Review Article

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The role of the chemokine receptor CCR7 in cancer progression

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Abstract

Metastasis is the most commonly reported cause of cancer-related mortality. Therefore, elucidating the mechanisms that regulate cancer metastasis is essential. Tumor cells are known to preferentially grow in organs that promote and provide an adequate niche. Tumor metastasis is a selective process rather than a random process, which means that it has an organ specificity. It has been proposed that different organs produce distinct chemotactic factors that can attract specific types of tumor cells to home to and arrest in a particular organ. Chemokines and chemokine receptors have garnered much attention due to their roles in tumor invasion and metastasis. The chemokine receptor that we focus on is CCR7, the receptor for both chemokines CCL19 and CCL21. CCR7 has been implicated in the migration and trafficking of malignant cells in numerous types of tumors, but the mechanisms underlying these functions of CCR7 remain unclear. This review summarizes relevant perspectives on the functional mechanisms and prognostic significance of CCR7 in cancer.

Keywords: CCR7; chemokine receptor; cancer progression; functional mechanism; therapeutic strategies.

Introduction

Chemokines are a large family of chemotactic cytokines comprised of more than 50 structurally related polypeptides that act on 22 heterotrimeric Gαi-protein-coupled receptors (GPCRs) [1, 2]. Based on the presence of key cysteine residues, chemokines are classified into four subgroups (C, CC, CXC, and CX3C). They control B-cell development, growth, and survival, and modulate levels of subsets of T-cells [3, 4]. Chemokines also have roles in organogenesis and immune responses and facilitate angiogenesis [5]. Researchers have shown that chemokines have pro-inflammatory functions. In the presence of inflammatory stimuli, chemokines directly induce leukocyte recruitment to a site of an injury [5]. Chemokine receptors belong to the GPCR superfamily, which is characterized by the presence of seven transmembrane domains. After binding with their corresponding ligands, GPCR receptors are involved in a variety of physiological and pathological processes, such as cell growth, differentiation, and apoptosis. Effector molecules that are regulated by chemokines and their receptors regulate cell chemotaxis, proliferation, and motility to promote pathological mechanisms of tumors [6, 7].

The CC subfamily of chemokines is a group of cytokines with members named CCL1–28 [8, 9]. CCL1–28 function as ligands for 10 chemokine receptors (CCR1-10). The gene that encodes CCR7 is located on human chromosome 2q21 and is composed of 352 amino acids. CCR7 is commonly expressed in semi-mature and mature DCs, and activated B and T lymphocytes. It affects lymphocyte cell trafficking and homing to lymphoid glands [10-14].

The precise mechanism of CCR7 binding to CCL19 (also named EBV-induced gene 1 ligand chemokine, macrophage inflammatory protein-3 (MIP-3), and Exodus-3) and CCL21 (also named secondary lymphoid tissue chemokine (SLC), 6Ckine, or Exodus-2) [10, 15-18] involves two key steps. First, CCL19 and CCL21 interact with the N-terminus of CCR7, which causes a conformational change in CCR7. Second, CCL19 and CCL21 enters CCR7's binding pocket. The binding of the ligand to the receptor causes additional conformational changes that lead to the dissociation of a G-protein that was associated with CCR7, and facilitates signal transmission in the cytoplasm [19-21].

Conformational changes to CCR7 induce pseudopodia formation and actin polymerization, resulting in increased levels of cellular motility [22, 23]. Overexpression of CCR7 has been linked to lymph node metastases in several cancers. Further, CC chemokines play an important role in neoplasia as a result of their pro- or anti-cancer characteristics [9, 24-26]. In this review, we will summarize relevant researches on the roles of

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CCR7 and its ligands CCL19 and CCL21 in cancer progression.

