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REVIEW

How do glycolytic enzymes favour cancer cell proliferation by nonmetabolic functions?

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Cancer cells enhance their glycolysis, producing lactate, even in the presence of oxygen. Glycolysis is a series of ten metabolic reactions catalysed by enzymes whose expression is most often increased in tumour cells. HKII and phosphoglucose isomerase (PGI) have mainly an antiapoptotic effect; PGI and glyceraldehyde-3-phosphate dehydrogenase activate survival pathways (Akt and so on); phosphofructokinase 1 and triose phosphate isomerase participate in cell cycle activation; aldolase promotes epithelial mesenchymal transition; PKM2 enhances various nuclear effects such as transcription, stabilisation and so on. This review outlines the multiple non-glycolytic roles of glycolytic enzymes, which are essential for promoting cancer cells' survival, proliferation, chemoresistance and dissemination.

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INTRODUCTION

In normal tissue, the vast majority of nonproliferating differentiated cells use oxidative phosphorylation (OXPHOS) for ATP production. These cells metabolise glucose to pyruvate through glycolysis, then oxidise this pyruvate through the tricarboxylic acid cycle, generating ATP through ATP synthase, the rate of the production being coupled with proton transport and on oxygen respiration.[1] In contrast, rapidly proliferating tumour cells consume glucose at a higher rate compared to normal cells and part of their glucose carbon is converted into lactate, even in oxygen-rich conditions; this is referred to as the 'Warburg effect' or 'aerobic glycolysis'. For ATP production, cancer cells may enhance the β-oxidation of lipids, the oxidative use of glutamine and/or lactate.[2–4] Furthermore, amino-acid uptake (alanine, aspartate, methionine and so on) is essential to replenish the tricarboxylic acid.[5] The Warburg effect seems to be a consequence to uncoupling between glycolysis and tricarboxylic acid-OXPHOS due to pyruvate dehydrogenase inactivation and lactate dehydrogenase activation, in relation to HIF-1 and c-Myc activation.[6,7] Since 2011, it is widely acknowledged that metabolic reprogramming is a hallmark of cancer,[8] providing tumour cells with all the metabolites (such as serine), derived from glucose and glutamine metabolism,[9,10] they need for growth and proliferation, such as nucleotides, macromolecules, lipids and also NAD^+, $NADPH,H^+$ cofactors. Currently, a large body of evidence supports the idea that activated oncogenes, inactivated tumour suppressors and transcriptional factors are linked directly or indirectly to the cellular metabolic reprogramming, establishing a relationship between genetic alterations and glucose metabolic phenotype.[5,6,11–13] The glycolytic pathway is a series of ten metabolic reactions catalysed by multiple enzymes or enzyme complexes whose expression is most often increased in tumour cells. The aim of this review is to emphasise their non-glycolytic functions such as their nuclear role (DNA repair, transcription and so on) and their implications in many other functions, such as apoptosis, detoxification, cell cycle control, signalling pathways and so on.

Hexokinases

In the cytosol, glucose (or fructose) is phosphorylated by hexokinases (HK) (glucose kinase or fructose kinase) to glucose-6-phosphate (G6P). HK catalye the first irreversible reaction of glycolysis. Among the four mammalian HK isoenzymes (HKI to HKIV), HKII is highly expressed in many cancers.[14,15] This predominant isoform has no regulatory site,[16] a characteristic favouring resistance to the Pasteur effect. HKII involved in the diversion of glucose towards glycolysis or pentose phosphate pathway (PPP) that sustain anabolic pathways such as glycerol and serine or nucleotide biosynthesis, respectively.[17] Moreover, HKII is bound to outer mitochondrial membrane porins (voltage-gated anion channels) to facilitate access for newly synthesised ATP for phosphorylation glucose.[18] This binding of HKII to the mitochondria decreases the negative feedback of G6P on HK, increasing glucose metabolism via glycolysis in tumours.[19]

The interaction of HKII with the voltage-gated anion channels depends on glucose uptake. Glucose deprivation prevents this interaction in the outer mitochondrial membrane, which modifies mitochondrial membrane potential leading to apoptosis through the release of apoptogenic molecules.[20,21] These mechanisms could be implied in BH3-only molecules, in particular Bad and Bid,[22–24] which may link glycolysis and apoptosis in response to glucose uptake.[25]

