6 Metabolic Plasticity of Tumor Cells: How They Do Adapt to Food Deprivation

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Abstract

Dysregulated metabolism is a key hallmark of cancer cells and an enticing target for cancer treatment. Since the last 10 years, research on cancer metabolism has moved from pathway attention to network consideration. This metabolic complexity continuously adapt to new constraints in the tumor microenvironment. In this review, we will highlight striking changes in cancer cell metabolism compared to normal cells. Understanding this tumor metabolic plasticity suggests potential new targets and innovative combinatorial treatments for fighting cancer.

Keywords

Metabolic reprogramming · Bioenergetics · Glycolysis · Mitochondria · Amino acid · Fatty acid · Hypoxia · Acidosis · Combined therapies

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6.1 Introduction

Cancer metabolism is under the spotlight since almost one century when Otto Warburg first observed an increase in glucose consumption in tumors in comparison with non-proliferating normal tissues (Warburg 1956a, b). Numerous studies on different tumor models and in patients confirmed that tumors present a high glucose consumption and lactate production regardless of oxygen availability (DeBerardinis and Chandel 2016). This phenomenon is called aerobic glycolysis and the resulting increased glycolytic flux was demonstrated to provide new biomass in order to fuel cancer cell growth. However, more recently, new investigation and new biochemical tools highlighted that tumors do not only depend on glucose as a major source of energy. New evidence demonstrated that mitochondrial activity still participates in tumor energy production. In order to survive and proliferate, cancer cells adapt their metabolism to acquire necessary nutrients from nutrient-poor environment or hostile environment like acidosis. Depending on cell type or microenvironment modification, tumor cells can rely on glucose, on specific amino acids (such as glutamine or serine) and/or on lipid metabolism (Fig. 6.1) (Corbet and Feron 2017a). These recent findings underscore the complexity of metabolic flexibility presented by cancer cells and the important role that this plasticity may play in cancer development.

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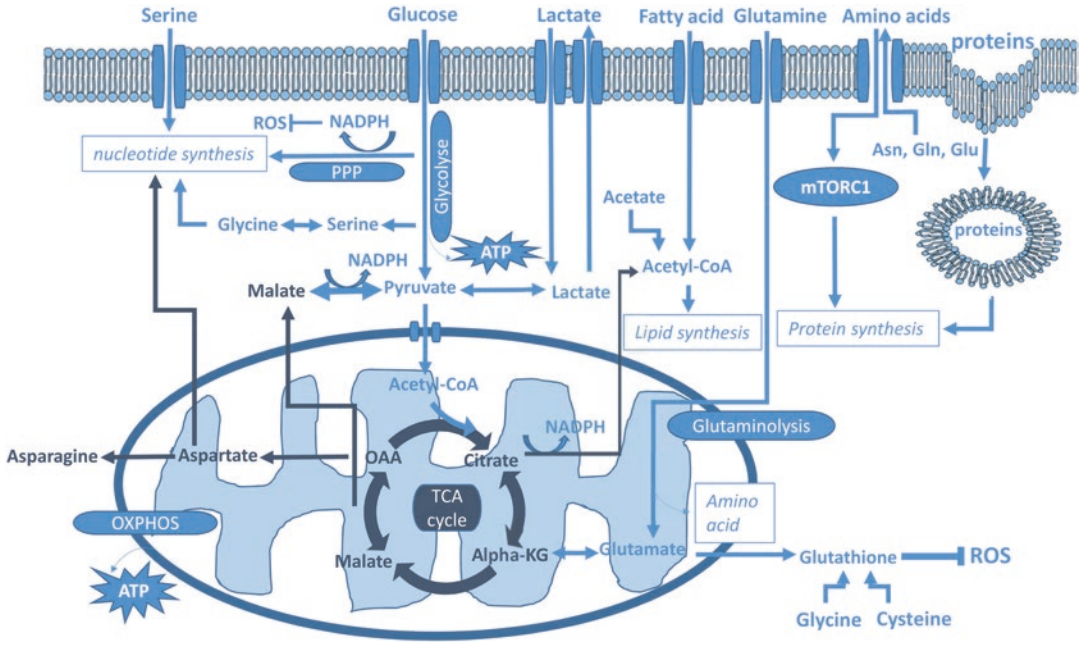

