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Research on the Mechanism by which Lactate Receptor GPR81 Mediates Differential Regulation of Immune Cell Subsets to Promote Tumor Immunosuppression

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Abstract

G protein-coupled receptor 81 (GPR81) is a lactate receptor that is upregulated in various malignant tumors. The specific mechanism by which it mediates immunosuppression in the tumor microenvironment has not been fully elucidated. This article systematically reviews the research progress on the activation of tumor cells by lactic acid and the differential regulation of GPR81 on the surface of immune cells by various immune cell subpopulations, thereby promoting tumor immune escape. Lactic acid activates GPR81 on tumor cells to upregulate the expression of a variety of inhibitory molecules, thereby inhibiting $CD8^+$T cell function and promoting the recruitment of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). It binds to GPR81 on the surface of immune cells to inhibit the antigen presentation function of dendritic cells (DCs), polarizes macrophages toward the M2 type, and induces MDSCs to express immunosuppressive mediators. The above regulatory functions ultimately inhibit anti-tumor immunity. In-depth elucidation of the immune cell regulatory network mediated by GPR81 will provide an important theoretical basis for the development of combined immunotherapy strategies targeting the lactate signaling pathway.

Keywords

lactate, GPR81, tumor immune microenvironment, immune cell subsets, immunosuppression

1. Introduction

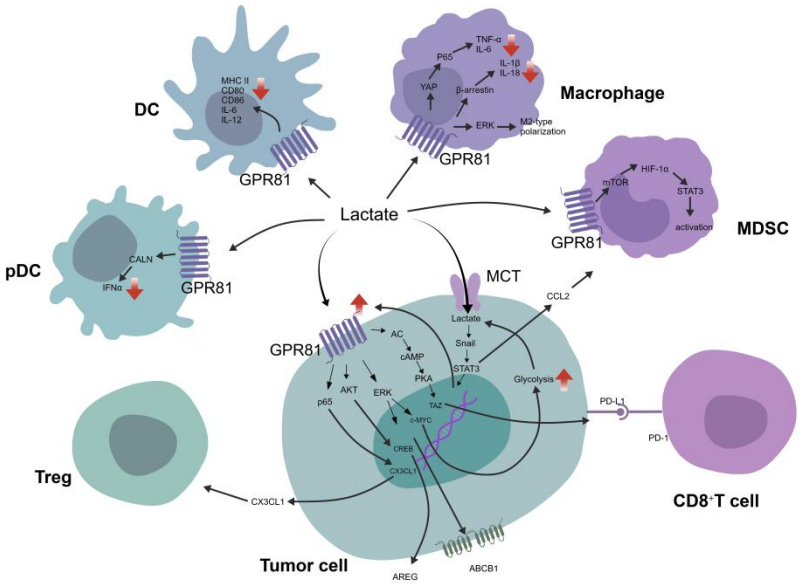
Tumor cells undergo metabolic reprogramming, preferentially engaging in glycolysis even under aerobic conditions, and converting the resulting pyruvate into large amounts of lactate via lactate dehydrogenase (LDHA). This phenomenon is known as the Warburg effect. Existing research has shown that lactic acid is not merely a metabolic waste product of glycolysis, but also plays an important role in tumor growth, metastasis, and immunosuppression. Lactic acid is transported across the membrane between tumor cells and the tumor microenvironment (TME) via monocarboxylic acid transporters (MCTs), accumulating in the TME and causing microenvironment acidification, which in turn leads to immune landscape remodeling. At the same time, lactic acid can also serve as an energy source, a substrate for oxidative phosphorylation in aerobic cancer cells, or a substrate for protein lactation [1]. In addition, the function of lactate as a signaling molecule has been confirmed, and GPR81 as its receptor has also received widespread attention.

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G protein-coupled receptor 81 (GPR81, also known as HCAR1) belongs to the hydroxycarboxylic acid receptor (HCAR) family and is a specific membrane receptor for lactate. GPR81 was initially thought to be expressed at high levels only in adipocytes and at low levels in secondary lymphoid tissues, intestines, brains and kidneys. It regulates lipolysis by coupling with the inhibitory G protein α subunit (Gαi), inhibiting the activity of adenylyl cyclase, reducing intracellular cyclic adenosine monophosphate (cAMP) levels, and inhibiting the activity of protein kinase A (PKA) [2]. Recent studies have shown that GPR81 is highly expressed in cell lines of various tumors, including breast cancer, lung cancer, gastric cancer, cervical cancer, colorectal cancer, and pancreatic cancer. Downregulating its level can inhibit lactic acid secretion and cancer growth [3]. GPR81, as a lactate receptor, plays multiple regulatory roles in the tumor microenvironment and has shown potential as a target for inhibiting the lactate signaling pathway in combination with immunotherapy.

