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Review

The metabolic cooperation between cells in solid cancer tumors

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ABSTRACT

Cancer cells cooperate with stromal cells and use their environment to promote tumor growth. Energy production depends on nutrient availability and O_2 concentration. Well-oxygenated cells are highly proliferative and reorient the glucose metabolism towards biosynthesis, whereas glutamine oxidation replenishes the TCA cycle coupled with OXPHOS-ATP production. Glucose, glutamine and alanine transformations sustain nucleotide and fatty acid synthesis. In contrast, hypoxic cells slow down their proliferation, enhance glycolysis to produce ATP and reject lactate which is recycled as fuel by normoxic cells. Thus, glucose is spared for biosynthesis and/or for hypoxic cell function. Environmental cells, such as fibroblasts and adipocytes, serve as food donors for cancer cells, which reject waste products (CO_2, H^+, ammoniac, polyamines…) promoting EMT, invasion, angiogenesis and proliferation. This metabolic-coupling can be considered as a form of commensalism whereby non-malignant cells support the growth of cancer cells. Understanding these cellular cooperations within tumors may be a source of inspiration to develop new anti-cancer agents.

Contents

1. Introduction

Cancer tumors are composed of an ecosystem of evolving clones competing and cooperating with each other and with other cells within their microenvironment. They include a mixture of cancerous and non-cancerous cells such as stromal cells, adipocytes and macrophages, all cooperating towards promoting division, invasion and dissemination. Life results from symbiotic cooperation: animal cells are heterotrophs and absorb sugars and oxygen, whereas they emit CO_2 and water; plant cells are autotrophs, absorb CO_2, emit oxygen and form sugars. Thus, cells that breathe need cells that photosynthesize and vice versa. In this review, we have endeavored to clarify the cooperation that seems to take place in tumors, emphasizing the fact that cancer cells

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optimize the resources present in their environment to proliferate. We demonstrate that environmental cells, such as adipocytes and fibroblasts, may serve as food donors for cancer cells which reject waste products (CO_2, H^+, ammoniac, polyamines…), promoting proliferation and dissemination. The rate of proliferation would be dependent on the dynamic reconstitution of ATP and cofactors (NAD^+, NADPH, H^+), which is controlled by the HIF-1/HIF 2 ratio, which decreases gradually with O_2 concentration [1–4]. The signaling pathways (activation of oncogenes such as c-Myc, inhibition of suppressor genes such as P53 and PTEN) that support tumor proliferation are not presented in this review and readers are referred to several other reviews [5–11]. In our paper we focus on understanding the biochemical pathways that support this type of commensalism, which may be a source of inspiration for developing new anti-cancer treatment options.

2. Cancer cells adapt their proliferation in relation to O_2 concentration

Cancer cells demonstrate extraordinary plasticity to adapt to variations in the conditions of their microenvironment. Cancer cell proliferation is dependent on O_2. Well-oxygenated cells, which are located close to blood vessels, proliferate at a higher rate, because they are supplied by nutrients, growth factors and O_2 in abundance. Their biosynthesis is efficiently supported by ATP, which is produced by mitochondrial oxidative phosphorylation (OXPHOS). In contrast, less oxygenated cells rely more on glycolysis [1,12–16], which may become the main, if not the unique cause of ATP generation. Hypoxia forces cells to develop strategies to survive and proliferate, but at a lower rate [1,3,17–19]. Thus, it is not surprising that these "robust" cells correspond to higher malignancy grades [20,21] and chemoresistant cells [22,23].

2.1. Normoxic cancer cells divide rapidly

The capability of well-oxygenated cells to produce ATP is maximal when OXPHOS–ATP is functioning well. Various growth factors, such as angiogenic factors, are secreted by cancer cells, stimulating the formation of new blood vessels. The angiogenesis phenomenon provides more oxygen and nutrients [24] and favors cell division in a positive feed-back loop. Glucose, alanine (Ala) and glutamine (Gln) serve as essential nutrients and as elementary "bricks" for building new cells [25–30]. To divide, cells need to reorient the glucose metabolism towards synthesis. Thus, other sources, such as glucose, are needed to produce pyruvate, such as Ala, oxaloacetate (OAA) and lactate. These molecules sustain the tricarboxylic cycle (TCA), coupled with the production of ATP by oxidative phosphorylation (OXPHOS). Glucose transformation towards anabolic pathways is favored by the re-expression of the M2 embryonic form of pyruvate kinase (PKM2). The switch from the inactive (dimeric) isoform of PKM2 to the active (tetrameric) form seems to be an oscillating process, controlled by allosteric regulation implying the concentration of fructose 1,6 diphosphate (F1,6P) [31,32]. When the dephosphorylated tetrameric form of PKM2 is activated, glucose transformation leads to ATP and lactic acid production [32–37] (Fig. 1). In contrast, dimeric PKM2 preponderance leads to an accumulation of intermediate molecules upstream of PKM2, which are diverted towards the pentose phosphate pathway (PPP) and towards the formation of metabolites such as glycerol and serine. PPP produces ribose and NADPH,H^+, whereas glycerol serves lipid synthesis and serine, the latter molecule sustaining tetrahydrofolate and nucleotide synthesis. Thus, the major share of the pyruvate entering the TCA cycle in cancer cells may derive from the transformation of Ala and Gln, which originate from muscle proteolysis, participating in cachexia [25,38]. Note that dimeric PKM2 could have a nuclear kinase activity, phosphorylating the STAT3 transcription factor, which activates several oncogenic genes such as *c-myc*, *bcl-x_L* [33,39,40] and *mek5* [41].

