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Original Article

The Mechanism of CCR5 in Tumors and Therapeutic Strategies

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Abstract:
With the continuous development of immunotherapy technology, immunotherapy has gradually become a key means of cancer treatment. Among them, chemokine receptor 5 (CCR5) can regulate immune responses and is an important target for a variety of tumor immunotherapies. CCR5 belongs to the β chemokine receptor family, a seven-transmembrane G protein-coupled receptor that is widely expressed in a variety of immune cells and tumor cells and is involved in tumorigenesis and tumor progression. CCR5 is aberrantly expressed in a variety of solid tumors (such as breast cancer, gastrointestinal cancer, pancreatic cancer, colon cancer, prostate cancer, melanoma) and hematologic malignancies, and is closely related to the poor prognosis of tumors by recruiting immune cells and regulating the tumor microenvironment, promoting tumor proliferation, invasion and metastasis. At present, initial results have been achieved in the treatment of CCR5-targeted tumors, and small molecule inhibitors of CCR5 such as leronlimab, maraviroc and vicriviroc have entered clinical studies. This article reviews the mechanism of CCR5 in tumorigenesis and progression, as well as the development history and application prospects of CCR5-targeted therapy strategies.

Keywords: CCR5; Cancer treatment; CCL5/CCR5 axis; Tumor microenvironment; gene therapy

Introduction

In recent years, immunotherapy has become a fundamental approach for treating various tumors[1]. C-C chemokine receptor 5 (CCR5) has attracted widespread attention as an important target in cancer therapy due to its ability to regulate immune responses. CCR5 belongs to the family of β chemokine receptors and is a seven-transmembrane G protein-coupled receptor that has high affinity for CCL5, CCL3, CCL4, and CCL8 (monocyte chemoattractant protein 2, MCP2), participating in various physiological, pathological, and tumor processes (see Table 1). During ligand binding, CCR5 activation leads to the activation of G proteins and a signaling cascade, such as the protein kinase B (PKB, also known as Akt) and NF-kB pathways, as well as cytoskeletal rearrangement and chemotactic cell migration[2, 3]. CCR5 is mainly expressed on activated T cells (Th1 and Th17), B cells, monocytes, macrophages, dendritic cells, myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and natural killer cells. Additionally, CCR5 expression has been observed in microglia, astrocytes, osteoclasts, hepatic stellate cells, endothelial cells, vascular smooth muscle cells, various tumor cells, and cancer-associated fibroblasts[4-7].

It has currently been found that CCR5 is abnormally expressed in various solid tumors (such as breast cancer, cervical cancer, ovarian cancer, colon cancer, prostate cancer, and melanoma) as well as hematologic malignancies (such as Hodgkin lymphoma and multiple myeloma), and is closely related to tumor occurrence, progression, and poor prognosis [8]. In

summary, CCR5 regulates tumor proliferation, invasion, and metastasis through multiple pathways, making it a potential target for tumor therapy. This article first explains the mechanisms of CCR5 in various tumors, providing a systematic theoretical basis for developing CCR5-based tumor therapies; it then summarizes the current research progress of CCR5 in tumor treatment and discusses potential future directions of CCR5 in the field of tumor therapy.

Table 1 The Physiological Functions of CCR5 and Its Ligands [8-11]

CCR5 Ligands	Physiological and Pathological Functions
CCL3	Immune Cell Migration:; Inflammation Regulation; Antiviral Response
CCL4	Chemotaxis; Immune Modulation
CCL5	Antiviral Defense; Inflammatory Response; Tissue Repair
CCL8	Immune Cell Recruitment; Tumor Microenvironment Regulation

2. Mechanism of CCR5 in Tumors

Chemokines play an important regulatory role in the body's defense system. Among them, CCR5 can promote immune responses by recruiting immune cells to sites of inflammation or tumors and participate in tumor cell proliferation, invasion, and migration through multiple mechanisms. In addition, CCR5 also promotes tumor occurrence and progression by recruiting regulatory T cells and myeloid-derived suppressor cells, thereby contributing to the formation of an immunosuppressive tumor microenvironment (TME).

The CCL5/CCR5 axis is a key signaling pathway in immunology and diseases. Tumor cells secrete CCL5 to recruit CCR5 monocytes/macrophages [12, 13]; these cells induce angiogenesis by secreting VEGF, a critical mediator of tumor angiogenesis [14, 15]. In addition, CCR5 is also involved in the DNA damage repair process in tumor cells. Studies show that CCR5 promotes chemotherapy resistance and enhances cancer cell survival by stimulating DNA repair mechanisms and enhancing anti-apoptotic mechanisms [16].