Function of CCR7 in tumor growth and metastasis

Chemokine receptors facilitate tumor diffusion at different stages of tumor metastasis, including vascular extravasation, adherence to the endothelium, proliferation and colonization of tumor cells, and angiogenesis [27, 28]. A growing body of literature has recognized the contribution of CCR7 to malignant cell survival, proliferation, and chemotaxis. Crosstalk occurs between CCR7 and intracellular signaling pathways. For example, the activation of CCR7 stimulates multiple cellular pathways capable of initiating a variety of cellular responses. At the same time, various triggers regulate CCR7 expression. Ultimately, cancer cell biology is affected by a variety of factors, particularly with regard to promoting tumor metastasis.

Cell migration is determined by biochemical and physical characteristics of cells, as well those of the extracellular matrix [29]. CCR7 promotes cancer progression by controlling the tumor microenvironment, affecting immune tolerance, inflammatory responses, and T cell activation [30, 31]. In combination with CCR7, both CCL19 and CCL21 induce calcium mobilization, G-protein activation, and cell migration. Furthermore, as a chemoattractant, CCL21 creates a concentration gradient that promotes tumor lymphocyte-infiltration, which likely promotes tumor progression [32].

Hypoxic stress may enhance expression of CCR7, which has been shown to lead to an obvious increase in VEGF levels [33-36]. This promotes lymphangiogenesis, and cancer cells that overexpress CCR7 enter lymphatic vessels. Subsequently, the cells migrate to lymph nodes due to the high expression levels of CCL21 and CCL19 in lymph nodes. In addition to hypoxia, other factors that affect CCR7 expression levels in the tumor microenvironment include TNF, NF-κB, and cyclooxygenase-2 (COX-2) [37-41]. Accumulating literature has shown that chemokine responses are activated via various signaling pathways, such as JAK/STAT, PI3K/Akt, JNK, extracellular signal-regulated kinase (ERK) 1/2, GSK-3α/β, Rho/Rac, and MAPK [42-58]. Recent evidence suggests that the CCL21/CCR7 axis can promote phosphorylation of the PI3K/Akt pathway. Subsequently, a variety of intracellular targets inhibit cellular apoptosis and induce cellular survival in different types of tumor cells [59, 60]. In human non-small cell lung cancer, CCR7 prevents apoptosis via activation of the ERK pathway [61]. In leukemic cells, CCR7 enhances expression of the protooncogene c-Fos via activation of the JAK/STAT signaling pathway [62]. Further, there appears to be a correlation between CCR7 activity and that of other signaling cascades, such as NOTCH [63], twist [64], and WNT [65].

The CCL19/CCL21-CCR7 axis plays a significant role in the endothelial-mesenchymal transition (EMT) that occurs throughout tumor progression [49, 64, 66-69] by inducing mesenchymal phenotypes. CCR7 promotes the EMT via multiple approaches, including the upregulation of vimentin and N-cadherin levels, the downregulation of E-cadherin [45, 64], and enhancing the phosphorylation of ERK, which subsequently regulates NF-κB [47, 70, 71]. Thus, an inhibitor of CCR7 would likely suppress EMT and attenuate tumor cell proliferation and metastasis [45, 72]. Anti-cancer effects of CCL19/CCL21-CCR7 have been reported; however, they are not well understood. Several studies have suggested that high levels of either CCL19 or CCL21 in tumors are associated with increased infiltration of anti-cancer tumor infiltrating lymphocytes (TILs), which improves prognosis [73-76].

In brief, CCR7, promotes lymph node cancer metastasis via multiple functional mechanisms. However, mechanistic details regarding the role of CCR7 in cancer remain poorly understood.

Expression of CCR7 throughout cancer progression

In 2001, Müller [22] suggested that the upregulation of CCR7 expression enables cancer cells to metastasize along CCL21 and CCL19 concentration gradients that increase as they approach lymph nodes. CCR7 has been reported to be associated with lymphatic metastases and poor prognosis in several cancers, including malignant melanoma [77], breast cancer [78], gastric cancer [79], lung cancer [65], head and neck carcinoma [80], colorectal cancer [81], esophageal squamous cell carcinoma [83], and pancreatic ductal adenocarcinoma [83].

