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Not only P-glycoprotein: Amplification of the *ABCB1*-containing chromosome region 7q21 confers multidrug resistance upon cancer cells by coordinated overexpression of an assortment of resistance-related proteins

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ABSTRACT

The development of drug resistance continues to be a dominant hindrance toward curative cancer treatment. Overexpression of a wide-spectrum of ATP-dependent efflux pumps, and in particular of *ABCB1* (P-glycoprotein or MDR1) is a well-known resistance mechanism for a plethora of cancer chemotherapeutics including for example taxenes, anthracyclines, *Vinca* alkaloids, and epipodopyllotoxins, demonstrated by a large array of published papers, both in tumor cell lines and in a variety of tumors, including various solid tumors and hematological malignancies. Upon repeated or even single dose treatment of cultured tumor cells or tumors *in vivo* with anti-tumor agents such as paclitaxel and doxorubicin, increased *ABCB1* copy number has been demonstrated, resulting from chromosomal amplification events at 7q11.2-21 locus, leading to marked P-glycoprotein overexpression, and multidrug resistance (MDR). Clearly however, additional mechanisms such as single nucleotide polymorphisms (SNPs) and epigenetic modifications have shown a role in the overexpression of *ABCB1* and of other MDR efflux pumps. However, notwithstanding the design of 4 generations of *ABCB1* inhibitors and the wealth of information on the biochemistry and substrate specificity of ABC transporters, translation of this vast knowledge from the bench to the bedside has proven to be unexpectedly difficult.

Many studies show that upon repeated treatment schedules of cell cultures or tumors with taxenes and anthracyclines as well as other chemotherapeutic drugs, amplification, and/or overexpression of a series of genes genomically surrounding the *ABCB1* locus, is observed. Consequently, altered levels of other proteins may contribute to the establishment of the MDR phenotype, and lead to poor clinical outcome. Thus, the genes contained in this *ABCB1* amplicon including *ABCB4*, *SRI*, *DBF4*, *TMEM243*, and *RUNDC3B* are overexpressed in many cancers, and especially in MDR tumors, while *TP53TG1* and *DMTF1* are *bona fide* tumor suppressors. This review describes the role of these genes in cancer and especially in the acquisition of MDR, elucidates possible connections in transcriptional regulation (co-amplification/repression) of genes belonging to the same *ABCB1* amplicon region, and delineates their novel emerging contributions to tumor biology and possible strategies to overcome cancer MDR.

Introduction

The development of drug resistance limits the effectiveness of chemotherapeutic drug treatment in cancer, with over 90% treatment failure rate in metastatic tumors. Many mechanisms, either intrinsic or acquired, operate to confer drug resistance (Goler-Baron and Assaraf, 2011; Gonen and Assaraf, 2012; Gottesman, 2002; Holohan et al., 2013; Housman et al., 2014; Ifergan et al., 2005; Longley et al., 2006; Wijdeven et al., 2016; Zhitomirsky and Assaraf, 2016). Poor drug solubility and toxicity to normal tissues limit the doses of chemotherapeutic drugs that can be administered to cancer patients, while pharmacokinetic effects, i.e. absorption, distribution, metabolism and

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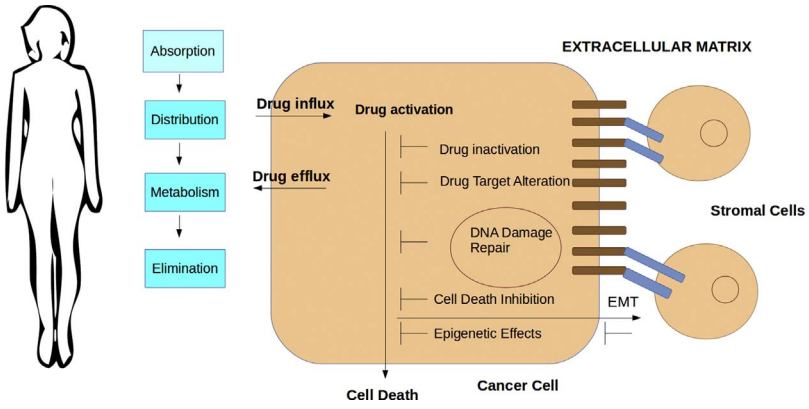

Fig. 1. Mechanisms that confer drug resistance upon human cancer cells. Left: pharmacokinetic factors, i.e. drug absorption, distribution, metabolism and elimination (ADME), limit the effective concentration of the drug that reach the cancer. Center and right: Drug influx and efflux limit the amount of drug that enters the tumor cell; multiple documented mechanisms, such as drug inactivation, drug target alteration, drug compartmentalization, enhanced DNA damage repair, cell cycle/checkpoint alterations, apoptosis inhibition and epigenetic alterations limit tumor cell death; epithelial-to-mesenchymal transition and metastasis are also possible escape routes of tumor cells (Alizadeh et al., 2015; Gonen and Assaraf, 2012; Holohan et al., 2013; Housman et al., 2014; Wijdeven et al., 2016; Zhitomirsky and Assaraf, 2016).

elimination, limit the actual amount of drug that reaches the tumor. Furthermore, at the level of the tumor, several established mechanisms confer resistance to one or more chemotherapeutic agents including impaired drug uptake due to decreased expression and/or loss of drug influx transporters, enhanced drug efflux, alterations in plasma membrane lipid composition, inhibition of apoptosis, enhanced DNA damage repair, cell cycle and/or checkpoint alterations, drug compartmentalization away from the drug target, increased drug metabolism and inactivation, drug target alteration, and epithelial-mesenchymal (EMT) transition (Bram et al., 2009; Debatin and Krammer, 2004; Fojo and Bates, 2003; Goler-Baron et al., 2012; Gonen and Assaraf, 2012; Holohan et al., 2013; Housman et al., 2014; Ifergan et al., 2005; Lowe et al., 2004; Maier et al., 2005; Raz et al., 2014; Stark et al., 2011; Zhitomirsky and Assaraf, 2016) (Fig. 1). Some of these mechanisms confer resistance to single agents, thus allowing possible effective treatment with alternative chemotherapeutic drugs, while other confers resistance to multiple, structurally unrelated chemotherapeutic drugs (i.e. multidrug resistance, MDR), thereby rendering the tumor refractory to drug treatment, hence markedly decreasing cure rates. Moreover, tumor heterogeneity is an important determinant in the development of drug resistance (Alizadeh et al., 2015; Andor et al., 2016; Lawrence et al., 2013; Swanton, 2012): both genetic and non-genetic mechanisms contribute to the generation of different subpopulations of cancer cells within individual tumors, and clonal selection upon treatment can account for positive selection of drug-resistant tumor populations. In particular, the presence of cancer stem cells (CSCs) in the tumor is a critical factor for the acquisition of chemoresistance. CSCs constitute a minor subpopulation of cells intrinsically resistant to chemotherapeutic drugs, due to epigenetic mechanisms that determine increased expression of anti-apoptotic proteins and of ATP-binding cassette (ABC) transporters, which mediate multidrug efflux, and their inherent quiescence (Al-Hajj et al., 2004; Dean, 2009; Feuerhake et al., 2000; Lerner and Harrison, 1990; Peters et al., 1998; Shibue and Weinberg, 2017; Zhou et al., 2001). Since the drug treatment affects only the sensitive population, the drug-resistant cell subpopulation survives and eventually spreads, making the cancer treatment ineffective.

MDR efflux pumps of the ABC superfamily of transporters

Among the mechanisms of drug resistance, the predominant one in cancer cells and possibly the most studied one is the drug efflux by proteins of a large superfamily of ATP-dependent efflux pumps, i.e. the ATP-binding cassette (ABC) transporters (Li et al., 2016b). This superfamily is composed of 48 genes and 3 pseudogenes (HUGO Gene Nomenclature Committee, http://www.genenames.org/cgi-bin/genefamilies/set/417), belonging to 7 subfamilies (*ABCA through ABCG*), mostly ATP-dependent transporters of metabolites, xenobiotics and signaling molecules through cell membranes against their concentration gradients (Dean, 2005; Fletcher et al., 2010; Fletcher et al., 2016). ABC transporters belong to one of the largest and more diffused superfamily, with representatives in all phyla, from prokaryotes to humans (Wilkens, 2015). ABC transporters can be grouped into exporters (which export lipids, sterols, drugs, and a large variety of primary and secondary metabolites) and importers (which take up a large variety of nutrients, biosynthetic precursors, trace metals and vitamins); bacteria use both ABC importers and exporters, while all eukaryotic ABC pumps are exporters, except for ABCA4 (Quazi et al., 2012).

Structural organization of ABC transporters

Canonically, ABC transporters are organized in four domains, i.e. two nucleotide-binding well conserved domains (NBD) or subunits and two transmembrane domains (TBD) or subunits, that can be more heterogeneous (Fig. 2). Prokaryotic ABC transporters are often assembled from separate protein subunits, composed of two NBDs and two TMDs, either identical (homodimeric) or different (heterodimeric); most importers have additional substrate-binding domains or proteins, which bind the substrate in the periplasm (Gram-negative bacteria) or external space (Gram-positive bacteria and Archaea) and deliver it to the TMDs. Eukaryotic exporters are composed of one rather large polypeptide containing two NBDs and two TMDs (e.g., *ABCB1*), or consist of two polypeptides, each of which contains an NBD and a TMD as in the prokaryotic exporters (Biemans-Oldehinkel et al., 2006; ter Beek et al., 2014).

The NBDs are ABC components, i.e. ATPase domains that bind and hydrolyze ATP, about 200-amino acid long, with two subdomains, a RecA-like domain and a α-helical domain (Fig. 2A). NBDs are characterized by the presence of the following motifs: 1) An A-loop, with a conserved aromatic residue (often a tyrosine), that serves to position the ATP by stacking with the adenine ring; 2) the P-loop or Walker A motif (GXXGXGK(S/T)), a phosphate-binding loop with a highly conserved lysine residue, whose backbone amide nitrogens and the ε-amino group form a network of interactions with β- and γ-phosphates of ATP; 3) the Walker B motif (ϕϕϕϕDE, where ϕ is a hydrophobic amino acid) which coordinates the magnesium ion via the conserved aspartate residue, while the second acidic residue at the end (usually a glutamate residue) is the general base that polarizes the attacking water molecule (Oldham and Chen, 2011); 4) the D-loop (consensus motif: SALD); 5) the H-loop (or switch region), with a highly conserved histidine that interacts with the conserved aspartate from the D-loop, the glutamate residue of the Walker B motif and with the γ-phosphate of the ATP, and helps positioning of the attacking water, of the general base and of the magnesium ion; 6) the Q-loop, containing eight residues with a conserved N-terminal glutamine, located at the interface between the RecA-like subdomain and the α-helical subdomain, in contact with the TMDs; the glutamine residue can move in and out of the active site during the ATP hydrolysis cycle, forming the active site upon Mg-ATP binding and disrupting upon ATP hydrolysis; 7) the ABC signature motif (or C motif, LSGGQ) is located at the α-helical subdomain, a characteristic feature of the ABC superfamily, not present in other P-loop

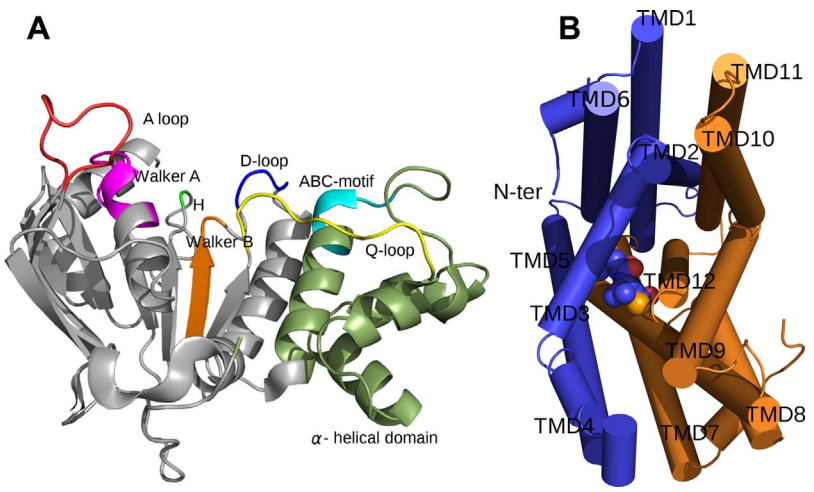

Fig. 2. Structure of a Nucleotide Binding Domain (NBD) and a Transmembrane Domain (TMD) of *ABCB1* (PDB code: 4M2T). A. Structure of NBD: domains and highly conserved sequence motifs are color-coded: Green, α-helical domain; Gray, regulatory C-terminal domain; Red, A-loop; Magenta, Walker A; Orange, Walker B; Blue, D-loop; Green, H-loop; Cyan, ABC motif; Yellow, Q-loop. B: Structure of *ABCB1* TMD dimer, view along the two-fold symmetry axis from the inward side (the NBD domain is not represented): the two TMDs of an ABC transporter are colored in blue and orange. α-helices are numbered TMD1-12. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

NTPases such as the F1-ATPase (Hanekop et al., 2006; Li et al., 2016b; Smith et al., 2002; ter Beek et al., 2014; Verdon et al., 2003).

Two ATP binding sites are formed by the two NBDs of each ABC transporters; however, it is yet unclear whether or not the hydrolysis of two ATP molecules is needed for each transport cycle. In the bacterial maltose transporter $MalEFGK_2$ two functional ATP sites are needed, while only one functional ATP site is needed in the histidine transporter $HisP_2MQJ$, and some ATP transporters have only a single ATPase site, while the second one is degenerated (Davidson and Sharma, 1997; Jones and George, 2013; Nikaido and Ames, 1999; Procko et al., 2009). The two NBDs can assume a closed conformation if tightly packed together, or an open conformation if more distant. ATP hydrolysis can take place only in the closed conformation; the release of ADP and phosphate destabilizes the NBD dimer, the RecA-like and α-helical domains move apart, the NBD dimer dissociates, and the movement can be transmitted to the TMDs.

TMDs are more heterogeneous. In ABC exporters, however, TMDs have a common structural fold, based on the presence of a six transmembrane helix-based core (Fig. 2B), which considerably stretches out into the cytosol, where a short coupling helix protrudes from the TMD and fits in a groove of NBD between the RecA-like and α-helical domains, containing the Q-loop, allowing the transduction of the ATP-dependent movement of NBD to TMD (Dawson and Locher, 2006; Hollenstein et al., 2007). The transmembrane helices of the two TMDs usually form a pore that can either be accessible from the cytoplasm (inward facing) or from outside the cell (outward facing) (Figs. 2 and 3): according to the alternating-access model, alternation between these conformations occurs during the catalytic cycle, to allow substrate binding and its transport across the membrane, against its chemical gradient (Ward et al., 2007).