In summary, CCR5, as a chemokine receptor, plays an important role in the occurrence and development of various tumors, the tumor microenvironment, tumor immune tolerance mechanisms, and tumor metastasis and dissemination (as shown in Table 2).

Table 2 Summary of the Mechanisms of CCR5 in Tumors

Tumor	The Function of CCR5	The Mechanism of Action of CCR5
Breast cancer	Regulates metabolism and TEM; Promoting angiogenesis and tumor growth; Participating in tumor metastasis and spread	Increasing the expression of GLUT-1 and stimulating glucose uptake; Promoting the secretion of VEGF; Enhancing the activation of the mTOR/Akt pathway; Synergistic action with the CCL5 ligand
Melanoma	Stimulating tumor proliferation	Downregulating TGF-β to modulate

	and metastasis; Participating in the TEM and immune suppression	the EMT pathway; Recruiting MDSCs cells; Synergistic action with the CCL5 ligand
Gastrointestinal cancer	Closely related to the patient's overall survival rate and poor prognosis	Synergistic action with the CCL5 ligand
Colorectal cancer	Participating in tumor occurrence and progression; Participating in the TEM	Synergistic action with the CCL5 ligand; Recruiting Treg cells and $CD8^+$ T
Prostate cancer	Participating in the TEM Promoting tumor growth	Recruiting MDSCs cells;

2.1 The Mechanism of CCR5 in Breast Cancer

CCR5 mainly participates in tumor growth, angiogenesis, tumor microenvironment, tumor metastasis, and immune evasion mechanisms in breast cancer.

Tumor growth depends on its ability to supply metabolic energy, and CCR5 participates in the metabolic processes of breast cancer cells through various mechanisms to promote tumor growth. Studies have shown that CCR5 promotes glucose uptake across the cell membrane by increasing the expression of glucose transporters (GLUT-1) on the cell surface, thereby maintaining the normal growth of breast cancer cells [2, 17]. In addition, CCR5 is also involved in inducing Akt phosphorylation, stimulating glucose uptake, glycolysis, the pentose phosphate pathway, fatty acid synthesis, and glutamine metabolism, thus activating metabolic pathways and providing metabolic energy for tumor growth [18].

CCR5 is still a key factor in promoting breast cancer angiogenesis. CCR5 activates protein kinase C delta (PKC δ), initiating the expression of the proto-oncogene tyrosine-protein kinase (Src) and hypoxia-inducible factor-1 (HIF-1), thereby stimulating the secretion of VEGF [14, 19]. Further studies have found that experiments in the mouse EO771 breast cancer model showed that endothelial cells expressing CCR5 promoted the growth of breast cancer tumors in the breast tumor microenvironment [20].

In addition, CCR5 is closely associated with the metastasis and immune escape mechanisms of breast cancer. Studies have found that stimulation with CCL5 in human breast cancer cell lines expressing CCR5 shows increased migration and invasion characteristics [21]. Additionally, the CCL5/CCR5 axis mediates cancer cells to evade the immune system by reprogramming TAMs into M2 macrophages and enhances the expression of PD-L1 [22].

2.2 Melanoma

CCR5 plays an important role in the proliferation and metastasis of melanoma cells. Compared with non-tumor cells, CCR5 mRNA and protein expression are significantly elevated in mouse melanoma cells. When CCR5-deficient mouse melanoma cells (CCR5-/-) B16F10 were injected into mice, it was found that CCR5 deficiency led to delayed tumor growth and inhibition of lung metastasis. In contrast, compared with the control group, overexpression of CCR5 in B16F10 cells stimulated tumor growth and lung metastasis [23].

Epithelial-Mesenchymal Transition (EMT) is one of the key factors in tumor metastasis. In mouse melanoma cells, the absence of CCR5 triggered a morphological transition from mesenchymal to epithelial phenotype by downregulating TGF-β, one of the key drivers of EMT [24].

In addition, some studies have found that in melanoma mouse models, MDSCs expressing CCR5 are enriched in tumor lesions and,

compared with CCR5- MDSCs, CCR5+ MDSCs exhibit higher immunosuppressive potential. Moreover, the study also found that inhibiting the CCL5/CCR5 axis can prolong the survival of tumor-bearing mice and reduce the immunosuppressive activity of MDSCs [25].

2.3 Gastrointestinal Cancer

The mechanism of CCR5 in gastrointestinal cancer has not yet been clearly studied, but the abnormal expression of CCR5 is closely related to the overall survival rate and poor prognosis of patients with gastrointestinal cancer.