CCR7 expression in breast cancer

The CCL19/CCL21-CCR7 axis has been reported to stimulate lymphangiogenesis and angiogenesis via the upregulation of VEGF-C in breast cancer. In turn, downregulation of VEGF-C reduced CCR7 expression by modulating ERK, MAPK, and Akt/PKB signaling pathways [84]. Zlotnik [85, 86] suggested that CCR7 may promote lymph node metastasis because breast cancer cells express CCR7, while CCL21 and CCL19 are abundant whithin lymphatic cells. Hypoxia can increase CCR7 expression in breast cancer by stimulating hypoxia-inducible factor 1 [87]. The CCL19/CCL21-CCR7 axis may control EMT progression and facilitate the invasion and migration of breast cancer cells by inducing several signaling pathways [88]. Müller [22] suggested that functions of CCR7 including chemotaxis, actin polymerization, and invasion are induced by stimulation with CCL21. In their model, breast cancer cells expressing CCR7 that were stimulated with CCL21 displayed increased F-actin polymerization, pseudopodia formation, and directional migration and invasion.

In breast cancer, CCR7 induces cytoskeleton remodeling and chemotaxis. However, these effects have only been observed in malignant breast cancer cells [89]. Chemotaxis in non-malignant cells is not inducible because functional Gαi signaling is only observed in invasive cancer cells after CCL19 treatment [90]. A recent study by Gurgel (2020) [91] assessed the difference between CCR7 expression in the cytoplasm and membranes and revealed a correlation between CCR7 expression and prognosis in breast cancer patients. Findings indicated that overexpression of cytoplasmic CCR7 is positively associated with breast cancer recurrence. Likewise, Liu [92] found that elevated expression of cytoplasmic CCR7 is associated with reduced rates of survival. Thus, inhibitors of CCR7 have

the potential to improve outcomes of breast cancer treatment when used in combination with classic chemotherapy or immunotherapy. Further studies will be needed to clarify mechanistic details of effects of CCR7 inhibitors.

CCR7 expression in colorectal cancer

The relationship between the CCL19/CCL21-CCR7 axis and colorectal cancer metastasis remains controversial [93]. A recent study reported an association between increased infiltration of CCR7+ T-cells and advanced colorectal cancer [94]. Günther et al. [95] also revealed a close connection between CCR7 expression and lymphatic metastasis in colorectal cancer. In addition, CCR7 knockdown has been shown to reduce colorectal cell invasion in vitro and inhibit lymph node metastasis in an animal model [96]. However, some studies revealed no significant correlation between CCR7 and colorectal cancer metastasis [93]. Gao et al. [81] investigated the correlation between CCR7 and Cetuximab resistance in colorectal cancer cell lines. Cetuximab, a monoclonal antibody that inhibits the epidermal growth factor receptor (EGFR), is routinely used in the treatment of colorectal cancer [97]. Their finding revealed (1) the CCL21/CCR7 axis promotes the EMT in colorectal cancer cells, (2) CCL21 may stimulate EGFR expression, and (3) CCR7 facilitates Cetuximab resistance via the PI3K/AKT pathway. These results suggest that CCR7 plays a crucial role in Cetuximab resistance. Therefore, inhibitors of CCR7 or CCL21 could be effective for inhibiting both the EMT and Cetuximab resistance in colorectal cancer. Additionally, a recent study showed that chemokines promote EGFR activation by inducing the production of reactive oxygen species [98]. This could explain why overexpression of CCL21 promotes colorectal cancer invasion.

CCR7 expression in melanoma

CCR7 expression has been identified as an independent predictor of poor survival and is closely linked with lymphatic dissemination in uveal melanoma [99]. In a study conducted by Cristiani [77], both overexpression of CCR7 and CCL19 secretion were observed in melanoma cell lines. Researchers found that CCR7 was expressed more highly in metastatic tumors than primary tumor lesions. Moreover, the more advanced the stage of melanoma, the higher the CCL19 level tended to be in serum, a finding that may have been due to the increased number of cancer stem cells present at advanced stages of disease. As a result of combined effects of CCR7 overexpression in cancer stem cells and high levels of CCL19 in blood, cancer stem cells migrate from the skin to peripheral blood. Thus, melanoma cell metastasis relies on the expression of CCR7 [77]. These results provide further support for the hypothesis that the use of a CCR7 inhibitor could interfere with the progression and metastasis of melanoma.

