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Interaction Between Cancer Metabolic Reprogramming and Immune Response

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Abstract:

Cancer cells undergo metabolic reprogramming to adapt to the harsh tumor microenvironment, allowing for their rapid proliferation and high survival rates. Metabolic reprogramming is one of the top ten characteristics of tumors and plays a key role in promoting tumorigenesis and progression. Glucose metabolism disorders are the most representative metabolic features. Unlike normal cells that rely on oxidative phosphorylation under aerobic conditions, cancer cells predominantly utilize aerobic glycolysis, a phenomenon known as the Warburg effect. This shift in metabolism in cancer cells not only enhances ATP production but also generates metabolites like lactate that may lead to an acidic tumor microenvironment (TME), which could further promote the proliferation and invasion of cancer cells. Metabolites like lactate, glutamine, arginine, tryptophan, and cholesterol not only provide energy and build blocks for cancer cells but also reprogram immune cell responses, facilitating immune evasion. This review explores the complex interactions between cancer cell metabolism and the immune system, highlighting how metabolites of cancer cells modulate immune responses and contribute to cancer progression. Understanding these interactions can provide insights into potential therapeutic strategies that target both cancer metabolism and immune evasion mechanisms.

Keywords: Cancer cell; metabolic reprogramming; tumor microenvironment; immune system.

1. Introduction

Energy metabolism reprogramming has been recognized as an emerging hallmark of cancer by modulating energy metabolism to promote rapid cell growth and proliferation in normal cells, metabolism can occur in two conditions, based on different cellular microenvironments. Under aerobic condition, normal cells utilize glucose in food to fuel glycolysis, which coverts glucose to pyruvate [1]. Then, pyruvate enters mitochondria where it is processed further over several cycles to final produce ATP, which is then stored for use by the cells whenever energy is needed. Different from aerobic condition, cells in anaerobic condition convert pyruvate to lactate, which generates less efficient energy. Even though these

two metabolic pathways in normal cells produce energy in different ways, they both play a crucial role in supporting cells to adapt different environments under varying oxygen levels [1]. However, cancer cells have developed quite different metabolic reprogramming from that of normal cells. Cancer cells exhibit changed metabolic pathway, called Warburg effect, which supports their rapid proliferation, survival, and invasion. Different from the metabolic pathway of normal cells, cancer cells tend to use aerobic glycolysis in most of the time, rather than using oxidative phosphorylation (OXPHOS) even when there is sufficient oxygen. Since more energy is needed in the growth of cancer cells, using aerobic glycolysis instead of oxidative phosphorylation accelerates the production of ATP, which generates more and more energy [1]. Those energy are "fuels" for synthesizing many basic molecules, such as amino acids for supporting cancer cells proliferation [2]. Another interesting metabolic pathway observed in cancer cells is metabolic plasticity. When the microenvironment is harsh, for example, cancer cells meet insufficient nutrients or low levels of oxygen, they use other substrates, such as glutamine to sustain their growth [3]. This means cancer cells can alter their ways of generating energy in response to different microenvironment [4]. Thus, this high level of metabolic plasticity can help cancer cells invade from immunity, even change the whole environment in immune system [3].

To fight with cancer cells, the immune system, which includes mainly innate immune system and adaptive immune system, has developed many cells and metabolic reprogramming [1]. In some activated immune cells, such as activated T cells, their metabolic pathways are like cancer cells [5]. These activated immune cells use Warburg effect to stimulate cell proliferation and produce molecules that are necessary for the synthesis antibodies and cytokines, which are important in activating immune response [3]. Indeed, the important role of immune system is sensing TME and fighting with cancer cells [1]. However, several studies have demonstrated that cancer metabolic reprogramming may significantly affect immune functions, such as competing glucose with immune system, altering enzymes and proteins, and changing metabolic pathways on tumor immunity, including mTOR pathway, AMPK signaling pathway, and adenosine signaling pathway [1,3]. Therefore, understanding how immune response interacting with cancer metabolic reprogramming is important for advancing cancer research and cancer treatments.