Several in vitro studies have shown that in various gastrointestinal cancers (including esophageal cancer, gastric cancer, and colorectal cancer) in mouse and human cancer cell lines, the mRNA and protein expression levels of CCR5 are significantly increased [24], and CCR5 expression is higher in gastrointestinal cancers with lymph node metastasis than in those without lymph node metastasis [26]. Studies have indicated that stimulation with CCL5 can further promote cancer cell proliferation and invasion, and upregulate CCR5 mRNA and protein levels in gastric cancer [27-31]. Moreover, research has shown that compared with gastric cancer patients whose tumor cells do not express CCR5, patients with increased CCR5 immunohistochemical staining in tumor cells after primary tumor resection have poorer overall survival, and this association remains significant in multivariate analysis [32].

2.4 Colorectal Cancer

Similar to gastric cancer, CCR5 also shows significant abnormal expression in colorectal cancer. In addition, CCL5, as the ligand of CCR5, is also overexpressed in primary colorectal cancer (CRC) tumors and distant liver and lung metastases. As early as 2011, Cambien and colleagues confirmed that the CCL5/CCR5 axis plays a crucial role in the pathogenesis of colorectal cancer [33]. Their study further found that compared to the primary tumor site, the expression of CCL5/CCR5 was higher in liver metastases. Furthermore, after inoculating a mixture of CCR5 high-expressing colorectal cancer cell lines and mesenchymal stem cells into immunodeficient mice, the tumor burden increased compared to mice injected with only HCT116 control cells [27]. Abnormal expression of the CCL5/CCR5 axis also leads to increased immunosuppressive effects of Tregs, thereby promoting the development of colorectal tumors. CD103 Tregs are a type of regulatory T cell expressing CD103, playing an important role in immune regulation. Studies have shown that compared to CCR5+ CD103+ Tregs, CCR5- CD103+ Tregs have impaired tumor-infiltration potential [34]. Compared with BALB/c mice, CCR5-deficient mice show a significant reduction in the numbers of Tregs and apoptotic CD8+ T cells in the tumor microenvironment [35]. In summary, in colorectal cancer, researchers are more focused on the role and mechanisms of CCR5 in tumor progression and the tumor microenvironment.

2.5 Prostate Cancer

The mechanism of CCR5 in prostate cancer mainly involves promoting tumor growth and regulating the tumor microenvironment. Vaday et al. found that the cell surface and protein expression of CCR5 were significantly increased in human prostate cancer cell lines and tissues [36]. Another study showed that CCR5 mRNA was detected in 89% of human prostate cancer samples, confirming the abnormal expression of CCR5 in prostate cancer [37]. Sicoli et al. found that, in an immunocompetent mouse model, v-Src-induced prostate cancer activated the CCR5 signaling pathway [38]. It has been reported that in mouse models, after the implantation of prostate cancer cell lines, MDSCs in the bone marrow express CCR5. Upon ligand binding, CCR5 MDSCs proliferate and migrate to the tumor site, forming an immunosuppressive tumor

microenvironment, thereby promoting tumor growth [33].

2.6 Pancreatic Cancer

Research on CCR5 in pancreatic cancer is limited, and its mechanism of action has not yet been clearly studied. A tissue microarray analysis of patients with pancreatic cancer showed that, compared with non-tumor pancreatic tissue, CCR5 expression in the nucleus and membrane of pancreatic cancer cells was increased. Moreover, the intensity of CCR5 expression was associated with the degree of tumor differentiation: moderately differentiated pancreatic cancer showed weaker CCR5 staining, while poorly differentiated pancreatic cancer had higher CCR5 expression [32]. Tan et al. also demonstrated that, in human pancreatic cancer and mouse pancreatic cancer models, the levels of chemokines secreted by tumor cells were increased, and these chemokines had binding affinity for the CCR5 receptor [39].

3. The Application of CCR5 in Tumor Therapy

CCR5, as a chemokine receptor related to immune function, has been detected to be overexpressed in many types of tumor cells. In addition, CCR5 plays an important regulatory role in various metastatic cancers, affecting tumor occurrence and development, influencing tumor immunosuppression and the tumor microenvironment, and is closely related to tumor prognosis and overall survival[6]. Therefore, inhibiting or knocking out the overexpression of CCR5 in cancer has become an important research direction in cancer treatment.

It is worth mentioning that the concept of CCR5 blockade therapy was initially aimed at HIV-infected patients. By inhibiting the expression of the co-receptor CCR5 in the body, it blocks the interaction between HIV and host cells [40]. Based on studies on the mechanisms of CCR5 in various tumors, this strategy has gradually been applied to cancer treatment. CCR5 small-molecule inhibitors have a small molecular weight, can effectively penetrate tumor tissue, bind to CCR5 receptors, and influence the occurrence, development, metastasis, and spread of tumors.