Fig. 6.1 Bioenergetics of cancer cells
Cancer cells can take up glucose, glutamine, serine, amino acids, fatty acids, acetate, lactate and extracellular proteins to support proliferation. Glucose metabolism through glycolysis produces ATP and carbon intermediates to sustain proliferation such as intermediates for the pentose phosphate pathway (PPP) and for de novo serine synthesis. PPP generates NADPH (defense against reactive species of oxygen, ROS) and is involved in nucleotide synthesis. Extracellular and de novo serine also participate in nucleotide synthesis. The end-product of glycolysis, pyruvate, can be converted into lactate or acetyl-coA. Lactate is exported out of the cells and acetyl-coA fuels tricarboxilic acid (TCA) cycle. In some cancer cells, lactate can be taken up and use as carbon substrate for pyruvate production. TCA cycle produces carbon intermediate for cellular proliferation such as aspartate, asparagine, glutamate and precursors for lipid synthesis. In the presence of oxygen, TCA cycle via oxidative phosphorylation (OXPHOS) produces ATP. TCA cycle can also be fueled by glutamate. Glutamate is the result of glutamine metabolism, glutaminolysis. Glutaminolysis is also involved in amino acid synthesis and in concert with glycine and cysteine, glutathione production (defense against ROS). Cancer cells can import fatty acids from extracellular and, via fatty acid oxidation (FA0), generate ATP and acetyl-CoA. Fatty acids can also be synthetized de novo via an acetyl-coA sources provide from citrate or acetate. Glutamine (Gln), glutamate (Glu) and asparagine (Asn) can act as exchange substrate for antiporter that allow the entrance of extracellular amino acids. The level of intercellular amino acid regulate mTORC1 activity, which in turn regulates protein synthesis. In case of depleted nutrient medium, cancer cells can import entire protein via micropinocytosis and through lysosomal degradation release free amino acids.

6.2 Bioenergetics of Cancer Cells

The metabolic needs of the proliferating cancer cells significantly differ from the quiescent cells. To support rapid proliferation, tumor cells must undergo metabolic reprogramming. Understanding the different metabolic strategies developed by the cancer cells to acquire necessary nutrients can build up promising strategies that may lead to food starvation or prevent their metabolic flexibility.

6.2.1 Aerobic Glycolysis and TCA Cycle Dependency

In most healthy cells, glucose is metabolized into pyruvate (glycolysis) and then oxidized in the mitochondria through tricarboxylic acid (TCA) cycle in order to produce energy via OXPHOS (Fig. 6.1). In the absence of oxygen, pyruvate is converted into lactate in the cytosol. Otto Warburg observed that this physiological response to hypoxia also occurs in cancer cells even in the

presence of oxygen. This phenomenon is called aerobic glycolysis. Warburg first explained this phenomenon by an impaired mitochondrial function in tumor cells leading to a non-coupling of glycolysis to energy production from mitochondria (Warburg 1956a, b). However, the Warburg hypothesis has been now reassessed because only a few mutations of mitochondrial metabolic enzymes have been described, and this true only in some cancer cell lines (San-Millan and Brooks 2017; Laurenti and Tennant 2016). Moreover, recent studies have shown that various cancer cell types rely on mitochondrial respiration and that mitochondrial metabolism is necessary for cancer tumorigenesis (Weinberg et al. 2010). Nevertheless, Warburg's observation that cancer cells consume a large amount of glucose has been validated in many cancer patients. Today, it is clear that the exacerbated glycolytic flux is due to the loss of tumor suppressors and activation of oncogenes that modulate the expression or activity of proteins (transporters, enzymes, cofactors) involved in glycolysis (DeBerardinis and Chandel 2016). It has been demonstrated that one advantage of the resulting increase in glycolytic intermediates is to provide new precursors for anabolic pathways in order to fuel cancer cell growth, especially through the pentose phosphate pathway (PPP), a pivotal biosynthetic pathway branched to glycolysis (De Preter et al. 2016). PPP produces NADPH against oxidative stress and also produces pentose phosphate for nucleotide synthesis (Fig. 6.1). De Preter et al. demonstrated that reduction of PPP activity decreases cancer cells proliferation with a profound effect in Warburg-phenotype cancer cells. In addition, she found that inducing a switch of glycolytic cancer cells to a more oxidative phenotype led to a decreased proliferation (De Preter et al. 2016). This result confirmed the pivotal role of aerobic glycolysis in cancer proliferation.

The observation that mitochondria are still active in many cancers is explained by the fact that these organelles (which are at the crossroad of many essential metabolic pathways) can be fueled by other nutrients than glucose (DeBerardinis and Chandel 2016). Amino acids and fatty acids can supply substrates to TCA cycle in cancer cell lines (Fig. 6.1). Like glycolytic intermediates, TCA cycle intermediates also provide new precursors for anabolic pathways (Ahn and Metallo 2015). Due to tumor heterogeneity, different metabolic preferences could coexist within a tumor. Local microenvironment could influence which fuel is used by the cancer cells to sustain tumor growth (Boroughs and DeBerardinis 2015; Ahn and Metallo 2015). For instance, it has been demonstrated that lactate release by hypoxic tumors can be taken up by oxidative tumors and then oxidized into pyruvate for fueling TCA cycle (Corbet and Feron 2017a).

6.2.2 Amino Acid Metabolism

In addition to the increased glucose consumption, various cancer types exhibit an increased demand for specific amino acids and become dependent either on an exogenous supply or on an upregulated *de novo* synthesis (Lukey et al. 2017).

