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Review

Doxorubicin and other anthracyclines in cancers: Activity, chemoresistance and its overcoming

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ABSTRACT

Anthracyclines have been important and effective treatments against a number of cancers since their discovery. However, their use in therapy has been complicated by severe side effects and toxicity that occur during or after treatment, including cardiotoxicity. The mode of action of anthracyclines is complex, with several mechanisms proposed. It is possible that their high toxicity is due to the large set of processes involved in anthracycline action.

The development of resistance is a major barrier to successful treatment when using anthracyclines. This resistance is based on a series of mechanisms that have been studied and addressed in recent years. This work provides an overview of the anthracyclines used in cancer therapy. It discusses their mechanisms of activity, toxicity, and chemoresistance, as well as the approaches used to improve their activity, decrease their toxicity, and overcome resistance.

1. Anthracyclines: chemical structures and synthesis

Anthracyclines are aromatic type II polyketides, defined by Brockmann as yellow-red or red, optically active dyes consisting of a linear tetracyclic 7,8,9,10-tetrahydro-5,12-naphtacenoquinone scaffold, with a polyhydroxy anthraquinone structure (rings B, C and D) fused to a fourth saturate substituted ring (A), which constitutes the aglycone moiety, which is decorated with one or more sugar moieties (Brockmann, 1963) (Fig. 1).

The first, most used anthracyclines were isolated by members of the genus *Streptomyces*. The rhodomycins were the first anthracycline compounds, identified by Brockmann and Bauer, originally studied as potential antibiotics, and found effective vs. *Staphylococcus aureus* (Brockmann and Bauer, 1950) (Fig. 2).

Daunorubicin (Dau) was isolated from *Streptomyces (S.) peucetius* in 1960 and was shown to be extremely active against acute leukemia (Camerino and Palamidessi, 1960; di Marco et al., 1981; Tan et al., 1967).

Doxorubicin (Dox) was subsequently obtained from a randomly mutagenized strain of *S. peucetius* and was shown to be even more potent than Dau. (Arcamone et al., 1969; di Marco et al., 1981). The search for more potent anthracyclines led to the isolation of many other molecules from Streptomyces species, including nogalamycin from *S. nogalater*, which is highly active against Gram-positive bacteria and several cancer lines but very toxic; aclacinomycin A from *S. galilaeus*, which has potent antileukemia activity and low cardiotoxicity and is currently only prescribed in Japan and China; and steffimycin B from *S. steffisburgensis* (Wiley et al., 1968; Oki et al., 1975; Weiss, 1992).

Streptomycetes have a complex, multicellular lifestyle, that involves the production of secondary metabolites, in particular when environmental conditions become limiting and when they undergo morphological differentiation (Bibb, 2005). Streptomycete genomes contain many biosynthetic gene clusters (BGCs), which group together the genes involved in secondary metabolite production (Bentley et al., 2002) and make possible the production of a series of bioactive molecules, including antibiotics that play a role in the defense of Streptomycetes against other competitors. Anthracyclines often have antibiotic activity against Gram-positive bacteria. On the one hand, they effectively fight

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other bacteria that compete with Streptomycetes in a nutrient-deprived environment. On the other hand, they can trigger programmed cell death in the Streptomyces species itself, with the onset of a process of autolytic degradation of the old bacterial mycelium and development of aerial hyphae. This process involves morphological and chemical differentiation and is a hallmark of multicellular bacteria (Claessen et al., 2014; van der Heul et al., 2018; Tenconi and Rigali, 2018).

In addition, anthracyclines reduce DNA phage infection by intercalating into DNA (Kronheim et al., 2018). They are also useful in intra- and interspecies communication (Challis and Hopwood, 2003). Overall, the synthesis of anthracyclines represents a competitive advantage for Streptomycetes, which have resistance mechanisms based on efflux by ABC-transporters, sequestration, chemical modification, programmed cell death, and metabolic dormancy (Tenconi and Rigali, 2018).

Anthracyclines are synthesized by multienzymatic pathways in BCGs (Hulst et al., 2022), formed by tens of biosynthetic genes, under the control of a series of regulatory genes. First, an anthracyclinone carbon scaffold is formed, which is then tailored in a species-specific fashion and decorated with one or more carbohydrate groups.

The aglycone backbone is formed by at least three proteins, forming the so-called minimal polyketide synthase, composed by an acyl carrier protein (ACP) and two ketosynthase subunits (KSα and KSβ). The reaction is based on iterative additions of malonyl units to an acetyl or propionyl group linked to a phosphopantetheine prosthetic group derived from CoA of ACP; the growing polyketide is transferred from the ACP to the active cysteine of KSα. After transfer to the KSα, the ACP supplies malonyl units, which are incorporated in the growing chain in a Claisen condensation reaction catalyzed by KSβ, and the polyketide is simultaneously transferred back to the ACP. Nine extension rounds are necessary to obtain the anthracycline decaketide structure (Fig. 3A). Consequently, the polyketide undergoes a series of modification reactions catalyzed by ketoreductases, aromatases, cyclases, oxygenases, methyltransferases and short-chain dehydrogenases/reductases, leading to closure of the rings and formation of the structures of many different tetracyclic aglycones, tailored with different groups and with different stereochemistry.

The aglycones are subsequently glycosylated. Often 6-deoxysugars are added to position 7 in ring A (R1 substituent in Fig. 1), such as the 3-amino-2,3,6-trideoxy-α-l-lyxo-hexopyranose (daunosamine) sugar of Dau and Dox. The biosynthesis of 6-deoxysugars starts with the attachment of thymidine monophosphate to glucose-1-phosphate, that results in thymidine diphosphate (TDP)-D-glucose (Fig. 3B). This is followed by two consecutive dehydration reactions, to yield a 3,4-diketo intermediate. TDP-L-daunosamine is produced by pyridoxal-5′-phosphate dependent enzymes, which catalyze a 3-transamination reaction and a 5-epimerization reaction, and by a NADPH stereospecific 4-ketoreductase (Fig. 3C). While Dau is produced by a number of strains, its immediate biosynthetic product Dox is produced only by strain *Streptomyces peucetius caesius* ATCC 27952, whose complete genome was recently sequenced. Scaling up the production of Dox has proven to be challenging.

Hundreds of anthracycline analogues have been produced using modified bacteria. Many other molecules have been produced by semisynthesis, such as Dox, epirubicin (Epi), idarubicin (Ida), valrubicin (Val) and pirarubicin, all which are in clinical use (Fig. 4) (van der Zanden et al., 2021). For example, Dox is industrially prepared by semi-synthesis from Dau, through a chemical bromination at C-14, followed by displacement of the bromine by hydroxide under treatment with a mild base (Dhakal et al., 2018).

In addition, the totally synthetic amrubicin (Amr), which includes a minimalistic form of the daunosamine sugar, is used in lung cancer chemotherapy in Japan (Fig. 4) (Kurata et al., 2007).

Genome mining strategies for the discovery of novel BCGs, techniques of metabolic engineering and combinatorial biosynthesis have yielded a number of anthracyclines and anthracycline-related molecules.

The use of several techniques, based on rational strain development methods, with approaches focusing on modification of regulatory networks, deletion of genes for competing pathways, increasing precursor availability, increasing expression of rate-limiting biosynthetic enzymes, increasing product tolerance, combinatorial biosynthesis, and use of heterologous hosts, has led to an increased production of molecules with medical and economic value (Hulst et al., 2022).

2. History and use of anthracyclines

Daunomycin was first described by Di Marco and coworkers, at Farmitalia Research Laboratories in 1960s. They isolated it from the bacterium *S. peucetius*. Daunomycin was later renamed Daunorubicin (Dau) as a combination of daunomycin and rubidomycin, the latter being an identical compound that was isolated and identified by Dubost and colleagues at Rhone-Poulenc from *S. coerubleorubidus*. The first clinical trials of Dau on solid tumors were not very successful, but its use in lymphomas had astonishing results. This prompted studies on other similar molecules.

Dox was discovered soon after at Farmitalia. It was produced using a mutated variant of the bacterium *S. peucetius* var. *caesius*. This molecule (also sold under the name of adriamycin) was surprisingly active against various types of solid tumors in animals and in clinical trials and was soon implemented in clinical settings. Although the anthracyclines were discovered more than 50 years ago, they are still significantly used in various types of solid tumors and hematologic cancers. Indeed, these agents are still among the most effective anticancer drugs to date. Their importance is witnessed by the huge number of clinical trials registered on the clinicaltrial.gov website at the date of Apr 27th, 2023, reported in Table 1, where anthracyclines already approved by the FDA are

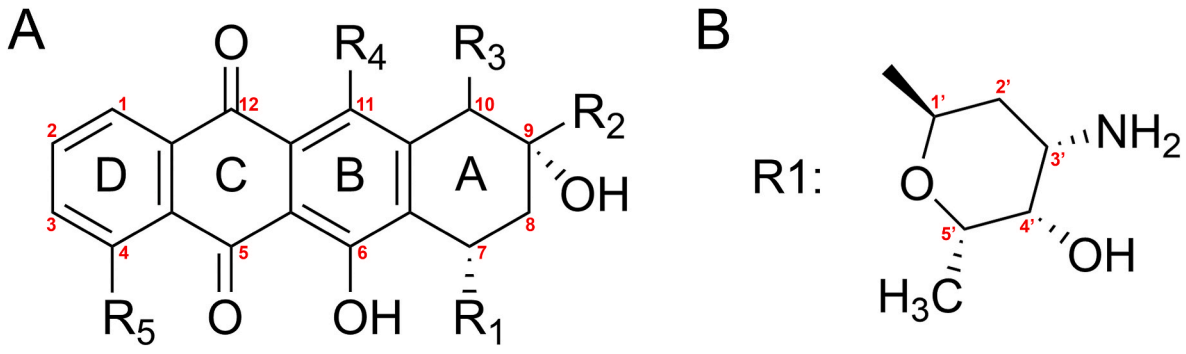


Fig. 1. A. General structure of anthracyclines, with 4 conjugated rings indicated as A-D. Substituents are indicated as R1-R5; R1 is often a sugar. Positions in the aglycone moiety are indicated as red numbers 1–12; B. the daunosamine ring bound to C7 in Daunorubicin and Doxorubicin; the carbons of the ring are indicated as red numbers 1′-5’.

highlighted in blue.

Dox and Dau were approved for clinical use by the FDA in the 1970s. They are now used to treat a variety of cancers, including acute lymphocytic and myelogenous leukemia, Hodgkin's and non-Hodgkin's lymphomas, bladder, gastric and breast cancers, and metastatic cancers such as ovarian cancer, osteogenic, Ewing and soft tissue sarcomas, thyroid cancer, Wilms' tumor, small cell lung cancer and neuroblastoma. However, both Dox and Dau have strong cardiotoxicity. This prompted the attempt to produce a variety of analogues to find compounds with improved therapeutic applications. However, only a few of them have been adopted for worldwide use, i.e., Epi, Ida and Val.

Epi has similar activity to Dox with reduced cardiotoxic effects (Paul Launchbury and Habboubi, 1993). The first trial of Epi in humans was published in 1980 (Bonfante et al., 1980), and the FDA approved its use in node-positive breast cancer as a component of adjuvant therapy in 1999.

Ida, initially approved in 1990 for acute myelogenous leukemia (AML), is a lipophilic variant of Dau that has significant oral bioavailability (approx. 30%) (Cersosimo, 1992). This feature makes Ida particularly attractive for the treatment of elderly patients, who are often unable to tolerate the side effects of intravenous chemotherapy (Crivellari et al., 2004).

Val, approved in 1998, was originally used under the trade name Valstar® in late 1990s for intravesical therapy of Bacillus Calmette-Guérin-refractory carcinoma in patients at risk of morbidity or mortality following cystectomy (Steinberg et al., 2000); it was withdrawn from the market in 2002 due to manufacturing issues, and relaunched in 2009.

Although most of the anthracyclines possess significant anticancer activities as single agents, they are mostly used in combination chemotherapy or in nanoformulations to improve therapeutics efficacy and to reduce toxicity.

For instance, commonly used Dox-containing regimens are CA (cyclophosphamide, Adriamycin), TAC (Taxotere, CA), ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine), CHOP (Cyclophosphamide, Adriamycin, Vincristine, Prednisone) and FAC (5-Fluorouracil, Adriamycin, Cyclophosphamide), whereas Epi is present in the combination chemotherapy Fluorouracil, Epi and cyclophosphamide (FEC) that a meta-analysis of anthracycline trials has demonstrated to be superior to cyclophosphamide, methotrexate and 5-fluorouracil (CMF) (Earl and Iddawela, 2004).

3. Anthracyclines: new modes of administration

3.1. Liposomal formulations

In addition to naked anthracyclines, different nanoformulations are in use. Several liposomal Dox formulations have been approved, including PEGylated (biochemically modified with polyethylene glycol (PEG)) forms, such as Doxil®/Caelix®, Lipodox®, and non-PEGylated (Myocet®) forms. PEGylated liposomal Dox is the first FDA-approved anthracycline nano-drug (1995). It is currently marketed by Janssen as Doxil in the United States/Japan and as Caelyx in the rest of the world. The current licensed product indications include (worldwide) AIDS-related Kaposi's sarcoma, ovarian carcinoma, multiple myeloma (in combination with bortezomib), and, in the European Union, breast carcinoma in patients at risk of anthracycline cardiotoxicity. Doxil/Caelix is a complex, sterically stabilized liposome, that was developed based on three principles: (i) prolonged drug circulation time and reduced clearance by the reticuloendothelial system (RES), due to the use of PEGylated nano-liposomes; (ii) high and stable content of Dox

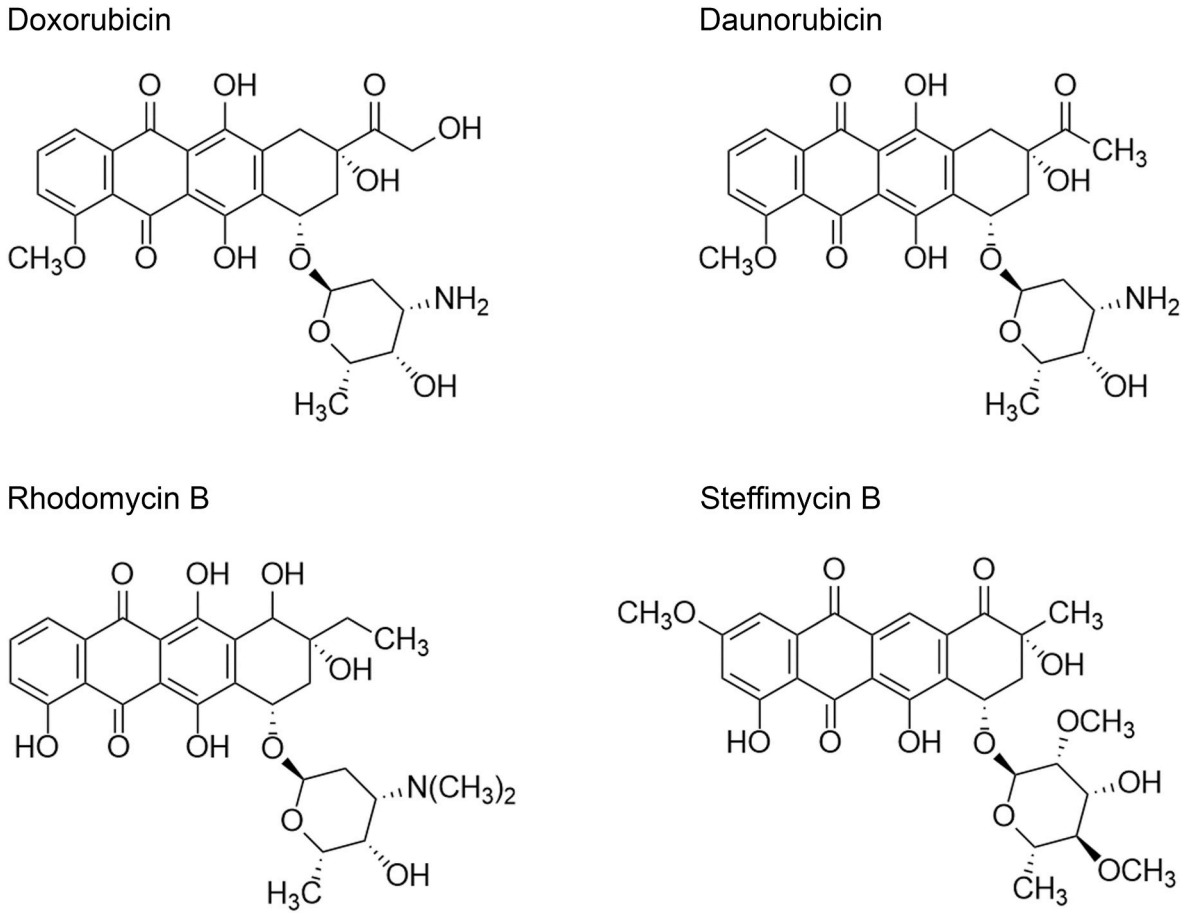


Fig. 2. Chemical structures of some classical anthracycline molecules. Doxorubicin (Dox), Daunorubicin (Dau), Rhodomycin B and Steffimycin B are indicated.

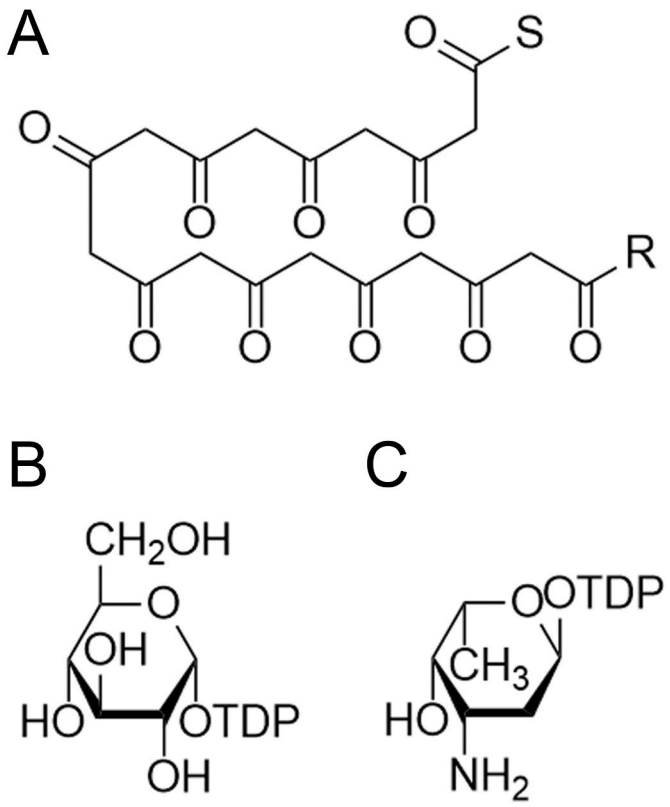


Fig. 3. Chemical structures involved in the synthesis of anthracyclines. **A)** the linear decaketide at the basis of anthracyclines synthesis; **B)** TDP-D-glucose, the first intermediate in the synthesis of anthracyclines carbohydrates; **C)** TDP-L-daunosamine, the sugar bound in position 7 (R1 substituent in Fig. 1) in both Dau and Dox.

driven by a transmembrane ammonium sulfate gradient, which also allows for drug release at the tumor; and (iii) liposome lipid bilayer in a "liquid ordered" phase composed of high-Tm (53 °C) phosphatidylcholine, and cholesterol. Due to the enhanced permeability and retention (EPR) effect, Doxil/Caelix is "passively targeted" to tumors. This means that it accumulates in tissues that offer increased vascular permeability, such as in sites of inflammation or cancer. At the tumor, Dox is effectively released and becomes available to tumor cells (Barenholz, 2012). Even after expiring of the FDA license in 2010, the development of a bioequivalent version of the drug proved to be difficult, until Sun Pharmaceutical Industries Ltd. (SPIL) developed Lipodox (SPIL Dox HCl liposome injection).

Myocet (Cephalon) is a non-PEGylated liposomal formulation of doxorubicin (Dox). It is approved for the first-line treatment of metastatic breast cancer in Europe and Canada.

The pharmacokinetics of conventional Dox and of the different liposomal formulations differ. Plasma levels of total Dox are substantially higher with liposomal Dox forms, while the peak plasma levels of free Dox are higher with conventional Dox. PEGylated liposomal Dox may accumulate in the skin and is associated with a particularly unpleasant form of palmar–plantar erythrodysesthesia, that occurs rarely with non-PEGylated Dox. Further, in contrast to pegylated liposomal Dox, non-pegylated Dox is phagocytized by mononuclear phagocytes.

In cancer patients who have a high risk of cardiac disease, pegylated liposomal Dox has been shown to increase survival compared to conventional Dox. It also has a better safety profile, with less cardiotoxicity, nausea and vomiting, and less myelosuppression (Chatterjee et al., 2010; Leonard et al., 2009; Liu et al., 2020a; O'Brien et al., 2004; Rahman et al., 2007), possibly due to greater accumulation of liposomal Dox in tumor tissue (and lesser amounts in other tissues) through EPR effect.

Liposomes can be functionalized with peptides and antibodies to increase their selectivity for tumor cells. This has been shown to reduce adverse effects, improve cytotoxicity, and even overcome multi-resistance in the treatment of tumors such as non-Hodgkin's lymphoma, glioma, melanoma, breast cancer, colon, and lung carcinoma (Arabi et al., 2015a, 2015b; Biswas et al., 2013; Chang et al., 2013; Chen et al., 2012a, 2012b, 2012c, 2012d; D'Angelo et al., 2022; Lowery et al., 2011; Mamot et al., 2012; Reynolds et al., 2012; Shahin et al., 2013; Shroff and Kokkoli, 2012; Wang et al., 2012; Zong et al., 2014).

In addition to peptides and antibodies, liposomes can also be functionalized with sugars, folate, lactoferrin, and E-selectin. These functionalizations can also improve the targeting of liposomes to tumor cells (D'Angelo et al., 2022). Stimuli-specific functionalizations have also been developed to promote the release of anthracyclines in tumor regions. These functionalizations include photosensitive, redox-sensitive, pH-sensitive, magnetic, temperature-sensitive, and ultrasound-specific liposomes. These liposomes have been used in different cancer models with promising results (Agarwal et al., 2011; Al-Jamal et al., 2012; de Smet et al., 2013; Dicheva et al., 2014; Li et al., 2019a; Li et al., 2013; Ta et al., 2014; Tagami et al., 2011; van Elk et al., 2014; Xu et al., 2015).

3.2. *Nanoformulations*

In addition to liposomal formulations, other nanoformulations of anthracyclines have been engineered to achieve higher solubility, provide more control over the drug's release and distribution, improve tumor cytotoxicity, and reduce side effects on neighboring healthy cells. A variety of experimental approaches have been used in recent years, including: polymeric vesicles; micro- and nano-emulsion systems; synthetic or natural polymeric nanoparticles (based on PEG or polylactic-*co*-glycolic acid, or dendrimer-based, among others); hydrogel nanoparticles; alginate-based nanoparticles; metal-organic frameworks. These nanoformulations have the potential to improve the efficacy and safety of anthracyclines for cancer treatment. However, more research is needed to optimize these formulations and to determine their long-term safety (for a review, see D'Angelo et al., 2022; El-Say and El-Sawy, 2017; Ibrahim et al., 2022; Lakkakula et al., 2021).