Numerous studies indicate that HKII overexpression has a central role in the development of cancers and is associated with oncogenic transformation and poor prognosis.[26–29] This upregulation has been demonstrated to be induced by HIF-1α in certain tumours[23] and is also believed to be due to the c-Myc oncogene.[30,31] Furthermore, mRNA and protein expression levels of HKII are regulated by microRNAs (miRs). The overexpression of

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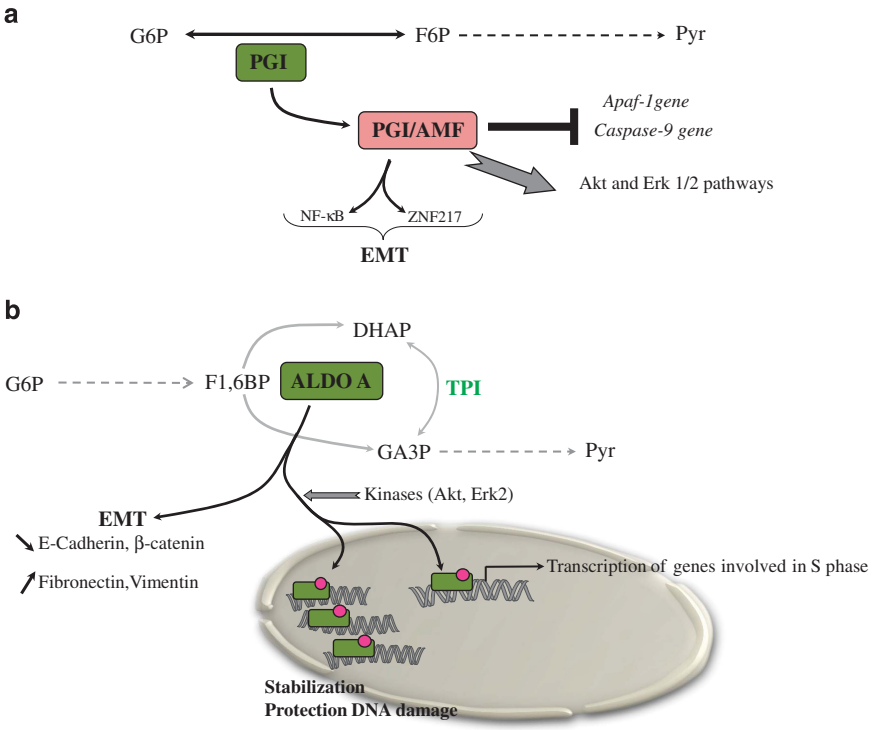

Figure 1. Schematic representation of non-glycolytic functions of PGI and aldolase A (ALDO A). (**a**) PGI acts as cytokine outside the cell with properties of the autocrine motility factor (AMF) referred to as PGI/AMF. It indirectly regulates expression of *Apaf-1* and *caspase-9* genes, blocking the formation of apoptosome. PGI/AMF could induce cell proliferation and reduce apoptosis through PI3K/Akt and Erk1/2 pathways. Expression of PGI/AMF is implied in the epithelial-to-mesenchymal transition (EMT) through the upregulation of NF-κB factor and ZNF217 factor. (**b**) ALDO A may be phosphorylated by Akt or Erk 2 kinases then may translocate in the nucleus. In this compartment, ALDO A is involved in the regulation of transcription of genes implied in cell cycle progression, but also in the stabilisation of transcripts by linking with AT-rich DNA sequences, and in the protection of DNA in response to DNA damage. In cytosol, ALDO A is implied in the EMT through modifications in the expression of markers of this process.

miR-143, tumour-suppressive miRNA or anti-oncomiR, inhibits both mRNA and protein expression of HKII, and represses metabolism in cancer cells.[32,33] In prostatic and breast tumours, an inverse correlation has been found between miR-143 expression and HKII level, such as a decrease in miR-143 expression linked to an increase in HKII expression.[32] This miR-143 has been found to be under indirect control of miR-155,[33] which is an oncomiR-repressing tumour suppressor gene.[34]

Phosphohexose isomerase (phosphoglucose isomerase, PGI)