Warburg observed in the 1920s [42] that oxygenated cancer cells could produce lactate. This aerobic glycolysis contrasts with the regulation which takes place in normal cells, where lactate formation is stopped in the presence of O_2 (Pasteur effect). This regulation is due to the mitochondrial production of citrate and ATP, which exercise a negative feedback control on phosphofructokinase1 (PFK1), arresting glycolysis [43]. The switch from glycolysis to TCA cycle activation is under the control of HIFα, which is inactivated by prolyl hydroxylase (PHD) in the presence of oxygen [44]. Cancer cells lose this regulation because HIF 1α remains activated, even in normoxia, due to inactivation of PHD by various mechanisms, such as accumulation of intermediates of the TCA cycle (succinate, fumarate, α-ketoglutarate (α-keto)) [45,46]. Lactate production should be explained principally as the activation of lactate dehydrogenase-5 (LDH-5) associated with the inhibition of pyruvate dehydrogenase (PDH), which is inactivated by pyruvate dehydrogenase kinase 1 (PDK1). The latter enzyme is activated by HIF-1 [17]. To explain the loss of Pasteur effect regulation, we hypothesized that citrate was at low concentration in proliferative cancer cells and did not exercise a negative feed-back on phosphofructokinase (PFK). This hypothesis was recently confirmed in clinical studies showing that citrate concentration is drastically reduced in prostate cancer cells and correlated with aggressiveness [47]. We demonstrated that citrate administration arrests cancer cell proliferation and renders cells sensitive to chemotherapy [48–50].

2.1.1. Glutaminolysis sustains OXPHOS–ATP production, nucleotides and lipid biosynthesis

In normoxia, the TCA of cancer cells would be preferentially sustained by Gln oxidation due to PDH inactivation. Gln is the preferential mode of blood nitrogen transportation (NH_4^+), since 90% of the body's glutamine is stored in muscle. Gln is transported at the plasma membrane by ASCT2 (SLC1A5), a Na^+-dependent amino acid transporter which is essential for glutamine uptake by fast epithelial growing tumor cells [51,52]. By cytosolic glutaminase (GLS), Gln provides glutamate (Glu) and/or amine groups for nucleotides, amino acids (e.g. serine), tetrahydrofolate and glutathione synthesis. Gln is also converted by the mitochondrial GLS into Glu, a reaction that produces ATP. Glu is transformed by glutamate dehydrogenase (GDH) into α-keto which replenishes the TCA, leading to the production of several intermediates such as oxaloacetate (OAA) [53,54] (Fig. 1). OAA is at very low concentration in mitochondria and must be regenerated at each cycle. In the case of lack of glutamine, cells might obtain OAA through pyruvate carboxylation, by activating pyruvate carboxylase (PC) [55,56]. Then, citrate synthase (CS) condenses OAA and acetyl-CoA into citrate which is exported in the cytosol by a transporter [57]. This exportation could be due to aconitase inhibition in response to diffusible products of nitric oxide (NO) [2,58–60] probably produced by cells from a hypoxic environment, in particular macrophages [61]. ATP-citrate lyase (ACLY) over-expression has been reported in numerous cancer cells for review [62,63]. ACLY reforms acetyl-CoA and OAA in the cytosol. Acetyl-CoA sustains de novo lipogenesis which is one of the major metabolic pathways required by cancer cells to divide [64,65], and also serves the acetylation of proteins such as histones. The regulation that orients acetyl-CoA towards one pathway rather than another remains to be investigated (Fig. 2). Modifications in pH, described later, could influence enzymatic activities such as histone acetyl transferase (HAT) [18]. Histone deacetylations are thought to support proliferation by inactivation of suppressors and activation of oncogenic genes. The decrease in HAT activity and/or in citrate concentration (and thus in acetyl-CoA) could play a major role in acetylation processes associated with genetic and epigenetic modifications. As such, a decrease in citrate could be associated with mutations, since it has been reported in glucose deprivation, which was found to be linked with K-Ras mutations [66].

In contrast, OAA derived from citrate transformation by ACLY is converted into aspartate by aspartate amino transferase (ASAT) or into malate by malate dehydrogenase (MDH) (Fig. 2). As a result, glutamine catabolism sustains the transaminase reactions producing pyruvate and aspartate by alanine amino transferase (ALAT) and ASAT, respectively.

