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A Study on the Regulation of PD-L1 Immune Escape by Gastric Cancer CAF Subsets Based on Metabolic Heterogeneity through Lactation Modification

Enpei Zhang*

School of Clinical and Basic Medical Sciences, Shandong First Medical University, Jinan 250117, China

**Corresponding author: Enpei Zhang.*

Abstract

High-glycolytic iCAFs in the gastric cancer tumor microenvironment exhibit significant metabolic heterogeneity and can secrete large amounts of lactate through the reverse Warburg effect, thus constructing an immunosuppressive microenvironment. Lactic acid is transported into tumor cells via MCT1 and regulates PD-L1 expression through a dual mechanism: AARS1-mediated histone lactation can upregulate PD-L1 transcription, while HAT1-catalyzed lactation at PD-L1 sites can block ubiquitination degradation and maintain protein stability. Highly expressed PD-L1 binds to PD-1 on $CD8^+$T cells and inhibits T cell killing function, mediating immune escape and immune resistance in gastric cancer. Targeting lactate metabolism and lactation modification can effectively reverse drug resistance and has synergistic therapeutic value with immunosuppressants. Currently, this field still suffers from shortcomings such as insufficient mechanistic evidence, a lack of gastric cancer-specific research, and limitations in detection technology.

Keywords

cancer-associated fibroblasts, metabolic heterogeneity, lactation modification, PD-L1, immune escape

1. Introduction

Stomach cancer is a common malignant tumor of the digestive tract worldwide, and it has received widespread attention due to its high mortality rate. Currently, research on immune checkpoint blockade therapy (ICB) has made significant progress, with inhibitors targeting the PD-1/PD-L1 pathway being one of the main treatment methods. However, the mortality rate of gastric cancer remains high. Although the therapy has made progress, the clinical durable response rate is still low, and many patients develop primary or acquired resistance. In-depth research into its underlying mechanisms revealed that the main factor limiting the therapeutic effect is the immunosuppression of the tumor microenvironment (TME). Among them, cancer-associated fibroblasts (CAFs) are the most numerous mesenchymal cells in the TME. These cells can interact with tumor cells and other surrounding cells, shaping an immunosuppressive microenvironment, which may be a key factor in inducing immune escape.

In recent years, targeted elimination of CAFs in cancer treatment has yielded diametrically opposed results, leading to the realization that it is inaccurate to regard CAFs as a homogeneous population of cells. With the application of single-cell RNA sequencing technology, researchers have discovered that CAFs are not

homogeneous cells, but can be divided into multiple cell subtypes e.g., myCAF, iCAF, apCAF. They exhibit extremely high heterogeneity, with some subpopulations playing a role in tumor suppression and preventing cancer cell metastasis, while other subpopulations promote cancer cells to evade immune surveillance and metastasis. These subgroups also have different metabolic characteristics. For example, in the study of pancreatic ductal adenocarcinoma, cross-species single-cell analysis identified CAFs subpopulations with different metabolic characteristics. Some of these subpopulations exhibited strong glycolytic characteristics and were able to secrete large amounts of lactic acid into the microenvironment through the reverse Wardurg effect. This finding suggests that certain CAF subsets can influence the pH of the TME to create an immunosuppressive environment. Traditional views hold that lactic acid is merely a metabolic waste product, but current research indicates that lactic acid can also serve as a substrate to mediate lysine lactation (Kla) modification of histones and non-histone proteins.

Recent studies have shown that lactate can induce lactation modification of PD-L1 protein in tumor cells, enhance its protein stability, reduce its degradation, and ultimately lead to upregulation of PD-L1 expression on the surface of tumor cells, promoting immune escape [1]. The mechanism chain of CAFs-lactic acid-lactic acidification modification-PD-L1 upregulation is still lacking systematic explanation. Different metabolic types of CAFs, especially high-glycolytic type, in the gastric cancer microenvironment are important drivers of the formation of an immunosuppressive environment. They induce lactation modification of PD-L1 and related proteins in tumor cells by secreting lactate, upregulate the expression and stability of PD-L1, and ultimately promote the immune escape of tumor cells. This article aims to systematically review the metabolic heterogeneity characteristics of CAF subpopulations and discuss the specific molecular mechanism of "CAFs-lactic acid-tumor cell lactation-PD-L1." It focuses on analyzing how CAFs mediate the lactation modification of PD-L1 through lactate, providing new theoretical basis and solutions for gastric cancer immunotherapy.