One of the most promising approaches to improving the efficacy and safety of anthracyclines is the encapsulation of these drugs in ferritins and ferritin derivatives. Ferritin is a protein cage composed of 24 subunits that possesses a cavity that can store up to 4500 Fe(III) ions. Ferritin has several desirable properties for cancer therapy, including high biocompatibility, ability to pass body barriers, high thermal stability and acid/base resistance, natural cell-targeting ability (due to specificity for the transferrin receptor TfR1, which is overexpressed in many cancer cells), and easily modifiable surfaces. These properties make ferritin a promising carrier for anthracyclines. By encapsulating anthracyclines in ferritin, it is possible to improve the solubility, stability, and targeting of these drugs. This could lead to more effective and less toxic cancer treatments (Cheng et al., 2020; Fan et al., 2013, 2018; Mainini et al., 2021; Tesarova et al., 2020; Wetz and Crichton, 1976; Xu et al., 2022).

The incorporation of Dox into horse spleen ferritin nanocages was first reported in 2005 (Simsek and Akif Kilic, 2005). Since then, heavy chain human ferritin has been used, either as it is (Liang et al., 2014) or modified with stimuli-sensitive sequences, that on the one hand allow long circulation and on the other hand are removed by tumor matrix-metalloproteases, increasing the potential for targeted delivery of Dox or Mitoxantrone (Falvo et al., 2018; Fracasso et al., 2016).

The co-delivery of anthracyclines with other drugs in a liposomal system has also been shown to be promising. In some cases, this approach reduced side effects of both drugs and synergistically improved the therapy. For example, co-delivery of Dox with molecules such as ceramide, lovastatin, CXCR4 antagonist, disulfiram, curcumin and rapamycin has shown promise to treat different tumors (Chen et al., 2019a; Liu et al., 2019b; Liu et al., 2014b; Rolle et al., 2020; Sesarman

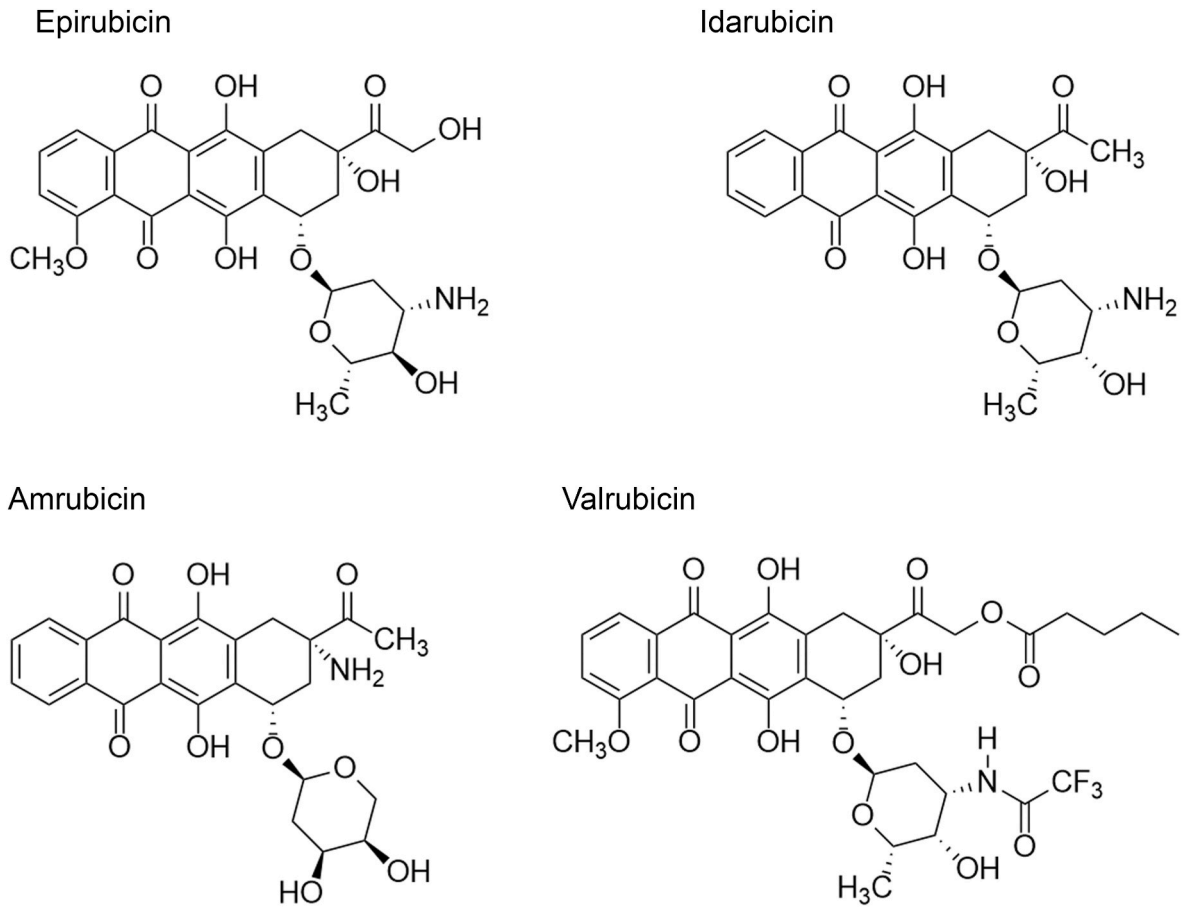


Fig. 4. Semisynthetic and synthetic anthracyclines used as anticancer drugs. The structures of Epirubicin (Epi), Idarubicin (Ida), Amrubicin (Amr) and Valrubicin (Val) are indicated.

Table 1
Clinical trials listed on the Clinicaltrials.gov database (Apr 27th, 2023).

Drug	Number of trials	Main Clinical Conditions	General Information
Doxorubicin*	2478	Lymphomas and soft tissue sarcoma, breast, genitourinary, ovarian, gastrointestinal, liver, and hematologic cancers	Naturally fluorescent anthracycline antibiotic
Daunorubicin**	457	Leukemias, lymphomas, lymphoproliferative disorders	First identified anthracycline
Epirubicin	586	Breast, gastrointestinal, genitourinary, lymphoma and sarcomas	Different spatial orientation of the hydroxyl group at the 4′ carbon of the sugar, fewer side effects
Idarubicin***	296	Leukemias and lymphomas, gastrointestinal and liver cancer	Soluble anthracycline, increased cellular uptake
Valrubicin (Valstar®)	13	Bladder, urogenital cancer	Semisynthetic analog of Doxorubicin, administered by direct infusion into the bladder
Pirarubicin	37	Epithelial, gastrointestinal, liver, breast, lymphomas	Less cardiotoxic than Doxorubicin, exhibits activity against some Dox-resistant cell lines
Amrubicin (Calsed®)	22	Lung and thoracic cancers, small cell lung carcinoma	First anthracycline derivative created by de novo synthesis
Aldoxorubicin	20	Gastrointestinal, endocrine, and pancreatic cancers, sarcomas	Doxorubicin linked to 6-maleimidocaproyl) hydrazone
Aclarubicin	17	Leukemias and lymphomas	Less cardiotoxic than Doxorubicin
Annamycin	8	Leukemias and lymphomas	Second generation anthracycline, less cardiac toxicity
Esorubicin (Deoxydoxorubicin)	5	Myeloma and breast cancer	Synthetic derivative of doxorubicin, less cardiotoxic but may cause severe myelosuppression
AEZS 108 (Zoptarelin doxorubicin)	5	Endometrial and breast cancer	Doxorubicin linked to a small peptide agonist to the luteinizing hormone-releasing hormone
Berubicin	4	Glioblastoma	Able to cross the blood-brain barrier and reach brain tumors
Sabarubicin (MEN-10755)	3	Prostate cancer, solid tumors	Disaccharide analog of doxorubicin
Camsirubicin (GPX-150)	2	Soft tissue sarcoma, solid tumors	Synthetic non-cardiotoxic analog of Doxorubicin
Cytarabine + Daunorubicin (CPX-351)	70	Leukemias and lymphomas	Liposomal formulation of cytarabine and Daunorubicin at a fixed 5:1 M ratio
Thermodox®	14	Gastrointestinal, bladder, liver, and breast cancers	Lysolipid thermally sensitive liposomal Doxorubicin

* Includes Doxorubicin, Adriamycin PFS, Adriamycin RDF, Doxil, Caelyx (Pegylated liposomal formulation).
** Includes Daunomycin, Cerubidine, and Rubidomycin.
*** Includes 4-Demethoxydaunorubicin, Idamycin, and 4-DMDR.

et al., 2019; Wang et al., 2019).

3.3. Other formulations

Many chemical modifications have been attempted to overcome the limitations associated with anthracyclines, such as their short retention time, cardiotoxicity, multidrug resistance and rapid excretion. These modifications have resulted in changes in the pharmacokinetics of the compounds, which has in turn affected their toxicity and side effects (Denel-Bobrowska and Marczak, 2017). Compounds as cholesterol-Dox, Dox-fatty acyl derivatives, hydrazone derivatives, formamidino-Dox derivatives, dexamethasone derivatives, hybrid compounds with arimetamycin scaffolds, steroidal anti-estrogen-Dox bioconjugates have been designed and synthesized. These compounds have shown changes in efficacy compared to Dox, with some being more effective and others being less toxic (Choi et al., 2017; Graeser et al., 2010; Peter et al., 2022). One example of a promising compound is INNO-206, a 6-maleimidocaproyl hydrazine derivative of Dox. INNO-206 is an albumin-binding prodrug of Dox with acid-sensitive properties. The prodrug binds rapidly to circulating serum albumin and releases Dox selectively at the tumor site. This results in higher antitumor efficacy compared to Dox in different tumor xenograft models and in an orthotopic pancreas carcinoma model (Graeser et al., 2010). Hybrid compounds of Dox conjugated with ferulic and caffeic acid, designed to be endowed with antioxidant activity, displayed high cytotoxicity vs. breast cancer cell, while being less toxic than Dox vs. cardiomyocytes (Chegaev et al., 2022).

Recently, Liu et al. designed and synthesized a photoresponsive hybrid prodrug with Dox and combretastatin A4 functions, which was effective vs. tumor neovasculature, with drug release performance triggered by sequential irradiation with two light wavelengths; the prodrug showed higher cytotoxicity compared with the two individual drugs towards MDA-MB-231 breast cancer cells, indicating that a synergistic effect was achieved (Liu et al., 2019c).

4. Molecular mechanisms of anthracyclines action in cancer

Anthracyclines are mostly taken up by cells through passive diffusion, although organic cation transporters can also contribute to drug uptake. Once inside the cell, anthracyclines can bind to the 20S subunit of the proteasome, a protein complex that breaks down proteins. Anthracyclines can also enter the nucleus through the nuclear pores (Kiyomiya et al., 2002). The exact mechanisms by which anthracyclines act on tumors are not fully understood, but they are thought to involve a number of different pathways (Fig. 5).

4.1. DNA intercalation and chromatin damage

Anthracyclines act on cancer cells by different mechanisms, many of which depend on drug binding to DNA: anthracyclines are mostly planar, aromatic molecules, able to bind DNA by intercalating with their aglycone moieties between DNA base pairs, thereby pushing apart the neighboring base pairs, and to be anchored to the DNA minor groove by one or more sugars (Fig. 6). Anthracyclines bind DNA with high affinity. This binding can be used to visualize chromosomes, as the fluorescence of Dau can be used to stain chromosomes (Comings and Drets, 1976). In circular DNA, such as plasmids, intercalation of anthracyclines produces strand separation that unwinds the DNA double helix and increases torsional stress. Eukaryotic cells have linear genomic DNA that is partitioned by proteins, such as nucleosomes and the transcriptional repressor CTCF. These proteins topologically constrain the DNA, which means that it cannot be easily unwound (Dixon et al., 2012). Cellular processes such as DNA replication, transcription, recombination, and repair require access to DNA and produce torsional stress. Binding of one Dox molecule relaxes the double helix twist by −27°, which determines local DNA unwinding. This unwinding needs to be compensated by positive upstream torsional strain (Salerno et al., 2010). Anthracycline intercalation produces torsional stress that affects DNA-dependent processes, and alters the structure and dynamics of nucleosomes, resulting

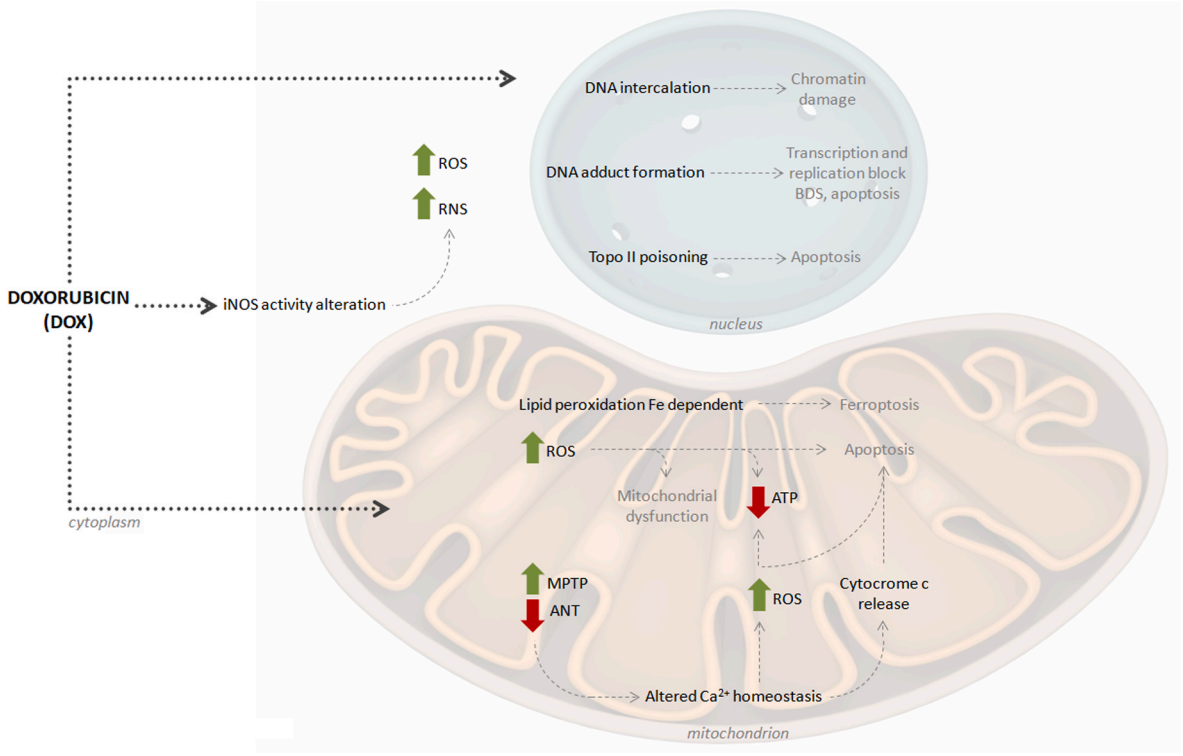


Fig. 5. The molecular mechanisms of anthracyclines (DOX) action in cancer cells are shown in the figure. The different mechanisms are shown within the cellular districts in which they mainly act. The green upward arrows and the red downward arrows indicate increases and decreases, respectively. The dashed light gray arrows point to the final consequences of each alteration.

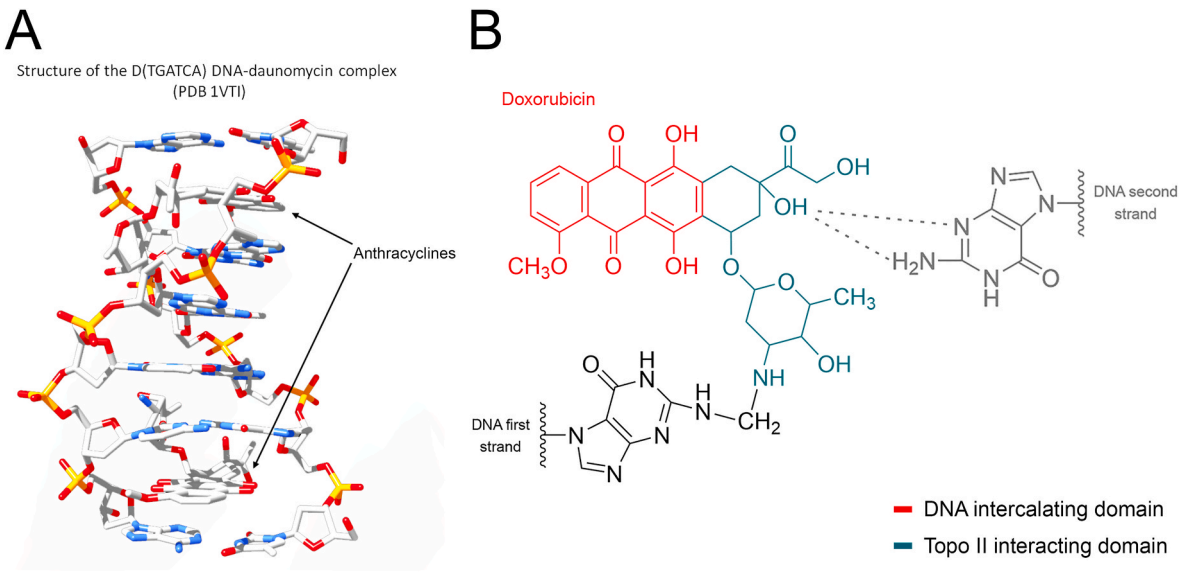


Fig. 6. Structures of anthracycline-DNA complexes and adducts. **A)** crystal structure of DNA sequence TGATCA complexed with two molecules of Dau. Dau intercalates in the major groove with its planar aromatic domain, and binds the minor groove with its sugar moiety, resulting in DNA torsional stress (Nunn et al., 1991); **B)** structure of the Dox-DNA complex. Dox forms a covalent bond mediated by formaldehyde with guanine on one strand of DNA, and hydrogen bonds with guanine on the opposing strand. Binding sites of anthracycline moieties relevant for pharmacological activity are indicated: the "DNA intercalating domain" is represented in red, the interaction domain with topoisomerase II is shown in green.

in increased release of nucleosomes (also called nucleosome eviction) and inducing structural changes in the nucleosomes themselves, increasing the dissociation of the H2A/H2B dimers from the tetrameric histone core (Bancaud et al., 2006, 2007; Gupta et al., 2009; Martins-Teixeira and Carvalho, 2020).

The sugar moiety of anthracyclines, which points towards the minor groove of DNA, also competes with histones. Anthracycline-induced histone eviction is probably due to both DNA intercalation of the anthraquinone group and nucleosome destabilization by the sugar moiety. Many anthracyclines, including Dox, cause nucleosome dissociation in an ATP-, transcription-, and histone chaperone-independent fashion. In contrast, doxorubicinone, a Dox metabolite that lacks the sugar moiety, causes little nucleosome eviction, suggesting that the sugar moiety plays a critical role in histone dissociation. Histone eviction is not observed for other DNA intercalators, such as ethidium bromide, or other chemotherapeutic drugs, such as the topoisomerase II inhibitor etoposide (Nesher et al., 2018; Pang et al., 2013a; van der Zanden et al., 2021; Yang et al., 2013a).

Nucleosome eviction has been demonstrated to be induced by different anthracyclines, at concentrations used in chemotherapy, independently of the DNA damage response proteins p53 and ATM, and in topoisomerase II α-depleted cells, showing that the effect is in large part directly dependent on drug binding and the consequent DNA torsional stress (Jackson et al., 2012; Jiang et al., 2009; Pang et al., 2013a). In anthracycline treatment, nucleosome eviction has multiple consequences, which are collectively called chromatin damage. These consequences include epigenomic and transcriptional alterations and reduced double strand breaks repair. Upon anthracycline-dependent histone H2AX eviction, this histone is unavailable for phosphorylation by the master regulators of DNA damage response ATM and ATR following DNA breaks: anthracyclines therefore reduce DNA repair with respect to etoposide-treated cells, where histones are not evicted. Further, anthracyclines alter the epigenetic code, because the evicted histones are replaced by new ones after anthracycline exposure, and can be considered epigenetic modifiers, rather than simple DNA damaging agents (Pang et al., 2013a, 2015).

Anthracyclines have different sequence specificity and binding affinities: Dau and Dox preferentially bind sequences with two GC pairs and an AT (e.g. GCATGC), intercalating in GC bases of DNA and establishing hydrogen bonds between hydroxyl group on C9 of Dau/Dox and N2 and N3 of guanine. This preference to GC base pair also explains the increase in binding affinity of the drug with an increase in GC content of DNA, and the high affinity for both nuclear and mitochondrial DNA (Ashley and Poulton, 2009; Chaires et al., 1987; Wang et al., 1987; Nunn et al., 1991).

Anthracyclines evict histones with distinct preferences. When chromatin is fully condensed, as in mitosis, histones are not evicted by anthracyclines, while histones are preferentially evicted by transcriptionally active genes, particularly in regions around transcription starting sites. Dau preferentially evicts histones from Lys36-trimethylated histone H3 (H3K36me3)-marked chromatin regions, which are rich in GC bases and generally associated with transcriptionally active gene bodies. In contrast, Acl evicts Lys27-trimethylated histone H3 (H3K27me3)-marked chromatin regions, relatively more condensed, enriched in AT bases, and identified as facultative heterochromatin sites. This chemical profiling of anthracyclines suggests possible anticancer drug selectivity. Diffuse large B-cell lymphoma cells that harbor histone methyltransferase EZH2 activating mutations, with corresponding elevated levels of H3K27me3, are about tenfold more sensitive to Acl than to Dau treatment (Pang et al., 2015; Yang et al., 2013a).

4.2. *DNA adduct formation*

Anthracyclines form adducts with DNA, through covalent bonds and hydrogen bonds with the two strands. While a filament forms covalent bonds with the molecule, this interaction is stabilized through the formation of hydrogen bonds on the other filament (Bilardi et al., 2012).

Structurally, anthracyclines intercalate preferably at GC base pairs. This is because the guanine base has a larger surface area than the other DNA bases, which makes it more likely to interact with the anthracycline molecule (Chaires et al., 1987, 1990; Chen et al., 1986). Dox-guanine covalent bonds can be formed at clinically used anthracycline concentrations, suggesting that DNA adducts can be formed in treated patients. However, this is not the main mechanism of Dox action, because only a small fraction of total bound drug forms DNA adducts at clinical doses (Coldwell et al., 2008; Forrest et al., 2012; Yang et al., 2013a).

Anthracycline adducts are often mediated by cellular formaldehyde,

which is formed by free radical reactions of polyamines and lipids, and is overproduced in Dox-sensitive cancer cells with respect to normal cells and resistant cancer cells. In addition to covalent Dox-DNA binding, a guanine on the opposite DNA strand can bind Dox with a hydrogen bond (Fig. 6B) (Kato et al., 2001; Taatjes et al., 1996, 1997).

In addition to their antitumor effect, anthracyclines that are bound to DNA are sequestered, preventing them from cycling and enzymatic degradation, which would generate ROS and toxic metabolites (see below) (Rephaeli et al., 2007).

DNA-drug adducts have different effects, such as transcriptional block, replication block, double-stranded breaks (DSBs) formation, and induction of apoptosis. *In vitro* transcription experiments show the ability of Dox (pre-activated with formaldehyde) to interfere with the transcription process by forming blocks along the transcription chain (Cullinane and Phillips, 1990). These blocks are found to be greater nearby the GpC sites, probably caused by the interaction between the drug and guanine (G) and by the formation of an inter-strand G-Dox-G cross-link. Similar results have been obtained testing other anthracyclines, such as cyano-morpholino-adriamycin (Cullinane and Phillips, 1992) or barminomycin for their ability to cause transcription blockage in *in vitro* experiments (Perrin et al., 1999). Barminomycin blocks transcription near GC sites and forms inter-filament bonds. Heat treatment at 90 °C reduces the number of bonds formed between DNA and drug by about 60%, which suggests that these adducts are considerably thermoresistant. However, while Dox requires formaldehyde pre-treatment to form adducts, barminomycin can exert its effects without activation.