Several catalytic mechanisms have been proposed for ABC transporters (Higgins and Linton, 2004; Jones and George, 2014; Linton and Higgins, 2007; Sauna et al., 2007; Senior et al., 1995). For eukaryotic ABC exporters, the catalytic cycle has the following steps: substrate binding to the inward face of TDMs, binding of two ATP molecules to NBDs, dimerization of the NBDs, conformational change of TMDs from inward facing to outward facing, ATP hydrolysis, release of substrate from the outward face of TMDs and of ADP and phosphate from NBDs and NBD dissociation (Wilkens, 2015). However, it is likely that not all ATP transporters function based on the very same mechanisms (Locher, 2016): lipid transporters as PglK and ABCA1 have been proposed to have only outwardly-facing conformations, and possibly a lateral access mechanism (Perez et al., 2015; Qian et al., 2017). The substrate-binding site is rather poorly defined in ABC exporters, and multiple and flexible sites can be present, therefore making them multidrug transporters and generating overlapping exporting function among them.

ABC transporters and MDR

Enhanced efflux of chemotherapeutic drugs by at least 15 ABC exporters has been shown to mediate MDR in cancer cells (Fletcher et al., 2016; Li et al., 2016b; Szakacs et al., 2006). The most important human ABC transporter involved in drug disposition and in MDR is *ABCB1* (also known as MDR1, P-glycoprotein, P-gp), while an important role is recognized also for ABCG2 (Breast cancer resistance protein, BRCP) and for ABCC1 (Multidrug Resistance Protein 1, MRP1), ABC exporters with broad substrate and inhibitor specificity, and wide tissue and cellular distribution, especially in physiological epithelial/endothelial barriers, partially overlapping with those of *ABCB1* (Fletcher et al., 2016; Mao and Unadkat, 2015; Natarajan et al., 2012; Zhang et al., 2015).

ABCB1 (MDR1, P-glycoprotein, P-gp)

ABCB1 has been discovered more than 40 years ago (Juliano and Ling, 1976). In humans, the *ABCB1* and *ABCB4* genes, originating from an endoduplication event, are located adjacent to each other on the long arm of chromosome 7 (7q21) and encode two similar proteins (78% identity) (Callen et al., 1987; Chin et al., 1989). In rodents, a further duplication gave rise to the genes *ABCB1a* and *ABCB1b*, with largely overlapping substrate specificities.

ABCB1 structure and function

ABCB1 is expressed at low levels in most human and rodent tissues, while high expression levels are present in the apical surface of epithelial cells, such as intestine, liver bile ductile, kidney proximal tubules, pancreatic ductules, adrenal gland, placenta, testis (blood-testis barrier) and brain capillaries (blood-brain barrier), oriented towards the lumen or the blood (Chin et al., 1989; Cordon-Cardo et al., 1990; Cordon-Cardo et al., 1989; Fojo et al., 1987; Schinkel, 1999; Thiebaut et al., 1987).

To characterize the function of *ABCB1*, knockout mice were generated harboring a disruption of the *ABCB1a* gene, the *ABCB1b* gene, or both the *ABCB1a* and *ABCB1b* genes together (Schinkel et al., 1997; Schinkel et al., 1994). These three mouse strains were healthy and fertile, with no abnormalities in anatomy, lifespan and in many other parameters, with respect to wild type mice under normal conditions; however, they displayed drastic pharmacokinetic differences upon administration of drugs, with marked reduction of the intestinal, hepatobiliary and urinary excretion of drugs (Schinkel et al., 1997; Schinkel et al., 1994; Smit et al., 1998; Sparreboom et al., 1997; van Asperen et al., 1996; van Asperen et al., 1999). Altered pharmacokinetics and increased accumulation of paclitaxel, doxorubicin and vinblastine, i.e. some of the most important chemotherapeutic drugs, administered

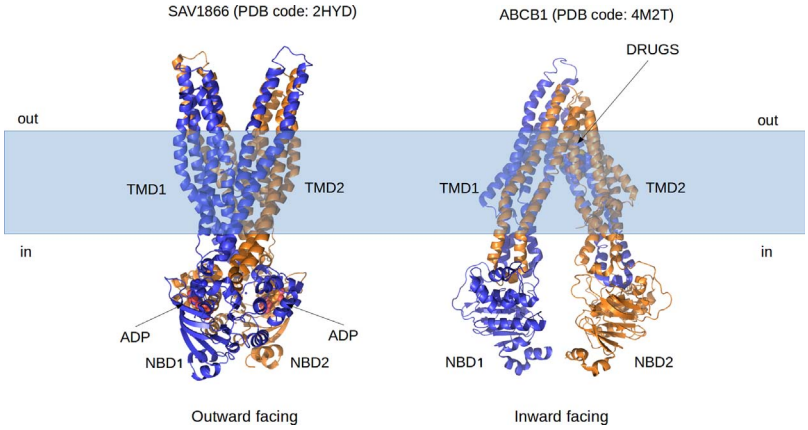

Fig. 3. Structures of ABC exporters in outward-facing and inward-facing conformations. Left: structure of *Staphylococcus aureus* SAV1866 in complex with ADP (PDB code: 2HYD), in outward-facing conformation. Right: Structure of mouse *ABCB1* (MDR1) in inward-facing conformation, in complex with two molecules of an analog of dendroamide-A (PDB code: 4M2T) (Dawson and Locher, 2006; Li et al., 2014).

against a number of cancers, was demonstrated in these mice (Sparreboom et al., 1997; van Asperen et al., 1996; van Asperen et al., 1999). In addition, ivermectin, loperamide, doxorubicin, digoxin, vinblastine, paclitaxel, erythromycin and many other drugs, which in wild type mice (and in humans) do not accumulate in the brain and are not neurotoxic, penetrate the blood-brain barrier and have serious neurotoxic effects in the CNS of *ABCB1(-/-)* mice (Schinkel et al., 1994; Schinkel et al., 1996; Schinkel et al., 1995; Schuetz et al., 1998; van Asperen et al., 1997).

Thus, both localization and characterization indicate an important role of *ABCB1* in the protection of the brain, the testis and of the fetus from toxic xenobiotics. *ABCB1* is responsible for the extrusion of xenobiotics and metabolites into the gut lumen, into the bile and urine, thus reducing their absorption, toxicity and bioavailability and hence making a major contribution to their ADME (absorption, distribution, metabolism and excretion). *ABCB1* possibly plays a role in the transport of endogenous molecules and metabolites (such as phospholipids, glycolipids, platelet-activating factors, amyloid β-peptides, and cytokines) and in exporting hormones such as aldosterone and progesterone, from the adrenal gland and the uterine epithelium (Sharom, 2008, 2011; Silva et al., 2015).

Several crystal structures of eukaryotic *ABCB1* proteins from mouse, *Cyanidioschyzon merolae* and *Caenorhabditis elegans* have been reported (Aller et al., 2009; Esser et al., 2017; Jin et al., 2012; Kodan et al., 2014; Li et al., 2014; Szewczyk et al., 2015; Verhalen et al., 2017; Ward et al., 2013; Wen et al., 2013), and showed that the overall structure of *ABCB1* is similar to that of other ABC transporters (Fig. 3). Since ABCB1 is expressed as one gene product containing both halves, similar but not identical, its structure is intrinsically asymmetric (Wen et al., 2013). Structures of mouse ABCB1a (87% identical to human *ABCB1*) in the apo-form, of mutant forms and in the presence of rationally designed ligands yielded insight on the "polyspecificity" of *ABCB1* in substrate interactions, on mechanism of ligand entry and on atomistic models of ATP-coupled transport (Fig. 4). All structures belong to a wide range of inward-facing conformations, with highly flexible TMDs and various distances between the two NBDs, which can determine opening and closing motion of the ABC exporter and thereby a number of possible binding sites due to the exposure of several flexible hydrophobic surfaces in the vicinity of the membrane (Esser et al., 2017; Szewczyk et al., 2015; Verhalen et al., 2017; Ward et al., 2013). A recent work by McHaurab and colleagues used double electron–electron resonance and molecular dynamics simulations to model *ABCB1* in the outward-facing conformation and to model energy-dependent movement and substrate efflux (Fig. 4). In this model, most *ABCB1* molecules in the cell are inward-facing, with dissociated and fully ATP-bound NBDs (Fig. 4, step 1), ready to bind the substrate with its high-affinity substrate pocket exposed to the cytoplasmic leaflet of the membrane (Fig. 4, step 2); drug extrusion requires a two-stage hydrolysis (Fig. 4, steps 3 and 4), and substrate release outside the cell by outwardly-facing *ABCB1*, a conformation with lower affinity for the substrate (Verhalen et al., 2017).

ABCB1 expression in cancers and MDR

In various cancer cell lines of distinct tissue lineage, *ABCB1* expression increases upon repeated drug treatment cycles with various chemotherapeutic drugs, rendering them MDR (Juliano and Ling, 1976; Ueda et al., 1987a; Assaraf et al., 1989a, 1989b). In addition, many early studies showed high overexpression of *ABCB1* in colon, kidney, ovary, adrenocortical and hepatocellular tumors (Bourhis et al., 1989; Fojo et al., 1987; Goldstein et al., 1989; Pirker et al., 1989). Direct association between *ABCB1* expression levels, drug resistance and poor prognosis have been found in acute myelogenous leukemia (AML) (Broxterman et al., 1999; Dorr et al., 2001; Grogan et al., 1993; Han et al., 2000; Leith et al., 1999; Michieli et al., 1999; van der Kolk et al., 2000; Zhou et al., 1995), breast cancer (Burger et al., 2003; Dexter

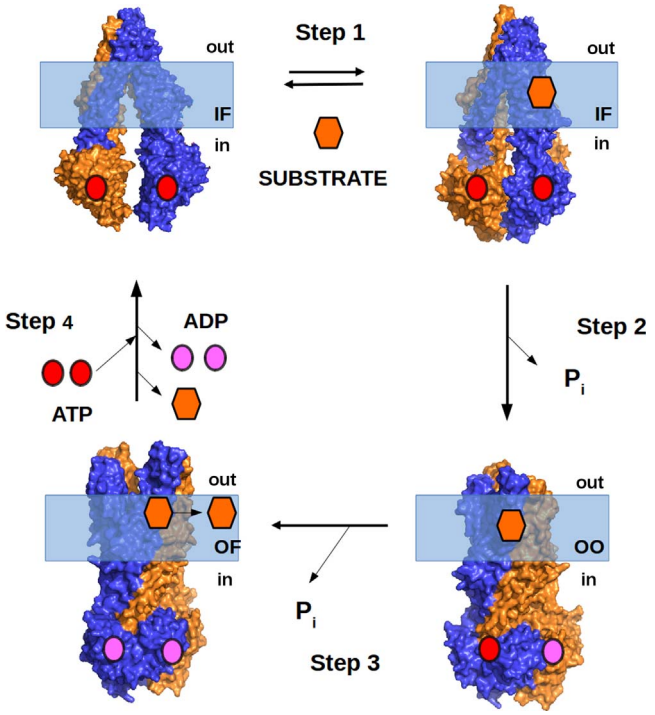

Fig. 4. Mechanism of action of *ABCB1*. Top-left: inward-facing (IF), ATP-bound *ABCB1* with non-dimerized NBDs; top-right: upon substrate binding, NBDs dimerize; bottom-right: hydrolysis of the first ATP occurs, and a doubly occluded (OO) transition state is formed; bottom-left: after hydrolysis of the second ATP, an outward-facing (OF) transition state is formed, and release of the substrate outside the cell occurs (Verhalen et al., 2017).

et al., 1998; Kao et al., 2001; Nooter et al., 1997; Sun et al., 2000; Trock et al., 1997; Vecchio et al., 1997), osteosarcoma (Chan et al., 1997), bladder cancer (Clifford et al., 1996; Nakagawa et al., 1997; Park et al., 1994; Tada et al., 2002), ovarian cancer (van der Zee et al., 1995), central nervous system (Abe et al., 1998; Perri et al., 2001) and other tumors and diseases.

In the Guidance Compliance Regulatory Information for the evaluation of drug interactions (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf), the US Food and Drug Administration (FDA) recommends that all investigational drugs should be evaluated *in vitro* to determine whether or not they are transport substrates of *ABCB1* (P-glycoprotein) or ABCG2 (BCRP); the International Transporter Consortium recommends *in vitro* analysis of interaction with *ABCB1* as a major bottleneck for filing a new drug application (International Transporter et al., 2010).

ABCB1 mutations and polymorphism

In the last years, a number of mutations and polymorphisms in the human *ABCB1* gene have been described, although sometimes with conflicting results (Schwab et al., 2003; Wolking et al., 2015). The NCBI dbSNP single nucleotide polymorphisms database currently (September 11th, 2017) lists 24289 nucleotide variants, including 1563 coding sequence variants (639 missense and 924 synonymous variants). Among the identified single nucleotide polymorphisms (SNPs), the dbSNP database counts only 1 pathogenic SNP, i.e. c.554G > T, yielding the G185V mutation (Choi et al., 1988; Safa et al., 1990). In addition, at least 14 SNPs, occurring only at low allele frequencies of <0.01, are reported to be associated with alterations in *ABCB1* functions (Wolf et al., 2011), concerning pharmacokinetics, treatment response and drug-related toxicity; the analysis of the literature show that no conclusive results are available (Wolking et al., 2015).

Epigenetic regulation of ABCB1 expression in drug response

Deregulation of epigenetic programs, in terms of DNA methylation and post-transcriptional regulation of histone proteins, cooperates with genetic alterations towards the establishment and progression of cancer as well as the development of the classical MDR phenotype mediated by *ABCB1* (Baker et al., 2005; Chen et al., 2005; Scotto, 2003). The binding of specific transcription factors to their DNA-response elements located in 'distal' and 'proximal' promoter regions of the *ABCB1* gene (Ueda et al., 1987b), and the methylation/demethylation status of this genomic locus, determine the repression or transactivation of *ABCB1* expression, associated with survival and treatment response (Arrigoni et al., 2016; Dejeux et al., 2010; Mencalha et al., 2013; Reed et al., 2010). In AML for example, an inverse correlation between methylation and *ABCB1* expression in clinical samples has been described; the hypomethylated status of *ABCB1* promoter region was proposed as a necessary condition for *ABCB1* gene overexpression and for the establishment of P-glycoprotein-mediated MDR in AML patients (Nakayama et al., 1998). In bladder cancer as well, the degree of methylation in the *ABCB1* promoter region appears to be closely associated with *ABCB1* gene expression and the emergence of the MDR phenotype (Tada et al., 2000). In breast cancer, the acquisition of drug resistance appears to be related to the methylation of the *ABCB1* downstream promoter accompanied by a regional genomic amplification of a locus in chromosome 7 containing the *ABCB1* gene and its *ABCB4* neighbor gene (Reed et al., 2008).

