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The role of glycolysis in tumorigenesis: From biological aspects to therapeutic opportunities

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ABSTRACT

Glycolytic metabolism generates energy and intermediates for biomass production. Tumor-associated glycolysis is upregulated compared to normal tissues in response to tumor cell-autonomous or non-autonomous stimuli. The consequences of this upregulation are twofold. First, the metabolic effects of glycolysis become predominant over those mediated by oxidative metabolism. Second, overexpressed components of the glycolytic pathway (i.e. enzymes or metabolites) acquire new functions unrelated to their metabolic effects and which are referred to as "moonlighting" functions. These functions include induction of mutations and other tumor-initiating events, effects on cancer stem cells, induction of increased expression and/or activity of oncoproteins, epigenetic and transcriptional modifications, bypassing of senescence and induction of proliferation, promotion of DNA damage repair and prevention of DNA damage, antiapoptotic effects, inhibition of drug influx or increase of drug efflux. Upregulated metabolic functions and acquisition of new, non-metabolic functions lead to biological effects that support tumorigenesis: promotion of tumor initiation, stimulation of tumor cell proliferation and primary tumor growth, induction of epithelial-mesenchymal transition, autophagy and metastasis, immunosuppressive effects, induction of drug resistance and effects on tumor accessory cells. These effects have negative consequences on the prognosis of tumor patients. On these grounds, it does not come to surprise that tumor-associated glycolysis has become a target of interest in antitumor drug discovery. So far, however, clinical results with glycolysis

Abbreviations: 2DG, 2-deoxyglucose; ABC, ATP-binding cassette; ALDO, aldolase; AMPK, 5′ AMP-activated protein kinase; ATP, adenosine triphosphate; BRAF, V-Raf murine sarcoma viral oncogene homolog B1; CDK, cyclin-dependent kinase; CRC, colorectal cancer; CSC, cancer stem cell; DCA, Dichloroacetate; DDR, DNA damage repair; dNTP, deoxynucleotide triphosphate; DSB, double-strand break; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; ENO, enolase; FADH, flavin adenine dinucleotide reduced; FOX, forkhead box protein; G6P, glucose 6-phosphate; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GBM, glioblastoma multiforme; GLUT, glucose transporter; GPI, glucose 6-phosphate isomerase; HCAR1, hydroxycarboxylic acid receptor 1; HCC, hepatocellular carcinoma; HER, human epidermal growth factor receptor; HIF, hypoxia inducible factor; HK, hexokinase; HR, homologous recombination; ICI, immune checkpoint inhibitor; ICP, immune checkpoint; IDH, isocitrate dehydrogenase; LDH, lactate dehydrogenase; lncRNA, long non-coding RNA; KRAS, Kirsten rat sarcoma virus; MCT, monocarboxylate transporter; miRNA, microRNA; mTOR, mechanistic target of rapamycin; NAD^+, nicotinamide adenine dinucleotide oxidized, NADH, nicotinamide adenine dinucleotide reduced; NP, nanoparticle; NSCLC, non-small cell lung cancer; OS, overall survival; OXPHOS, oxidative phosphorylation; PDAC, pancreatic ductal adenocarcinoma; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinases; PD-L1, programmed death ligand 1; PFK, phosphofructokinase; PFKP, PFK platelet; PFKFB, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase; PGI, phosphoglucose isomerase; PGK, phosphoglycerate kinase; PGM, phosphoglycerate mutase; PI3K, phosphoinositide 3-kinase; PK, pyruvate kinase; PPP, pentose phosphate pathway; RCC, renal cell carcinoma; ROS, reactive oxygen species; SIRT1, sirtuin-1; TCA, tricarboxylic acid; TF, transcription factor; TME, tumor microenvironment; TNBC, triple negative breast cancer; TPI, triosephosphate isomerase.

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inhibitors have fallen short of expectations. In this review we propose approaches that may allow to bypass some of the difficulties that have been encountered so far with the therapeutic use of glycolysis inhibitors.

Introduction

Glycolysis converts glucose to pyruvate. Pyruvate can be further metabolized along two different pathways. In the presence of oxygen, it enters oxidative metabolism (Fig. 1), where it is metabolized to CO_2, nicotinamide adenine dinucleotide reduced (NADH) and flavin adenine

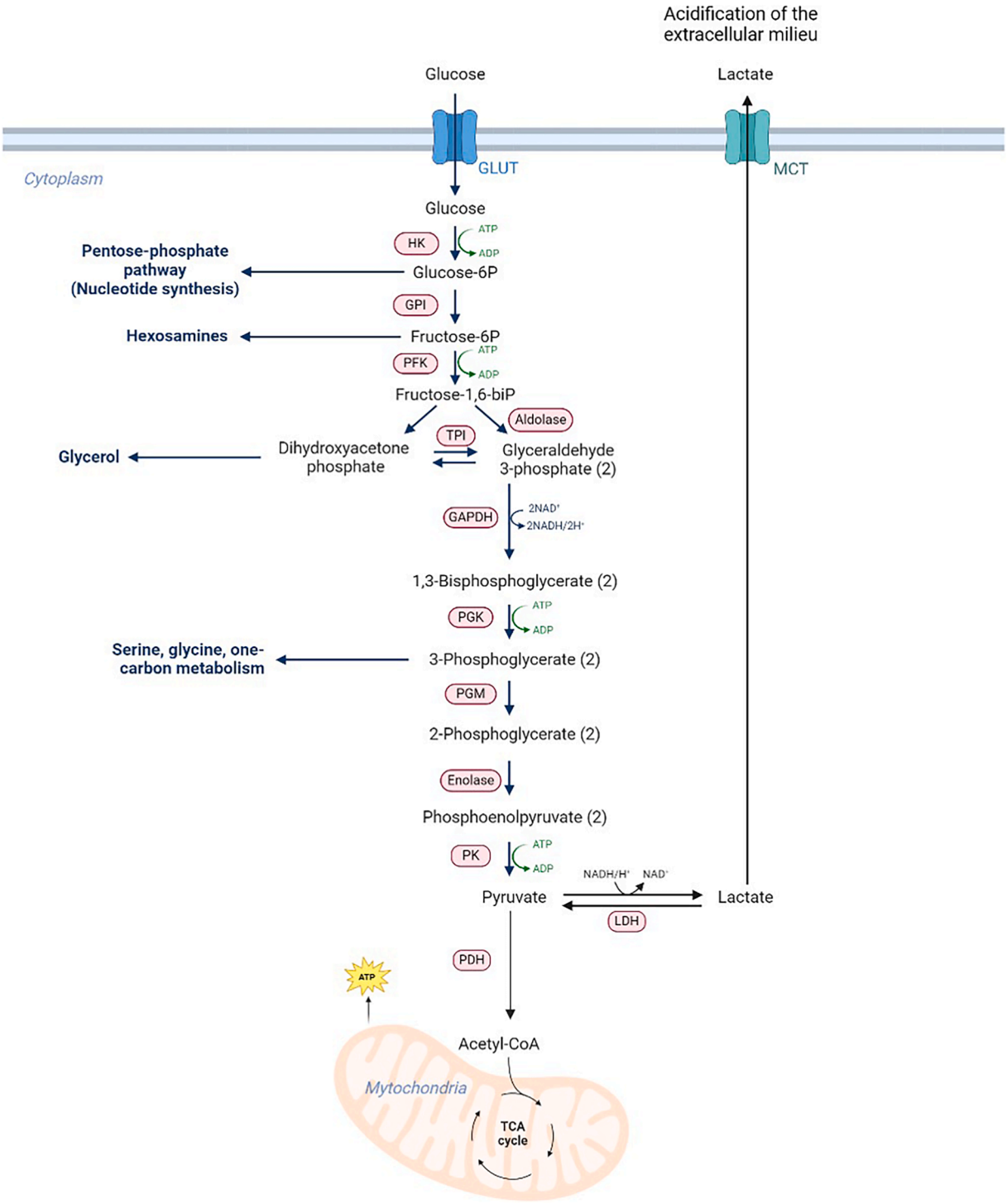

Fig. 1. Glycolytic metabolism. The figure shows glycolytic enzymes and metabolites as well as metabolic pathways that branch off from glycolysis. ATP, adenosine triphosphate; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GPI, glucose 6-phosphate isomerase; GLUT, glucose transporter; HK, hexokinase; LDH, lactate dehydrogenase; MCT, monocarboxylate transporter; NAD+, nicotinamide adenine dinucleotide oxidized; NADH, NAD reduced; PDH, pyruvate dehydrogenase; PFK, phosphofructokinase; PGK, phosphoglycerate kinase; PGM, phosphoglycerate mutase; PK, pyruvate kinase; TCA, tricarboxylic acid; TPI, triosephosphate isomerase.

dinucleotide reduced (FADH) in the tricarboxylic acid (TCA) cycle. These molecules then enter oxidative phosphorylation (OXPHOS) where large amounts of free energy are generated in the form of adenosine triphosphate (ATP) (up to 36 molecules per glucose molecule) [1]. In the absence of oxygen, pyruvate is reductively metabolized (fermented) to lactate in a reaction catalyzed by lactate dehydrogenase (LDH). Glycolysis coupled to pyruvate fermentation, however, is much less efficient in generating ATP since its production relies exclusively on ATP generated during glycolysis (2 ATP molecules per glucose molecule). Thus, under aerobic conditions, cells rely on oxidative metabolism for energy production, while switching to the much less efficient glucose fermentation under hypoxic conditions. In fact, oxidative metabolism has been shown to generate >90 % of ATP in aerobic conditions [2].

In seminal studies published one century ago Otto Warburg reported that tumor cells use predominantly glycolysis for energy production even under aerobic conditions with most glucose being converted to lactate (referred to as aerobic glycolysis) [3]. These observations led Warburg to speculate that cancer cells harbor defects in oxidative metabolism that force them to use glycolysis for energy production. In the following, however, it was shown that in most cases, mitochondrial respiration is not compromised in tumor cells [4]. More recent studies showed that tumor cells relying on glycolysis for energy production have a growth advantage compared to similar cells relying on oxidative metabolism [5]. Moreover, it was found that glycolysis followed by lactate production is also observed in non-transformed cells undergoing rapid proliferation like mouse fibroblasts [6] or mitogen-stimulated mouse lymphocytes [7].