Currently, the metabolic reprogramming of cancer cells and their impacts on immune system responses have become a focus in cancer research. Although the specific mechanism of the interaction between cancer metabolic reprogramming and immune system remains unclear, scientists have made huge progress in exploring how cancer cells sustain their survival and proliferation via cancer reprogramming [1]. This review mainly discusses how the metabolic reprogramming of cancer cells affects immune system.

2. Metabolic Pattern of Tumor Cells

Cancer cells have a complicated metabolic pattern that allows them to choose which metabolic reprogramming to employ in response to different microenvironments [6]. The most famous metabolism way of cancer cells is called Warburg effect, or aerobic glycolysis [1]. The Warburg effect, proposed by Otto Warburg in the 1920s, is a phenomenon that described how cancer cells produce energy [7]. Unlike normal cells, which mainly use OXPHOS as metabolic pathway, cancer cells tend to produce effective energy through aerobic glycolysis, which transfers glucose into lactate, accelerating both the rates of glucose intake and production of lactate [7]. Under such mechanism, more and more energy conversion happen even when the oxygen levels are sufficient [1]. In addition, because of high levels of lactate production, the microenvironment becomes more acidic, which creates an appropriate condition for proliferation of cancer cells [8]. Therefore, Warburg effect allows cancer cells to become more adaptive to various environments, even under hypoxic conditions, such as insufficient nutrients or low levels of oxygen [7]. Besides, glucose intake of cancer cells increases significantly, leading to the competition of energy with other cells, such as immune cells. Because of this energy competition, cancer cells can deprive the energy of immune cells from producing molecules, such as cytokines, which are essentials for maintaining normal immune functions [1]. Thus, investigating the Warburg effect is crucial for understanding the interaction between cancer metabolic mechanisms and immune system, as well as serving as a foundation for future research in the field of cancer biology.

Another two metabolic reprogramming ways that cancer cells use are pentose phosphate pathway (PPP) and serine metabolism pathway [1]. PPP first begins with glucose been phosphorylated to form glucose-6-phosphate (G6P), which is then oxidized by an enzyme called 6-phosphogluconate dehydrogenase (G6PD) [9]. The whole PPP is controlled tightly by G6PD, and this enzyme can further generate other enzymes, such as ribose-5-phosphate (R5P) for further reductive biosynthesis of nicotinamide adenine dinucleotide phosphate (NADPH) [9]. PPP is highly regulated by G6PD, which is served for synthesizing other basic molecules, such as nucleotides and lipids, and these molecules are fundamental for cancer cell growth [9].

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According to Jiang et al., this PPP regulated by G6PD provides basic demands for cancer cells proliferation and cellular division [9]. Although PPP does not directly participate in providing ATP, it promotes cancer cell proliferation by meeting demands for NADPH and ribose sugar [10]. The second metabolic reprogramming that utilized by cancer cells is serine metabolism pathway [11]. Aberrant serine mechanism pathway has been observed in many TMEs [11,12]. In cancer cells, one of the most unique characteristics is the increased serine expression level, which is produced by serine metabolism pathway. The serine metabolism pathway mainly contains three enzymes, phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase (PSAT1), and phosphoserine phosphatase (PSPH), which transfer glycolytic intermediate 3-phosphoglycerate (3PG) into final product, serine [11]. According to recent research, this metabolism of producing serine is upregulated in many cancer cells for supporting their rapid proliferation and cell division [12]. Interestingly, tumor cells will choose different metabolic methods to produce ATP and biomacromolecules for their own use according to the concentration of external nutrients and different stress conditions.

3. Interactions between cancer metabolites and immune cells

In addition to nutrient depletion, metabolites produced by cancer cells can have a significant impact on immune cells in the microenvironment. However, there are more immune cells in the immune system than just T cells and NK cells. The metabolites produced by tumor metabolic reprogramming are complex and variable. Although tumor cells mainly provide energy through the aerobic glycolysis of glucose, there are also other metabolic modalities, such as amino acid metabolism, glutamine metabolism, fatty acid metabolism, cholesterol metabolism, etc.