CCR7 expression in lymphoma and leukemia

Research by Rehm et al. [100] revealed that lymphoma cells and fibroblastic reticular cells interact. CCR7-positive lymphoma cells localize to lymph nodes, while CCL19 and CCL21 are secreted by fibroblastic reticular cells. Lymphotoxins secreted by lymphoma cells stimulate lymphotoxin receptor-positive fibroblastic reticular cells. Therefore, CCR7-negative lymphoma cells have a survival disadvantage over CCR7-positive lymphoma cells. In human T-cell leukemia, a high level of CCR7 expression was found to be associated with distant dissemination [53].

CCR7 expression in other cancers

The anticancer effects of CCR7 are controversial. A recent meta-analysis showed that CCR7 expression is a prognostic factor for poor survival in patients with gastric cancer [101]. Zhang et al. [102] suggested that the CCL19/CCR7 axis induces the EMT and promotes tumor progression in gastric cancer. Conversely, CCL19 overexpression has been shown to inhibit proliferation and metastasis in gastric cancer cells by upregulating the CCR7/ Absent in melanoma 2 pathway [79]. Further, a different study found no correlation between CCR7 expression and lymph node metastasis in gastric cancer [103].

A similar situation exists in non-small cell lung cancer, within which CCR7 has been implicated in the EMT, lymphangiogenesis, and apoptosis [14, 69, 104]. CCR7 inhibition suppressed the EMT and facilitated NF-κB-dependent apoptosis in lung cancer cells. Xu et al. [105], indicating that CCR7 activation promotes cellular proliferation by enhancing ERK, cyclin A, and cyclin B1 phosphorylation. However, different viewpoints exist. CCR7, in a separate study, was linked to improved postoperative prognosis in lung cancer patients [106], a completely contradictory result. These findings indicate that the role of CCR7 in the progression of non-small cell lung cancer is complex, and further studies will be needed to discern its precise role in disease progression. In conclusion, many lines of evidence indicate that CCR7 expression correlates with cancer metastasis, however, contradictory findings have been reported. Observed inconsistencies may be due to the varying characteristics and stages of cancer cells assessed [36, 107,108].

Therapeutic strategies based on the inhibition of CCR7 expression

Metastasis is one of the principal causes of cancer-related mortality [109]. However, most treatments targeting metastatic cancer continue to target the primary disease, rather than the metastatic process. Targeted cancer therapy involving the inhibition of CCR7 expression has garnered increasing attention. The use of monoclonal antibodies, small molecule antagonists, and targeted siRNA are options for inhibiting metastatic progression. Yu et al. [96] revealed that CCR7 siRNA may inhibit colon cancer metastasis. In another study, a potential regulator of tumor growth, miRNA let-7a, reduced levels of CCR7 expression in breast cancer [110]. Anti-CCR7 antibodies have also been used in cancer treatment. In T-cell acute lymphoblastic leukemia, anti-CCR7 antibodies inhibited leukemia cell migration to the central nervous system by blocking CCR7 activity [111]. In addition, the monoclonal CCR7 inhibitory antibody has already been shown to have significant anti-tumor effects against MCL and CLL [112, 113]. To date, few small-molecule antagonists of CCR7 have been reported. Cosalane has been identified as a relatively potent inhibitor of CCR7 [114]; however, other potential small molecule inhibitors of CCR7 have not yet been tested [115].

Conclusion

In summary, the regulation of expression levels of the chemokine receptor CCR7 plays a crucial role in oncogenesis and tumor progression. Increased CCR7 expression is associated with poor survival and has the potential to be used as a prognostic

marker for numerous types of cancers. The targeted blockade of CCL21/CCL19-CCR7 pathways will likely serve as an important mechanism for developing novel cancer therapies in the future. However, the role of CCR7 in cancer is not completely understood, and possible mechanisms by which CCR7 affects different cancers require further clarification.

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