Recently, also the histone methylation and acetylation, occurring on lysine residues within histone tails, are emerging as relevant players for the epigenetic regulation of *ABCB1* gene expression and chemotherapy drug response (Henrique et al., 2013). Huo et al., evidenced that transcriptional activation of *ABCB1* gene expression is accompanied by increased methylation on lysine 4 of histone H3 (H3K4), and that the histone methyltransferase MLL1 is involved in this regulation. In this respect, knockdown of MLL1 decreased the constitutive expression of *ABCB1*, increased cellular retention of *ABCB1* substrates, and sensitized cancer cells to chemotherapeutic agents (Huo et al., 2010). An induction of H3K4 methylation within the coding regions of the *ABCB1* gene was also evidenced after treatment with the histone deacetylase (HDAC) inhibitor Trichostatin A (TSA), resulting in upregulation of *ABCB1* (Baker et al., 2005; Jin and Scotto, 1998). Interestingly, it was also shown that TSA treatment induced an increase in *ABCB1* expression in drug-sensitive small cell lung carcinoma (SCLC) cells, but strongly decreased its expression in drug-resistant cells through a transcriptional mechanism, independently from promoter methylation (El-Khoury et al., 2007). Moreover, in colon and pancreatic cancer cell lines, it was demonstrated that the increase in *ABCB1* mRNA expression observed after TSA treatment is not associated with an active P-gp protein expression, suggesting that well tolerated HDAC inhibitors may represent a potential therapeutic avenue to potentiate the effects of anti-tumor drugs that are P-glycoprotein substrates (Balaguer et al., 2012). In T-cell leukemia, the transcriptional control of *ABCB1* expression is achieved by two molecular mechanisms: when densely methylated, *ABCB1* is transcriptionally silent via a mechanism that is TSA independent. TSA induced significant acetylation of histones H3 and H4 but did not activate transcription, whereas 5-azacytidine, inducing DNA demethylation, lead to partial relief of transcriptional repression. *ABCB1* expression was significantly increased following the combination of 5-azacytidine and TSA treatments suggesting that, upon demethylation, activation of *ABCB1* is mediated by HDAC (El-Osta et al., 2002). Of note, the use of depsipeptide, an HDAC inhibitor, in combination with retinoic acid (RA) treatment, in Acute Promyelocytic Leukemia (APL) cells, prior to doxorubicin treatment, prevents doxorubicin-induced apoptosis in NB4 APL cells, by inducing the *ABCB1* gene and *ABCB1* expression, partially through CCAAT box-associated histone acetylation (Tabe et al., 2006). On the contrary, combined treatment of depsipeptide and RA following doxorubicin treatment, lead to enhanced doxorubicin-induced apoptosis. These results underline the critical importance of modulation of *ABCB1* expression by the use of epigenetics modulating drugs, and indicate that this is a critical point to take into consideration for the future design of clinical trials that combine epigenetics modulators and chemotherapeutic agents.

Post-transcriptional regulation of ABCB1 expression by microRNAs in drug response

miRNAs are small ($\approx$22 nucleotides long) noncoding RNAs which are evolutionary conserved and play a key role in the regulation of gene expression; miRNAs are significantly deregulated in cancer, and each cancer phenotype is defined and characterized by a unique miRNA signature, highlighting miRNAs as relevant molecules for cancer diagnostics and possible therapeutic interventions (Blandino et al., 2014). miRNAs can act by targeting a spectrum of distinct players, involved in the establishment of cancer MDR (Zhang and Wang, 2017). Of note, since many drugs need the expression of specific genes to exert their antineoplastic activity, miRNAs which affect the post-transcriptional regulation of pharmacogenomics-related genes, such as those responsible for drug metabolism or transport as well as those directly targeted by the drugs, are also emerging as potent regulators of drug efficacy (Rukov and Shomron, 2011). Several miRNAs are involved in different regulatory pathways that confer chemoresistance to cancer cells, as the ID4-miR-9*-SOX2-ABCC3/ABCC6 pathway which imparts stemness potential and chemoresistance in glioma cells (Jeon et al., 2011), and the miR27b-CCNG1-p53-miR-508-5p axis which regulates MDR in gastric cancer (Shang et al., 2016).

The identification of the expression levels of miRNAs targeting genes involved in the binding or in the transport of chemotherapeutic drugs may be extremely useful to identify the possible acquisition of drug resistance during cancer treatment (Yamamoto et al., 2011). For example, Pan et al. found that miR-328, which targets the ABCG2 gene,

encoding for a MDR efflux transporter of the ABC superfamily, may affect the transport of the anticancer drug mitoxantrone (MX) across the plasma membrane and the sensitivity of MCF-7 breast cancer cells to this anthracycline drug (Pan et al., 2009). Also miR-345 and miR-7, targeting ABCC1 gene, which encodes for the human multidrug resistance-associated protein 1 (MRP1), were associated with acquired resistance of MCF-7 breast cancer cells to cisplatin (Pogribny et al., 2010).

Moreover, different miRNAs were described with a functional role in the regulation of the expression and activity of *ABCB1*, the founding member of the ABC superfamily of multidrug efflux transporters that is a dominant pump responsible for MDR (Garofalo and Croce, 2013; Li et al., 2016b; Livney and Assaraf, 2013; Wijdeven et al., 2016). As described above, the plasma membrane overexpression of *ABCB1* in cancer cells leads to an increased drug efflux and impairs the achievement of an intracellular cytotoxic drug concentration. Of note, various miRNAs targeting this ABC superfamily member were described to be involved in the regulation of drug efflux activity of this transporter as well as in drug response (Geretto et al., 2017; Lopes-Rodrigues et al., 2014). It has been shown that 3′-UTR variants of *ABCB1* with shortened length may be synthesized during the acquisition of drug resistance and this may lead to the loss of miRNA binding sites and hence alleviating this miRNA-based repression of *ABCB1* expression (Bruhn et al., 2016). However, altered levels of miRNAs affecting *ABCB1* expression were also recently described. For example, in human intestinal epithelial cells miR-145 negatively regulates the expression and function of *ABCB1* through direct interaction with its mRNA 3′-UTR (Ikemura et al., 2013), while in ovarian cancer the development of cisplatin resistance was related to the up-regulation of miR-130a, resulting in *ABCB1*-mediated MDR (Li et al., 2015; Yang et al., 2012). By targeting *ABCB1*, miR-873 and miR-595 also contribute to the regulation of drug resistance and the activity of cisplatin in inhibiting tumor growth in ovarian cancer (Tian et al., 2016; Wu et al., 2016). Interestingly, miR-27a and miR-451 induce the activation of *ABCB1* expression and their modulation with antagomirs enhances the sensitivity of ovarian cancer cells via enhanced intracellular accumulation of doxorubicin (Zhu et al., 2008). In contrast, in colorectal cancer, restoration of miR-451 decreases *ABCB1* expression and results in sensitization to irinotecan (Bitarte et al., 2011); whereas, up-regulation of miR-27a in hepatocellular carcinoma cells decreased the *ABCB1* expression via FZD7/β-catenin signaling pathway, enhancing the sensitivity of these cells to 5-fluorouracil resulting in 5-fluorouracil-induced apoptosis (Chen et al., 2013b). Moreover, in breast cancer cells as well, miR-451 was reported to mediate down-regulation of *ABCB1* gene expression, resulting in increased sensitivity of tMCF-7 breast cancer cells to doxorubicin (Kovalchuk et al., 2008). In hepatocellular carcinoma cells, a novel role for miR-491-3p was identified resulting in *ABCB1*-mediated MDR, suggesting the potential application of miR-491-3p as a therapeutic strategy for repression of P-glycoprotein-dependent MDR tumors (Zhao et al., 2017). In gastric cancer, the overexpression of miR-508-5p, targeting the 3′-UTR of *ABCB1*, was sufficient to reverse MDR in cancer cells to multiple chemotherapeutic drugs, both *in vitro* and *in vivo*, and, interestingly, miR-508-5p might act as a prognostic factor for overall survival in this tumor (Shang et al., 2014). In neuroblastoma cells, it was shown that epigenetic silencing of miR-137 in doxorubicin-resistant cells contributes to overexpression of the constitutive androstane receptor (CAR) and, in turn, *ABCB1*, and that treatment with the 5-azacytidine, a methylation inhibitor, increased miR-137 expression and sensitized doxorubicin-resistant neuroblastoma cells to this anthracycline (Takwi et al., 2014). Moreover, the hyper-methylation of the promoter region of miR-129-5p is recently gaining relevance in the development of drug resistance in gastric cancer cells and this miRNA, by targeting MDR-related ABC transporters as *ABCB1,* was proposed as a potential therapeutic target to enhance drug sensitivity of gastric cancers (Wu et al., 2014). In gastric cancer, it was also evidenced that miR-129 was able to reverse cisplatin-resistance through repression of *ABCB1* gene expression and activation of the caspase-mediated intrinsic apoptotic pathway (Lu et al., 2017). Of note, the nanoparticles-mediated co-delivery of miR-129-5p and doxorubicin significantly increased miR-129-5p expression in doxorubicin-resistant MCF-7 breast cancer cells, which effectively overcame MDR achieving a 100-fold increase in *ABCB1* gene expression, thereby increasing intracellular drug accumulation and cytotoxicity in this tumor cell line model (Yi et al., 2016). This synergistic therapeutic option was also recently reported for miR-375 in hepatocellular carcinoma (Fan et al., 2017). Moreover, in breast cancer it was further reported that the overexpression of miR-298 as well results in down-regulation of *ABCB1* gene expression, increasing nuclear accumulation of doxorubicin and cytotoxicity in doxorubicin-resistant cells (Bao et al., 2012). In mouse leukemia cells it was reported that the restored expression of miR-381 or miR-495 in doxorubicin-resistant K562 cells correlates with a decreased *ABCB1* gene expression and with an increased drug uptake by these cells (Xu et al., 2013). More recently, in the same cellular system, restoration of miR-9 expression was also able to reverse cancer cell drug resistance *in vitro* and sensitized tumors to chemotherapy *in vivo* by targeted repression of *ABCB1* gene expression (Li et al., 2017). In addition, in gallbladder cancer, miR-218-5p enhanced sensitivity of gemcitabine by abolishing PRKCE-induced up-regulation of *ABCB1* (Wang et al., 2017). Table 1 shows miRNAs acting on *ABCB1* in MDR (vs. non-MDR) tumors.

Transport substrates of ABCB1

ABCB1 is able to bind and extrude out of cells a plethora of chemically, structurally and pharmaceutically distinct compounds including drugs used as anti-cancer chemotherapeutics, inflammation, immunosuppression, infection, allergy, hypertension, and arrhythmia (Table 2); more than one thousand compounds have been described as *ABCB1* substrates (Didziapetris et al., 2003). The high flexibility, fuzziness and complexity of drug substrate binding sites of *ABCB1* (Esser et al., 2017; Szewczyk et al., 2015; Verhalen et al., 2017; Ward et al., 2013) explain the wide number of drug classes of these *ABCB1* substrates, which include small molecules, as cations, amino acids and carbohydrates, larger molecules, as chemotherapeutic drugs, ionophores, fluorescent dyes and steroids and larger molecules such as peptides, polysaccharides and proteins (Borgnia et al., 1996; Didziapetris et al., 2003; Eytan et al., 1994; Sharom, 2011; Silva et al., 2015; Zhou, 2008). Many of these substrates are relatively hydrophobic and weakly amphipathic, typically contain aromatic rings and a positively charged nitrogen, and often their binding occurs with K_D values of 10 μM–1 mM (Morrissey et al., 2012). This substrate "polyspecificity" is crucial for *ABCB1* to exert its role as a xenobiotics efflux pump, able to protect cells from a high number of cytotoxicants. In addition, substrates binding to *ABCB1* partially overlap to those bound by other ABC transporters, such as ABCC1, ABCC2 and ABCG2, and by cytochrome P450 3A enzymes, in particular CYP3A4: a coordinate interplay between these proteins can operate to protect cells as a barrier in the bioavailability of drugs, especially when orally administered (Cascorbi, 2006; Cummins et al., 2002; Kim et al., 1999).

ABCB1 transport inhibitors

The induction of *ABCB1* upon exposure to cancer chemotherapeutics is an important cause of MDR; conversely, inhibition of *ABCB1* transport is one the most studied clinical strategies to counteract MDR, with the aim to interfere with chemotherapeutic drug efflux, thereby increasing their accumulation and hence their cytotoxic effect in cancer cells. Mechanistically, *ABCB1* inhibitors may exert their activity by binding and blocking the substrate binding site of the transporter, either in competitive, non-competitive or allosteric fashion, by interfering with ATP hydrolysis, by binding the transporter in site independent of the drug binding site which allosterically alters the intact structure and function of *ABCB1*, or by altering the integrity and functionality of cell

Table 1
miRNA acting on *ABCB1* in MDR (vs. non-MDR) cancers.

miRNA	Direct expression	*ABCB1* target	Effect on		Cancer
			expression	drug resistance	
miR-9	↓	*ABCB1*	↑	↑ Adriamycin	MDR chronic myelogenous leukemia vs. non-MDR
miR-27a	↑	?	↑	↑ Doxorubicin, vinblastine	MDR ovarian cancer vs. non-MDR
	↓	FZD7/β-catenin	↑	↑ 5-fluorouracil	MDR hepatocellular carcinoma vs. non-MDR
miR-129	↓	*ABCB1*	↑	↑ Cisplatin	MDR gastric cancer vs. non-MDR
miR-129-5p	↓	*ABCB1*	↑	↑ Vincristine, 5-fluorouracil, cisplatin	MDR gastric cancer vs. non-MDR
	↓	*ABCB1*, CDK6	↑	↑ Doxorubicin	MDR breast cancer vs. non-MDR
miR-130a	↓	*ABCB1*	↑	↑ Cisplatin	MDR ovarian cancer vs. non-MDR
miR-137	↓	CAR	↑	↑ Doxorubicin	MDR neuroblastoma vs. non-MDR
miR-145	↓	*ABCB1*	↑		Intestinal epithelial cells vs. ischemia-reperfusion cells
miR-218-5p	↓	PRKCE	↑	↑ Gemcitabine	Gallbladder cancer vs. non cancer
miR-298	↓	*ABCB1*	↑	↑ Doxorubicin	MDR breast cancer vs. non-MDR
miR-375	↓	*ABCB1*, AEG1, YAP1, ATG7	↑	↑ Doxorubicin	MDR hepatocellular carcinoma vs. non-MDR
miR-381	↓	*ABCB1*	↑	↑ Doxorubicin	MDR chronic myelogenous leukemia vs. non-MDR
miR-451	↑	?	↑	↑ Doxorubicin	MDR ovarian cancer vs. non-MDR
	↓	COX2/Wnt	↑	↑ Irinotecan	MDR colonspheres vs. non-MDR
	↓	*ABCB1*	↑	↑ Doxorubicin	MDR breast cancer vs. non-MDR
miR-491-3p	↓	*ABCB1*, Sp3	↑	↑ Doxorubicin, vinblastine	MDR hepatocellular carcinoma vs. non-MDR
miR-495	↓	*ABCB1*	↑	↑ Doxorubicin	MDR chronic myelogenous leukemia vs. non-MDR
miR-508-5p	↓	*ABCB1*, ZNRD1	↑	↑ Adriamycin, Vincristine, 5-fluorouracil, cisplatin	MDR gastric cancer vs. non-MDR
miR-595	↓	*ABCB1*	↑	↑ Cisplatin	MDR ovarian cancer vs. non-MDR
miR-873	↓	*ABCB1*	↑	↑ Cisplatin	MDR ovarian cancer vs. non-MDR

Table 2
Classes of *ABCB1* substrates.
Data from: Didziapetris et al. (2003), Sharom (2011), Silva et al. (2015), Zhou (2008).

