Different Tumor Microenvironments Lead to Different Metabolic Phenotypes

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Keywords

Tumor microenvironments · Metabolic phenotypes · Fatty acid oxidation · Metabolic processes · Heterogeneity of cancer

Abbreviations

ACC	Acetyl-CoA carboxylase
AMPK	AMP-activated protein kinase
ATP	Adenosine triphosphate
CAF	Cancer-associated fibroblasts
Cav-1	Caveolin-1
CSC	Cancer stem cell
ETC	Electron transport chain
FABP4	Fatty acid-binding protein 4
FAO	Fatty acid oxidation
FASN	Fatty acid synthase
GLS	Glutaminase
GLUT1	Glucose transporter 1
HBx	Hepatitis B virus X protein
HCC	Hepatocellular carcinoma
hMSCs	Human mesenchymal stem cells
KRAS	Kirsten rat sarcoma viral oncogene homolog
MCT4	Monocarboxylate transporter 4
mTORC1	Mammalian target of rapamycin complex 1
NADPH	Nicotinamide adenine dinucleotide phosphate
NSCLC	Non-small cell lung cancer
OAA	Oxaloacetate
PanNET	Pancreatic neuroendocrine tumors
ROS	Reactive oxygen species
SCD1	Stearoyl-CoA desaturase 1
TCA	Tricarboxylic acid
TME	Tumor microenvironment
TSC½	Tuberous sclerosis proteins ½
VHL	Von Hippel-Lindau
α-KG	α-Ketoglutarate

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Key Points

- Cancer cells adapt to changes in nutrient and oxygen availability by adopting alternative metabolic pathways.
- Fatty acid oxidation in cancer cells is a survival mechanism under glucose deprivation.
- Lipid scavenging is utilized to enable cancer cells to survive periods of tumor regression.
- There is persistent glutamine oxidation under hypoxic and glucose deprivation conditions.
- Nutrient utilization can predict a tumor's metabolic dependencies in vivo.
- Distinct, and often complementary, metabolic processes operate concurrently within a single tumor.

1 Introduction

The beginning of the twenty-first century offered new advances in cancer research, including new knowledge about the tumor microenvironment (TME). Because TMEs provide the niches in which cancer cells, fibroblasts, lymphocytes, and immune cells reside, they play a crucial role in cancer cell development, differentiation, survival, and proliferation. Throughout cancer progression, the TME constantly evolves, causing cancer cells to adapt to the new conditions. The heterogeneity of cancer, evidenced by diverse proliferation rates, cellular structures, metabolisms, and gene expressions, presents challenges for cancer treatment despite the advances in research. This chapter discusses how different TMEs lead to specific metabolic adaptations that drive cancer progression.

2 The Tumor Microenvironment

The TME, the environment surrounding the cancer cells, is a heterogeneous mixture of immune cells, endothelial cells, materials secreted from cells and their organelles, and fibroblasts [1] (Fig. 1). Within this miniscule niche, the tumor survives in seemingly hostile conditions—hypoxia, nutrient deficiency, and necrosis—thanks to metabolic reprogramming [2]. The question is: How does a tumor microenvironment offer advantages for cancer cell survival under such conditions?

Hanahan and Weinberg suggest that there are six general characteristics of cancerous cells important for advancements toward malignant growth: (1) self-sufficiency in growth signals, (2) insensitivity to anti-growth signals, (3) evasion from apoptosis, (4) limitless replication potential, (5) sustained angiogenesis, and (6) tissue evasion and metastasis [3]. Despite the diversity of outcomes in tumor progression, these same capabilities are shared by most, if not all, tumor types. Moreover, these features develop differently in various tumor types through distinct mechanisms and at different time points during the multistep tumorigenesis enabled by genomic instability in cancer cells and tumor-promoting inflammation [4]. The hallmarks of cancer provide further insight into potential opportunities for early interventions for cancer treatment.

Among their basic needs, cancer cells require rapid ATP generation, biosynthesis of macromolecules, and maintenance of cellular redox status [5]. The insidious nature of cancer cells does not stop at their determination to live but also extends to the factors that sacrifice adjacent living tissue to propagate cancerous cells. Tumors create alternate pathways for nourishment and, most importantly, survival.

