CCL7 Signaling in the Tumor Microenvironment

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Abstract

The tumor microenvironment is the primary location in which tumor cells and the host immune system interact. There are many physiological, biochemical, cellular mechanisms in the neighbor of tumor which is composed of various cell types. Interactions of chemokines and chemokine receptors can recruit immune cell subsets into the tumor microenvironment. These interactions can modulate tumor progression and metastasis. In this chapter, we will focus on chemokine (C-C motif) ligand 7 (CCL7) that is highly expressed in the tumor microenvironment of various cancers, including colorectal cancer, breast cancer, oral cancer, renal cancer, and gastric cancer. We reviewed how CCL7 can affect cancer immunity and tumorigenesis by describing its regulation and roles in immune cell recruitment and stromal cell biology.

Keywords

CCL7 · Tumor microenvironment · CCRs · Pro-tumor effect · Antitumor effect · Cancer-associated fibroblast · Cancer-associated adipocytes · Proliferation · Metastasis · Immune cell infiltration · Tumor-associated macrophage · Prognosis · Immunotherapy · Combination treatment · Clinical trials

4.1 Physiological Roles of CCL7

Chemokines comprise a large superfamily of at least 46 cytokines initially described based on their ability to bind to seven transmembrane domain G protein-coupled receptors to induce directed migration of leukocyte subsets to sites of inflammatory site or tumor microenvironment (TME) [1]. Their ligands can bind to extracellular N-terminus of receptors and lead to phosphorylation of serine/threonine residues on their cytoplasmic C-terminus, causing signaling and receptor desensitization [1]. Chemokine and chemokine receptor pairs not only mediate cellular migration but also affect many cellular functions, including survival, adhesion, invasion, and proliferation by regulating chemokine levels [2, 3]. Chemokines are classified into four groups (CXC, CC, C, and CX3C) based on the position of the first two cysteines [4, 5]. CXC chemokines act predominantly on neutrophils and T lymphocytes while CC chemokines are active on

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various cell types, including monocytes and lymphocytes [6–8]. Chemokine (C-C motif) ligand 7 (CCL7), also known as monocyte chemotactic protein 3 (MCP-3), is a member of chemokine ligand subfamily first characterized from osteosarcoma supernatant [9]. CCL7 is expressed in various types of cells (including stromal cells, immune cells, and airway smooth muscle cells) under physiological conditions and tumor cells under pathological conditions. CCL7 is a potent chemoattractant for a variety of leukocytes, including monocytes, eosinophils, basophils, dendritic cells (DCs), natural killer (NK) cells, and activated T lymphocytes [10, 11]. CCL7 is also highly expressed in advanced renal cancer, gastric cancer, colorectal cancer, and squamous cancer cells [12–15]. Ligands for chemokine receptors CCR1, CCR2, CCR3, and CCR5 can recruit macrophages to the TME [16]. Neutrophils and myeloid-derived suppressor cells (MDSCs) are recruited to the tumor through ligands for CCR2, CCR3, CXCR1, CXCR2, and CXCR4. Tregs express chemokine receptors CCR2, 3, 4, 6, 7, 8, and 10, CXCR3, and CXCR4 [17–25]. Among these receptors, CCR1, CCR2, CCR3, and CCR5 are widely known as the main functional receptors of CCL7 [26–28]. In this chapter, we will describe the role of CCL7 and its receptors in TME. We will also review how CCL7 and its receptors can affect cancer immunity and tumorigenesis in various types of tumor.

4.2 Opposite Role of CCL7 Signaling in the Tumor Microenvironment

Cross talk between tumor cells and their environment in peripheral TME is an important factor that affects tumor progression. Stromal cells including fibroblasts, macrophages, adipocytes, and others are components of the TME [29, 30]. Interactions between stromal cells and tumor cells are formed by a variety of soluble factors including inflammatory cytokines, growth factors, and chemokines secreted by tumor cells or stromal cells [31, 32]. CCL7 is an important molecular regulator in the reciprocal interaction between stromal cells and tumor cells. It not only participates in tumorigenesis (Table 4.1) but also exerts antitumor responses in particular contexts [33].