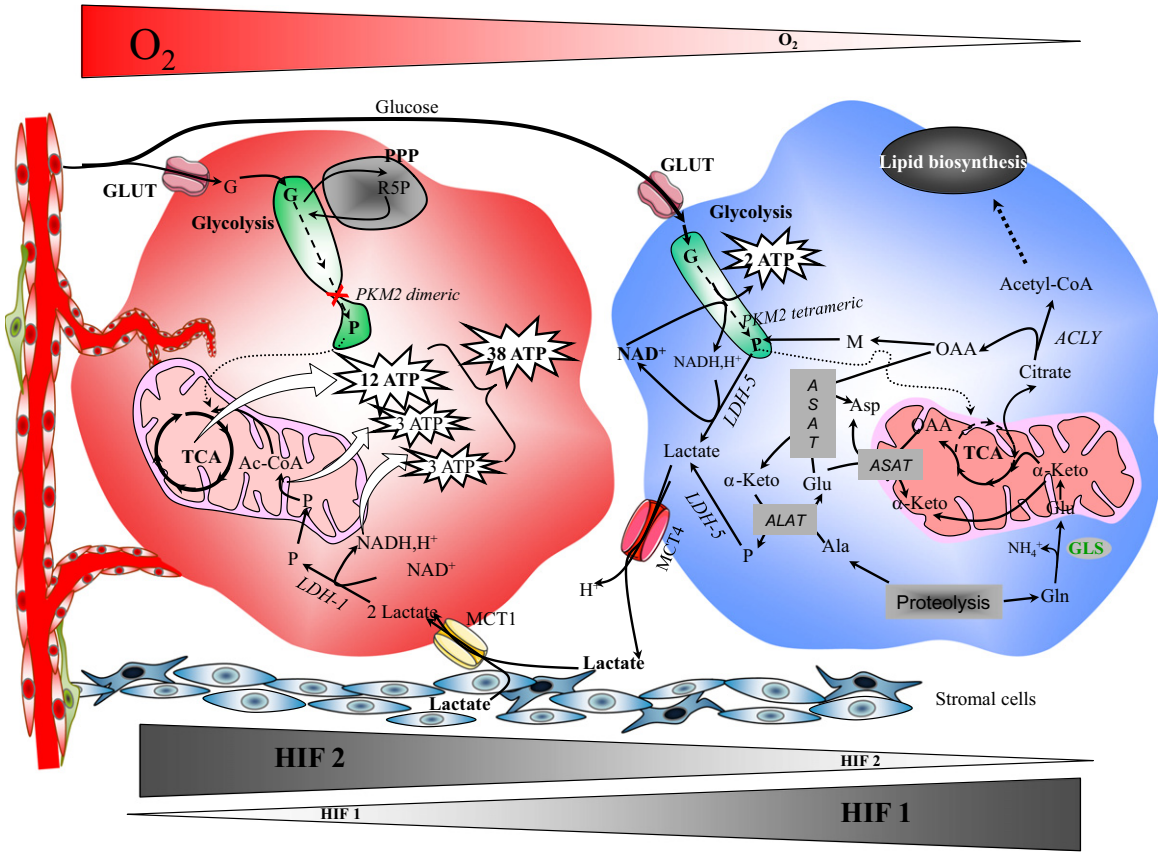

Fig. 1. The cooperative glucose metabolism between normoxic and hypoxic cancer cells. In normoxic cancer cells, dimeric PKM2 expression favors the accumulation of glycolysis intermediates (diverted towards anabolic synthesis) and spares glucose for hypoxic cancer cell glycolysis. In these cells, the expression of tetrameric PKM2 induces ATP and pyruvate formation through glycolysis. Proteolysis sustains biosynthesis via the production of citrate (entering lipid synthesis) and of aspartate (entering nucleotides). Pyruvate also derives from ALAT or malate decarboxylation by ME. Hypoxic cells transform pyruvate into lactate through LDH-5 and export lactate and H^+ by MCT4. H^+ acidifies the microenvironment, whereas lactate is captured by the MCT1 of normoxic cells, and forms pyruvate by LDH-1. Then pyruvate enters into the TCA coupled with OXPHOS, producing ATP. As a result, the lactate shuttle leads to cooperation between cells to optimize the production of ATP (one molecule of glucose furnishes 38 ATP). Ac-CoA: Acetyl-CoA, ACLY: ATP-citrate lyase, ALAT: alanine transaminase, ASAT: aspartate transaminase, Asp: aspartate, G: glucose, Gln: glutamine, Glu: glutamate, GLUT: glucose transporter, GS: glutaminase, HIF: hypoxia induced factor, IDH: isocitrate dehydrogenase, α-Keto: α-ketoglutarate, M: malate, ME: malic enzyme, MCT 1 and 4: monocarboxylate transporter 1 and 4, NAD: nicotinamide adenine dinucleotide, P: pyruvate, PKM2: pyruvate kinase isoform M2, PPP: pentose phosphate pathway, TCA: tricarboxylic cycle.

Nucleotide synthesis is then replenished by aspartate, whereas pyruvate sustains the LDH-5 reaction producing lactate. Finally, up to 60% of Gln would be converted into lactate (glutaminolysis), whereas the remaining Gln furnishes precursors for nucleotide synthesis [53].

2.1.1.1. Polyamine synthesis. This pathway is coupled with nucleotide synthesis and supports cellular proliferation and dissemination. Normoxic cells orient arginine transformation through polyamine (putrescine, spermidine, and spermine) synthesis via ornithine production (Fig. 3). Polyamines are involved in various biological processes such as: decreased apoptosis [67], DNA synthesis and stability, maintenance of chromatin conformation and regulation of specific gene expression [68]. Arginine is transformed into polyamines or nitric oxide (NO), depending on O_2 concentration, a crossroads that is regulated by the HIF-1α/HIF-2α ratio [2] (Fig. 3). In normoxia, HIF-2α activity is preponderant and favors polyamine synthesis, which starts with the transformation of arginine into ornithine via arginase 1 [69,70]. Then, ornithine is decarboxylated by ornithine decarboxylase (ODC) in putrescine which sustains spermine and spermidine formation via S-adenosine decarboxylase (SAM decarboxylase) producing 5 methylthioadenosine (MTA) [71]. MTA phosphorylase catalyzes the transformation of MTA into L-methionine and adenine (Fig. 3). L-methionine regenerates S adenosine methionine (SAM) by SAM synthase. Thus, decarboxylation of SAM sustains the methylation of polyamines, a process which decreases the SAM pool [71]. This deficiency promotes carcinogenesis via various effects, such as DNA hypomethylation [72], resistance to apoptosis [73] and impairment of GSH detoxification [74]. It is noteworthy that cancer cells are frequently dependent on extracellular arginine because arginosuccinate synthase (ASS1) is often inactivated [75,76] (Fig. 3). This blockage leads to an accumulation of aspartate, derived towards pyrimidine synthesis. Aspartate derives from arparagine transformation by asparaginase or from transaminase reactions. Thus, deprivation diet and arginine-depleting enzymes have been proposed to alter cancer cell growth [75]. Furthermore, N-acetyltransferase (SSAT) catalyzes the polyamine catabolism which reconstitutes putrescine and forms 1,3 diaminopropane which replenishes the transaminase reaction, producing pyruvate and Glu (Fig. 3). Finally the complex metabolism of methionine sustains proliferation via the synthesis of polyamines, pyruvate and Glu.