2. Heterogeneity and Metabolic Characteristics of CAFs in Gastric Cancer

Cancer-associated fibroblasts (CAFs) are not a homogeneous group of cells, but rather a collective term for a class of cells with high heterogeneity. They come from a variety of sources, such as resting fibroblasts, mesenchymal cells, tumor cells that have undergone epithelial-mesenchymal transition (EMT), and activated stellate cells, etc. They can be divided into several subtypes. With the widespread application of single-cell RNA sequencing (SCRNA-seq) technology, researchers have divided CAFs into three major subtypes based on cell characteristic markers and functional status: myofibroblast-like CAFs (myCAFs), inflammatory CAFs (iCAFs), and antigen-presenting CAFs (apCAFs). Among them, myCAFs highly express contractile proteins such as α-SMA and are mainly involved in the remodeling of the extracellular matrix and the process of increasing tumor stiffness. iCAFs highly secrete inflammatory factors such as IL-6 and LIF and play an important role in immune regulation. apCAFs highly express MHC class II molecules and may be involved in the antigen presentation process.

This heterogeneity in functional types is closely related to the heterogeneity in cellular metabolism. Different subtypes of CAFs exhibit different metabolic characteristics to adapt to and alter different tumor microenvironments. Among them, the iCAFs subtypes exhibit active glycolysis. They highly express glucose transporter 1 (GLUT1) and lactate dehydrogenase A (LDHA), and still preferentially carry out glycolysis under sufficient oxygen conditions, producing a large amount of lactic acid. This phenomenon is known as the "reverse Warburg effect." The lactic acid produced in the above process is pumped out of the cell through monocarboxylic acid transporters (MCTs), leading to an increase in lactic acid content in the TME. Compared with iCAFs, other subtypes of CAFs may rely more on oxidative phosphorylation and other metabolic mechanisms to affect TME by competing for nutrients [2]. Therefore, the metabolic heterogeneity of CAFs is the material basis for their functional heterogeneity, and the lactate secreted by high-glucose glycolytic CAFs becomes a key metabolic signaling molecule that regulates the immune status of TME.

3. Lactic Acidification Modification

Lactic acid has long been considered the final metabolic waste product of glycolysis. However, recent studies have found that lactate can be used as a substrate and, under the catalysis of histone acetyltransferase p300, binds to histone lysine residues to form a post-translational modification called histone lactylation (Kla) [3]. It is worth noting that the conclusion that p300 is a lactate transferase remains controversial. Studies have

shown that the intracellular concentration of lactyl-CoA is about 1,000 times lower than that of acetyl-CoA, questioning whether p300 is a true lactate transferase. The recent discovery of novel lactate transferases such as AARS1 has provided a new explanation for the identity of lactate transferases. Studies have found that isopropionyl-tRNA synthetases include AARS1 and AARS2, which can directly recognize lactate and synthesize lactylAMP under the action of ATP, and covalently modify substrate proteins [4]. This discovery shows that lactic acid is not only a metabolic waste product, but can also act as a signaling molecule to regulate cellular epigenetics and affect life activities.

Lactic acidification has a complex mechanism. It can occur on histones, affecting gene transcriptional activity, or on non-histone proteins, affecting protein stability and activity. In the tumor microenvironment, lactation modification promotes the polarization of tumor-associated macrophages (TAMs) towards the M2 type and inhibits the function of T cells, thereby creating an immunosuppressive environment. For example, studies have found that a high lactate environment can induce histone lactation in the promoter region of the arginase 1 (Arg1) gene in TAMs, promoting its transcription and thus inhibiting T cell activity [5]. On the other hand, it can also maintain the characteristics of tumor cells stem cells and promote tumor invasion and metastasis. In gastric cancer, lactic acid accumulation is significantly associated with poor prognosis, suggesting that lactic acid is a key factor in the progression of gastric cancer [6]. CAFs are important producers of lactate in the TME. The lactate they produce may be utilized by tumor cells as a substrate to induce lactation modification of key tumor cell proteins such as PD-L1, thereby altering their stability, activity, or function.

