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Review

A global view of the biochemical pathways involved in the regulation of the metabolism of cancer cells

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ABSTRACT

Cancer cells increase glucose uptake and reject lactic acid even in the presence of oxygen (Warburg effect). This metabolism reorients glucose towards the pentose phosphate pathway for ribose synthesis and consumes great amounts of glutamine to sustain nucleotide and fatty acid synthesis. Oxygenated and hypoxic cells cooperate and use their environment in a manner that promotes their development. Coenzymes (NAD^+, $NADPH,H^+$) are required in abundance, whereas continuous consumption of ATP and citrate precludes the negative feedback of these molecules on glycolysis, a regulation supporting the Pasteur effect. Understanding the metabolism of cancer cells may help to develop new anti-cancer treatments.

Contents

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1. Introduction

In contrast to normal cells which arrest glycolysis in the presence of oxygen and favor oxidative phosphorylation-ATP production (OXPHOS), cancer cells lose this regulation and favor glycolysis-producing lactate. This "aerobic glycolysis" was first observed by Otto Warburg in the 1920s [1]. The Warburg effect has led to increasing data focusing on the signaling pathways that conduct this reprogramming [2–6]. Understanding the biochemical routes that redirect the metabolism towards biosynthesis may be a source of inspiration for developing new anticancer treatments. The aim of this review is to dissect the main biochemical routes involved, although some of them remain partly deductive, emphasizing the importance of molecules such as NAD^+, ATP and citrate, for regulating and driving these pathways.

2. The metabolism of cancer cells: The importance of the Warburg effect and loss of the Pasteur effect

The biochemical metabolism of cancer cells is disrupted in order to promote the production of lactate, despite the presence of O_2.

2.1. The Warburg effect

Cancer cells synthesize great amounts of nucleotides, macromolecules and lipids, and these biosynthesis require continuous production of NAD^+, $NADPH,H^+$ and ATP. They consume at least 10 times more glucose than normal cells [5,7,8] and produce lactic acid, even in the presence of oxygen. High rates of glucose uptake have been clinically used to detect tumours by positron emission tomography with a glucose analogue tracer (PET) [9]. Aerobic glycolysis was considered by Warburg as a defect in mitochondrial respiration [8] and/or in ATP production by others (for review [5]) implying: - F1/F0 ATPase defect or mitochondrial content depletion [10]–SCO2 (synthesis of cytochrome c oxidase 2) defect, since aerobic glycolysis is reversed by re-expressing SCO2, an assembly factor controlled by p53 entering in complex IV [11]; an abrogation of proton gradient by uncoupling proteins (UCP) such as UCP2, which are overexpressed in various cancer cells [12,13]; cardiolipin abnormalities also favoring the dissipation of energy [14]; and mutations in certain electron transport chain (ETC) complexes encoded by mtDNA exposed to ROS damage because mtDNA is not surrounded by histones [15–18]; however, mitochondrial mutations are inconsistently observed [19–26] or remain silent [27].

In contrast to these hypotheses, many cancer lines may not be inherently more glycolytic than normal cells [28], and/or may not generate defective OXPHOS production [29]; their aerobic glycolytic phenotype could be a normal adaptation to a hypoxic environment. The ATP production mode of cancerous and normal cells of the same origin should be compared [28–30], and it is likely that the part of glycolysis depends on the type of cancer cell and on microenvironment, which may or may not provide oxygen and nutrients in abundance. Interestingly, the Warburg effect is not believed to exclusively concern cancer cells, but also embryonic proliferative cells [21].

Cancer cells located in well-oxygenated areas divide the most rapidly, thus favoring OXPHOS production of ATP, in contrast to more hypoxic cells [29,31–33], which need to consume larger amounts of glucose, since OXPHOS is slowed down or arrested, a downregulation which might avoid excessive ROS production [34,35]. In the highly hypoxic core areas of tumors [36,37], glycolysis necessarily becomes the main, if not the unique cause of ATP generation. It is not so surprising that these "hardy cells" correspond to higher malignancy grades [32,38], because hypoxia forces them to adapt and develop several strategies to avoid apoptotic or necrotic death: overexpression of oncogenes, such as hypoxia-inducing factor-1 (HIF-1) which promotes hypoxic metabolism [39,40]; overexpression of UCP2 which can reduce ROS production [12,13]; over-activation of cytosolic dehydrogenases, in particular of lactate dehydrogenase A (LDH-A) which produces more NAD^+ which is crucial for glycolysis function [13,41–43]; overexpression of anti-apoptotic proteins such as Mcl-1 and Bcl-x_L [44–46]; and activation of a mitochondrial autophagy protective effect [47–50].

2.2. Lactic acid production

Lactate production is an essential feature of cancer cells. The isoform LDH-M, which is regulated by the c-Myc [51] and/or HIF-1 target gene *LDH-A* [43], transforms pyruvate into lactate. This route is favored because the conversion of pyruvate in acetyl-CoA through pyruvate dehydrogenase (PDH) is inactivated by pyruvate dehydrogenase kinase 1 (PDK1) [52–54]. This blockade leads to an uncoupling between glycolysis and the TCA cycle (Fig. 1), which drives pyruvate away from acetyl-CoA generation and causes a reduction in the quantities of NADH and $FADH_2$ delivered to ETC, decreasing ROS production, especially when limited levels of O_2 are present [18,43].