Classes of *ABCB1* substrates	
Substrate class	Examples
Anti-arrhythmics	Digoxin, quinidine, verapamil.
Antibiotics (antimicrobial drugs)	Clarithromycin, doxycycline, erythromycin, gramicidin A, grepafloxacin, itraconazole, ketoconazole, levofloxacin, rifampicin, sparfloxacin, tetracycline, valinomycin.
Anticancer chemotherapeutic drugs	Alkylating agents: chlorambucil, cisplatin Antibiotics: actinomycines (actinomycin D), anthracyclines (daunorubicin, doxorubicin), mitoxantrone, mytomicin C. Antimetabolites: cytarabine, 5-fluorouracil, hydroxyurea, methotrexate. Camptothecins: irinotecan, topotecan. Epidermal growth factor receptor inhibitors: erlotinib, gefitinib Epipodophyllotoxins: etoposide, teniposide Taxanes: docetaxel, paclitaxel. Tyrosine kinase inhibitors: imatinib, nilotinib Vinca alkaloids: vinblastine, vincristine Others: bisantrene, tamoxifen.
Anticonvulsants and anti-epileptics	Carbamazepine, phenobarbital, phenytoin, topiramate.
Antidepressants	Amitriptyline, doxepin, nortriptyline.
Anti-diarrheal drugs	Loperamide (opioid), octreotide
Antiemetics	Domperidone, ondansetron.
Antigout drugs	Colchicine
Antihelmintics	Ivermectin
Antihistamine	Fexofenadine, terfenadine.
Anti-HIV	Amprenavir, indinavir, nelfinavir, ritonavir, saquinavir.
Antihypertensives	Celiprolol, debrisoquine, losartan, prazosin, reserpine, talinolol.
Calcium channel blockers	Azidopine, diltiazem, nicardipine nifedipine, verapamil.
Calmodulin antagonists	trans-flupentixol, trifluoperazine.
Cardiac glycosides	Digitoxin, digoxin.
Cyclic peptides	Beauvericin, valspodar (PSC-833).
Fluorescent dyes	Calcein AM, Hoechst 33342, Rhodamine 123.
Histamine H_2-receptor antagonists	Cimetidine, ranitidine
Hypocholesterolizing drugs	Lovastatin, simvastatin
Immunosuppressive agents	Cyclosporin A, sirolimus, tacrolimus, valspodar (PSC-833)
Linear peptides	ALLN (Acetyl-leucyl-leucyl-norleucine), leupeptin, pepstatin A
Neuromuscular blocking agents	Vecuronium
Natural products	Curcumin, Flavonoids.
Neuroleptics	Chlorpromazine, phenothiazine
Pesticides	Endosulfan, methylparathion, paraquat.
Steroid hormones	Aldosterone, corticosterone, cortisol, dexamethasone, estradiol, methylprednisolone.
Others	Amino acids, bilirubin, carbohydrates, cations, polysaccharides

Table 3
Classes of *ABCB1* inhibitors.
Data from Palmeira et al. (2012a), Silva et al. (2015).

Classes of *ABCB1* inhibitors	
Inhibitor class	Examples
First generation	
Analgesics	Meperidine, pentazocine
Anesthetic drugs	Benzyl alcohol, chloroform, diethyl ether, propofol
Antibiotics	Azithromycin, bafilomycin, brefeldin A, cefoperazone, ceftriaxone, clarithromycin, erythromycin, nigericin, salinomycin, valinomycin
Anticancer drugs	Antiandrogen; bicalutamide, mitotane Estrogen receptor antagonists: tamoxifen Farnesyl trasferase inhibitors: lonafarnib, tipifarnib Tyrosine kinase inhibitors: erlotinib, gefitinib, lapatinib
Antifungal drugs	Aureobasidin A, dihydroptychantol A, econazole, itraconazole, ketoconazole
Antihistaminic drugs	Astemizole, azelastine, benzquinamide, terfenadine, tesmilifene
Anti-inflammatory drugs	Zomepirac, indomethacin, SC236, curcumin, ibuprofen, NS-398
Antidepressants	Amoxapine, loxapine, sertraline, paroxetine, fluoxetine
Antiprotozoal drugs	Hycanthone, metronidazole, monensin, quinine
Antiviral drugs	Concanamycin A, nelfinavir, ritonavir, saquinavir
Anxiolytics	Midazolam
Cardiac drugs	Antiarrhythmics: amiodarone, propafenone, quinidine Calcium channel blockers: amiodarone, bepridil, deverapamil, diltiazem, emopamil, felodipine, isradipine, lomerizine, mibefradil, nicardipine, nifedipine, niguldipine, nimodipine, nitrendipine, propaphenone, quinidine, tetrandrine, verapamil. Antiplatelet drug: dipyridamole Antihypertensives: carvedilol, doxazosin, prazosin, reserpine.
CNS stimulators	Amoxapine, caffeine, cotinine, loxapine, nicotine, pentoxifylline, sertraline
CNS depressants	Chloropromazine, trans-flupentixol, haloperidol, perospirone, perphenazine, prochloropromazine, trifluoperazine
Cholesterol-lowering drugs	Atorvastatin,
Immunosuppressant drugs	Cyclosporin A, tacrolimus, sirolimus
Phosphodiesterase inhibitors	Vardenafil
Steroid hormones	Cortisol, medroxiprogesterone, methylprednisolone, mifepristone, progesterone, SB4723, SB4769, tirilazad, U-74389F
Others	Bromocriptine, disulfiram, methadone, tetrabenazine
Second generation	BIBW22BS, biricodar (VX 710), CGP 42700, cinchonine, dexverapamil, dexniguldipine, dofequidar (MS-209), hydro-cinchonine, KR-30031, MM36, PAK-104P, quinine homodimer Q2, RO44-5912, S9788, SB-RA-31012 (tRA96023), stipiamide homodimer, timcodar (VX-853), toremifene, valspodar (PSC 833), WK-X-34
Third generation	Annamycin, CBT-1, DP7, elacridar (GF120918), laniquidar (R101933), mitotane, ontogen (OC144093), PGP-4008, tariquidar (XR9576), zosuquidar (LY335979),
Fourth generation	
Natural products	Alkaloids: ellipticine, pervilleine F Cannabinoids: cannabidiol Coumarins: cnidiadin, conferone, DCK, praeruptorin A, rivulobirin A Diterpenes: euphodendroidin D, jolkinol B, pepluanin A, portlanquinol Flavonoids: baicalein heptamethoxyflavone, nobiletin, quercetin, sinensetin, tangeretin Ginsenosides: 20S-ginsenoside Lignans: nirtetralin, schisandrin A, silibinin Polyenes: pentadeca-(8,13)-dien-11-yn-2-one Sesquiterpenes: dihydro-β-agarofuransesquiterpenes Taccalonolides: taccalonolides A Triterpenes: oleanolic acid, sipholenol A, sipholenone E, uvaol
Peptidomimetics	Peptide 15, reversin 121, reversin 205, XR9051
Surfactants and Lipids	Cremophor EL, Nonidet P40 Pluronic P85, poly(ethylene glycol)-300 (PEG-300), Tween-20, Triton X-100,
Dual ligands	Dual inhibitors of *ABCB1* and tumor cell growth (e.g.: aminated thioxanthones)

membrane lipids, or by altering plasma membrane fluidity (Drori et al., 1995; Shapiro and Ling, 1997; Silva et al., 2015; Varma et al., 2003).

Classification into four generations of *ABCB1* inhibitors according to their potency, selectivity and drug–drug interaction potential (Palmeira et al., 2012a), rather than to their chronology of discovery and characterization, is useful (Table 3). The first generation of *ABCB1* transport inhibitors comprises classical inhibitors such as the founding member verapamil as well as cyclosporine A and all compounds which were previously described as having other therapeutic applications. The first identified *ABCB1* transport inhibitor has been the calcium channel blocker verapamil, able to increase the intracellular accumulation of chemotherapeutic drugs as doxorubicin, vincristine and vinblastine by competing with these drugs (Miller et al., 1991; Tsuruo et al., 1981). Verapamil, as many other of first-generation ABCB1 substrate, and presumably acts by competing for efflux with other ABCB1 substrates (Varma et al., 2003; Yusa and Tsuruo, 1989). Verapamil sensitizes cancer cells to several anticancer drugs, such as doxorubicin, increasing their cytotoxic activity (Futscher et al., 1996); many clinical studies on the use of verapamil, alone and in combination regimens, against various cancers and other diseases have been carried out, and some are still ongoing (https://clinicaltrials.gov/). A number of “already-in-clinical-use” *ABCB1* inhibitors have been discovered, belonging to several classes, such as calcium channels blockers (e.g., verapamil), anti-malarial drugs (e.g., quinine), immunosuppressants (e.g., cyclosporine A), anesthetics (e.g., chloroform), antibiotics (e.g., erythromycin, and ceftriaxone), antifungal drugs (e.g., ketoconazole), antivirals (e.g., nelfinavir, and saquinavir), CNS stimulators or anti-depressants (e.g., caffeine, nicotine, and chlorpromazine), as well as steroids (e.g., cortisol, and progesterone). In addition, some *ABCB1* transport inhibitors are themselves anticancer drugs, such as tamoxifen, and tyrosine kinase inhibitors as erlotinib and lapatinib (Table 3) (Palmeira et al., 2012a; Sharom, 2011; Silva et al., 2015; Zhou, 2008). Often, the clinical use of these *ABCB1* inhibitors is hampered by their intrinsic toxicity, because high concentrations of these drugs are needed to inhibit *ABCB1* efflux

activity, given their low affinity for *ABCB1*. Further, since many first-generation *ABCB1* inhibitors are also substrates of other transporters and/or enzymes, pharmacokinetic interactions are complex and sometimes unpredictable (Ambudkar et al., 1999).

Second-generation *ABCB1* transport inhibitors were designed from compounds with another recognized activity, but which were subjected to structural modifications in order to decrease their principal therapeutic activity and to enhance *ABCB1* inhibitory activity, in order to achieve decreased toxicity and higher potency (Kathawala et al., 2015; Palmeira et al., 2012a; Silva et al., 2015). These compounds include derivatives of anticancer, cardiovascular and immunosuppressive agents (Table 2). For example, valspodar (PSC-833) is a non-immunosuppressive derivative of cyclosporine A; although it is 5- to 20-fold more potent than its parent compound, and also exhibited promising pre-clinical results, its administration in combination with anticancer drugs inhibits the metabolism and extrusion of such cytotoxic agents, thus leading to unacceptable toxicity which requires chemotherapy dose reduction (Advani et al., 2001; Advani et al., 2005; Bates et al., 2001; Bauer et al., 2005; Chico et al., 2001). In addition, many of these compounds inhibit cytochrome P450 enzymes, resulting in unpredictable pharmacokinetic interactions.

Third-generation *ABCB1* inhibitors (Table 3) were developed by using quantitative structure-activity relationships (QSAR) and combinatorial chemistry, which specifically and potently inhibit the ABC exporter at nanomolar concentrations, without affecting cytochrome P450 enzymes (Coley, 2010; Dantzig et al., 2001; Palmeira et al., 2012a; Silva et al., 2015). Often these compounds inhibit *ABCB1* based on a non-competitive mechanism; the most promising ones are possibly tariquidar, elacridar and zosuquidar (Akhtar et al., 2011; Dantzig et al., 2001; Fox and Bates, 2007; Hyafil et al., 1993; Weidner et al., 2016). Zosuquidar, a difluoro-cyclopropyl dibenzosuberane derivative, is very potent, is effective at nanomolar concentrations and has no interaction with cytochrome P450 and with other drug efflux pumps (Bihorel et al., 2007; Dantzig et al., 2001; Dantzig et al., 1999; Green et al., 2001; Kemper et al., 2004). However, third-generation *ABCB1* inhibitors have encountered unexpected toxicity problems, and clinical trials have yielded modest results (Pusztai et al., 2005; Ruff et al., 2009); for example, a phase III trial for the treatment of AML and myelodysplastic syndrome (MDS) using zosuquidar did not meet its primary endpoint (Cripe et al., 2010).

Fourth-generation *ABCB1* inhibitors (Table 3) include various classes of compounds, i.e. natural compounds, surfactants and lipids, peptides and molecules with dual activity (Palmeira et al., 2012a). Hundreds of natural compounds, obtained from several natural sources, and belonging to many chemical families, such as alkaloids, flavonoids, coumarins, resins, saponins and terpenoids (Dewanjee et al., 2017), have been described thus far as acting on ABC transporters, thereby offering potential for semi-synthetic modification to produce new scaffolds which could serve as valuable tools to evade the systemic toxicities shown by synthetic counterparts. However, reports in the literature are sometimes contradictory: for example quercetin has been reported to have opposite effects on *ABCB1* and MDR (Critchfield et al., 1994; Phang et al., 1993; Rodgers and Grant, 1998) perhaps also due to its inhibition of Cytochrome P-450 enzymes.

Surfactants have complex relationship with *ABCB1*-dependent drug efflux and MDR; they alter membrane fluidity, perturbing lipid bilayers, and drug-membrane partitioning; they also interact with *ABCB1*, inflict modifications in secondary and tertiary enzyme structure, inhibit ABC transporter activity and increase cellular drug accumulation (Regev et al., 2007; Sharom, 2014; Shieh et al., 2011; Shukla et al., 2017).

Some peptides, such as reversins, are able to potently inhibit *ABCB1* in a non-competitive manner (Arnaud et al., 2010); they have been recently used as conjugate copolymers with anthracyclines to overcome MDR (Koziolova et al., 2016; Sivak et al., 2017).

Dual ligands, able to simultaneously modulate *ABCB1* and other enzymes, have been recently described. Apart from their ability to inhibit other ABC transporters shown by several inhibitors, dual ligands include aminated thioxanthones, targeting *ABCB1* and DNA-intercalating, and verapamil-like compounds, targeting *ABCB1* and NO synthase (Colabufo et al., 2011; Namanja-Magliano et al., 2017; Palmeira et al., 2012b).

Other strategies to overcome ABCB1-dependent MDR

Collateral sensitivity (CS) is the ability of compounds to selectively kill MDR cells over parental cells from which they were derived (Pluchino et al., 2012). CS agents are MDR-selective compounds that can act with different mechanisms; one of such mechanisms is apoptosis via reactive oxygen species (ROS) overproduction following futile ATP hydrolysis cycles in cells with high-*ABCB1* levels, induced by iron-chelating compounds such as Dp44mT or N-(2-hydroxy acetophenone) glycinate (Ganguly et al., 2010; Jansson et al., 2010); Dp44mT also acts by hijacking lysosomal *ABCB1* (Jansson et al., 2015; Seebacher et al., 2016). Other CS-inducing drugs exploit increased sensitivity to bioenergy states: treatment with 2-deoxy-D-glucose, a hexokinase II inhibitor, induces apoptosis in MDR cells, that rely on glycolysis for ATP generation due to the Warburg effect resulting from hypoxia in tumor microenvironment (Bell et al., 1998; Kaplan et al., 1991).