2.2. Hypoxic cancer cells: the most chemoresistant cells

Hypoxic cells develop in O_2 concentrations lower than 2%. In hypoxia, cells slow down or arrest their proliferation, whereas they enhance their glycolysis, which becomes the preferential source of ATP: two molecules are formed via the reaction catalyzed by phosphoglycerate kinase 1 (PGK1) [48,77] and two others via that of the tetrameric form of PKM2. Glycolysis and the tetrameric form of PKM2 are stimulated by the increase in HIF-1 [2,33]. Other sources of ATP could be represented in hypoxic conditions, by glutaminase which catalyzes the deamination of Gln in Glu, or by the acetyl-CoA synthase 2 (ACSS2), when functioning in the reversed manner, producing acetate and ATP from acetyl-

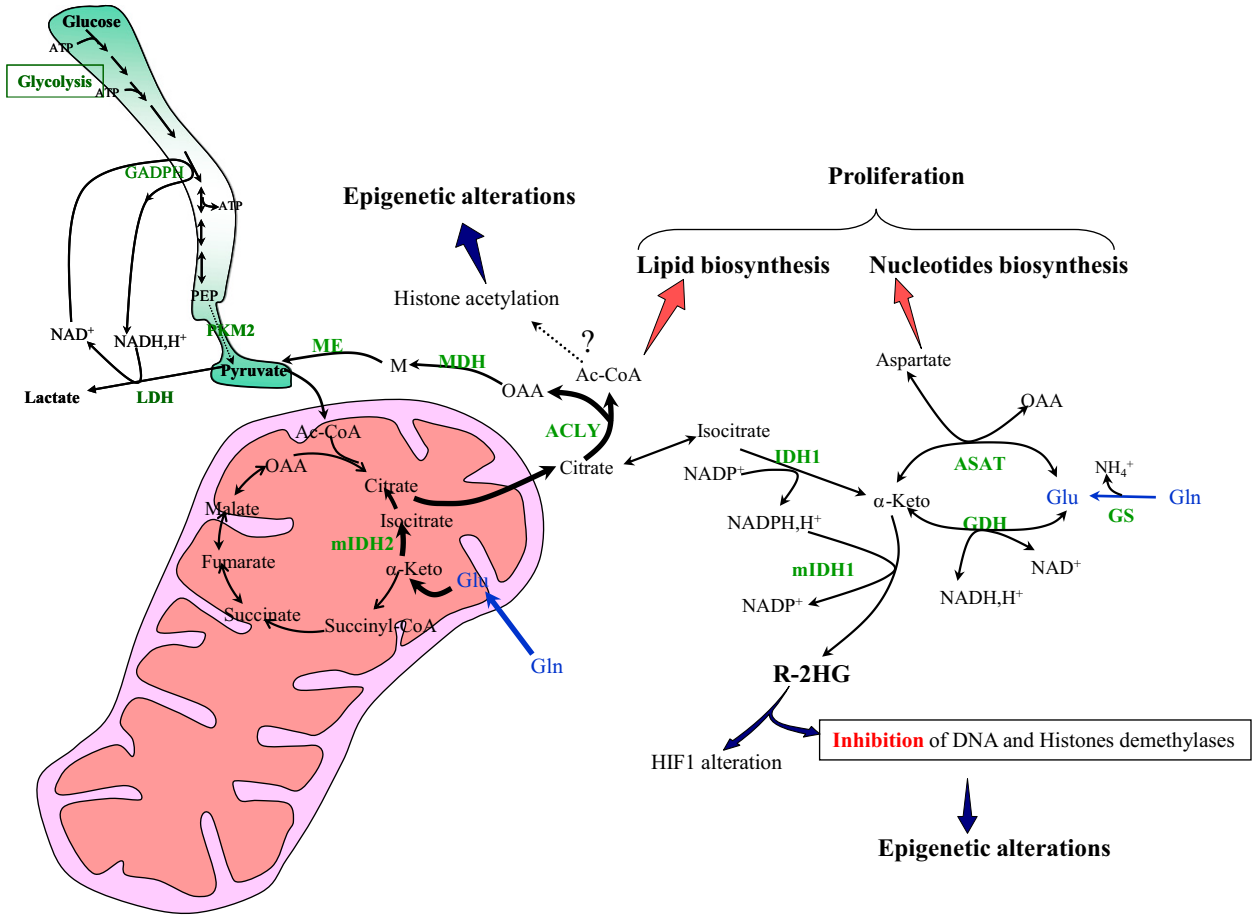

Fig. 2. The formation of citrate and acetyl-CoA in cancer cells and their utilizations. In dividing cancer cells, citrate produced by the TCA cycle is exported outside mitochondria to feed ACLY activity, producing acetyl-CoA and OAA. OAA feeds ASAT, sustaining nucleotide synthesis, lactate exportation (when PDH is blocked) and/or pyruvate cycle, regenerating mitochondrial citrate (when PDH remains activated). Acetyl-CoA molecules are consumed in de novo lipid synthesis, and/or serve acetylation processes such as histone acetylation. The imbalance between pathways remains to be investigated, but could be influenced by modifications in cytosolic pH. Note that glutamine transformation may sustain mitochondrial formation of citrate via a reversed mIDH2 route which is particularly activated in hypoxia. Cytosolic citrate may be partially engaged in an IDH1 route, sustaining ASAT and feeding nucleotide synthesis in Asp. Mutation of IDH 1 and 2 may lead to the production of R-2HG, a molecule favoring epigenetic and genetic alteration. Ac-CoA: Acetyl-CoA, ACLY: ATP-citrate lyase, GAPDH: glyceraldehyde-3-phosphate dehydrogenase, GDH: glutamate dehydrogenase, MDH: malate dehydrogenase, ME: malic enzyme, mIDH: mutant isocitrate dehydrogenase, OAA: Oxaloacetate, PKM2: pyruvate kinase isoform M2, R-2HG: R-2-hydroxyglutarate.

CoA and AMP [78]. However, if hypoxia is too severe and ATP production is also insufficient, necrotic death or necroptosis occurs [79–81].

Hypoxic cells reject waste products (lactate, CO_2, H^+, NH_4^+,...) which sustain the proliferation of surrounding oxygenated cells, leading to a symbiotic cooperation, optimizing ATP production and sparing glucose. Indeed, the glycolysis of hypoxic cells produces only two ATPs and rejects two molecules of lactate through a monocarboxylate transporter (MCT4). Lactate is captured by the MCT1 of normoxic cells to form pyruvate by LDH-1, which enters into the TCA, producing 18 ATP [82,83] (Fig. 1). This lactate shuttle optimizes ATP production, spares glucose for ribose synthesis and activates HIF-1, NF-κB, VEGF and IL-8, hence supporting angiogenesis and proliferation [82].