PGI (also referred to as phosphohexose isomerase or G6P isomerase) is a second glycolytic enzyme that catalyses the isomerisation of G6P into fructose-6-phosphate. PGI has other biological roles when secreted as an extracellular cytokine with properties that include autocrine motility factor (AMF), also referred to as PGI/AMF.[35,36] Overexpressed secretion of PGI/AMF has been observed in the serum and urine of patients with gastrointestinal, kidney and breast cancers.[36,37] PGI/AMF induces the transformation and survival of NIH-3T3 fibroblasts,[38] promotes cell motility[39] and is associated with cancer progression and metastasis,[40,41] notably through ERK activation that produces IL-8 in response to PGI/AMF.[42] Moreover, PGI/AMF inhibits expression of *Apaf-1* and *caspase-9* genes, and indirectly regulates the formation of the apoptosome that induces tumour resistance to apoptosis. The relationship between PGI/AMF and inhibition of Apaf-1 and caspase-9 expressions remains to be studied[43] (Figure 1a). PGI/AMF could also reduce apoptosis through PI3K/Akt signalling pathway activation. This action seems a consequence of an interaction between PGI/AMF and HER2, inducing HER2 phosphorylation. This pathway activates phosphoinositide-3-kinase and mitogen-activated protein kinase signalling leading Akt activation.[38,44] This activation is generally associated with increased tumour progression, tumour cell invasiveness and antiapoptosis.[45] Downregulation of PGI/AMF decreases the expression of Akt and Erk1/2[46] and induces epithelial–mesenchymal transition (EMT), hence reducing malignancy.[47] Thus, PGI/AMF is implied in the regulation of EMT, a phenomenon that is associated with acquisition of invasive phenotype by cancer cells.[48] PGI/AMF upregulates the NF-κB transcription factor and ZNF217 factor, which contribute towards the induction of EMT, and downregulates the mi-R-200 family, which is involved in the inhibition of this process[49,50] (Figure 1a).

Phosphofructokinase 1 (PFK1)

PFK1 converts fructose-6-phosphate into fructose-1,6-bisphosphate. This is the second irreversible reaction of the glycolytic pathway and a major glycolysis checkpoint.[11] PFK1 is stimulated by ADP/AMP, whereas citrate, long-chain fatty acids, lactate and ATP act as strong inhibitors, providing negative feedback for glycolytic rate,[51,52] (for a review, refer to Ros and Schulze[53]). Moreover, in response to hypoxia, the O-linked β-*N*-acetylglucosamine (O-GlcNAc) post-translational modification is dynamically induced at Ser529 of PFK1, hence inhibiting its activity.[54] This regulation reorients a great share of glucose flux through the PPP, and results in an increase in NADPH, which is an essential cofactor for lipogenesis and also contributes towards GSH, reducing power regeneration and conferring cancer cells with a growth advantage.

The most potent allosteric activator of PFK1 is fructose-2,6-bisphosphate (F2,6BP), which induces PFK1 activity even in the presence of ATP, suggesting that it could have a role in PFK1 upregulated activity in many tumours.[55] The synthesis and degradation of F2,6BP depend upon 6-phosphofructo-2-kinase (PFK2)/F2,6BPase (PFK2), which includes both kinase and phosphatase activities. There are four mammalian PFKFB isoenzymes (PFKFB 1 to 4).[56] The PFKFB3 isoenzyme has the highest kinase/phosphatase activity ratio (740/1) and thus leads to elevated F2,6BP levels, which in turn sustain high glycolytic rates. In contrast, it has been shown that F2,6BPase overexpression induces a decrease in the rate of F2,6BP,thereby blocking glycolysis. F2,6BP expression is high in a number of aggressive cancers (e.g. breast, colon and ovarian)[57] and is induced by hypoxia in cultured human colon adenocarcinoma cells.[58] PFKFB3 overexpressed activity induces the expression of several cell cycle regulators such as phosphatase, Cdc 25C, and cyclin D3 and represses the cell cycle inhibitor p27, all of which contribute towards an increase in CDK1 activity.[59,60]

Aldolase (ALDO) and Triose phosphate isomerase (TPI)

Fructose-bisphosphate ALDO catalyzes the reversible reaction of fructose-1,6-bisphosphate to glyceraldehyde-3-phosphate and dihydroxyacetone phosphate. In human tissue, three ALDO isozymes are expressed in a tissue-dependent manner: ALDO A (mainly in muscles), ALDO B (mainly in liver) and ALDO C (expressed in neuronal tissue).[61] ALDO A is the most commonly expressed in tumour tissue[62] and is overexpressed in various cancers such as squamous cell lung cancer[63,64] and hepatocellular carcinoma.[65]