In addition to becoming the predominant energy-producing pathway, tumor glycolysis is also upregulated compared to normal tissues [8]. This upregulation is of crucial importance for the appearance of non-metabolic effects (so-called “moonlighting” functions) [9] that have been ascribed to individual components (e.g. enzymes) of the glycolytic pathway. This upregulation is the result of quantitative (e.g. overexpression of glucose transporters (GLUT) or glycolytic enzymes or overproduction of metabolites) and/or qualitative (e.g. post-translational modifications or expression of embryonic isoforms of glycolytic enzymes) changes in the glycolytic pathway [10]. Upregulated glycolysis in a limited number of tumor cells can be propagated to other cells through intercellular communications [11]. Upregulation often affects, initially, an individual enzyme, but this change leads, in the following, to an overall upregulation of glycolysis [10]. Quantitative upregulation of a glycolytic enzyme may also promote its localization to an unusual subcellular location, e.g. the nucleus [12] and it is this subcellular location that may endow it with “moonlighting” functions.

It should also be noted that upregulated glycolysis is not synonymous with aerobic glycolysis leading to lactate production. In fact, as already mentioned, glucose can enter oxidative metabolism upon oxidation to pyruvate or it can feed other pathways that branch off like, for example, the pentose phosphate pathway (PPP) upon phosphorylation to glucose 6-phosphate (G6P), thereby promoting the synthesis of precursors (e.g. nucleotides) for biomass generation [13].

Lastly, a semantic issue. *Stricto sensu*, the term glycolysis refers to the metabolic steps that generate pyruvate. Nevertheless, for the sake of clarity and in consideration of the historical use of the term, glycolysis is used herein to include also the metabolic step that leads to the fermentation of pyruvate to lactate (anaerobic glycolysis in the absence of oxygen, aerobic glycolysis in its presence).

Putting upregulated glycolysis in context – Metabolic heterogeneity

During the last decades it has become clear that upregulated glycolysis, while being a characteristic feature of tumor cell metabolism [14], is not as overarching as originally thought. First, tumor cells that rely on glycolysis may coexist, within the same cell population, with tumor cells that rely on oxidative metabolism [15]. Thus, triple negative breast cancer (TNBC) cells relied mainly, but not exclusively (for 62-75 %), on oxidative metabolism for ATP production, while other breast cancer cell lines depended to a similar degree on glycolytic and oxidative metabolism [16]. As expected, hypoxia led in all tested cell lines to an upregulation of glycolysis. Among leukemia cell lines, some were found to rely mainly on glycolytic, others on oxidative metabolism [17]. Metabolic heterogeneity was confirmed *in vivo*, in non-small cell lung cancer (NSCLC) patients, using intraoperative ^{13}C-glucose infusions to compare metabolism between tumors and normal lungs [8]. The results showed that both glycolytic as well as oxidative metabolism were upregulated in tumors. In fact, several observations suggest that both glycolytic and oxidative metabolism are required in many cases to support full tumorigenicity. Thus, inhibition of glycolysis in aggressive tumors did not completely suppress but, rather, reduced tumor growth [18]. In breast cancer cells reprogramming from oxidative to glycolytic metabolism impaired tumorigenesis, suggesting that upregulated glycolysis alone was not sufficient to support tumor growth [19]. Simultaneous upregulation of glycolytic and oxidative metabolism was also crucial for melanoma progression [20].

When aerobic glycolysis is at work, affected cells release lactate in the extracellular milieu together with stoichiometric amounts of H^+ ions, thereby leading to acidification of the surrounding tumor microenvironment (TME) [21]. Lactate can then enter tumor cells to be metabolized along the TCA cycle/OXPHOS pathway [8,22,23]. This has been shown to protect glioblastoma multiforme (GBM) cells from nutrient deprivation by increasing histone acetylation and chromatin accessibility [24]. Lactate can also induce increased expression of genes involved in lipid metabolism in tumor cells, thereby increasing intracellular lipid accumulation and providing acetyl moieties for histone acetylation [25]. As we will discuss in the following, lactate can also signal through specific cell-surface receptors that are overexpressed on tumor cells. Proton export has another consequence on tumor cell metabolism. It leads to intracellular alkalization and this has been shown to activate metabolic enzymes that upregulate glycolytic metabolism and the PPP pathway and increase tumor cell proliferation [26].

The coexistence between glycolytic and oxidative metabolism, however, is not uniformly distributed throughout tumor tissues. Instead, an intratumor partition of glycolytic and oxidative metabolism has been proposed, with glycolytic metabolism occurring mainly in the interior tumor regions and oxidative metabolism in the lateral regions [27]. Moreover, metabolic heterogeneity has also been proposed to exist between tumor cells and non-transformed, accessory cells of the TME. Thus, cancer-associated fibroblasts (CAF) were shown to rely predominantly on aerobic glycolysis and to release lactate in the TME which is then used to feed oxidative metabolism in tumor cells. This effect has been referred to as “reverse Warburg effect” [28,29]. Tumor cells relying predominantly on aerobic glycolysis can also switch back to oxidative metabolism in the presence of low glucose concentrations [30] or in response to other stressors [31]. Chemosensitive tumor cell lines displaying a predominantly glycolytic phenotype shifted towards oxidative metabolism upon acquisition of chemoresistance and retained the ability to switch between the two metabolic phenotypes [32].

Moreover, metabolic heterogeneity can exist even within individual tumor cells. In fact, individual tumor cells can exist in a hybrid metabolic state in which both aerobic glycolysis and oxidative metabolism are used [33,34]. Oxidative metabolism was mainly used in the G1 phase and aerobic glycolysis in the S phase of the cell cycle [33,35]. Such a hybrid metabolic state may be advantageous in supporting tumor cell proliferation and tumor growth, as well as metastasis and therapy resistance [19,33].

Overall, these observations together with those previously referred to, showing that aerobic glycolysis can feed oxidative metabolism through the release of lactate, suggest that tumor metabolism is inherently routed towards a symbiotic relationship between fermentative and oxidative metabolism. In fact, the cooperative role of glycolytic and oxidative metabolism in shaping the overall metabolic phenotype of

tumors is also demonstrated by reports showing that simultaneous inhibition of glycolytic and oxidative metabolism yields superior antitumor effects *in vivo* compared to inhibition of each pathway separately, e.g. [36–38].

Stimuli involved in the upregulation of aerobic glycolysis in tumor cells

Upregulation of aerobic glycolysis in tumor cells occurs in response to different classes of stimuli. First, the expression of a predominantly glycolytic phenotype has been suggested to depend, at least in part, on the tissue from which a given tumor originates [39], possibly because lineage-specific transcription factors (TF) are involved in the regulation of tumor metabolism [40,41].

Second, upregulation of glycolysis is promoted by tumor cell-intrinsic or-extrinsic stimuli. As regards tumor cell-intrinsic stimuli, some of these are directly involved in neoplastic transformation and tumor growth. Thus, many oncoproteins have been shown to upregulate glycolysis: e.g. V-Raf murine sarcoma viral oncogene homolog B1 $(BRAF)^{V600E}$ [42,43], Kirsten rat sarcoma virus (KRAS) [13,44,45], epidermal growth factor receptor (EGFR) [46], the phosphoinositide 3-kinase (PI3K)/AKT/mechanistic target of rapamycin (mTOR pathway) [47], human epidermal growth factor receptor (HER)2 [13], EWS-FL1 [48], WNT/β-catenin [49], c-MYC [50–52], SRC, and oncogenic viruses [53]. Oncosuppressive proteins can play a similar role if they bear mutations leading to the loss of their oncosuppressive function and/or acquisition of oncogenic functions [54].

Other tumor cell-intrinsic stimuli that upregulate glycolysis do not play a causative role in tumorigenesis but facilitate tumor progression. Thus, immune checkpoint molecules (ICP), immunosuppressive cell surface molecules that are often overexpressed on tumor cells, can upregulate glycolysis [55,56]. The purinergic P2RY2 receptor is overexpressed on pancreatic ductal adenocarcinoma (PDAC) cells and upregulates glycolytic enzymes and transporters [57]. Upregulated reactive oxygen species (ROS), as those occurring in AML cells, upregulated the glycolysis activator 6-phosphofructo-2-kinase/fructose-2, 6-biphosphatase (PFKFB) 3 and, consequently, glucose uptake and glycolysis [58]. Caveolin-1, the main component of caveolae plasma membranes, was overexpressed in hepatocellular carcinoma (HCC) cells where it upregulated expression of HK2 and glycolytic metabolism [59]. Aldehyde dehydrogenase 1 family member 3 (ALDH1A3) activated PI3K/AKT/mTOR and its downstream target peroxisome proliferator-activated receptor (PPAR) γ, thereby leading to increased expression of HK2 and upregulation of glycolysis [60]. Overexpression of the epithelial-mesenchymal transition (EMT) transcription factor (TF) Snail in PDAC cells induced EMT and caused upregulation of glycolysis and downregulation of oxidative metabolism [61]. Overexpression of the TF forkhead box protein (FOX) M1 upregulated the expression of LDHA and aerobic glycolysis in PDAC cells [62]. The closely related fasting/starvation-induced TFs FOXK1 and FOXK2 upregulated expression of several glycolytic enzymes and glycolysis and downregulated oxidation of pyruvate by increasing the expression and activity of pyruvate dehydrogenase kinases (PDK) 1 and 4 [63].

Metabolic stimuli can also upregulate tumor glycolysis. This occurs, for example, when oxidative metabolism becomes inhibited or obstructed or when the capacity to drive fluxes or generate metabolites linked to oxidative metabolism is exceeded (metabolic "overflow"). This has been demonstrated in response to pharmacological inhibition of oxidative metabolism [64,65], upon shortage of molecules that replenish oxidative metabolism [66], upon mitochondrial uncoupling [67], when the rate of NADH generation exceeds the maximum rate at which NADH can be oxidized in mitochondria [68], in response to a fragmented mitochondrial state [43], in the presence of isocitrate dehydrogenase (IDH) mutations [69] or upon inactivation of mitochondrial DNA due to fumarate accumulation in hereditary leiomyomatosis and renal cell carcinoma (HLRCC) [70]. The products of IDH mutations, hydroxyglutarate, together with fumarate and succinate, have been defined as oncometabolites because of their tumorigenic properties [71] which are the consequence of their capacity to inhibit α-ketoglutarate (αKG)-dependent dioxygenases because of their structural similarity with αKG. Consequences of this inhibition are the induction of pseudohypoxic responses and epigenetic dysregulation leading, among others, to the induction of EMT in tumor cells [71].