Another strategy to overcome MDR in *ABCB1*-overexpressing cells is the use of nanoparticle delivery of anticancer drugs. Nanoparticles that are taken up by the cell via endocytosis often bypass and evade the ABC transporters responsible for efflux of cytotoxic drugs once released into the cytoplasm (Bar-Zeev et al., 2016; Bar-Zeev et al., 2017; Cerqueira et al., 2015; Fracasso et al., 2016; Huang et al., 2011; Livney and Assaraf, 2013; Shapira et al., 2011; Song et al., 2010; Yuan et al., 2016).

Drug inducers of ABCB1 expression

Cells exposed to a P-glycoprotein cytotoxic drug substrate either upon stepwise selection or single dose exposure, frequently display the MDR phenotype often due to high overexpression of *ABCB1* levels, frequently due to gene amplification or increased transcription (Assaraf and Borgnia, 1994; Assaraf et al., 1989a, 1989b; Borgnia et al., 1996; Fojo et al., 1985; Roninson, 1992; Roninson et al., 1986; Scotto et al., 1986; Shen et al., 1986).

Many molecules (Table 4), and in particular many chemotherapeutic drugs, induce *ABCB1* overexpression *via* multiple mechanisms, involving genomic amplification, upregulation of transcription, mRNA splicing, transport and stability. Constitutive *ABCB1* transcription mostly depends on a few elements, i.e. two GC-rich regions (GC-boxes), located from −110 to −103 and from −56 to −45 bases upstream of the major +1 start site in the human *ABCB1* promoter, the CCAAT box (Y-box), the p53 element and possibly the AP-1 and T-cell factor elements (see above, for a review see (Silva et al., 2015)). In addition, stress-induced upregulation of *ABCB1* expression occurs, depending on ROS, heat shock, inflammation and ionizing radiations, acting via a wealth of transcription factors, such as phosphoinositide 3-kinase (PI3K)/Akt, extracellular signal-regulated kinases (ERKs; or mitogen-activated protein kinases, MAPKs), c-Jun NH2-terminal protein kinase (JNK), protein kinase C (PKC) and nuclear factor-κB (NF-κB), cyclic adenosine monophosphate responsive element (CRE) and heat-shock factor (HSF), acting on several pathways in a very complex manner (Callaghan et al., 2008; Chin et al., 1990; Krishnamurthy et al., 2012; Labialle et al., 2002; Miyazaki et al., 1992; Nwaozuzu et al., 2003; Scotto, 2003; Scotto and Egan, 1998; Silva et al., 2015; Vilaboa et al., 2000; Wong et al., 2010; Zhou and Kuo, 1997).

ABCB1 can be induced by several stimuli, acting on these regulatory elements, directly or indirectly. Apart from the stress conditions abovementioned, many molecules are able to induce *ABCB1* overexpression. Table 4 reports a list of *ABCB1* inducers, the mode they have been described to act through, and the level of induction observed upon cell treatment: these compounds are rather heterogeneous in

Table 4
Drugs inducing ABCB1 expression.

Drugs inducing ABCB1 expression	
Inducer	Action
Abacavir	1.5-fold ABCB1 induction upon 15 μM treatment for 72 h in hCMEC/D3 cells (Chan et al., 2013)
N-Acetoxy-2-acetylaminofluorene	3.2-fold ABCB1 expression increase upon 40 μM treatment for 8 h in HepG2 cells (Kuo et al., 2002)
2-Acetyl-aminofluorene	7.5-fold ABCB1 induction upon 100 μM treatment for 24 h in rat hepatoma cells (Deng et al., 2001)
Actinomycin D	2.5-fold *ABCB1* mRNA induction upon 400 ng/mL treatment for 72 h in human T lymphoblastoid CCRF-CEM cells (Gekeler et al., 1988)
Aflatoxin B1	*ABCB1* mRNA induction upon 3 mg/kg i.p. treatment for 48 h in Fischer rats (Burt and Thorgeirsson, 1988)
Ambrisentan	2.3-fold ABCB1 expression upon 50 μM treatment for 96 h in LS180 cells (Weiss et al., 2013)
Amiodarone	2.4-fold ABCB1 induction upon 10 μM treatment for 72 h in LS180 cells (Schuetz et al., 1996)
Amprenavir	3.5-fold ABCB1 induction upon 10 μM treatment for 72 h in LS180 cells (Perloff et al., 2000)
Arsenite	3-fold ABCB1 induction upon 250 nM treatment for 24 h in TRL1215 cells (Liu et al., 2001)
Artemisinin	13.5-fold *ABCB1* mRNA induction upon 10 μM treatment for 6 h in Caco-2 cells (Riganti et al., 2009b)
Asiatic acid	2.6-fold ABCB1 induction upon 25 μM treatment for 48 h in LS180 cells (Abuznait et al., 2011b)
Atazanavir	2.5-fold ABCB1 induction upon 10 μM treatment for 72 h in hCMEC/D3 cells (Zastre et al., 2009)
Atorvastatin	4-fold *ABCB1* mRNA induction upon 10 μM treatment for 72 h in T84 cells (Haslam et al., 2008a)
Avermectin	2.6-fold ABCB1 induction upon 0.5 μM treatment for 12 h in Drosophila S2 cells (Luo et al., 2013)
Beclometasone	2.1-fold ABCB1 expression increase upon 50 μM treatment for 72 h in Caco-2 cells (Crowe and Tan, 2012)
Benzopyrene	Increased ABCB1 expression upon 50 μM treatment for 72 h in Caco-2 cell (Sugihara et al., 2007)
Bethametasone	4-fold ABCB1 induction upon 0.4 μM treatment for 24 h in placenta cells (Manceau et al., 2012)
Bilirubin	18-fold *ABCB1* mRNA induction upon 100 μM treatment for 24 h in T84 cells (Naruhashi et al., 2011)
Bosentan	3.7-fold ABCB1 induction upon 50 μM treatment for 96 h in LS180 cells (Weiss et al., 2013)
Bromocriptine	10-fold ABCB1 induction upon 100 μM treatment for 24 h in rat Reuber H35 cells (Furuya et al., 1997)
Budesonide	1.6-fold ABCB1 induction upon 50 μM treatment for 72 h in Caco-2 cells (Maier et al., 2007)
Cadmium	3.7-fold ABCB1 induction upon 10 μM treatment for 72 h in Caco-2 cells (Thevenod et al., 2000)
Caffeine	Increased ABCB1 expression upon 5–100 μM treatment for 48 h in LS180 cells (Abuznait et al., 2011a)
Capsaicin	2-fold ABCB1 induction upon 50 μM treatment for 72 h in Caco-2 cells (Han et al., 2006)
Carbamazepine	7.6-fold ABCB1 induction upon 50 μM treatment for 72 h in human blood lymphocytes (Owen et al., 2006)
Catechine	2.3-fold ABCB1 induction upon 10 μM treatment for 4 weeks in Caco-2 cells (Lohner et al., 2007)
Celiprolol	3.2-fold ABCB1 induction upon 100 μM treatment for 72 h in Caco-2 cells (Anderle et al., 1998)
Cembratriene	3-fold ABCB1 induction upon 25 μM treatment for 48 h in LS180 cells (Abuznait et al., 2011b)
Cholate	1.8-fold *ABCB1* mRNA induction upon 100 μM treatment for 24 h in T84 cells (Naruhashi et al., 2011)
Chrysin	2.8-fold ABCB1 induction upon 10 μM treatment for 4 weeks in Caco-2 cells (Lohner et al., 2007)
Ciclesonide	1.7-fold ABCB1 induction upon 50 μM treatment for 72 h in Caco-2 cells (Crowe and Tan, 2012)
Cisplatin	2.7-fold ABCB1 expression upon 3 mg/kg treatment for 96 h in liver and kidney of Sprague-Dawley rats (Demeule et al., 1999)
Clotrimazole	4.1-fold ABCB1 induction upon 10 μM treatment for 72 h in LS180 cells (Schuetz et al., 1996)
Colchicine	1.8-fold ABCB1 induction upon 100 μM treatment for 24 h in Caco-2 cells (Silva et al., 2014)
Colupulones	1.3-fold ABCB1 induction upon 1 μM treatment for 48 h in LS180 cells (Bharate et al., 2015)
Cyanidin	2.7-fold ABCB1 induction upon 10 μM treatment for 4 weeks in Caco-2 cells (Lohner et al., 2007)
Cycloheximide	27-fold *ABCB1* mRNA induction upon 10 μM treatment for 24 h in RC3 cells (Gant et al., 1992)
Cyclosporine A	2-fold *ABCB1* mRNA induction upon 5 μg/mL treatment for 48 h in LS180 cells (Herzog et al., 1993)
Cytarabine	1.3-fold ABCB1 induction upon 0.5 μM treatment for 24 h in HL60 leukemia cells (Prenkert et al., 2009)
Dadzein	1.7-fold ABCB1 induction upon 10 μM treatment for 4 weeks in Caco-2 cells (Lohner et al., 2007)
Daunorubicin	3-fold ABCB1 induction upon 1.5 μg/mL treatment for 4 h in CEM/A7R cells (Hu et al., 1995)
Daurunavir	1.7-fold ABCB1 induction upon 10 μM treatment for 72 h in hCMEC/D3 cells (Chan et al., 2013)
Depsipeptide	6.3-fold *ABCB1* mRNA induction upon 5 ng/mL treatment for 72 h in 108 renal carcinoma cells (Robey et al., 2006)
Dexamethasone	2.9- and 1.9-fold ABCB1 expression upon 50 mg/kg7day treatment for 96 h in intestine and liver, respectively, of Wistar rats (Kageyama et al., 2006)
Digoxin	92-fold *ABCB1* mRNA induction upon 1 μM treatment for 72 h in T84 cells (Haslam et al., 2008b)
1,25-Dihydroxyvitamin D3	5.9-fold ABCB1 induction upon 2.5 μg/kg/day treatment for 8 days in fxr(-/-) mice kidney (Chow et al., 2011)
Diltiazem	4-fold *ABCB1* mRNA induction upon 10 μg/mL treatment for 48 h in LS180 cells (Herzog et al., 1993)
Docetaxel	Increased *ABCB1* expression upon 10 μM treatment for 48 h in LS180 cells (Harmsen et al., 2010)
Doxorubicin	Increased ABCB1 and *ABCB1* mRNA expression upon 3 μM treatments in MCF-7 cells (Mealey et al., 2002)
Doxycycline	8-fold increased ABCB1 expression upon 100 μg/mL treatment for 12 weeks in MCF-7 cells (Mealey et al., 2002)
Efavirenz	8-fold increased ABCB1 expression upon 10 μM treatment for 72 h in hCMEC/D3 cells (Chan et al., 2013)
Epigallocatechin-3-gallate	2.2-fold ABCB1 induction upon 10 μM treatment for 4 weeks in Caco-2 cells (Lohner et al., 2007)
Epirubicin	3-fold ABCB1 induction upon 1.5 μg/mL treatment for 8 h in CEM/A7R cells (Hu et al., 1995)
Eriodictyol	2.1-fold ABCB1 induction upon 10 μM treatment for 4 weeks in Caco-2 cells (Lohner et al., 2007)
Erlotinib	2.9-fold ABCB1 induction upon 10 μM treatment for 48 h in LS180V cells (Harmsen et al., 2013)
Erythromycin	3.3-fold ABCB1 induction upon 15 mg/kg treatment for 7 days in Rhesus monkey livers (Gant et al., 1995)
β-Estradiol	4-fold *ABCB1* mRNA induction upon 50 μM treatment for 48 h in LS180 cells (Abuznait et al., 2011a)
Ethinylestradiol	1.6-fold ABCB1 induction upon 0.5 pM treatment for 48 h in Caco-2 cells (Arias et al., 2014)
Fascaplysin	7-fold ABCB1 induction upon 1 μM treatment for 48 h in LS180 cells (Manda et al., 2016)
Flavone	3-fold ABCB1 induction upon 10 μM treatment for 4 weeks in Caco-2 cells (Lohner et al., 2007)
5-Fluorouracil	4.5-fold ABCB1 induction upon 2 μg/mL treatment for 72 h in CEM/A7R cells (Hu et al., 1999)
Fluticasone	+87% ABCB1 induction upon 50μM treatment for 72 h in Caco-2 cells (Crowe and Tan, 2012)
Gefinitib	3-fold ABCB1 induction upon 10 μM treatment for 48 h in LS180V cells (Harmsen et al., 2013)
Genistein	2-fold ABCB1 induction upon 10 μM treatment for 4 weeks in Caco-2 cells (Lohner et al., 2007)
Hyperforin	3-fold ABCB1 induction upon 150 nM treatment for 48 h in LS180 cells (Abuznait et al., 2011a)
Hypericin	7-fold ABCB1 induction upon 3 μM treatment for 72 h in LS180V cells (Perloff et al., 2001)
Idarubicin	4-fold ABCB1 induction upon 0.1 μg/mL treatment for 24 h in CEM/A7R cells (Hu et al., 1999)
Indinavir	1.6-fold ABCB1 induction upon 10 μM treatment for 72 h in LS180V cells (Perloff et al., 2000)
Insulin	+89% ABCB1 induction upon 10 U/kg/day treatment for 5 weeks in Sprague-Dawley rats (Liu et al., 2008)
Ivermectin	2-fold ABCB1 induction upon 10 μM treatment for 72 h in JWZ murine hepatic cells (Menez et al., 2012)
Lopinavir	2.3-fold ABCB1 induction upon 10 μM treatment for 72 h in hCMEC/D3 cells (Chan et al., 2013)

(*continued on next page*)

Table 4 (*continued*)