6.2.2.1 Glutamine Metabolism

This non-essential amino acid is the most abundant amino acid present in the plasma and is used by the cell for energy generation and biomass production (Altman et al. 2016). Glutamine enters into the cells via many transporters, such as SLC1A5 which is upregulated in several cancer types (Bhutia et al. 2015). Then, it can be exported via the efflux of glutamine through LAT1 antiporter (Pavlova and Thompson 2016). Glutamine can also be metabolized through glutaminolysis to generate glutamate and subsequently alpha-ketoglutarate that fuels the TCA cycle (DeBerardinis and Chandel 2016). Two different routes may be used by the TCA cycle to metabolize the alpha-ketoglutarate: the canonical oxidative decarboxylation pathway and the reductive carboxylation pathway. The oxidation of alpha-ketoglutarate produces energy, anaplerotic nutrients and pyruvate through malic enzyme (Fig. 6.1). On the other hand, the reduction of alpha-ketoglutarate leads to citrate which supports the fatty acid synthesis (Altman et al. 2016). In addition, glutamine via its conversion into glutamate is an important source of nitrogen,

which supports the production of amino acids and the biosynthesis of nucleotides. Glutamate can also induce cysteine uptake by acting as an exchange substrate for the cysteine antiporter xCT (Pavlova and Thompson 2016). Glutamine metabolism is also involved in protein synthesis, mTORC1 regulation (a major positive regulator of cell growth), production of defense against reactive oxygen species (through glutathione synthesis and NADPH production) and autophagy.

As a consequence of these different reactions and pathways, glutamine is theoretically an ideal substrate for the development of cancer cells. Experimental studies have confirmed its pivotal role. In 2007, Yuneva et al. already described that some cancer cells were sensitive to glutamine depletion (Yuneva et al. 2007). Several experimental ^{13}C-NMR studies have shown that glutamine is used to replenish TCA cycle in cancer instead of glucose (DeBerardinis et al. 2007; Fan et al. 2013; Altman et al. 2016; Jones and Bianchi 2015). In different cancer cell lines, it has been demonstrated that glutamine supports OXPHOS and that OXPHOS remains the largest quantitative contributor for ATP production, a fact that is also true in hypoxia (Fan et al. 2013; Le et al. 2012). In glioblastoma, it has been shown that glutamine also serves as a carbon source for biosynthetic pathways. First, the decarboxylation of glutamine leads to pyruvate production through malic enzyme, consistent with NADPH production. Pyruvate can then be used as anaplerotic nutrient to replenish TCA cycle intermediates during citrate export while NADPH serves as an electron donor for reductive reaction in lipid synthesis. Second, glutamine decarboxylation feeds the production of oxaloacetate that supplies anabolism as oxaloacetate can be converted into aspartate, a required precursor for the synthesis of nucleotides (DeBerardinis et al. 2007). More recently, glutamine has been identified as a major source of citrate in cancer cells when the TCA cycle function is altered by hypoxia (Metallo et al. 2011). In these circumstances, glutamine preferentially undergoes reductive metabolism to produce citrate through the TCA cycle, then can be converted into acetyl-CoA for lipid synthesis (Zhang et al. 2014; Metallo et al. 2011; Wise et al. 2011; Mullen et al. 2011). Some studies reported circumstances where reductive and canonical metabolism of glutamine co-exist, depending on the tumor microenvironment (acidic pH) or mutations of oncogenes regulating the mitochondrial metabolism (McGuirk et al. 2013; Corbet et al. 2014). This ability to easily switch from one mode to another mode of glutamine metabolism offers to the tumor cells a metabolic plasticity advantage to rapidly adapt to new environmental constraints.

6.2.2.2 Serine Metabolism

Besides glutamine, the availability of other amino acids is also a limiting factor for cancer cell proliferation (Kory et al. 2018). Many cancer cells are dependent on serine, a non-essential amino acid involved in several metabolic processes that are crucial for cell growth (Yang and Vousden 2016). Serine can be synthesized *de novo* via a glycolysis-diverting pathway: the glycolytic intermediate 3-phosphoglycerate is converted into serine following a three-step enzymatic reaction (Amelio et al. 2014). Metabolic studies have shown that cancer cells may use as much as 50% of glucose-derived carbon in serine biosynthesis and downstream metabolism (Pavlova and Thompson 2016). Serine can also be imported from the extracellular medium via different transporters (Yang and Vousden 2016). After glucose and glutamine, serine is the third most consumed metabolite in mammalian cells (Frezza 2016; Hosios et al. 2016). Serine, through its conversion into glycine, is a major donor of one-carbon unit to the folate cycle which is essential for the synthesis of nucleic acids and contributes to NAPDH formation and methylation reaction (DNA, RNA, proteins and lipids). Of note, antifolate chemotherapies are currently used in cancer treatment. Serine is also involved in the production of cysteine and glutathione (Yang and Vousden 2016). In various cancer types, the first enzyme of *de novo* serine synthesis (PHGDH) was found to be overexpressed, opening new opportunities for cancer treatment (Yang and Vousden 2016).

