Seminars in Cancer Biology 91 (2023) 143–157

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

The metabolic crosstalk between PIN1 and the tumour microenvironment

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ARTICLE INFO

Keywords:
PIN1
Cancer
Metabolism
Tumor microenvironment
Molecular signaling

ABSTRACT

Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (PIN1) is a member of a family of peptidyl-prolyl isomerases that specifically recognizes and binds phosphoproteins, catalyzing the rapid cis–trans isomerization of phosphorylated serine/threonine-proline motifs, which leads to changes in the structures and activities of the targeted proteins. Through this complex mechanism, PIN1 regulates many hallmarks of cancer including cell autonomous metabolism and the crosstalk with the cellular microenvironment. Many studies showed that PIN1 is largely overexpressed in cancer turning on a set of oncogenes and abrogating the function of tumor suppressor genes. Among these targets, recent evidence demonstrated that PIN1 is involved in lipid and glucose metabolism and accordingly, in the Warburg effect, a characteristic of tumor cells. As an orchestra master, PIN1 finely tunes the signaling pathways allowing cancer cells to adapt and take advantage from a poorly organized tumor microenvironment. In this review, we highlight the trilogy among PIN1, the tumor microenvironment and the metabolic program rewiring.

1. Introduction

Metabolic transformation represents a hallmark of tumour initiation and progression [1]. The first observations made by Otto Warburg, awarded with the Nobel Prize in 1931 in Physiology or Medicine, goes back in 1928 with the paper "The Chemical Constitution of Respiration Ferment" [2]. In a later paper, he raised the observation that in the tumors the oxygen utilization for energy production (i.e. ATP) is shifted to the fermentation of glucose and in turn, the secretion of lactate as a consequence of defective oxidative metabolism [3]. Warburg observed that cancer cells avidly use glucose via aerobic glycolysis (skipping the oxidative phosphorylation), even when they are in the presence of an

Abbreviations: AMP, activated protein kinase, acetyl CoA carboxylase, pyruvate kinase2; AGPAT2, 1-Acylglycerol-3-Phosphate O- Acyltransferase 2; 2-DG, 2-deoxy- glucose; 3PG, 3- phosphoglycerate; PFKFB3, 6- phosphofructo-2-kinase/ gructose-2,6-bisphosphate- 3; ACC, Acetyl-CoA carboxylase; AML, Acute myeloid leukemia cells; ALD-A,C 47], C, Adenylate 80, kinase-3aldolase-A; ATGL, Adipose triglyceride lipase; LDOA, Aldolase A; ACLY, ATP-citrate lyase; BCAA, Branched-chain amino acid; BCAT, Branched-chain aminotransferases; BAT, Brown adipose tissue; ENO1, Carbonic anhydrase-9, enolase-1; CPT1A, Carnitine Palmitoyltransferase 1 A; EMT, Epithelial-Mesenchymal Transition; FANS, Fatty acid synthase; Glut-1, 3, Glucose transporter-1,3; G- 6-P, Glucose-6-phosphate; GDH, Glutamate dehydrogenase; GS, Glutamine synthetase; GSH, Glutathione; GAPDH, Glyceraldehyde phosphate dehydrogenase; HK1, 2, Hexokinase 1,2; HK1 and HK2, Hexokinases; HIG2, Hypoxia-inducible gene 2; GLS1, Isozyme of glutaminase 1; LDH, Lactate dehydrogenase; LCAD, Long Chain Acyl CoA Dehydrogenase; MCAD, Medium-Chain Specific Acyl-CoA Dehydrogenase; MCT, Monocarboxylate transporter; NHE1, Na+/H+ exchanger isoform 1; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; Nrf2, Nuclear factor-erythroid factor 2- related factor 2; OAA, Oxaloacetate; PPP, Pentose phosphate path- way; PLIN2, Perilipin 2; PGC, Peroxisome proliferator-activated receptor-gamma coactivator; PEP, Phosphoenolpyruvate; PFKL, Phosphofructokinase L; PGK1, Phosphoglycerate kinase 1; PML, Promyelocytic leukemia protein; PDH, Pyruvate dehydrogenase; PDK1, Pyruvate dehydrogenase kinase 1; PK, Pyruvate kinase; PKM, Pyruvate kinase M; R-2HG, R-2- hydroxyglutarate; SSP, Serine synthesis pathway; SREBP1c, Serum Response Element Binding Protein 1c; SIAH2, Siah E3 Ubiquitin Protein Ligase 2; ASCT2, Sodium- dependent neutral amino acid transporter type 2; TRX, Thioredoxin; TAGs, Triacylglycerols; WAT, White adipose tissue; αKGDH, α-ketoglutarate dehydrogenase complex.

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https://doi.org/10.1016/j.semcancer.2023.03.001
Received 12 September 2022; Received in revised form 20 February 2023; Accepted 2 March 2023
Available online 4 March 2023

abundant amount of oxygen [4]. Over the years, this phenomenon was confirmed and expanded by many in vivo and in vitro studies, which demonstrated a vast cancer metabolic reprogramming, referred to as the Warburg effect, necessary to support cancer cell growth and proliferation [5,6]. Although accepted from the scientific community, the issue if the metabolic changes drive the cancer progression or begins the tumorigenic status is still an unresolved debate [7].

In most tumor cells, several conventional waste products represent the main nutrient sources. For instance, the quantity of lactate in tumors derived from a balance among the amount produced, exported to extracellular space by monocarboxylate transporters 4 (MCT4) and imported through MCT1 [7].

The inter-conversion between pyruvate and lactate is mediated by the nicotinamide adenine dinucleotide (NAD^+) oxidoreductase lactate dehydrogenase (LDH) enzyme. LDHA preferentially reduces pyruvate to lactate in the cytosol, while LDHB (mitochondria) supports the conversion of lactate to pyruvate in cells that utilize lactate as a nutrient source for oxidative metabolism or gluconeogenesis. At the molecular level, LDH regulates several oncogenes and tumor suppressor genes involved in the metabolic switch from oxidative phosphorylation (OXPHOS) toward an altered glycolysis in tumor cells [8]. At the cellular level, the lactate increases during cancer progression and the acidification of the tumor microenvironment promotes among different biological effects, the immune suppression [9,10] and positively correlates with radio-resistance [11].

Beyond lactate, several cellular products as acetate and ketone bodies are used from cancer cells as nutrients and utilized in the TCA cycle by specific enzymes that catalyze the formation of acetyl-CoA [12,13], which is oxidized to produce energy. Other unconventional nutrients as the ammonia and exogenous proteins have been identified as a source of nitrogen to fuel tumor growth [14]. Their catabolism represents a pool of different carbon and nitrogen intermediates and the ATP produced through the glycolysis and TCA cycle fuels the anabolic processes that support the synthesis of the biomass [15], since in malignant cells the metabolism is unbalance toward the anabolism [16].

Recent studies have shown that PIN1 binds to a variety of metabolic regulators, such as AMP-activated protein kinase, acetyl CoA carboxylase, pyruvate kinase2 and others that will be discussed later, indicating that PIN1 has major impacts on lipid and glucose metabolism in cancer cells. Since emerging studies indicated the relation between the tumor microenvironment (TME) and the metabolic rewiring as a crucial point for the initiation and progression of cancer [17], in this review we focused on three main aspects: the tumor cell metabolism with the associated TME and PIN1 as an orchestra master of this interplay.

2. Tumor cell metabolism

The aberrant proliferation of cancer cells is supported by the enhanced adaptation to nutrients from the microenvironment, which derives from alterations in the energy metabolism. Metabolic reprogramming is believed to be the direct and indirect consequence of oncogenic mutations, genomic instability, chronic tumor inflammation, immune evasion, and the interactions with the microenvironment.

A common feature of tumor cell metabolism is the ability to obtain several key nutrients including lactate, acetate, ketone bodies, ammonia, and exogenous proteins from the absorption and digestion of extracellular products [10,18–20]. Cancer cells, which are often located far from blood vessels are subject to a chaotic proliferation and try to adapt to the new needs. The process requires not only the reprogramming of catabolism with “the aerobic glycolysis” (as mentioned before) but also to turn on different new anabolic programs to increase its biomass, initiates the angiogenic switch to overcome the hypoxic conditions and stabilizes its own microenvironment, as discussed later.

2.1. The catabolic reprogramming of tumor cells

2.1.1. Glucose catabolism

The aerobic glycolysis, termed the Warburg effect, represents one of the hallmarks of cancer cells, widely accepted as a common feature of metabolic reprogramming for malignant transformation and tumor development, including metastasis and invasion [21].

Cancer cells appear to engage the glycolytic metabolism even before they are exposed to hypoxic conditions [4], generating a large amount of lactate from glucose via pyruvate synthesis [19], which is similar to the anaerobic glycolysis in normal differentiated cells. Cancer cells are highly dependent from the glycolytic pathway and prefer glucose fermentation over mitochondrial oxidation in which the oxidative phosphorylation (OXPHOS) is replaced by aerobic glycolysis. Instead of producing theoretically 38 molecules of ATP from the complete oxidation of 1 molecule of glucose, only 4 molecules are produced through the aerobic glycolysis [22]. This apparent “inefficiency” represents the tumor ability to set up adaptative metabolic capacities which are summarized in Table 1.