The differences in cancer origin and stage of progression ultimately lead to the heterogeneity of cancer and the corresponding components involved in cancer metabolism.

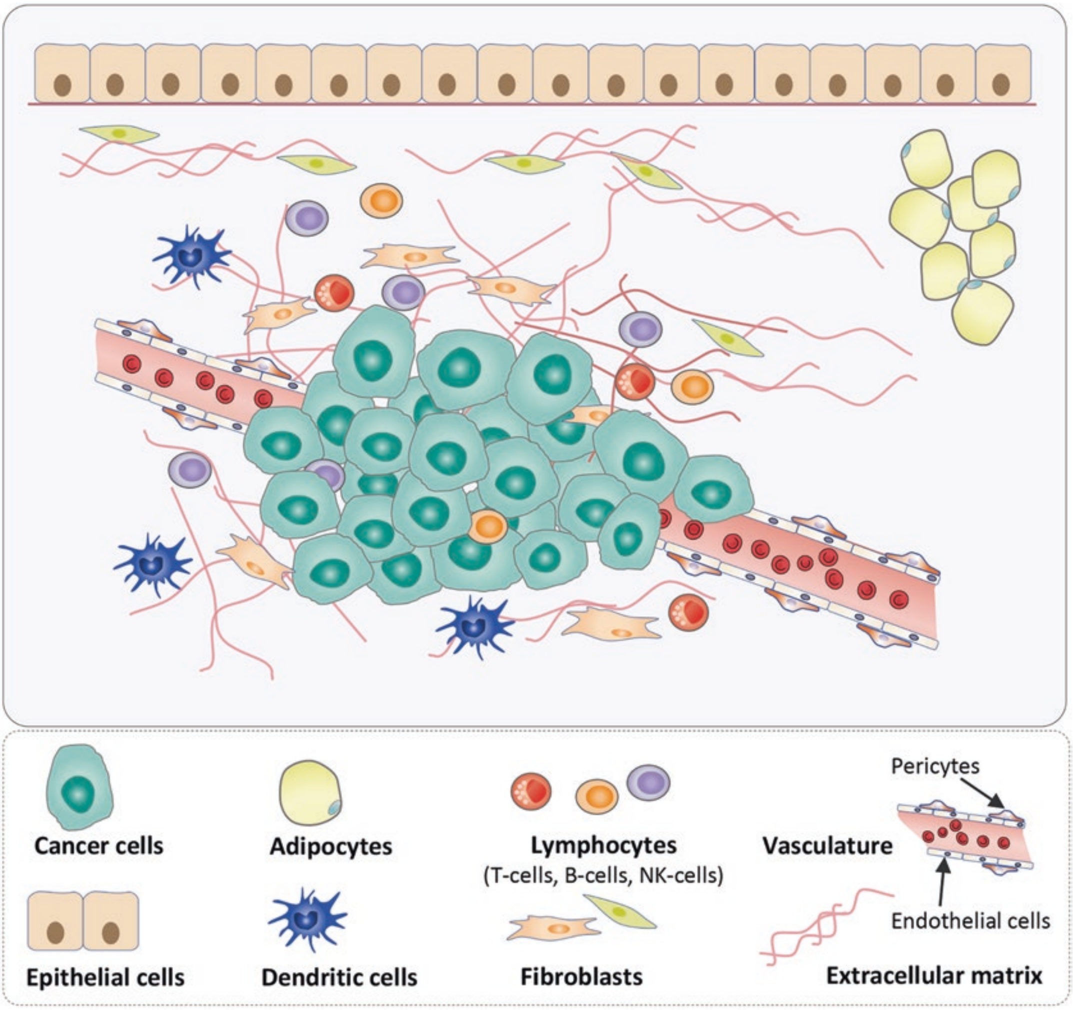

Fig. 1 The tumor microenvironment is composed of several components such as lymphocytes, adipocytes, fibroblasts, and dendritic cells