While the stimuli discussed so far upregulate glycolytic metabolism, in some cases also glycolysis downregulation has been reported in response to intracellular cues. Thus, in NSCLC cells, phosphoglycerate kinase (PGK) 1 was ubiquitinated and committed to degradation by Rab-family of interacting proteins (FIP) 2 [72]. Phosphofructokinase platelet (PFKP) was targeted for ubiquitination and degradation in breast cancer cells [73]. Phosphatase and tensin homolog (PTEN), a negative regulator of the PI3K/AKT pathway, inhibited phosphoglycerate kinase (PGK) 1 leading to downregulation of glycolysis in tumor cells [74].

A separate class of intracellular stimuli that downregulate glycolysis are microRNAs (miRNA). These single-stranded, non-coding RNA molecules of 12-23 nucleotides length negatively regulate post-transcriptional gene expression, including genes encoding glycolytic enzymes. These miRNAs are often downregulated in tumor cells, leading to overexpression of glycolytic enzymes. MiRNAs that have been described to downregulate the expression of glycolytic enzymes include: miRNA-215-5p targeting PGK1 in PDAC cells [75], miR-138 targeting PDK1 in colorectal cancer (CRC) cells [76], miR-644 targeting glycolytic genes in castration-resistant prostate cancer (CRPC) cell lines [77], miR-505 targeting HK2 in PDAC cells [78]. The activity of miRNAs, in turn, is negatively regulated by long non-coding RNAs (lncRNA). Consequently, the expression of genes encoding glycolytic enzymes that are downregulated by miRNAs is upregulated in response to lncRNAs. This has been shown, for example, for HK2 [78]. A different mechanism of action has been ascribed to the lncRNA Actin Gamma 1 Pseudogene which bound and stabilized PFKFB3 by preventing its ubiquitination and degradation, thereby upregulating glycolysis [79].

Extracellular, tumor-associated stimuli that upregulate glycolysis include hypoxia and compressive stress occurring in response to insufficient vascularization [80,81]. Hypoxia is, in fact, the prototypic inducer of (anaerobic) glycolysis. Extracellular matrix composition, in particular hyaluronan concentration, can also act as a modulator of tumor glycolysis [82]. High glucose concentration also upregulates glycolysis [83]. Glucose starvation can select for clones with upregulated glycolysis and increased lactate production [84]. Interestingly, lactate itself upregulated glycolysis upon interaction with its cell surface receptor hydroxycarboxylic acid receptor 1/G protein-coupled receptor 81 (HCAR1/GRP81) overexpressed on breast cancer cells [85]. Thus, lactate can have two apparently contradictory effects on tumor metabolism: on one hand it can feed oxidative metabolism (see above) and, on the other hand, upregulate glycolytic metabolism. Other extracellular stimuli that have been reported to upregulate glycolysis include bacterial infections, ultraviolet radiation, antitumor therapeutics, ROS, cytokines or exosomes derived from accessory cells of the TME [86–91]. Of note, tumor cells have been shown to preserve upregulated glycolysis in the presence of stimuli that downregulate glycolysis in non-transformed cells. Thus, while non-transformed cells downregulated glycolysis when they were transferred from stiff to soft substrates, tumor (NSCLC) cells were insensitive to this transfer and retained a high glycolytic metabolism [92]. Tumor cell-intrinsic and -extrinsic stimuli can cooperate in the upregulation of tumor-associated glycolysis [93,94].

Consequences of upregulated glycolysis in tumors

Molecular effects of upregulated glycolysis

Metabolic consequences of upregulated glycolysis

Upregulated glycolysis has several features that may make it the preferred metabolic pathway, over oxidative metabolism, to support

tumor cell proliferation and growth. This appears counterintuitive because, as already discussed, glycolysis-induced ATP production is much less efficient as compared to oxidative metabolism. Aerobic glycolysis, however, can generate ATP at a faster rate than oxidative metabolism [95] (Fig. 2). In fact, in contrast to rapidly proliferating cells, slow-cycling or quiescent cells rely more on oxidative metabolism than glycolysis [96,97] and blocking glycolysis with bromopyruvate was efficient on rapidly proliferating cells but less so on slowly proliferating cells [96,97]. In addition to ATP generation, rapidly proliferating cells, including tumor cells, may use glycolysis also for other metabolic purposes. It has been suggested that a major function of glycolysis in rapidly proliferating cells is to provide high levels of glycolytic intermediates to support anabolic reactions and generate biomass [1,98,99]. Thus, G6P can enter the PPP in order to generate nucleotides and antioxidants [100,101]. Glycolysis may also protect tumor cells from oxidative stress by reducing the impact of OXPHOS, which is a major source of ROS. More recently, it has been shown that aerobic glycolysis can be driven when the demand for NAD^+ to support oxidation reactions exceeds the rate of ATP turnover [102]. In this case, the quantity of NAD^+ becomes limiting, thereby favoring fermentation of pyruvate to lactate even when oxygen is available.

The view that upregulation of glycolysis does not occur mainly for ATP production, but for other metabolic purposes, has received strong support by recent results [103], which showed that oxidative metabolism was inhibited in primary solid tumor models, while glycolysis was increased compared to healthy tissues, but not to a degree that compensated for downregulated oxidative metabolism in terms of ATP production. This suggests that primary tumors upregulated glycolytic metabolism and downregulated oxidative metabolism in order to supply glycolysis-generated metabolites rather than ATP.

Non-metabolic, "moonlighting" functions of upregulated glycolysis

In addition to the metabolic effects, upregulated glycolysis has a large number of tumor-promoting effects which, in many cases, are mediated by overexpressed glycolytic enzymes or overproduced metabolites through non-metabolic, so-called "moonlighting" functions [9] (Fig. 2).

Induction of tumor-driving mutations or other tumor-initiating events. Several reports have suggested that upregulated glycolysis might play a role in promoting tumor initiation. Thus, an increase in phosphoglycerate mutase (PGM) or phosphoglucose isomerase (PGI) activity in mouse embryonic fibroblasts induced indefinite proliferation of these cells [104]. Later, it was shown that glycolysis activated the IκB kinase (IKK)-nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway and its hyperactivation due to p53 loss was important for oncogenic RAS-induced cell transformation [105]. In a switchable model of MYC-driven liver cancer, metabolic changes, including pyruvate conversion to lactate, preceded tumor formation and were rapidly inhibited as tumors began to regress [106]. A model has also been proposed whereby convective disturbance in cells leads to metabolic reprogramming towards glycolysis also in aerobic conditions, and such reprogramming causes disruption of microtubule dynamics and induces genomic instability giving rise to tumorigenic events [107].

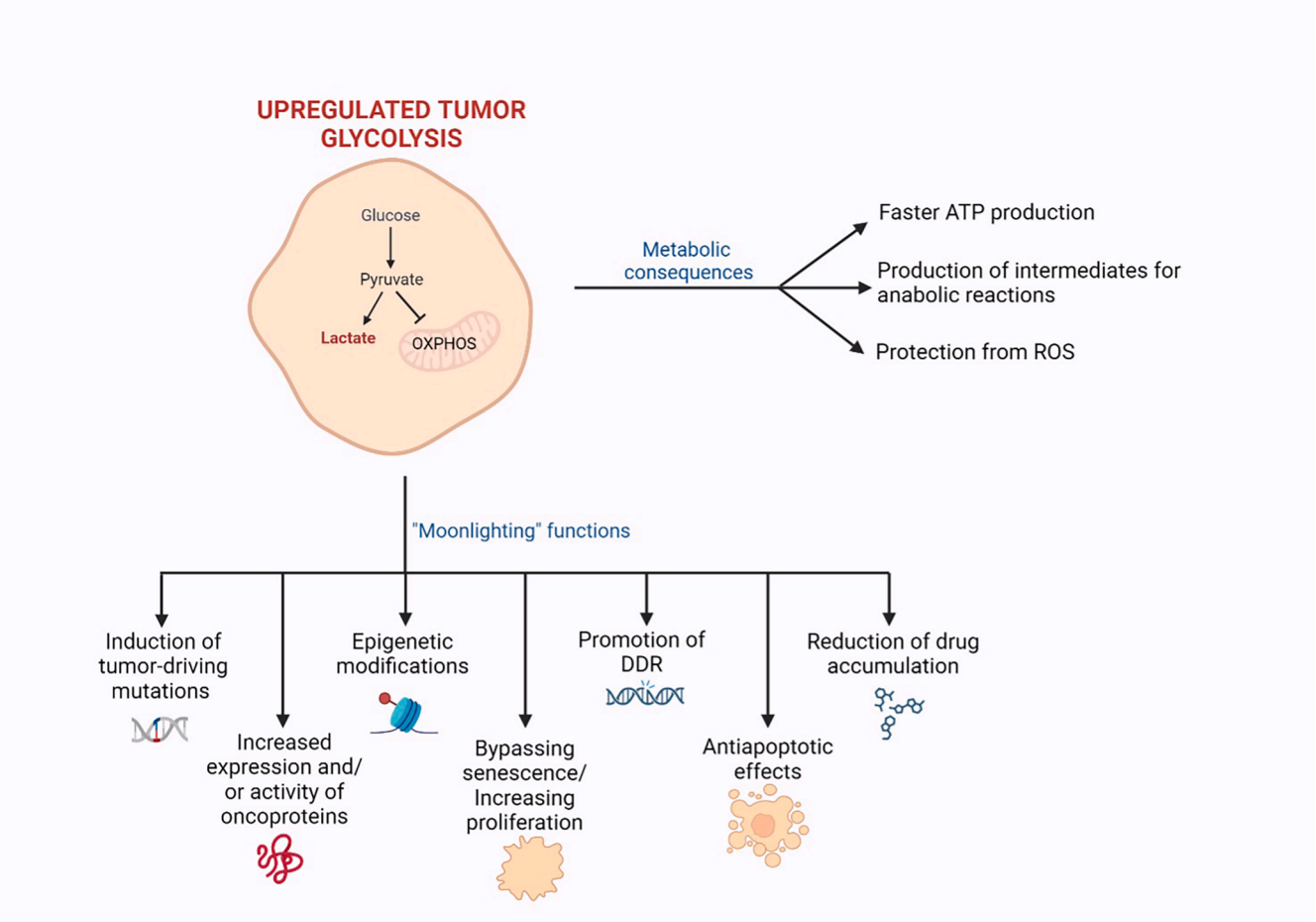

Fig. 2. Molecular effects of upregulated tumor glycolysis. These effects can be broadly classified into two categories: metabolic consequences and induction of "moonlighting" functions which, in turn, are classified into the indicated subcategories. ATP, adenosine triphosphate; DDR, DNA damage response; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species.