2.3. The main role of HIF-1α in the loss of the Pasteur effect

In the presence of O_2, normal cells arrest glycolysis (Pasteur effect) in favor of OXPHOS, producing 18 times more ATP than glycolysis. This effect may be related to HIF-1α [40,43,55], which modifies the expression of numerous genes involved in glycolysis, lactate production and extrusion, angiogenesis and metastasis [56,57]. The kinase mTOR stimulated by AKT favors HIF-1α transcription [58]. HIF-1α is a major determinant of the glycolytic phenotype because it activates glucose transporters (GLUT), several key enzymes of glycolysis such as hexokinase II (HKII), phosphofructokinase (PFK) and pyruvate kinase M2 (PKM2) [4,6,43,52,55,59–61]. It also stimulates LDH-A and PDK1, promoting lactic acid production [52,53,59,62]. HIF-1α is normally inactivated in an oxygen-dependent manner by prolyl hydroxylase domain protein (PHD), which allows HIF-1α recognition by the von Hippel–Lindau (VHL) protein complex, the latter addressing HIF-1α for poly-ubiquitylation and destruction at the proteasome [63,64]. In hypoxia (defined as $\leq$2% O_2), HIF-1α protein expression levels increase gradually with O_2 concentration [32,65,66]. The potential reasons for HIF-1α escaping inactivation in normoxia include mutation of the von Hippel–Lindau (VHL) protein [67] and inhibition of PHD by succinate and fumarate as a result of mutations in succinate dehydrogenase (SDH) and/or fumarate hydratase (FH) [68–70], which act as suppressor genes since their mutations lead to the development of many tumours [71,72]. Moreover, pyruvate or oxaloacetate (OAA), which accumulate in hypoxia, activate HIF-1α in a feedback loop, even upon re-oxygenation [73]. Lactate also induces HIF-1α activation [74].

3. Major catabolic pathways

3.1. Glycolysis

To provide essential molecules (ribose, glycerol, serine, etc.) for biosynthesis, glycolysis is slowed down at its end, where pyruvate kinase (PK) converts phosphoenolpyruvate (PEP) into pyruvate, which leads to the production of ATP. This blockade is related to re-expression of PK in its embryonic form (PKM2), which is less active than the adult form. PKM2 plays a key role in the Warburg effect [75–77], and favors the transcription of HIF-1α in the nucleus [78]. The dimeric phosphorylated form of PKM2 is inactive and causes a bottleneck, favoring glucose metabolism towards biosynthesis. In contrast, the dephosphorylated tetrameric form leads to ATP and lactic acid production [21,76,77]. The switch from the inactive to the active form is an oscillating process, controlled by allosteric regulation implying the concentration of F1,6P and serine [79,80], and by covalent regulation through protein kinase A [75,76,79]. The binding of phosphotyrosine peptides to PKM2 results in the release of its main allosteric activator F1,6P [81,82], whereas phosphatase PP2A deficiency is thought to play a key role in the modulation activity of PKM2 [22]. Due to PKM2 dimeric preponderance in

cancer cells [80], pyruvate production derived from glucose is reduced and other sources of pyruvate are needed to sustain LDH activity. Pyruvate may derive from alanine by transamination (ALAT) and/or from malate decarboxylation by ME [83]. PEP, which accumulates above the bottleneck, acts as a feedback inhibitor of triose phosphate isomerase (TPI) [60]. This inhibition results in equal production of dihydroxyacetone phosphate (DHAP) and glyceraldehyde 3-phosphate (GA3P). DHAP feeds glycerol formation for triglyceride synthesis, whereas GA3P sustains PPP for ribose synthesis [60]. GA3P also sustains 3-phosphoglycerate (3-PG) production involved in serine synthesis [84]. PEP may bypass the PKM2 bottleneck and be converted into pyruvate, through an alternative pathway that does not generate ATP, hence avoiding the negative control on PFK1 [85]. Because alternative oscillation between the active and inactive forms of PKM2 is required to produce ATP (but only 2 molecules per glucose), it is likely that other sources of ATP are involved, through mitochondrial oxidation of glutamine or fatty acids.

3.2. Other routes for glucose: Pentose phosphate pathway (PPP) and glycogen storage

Glucose 6-phosphate (G6P) can be used by the PPP to produce ribose 5-phosphate (R5P) which is required in abundance for nucleotide synthesis [86]. If the oxidative part of PPP is involved, it also produces $NADPH,H^+$, required for DNA, fatty acid synthesis and the redox system. The balance between the engagement in the oxidative or the non-oxidative part of PPP is regulated by the availability of glucose 6-phosphate (G6P) and $NADPH,H^+$ [87] which control glucose 6-phosphate dehydrogenase (G6PDH), the first enzyme in the oxidative part of PPP. F1,6P which accumulates above the PKM2 bottleneck may inhibit G6PDH, limiting the participation of the oxidative branch of the PPP in R5P synthesis [83]. In addition, GA3P is converted into R5P by transketolase (TKTL) and aldolase of the non-oxidative part of PPP. TKTL1 isoform is activated and overexpressed in various cancers, correlating with invasiveness and poor outcome [83,88,89]. Another mechanism could promote the non-oxidative branch of PPP: the inhibition of PFK1 activity results in an increase in F6P that can be channeled into the non-oxidative branch of PPP [90]. Glucose can be stored as glycogen in tumours [91], through glycogen synthase activity, which is inhibited through phosphorylation by glycogen synthase kinase-3 (GSK3). The latter enzyme is thought to play a suppressor role [92], and is inhibited by the PI3K/AKT signaling pathway [93]. Due to GSK3 inactivation, cancer cells may store glycogen in abnormal quantities, which could be used when their microenvironment is impoverished in glucose [30] by glycogen phosphorylase activation [94].

3.3. Proteolysis provides intermediates for the TCA cycle and base synthesis, and sustains the LDH reaction

Cancer cells consume great quantities of amino acids, especially glutamine (Gln) [83,90,95–97], which is the preferential mode of transportation of blood nitrogen (NH_4), and alanine derived from muscle proteolysis, hence favoring cachexia [98]. The rate of consumption is not explained by protein synthesis because it 10 times in excess of the need for essential amino acids [95]. This could be related to the proteolysis-inducing factor (PIF), a catabolic factor produced by tumors which stimulates proteolysis in skeletal muscle [99]. Gln is transported at the plasma membrane [100] and provides amine groups for nucleotides, amino acids, tetrahydrofolate and gluthation synthesis. Gln is converted by the mitochondrial enzyme glutaminase (GLS) into glutamate (Glu), which is transformed by glutamate dehydrogenase (GDH) into α-KG. This intermediate could replenish the TCA cycle, producing OAA, or be expelled outside mitochondria to feed the transaminase reactions that produce aspartate (ASAT) and pyruvate (ALAT) (Fig. 1). Finally, up to 60% of Gln can be converted into lactate [101]. Although the conversion of Gln and Glu is typically bidirectional, the reaction towards Glu is favored by a high Gln input and by overexpression of GLS under c-Myc control [102] and/or suppression of glutamine synthase (GS) [83,103,104].