3 Different Tumor Microenvironments (TMEs) Lead to Different Metabolic Phenotypes

3.1 Cancer Cells Adapt to Changes in Nutrient and Oxygen Availability by Adopting Alternative Metabolic Pathways (Fig. 2)

The harsh tumor microenvironment (TME), hypoxia, low pH, and low nutrient concentrations are key characteristics in determining metabolic phenotypes. Various studies have demonstrated that cancer cells adapt to changes in nutrient and oxygen availability by adopting alternate metabolic pathways in order to continue providing the energy and macromolecules needed for cell proliferation. These pathways include fatty acid oxidation, lipid scavenging, and alternative cellular respiration pathways adopted by cancer cells under different TMEs [6–9].

The nutrient- and oxygen-poor internal conditions of TMEs incite cancer-friendly metabolic

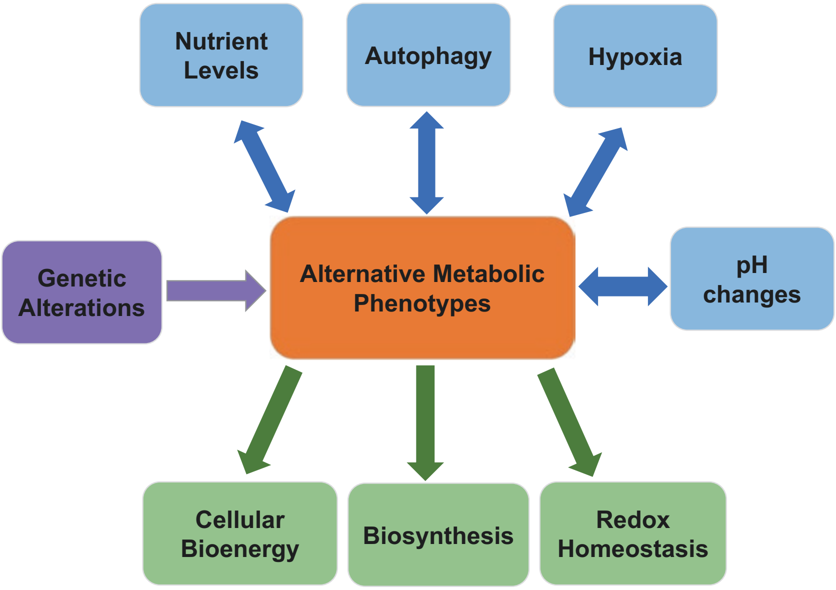

Fig. 2 The fundamental concept of how the tumor microenvironment (blue) leads to different metabolic phenotypes. Genetic alterations also contribute to the metabolic phenotype. The metabolic phenotype then propels bioenergetics, biosynthesis, and redox reactions in the tumor cells

changes to help cancer cells survive in these harsh environments [10]. Under hypoxic conditions, oxidative phosphorylation or other aerobic reactions are limited. This state disrupts the redox balance and affects cell signaling. An increase in the levels of reactive oxygen species (ROS) is defined as oxidative stress [11]. Due to decreased oxygen tension, hypoxic cells depend mainly on anaerobic glycolysis for energy production, while their low oxygen supply allows limited ATP production via oxidative phosphorylation [12]. For example, breast cancer growth is attributed to the TME, which reacts to oxidative stress leading to the production of ROS [13, 14]. Similarly, a study by Le et al. found that there is an increase in ROS production in response to oxidative stress under hypoxia [15]. Thus, this study concluded that cancer cells become dependent on glutamine for bioenergetics and redox homeostasis as a way to survive in hypoxia [15].

Extracellular acidity is another crucial component of the TME [16]. When cancer cells undergo anaerobic glycolysis in hypoxia, lactic acid levels increase, causing the TME's extracellular pH (pH_e) to diminish. This reaction generates an acidic TME [16]. Tumors that have an acidic TME have been shown to display more malignant phenotypes. Rofstad et al. treated melanoma cells with an acidic medium resulting in increased melanoma cells metastasizing to the lungs in mice [17]. The results seen in the study suggest that lower pH_e can exacerbate malignant metastasis.