In addition to its glycolytic function, ALDO A is involved in several functions, which are distinct from its glycolytic role, such as signal transduction,[66] vesicle trafficking,[67] and cell motility.[68] Several studies have demonstrated that ALDO A interacts with the F-actin, which is involved in cell division during cytokinesis. Thus, ALDO A knockdown reduces cell proliferation but is apparently not effective on glycolytic flux, and increases multinucleation.[69] Recently, ALDO A overexpression has been shown to promote EMT and cell migration by decreasing E-cadherin and β-catenin, and by concomitantly increasing fibronectin and vimentin, all processes that favour tumorigenicity[63] (Figure 1b). ALDO A has also been found in the nuclear localisation of many types of tumour,[70,71] whereas decreased proliferation has been shown to induce a reduction in ALDO in the nucleus.[69] The mechanisms involved in the subcellular localisation of ALDO A are not yet clearly known and it might act as a cofactor favouring proliferation. Its transport towards the nucleus may be regulated by phosphorylation as described *in vitro* by PKCμ and ERK2.[72] The inhibition of kinases, such as Akt and PKC that are frequently overexpressed in carcinogenesis[73] have been shown to alter ALDO A nuclear localisation.[74] In the nuclear compartment, ALDO A associates with nucleic acids, particularly with AT-rich DNA sequences.[71,75] This association may have a role in the stabilisation of transcripts[76] and could also be involved in agents such as ultraviolet radiation[77] (Figure 1b). ALDO A seems to be related with the activation of transcription of certain genes involved in S phase and may also be correlated with proliferative cell activity (for example, DNA replication)[69,74,75] (Figure 1b).

TPI is an homodimeric enzyme that converts dihydroxyacetone phosphate into glyceraldehyde-3-phosphate, and only the latter can complete glycolysis and thus prevent the accumulation of dihydroxyacetone phosphate.[78] TPI has been found in increased levels in lung cancers,[79] squamous cell lung carcinomas[80] and urinary cancers.[81] It has also been shown to be upregulated in chemoresistant ovarian carcinoma compared to sensitive parental cell lines.[82] *In fine,* activation of this enzyme is responsible for ATP production by glycolysis, whereas its inhibition or slow-down orients dihydroxyacetone phosphate towards the PPP,[83] which is a key source of reduced NADPH, a cofactor for anabolic pathways (for example, fatty acid biosynthesis) and in maintaining the redox balance.[84] Moreover, PPP produces ribose and is involved in the transcription of gene expression during stress conditions.[85] Thus, TPI regulates the distribution of metabolites between glycolysis or PPP, by coordinating $NADPH,H^+$ and ATP production with redox metabolism depending on reactive oxygen species production. Gruning *et al.* demonstrated that an accumulation of phosphoenolpyruvate inhibits TPI activity,[83,86] which in turn promotes the PPP pathway, protecting cells against oxidants and, consequently, preventing reactive oxygen species accumulation. In contrast, the loss of TPI catalytic activity is a consequence of phosphorylation of this glycolytic enzyme by the cyclin A/Cdk2 complex, resulting in disrupted energy production in etoposide-treated HeLa cells, rendering these cells sensitive to apoptosis.[87] Interestingly, upregulation of TPI expression could partially reverse the multidrug-resistant phenotype of SGC7901/VCR, suggesting that TPI may be an anti-drug-resistant agent in gastric cancer and a target candidate for developing novel therapeutics for better treatment of gastric cancer.[88]

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH)

GAPDH is one of most the important enzymes involved in cell energy metabolism as it produces glycerate-1,3-biphosphate and $NADH,H^+$, an essential cofactor required for ATP production by OXPHOS, and/or to sustain lactate dehydrogenase-5 activity. It is noteworthy that lactate dehydrogenase-5 activity, which is stimulated by $HIF1^3$ and is crucial to regenerate NAD^+, required for GAPDH activity. The *GAPDH* gene is classically used as a housekeeping gene, but it is known to be overexpressed in many tumours compared to in normal tissue, and correlated with poor prognosis or tumour aggressiveness (for example breast, colorectal, glioma, lung, melanoma ovarian, pancreatic, prostatic and renal cancer) (for a review, refer to Guo *et al.*[89]), and increased drug resistance.[90]

Various non-glycolytic functions of GAPDH have been reported in cancer, such as involvement in cell death,[91–94] DNA repair,[95,96] immunity[97] (for a review, refer to Tristan *et al.*[98]) and cancer cell senescence.[99] These functions are dependent on the localisation of the enzyme (mainly located in cytoplasm, but also in nucleus, mitochondria and vesicular fractions).[98,100,101] Exposure to various stresses (for example, DNA damage, *S*-nitrosylation),[92] (for a review, refer to Huang *et al.*[102]) modification of conformation (homo-oligomerisation, tetrameric structure) and post-translational modifications of GAPDH such as acetylation[103–106] and phosphorylation[107] influence the localisation and function of this enzyme. It has been reported that GAPDH overexpression is associated with cell proliferation via its effect on cyclin B-cdk1 activity.[108] Moreover, in the case of abundant glucose, GAPDH links its substrate, glyceraldehyde-3-phosphate, liberating the small GTPase Rheb that is recognised as an important positive regulator of mTORC1,[109] a crucial pathway regulating many cellular responses to growth factors[73] (Figure 2).