Table 4.1 Pro-tumoral effect of CCL7 in the tumor microenvironment

Cancer type	Cancer cell types	Producer (stimulator)	Recipient/signaling type (receptor)	Physiological effects	Ref.
Colorectal cancer	Patient sample	Colorectal cancer cells	Autocrine (CCR1, 2, 3, 5)	Enhances liver metastasis	[14]
Colorectal cancer	HCT116, HT29	Colorectal cancer cells	Autocrine (CCR3)	Enhances proliferation and promote migration, metastasis	[35]
Colorectal cancer	LS174T, CL-188	Kupffer cells	Hepatic stellate cells	Enhances liver metastasis	[46]
Oral cancer	YD-10B, YD-38, HSC-2, HSC-3	Cancer-associated fibroblast	Oral cancer cells (CCR1,3)	Enhances invasion	[12]
Oral cancer	YD-10B, YD-32, YD-38, HSC-2	Cancer-associated fibroblast	Oral cancer cells	Enhances cancer progression	[59]
Renal cancer	Patient sample	Renal cancer cells	Tumor-associated macrophage (CCR2)	Enhances brain metastasis	[13]
Renal cancer	A498, 769P, 786O, Caki-1, Caki-2	Renal cancer cells	Autocrine, endocrine	Enhances macrophage infiltration, tumor growth, metastasis	[34]
Gastric cancer	N.D.	Gastric cancer cells	Autocrine	Enhances lymph node metastasis and poor prognosis	[15]
Gastric cancer	C57BL6 mouse tissues	Adipose tissue	Paracrine, endocrine	Enhances macrophage recruitment	[67]

(continued)

Table 4.1 (continued)

Cancer type	Cancer cell types	Producer (stimulator)	Recipient/signaling type (receptor)	Physiological effects	Ref.
Breast cancer	Cal51, mda-mb-231, HFFF2	Cancer-associated fibroblast	Breast cancer cells (CCR1)	Enhances proliferation	[58]
Breast cancer	MDA-MB-231	Astrocytes	Breast cancer (CCR1)	Enhances self-renewal of tumor-initiating cells	[68]
Prostate cancer	LNCaP, C4-2B, Du-145, PC-3	Cancer-associated adipocytes	Prostate cancer cells (CCR3)	Enhances migration	[66]
Lung cancer	H1650	Neutrophils	Lung cancer cells	Enhances tumorigenic properties	[48]
Hepatocellular carcinoma	Huh-7, PLC	Cancer-associated fibroblast	Hepatocellular carcinoma cells (CCR1,2,3,5)	Enhances metastasis	[56]
Melanoma	B16-F0	Tumor cell-derived exosomes-educated mesenchymal stromal cells	Melanoma cells (CCR2)	Enhances macrophage recruitment and tumor growth	[71]
Laryngeal squamous cell carcinoma	Patient sample	Cancer-associated fibroblast	Laryngeal carcinoma cells (CXCR4)	Enhances tumor-supporting	[57]

Table 4.2 Antitumoral effect of CCL7 in the tumor microenvironment

Cancer type	Cancer cell types	Producer (stimulator)	Physiological effects	Ref.
Cervical carcinoma	HeLa	Cervical carcinoma cells	Enhances infiltration of macrophage, dendritic cells, and NK cells	[73]
Mastocytoma	P815	Mastocytoma cells	Enhances T cell activation and tumor rejection	[74]
Melanoma	B16, K1735	Melanoma cells	Enhances depletion of CD4, CD8, and NK cells	[75]
Pancreatic cancer	Panc-1	Pancreatic cancer cells	Enhances NK cell infiltration	[76]
Colorectal cancer	CMT93	Colorectal cancer cells	Enhances immune cell infiltration	[77]

Increased CCL7 levels can recruit monocytes to sites at the tumor periphery. This helps in the formation of an environment suitable for carcinoma progression and promotes monocytes to complete phenotypic transformation. CCL7 can also recruit leukocytes and activate antitumor immune responses (Table 4.2). Here, we will focus on the opposite roles of CCL7 based on original cells of CCL7 in various tumor types.