Cancer cells must increase the import of nutrient sources from the environment and an important mechanism shared among many types of cancers is the increased uptake of glucose. Several studies demonstrated that many oncogenes including the hypoxia-inducible factor (HIF1α) [46], c-Myc [47], Ras [48] and PI3K/Akt [49] pathways induce the up-regulation of GLUT1 expression. To corroborate these molecular evidence, GLUT1 is a glucose transporter upregulated in most of the tumors [31,50–53], and its expression correlates with poor prognosis, survival [54] and cancer therapy resistance [55].

Other key proteins involved in this process are MCT1 and 4, a family of proteins which regulate glycolysis and are responsible for the import/export of lactate [56]. Several studies demonstrated a significant increase of MCT1 and MCT4 expression in tumors, not only in cancer cells but also in stromal cells [57]. An enhanced glycolysis leads to an increased formation of intracellular lactate that is exported to the extracellular environment by MCT4 even under aerobic conditions [58]. The increased level of MCT4 and the resulting lactate export are necessary for sustaining a high level of glycolysis, specifically in stromal cells such as macrophages. The overexpression of MCT4 is a necessary mechanism through which these cells can avoid an intracellular accumulation of lactate and the resulting intensification of extracellular acidification, a common feature of inflammatory processes and tumors.

A low pH has been shown to act on monocytes and macrophages by inducing the activation of the inflammasome. Actually, the aberrant activation of the inflammasome and the concurrent overexpression of their effector molecules have been observed in several types of human malignancies [57,59]. The lactate exported by the MCT4-expressing glycolytic cancer cells (high level of glycolysis) is picked up by MCT1-expressing oxidative cancer cells (OXPHOS and glutaminolysis) that preferentially use lactate instead of glucose [60]. This synergism has been described as “metabolic symbiosis” [61,62] in which, in addition to MCTs, the lactate is transferred trough intercellular channels made up by connexin 43 (Cx43) [57,63]. Dovmark T.H. et al. demonstrated that the knockdown of Cx43 increased the retention of lactate in the cytoplasm of COLO357 spheroids (diameter ~150 μm). In a pancreatic cell line, which is Cx43-negative, showed a markedly increased of Cx43-immunoreactivity in the areas of invasion in an orthotopic xenograft mouse model. These tissue areas were associated with chronic extracellular acidosis (as indicated by the marker LAMP2 near/at the plasmalemma), which can explain the advantage of using intercellular channels over MCT-dependent mechanism in vivo. The authors proposed that Cx43 channels are important conduits for dissipating lactate anions from glycolytic pancreatic cells [63] (Fig. 1).

The metabolic symbiosis provides a heterogeneous system, which mainly combine the MCT-4 positive cells with a high level of glycolysis and MCT-1 positive cells that are engaged in OXPHOS and glutaminolysis, which function as prominent sources of reactive oxygen

Table 1
The most important players in cancer metabolism.

Name	Role	Mechanism	Implication in metabolic reprogramming	Ref.
Redox stress and robust ROS-defense	Presence of high levels of ROS in cancer cells and TME	High levels of ROS lead to the oxidative damage of the cellular lipid components	Increased ROS levels promote cell invasiveness and metastasis	[23]
Hypoxia	Low levels of oxygen	Hypoxia signaling operated by HIFs to reprogram cancer metabolism	HIF-1α induces the over-expression of: adenylate kinase-3; aldolase-A,C (ALD-A,C); carbonic anhydrase-9; enolase-1 (ENO1); glucose transporter-1,3 (Glut-1,3); glyceraldehyde phosphate dehydrogenase (GAPDH); hexokinase 1,2 (HK1,2); lactate dehydrogenase-A (LDHA); phosphofructokinase L (PFKL); phosphoglycerate kinase 1 (PGK1); and 6-phospho-fructo-2-kinase/gructose-2,6-bisphosphate-3 (PFKFB3); pyruvate dehydrogenase kinase 1 (PDK1), which phosphorylates and consequently inhibits pyruvate dehydrogenase (PDH)	[24–27]
Low pH	Extracellular acidity	Low level of pH in TME compared to intracellular pH	Acidity activates the sterol regulatory element-binding protein 2 (SREBP2) promoting tumor growth and correlates with decreased survival in different groups of cancer patients	[28,29]
Lactate	Accumulation of lactate	Tumor cells uptake high amounts of glucose, producing large quantity of lactate even in the presence of oxygen	Accumulation of lactate leads to low pH; high expression of MCT (s) is correlated to tumor progression and poor clinical outcomes	[30]
GLUT1	Glucose transporter	Up-regulated in cancer cells	Overexpression of GLUT-1 is induced by HIF1-alfa, PI3K/Akt pathway, AMPK and is related to cancer therapeutic resistance	[31–35]
MCT1	Lactate import transporter	Up-regulated in cancer cells	Overexpression is induced by lactate, obesity and chronic hypoxia	[36–39]
MCT4	Lactate export transporter	Up-regulated in cancer cells	Overexpression is induced by chronic hypoxia, weight loss, exercise and obesity	[40–42]
ASCT2 (sodium-dependent neutral amino acid transporter type2)	Glutamine transporter	Glutamine accumulation	Glutamine accumulation is promoted by c-Myc	[43]
SN2 (Isoform of system N)	Glutamine transporter	Glutamine accumulation	Glutamine accumulation is promoted by c-Myc	[43]
GLS1	Glutaminase 1	c-Myc induces overexpression of GLS1 in cancer	Catalyze the conversion of glutamine to glutamate	[44]
GLS2	Glutaminase 2	p53 induces the expression of GLS2 in normal condition, downregulated in cancer	Catalyze the conversion of glutamine to glutamate; tumor suppression activity	[45]

species (ROS) within the cell, thus increasing the oxidative stress. The relationship between ROS levels and cellular metabolism is tightly regulated and several oncogenes have been linked to this process. Exogenous expression of activated H-Ras (G12V) has been shown to increase the mitogenic activity of 3T3 fibroblasts, and this activity was even dependent on ROS production [64]. In immortalized murine embryonic fibroblasts (MEFs) through a dominant negative form of p53, the expression of Myr-Akt, H-RasG12V, or K-RasG12D conferred a ROS-dependent anchorage independent growth of cancer cells [65]. The mitochondrial ROS activate a HIFs dependent transcriptional network to allow tumor cells to adapt to their diminished oxygen microenvironment. This condition is a prominent feature of the tumor mass due to a mismatch between the high proliferative rate of tumor cells and the ability of the blood supply to provide nutrients including oxygen. The hypoxic condition activates HIF1α, which promotes the lactate production and the generation of electron acceptor NAD^+ molecules by up-regulating LDHA expression [66], the activation of GLUT1 and GLUT3 glucose transporters to increase glycolytic flux [67], the increase expression of PDK1 to divert glycolytic carbon away from the mitochondria [24] and inducing the expression of glycolytic enzymes, including hexokinases (HK1 and HK2) and PGK1 [68]. HIF1α has also been shown to induce microRNA-210, a multiplayer capable to decrease the expression of the iron-sulfur cluster assembly proteins ISCU1/2 (critical for electron transport and mitochondrial oxidation-reduction reactions) and mitochondrial oxygen consumption, increase the lactate production and ROS levels [69]. Given the wide impact of miR-210 on hypoxic cell metabolism, it has been named as a master miRNA of the hypoxia response (hypoxamiR) [70].

2.1.2. Amino acids catabolism

In addition to metabolites such as lactate, many studies have also found acetate, ketone bodies, ammonia, and exogenous proteins as source of nutrients. The acetate derives from exogenous and endogenous sources as mentioned below: dietary source, liver metabolism and even the commensal microbiota. During fasting, an epatic acetyl-CoA hydrolase generates free acetate from acetyl-CoA that can be released into the circulation and metabolized elsewhere in the body as needed [71,72]. Also, the commensal microbiota represents the main source of short-chain fatty acids (FAs) in the gut, the most abundant of which is acetate [73]. Furthermore, a more localized production of acetate comes through the deacetylation of histones by specific lysine deacetylases (KDACs), such as Zn^{2+}-containing KDACs (Zn-KDACs), to regenerate acetate [74,75]. The acetate is taken from cells by passive diffusion of the protonated form of acetate [76], which is facilitated by the high level of acetate and the relatively low pH in the proximal colon and caecum. The active transport of acetate is promoted by MCTs transporters, in which acetate is co-transported with Na^+ or H^+ or exchanged for $HCO3^-$ [77–79] (Fig. 2).

Ketone bodies (3-hydroxy-butyrate, aceto-acetate and acetone) are naturally occurring mitochondrial fuels that are normally produced in the liver during periods of starvation. Then, they are shuttled via the blood stream to the brain, where neuronal cells have the capacity to convert them back into acetyl-CoA and re-utilize them as mitochondrial fuels when nutrients are scarce. Locally, astrocytes also have the capacity to generate ketone bodies, to protect the mitochondrial metabolism of neurons. This biological process is known as “neuron-glia metabolic coupling” [80].