6.2.2.3 Role of Other Amino Acids

To sustain their need for amino acids, cancer cells have developed means to either increase the import or the biosynthesis of these amino acids. By acting as an exchange substrate for the antiporter LAT1, glutamine is involved in the import of many essential amino acids through this antiporter (Pavlova and Thompson 2016). Fuchs et al. demonstrated that the expression of LAT1 was increased in several cancer types and that the expression of this antiporter was correlated with tumor growth (Fuchs and Bode 2005). The metabolism of serine and glutamine is involved in the biosynthesis of all non-essential amino acids (Zhang et al. 2017). These amino acids are essential for protein synthesis, and like glutamine and serine, they participate in other cellular functions. For instance, Krall et al. observed that asparagine level regulates the uptake of amino acids and mTORC1 activity. More specifically, asparagine regulates the serine uptake and influences the serine metabolism as well as nucleotides synthesis (Krall et al. 2016). The asparagine biosynthesis is the result of glutamine oxidation into aspartate which is metabolized into asparagine. Sullivan et al. demonstrated that a major role of glutamine oxidation for respiration was to provide access to electron acceptors to support aspartate biosynthesis. They demonstrated that aspartate supported cancer proliferation through its contribution to nucleotide synthesis (Sullivan et al. 2015). This data highlight the importance of the *glutamine-aspartate-asparagine* axis in cancer proliferation. In many tumor cells, some non-essential amino acids become essential because of the high metabolic demand (such as glutamine and serine) or mutations in specific metabolic enzymes (Geck and Toker 2016). For example, arginine auxotrophic tumors have been described. These tumors cannot synthesize arginine due to a lack of argininosuccinate synthase (Geck and Toker 2016). This feature is interesting for cancer therapy because healthy cells do not need extracellular sources of non-essential amino acids and starvation therapy is under consideration. In the absence of glutamine and other amino acids, cancer cells have developed a third way to obtain proper resources via the micropinocytosis of extracellular proteins, phagocytosis of apoptotic bodies and entosis living cells (Zhang et al. 2017; Pavlova and Thompson 2016). After lysosomal degradation, cancer cells recover free amino acids and therefore survive in unfavorable environment.

6.2.3 Fatty Acids Synthesis and Oxidation

Lipids are important building blocks for producing new cells. They are major components of membranes and they are also involved in lipidation reactions and cellular signaling (DeBerardinis and Chandel 2016). Fatty acids can be obtained from extracellular media or synthesized *de novo*. Fatty acid synthesis requires a source of acetyl-coA and the reducing factor NADPH. Depending on the microenvironment and the availability, glucose, glutamine or acetate are the major source of acetyl-coA while the NADPH mainly comes from PPP (DeBerardinis and Chandel 2016). While the *de novo* synthesis of fatty acids is low in most healthy cells, tumorigenesis is associated with high lipid synthesis (Pavlova and Thompson 2016). In the presence of abundant extracellular nutrients and oxygen, most tumors rely on *de novo* fatty acid production (Boroughs and DeBerardinis 2015). Moreover, the three major components involved in fatty acid synthesis are frequently upregulated in various cancer types (Pavlova and Thompson 2016). However, under some condition such as hypoxia, cancer cells are not able to synthesize fatty acids and need to import lipids from the extracellular environment. Fatty acids also supply energy, as mitochondrial fatty acid oxidation produces more than twice much ATP per mole than oxidation of glucose or amino acids (Boroughs and DeBerardinis 2015). To conclude, like for amino acid metabolism, cancer cells have developed various mechanisms to exploit lipid metabolism in order to sustain growth in unfavorable microenvironment.

6.3 Metabolic Reprogramming

Tumors adapt to different sources of energy to survive and proliferate. However, what dictates which pathway is used and when? It has been established that the metabolic phenotype of tumor is controlled by intrinsic genetic mutations and external response to microenvironment (Cairns et al. 2011). Intrinsic mutations lead to modification of metabolic pathways to optimize cancer proliferation (Obre and Rossignol 2015; Cairns et al. 2011). Here, we will describe illustrative examples of metabolic plasticity induced by the microenvironment, namely pH, oxygen and nutrient deprivation. We will also focus on metabolic changes that are induced by anticancer treatments.

6.3.1 Influence of Tumor Microenvironment on Tumor Plasticity: Illustrative Examples

Abnormal and heterogeneous microenvironment impose constraints on fast-growing tumors. Limited access to vasculature lead to local hypoxia and nutrient deprivation. The increase in metabolic needs lead to acidification of the tumor microenvironment. These constraints lead to profound cancer cells metabolic adaptation that need to be integrated together in order to develop efficient strategies to control tumor progression.