In the following it was shown that upregulated glycolysis can promote the acquisition of tumor-driving mutations [108]. Thus, upregulated glycolysis promoted the acquisition of mutations in *KRAS* or *BRAF* in a minority of CRC clones that had been grown in low glucose conditions and showed a permanent upregulation of GLUT1 [109]. However, since only a minority of clones had acquired mutations, other undefined factors were required for the induction of mutations in a larger fraction of clones. Moreover, in mouse CRC models loss of the gene encoding the mitochondrial pyruvate carrier 1 (*Mpc1*) led to upregulation of glycolysis and this, in turn, increased the frequency of adenomatous polyposis coli (*Apc*) loss of heterozygosity, the key tumorigenic alteration in this model [110]. This effect promoted further mutational events facilitating the shift from a benign adenoma into an invasive adenocarcinoma.

Glycolysis can also play other roles in tumor-initiating events. Thus, LDHA and the oncoprotein RNA terminal phosphate cyclase like 1 (RCL), a N-glycoside hydrolase, induced the anchorage-independent growth of Rat1a fibroblasts and formed tumors in nude mice when acting together but not either alone [111]. LDHA overexpression was also required for c-Myc-induced transformation of fibroblasts and lymphoma cell lines [112]. In a model of HER2-driven mammary tumor, knockdown of LDHA greatly diminished the tumorigenicity of the tumor cells [113]. LDHA had an oncogenic effect in breast cancer cells by binding to the active, small GTPase Rac1 and this interaction inhibited Rac1 binding to its negative regulator, keeping Rac1 in its active state [114]. Old *Drosophila* flies were shown to undergo metabolic reprogramming towards aerobic glycolysis [115]. This induced hyperplasia of intestinal stem cells similar to that induced by the oncogene Ras^{V12} [116] which requires at least one other signal (e.g., mutation of an oncogene) in order to induce a malignant tumor. These results suggest that upregulated glycolysis can act as a signal which, in concert with other signal(s) can give rise to full-blown tumors [10].

Glycolysis and cancer stem cells (CSC). The role of glycolysis in tumor initiation brings us to a closely related topic, i.e. CSCs. The term CSCs, as nowadays used, encompasses both true tumor-initiating cells as well as tumor cells which undergo phenotypic changes (e.g. EMT) allowing them to survive to potentially lethal stressors from the TME and give rise to a new offspring of tumor cells [117–119]. While these cells have some properties of true tumor-initiating cells, they represent a separate entity because they derive from differentiated, proliferating tumor cells that have undergone a phenotypic switch.

Given that premise, a large number of contradictory reports have been published on the metabolic phenotype of CSCs. Many reports claim that CSCs, whether from solid or hematological tumors, rely mainly on oxidative metabolism for their survival [120–126], with some reports showing differences between CSCs and the bulk of cancer cells, with the first relying mainly on oxidative metabolism and the second on glycolytic metabolism [127,128]. There are, however, also many reports claiming that CSCs of different tumor types rely mainly on glycolytic metabolism [12,46,129–132]. In some cases, the effect on CSCs was shown to be the consequence of glycolysis-induced enhancement of the activity or expression of stem cell TFs such as, for example, Oct-4, NANOG, sex determining region Y-box 2, and B lymphoma Mo-MLV insertion region 1 homolog [129,130,133].

In addition to the many reports showing that either oxidative metabolism or glycolysis are crucial for CSCs, there are also some reports claiming that both oxidative and glycolytic metabolism are involved in CSC biology [134,135]. In one case it was shown that CSC metabolism can shift from glycolytic to oxidative metabolism and vice versa, depending on the stemness grade of the cells [136].

Now, how can we reconcile these apparently contradictory results? A possible explanation derives from the knowledge that CSCs are, themselves, a heterogeneous cell population that encompasses both quiescent and proliferating cells [137]. As we have already discussed, quiescent cells, whether neoplastic or non-transformed, rely mainly on oxidative metabolism [97,138,139]. On the other hand, as will be discussed in more details in the next section, there is an equally large body of evidence showing that proliferating cells rely mainly on glycolytic metabolism. The balance between these two states, i.e. quiescence and proliferation of CSCs, may vary according to the need to replenish or not the pool of differentiated and proliferating tumor cells and this may tilt the balance towards a predominantly glycolytic or oxidative metabolism, respectively.

Glycolysis-induced increase of the expression or activity of oncoproteins. In addition to a direct role in the induction of tumorigenesis, upregulated glycolysis can increase the expression and/or activity of oncoproteins. In the following we describe some examples of oncoproteins that are increased and/or activated in response to upregulated glycolysis.

Some of these proteins are tumor-promoting TFs such as signal transducer and activator of transcription 3 [140,141], EMT TFs [142], or transcriptional coactivators like Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) [143].

As regards proteins other than TFs, upregulated glycolytic enzymes or metabolites have been shown to activate and/or increase the activity of components of the PI3K/AKT/mTOR pathway, one of the signaling pathways most commonly involved in tumorigenesis [144]. Thus, PKM2 led to activation of mTORC1 in renal cell carcinoma (RCC) cells [145]. An aldolase (ALDO) metabolite, dihydroxyacetone phosphate (DHAP), activated mTORC1 in a manner independent of energetic stress [146]. An acetylated PFK1 platelet isoform interacted with p85 upon localization to the plasma membrane, and this led to activation of PI3K/AKT in GBM cells driven by EGFR signaling [147]. Upregulated PFKFB4 increased the expression of the histone acetyltransferase GNC5 and activated PI3K/AKT signaling in thyroid cancer cells [148]. Enolase (ENO) 1 activated AKT signaling in human gastric cancer cells [149]. If we consider this section together with section 3, it will be appreciated that the PI3K/AKT/mTOR pathway acts both as a stimulus for the upregulation of glycolysis and is itself a target that is upregulated in response to glycolysis, suggesting the existence of a feed-forward loop between these two players.

Other interactions involve oncoproteins not belonging to the PI3K/AKT/mTOR pathway. PFKFB4 stimulated SRC-3 and this funneled glucose through the PPP and promoted purine synthesis [150] . PKM2 phosphorylated histone H3, thereby facilitating EGF-induced expression of cyclin D1 and c-MYC in GBM cells [151]. Interestingly, PKM2 interacted with prolyl hydroxylase 3 (PHD3) and this interaction enhanced PKM2 binding to hypoxia inducible factor (HIF)-1α and promoted transactivation of HIF-1 target genes by enhancing HIF-1 binding and p300 recruitment to hypoxia response elements [152]. Since *PKM2* transcription is a target of HIF-1, these results suggest the existence of a positive feed-forward loop. An interesting, double role has been reported for PGK1 in PDAC cells [153]. In the nucleus PGK1 promoted metastasis via upregulation of OXPHOS, whereas cytoplasmic PGK1 increased tumor cell proliferation due to its role in glycolytic metabolism. Nuclear LDHA promoted hypermethylation of histone H3K79 leading to the activation of antioxidant responses and Wnt signaling in human papilloma virus (HPV)-positive cervical tumor cells [154]. ALDOA promoted the formation of lysosomal complexes containing vacuolar-type ATPase (v-ATPase), Ragulator, AXIN, liver kinase B1 (LKB1) and 5′ AMP-activated protein kinase (AMPK) when ALDOA was not occupied by its substrate fructose 1,6-bisphosphate (F1,6BP) [155]. These complexes supported AMPK activation and autophagy in the presence of glucose starvation.

While most of the interactions described so far have tumor-promoting effects, some have been reported to induce antitumor effects. Thus, glyceraldehyde 3-phosphate dehydrogenase (GAPDH) underwent S-nitrosylation in response to nitric oxide generated in response to an apoptotic stimulation [156]. This modification increased the

binding of GAPDH to the E3 ubiquitin ligase Siah2 leading to its stabilization, nuclear translocation and degradation of nuclear proteins, thereby promoting apoptosis. In the following the same group showed that GAPDH itself could promote nitrosylation of nuclear proteins, including the deacetylating enzyme sirtuin-1 (SIRT1), histone deacetylase-2 (HDAC2) and DNA-activated protein kinase (DNA-PK) [157].

Glycolysis-induced epigenetic and transcriptional modifications. Upregulated glycolysis can induce changes at the epigenetic and/or transcriptional level. These changes can contribute to tumor initiation and progression at different levels. Thus, epigenetic changes can prime epithelial cells for neoplastic transformation [158]; promote the accumulation of DNA mutations [159]; increase chromatin accessibility, thereby facilitating DNA repair and promoting drug resistance [160, 161]; increase the expression of oncogenes [162]; promote the emergence of stress-resistant cancer cell subpopulations [163]; remodel the TME [164]; facilitate immune evasion of tumor cells [165].

Glycolysis can increase chromatin accessibility by inducing histone lactylation [166] in tumor cells or tumor-associated cells [167], leading to a wide range of tumor-promoting effects (reviewed in [168]). Another histone modification, acetylation, occurs upon transfer of an acetyl-group from acetyl-CoA to histone Lys residues [169]. Acetyl moieties for histone acetylation can be derived from PDH-catalyzed decarboxylation of pyruvate generating acetyl-CoA, from fatty acid metabolism or, as already discussed, from lactate-induced intracellular lipid accumulation [25]. Histone acetylation can also induce an open chromatin configuration which is required for an efficient DNA damage repair (DDR) [170] that can have tumorigenic effects due to increased expression of oncogenes [171] or telomerase reverse transcriptase (TERT) leading to increased tumor cell proliferation [172]. An increased open chromatin conformation was also induced by HK2 [12]. Furthermore, 3-phosphoglycerate, an intermediate of glycolysis, is a precursor for serine and glycine biosynthesis, which provides one-carbon units for the synthesis of S-adenosylmethionine (SAM), which transfers methyl groups on proteins like histones, DNA, RNA and intermediary metabolites, thereby affecting gene regulation and expression of the corresponding proteins [173].