Recently, it was provided evidence that human tumors may also share the same type of metabolic wiring as the brain. It was proposed that catabolic fibroblasts, with mitochondrial dysfunction, produce ketone bodies in the tumor stroma [81]. Ketone bodies are re-utilized by adjacent cancer cells, which process them as mitochondrial fuels for oxidative phosphorylation (OXPHOS), to drive anabolic tumor growth [82] (Fig. 2).

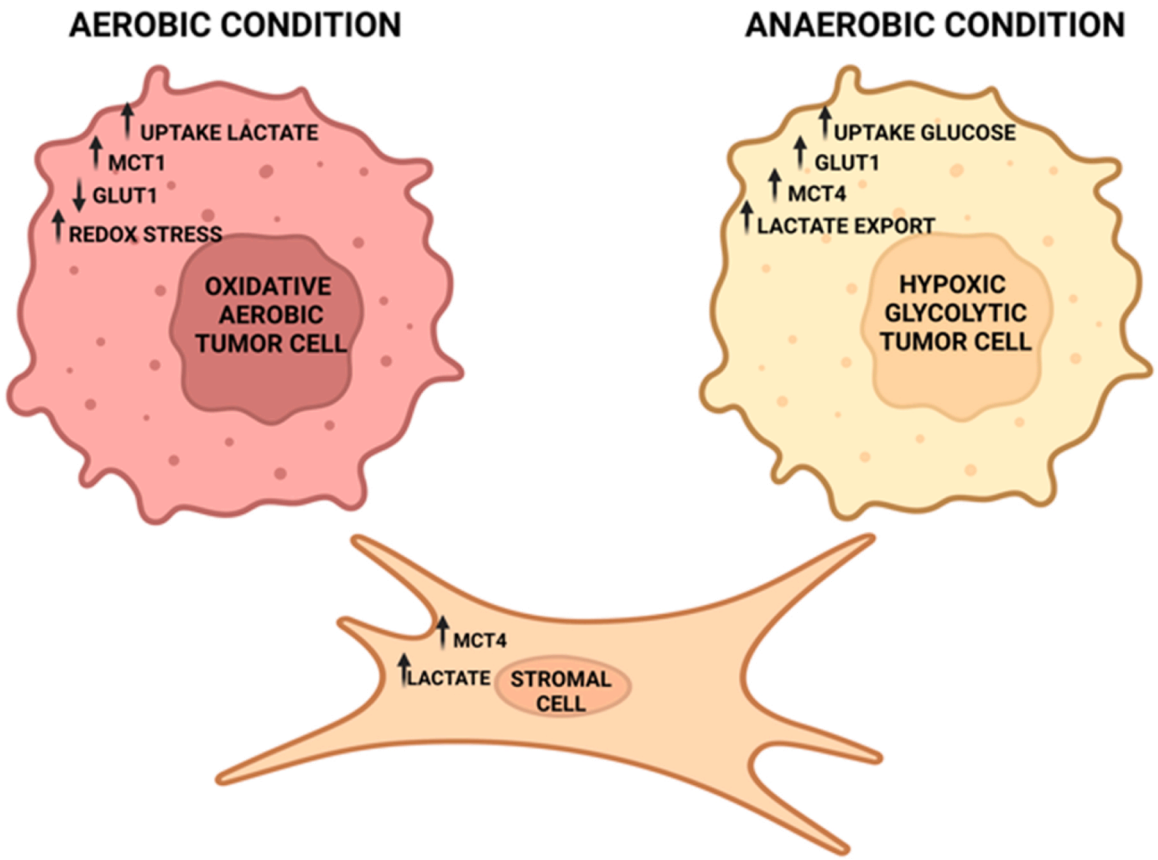

Fig. 1. The metabolic symbiosis in the tumor environment. A scheme summarizing the main changes in metabolic management between oxidative/tumor cells and hypoxic/glycolytic cells in TME. The tumor heterogeneity induces a lactate shuttle between hypoxic and oxidative cancer cells. MCT4-positive hypoxic cells contribute to the formation of an acidic microenvironment by aerobic glycolysis and the secretion of lactate. MCT1-expressing oxidative cells decrease the GLUT1 transporter while increase MCT1-mediated lactate import for the utilization of lactate as a substrate of the TCA cycle. Other cells of the TME as CAF and immune cells give a great contribution in the acidification of the environment by means of MCT4-mediated lactate export.

Among the nutrient supplies, glutamine has been described crucial for many types of tumors. It is a circulating source of nutrients in the blood and muscles providing a ready source of carbon and nitrogen to support the biosynthetic processes, energy and cellular homeostasis that cancer cells may exploit to drive tumor growth. Upon entry into the cell via transporters, glutamine is converted by mitochondrial glutaminases to ammonium ions and glutamate, which can contribute to the synthesis of glutathione or be converted to α-ketoglutarate (α-KG), which enters in the tricarboxylic acid (TCA) cycle and provide energy for the cell (Fig. 2). Oncogenic alterations lead to the reprogramming of glutamine metabolism where the proto-oncogene c-Myc binds the promoter regions of high-affinity glutamine transporters ASCT2 (sodium-dependent neutral amino acid transporter type 2) and SN2 (isoform of system N) resulting in the high uptake of glutamine [43]. Furthermore, c-Myc promotes the expression of isozyme of glutaminase 1 (GLS1), which catalyzes the conversion of glutamine in glutamic acid, increasing glutaminolysis, intracellular levels of glutamate and α-KG, oxygen consumption and mitochondrial respiration. In contrast, the tumor suppressor p53 induces the expression of GLS2, which exhibits contrasting functions during tumorigenesis compared to GLS1. The induction of GLS2 by p53 has tumor suppressor activity [45] and could help to rewire the cellular metabolism [83]. Indeed, cancer cells typically exhibit downregulation of GLS2 in p53-deficient cells compared to p53 wild-type cells [84].

Other genes are involved in glutamine reprogramming metabolism as highlighted by the research group of Chiaradonna [85]. Kras-transformed cells downregulate the expression of glutamate dehydrogenase (GLUD) and upregulate the expression of glutamate-oxaloacetate transaminase (GOT) resulting in the accumulation of cytoplasmatic aspartate and malate leading to an efficient utilization of nitrogen into biopolymers (amino acids and nucleotides) as discussed later, and glutathione, sustaining the growth and the ability to quench ROS production and promote cancer cell proliferation and/or survival.

The ammonium produced as a by-product of glutaminolysis may diffuse into the tumor cell microenvironment and amplify autophagy in stromal cells, facilitating tumor growth by providing metabolic and energetic substrates to cancer cells [86]. Specifically, ammonium ions are produced by glutaminase and glutamate dehydrogenase (GDH) from glutamine and glutamate in mitochondria and utilized by glutamine synthetase (GS) to produce glutamine (see Fig. 2). Furthermore, some studies showed the accumulation of ammonia in the tumor microenvironment where it is captured from CAF cells to synthesize glutamine to be converted in nucleotide synthesis and TCA cycle metabolites [87]. Additionally, altered lipid metabolism contributes to cancer cell growth, including the biosynthesis and oxidation of fatty acids (FAs)[88].

2.1.3. Lipid catabolism

Most of lipids, derived from FAs are acquired from cells through de novo synthesis or exogenously up taken, using multiple transporters [89] including CD36, FATPs, and FABPpm. FAs and their synthetic products can be stored as lipid droplets (LDs) and used to generate NADPH and acetyl-CoA through the beta-oxidation process resulting in citrate production. A quote of citrate is included in the TCA cycle and the rest is converted to palmitate through the enzymatic activities of ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC) and fatty acid