The heterogeneity of nutrient and oxygen supply and uptake within individual tumors, in conjunction with the evidence of the adaptive process of cancer cells in response to differing conditions, illustrates that cancers are composed of many different cells that are each capable of employing distinct metabolic pathways to supply energy and fuel biosynthesis as a means of maintaining tumorigenesis. Thus, the local TME holds the determining factors by which metabolic adaptation is acquired [8, 9, 12, 13].

The hypoxic conditions lead to pathways that would only be present due to the alterations made necessary by metabolic stress. Other cells respond to glucose deprivation by requiring less energy to survive or utilize alternative compounds to take glutamine's place in the tricarboxylic acid (TCA) cycle [15]. However, different cancer cells take varying initiatives in order to survive, further exemplifying the heterogeneity of cancer metabolism.

3.2 Fatty Acid Oxidation (FAO) Is Used as a Survival Response to Glucose Deprivation

Recently, with further study of the fatty acid oxidation pathway, there has been significant evidence presented to support a “lipolytic phenotype” of cancer. FAO is a part of various steps of tumorigenesis, including cancer cell growth and survival [18, 19]. In addition, FAO also occurs in tumor-associated immune cells, endothelial cells, and adipocytes, which may lead to immune suppression in the tumor microenvironment [18]. As stated before, adipocytes are major elements of various tumor microenvironments. In a study of invasive melanoma by Lazar et al., adipocytes were found to secrete high numbers of exosomes, which are integrated by cancer cells, subsequently contributing to their migration and invasion [20]. Lazar et al. observed that the presence of adipocyte exosomes increased FAO in melanoma cells. Therefore, through the uptake of fatty acids from surrounding adipocytes, FAO was promoted in cancer cells [20]. Similarly, in a study by Wen et al., adipocytes promoted xenograft colon tumor growth in vivo [21]. In addition, they observed that adipocytes are crucial components for cancer stem cell (CSC) gene expression and downregulated intestinal epithelial cell differentiation gene expression in vitro [21]. Furthermore, Wen et al. also demonstrated how adipocytes within the tumor microenvironment lead to cancer cell proliferation and survival due to fatty acid uptake and FAO promotion [21]. Lazar et al. and Wen et al. both demonstrate how a lipolytic phenotype is promoted by the tumor microenvironment’s associated components. Their findings suggest potential players to target within the FAO metabolic pathway to prevent tumorigenesis.

Cancer cells employ FAO as a means to survive in response to glucose deprivation [6, 7]. FAO is utilized by tumor cells to produce ATP as an energy source [7, 22]. Over twice the amount of ATP can be made under mitochondrial oxidation of one mole of fatty acid as compared to oxidation of one mole of glucose [7]. Due to harsh TME conditions, for example, lack of nutrition, cancer cells adapt different metabolic phenotypes, such as transitioning from glycolytic to fatty acid oxidation phenotype [6, 22]. The lack of nutrition also enhances both fatty acid synthesis and lipid droplet biogenesis to propel lipid oxidation for the maintenance of energy levels [6].

In a study conducted by Wang et al., the roles of the hepatitis B virus X protein (HBx) in hepatocellular carcinoma (HCC) adaption to metabolic stress were investigated. Wang et al. found that HBx activates FAO in glucose withdrawal [6], maintaining nicotinamide adenine dinucleotide phosphate (NADPH) and adenosine triphosphate (ATP) homeostasis. HBx promotes dynamic equilibrium, mobilizing, and oxidizing lipids to meet the demands for ATP [6]. These results suggest that HBx plays a key role in maintaining redox and energy levels by activating FAO, a necessary part of HCC cell survival under metabolic stress.

Most cancer cells synthesize de novo fatty acids during normoxia without nutrition deprivation [7, 22]. Fatty acid synthesis is a crucial step for tumor cell survival [22]. Cancer cells synthesize de novo fatty acids in order to sustain proliferation and energy production through FAO. Acetyl-CoA carboxylase (ACC) and fatty acid synthase (FASN) are essential enzymes in de novo fatty acid synthesis. Acidic and hypoxic environments induce FASN expression in cancer cells, which is an observable phenotype in a variety of human cancers [22].