6.3.1.1 Hypoxia Enhanced Metabolic Plasticity

Hypoxia takes place when cancer cells have limited access to oxygen or when the balance between oxygen supply and consumption is disrupted. Several factors contribute to the occurrence of tumor hypoxia where co-exist chronic hypoxia (diffusion-limited hypoxia and hypoxemic hypoxia) and acute hypoxia (due to temporal fluctuations in red blood cell flux) (Bayer and Vaupel 2012). The main physiological response to hypoxia is the stabilization of the transcription factor HIF-1α (hypoxia-inducible factor 1 alpha), a common feature observed in hypoxic cancer cells (Nakazawa et al. 2016). HIF-1α activity upregulates almost all enzymes of glycolysis and glucose transporters thereby facilitating increased glycolytic flux (Eales et al. 2016). HIF-1α also prevents oxidative mitochondrial activity by controlling the glycolytic pyruvate fate. First, HIF-1α enhances pyruvate reduction into lactate (upregulation of LDHA) and increases lactate export (upregulation of MCT4). Second, HIF-1α prevents oxidation of pyruvate via the upregulation of PDK-1 and PDK-3 which inhibit the conversion of pyruvate into acetyl-CoA (Lu et al. 2008). In addition to the decreased mitochondrial respiration, the decrease in acetyl-CoA entering into TCA cycle affects other metabolic pathways as it decreases the level of TCA cycle intermediates required for biomass production and synthesis of non-essential amino acids. Glucose-derived acetyl-CoA is also the starting point for fatty acid synthesis (Nakazawa et al. 2016). Therefore, hypoxic cancer cells exhibit an increase in glutamine consumption to compensate the decrease in glucose contribution to TCA cycle (Nakazawa et al. 2016). As previously described, both oxidative and reductive glutamine metabolism can sustain TCA cycle. It has been shown that HIF-1α can shift glutamine metabolism from oxidative to reductive carboxylation to support lipid synthesis (Metallo et al. 2011).

There is increasing evidence that, under hypoxia, cancer cells rely on carbon sources other than glutamine and glucose (Eales et al. 2016). Under hypoxia, several cancer cells lines increased their uptake of extracellular lipids (Kamphorst et al. 2013). Hypoxia upregulates an enzyme involved in acetate metabolism (ACSS2, acetate to acetyl-CoA) (Schug et al. 2015). As a consequence, a large fraction of fatty acid carbon is derived from acetate (Kamphorst et al. 2014). Overall, specific mutations induced by hypoxia in acetate metabolism and/or fatty acid uptake influence the fuel choice. The acetate assimilation to maintain lipogenesis together with the increased uptake of fatty acid support the rapid proliferation of tumor cells under hypoxia. Serine metabolism under hypoxia was also investigated by Ye et al. They found that SHMT2, the enzyme that converts serine into glycine in mitochondria,

was induced under hypoxia through HIF-1α. They also observed that depletion of this enzyme in hypoxic cells increased ROS levels, led to cell death *in vitro* and decreased tumor growth *in vivo*. They concluded that this enzyme was crucial to connect serine metabolism to mitochondrial redox control of cancer and to maintain cell survival (Ye et al. 2014).

Hypoxia is heterogeneous in solid tumors, a feature that can enhance metabolic cooperation between different microenvironment and cell types. For example, De Bock et al. demonstrated that tumor vascular endothelial cells rely on glycolysis rather than on oxidative phosphorylation for ATP production. This allows oxygen to permeate further into the tumor instead of being directly consumed by proximal endothelial cells (De Bock et al. 2013). Another example of metabolic cooperation is the symbiosis existing between hypoxic and oxygenated cancer cells within a tumor (Sonveaux et al. 2008): the lactate released by hypoxic highly glycolytic cancer cells is metabolized by normoxic cancer cells. As a consequence, glucose freely diffuses through the oxygenated tumor cell sheath to fuel glycolysis of distant, hypoxic tumor cells. Of note, this metabolic symbiosis can be disrupted by MCT1 inhibition (Sonveaux et al. 2008).