Although the role of GPR81 in tumor immunosuppression has received widespread attention, the progress of existing research in different immune cell subsets is uneven: the mechanism research in dendritic cells and macrophages is relatively in-depth, the research in myeloid-derived suppressor cells and T cells is still accumulating, while the function of GPR81 in subsets such as NK cells, neutrophils, and B cells is still blank. Furthermore, the heterogeneity of GPR81 expression in different cancer types and its association with immunotherapy response still lack systematic analysis. Based on this, this article systematically reviews the differential regulatory mechanisms of lactate/GPR81 signaling in dendritic cells, macrophages, myeloid-derived suppressor cells, and T cells, using immune cell subsets as clues, and explores its clinical translational potential, in order to provide a theoretical reference for combined immunotherapy targeting the lactate pathway.

Figure 1: Lactate/GPR81 Signaling Pathway in the Tumor Microenvironment



2. Lactic acid/GPR81 Signaling Pathway

GPR81 is upregulated in both tumor cells and stromal cells and is activated by lactate present in the tumor microenvironment. After the lactate secreted by tumor cells through aerobic glycolysis is transported to the extracellular space, it can bind to its own GPR81 through autocrine action. In tumor cells, lactate binds to GPR81 and then phosphorylates binding protein (CREB) through the phosphatidylinositol 3-kinase (PI3K)/Akt-cAMP pathway, upregulating the angiogenesis mediator dual regulator protein (AREG) and promoting angiogenesis in tumor tissue [2]. Meanwhile, lactate binds to GPR81 and activates phospholipase C (PLC), which in turn activates protein kinase C (PKC), phosphorylates extracellular signal-regulated kinase 1/2 (ERK1/2), and ultimately upregulates the transcription of ATP-binding cassette transporter B1 (ABCB1) [2]. ABCB1 is a drug delivery transporter, and increased expression and activity of it can lead to increased

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resistance to chemotherapy in tumors. In addition, GPR81 signaling enhances the expression of various DNA repair proteins, which also benefits chemical resistance. Although the tumor cell-initiated GPR81 signaling does not directly act on immune cells, the induced secretion of chemokines and upregulation of immune checkpoint molecules lay the foundation for the formation of the subsequent immunosuppressive microenvironment.

Lactic acid released into the tumor microenvironment can also bind to adjacent tumor cells or stromal cells in a paracrine manner, including cancer-associated fibroblasts (CAFs), endothelial cells, cancer-associated adipocytes (CAAs), dendritic cells (DCs), and tumor-associated macrophages (TAMs) with GPR81 upregulation, and exert certain regulatory effects on them, which will be detailed later.

In addition, lactate/GPR81 is also regulated by a variety of factors. Firstly, once endogenous or exogenous lactate enters the cell, it can mediate the upregulation of transcription factor Snail and the synthesis of STAT3. STAT3 can upregulate the transcription of GPR81 by binding to the promoter [4]. Secondly, the effluxed lactate acts on the tumor cell's own GPR81 in an autocrine manner, activating the ERK-c-MYC signaling axis: ERK phosphorylates the Ser62 site of c-MYC, preventing it from being recognized and degraded by FBW7 ubiquitin ligase, thereby stabilizing the c-MYC protein. The stabilized c-MYC further transcribes and upregulates key glycolysis genes such as LDHA, GLUT1 and HIF1α, and maintains high lactate output [5]. The positive feedback loop of "lactate–STAT3–GPR81–MYC–lactate" formed by the two can further amplify the signal response.

3. The Regulatory Effect of Lactate Receptor GPR81 on Dendritic Cells

Under normal conditions, activated DCs will highly express MHC II and co-stimulatory molecules such as CD40, CD80, and CD86, thereby inducing T cell activation and functional differentiation, or producing a variety of cytokines. GPR81 is upregulated in tumor tissues and dendritic cells (DCs), so lactate in the tumor microenvironment can directly act on this receptor on DCs. In conventional dendritic cells (cDCs), treatment with the GPR81 agonist CHBA significantly reduced the number of cDCs with high MHC II expression (from 42% to 19%), suggesting that GPR81 can inhibit MHC II. This change is achieved by GPR81 activation reducing cAMP levels and downregulating CIITA (MHC II transcription coactivator) mRNA [6]. Meanwhile, the expression of CD86 and CD80 also decreases, while the expression of CD40 shows no significant change. In addition, activation of GPR81 also reduces the secretion of pro-inflammatory factors IL-6 and IL-12. In plasmacytoid dendritic cells (pDCs), it was found that GPR81 coupled with the G protein βγ subunit (Gβγ) subunit induces cytoplasmic Ca2+ mobilization and regulates downstream gene expression through calcineurin (CALN), thereby reducing the secretion of IFNα by pDCs [7]. The aforementioned regulatory effects of GPR81 on DCs reduce the antigen-presenting capacity of dendritic cells, making it unable to effectively activate $CD8^+$ T cells. This weakens the inhibitory capacity of DCs on Tregs, reduces the paracrine activation of NK cells and macrophages, and weakens the anti-tumor immune response.