GAPDH seems to have controversial action on apoptosis. Certain studies have reported a proapoptotic function[92,105] when GAPDH is located in the mitochondria and associated with the voltage-dependent anion channel 1 to induce apoptosis.[94] Contrariwise, others have described a protective role and its implication in tumour progression[110] (for a review, refer to Colell *et al.*[91]).

Phosphoglycerate mutase (PGAM)

PGAM catalyses the interconversion of 3-phosphoglycerate (3-PG) and 2-phosphoglycerate (2-PG), corresponding to the eighth reaction of glycolysis. PGAM activity is commonly upregulated in many human cancers[80,111,112] and its inhibition is lethal to cancer

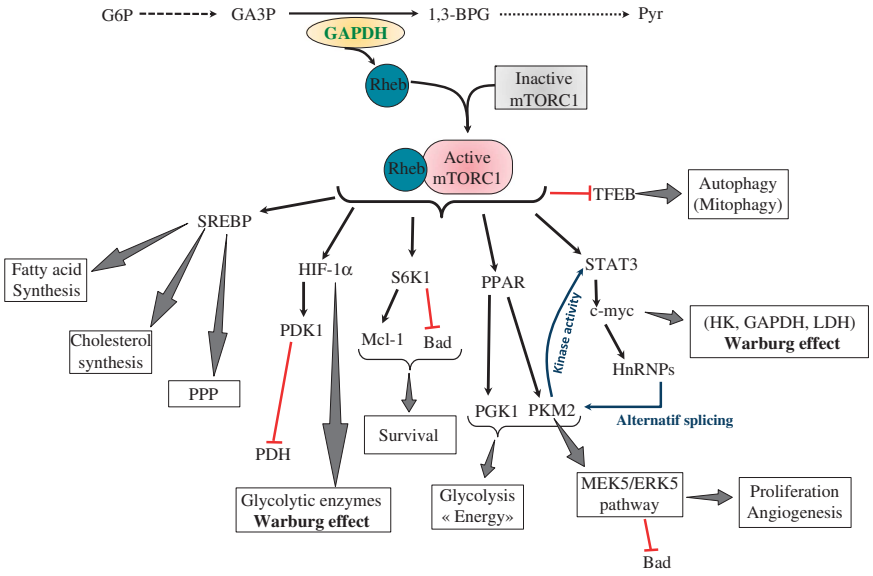

Figure 2. Multifaceted functions of GAPDH. GAPDH is a crucial factor linking metabolism and tumour growth. When glycolysis is stimulated, GAPDH releases, in cytosol, the small GTPase Rheb that is a positive regulator of mTORC1, a crucial signalling pathway for stimulating cell growth. The Rheb-mTORC1 complex regulates several phenotypic characteristics of cancer cells supporting proliferation and survival: metabolic reprogramming (Warburg effect) furnishing energy to anabolic biosynthesis sustaining division (PPP, fatty and cholesterol synthesis); apoptotic protection and various mechanisms such as autophagy, mitophagy and angiogenesis, which sustain cell metabolism.