Glutaminolysis may be the main source of OAA required for TCA cycle function [105], which requires this molecule to be reformed at each cycle. Pyruvate carboxylase (PC), which forms OAA from pyruvate [106,107], is thought to be relatively inactive in cancer cells, because acetyl-CoA, its allosteric activator, is consumed by high CS activity [108]. Finally, glutamine provides a great proportion of citrate, either through glutaminolysis [90] or through the IDH route in case of defective OXPHOS [105]. Citrate subsequently sustains *de novo* lipid synthesis, the LDH route and/or the transaminases cascade (ALAT and ASAT) in a direction that consumes glutamine and alanine.

3.4. Lipolysis may produce an essential part of ATP

The consumption of lipids by cancer cells remains to be further investigated. Cancer cells induce lipolysis in adipose tissues, a characteristic of cachexia, by producing lipid mobilization factors [99]. It is often considered that β-oxidation is suppressed in tumor cells because glycolysis is physiologically activated while β-oxidation is inactivated (and vice versa), and because the PI3K/AKT signaling pathway promotes glycolysis and lipid synthesis [109]. However, from a theoretical point of view, the products of β-oxidation (i.e. acetyl-CoA, $NADH,H^+$ and ATP) inhibit PDH, whereas ATP inhibits PK [87,110,111]. Both retroactions reinforce the PK bottleneck and the aforementioned PDH inactivation. Therefore, β-oxidation could be active concurrently to glycolysis in cancer cells, producing a large share of the acetyl-CoA that feeds the CS reaction, rather than pyruvate, which is directed towards lactate production. β-Oxidation is a highly energetic pathway, the complete oxidation of palmitate, a common fatty acid of 16 carbons, resulting in the formation of 106 ATP. It has recently been reported that environmental adipocytes may act as an essential energy storage solution for ovarian cancer cells, providing cancer cells with fatty acids [112]. Therefore, the inhibition of β-oxidation could offer a new therapeutic strategy for counteracting cancer growth, given that the inhibition of the mitochondrial transport of fatty acid may induce cancer cell death [113].

4. Citrate, cofactors (NAD^+, $NADPH,H^+$) and waste products sustain and promote biosynthesis

4.1. The role of citrate in ATP production

Complete oxidation of glucose and of glutamine (glutaminolysis) produces 36 ATP and 9 ATP respectively. Glycolysis is fundamental because it provides intermediates required for proliferation (ribose for nucleotides, glycerol for membrane and serine for tetrahydrofolate synthesis). Although glycolysis is an inefficient way to produce energy (2 ATP products per metabolized glucose), its capacity to very quickly adjust ATP production to the considerable input of glucose could give a selective advantage to proliferative cells [2,114]. Furthermore, ATP is maintained at a low level, precluding the negative feedback of ATP on PFK1. To override this inhibition, PFK2 (also referred to as PFKB3) activation appears fundamental in cancer cells [87,115], and could play a major role in the deregulation that leads to the loss of the Pasteur effect. PFK2 interconverts fructose-6-phosphate into fructose 2,6-bisphosphate (F2,6P), which is a powerful allosteric activator of PFK1, promoting glycolysis, whereas its nuclear overexpression promotes the cell cycle [116–118]. F2,6P is a p53 target which represses glycolytic flux by promoting TIGAR synthesis (TP-53 induced glycolysis and apoptotic regulator) which dephosphorylates F2,6BP [47,119]. PFK1 and PFK2 are also dependent on citrate [120,121], which is a powerful physiological censor of ATP production, allowing close adjustment of metabolic flow

through feedback reactions on key regulator enzymes, not only of glycolysis but also of TCA cycle (PDH, SDH, and malate dehydrogenase: MDH) [122–124]. Therefore, in normal cells, when sufficient quantities of citrate are produced by mitochondria, citrate accumulates outside mitochondria and blocks PFK1 and PFK2 [120,121], whilst simultaneously blocking the TCA cycle which results in the arrest of ATP synthesis [115]. It is likely that cancer cells avoid this citrate feedback on PFK, supporting the Pasteur effect, presumably because citrate is continuously catalyzed by ATP citrate lyase (ACLY) or by isocitrate dehydrogenase (IDH). As expected, ACLY inhibition [125] or cancer cell exposure to citrate blocks glycolysis and leads to cell death in a dose-dependent manner [126,127].

The ACLY route is presumably favored in cancer cells because the TCA flux may be slowed down or inactivated below CS at various levels: aconitase, could be inactivated by HIF1-α [39] or by nitric oxide (NO) [128]; α-ketoglutarate dehydrogenase (α-KDH), an enzyme very similar to PDH could be inactivated by the same mechanisms; and SDH could be inactivated either by citrate [123], malonate (derived from malonyl-CoA)[87] or by mutations [71,72].

The ACLY reaction provides abundant acetyl-CoA for enhanced *de novo* lipid synthesis, the first enzyme involved in this synthesis – acetyl-CoA carboxylase (ACC) – being activated by citrate [87]. ACLY also provides OAA, which is transformed into malate by MDH, producing cytosolic NAD^+ [83]. Malate returns into mitochondria through the malate/aspartate shuttle (Fig. 1), or is preferentially transformed into pyruvate by malic enzyme (ME), producing $NADPH,H^+$ [83]. In hypoxic cancer cells, it is likely that the malate/aspartate shuttle is unprimed [22], because TCA-OXPHOS function is slowed down or arrested. In normoxia, glutamine oxidation feeds the TCA cycle which results in producing OAA which feeds nucleotide synthesis through the aspartate shuttle. Of note, enhanced ACLY activity lowers the cytosolic citrate level, avoiding its negative feedback on PFK. However, when *de novo* lipid synthesis is slowed down or inactivated, citrate could be transformed into isocitrate by aconitase and then into α-ketoglutarate (α-KG) by IDH. α-KG could feed the TCA cycle or could be diverted towards alanine aminotransferase (ALAT), producing glutamate and pyruvate. It could also be used by mutant IDH, producing 2 hydroxyglutarate (2-HG), a product presenting oncogenic properties [129,130]. Interestingly, in hypoxic situations, the IDH route could be used in a reversed manner to produce citrate, from glutamine-derived α-KG [105].