Dox treatment of mouse breast cancer cells leads to blocking of [8H]-thymidine incorporation, disruption of DNA replication and cell cycle arrest, highlighting the ability of Dox to interfere with replicative processes of the cell (Bilardi et al., 2012; Kanno et al., 1985). Furthermore, during DNA replication processes, the replication machinery may stall at the points of adduct formation and contribute to the collapse of the replication fork by increasing the likelihood of DSBs and DNA damage (Bilardi et al., 2012). Forrest and colleagues investigated the behavior of DNA damage response proteins following treatment with Dox-DNA adducts. They found that the phosphorylation of p53 was not affected by the adducts. However, increased sensitivity to adducts was observed when the signaling of ATM and ATR protein kinases (two serine/threonine kinases that regulate cell cycle checkpoints and are involved in DNA repair) was lost. ATR is necessary, in the response to adducts, in the G2/M checkpoint, while ATM seems to be important during the G1 phase (Forrest et al., 2012).

Inter-strand crosslinks generated by Dox or other anthracyclines represent a major challenge for DNA damage response and repair proteins. Spencer and colleagues tested the main pathways of DNA repair (mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER), homologous recombination (HR) and non-homologous end-joining (NHEJ) using Dox, barminomycin and Doxoform (a Dox-formaldehyde conjugate)) on colorectal cancer cells. Cell lines with alterations in MMR, BER and NHEJ repair pathways were equally sensitive to the treatments as compared to control cell lines, suggesting an unlikely involvement of these pathways in the repair of adduct damage. In contrast, defective lines in the NER and HR repair pathway showed lower or higher sensitivity, respectively, compared with the control lines, indicating an involvement of these pathways in the response to adduct-induced DNA damage (Spencer et al., 2008).

Despite these evidences, however, the consequences of exposure to Dox alone or pre-activated with formaldehyde appear to be substantially different. While Dox treatment alone mainly interferes with topoisomerase II and can easily lead to DSBs, administration of pre-activated Dox with formaldehyde forms adducts with the DNA without causing it to rupture. Dox-DNA adducts, formed by the simultaneous administration of Dox and "formaldehyde-releasing" drugs, induce a cytotoxic response, greater than Dox administered alone. Furthermore, DNA fragmentation, induced by pre-activated Dox, is much lower in topoisomerase-defective cells or following co-administration with catalytic inhibitors of topoisomerase II compared to control cells. Finally, the apoptosis induced by the Dox-DNA adducts is initiated by the action of caspases and reversed by the overexpression of Bcl2. Taken together, these data suggest that adducts can induce apoptosis independently of the action of topoisomerase II (Swift et al., 2006).

In order to improve the antitumor activity of anthracyclines, approaches that increase the level of formaldehyde have been developed. These approaches include using compounds that release formaldehyde, such as butyroyloxymethyl-diethyl phosphate, pivaloyloxymethyl butyrate and hexamethylenetetramine, in combination with Dox. They also include using Dox-formaldehyde conjugates, such as Doxoform, and prodrugs, such as Doxsaliform (a Dox- salicylamide N-Mannich base that releases the Dox-formaldehyde conjugate). pH-responsive acrylate-based polymer formaldehyde-Dox prodrugs have also been produced, designed to release formaldehyde at a specific pH, which could improve the delivery of Dox to cancer cells (Barthel et al., 2016; Cutts et al., 2001; 2005; Engel et al., 2006; Ordonez et al., 2021; Post et al., 2005; Rephaeli et al., 2007).

4.3. Topoisomerase II poisoning

Mammals have two types of highly conserved topoisomerases: the monomeric type I topoisomerase, which generates single-strand breaks in DNA, and the dimeric type II topoisomerase, that forms DSB. Topoisomerases bind DNA supercoils, introduce breaks in DNA, release torsional stress, and reseal the breaks, facilitating DNA transcription, replication, repair and other processes.

Anthracyclines poison the topoisomerase II enzyme function and induce irreversible DNA damage by forming an abortive anthracycline-topoisomerase-DNA ternary complex. This complex stabilizes the DNA-topoisomerase II complex, possibly trapping the enzyme at the cleavage site and preventing topoisomerase from properly regenerating the broken phosphodiester bonds. Therefore, anthracyclines subvert the physiological function of topoisomerase II, transforming it into a DNA-breaking nuclease, which leads to genomic instability and triggers apoptotic cell death. Topoisomerases inhibitors are lethal toxins, that lead rapidly dividing cells to apoptosis. In anthracycline intercalation, the planar ring of the aglycone binds to DNA bases of the major groove, while the A ring and the C9 substituents bind the minor groove and interact with the topoisomerase II (Fig. 6B) (Nitiss, 2009; Pommier et al., 2010; Visone et al., 2020). The presence of a 4-methoxy group and the sugar moiety at position 3 play a role in anthracycline efficacy, in its interaction with DNA and topoisomerase II, and in the side effects of the drug, particularly in cardiotoxicity. Interestingly, cardiomyocyte-specific topoisomerase IIβ deletion protects mice from developing Dox-induced heart failure, while topoisomerase II inhibitors protect cardiomyocytes from toxicity induced by Dox (Vavrova et al., 2013; Zhang et al., 2012).

Epi, where the configuration of the C4′ hydroxyl group is inverted with respect to Dox, and the substituent is in the equatorial orientation (Fig. 4), is about 30% less cardiotoxic than Dox, since its pharmacokinetic profile is altered by detoxification as a 4′-glucuronide. Although less potent than Dox, Epi retains significant anticancer properties and is often used against non-Hodgkin lymphoma and breast cancer. It is better tolerated, and the cumulative maximal dose of Epi is about double that of Dox (Minotti et al., 2004).

Amr lacks the 4-methoxy group of the aglycone and the 3' amino group of the carbohydrate, which is a minimalist version of daunosamine. Amr also possesses an amino group at position 9 instead of a hydroxyl group (Fig. 4). Amr is less cardiotoxic than Dox and Epi. It is a prodrug, activated by enzymatic reduction of the carbonyl group at the side chain into a hydroxyl group. The active metabolite of Amr is very potent and stabilizes the topoisomerase II-DNA complex (Horita et al., 2016; Kurata et al., 2007).

4.4. Redox-mediated mechanisms

Anthracyclines can alter the redox state of a cell by iron-dependent lipid peroxidation, which can lead to an apoptotic process known as "ferroptosis", caused by the accumulation of lipid-based reactive oxygen species (ROS), and regulated by glutathione perodixase 4 (GPX4). Anthracyclines can form reactive adducts defined "iron-Dox" such as Dox-Fe^{2+} or Dox-Fe^{3+}, that can interconvert with each other and participate in ROS formation (Fang et al., 2019). Anthracyclines downregulate GPX4 and are able to drive the accumulation of iron directly within the mitochondria, accompanied by the downregulation of the ABCB8 transporter, an efflux pump for iron from the mitochondria, leading to excessive lipid peroxidation; the overexpression of ABCB8 protects against Dox-induced damage and preserves the structure of the mitochondria while its absence lowers Dox efflux, increases Dox-induced toxicity, and reduces cardiomyocytes viability (Menon and Kim, 2022). In melanoma cells silenced for *ABCB8*, resistance to Dox is decreased, compared to control cells, an effect found to be specific against anthracyclines and not against other commonly used chemotherapeutic molecules (Elliott and Al-Hajj, 2009). In lung cancer cells, ABC transporters inhibitors significantly increase ROS levels and induce cell death, underlining the importance of these transporters in cells detoxification (Yuan et al., 2022).

4.5. Altered calcium homeostasis

Anthracycline administration to cells can alter calcium homeostasis. This is possibly due to the dysregulation of calcium binding proteins and channels, such as ryanodine receptor, sarco/endoplasmic reticulum ATPase (SERCA), L-type Ca^{2+} channel and Sorcin (SOluble Resistance-related Calcium binding proteIN) (Hanna et al., 2014a; Keung et al., 1991a; Genovese et al., 2017a).

Mitochondrial calcium homeostasis is also altered by anthracyclines. Dox treatment can increase the permeability of the Mitochondrial Permeability Transition Pore (MPTP) and inhibit the calcium conducting Adenosine Nucleotide Translocase (ANT), which impairs the mitochondria's ability to obtain calcium from the cytosol (Wallace, 2007). Dox treatment triggers persistent calcium release, suppresses the prosurvival ERK1/2 pathway and induces cell migration, in a Ca^{2+}-dependent fashion (Abdoul-Azize et al., 2018).

Alteration in intracellular calcium levels by anthracycline treatment is one of the major causes of cardiotoxicity (see below). Increase in cellular Ca^{2+} concentration contributes to further generation of ROS, increase of mitochondrial permeability due to MPTP, and increase of cytochrome *c* release, which triggers apoptosis (Kim et al., 2006; Petrosillo et al., 2004; Przygodzki et al., 2005; Waring, 2005).

4.6. ROS generation and mitochondrial dysfunction

Due to the high energy requirements for contractile function, cardiomyocytes contain a high number of mitochondria, which can occupy up to 50% of their volume. Notably, Dox accumulates in mitochondria 100 times more than in cytosol. Dox can cause mitochondrial impairment through a number of mechanisms.

Inhibition of the mitochondrial respiratory chain can be due to the redox cycling capacity of Dox, which causes the generation of superoxide anion and reactive oxygen species (Davies and Doroshow, 1986; Doroshowsb and Daviesn, 1986). One of the best understood mechanisms of action of anthracyclines is their production of ROS. ROS are very reactive molecules that are generated during several metabolic processes, the main one being the electron transport chain of the oxidative phosphorylation (Oxphos) for ATP production, on the inner membrane of the mitochondria. ROS can also act as signal molecules, but when in excess they can damage membranes, biological macromolecules, and cell structures, leading to cellular dysfunction and apoptosis. Anthracyclines, and in particular Dox, can accumulate near the inner membrane of the mitochondria, thus affecting their functionality and altering the electron transport chain. Interestingly, Dox-treated mice show significant alterations in the expression of NDUFA3 (the 1a subcomplex of NADH dehydrogenase 3), SDHA (subunit a of succinate dehydrogenase complex II) and ATP5a1, the subunit a of ATP synthase (Zhang et al., 2012).

In Ehrlich cancer cells, Dox increases the production of superoxide anion in a dose-dependent manner. This happens through a cyclic process in which electrons pass from NADPH to Dox, which is transformed into Dox semi-quinone (SQ-Dox) by NADPH:cytochrome P-450 reductase, and subsequently to an oxygen molecule (O_2), producing superoxide anion (O_2-·) and re-obtaining a Dox molecule. At this point the cycle can start again. The superoxide anion can be converted into hydrogen peroxide (H_2O_2) by the super oxide dismutase (SOD) which can in turn be transformed into hydroxyl radicals via the Fenton reaction (Doroshow, 2019). Via this mechanism, anthracyclines such as Dox, Dau and bleomycin, alter ROS production by directly interfering with the electron transport chain complexes (Pourahmad et al., 2016). A consequence of this is the subtraction, from the transport chain, of the electrons destined to produce ATP.

Dox can also increase the levels of intracellular ROS via NADPH oxidase, an enzyme which produces O_2-· using NADPH as a cofactor. Through a mechanism similar to that described above, NADPH, transfers an electron to Dox to form SQ-Dox, that releases the electron to an O_2 molecule to form O_2-· (Ghigo et al., 2016). Dox is also able to alter the activity of NADPH oxidase, consequently increasing the intracellular ROS levels. The increased activity of NADPH oxidase by Dox has been shown induce apoptosis in H9c2 cells (Gilleron et al., 2009). Dox treatment of *NADPH oxidase 2*-knockout mice led to fewer adverse effects, such as induced contractile dysfunction, alterations in diastolic and systolic function, myocardial atrophy, cardiomyocyte apoptosis, compared to wild type control mice. These alterations were associated with changes in NADPH oxidase activity and consequently in ROS level (Zhao et al., 2010).

Anthracyclines can also play an important role in the production of reactive species by interfering with the iNOS enzyme, which produces nitric oxide (NO) using NADPH as a cofactor. In this case, an electron is transferred to a Dox molecule, forming SQ-Dox and producing NO from O_2 and L-Arginine. SQ-Dox can then release the electron to an O_2 molecule producing O_2-·. Finally, from the reaction between NO, produced by iNOS, and the superoxide anion, produced by the conversion of SQ-Dox into Dox, reactive nitrogen species (RNS) such as peroxynitrite ($ONOO^-$), which are highly reactive and dangerous for cells, can be formed (Ghigo et al., 2016).

Moreover, it seems that the increase in the activity of iNOS is also necessary for the immunogenic effects of the drug. In human Dox-resistant and iNOS-silenced colon cancer cells, Dox shows less accumulation and is less toxic, and is unable to induce NO synthesis, compared to Dox-sensitive cells (de Boo et al., 2009). Furthermore, anthracyclines can increase the expression and activity of iNOS via NADPH oxidase, increasing the amount of NO and consequently of RNS levels (Aldieri et al., 2002; Öktem et al., 2006; Sabbatino et al., 2021). In addition, NO can act as a mediator of drug toxicity and as a chemosensitizing agent, by decreasing the efflux of Dox outside the cell via the ABCB4 efflux pump (Wen et al., 2019a).

Dox has a strong affinity for cardiolipin, a diphosphatidylglycerol lipid located in the inner mitochondrial membrane. When Dox binds cardiolipin, this lipid cannot serve as an anchor for cytochrome *c* and for other mitochondrial proteins such as ANT, possibly altering their function (Goormaghtigh et al., 1990).

Oxidative damage and calcium overload can induce the MPTP opening, thus causing solutes of molecular weight <1500 Da to freely permeate mitochondria, resulting in mitochondrial swelling, efflux of Ca^{2+}, uncoupling of the respiratory chain, membrane potential collapse, and release of small pro-apoptotic proteins (Bernardi et al., 2015). Dox is known to induce MPTP opening in a dose-dependent manner

(Montaigne et al., 2010), which can be reduced by immune-suppressant cyclosporin-A, a MPTP desensitizer (Broekemeier and Pfeiffer, 1989).

A further mechanism by which anthracyclines can cause mitochondrial impairment is the preferential accumulation of 8-hydroxydeoxyguanosine (8OHdG) adducts in cardiac mitochondrial DNA following acute intoxication (Serrano et al., 1999). In long term treatments with Dox, the concentration of 8OHdG adducts remained constant between 1 and 5 weeks following the last injection; conversely, a rapid repair of 8OHdG adducts was observed during the first days following an acute intoxicating Dox dose (Serrano et al., 1999).

Dox could also induce interference with mitochondrial function via an indirect mechanism involving inhibition of topoisomerase IIβ in cardiomyocytes, which results in nuclear damage, p53 activation, and downstream inhibition of mitochondrial function and defective mitochondrial biogenesis. Notably, deletion of topoisomerase IIβ has cardioprotective effects (Zhang et al., 2012).

Dox can also impact mitochondrial dynamics. Fusion and fission of mitochondria are in constant equilibrium; an unbalance towards fission can cause mitophagy, apoptosis and cell proliferation, whereas excess fusion can impair the mitophagy process. In the liver, Dox treatment can decrease mitochondrial fusion but does not alter fission, and may result in mitochondrial fragmentation (Dirks-Naylor et al., 2014).

4.7. Induction of apoptosis

Due to the mechanisms described above, anthracyclines can lead to cell death in both normal and tumor cells. Indeed Dox, used as a therapeutic agent in anticancer therapies, can induce cardiotoxicity in patients. This adverse effect is caused by the induction of cell death in cardiomyocytes and endothelial cells, triggered by damage to biological macromolecules or cellular structures. Dox can induce controlled cell death by different mechanisms, such as autophagy, ferroptosis, nephroptosis, pyroptosis and apoptosis (Christidi and Brunham, 2021), depending on the cell line studied and on the concentration of the drug.

In H9c2 rat myocardial cells, the administration of Dox causes the activation of the protein AMPK (protein that functions as a sensor for the energy state of cell and as a regulatory protein in the oxidative stress response) in response to ROS accumulation. The activation of AMPK leads to the phosphorylation of p53 and consequently to apoptosis. The activation of p53 leads to the migration of Bax from the cytosol to the mitochondrial surface where it forms the Bax/Bcl-2 complex, that triggers cytochrome *c* release and its binding to Apaf-1 and procaspase-9, leading to the activation of caspase-9 and caspase-3 first and caspase-6 and caspase-7 subsequently, that leads to apoptosis (Chen et al., 2011a, 2011b).

Wang and colleagues (Wang et al., 2004) tested the proapoptotic effects of Dox on various normal and tumor cell lines, i.e., normal bovine aortic endothelial cells (BAEC), adult rat cardiomyocytes (ARCMs), human ovarian teratocarcinoma (PA-1) and human breast adenocarcinoma cell lines (MCF-7). While p53 expression was more induced in tumor lines than in normal ones, the fraction of apoptotic cells was higher in the latter, suggesting that Dox-induced apoptosis is independent of p53 in normal cells while it is p53-dependent in cancer cells.

In breast cancer cells, Dox causes the activation of extracellular signal-regulated kinase-2 (ERK2), which in turn phosphorylates p53 at position Thr55. Pretreatment of cells with a chemical inhibitor of ERK2 blocks the Dox-induced p53 activation and suppresses p53 phosphorylation at Thr55. The mutation of Thr55 blocks p53 activation and desensitizes the cells to Dox, increasing resistance to the drug (Yeh et al., 2004). In p53, phosphorylation of Ser15 occurs a few minutes after exposure to Dox, while Thr55 is phosphorylated later; it is unclear whether phosphorylation of Ser15 is necessary for phosphorylation to occur at Thr55 (Appella and Anderson, 2001; Shati, 2020).

Dox can also induce apoptosis through the NFAT/Fas/FasL axis. A study carried out on Wistar rats evaluated the apoptotic effect of Dox on cardiomyocytes: in addition to altering the protein levels of cytochrome *c*, Bax and caspase-3, treatment with Dox reduces the activity of mTOR and the levels of Bcl-2, and increases the levels of ERK1/2, MAPK and JNK. Furthermore, Dox modulates the nuclear factor-activated T cell 2/3/4 (NFAT 2/3/4), increasing the levels of Fas/FasL, membrane receptors belonging to the tumor necrosis factor (TNF) family. Fas/FasL can lead to programmed cell death through caspase-8 (Shati, 2020).

It seems that the concentration of Dox can affect the specific apoptotic pathway that is triggered. Indeed, apoptosis and catastrophe of the mitotic spindle are obtained by administering Dox either at low or high concentrations. At low concentrations, Dox can induce apoptosis through the activation of AMPK and p53, and loss of integrity of the membranes occurs right after treatment. However, at high concentrations, Dox can induce apoptosis through the activation of NF-kB, p38, and caspases, and loss of integrity of membranes occurs in later stages of the process (Eom et al., 2005a).

In the future, a better understanding of the specific signaling pathways that lead to programmed cell death in different cell lines could help to improve or maximize the anticancer effects of anthracyclines, while at the same time reducing adverse effects on non-tumor cells.

4.8. Cell membrane alterations and lipid dysfunction

Anthracyclines, and especially Dox, can damage cell membranes. Dox decreases the fluidity and lipid organization of biological membranes (Murphree et al., 1981; Siegfried et al., 1983), and alters cell membrane composition and function. Dox inhibits phosphatidylserine decarboxylase, that catalyzes the synthesis of phosphatidylethanolamine (PE) from phosphatidylserine (PS). This can lead to a decrease in the PS/PE ratio, especially in the mitochondrial membrane, which can make the membrane more susceptible to damage (Bellance et al., 2020).

Dox largely localizes to the mitochondrial compartment, due to the high affinity for negatively charged membranes, which enables it and other anthracyclines to bind to the inner mitochondrial membrane, where lipid peroxidation can occur. Dox conversion to a lipophilic aglycone makes it able to diffuse through the outer mitochondrial membrane, and to rapidly accumulate into mitochondria (Nohl, 1988; Tacar et al., 2013). In the mitochondria, the aglycone activates many reactions, which release electrons and generate ROS, that are responsible for collateral damage in tumor chemotherapy due to oxidative stress in non-targeted tissues. This may result in mitochondrial dysfunction, especially in cardiomyocytes, accompanied to an increase in proteotoxic burden, due to protein degradation at the endoplasmic reticulum and mitochondria (Chen et al., 2007; Lv et al., 2012).

Ceramides (Fig. 7), i.e., the basic structural units of the sphingolipids, play a role in activating cell death signals initiated by cytokines, chemotherapeutic agents, and ionizing radiation. Ceramides are produced by serine palmitoyltransferase in the endoplasmic reticulum via the condensation of L-serine and palmitoyl-CoA to form 3-ketodihydrosphinganine, which in turn is reduced to dihydrosphingosine, which is then N-acylated and undergoes desaturation to form the ceramide (Hanada, 2003, 2006). Ceramides are bioactive lipids, since they participate in a wealth of cellular signaling, including regulating differentiation, proliferation, growth arrest, senescence and apoptosis (Hannun and Obeid, 2008). Ceramides, such as N-hexanoyl--sphingomyelin, are potent enhancers of the uptake of Dox, Epi and other

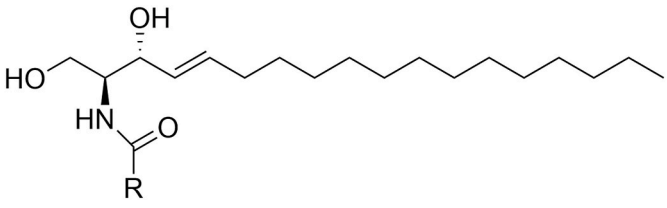


Fig. 7. Representation of ceramide structure. R represents the alkyl portion of a fatty acid.

anthracyclines. They act by modulating the degree of plasma membrane lipophilicity, facilitating transbilayer diffusion of amphiphilic drugs. By this mechanism, ceramides administration increases Dox uptake to cultured endothelial and cancer cell lines, decreasing its toxicity (Veldman et al., 2004). Anthracycline cytotoxicity is decreased upon impairment of ceramide generation, while it is increased upon blockage of ceramide degradation (Senchenkov et al., 2001). Glucosylceramide synthase, an enzyme that catalyzes ceramide glycosylation, activated by ceramide, is overexpressed in Dox-resistant cells, and drives resistance to Dox and other anthracyclines (Liu et al., 2008).

4.9. Immune modulation

Anthracyclines can induce immunomodulation, i.e., thay can change the immune system in a way that helps to fight cancer. Anthracyclines can induce a type of cell death called immunogenic cell death, increasing the production of interleukins (IL) and IFN gamma and inducing dendritic and T-cell tumor infiltration (Ma et al., 2013, 2020; Mattarollo et al., 2011). Peritoneal exudate cells from Dox-treated mice produce TNF alpha, IL1, and IFN gamma; Dox treatment increases the levels of TNF alpha mRNA and decreased the levels of IL6 mRNA and protein (Ujhazy et al., 2003).

Anthracyclines can also induce the release of danger-associated molecules (DAMs). DAMs are molecules that are released from dying cells and can signal to the immune system that there is a problem. Some of the DAMs that can be released by anthracyclines include: i) the calreticulin complex, that translocates from the endoplasmic reticulum to the plasma membrane, and provides an “eat-me” signal, ii) the nuclear alarmin HMGB1, released to engage TLR-4, required for cross-presentation of dying tumor cells, on dendritic cells, and iii) ATP, that when released triggers the inflammasome via P2X7 purinergic receptors on dendritic cells, activating the secretion of proinflammatory IL-1β (Obeid et al., 2006; Apetoh et al., 2007).

