

Research Progress in Inhibiting Tumor Cells Through Sugar Metabolism in the TME

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Abstract. In the immune microenvironment, the sugar metabolism of tumor cells determines their own growth, and the disturbance of metabolic process is considered as an important feature of tumor cell growth. Compared with normal cells, the greatest change in the metabolic process of tumor cells is the occurrence of aerobic glycolysis. Even under sufficient oxygen conditions, tumor cells will still absorb a lot of glucose through glycolysis to provide energy for cells, and many important rate-limiting enzymes in the glycolysis process are expressed in different forms in tumor cells and have an important impact on tumor growth. However, the specific mechanism of this conversion and the targeted enzyme's process are not clear. This article analyzes the difference in sugar metabolism between tumor cells and normal cells, specifically summarizes and analyzes the inhibitory effect mechanism of pyruvate kinase and lactate dehydrogenase on tumors, and obtains the conclusion that targeted inhibition of PKM and LDH can inhibit the growth and reproduction of tumor cells. Exploring the inhibition of tumor cell dependence on glucose, studying the glycolysis pathway of tumor cells and targeted drugs inhibiting key enzyme activity can help us further understand the metabolic characteristics and growth mechanism of tumor cells, provide new targets and strategies for tumor treatment, and provide a reference for anti-tumor combination therapy and individualized treatment for patients. However, at present, the research on targeted drug toxicity and side effects has not been solved, and the potential side effects and toxicity are not studied enough. Future research should focus on individualized treatment for patients, pay attention to the differences in the activation degree of glycolysis pathway in tumor cells, and bring better treatment results to tumor patients.

Keywords: Tumor cell sugar metabolism; tumor microenvironment; sugar fermentation way; key enzyme of sugar fermentation.

1. Introduction

Current research in the field of tumor metabolism indicates that abnormal glucose metabolism in tumor cells is closely related to tumor development, growth, and metastasis. Inhibiting the glucose metabolism of tumor cells may enhance the effect of immunotherapy. However, there are still deficiencies in the study of glucose metabolism mechanisms in tumor cells, and further research is needed to study the regulation mechanism of glucose metabolism pathways in tumor cells and their interaction with other biological processes, laying a foundation for targeted treatment. The transport protein, key rate-limiting enzyme, and metabolites such as pyruvate, lactate, and ATP in the glycolysis process can affect tumor growth and development through different mechanisms, including inhibiting apoptosis and inducing autophagy. Understanding the mechanism of tumors and related molecular processes in glycolysis provides direction for basic and clinical research on targeted drugs for tumors [1]. Glycolysis is an important link in glucose metabolism. Under sufficient oxygen supply, tumor cells will still absorb a large amount of glucose through glycolysis process to provide energy for cells and secrete lactate, showing an active aerobic glycolysis phenomenon. It is now known that the abnormal glucose metabolism of tumor cells is related to various mechanisms, such as hypoxia-inducible factor (HIF) can activate glycolysis-related enzymes, which is beneficial for tumor cells to take glycolysis for energy; mitochondrial dysfunction or reduction can inhibit glucose oxidative phosphorylation pathway to a certain extent; activation of some oncogenes and inactivation of tumor

suppressor genes also participate in regulating mitochondrial oxidative respiratory chain and glycolysis-related enzymes to affect glucose metabolism process; tumor cells oxidative phosphorylation-related enzyme synthesis is inhibited, etc[2]. Therefore, abnormal glucose metabolism plays an important role in the growth, invasion, and metastasis of tumor cells. In addition, in the glycolysis process, a variety of key rate-limiting enzymes are expressed in tumor cells in different forms. Through in-depth exploration of the key enzyme targets and regulation, the growth of tumor cells can be effectively inhibited. In this article, we have summarized and analyzed the regulation pathways of tumor cell glucose metabolism in recent years.