Further treatment strategies involve combining CCR5 inhibitors with other anti-tumor drugs, such as immune checkpoint inhibitors, other chemokine receptor inhibitors, EGFR or VEGF inhibitors, and chemotherapeutic drugs like paclitaxel, all of which can effectively enhance anti-tumor treatment effects [2, 16].

Based on CCR5's role in recruiting immune cells and its regulatory mechanisms in the tumor microenvironment, targeting CCR5 through gene editing technology to enhance the efficacy of cell therapy in tumor cells is one of the most promising cancer treatment strategies.

3.1 CCR5 Small Molecule Inhibitor

CCR5 antagonists, such as leronlimab, maraviroc, and vicriviroc, have been shown to alleviate the effect of CCR5 on tumor progression and block the metastasis process[6]. Metastasis experiments from human breast cancer xenografts to immunodeficient mice were blocked by the three CCR5 antagonists leronlimab, maraviroc, and vicriviroc through the inhibition of homing, thereby preventing tumor transplantation progression and enhancing the cytotoxic effects of DNA-damaging chemotherapeutic agents[41]. Recent studies indicate that treating cells with the CCR5 small-molecule inhibitor maraviroc blocks their proliferative capacity, suggesting that CCR5-CCL4 chemotaxis plays a key role in lung cancer metastasis[38]. Another study showed that in immunocompetent mice, maraviroc and vicriviroc reduced the metastasis of prostate cancer cells to bone, brain, and visceral organs[42]. Maraviroc can also reduce the growth of orthotopically injected colon cancer cells by limiting the accumulation of cancer-associated fibroblasts. Research in cancer patients showed that maraviroc mediates cytotoxic and apoptotic

effects in colorectal cancer cells, decreases the likelihood of gastric cancer cell dissemination, and inhibits the metastatic potential of prostate and breast cancer cells[43, 44]. Furthermore, recent reports indicate that maraviroc blockade of CCR5 can induce the repolarization of tumor-associated macrophages and produce beneficial clinical responses in colorectal cancer patients with liver metastases [1].

Another possibility includes the application of receptor-based fusion proteins or neutralizing antibodies targeting CCR5 and its ligands. In addition to the aforementioned CCR5 humanized monoclonal antibody leronlimab, it has also been reported that blocking CCR5 with anti-CCR5 antibodies in mice can inhibit the growth of B16 melanoma and the accumulation of MDSCs in tumor tissues. Furthermore, targeting the chemokine CCL5 can reduce the apoptosis of tumor-infiltrating CD8 T cells in mouse colorectal tumor models and decrease the immunosuppressive activity of MDSCs in mouse breast cancer, leading to inhibition of tumor progression in both tumor models [35, 45, 46].

These research data indicate that CCR5 small molecule inhibitors can block tumor progression and migration by preventing CCR5 from binding to its ligands, making them a promising therapeutic approach.

3.2 CCR5 inhibitor combined with other biologics treatment strategy

Programmed cell death protein 1 (PD-1) and its ligand 1 (PD-L1) signaling pathway is a key immune checkpoint that plays a critical regulatory role in tumor immune evasion. CCR5 participates in promoting tumor occurrence and development through a mechanism different from conventional immune checkpoints. Surprisingly, CCR5 inhibitors can synergize with immune checkpoint inhibitors to produce a stronger anti-tumor effect. For example, in a glioma mouse model, co-inhibition of chemokine receptors CCR2 and CCR5 increased survival and exhibited a strong synergistic effect with anti-PD-1 therapy [47]. Another study indicated that CCL5 binds to the receptor CCR5 on prostate cancer cells and activates the AKT signaling pathway, leading to upregulation of AR and PD-L1. The CCR5 antagonist maraviroc inhibits the CAF-mediated CCL5 signaling pathway, effectively reducing the expression of AR and PD-L1 and enhancing the efficacy of enzalutamide [48].

In addition, three clinical studies targeting CCR5 have been approved by the FDA for the treatment of metastatic cancer. Each study combined a drug and a biologic to treat CCR5-positive metastatic cancer. The first is a Phase I study of pembrolizumab combined with maraviroc in patients with refractory microsatellite-stable (MSS) colorectal cancer [49]. The second is a Phase II study evaluating the safety and efficacy of vicriviroc combined with pembrolizumab (MK-3475) in patients with advanced metastatic MSS colorectal cancer [50]. The third is a Phase Ib/II study using carboplatin and leronlimab to treat CCR5 metastatic triple-negative breast cancer (TNBC) [51]. This study is assessing the impact on progression-free survival, with secondary endpoints including overall response rate, circulating tumor cell counts, and benefits based on new metastasis occurrence times. These combination treatment strategies may further enhance the efficacy of CCR5 inhibitor blockade therapy by modulating the tumor immune microenvironment, inducing immune tolerance, and counteracting anti-tumor immune evasion mechanisms.