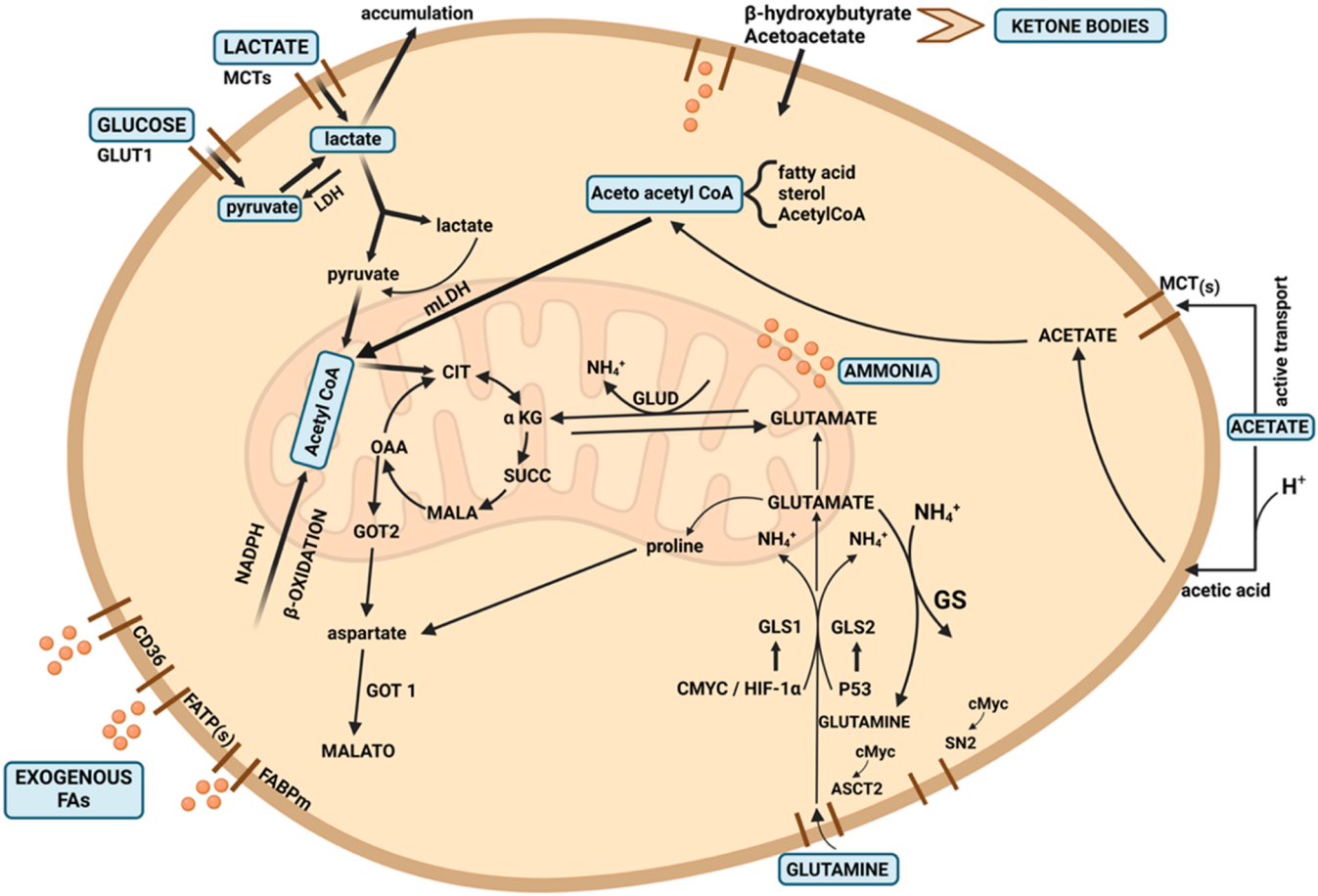

Fig. 2. The transporters of nutritional sources in cancer cells. Cancer cells increase glucose and glutamine uptake and many other nutrients as acetate, ketone bodies, exogenous fatty acids and ammonia to fuel growth and proliferation. During the metabolic reprogramming, the activation of glycolysis includes the transcriptional regulation and increased expression of glucose transporters (MCTs). The figure displays the critical transporters ASCT2, SN2 and GLS1, GLS2 enzymes involved in glutaminolysis, the metabolic recycling of ammonia, a waste product of this process to support cancer biomass. The acetate is imported by active transporters MCT(s) or passively converted to acetoacetate and then in Aceto AcetylCoA in the cytosol as precursor of fatty acids, sterols and AcetylCoA. A quote of AcetylCoA from Aceto AcetylCoA is transported in mitochondria and included in the TCA cycle. Even the exogenous FAs are imported in the cytoplasm by different transporters: CD36, FATP(s), FABP(m) located on the plasmatic membrane. The FAs are metabolized by β-oxidation and different end-products are produced, among which is AcetylCoA included in TCA. A quote is exported outside of the mitochondria as citrate. In the cytosol, citrate could be converted back into acetyl-CoA for lipid synthesis. Mitochondria are not in scale and the nucleus is omitted.

synthase (FANS). The increased up-take of FAs is mediated by HIF1α, which induces the upregulation of FABP1–6. Furthermore, the upregulation of lipogenesis and cholesterol biosynthesis is regulated by sterol regulatory element binding proteins (SREBPs) [90], that regulate genes involved in FAs synthesis to promote their expression under the control of many oncogenes and tumor suppressor genes. In general, the PI3K/AKT signaling axis promotes the lipid synthesis over lipolysis and beta-oxidation [91] and induces the production of Acetyl-CoA from citrate [92] (Fig. 2).

PI3K signaling is also closely linked to mTORC1 and mTORC2 promoting the expression of lipogenic enzymes, including ACLY, FASN and ACSS2. Furthermore, the activation of mTORC2 supports the lipogenesis through AKT-dependent and independent mechanisms [93,94].

It is possible to conclude that stress factors such as hypoxia, oncogenic mutations, and altered signaling induce the up-regulation of anabolic processes and the suppression of catabolic pathways, which finally sustain the success of cancer cells.

2.2. *The anabolic reprogramming of tumor cells*

The biosynthetic pathways are fundamental to sustain cell proliferation and biomass synthesis and indeed, are an essential aspect of cancer metabolism. The cells produce the macromolecules, essentially proteins, lipids, and nucleic acids through ATP-dependent processes. Among the main biosynthetic pathways, the pentose phosphate pathway (PPP) provides biomass including lipids, nucleotides and NADPH that are under the control of Nrf2 (Nuclear factor-erythroid factor 2-related factor 2), which drives anabolic reactions and supports the antioxidant capacity, maintaining the balance of ROS levels and allowing tumor progression and metastasis [95]. The serine synthesis pathway (SSP) represents one of the branches from glycolysis at the point of 3-phosphoglycerate and induces an elevated flux through the *de novo* SSP, which is a common phenomenon in cancer cells. This is induced in response to metabolic stresses, such as glucose, glutamine and serine depletion and produces serine, glutathione, and nucleotides (Fig. 3).

The branched-chain amino acid (BCAAs)- leucine, isoleucine and valine are essential amino acids, which are metabolized directly in the muscle to generate energy for work activities. These three aminoacids are absorbed through diet or from protein degradation and represent a nitrogen and/or carbon source for cell growth and proliferation. In cancer cells, two branched-chain aminotransferases, BCAT1 (in the cytoplasm) and BCAT2 (in the mitochondria) transfer the alfa-amino group onto alpha-ketoglutarate and provide glutamate, which serves as an indirect nitrogen source for nucleotide and non-essential amino