By analyzing the different pathways of glucose metabolism in tumor cells, we further propose effective methods to fight tumors. Starting from the glucose metabolism pathway of tumor cells, we have summarized the various factors that affect tumor cells in the TME and various immunotherapy strategies that target metabolic pathways and future prospects. It is found that inhibiting the activity of key enzymes can enhance immune response and promote immune anti-tumor effect. By studying the glucose metabolism mechanism of tumor cells, new targets can be provided for tumor treatment to effectively achieve individualized treatment of tumors.

2. Metabolism of Tumors in the Immunological Microenvironment

2.1. Normal Tissue Metabolism

Energy metabolism refers to the process of energy production, release, transfer, storage, and utilization that occurs during the metabolic process of substances. The main source of energy for tissues and cells comes from the conversion of glucose. Under conditions of sufficient oxygen, the process of glucose completely oxidizing into water and carbon dioxide is called aerobic oxidation, which is the main way of sugar oxidation and also the main process for most cells to obtain energy. Under anaerobic conditions, glucose or glycogen is decomposed into lactic acid with energy production, which is called anaerobic glycolysis.

2.2. Cancer Cell Metabolism

Research has shown that tumor cells transport extracellular glucose into the cytoplasm through glucose transporters distributed on the cell membrane. With the help of enzymes such as hexokinase, phosphoglucose isomerase, and phosphofructokinase, glucose is metabolized and broken down to produce ATP. After multiple steps of metabolism, the product is pyruvate. When tumors are under hypoxia, pyruvate is converted to a large amount of lactate-by-lactate dehydrogenase (LDH), and lactate is secreted to the extracellular space through the monocarboxylate transporter on the cell membrane. Lactate accumulates locally and forms a local acidic environment for tumor growth, which is beneficial to the invasion of tumor cells to surrounding tissues [3]. Lactic acid can also enter the blood circulation and reach the liver, where it is converted into glucose through gluconeogenesis, ultimately generating liver glycogen or blood glucose, forming the lactate cycle [4]. In the oxygen-rich areas of tumors, cancer cells also possess the same tricarboxylic acid cycle energy metabolism pathway as normal cells, where the metabolic product pyruvate is transported into the mitochondria through a transporter protein and oxidized and decarboxylated to generate acetyl coenzyme A, which is then metabolized through the tricarboxylic acid cycle and oxidative phosphorylation for energy metabolism.

3. Key Enzyme in Glycolysis

3.1. Inhibition of Pyruvate Kinase (PK)

In an aerobic environment, tumors engage in glycolysis to accelerate glucose uptake in the tumor microenvironment and produce a large amount of lactate, providing the required energy for tumor cell proliferation and inhibiting the function of immune cells to promote tumor cell metastasis [5].

Suppressing tumor cell glucose metabolism is a potential therapeutic method for tumors, which can be achieved by inhibiting key enzymes in glucose metabolism. Tumor cells contain some key enzymes, such as phosphofructokinase (PFK) and pyruvate kinase (PKM), which play a crucial role in glucose metabolism. PKM2 is one of the key enzymes in the glycolytic process, catalyzing the conversion of phosphoenolpyruvate to pyruvate. PKM2 expression levels are usually high in tumor cells, and its activity is also regulated by various factors. By inhibiting the activity of PKM2, the glucose metabolism process of tumor cells can be interfered with, thereby inhibiting tumor cell growth and proliferation. Inhibition of PKM2 activity can be achieved by directly inhibiting the activity of PKM2 and by regulating the expression level of PKM2 to inhibit tumor cell glucose metabolism. Some drugs can reduce the expression level of PKM2 to inhibit tumor cell glucose metabolism by regulating the expression level of PKM2. For example, some synthetic drugs can bind to the transcription factor of PKM2, inhibit its transcription activity, and thereby reduce the expression level of PKM2. Suppressing the activity of these key enzymes can interfere with the glucose metabolism process of tumor cells and block their growth. Therefore, inhibiting tumor cell glucose metabolism key enzyme PKM can inhibit cancer cell growth.