Anthracyclines can be combined with immunotherapy to improve the effectiveness of immunotherapy. Dox and Doxil synergize with anticancer immunotherapies as anti-PD-1 and CTLA-4 monoclonal antibodies, increasing their antitumor response in mice models; these anthracyclines activate an antitumor T-cell response, inducing tumor-infiltrating CD8(+) T cells and increasing the expression of CD80 in dendritic cells (Rios-Doria et al., 2015). Anthracyclines can help to sensitize cancer cells to immunotherapy by upregulating the expression of activating ligands on the cancer cells. This makes the cancer cells more susceptible to killing by immune cells. The death ligand tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) binds to the TRAIL-R1 and -R2 receptors, which trigger an apoptotic signal initiated by cleavage of caspase-8. Combining Dox with TRAIL-targeted therapy sensitizes tumors to killing by recombinant TRAIL. The treatment with a sublethal dose of Dox promotes tumor susceptibility to NK and T lymphocytes, by increasing the TRAIL receptor signaling: an increased expression of TRAIL-R2 is observed in Dox-treated cancer cells, together with a downregulation of the cellular FLICE inhibitory protein, inhibitor of death receptor-mediated apoptosis (Vaculova et al., 2010; Wennerberg et al., 2013).

4.10. Autophagy and senescence

Autophagy is a process, based on lysosomal hydrolytic enzymes, that cells use to recycle macromolecules, cellular materials, and organelles. Anthracyclines can induce autophagy, which can have both protective and harmful effects.

Autophagy can protect cells from damage by ROS and other stressors. Autophagy is activated by anthracyclines due to ROS-dependent oxidative stress, that leads to mitochondrial dysfunction, activation of AMPK and of the calmodulin-dependent kinase. Upregulation of AMPK inhibits mTOR and activates JNK, leading to the activation of Ulk-1 (Unc-51-like kinase 1) and to the dephosphorylation of Atg13 (Autophagy related protein 13) and FIP200 (Family Interacting Protein of 200 kD), needed for pre-autophagosome formation. Further, anthracycline treatment leads to the formation of a complex of Vps15, Vps34 and Beclin-1, which is needed for the maturation of the autophagosome, that can be formed upon dissociation of Beclin-1 from Bcl-2, triggered by activated JNK (Meredith and Dass, 2016; Terman and Brunk, 2005; Zhou et al., 2015b).

Anthracyclines can cause autophagy triggering PARP-1, and therefore inducing ATP and NAD^+ depletion and the activation of the key autophagy regulator mTOR (Muñoz-Gámez et al., 2009).

Anthracycline-induced cardiotoxicity depends at least in part on autophagy. Dox induces myocyte injury by impairing lysosomal function and signaling, repressing the expression of the transcription factor TFEB and impairing lysosome acidification. Loss of TFEB is associated with reduction in macroautophagy protein expression, inhibition of autophagic flux, impairments in lysosomal cathepsin B activity, and activation of cell death (Bartlett et al., 2016; Li et al., 2016a). However, autophagy upregulation (by administration of rapamycin) attenuates anthracycline-dependent cardiotoxicity in rat cardiac myoblasts, possibly down-regulating the pro-apoptotic protein caspase-3 (Sishi et al., 2013). Stimulation of autophagy can be either a protective mechanism or a process that contributes to cell death during apoptosis, depending on the level of activation, and on the pathways triggered: while high levels of autophagy promote apoptosis, low levels of autophagy may support cell survival and prevent apoptosis (Hsieh et al., 2009).

Anthracyclines can also induce senescence, which is a state of cellular arrest. Senescence can be protective, as it can prevent cells from dividing and becoming cancerous. However, senescence can also be harmful, as it can lead to the accumulation of senescent cells in tissues. Senescence involves pathways similar to those of cell death. In breast tumor, Dox induces p53, and consequently upregulates p21 and downregulates CDC2/CDK1, resulting in accelerated senescence (Di et al., 2009). In different cellular contexts, or upon administration of different doses of drug, anthracyclines induce different modes of cell death, i.e., apoptosis (induced by high doses of Dox) or mitotic catastrophe accompanied by senescence-like phenotype: inhibition of apoptosis leads to increased cellular senescence (Eom et al., 2005b; Rebbaa et al., 2003). Senescence is linked to the immune properties of anthracyclines and can represent a therapeutic strategy: breast cancer brain metastasis (BCBM) senescent cells, induced by Dox, trigger the recruitment of PD1-expressing T cells to the brain. Anthracycline-dependent induction of senescence was shown to improve the efficacy of immunotherapy with anti-PD1 in BCBM in a CD8 T cell-dependent manner, thereby providing an advantage for immune-based treatments of this pathology (Uceda-Castro et al., 2022).

4.11. Induction of necrosis

Necrosis is a type of cell death that is characterized by the uncontrolled rupture of the plasma membrane and nuclear/cellular swelling. This can lead to the release of cellular contents and the activation of the immune system.

Anthracyclines can induce necrosis in cells by a number of mechanisms. Anthracyclines can damage DNA, which can lead to the activation of PARP1. A “regulated” form of necrosis is induced by PARP1, especially when ATP levels are depleted, a condition that decreases the chances of the cell to survive (Shin et al., 2015). Many tumors have mutations that inhibit apoptosis and allow cells to continue growing past normal growth cycle checkpoints. In these cases, necrosis in response to DNA damage may explain how anthracyclines still induce cell death, triggered by PARP1, when other pathways are hindered (Zong et al., 2004).

The anthracyclines can trigger a programmed necrosis, triggered by death receptor proteins, such as TNF and TRAIL, that activate the Receptor-Interacting Protein RIP by inhibiting caspase 8 (Holler et al., 2000).

4.12. Mechanisms of selectivity of anthracyclines to cancer cells

Tumorigenesis affects many metabolisms and cellular features, such that there are a series of hallmarks that make tumor cells different from normal cells (Hanahan and Weinberg, 2011). Some of these features contribute to the selectivity of anthracyclines to cancer cells. Such selectivity mostly depends on the fast metabolism of tumors. Anthracyclines act on the processes of DNA replication, that are strongly increased in the rapidly dividing cancer cells.

Tumorigenesis determines a complete reprogramming of cell metabolism. This includes the increased expression of topoisomerase II. Cancer cells often have higher levels of topoisomerase II than normal cells (Cox and Weinman, 2016; Nitiss, 2009). This makes them more susceptible to the damage caused by anthracyclines.

Another mechanism of selectivity is the reduced levels of DNA repair in cancer cells, dependent on the differential expression or mutation of proteins such as p53, PARP and APC in tumors (Hanahan and Weinberg, 2011). This makes cancer cells more susceptible to the damage caused by anthracyclines.

Further, anthracyclines have been shown to inhibit the growth of cancer cells by targeting mitochondria, which are the powerhouses of cells and play a role in cell death. Energy metabolism is more stressed in cancer cells than in normal cells. By targeting mitochondria, anthracyclines can induce apoptosis in cancer cells.

5. Side effects, toxicity and adverse drug interactions of anthracyclines

5.1. Side effects of anthracyclines

Anthracyclines are toxic to both tumor cells and other rapidly dividing cells, such as those in the bone marrow and the heart. This is why anthracyclines can have serious side effects, such as bone marrow suppression and cardiotoxicity.

However, the difference in relative toxicity between tumor and normal cells constitutes the so-called “therapeutic window,” which allows the use of chemotherapy against tumors. The therapeutic window is the range of doses in which the drug is effective at killing tumor cells without causing unacceptable toxicity to normal cells.

Anthracycline use is associated with many side effects, ranging from generally acute and reversible chemo-related phenomena, such as nausea, vomiting, diarrhea, stomatitis, mucositis, alopecia, gastrointestinal disturbances, rash and bone marrow suppression, to long-term side effects, as cardiotoxicity, therapy-related malignancies and gonadotoxicity, that severely impact patients’ quality of life and strongly limit anthracycline use. The risk of side effects from anthracyclines depends on the dose of the drug, the length of treatment, and the patient’s individual risk factors.

5.2. Cardiotoxicity

Cardiotoxicity is the most important and best studied side effect of anthracycline treatment. The use of the anthracyclines is limited by a multifactorial, severe, dose-dependent and irreversible cardiotoxicity, that may result in cardiac contractile dysfunction, cardiomyopathy, ventricular dysfunction, pericarditis-myocarditis syndrome, arrhythmias and heart failure (Shinlapawittayatorn et al., 2022; Weingart et al., 2018). Cardiac toxicity may have an early onset or a late onset. The acute form is characterized by abnormal electrocardiographic alterations such as arrhythmias and ST- and T-wave alterations. An acute myocardial damage can result in the “pericarditis-myocarditis syndrome”, which begins a few days after infusion, and is characterized by severe disturbances in impulse conduction and congestive heart failure. In the long term, administration of anthracyclines may induce chronic, cumulative, dose-related toxicity progressing to congestive heart failure.

No management or medicines are available to relieve anthracycline-induced cardiotoxicity, and heart transplantation is the only option for patients with severe symptoms. Patients with heart disease or malfunctions, and old patients are often excluded by anthracycline treatments; cardiotoxicity limits Dox use to a cumulative dose of 450–550 mg/m^2 (Lotrionte et al., 2013; Shan et al., 1996; Swain et al., 2003).

The molecular mechanisms of the anthracycline-dependent cardiotoxicity are practically the same than those of drug action on tumors, including DNA intercalation, topoisomerase II inhibition, induction of oxidative stress, inflammatory cytokines, apoptosis, mitochondrial dysfunction and Ca^{2+} dyshomeostasis.

Specific factors increase the toxicity towards the heart with respect to other tissues. Abnormal Ca^{2+} homeostasis is especially important, for the nature of the contractile activity of the heart, which is strictly dependent on the cation. Anthracyclines dysregulate expression and/or function of L-type Ca^{2+} channel, ryanodine receptor (RyR), Sorcin, sarco/endoplasmic reticulum ATPase (SERCA), and dysregulating mitochondrial calcium fluxes, impairing cardiac mitochondrial calcium homeostasis and disrupting cation regulation: this leads to cardiac intracellular Ca^{2+} overload, increased diastolic calcium concentration, a decrease in Ca^{2+} transients amplitude and, overall, to the impairment of calcium contractile function (Battista et al., 2020; Bühner et al., 1980; Dhingra et al., 2020; Gambliel et al., 2002; Hanna et al., 2014b; Keung et al., 1991b; Louisse et al., 2017; Montaigne et al., 2011; Olson et al., 2005; Solem et al., 1996).

Further, anthracyclines increase ROS production and oxidative stress: this, on the one hand leads by itself to impaired cardiac contractile function, and on the other hand reduces the expression of RyR, SERCA and phospholamban (Olson et al., 2005).

Many studies indicate that the cardiac mitochondrial Ca^{2+} overload and dysfunction could represent the main cause of cardiac contractile dysfunction. Dox induces the release of cytochrome *c* from mitochondria, and impairs cardiac mitochondrial respiration, leading to loss of ATP production, apoptosis and cell death (Pereira et al., 2019).

5.3. Therapy-related tumorigenesis

Anthracycline-dependent tumorigenesis is a possible long-term side effect, and in some cases AML, acute promyelocytic leukemia (APL), sarcoma, breast cancer and thyroid tumors have been attributed to anthracycline treatment. Anthracycline therapy-related AMLs are often aggressive, developing with a short (1–3 years) latency and with poor prognosis: they are commonly associated with balanced chromosomal translocations at site 11q23 or 21q22, involving *MLL1* and *AML1/CBFA2/RUNX1* genes, respectively (Cowell and Austin, 2012; Larson et al., 1992; Pedersen-Bjergaard and Philip, 1991).

Anthracycline-induced APLs also often have a short latency, and involve a balanced t(15; 17) chromosomal translocation, that results in a PML-RARα fusion protein. Treatment with all-trans retinoic acid- and anthracyclines results in a 5-year survival rate of about 80% (Beaumont et al., 2003; Rashidi and Fisher, 2013). Mutations can be induced by a series of mechanisms, among which obviously the misrepaired double strand breaks resulting by topoisomerase II hijacking and by the eviction of histone H2AX (Felix et al., 2006; Mays et al., 2010; Pang et al., 2013b).

Selective histone eviction can be associated with epigenetic alterations: e.g., MLL1 is a H3K4 methyltransferase, and *MLL1* translocations are correlated with reduced H3K4 histone methylation. Anthracyclines with distinct histone eviction profiles, such as Acl, dimethyl-Dox and dimethyl-Epi may represent alternative options for Dox-resistant AML (del Rizzo and Trievel, 2011; Liu et al., 2015a; Xu et al., 2016a; Qiao et al., 2020).

5.4. Gonadotoxicity

Among the tissues with high proliferating rate, gonads are often affected by anthracycline-dependent toxicity. Although in many cases

gonadal damage may be reversible, and gonads often regain function within months from treatment, gonadotoxicity can produce damages, as shortened reproductive lifespan, effects on pregnancy and irreversible function loss. Further, gonadotoxicity also increases the risk of osteoporosis, infertility and cardiovascular disease. Cryopreservation of gametes or embryos is the most used option to counteract gonadotoxicity, for patients in a reproductive age (Anderson et al., 2015; Byrne et al., 1992; Delessard et al., 2020; Green et al., 2002; Webber et al., 2016).

Several classes of compounds have been proposed against anthracycline-dependent gonadotoxicity, including hormone agonists, antioxidants, proteasome inhibitors, tyrosine kinase and DNA damage repair inhibitors. However, since most tests are carried out in mice models, these compounds need validation both on the effect on gonads and on the anthracycline efficacy against tumors (Kropp et al., 2015; Manabe et al., 1997; Roti et al., 2014; Tuppi et al., 2018).

A second, preferable approach would be the development of anthracyclines where the antitumoral effect is preserved, while the side effects are limited (see below).

Gonadotoxicity can be attributed mostly to the double strand DNA breaks induced by the drug and the subsequent damage and cell death of both germ cells, and somatic cells, as those of vasculature and of the gonad's stromal compartments. Acl and dimethyl-Dox, with reduced DNA-damaging activity, display reduced follicles apoptosis in female mice (Beaud et al., 2017; Marcello et al., 1990; Qiao et al., 2020; Roti and Salih, 2012). Therefore, the anthracycline-dependent DNA-damaging activity seems to be the most important cause for gonadotoxicity, especially in females, while the lack of effect of antioxidants seem to rule out oxidative stress as a major cause (Hou et al., 2005; Levi et al., 2015).

6. Mechanisms of intrinsic and acquired resistance to anthracyclines

Drug resistance is the main cause for failure in cancer chemotherapy (Holohan et al., 2013; Housman et al., 2014). Many mechanisms participate in conferring resistance to anthracyclines (Fig. 8), not all of them fully understood (Gatti and Zunino, 2005). Resistance may be intrinsic, i.e., pre-existent to treatment, or induced by chemotherapy (acquired resistance).

6.1. Alterations/mutations of topoisomerase II

Mutations or abnormal expression of the topoisomerase IIα, which is essential in mammals, is a major target of anthracyclines.

Cells overexpressing topoisomerase II are drug-sensitive, while cells with reduced levels of the enzyme are resistant to topoisomerase II poisons (Nitiss and Beck, 1996). Suppression of topoisomerase IIα by RNA interference confers resistance to Dox *in vitro* and *in vivo*. Reduced topoisomerase II levels determine a decrease in topoisomerase-DNA cleavage complexes, and hence in DNA damage signal and response, resulting in less DNA damage. Cytoplasmic rather than nuclear localization of topoisomerase IIα and suppression of topoisomerase II-linked apoptotic signaling also contribute to Dox resistance (Burgess et al., 2008). Conversely, relapsed tumors often have altered topoisomerase expression with respect to the parental tumor, suggesting that topoisomerase expression levels are important factors in the response to therapy.

Topoisomerase II poisons can induce a certain amount of degradation of topoisomerase IIα; its degradation can be blocked by either proteasome or transcription inhibitors (Nitiss, 2009).

The link between anthracycline sensitivity and topoisomerase II is not well understood. High expression of topoisomerase II is sometimes associated with a downregulation of the apoptotic program commonly triggered by DNA strand breaks (Cox and Weinman, 2016). Another study showed that high expression levels of topoisomerase II are linked to the development of catalytically active mutations in this enzyme (mutations K798L and K798P, that also confer resistance to etoposide), which result in decreased Dox sensitivity (Okada et al., 2001). Further, increase in the β-isoform of topoisomerase II also decreases sensitivity to Dox (Cox and Weinman, 2016). However, some studies show the possibility of cancer type-dependent effects: resistant hepatocellular carcinoma cell lines have an increased topoisomerase IIα expression, while breast cancers with decreased topoisomerase IIα display increased resistance to Dox (Pang et al., 2005; Press et al., 2011).

6.2. Alterations in intracellular drug concentration

The basis of chemotherapy is the capacity of the drugs to effectively reach the cellular targets, where they exert their action, killing tumor cells. However, there are distinctive mechanisms that can limit the

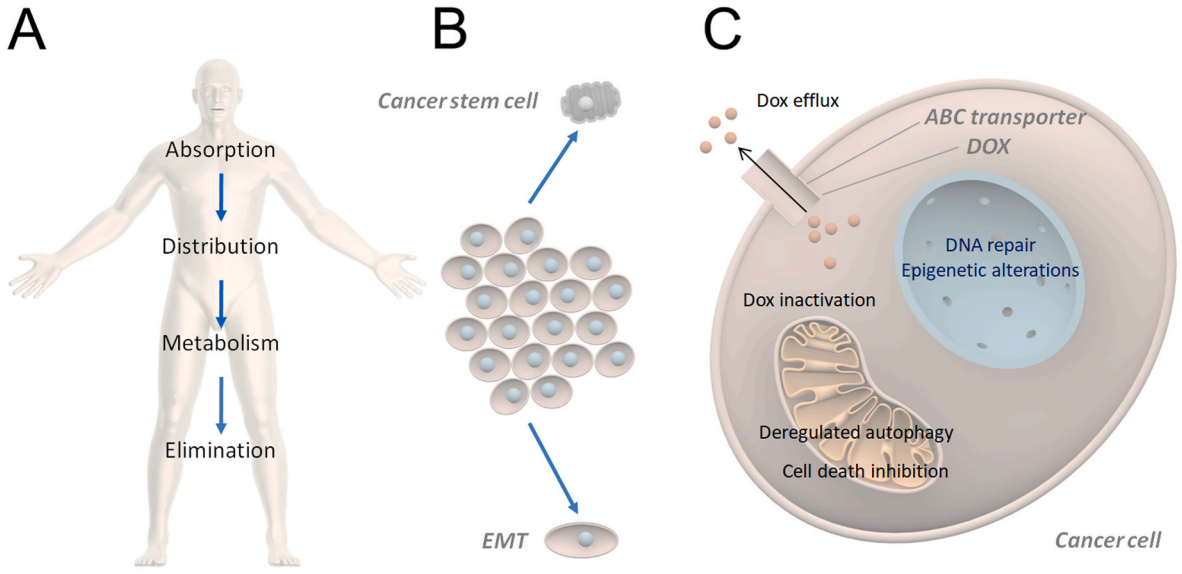


Fig. 8. Mechanisms that confer drug resistance in tumors. **A)** anthracycline pharmacokinetics; **B,C)** molecular mechanisms of anthracycline resistance in cancer cells by: **B)** induction of the epithelial-to-mesenchymal transition (EMT) and cancer stem cells (CSCs); **C)** increase of drug efflux through ABC transporters, drug inactivation, deregulation of autophagy pathways and cell death inhibition, increase of DNA damage repair systems and epigenetic alterations.

intracellular drug concentration and result in decreased effect of the drug and/or in resistance to anthracyclines.

6.2.1. Drug efflux pumps

The ATP-binding cassette (ABC) transporters are a superfamily of proteins that are involved in the transport of a wide variety of molecules across cell membranes. These transporters are found in all living cells, and they play an important role in protecting cells from toxic substances.

In cancer cells, ABC transporters can be overexpressed, which can lead to increased efflux of anthracyclines out of the cell. This can reduce the intracellular drug concentration and make the cancer cells more resistant to anthracycline therapy.

The ABC transporters are expressed by 48 different genes, belonging to subfamilies ABCA through ABCG (Fletcher et al., 2016; Li et al., 2016c).

ABC transporters contain four domains, i.e., two NBD domains (nucleotide-binding ATPase domains), that bind and hydrolyze ATP, and two TMD domain (transmembrane domains), with transmembrane helices forming a pore that can assume two conformations: an inward-facing conformation, accessible from the cytosol, and an outward conformation, accessible from the extracellular space (Fig. 9). A shift between the conformation occurs upon substrate binding, that allows its transmembrane transport against its physicochemical gradient (Ward et al., 2007).

ABC transporters are highly expressed in sensitive tissues, as the blood-brain barrier, the gastrointestinal region, liver, ovary, placenta and kidney, and are responsible for the protection of the organism from many toxic compounds, since they are rather non-specific; they can bind and extrude a diversity of substances (Mizuno et al., 2003; Thiebaut et al., 1987).

Altered membrane transport by overexpression of ABC transporters is the most important source of multidrug resistance (MDR), i.e., the decrease of sensitivity of tumors towards chemotherapy. MDR in cancer cells was demonstrated to occur depending on the expression of at least 15 ABC transporters (Fletcher et al., 2016; Li et al., 2016c; Szakács et al., 2006a). Anthracycline export is especially mediated by ABCB1 (also identified as MDR1, P-glycoprotein or P-gp), ABCG2 (Breast cancer resistance protein, BRCP) and ABCC1 (Multidrug Resistance Protein 1, MRP1), pumps with wide substrate specificity, able to transport planar, hydrophobic, polyaromatic molecules (Fig. 10). These pumps have ample cellular and tissue distribution, and are especially located in physiological epithelial/endothelial barriers, thereby protecting brain, testis and the fetus from toxic xenobiotics, by extruding xenobiotics and metabolites from the cells, into the gut lumen, the bile and urine, thus reducing their absorption, toxicity and bioavailability (Fletcher et al., 2016; Khatami, 2018; Mao and Unadkat, 2015; Sharom, 2008; Silva et al., 2015; Zhang et al., 2015).

ABCB1 is the most important efflux pump, highly expressed in the apical region of epithelial cells (such as intestine, kidney proximal tubules, liver and pancreas ductules), testis (blood-testis barrier), placenta and brain capillaries (blood-brain barrier), oriented towards the lumen or the blood (Schinkel, 1999). In addition, ABCB1 is highly expressed in many tumors, as adrenocortical, colon, kidney, ovary, AML, breast cancer, osteosarcoma, bladder tumor, hepatocellular tumors, central nervous system cancers and many other tumors; correlation between ABCB1 expression levels, drug resistance and poor prognosis has been described in a plethora of tumors (Abe et al., 1998; Bourhis et al., 1989; Broxterman et al., 1999; Burger et al., 2003; Clifford et al., 1996; Del Vecchio et al., 1997; Dexter et al., 1998; Dorr et al., 2001; Fojo et al., 1987; Goldstein et al., 1989; Grogan et al., 1993; Han et al., 2000; Kato et al., 2001; van der Kolk et al., 2000; Leith et al., 1999; Michieli et al., 1999; Nakagawa et al., 1997; Nooter et al., 1997; Park et al., 1994; Pirker et al., 1989; Sun et al., 2000; Tada et al., 2002; Trock et al., 1997; van der Zee et al., 1995; Zhou et al., 1995). ABCB1 is the most studied ABC transporter: it is highly polyspecific, due to high fuzziness and plasticity of its binding sites, and can bind and export out of cells more than 1000 different molecules, ranging from small cations, sugars and amino acids to peptides, polysaccharides and proteins: chemotherapeutic drugs, often hydrophobic, weakly amphipathic, aromatic and with positively charged nitrogens, are among the most important substrates of ABCB1 and other ABC transporters, that can thus protect the cells from a number of cytotoxic compounds (Alam et al., 2018, 2019; Didziapetris et al., 2003; Esser et al., 2017; Le et al., 2020; Morrissey et al., 2012; Szewczyk et al., 2015; Verhalen et al., 2017; Ward et al., 2013). Many anthracyclines are good substrates of ABCB1 and are efficiently released by many cancer cell lines. Upon ABCB1 substrates administration, including anthracyclines, many tumor cells become multidrug resistant, by different mechanisms, such as ABCB1 overexpression, *ABCB1* gene amplification, or increased transcription, mRNA splicing, or protein stability.