According to Ackerman and Simon, adipocytes within TMEs play a key role in increasing lipolysis and secreting fatty acids for energy production, contributing to an aggressive growth phenotype [23]. Lipids produced from adipocytes were used by ovarian cancer cells in order to help tumor growth. These findings suggest that adipocytes are key players in tumor growth by supplying fatty acids [24]. Moreover, this study uncovered fatty acid-binding protein 4 (FABP4) as a potential target for cancer therapy.

3.3 Lipid Scavenging Is Utilized to Enable Cancer Cells to Survive Periods of Tumor Regression

Under hypoxic conditions, oncogenic Kirsten rat sarcoma viral oncogene homolog (*KRAS*) regulates lysophospholipids to replenish lipids for growth. The inhibition of stearoyl-CoA desaturase 1 (SCD1), which catalyzes the bypassing of saturated de novo fatty acids into lipids, was resisted by *KRAS*-derived tumor cells because of their adaption of lipid scavenging [7]. The increase in protein synthesis and a decrease in lipid desaturation ultimately resulted in cell death [25, 26]. During tumor regression, cancer cell survival is made possible by FAO and other oxidative mitochondrial pathways. As demonstrated by *KRAS*-driven pancreatic cancer, tumor regression caused by kinase inhibitors or *KRAS* withdrawal resulted in inhibited oxidative respiration in tumor cells [27]. Lipid scavenging is an alternative pathway to gain fatty acids in hypoxia and fulfill the requirements for cell monounsaturated fatty acids by Ras-driven cancer cells [28]. The reduction of the need for de novo fatty acid synthesis is attributed to the increase in fatty acids being brought into the TME. Ras-driven cancer cells become immune to SCD1 inhibition, demonstrating the lipid scavenging phenotype [28].

3.4 Persistence of Glutamine Oxidation Under Hypoxic and Glucose Deprivation Conditions

As established in previous chapters, the tricarboxylic acid (TCA) cycle is crucial for producing energy and biosynthesis [29, 30]. However, how hypoxic TMEs influence the TCA cycle is still being investigated. Le et al. determined how hypoxic conditions could influence glutamine metabolism [15]. Their study showed that when deprived of glucose and oxygen, B-cell lymphoma exhibit an addiction to glutamine, where glutaminolysis is employed with a glucose-independent TCA cycle to fuel cell proliferation [15]. In this scenario, the glucose-independent TCA cycle is supported by glutamine. Similarly, hypoxic cells use glutamine to generate citrate from α-ketoglutarate (α-KG) in response to a reduced supply of glucose-derived citrate [15]. Targeting glutamine metabolism was further investigated not only by their follow-up works [31–33] but also by other teams [34–36]. This dependence of cancer cells on glutamine metabolism has translated into clinical trials as a novel therapy for cancer patients. Collectively, these findings offer a cautionary note that therapeutic strategies targeting cancer metabolism should consider the metabolic heterogeneity in hypoxic cancer cells, particularly the non-Warburg cells that have so far been underrepresented in the cancer metabolism literature [37].

4 Nutrient Utilization Can Predict a Tumor's Metabolic Dependencies In Vivo [38]

As described by Sir Hans Kornberg, anaplerosis is the reloading of metabolic intermediates in the TCA cycle, which is a crucial part of energy production and biosynthetic pathways. Glutamine and glucose both contribute to TCA anaplerosis in non-small cell lung cancer (NSCLC) cells [38]. In this study by Davidson et al., the authors found that glucose is a carbon source of the metabolites in the TCA cycle, which is needed for tumorigenesis.

For continuous proliferation, cancer cells must maintain the necessary precursors of biosynthetic pathways, and glutamine serves as a major substrate for anaplerosis in many cancer cells [30]. For example, both hypoxic and normoxic renal cell carcinomas with a mutation in the von Hippel-Lindau (VHL) tumor-suppressor gene sustain lipogenesis by converting α-KG, derived from glutamine, to acetyl-CoA, which then allows them to utilize the glucose-independent TCA cycle as a means of energy production [8, 9]. On the other hand, when glutaminase is inhibited, the breakdown of glutamine is partially prevented and some cancer cells employ pyruvate carboxylase and use glucose-derived pyruvate as a substitute for glutamine to fuel anaplerosis [8].