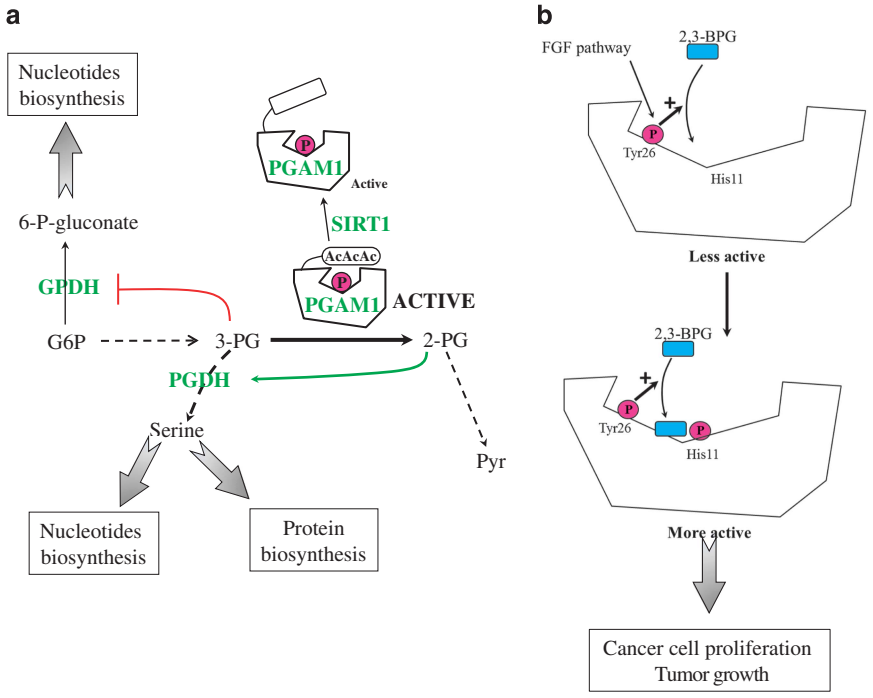

Figure 3. (**a**) PGAM regulation and allosteric action of PGAM1. PGAM1 regulates glycolytic flux and serine synthesis. Acetylation of PGAM1 stimulates its glycolytic activity and enhances glycolysis. In return, the 3-PG level is decreased, abrogating its inhibition to glucose-6-phosphate dehydrogenase, while 2-PG level is increased. This molecule favours serine synthesis by activating phosphoglycerate dehydrogenase. Of note, SIRT1 level leads to deacetylation of PGAM1 and decreases its enzymatic activity. (**b**) Control of PGAM1 activation. Tyrosine 26 phosphorylation of PGAM1 (due to growth factors such as fibroblast growth factor) contributes towards favouring 2,3-bisphosphoglycerate (2,3-PG) binding and stabilisation on PGAM1. In this setting, PGAM1 is more active and promotes cancer cell proliferation and tumour growth.

cells in culture.[113] PGAM plays a crucial role in coordinating glycolysis and biosynthesis of pathways to promote cancer cell proliferation, particularly in hypoxia. Indeed, under hypoxic conditions, the expression of the *PGAM* gene is induced, resulting in increased protein expression and concomitant elevation of PGAM enzymatic activity.[114,115] This induction might contribute towards the regulation of glycolytic flux and cell adaptation hypoxia.[116] PGAM is a critical regulatory step in glycolysis as PGAM inhibition by epoxide inhibitors is lethal to cancer cells.[117] Overexpressed PGAM can maintain its substrate (3-PG) at low