3.1.1. Inhibition effect of small molecular compounds on PKM2

The key step of glycolysis is catalyzed by PKM to convert phosphoenolpyruvate (PEP) to pyruvate. There are four isoforms of pyruvate kinase, L2, M1, and M2. Among them, M2 is the main isoform in tumor cells. Compared to other isoforms, PKM2 has low activity in tumor cells, resulting in the accumulation of upstream intermediates of glycolysis. Efficient inhibitors of PKM2 can completely inhibit glycolysis metabolism and ATP production. Although PKM1 and PKM2 are highly homologous and have the same catalytic site, PKM2 contains a unique allosteric regulatory site [6]. The transition between PK active and inactive forms is facilitated by the symmetric rocking of the A, C center regions of the PK subunit. Some compounds can interfere with the formation of key salt bridges and thereby prevent the formation of the enzyme's active conformation. Therefore, PKM2 can serve as a new target for cancer treatment by seeking small molecule compounds that can specifically bind to PKM2 protein and inhibit its catalytic activity in tumor cell glycolysis, interrupting glycolysis will effectively improve the therapeutic effect of tumors. It can also be concluded through the PKM2 site that small molecule inhibitors can bind to the active site of PKM2 and inhibit its ability to catalyze the production of pyruvate from phosphoenolpyruvate, based on studies of the PKM2 site and the mechanism of action of small molecule inhibitors. Through understanding the structure and function of the PKM2 active site, small molecule inhibitors can be designed and synthesized to bind to it. Inhibition of PKM2 by small molecules binding to its active site alters the enzyme's conformation and prevents it from binding to substrates, thereby inhibiting its catalytic activity. Tumor cells typically have abnormal glucose metabolism and increased demand and utilization of glucose. By inhibiting the activity of PKM2, the utilization of glucose and energy supply by tumor cells can be reduced, thereby inhibiting their growth and proliferation. This conclusion provides a theoretical basis for the development of small-molecule inhibitors against PKM2 as antitumor drugs.

A study used qRT-PCR and WB to detect the expression levels of PKM2 mRNA and protein in cells, MTT assay to detect changes in cell proliferation, and Transwell and scratch assays to detect cell invasion and migration abilities. The results showed that the positive expression rate of PKM2 protein in bladder cancer tissue was significantly higher than that in normal bladder tissue, and was associated with pathological grading and clinical staging. Compared with the blank control and negative control, the experimental group had reduced expression of PKM2 mRNA and protein in cells ($P < 0.05$), reduced cell proliferation ability ($P < 0.05$), decreased number of invasive cells ($P < 0.05$), and reduced migration ability ($P < 0.05$). It can be inferred that the overexpression of PKM2 may play an important role in the development and progression of bladder cancer, and downregulating PKM2 gene expression can inhibit the proliferation, invasion, and migration of bladder cancer cells [7]. The study [8] investigated the regulatory mechanism of M2-type PKM on the inhibitory function of FOXP3 (Forkhead box P3) protein and Treg cells. The results showed that the expression level of PKM in

Treg cells was significantly lower than that in Teff cells, and overexpression of PKM2 could downregulate the stability of FOXP3 protein, thereby affecting the phenotype of Treg cells. Inhibition of PKM2 activity could enhance the stability of FOXP3 protein and promote the inhibitory function of Treg cells. The experiment also found that PKM2 could promote the polyubiquitination modification of FOXP3 mediated by Stub1, leading to its degradation, thereby regulating the protein level of FOXP3 and inhibiting the function of Treg cells. Therefore, a new mechanism was discovered that PKM2 reduced the level of FOXP3 in Treg cells by regulating its ubiquitination modification, and the regulation of PKM2 activity could also change the protein level of FOXP3 and the phenotype of Treg cells. Therefore, inhibitors or activators of PKM2 activity are expected to achieve the goal of treating autoimmune diseases, inflammation, and tumors in clinical studies by changing the stability of FOXP3 and the inhibitory function of Tregs. Through two different experiments, it can be concluded that regulating PK can enhance T-cell activation and anti-tumor immune sensitivity, which can affect the efficiency and energy supply of the glycolysis pathway, thereby affecting T-cell activation and proliferation. It can provide sufficient energy to promote T-cell activation and proliferation. PK activity is also closely related to immune memory. In the process of immune memory, memory T cells can recognize and attack antigens that have been encountered again, and produce stronger immune responses. By regulating the activity of PK, the production and function of memory T cells can be affected, and then the strength and direction of immune memory can be regulated.