4.2. NAD^+ production is crucial for cancer cell growth regulation

Cancer cells require an abundance of NAD^+, which must be regenerated by cytosolic dehydrogenases such as MDH, LDH and glycerol phosphate dehydrogenase (GPDH). The influence of NADH oxidase, which plays a role in inhibiting reactive oxygen species (ROS), to restore the NAD^+ pool remains to be studied. NAD^+ supports glycolysis at glyceraldehyde 3-phosphate dehydrogenase (GAPDH) level, and pyrimidine synthesis at the dihydro-orotate dehydrogenase reaction. NAD^+ also controls the differential regulation of HIF-1α and HIF-2α by sirtuin 1 (SIRT1), an NAD^+-dependent deacetylase [39]. High levels of NAD^+ activate SIRT1, which results in decreased HIF-1α transcriptional activity and enhanced HIF-2α-mediated stimulation of target genes, including erythropoietin, angiogenic factors and aconitase stimulation[39,131]. Although HIF-1α and HIF-2α share certain redundant functions, they exhibit unique and even opposing activities in cell growth, metabolism, angiogenesis, nitric oxide production and other processes that affect tumor growth [39]. For example, HIF-1α stimulates NO production by nitric oxide synthase (iNOS) aimed at restoring local pO_2, in contrast to HIF-2α.

NAD^+ is also required by poly(ADP-ribose) polymerase (PARP) for efficient base-excision repair of apurinic sites, since cancer cells present frequent DNA breakage that requires repair [79,132,133]. Thus, the metabolic Achilles' heel of the tumor metabolome could be its sensitivity to a reduction of NAD^+ levels caused by activation of poly(ADP-ribose) polymerase after DNA damage [79]. Interestingly, Weinhouse contested Warburg's ideas, arguing that cancer cells may have normal OXPHOS capacity if supplemented with NAD^+ [30,134].

4.3. $NADPH,H^+$ production sustains lipid synthesis and the redox system

$NADPH,H^+$ is consumed in large quantities by reductive biosynthesis of fatty acids, nucleotides and amino acids [2,3,6,21,22,59,132]. For example, palmitate synthesis – a major lipid constituent of membrane – requires 14 molecules of $NADPH,H^+$. This cofactor also plays a major role as an anti-oxidant, maintaining the pool of reduced glutathione (GSH), a molecule that plays a key role in the detoxification system. ROS promote proliferation via several mechanisms (DNA mutations, phosphatase inhibition generating a brake on protein kinases, etc.) [135,136]. However, when present in excess, ROS create oxidative damage that leads to cell death. $NADPH,H^+$ is also required for the redox state of cytochrome *c*, the lack in oxidized cytochrome *c* preventing apoptosis induction [137]. For that purpose, $NADPH,H^+$ must be continuously regenerated either by the oxidative part of PPP and/or by malic enzyme (ME), the contribution of the latter becoming essential in cells favoring non-oxidative PPP through TKTL1 activation [83,101]. The role of enzymes such as isoforms of IDH [138,139,79] in NADPH, H^+ production remains to be investigated, given that IDH mutations may be associated with better survival in glioblastoma [140].

4.4. Waste products and cooperative symbiosis sustain survival and proliferation

Acidosis is often associated with hypoxia, but can also be observed in the microenvironment under normoxia conditions [141]. This acidification could be the “raison d'être” of the Warburg effect, promoting cancer cell invasion and spread [142–146], favoring extracellular degradation and selecting phenotypes that are resistant to apoptosis [142,147–149]. In order to acidify their microenvironment, cells extrude lactate via the monocarboxylate transporter 4 (MCT4), regulated by HIF-1 [150] (Fig. 2) and eject protons through several systems, such as the V-ATPase [3] or the sodium-proton exchanger 1 (NHE1) [151–153]. This anti-porter requires to be coupled with the sodium-potassium (Na^+/K^+)-ATPase to avoid the accumulation of sodium in the cytosol [154–156]. Because ATP hydrolysis has been found to be proportionate to lactate formation [157], the overall activity of the (Na^+/K^+)-ATPase observed in fully oxygenated cancer cells could be due to increased lactic fermentation rates, as observed in non-transformed muscle cells [30,158]. To avoid intracellular acidification leading to restricted ribosomal biogenesis [159] and cell cycle arrest [160], it is crucial for cancer cells to export protons. CO_2 produced mainly by oxygenated cancer cells is both a source of microenvironment acidification and of cell cytoplasm alkalinization. It is evacuated and hydrated by carbonic anhydrase-9 (CA-9), a transmembrane enzyme which is overexpressed in various cancer cells [161,162]. CA-9 converts CO_2 into $HCO3^-$ and H^+ which acidifies the microenvironment, whereas $HCO3^-$ returns inside cells to maintain a neutral or alkaline pH which favors LDH-5 and PFK1 activities [163,164].