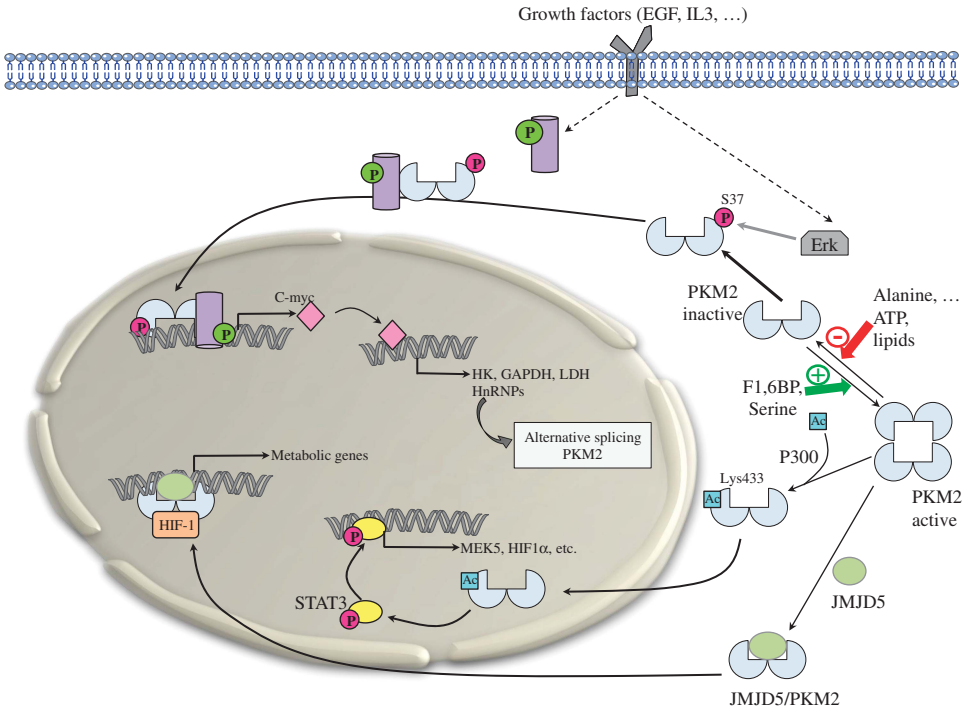

Figure 4. Schematic representation of non-glycolytic functions of PKM2. The regulation between tetrameric and dimeric PKM2 form is an oscillating phenomenon subject to allosteric regulation: glycolytic intermediate F1,6BP and the biosynthetic by-product serine induce the active form of PKM2 whereas high concentration of ATP and/or of downstream biosynthetic products (amino acids and lipids) lead the inactive dimeric form of PKM2. This form can be translocated from cytoplasm to nucleus in response to various processes such as phosphorylation, acetylation on lysine 433 and interaction with a dioxygenase/demethylase, Jumonji C domain-containing dioxygenase (JMJD5). In the nucleus, JMJD5/PKM2 acts as a direct transcriptional coactivator of the metabolic genes under control of HIF1α. Nuclear PKM2 dimeric also induces c-Myc expression, leading to the upregulation of glycolytic genes and of HnRNPs, which favours the alternative splicing of the PK isoform M2. Acetylation of PKM2 on lysine 433 leads to STAT3 phosphorylation, which enhances the transcription of genes such as *mek5* and *hif1-α* genes, which are essential for tumour cell proliferation, migration and adhesion.

levels, abrogating its inhibition of the G6P dehydrogenase enzyme involved in PPP. Furthermore, the increase in 2-PG activates the phosphoglycerate dehydrogenase enzyme, which diverts the 3-PG to serine biosynthesis, thus contributing towards the needs of rapidly growing tumours[9,118] (Figure 3a).

Acetylation and phosphorylation are post-translational modifications in cells and the majority of enzymes participating in glycolysis are acetylated on lysine residues, including PGAM.[119] Thus, PGAM1 regulates anabolic biosynthesis by controlling intracellular levels of substrate, the 3-PG, and product, the 2-PG. Acetylated PGAM displays enhanced activity, whereas Sirt1, a member of the NAD^+-dependent protein deacetylases, leads to PGAM deacetylation and downregulation of mutase activity.[120] This deacetylation maintains a high level of intracellular 3-PG, which in turn reduces PPP level by inhibiting G6P dehydrogenase. Phosphorylated PGAM (Tyr26) by fibroblast growth factor receptor 1 induces release of inhibitory Glu19 by facilitating access to the active site and by stabilising active conformation[121] (Figure 3b). This phosphorylation is crucial for the mutase reaction, transforming 3-PG to 2-PG in glycolysis[118,122] and inducting the 2-PG level, which in turn sustains phosphoglycerate dehydrogenase. This enzyme diverts 3-PG from glycolysis to serine synthesis and contributes towards maintaining a low level of 3-PG in cancerous tumours. Moreover, the phosphoenolpyruvate pyruvate kinase (PK) substrate can phosphorylate PGAM at the catalytic His11 (H11), producing pyruvate (the same applies in the absence of PKM2 activity)[123] and 2,3-BPG, which is a cofactor for phosphorylating His11[122] (Figure 3b).

Pyruvate kinase

PK catalyses the tenth and last reaction of glycolysis, which also is an irreversible reaction by transferring the phosphate from phosphoenolpyruvate to ADP to produce ATP and pyruvate.[124] There are two distinct PK genes: *PKL/R* (pyruvate kinase, liver and red blood cells) and *PKM2* (pyruvate kinase, muscle), which express four PK isoforms: L, R, M1 and M2,[125,126] (for a review, refer to Mazurek[127]). PKM1 and PKM2 are encoded by alternative splicing of the *PKM* gene[125,128] which is notably regulated by three heterogeneous nuclear ribonucleoproteins (hnRNPA1, A2 and I), themselves regulated by c-Myc.[129–131] Elevated PKM2 expression is now known as a common characteristic of all cancers[132] and is closely associated with poor prognosis in certain tumours[133–136] (for a review, refer to Wong *et al.*[132]).