4. Regulatory Role of Lactate Receptor GPR81 in Macrophages

Lactic acid also regulates macrophage function by directly acting on GPR81 on macrophages. At the mechanistic level, activation of GPR81 signaling inhibits the pro-inflammatory response of macrophages through multiple downstream pathways. First, activation of GPR81 can inhibit the classical NF-κB signaling pathway. Studies have found that lactate activates the AMPK-LATS pathway through GPR81, which can promote the phosphorylation and inactivation of YAP protein. This not only weakens the interaction between YAP and the NF-κB subunit p65, but also directly inhibits the nuclear translocation of p65, ultimately significantly reducing the production of pro-inflammatory factors such as TNF-α and IL-6 in macrophages under LPS stimulation [7]. Second, GPR81 signaling can also reduce the secretion of IL-1β and IL-18 by limiting the activation of the β-arrestin/inflammatoric pathway, thereby inhibiting the inflammatory response of monocytes and macrophages [7].

At the functional level, GPR81 signaling can induce macrophages to polarize towards the M2 type. In a study of clear cell carcinoma (ccRCC), it was shown that tumor cells efflux lactate in large quantities through MCT4, which activates GPR81 on the surface of tumor-associated macrophages (TAMs), triggers ERK

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phosphorylation, and thus promotes TAMs to polarize to the M2 type [5]. This change will suppress toxic T cell activity, induce their depletion, and promote tumor angiogenesis.

5. Regulatory Role of Lactate Receptor GPR81 in MDSCs

MDSCs are a type of immature myeloid cells that proliferate abnormally under pathological conditions. They promote the immunosuppressive effects of Tregs and inhibit cytotoxic T cells and NK cells, as well as have direct tumor-promoting effects such as angiogenesis and metastasis, thus promoting further tumor development. Lactic acid/GPR81 can regulate MDSCs through both autocrine and paracrine pathways.

On the one hand, lactate/GPR81 recruits MDSCs through an autocrine pathway. In colorectal cancer cells, GPR81 induces transcriptional upregulation of C-C motif chemokine ligand 2 (CCL2) and C-C motif chemokine ligand 7 (CCL7) through the scaffold protein 14-3-3ζ-transcriptional activator protein 3 (STAT3) pathway, thereby promoting the recruitment of CCR2+ polymorphic nuclei MDSCs (PMN-MDSCs), increasing the infiltration of MDSCs in the tumor microenvironment and promoting the formation of an immunosuppressive environment. Meanwhile, the study also found that reserpine can promote anti-tumor immunity by inhibiting GPR81 and blocking downstream pathways [8]. Extensive infiltration of MDSCs leads to arginine depletion in $CD8^+$ T cells and promotes Treg recruitment.

On the other hand, tumors can enhance the immunosuppressive function of MDSCs through paracrine pathways. In pancreatic cancer, tumor-derived lactate binds to GPR81 on MDSCs, activating mammalian target of rapamycin (mTOR), which in turn activates downstream hypoxia-inducible factor-1α (HIF-1α), upregulating STAT3 and ultimately activating MDSCs [1]. Activation of this pathway can induce MDSCs to express immunosuppressive mediators, thereby inhibiting the antitumor effects of cytotoxic T cells.

6. Regulatory Effect of Lactate Receptor GPR81 on T Cells

There is currently insufficient evidence to suggest that GPR81 is directly expressed on the surface of T cells and mediates direct signal transduction. The regulation of T cells by GPR81 is mainly achieved through indirect mechanisms by tumor cells and other stromal cells.

6.1 Tregs

Tregs are a type of immunosuppressive cell that can suppress the function of cytotoxic T cells by secreting anti-inflammatory factors such as IL-10 and TGF-β, playing an important role in the formation of the immunosuppressive microenvironment. A study on gastric cancer showed that lactate activation of tumor cells GPR81 can phosphorylate p65 and translocate to the promoter of C-X3-C motif chemokine ligand 1 (CX3CL1), thereby upregulating its expression [9]. CX3CL1 is a chemokine that can promote the infiltration of Tregs in the tumor microenvironment, thereby inhibiting the tumor-suppressing function of $CD8^+$T cells. In addition, GPR81 can also indirectly play a role in recruiting Tregs by recruiting MDSCs and promoting their function. Extensive Treg infiltration can suppress the function of DC, NK, and $CD8^+$T cells, stimulate excessive collagen deposition in CAFs, block anti-tumor immunity, and induce epithelial-mesenchymal transition, thus promoting tumor migration.