3.2. LDH

3.2.1. The relationship between LDH and tumors

As a key enzyme in aerobic glycolysis, LDH is composed of two subunits, LDHA and LDHB. Numerous studies have shown that abnormal expression of LDHB is associated with malignant progression in various tumors. Phosphorylation of LDHA can change cell metabolism patterns, thereby promoting the metastatic process of tumors. Previous studies have shown that human epidermal growth factor receptor 2 (HER2) and avian sarcoma virus oncogene v-src homologous (SRC) activate LDHA through phosphorylation at tyrosine residue 10, further promoting invasion and metastasis of tumor cells [9]. In tumor cells, LDHA can be phosphorylated at tyrosine residues by fibroblast growth factor receptor 1 (FGFR1), which phosphorylates all four tyrosine residues. FGFR1 tyrosine phosphorylation has different regulatory effects on LDHA and LDHB. FGFR1 tyrosine phosphorylation can increase the stability of LDHA. For LDHB, FGFR1 tyrosine phosphorylation can reduce LDHB expression by methylation of the promoter [10].

3.2.2. Promotion and inhibition of LDH on tumors

LDH plays different roles in different tumors, which can promote or inhibit the occurrence and development of tumors. LDH can promote tumor growth by enhancing aerobic glycolysis in tumor cells, providing energy for tumor cells and promoting their growth and proliferation. In addition, LDH can also inhibit the invasion and metastasis of tumor cells, which may be related to its ability to regulate the degradation of extracellular matrix.

3.2.3. Promotion mechanism of LDH in cancer

The mechanism of LDH's promotion of cancer can be demonstrated by its role in promoting cancer through lactate metabolism. In malignant tumor cells, glucose is metabolized through the glycolysis pathway to produce lactate. This process generates a large amount of lactate. Malignant tumor cells use special lactate transporters to transport lactate from inside the cell to outside the cell. Extracellular lactate can cause acidification of the extracellular fluid. Acidic environment promotes the proliferation, invasion, and metastasis of tumor cells. Lactate can be used as an energy source for tumor cells to survive and proliferate through liquid endocytosis. Lactate promotes the survival and proliferation of tumor cells by activating intracellular signaling pathways. For example, lactate can activate the HIF-1 α pathway, which promotes tumor cell survival. Therefore, it can be concluded that LDH provides the energy required for tumor cell survival and proliferation by promoting lactate

production, transport, and acidification of the tumor microenvironment, and activating survival signaling pathways to promote tumor cell survival and proliferation.

Silencing LDHB has been found to reduce aerobic glycolysis in thyroid papillary cancer [11], non-small cell lung cancer [12], and pancreatic cancer cells [13], inhibiting cancer cell growth in relevant studies at the cellular level. In addition, upregulation of LDHB expression promotes osteosarcoma cell proliferation, migration, and invasion activity, inhibiting cell apoptosis [14].

This conclusion is based on studies of PTC, NSCLC, and PCA, as well as observations of LDH expression in osteosarcoma cells. Inhibition of aerobic glycolysis was found to inhibit cancer cell growth, while upregulation of LDH expression was associated with osteosarcoma cell proliferation and inhibition of apoptosis. It can be concluded that LDH promotes aerobic glycolysis in tumor cells, providing energy for tumor cell growth and proliferation; it can also affect tumor cell apoptosis, promoting tumor cell survival and proliferation; and it can promote tumor angiogenesis, providing nutrients and oxygen for tumor cells, further promoting tumor cell growth and proliferation.