4. Mechanism of Action of CAFs-lactation-modified PD-L1 in Gastric Cancer Immune Escape

Cancer-associated fatty acids (CAFs) are important influencers of the tumor microenvironment (TME). Some CAFs (iCAFs) mainly metabolize through glycolysis, producing a large amount of lactate that is secreted into the TME, forming a lactate pool. Lactic acid is taken up by tumor cells and used to modify proteins such as PD-L1. This process upregulates the expression of PD-L1 and enhances its stability, deepens immunosuppression, and promotes the occurrence of immune escape. The lactate produced by CAFs modifies the PD-L1 immune escape axis of tumor cells, which can be mainly divided into three steps, “uptake–modification–stabilization.”

4.1 Tumor Cells Uptake of Lactic Acid from TME

High concentrations of lactate in TME can be efficiently transported into the cell via monocarboxylate transporters (MCTs) on tumor cells. Studies have shown that MCT1 is highly expressed in gastric cancer cells and is the main carrier for tumor cells to take up TME lactate. MCT4 mainly mediates the expulsion of lactate from inside and outside the cell. Lactate and protons work together to cross the membrane from the TME lactate pool into tumor cells via MCT1 [3]. This transport not only maintains pH homeostasis within tumor cells, but also provides substrates for subsequent modifications.

4.2 Modification of Lactic Acid

Intracellular lactate regulates PD-L1 through a dual mechanism of epigenetic modification and protein post-translational modification (PTM). At the transcriptional level, AARS1, as a non-classical lactate transferase, can directly utilize lactate and ATP to catalyze the lactation modification of proteins. Studies by Ju et al. have confirmed that AARS1, as a non-classical lactyl transferase, can mediate lactylation modification of histones, such as H3K18la [4]. Given that histone lactation, such as H3K18la, can accumulate in specific gene promoter regions and regulate the transcription of downstream target genes by relaxing chromatin structure and recruiting transcriptional machinery, AARS1-mediated lactation modification may be involved in the transcriptional regulation of PD-L1, but this direct association still needs further experimental verification. At the protein level, lactation specifically targets specific lysine residues in the extracellular domain of PD-L1. The study by Gao et al. clearly identified histone acetyltransferase 1 (HAT1) as a lactate transferase that directly catalyzes lactation modification of key sites (K75 and K178) of PD-L1 [7]. Normally, PD-L1 is easily degraded by ubiquitination, while lactation modification competitively occupies lysine sites, hindering the ubiquitination process. This effect significantly prolongs the protein half-life of PD-L1, causing it to

accumulate in large quantities on the surface of tumor cells and remain highly stable, thereby forming a persistent immunosuppressive signal [8].

4.3 Beneficial to Immune Escape

PD-L1, which is modified with lactate and stabilized, forms a dense immune checkpoint barrier on the surface of tumor cells, exerting a strong inhibitory effect on effector T cells. After stable PD-L1 binds to the PD-1 receptor on the surface of CD8+ T cells with high affinity, it can recruit phosphatases such as SHP-2, block downstream signaling pathways of TCR, such as PI3K-AKT and RAS-MAPK, inhibit T cell proliferation, secretion of cytokines, such as IFN-γ and TNF-α, and killing activity, and induce T cells to enter a state of functional exhaustion [7]. The lactic acid continuously secreted by CAFs maintains the high stability of PD-L1 through the above mechanism, enabling tumor cells to evade the surveillance and clearance of the body's immune system for a long time. In summary, lactate from CAFs enters gastric cancer cells via MCT transport, may promote PD-L1 transcription through histone lactation, and inhibit its ubiquitination and degradation through PD-L1 protein lactation, thereby establishing high expression and high stability of PD-L1 at both the transcriptional and protein levels, ultimately leading to immunotherapy resistance.