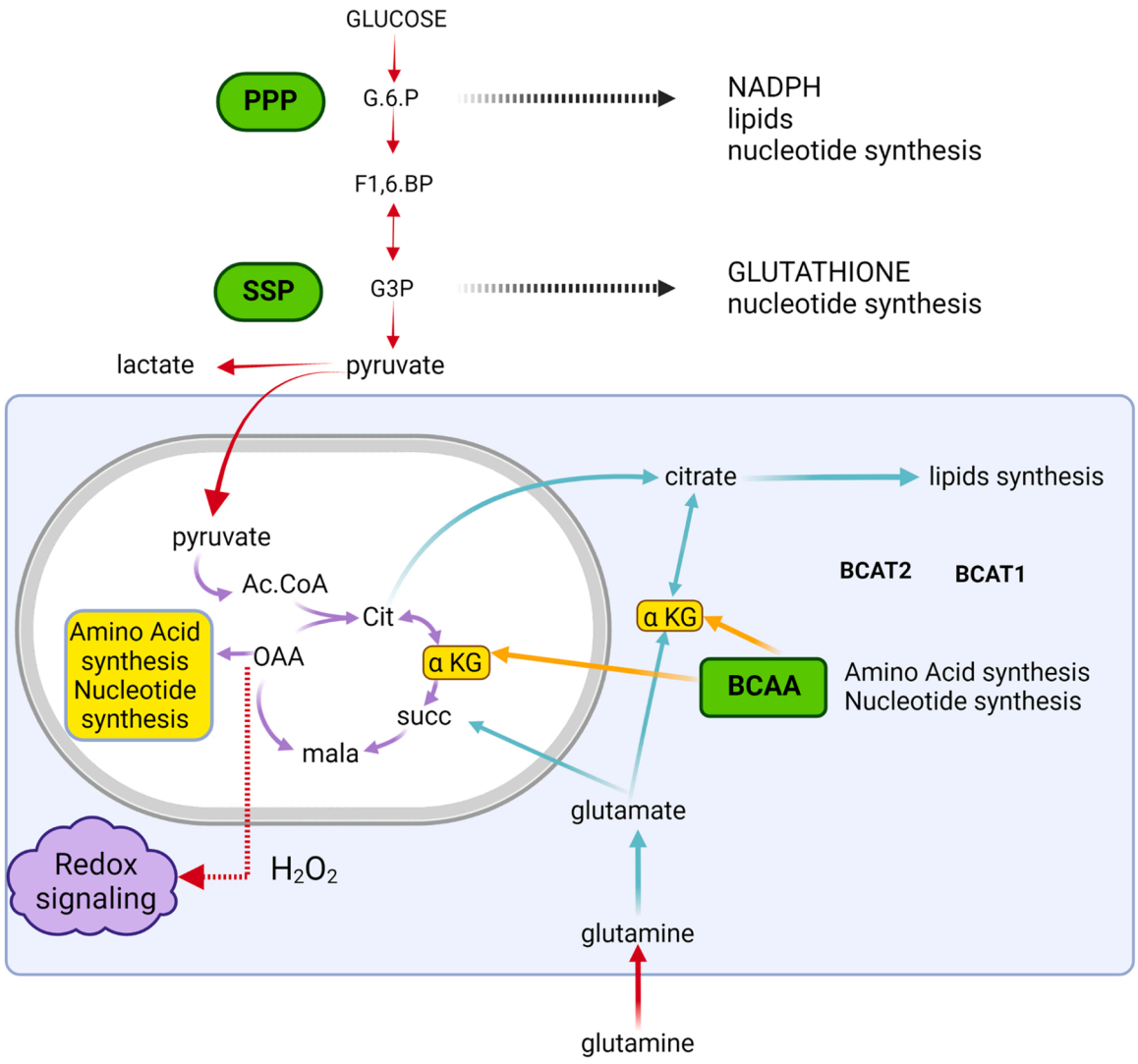

Fig. 3. Biomass synthesis in cancer progression. This scheme illustrates the synthesis of main products for tumor biosynthesis. The increased glucose consumption is used as a carbon source for anabolic processes needed to support cell proliferation. The excess of carbon is used for the de novo generation of nucleotides, lipids, and proteins and can be diverted into multiple branching PPP, SSP and BCAA pathways that emanate from glycolysis [20–22,31,43,23,25–28,32,38–41,96,97].

acid syntheses [98,99].

The anabolic processes of cancer cells employ the cytoplasmatic intermediates from glucose metabolism, such as glucose-6-phosphate (G-6-P), which is at the intersection of glycolysis, glycogen synthesis and PPP metabolic pathways. Another intermediate, the 3-phosphoglycerate (3PG is the major entry point of the serine synthesis pathway for nucleotide synthesis and the oxaloacetate (OAA) and citrate are used to generate cytosolic aspartate and acetyl-CoA for nucleotide and lipid syntheses. The glucose uptake and the mitochondrial citrate metabolism are reprogrammed by the PI3K/AKT oncogenic activity. AKT facilitates the conversion of cytosolic citrate in acetyl-CoA for fatty acids, cholesterol and isoprenoid synthesis by ACLY [100,101]. The PI3K/AKT/mTOR signaling enhance the protein synthesis through a variety of deamidation and transamination reactions, which produce several non-essential amino acid precursors from the intermediates derived from the accumulation of glutamate pool and glutamine up-take [102,103].

The anabolic growth is supported by metabolic enzymes, which are evolved in different isoforms such as M2 isoform of pyruvate kinase M (PKM2), predominant in embryonic and cancer tissues compared to M1 isoform of pyruvate kinase M (PKM1) found in differentiated tissues [104]. PKM2 is a glycolytic enzyme that converts phosphoenolpyruvate (PEP) to pyruvate. Normally, PKM2 is activated by the glycolytic intermediate fructose 1,6-bisphosphate. However, the phosphorylation of PKM2 in the Tyr105 has been found to reduce its binding affinity to fructose 1,6-bisphosphate, resulting in a lower PKM2 activity, a slow conversion of PEP to pyruvate bringing to the accumulation of glycolytic intermediates for anabolic pathway feeding. Some evidence suggest that the decreased activity of PKM2 facilitates the anabolic metabolism [105], through for example, the PI3K/AKT/mTOR pathway that is implicated in the control of PKM2 expression levels. Cells treated with rapamycin (mTOR inhibitor) have been found to display decreased PKM2 expression levels [106]. The ratio between high- (tetrameric active conformation) and low-activity (dimeric conformation) of PKM2 is allosterically controlled by substrate availability [107]. Metabolites such as fructose 1–6 bisphosphate bring PKM2 in an active conformation with the production of pyruvate from PPE. Contrary, inhibitory cell signaling decrease the PKM2 activity, which is converted in the dimeric conformation resulting in a less rapid conversion of PEP to pyruvate bringing to the accumulation of glycolytic intermediates and shunting of these biomolecules in anabolic pathways.

In summary, the metabolic shift termed aerobic glycolysis or Warburg effect is required to sustain the anabolic needs of tumor cells. Glucose metabolism can be diverted from glycolysis to PPP, SSP and

BCAA to supply anabolic components (e.g. nucleotides, aminoacids, fatty acids) to the rapidly growing tumor cells.

2.3. PIN1 and the cancer metabolic reprogramming

2.3.1. PIN1 and glycolysis

PIN1 is a PPIase that binds phosphorylated Serine/Threonine-Proline (pSer/Thr-Pro) motifs, regulating folding, stability, subcellular localization, and activity of multiple targeted proteins [103–106,108]. According to several studies, PIN1 down-regulates numerous tumor suppressor genes and up-regulates more than 50 oncogenes [108–111].

PIN1 facilitates the activation of multiple cancer-driving pathways, sustaining the proliferation [112], division [113,114] apoptosis [115] and cancer cell invasion and metastasis [116]. Furthermore, PIN1 supports aberrant angiogenesis to maintain the nutrient source and oxygen, as well as the elimination of metabolic waste [117], chronic inflammation by regulating the inflammatory response [118] and helps cancer cells to evade immune destruction by controlling the (TLRs) Toll-like receptors signals [119]. In addition, PIN1 regulates the metabolic reprogramming of tumors by interacting directly with crucial proteins that are highlighted in Table 2.

Table 2
PIN1 implication in the "Warburg effect".

Direct targets and cellular localization	PIN 1 binding motifs	Molecular consequence of PIN1 binding to targets	Bibliography
p-PKM2 (cytosol)	Binding and increasing the nuclear localization of p-PKM2	p-PKM2 promotes acetylation of H3-K9 histone on CyclinD1 and c-Myc target genes. p-PKM2 is a coactivator of β-catenin	[120–122]
p-PGK1 (cytosol)	Binding and increasing mitochondrial translocation of p-PGK1	p-PGK1 phosphorylates and activates PDHK1 suppressing PDH and the tricarboxylic cycle	[123,124]
IRS-1 (cytosol) in normal diet	PIN1 binds to the Ser-434-containing motif of IRS-1 in the SAIN domain, via its WW domain	Phosphorylation of IRS1 and PI3K/AKT activation, inducing: increased glucose uptake into muscle; increased lipid synthesis in the liver; increased adipogenesis	[125]
HIF-1α (Nucleus)	Up-regulation of HIF-1α/Ser641, Ser643	Activation of target genes (VEGF, GLUT1, KLH20)	[126–128]
c-Myc (Nucleus)	Binding and upregulation of the transcriptional activity of c-Myc/Thr58, Ser62	c-Myc activates GLUT1 and HK2 target genes involved in the controls of glutamine metabolism process	[43,129, 130]
β-catenin (cytosol)	Binding and upregulation of the transcriptional activity of β-catenin/Ser246	Nuclear accumulation of β-catenin and target genes activation (STAT3, CyclinD1, cMyc, RTK, PDH, MMP2, MMP9)	[131]
AKT (cytosol)	PIN1 binds and activates AKT	AKT protein stabilization (PI3K/AKT/mTor/HIF-1/c-Myc)	[132–134]
Cyclin D1 (cytosol)	PIN1 binds to the phosphorylated GSK-3β Thr286 motif of Cyclin D1	Increased cyclin D1 stability and nuclear accumulation.	[135]
AMPK (cytosol)	Binding and suppressing AMPK phosphorylation	Stabilization of ACC1	[136,137]
ACC1 (cytosol)	Binding and degradation suppression of ACC1	The stabilization of ACC1 enhances lipid synthesis	[138-140]

PIN1 binds and increases the nuclear localization of phosphorylated p-PKM2 [120], which in turn phosphorylates histone H3-T11 leading to histone H3-K9 acetylation of the promoter of Cyclin D1 and c-Myc target genes [121]. The expression of cyclin D1 and c-Myc is also stimulated by the β-catenin transcription factor under the PIN1 control. Hence, PIN1 acts directly on PKM2 that in turn up-regulates cyclinD1 and c-Myc or trough β-catenin interaction, a partner of PKM2, to promote the expression of glucose transporter 1 (GLUT-1) and lactate dehydrogenase A (LDH-A) to enhance the lactate accumulation and the "Warburg effect" [122].

PIN1 increases the mitochondria translocation of PGK1 that phosphorylates and activates the pyruvate dehydrogenase kinase 1 (PDHK1), which inactivates the pyruvate dehydrogenase (PDH) and the tricarboxylic cycle [123,124].