Cell stress induce ABCB1 overexpression, via transcription factors including ERKs (extracellular signal-regulated kinases), MAPKs (mitogen-activated protein kinases), JNK (c-Jun NH_2-terminal protein kinase), PKC (protein kinase C), PI3K (phosphoinositide 3-kinase)/Akt, AMPK, NF-κB, NF-Y, members of the Sp family, AP-1, HIF-1α and the heat-shock factor HSF, in addition to miRNA34a and miRNA-222-3p (Callaghan et al., 2008; Chin et al., 1990; Krishnamurthy et al., 2012; Mirzaei et al., 2021b; Miyazaki et al., 1992; Osborn and Chambers,

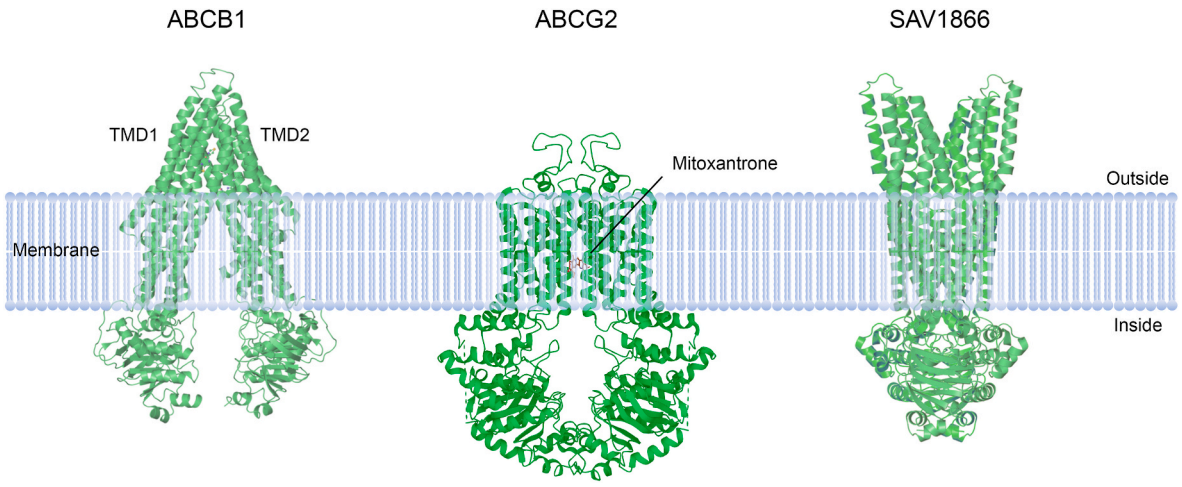
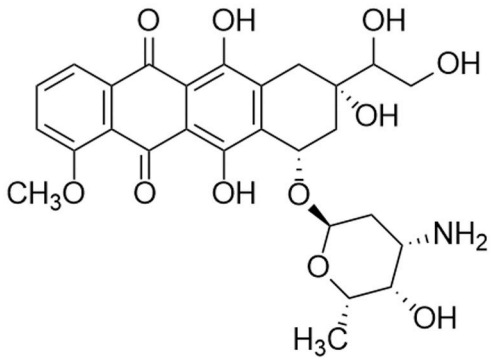
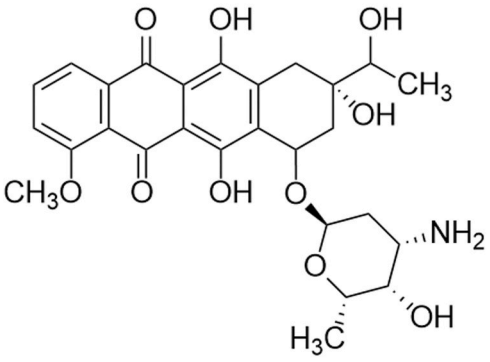


Fig. 9. Structures of ABC efflux pumps. Left: Structure of mouse inward-facing ABCB1, in complex with two molecules of a dendroamide-A analog (PDB code: 4M2T). Center: Structure of ABCG2 in complex with mitoxantrone (PDB code: 7NFD). Right: structure of outward-facing conformation *Staphylococcus aureus* SAV1866 in complex with ADP (PDB code: 2HYD).

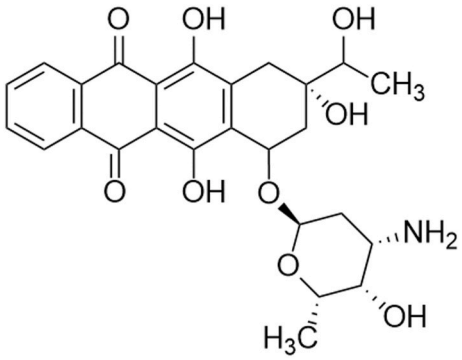
Doxorubicinol



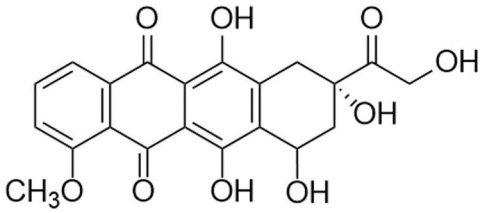
Daunorubicinol



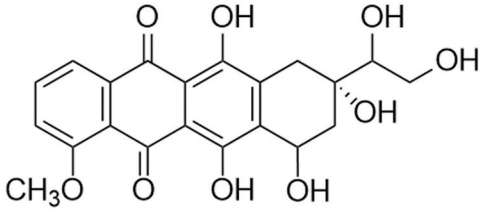
Idarubicinol



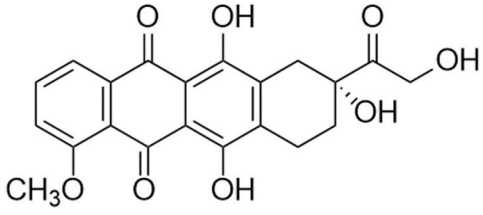
Doxorubicinone



Doxorubicinolone



7-Deoxydoxorubicinone



7-Deoxydoxorubicinolone

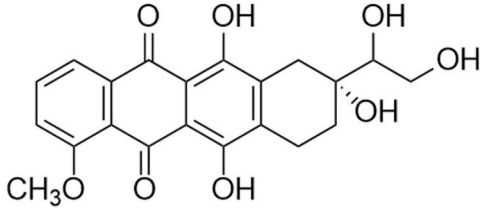


Fig. 10. Chemical structures of some anthracyclines modified via three main metabolic pathways (hydroxylation, semiquinone and deoxyaglycone formation): Doxorubicinol (Doxol), Daunorubicinol, Idarubicinol, Doxorubicinone, Doxorubicinolone, 7-Deoxydoxorubicinone and 7-Deoxydoxorubicinolone are indicated.

1996; Roninson et al., 1986; Scotto, 2003; Scotto et al., 1986; Shen et al., 1986; Silva et al., 2015; Vilaboa et al., 2000; Wong et al., 2010; Zhou and Kuo, 1997).

Anthracycline-dependent *ABCB1* gene amplification is accompanied by the amplification of surrounding genes in chromosome 7q21.1 region, in particular ABCB4 (MDR3) and Sorcin (Genovese et al., 2017b; Januchowski et al., 2017; Kitada and Yamasaki, 2007; Patch et al., 2015). ABCB4 (MDR3), similarly to ABCB1, is an ABC transporter, is overexpressed in Dox-treated cells, is important in the MDR phenotype and in particular in the onset of resistance to anthracyclines (Gottesman et al., 2002; Januchowski et al., 2017; Januchowski et al., 2014a, 2014b; Thomas and Coley, 2003; Torigoe et al., 1995; ; van der Bliek et al., 1987, 1988). Sorcin is a protein involved in calcium homeostasis and tumorigenesis, overexpressed in many human cancers, and in particular in MDR tumors. Sorcin regulates calcium fluxes in the cells, is a marker of endoplasmic reticulum and mitochondrial stress, participates in cell cycle regulation and also binds with high affinity Dox and other chemotherapeutic drugs (Battista et al., 2020; Franceschini et al., 2008; Genovese et al., 2018; Genovese et al., 2017a; He et al., 2011a, 2011b; Ilari et al., 2015; Lalioti et al., 2014; Liu et al., 2014a; Mella et al., 2003; Qinghong et al., 2015; Tito et al., 2023; Zamparelli et al., 2010; Zhou et al., 2006).

Activity of Cox-2 has also been involved in the control of ABCB1 expression, since celecoxib, an inhibitor of Cox-2, lowers ABCB1 expression in MDR hepatocellular cancer cells and other tumors (Fantappiè et al., 2007; Mazzanti et al., 2009).

In addition to ABCB1, ABCC1 and ABCG2 are important pumps involved in the onset of resistance to anthracyclines, highly expressed in solid tumors and hematologic malignancies, with levels correlated with poor clinical outcome (He et al., 2011b; Moiseeva et al., 2022; Stacy et al., 2013). No structures of ABC transporters in complex with anthracyclines have been solved. However, the structure of ABCG2 in complex with mitoxantrone (Fig. 9), chemically similar to anthracyclines, and the docking studies of ABCB1 with Dox show that π-stacking between the phenyl ring of a phenylalanine and the polycyclic moiety of the drug and hydrogen bond formation are essential for substrate binding, and that substrate binding involves reduced dynamics of the NBD domains, suggesting that this may represent the mechanism of the drug-induced ATPase stimulation of ABC transporters (Kowal et al., 2021; Orlando and Liao, 2020; Wang et al., 2020b).

6.2.2. Drug influx transporters

For long time, anthracycline influx was thought to be dependent only on passive diffusion (Dalmark and Storm, 1981). However, a series of studies have demonstrated that the cellular uptake of Dox and other anthracyclines is also mediated by organic cation transporters (OCT) OCT1, OCT2, OCT3, OCT6, OCTN1, and by the organic anion transporting polypeptide (OATP) OATP1A2. In addition, OCT1, OCT3, and OATP1A2 are expressed in human heart and in breast cancer tissues. Dox uptake in cells expressing OATP1A2 variants is markedly reduced, and OATP1A2 and OCT transporters inhibition decreases Dox-mediated cytotoxicity and increases drug resistance in cancer cell lines (Durmus et al., 2014; Huang et al., 2021; Lal et al., 2007; Lee et al., 2017; Novak et al., 2015; Okabe et al., 2005, 2008; Otter et al., 2021).

6.3. Altered cellular distribution, absorption, distribution, metabolism and excretion

The absorption and distribution of drugs drive their cellular function and response in the human body. ABC transporters are major contributors to the ADME (absorption, distribution, metabolism, and excretion) of chemotherapeutic drugs. They can also transport drugs within organelles, such as lysosomes, away from their target sites, reducing their effective concentration. This can trap the drugs and facilitate their disposal by neutrophils (Fletcher et al., 2016; Khatami, 2018; Mao and Unadkat, 2015; Noack et al., 2018; Sharom, 2008; Silva et al., 2015; Zhang et al., 2015).

Drug-metabolizing enzymes can biotransform many xenobiotics, including antineoplastics, determining their activation or detoxification. Cytochrome P450 (CYP) enzymes are involved in the metabolism of many antitumor drugs. CYP alterations may change the breakdown of the drugs, and significantly increase their secretion. For example, the CYP3A inhibitor cyclosporin increases plasma Dox and etoposide concentrations, possibly inhibiting both CYP and ABCB1-mediated drug elimination (Kivisto et al., 1995).

In tumor cells, impaired detoxification promotes resistance, generating an ineffective drug response. Glutathione S-transferase (GST) generates drug resistance by acting on multiple cellular processes, such as cell proliferation, differentiation and apoptosis (Estrela et al., 2006). Reduced glutathione (GSH) levels are often increased in drug-resistant cells. GSH can bind and/or react with several drugs, interacts with ROS, prevents DNA/protein damage, and is highly produced in tumors, especially those exposed to Dox (Hochwald et al., 1997). High levels of GST favor tumor growth. The promoters of the γ-glutamylcysteine synthetase and GST genes contain binding sites for transcriptional regulators such as AP-1, AP-2, NF-kB, and Nrf-2. In the presence of oxidative stimuli, Nrf-2 dissociates from its negative regulator Keap1 and translocates to the nucleus, where it binds to Maf proteins and to antioxidant responsive element (ARE) sequences, triggering a cytoprotective response by upregulating detoxification and cytoprotective proteins as glutathione reductase, GST, ferritin, heme oxygenase-1 and phase-I drug oxidation enzyme NAD(P)H:quinone oxidoreductase 1. Alterations in Nrf-2 and Keap1 promote the constitutive expression of cytoprotective (prosurvival) genes in cancer cells due to continuous activation of Nrf-2, which contributes to drug resistance (Dhakshinamoorthy and Jaiswal, 2000; Rushworth et al., 2008; Shibata et al., 2008).

6.4. Pharmacokinetics and metabolism

Anthracyclines are a class of chemotherapy drugs that are administered intravenously. They are not well absorbed orally, except for Ida, which can be given orally. Intravenous infusion must be performed with care to avoid extravasation, which can seriously damage surrounding tissues. Dox and Epi can be injected rapidly, while Dau must be infused slowly. The drugs are rapidly removed from the plasma due to their uptake in the heart, kidneys, lungs, liver, and spleen. The terminal half-life of Dox and Dau is 30 h, while Ida has a half-life of 15 h. Anthracyclines are unable to cross the blood-brain barrier. Val is used exclusively for intravesical instillation to treat bladder cancer, and less than 10% is absorbed systemically.

After administration, there is a rapid initial decrease in plasma concentration, followed by a slower decline. This is partially due to protein binding, especially to albumin (Finlay and Baguley, 2000; Liston and Davis, 2017; Patel et al., 2013).

Anthracyclines are not uniformly distributed in the body. They accumulate in healthy tissues, particularly the heart, liver, spleen, and kidney. This accumulation is responsible for most of the side effects of anthracyclines (Nicoletto and Ofner, 2022; Patel et al., 2013).

In humans, about 50% of Dox is eliminated from the body unchanged. The remaining 50% is metabolized via three main pathways: hydroxylation, semiquinone formation, and deoxyaglycone formation. These pathways occur in various tissues, including the liver, heart, kidney, and blood (Edwardson et al., 2015).

Hydroxylation of anthracyclines at C13 (the first carbon of substituent R2, in Fig. 1) is a NADPH-dependent aldo-keto reduction of the C13 carbonyl group. This produces secondary alcohol metabolites, such as doxorubicinol (Doxol) in the case of Dox (Fig. 10). Doxol is up to 50 times more potent than the original compound. Other secondary alcohol metabolites include daunorubicinol and idarubicinol, which are formed from Dau and Ida, respectively (Octavia et al., 2012; Siebel et al., 2020).

The anthracycline semiquinone formation is the “one electron reduction” of the quinone moiety of the drug, catalyzed by many cellular

NADH- and NADPH-dependent reductases. The semiquinone can then react with oxygen to form a ROS, which can damage DNA and other cellular components.

The deoxyaglycone formation is the cleavage of the sugar moiety from the anthracycline molecule. This produces a highly toxic compound that is rapidly eliminated from the body.

Dox and Doxol may undergo deglycosidation of the daunosamine sugar moiety at C7, producing the doxorubicinone and doxorubicinolone 7-deoxyaglycone forms, respectively, characterized by the presence of a hydroxyl group at C7, that may be further metabolized to produce 7-deoxydoxorubicinone and 7-deoxydoxorubicinolone, respectively (Fig. 10) (Arnold et al., 2004).

The microbiome has an impact on the anthracycline metabolism and can reduce Dox toxicity. Anthracyclines are anaerobically degraded by *Klebsiella pneumoniae* and *Escherichia coli BW25113*, isolated by gut microbiome, and are inactivated under anaerobic conditions by the intestinal *Raoultella planticola*, that deglycosylates Dox to 7-deoxydoxorubicinol and 7-deoxydoxorubicinolone metabolites via a reductive deglycosylation mechanism, using molybdopterin-dependent enzymes (Yan et al., 2018). Dox deglycosylation mediated by the NADH dehydrogenase component of respiratory electron transport complex I of a *Streptomyces* strain has also been described (Westman et al., 2012).

6.5. Deregulation of proliferation, signaling pathways and cell death

Anthracyclines act primarily by poisoning topoisomerase II, generating DNA breaks and interfering with chromatin integrity. The cellular actions of anthracyclines directly or indirectly lead to cellular death, usually by apoptosis. However, cells can counteract such actions, altering many functions and pathways, and therefore generating resistance to the administered drug.

6.5.1. Altered cell cycle progression and proliferation pathways

Several studies have shown that resistance to anthracyclines can be generated by inducing proliferation and/or cell cycle progression, and by inhibiting apoptosis.

Signaling via the Ras/Raf/MEK/ERK, Jak/STAT and Ras/PI3K/PTEN/Akt/mTOR pathways is carefully regulated by many kinases, phosphatases and exchange proteins. Mutations and alterations in elements of these pathway, such as Jak2 kinase, Flt3, Kras, Nras and PI3K/Akt, can generate resistance to chemotherapy and radiotherapy, promoting proliferation and accelerating cell cycle progression (Abrams et al., 2010; Ligresti et al., 2009; McCubrey et al., 2007, 2008; Meshinchi et al., 2003; Stirewalt and Radich, 2003).

The levels and/or the action of many other players of the cell cycle regulation are altered in anthracycline-resistant cells. Among these proteins, the zinc finger E-box-binding homeobox 1 (ZEB1) is an important driver of resistance, regulated by the E3 ubiquitin ligase checkpoint with forkhead and ring finger domains (CHFR), as well as p62, Wnt, and ADAM10 (Kessler et al., 2013; Luo et al., 2021; Wei et al., 2011; Yang et al., 2012).

Further, the E2F transcription factors, which are 10 proteins (E2F1, E2F2, E2F3a, E2F3b, E2F4, E2F5, E2F6, E2F7a, E2F7b, and E2F8) that bind a so-called E2F-response element (TTTSSCGC), were identified as key regulators of sensitivity to anthracyclines. E2F family members regulate proliferation, differentiation, survival, apoptosis, and DNA damage responses. E2F1 and E2F7 have proliferative and anti-apoptotic functions and drive resistance to anthracyclines by activating the sphingosine kinase-1 (SPHK1) and Rac GTPase activating protein 1 (RACGAP1) pathways. Exportin1 relocalizes E2F1 and E2F7 from the nucleus to the cytoplasm, driving resistance to anthracyclines. Re-sensitization occurs by inhibiting Exportin1 (Hazar-Rethinam et al., 2015a, 2015b; Saenz-Ponce et al., 2018).

6.5.2. Altered apoptotic regulators/effectors

Cell survival to the effects of anthracycline on DNA can involve adaptive suppression of the downstream apoptosis programs that are usually triggered by DNA strand breaks. Overall, the equilibrium between proliferation and cell death can be shifted towards proliferation, generating resistance.

The tumor suppressor p53 is an important sensor of DNA damage, is a transcriptional activator of pro-apoptotic proteins such as Bax, Bak, CD95 and TRAIL, and a repressor of anti-apoptotic proteins such as Bcl-2 and Survivin (Ryan et al., 2001). Dox and other anthracyclines upregulate p53 via DDR kinases-dependent phosphorylation, inhibiting its binding to and phosphorylation by MDM2, a member of the ubiquitination and proteosomal degradation pathway, that normally maintain a low steady-state p53 level (Bunz et al., 1999; Khanna and Jackson, 2001). Nutlin-3, an inhibitor of the interaction between MDM2 and p53, increases p53 activation and stabilization, and increases Dox sensitivity in hepatocarcinoma cells (Zheng et al., 2010). p53 deletion or mutation, or disruption of p53 activation, commonly occur during tumorigenesis, providing a molecular basis for resistance to Dox. Experimental p53 re-expression promotes apoptosis upon Dox treatment (Zhao et al., 2007). For example, human squamous cell carcinoma cancer resistant to Dox showed overexpression of mutated p53-Arg273His, which determines downregulation of procaspase-3. Knockdown of p53-Arg273His increases procaspase-3 level and re-sensitizes the cells to drug-induced apoptosis, while overexpression of p53-Arg273His decreases procaspase-3 levels and increases resistance (Wong et al., 2007). Several missense p53 mutations, localized within the region encoding the DNA-binding domain of the protein, have been identified in pediatric acute lymphocytic leukemia (ALL) resistant to Dox. When tumor suppression functions of p53 were chemically restored, the p53 transcriptional targets PUMA (P53-Upregulated Modulator of Apoptosis), p21 (Cyclin Dependent Kinase Inhibitor 1A, CDKN1), and NOXA were induced, together with Dox sensitivity (Demir et al., 2020).

NF-κB is a transcription factor that can act in tumor suppression or promotion, depending on the cellular context. NF-κB is activated by DNA damage and regulates genes as Bcl-XL and XIAP, increasing resistance to anthracycline-dependent cell death (Fan et al., 2008). NF-κB is activated in response to anthracycline-induced double-strand breaks by different mechanisms: the transcriptional activity of NF-κB is potentiated by the anti-apoptotic gene BAG-1 and by the HBV protein HBx, or by the reduced expression of miR-26b that suppresses NF-κB (Liu et al., 2011; Ni et al., 2013; Zhao et al., 2014a).

FOXO3a is another substrate of MDM2 that accumulates in the nucleus in response to Dox, promoting apoptosis in several tumor cell types, such as neuroblastoma, osteosarcoma, breast cancer and lung cancer (Chen et al., 2010; Dieudonné et al., 2012; Ho et al., 2012; Wang and Li, 2010). FOXO3 induces Dox-dependent apoptosis by transcriptionally repressing miR-21, thereby reducing translation of Fas-L, repressing apoptotic Bcl-2 family members such as Bcl-2 and Survivin, and upregulating Bim, a pro-apoptotic Bcl-2 protein (Hagenbuchner et al., 2012; Li et al., 2016b; Obexer et al., 2009). Paradoxically, FOXO3 can either be a cell survival factor and a cell death factor. Increased FOXO3 expression has been observed in Dox-resistant breast cancer and leukemias, possibly linked to FOXO3's ability to transcriptionally activate ABCB1 (Chen et al., 2010; Hui et al., 2008a, 2008b). The FOXO3 pro-death vs. pro-survival activity is possibly controlled by specific post-translational modifications. In the unphosphorylated state, FOXO3 activates an anti-oxidant transcriptional pathway; p38-dependent FOXO3 phosphorylation at position Ser7 determines its translocation to the nucleus in response to Dox administration, while phosphorylation at Ser574 determines the binding of FOXO3 to pro-apoptotic promoters and induces cell death. Dox-sensitive tumors have higher nuclear FOXO3 content than Dox-resistant tumors (Li et al., 2016b).

Sirtuins are other proteins participating to the MDR phenotype. SIRT1 is often found overexpressed in hepatocarcinoma tumors resistant to Dox, as SIRT4, 5, 6 and 7 in breast cancers resistant to Epi. The mechanism of Sirtuin-mediated resistance is not fully known, but it may involve the deacetylation of p53, FOXO3, or YAP2, and consequently the

inhibition of apoptosis (Brunet et al., 2004; Chen et al., 2012c; Chen et al., 2011a, 2011b; Luo et al., 2001).