To divide in hypoxic conditions, cells need a continuous formation of citrate, which is required for lipid synthesis. This molecule derives from the reductive carboxylation of Glu, followed by a reversed isocitrate dehydrogenase 2 reaction (IDH 2) [84] (Fig. 2). This reversed IDH route should be linked with poor prognosis, since aggressive cancer cells demonstrate an inhibition of citrate synthase (CS) expression activity, linked with epithelial–mesenchymal transition (EMT) phenotype [85]. Note that, α-keto could also be used by mutant IDH, producing R-2-hydroxyglutarate (R-2-HG), an "oncometabolite" which stimulates cellular transformation and growth, particularly in glioma and acute leukemia [86–88] (Fig. 2).

In hypoxic environments, HIF1α is preponderant and the increase of HIF1α/HIF2α ratio orients the arginine metabolism towards NO production [2], a process which stimulates the proliferation of surrounding cells, by activating expression of genes such as HIF [36,89] and PKM2 [34,36], while it favors the efflux of citrate [60]. NO reinforces the Warburg effect, because it stimulates glycolysis via PFK1 through HIF-1α activation [44,90–92]. NO production by nitric oxide synthase (NOS) is favored in hypoxic cells and reduces the L-arginine available for polyamine synthesis (Fig. 3). This mechanism favors DNA instability, chromatin breakpoint and epithelial mesenchymal transition (EMT), all processes that increase the malignancy of these cells [68]. Note that polyamines secreted by normoxic cells decrease the expression of adhesion molecules, such as E-cadherin, on the surface of hypoxic cancer cells, favoring EMT and dissemination [68,93], and attenuate the cytotoxic activities of immune cells [94]. Thus, the cooperation established between cells and involved in the metabolism of polyamines increases malignancy, proliferation and dissemination.

2.3. The major role of NAD^+ and $NADPH,H^+$

Proliferation rate would depend on factors such as O_2 and nutrient availability, which regulate the rate of reconstitution of NAD^+, NADPH, H^+ and ATP, sustaining anabolic pathways.