6.2 $CD8^+$T Cells

As the most important effector cells in anti-tumor immunity, $CD8^+$T cells have an extremely complex regulatory network. GPR81 indirectly regulates $CD8^+$T cells through its effects on tumor cells and other stromal cells. Lactic acid binds to GPR81 on the surface of tumor cells, which can activate the transcriptional cofactor TAZ through the classical Gαi-cAMP-PKA pathway. TAZ interacts with the transcription factor TEAD, thereby upregulating the expression of PD-L1 in tumor cells. PD-L1 binds to PD-1 on the surface of T cells, inhibiting the production of effector cytokines and inducing $CD8^+$ T cell apoptosis [1]. Therefore, the combined use of GPR81 receptor blockers can have a synergistic effect with immune checkpoint therapy. In one study, it was found that the combination of GPR81 antagonist 3-OBA and PD-1/PD-L1 pathway blockers can significantly enhance the anti-tumor effect of metformin, providing a new approach to overcoming tumor drug resistance [10]. Furthermore, in breast cancer, GPR81 was found to mediate glucose metabolism reprogramming through the Hippo-YAP pathway, resulting in a decrease in the proportion of $CD8^+$T cells and

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an increase in the proportion of FOXP3$^+$Treg cells in the tumor microenvironment, further supporting the indirect regulatory role of GPR81 in T cell subset balance.

In addition, as upstream cells of CD8$^+$T cells in the anti-tumor immune response, the regulation of the former by GPR81 will also indirectly affect the latter. For example, in antigen-presenting cells, GPR81 signaling inhibits the expression of MHC II and co-stimulatory molecules CD80 and CD86 on the surface of DCs and reduces the secretion of pro-inflammatory cytokines such as IL-12, resulting in a decrease in the antigen-presenting capacity of DCs and a significant reduction in their ability to activate naïve T cells, thus failing to effectively induce the proliferation and differentiation of CD8$^+$ T cells. Meanwhile, the reduction in GPR81-mediated IFNα secretion in pDC further weakens the initiation of the anti-tumor immune response. In addition, GPR81-induced macrophage M2 polarization reduces its antigen-presenting ability and secretes more inhibitory factors, which significantly reduces the tumor cell killing rate of CD8$^+$T cells. MDSCs express immunosuppressive mediators after GPR81 signaling activation, directly inhibiting the cytotoxic function of CD8$^+$T cells. In summary, GPR81 systematically inhibits the anti-tumor effect of CD8$^+$T cells through a multi-level, multi-cell-type indirect regulatory network, thereby promoting tumor immune escape.

7. Conclusions

Lactic acid, as a key metabolite in the tumor microenvironment, has transcended its traditional role as an energy substrate and become an important signaling molecule regulating tumor immune escape. GPR81, as a specific membrane receptor for lactate, is differentially expressed in tumor cells and various stromal cells, constituting the core molecular basis of lactate-mediated tumor immunosuppression. GPR81 suppresses anti-tumor immunity by regulating multiple immune cells, and promotes tumor growth and drug resistance. In summary, the GPR81-mediated lactate signaling pathway is a key bridge connecting tumor metabolic reprogramming and immunosuppression. In-depth analysis of the differential regulatory mechanisms of GPR81 in different immune cell subsets not only helps to elucidate the metabolic-immune cross-network of tumor immune escape, but also provides an important theoretical basis for developing combined immunotherapy strategies targeting the lactate/GPR81 pathway.

However, current research on GPR81 mainly focuses on a few cell subpopulations such as DCs, macrophages, MDSCs and T cells, while its function in important components of the tumor microenvironment such as NK cells, neutrophils, and B cells remains to be elucidated. Meanwhile, as an emerging epigenetic regulatory mechanism, the interaction between lactation modification and the GPR81 signaling pathway warrants further investigation. Furthermore, developing highly selective, high-affinity GPR81 small molecule antagonists or monoclonal antibodies is key to advancing clinical translation. Based on existing research, the combination of GPR81 blockers and PD-1/PD-L1 immune checkpoint inhibitors has shown potential for synergistic effects. In the future, its efficacy needs to be validated in more cancer types and preclinical models, and the best combination regimen with strategies such as chemotherapy, radiotherapy, metabolic intervention and CAR-T cell therapy needs to be explored.

Finally, the heterogeneity of GPR81 expression in different tumor types and individual patients suggests that screening tumor populations with high GPR81 expression as advantageous groups for precision treatment and establishing the correlation between GPR81 expression levels and patient prognosis and immunotherapy response will be an important prerequisite for achieving personalized GPR81-targeted therapy. A thorough analysis of the GPR81-mediated immune metabolic regulatory network is expected to provide new theoretical basis and therapeutic breakthroughs for overcoming drug resistance in tumor immunotherapy and reshaping anti-tumor immune responses.

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Conflicts of Interest

The authors declare no conflict of interest.

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