6.3.1.2 Interplay Between Cancer Metabolism and Extracellular pH

Aerobic glycolysis and hypoxia are responsible for this extracellular acidification (Corbet and Feron 2017b). The increase in glycolytic flux leads to the production of lactate and protons that need to be exported outside the cells to avoid cytoplasm acidity and to maintain cellular function. Therefore, cancer cells have developed different mechanisms to export protons outside the cell. It has been shown that HIF-1α upregulates plasma membrane ion pumps and transporters (Taddei et al. 2013). Lactate and H^+ are exported to the extracellular media through the MCT4 transporter. Protons can also be exported outside the cells by Na^+/H^+ exchangers and H^+-ATPases. Of note, oxygenated areas are also involved in extracellular acidification because CO_2 produced by cellular respiration diffuses outside the cell and is hydrated in the extracellular medium in bicarbonate and proton. The disorganized tumor vasculature prevents an efficient wash-out of H^+ ions released into the extracellular medium and contributes to its acidification (Corbet and Feron 2017b). Extracellular acidosis has been largely described promoting cancer cells migration, invasion and metastasis (Taddei et al. 2013). Acidosis can also play a role in tumor metabolism reprogramming (Corbet and Feron 2017b). In 2008, Chen et al. performed a genome-scale gene expression study in breast cancer to measure response to lactic acidosis: low-risk breast cancer patients exhibited a preference for aerobic respiration and a repression of glycolysis gene expression (Chen et al. 2008). In another study, Chen demonstrated that acidosis abolished stabilization of HIF-1α (Tang et al. 2012). In 2013, Lamonte et al. performed stable-isotope tracers of glucose, glutamine and palmitate under acidosis. They observed that acidosis redirected glucose away from glycolysis and increased respiratory metabolism (Lamonte et al. 2013). They also found that acidosis promoted an increase in glutamine uptake and consumption leading to the ATP generation. They measured an increase in fatty oxidation which, together with glutaminolysis, increased ROS production. Interestingly, acidosis also redirected glucose away from glycolysis towards the oxidative branch of the PPP to produce NADPH resulting in ROS neutralization (Lamonte et al. 2013). More recently, Corbet et al. described that acidosis is leading to a metabolic reprograming towards glutamine and fatty acid metabolism. They found that the main source of acetyl-CoA was fatty acid oxidation in acidic pH-adapted cancer cells. Acetyl-CoA fuels the TCA cycle and supports tumor cell respiration under acidosis. By mitochondrial protein hyperacetylation, acetyl-CoA also restrains complex I activity and ROS production (Corbet et al. 2014, 2016). Another recent study has shown that chronic acidosis increased acetate metabolism. It was found that extracellular acidic pH triggered activation of SREBP2 by stimulating nuclear translocation and promoter

binding to its targets, namely ACSS2 that promotes conversion of acetate into acetyl-CoA (Kondo et al. 2017). In summary, in order to reduce proton production, cancer cells shift their metabolism away from glycolysis and rely on glutamine and fatty acid metabolism. Even if hypoxia and acidosis are often considered as a whole and often present similar adaptation, some metabolic reprogramming are specific to each hallmark. Moreover, different studies demonstrated areas of hypoxia and acidosis do not overlap in all tumors (Corbet and Feron 2017b). Consequently, these similarities and differences should be taken into account for the development of strategies targeting tumor metabolism.

6.3.1.3 How the Cancer Cell Escape to Nutrient Deprivation

Even if acidosis and hypoxia regulate cell preferences in nutrients, the presence of nutrients themselves is a limiting factor for cell function. While some tumors regions are well vascularized, some others are poorly perfused leading to decreased availability of oxygen and of exogenous nutrients. Nutrient availability also fluctuates during tumor development. It has been established that, when tumors become deprived of nutrients, they decrease their demand in ATP in order to keep an adequate ATP/ADP ratio to drive unfavorable reactions (DeBerardinis and Chandel 2016). The mTOR pathway, which controls cell proliferation, regulates this energy demand. Indeed, under nutrient-rich conditions, mTORC1 promotes cell growth by stimulating biosynthetic pathways and repressing autophagy. On the opposite, when amino acid level is low, mTORC1 is inhibited and cell proliferation is consequently reduced while autophagy is activated (Kim and Guan 2019; Rabanal-Ruiz et al. 2017). Moreover, Palm et al. demonstrated that the mTORC1 inhibition in a nutrient depleted microenvironment led to an increased micropinocytosis and lysosomal degradation resulting in free amino acids liberation (Palm et al. 2015). In response to specific nutrient limitations, cancer cells can shift their metabolism to other sources of energy. Polet et al. demonstrated that glutamine deprivation in leukemia cells led to the upregulation of the serine pathway independently from glucose metabolism. They observed that glutamine depleted medium induced the upregulation of serine metabolism enzymes (Polet et al. 2016). Another example of metabolic plasticity induced by specific food deprivation is provided by the glutamine metabolism that is increased when using a glucose depleted medium (Le et al. 2012).

Cancer cells may also benefit from a symbiosis with other cells in the microenvironment (Lyssiotis and Kimmelman 2017). By-products of one type of cell could serve as a carbon source for another type of cell. We already described two examples of metabolic symbiosis that occurs upon hypoxia: lactate/glucose between normoxic and hypoxic cancer cells and oxygen/glycolysis between endothelial cells and cancer cells (Sonveaux et al. 2008; De Bock et al. 2013). Independently from hypoxia, another symbiosis was observed in pancreatic cancer: pancreatic cancer-associated fibroblasts (CAFs) excrete alanine in response to interaction with pancreatic cancer cells. The alanine is taken up by pancreatic cancer cells and used to fuel TCA cycle. Moreover, alanine can outcompete glucose and glutamine to fuel metabolism and decrease tumor dependency to glucose and glutamine which are limited in the pancreatic tumor microenvironment (Sousa et al. 2016; Kamphorst et al. 2015). Comparably, it has been shown that ovarian CAFs produce glutamine for ovarian cancer cells and that the disruption of CAF glutamine production delays tumor growth (Yang et al. 2016). It has been hypothesized that CAFs consume glutamate and lactate, the waste products of ovarian cancer cells, in order to produce glutamine (Tajan and Vousden 2016). In a similar way, in glutamine-restricted microenvironment, astrocytes produce glutamine for glioblastoma (Tardito et al. 2015) and adipocytes produce glutamine for pancreatic cancer cells (Meyer et al. 2016). These results warrant further research on glutamine symbiosis in different cancer types as a potential niche for new therapies.