2.3.2. PIN1, cMyc and β-catenin

Sears and colleagues found that PIN1 overexpression increases the transcriptional activity of c-Myc [129] and promotes the c-Myc interaction to the promoters of target metabolic genes GLUT1 and HK2 as described by Dang C. [130]. PIN1 can regulate indirectly c-Myc through the binding of insulin receptor substrate 1 (IRS1), which acts upstream of the IRS-1/PI3K/AKT/mTor/c-Myc axis [132,133] or by interacting with AKT [134]. As described by Yusuke Nakatsu and Asano, PIN1 shows a biphasic regulation on insulin signaling. In mice fed with normal diet, PIN1 binds to the Ser-434-containing motif of IRS-1, which is located in the SAIN domain, via its WW domain. The authors speculated that PIN1 modifies the conformation of the SAIN domain and thereby enhances IRS-1 tyrosine phosphorylation through the insulin receptor, leading to glucose uptake. In high fed diet, PIN1 binds to JNK and S6K increasing their kinase activities, thereby triggering the inhibition of IRS1, decreasing the glucose uptake and contributing to insulin resistance [141,142]. In addition, PIN1 stabilizes the acetyl CoA carboxylase (ACC1) and fatty acid synthase (FASN) two responsive enzymes to insulin stimulation, which favor an adequate supply of fatty acids essential for cancer cell proliferation [143,138,139].

PIN1 regulates β-catenin tournover and its subcellular localization. The direct binding of PIN1 increases the translocation of β-catenin into the nucleus and activates the transcription of STAT3, CyclinD1, cMyc, RTK, PDH, MMP2 and MMP9 target genes [131].

2.3.3. PIN1 and HIF1α

In addition, PIN1 directly interacts with HIF-1α, β-catenin, and modulates their functions to support cancer metabolism. Hypoxia, a common condition in cancer, leads to the activation of HIF1α, which turn on many glycolytic enzymes including hexokinase, GLUT1 expressions and angiogenesis [126–128]. As other regulators, also HIF-1α is controlled directly and indirectly by PIN1 [128]. Under normal oxygen condition, HIF-1α protein is polyubiquitinated by an E3 ligase complex and degraded by the proteasome [144,145]. During hypoxic conditions, HIF1α protein is not ubiquitinated but phosphorylated by the MAPK kinase. In this condition, PIN1 binds directly to phosphorylated HIF1α and sustains its activity on the promoter of target genes including VEGF, GLUT1 and KLH20 [146]. PIN1 also could bind and isomerize promyelocytic leukemia protein (PML), enhance the association between KLHL20 and PML, resulting in the downregulation of PML expression and up-regulation of HIF1α protein with an increase of KLH20 transcriptional activity in a positive feedback loop.

2.3.4. PIN1, AMPK and ACC1

PIN1 suppresses the activity of cytosolic AMPK. PIN1 overexpression was showed to remarkably decrease the AMPK phosphorylation, while PIN1 knockdown enhanced AMPK phosphorylation by 2-deoxy-glucose (2-DG). Normally, AMPK phosphorylates and inhibits the activities of ACC1 and ACC2, indirectly upregulates fatty acid oxidation, which results in lipid depletion. AMPK activators as metformin have been used

for treating metabolic syndrome [147]. In this contest, PIN1 represents a negative regulator of AMPK as demonstrated by Nakatsu et al. [148]. The AMPK-PIN1 interaction leads to a hypo-phosphorylation of S79 residue in ACC1 and thereby elevates ACC1 activity increasing the concentration of malonyl-CoA, an inhibitor of fatty acid oxidation as observed in muscle from obese and type 2 diabetes patients [128,149, 136,137]. In summary, PIN1 promotes the lipid biosynthesis by enhancing the activity of ACC1 preventing its degradation (direct interaction) [150] and indirectly through AMPK suppression, an inhibitor of ACC1.

2.3.5. PIN1 and SREBP1c

The accumulation of lipids is also favored by the involvement of PIN1 in the regulation of the transcriptional activity of the Serum Response Element Binding Protein 1c (SREBP1c), induced by PIN1 through the PI3K/AKT/mTOR pathway in response to EGF signaling [143].

Mouse model studies showed that PIN1 is upregulated in response to high glucose, insulin and high-fat diet that stimulates to metabolic switch [131,151,152,125]. As mentioned by Zannini et al., [146] PIN1 was described also as a metabolic adaptor ready to be engaged from different stimuli as diet and fat's control, speculating its implication in tumor reprogramming [141].

3. The metabolic reprogramming, TME and PIN1

Cancer is surrounded by complex environmental active components that represent a heterogeneous collection of infiltrating and resident host cells, secreted factors and extracellular matrix, which support the tumor growth and progression. The tumor microenvironment is a complex and continuously evolving entity in a dynamic cooperation among components [153,154].

The nature of the tumor microenvironment varies between different tumor types, but hallmark features include immune cells, stromal cells, blood vessels, and extracellular matrix. It is believed that the "tumor microenvironment is not just a silent environment, but rather an active promoter of cancer progression". The interactions among cancer cells and structural components of the TME allow them to become more aggressive and disseminate from the primary site to distant locations, through a complex and multistep metastatic cascade. The TME is complex and includes social and physical interactions. During cancer initiation and progression, the social community will require nutrients and oxygen, which are limited in the hypoxic status, the central characteristic of almost all solid tumors during progression [17]. The hypoxia together with reprogrammed glycolysis and insufficient blood perfusion contribute to the acidity of the tumor microenvironment, which is under a constant oxidative stress due to the increased metabolism rate, which drives the tumor growth.

3.1. Hypoxia in the TME

Hypoxia is a common event in cancer, a central adaptation to a low O_2 concentration and is driven by HIF1α, which induces the expression of glycolytic genes such as hexokinases (*HK1* and *HK2*), phosphofructokinase 1 (*PFK1*), and phosphoglycerate kinase 1 (*PGK1*) [155]. HIF1α also regulates a rapid response for energy production by guarantying an adequate glucose uptake by inducing GLUT1 and GLUT3 glucose transporters, which are required for glucose internalization [48]. In addition, an end-product of glycolysis, *the* lactate, is efficiently removed from the cell through the action of HIF1α-inducible plasma membrane MCT4 [78]. However, HIF1α also actively represses mitochondrial function and oxygen consumption by inducing PDK1. Specifically, it inhibits the conversion of glucose-derived pyruvate into acetyl-CoA by PDH complex in mitochondria via the upregulation of LDHA and PDK1 [24,64]. Under hypoxic condition, HIF1α binds its partner HIF1β [156], translocates into the nucleus and forms a complex with the transcriptional co-activators CBP/p300 and binds to hypoxia response element (HRE) DNA domains [157], resulting in the transcription of many genes involved in cancer metabolic reprogramming correlated to glycolysis as HK2, ALDOA (aldolase A), PK (pyruvate kinase), PGK1, LDHA and GLUT-1 (Fig. 4).

As demonstrated by Han et al., under hypoxic condition, the levels of PIN1 and HIF1α proteins are significantly increased and the interaction between the two molecules stabilizes HIF1α, promoting angiogenesis. The stabilization of HIF1α by PIN1 leads to a hypoxic adaptation of the tumor. PIN1 depletion decreases the expression of genes implicated in angiogenesis (VEGF) and the glycolytic pathway (GLUT1 and PGK1), two mechanisms known to play an important role in cancer progression [158]. Under hypoxic conditions, genetic and pharmacological inhibition of PIN1 by PiB compound accelerate the degradation of HIF1α, in turn reducing VEGF expression and angiogenesis. The anti-angiogenic activity of PiB may account for its capability to inhibit tumor growth in a xenograft model [158].

In order to decrease the consumption of oxygen and ROS production, hypoxic signals mediated by HIF1α regulate the lipid metabolism. HIF1α can promote the expression of PDK1 [159], which inhibits the pyruvate dehydrogenase complex and blocks the conversion of pyruvate to acetyl-CoA, which normally feeds the TCA cycle by producing citrate, suppressing fatty acid incorporation into mitochondria and β-oxidation [160,161]. The FA metabolism needs to be modified under hypoxia to fuel other biological processes other than energy production. Since the conversion of glucose into citrate—the major source of cytoplasmic acetyl-CoA and FA precursor—is decreased under hypoxia due to the inhibition of the TCA cycle, alternative sources of FA precursors must be exploited. In tumor cells, which usually grow in a hypoxic microenvironment, these hypoxia-mediated changes in lipid metabolism are especially important to maintain the high proliferation rate. The uptake of extracellular FA is promoted under hypoxia by the activation of the transcription factor PPARγ, directly activated by HIF1α at genomic level [162], and the increased expression of FABPs 3, 4 and 7 [162,163]. Hypoxia increases FA uptake in breast cancer, ovarian cancer and glioblastoma cells by inducing the expression of FA-binding proteins (FABP3, FABP7 or FABP4), which are involved in the uptake and subcellular trafficking of FAs [163–165]. Hypoxic cancer cells are known to accumulate lipid droplets [166] either by endogenous synthesis or by exogenous uptake. Bensaad et al. reported that the hypoxic accumulation of lipid droplets in breast cancer and glioblastoma cells is mediated by FABP-dependent FA uptake [163]. In addition, HIF1α could promote the endocytosis of lipoproteins, by upregulating the expression of low-density lipoprotein receptor–related protein (LRP1), a receptor that internalizes LDL in vascular smooth muscle cells, as well as the expression of VLDL receptor (VLDLR) in cardiomyocytes [167,168]. To maintain the de novo FA synthesis under hypoxia, the preservation of citrate levels and the synthesis of acetyl-CoA are achieved by the stimulation of reductive glutamine metabolism, mediated, at least in part, by the induction of GLS1 [169] and the proteolysis of the OGDH2 E2 subunit of the α-ketoglutarate dehydrogenase complex (αKGDH) by Siah E3 Ubiquitin Protein Ligase 2 (SIAH2) [170]. αKGDH consists of E1 (oxoglutarate dehydrogenase, OGDH), E2 (dihydrolipoamide succinyltransferase DLST), and E3 (dihydrolipoamide dehydrogenase, DLD) components that collectively convert αKG to succinyl-CoA and NADH. Under hypoxia, OGDH2 is specifically degraded to reprogram the cycle to support the lipid synthesis [170]. Normally, αKGDH oxidizes αKG to succinate (standard TCA cycle reaction). In cells where HIF1α is stabilized, the reductive cycle (reverse TCA cycle) of αKG by isocitrate dehydrogenase to isocitrate and then to citrate is favored.