Drugs inducing ABCB1 expression	
Inducer	Action
Mangiferin	2.4-fold ABCB1 induction upon 200 μM treatment for 72 h in HK2 cells (Chieli et al., 2010)
Methylprednisolone	+50% ABCB1 induction upon 50 μM treatment for 72 h in Caco-2 cells (Crowe and Tan, 2012)
Midazolam	5.9-fold ABCB1 induction upon 10 μM treatment for 72 h in LS180 cells (Schuetz et al., 1996)
Mitoxantrone	30/100-fold *ABCB1* mRNA induction upon 1 μg/mL treatment for 8 h in NIH 3T3 cells (Schrenk et al., 1996)
Morphine	2-fold ABCB1 induction upon 20 mg/kg/day treatment for 5 days in Sprague-Dawley rat brains (Aquilante et al., 2000)
Myricetin	2.5-fold ABCB1 induction upon 10 μM treatment for 4 weeks in Caco-2 cells (Lohner et al., 2007)
Naringenin	1.8-fold ABCB1 induction upon 10μM treatment for 4 weeks in Caco-2 cells (Lohner et al., 2007)
Nelfinavir	3.5-fold ABCB1 induction upon 10 μM treatment for 72 h in LS180V cells (Perloff et al., 2000)
Nevirapine	1.6-fold ABCB1 induction upon 15 μM treatment for 72 h in hCMEC/D3 cells (Chan et al., 2013)
Nicardipine	6-fold *ABCB1* mRNA induction upon 10 μM treatment for 48 h in LS180 cells (Herzog et al., 1993)
Nifedipine	4-fold *ABCB1* mRNA induction upon 5 μg/mL treatment for 48 h in LS180 cells (Herzog et al., 1993)
Nilotinib	3.6-fold *ABCB1* induction upon 10 μM treatment for 48 h in LS180V cells (Harmsen et al., 2013)
Oleocanthal	2.3-fold *ABCB1* induction upon 25 μM treatment for 48 h in LS180 cells (Abuznait et al., 2011b)
Ouabain	3.4-fold *ABCB1* mRNA induction upon 1 μM treatment for 24 h in HT29 cells (Riganti et al., 2009a)
Oxycodone	4-fold ABCB1 induction upon 5 mg/kg/day treatment for 8 days in Sprague-Dawley rat livers (Hassan et al., 2007)
Paclitaxel	Increased ABCB1 expression upon 10 μM treatment for 48 h in LS180 cells (Harmsen et al., 2010)
Parthenolide	6-fold *ABCB1* mRNA induction upon 10 μM treatment for 6 h in HT29 cells (Riganti et al., 2009b)
Phenobarbital	14-fold ABCB1 induction upon 1 mM treatment for 72 h in LS180 cells (Schuetz et al., 1996)
Phenothiazine	6.5-fold ABCB1 expression upon 50 mg/kg/day treatment for 72 h in bile canalicular membrane vesicles of Wistar rats (Watanabe et al., 1995)
Phenytoin	ABCB1 induction upon 50 mg/kg/day treatment for 21 days in Sprague-Dawley rat brains (Wen et al., 2008)
Piperine	2-fold ABCB1 expression upon 100 μM treatment for 72 h in Caco-2 cells (Han et al., 2008)
Pregnenolone-16α- carbonitrile	+53% ABCB1 expression upon 5 μM treatment for 6 h in brain capillaries from CB6F1 rats (Bauer et al., 2006)
Propranolol	4-fold ABCB1 induction upon 200 μM treatment for 24 h in LS180 cells (Collett et al., 2004)
Quercetin	2.5-fold ABCB1 induction upon 10 μM treatment for 4 weeks in Caco-2 cells (Lohner et al., 2007)
Rapamycin	4.9-fold ABCB1 induction upon 10 μM treatment for 72 h in LS180 cells (Schuetz et al., 1996)
Reserpine	29-fold ABCB1 induction upon 10μM treatment for 72 h in LS180 cells (Schuetz et al., 1996)
Retinoic acid	20-fold *ABCB1* mRNA induction upon 5 μM treatment for 72 h in SK-N-SH cells (Bates et al., 1989)
Rifampicin	16-fold ABCB1 induction upon 10 μM treatment for 72 h in LS180 cells (Schuetz et al., 1996)
Ritonavir	4.2-fold ABCB1 induction upon 10 μM treatment for 72 h in LS180V cells (Perloff et al., 2000)
Saquinavir	2.4-fold ABCB1 induction upon 10 μM treatment for 72 h in LS180V cells (Perloff et al., 2000)
Sildenafil	2.1-fold ABCB1 induction upon 5 μM treatment for 96 h in LS180 cells (Weiss et al., 2013)
Tacrolimus	3.2-fold ABCB1 induction upon 10 μM treatment for 72 h in LS180 cells (Schuetz et al., 1996)
Tadalafil	3.3-fold ABCB1 induction upon 20 μM treatment for 96 h in LS180 cells (Weiss et al., 2013)
Tamoxifen	6-fold ABCB1 induction upon 50 mg/kg/day treatment for 7 days in Rhesus monkey livers (Gant et al., 1995)
Taxifolin	1.8-fold ABCB1 induction upon 10 μM treatment for 4 weeks in Caco-2 cells (Lohner et al., 2007)
γ-Tocotrienol	2.4-fold ABCB1 induction upon 25 μM treatment for 48 h in LS180 cells (Abuznait et al., 2011b)
Trichostatin A	20-fold *ABCB1* mRNA induction upon 100 ng/mL treatment for 24 h in SW620 cells (Jin and Scotto, 1998)
Verapamil	3-fold ABCB1 induction upon 10 μM treatment for 72 h in Caco-2 cells (Anderle et al., 1998)
Vinblastine	7.5-fold ABCB1 induction upon 0.011 μM treatment for 72h in Caco-2 cells (Anderle et al., 1998)
Vincristine	ABCB1 induction upon 0.1 μM treatment for 48 h in LS180 cells (Harmsen et al., 2010)

nature, structure and origin. *ABCB1* inducers include many drugs (among which several chemotherapeutic drugs and tyrosine kinase inhibitors, usually also *ABCB1* substrates), natural compounds and marine compounds, and phosphodiesterase-5 inhibitors.

The *ABCB1* amplicon

MDR and the genes in the human ABCB1 amplicon

The human *ABCB1* (*MDR1*) gene resides in chromosome 7q21.1 region (Callen et al., 1987); its ability to confer MDR when overexpressed or amplified (Callen et al., 1987; Fojo et al., 1987; Schoenlein, 1993; Scotto et al., 1986; Van der Bliek et al., 1986b) and the increase in *ABCB1* expression upon chemotherapeutic drug treatment (Abolhoda et al., 1999; Atalay et al., 2006; Brugger et al., 2002; Chin et al., 1990; Gekeler et al., 1988; Hu et al., 1995; Liu et al., 2002; Park et al., 1994; Schneider et al., 1993) have been largely reported throughout the years.

The amplification of chromosome 7q21 region in neuroblastoma cancer cell lines (Flahaut et al., 2006), as well as the increased copy number of 7q21.12 region (including *ABCB1* gene) in lung cancer cells (Kitada and Yamasaki, 2007) and in leukemia cells (Kadioglu and Efferth, 2016) correspond to drug resistance, suggesting the possible participation of other genes in the development of the MDR phenotype.

Genomic instability and chromosomal rearrangements often affect cancer cells, resulting in genomic amplification, frequently translated in an increased copy number of the *ABCB1* gene that leads to a marked transactivation of *ABCB1* gene overexpression (Chen et al., 2002; Duesberg et al., 2007; Katoh et al., 2005; Kim et al., 2015; Mickley et al., 1997; Pang et al., 2005). These genomic rearrangements may either occur in upstream regions far from the *ABCB1* promoter or may affect genomic alterations along the 7q chromosomal arm that can correlate with *ABCB1* activation (Chen et al., 2002; Knutsen et al., 1998).

Genomic investigations focusing on the *ABCB1* amplicon have been undertaken in order to understand whether or not the surrounding genes might have some role in the development of the MDR phenotype or if they were co-amplified or suppressed in resistance-induced cancer cell lines. *ABCB1* gene expression can be increased up to 1000-fold in lung cancer cells with acquired paclitaxel resistance, showing a surprising discrepancy between the gene copy number and the expression level. Along with *ABCB1* gene expression enhancement, within the same amplicon (7q21.12), there is a concomitant co-amplification of *RPIB9* (*RUNDC3B*) and *ADAM22* with an increased fold change of 38.5 and 27.7, respectively (Yabuki et al., 2007).

Taxane-induced MDR ovarian cancer cell lines showed a regional activation on chromosome 7q21.11-13 of about 22 co-expressed genes over an area of 8Mb, surrounding the *ABCB1* gene. These genes include *SRI* (Sorcin), *MGC4175* (*TMEM243*), *DMTF1*, *CROT*, *ABCB1*, *ABCB4*, *ADAM22*, *RUNDC3B*, *DBF4* and the regional activation was driven by

gene copy number gains (Wang et al., 2006). Another study on taxane-resistant breast cancer cell lines reported gains in gene copy number on chromosome 7, specifically concerning ABC transporters (*ABCB1*, *ABCB4*), *SRI*, *DMTF1*, *SLC25A40* and *CROT*, all belonging to the *ABCB1* amplicon (Hansen et al., 2016). Furthermore, a whole-genome characterization study on chemoresistant ovarian cancer cells reported an intergenic deletion between *ABCB1* and *SLC25A40* genes and that results in the creation of a fused transcript, with no evidence of this event in drug-sensitive tumor samples. Additional transcriptome investigations showed the increase of *ABCB1-SLC25A40* fused transcript in chemoresistant human ovarian cancer samples and the decrease of SLC25A40 in drug sensitive specimens (Patch et al., 2015).

However, the genomic rearrangements and the high copy number cannot explain by themselves the unexpected high level increase in gene expression, suggesting that other mechanisms as such transcriptional upregulation, mRNA stabilization, post-transcriptional regulation and epigenetic modifications may contribute to this enhanced gene expression. Interestingly, non-coding RNAs as miRNAs and long non-coding RNAs (lncRNA) may exert post-transcriptional regulatory functions in cancer cells, giving rise to metastatic or drug-resistant phenotypes. Indeed in the *ABCB1* amplicon a lncRNA (*TP53TG1*) resides, reported to be down-regulated in A549 cisplatin-resistant lung cancer cells (Yang et al., 2013). On the other hand, deletions in the *ABCB1* genes locus in breast cancer patients determine a 2–8-fold decreased expression of these MDR locus-related genes; cancer patients harboring these deletions display a better response to neoadjuvant chemotherapy (Litviakov et al., 2016).

Overall, many published studies report that a genomic amplification of chromosome 7q21.12 region, where *ABCB1* and related genes reside (Fig. 5), occurs in MDR tumors, and that amplification and or overexpression of these genes contributes to the MDR phenotype (Bonte et al., 2008; Chao et al., 1991; Cheng et al., 2013; Finalet Ferreiro et al., 2014; Flahaut et al., 2006; Hansen et al., 2016; Januchowski et al., 2017; Kadioglu and Efferth, 2016; Kitada and Yamasaki, 2007; Lee et al., 2017; Litviakov et al., 2016; Patch et al., 2015; Sasi et al., 2017; Torigoe et al., 1995; Van der Bliek et al., 1988; Van der Bliek et al., 1986a; Van der Bliek et al., 1986b; Yabuki et al., 2007). The core of the amplicon is formed by the genes *Sorcin (SRI), ADAM22, DBF4, SLC25A40, RUNDC3B (RPIP9), ABCB1, ABCB4, CROT*, *TP53TG1 lncRNA, TMEM243 (MGC4175)* and *DMTF1 (DMP1)* (Fig. 5). All of these genes have been found to be associated with tumorigenesis and MDR; very important contributions to the MDR phenotype are due in particular to the overexpression of DBF4 and Sorcin, which are considered as important markers of poor prognosis and drivers of MDR in several types of cancers, acting on different mechanisms with respect to *ABCB1*. Selective inhibitors of Sorcin expression and of CDC7-DBF4 activity have been recently developed, and are considered good potential anti-tumor candidates (see below).

ABCB1 amplicon genes: regulation, cancer and MDR

Sorcin (SRI)

Sorcin was originally isolated by Meyers and Biedler in 1981 as a soluble, low molecular weight protein in hamster lung cancer cell line resistant to vincristine, and this feature was used to give sorcin the name of Sorcin (SOluble Resistance-related Calcium binding protein) (Meyers and Biedler, 1981). Sorcin belongs to the penta EF-hand (PEF) protein family; as other members of this family, upon calcium binding, Sorcin undergoes a conformational change, leading to the exposure of hydrophobic surfaces that enable the interaction with membranes and other binding partners (Ilari et al., 2015). Among them, Sorcin binds and controls proteins involved in the regulation of intracellular calcium concentration as Ryanodine Receptors (RyRs), Sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA pumps) and Na^{+}/Ca^{2+} exchanger (NCX), leading to the termination of contraction and the onset of relaxation (Colotti et al., 2014; Franceschini et al., 2008; Zamparelli et al., 2010). Sorcin is phosphorylated by several kinases involved in cell cycle progression or calcium homeostasis, regulating calcium load in storage organelles and vesicle trafficking (Lalioti et al., 2014).

Sorcin is overexpressed in many cancers of distinct tissue origin, especially those displaying the *ABCB1*-dependent MDR phenotype. The *Sorcin* gene resides in the same amplicon of *ABCB1* and was identified as a resistance–related gene because its genomic locus is co-amplified along with *ABCB1* in cancer cells displaying the MDR phenotype (Van der Bliek et al., 1986a). Although for many years Sorcin overexpression was thought to be an accidental by-product of this genomic co-amplification process (Van der Bliek et al., 1988), a large body of published studies considered Sorcin both as a marker and a cause of MDR. Sorcin is found overexpressed in many human tumors including lymphoma, leukemia, gastric cancer, lung cancer, adenocarcinoma, breast cancer, nasopharyngeal cancer and ovarian cancer, particularly in malignancies with the *ABCB1*-dependent MDR phenotype (Deng et al., 2010; Gao et al., 2015; Padar et al., 2004; Qi et al., 2006; Qu et al., 2010; Sun et al., 2017; Tan et al., 2003; Yamagishi et al., 2014; Yang et al., 2008; Zhou et al., 2006).

Many studies have dissected the role of Sorcin in MDR cancer types, indicating its role as an oncoprotein. In doxorubicin-resistant K562/A02 leukemia cell lines, Sorcin was found consistently up-regulated compared to the drug-sensitive parental cell line, and the overexpression in the resistant line conferred MDR (Hu et al., 2013; Qi et al., 2006; Sun et al., 2017; Yamagishi et al., 2014; Zhou et al., 2006). Sorcin expression levels in leukemia patients generally correlate with low-response to chemotherapies and poor prognosis. Moreover, Sorcin overexpression by gene transfection resulted in increased drug resistance to a variety of chemotherapeutic agents, including doxorubicin, etoposide, homoharringtonine and vincristine in K562 cells; and conferred drug resistance to vincristine, adriamycin, paclitaxel and 5-fluorouracil in SGC7901 cells, ovarian and breast cancer, thereby confirming the ability of Sorcin overexpression to enhance drug resistance. Consistently, inhibition of Sorcin expression by RNA interference techniques led to reversal of MDR in many tumor cell lines, as MDR K562/A02 and Sorcin-transfected K562, MCF-7/A02, HeLa, colorectal cancer and CNE2/DDPls (Colotti et al., 2014; Dabaghi et al., 2016; Gao et al., 2015; Gong et al., 2014; Hamada et al., 1988; He et al., 2011; Hu et al., 2013; Hu et al., 2014; Kawakami et al., 2007; Liu et al., 2014; Maddalena et al., 2011; Parekh et al., 2002; Sun et al., 2017; Zhou et al., 2006).