Similarly, a study by Cheng et al. demonstrated that "glutamine-addicted" cells accomplished anaplerosis by utilizing pyruvate carboxylase [8, 39]. It was found that the glutamine-addicted cells utilized glucose-derived pyruvate for anaplerosis when glutaminase (GLS) was silenced. The data from this study supported the model of pyruvate carboxylase's role in cancer cell resistance against GLS inhibition or glutamine deprivation. Cells such as a hepatocellular carcinoma cell line, Huh-7, use pyruvate carboxylase as a primary mechanism to resist the treatment of glutamine metabolism inhibition [8].

4.1 Inhibition of mTORC1 Decreases Energy Consumption for Cancer Cell Survival

The mammalian target of rapamycin complex 1 (mTORC1) is a protein that translates the TME into a growth phenotype through its control of autophagy and fatty acid oxidation (FAO). The inhibition of mTORC1 represses the AMPK-dependent activation of tuberous sclerosis proteins ½ (TSC½) as a result of the withdrawal of glucose [9]. When energy consumption is reduced, oxaloacetate (OAA) or methyl pyruvate (MP) can be substituted for glutamine and still be able to maintain ATP levels and prevent cell death. The TSC-mTORC1 pathway balances energy supply and demand in a way that leads to a reduction of the energy needed to survive [9]. Choo et al. demonstrated that, under glucose deprivation, a decrease in anabolic reactions occurs in order to prevent cell death [9]. As shown with the decrease of energy consumption, the balance keeps the cancer cells alive through the dependence of TSC½ cells on glutamate dehydrogenase-dependent glutamine metabolism [9]. The results found in this study support the concept that tumor cells under stress create alternative pathways out of necessity. With glucose or glutamine metabolism inhibition, the potential treatment of TSC-deficient tumors may be possible.

4.2 Cancer Cells with Functionally Defective Mitochondria Employ Glutamine-Dependent Reductive Carboxylation as an Alternative to Normal Oxidative Metabolism

In normal cells, mitochondria play vital roles in regulating metabolic pathways and physiological states of the cell: they generate cellular energy, monitor cellular redox, and initiate cellular apoptosis. However, through investigation of mitochondria in cancer cells, it has become evident that mutations in mitochondrial genes correlate with tumorigenesis and metabolic adaptability [40]. Mitochondria in cancer cells subjected to hypoxia respond by releasing metabolites and proteins regulating metabolic pathways [40].

Cancer cells with functionally defective mitochondria employ glutamine-dependent reductive carboxylation, where glutamine is converted to citrate and then to acetyl-CoA and oxaloacetate, as an alternative to normal oxidative metabolism. Oxidative metabolism is favored in cells with normal mitochondria and provides the acetyl-CoA needed for lipogenesis and production of other metabolites of the TCA cycle, which serve as precursors of other biosynthetic pathways. Even in cells with altered mitochondrial function, the glutamine-dependent reductive metabolism still allows for the formation of these necessary metabolic precursors [41]. The glutamine-dependent reductive pathway permits glutamine to support cancer cell growth [41].

5 Distinct, and Often Complementary, Metabolic Processes Operate Concurrently Within a Single Tumor

The particular alternative metabolic pathways adopted by cancer cells are associated with specific genetic alterations that allow the cancer cells to express certain enzymes in higher than usual amounts. The production of these enzymes allows cancer cells to use the available nutrients in their microenvironment to fuel cell survival and proliferation. For example, genetic alterations that result in the deactivation of caveolin-1 (Cav-1) expression lead to autophagy and aerobic glycolysis in cancer-associated fibroblasts [42]. Subsequently, lactate, glutamine, and other metabolites that fuel biosynthesis are synthesized and exported to initiate oxidative metabolism in neighboring cancer cells [42].