3.2.4. LDH's anti-cancer effect

LDH enhances T-cell activation and enhances anti-tumor immune sensitivity. The study investigated whether phospholipase C (PLC) is involved in aerobic glycolysis and proliferation of bladder cancer T24 cells through the LDHA pathway, as well as its regulatory mechanism. Experiment [13] concluded that the protein and mRNA expression of PLC ϵ and LDHA in bladder cancer tissue were significantly higher than in adjacent tissues. PLC ϵ may regulate the expression of LDHA to affect glucose consumption, lactate production, and proliferation of bladder cancer T24 cells. PLC ϵ may regulate the expression of LDHA by affecting the activation of STAT3. In vivo experiments, knockdown of PLC ϵ can inhibit the growth of bladder cancer T24 cell xenografts in nude mice, and knockdown of PLC ϵ can down-regulate the expression of PLC ϵ and LDHA in nude mouse xenografts. Glycolysis experiments and CCK-8 experiments showed that overexpressed LDHA can promote glucose consumption, lactate production, and proliferation of T24 cells. Moreover, the overexpression of LDHA can reverse the decrease in glucose consumption, lactate production, and proliferation caused by the knockdown of PLC ϵ in T24 cells. Western blot analysis showed that compared to the control group, the knockdown of PLC ϵ significantly inhibited the phosphorylation of STAT3 in bladder cancer T24 cells, without affecting the expression of total STAT3. The WB experiment found that STAT3 inhibitor Stattic can inhibit the phosphorylation of STAT3 and the expression of LDHA protein in T24 cells. Glycolysis experiments and CCK-8 experiments found that the inhibitor Stattic can inhibit glucose consumption, lactate production, and proliferation of T24 cells. The results of experiment [15] suggest that PLC ϵ may regulate aerobic glycolysis through the LDHA pathway, thereby affecting the proliferation of bladder cancer T24 cells. Therefore, the mechanism study conclusion shows that LDH can regulate energy metabolism, and LDH catalyzes the production of lactate. The activity of LDH is closely related to the energy metabolism of T cells. By regulating the activity of LDH, sufficient energy can be provided, the efficiency and energy supply of the glycolysis pathway can be affected, and the activation and proliferation of T cells can be promoted. In conclusion, the upregulation of LDH expression may promote the proliferation of osteosarcoma cells and inhibit apoptosis. Therefore, inhibiting LDH can reduce the energy supply of tumor cells, thereby inhibiting tumor growth and proliferation. Regulating LDH can enhance T-cell activation and enhance anti-tumor immune sensitivity, acting by regulating energy metabolism.

4. Development of Targeted Anti-Tumor Drugs and Clinical Applications Based on the Glycolysis Pathway

The integrated inhibition of tumor cell glucose metabolism and the enhancement of key enzyme activity in glycolysis can use the targeted regulation mechanism of glycolytic enzymes to reduce tumor glucose uptake and achieve targeted therapy for tumors. Targeted drugs refer to drugs that inhibit the growth and spread of tumor cells by specifically interfering with the function of target molecules. PKM and LDH play important roles in the energy metabolism of tumor cells, so the

inhibition of these two enzymes can be a targeted therapeutic approach. Targeting the metabolic pathways and key enzymes related to glycolysis can become a new target for cancer treatment [16]. Glycolytic enzymes such as hexokinase, pyruvate kinase, and LDH can be inhibited to reduce tumor glucose uptake and target tumor treatment. The targeted regulation of glycolytic pathways to develop targeted anti-tumor drugs is a challenging research field. By developing drugs that specifically inhibit these enzymes, the sugar metabolism process of tumor cells can be interfered with and tumor cell growth can be inhibited. At present, low-sugar treatment has also been applied to clinical practice as a new tumor treatment method. Targeting energy metabolism is a new direction of cancer treatment. Tumor cells provide energy and precursor substances for the synthesis of biological macromolecules through the glycolysis pathway. Therefore, some enzymes and metabolites in the glycolysis pathway have become important targets for tumor treatment. Currently, some anti-tumor drugs based on glycolysis pathway have been applied in clinic, such as a drug named 3-bromopyruvate (3-BrPA), which was found to inhibit PKM2 activity [17]. 3-BrPA inhibits tumor cell glycolysis process by binding to the active site of PKM2 and preventing it from catalyzing phosphoenol pyruvate to pyruvate. It can inhibit the energy supply of tumor cells and achieve the purpose of inhibiting tumor growth. This drug shows growth inhibition effect on multiple tumor cells and has less impact on normal cells compared with traditional chemotherapy drugs. This study shows that 3-BrPA can become a new and effective anti-tumor drug. 2-Deoxy-D-glucose (2-DG) can inhibit the kinase activity of hexokinase in glycolysis pathway, reduce the energy supply of tumor cells, and achieve the purpose of inhibiting tumor growth. However, the use of these drugs needs to carry out individualized treatment according to the specific situation of patients and also needs to pay attention to drug adverse reactions and drug interactions and other issues.