6.3.2 Influence of Treatment in Metabolic Reprogramming

With the advent of treatment targeting cancer metabolism, it is now crucial to evaluate if the treatment itself may promote changes in metabolism. The study of Polet et al. we described earlier is an example of metabolic adaptation to a treatment as they demonstrated that glutamine inhibition enhanced serine metabolism (Polet et al. 2016). Indeed, they also treat leukemia cells with pharmacological inhibitors of glutamine metabolism. They observed that these inhibitors decrease leukemia cells growth and that the addition of serine deprivation increased the antiproliferative effect of these pharmacological inhibitors. Consequently, they demonstrated that treatment against one major metabolic pathway for cancer cell growth induces a metabolic reprogramming to another pathway that cancer cells exploit to sustain their proliferation. Other adaptations were observed in other cancer cell lines. For instance, the metabolic adaptation to antiglutamine therapies has also been described in pancreatic cancer cells that are dependent on glutamine pathway (Biancur et al. 2017). When testing glutaminase inhibitors (GLSi, conversion of glutamine into glutamate), they observed effects only at an early stage, effects that were overcome in long-term proliferation assays. After GLSi treatment, they observed a decrease in glutamate derived from glutamine but concomitantly they also found an increase in glutamate not derived from glutamine. These results indicated an adaptive response to GLSi as an alternative pathway was used by treated pancreatic tumor cells. They identified multiple compensatory pathways that may explain the resistance to GLSi such as an alteration in metabolic enzymes involved in TCA cycle, lipid metabolism and amino acid metabolism. Finally, they demonstrated that combining inhibitors of these pathways with GLS inhibitors may have therapeutic utilities. They concluded that individual tumors may have unique kinetics or metabolic adaptations to the same metabolic perturbation (Biancur et al. 2017). This underlines the need to find biomarkers of response in order to perform personalized medicine. Another study identified a metabolic adaptation upon pharmacological glycolysis inhibition (Pusapati et al. 2016). They used the glucose analog 2-deoxy-D-glucose (2DG) that blocks the glycolysis by competitively inhibiting glucose-6-phosphate isomerase (the second enzyme of the glycolysis). The treatment was effective in blocking glycolysis but did not have significant therapeutic benefit *in vivo*. As expected, they observed a decrease in fructose 1,6-bisphosphate, a 2DG downstream glycolytic metabolite. Interestingly, they also observed an increase in PPP metabolites under 2DG treatment. PPP is fueled by glucose-6-phosphate which results from the conversion of glucose by the first enzyme of the glycolysis. They observed that 2DG induced a glucose-6-phosphate flux into the PPP. However, the PPP product, pentose 5-phosphate, re-entered in the glycolysis at a lower step by producing glyceraldehyde 3-phosphate. By redirecting the flux of the first step directly into PPP and reinjecting PPP products lower in glycolysis, resistant cancer cells can bypass the inhibition of 2DG. They demonstrated that cancer cells, that are resistant to 2DG, rely on mTORC1 for survival and that mTORC1 induced the expression of the rate-limiting enzyme in the PPP. Finally, they found that combining 2DG together with inhibition of mTORC1 signaling decreased tumor growth in cells that were resistant to 2DG.

Taken together, these three illustrative examples of metabolic reprogramming induced by pharmacological inhibitors highlight the high metabolic plasticity of cancer cells. These results prone the use of combined strategies to potentiate the effects of treatments targeting cancer metabolism.

6.4 Futures Directions: Understanding Metabolic Plasticity to Rationalize Combinatorial Treatments

This review highlights the ability of tumor cells to rapidly shift their metabolism and adapt to new microenvironment constraints such as nutrient deprivation, acidosis, hypoxia and

pharmacological inhibitors. Therefore, treatments that target a single pathway or a single cancer hallmark seems to be old fashion. Nowadays, new therapies should be based on strategies such as combined therapies that are able to control tumor progression and their adaptation in order to prevent resistance. Chemotherapeutics agents together with surgery and radiotherapy are standard of care treatments to treat (or cure) most tumors. Despite significant results in early tumor regression, many tumors develop resistance to chemotherapy. Even if genetics and epigenetics are widely studied to understand the origins of resistance, the tumor microenvironment, such has hypoxia, has emerged as a key player in the development of these resistances (Agarwal and Kaye 2003; Senthebane et al. 2017) and metabolic modulators are increasingly considered in the treatment armamentarium.