6.5.3. Altered DNA damage repair

Resistance to anthracyclines is linked to alteration of DNA damage, which can occur in several different ways. As mentioned above, the p53-dependent response to DNA damage is altered by Dox treatment, resulting in resistance. Another mechanism linking anthracycline resistance to DNA damage concerns the Adenomatous Polyposis Coli (APC) tumor suppressor, which is mutated or hypermethylated in most breast cancers. APC loss increases resistance to Dox, by decreasing the activation of DNA damage response proteins (ATM, Chk1, and Chk2). This resistance can be reduced by using inhibitors targeting DNA damage repair kinases such as ATM, ATR, and DNA-PK. This suggests a potential clinical use of DNA repair inhibitors in combination therapy with anthracyclines (Stefanski et al., 2019; VanKlompenberg et al., 2016).

Resistance to Dox can also be induced by the kinase CK2α/CSNK2A1, via SIRT6-mediated activation of the DNA damage repair pathway. Tumors resistant to Dox have high expression of CSNK2A1, associated with highly phosphorylated SIRT6, and short survival in osteosarcoma patients. CSNK2A1- and SIRT6-mediated resistance to Dox is reduced by mutation of the Ser338 phosphorylation site of SIRT6. Emodin, a CSNK2A1 inhibitor, potentiates the cytotoxic effects of Dox in osteosarcoma cells (Hussein et al., 2021).

6.6. Epigenetic and post-translational alterations

Resistance to chemotherapy can arise from the accumulation of epigenetic alterations in cancer cells. Tumor cells can change their epigenomic landscapes to resist anti-cancer therapy by remodeling their DNA methylation pattern or modifying histone proteins.

DNA methylation is the covalent addition of a methyl group to the C5 position of the cytosine of a CpG dinucleotide by DNA methyltransferases. Hypomethylation of the promoters of genes involved in drug efflux, such as ABCB1 and ABCG2, can lead to their overexpression and acquisition of resistance via increased drug efflux (Abolhoda et al., 1999; Bram et al., 2009; Pajic et al., 2009; Zappe and Cichna-Markl, 2020).

In triple-negative breast cancer, the tumor suppressor ZMYND8 protein forms a repressor complex with KDM5C and EZH2, which increases the amount of H3K27me3 on the promoters of ABCB1, ABCC1, and ABCC2, thereby repressing their expression (Mukherjee et al., 2020).

Histone acetylation is important for resistance to anthracyclines. Tabe and coworkers showed that histone deacetylase inhibitors induce resistance to Dox by up-regulating ABCB1 in APL cells (Tabe et al., 2006). However, the phenomenon is complex, and some oncogenes, such as Myc and insulin-like growth factor receptor 2 (IGF-2), are also upregulated by epigenetic mechanisms. Histone deacetylases increase the expression of Myc, E2F, and other G2M cell cycle genes, and contribute to increase resistance of breast cancer cells to Dox-induced growth arrest (Merino et al., 2018).

In breast cancer, epigenetic inactivation of the mismatch repair gene MSH2, due to promoter hypermethylation, is associated with acquisition of resistance to Dox. This is accompanied by aberrant expression of epigenetic regulatory genes, and a significant increase in H3 acetylation and methylation (Ponnusamy et al., 2018).

Epigenetic changes therefore result in global dysregulation of gene expression, which in some cases can lead to the acquisition of resistance to chemotherapy (Crea et al., 2009; Zeller and Brown, 2010).

6.7. Altered autophagy

Autophagy is an evolutionarily conserved process in which damaged organelles, misfolded or damaged proteins, and other cellular parts are transported to the lysosomal system and degraded, with subsequent recycling of degraded materials. The first events of autophagy are the formation of a phagophore, followed by the preautophagosome. Then, ATG (autophagy-related genes) proteins, LC3, and other components form the autophagosome, which fuses with the lysosome to form an autolysosome. Autophagy directly affects the invasion, metastasis, and proliferation of cancer cells, and can mediate the process of chemoresistance in the tumor microenvironment.

ATG5 is involved in resistance to anthracyclines in gallbladder cancer. The long non-coding RNA GBCDRlnc1 (gallbladder cancer drug resistance-associated lncRNA1) is upregulated in Dox-resistant gallbladder cancer tissues and cells, and interacts with PGK1 (phosphoglycerate kinase 1), preventing its ubiquitination and degradation. This leads to the downregulation of the autophagy initiator ATG5-ATG12 complex, and increased drug resistance (Cai et al., 2019b). In AML cells, downregulation of ATG7 increases apoptosis and decreases resistance to cytarabine and Ida (Piya et al., 2016).

In osteosarcoma cells, the activation of HSP90AA1, which regulates the activation of autophagy through the PI3K/Akt/mTOR pathway, is a driver for resistance to anthracyclines and other drugs (Xiao et al., 2018).

The high mobility group box 1 protein (HMGB1) is another key regulator of autophagy, which plays an important role in DNA replication and DNA repair mechanisms. Cancer cells acquire sensitivity to anthracyclines upon blockage of both autophagy and HMGB1. Upon Dox administration, mRNA and protein levels of HMGB1 are increased. HMGB1 competes with Bcl-2 for Beclin1 binding. The complex between Beclin1 and PtdIns3KC3 induces autophagosome formation and triggers autophagy (Chen et al., 2018).

6.8. Intra-tumor heterogeneity

Intra-tumor heterogeneity (ITH) is an important driver of drug resistance. Single-cell sequencing studies have identified multiple genetically distinct variants within human tumors, demonstrating the heterogeneous nature of human cancers. The main factors of ITH are genetic variation, stochastic processes, the microenvironment (see next section) and cell/tissue plasticity. These factors can all determine drug resistance by selecting a subpopulation of cells that are resistant to the drug.

Subpopulations of tumor cells expressing high amounts of ABC transporters can develop resistance to anthracyclines. For example, melanomas resistant to Dox have been described to develop from ABCB1-, ABCB5- and ABCB8-positive subpopulations of cells (Elliott and Al-Hajj, 2009; Frank et al., 2005).

Stromal infiltration, due to laminin or integrin expression, can activate intracellular pathways such as NF-κB, MAPK/ERK, PTEN/PI3K/Akt. This activation can protect tumor cells from apoptosis and lead to resistance to Dox in lung cancer (Sethi et al., 1999).

ITH in Dox binding to chromatin in ovarian cancer cells, possibly due to epigenetic differences in subpopulations, has been shown to be responsible for the onset of resistance to anthracyclines in different metastases in the same mouse and in different regions of the same metastasis (Sparks et al., 2018).

6.9. Altered tumor microenvironment

In addition to containing heterogeneous tumor cells, cancers contain various types of cells (such as immune cells, inflammatory cells and fibroblasts), blood vessels, extracellular matrix (ECM), and many nutrients and signaling molecules. These components together play key roles in tumor growth and survival, and contribute to the hallmarks of cancer (Hanahan and Coussens, 2012; Hanahan and Weinberg, 2011).

The tumor microenvironment (TME) also contributes to resistance to chemotherapeutic drugs, and anthracyclines in particular, by different mechanisms.

One important mechanism is pH modulation. In normal cells and

tissues, the extracellular pH is usually slightly more alkaline than intracellular pH (external pH 7.3–7.5 vs. internal pH 6.8–7.2) (Casey et al., 2010). However, in cancer, a pH gradient reversal is observed, with higher intracellular pH and lower extracellular pH. This is due to proton pumping mediated by proton transporters and the modulation of pH sensors (Sharma et al., 2015). The acidification of the extracellular milieu (external pH 6.5–7.1) impairs the distribution of weak base anticancer drugs, such as most anthracyclines. This phenomenon, known as "ion trapping", allows cancer cells to evade apoptosis and increases resistance to chemotherapeutic drugs (Taylor et al., 2015; Webb et al., 2011).

Approaches aiming to increase microenvironment pH, such as the use of proton pump inhibitors, have shown efficacy in shrinking tumor and sensitizing cancer cells to chemotherapy drugs. Lansoprazole, a proton pump inhibitor, is not toxic to tumor cells but potentiates Dox toxicity and increases its penetration through multilayered cell cultures. In solid tumors, lansoprazole improves Dox distribution and increases drug activity in the cancer, reducing the onset of resistance (Yu et al., 2015).

In the TME, the basic fibroblast growth factor (bFGF) stimulates endothelial cells to produce Raf-1, which forms a complex with the proapoptotic kinase ASK1. This complex induces resistance, protecting endothelial cells from Dox-induced apoptosis (Alavi et al., 2007).

Fluctuating hypoxia and reoxygenation, which are typical of the TME, produce oxidative stress that may induce DNA damage in cancer cells. This can affect anthracycline effect and resistance (possibly via hypoxia-induced ABCB1), and can also provide genetic instability that in turn leads to the accumulation of mutations and to increased divergent subpopulations (Bindra and Glazer, 2005; Comerford et al., 2002; Hamdan and Zihlif, 2014; Reynolds et al., 1996).

In addition, TME cells, as tumor-associated macrophages, release miRNA-containing exosomes, contributing to tumor heterogeneity and to the onset of resistance (Challagundla et al., 2015). Anthracyclines activate different resistance pathways associated with different types of TME cells. For example, in myeloid-derived suppressor cells, Dox activates the PGE2/miR-10/AMPK signal, while in osteosarcoma mesenchymal stem cells-derived IL-6 activates the JAK2/STAT pathway, with ABCB1 and ABCC1 overexpression. In acute lymphoblastic lymphoma, cancer-associated adipocytes express Dau-metabolizing enzymes, and in breast cancer tumor-associated adipocytes express increased amounts of efflux pumps (Lehuédé et al., 2019; Rong et al., 2016; Sheng et al., 2017; Tu et al., 2016).

Further, in endothelial cells (ECs), different mechanisms of resistance to anthracyclines are activated by Dox in different tumors. For example, in B cell lymphoma, ECs induce Notch2 and downregulate the PI3K/AKT/mTOR pathway. In breast cancer and melanoma, ECs activate the NF-κB pathway, while in hepatocarcinoma they activate the FGFR1-ETS2 pathway (Acharyya et al., 2012; Bent et al., 2016; Cao et al., 2014; Tavora et al., 2014).

6.10. *Extracellular vesicles-dependent intercellular communication/ signaling*

Extracellular vesicles (EVs) are mediators of resistance towards many chemotherapeutic drugs, including anthracyclines. There are a number of different mechanisms by which EVs can mediate resistance (Namee and O'Driscoll, 2018). Historically, the first studies on the role of EVs in resistance were carried out in breast cancer cells resistant to Dox and mitoxantrone (structurally similar DNA-intercalating chemotherapeutic agents). These studies showed that EVs can sequester the drugs, removing them from the cytosol of resistant cells via ABCG2, thereby decreasing the intracellular concentration of the drugs (Ifergan et al., 2005; Shedden et al., 2003).

In ALL cells, resistance to Dau depends on the presence of ABCB1 on the surface of EVs. These EVs transfer the efflux pump to drug-sensitive cells, which then become resistant to the drug (Bebawy et al., 2009). Similarly, in ovarian cancer and in osteosarcoma, the transfer of EVs mediates onset of resistance by means of the transfer of ABCB1. In leukemia, ABCC1 and ABCA3 are transferred via EVs (Bouvy et al., 2017; Chapuy et al., 2008; Torreggiani et al., 2016; Zhang et al., 2014).

In breast cancer, paracrine modulation of drug resistance by horizontal transmission of EVs is responsible for Adriamycin resistance. This can occur through a number of different mechanisms. For example, EVs rich in miR-100, miR-30a and miR-222 has been shown to be involved in pathways of cancer pathogenesis and membrane vesiculation. The presence of the transient receptor potential channel 5 (TrpC5) on the cell surface of EVs has also shown to be responsible of the transfer of drug-resistant properties between breast cancer cells (Chen et al., 2014; Ma et al., 2014). High expression and transfer of exosomal miR-21 in squamous cell carcinoma is also linked to tumor progression, drug resistance and poor prognosis (Tanaka et al., 2013).

In hepatocellular carcinoma (HCC), TGFβ-dependent chemoresistance to Dox has been observed. TGFβ increases resistance to Dox and alters release of EVs and of long non-coding RNAs (lncRNA) within these vesicles. LincRNA-ROR (linc-ROR), a stress-responsive lncRNA, is highly expressed in HCC cells and enriched within EVs derived from tumor cells. These EVs have a role in intercellular signaling in response to TGFβ and in chemoresistance. Incubation with HCC-derived EVs increases linc-ROR expression and reduces Dox-induced cell death in recipient cells. EV-lncRNA thus mediates drug resistance, and targeting linc-ROR may help to restore sensitivity to anthracyclines (Takahashi et al., 2014).

6.11. *Epithelial-to-mesenchymal transition*

Normal epithelial cells cannot migrate because of the presence of intracellular junctions, including adherens, tight, and gap junctions. The ability to migrate depends on the loss of intracellular junctions, and the consequent acquisition of mesenchymal features such as high motility, lack of apical-basal polarity, and detachment from basement membrane. This process is known as epithelial-to-mesenchymal transition (EMT).

EMT is important in cancer progression and depends on a series of pathways that act as EMT markers. Epithelial E-cadherin level decreases, while N-cadherin and vimentin levels increase. Most EMT markers are growth factors, such as transforming growth factor β (TGF-β), epidermal growth factor (EGF), hepatocyte growth factor (HGF) and fibroblast growth factor (FGF), and proteins, such as Wnt, ZEB1, ZEB2, interleukins, Slug, STAT3, SNAIL and TWIST. Upregulation of SNAIL and TWIST triggers EMT-mediated metastasis, while their downregulation reduces migration and invasion of tumor cells (for a review, see Mirzaei et al., 2021a).

The onset of EMT increases the viability of tumor cells, enhances malignancy, invasion, and metastasis, and resistance to chemotherapy. It also represents a negative factor for cancer patients' prognosis. Exposure to anthracyclines can induce EMT and its markers, such as vimentin and SEMA4A, in several tumors. In hepatocellular carcinoma, silencing of SEMA4A reduces EMT and increases sensitivity to Dox (Pan et al., 2016). Cells that survive treatment develop EMT features, are senescence-averse and are drug-resistant (Han et al., 2013; Ponnusamy et al., 2017; Yang et al., 2017a).

One of the pathways that affect anthracycline resistance is PTEN/PI3K/AKT. PTEN is a tumor suppressor that regulates the PI3K/AKT pathway. Cells with overexpressed AKT produce a transcription factor, Snail, that represses the expression of E-cadherin, activating EMT and generating resistance via different mechanisms, such as expression of efflux pumps. PTEN signaling reduces ABCB1 activity in colon cancer cells and increases sensitivity to Dox. MicroRNAs as miR-93 and miR-29a act on PTEN signaling, affecting EMT and drug resistance (Chu et al., 2017; Larue and Bellacosa, 2005; Shi et al., 2020).

miR-200c downregulates the E-cadherin repressors ZEB1 and ZEB2, increasing E-cadherin, inhibiting EMT, and decreasing resistance to anthracyclines (Chen et al., 2013). C-Myc triggers EMT by decreasing

the expression of miR-200c, inducing resistance to anthracyclines in nasopharyngeal tumor. In lung cancer, miR-451a inhibits c-Myc, increasing epithelial markers such as E-cadherin and decreasing mesenchymal markers such as vimentin and N-cadherin, thereby inhibiting EMT and increasing resistance to Dox (Tao et al., 2020; Yang et al., 2020).

Sensitivity to Dox is also achieved by overexpression of miRNA-33a-5p, which inhibits EMT in breast cancer cells by downregulating the translation initiation factor eIF5A2, or by expression of miR-137, which regulates DUSP4, whose silencing decreases the onset of EMT (Du et al., 2019; Guan et al., 2019). On the contrary, miR-223 decreases the level of FBXW7, a tumor suppressor that is part of a ubiquitin ligase complex that regulates a network of proteins important in cell division, cell growth, and differentiation. This induces EMT and increases resistance to Dox in colorectal cancer (Ding et al., 2018).

Increased resistance to anthracyclines via EMT can also be due to the overexpression/activation of β-catenin signaling, Notch, ARK5, P300, FSCN-1 and other EMT-activating proteins (Han et al., 2013; Han et al., 2014; Tian et al., 2020; Wang and Zhao, 2021; Yang et al., 2017b).

6.12. Cancer stem cell alterations

Cancer stem cells (CSCs) have special properties that make them resistant to chemotherapy. These properties include: EMT (epithelial-to-mesenchymal transition), which allows CSCs to become more motile and invasive; high expression of drug efflux pumps and detoxification enzymes, which allows CSCs to expel chemotherapeutic drugs from the cell; quiescence, which allows CSCs to enter a state of dormancy and avoid cell death; apoptosis resistance, which makes CSCs less likely to die in response to chemotherapy; epigenetic alterations, which can change the expression of genes involved in drug resistance. These properties allow CSCs to survive chemotherapy and form new tumors (Li et al., 2008; Vu et al., 2013).

Twist, Slug, and Snail are transcription factors that induce EMT. They also trigger stem cell-like features in tumor cells, which are associated with drug resistance (Shibue and Weinberg, 2017).

CD13, CD44, CD133, and EpCAM are markers of CSCs in liver cancer. They are overexpressed in tumor foci and in cells that survive chemotherapy. These markers are linked to resistance to several chemotherapeutic drugs. For example, CD13 reduces ROS-induced drug-dependent DNA damage and protects cells from apoptosis. This makes cells resistant to anthracycline treatments and favors metastasis (Haraguchi et al., 2010; Zeng et al., 2012). CD133 is overexpressed in CSCs from hepatocarcinoma resistant to Dox, where it induces survival proteins of the AKT/PKB and the Bcl-2 pathways. Treatment of CD133+ cells with AKT inhibitors reduces the expression of the survival proteins; treatment of unsorted hepatocarcinoma cells with Dox enriches the stem-like CD133+ population (Ma et al., 2008).

ABC transporters as ABCB1, ABCC1 and ABCG2 are expressed at high levels in CSCs of many solid tumors, making them intrinsically resistant to chemotherapeutic drugs. For example, down-regulation of ABCG2 has been reported to increase the sensitivity towards Dox of breast and liver CSCs. In particular, the CSCs marker Oct4, a transcriptional factor of pluripotent cells, induces chemoresistance towards anthracyclines and other chemotherapeutic drugs via Oct4-TCL1-AKT-ABCG2 pathway (Das et al., 2019; Wang et al., 2010).

MicroRNAs are also involved in the generation of anthracycline resistance or sensitivity in tumors (see next section) and in CSCs. For example, miR-199a suppresses CD44, and therefore reduces the expression of ABCG2. This increases the sensitivity to adriamycin in ovarian CSCs (Sukowati et al., 2015).

6.13. MicroRNA alterations

Non-coding RNAs, and in particular microRNAs (miRNAs), have been shown to be associated with anthracycline resistance in many cancer types. MiRNAs that determine repression of targets involved in proliferation pathways such as oncoproteins or tumor suppressors and their regulators, or in xenobiotic efflux, can have important effects on anthracycline resistance and sensitivity (Blower et al., 2008; Cox and Weinman, 2016; Si et al., 2022; Zangouei et al., 2021) (Table 2). Dysregulation of the miRNAome is observed in breast cancer cells, with miR-200c, miR-451, miR-27 levels reduced in Dox-resistant cells. These microRNAs regulate the expression of ABCB1, and transfection of resistant cells with miRNA-451 results in increased drug sensitivity (Chen et al., 2012a; Kovalchuk et al., 2008; Zhu et al., 2008).

In hepatocellular carcinoma, the liver-specific miR-122, that represents a large part of total miRNAs expressed in the liver, is often downregulated, especially in tumors resistant to Dox. MiR122 affects anthracycline resistance by modulating p53 activity and ABCB1 expression. Transfection with miR-122 restores the miRNA level, resensitizing hepatocarcinoma cells towards the drugs (Fornari et al., 2009; Xu et al., 2011).

MiR-223 binds to the 3′UTR of the *ABCB1* gene suppressing MDR1 expression in many hepatocarcinoma cell lines, downregulating ABCB1

Table 2
The roles of miRNAs in anthracycline resistance.

Resistance mechanism	Target protein/ process	miRNA
Drug efflux	ABCB1	miR-451, miR-27, miR-122, miR-137, miR-195, miR-200c, miR-223, miR302s, miR-381, miR-495, miRNA-508-5p
	ABCC1	miR-134, miR-145, miR-199a, miR-326, miR-451, miRNA-1291
	ABCC4	miR-124-3p
	ABCA1	miR-760
	ABCG2	miR-132, miR-212
Cell survival, apoptosis and autophagy	p53	miR-22
	p21	miR-519d
	PI3K/Akt pathway	miRNA-205, miR-222
	PTEN/Akt	miR-21, miR-29a, miR-93, miR-132, miR-212, miR-222, miR-519d
	Akt	miRNA-17/20, miRNA-181
	HER3	miRNA-450-3p
	Bcl-2	miRNA-135a-5p, miRNA-149, miRNA-205
	MCL1	miRNA-193b
	SIRT1	miRNA-204
	ULK1	miRNA-22, miRNA-26a, miRNA-26b, miRNA-142, miRNA-489
	LAPTM4B	miRNA-489
	ATG4A and ATG5	miRNA-22, miRNA-142
	ATG16L1	miRNA-410
	Beclin-1	miRNA-30a
Epithelial-to-mesenchymal transition	Vimentin, cadherin	miR-25, miR-93, miR-124, miR-137, miR-181c, miR-448, miR-489
	Twinfilin1	miR-30c
	IL-11	miR-30c
	ST8SIA4	miR-181c
	IGF-1R	miR-520b
	eIF5A2	miR-33a-5p
	ZEB-1	miRNA-200b, miRNA-200c, miRNA-431, miRNA-708-3p
	ZEB-2	miRNA-138
Cell cycle and proliferation	Cyclin G1	miR-122
	REV1	miRNA-30c
	CK1	miR23a, miR24, miR-222
	Wnt1 and Wnt cascade	miR-140-5p, miRNA-214-3p, miRNA-452
	Notch1	miR-34a
	Ankyrin 1	miRNA-486
	Aurora kinase A	miRNA-26a-5p
	Ras/MAPK/ ERK pathway	miRNA-187, miRNA-217, miRNA-302a/b/c/d
DNA repair	PARP-1	miRNA7-5p
Epigenetic	HDAC-1	miRNA-520h

both at mRNA and at protein levels. Over-expression of miR-223 increases cell sensitivity to anthracyclines, while inhibition of miR-223 has the opposite effect (Yang et al., 2013b). Other microRNAs act on different transporters: the ABCC1 pump is the target of miR-134, miR-199a and miR-145, while the ABCC4 pump is downregulated by miR-124-3p in breast cancer (Chang et al., 2018; Gao et al., 2016; Lu et al., 2015a).

Many signaling pathways that induce proliferation are targeted by other microRNAs, as NF-κB, Wnt1, FSTL1, NOTCH1, NANOG, the PI3K/AKT pathway and the MAPK pathways (for a review, see Cox and Weinman, 2016; Si et al., 2022; Zangouei et al., 2021).