3.1 Lactate

Cancer cells generate many metabolites through its special metabolic reprogramming, the Warburg effect, or aerobic glycolysis. This abnormal glycolysis causes increase in consuming glucose and producing more and more lactate [13]. Then, accumulated lactate is transported into extracellular environment through monocarboxylate transporter 4 (MCT4) [1]. As lactate levels rise, MCT4 eventually transforms the entire cellular milieu, producing an acidic TME that is favorable for the proliferation of cancer cells. Recent research has shown that this acidic TME can enhance cancer cells proliferation and, in the same time, can alter normal functions of both adaptive immune cells and innate immune cells. For instance, lactate production can greatly change the function of T cells, such as activated effector T cells and regulatory T cell [1,14]. In effector T cells, high levels of lactate may disrupt infiltrations from T cells to attack cancer cell, which slows down the rate of eliminating cancer cells in the body. In addition, acidic TME affects the ability of producing effective cytokines, such as IFN-γ in effector T cells [1]. What's more, high levels of lactate are present in both human and rat melanoma, such as in immunocompetent mice, reducing lactate production can slow down their tumorigenesis, and the infiltration of IFN-γ-secreting CD8+ T cells and NK cells in the tumor is significantly increased. The other T cell type, regulatory T cells (Tregs), is an immunosuppressive immune cell that relies on lactate production for growth [14]. When the levels of lactate increase, more and more Tregs will produce immunosuppressive cytokine IL-10, which suppresses other immune cells to attack cancer cells, and indirectly supports cancer cells to evade from immune system [14]. Acidic TME not only affects adaptive immune cells, but also changes the expression ways of innate immune cells, such as macrophages. M1 and M2 macrophages are two types macrophages with different functions in response to defense cancer cells. M1 is responsible for activating T cells and supporting anti-tumor immunity [13]. While countering acidic TME, macrophages change their types from M1 to M2, which supports proliferation of cancer cells through producing immunosuppressive cytokines, such as IL-10 and TGF-β [13,14]. Taken together, these findings suggest that higher lactate levels in tumors and concomitant acidified TME inhibit immune cell function and dismantle immune surveillance in cancer, ultimately leading to immune evasion.

3.2 Glutamine

Glutamine is an amino acid that used for many functions, such as generating foods for cells in both immune cells and cancer cells [1]. For example, overactivation of the oncogene RAS can promote endocytosis, where cancer cells remove extracellular proteins and degrade them into amino acids, including glutamine, to provide nutrients to cancer cells [15]. Indeed, several studies have suggested that most immune cells are tightly regulated by glutamine, for instance, in both adaptive immune cells, such as T cells, and innate immune cells, such as macrophages [16]. According to Calder, the proliferative T cells in both animals and human are dependent on glutamine, otherwise, the proliferation function in T cells is abnormal and the number of T cells in immune system may decrease. Furthermore, research has shown that glutamine is an important amino acid in controlling cytokine production of

T cells. Interleukin-2 (IL-2) is one of the crucial cytokines that are produced by T cells, and it not only regulates the proliferation of T cells, but also connects the communication bridge between T cells and the activation of other immune cell. In animal experiment, Calder has pointed out that deficiency in glutamine could greatly affect the production of IL-2. Different from highly proliferative T cells, the main function of macrophages is phagocytosis. Interestingly, the concentrations of glutamine in blood are closely related to phagocytosis, and if glutamine levels are high, macrophages can increase their effect of phagocytosis. In addition to phagocytosis, as antigen presenting cells, macrophages can also deliver antigens to other adaptive immune cells, such as T cells. And this antigen presentation of macrophages is associated with expression of glutamine, according to Calder's research [16].

Not only in immune cells, cancer cells also need glutamine to maintain their basic needs [17]. To satisfy their exponential proliferation, cancer cells require a lot of energy to support growth, even when the energy is insufficient, they can try to find another way to break down energy for their own use. Under hypoxic condition, such as nutrients deficiency, cancer cells use glutamine for their highly biosynthetic requirements. However, this highly glutamine requirement in cancer cells competes glutamine requirements that are needed in immune cells, creating a metabolic competition that greatly affects immune cell functions. Also, this cancer-derived glutamine metabolite may reprogram the way of immune cell responses, and even suppress immune cell growth and proliferation to satisfy cancer cells their own growing requirements [1]. In addition, by blocking the glutamine pathway in cancer cells, the content of amino acids in the tumor microenvironment can be increased, enhancing the killing effect of immune cells. Targeting glutamine metabolism may be a new cancer treatment [18].