Cells reject lactate, hence favoring tumor angiogenesis [74], reducing cell adherence by stimulating the production of hyaluronan [146] and playing an immunosuppressive role against cytotoxic T cells [165]. Cells also reject alanine and glutamine when in excess, and it has been estimated that more than half of glutamine-derived carbon could be secreted as lactate and alanine [96,101]. These molecules may serve to reproduce glucose by liver gluconeogenesis (Cori cycle). Lactate can be used by oxygenated cancer cells as oxidative fuel. For that purpose, it may be transported by MCT1 in well-oxygenated cells and used to reform pyruvate (through LDH-1 encoded by *LDH-B*)

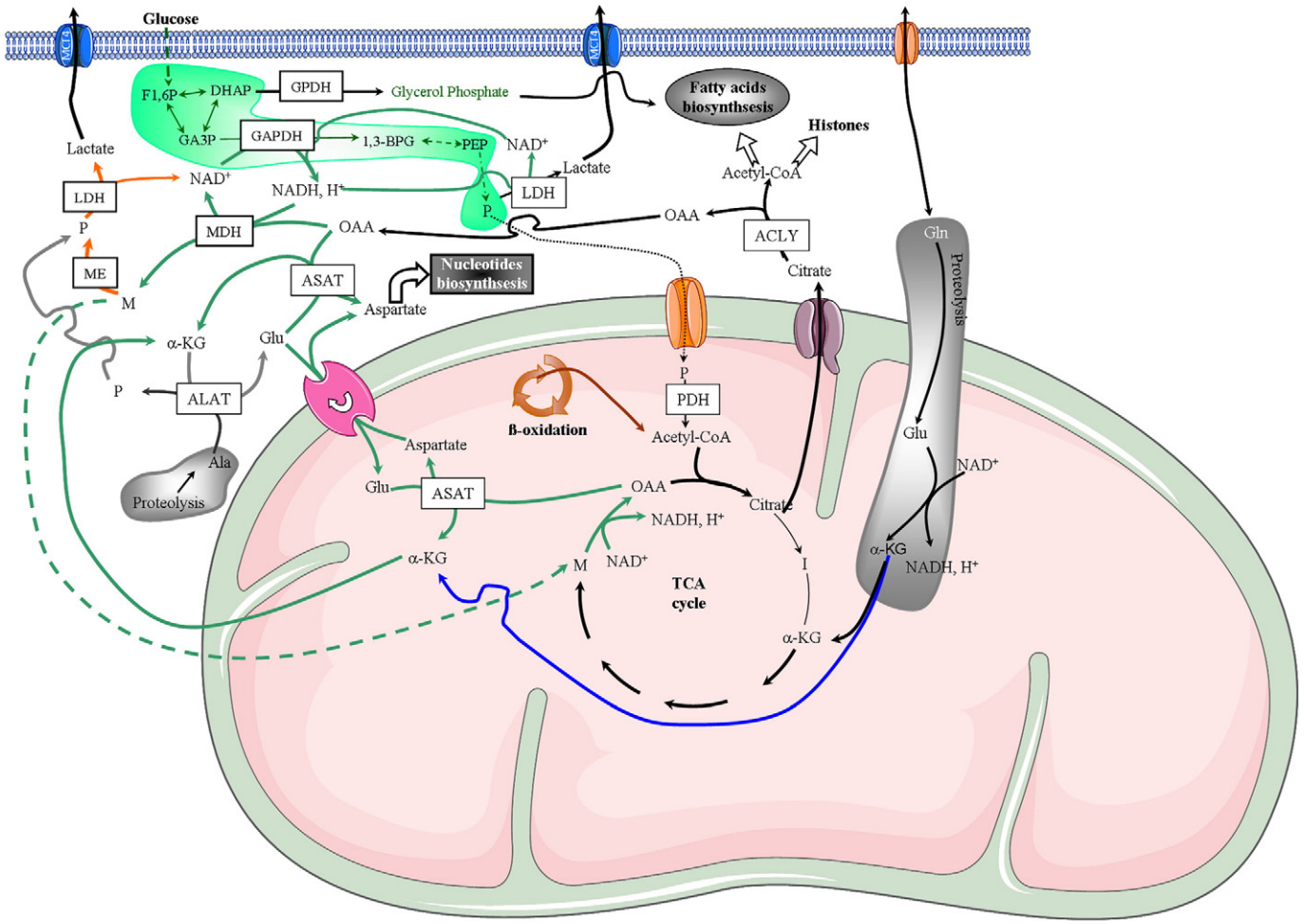

Fig. 1. A model of the biochemical pathways in cancer cells. Well-oxygenated cells proliferate at a higher rate and consume great amounts of substrates to proliferate. The low activity of PKM2 creates a bottleneck at the end of glycolysis, diverting glucose transformation towards biosynthesis (nucleotides, lipids, etc.) rather than pyruvate formation. PDH slowdown favors an uncoupling between glycolysis and TCA, which is supplemented preferentially by glutaminolysis and/or β oxidation resulting in α-keto and acetyl-CoA production, feeding aspartate (derived from OAA) and citrate formation. Citrate moves outside mitochondria, where ACLY reforms acetyl-CoA and OAA. Acetyl-CoA feeds lipid synthesis and target acetylation (histones, proteins, etc.). OAA is converted into malate by MDH or into aspartate by ASAT, which feeds nucleotide synthesis. Malate may return into mitochondria through the malate/aspartate shuttle or may be preferentially transformed into pyruvate by ME, feeding the LDH reaction. The malate/aspartate shuttle operates with two antiporters: one enters malate in mitochondria in exchange for α-KG, whilst the other releases aspartate from the mitochondria in exchange for glutamate. Cytosolic dehydrogenases (MDH, LDH, GPDH) regenerate NAD^+, whereas the oxidative part of the PPP, and/or ME provides $NADPH,H^+$. ACLY: ATP citrate lyase, Ala: alanine, ALAT: alanine amino transferase, ASAT: aspartate amino transferase, 1,3BPG: 1,3-bisphosphoglycerate, DHAP: dihydroxyacetone phosphate, F1,6P: fructose 1,6 diphosphate, GA3P: glyceraldehyde 3-phosphate, GAPDH: glyceraldehyde 3-phosphate dehydrogenase, Gln: glutamine, Glu: glutamate, GPDH: glycerol phosphate dehydrogenase, α-KG: α-ketoglutarate, LDH: lacticodehydrogenase, M: malate, MCT 4: monocarboxylate transporter 4, MDH: malate dehydrogenase, ME: malic enzyme, NAD^+: nicotinamide adenine dinucleotide, NADPH, H^+: nicotinamide adenine dinucleotide phosphate, OAA: oxaloacetate, P: pyruvate, PDH: pyruvate dehydrogenase, PEP: phosphoenolpyruvate, PG: phosphoglycerate, PKM2: pyruvate kinase isoform M2, PPP: pentose phosphate pathway, R5P: ribose 5-phosphate, TCA: tricarboxylic acids cycle.