In breast cancer, miR-140-5p is frequently downregulated, enhancing resistance to anthracyclines. MiR-140-5p downregulates the Wnt1 mRNA and protein levels and increases the sensitivity of Dox via Wnt1 and ABCB1 pathways, both *in vitro* and *in vivo* (Wu et al., 2019). Dysregulation of miR-34a plays a critical role in the acquired resistance of breast cancer towards anthracyclines, at least in part by targeting and degrading Notch1. Overexpression of miR-34a sensitizes MCF-7 breast cancer cells to adriamycin (Li et al., 2012). Mir-222, miR-21, miR-93, miR-132, miR-212 and miR-29a have been identified as regulators of the PTEN/Akt pathway, able to confer resistance to anthracyclines. These miRNAs are overexpressed in many tumor cell lines and cancer patients, decreasing the levels of the tumor suppressor phosphatase PTEN, and consequently increasing phosphorylation of signaling proteins as Akt, GSK3β and NF-κB, increasing proliferation; silencing of miR-132 and miR-212 also decreases the levels of efflux pumps as ABCB1 and ABCG2, and increases drug concentration, leading to resensitization towards anthracyclines (Chu et al., 2017; H. Shen et al., 2016, 2017; Wang et al., 2011; Xie et al., 2018).

In hepatocarcinoma, overexpressed miR-519d inhibits apoptosis and promotes tumor growth by decreasing the expression of tumor suppressor proteins as p21 and PTEN, also leading to resistance to Dox (Fornari et al., 2012).

MiR-30c regulates other important proteins as twinfilin1 (TWF1), an actin-binding protein, and interleukin-11, that promote EMT, and the tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta polypeptide, that codes for the anti-apoptotic protein 14-3-3ζ, that binds and stabilizes key proteins involved in signal transduction, cell proliferation, and apoptosis, including EGFR, HER2, PKC, β-catenin, and RAF-1, and reduces the activation of the p38MAPK signal pathway (Bockhorn et al., 2013; Fang et al., 2014).

On the contrary, miR-181c is downregulated in drug-resistant chronic myelocytic leukemia cell lines. Upregulation of miR-181c inhibits chemoresistance by targeting ST8SIA4 (a sialyltransferase required for the synthesis of polysialic acid, a modulator of the adhesive properties of neural cell adhesion molecule NCAM1), whose expression is increased in many carcinomas, and highly correlates with leukemia multidrug resistance (Zhao et al., 2016a). MiR-26b, that suppresses the NF-κB activators TAK1 and TAB3, is overexpressed in hepatocarcinoma cells, inhibiting NF-κB and increasing Dox sensitivity (Zhao et al., 2014a). The downregulation of miR-101, miR-199a–3p and miR-215 is also associated with anthracycline resistance in hepatocarcinoma, while high levels of these miRNAs are associated with sensitivity to drug. Restoring their expression in miRNA-deficient cells increases Dox sensitivity (Fornari et al., 2010; Wang et al., 2015; Xu et al., 2014).

Other miRNAs target proteins involved in cell cycle, as cyclins and kinases, in epithelial-to-mesenchymal transition, in metastatization, in exosomes and in other cellular pathways are implicated in the mechanisms of resistance to anthracyclines and other chemotherapeutic drugs (Cox and Weinman, 2016; Si et al., 2022; Zangouei et al., 2021).

7. Overcoming anthracycline resistance

Drug resistance and multidrug resistance are the most important causes for anthracycline-based chemotherapy failure. Many patients fail to respond to repeated treatments or develop resistance, that determine relapse and/or metastatization. Several strategies have been exploited for overcoming resistance to anthracyclines.

7.1. Increasing anthracyclines solubility

One of the strategies to overcome resistance is to increase drug solubility and/or drug delivery.

Highly soluble anthracyclines have been studied, with the goal of obtaining compounds that are more available, more efficacious, and less likely to induce resistance.

Anthracyclines that are hydroxylated at the C13 position are more polar and water-soluble than the parent compounds. However, contrary to what might be expected, these compounds are often considerably less potent antineoplastic agents. They also have lower excretion and higher cardiotoxicity, due to their enhanced ability to accumulate in cardiac tissue relative to the parent compounds (Reszka et al., 2005). Since the 13-hydroxylation of anthracyclines by the aldo-keto reductase (AKRs)-dependent "two-electron reaction" reduces their cytotoxicity, blocking the formation of hydroxylated metabolites is a strategy to improve the efficacy of anthracyclines. AKR inhibitors (in particular AKR1B10 inhibitors) such as 2-hydroxyflavanone, beta-cholanic acid, emodin, oleanoic acid, and 3-(4-hydroxy-2-methoxyphenyl-1)acrylic acid 3-(3-hydroxyphenyl)propyl ester increase anthracycline cytotoxicity in anthracycline-resistant cell lines overexpressing AKRs. However, no improvement in clinical response in tumor patients resistant to anthracyclines has been reported to date using these compounds (Awasthi et al., 2018; Heibein et al., 2012; Hintzpeter et al., 2016; Morikawa et al., 2015; Veitch et al., 2009).

The carbonyl reductase CBR1 inhibitor 7-mono-O-(β-hydroxyethyl)-rutoside (monoHER) was used in a phase II study with Dox in metastatic cancer patients. MonoHER increases Dox cardioprotection, possibly by reducing the production of the cardiotoxic metabolite Doxol by "two-electron reaction". It also increases Dox cytotoxicity in human liposarcoma cells by reducing NF-κB activation and promoting Dox-induced apoptosis, while not interfering with the antitumor activity of Dox (Bruynzeel et al., 2007; Jacobs et al., 2011).

Increasing solubility of anthracycline may represent a possible solution to obtain a more effective drug.

7.2. Increasing anthracyclines delivery to tumors

The use of nanomaterials for the delivery of anthracyclines also may help overcoming resistance. Nanoparticle (NP)-based drug delivery systems exhibit many advantages in cancer therapy, including good pharmacokinetics, tumor targeting, decreased side effects, and decreased drug resistance (Palazzolo et al., 2018). Many types of NPs are available for cancer therapy, some of which have been described in section 3.2, especially as regards liposomal and ferritin-based NPs. A description of the approaches used exceeds the scope of the present paper; for a review, see Yao et al. (2020). Anthracycline delivery has been obtained via organic NPs, inorganic NPs and hybrid NPs. The organic NPs include liposome-based NPs, polymer-based NPs and dendrimers. Many different inorganic NPs have been described, among which gold NPs (Au NPs), carbon nanotubes, silica NPs, magnetic NPs, and quantum dots. Hybrid NPs combining the advantages of different NPs, include lipid-polymer hybrid NPs, organic-inorganic hybrid NPs, and cell membrane-coated NPs.

Passive and active delivery strategies have been pursued to overcome drug resistance. For example, a temperature-, pH-, and redox-responsive drug delivery system was synthesized based on methacrylic acid, poly (N-isopropylacrylamide), 2-hydroxyethylmethacrylate, and N,N′-bis (acryloyl)cystamine. Dox was effectively loaded into NP that remain stable in blood circulation and accumulate at tumor tissues, where pH-response and temperature-response favor entry into tumor tissues by endocytosis, cleavage by glutathione, and drug release (Yu et al., 2018). Stimuli-sensitive ferritin-based NPs proved to be highly effective in

specific anthracycline delivery to tumors, targeting CD71, which is highly expressed in most human cancers (Falvo et al., 2018; Fracasso et al., 2016).

Combination therapy is a very promising strategy to overcome anthracycline resistance and improving the efficacy of the treatment. For example, multifunctional micelles for the co-delivery of Dox with efflux pumps inhibitors were demonstrated to be effective (Qin et al., 2018). Co-delivery of ABCB1-targeted siRNA and anthracyclines (e.g., miRNA-495 and Dox) by membrane-coated silica NPs restores drug sensitivity in a drug-resistant lung cancer by down-regulating ABCB1 expression (He et al., 2019). Co-delivery of ABCC1-targeting siRNAs and Bcl-2 with Dox was performed using cationic liposomes, inducing cell death and drug resistance in MDR lung cancers (Saad et al., 2008).

Co-delivery of Cox2 inhibitors and Dox by disulfide-containing poly (β-amino ester) NPs overcomes the MDR phenotype of breast cancer cells (Zhang et al., 2019), while co-delivery of Dox and resveratrol in PLGA NPs overcomes Dox resistance in breast cancer cells by inducing apoptosis via the downregulation of Bcl-2 and NF-κB expression, and via the inhibition of efflux pumps expression (Zhao et al., 2016c).

EVs can modulate chemoresistance by transferring vesicular content, and especially microRNAs that activate anti-apoptotic signaling and DNA damage repair. They can also alter processes such as chemotherapeutic drugs efflux, immunosuppression, cytosolic pH and EMT. Inhibition of exosome release is a strategy to reduce resistance to anthracyclines. For example, the inhibitor GW4869, which blocks ceramide-mediated exosome biogenesis, increases the effect of PEGylated liposomal Dox and reduces resistance in AML cells (Hekmatirad et al., 2021). Pantethine, which inhibits cholesterol synthase and fatty acids synthesis, thus blocking EVs synthesis, increases sensitivity towards Dox in breast cancer cells (Roseblade et al., 2015). Inhibition of vesicle biogenesis in B-cell lymphoma increases the accumulation of anthracyclines, dependent on the expression of ABCA3. Genetic or chemical depletion of ABCA3 increased the intracellular retention of the chemotherapeutic agents, and also EVs spread, overcoming resistance (Koch et al., 2016). Ketotifen (an antihistamine compound) inhibits EVs release by acting on calcium homeostasis and sensitizes breast cancer cells resistant to Dox (Khan et al., 2018).

Alternatively, administration of Dox-loaded EVs reduces anthracycline cardiotoxicity and enhances sensitivity of breast and ovarian cancer, increasing the therapeutic index of Dox (Hadla et al., 2016).

In breast cancer resistant to anthracyclines, administration of the farnesoid X receptor antagonist guggulsterone and the retinoid-X receptor agonist bexarotene induced exosomes by increasing the levels of ceramide, and strongly reduced the cellular levels of BCRP/ABCG2 by inducing its association and secretion with exosomes, resensitizing cancer cells towards Dox (Kong et al., 2015).

Both combination therapy and active delivery may represent strategies of choice in the future.

7.3. Reducing anthracyclines toxicity

All strategies for reducing anthracycline toxicity, and in particular cardiotoxicity, imply the principle that increasing the limits of drug use also decreases the onset of resistance.

Reducing anthracycline cardiotoxicity using liposomal formulations of Dox or Dau to selectively target tumor tissue as a result of the enhanced permeability and retention (EPR) effect not only has similar or better performance vs. tumors, but also overcomes cardiotoxicity and myelosuppression, and improves drug effectiveness in Dox-resistant ABCB1-expressing tumors (Füredi et al., 2017; Rafiyath et al., 2012).

Prevention of anthracycline-dependent cardiotoxicity includes the co-administration of cardioprotective molecules, as dexrazoxane, ascorbic acid, and neuregulin (Jay et al., 2013; Sargent et al., 2001; Viswanatha Swamy et al., 2011). The iron chelator dexrazoxane reduces the anthracycline-dependent ROS generation, oxidative stress and DNA double-strand breaks. It has significant clinical efficacy, decreasing cardiac toxicity without reducing anthracycline activity or enhancing secondary malignancies. Dexrazoxane is the only FDA- and EMA-approved cardioprotective treatment for anthracycline cardioprotection. It is also approved for use as treatment of extravasation, an adverse event in which chemotherapies containing anthracylines leak out of the blood vessel and necrotize the surrounding tissue. Importantly, dexrazoxane also reduces Dox resistance in leukemia, possibly by long-term decreased expression of ABCB1 (Kane et al., 2008; Marty et al., 2006; Reichardt et al., 2018; Sargent et al., 2001).

Other agents with cardioprotective effects include statins, beta blockers, ACE inhibitors and COX inhibitors. Statins (inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase) act by upregulating NO synthesis and IKKα phosphorylation and decreasing the amount of IkBα. Statins increase the effect of anthracyclines and increases sensitivity to the drug in many cancers. They downregulate and inhibit ABCB1 and ABCB4, and consequently increase the nuclear levels of the drug and the effect on topoisomerase II (Riganti et al., 2006; Werner et al., 2013).

7.4. Acting on topoisomerase II

Topoisomerase II catalytic inhibitors can act via different mechanisms, such as competition for ATP binding (e.g., novobiocin), DNA cleavage impairment (e.g., merbarone) and inhibition of ATP hydrolysis (e.g., dexrazoxane). Apart being an iron chelator, dexrazoxane is a topoisomerase II catalytic inhibitor. It binds to the ATPase domains in the N-terminal region of topoisomerase II, which reduces topoisomerase activity and stability. This can lead to DNA damage and anthracycline cardiotoxicity (Classen et al., 2003). However, secondary resistance to topoisomerase II inhibitors can develop. This can happen through overexpression of efflux pumps, altered expression or cytoplasmic accumulation of topoisomerase II, altered DNA repair mechanisms, or altered apoptotic signaling.

Dual-target inhibitors have been designed to overcome these problems, and may prove effective in the future. One example is F14512, which is composed of an epipodophyllotoxin moiety that interacts with topoisomerase II, coupled via a glycine linker to a spermine side chain that facilitates the uptake and accumulation of molecule in tumor cells expressing the polyamine transport system, and reinforces the interaction with DNA due to its positive charge. F14512 has high cell selectivity, provides high affinity binding and stability to the ternary topoisomerase II-drug-DNA complex, and triggers less but unrecoverable DNA damage than the parent drug etoposide. It is an efficient, highly cytotoxic drugthat can overcome resistance to topoisomerase II inhibitors (Kruczynski et al., 2013).

The quinolone derivative Vosaroxin targets topoisomerase II and induces site-selective DSBs in DNA. This leads to tumor cell apoptosis. Vosaroxin lacks cytotoxicity due to metabolic activation and oxidative stress, since it forms stable complexes with Fe^{3+}, preventing formation of ROS. Vosaroxin has the potential to remain active in tumors refractory to anticancer drugs, since it does not determine DSBs in the S-phase of the cell cycle. This prolongs the S-phase, possibly due to torsional stress from cleavage complexes near sites of DNA replication that cause the replication fork to stall. Vosaroxin also seems to evade two resistance mechanisms, namely p53 alteration and ABC transporter upregulation. It has good activity against AML patients resistant to therapy, and has been proposed as a useful resource in anthracycline-resistant tumors (Jamieson et al., 2016).

Histone deacetylase (HDAC) inhibitors can resensitize tumor cells to topoisomerase II inhibitors such as anthracyclines. They do this by increasing the access and binding of the topoisomerase to DNA. Molecules as vorinostat and valproic acid regulate chromatin structure by increasing the acetylation of histones and chromatin decondensation. This potentiates the DNA-damaging action of topoisomerase II. HDAC inhibitors are efficient in combination with Dox in relapsed or refractory multiple myeloma, ALL, sarcoma and breast cancer (Dumont et al.,

2014a; Marchion et al., 2005a; Tu et al., 2014; Waldschmidt et al., 2018).

7.5. Modulation of drug efflux pumps

High levels of ABC transporters are responsible for most cases of resistance to anthracyclines and of poor outcome in many different tumors. This is because the chemotherapeutic drugs are substrates of the efflux pumps ABCB1, ABCC1 and ABCG2, which are overexpressed in many tumor cells. Further, upregulation of ABCB1 and other efflux pumps in cancer cells, *in vivo* and in clinical setting, following anthracyclines administration, further worsens the outcome, with the onset of resistance and relapses. Three types of strategies for reversing and overcoming multidrug resistance by targeting ABCB1 and other efflux pumps have been used in cancers, mostly by using the "three Es", namely the use of cytotoxic molecules that are not substrates for ABC transporters and can circumvent the efflux processes (Evade), the inhibition of the efflux pumps (Engage), and methodologies based on the sensitivity of resistant cells to certain molecules (Exploit) (Szakács et al., 2006b).

Administration of non-substrates of ABC transporters has been carried out by using molecules as cisplatin, cyclophosphamide, epothilones, or second- and third-generation taxanes, with low affinity for ABCB1 (Altmann, 2003; Galletti et al., 2007; Ojima et al., 2018).

The use (alone or in coadministration with anthracyclines) of inhibitors of ABC transporters has been attempted for decades. Efflux pump inhibitors act with different mechanism, such as by blocking the substrate binding site of the transporter (competitively, non-competitively or allosterically), by decreasing ATP hydrolysis, or by altering the integrity and functionality of cell membrane lipids, or by altering plasma membrane lipids/fluidity. They aim to block the efflux of chemotherapeutic drugs, increasing the intracellular drug concentration, and consequently the cytotoxic effect. The inhibitors of ABC transporters (in particular ABCB1) have been divided in four categories (four generations), based on their potency, selectivity and origin (Palmeira et al., 2012; Silva et al., 2015). First generation inhibitors are a heterogeneous class of compounds, including antitumor drugs (e.g., erlotinib and lapatinib), calcium channels blockers (such as verapamil), anti-malarial drugs (quinine), antibiotics (e.g., erythromycin), antifungal drugs (e.g., ketoconazole), antivirals, immunosuppressants, anesthetics, steroids, CNS stimulators or anti-depressants: usually these compounds are poor inhibitors at low concentration, are rather toxic and non-specific. Second generation inhibitors are based on first-generation compounds, modified to increase their inhibition potency and decrease their toxicity, such as valspodar, derived from the immunosuppressant cyclosporine A. Third generation inhibitors (e.g., zosuquidar, tariquidar) are non-competitive ABCB1 inhibitors, potent and more specific (they do not inhibit cytochrome P450 enzymes). Fourth generation inhibitors are a heterogeneous group of efflux pumps inhibitors, mostly derived from natural sources, such as natural compounds, peptides, lipids, surfactants and other molecules (Genovese et al., 2017b). Some second- and third-generation inhibitors have been relatively successful.

Some compounds act not only as inhibitors of efflux pumps. For example, decursin, a pyranocoumarin compound obtained from the roots of *Angelica gigas*, also stimulates apoptosis, by triggering the caspase cascade (Choi et al., 2016). Schisandrin A, a bioactive lignan obtained from *Schisandra chinensis*, upregulates caspase-9 and PARP1 (Zhang et al., 2018). Canagliflozin, an anti-diabetic compound, decreases ATP levels, thereby impairing ABC transporters activity, increasing anthracycline internalization and resensitizing adriamycin-resistant hepatocarcinoma cells (Zhong et al., 2020). Many compounds, such as pioglitazone, tanshinone IIA, the epigallocatechin gallate derivative Y6, alantolactone, costunolide, statins and phenothiazines, are considered potent chemosensitizers, effective against anthracycline-resistant tumor cell lines by decreasing ABCB1 expression, usually acting at mRNA level; some compounds are also effective in animal set-ups (Cai et al., 2019a; Higuchi et al., 2019; Li et al., 2019b; Maryam et al., 2017; Środa-Pomianek et al., 2019; Wen et al., 2019a, 2019b). Curcumin induces Dox chemosensitization in colon adenocarcinoma cells by decreasing the expression of ABCB1 and acting on COX-2 (Jayarajan et al., 2020).

Nanomedicine strategies aimed at modulating efflux pumps have also been used. For example, curcumin-loaded solid lipid NPs increase Dox sensitivity by 5–10 times with respect to curcumin alone (Abd-El-latef et al., 2020).

The co-delivery of Dox and siRNAs against ABCB1 via folic acid-modified liposomes on the one hand improves nuclear delivery of Dox, increasing DNA damage and cell death, and on the other decreases ABCB1 levels, further improving Dox effect and increasing tumor chemosensitivity (Wu et al., 2016). Similarly, nanoparticles functionalized with aptamers (short oligonucleotides targeting specific receptors) have been used for the co-delivery of Dox with anti-ABCB1 siRNA to breast cancer cells, leading to improved Dox penetration and resensitization towards anthracyclines (Chandra et al., 2020). Co-delivery of Dox with the steroidal alkaloid cyclopamine in albumin NPs, or with resveratrol in polymeric NPs decreases tumor resistance by downregulating ABCB1 (and possibly ABCG2) (Lu et al., 2019; Zhao et al., 2016c).

Many studies aim to increase sensitivity to anthracyclines by acting on efflux pumps activity and expression, in particular acting on surface modification of NPs to increase their cellular uptake by tumor cells, by increasing the stability of nanocarriers and their efficiency of encapsulation (Sanità et al., 2020).

In addition, since the expression of efflux pumps is predominantly regulated at transcriptional levels (e.g., the *ABCB1* gene contains multiple sites for activating transcription factors, including Myc, Sp1, AP-1, NF-κB, TCF, Sp3, OCT-4 and PITX2), repression of their expression can be obtained by acting on the regulation of stress-regulated transcription factors (see also below) (Lee and Thévenod, 2021).

7.6. Epigenetic modifiers

Remodeling DNA methylation patterns or modifying histone proteins can reorient the epigenomic landscape of cancer cells, driving them towards chemosensitization.

One mechanism of resensitization is the disruption of pro-survival signaling pathways, such as those that involve growth factors, their receptors and downstream pathways. HDAC inhibitors can act both by increasing the access and binding of topoisomerase II to DNA (see also section 7.4) and by altering survival pathways. Molecules as vorinostat and valproic acid are efficient in combination with Dox or Epi in a variety of resistant cancers (Dumont et al., 2014b; Marchion et al., 2005b; Münster et al., 2007).

The chromatin reader protein ZMYND8 (zinc-finger MYND type-8) is a potent chemosensitizer, able to overcome Dox-dependent drug resistance in metastatic breast cancer. It modulates a series of oncogenes via its association with corepressors such as KDM5A and EZH2, and alters the tumor-promoting gene expression profile of cancer cells. Its silencing determines the overexpression of markers of drug resistance (ABCB1, ABCC1, ABCC2), pluripotency (SOX2, BMI1, SOX9, POUSF1, NANOG, NOTCH1), EMT (TWIST1, ZEB1, SNAI2, VIM), and stemness (CD24, CD44). Its overexpression via lentiviral production decreases the tumor-promoting markers. Regulation of expression or activity of ZMYND8 and its binding partners is considered a potential strategy to revert drug resistance (Mukherjee et al., 2020).

Among the epigenetic modifiers, the enhancers, and in particular the so-called super-enhancers (SEs) deserve special attention. The enhancers are cis-regulatory elements of genes; SEs are long enhancers enriched in transcription factors, cofactors, mediators, RNA Pol-II, Lys27-acetylated histone H3 (H3K27ac), Lys4-methylated histone H3 (H3K4me1), cyclin-dependent kinase 7 (CDK7) and bromodomain-containing protein 4 (BRD4) with respect to standard enhancers. SEs regulate the expression

of multiple genes, controlling cell identity and defining its fate, and in particular drive chemoresistance (Li et al., 2021; Shang et al., 2019; You and Jones, 2012). SEs involved in the resistance to anthracyclines have been recently studied in small cell lung cancer, showing the differential expression of a series of proteins, in particular transcription factors that regulate downstream pathways, among which FOXP1, IRF1, SP1 (Bao et al., 2019). In breast cancer resistant to Dox, alteration of chromatin accessibility and of transcriptome landscape is associated with a series of differentially expressed genes, among which many histone-modifying genes (Wang et al., 2021). SE inhibitors are a possible strategy to overcome resistance. Several approaches have been used, such as small-molecule BRD4 inhibitors, histone acetylation inhibitors and CDK inhibitors. The CDK12 inhibitor THZ531 decreases DNA damage repair and increases Dox sensitivity of anaplastic thyroid carcinoma cells (Geng et al., 2019).

7.7. Preventing CSC development

The CSCs' self-renewal ability and intrinsic resistance to chemotherapeutic agents drives the selection and the spread of a resistant phenotype, primarily due to high drug efflux pump activity, DNA repair, microvascularization and high ROS levels. Tumor relapse can also occur due to the reconversion of non-CSCs to CSCs, that can be triggered by EMT, the tumor microenvironment, autophagy and EVs (Zhou et al., 2021).

Targeting CSC-specific proteins and pathways is a promising strategy for overcoming resistance to anthracyclines. CD13 (aminopeptidase N) is a surface marker of CSCs, that is associated with cell growth, invasion and metastasis. Anti-CD13 antibodies and the CD13 inhibitor ubenimex are effective in increasing the sensitivity of hepatocellular carcinoma to Dox (Haraguchi et al., 2010; Yamashita et al., 2016).