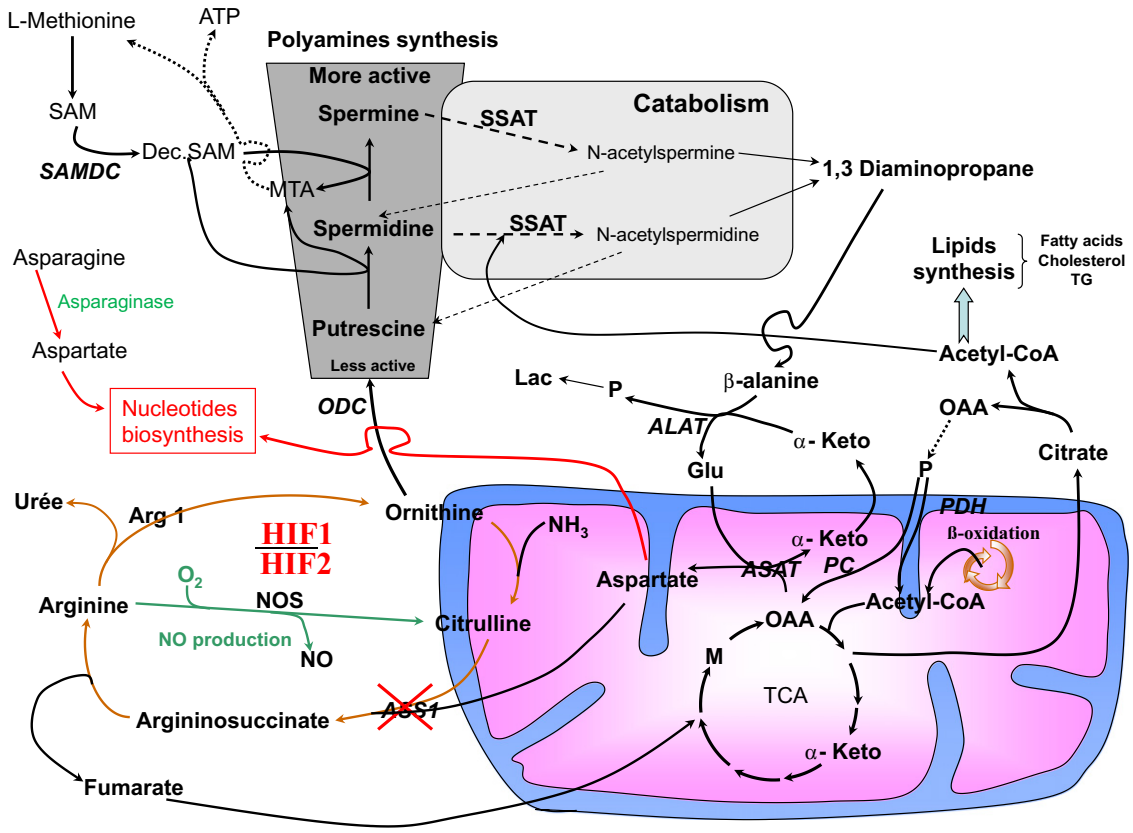

Fig. 3. Polyamines and NO synthesis. Polyamines (putrescine, spermidine, and spermine) and NO synthesis sustain proliferation. The polyamine cycle is partially coupled with urea and TCA cycle. Because ASS1 is deficient in cancer cells, arginine is oriented towards polyamine synthesis, which decreases the SAM pool. This decrease promotes carcinogenesis through various effects. ASS1 blockage also leads to an accumulation of aspartate, sustaining pyrimidine synthesis. In hypoxic cells, polyamine synthesis is decreased whereas NO production increases, reinforcing glycolysis in these cells. Argininosuccinate degradation produces fumarate which replenishes the TCA cycle producing citrate. This pathway generates acetyl-CoA molecules in the cytosol, which serve polyamine catabolism. Acetyl-polyamines are reengaged in the synthesis of polyamines and the 1,3 diaminopropane sustains ALAT activity, producing lactate and glutamate. ALAT: alanine transaminase, Arg 1: arginase 1, SAT: aspartate transaminase, ASS1: arginosuccinate synthase, Glu: Glutamate, HIF: hypoxia induced factor, α-Keto: α-ketoglutarate, Lac: lactate, M: malate, MTA: 5-methylthioadenosine, NO: nitric oxide, NOS: nitric oxide synthase, OAA: oxaloacetate, ODC: ornithine decarboxylase, P: pyruvate, PC: pyruvate carboxylase, PDH: pyruvate dehydrogenase, SAM: S-adenosine methionine, SAMDC: S-adenosine methionine decarboxylase, SSAT: N-acetyltransferase, TG: triglycerides.

NAD$^+$ supports essential reactions such as glycolysis (GAPDH), pyrimidine synthesis and the Poly ADP-Ribose Polymerase (PARP) reaction, required to repair frequent DNA breakage [95–97]. High levels of NAD$^+$ activate sirtuin1 (SIRT1) results in decreased HIF-1α transcriptional activity and enhanced HIF-2α-mediated stimulation of target genes, including erythropoietin, angiogenic factors, bringing more nutrients and O_2 to tumor cells [2,70,98]. In contrast to HIF-2, HIF-1α expression increases gradually with decreased O_2 concentration [1,99,100]. It stimulates NO production by NOS aimed at restoring local pO_2 in favor of various processes such as angiogenesis [101,102]. The conversion of lactate to pyruvate by LDH-5 supports the pyruvate-mediated inhibition of PHD2, and, consequently, HIF-1 activation, independently of hypoxia [82,103,104]. Lactate, as an oxidative fuel, would favor tumor growth, while blocking glycolysis [105–107]. This blockage reorients glycolytic intermediates towards anabolic pathways and spares NAD$^+$.

Thus, an excess in NAD$^+$ stimulates proliferation and angiogenesis through HIF-2α stimulation, in contrast to a lack of this cofactor. As a consequence, NAD$^+$ must be continuously regenerated by cytosolic dehydrogenases, such as MDH, LDH and glycerol phosphate dehydrogenase (GPDH), which may play a predominant role, particularly in hypoxic cancer cells, through deactivation of the malate/aspartate shuttle, either due to TCA cycle arrest [36] or to inactivation of PDH or CS [85]. In normoxic cells, this shuttle could regenerate cytosolic NAD$^+$, allowing the transfer of H$^+$ from cytosolic NADH to mitochondria. The nicotinamide phosphoribosyltransferase (Nampt) and NADH oxidase could also be essential for maintaining adequate intracellular NAD$^+$ level [108]. NADH oxidase yields to the formation of reactive oxygen species (ROS), which activate a cascade leading to NF-κB activation [82,109].

Finally, sensitivity to a reduction in NAD$^+$ level is dependent on O_2 concentration, hypoxia enhancing the activity of the aforementioned dehydrogenase reactions to restore NAD$^+$. Thus, NAD$^+$ concentration has been considered as the metabolic Achilles' heel of the tumor metabolome. When Weinhouse contested Warburg's ideas, he argued that the Warburg effect could be reversed if cancer cells are supplemented with NAD$^+$ and, beyond a given threshold, a normal OXPHOS capacity would be restored [110–112].

NADPH,H$^+$ is a major cellular anti-oxidant that maintains the pool of reduced glutathione, a key factor in the detoxification system which prevents oxidative damage created by ROS. These ROS favor proliferation at low concentration, but become toxic at high concentration [113,114]. NADPH,H$^+$ is also required for the reductive biosynthesis of fatty acids, nucleotides and amino acids, and is crucial for cells to inhibit apoptosis [115]. Therefore, this cofactor must be continuously regenerated either by the oxidative part of PPP or the malic enzyme (ME).

3. Microenvironment and tumoral stroma

The tumor microenvironment is a complex scaffold of extracellular matrix molecules and various cell types, including stromal cells and adipocytes. Tumor stromal cells principally include cancer-associated fibroblasts (CAFs), tumor endothelial cells (TECs), and tumor-associated macrophages (TAMs). These cells secrete factors that sustain tumor

growth, hence promoting angiogenesis, invasion and metastasis. A metabolic-coupling is formed, where environmental stroma cells [116,117] and adipocytes [118] are used by cancer cells as "food donors". This can be seen as a form of commensalism, via which non-malignant cells support the growth of cancer cells (Fig. 4).

3.1. Adipocytes

The consumption of lipids by cancer cells may play an essential role in cancer growth, as reported for breast, peritoneal and ovarian cancer cells [118]. This phenomenon concerns both distant and environmental adipocytes. Lipolysis, characteristic of cachexia, is favored by lipase activation in response to factors such as catecholamines [119–121]. Note that cachexia is a complex phenomenon implying various mechanisms such as the Cori cycle (i.e. the recycling of lactate in liver neoglucogenesis, a pathway consuming ATP) [121,122]. Adipocytes also secrete proangiogenic factors [123,124] and favor the recruitment of macrophages through adipokine secretion which is involved in tumoral progression and immune response [125,126]. Furthermore, they may act as an essential energy storage, furnishing fatty acids [118] which are transported to tumors via macrophages and are used for building membranes, or are catabolized by β-oxidation. This process may also generate ketone bodies which are an ideal substrate for ATP generation in aggressive cancer cells, since ketone bodies furnish more ATP with less oxygen consumption than glucose [127,128].