Adequate FA supply is further supported by the activation of SREBP-1, which in turn upregulates the expression of FASN [171]. To avoid lipotoxicity and/or replenish lipid stores, FAs are converted to neutral triacylglycerols (TAGs), which are stored in lipid droplets (LDs). The formation of LDs under hypoxia is favored by the upregulation of the TAG biosynthesis pathway enzyme 1-Acylglycerol-3-Phosphate

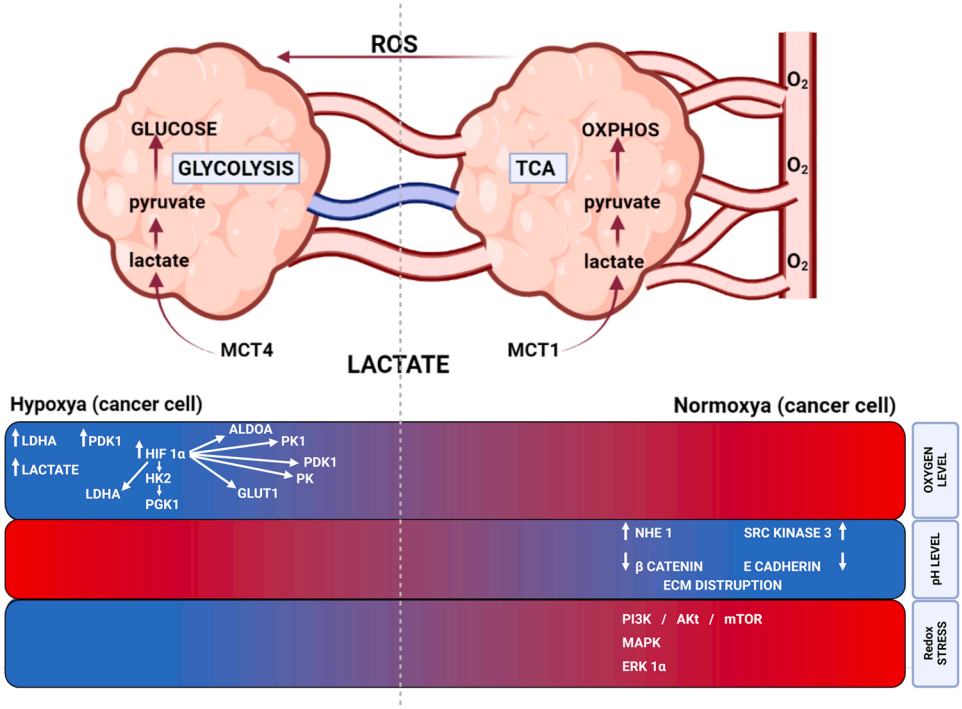

Fig. 4. The tumor microenvironment and the metabolic crosstalk. This illustration encompasses the principal hallmarks that govern the metabolic alterations in the tumor microenvironment. Aberrantly activation of oncogenes and loss of tumor suppressor genes deregulate the import of glucose and its metabolism, alter the hypoxia, pH and redox status inside and outside of cancer cells. In turn, it is deregulated the chemical composition of the extracellular matrix, which induces pleiotropic effects on the phenotypes of normal cells that reside in the vicinity of the tumor.

O-Acyltransferase 2 (AGPAT2) and lipin-1 [166,172], and the LD membrane proteins Perilipin 2 (PLIN2) and hypoxia-inducible gene 2 (HIG2) [173,174]. Finally, lipid accumulation under hypoxia is additionally supported by the inhibition of β-oxidation through down-regulation of Peroxisome proliferator-activated receptor-gamma coactivator (PGC)− 1alpha, PGC-1β, Carnitine Palmitoyltransferase 1 A (CPT1A), Medium-Chain Specific Acyl-CoA Dehydrogenase (MCAD) and Long Chain Acyl CoA Dehydrogenase (LCAD) [160,175].

In the lipid metabolism, PIN1 has a crucial role through the direct interaction with ACC1. In cancer tissues, it is suggested that elevated levels of PIN1 constitutively upregulates ACC1 protein, resulting in lipogenesis and inhibition of the citric acid cycle, thereby leading to adipogenesis. The ablation of PIN1 gene or chemical inhibition reduces the storage of lipid droplets and the expression of mature adipocyte markers in both 3T3-L1 and MEF cells [125,176].

A recent study demonstrated that PIN1 associates with PPARγ, a master regulator of adipogenesis, enhancing its transcriptional activity by changing the ligand binding affinity [177].

3.2. High redox stress in TME

The Warburg effect only partially explains the complexity of tumor metabolism. The TME has been associated to the phenomena called “reverse Warburg effect”, where aerobic glycolysis in cancer cells supports adjacent cells, establishing a complex interplay between different metabolic compartments. There is a metabolic heterogeneity within tumors, with some cells maintaining a glycolytic phenotype while others predominantly utilize OXPHOS with a transfer of catabolites, which induces stromal-cancer cells metabolic coupling, allowing tumoral cells to generate ATP, increase proliferation and reduce cell death [178].

Catabolites implicated in metabolic coupling include the monocarboxylates lactate, pyruvate and ketone bodies. Monocarboxylate transporters are critically necessary for the release and uptake of these catabolites. MCT4 is highly expressed in cancer-associated fibroblasts and it is regulated by catabolic transcription factors such as HIF1α and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [179].

The accelerated metabolism driven by oncogenic mutations coupled with cellular respiration and the aerobic metabolism [180–182] generates a large quantity of ROS [183], compared to normal cells, which regulates cell proliferation, transformation [184], differentiation and immune response. Increased ROS levels, hyper-activate cellular signaling including the PI3K/AKT/mTOR and MAPK/ERK pathways, which induced a reprogramming of gene expression [64,185]. In a positive feedback loop, hypoxia-ROS-HIF-α [186] are implicated in different tumoral processes. Hypoxia stimulates the production of mitochondrial ROS (mROS) via the transfer of electrons from ubisemiquinone to molecular oxygen at the Q_o site of complex III of the mitochondrial electron transport chain. Increased mROS induce and stabilize HIF1α, which enhances the survival and progression of tumor cells by upregulating genes involved in tumor angiogenesis, metabolism, metastasis, and chemoresistance [187–189].

In the TME are present oxidative molecules such as H_2O_2, NO, or even O_2, which can induce the damage of intracellular constituents such as lipids, which, in turn, can lead to the loss of cellular integrity. For these reasons, a number of antioxidant defense mechanisms such us the glutathione (GSH) and the thioredoxin (TRX) systems are activated to protect cancer cells from the oxidative damage. In this context, PIN1 regulates the redox balance and the inhibition of PIN1 significantly increased ROS production. PIN1 maintains the redox balance via the synergistic activation of the c-Myc/NRF2/ARE axis protecting the basal mitochondrial function from KRAS/ERK induced oxidative injury and maintains the redox balance by increasing the expression of ARE-driven genes. Under stress conditions, the activation of NRF2 predominantly regulates the antioxidant program that tightly controls the levels of ROS [190]. cMyc in complex with PIN1 induces the expression of NRF2, which translocates in the nucleus to increase the expression of a cohort of cytoprotective enzymes [191].

3.3. Low pH in TME

The tumor microenvironment due to hypoxia, inflammation, glycolytic cell metabolism, lactate accumulation and insufficient blood perfusion is mild acidic [6,192,193]. Acidosis can have many effects on the malignancy and development of a tumor. In tumor cells the secretion of lactate is coupled with the export of one proton resulting in

accumulation of lactate and acidification of the tumor microenvironment [193].