3.3 Tumor treatment strategies based on CCR5 gene editing

With the development of gene editing technology, gene therapy has become a new direction for cancer cure. Researchers have reported that CCR5 clustered regularly interspaced short palindromic repeats (CRISPR) gene editing can redirect NK cells in vivo, and this strategy has the potential to

enhance the effectiveness of adoptive NK cell immunotherapy against hematologic and solid tumors[52]. In another study, the combination of CCR5 gene editing with targeted insertion of mDHFR variants was able to effectively select CCR5-disrupted T cells, which can be easily modified for cancer immunotherapy, establishing a drug selection platform applicable to clinical T cell gene therapy[53]. Recent studies have shown that the strategy of CRISPR/Cas9 CCR5 knockout hematopoietic stem cell transplantation can simultaneously treat HIV infection and patients with hematologic malignancies[54].

CCR5 also plays a significant role in tumor immunotherapy. Studies have shown that breast tumors induced by the middle T antigen of mouse mammary tumor virus and polyoma virus (MMTV-PyMT) occur with a delay and are smaller in CCR5-/- mice[55]. Immunotherapy combined with gene editing technology has produced one of the most promising tumor treatment methods—CAR-T cell therapy. A recent study, aiming to overcome the limitations of the solid tumor microenvironment on CAR-T therapy, designed an enhanced CAR-T cell co-expressing CCR5 and IL-12 (CARTmeso-5-12). The study found that CARTmeso-5-12 cells increased CAR-T cell migration and tumor infiltration through CCR5 expression and enhanced T cell proliferation and cytotoxic activity through IL-12 overexpression, while reducing the inhibitory effects of the tumor microenvironment, thereby improving the efficacy of CAR-T cell therapy[56].

4. Outlook

Abnormal expression of CCR5 in various tumors indicates its significant clinical application potential. By targeting CCR5, the proliferation, migration, and immune evasion of tumor cells can be effectively inhibited, enhancing anti-tumor immune responses. As the mechanism of CCR5 in tumors has been gradually elucidated, based on extensive clinical experience with CCR5 inhibitors in the treatment of HIV patients, CCR5 inhibitors have further been used for cancer prevention and the treatment of metastatic cancers, showing good therapeutic effects in various cancers such as breast cancer, gastric cancer, and pancreatic ductal adenocarcinoma[2, 57, 58]. Furthermore, existing clinical treatment experience indicates that combination therapy strategies of CCR5 small molecule inhibitors with other drugs (immune checkpoint inhibitors, CCR5 monoclonal antibodies, chemotherapeutic agents, etc.) may be one of the most effective approaches for treating these tumors. Of course, these treatment methods also require more clinical studies and experimental data to verify their safety and efficacy.

With the discovery of the CRISR/Cas gene editing system, gene editing therapy has become a key technological approach to cancer treatment. Optimizing immune cells through gene editing technology, such as CAR-T cell therapy, has successfully broken through in hematologic tumors[59]. The presence of the tumor microenvironment in solid tumors severely suppresses the efficacy of general drugs and CAR-T cell therapies. Since CCR5 regulates tumor microenvironment immunosuppression in various tumors, some researchers hope to use this as a breakthrough to target CCR5 gene therapy for solid tumors through gene editing technology. Reports indicate that CCR5 gene knockout cell transplantation has achieved multiple cases of permanent cure for HIV[60]. Currently, clinical trials of CCR5 antagonists have shown that blocking or inhibiting CCR5 expression in tumor cells has a significant anti-tumor effect. Therefore, by drawing on successful cases of CCR5 gene editing technology in HIV treatment and biosafety verification, applying CCR5 gene editing strategies to cancer therapy may hold new application prospects. According to existing research reports, mature gene editing techniques targeting the chemokine receptor CCR5 of

immune cells (T lymphocytes, NK cells, B lymphocytes, etc.) can block CCR5's regulatory effect in tumors while enhancing the efficacy of immune cell therapy. This new approach combining gene therapy and immunotherapy appears to be the most promising tumor treatment strategy

In summary, research on CCR5 in tumor therapy has been increasing over the past few decades and shows a promising development trend. These studies also continue to remind us that in the near future, CCR5 may play a key role in the treatment of various tumors.

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