Of note, while upregulated glycolysis induces changes in chromatin accessibility, increased chromatin accessibility upregulated the expression of glycolytic enzymes and metabolism, suggesting the existence, also in this case, of a feed-forward loop. Thus, loss of AT-rich interaction domain 1A (ARID1A), a subunit of the mammalian SwItch/Sucrose nonfermentable (SWI/SNF) complex increased chromatin accessibility and enhanced HIF-1α-induced expression of several glycolytic enzymes in a mouse model of lung cancer [174].

Glycolysis-induced bypassing of senescence and induction of proliferation. Upregulated tumor glycolysis can deliver signals to bypass senescence, an antitumor mechanism that avoids indefinite proliferation [175]. Several glycolytic enzymes or metabolites deliver a senescence-bypassing signal. Thus, upregulated PGM and glucose 6-phosphate isomerase (GPI) enhanced glycolysis and promoted indefinite proliferation of mouse embryonic fibroblasts. Their knockdown triggered premature senescence [104]. Later, the same authors showed that unlimited proliferation of embryonic stem cells correlated with upregulated glycolysis, while differentiating stem cells showed a decrease in glycolysis [176]. Upregulated GAPDH allowed to bypass senescence induced by the oncoprotein $BRAF^{V600E}$ [42]. Lactate suppressed oncogene-induced senescence through upregulation of the EMT master TF Snail [177] which, in turn, inhibited expression of $p16^{INK4a}$, a tumor suppressor that inhibits cyclin-dependent kinase (CDK) 4/6 and cell cycle progression.

Bypassing senescence is an indirect mechanism that promotes tumor cell proliferation. In addition, upregulated glycolysis can also directly promote cell division and proliferation. Thus, overexpressed PFKFB3 was found to localize to the cell nucleus and increase cell proliferation via increased expression of CDKs and decreased expression of the cell cycle inhibitor p27 [178]. More recently, it was found that lactate bound and inhibited the SUMO protease sentrin isopeptidase (SENP) 1 to govern the E3 ligase activity of the anaphase-promoting complex, thereby facilitating mitotic exit in proliferating cells and overcoming mitotic arrest induced by the anti-mitotic drug nocodazole [179]. On the other hand, depletion of lactate prolonged mitosis.

Promotion of DDR or prevention of DNA damage. Upregulated tumor glycolysis promotes DDR, thereby facilitating cell survival and unrestrained proliferation. Several glycolytic enzymes (PFKFB3, PGM1, PKM2, PGK1) or metabolites (pyruvate, lactate) have been shown to induce DNA-repairing activity through different mechanisms of actions. Thus, PFKFB3 localized to nuclear foci after induction of double-strand breaks (DSB) by irradiation [180]. PFKFB3 promoted the generation of a local pool of deoxynucleotide triphosphates (dNTP) at the site of DNA damage, thereby supporting DNA synthesis during DNA repair. Similarly, PGM1 facilitated homologous repair of DSBs in cancer cells by securing the intracellular dNTP pool [181]. ALDOA upregulated PPP and this led to increased nucleotide metabolism which protected breast cancer cells from DNA damage [182]. Knockdown of PGK1 inhibited the proliferation of endometrial cancer cells and reduced the expression of proteins involved in DDR [183]. Phosphorylated PKM2 localized to the nucleus where it phosphorylated the C-terminal-binding protein 1 (CtBP)-interacting protein (CtIP) leading to increased recruitment of CtIP at DSBs and consequent promotion of homologous recombination (HR)-mediated DDR. Inhibition of this pathway increased susceptibility of cancer cells to DNA-damaging agents [184]. Pyruvate facilitated chromatin loading of γH2A histone family member X (γH2AX) thereby promoting DDR in GBM cells [185]. Lactate protected from cisplatin cancer cells selected for growth under glucose-deprived conditions. Cisplatin showed reduced efficacy, induced less DNA damage, and the cells had increased expression of DNA repair genes [186]. Lactate promoted also the lactylation of the HR protein MRE11 in response to DNA damage and this facilitated binding to DNA, DNA end resection and HR [187]. Upregulated glycolysis can also prevent DNA damage. Thus, NADPH generated during the oxidative phase of the PPP promoted the generation of the reduced form of glutathione and thioredoxin, both of which can scavenge ROS, thereby preventing their DNA-damaging activity [188]. Pyruvate was shown to directly scavenge free radicals [189].

It should be noticed that while the vast majority of reports suggest that upregulated glycolysis induces DDR, a few reports have described that some glycolytic enzymes, e.g. PKM2 [190] and ALDOB [191] can induce DNA damage.

Antiapoptotic effects. Upregulated glycolysis can exert antiapoptotic effects through different mechanisms of action. Thus, it caused overexpression of the antiapoptotic molecule myeloid cell leukemia-1 (Mcl-1) [192]. PKM2 caused overexpression of the anti-apoptotic proteins B-cell lymphoma 2 (Bcl-2) [130] and B-cell lymphoma extra-large (Bcl-xL) [193]. Under conditions of oxidative stress, PKM2 was redirected to mitochondria where it phosphorylated and stabilized Bcl-2 [194]. HK2 inhibited mitochondrial apoptosis by direct insertion in the outer mitochondrial membrane and inhibition of cytochrome c release upon interaction with the voltage-dependent anion channel [195]. F2,6BP, the enzymatic product of the glycolysis activator PFKFB3, induced CDK-induced phosphorylation of the Cip/Kip protein p27. This caused ubiquitination and degradation of p27, a suppressor of G1/S transition and activator of apoptosis [178]. Lactate induced lactylation of adenylated kinase 2 which downregulated the intrinsic apoptosis pathway [196].

Upregulated glycolysis can also have antiapoptotic effects through

induction of protective autophagy. This was demonstrated with GAPDH-overexpressing HeLa cells which showed upregulation of glycolysis and enhanced autophagy which cooperated in protecting the cells from caspase-independent cell death [197].

Inhibition of drug influx or increase of drug efflux. Upregulated glycolysis can reduce the accumulation of drugs inside tumor cells through two different mechanisms. First, through inhibition of drug influx. Thus, the inversed pH gradient on each side of the membrane of glycolytic tumor cells reduced the uptake of weakly basic antitumor drugs (e.g., doxorubicin or mitoxantrone) into tumor cells [198]. Moreover, the acidification of the extracellular tumor milieu lowered the cytotoxicity of these drugs [199].

Second, upregulated glycolysis may also increase the efflux of drugs out of tumor cells. This efflux is executed by the ATP-binding cassette (ABC) transporter family of transmembrane proteins. Efflux activity of ABC transporters is highly dependent on cellular ATP levels [200] and the ATP generated in tumor cells due to upregulated glycolysis activated ABC transporters [201]. Binding of lactate to HCAR1 led to upregulation of the ABCB1 transporter which promoted drug efflux and resistance [202]. Pyruvate increased the expression of the ABC transporter multi-drug resistance 1 (MDR1) and this caused an increased efflux of chemotherapeutics. Acidification of the extracellular milieu can also lead to increased activity of efflux pumps [203].

Biological effects of upregulated glycolysis

In the previous sections we have addressed the molecular effects of upregulated tumor glycolysis. In the following sections we discuss the biological consequences of these effects on the different stages and phenotypes of tumorigenesis Fig. 3.

Effects on tumor initiation

Upregulated glycolysis may represent, by itself, a stimulus that promotes and facilitates tumor initiation. In the previous sections we have already discussed the effects of upregulated glycolysis in promoting tumor initiation. We have recently reviewed this field [108] and we have proposed that upregulated glycolysis may have a two-pronged effect in promoting tumor initiation. First, upregulated glycolysis may play a permissive role through the induction of modifications of chromatin conformation as a result of histone acetylation and lactylation. This permissive effect may be followed by glycolysis-induced executioner effects (e.g. induction of mutations, bypassing senescence, promotion of DDRs, anti-apoptotic effects). Upregulated glycolysis, however, is just one way whereby tumor initiation can be induced since tumor-initiating permissive and executioner effects can also be caused by glycolysis-unrelated mechanisms. To this regard, it is interesting to note that, in several instances, also oxidative metabolism has been suggested to act as a tumor-initiating mechanism [204,205].

Glycolysis, tumor cell proliferation and primary tumor growth

There is now ample evidence suggesting that upregulated glycolysis supports tumor cell proliferation and primary tumor growth [1,3,98,100,206,207]. In addition to rapid ATP generation, this may be the result of the generation of metabolic intermediates serving as macromolecular precursors, but also of “moonlighting” functions (e.g. such as