PK is expressed in most cells and exists as inactive monomers, less active dimers and active tetramers. The balance between tetrameric and dimeric PKM2 is an oscillating phenomenon subject to allosteric regulation: it is activated by the glycolytic intermediate F1,6BP and by the biosynthetic by-product serine and it is inactivated by the concentration of ATP and downstream biosynthetic products (alanine, amino acids and lipids) increases[3,127,137–140] (Figure 4). Furthermore, PK is downregulated by phosphorylation on Tyr105 by fibroblast growth factor receptor 1, Bcr-Abl and JAK2.[141,142] Although dephosphorylated PKM2 tetramers orient pyruvate towards the tricarboxylic acid cycle to produce ATP by OXPHOS, phosphorylated PKM2 dimers induce a bottleneck that favours a high rate of biosynthesis, such as nucleotides, phospholipids and amino acids[5,143] but also indirectly sustain the Warburg effect by regulating gene expression.[144]

Besides phosphorylation, acetylation plays a role in the regulation of PKM2, as acetylation on Lys305 decreases PKM2 activity,[145,146] (for reviews, refer to Huang *et al.*[102] and Yang and Lu[147]).

The relationship between dimeric or tetrameric PKM2 state allows the proliferating cells to regulate their needs for anabolic and catabolic pathways and is controlled by oncogenes and tumour suppressors.[129,137,148,149] MUC1 (mucin 1) is an oncoprotein that is overexpressed in many epithelial cancers[150] (for a review, refer to Kufe[151]). MUC1-cytoplasmic domain (MUC1-CD) is translocated to the cell nucleus where it directly interacts with multiple transcriptional factors and also acts as a transcriptional coactivator by linking transcription factors, for example, STAT3, NF-κB, β-catenin and HIF1-α (refer to the recent review by Nath and Mukherjee[152]). Indeed, it is implied in the regulation of PKM2 activity by directly associating with PKM2 to enhance its activity, whereas tyrosine phosphorylation of MUC1-CD decreases its activity.[153]

PKM2 can be translocated from cytoplasm to cell nucleus under certain conditions such as apoptotic signals,[154] interleukin-3 response,[155] phosphorylation by ERK1,[156] acetylation on Lys 433[146] and interaction with a dioxygenase/demethylase, Jumonji C domain-containing dioxygenase (JMJD5)[157] (for a review, refer to Yang and Lu[147]) (Figure 4). In this compartment, PKM2 acts as (1) a transcriptional coactivator, such as JMJD5/PKM2, which modulates the HIF1α-mediated transcriptional reprogramming of metabolic genes;[157] nuclear PKM2 interacts with Oct-4 to enhance Oct-4-mediated transcription potential[158] and also with phosphorylated β-catenin to induce c-Myc expression leading to the upregulation of glycolytic genes[156,159] that promote tumorigenesis; (2) a kinase protein activates STAT3 via phosphorylation on Tyr305 with phosphoenolpyruvate as a phosphate donor[144] and enhances the transcription of genes that are essential for tumour cell proliferation, such as *mek5* and *hif1-α* genes[160] (for a review, refer to Demaria and Poli[161]) but also promotes cell migration and adhesion in a STAT3-dependent manner (Figure 4). These effects are due to repression of E-cadherin by induction of Snail-2 expression,[162,163] upregulation of matrix MMP-2 and MMP-9 (metalloproteinases-2 and -9)[162] and could be responsible for metastatic progression (for review on MMP-2 and -9, refer to Bauvois[164]). Finally, PKM2 phosphorylates histone H3 on Thr11, a process that is required for histone H3 acetylation on Lys9; they also remove histone deacetylase 3 (HDAC3) from *CCDN1* and *MYC* promoter.[165] All these effect favour cell proliferation, invasion, metastasis and epigenetic regulation of gene expression.

CONCLUSIONS

Dysfunctions in oncogenes and or tumour suppressor genes cause modifications in various intracellular signalling pathways, which reprogramme tumour cells metabolism to allow enhanced survival and growth. Enhanced aerobic glycolysis has a key role in this metabolic reprogramming. The complex process of cancer growth needs a flexible cell metabolism, in which the nonenzymatic functions of most enzymes of glycolysis may offer an important contribution. Although each enzyme may have multifaceted roles, roughly HKII and PGI have mainly an antiapoptotic effect, PGI and GAPDH activate survival pathways (Akt and so on), PFK1 and TPI participate in cell cycle activation, ALDO promotes EMT and PKM2 enhances various nuclear effects such as transcription, stabilisation and so on. These multifaceted roles of enzymes participate towards linking the plastic metabolism of cancer cells with various processes sustaining cancer cell growth and implied in tumour relapse, while potentially contributing towards the link between obesity with shortened life span or cancer. Further studies should consider these functions linking glycolysis and tumour growth which very likely will allow to develop new anticancer strategies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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