3.3 Arginine

In normal cells, arginine can be synthesized by two enzymes, both argininosuccinate synthase 1 (ASS1) and argininosuccinate lyase (ASL). These two enzymes change citrulline and aspartate into arginine through many pathways under the intracellular environment of normal cells. However, the utilized ways of arginine are quite different between normal cells and cancer cells. Under different conditions, such as hypoxic conditions, cancer cells tend to use various metabolic ways to satisfy their high demand of energy and nutrients. Different from normal cells, cancer cells are deficient in synthesizing arginine by their own. Due to this defect, cancer cells need a large amount of external arginine sources to support their rapid proliferation [19]. Arginine metabolism also plays a crucial role in T cell activation and regulation of immune responses. For example, arginine supplementation stimulates cytotoxicity and effector cytokine production in T cells and NK cells in vitro [20].

Except from cancer cells, as a major amino acid, arginine is highly used in many immune cells, both adaptive immune cells and innate immune cells. In T cells, for instance, many activities, including the activation, cell division, and proliferation of T cells depend on arginine production. In Martí i Líndez & Reith study, the availability of arginine could greatly affect many cellular activities in CD4+ cells and CD8+ cells [21]. In their study, arginine was necessary in regulating the cell proliferation and cell memory in adaptive immune cells. Arginine is also important in regulating cellular functions in many innate immune cells, such as macrophages. There are two types of macrophages, M1 macrophages and M2 macrophages, and their arginine pathways act in quite different ways [21]. Through several pathways, arginine is converted into nitric oxide (NO) by an enzyme called nitric oxide synthase (iNOS), which is an important enzyme that boosts immune system to attack cancer cells. However, M2 macrophages utilize arginase-1 (ARG-1) to transfer arginine into ornithine and urea, which decreases arginine levels in TME to suppress immune system, and provides an appropriate environment that supports cancer cells proliferation. Under this way, cancer cells use ARG-1 to deplete arginine in TME, in the same time, competing arginine requirements with immune cell, which creates a nutrients-starved environment for immune cells and supports cancer cells their growth and proliferation. Therefore, supplementing arginine in TME and preventing arginine degradation is an effective strategy to reactivate T cell and NK cell-mediated immune responses [22].

3.4 Tryptophan

Another essential amino acid for a variety of cellular processes is tryptophan, which is required by many cells to continue operation [1]. In T cells, tryptophan is mainly been metabolized by two enzymes, indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO2), which help the conversion from tryptophan to other important metabolites, such as kynurenine. Kynurenine is important in regulating many T cell activities, such as promoting Tregs differentiation so that preventing excessive inflammation in immune system. Just like these immune cells, cancer cells also need IDO and TDO2 to create an immunosuppressive environment, which promotes their rapid proliferation [23]. Research has shown that the levels of both IDO and TDO2 are highly expressed in can-

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cer cells, so that they can transfer tryptophan into more and more kynurenine. The accumulation of kynurenine encourages cancer cells survival and rapid proliferation. Moreover, kynurenine can also serve as a oncometabolite that inhibits immune cell functions, and facilitate cancer cells to escape from surveillance and attack of immune system. Cancer cells produce more and more kynurenine inside the body, which leads to change in TME. Once TME has been altered, some cytotoxic T cells can't work efficiently, and the cancer cells in TME promote the expansion of some immunosuppressive cells, such as Tregs and myeloid-derived suppressor cells (MDSCs), which inhibit the whole immune system to fight with cancer cells and further accelerate cancer cell growth [23]. In addition to escaping from immune system, cancer cells compete tryptophan with other immune cells, such as T cells. Under this competition, cancer cells create a local environment that rich in both tryptophan and its metabolites, kynurenine, this not only changes other immune cells activities, but also contributes to immune evasion by promoting the differentiation of Tregs and inhibiting cytotoxic T cells. Ultimately, the whole TME has been changed by cancer cells, and those cancer cells can complete their proliferation easily and become more readily to metastasize [24].