4.2.1 Pro-tumor Effect of CCL7

4.2.1.1 Signaling Induced by Tumor-Derived CCL7

CCL7 can act as a tumor-induced factor that can promote tumor growth, invasion, and metastasis by autocrine in metastatic renal cell carcinoma (RCC) rather than in primary RCC [13]. High CCL7 expression in RCC evokes the recruitment of tumor-associated macrophages (TAMs) that present CCR2 on their surface membrane, thus increasing vascular permeability. RCC cells can cross through blood-brain barriers to brain tissues [13]. microRNA Let-7d can specifically bind to the 3′UTR (untranslated region) of CCL7 mRNA and modify the expression of CCL7 in a negative feedback manner. The expression of let-7d is reduced in RCC, resulting in a large amount of CCL7 [34]. As a result, CCL7 plays an indirect role in RCC metastasis through the let-7d-CCL7-TAM axis. Pro-tumorigenic properties of CCL7 have also been confirmed in colorectal cancer (CRC) cells [14]. In vitro and in vivo CCL7 overexpression by lentiviral transduction can increase the proliferation, migration, and invasion of CRC cells [35]. In addition, by

binding to CCR3, CCL7 overexpression can activate the ERK/JNK signaling pathway that converges on downstream pathways of the MAPK cascade, thereby participating in the epithelial-mesenchymal transition (EMT) process that is sufficient to enhance cancer cell metastasis. Clinical studies have shown that CCL7 expression is higher in liver metastatic tumor tissues compared to primary CRC tissues, suggesting that CCL7 can promote CRC liver metastasis [14, 35]. In prostate cancer, PC3 cells can secrete more pro-metastatic factors, including CCL7 and TGF-β, thus accelerating the growth of prostate cancer and the rate of bone metastasis [36].

4.2.1.2 Signaling Induced by Immune Cells-Derived CCL7

Immune cells in the TME can promote tumor angiogenesis and suppress antitumor reaction of several activated immune cells, thus positively affecting tumor development process. Chemokine CCL7 was initially identified as a cytokine in mononuclear cells [37]. It can act on a variety of target cells, including neutrophils, eosinophils, basophils, NK cells, T lymphocytes, other inflammatory cells, DCS, and mononuclear cells, particularly monocytes [37–39]. In the last decade, many studies have shown that TAMs are closely related to tumor progression [40]. It has been found that TAMs differentiated through interaction with tumor cells are involved in immunosuppression, migration, and metastasis [41, 42]. Consistently with these functions of TAMs, studies using human tumor samples have shown that high density of TAMs with M2 phenotypes is closely linked to worse clinical prognosis, especially in many types of malignant tumors such as lung cancer, breast cancer, ovarian cancer, and bladder cancer [40–43]. Polarization signaling of TAM and TAM itself are new immunotherapeutic targets for malignant tumor treatment [44, 45]. Alcoholic liver damage is considered a high risk factor for colorectal cancer liver metastasis (CRLM) [46]. Overexpression of CCL7 in Kupffer cells (KCs), human liver macrophages, can create a favorable microenvironment for CRLM. The cascade begins with CCL7 and alcohol-stimulating KCs which express anti-inflammatory cytokine [46]. These stimuli can promote the potential ability of hepatic stellate cells (HSC) and enable the liver to become an important component of the metastatic niche. In pancreatic cancer, CCL7 mRNA levels are markedly increased after stimulating monocytes with thymic stromal lymphopoietin which is produced by activated cancer-associated fibroblast (CAF) [47]. CCL7 secretion by monocytes contributes greatly to the recruitment of basophil to tumor-draining lymph nodes (TDLN). Neutralizing antibody of CCL7 can partially block the recruitment of basophils to the TDLN. IL-4-positive basophils show greater accumulation in TDLNs than in non-TDLNs. This is relevant to Th2 inflammatory responses, indicating poor prognosis in pancreatic cancer patients with high proportion of basophils [47]. CCL7 is also secreted irregularly by neutrophils. It can increase the movement of human non-small cell lung cancer (NSCLC) cells so that cancer cells can metastasize to bone tissues [48, 49].

4.2.1.3 Signaling Induced by CAF-Derived CCL7

Cancer cells participate in the creation of a favorable microenvironment by interacting with stromal cells and triggering the homing of a variety of cells to the tumor site. Among cells affected by cancer cells, CAFs have both fibroblastic and mesenchymal stromal cell (MSC) origin [50, 51]. CAFs can promote tumor growth through direct stimulation of cancer cell proliferation, increasing angiogenesis, and recruitment of immune cells into TME [52]. Via interacting with tumor cells, activated CAFs can enhance the secretion of matrix metalloproteinase (MMP), chemokines, and growth factors to promote tumor migration [53, 54]. Compared to normal fibroblasts, CAFs are more numerous. In addition, they express higher quantities of mesenchymal markers such as E-cadherin. Furthermore, CAFs can significantly increase hepatocellular carcinoma (HCC) cell migration by inducing epithelial mesenchymal transition (EMT) in HCC cells in vitro [55]. CAFs also have powerful effects on HCC metastasis in vivo. CCL7 can activate the