CD44 is another surface marker of CSCs that has been targeted in an effort to overcome anthracycline resistance and to improve drug activity. Dual aptamers-Dox conjugated liposomes were used to fight CSCs in breast cancer, anti-CD44 monoclonal antibodies were administered with liposomal Dox in colon carcinoma cells, hyaluronic acid-MP conjugated micelles for intracellular delivery of Dox were used in colon cancer, and hyaluronan-decorated fullerene-silica multifunctional nanoparticles were employed for the delivery of Dox to breast cancer cells (Arabi et al., 2015b; Debele et al., 2018; Kim et al., 2019; Wang et al., 2016b).

Aptamers against EpCAM, another CSC surface marker, have also been conjugated with Dox. These aptamers efficiently deliver Dox and lead to increased survival and tumorigenic latency in *in vitro*, *ex vivo* and *in vivo* colorectal cancer models, transforming the anthracycline in a CSCs killer (Xiang et al., 2017). The Stat3 inhibitor WP1066 has also been shown to overcome Dox resistance by decreasing the enrichment of CSCs in triple-negative breast cancer cells (Cheng et al., 2018).

7.8. Targeting signal pathways involved in proliferation or cell death

Loss of function of tumor suppressors contributes to chemoresistance by many mechanisms, such as inhibition of apoptosis, increased drug efflux and EMT. The list of tumor suppressors involved in these mechanisms includes p53, SST, HOXA9, DAPK, caspases, PTEN, E2F7, NOTCH1, TRAILR1/2, CDH1, RB1 and numerous other proteins. Restoration of tumor suppressor gene function is a possible strategy for overcoming anthracycline resistance (Gao et al., 2021).

The reactivation of mutated p53 is an important goal in overcoming anthracycline resistance (Cao et al., 2020). Reactivation of p53 was attempted by expressing it using adenoviral vectors and, possibly with more success, by using small molecules. For example, ARP-246 (a methylene quinuclidinone prodrug) is able to restore wild-type-like conformation of p53 bearing some inactivating mutations, and has been shown to overcome Dox resistance in ovarian cancer and ALL (Demir et al., 2020; Mohell et al., 2015). Zinc supplementation has also been shown to restore the response of mutant p53 to adriamycin-resistant breast cancer and glioblastoma, by acting on p53 conformation (Puca et al., 2011). Nutlin-3, a small-molecule inhibitor of the p53-MDM2 interaction, displaces p53 from MDM2, reactivating p53 and avoiding its proteasomal degradation. This leads to cell cycle arrest and apoptosis, and has been shown to potentiates Dox activity in sarcoma, leading to reversal of resistance (Ohnstad et al., 2011).

In addition to p53, other tumor suppressors have also been targeted in an effort to overcome anthracycline resistance. For example, the pterocarpanquinone LQB-118 induces apoptosis in cells from chronic myeloid leukemia patients exhibiting MDR phenotype, by targeting the inhibitor of apoptosis proteins (IAPs). This leads to downregulation survivin and FOXO3a, another substrate of MDM2 that accumulates in the nucleus in response to Dox, promoting apoptosis in a number of different tumor cell types (de Moraes et al., 2014).

A CDK4-specific small-molecule inhibitor (RO050124) reduces neuroblastoma cell viability upon Dox treatment by acting on the CDK4/cyclin D-RB1 axis, thereby resensitizing cells to anthracyclines (Gogolin et al., 2013).

Exportin-1 transports its cargo, including p53 and BCR-ABL, from the nucleus to the cytoplasm. Dysregulation of exportin-1 is associated with drug resistance induced by mislocalization of tumor suppressors, such as anthracycline resistance mediated by mislocalization of the transcription factor E2F7. Selinexor, an inhibitor of exportin-1, reverses anthracycline resistance in head and neck squamous cell carcinoma by relocalizing E2F7 into the nucleus, thus allowing it to exert its transcriptional inhibitory effect upon Dox treatment (Saenz-Ponce et al., 2018).

7.9. Targeting metabolic alterations

Metabolic plasticity is a hallmark of cancer, characterized by a glycolytic phenotype (the so-called Warburg effect, that includes increased uptake of glucose and hyperactivated glycolysis), and/or mitochondrial energy reprogramming. This means that cancer cells rely more on aerobic glycolysis, a less efficient way of generating ATP, to meet their high energy demands. This is because cancer cells are rapidly proliferating and require a lot of energy to support cell growth and division. In addition, the increased energy demand is in line with the increased activity of drug efflux and drug detoxification mechanism in cancer cells that are resistant to therapy. Targeting key glycolytic enzymes can "rewire" tumor metabolism and resensitize cancers to chemotherapy (Varghese et al., 2020).

For example, the transcription factor HIF-1α (hypoxia-inducible factor-1α), under the control of the PI3K/AKT/HIF-1α signaling pathway increases the expression of the key transporters and glycolytic enzymes, supporting tumor progression, and of efflux pumps, supporting resistance to chemotherapeutic agents (Lee et al., 2009). Sensitization to anthracyclines of many different cancer cell lines was obtained by targeting the PI3K/AKT/HIF-1α signaling pathway with agents as PX478, Tanshinine I, salidroside, quercetin, nuciferin and microRNAs such as miR-124, miR-194-5p and miR-199a-5p (Hassan et al., 2020; Jin et al., 2020; Li et al., 2022; Liu et al., 2019a; Liu et al., 2020b; Wilson and Hay, 2011; Xia et al., 2021; Zeng et al., 2022; Zhao et al., 2022a).

Downregulation of glycolysis and inhibition of GRP78, a regulator of ER stress and aerobic glycolysis, was obtained by using a combination of DT-010, a conjugate of danshensu and tetramethylpyrazine: such agents increased the therapeutic efficiency of Dox and the sensitivity of breast cancer cells to anthracyclines (Wang et al., 2016c).

The metabolic change associated with glycolysis has been targeted using glycolytic inhibitors, such as 2-deoxy-D-glucose. This molecule acts synergistically with Dox and is efficient against highly glycolytic CSCs (Ciavardelli et al., 2014).

Insulin has also been used to chemosensitize breast cancer cells towards Adr and other drugs. Metformin, another antidiabetic drug, is able to sensitize the MDR phenotype toward Dox in breast cancer cells, by acting on the IFN-α signaling pathway and inducing oxidative stress

(Lasalvia-Prisco et al., 2004; Marinello et al., 2019).

7.10. Targeting tumor microenvironment

Targeting tumor microenvironment (TME) is another strategy to overcome resistance towards anthracyclines. Abnormal vasculature results in impaired delivery of systemic therapy, immunological effectors, and oxygenated blood. Strategies for resensitization include the use of antiangiogenic therapies, such as liposomal prednisolone phosphate and the thyroid hormone-like tetraiodothyroacetic acid. PEGylates liposomes themselves increase resistance to Dox also by acting on angiogenesis (Kibria et al., 2016; Licarete et al., 2020; Rebbaa et al., 2008).

Losartan, a stroma-depleting agent, determines reduction of the extracellular matrix, facilitating the delivery of liposomal Dox to triple negative breast cancer, pancreatic and skin tumors, and increasing tumor chemosensitivity (Diop-Frimpong et al., 2011; Zhao et al., 2022b).

Maspin, a serpin protease inhibitor, once secreted leads to altered degradation and deposition of extracellular matrix, increasing the formation of dense-matrix tumors resistant to chemotherapy, since collagen accumulation is associated with decreased drug delivery and efficacy. The use of maspin inhibitors may represent a strategy to resensitize breast and ovarian carcinomas towards anthracyclines (Triulzi et al., 2014).

7.11. Targeting EMT

There are a number of factors that can promote EMT, including the expression of transcription factors such as ZEB proteins, microRNAs, and Twist1. These factors can activate signaling pathways that lead to changes in gene expression, cell morphology, and adhesion, can lead to increased cell motility, invasion, and metastasis. EMT can also contribute to resistance to anthracyclines. EMT can be regulated by molecular pathways involving are PTEN, PI3K/Akt, ERK, c-Myc, ncRNAs and PDCD5 (Mirzaei et al., 2021a). Several approaches have been shown to inhibit EMT and sensitize cancer cells to anthracyclines.

Some of the signaling pathways that are involved in EMT can be targeted with drugs or other agents. For example, the estrogen receptor β inhibits the PI3K/Akt signaling, which can lead to EMT, and is able to resensitize triple negative breast cancer cells to anthracyclines chemotherapy (Lei et al., 2020). Small molecule calcium channel blockers as lercanidipine and amlodipine inhibit the ERK/TGF-β pathway, and sensitize gastric cancer cells to Dox (Panneerpandian et al., 2021). The polyphenol honokiol overcomes resistance to anthracyclines in breast cancer cells by decreasing the expression of c-Myc (Yi et al., 2021).

Certain phytochemicals have been shown to inhibit EMT and sensitize cancer cells towards anthracyclines. Resveratrol stimulates PTEN and inhibits Akt, suppressing EMT, inducing cell cycle arrest and apoptosis, while curcumin decreases the expression of TGF-β and PI3K/Akt, and inhibits EMT, increasing E-cadherin and decreasing N-cadherin, leading to increased anthracycline sensitivity (Guo et al., 2020; Xu et al., 2017). In breast cancer cells, melatonin inhibits the EMT and metastatization, by decreasing the expression of Twist1, increasing sensitivity to Dox administration (Menéndez-Menéndez et al., 2019). Salinomycin, an ionophore antibiotic, decreases resistance to anthracyclines in hepatocellular carcinoma, inducing EMT via FOXO3a (Zhou et al., 2015a). Other compounds as oleuropein, isocorydine, ascochlorin, NSC74859, and GC7 increase anthracycline efficacy in many different cancers by inhibiting the EMT and represent possible approaches for overcoming resistance (Cheung et al., 2020; Choupani et al., 2019; Dai et al., 2016; Liu et al., 2018; Pastushenko et al., 2020). The natural compound formononetin and the traditional Chinese herbal formula Pien Tze Huang resensitize tumor cells towards Dox by suppressing EMT, preventing the expression of HDAC5 and decreasing the expression levels of TGF-β1, respectively (Chen et al., 2019b; Liu et al., 2015b).

Some non-coding RNAs have been shown to inhibit EMT and sensitize cancer cells to anthracyclines. For example, miR-520b inhibits IGF-1R, while miR-33a-5p downregulates eIF5A2 (the eukaryotic translation initiation factor 5A2) in breast cancer. Again, miR-451a inhibits c-Myc in lung cancer cells, increases the level of the epithelial marker E-cadherin, and decreases the mesenchymal markers N-cadherin and vimentin, and miR-137 suppresses EMT by inhibiting DUSP4 in breast cancer (Du et al., 2019; Guan et al., 2019; Tao et al., 2020; Zhang et al., 2021).

7.12. Targeting autophagy

Autophagy can play a dual role, either as a mechanism that inhibits tumor progression or as a pathway that promotes tumor growth, depending on the nature of the cancer and of the metabolic stress induced (Chen et al., 2018). The role of autophagy in anthracycline resistance is not fully understood, but it is thought that autophagy can help cancer cells to survive chemotherapy by clearing damaged cells and by providing cells with nutrients. There are a number of ways to target autophagy to overcome anthracycline resistance. Some of these approaches include inhibiting autophagy, by using drugs that block the formation of autophagosomes or the fusion of autophagosomes with lysosomes, or promoting autophagy, by using drugs that activate autophagy or by increasing the expression of autophagy-related proteins.

In papillary thyroid cancer, RAD001, a potent activator of autophagy, increases Dox sensitivity via Met dephosphorylation (Lin et al., 2010). 3-methyladenine, an inhibitor of phagophore formation, in combination with Dox, leads to necroptosis, a form of cell death, increasing sensitivity to anthracyclines in breast cancer (Aydinlik et al., 2017). Chloroquine inhibits autophagolysosome formation, and is highly effective in restoring anthracycline sensitivity in Dox-resistant breast cancer cells (Guo et al., 2016). A pH-responsive self-assembled nanovesicle based on the amphiphilic copolymer poly[$(PEG)_x$(4-aminomethyl-2-benzyloxy-[1,3]-dioxolan)$_y$phosphazene]$_n$ (PPAP) was also recently constructed to load Dox and chloroquine, in order to improve the anti-tumor effect of the drug and reverse anthracycline resistance by accomplishing autophagy inhibition (Wang and Qiu, 2022).

A CD133 aptamer for targeted delivery of Dox into liver cancer stem cells has been used recently in combination with ATG5 siRNA to overcome chemoresistance by inhibiting autophagy (Yin et al., 2022). The lncRNA CTA is downregulated in osteosarcoma, and in particular in anthracycline-resistant osteosarcoma cells; overexpression of CTA decreases autophagy by competitively binding miR-210 and overcomes Dox resistance of osteosarcoma both *in vitro* and *in vivo* (Wang et al., 2017). The steroidal ginsenoside Rg3 inhibits late-stage autophagy and sensitizes hepatocellular carcinoma towards Dox (Kim et al., 2014a).

In other cellular contexts, excessive autophagy can lead to autophagic cell death, resulting in increased sensitivity to anthracyclines. For instance, NVP-BEZ235, a PI3K/mTORC1 inhibitor, increases autophagy and consequently Dox-induced apoptosis in neuroblastoma cells, potentiating sensitization to Dox (Westhoff et al., 2013). Molecules as Psammaplin A, that increase the expression of autophagy-dependent proteins such as DRAM, and the alkaloid voacamine, also overcome resistance to anthracyclines by inducing autophagic cell death in cancer cells (Kim et al., 2015; Meschini et al., 2007).

7.13. EVs as delivery systems; EVs targeting

EVs are among the causes of resistance to anthracyclines and have been targeted to overcome resistance. Inhibition of EVs biogenesis, release and uptake can induce chemosensitivity in resistant, and especially in multidrug resistant cancer cells (Hayatudin et al., 2021).

Indomethacin inhibits EVs biogenesis (and therefore the export of chemotherapeutic agents) in large B-cell lymphomas, by inhibiting the ABC transporter ABCA3, increasing tumor cell susceptibility to Dox and to the anthracenedione pixantrone (Koch et al., 2016).

The antihistamine Ketotifen inhibits EVs release by altering the

intracellular levels of calcium, inhibiting the expression of CDC42, Rac, Rho and the metalloprotease MMP-9. With this mechanism, Ketotifen overcomes resistance to Dox in breast cancer and cervical cancer cells (Khan et al., 2018; Kim et al., 2014b).

The vitamin B_5 derivative pantethine plays a role in lipid metabolism, reducing cholesterol synthesis and EVs formation. Pantethine treatment partially overcomes Dox resistance in breast cancer cells (Roseblade et al., 2015).

On the other hand, EVs have been used for the delivery of anthracyclines to tumors, similarly to Dox-loaded liposomes. Dox-loaded exosome-mimetic nanovesicles *in vitro* induce TNFα-stimulated endothelial cell death in a dose-dependent manner, while in mice models they are efficiently delivered to cancer tissues and reduce tumor growth and anthracycline resistance (Jang et al., 2013). Further, Dox-loaded exosomes are more effective than naked Dox against breast and ovarian cancer: they reduce the cardiotoxicity of the drug and increase its therapeutic index (Hadla et al., 2016; Toffoli et al., 2015).

7.14. siRNAs, miRNAs and other RNA-based approaches

In the context of anthracycline resistance, miRNAs and siRNAs have been shown to target a variety of pathways, including cell cycle regulation, apoptosis, drug efflux, and stemness. siRNAs and miRNAs represent possible strategies to overcome chemoresistance to anthracyclines and other anticancer drugs, as they possess gene-specific regulatory functions in many anthracycline-dependent pathways (Ashrafizaveh et al., 2021; Paskeh et al., 2022; Torki et al., 2021).

miRNA7-5p functions as a tumor suppressor, decreasing the anthracycline-induced DNA repair by targeting PARP1. In Dox-resistant lung cancer the expression level of miRNA-7-5p is reduced; its expression overcomes chemoresistance (Ashrafizaveh et al., 2021; Lai et al., 2019; Paskeh et al., 2022; Torki et al., 2021). HDAC1 down-regulation by anthracyclines, via miRNA-520h expression, enables gastric cancer to escape from Dox-dependent death. miRNA-520h inhibitors represent a possible strategy to improve anthracycline efficacy and to overcome chemoresistance (Shen et al., 2014). Overexpression of miRNA-15a and miRNA-16 resensitizes breast cancer cells towards anthracyclines by downregulating the transcriptional repressors BMI1, RING1A, RING1B, and EZH2 (Patel et al., 2017). miRNA-22 and miRNA-106b target p53 and CDNK1A, respectively, repressing p21, while miRNA-122 regulates p53 by inhibiting cyclin G1, sensitizing cancers towards Dox (Fornari et al., 2009; Ivanovska et al., 2008; Tsuchiya et al., 2011). miRNAs able to restore chemosensitivity to anthracyclines acting on cell cycle targets are miRNA-30c (targeting REV1), mRNA-16 (that regulates the p53-induced phosphatase 1 WIP1) and miRNA-486, acting on ankyrin 1 (Hall et al., 2016; Lin et al., 2019; Zhang et al., 2010). Other miRNAs acting on proliferative signaling pathways are miRNA-26a-5p, targeting Aurora kinase A, miRNA-205, that regulates the PI3K/Akt pathway, miRNA-450-3p, targeting HER3, miRNA-17/20 and miRNA-181, targeting Akt, miRNA-21 and miRNA-222, that target PTEN, also regulating the PI3K/Akt pathway. Expression of these RNAs overcomes anthracycline resistance in many types of cancer cells (Hu et al., 2016; Tao et al., 2011; Wang et al., 2016a; Yu et al., 2014; Yuan et al., 2019; Zhao et al., 2016a, 2014b). Molecules such as miRNA-217, miRNA-187 and miRNA-302a/b/c/d, target the Ras/MAPK/ERK pathway by downregulating KRAS, MAPK7 and MEKK1, respectively. These miRNAs restore sensitivity towards anthracyclines in different types of cancer (Liu et al., 2020a; Xiao et al., 2017; Zhao et al., 2016b).

Other microRNAs overcome resistance to anthracyclines regulating apoptotic pathways: miRNA-149, miRNA-205 and miRNA-135a-5p target Bcl-2 in neuroblastoma and gastric cancer, while miRNA-193b regulates MCL1 in breast cancer, and miRNA-204 targets SIRT1 in prostate cancer (Long et al., 2015; Mao et al., 2019; Pan et al., 2014; Shu et al., 2017; Verdoodt et al., 2013).

Regulation of autophagy also decreases resistance towards anthracyclines. This has been observed upon inhibiting autophagy by using miRNA-26a and miRNA-26b, that target ULK1 in hepatocellular carcinoma, miRNA-489, that suppresses ULK1 and LAPTM4B in breast cancer, miRNA-142 and miRNA-22, that target ULK1, ATG4A and ATG5, miRNA-410, that downregulates ATG16L1, and miRNA-30a, that targets Beclin-1 in osteosarcoma (Chen et al., 2017; Jin et al., 2017; Soni et al., 2018; Xu et al., 2016b; Zhu et al., 2020).

The expression of ABC transporters can also be modulated by miRNAs, thereby reducing drug efflux and increasing cancer cells sensitivity to Dox and other anthracyclines. ABCB1 expression is suppressed in neuroblastoma by miRNA-137 and miRNA-495, in gastric cancer by miRNA-508-5p, in leukemia by miRNA-381 and miRNA-495, and in breast cancer by miRNA-200c, miRNA-221-3p, miRNA-298 and miRNA-302a/b/c/d (Bao et al., 2012; Chen et al., 2012b, 2020; Takwi et al., 2014; Xu et al., 2013). ABCC1 expression is reduced by miRNA-134, miRNA-145 and miRNA-326 in breast cancer, and by miRNA-1291 in pancreatic carcinoma, thus increasing anthracyclines chemosensitivity (Gao et al., 2016; Liang et al., 2010; Lu et al., 2015b; Pan et al., 2013).

Other miRNAs regulate anthracycline-associated stemness. For example, miRNA-214-3p and miRNA-452 regulate the Wnt cascade, miRNA-34a downregulates PRK1 and NOTCH, and miRNA-873 suppresses PD-L1 (Gao et al., 2019; Kim et al., 2016; Park et al., 2014; Zheng et al., 2016). Anthracycline-dependent EMT is targeted by miRNA-200b, miRNA-200c, miRNA-431 and miRNA-708-3p, that regulate ZEB1 expression, and by miRNA-138, that targets ZEB2 (Kwok et al., 2019; Lee et al., 2018; Jin et al., 2016).

siRNAs have also been used to silence targets involved in establishing resistance to anthracyclines. Sensitivity to Dox and other drugs has been obtained by silencing p21, stemness targets Oct-4 and Nanog, apoptotic genes such as STAT3, Bcl-2, Bax, Notch and PUMA, ABC transporters and many other targets (al Hanjori et al., 2021; Aliabadi et al., 2013; Azimi et al., 2018; Huang and Rao, 2018; Joshi et al., 2021; Li et al., 2017; Li et al., 2018; Zhang et al., 2011; Zhou et al., 2018).

Some lncRNAs inhibit anthracycline resistance, by regulating different types of targets. For example, in thyroid cancer the lncRNA PTCSC3 inhibits STAT3, in liver cancer lncRNA GAS5 targets PTEN, and in osteosarcoma the lncRNA FENDRR down-regulates ABCB1 and ABCC1 (Kun-Peng et al., 2017; Wang et al., 2020a; Wang et al., 2018).

The use of these RNA-based target-specific molecules in combination with anthracyclines will represent an important factor in increasing drug efficacy and overcoming resistance in the future.

8. Conclusions

Anthracyclines are a class of chemotherapy drugs that have been used for the past decades as effective treatments against a number of cancers. Thanks to their several action modes, anthracyclines have been shown to be effective in counteracting cancer, inducing apoptosis, necrosis, mitochondrial dysfunction and other consequences that can kill cancer cells.

However, the use of anthracyclines has been hampered by severe side effects and toxicity that occur during or after treatment, such as cardiotoxicity. This is likely due to the large set of processes involved in anthracycline action.

Another important problem associated with the pharmacological use of anthracyclines for the treatment of tumors is drug resistance, which reduces the drugs' effectiveness. It is estimated that up to 50% of patients eventually become resistant to these drugs. The development of resistance is a major barrier to successful treatment when using anthracyclines and is also based on a series of mechanisms that have been studied and addressed in the last years. There are a number of mechanisms that can lead to anthracycline resistance, including increased drug efflux, because cancer cells can develop mechanisms to pump anthracyclines out of the cell, making them less effective and reduced drug accumulation, because cancer cells can become less sensitive to anthracyclines by reducing the amount of drug that accumulates in the cell.

Many approaches have been used to improve the efficacy of anthracyclines, starting from the use of liposomal formulations, which are more effective in targeting the molecule and simultaneously manage to reduce side effects such as cardiotoxicity.

Other methods to overcome anthracycline resistance include combination therapy and targeted therapy, and molecules targeting tumor microenvironment and EMT. The use of siRNAs, miRNAs and other RNA-based approaches could be effective in counteracting the appearance of anthracycline resistance.

Ultimately, a new frontier will be possible with the discovery of cancer-selective molecules, and in particular with tumor-selective delivery of drugs. We think that tumor vs. normal cells selectivity will be the next important barrier that needs to be overcome, and that anthracycline-containing stimuli-sensitive nanodrugs may represent a valid strategy for the future.

Continued research is needed to develop new strategies to overcome resistance and improve the efficacy of these drugs.

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