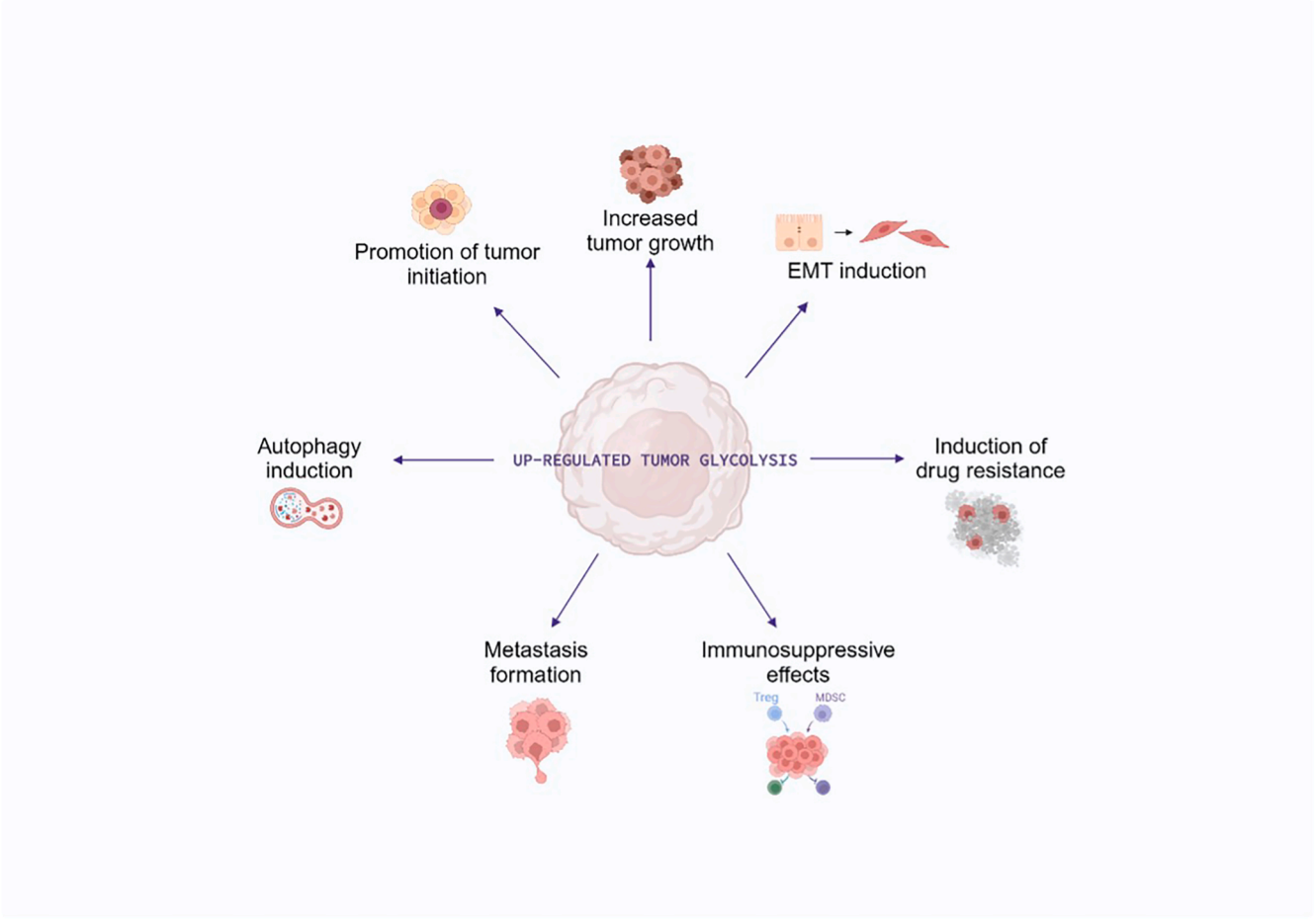

Fig. 3. Biological effects of upregulated tumor glycolysis. The molecular effects of upregulated tumor glycolysis translate into a series of biological effects that are depicted here and discussed under section 4.2. EMT, epithelial-mesenchymal transition.

those described under 4.1.2.3-4.1.2.7).

While glycolysis appears the most commonly used metabolic pathway to support tumor cell proliferation and primary tumor growth, there are circumstances where oxidative metabolism takes the center stage. Thus, proliferating tumor cells take advantage of oxidative metabolism under conditions of serum starvation [207], to support ATP-dependent drug efflux pumps [208], to supply ATP and NAD^+ for poly(ADP-ribose) polymerase-dependent DNA repair mechanisms [209] and, more generally, when there is requirement for high amounts of ATP [210], to support aspartate and asparagine biosynthesis [211,212], to regenerate mitochondrial NAD^+ and FAD^+ for the TCA cycle and pyrimidine synthesis [213], to promote immortalization of CSCs [205], and to support production of succinate as survival factor in leukemia cells [204]. Overall, while upregulated glycolysis appears to be the default pathway to support tumor cell proliferation, tumor cells may undergo reprogramming when specific metabolic requirements are better supported by oxidative metabolism.

Glycolysis and EMT

Upregulated glycolysis has been shown to induce EMT, i.e. the conversion of tumor cells with an epithelial phenotype into cells with a mesenchymal phenotype which is accompanied by the acquisition of malignant functionalities, including immunosuppressive effects, apoptosis resistance, formation of metastases and CSCs [119,214]. Of note, some known EMT inducers like EGF, have been claimed to do so through upregulation of glycolytic metabolism [215]. In fact, most glycolytic enzymes and glycolysis-induced acidosis have been shown to induce EMT in tumor cells (reviewed in [108]). Of note, overexpression of PGI induced EMT also in normal breast epithelial cells [216] showing that the EMT-inducing potential of upregulated glycolysis is not limited to transformed cells. Moreover, silencing of PGI induced the reverse process, i.e. mesenchymal-epithelial transition (MET), in osteosarcoma cells and suppressed the formation of pulmonary metastases [217]. The glycolysis-inducing enzyme PFKFB3 was found to induce EMT through increased ROS production [218]. Experiments measuring accumulation of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) in tumor tissues showed that accumulation in a human A431 xenograft tumor was highest in tumor cells undergoing EMT in hypoxic regions [219], suggesting that tumor cells that have undergone EMT display a pronounced glycolytic phenotype as had been previously shown *in vitro* with breast cancer cell lines [220]. On the other hand, loss of the TCA cycle enzyme citrate synthase led to a glycolytic switch which was accompanied by acquisition of an EMT phenotype [221]. The cross-talk and tight linkage existing between glycolysis and EMT has been documented in a report showing that EMT induction in CRC cells promoted nuclear translocation of PKM2 [222]. Nuclear PKM2 induced deacetylation of histone H3 and downregulated the transcription of the gene encoding E-cadherin, such downregulation being a hallmark of EMT. Moreover, glycolysis-derived metabolites can also promote EMT through stabilization of the EMT TF Snail [223].

Glycolysis and autophagy

Upregulated glycolysis has also been shown to induce autophagy, a phenotypic change that allows tumor cells to survive in response to cell-autonomous or non-autonomous stressors, including antitumor drugs. As for EMT induction, a multitude of glycolytic enzymes as well as acidosis have been shown to induce autophagy in tumor cells (reviewed in [108]). In the following we discuss briefly some findings of particular interest. Thus, in mouse embryonic fibroblasts, glucose starvation, but not amino acid starvation, induced GAPDH phosphorylation by AMPK [224] and its translocation to the nucleus where it interacted with and activated the deacetylase SIRT1. SIRT1 then activated several components of the autophagy pathway and induced autophagy. Other reports confirmed that glycolysis-induced autophagy occurred in the presence of glucose starvation [225,226]. The different outcomes occurring in the presence of glucose sufficiency or glucose starvation were investigated with bladder cancer cells stimulated with vitamin K [227]. In the presence of glucose sufficiency, this led to activation of PI3K/AKT and HIF-1α, upregulation of glycolysis and downregulation of oxidative metabolism. On the other hand, glucose starvation led also to upregulation of glycolysis but, in this case, it was accompanied by AMPK activation, mTORC1 inhibition and induction of autophagy. Others showed that AMPK negatively regulated aerobic glycolysis in cancer cells and exerted tumor-suppressive effects *in vivo* [228]. Moreover, inactivation of AMPK promoted metabolic reprogramming towards glycolysis in both transformed and non-transformed cells. Taken together with the results discussed in the previous section, these results suggest that upregulation of glycolysis in the presence of glucose sufficiency is accompanied by EMT, while in the presence of glucose starvation autophagy is induced [229].

Upregulated glycolysis can induce autophagy also in an AMPK-independent manner. Thus, HK2 induced autophagy in MCF-7 breast cancer cells upon interaction with and inhibition of the activity of mTOR [230], a negative regulator of autophagy [137]. Autophagy was induced also upon interaction of glycolytic enzymes with components of the autophagic cascade, leading to their activation and autophagy induction [231,232]. LDHB, the enzyme that preferentially catalyzes the conversion of lactate to pyruvate, was shown to promote autophagy by inducing lysosomal acidification, vesicle maturation and intracellular proteolysis [233].

Surprisingly, glycolytic enzymes have also been shown to inhibit autophagy in tumor cells (reviewed in [108]). In one case, autophagy inhibition was the result of the direct interaction of a glycolytic enzyme (PFKFB3) with a component of the autophagic pathway (ubiquitin-associated (UBA) domain of p62/sequestosome-1) [234]. Alternatively, autophagy inhibition was induced indirectly, e.g. through the interaction of PKM2 with the PI3K/AKT/mTOR pathway, a negative regulator of AMPK and autophagy induction [235].

On the other hand, autophagy and autophagy-inducing mediators have been shown to positively or negatively regulate glycolysis. Thus, Unc-51-like autophagy-activating kinases 1 and 2 (ULK1/2), mediators of stress signals to the autophagic machinery, have been shown to phosphorylate and activate glycolytic enzymes like HK, PFK1 and ENO1 in conditions of amino acid deprivation, thereby leading to increased glucose uptake and glycolysis [236]. Overall, these results underscore the cross-talk existing between upregulated glycolysis and autophagy in tumor cells [137,237].

Glycolysis and metastasis

EMT plays a crucial role in the early events that lead to metastasis formation, i.e. migration, invasion, dissemination and settlement in pre-metastatic niches. In a previous section we have discussed that upregulated glycolysis can induce EMT. Therefore, it is not surprising that much evidence has been reported about the role of glycolytic metabolism in promoting metastasis formation [103,238–240]. Also in this case, different glycolytic enzymes were involved.

On the other hand, there is also a long list of reports claiming a predominant role of oxidative metabolism in promoting tumor metastasis [126,241,242]. It has also been reported that upregulated oxidative metabolism in PDAC cells promotes metastasis formation but not tumor cell proliferation and primary tumor growth [243].

While, at present, it appears difficult to reconcile these contradictory results, it should be considered that metastasis formation encompasses a series of successive steps from the site of primary tumor growth to the site of metastatic seeding and growth. It appears reasonable to assume that tumor cells may rely on different metabolic pathways during the different steps of this journey. Thus, invasion and migration of tumor cells have been shown to depend on glycolysis-associated EMT (see 4.2.4). During the subsequent steps, in particular if one or more of these include phases of slow proliferation or even quiescence, oxidative metabolism may become predominant. Moreover, glycolytic and oxidative metabolism may also collaborate in the process of metastasis

formation. As already discussed, glycolysis-produced lactate released in the TME can be internalized by tumor cells and fuel oxidative metabolism. Interestingly, MCT1 inhibition decreased metastasis formation, but had little effect on the growth of primary subcutaneous melanomas [244].

Immunosuppressive effects

Tumor glycolysis has immunosuppressive effects. In the following we will discuss some examples.