feeding the TCA cycle of these cells, producing 18 ATP per lactate and sparing glucose for most anoxic cells [59,155,166–168]. This cooperation between hypoxic and normoxic tumor cells optimizes ATP production (as a result a molecule of glucose leads to 38 ATP) and allows cells to adapt efficiently to their environmental oxygen conditions [166–170] (Fig. 2). This "metabolic symbiosis" sustains tumor growth [76] and contributes to chemotherapy and radiotherapy resistance [32,38]. Cancer cells also reject several other end products, such as $NH4^+$, NO, glycocyamine, etc., which are likely to promote proliferation and/or re-expression of fetal genes [21]. $NH4^+$ derived from glutaminolysis appears as a diffusible autophagy regulator, mediating resistance to chemotherapy and oxidative stress in nutrient-poor regions of solid tumors [171].

5. Main anabolic pathways

Biosyntheses are necessarily enhanced by cancer cells to build new tumor substance. To save the ATP required by essential *de novo* synthesis, it is likely that cells promote salvage pathways, sparing ATP, and directly incorporate several molecules or macromolecules found in their environment [172]. Metabolic coupling occurs between cancer cells and environmental cells such as adipocytes [112] or autophagic stroma cells[97,173,174] that may serve as "food donors."

5.1. Lipid synthesis

Cancer cells are highly dependent on their *de novo* lipid synthesis [175], which is promoted by the PI3K/AKT/mTOR pathway [176], and reflected by increased expression of lipogenic enzymes, such as fatty acid synthase (FAS) [177–180]. Acetyl-CoA derived from citrate is converted into malonyl-CoA under the action of acetyl-CoA carboxylase (ACC), a key regulator enzyme activated by citrate [87]. FAS then catalyses the NADPH-dependent condensation of acetyl-CoA and malonyl-CoA in fatty acids, consuming great quantities of ATP and $NADPH,H^+$ [87,110,111]. Of note, acetyl-CoA feeds the acetylation of histone [181], favoring gene expression [2,21,22]. Enhanced CS activity promotes the lipid route rather than mitochondrial ketone body synthesis [182]. It is likely that the ketogenic route and histone acetylation are favored in