Other studies have revealed that distinct, and often complementary, metabolic processes operate concurrently within a single tumor. Hypoxic breast cancer cells and stromal cells in the TME exhibit a mutualistic relationship employing complementary metabolic processes [43]. When subjected to hypoxia, breast cancer cells demonstrate an increase in lactate secretion. The elevation in lactate concentration in the TME results in the migration of specific stromal cells called human mesenchymal stem cells (hMSCs) toward hypoxic tumor cells. These hMSCs, along with stromal cancer-associated fibroblasts (CAFs), consume the newly produced lactate and convert it to pyruvate to be used in the TCA cycle. Lactate consumption by stromal cells serves two purposes: the breakdown of lactate serves as an energy source for the proliferating cancer cells, and the conversion of lactate to pyruvate, and ultimately to α-KG in the TCA cycle, prevents acidification of the TME [43].

Another example of this phenomenon of cells in the TME pairing metabolic processes is evident in ovarian cancers. Adipocytes in breast cancer microenvironments employ lipolysis to release fatty acids which provide energy to fuel rapidly proliferating ovarian cancer cells [24]. Within one region of the TME, two different types of cells undergo vastly different, yet complementary, metabolic processes in order to fuel tumorigenesis, thus demonstrating the heterogeneity of cancer metabolism.

5.1 Metabolic Symbiosis as a Result of Tumor Angiogenesis Inhibition Can Be Stopped by mTOR Signaling Inhibition [44]

Coordinated metabolic pathways with respect to glucose and lactate metabolism between cells within the TME have been observed in various cancers [45]. Allen et al. observed metabolic symbiosis with their work in tumor angiogenesis inhibition [44]. When angiogenesis is targeted using VEGF inhibitors in mice bearing pancreatic neuroendocrine tumors (PanNET), cancer cells formed next to the remaining blood vessels [44]. The cancer cells compartmentalized in response to insufficient vascularization—creating distal hypoxic cells and proximal normoxic cells [44]. Upon further observation, increased glucose transporter 1 (GLUT1) and monocarboxylate transporter 4 (MCT4) were found in tumor cells far from blood vessels indicating glycolysis [44]. Moreover, signs of mTOR signaling, in the form of ribosomal protein s6 (p-S6) expression, were found in tumor cells near blood vessels [44]. In these metabolic pathways known as metabolic symbiosis, the hypoxic cells take up glucose and secrete lactate, which is then taken up and catabolized by normoxic cells [44]. As a result of increased lactate catabolism, the normoxic cells' mTOR signaling through glutamine metabolism is increased [44].

The metabolic symbiosis that Allen et al. found is due to the compartmental expression of GLUT1/MCT4 [44]. For metabolic symbiosis to occur, the lactate that is secreted must be taken up and used for energy metabolism by the normoxic cancer cells. Within their study, Allen et al. also demonstrated that normoxic cancer cells in vitro and in vivo take up and catabolize lactate—which reinforces the notion that lactate is used for energy metabolism [44].

Allen et al.'s experiments demonstrate how PanNET tumor cells adapt to evade targeted anti-angiogenesis therapy. While Allen et al. were able to target the metabolic symbiosis by inhibiting mTOR signaling [44], the initial adoption of metabolic symbiosis demonstrates how the tumor cells circumnavigate the initial treatment by creating new pathways for energy production. Furthermore, metabolic symbiosis as a result of tumor angiogenesis inhibition reflects how distinct and complementary metabolic processes occur within the same tumor.

6 Conclusion

As cancer cells seek to survive, alternate metabolic pathways adapt to different TME stresses. These adaptations, often through genetic alterations or coordination with other metabolic processes, illustrate how precisely the TME can alter metabolic characteristics. With the advancements in research into TMEs and the use of metabolomics technologies [46], there is a tremendous opportunity for uncovering new therapeutic targets and creating treatments that target TMEs [47, 48]. The heterogeneity of cancer metabolism is evident in genetic mutations in oncogenes and tumor-suppressor genes, as well as the diversity of the TME.

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