Additionally, a recent study showed that directed siRNA-Sorcin silencing decreased *ABCB1* protein levels in a H1299 lung cancer cell line, with a consequent increase in rhodamine123 efflux out of the cells, confirming a direct relationship between Sorcin and regulation of *ABCB1* transport activity in MDR cells. Besides, Sorcin is able to bind

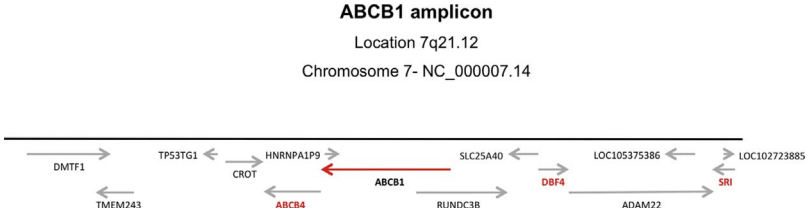

Fig. 5. The *ABCB1* amplicon. Genes in the 7q21.12 region are shown.

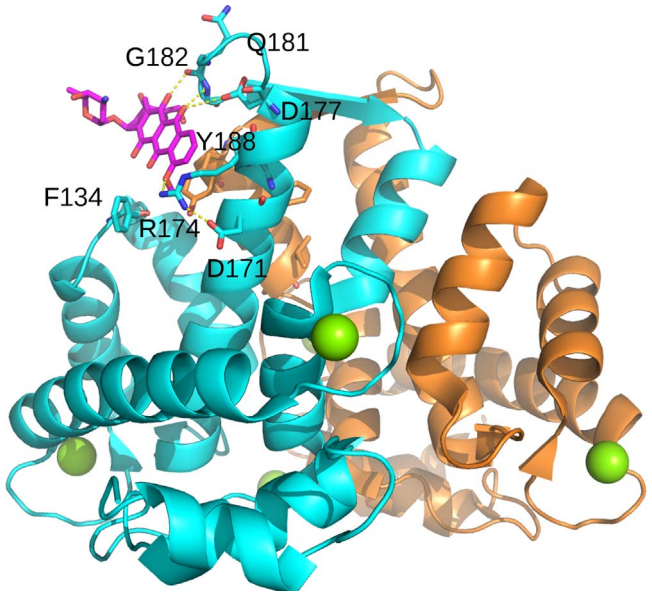

Fig. 6. Structure of Sorcin in complex with doxorubicin. The two monomers of Sorcin are indicated in cyan and orange, and doxorubicin in magenta sticks. The residues involved in doxorubicin binding are indicated and represented as sticks; calcium ions are represented as green spheres (Genovese et al., 2017). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

directly doxorubicin, paclitaxel, vinblastine and cisplatin, acting as a protein drug sink thus hampering nuclear uptake of doxorubicin, thus allowing cell survival (Genovese et al., 2017). Sorcin is highly expressed and is able to bind doxorubicin with high affinity on the EF5-hand (Fig. 6), which does not bind calcium and is involved in homodimer formation (Genovese et al., 2017).

Furthermore, Sorcin silencing inhibits the epithelial-to-mesenchymal (EMT) transition in the human breast cancer MDA-MB-213 cell line, possibly via E-cadherin and VEGF expression, and reduces breast cancer metastasis, while Sorcin overexpression increases migration and invasion *in vitro* (Hu et al., 2014). Sorcin expression levels are significantly up-regulated in hepatocellular carcinoma (HCC) tumors compared with matched adjacent non-tumor liver tissues and normal liver tissues, and expression levels correlate with HCC metastasis. HCC patients with high Sorcin expression had both shorter survival and higher recurrence than those with low Sorcin expression. Sorcin expression is therefore an independent and significant risk factor for survival and recurrence of HCC patients. Sorcin can promote HCC and colorectal cancer cell proliferation, migration, and invasion *in vitro*, and facilitate cancer growth, metastasis and EMT, by activating extracellular signal-regulated kinase (ERK) and/or PI3K/Akt signaling pathways (Lei et al., 2017; Tong et al., 2015).

Several groups are currently studying the role of Sorcin in the development of MDR in cancer cells, disclosing intriguing findings. Yamagishi and collaborators found that Sorcin expression correlates with *ABCB1* up-regulation, indeed Sorcin induced *ABCB1* expression through a cAMP response element (CRE) located within −716 and −709 bp in the *ABCB1* gene. Consistently, they found that up-regulation of Sorcin induces *ABCB1* expression through the inducible activation of CREB (cAMP response element-binding protein) pathway increasing the phosphorylation of CREB1 and its binding to the CRE binding site in the *ABCB1* promoter (Yamagishi et al., 2014).

A shorter isoform (18 KDa) of Sorcin, identified to be located in mitochondria, is the aim of the quality control system operated by ER-associated TRAP1. The latter protein is up-regulated in several human tumors and can modulate apoptosis; indeed, transfection experiments of a TRAP1 deletion mutant in TRAP1-silenced cells increased the expression of mitochondrial sorcin and protected cells from apoptosis upon treatment with ER stress agents and paclitaxel (Maddalena et al., 2013), suggesting a putative post-transcriptional regulation of sorcin expression. Sorcin, loading calcium in ER and mitochondria, participates in the prevention of ER stress and unfolded protein response, and increases cell escape from apoptosis (Lalioti et al., 2014; Maddalena et al., 2011; Maddalena et al., 2013), shifting the equilibrium between cell life and death towards proliferation in MDR cancer cells overexpressing Sorcin.

For these reasons, Sorcin is an interesting oncoprotein and MDR marker, able to bind several chemotherapeutic drugs, whose overexpression results in the MDR phenotype. Sorcin expression is directly linked to *ABCB1* up-regulation, and is itself involved in regulation of the *ABCB1*-dependent MDR phenotype. The modulation of Sorcin expression and activity (Li et al., 2016a; Sun et al., 2017) is emerging as a possible strategy for overcoming tumorigenesis, cancer-related EMT and MDR.

ADAM22

ADAM22 is a non-catalytic metalloprotease involved in both regulation of cell adhesion and spreading and inhibition of cell proliferation. It acts as a neuronal receptor for LGI1 and as a ligand with the integrin αvβ3 and also with integrin dimers containing α6 or α9 in the brain (D'Abaco et al., 2006), thus regulating synaptic transmission (Fukata et al., 2006; Liu et al., 2009). In ovarian cell lines and in two different human breast cancer cell lines, MCF-7 and MDA-MB-231, exposure to docetaxel induced resistance to the drug, accompanied by overexpression of ADAM22 and many other proteins of the *ABCB1* amplicon (Hansen et al., 2016; Wang et al., 2006). Microarray analysis uncovered that ADAM22 is overexpressed in doxorubicin-resistant osteosarcoma cell lines (Ma et al., 2017). ADAM22 is a target of SRC1, steroid co-activator protein 1; in this respect, SRC1 overexpression enhances ADAM22 expression in endocrine-sensitive MCF-7 breast cancer cells. An enrichment of SRC1 was found at the *ADAM22* promoter through chromatin immunoprecipitation (ChIP) experiments in endocrine-resistant breast cancer but not in the sensitive one, suggesting the ability of this protein to promote tumor progression. SRC1-dependent ADAM22 expression in response to tamoxifen has been observed; ADAM22 is considered a prognostic and therapeutic drug target in the treatment of endocrine-resistant breast cancer. Further, *ADAM22* gene methylation is associated with malignant transformation of ovarian endometriosis (Bolger and Young, 2013; McCartan et al., 2012; Ren et al., 2014).

DBF4

DBF4 is a positive regulatory subunit of the CDC7 kinase that plays a central role in DNA replication and cell proliferation, being essential for the progression through the S phase. Indeed, the DBF4-CDC7 complex phosphorylates the Mcm2 helicase at Ser40 and Ser53, thereby allowing the initiation of eukaryotic DNA replication. CDC7 levels appear to be constant throughout the cell cycle, whereas DBF4 levels have a burst in late G1 phase and decrease at the end of mitosis (Cheng et al., 2013; Pasero et al., 1999; Weinreich and Stillman, 1999). CDC7-DBF4 is essential for the initiation of DNA replication; during the G1 phase CDC7-DBF4 is down-regulated by RAD53-dependent phosphorylation of DBF4, which allows origin licensing and prevents premature replication initiation (Zegerman and Diffley, 2010), while in the S phase, the intra-S-phase checkpoint is activated by CDC7-DBF4, by removing the inhibitory activity of Mcm4 (Sheu and Stillman, 2010).

DBF4 has three motifs, N, M and C, which regulate its interaction with various binding partners. The N motif is located at the N-terminus of the protein and is believed to interact with ORC and RAD53, a kinase required for check-point mediated cell cycle arrest (Duncker et al., 2002). The C and N motifs are involved in the response towards genotoxic agents, while less is known about the M motif (Fung et al., 2002), even though it seems to have a role in cell proliferation, since it mediates the interaction with Mcm2 (Varrin et al., 2005).

Both CDC7 and DBF4 are overexpressed in many cancer cell lines and primary tumors; tumor cell lines with increased CDC7 protein levels also have increased DBF4, whose gene can be present in extra copies in some tumors (Bonte et al., 2008; Cheng et al., 2013). Overexpression of CDC7-DBF4 has been reported in many human tumors, including ovarian cancer, colorectal cancer, melanoma, diffuse large B-cell lymphoma, oral squamous cell carcinoma and breast cancer, and is correlated with poor prognosis and advanced grade tumor grade (Bonte et al., 2008; Chen et al., 2013a; Cheng et al., 2013; Choschzick et al., 2010; Clarke et al., 2009; Hou et al., 2012; Kulkarni et al., 2009; Nambiar et al., 2007). A high correlation between loss of p53 function and up-regulation of DBF4 and CDC7 is observed in primary breast cancer, suggesting that the increased amount of CDC7-DBF4 is presumably a common driver mutation for this malignancy (Bonte et al., 2008). Higher DBF4-expressing melanomas were associated with lower relapse-free survival, and higher proliferation (Nambiar et al., 2007). High expression of CDC7-DBF4 correlates with poor prognosis in patients with large B-cell lymphoma (Hou et al., 2012), and is a marker of resistance to DNA-damaging compounds in oral carcinoma (Cheng et al., 2013), and a marker of chemoresistance to cisplatin, mitomycin C, taxol, hydroxyurea and etoposide in lung adenocarcinoma and bladder cancer (Sasi et al., 2017). 6-fold overexpression of DBF4 was recently found in docetaxel-resistant prostate cancer cells with respect to docetaxel-sensitive cells (Lee et al., 2017), and overexpression of DBF4 was acquired during progression towards docetaxel resistance in taxane-treated breast cancer cells (Hansen et al., 2016).

MiR29a regulates BPDE-induced DNA damage response (and determines increased cell lethality) through repression of CDC7-DBF4 kinase expression in lung cancer cells, while overexpression of CDC7-DBF4 determines resistance to BPDE (Barkley and Santocanale, 2013). Further, CDC7-DBF4 is highly expressed in colorectal cancer and is considered a potential therapeutic target in cancers with high p53 expression and an independent prognostic biomarker in colorectal cancer enabling to select patients for adjuvant anti-CDC7-DBF4 treatment (Melling et al., 2015). Since the CDC7-DBF4 kinase is considered a novel and promising cancer target, inhibitors of the CDC7-DBF4 kinase have been recently developed, and are considered good potential antitumor candidates: in particular, the benzofuropyrimidinone XL413 is a selective inhibitor, able to arrest cell cycle and inhibit tumor growth in a Colo-2015 xenograft model (Koltun et al., 2012); pyridinyl-pyrrole derivative compounds (such as PHA-767491) have antitumor activity on glioblastoma, pancreatic cancer, breast cancer and other tumors (Erbayraktar et al., 2016; Montagnoli et al., 2008; Natoni et al., 2011; Sasi et al., 2017).

SLC25A40

SLC25A40 belongs to the solute carrier 25 (SLC25) nuclear-encoded protein family residing on mitochondrial membranes, and in some cases in other organelle membranes, and protects mitochondria from oxidative stress (Palmieri, 2013). These proteins are widely expressed in eukaryotic cells and they possess conserved structural features as, a tripartite structure, six hydrophobic transmembrane α-helices and a 3-fold repeated signature motif. Members of this family can vary by the nature and size of the transported substrates, for the modes of transport and driving force (Palmieri, 2013).

SLC25A40 mRNA and SLC25A40 protein are highly expressed in brain and central nervous system (Haitina et al., 2006). Valach and coworkers reported a relationship between SLC25A40 overexpression and tumorigenesis, and they found it to be also activated in cancer-associated fibroblasts (Valach et al., 2012).

SLC25A40 was reported to be overexpressed in drug-resistant cancer cell (Hansen et al., 2016), and an *ABCB1*-SLC25A40 fused transcript product was observed in resistant ovarian cancer cells (Patch et al., 2015); its precise role in MDR has not been fully elucidated yet.

RUNDC3B (RPIP9)

RUNDC3B (RUN domain-containing protein 3B) function has not been determined yet, but it is known to contain a RUN domain used to interact with RAP2 (explaining the alternative name RAP2 binding-protein 9, RPIP9), a RAS-protein involved in the MAPK cascade. RUNDC3B also contains a binding site for MAPK signaling pathway intermediates, being in the middle between RAP2 and MAPK pathway, thus it is likely to be involved in the RAS-like GTPase signaling pathway (Burmeister et al., 2017; Finalet Ferreiro et al., 2014).

Both RUNDC3B isoforms are highly expressed in brain tissue; RUNDC3B is activated in tumorigenic breast cancer cell lines and in the breast cancer primary tumor (Raguz et al., 2005).

RUNDC3B is in the same amplicon of *ABCB1* and is transcribed from the complementary DNA strand of the *ABCB1* gene (Fig. 5); it may interfere with alternative regulation of *ABCB1* promoter regulation. Treatment with histone deacetylases inhibitors (iHDACs) of colon and pancreatic carcinomas results in an increased expression of *ABCB1* and *RUNDC3B* mRNAs (Balaguer et al., 2012). In addition, both *ABCB1* and RUNDC3B overexpression was found in breast cancer cells compared to normal tissues, with a correlation between this overexpression and poor prognosis in breast cancer (Raguz et al., 2005).

Integrative genomic studies report an increased expression of RUNDC3B in paclitaxel-resistant ovarian cancer cells (Januchowski et al., 2017) and a correlation between tumor growth advantage and chemoresistance in hepatosplenic T-cell lymphoma where a gain of chromosome 7q arm corresponds to an up-regulation of RUNDC3B (Finalet Ferreiro et al., 2014).

ABCB4 (PGY3, MDR3)

ABCB4, a member of ABC transporters, is encoded by the *ABCB4 (MDR3)* gene, and is an ATP-dependent phospholipid efflux translocator and a positive regulator of biliary lipid secretion, acting as a phospholipid flippase which translocates phosphatidylcholine (PC) from liver hepatocytes into bile, thus being essential for bile formation. It can also influence the composition of lipids of the plasma membrane, recruiting PC, phosphatidylethanolamine (PE) and sphingomyelin (SM) towards non-raft membrane domain or contributing to cholesterol and SM-enrichment in raft membranes in hepatocytes (Morita and Terada, 2014). *ABCB4* cooperates with ATP8B1 to protect hepatocytes from the detergent activity of bile salts (Groen et al., 2011).