As an illustrative example, we may cite the use of dichloroacetate (DCA), a metabolic modulator that has been widely studied in several combined therapies (Han et al. 2018). DCA inhibits Pyruvate Dehydrogenase Kinase (PDK) and consequently shifts metabolism from glycolysis to glucose oxidation through PDH reactivation. Therefore, DCA redirects pyruvate back into the mitochondria and reduces lactate production (Kankotia and Stacpoole 2014). In 2007, Bonnet et al. showed that DCA reduced cancer cell proliferation via the induction of oxidative stress and apoptosis in various cancer cell types but not in healthy cells (Bonnet et al. 2007). In a study of hypoxia-induced chemoresistance in gastric cancer, researchers observed that the levels of HIF-1α and PDK-1 were higher in-patients who showed recurrence after chemotherapy (Xuan et al. 2014). They found that the expression of PDK-1 was positively correlated with HIF-1α expression, the factor that regulates hypoxic responses in cancer cells. Moreover, they observed *in vitro* that PDK-1 expression was higher under hypoxia. Finally, they observed that DCA treatment was able to re-sensitize resistant gastric cancer cells through the alteration of glucose metabolism (Xuan et al. 2014). This study revealed that the metabolic reprogramming induced by hypoxia was involved in chemoresistance. The results suggest that metabolic change induces by hypoxia, such as higher PDK-1 expression, could be a marker of chemoresistance as well as a target for DCA therapy. DCA has also been studied in combination with bevacizumab, an antiangiogenic drug (Kumar et al. 2013). Kumar et al. showed that glioblastoma cells that were rendered resistant to antiangiogenic therapy (after long term exposure to bevacizumab) enhanced HIF-1α related gene expression and consequently presented a shift from mitochondrial respiration to glycolysis. They showed that DCA reversed this shift induced by bevacizumab which highlighted the plasticity of tumor metabolism in response to therapeutic agents. These two studies underline the ability of DCA to counteract drug resistance induces by HIF-1α and the benefit of combining a metabolic modulator with another anti-cancer agent.

DCA is also studied in combination with other metabolic agents. For instance, the combination of DCA with metformin, a metabolic drug that inhibits mitochondrial respiration, shows promising results in anti-cancer therapies. Metformin suppresses tumor growth in different cancers via the inhibition of complex 1 of the electron transport chain and therefore enhance ROS production and apoptosis induction (Ward et al. 2017). In return, metformin is leading to an excessive lactate production and glucose consumption. Therefore, in order to reduce this side effect of metformin, several studies sought to evaluate the potential benefit of combining metformin and DCA. Different studies on glioblastoma, ovarian cancer and breast cancer have shown that DCA enhanced cytotoxicity of metformin via the reduction of metformin-mediated lactate accumulation. Indeed, it has been demonstrated that DCA reversed metformin-induced glycolytic metabolism and that this co-treatment synergistically reduced tumor growth (Haugrud et al. 2014; Li et al. 2016; Ward et al. 2017). Another recent study combined DCA with arginase in auxotroph tumors to arginine (Verma et al. 2019). As explained earlier, some tumors are dependent on external sources of arginine. Arginase has been found to inhibit the growth of

arginine auxotroph tumor. Verma et al. observed that this drug combination synergistically reduced tumor growth *in vitro* and *in vivo*. They observed an increase in genes involved in cell cycle and p53 signaling. Investigation is performed to understand the underlining mechanism of action leading to this synergy (Verma et al. 2019).

Using a similar approach, Bourdeau et al. studied the modulation of aerobic glycolysis via the inhibition of the enzyme that converts pyruvate into lactate (LDHA). They observed that some cancer cells were resistant to this inhibition or become rapidly resistant. They found that the resistance was due to a reduction of glycolysis and to an increase of OXPHOS. Therefore, they combined the LDHA inhibitor (GNE-140) with an OXPHOS inhibitor (phenformin) and observed that this combination re-sensitized the cell to GNE-140. Of note, this combination not only potentiated the effect of LDHA inhibitors but also prevented the emergence of cell resistance to LDHA inhibition (Boudreau et al. 2016).

These illustrative examples of combined therapies are mainly based on modulation of glycolysis or OXPHOS. Nevertheless, as described before, cancer cells can rely on other sources of energy and easily switch from one substrate to another due the metabolic plasticity. For instance, Imbert et al. have shown that targeting amino acid fluxes with pH regulators provides a promising therapeutic strategy (Imbert et al. 2018).

In the future, personalized medicine will benefit from specific biomarkers that will identify which sources of energy are used by cancer cells. Moreover, these biomarkers will tackle potential metabolic adaptation in the course of treatment. Overall, this will help to define the ideal combination of drugs that target metabolism in order to efficiently fight against cancer.

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