3.2. Fibroblasts and the extracellular matrix (ECM)

Cancer-associated fibroblasts (CAFs) are the major cell type present in cancer-associated stroma and secrete extracellular matrix proteins, pro-inflammatory cytokines and growth factors [129,130]. The delipidation of mature adipocytes dedifferentiates cells in preadipocytes and, potentially, in fibroblast-like cells [131]. Thus, in tumors growing in adipose tissue-dominated microenvironments, adipocytes dedifferentiate, whereas fibroblast-like cells accumulate.

CAFs may serve as a key source of glutamine to fuel cancer cell mitochondrial activity, driving a vicious cycle of catabolism between tumoral stroma and anabolic cancer cells. Epithelial cancer cells, which consume high levels of glutamine, generate ROS [132], a process that would be linked with a loss of stromal caveolin-1 (Cav-1) in CAFs [29,36,133,134] (Fig. 4). This condition is associated with poor clinical outcome in breast and prostate cancers [135–138]. This loss of Cav-1 leads to oxidative stress, activating certain key transcription factors (e.g. HIF1-α and NF-κB activation) and leading to the promotion of glycolysis in CAFs under normoxic conditions [134,139]. The loss of Cav-1 in adjacent fibroblasts leads to the induction of a mitophagic and autophagic

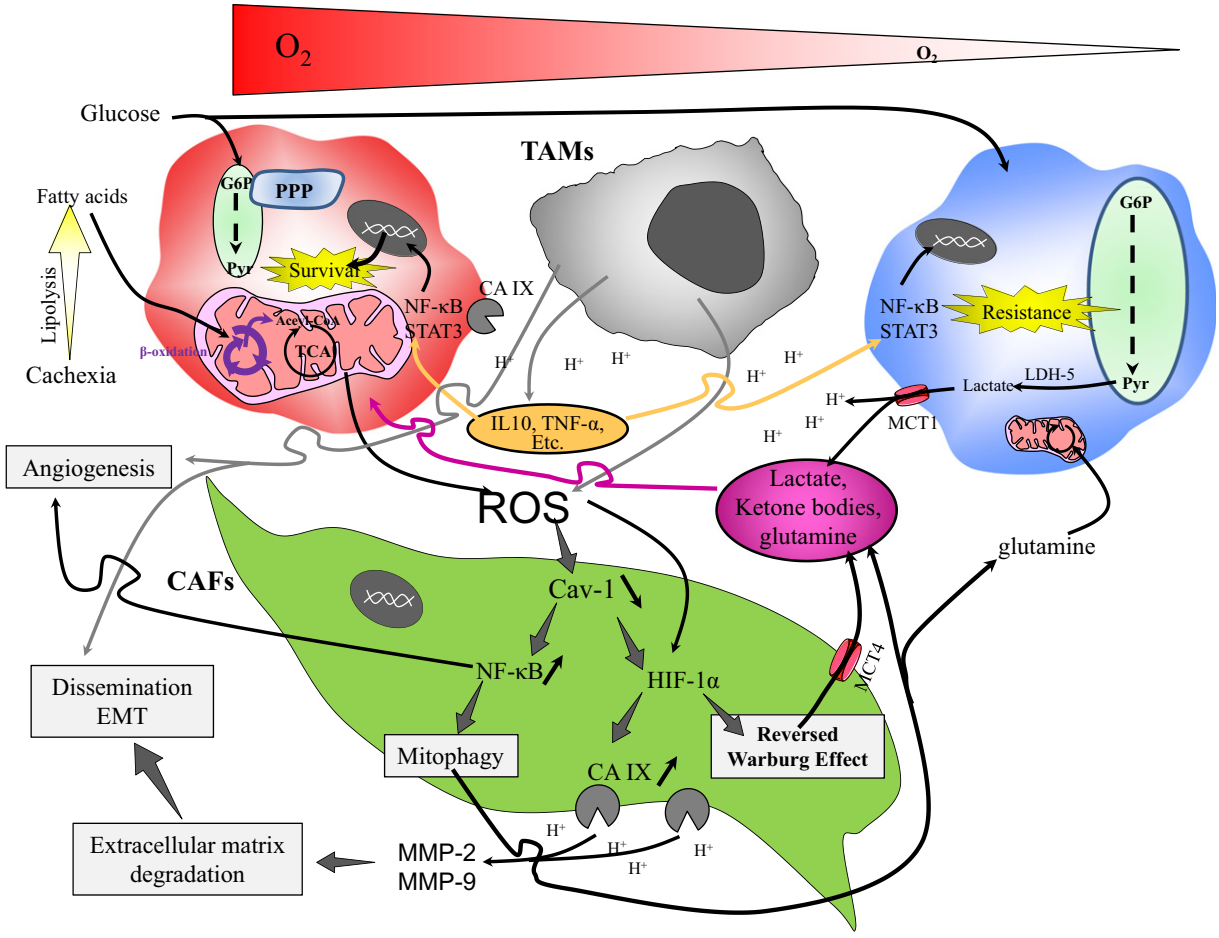

Fig. 4. Relationships between cancer cells and their microenvironment. The tumor microenvironment includes adipocytes and stromal cells (principally CAFs and TAMs), which secrete factors (lactate, ketone bodies, glutamine,…) that sustain the survival of hypoxic cancer cells and the growth of normoxic cancer cells. The loss of Cav-1 in CAFs is favored by ROS and promotes a reversed Warburg effect. This process is associated with mitophagic and autophagic transformations which furnish nutrients such as glutamine. A vicious glutamine cycle is established between CAFs and cancer cells. Due to CA IX stimulation, cancer cells and CAFs favor extracellular acidification which stimulates metalloproteinases, destroying the matrix. TAMs secrete growth factors (IL10, TNF-α,…) and ROS, promoting the loss of Cav-1, angiogenesis via NF-κB, and metastasis. All these factors favor EMT, angiogenesis and dissemination. CA IX: carbonic anhydrase IX, CAFs: cancer associated fibroblasts, Cav-1: caveolin-1, EMT: epithelial–mesenchymal transition, G6P: glucose 6-phosphate, HIF: hypoxia induced factor, IL: interleukin, MCT: monocarboxylate transporter, MMP: matrix metalloproteinases, NF-κB: nuclear translocation of nuclear factor kappa B, PPP: pentose phosphate pathway, Pyr: pyruvate, ROS: reactive oxygen species, STAT3: signal transducer and activator of transcription 3, TAMs: tumor associated macrophages, TAMs: tumors associated macrophages.