Lactate promoted immune evasion upon interaction with its specific receptor on stromal dendritic cells and tumor cells. This interaction induced upregulation of the immune checkpoint (ICP) molecule programmed death ligand 1 (PD-L1) on both dendritic and tumor cells [245, 246]. PD-L1 and other ICP molecules inhibit adaptive, antigen-specific immune responses [247]. Lactate enhanced the expression of PD-1 on immunosuppressive regulatory T (T_{reg}) cells upon internalization by MCT1, while dampening the expression on effector (T_{eff}) cells, thereby inducing resistance to anti-PD-1 therapy [248]. Acidosis of the TME suppressed immunotherapy-induced antitumor responses [249]. Upregulated PFKFB3 and HK2 led also to increased expression of PD-L1 on HCC cells, GBM cells and multiple myeloma (MM) macrophages [250]. Concurrent upregulation of glycolysis and PD-L1 as well as other ICPs has been observed in transcriptomic datasets as well as The Cancer Genome Atlas (TCGA) and found to correlate with shorter overall survival (OS) times in patients [251]. Moreover, patients who showed high tumor ^{18}F-FDG uptake and strong expression of GLUT1 had lower responses to immune checkpoint inhibitor (ICI) therapy. In one case, upregulated glycolytic metabolism contributed to the immunosuppressive effects leading to resistance to ICI therapy as part of a hypermetabolic phenotype that was also characterized also by upregulation of oxidative metabolism [252]. Overall, these results are of considerable clinical interest because ICI therapy has become, during the last decade, a therapeutic mainstay for the treatment of different tumor types, like melanoma and NSCLC [247]. Moreover, upregulated tumor glycolysis led to resistance to adoptive T cell therapy [253], another therapeutic approach that is becoming of increasing therapeutic relevance.

Upregulated glycolysis can also inhibit innate immune responses. Lactate and accompanying acidosis in the extracellular environment play also in this case a prominent role. They suppress inflammatory macrophage activation while promoting polarization towards an anti-inflammatory M2 phenotype [254,255]. Lactate inhibited interferon-α induction in plasmacytoid dendritic cells and enhanced kynurenine production, thereby promoting the induction of T_{reg} cells [256]. Glycolytic metabolism has also been shown to reduce the immunogenicity of tumor cells. Thus, replacing HK2 in HCC cells with the lower affinity glucokinase led to reactivation of innate immune responses and restoration of the sensitivity of HCC cells to natural killer (NK) cells [257].

While the vast majority of available evidence suggests that glycolytic enzymes or metabolites expressed in tumor cells have immunosuppressive effects, it is interesting to note that in one instance a glycolytic enzyme acted as an innate immune receptor able to detect bacterial peptidoglycan [258]. This result supports our hypothesis that components of upregulated glycolytic metabolism may act as danger signals able to activate innate immune responses [10]. It will be of obvious interest to discern the circumstances under which a glycolytic component may act as an inhibitor or inducer of immune responses.

It is also intriguing to note that when we consider the effects of glycolytic metabolism on the adaptive and innate immune system in a non-tumor setting, the effects of glycolytic metabolism are rather immunostimulating, rather than immunosuppressive [259–261]. It would go beyond the scope of this article to enter a detailed discussion about possible reasons of this apparent discrepancy but, again, it would be of interest to address this contradictory issue which, in some way, recalls the effects that have been reported for metformin (Glucophage) in tumor and non-tumor settings [262].

Glycolysis and drug resistance

Induction of drug resistance in tumor cells due to upregulation of glycolytic metabolism has been recently reviewed [10]. Briefly, drug resistance occurs in response to upregulated tumor glycolysis through several of the molecular mechanisms that have been described in previous sections: e.g. inhibition of apoptosis, induction of EMT or autophagy, inhibition of drug influx or stimulation of drug efflux, DDR, overcoming of mitotic arrest. Resistance can affect all main classes of antitumor drugs such as chemotherapeutics, high molecular weight (Mr) therapeutics like monoclonal antibodies (mAb) including ICIs, hormone antagonists, tyrosine kinase inhibitors and other targeted low Mr therapeutics, glucocorticoids and ionizing radiation. GLUTs, glycolytic enzymes as well as some glycolytic metabolites like pyruvate, lactate and ATP itself have been shown to mediate drug resistance.

As regards autophagy-induced drug resistance [263], LDHA promoted tamoxifen resistance in breast cancer cells through induction of autophagy, which was associated with the acquisition of EMT traits [232].

Lactate induced resistance to the pan-AKT inhibitor uprosetib in CRC cells [264]. Inhibition of lactate transport or oxidative metabolism increased uprosetib-induced apoptosis, suggesting that resistance was induced upon lactate import and its metabolisation along the TCA cycle/OXPHOS pathway. In fact, also upregulated oxidative metabolism has been shown to induce drug resistance in tumor cells as recently reviewed [265].

Effects on tumor accessory cells

So far, we have discussed the effects of upregulated glycolysis on tumor cells or cells of the immune system. There are, however, also effects on tumor accessory cells other than immune cells that have been described. Thus, PKM2 [266] and lactate [267] have been shown to induce tumor angiogenesis: PKM2 by upregulating the expression of angiogenic factors, and lactate by activating tumor-associated macrophages to adopt a pro-angiogenic phenotype. Inhibition of PFKFB3 induced tumor vessel normalization, improved vessel maturation and perfusion [268]. This caused reduced cancer cell invasion, intravasation, and metastasis. Tumor pericytes from NSCLC and HCC showing elevated HK2-induced glycolysis upregulated their contractility and their blood vessel-supporting function was impaired as compared to pericytes from normal tissues [269].

Consequences of upregulated tumor glycolysis on prognosis

A key question is whether upregulated tumor glycolysis impacts on the prognosis of cancer patients. The answer is yes, since all articles that investigated prognostic parameters like OS and/or progression-free survival (PFS) have reported a negative impact of upregulated glycolysis. In the following some examples. NSCLC patients with circulating tumor cells expressing high levels of HK2 had poor therapy responses and shorter PFS [270]. High serum LDH levels were associated with a reduction in OS in cancer patients [271]. High expression of lactate transporters in GBM tissues indicated a poor prognosis [27]. Upregulated ALDOA and ALDOB were associated with poor prognosis in CRC patients [272–274]. Upregulated PKM2 was associated with poor prognosis in patients with TNBC treated with neoadjuvant chemotherapy [275].

Therapeutic approaches to inhibit tumor glycolysis

In the previous sections we have discussed the effects of upregulated glycolysis in promoting primary tumor growth and metastatic dissemination. Given these effects it is not surprising that, over the years, efforts have been put in place in order to synthesize and develop therapeutically active compounds that inhibit glycolysis and its tumorigenic effects. As we will see in the following, however, only a few of them have progressed into clinical trials, and none of them has, so far, received regulatory approval. In this section we give a bird's eye view of the

current developmental status of glycolysis inhibitors. For a more detailed discussion of this topic the reader is referred to some excellent reviews that have been published in recent years [276–278].

One approach that has been pursued aims at reducing glucose uptake in tumor cells by inhibiting the activity of GLUTs. Different types of molecules have been investigated as GLUT inhibitors, including genistein, STF-31, fasentin, WZB117, phloretin, cytochalasin B, and ritonavir. These molecules had antitumor effects in *in vivo* preclinical models. However, since GLUTs are expressed ubiquitously in all cells, selective inhibition of glucose uptake by tumor cells remains a significant challenge [279,280]. In order to achieve such selective inhibition, one GLUT1 inhibitor, BAY-876, has been loaded onto nanoparticles (NP). In one case [281] the NPs were specifically targeted to GLUTs using glucose ligands. In another case, NPs activatable by the acidic TME were loaded with BAY-876 and modified with PD-L1 and cytotoxic T lymphocyte antigen-4 (CTLA-4)-antagonizing aptamers [282]. The results obtained with these compounds were encouraging and suggest that this is a promising strategy to achieve tumor targeting of glycolysis inhibitors.

HK, the enzyme that catalyzes the first rate-limiting step of glycolysis, is another potential target. HK inhibitors that have been reported include lonidamine, genistein-27, 2-deoxyglucose (2DG), chrysin, benitrobenzrazide, 3-bromopyruvate (3BP), astragalin and resveratrol [283]. Benitrobenzrazide is a putative HK2-selective inhibitor with sub-micromolar potency. 2DG is a glycolysis inhibitor that inhibits the activity of both HK and GLUT1. As will be shown later, this is one of the few glycolysis inhibitors that have been tested in clinical trials.

PFKFBs positively regulate glycolysis through their metabolite, F2,6BP. PFKFB inhibitors are 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3PO) and its derivative, 1-(4-pyridinyl)-3-(2-quinolinyl)-2-propen-1-one (PFK15). Both have been shown to possess activities consistent with their glycolysis inhibitory effect, including reduction of glucose uptake, lactate secretion and proapoptotic effects [284].

PDK is another potential target for glycolysis inhibition in cancer because it negatively regulates PDH, the enzyme that transforms pyruvate into acetyl-CoA, thereby feeding the TCA cycle and oxidative metabolism. Dichloroacetate (DCA) is a PDK inhibitor and, as will be seen in the following, it has progressed into clinical trials.

LDH catalyzes the conversion between pyruvate and lactate. The LDHA isoform preferentially catalyzes the pyruvate to lactate conversion, LDHB the opposite, i.e. the lactate to pyruvate conversion. Several LDHA inhibitors have been synthesized and investigated: FX11, a small catechol-containing compound; oxamate, a competitive inhibitor of pyruvate; GNE-140, a potent orally available LDH inhibitor.

Eventually, also transporters that cause predominantly lactate influx into the cells (monocarboxylate transporter (MCT) 1, or predominantly lactate efflux out of the cells (MCT4) have been identified as potential pharmacological targets. The MCT1 inhibitor AZ3965 has entered clinical investigation and, in fact, appears to be the only glycolysis inhibitor still in active clinical development.

Many of the glycolysis inhibitors discussed so far have shown significant antitumor activity in animal tumor models. It is, therefore, surprising that only a few of them have progressed into clinical trials (Table 1). In fact, only the HK inhibitor 2DG, the PDK inhibitor DCA and the MCT1 inhibitor AZ3965 have been tested in tumor patients. Moreover, several of these studies are outdated and have progressed only up to early-stage trials. These facts raise the obvious question as to which are the reasons for these disappointing results and why only a small number of available glycolysis inhibitors have progressed into the clinics.