It has been proposed that the exposure to chronic acidosis may facilitate the clonal evolution of cancer cells by inducing chromosomal instability, clastogenicity, and gene mutations [194,195]. In addition, the extracellular acidification may contribute to metastatic progression by degrading the extracellular matrix, essentially by the involvement of Na^+/H^+ exchanger isoform 1 (NHE1), which is known to play a key role in regulating intracellular pH and osmotic homeostasis and is functionally associated with cancer cell survival, migration and metastatic progression [194]. NHE1 overexpression in cancer cells is also suggested to favor the Epithelial-Mesenchymal Transition (EMT). Indeed, in prostate cancer cells, the expression of NEH1 is strongly correlated with the expression of Zeb1, a crucial transcription factor, which activates the mesenchymal gene expression program [196]. In breast cancer stem cells, Zeb1 is controlled by the PIN1/Rab2A/Erk pathway to regulate their expansion and tumorigenicity [197]. Furthermore, Zeb1 was found to bind to the promoter of NHE1 gene (SLC9A1) and support its expression. NHE1 up-regulation was even proposed to drive carcinogenesis [198]. NHE1 not only directs the proton traffic during tumor microenvironment acidification but also is involved in the trafficking of proteases from lysosomes to the plasma membrane/secretion involved in cancer cell invasion [196].

The acidic pH has also been demonstrated to participate to the acquisition, by cancer cells, of aggressive features that are characteristics of the EMT. During EMT, loss of cell junction molecules leads to perturbation of cell-cell interactions. This is considered the most critical step for cancer cells to dissociate from the primary tumor, invade surrounding tissues, and metastasize to secondary sites [199]. In normal cells, β-catenin promotes adherent junction (AJ) formation by binding to E-cadherin, but it can also function to induce EMT when released from the E-cadherin-β-catenin complex [200]. The extracellular acidic pH induces the loss of β-catenin from AJ in hepatocarcinoma cells through the activation of Src kinase, and the degradation of E-cadherin [201].

Chen and colleagues showed that the incubation of HepG2 cells in acidic medium (pH 6.6) induced cell dispersion from tight cell clusters, leading to the downregulation of β-catenin at cell junctions and a rapid activation of c-Src. Pre-treatment with a Src kinase inhibitor (PP2) prevented the acidic pH-induced downregulation of β-catenin at AJ and in the membrane fractions. The acidic pH-induced c-Src activation increased tyrosine phosphorylation of β-catenin and decreased the amount of β-catenin-associated to E-cadherin. Also, it enhances the endocytosis of E-cadherin and decreases the amount of E-cadherin available for cell–cell adhesion. All these factors might contribute to the disassembly of the AJ [202]. The depletion of membrane-bound β-catenin coincides with enhanced cell migration and invasion [201].

The acidic pH also participates to the acquisition of elongated mesenchymal cell phenotype, that is involved in an increased migratory activity [203] and an ECM degradative function that participate to the metastatic evasion/invasion of tissues [194]. Peppicelli et al. found that MSC exposed to a low pH medium and co-injected with melanoma cells into immunodeficient animals are able to increase the growth rate of melanoma xenografts more efficiently than MSC grown in standard pH media. The promoted tumorigenesis of melanoma cells co-injected with "acidic" MSC correlates with a mesenchymal-like phenotype compatible with an EMT program acquired by melanoma cells exposed to low pH-MSC medium. A clear elongated morphology, resistance to apoptosis and reduction in E-cadherin/N-cadherin ratio characterize melanoma cells exposed to low pH-MSC medium. The increased resistance to apoptosis of melanoma cells exposed to low pH-MSC medium might be due to a stimulated AKT activity [204]. It is known that melanoma cells transfected with N-cadherin acquire a fibroblast-like shape [205] and N-cadherin acting as an oncogene promotes malignancy. In addition, Alonso et al. showed that N-cadherin expression promotes the metastatic spreading of human melanoma cells [206]. Considering that PIN1 can act both on the regulation of the TME pH and the activity of E-Cadherin [207], β-catenin [131], c-Src and AKT [132–134] responsible of the here described phenotype, it could be interesting to further analyze its contribution in this context.

3.4. PIN1 and the metabolism of stromal cells

Looking more widely in the regulation of stromal cell metabolism, PIN1 is strictly controlled in adipocytes, and it is important for lipid mobilization. In obese mice (ob/ob), its protein level increases even when normal mice are fed with high-fat diet (HFD) in subcutaneous white adipose tissue (scWAT). In PIN1 adipose specific KO mice (ad-PIN1), the weight of scWAT, epididymal (EpiWAT) and brown (BAT) adipose tissues decrease compared to the control together with the liver triglyceride levels. When fed with HFD, ad-PIN1 KO mice increased glucose and insulin tolerance [208]. PIN1 downregulates lipolysis through the interaction and degradation, via the ubiquitin system, of adipose triglyceride lipase (ATGL), a rate-limiting enzyme involved in the catabolism of TAGs. Ad-PIN1 KO mice upregulate the expression of genes involved in the beta-oxidation and have an increase of lipolytic activity in EpiWAT. Even the glucose metabolism is more efficient [209]. It will be interested to untangle how PIN1 could orchestrate its targeted metabolic genes in cancer cells and in adipocytes to sustain tumor growth.

Bone marrow stromal cells support leukemogenesis, but the molecular mechanisms are still poorly understood. The oncometabolite R-2-hydroxyglutarate (R-2HG) promotes leukemogenesis but its effect on the bone marrow stromal cells is still unclear. Chen et al. demonstrated that R-2HG induced NF-κB activation in bone marrow stromal cells to create a supportive niche for acute myeloid leukemia cells (AML) cells. Specifically, R-2HG induces the interaction of PIN1 and ROS/ERK-dependent phosphorylated NF-$_K$B. This interaction stabilizes NF-$_K$B, which activates the transcription of target genes including IL-6, IL-8 and complement 5a to stimulate the proliferation of AML cells [210].

In the hypoxia/reoxygenation ischemia/reperfusion in vivo model, endothelial inflammation is driven by the ROS/NF-κB pathway. $p66^{Shc}$ adaptor protein is involved in ROS generation inside the mitochondria. PIN1 isomerizes phosphoSer36-$p66^{Shc}$, which leads to $p66^{Shc}$ dephosphorylation from PP2 phosphatase. Only isomerized and dephosphorylated p66Shc can translocate to the mitochondria and subsequently lead to ROS generation [211].

3.4.1. Future perspective

All current knowledge shows that the metabolic reprogramming is an event in which genetics and epigenetics factors trigger events, which allow cells to adapt to the new condition. It is therefore an adaptive response implemented by a community of cells and from its microenvironment that mutually feed themselves. These features were described by innumerable scientific studies published after Otto Warburg observations even if many aspects still remain to be investigated.

In this context, scientific data are supporting the involvement of PIN1 as a player indirectly involved not only in the tumorigenic process within the cell itself but also participating in all those events that metabolically affect the evolution of the tumor, placing itself at the interface between the triggering processes and the adaptation of the disease. PIN1 represents a valid candidate on which to act pharmacologically in order to intervene on different aspects of the oncogenic path where it is involved. Currently, we know a lot about the activity of PIN1 in cancer cells, however, as the tumor is an ecosystem composed of several components, it will be necessary to carry out in depth studies to grasp the action of PIN1 at every point of this complex system.

PIN1 has a strong impact on lipid and glucose metabolisms by modulating multiple signal transduction pathways and all these new aspects should be considered studying PIN1 in the tumorigenic process. It will be important to know in detail, in each type of cell that makes up the tumor microenvironment, the activity of PIN1 on the genes linked to metabolism, and to what extent the change in the microenvironment

influences the activity of PIN1 in the various components of the tumor.

Many tumors have been shown to increase PIN1 levels and PIN1 KO mice drastically exhibit tumor shrinkage [212]. Even pharmacological inhibition of PIN1 sensitizes cancer cells to chemo and target therapies as demonstrated in breast cancer [213,214] and also for hepatocellular carcinoma [215]. All these evidence suggest that PIN1 may be a valid drug target, which combined with the scientifically consolidated awareness of the influence of PIN1 on metabolism leads to propose it as a target player to hamper or at least slow down the tumor progression. PIN1 targeted therapies could lead to a metabolic rewrite of the tumor providing improved responses to current and next generation therapies increasing patient survival. Furthermore, considering the effects of nutrition on the biology of PIN1 and its involvement in the metabolism, this could provide important advances not only in the understanding of certain metabolic diseases including cancer but also advances in the knowledge of the mechanisms that are at the basis of the onset of tumorigenesis.

Funding source

All sources of funding should also be acknowledged and you should declare any involvement of study sponsors in the study design; collection, analysis and interpretation of data; the writing of the manuscript; the decision to submit the manuscript for publication. If the study sponsors had no such involvement, this should be stated.

Funding agencies

This research was funded by Fondazione AIRC per la Ricerca sul Cancro (Grant AIRC IG23566).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability

No data was used for the research described in the article.

Acknowledgments

Michele Gallo for supporting us in drawing the figures.

Author contributions

IC conceptualized, wrote and revised the text. TA and VC edited the final version. FR and VK conceptualized the work and edited the final version. All authors contributed to the article and approved the submitted version.

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