program, a process which is also favored by glutamine [140,141]. Due to the loss of mitochondria in CAFs [85], a reversed Warburg effect occurs in these cells (as in catabolic cancer cells), which secrete, via MCT4, energy-rich nutrients such as lactate, ketone bodies and glutamine [142]. These molecules are captured by MCT1 of anabolic cancer cells (i.e. well-oxygenated cells) to serve as a source of energy and/or as intermediates to biosynthesis. All these processes lead to metabolic coupling between cancer cells and stromal cell compartments, where catabolic cancer cells and CAFs may serve as food donors [142] (Fig. 4).

Moreover, CAFs secrete proline rich-molecules of collagens I and III, which accumulate and remodel the ECM leading to a desmoplastic reaction, significant in poor prognosis [143]. This strong fibrotic reaction is stimulated by HIF-1 [144,145], which activates lysyl oxidase (LOX) and enzymes implicated in tumor growth, invasiveness, and metastasis [146]. PDH inactivation and LOX activation, due to HIF-1, favor a cross-linking between collagen molecules [147], forming linear collagen fibers promoting cancer cell migration [143]. Collagens (types I and IV) are major constituents of the ECM and can induce chemoresistance by interacting with integrins on cancer cells [148]. Matrix rigidity increases interstitial fluid pressure and represents a physical barrier which may decrease drug delivery [149–151] and inhibit anti-tumor immune response [143,152].

3.3. Waste products favor acidification, proliferation and dissemination

NH_4^+, which derives from glutamine transformation in glutamate, diffuses freely in the microenvironment. It is a potent autophagic inducer of CAFs, and participates in resistance to chemotherapy and oxidative stress in nutrient-poor regions of solid tumors [29,153].

CAFs and anabolic cancer cells favor extracellular acidification due to stimulation of carbonic anhydrase IX (CA IX) [154,155], an enzyme located on the cell membrane and converting the CO_2 rejected by mitochondrial respiration into HCO_3^- and H^+ [18,82], and regulated by HIF-1α [18,154–158]. While HCO_3^- returns inside cancer cells to maintain a neutral or alkaline pH, which favors LDH-5 and PFK1 activities [159,160], extracellular acidification favors several proteases such as matrix metalloproteinases 2 and 9 (MMP2 and MMP9), destroying the matrix of normal cells and participating in EMT [143,161] (Fig. 4). Over and above CA IX, tumor cells have other "tools" to ensure proton exportation, such as MCT4 (with concomitant secretion of lactate), membrane-bound vacuolar ATPase (V-ATPase) and the NHE1 sodium proton exchanger [82,162]. It is likely that hypoxic cells preferentially use MCT4 to acidify the microenvironment [18,82]. This acidification could be one of the "raison d'être" [163] or a consequence of the Warburg effect, promoting extracellular cancer degradation, angiogenesis, cell invasion and spread [18,163–168], whereas it selects cancer cell phenotypes that are resistant to apoptosis [169–171].

3.4. The immune response

The microenvironment is modified by chronic inflammation which is favored by hypoxia [172], because HIF-1α is implicated in the release of NF-κB-regulated inflammatory cytokines in stimulated macrophages [173]. Chronic inflammation carries various types of infiltrating immune cells, which have different effects on tumor progression [174], whereas cancer cells secrete chemo-attractant molecules for immune cells [175,176]. Tumor-associated macrophages (TAMs), which are the major leucocytic cells, secrete an abundant source of growth factors such as cytokines (interleukins), whereas they provide ROS, which promotes angiogenesis and metastasis. TAMs over-express arginase 1, which reduces the NO level [177,178]. Leucocytes and macrophages decrease E-cadherin expression by inducing transcription factors from the nuclear factor of activated T cell (NFAT) family (e.g. NFATc1) [179], a process favoring the EMT phenotype [180]. Tumor-derived lactate acts as an immune suppressor and its accumulation near tumors disrupts T cell metabolism and function [181,182]. Moreover, it would inhibit innate immune response against tumor cells via the cytosolic function of NK cells [183]. This phenomenon is due to the decrease in perforin and granzyme B activity in these cells [184]. Moreover, the extracellular lactate taken up by monocytes results in an inhibition of TNF release, a mechanism contributing towards the immunosuppressive effect of lactate in wounds and tumor [181]. All these factors favor invasion and dissemination, and are associated with poor prognosis [185,186]. In contrast, immune response can be associated with good clinical outcome when cytotoxic $CD8^+$ cells are predominant (except for renal cell carcinoma) in contrast with $CD4^+$ infiltrates which are generally associated with poor prognostic [174,187]. Note that, cytotoxic T lymphocytes would be highly glycolytic cells relying on MCTs to secrete lactate [188], hence explaining the low capability of FDG-PET to differentiate cancer and inflammatory cells.

4. Conclusions

Recent advances in cancer biology lead to portraying cancer tumors as an ecosystem where malignant cells use non-tumoral cells and nutrients from their microenvironment to their own benefit. This review describes how this form of commensalism is supported by O_2 concentration, polyamine synthesis, lactate shuttle, NAD^+ and $NADPH,H^+$ availability and ROS production, all factors that promote cancer cell growth and survival. Concurrently, a massive catabolism occurs in adjacent non-cancerous cells (CAFs, adipocytes,…), supported by cellular interconnections and various signaling, mechanistic, and biochemical processes, such as loss of Cav-1, EMT and diminished immune response. Our knowledge of the metabolic cooperation between cells in solid cancer tumors is, as yet, limited. However, a deeper understanding of the mechanisms involved in this type of ecosystem will be fundamental for developing new treatment options.

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