5. Therapeutic Strategies Targeting CAF Metabolism and Lactation Modification

Intervening in the downstream metabolic pathway of cancer-associated fibroblasts (CAFs) and the lactation-modified PD-L1 pathway is a promising therapeutic strategy. Blocking lactate transport and metabolic coupling is the primary approach. As mentioned above, lactate mainly enters tumor cells through MCT1, thereby producing lactate-modified PD-L1. The use of the MCT1 selective inhibitor AZD3965 can block the metabolic coupling of lactate between CAFs and tumor cells, reduce the amount of lactate taken up by tumor cells, inhibit the modification of PD-L1 by lactate, reduce the stability of PD-L1, and thus block the immune escape process. In addition, inhibitors targeting LDHA, such as FX11 and GSK2837808A, can reduce lactate production in CAFs and tumor cells at the source, and also have intervention potential. At the level of enzymatic regulation of lactation modification, inhibiting lactation Writer enzyme can interfere with PD-L1 expression at the transcriptional level. In gastric cancer, lactate secreted by CAFs can activate AARS1 in tumor cells, mediating histone lactation modification, which may regulate PD-L1 expression at the transcriptional level.

Developing small molecule compounds, such as β-alanine analogs, that specifically inhibit AARS1 lactate transferase activity can block this process and downregulate PD-L1 expression at the transcriptional level. In addition, inhibitors targeting p300/CBP, such as A-485 and C646, may also exert their effects by inhibiting histone lactation, but their specificity still needs further evaluation. Corresponding to Writer, targeting lactate-induced Eraser enzymes provides another direction for intervention. Delactylases, such as SIRT1, SIRT2, and SIRT3, catalyze the delactation of lysine residues. Activating SIRT family members or using their agonists, such as resveratrol to activate SIRT1, may promote the delactation of PD-L1 and histones, reduce PD-L1 stability, and inhibit its transcription. The aforementioned strategies targeting lactate metabolism and lactation modification are not used in isolation, but can be combined with immune checkpoint inhibitors for treatment. These strategies, when used in combination with anti-PD-1/PD-L1 antibodies, can synergistically enhance the efficacy of immunotherapy by reducing PD-L1 expression levels in tumor cells and restoring T cell function, thereby overcoming primary or acquired drug resistance.

6. Conclusion

Specific metabolic subgroups, such as high-glycemic glycolytic iCAF, are the main source of lactate in the tumor microenvironment. The lactate they secrete is not only a metabolic waste product, but also a key signaling molecule. After being taken up by tumor cells, these lactates induce histones, such as H3K18la, causing the chromatin near the PD-L1 gene promoter to loosen and thus initiate transcription, upregulating PD-L1 expression or directly lactating non-histone proteins, such as PD-L1 itself. This has an effect on multiple levels, including epigenetics and protein stability, directly upregulating PD-L1 expression and thus helping tumor cells achieve immune escape. This “metabolism–epiota–immunity” regulatory network provides a new perspective for understanding drug resistance in gastric cancer immunotherapy. There are still some limitations in current research in this field. First of all, the direct causal evidence between lactate derived

from CAFs and lactation of tumor cells is not sufficient, and existing studies are mostly based on logical deduction rather than functional verification of CAFs specificity. Also, there is still a lack of direct experimental evidence whether AARS1-mediated histone lactylation directly targets the PD-L1 promoter, and the association between H3K18la and PD-L1 transcription needs to be further confirmed in the gastric cancer system. Moreover, single-cell level evidence of metabolic heterogeneity of CAFs in gastric cancer is relatively limited, and existing conclusions are mostly based on other tumor types such as pancreatic cancer. Finally, the detection technology of lactation modification still relies on antibody enrichment, and site specificity and quantitative accuracy need to be improved.

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Conflicts of Interest

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