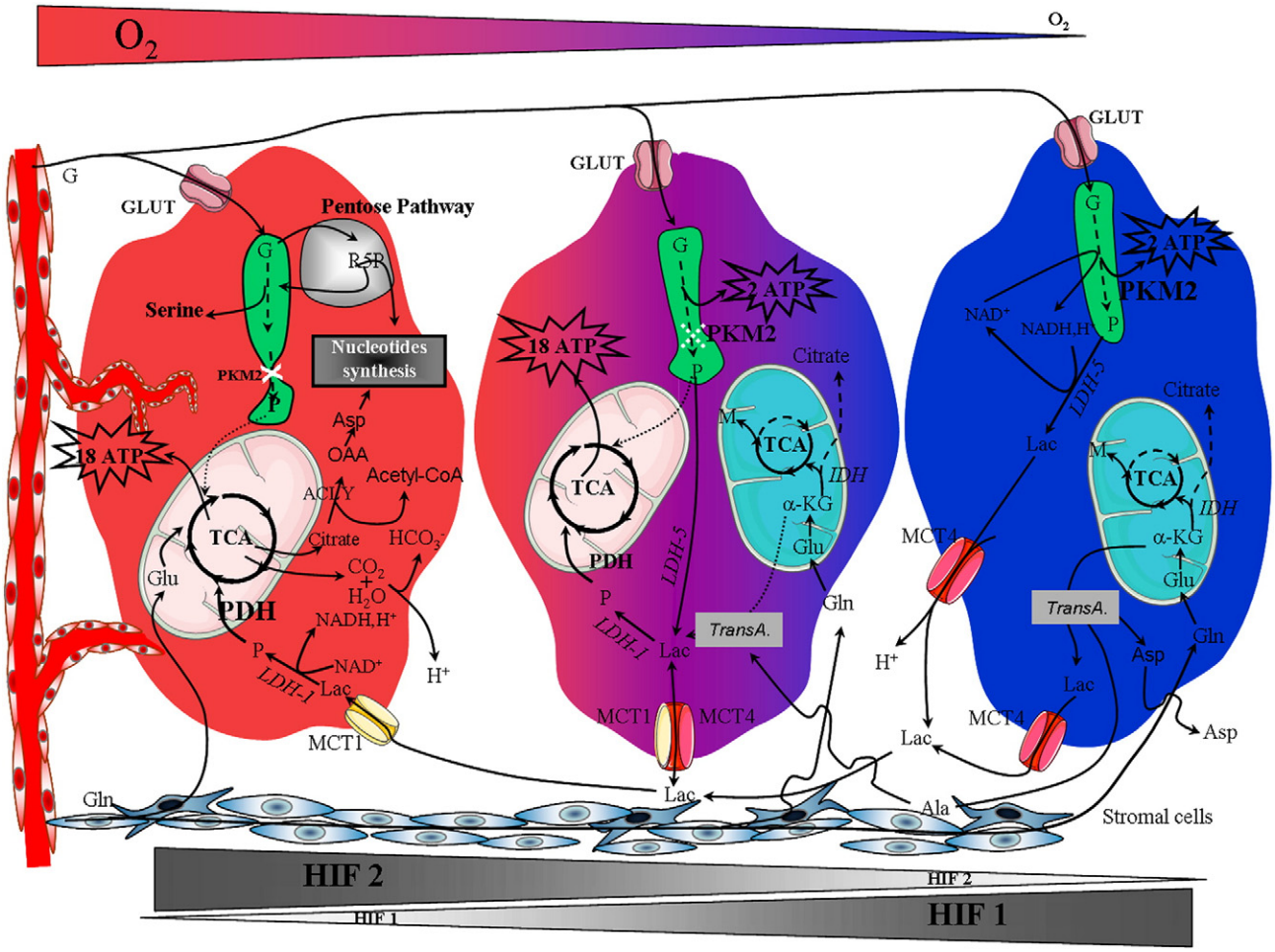

Fig. 2. A model of the symbiotic cooperation between normoxic and hypoxic cancer cells. In normoxia conditions, TCA functioning is coupled with OXPHOS for ATP and CO_2 production. Because cells produce great amounts of ATP, they proliferate at a higher rate. Inactive PKM2 favors the utilization of glucose towards biosynthesis pathways (ribose, serine, glycerol, etc.). Rejected CO_2 contributes towards the acidification of the environment, promoting invasiveness and dissemination. In the case of severe hypoxia or anoxia, OXPHOS-ATP production is arrested, and glycolysis becomes the unique source of ATP, which is used by cells to survive. Glucose is metabolized into pyruvate by active PKM2 dimeric form, the reaction producing ATP. In this condition, Ala and Gln sustain transaminases cascades (TransA), resulting in pyruvate feeding the LDH-5 reaction, and in aspartate, which is rejected as a waste product, since nucleotide synthesis is arrested due to lack of energy. For the functioning of glycolysis-producing pyruvate, NAD^+ is crucial and this cofactor is regenerated by LDH-5. Lactate is rejected by MCT4 transporter and acidifies the environment. Lactate may enter normoxic cells by MCT1 and could be used as an important fuel, feeding the TCA cycle after pyruvate transformation by LDH-1 (one lactate results in 18 ATP). In moderate hypoxia, cells proliferate at an intermediate rate, because the production of ATP by TCA-OXPHOS is reduced. Glycolysis is enhanced, the switch between the active and inactive form of PKM2, orienting glucose towards biosynthesis or towards ATP and pyruvate production. Ala and Gln sustain transaminases cascades (TransA), resulting in pyruvate and aspartate production, sustaining the LDH reaction and nucleotide synthesis respectively. Because of PDH slowdown or inactivation, citrate may come from Glu through a reversed IDH route, rather than OAA and acetyl-CoA condensation. The senses of fluxes depend on quantities of O_2 concentration and substrates. This cooperation between hypoxic and normoxic cancer cells optimizes ATP production, since one molecule of glucose results finally in 38 ATP (2 through glycolysis in severe hypoxic cells, and 36 through by TCA functioning in normoxic cells). ACLY: ATP citrate lyase, Ala: alanine, Asp: aspartate, G: glucose, GADPH: glyceraldehyde 3-phosphate dehydrogenase, GDH: glutamate dehydrogenase, Gln: glutamine, GLUT: glucose transporter, GPD: glycerol 3-phosphate dehydrogenase, GS: glutamine synthetase, G6PDH: glucose 6-phosphate dehydrogenase, G6P: glucose 6-phosphate, G3P: glycerol 3-phosphate, HAT: histone acetyl transferase, HIF: hypoxia inducible factor, IDH: isocitrate dehydrogenase, α-KG: α-ketoglutarate, LDH: lacticodehydrogenase, M: malate, MCT: monocarboxylate transporter, NAD^+: nicotinamide adenine dinucleotide, OAA: oxaloacetate, OXPHOS oxidative phosphorylation, P: pyruvate, PDH: pyruvate dehydrogenase, PKM2: embryonic isoform of pyruvate kinase, R5P: ribose 5-phosphate, TCA: tricarboxylic acid cycle, TransA: transaminases.

concert, since the ketone product β-hydroxybutyrate contributes to histone acetylation by inhibiting histone deacetylases [183]. Glycerol 3-phosphate (G3P) is crucial for triglyceride biosynthesis and is derived from DHAP by glycerol 3-phosphate dehydrogenase (GPDH). The glycerol phosphate shuttle, which transfers energetic electrons to complex II via $FADH,H^+$, could become the main cause of OXPHOS and ROS stimulation when the malate/aspartate shuttle is unprimed.

5.2. Nucleotide synthesis

ATP initiates *de novo* purine synthesis by stimulating the reaction forming 5-phosphoribosyl-1-pyrophosphate (PRPP) from R5P, whereas aspartate feeds the aspartate transcarbamylase reaction opening pyrimidine synthesis with carbamyl-phosphate derived from glutamine by carbamyl-phosphate synthase. Although PRPP is an allosteric activator of the latter enzyme, it enters the last part of pyrimidine synthesis. Nucleotide synthesis consumes great quantities of R5P produced by the oxidative and/or non-oxidative branches of the PPP (as seen above); aspartate derived from the transamination of OAA or from L-asparagine derived from diet and proteolysis by asparaginase, which is targeted in leukemia treatment [184]; glycine derived from serine favored by 3-PG accumulation above the PKM2 bottleneck; and glutamine derived essentially from proteolysis, except under glutamine depletion where it can be synthesized from Glu by GS [185]. Thymidine synthesis, which requires $NADPH,H^+$ for dihydrofolate reductase functioning, is coupled with the folate cycle which uses $NADPH,H^+$ and serine [186]. Ribonucleosides are transformed into desoxyribonucleosides by thioredoxine, also consuming $NADPH,H^+$.