ABCB4 and *ABCB1* belong to ABC transporters superfamily, and are encoded by fused genes, arising from an endoduplication event, and often co-amplified because of their genomic proximity (about 500 Kb); they share 80% nucleotide sequence identity, and 77% identity and 82% similarity in the amino acidic sequence (Callen et al., 1987; Torigoe et al., 1995; Van der Bliek et al., 1987; Van der Bliek et al., 1988).

ABCB4 is well expressed in the liver; its substrates are PC and some hydrophobic drugs, while in MDR cells *ABCB4* is particularly selective for paclitaxel and vinblastine (Gottesman et al., 2002; Thomas and Coley, 2003). *ABCB4* is co-amplified with *ABCB1* in several MDR cancer cell lines. In doxorubicin-resistant colon cancer cell lines, its mRNA is up-regulated up to 40-fold compared to parental cell lines, and this amplification is possibly due to the concomitant amplification of the *ABCB1* gene (Chao et al., 1991). A dose-dependent increase in *ABCB1 and ABCB4* levels is observed in doxorubicin-, paclitaxel- and vincristine-resistant cancer cell lines upon drug selection; further, in some of these tumor cell lines, up-regulation of *ABCB4* was higher than that of *ABCB1*, suggesting a compensatory mechanism in drug resistance when *ABCB1* is not overexpressed, and an active role for *ABCB4* in MDR, driven preferentially towards doxorubicin and paclitaxel (Januchowski et al., 2017; Januchowski et al., 2014a; Januchowski et al., 2014b).

The increased mRNA and protein levels of *ABCB4* along with those of *ABCB1* in acquired paclitaxel-resistant breast cancer cells highlights a role of *ABCB4* in taxane resistance, since it was shown that directed siRNA silencing towards *ABCB1* did not restore the complete paclitaxel

sensitivity in these cancer cell lines co-overexpressing both *ABCB1 and ABCB4* (Nemcova-Furstova et al., 2016). This matter is still conflicting, as while *ABCB4* silencing in paclitaxel-resistant ovarian cancer cells does not fully restore drug sensitivity, *ABCB1* silencing completely reverses MDR (Duan et al., 2004a). However, it seems that transcriptional regulation of *ABCB4* gene expression relies mostly on *ABCB1* co-amplification; nevertheless, *ABCB4* has a role in drug resistance, preferentially in taxanes, hence complementing the protective role of *ABCB1* against various MDR type anticancer drugs

CROT

Carnitine *O*-octanoyltrasferase is a peroxisomal protein that plays a role in lipid metabolism and fatty-acid beta-oxidation. DNA copy increase and increased expression of CROT, together with that of other proteins of the 7q21.11-13 chromosomal region, was observed upon progressive administration of paclitaxel and docetaxel to 18 ovarian cancer cell lines (Wang et al., 2006), and of docetaxel to the MCF-7 breast cancer cell line (Hansen et al., 2016). MiR-33 co-downregulates the expression of ABC transporters and CROT (Fernandez-Hernando et al., 2011).

TP53TG1 lncRNA

TP53TG1 is a p53-induced lncRNA, which is activated upon DNA damage and acts as a tumor suppressor, contributing to p53 response to DNA damage (Diaz-Lagares et al., 2016). It was reported to bind YBX1 DNA/RNA binding protein, preventing its nuclear localization and subsequent activation of oncogenes (Diaz-Lagares et al., 2016). The first evidence of its down-regulation came from microarray experiments performed on A549 cisplatin-resistant lung cancer cell lines (Yang et al., 2013). In colorectal cancer cells the *TP53TG1* promoter undergoes a hypermethylation that causes the release of the YBX1 protein and subsequent transcription of oncogenes, resulting in an MDR phenotype (Lizarbe et al., 2017). The same findings were reported by Diaz-Lagares and coworkers in other cancer cell lines (Diaz-Lagares et al., 2016).

Beside the epigenetic inactivation of *TP53TG1* transcription, its upregulation has been reported in T lymphocytes exposed to ionizing radiations, in colon cancer cells treated with bleomycin or cisplatin and in docetaxel-resistant breast cancer cells (Hansen et al., 2016; Kabacik et al., 2015; Takei et al., 1998). *TP53TG1* is the first lncRNA activated upon induction of double strand breaks (DSBs), confirming its activation upon cell stress and DNA damage (Kabacik et al., 2015). Additionally, overexpression of *TP53TG1* has been observed in glioma cells, compared to normal brain tissue. This up-regulation results in cell proliferation and migration, especially under glucose deprivation (Chen et al., 2017). Cellular *TP53TG1* lncRNA expression is up-regulated under stress conditions (and in docetaxel-resistant breast cancer cells), but its promoter can be epigenetically silenced in cancer cells leading to the development of MDR, suggesting a role in the development of intrinsic MDR.

TMEM243 (MM-TRAG, or MGC4175)

TMEM243 (MDR1- and mitochondrial taxol resistance-associated protein transmembrane protein 243) is a transmembrane protein that localizes at nuclei, mitochondria and cell membrane; it is expressed in all tissues with no reported differences between normal tissues and chemotherapy naïve cancer cells (Duan et al., 2004b), and is overexpressed in taxane-resistant ovarian cancer cells (Wang et al., 2006), a possible indication of a role in acquired MDR.

Microarray experiments reported an up-regulation in taxol- and doxorubicin-resistant cancer cell lines, compared to the non-treated cancer cells. Under these conditions, *TMEM243* is present as a single copy gene, and its overexpression is not due to genomic amplification or gene rearrangements (Duan et al., 2004b), suggesting a mechanism of acquired MDR. Furthermore its expression has been reported as associated with paclitaxel resistance in drug-resistant breast cancer cells (Dorman et al., 2016) and in doxorubicin-resistant osteosarcoma cell lines, where microarray and qPCR experiments showed a 2-fold upregulation (Rajkumar and Yamuna, 2008).

DMTF1 (DMP1)

DMTF1 (Cyclin-D binding myb-like transcription factor 1) is a transcriptional activator of CDN2A/ARF locus in response to RAS-RAF signaling promoting cell growth arrest p53-mediated. It binds to ARF activating its transcription and stimulating p53 quenching with oncogenic signaling pathways (RAS, HER2neu, C-MYC, cyclin D), thus acting as an oncosuppressor (Frazier et al., 2012; Fry et al., 2016). DMTF1 contains a cyclin D-binding domain, three central myb or myb-like domains, and two flanking acidic transactivation domains. The structure of the N-terminal, myb-like domain of DMTF1 has been solved by NMR (PDB accession code: 2LLK). In DMTF1, myb-like domains are able to bind both DNA and proteins. DMTF1 physically interacts with p53, preventing its ubiquitination by Mdm2, thus promoting nuclear localization of p53 (Frazier et al., 2012; Kendig et al., 2017). DMTF1 is highly expressed in terminally differentiated cells and experimental evidence showed that in hematopoietic cell lines, its repression occurred by WT1, which is expressed only in hematopoietic progenitors, thereby leading to leukemia (Tschan et al., 2008). Furthermore *DMTF1* mRNA is decreased in AML cell lines compared to normal granulocytes and treatment with ATRA restored normal levels of the *DMTF1* transcript (Inoue and Fry, 2016).

Van Dekken and collaborators reported a high level of amplification of genes residing on the 7q chromosome region in adenocarcinoma of the gastroesophageal junction, including *DMTF1* (van Dekken et al., 2006). Acquisition of docetaxel resistance in breast cancer cells correlates with overexpression of DMTF1, together with that of other proteins of the *ABCB1* amplicon (Hansen et al., 2016). On the other hand, the human *DMTF1* gene appears to be deleted in 40% of human non-small-cell lung carcinoma (NSCLC), that generally have normal levels of ARF and p53 (Sugiyama et al., 2008); corroborating results reported that *DMTF1* deletion in breast cancer cell lines brings about features of tumor aggressiveness renders p53 inactive (Fry et al., 2017). In addition, *DMTF1* transcription is repressed upon anthracycline treatment, thus leading to NF-kappaB-dependent repression of the Arf-p53 pathway; both *DMTF1*(-/-) and *ARF*(-/-) cells are anthracycline-resistant (Taneja et al., 2007).

Other researchers reported that *DMTF1* deletion cooperates with kRAS signaling for the development of cancer *in vivo*, and confirmed that it acts as a primary regulator of lung carcinogenesis, being a regulator of ARF-p53 pathway (Mallakin et al., 2007).

It has been observed that this deletion brings a consequent loss of *DMTF1* and leads to tumorigenesis in a mouse model as well; it has been noted that *DMTF1*(+/−) mice, harboring a copy of the gene, still developed tumors, suggesting a *DMTF1* haploinsufficiency (Inoue et al., 2007). The hemizygous copy of *DMTF1* gene is found at high frequency in breast cancer cells (Maglic et al., 2015), undergoing a fine post-transcriptional regulation. Indeed its mRNA is alternatively spliced to three variants (α,β,γ) that can exert different functions (Inoue and Fry, 2016). DMTF1γ has an unknown function, but interestingly α and β variants have two divergent functions; in breast cancer, the α variant is p53-dependent and acts as a tumor suppressor, whereas the β variant is p53-independent and acts as an oncogene. Furthermore, DMTF1 β/α ratio increases with neoplastic transformation, and high β variant expression is associated with a shorter survival rate in cancer. DMTF1β was also found overexpressed in primary breast cancer, with a negative impact on patients survival, and it does not activate ARF, suggesting that the β variant may antagonize α's dependent ARF activation, leading to cell proliferation and tumorigenesis (Inoue and Fry, 2016). Alternative splicing of DMTF1 transcript is a way for cancer cells to modulate survival and proliferation since it has been observed that 30% of breast cancer cells have higher amounts of β rather than α, and that the β mRNA is 43–55% higher in breast cancer while the β protein is increased by 60% in tumors, suggesting a fine post-transcriptional

regulation (Maglic et al., 2015). The DMTF1β variant can be thus considered a cancer biomarker, and proteins that activate the *DMTF1* promoter or stabilize the DMTF1α variant, lead to regression of tumor growth *in vitro* (Fry et al., 2017).

Another strategy of post-transcriptional regulation of the *DMTF1* gene is exerted by miR-155, an oncogenic microRNA. In bladder cancer tissues miR-155 reduces the expression of DMTF1, leading to cell cycle progression and enhancement of cancer cell growth (Peng et al., 2015).

DMTF1 expression regulation in cancer mainly relies on gene deletion, since it is generally considered as a haploinsufficient tumor suppressor, and also on post-transcriptional regulation that leads to its down-regulation, even though alternative splicing plays an intriguing role in the up-regulation of the oncogenic DMTF1 variant (Inoue and Fry, 2016).

Future perspectives

The idea of *ABCB1* as a major player in MDR is now outdated, and 4 generations of *ABCB1* transport inhibitors have been unexpectedly and disappointingly ineffective in the clinic. Emerging contributions to MDR in tumors continue to increase, and resistance to chemotherapeutic drugs is now considered a complicated puzzle, with an ever-increasing number of pieces, involved in many different functions, with complex and intricate connections, acting at multiple regulatory levels. Even at the single level of *ABCB1* expression, the co-amplification and/or co-expression of genes of chromosome 7q21 residing on the same amplicon is emerging as a factor that contributes and modulates MDR.

The contribution of *TP53TG1 lncRNA, TMEM243, SLC25A40, RUNDC3B, ADAM22,* and in particular of *SRI, ABCB4, DMTF1* and *DBF4* is now acknowledged as an important determinant of MDR. Deciphering their functions could pave the way for the development of novel clinically relevant strategies for therapeutic interventions in cancer. In addition, gene-targeting and expression modulation strategies, *e.g.* by the use of epigenetic drugs, non-coding RNAs or natural products can represent possible options, both for the improvement of the knowledge of the molecular basis of MDR and for drug discovery. CDC7-DBF4 inhibitors are already available and are considered good potential anti-tumor drug candidates: PHA-767491 and XL413 are selective inhibitors, with good antitumor activity vs. several tumors, such as glioblastoma, pancreatic cancer, colon and breast cancer (Erbayraktar et al., 2016; Montagnoli et al., 2008; Natoni et al., 2011; Sasi et al., 2017). The use of combined administration of drugs targeting *ABCB1*, Sorcin and CDC7-DBF4 could prove a viable and more effective therapeutic strategy against MDR tumors.

Conclusions

MDR continues to pose a dominant obstacle towards curative chemotherapy against various human cancers. ATP-driven efflux pumps, *ABCB1* in particular, are responsible for drug expulsion and have a significant role in conferring MDR upon various cancer cells, that develop cross-resistance to diverse anticancer drugs, resulting in the failure of chemotherapy in multiple malignancies (Ambudkar et al., 1999; Fletcher et al., 2016; Holohan et al., 2013; Li et al., 2016b; Sharom, 2011; Silva et al., 2015). Overexpression of *ABCB1* in tumors, particularly upon chemotherapeutic treatment, is possibly the major cause of treatment failure; notwithstanding the design of 4 generations of *ABCB1* transport inhibitors and the wealth of information on the biochemistry and substrate specificity of ABC transporters, translation of this knowledge from the bench to the bedside has proved to be unexpectedly difficult.

Many studies have shown that upon repeated treatment of cultured tumor cell lines with a plethora of anticancer drugs including for example taxenes, anthracyclines, *Vinca* alkaloids, epipodophyllotoxins and other chemotherapeutic drugs, amplification, and/or overexpression of a series of genes surrounding the genomic *ABCB1* locus is observed; altered levels of these proteins may correlate with the establishment of the MDR phenotype, and lead to poor clinical outcome. Genes in the *ABCB1* amplicon (with the exception of the tumor suppressor *TP53TG1* lncRNA) were generally up-regulated in many cancers, and especially in MDR tumors; all of these genes are directly involved in tumor growth and drug resistance and finely regulated in various modes, from canonical transcriptional upregulation to epigenetic and post-transcriptional control.

The genes in the *ABCB1* amplicon exert important roles for cell survival in cancer or MDR status, as p53-mediators of cell growth arrest (*TP53TG1* and DMTF1), cell cycle or cell proliferation regulators (DBF4 and ADAM22), mediators of signaling pathways (RUNDC3B), mitochondrial transmembrane proteins (SLC25A40 and TMEM243), ATP-driven pumps (*ABCB4*) or calcium and xenobiotic sensors (Sorcin). In particular, Sorcin is able to limit the cytotoxic activity of chemotherapeutic agents in tumor cells and to confer MDR via three known mechanisms: by direct binding to chemotherapeutic drugs as well as its overexpression on the one hand induces *ABCB1* overexpression and on the other hand activates pathways leading to EMT and metastasis.

In conclusion, the gain of knowledge about these genes and their role in cancer and chemoresistance can possibly pave the way towards the development of novel biomarkers as well as offer important information on tumorigenesis and MDR mechanisms. A possible strategy to overcome MDR in cancer could be by considering the targeting of these proteins, which are often co-overexpressed along with *ABCB1* in MDR tumors, and can be used as biomarkers of poor cancer patient outcome.

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