5. Conclusion

This article summarizes the research and analysis of the two key enzymes that play a critical role in the process of tumor cell glycolysis. Based on the understanding of the structure and function of PKM2 and the mechanism of action of small molecule inhibitors, it was found that the binding of inhibitors to the active site of PKM2 would change the conformation of the enzyme, inhibiting its activity. By inhibiting PKM2 activity, the utilization of glucose by tumor cells for energy production is reduced, thus inhibiting their growth and proliferation. Up-regulation of LDH expression may promote the proliferation of osteosarcoma cells and inhibit apoptosis. Therefore, inhibiting LDH can reduce the energy supply to tumor cells, forcing them to rely on other metabolic pathways, thereby inhibiting tumor growth and proliferation. By studying the inhibition of PKM and LDH to inhibit tumor cell growth, small molecule inhibitors targeted against PKM and LDH can be potential anti-tumor drugs. By inhibiting the activity of PKM and LDH, the energy supply of tumor cells can be reduced, and the growth and proliferation of tumor cells can be suppressed. By detecting the expression level and activity of key enzymes in tumor cells, targeted treatment of tumors can be achieved. For tumor cells with high expression or high activity of PKM and LDH, the use of corresponding inhibitors can improve the specificity and effectiveness of treatment. Glycolysis is one of the metabolic pathways of tumors, and multiple treatment strategies need to be comprehensively considered to improve the therapeutic effect. By targeting the inhibition of PKM and LDH pathways, the proliferation rate of tumor cells can be slowed down, thereby inhibiting tumor development. This can enhance the sensitivity of tumor cells to treatment, making them more sensitive to chemotherapy drugs and immunotherapy. Targeted inhibition of PKM and LDH pathway activation can weaken the ability of tumor cells to escape from immune response and enhance the effectiveness of immunotherapy.

Personalized therapy is a treatment plan designed based on a patient's individual genomic information and pathological characteristics. PKM and LDH may vary among different tumor types and individuals, so inhibiting these enzymes can customize treatment according to the patient's individual characteristics. This article has not yet analyzed the determination of targeted drugs through analysis of patients' genomic, protein expression, and metabolic features. In addition, it is necessary to further

understand the mechanism of PKM and LDH in cell energy metabolism to better develop inhibitors against these enzymes. Currently, targeted drugs for inhibiting LDH and PKM still lack selectivity, and these drugs may have side effects on normal cells while attacking tumor cells, leading to symptoms such as nausea and vomiting in patients. Therefore, more precise targeting and localization are needed to attack tumor cells while reducing damage to normal cells. Tumors can develop resistance to drugs, including through gene mutations in tumor cells and individual differences in patients. To address this issue, inhibitors can be combined with chemotherapy or immunotherapy to improve treatment outcomes and overcome drug resistance. Currently, there is no reliable method to predict a patient's sensitivity to targeted inhibitors. Therefore, multiple trials and genetic testing methods need to be used during the treatment process to accurately predict a patient's sensitivity to specific drugs. A lot of research and clinical trials are needed to achieve targeted drugs and personalized therapy, providing strong support for the development of targeted anti-tumor drugs for clinical application.

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