6. The reprogramming metabolism favors cancer cell growth

6.1. NO production, polyamine synthesis, and S-adenosylmethionine depletion

Arginosuccinate synthase (ASS) converts aspartate and citrulline into arginosuccinate, which is then transformed into fumarate and arginine. ASS1 is often inactivated in various types of cancer cells [187,188]. This inactivation has multiple consequences that favor cancer development, such as NO production, polyamine synthesis and S-adenosylmethionine (SAM) depletion. This blockage leads to aspartate accumulation and engages this molecule towards pyrimidine synthesis, whereas it induces cell dependence on extracellular arginine. This semi-essential amino acid is required in abundance by tumors and is diverted towards NO production through NO synthase or converted into ornithine via arginase1, this crossroad being regulated by the HIF1α/HIF2α ratio [39]. NO inhibits aconitase [128], favoring the ACLY route, and promotes several pathways that favor proliferation such as gene expression (HIF, PKM2) [21,189] and increased intracellular cGMP sustaining mitosis, the decreased cAMP/cGMP ratio stimulating glycolysis via PFK1 [190,191]. In contrast, ornithine feeds the polyamine pathway that is coupled with the production of 5 methylthioadenosine, leading to the formation of adenine [108]. For polyamine synthesis, ornithine is decarboxylated in putrescine by ornithine decarboxylase (ODC), and putrescine sustains spermine and spermidine polyamine formation via S-adenosine decarboxylase (SAM decarboxylase), a 5 methylthioadenosine-producing reaction [135]. As a result, arginine via this route sustains purine nucleotide synthesis, sparing ATP molecules. Thus, arginine deprivation diet and arginine depleting enzymes such as pegylated arginine deiminase may affect cancer cell growth [187]. Increased polyamine availability also enhances the capability of cancer cells to invade and metastasize to new tissues while diminishing the anti-tumor immune functions of immune cells [192]. Because polyamine synthesis is coupled with SAM decarboxylase, this process decreases the intracellular SAM pool [108]. SAM deficiency promotes carcinogenesis by DNA hypomethylation [193], resistance to apoptosis [194] and impairment of GSH detoxification, since SAM is a precursor of GSH [195].

6.2. Resistance to apoptosis

Glycolytic metabolism protects cancer cells from apoptosis [196,197]. Various links between resistance to apoptosis and glycolysis have been put forward: AKT has been found to promote growth factor-independent survival, to regulate multiple steps of glycolysis such as the glucose transporter 1 (GLUT1) and hexokinase 1 (HK1), and to prevent activation of Bax, which triggers apoptosis [198]. HK2 is overexpressed in cancer cells and linked to the outer membrane with the voltage-dependant anion channel (VDAC). It competes with Bcl-2 proteins for binding to VDAC and influences the balance of the pro- and anti-apoptotic proteins that control outer membrane permeabilization [61,199,200]. Overexpression of GAPDH promotes survival of cancer cells even when they have undergone mitochondrial permeabilization, an apoptosis-initiating process [201–203]. Glycolysis is also linked to the two anti-apoptotic proteins Mcl-1 and Bcl-x_L [45,204,205]. Mcl-1 expression is under GSK-3 control [206], and enforcement of glycolysis stabilizes Mcl-1 expression [46,126,207,208]. Bcl-x_L regulates mitochondrial respiration and metabolism and seems to block apoptosis by reducing citrate-derived acetyl-CoA production [209,210]. This decrease prevents the N-acetylation process which is required to activate multiple proteins including caspases [211]. Addition of citrate restores protein N-alpha-acetylation in Bcl-x_L expressing cells and sensitivity to apoptotic stimuli [212]. Glycolysis could also be associated with inactivation of several pro-apoptotic BH3-only proteins: inactivation of Bad may be critical for suppressing apoptosis and maintaining glycolysis. Bad is inactivated by phosphorylation which is JNK1-mediated and is required for maintaining normal glycolysis for cell survival via the activation of PFK-1 [213]. Noxa phosphorylation is Cdk5-mediated and promotes glucose uptake and directs glucose flux towards PPP [214]. Noxa also favors activation of the pro-apoptotic protein Bax whereas it neutralizes the anti-apoptotic Mcl-1. Under glucose deprivation, Cdk5 kinase activity is diminished. Consequently, unphosphorylated Noxa exerts a pro-apoptotic role [215], which involves Mcl-1 degradation and the concerted action of Bim [216]. Two other BH3-only proteins, Bim and PUMA, are downregulated by high glucose metabolism [197,217]. Bim is induced by ER stress, a consequence of glucose deprivation which promotes the accumulation of unfolding proteins [197].

6.3. The imbalance between oncogenes and suppressors redirects metabolism to support proliferation

The role of the signaling pathways that conduct the reprogramming metabolism has been extensively reported in recent years, in particular the role of HIF [39,40,218]. In brief, activated mitogenic pathways (PI3K/AKT/mTOR pathway, HIF-1α, c-Myc, etc.) are increased due to genetic mutations and stimulate proliferation [2–4,6,103,119,219] in association with the loss of anti-proliferative pathways (P53, P21, PTEN, LKB, AMPK). For example, AKT stimulates glucose uptake, glycolysis, PPP and fatty acid synthesis [220], whereas c-Myc promotes glutamine metabolism as well as purine and pyrimidine biosynthesis [221]. This reorientation of signaling pathways drives expression and/or activation of various enzymes which participate in the specific metabolism of cancer cells, promoting survival and proliferation.

In conclusion, cancer cells adopt a metabolism in a way that favors their development, whilst driving and adapting to their microenvironment in a manner that also promotes their development. Although many questions remain to be elucidated, understanding the biochemical pathways potentially involved helps us to develop new strategies for counteracting cancer proliferation. To induce cancer cell death, at least experimentally, it would be interesting to explore and/or combine different strategies: to inhibit regulator enzymes, notably those that open biochemical pathways, although to expect a significant effect, it would probably be necessary to block at least two pathways; to reduce ATP, NAD^+ and $NADPH,H^+$ production, particularly in hypoxic chemoresistant cells, by targeting the reactions implied in their production, such as PGK1, LDH or ME; to interfere with metabolites located at the crossroads of essential pathways, such as PEP, pyruvate, α-KG, aspartate, by using competitive inhibitors such as 3-bromopyruvate [208,222]; to block metabolite transporters such as MCT [166]; and to increase the level of citrate inside cells by inhibiting ACLY (a combination of alpha lipoic acid and calcium hydroxycitrate is efficient in mouse cancer models [223]) in an aim to reactivate the Pasteur effect, to block PFK and arrest glycolysis [126,127]. Finally, anti-metabolic strategies could be associated with current chemotherapies to improve their efficiency and to sap the mechanisms of chemoresistance.

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