3.5 Cholesterol

Cholesterol, one of the vital components that composed of cellular membranes, is important in maintaining membrane integrity and promoting synthesis of other basic molecules for cell survival, such as steroid hormones. There is growing evidence of the importance of cholesterol metabolism in the innate immune response. In cancer cells, the reprogramming mechanism of cholesterol can be elevated to support cancer cells proliferation, survival and evasion [25]. High cholesterol levels caused by tumor cells can promote the expression of T cell suppressive immune checkpoints, thereby losing their anti-tumor effects [26]. What's more, the researchers found that the concentration of cholesterol in tumor cells was much higher than in immune cells. In fact, high cholesterol can disrupt lipid metabolism networks in T cells, thereby exerting an immune-suppressing effect [27]. Cholesterol is produced by cancer cells through a mechanism called the mevalonate pathway, which transfers acetyl-CoA to produce the final product cholesterol through HMG-CoA reductase (HMGCR). In addition to cholesterol, its oxidative derivative, such as oxysterol, can further regulate other tumor pathways, such as Hedgehog, which acts as an important way that accelerates tumor progression and metastasis, which is bad for cancer prognosis. Interestingly, research has also shown that the cholesteryl esters (CEs) in lipid droplets could be utilized by cancer cells under hypoxic conditions to satisfy their high requirements in cholesterol [25]. In immune cells, however, cholesterol can be used in generating lipid rafts that are essential for immune cell signaling and proliferation. In T cells, research has shown that certain levels of cholesterol may help T cells activation and antigen presentation in communicating with other immune cells. According to Huang et al., the cholesterol mechanism within immune cells is controlled tightly by sterol regulatory element-binding proteins (SREBPs), a protein that is used for synthesizing cholesterol, and liver X receptors (LXRs), a protein that prevents excessive cholesterol accumulation. These two proteins keep balance with each other to maintain normal immune cell functions. However, when the cholesterol balance within TME is broken, those immune cell functions can be impaired, thus damaging anti-tumor response. Cholesterol, particularly its derivative, oxysterol, such as such as 25-hydroxycholesterol (25HC) and 25S-hydroxycholesterol (25HC) have shown a close relationship between impaired immune functions. In Huang's study, high levels of 25HC expression have been indicated that it could facilitate breast cancer progression and cancer metastasis. Furthermore, 25HC can attract other immunosuppressive cells, such as MDSCs to inhibit cytotoxic T cell functions. Not only in T cells, DCs can also be suppressed by oxysterols through downregulating C-C chemokine receptor 7 (CCR7) [25]. Therefore, the whole cholesterol metabolism can be manipulated by cancer cells in a different way than in immune cells. This unique cholesterol reprogramming creates an immunosuppressive TME that recruits many immunosuppressive cells, such as MDSCs and neutrophils to inhibit normal immune functions. In addition, cancer cells promote the secretion of other immunosuppressive cytokines, such as IL-10 and TGF-β, which then further inhibit cytotoxic T cell function in attacking cancer cells. Moreover, the accumulation of cholesterol created by cancer cells in TME can cause T cell exhaustion, charactering of increasing inhibitory receptors, such as TIM-3 and LAG-3, which further preventing T cells in fighting against tumors [25].

4. Conclusion

The interaction between cancer metabolic reprogramming and immune response is a critical area of study in cancer biology. Targeting cancer and/or immune cell metabolism can produce synergistic effects with anti-tumor immunity. Key metabolites like lactate, glutamine, arginine, tryptophan and cholesterol derivatives modulate immune cell function, promoting an immunosuppressive environment

that facilitates tumor immune evasion. Additionally, competition for critical nutrients like glucose and glutamine between cancer and immune cells creates metabolic bottlenecks that lead to immune cell exhaustion and reduced functionality. Although combinations of various metabolites and immunotherapies have been used in clinical trials, a better understanding of the metabolic mechanisms of tumor immune evasion and the metabolic demands of immune cells is essential to fully exploit the therapeutic potential of combination therapies. A deeper understanding of the interplay between cancer metabolism and immune modulation will pave the way for more effective cancer therapies and improved patient outcomes. Metabolic interventions can not only improve immune cell response to highly immunogenic cancers, but also increase the immunogenicity of cancer cells, thereby expanding the range of cancers that can be effectively treated with immunotherapy. Future research should focus on identifying key metabolic checkpoints and developing targeted therapies that can simultaneously disrupt cancer metabolism and enhance immune responses.

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