Three reasons can be envisaged. First, the first generation of compounds targeting glycolytic enzymes were directed against catalytic sites. It was realized that many of these compounds lacked specificity and/or had to be directed against hydrophobic catalytic sites. More recently, attention has been focused on allosteric inhibitors, which appear more promising in terms of specificity and synthetic feasibility [277]. Second, in many cases, inhibition of glycolysis is followed by metabolic rewiring and upregulation of oxidative metabolism. This suggests the need to target the two main metabolic pathways at the same time, with the obvious possibility that this will be accompanied by unacceptable side effects. Third, available glycolysis inhibitors target enzymes or transporters that are ubiquitously expressed. Again, any antitumor effect may be accompanied by side effects due to glycolysis inhibition in normal cells. Of particular concern are the effects on

Table 1
Glycolysis inhibitors that have been tested in clinical trials.

Molecular Target	Mechanism of Action	Compound(s)	Clinical Indication(s)	Phase	Effects observed in clinical trials	Clinicaltrials.gov Number	References
HK	Inhibition of HK	2DG	Metastatic solid tumors and hormone-refractory prostate cancer	I/II	Serious AEs recorded in 3/12 patients; no outcome reported.	NCT00633087	None
HK	Inhibition of HK	2DG + docetaxel	Advanced solid tumors	I	34 patients; most common AEs were fatigue, sweating, dizziness and nausea; 11 patients had SD, 1 PR, 22 PD.	NCT00096707	[285]
HK	Inhibition of HK	2DG + radiotherapy	Untreated patients with GBM	I/II	2DG administered p.o. 30 min before irradiation. Transient hypoglycemia in most patients., at 300 mg kg^{-1}, 2/6 patients were very restless. No damage to normal brain tissue during follow-up.	None	[286]
MCT1	Transporter mediating lactate influx into cells	AZ3965	Adult solid tumors, DLBCL, BL; patients with high MCT1.	I	AEs were primarily grade 1 or 2, 7 patients receiving ≥20 mg/day had DLTs: grade 3 cardiac troponin rise, ocular DLTs, grade 3 acidosis. On-target activity was demonstrated.	NCT01791595	[287]
PDK	Inhibition of PDK → upregulation of oxidative metabolism	DCA	Recurrent malignant brain tumors	I	8 patients completed at least 1 four-week cycle and remained clinically stable. No DLTs. 2 patients experienced grade 0-1 distal paresthesias.	NCT01111097	[288]
PDK	Inhibition of PDK → upregulation of oxidative metabolism	DCA	Advanced solid tumors	I	24 patients enrolled. No DLTs at 6.25 mg kg^{-1} BID. 3/7 patients had DLTs (fatigue, vomiting, diarrhea) at 12.5 mg kg^{-1} BID. No responses were observed, 8 patients had SD.		[289]

Abbreviations: 2DG, 2-deoxy-D-glucose; AE, adverse event; BID, twice daily; BL, Burkitt lymphoma; DCA, dichloroacetate; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; MCT, monocarboxylate transporter; PD, progressive disease; PDK, pyruvate dehydrogenase kinase; PR, partial response; SD, stable disease.

tumor-associated immune cells where glycolysis inhibition may lead to tumor-promoting immunosuppressive effects [277]. As we will discuss in the conclusive section, approaches targeting specifically glycolysis in tumor cells may offer a solution to bypass this problem.

Conclusions

In this article we have discussed the consequences of upregulated tumor-associated glycolysis that have been identified so far. There are, however, unresolved questions that have to be addressed in the future.

A first question is whether metabolic reprogramming towards glycolysis shows a positive association with one or more tumor types. We did not find such an association, although there are some exceptions, such as fumarate hydratase (FH)-deficient tumors or clear cell RCC where glycolysis is predominantly used because oxidative metabolism is obstructed (reviewed in [290]).

On the other hand, a positive association has been proposed between the expression of individual oncoproteins and a glycolytic phenotype as, for example, in AML, the presence of fms-like tyrosine kinase 3 (FLT3)-internal tandem duplication (ITD) (FLT3-ITD) [291] or in RAS-driven tumors [292]. For RAS-driven tumors, however, results in favor of a crucial role for oxidative metabolism have also been reported [101, 293], suggesting that the metabolic consequences of tumor-driving oncoproteins are context-dependent [294]. Overall, these results suggest that the metabolic phenotype of tumors is the result of a balance between stimuli (intracellular and/or extracellular, as described in section 3) that upregulate glycolysis and the tissue where the tumor originates (Fig. 4).

Eventually, a strong positive association has been observed between the metabolic tumor phenotype and the proliferative or quiescent status of tumor cells: proliferating tumor cells rely predominantly on glycolytic metabolism, while slowly proliferating or quiescent tumor cells rely predominantly of oxidative metabolism.

As to the therapeutic perspectives of inhibiting glycolytic metabolism in the cancer setting, the few clinical results that have been reported so far are rather disappointing (see section 5). In some way this is not surprising because, as we have pointed out throughout this article, tumors are characterized by a pronounced metabolic plasticity with the capacity to switch from a predominantly glycolytic to oxidative metabolism and vice versa.

A possible exception is represented by those rare tumors where oxidative metabolism is completely disabled and tumor cells rely exclusively on glycolytic metabolism for their metabolic needs. Thus, in the large majority of cases, it would be necessary to block both glycolytic and oxidative metabolism in order to inhibit overall ATP production and other metabolic outputs. There are, indeed, preclinical studies suggesting the feasibility of this approach [36,134], but it seems reasonable to expect that an approach of this kind would be accompanied by intolerable side effects, particularly upon prolonged or chronic administration, as is likely required for antitumor therapy. One possibility to avoid these downsides is to take advantage of targeting approaches, either using compounds that block both metabolic pathways encapsulated in nanoparticles that target antigens overexpressed or specifically expressed on tumor cells [295] or upon conjugation of these compounds to carriers (e.g. mAbs) that similarly recognize these tumor antigens [296]. In section 5 we have discussed a few articles that have pursued this approach. We feel that this road is worthwhile being explored further in order to harness the metabolic dependencies of tumors while

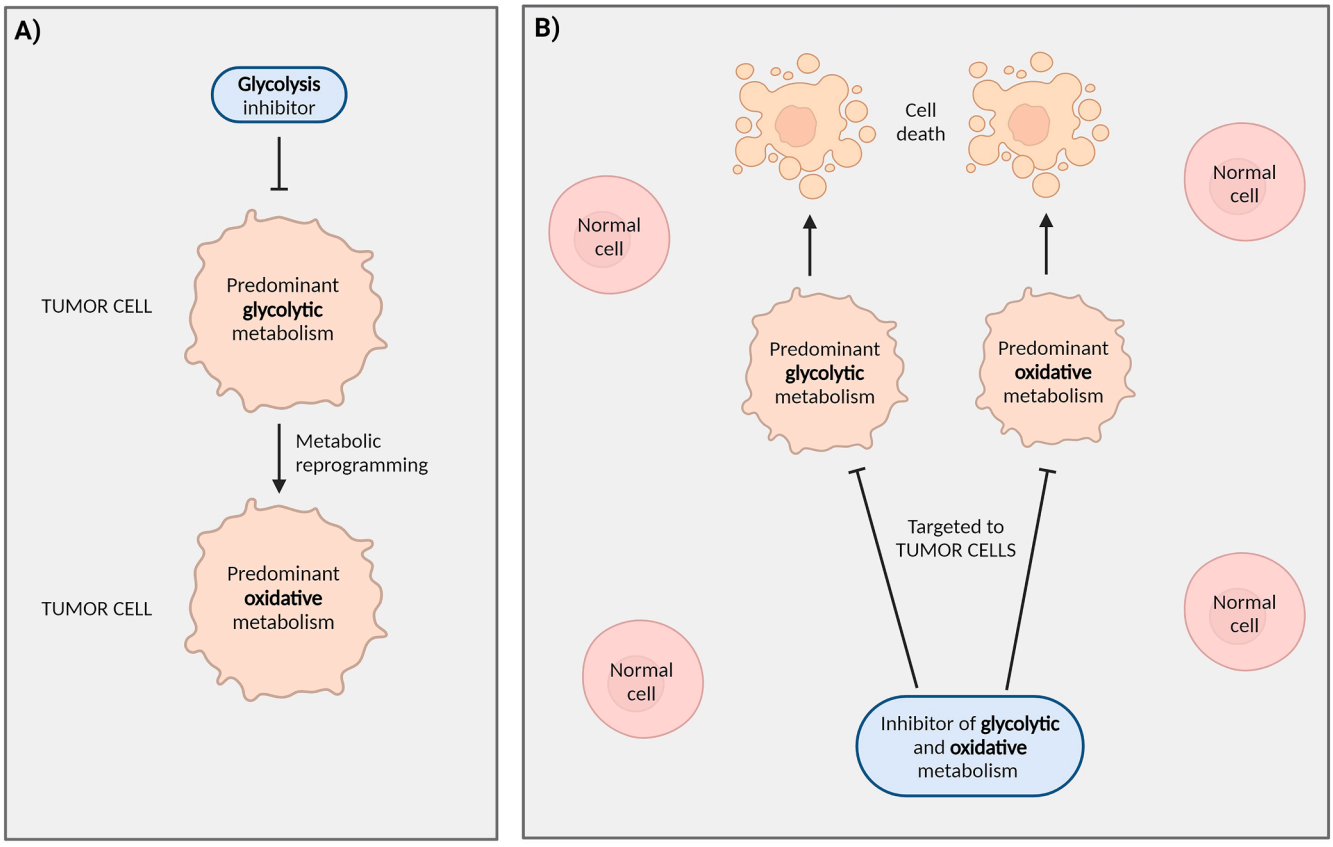

Fig. 4. Tumor targeting of inhibitors of glycolytic and oxidative metabolism. A) Administration of inhibitors of glycolytic metabolism may induce metabolic reprogramming towards oxidative metabolism in tumor cells allowing them to bypass the antitumor effects of the inhibitors. B) Administration of inhibitors that block both glycolytic as well as oxidative metabolism may be required in order to achieve efficacious antitumor activity. An approach of this kind however, may be accompanied by unacceptable side effects. In order to avoid these effects, it is proposed to take advantage of tumor targeting approaches, allowing to deliver the drug (s) preferentially to tumor cells while sparing normal cells.

limiting possible side effects.

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CRediT authorship contribution statement

Marco Cordani: Writing – review & editing. **Federica Michetti:** Writing – review & editing. **Ali Zarrabi:** Writing – review & editing. **Atefeh Zarepour:** Writing – review & editing. **Cristiano Rumio:** Writing – review & editing. **Raffaele Strippoli:** Writing – review & editing, Supervision. **Fabrizio Marcucci:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

All authors declare no conflict of interest.

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