TGF-β pathway by enhancing Smad2 phosphorylation. Blocking the TGF-β pathway markedly can inhibit effects of CCL7 on HCC tumor migration and invasion [56]. This study has highlighted the role of CCL7 in regulating tumor progression by influencing the TME via the TGF-β pathway [56]. In a coculture system of CAF and laryngeal squamous cell carcinoma, CCL7 protein levels are elevated, accompanied by rapid tumor cell proliferation with increasing CXCR4 expression [57]. A further study showed that CAF-derived CCL7 mainly promoted breast cancer cell proliferation by binding to its receptor CCR1 [58]. IL-1α secreted by oral squamous cell carcinoma (OSCC) can induce CCL7 release from activated stromal fibroblasts and stimulate CAF proliferation [59]. At the same time, CCL7 generated by CAF is the main promoter of OSCC cell migration and invasion. It guides cytoskeletal transformation and enhances cell dissemination and membrane disarrange [12, 59].

4.2.1.4 Signaling Induced by CAAs-Derived CCL7

It has been previously thought that obesity can serve as a risk factor of cancers such as breast cancer, prostate cancer, renal cancer, and gastrointestinal cancer [60]. Many studies have shown that cancer-associated adipocytes (CAAs) can produce cytokines, adipokines, chemokines, and MMP that can promote tumor initiation, progression, and metastasis [61, 62]. Furthermore, obese cancer patients show poor survival outcomes in prostate cancer, breast cancer, and CRC [63–65]. Inhibition of CCL7/CCR3 axis blocks the ability of adipocytes to enhance tumor cell migration. This means that CCL7/CCR3 interaction plays a crucial role in obese prostate cancer progression [66]. Increased expression of CCL7 can positively enhance proinflammatory reaction feedback loop and modulate immature monocytic myeloid cells mobilization in gastric TME [67]. Furthermore, in adipose tissue of obese mice, *Helicobacter felis* infection can induce macrophage accumulation and expression of CCL7 [67].

4.2.1.5 Signaling Induced by Other Cells-Derived CCL7

Astrocytes can secrete high levels of CCL7 when they are stimulated with cyclooxygenase 2 (COX2) and MMP-1 [68]. The axis of COX2-MMP-1/CCL7 can promote self-renewal of breast cancer and its brain metastasis [68]. Truncated CCL7 cleaved by MMP-13 can eliminate the action of its corresponding receptors. The cleaved CCL7 becomes part of the negative feedback loop, which in turn increases MMP-13 and osteolysis. Thus, malignant breast cancer MDA-MB-231 cells are easy to move to the bone [69]. CCL7 produced by bone marrow (BM) stromal cells can act as a chemoattractant for human multiple myeloid cells via CCL7/CCR2 interaction [70]. CCL7 plays a pivotal role in the recruitment of macrophages by tumor cell-derived exosome-educated mesenchymal stromal cells (MSCs) via binding to CCR2 on melanoma cells [71]. Overexpression of CCL7 by MSCs increases its interaction with neighboring immune cells and facilitates macrophage infiltration, making tumor microenvironment suitable for tumor self-renewing [72]. As shown in Fig. 4.1, CCL7-related signaling plays a pivotal role in tumor microenvironment to enhance tumorigenesis.

4.2.2 Antitumor Effect of CCL7

CCL7 is generally recognized as inflammatory cytokine. T lymphocytes and DCs activated by CCL7 play an important role in mobilizing immune responses to resist tumor growth. Transduced model of CCL7 using parvovirus which overexpresses CCL7 in cervical cancer tumor shows tumor regression and immune cell infiltration such as NK cells and macrophages in xenograft model [73]. Furthermore, CCL7 overexpression increases recruitment of leukocytes and triggers type I T cell-dependent reactions, evoking an antitumor cascade [74]. CCL7 gene transfer to mastocytoma cells causes reduced tumorigenicity, enhanced neutrophil recruitment to the tumor, and DC infiltration in peritumoral

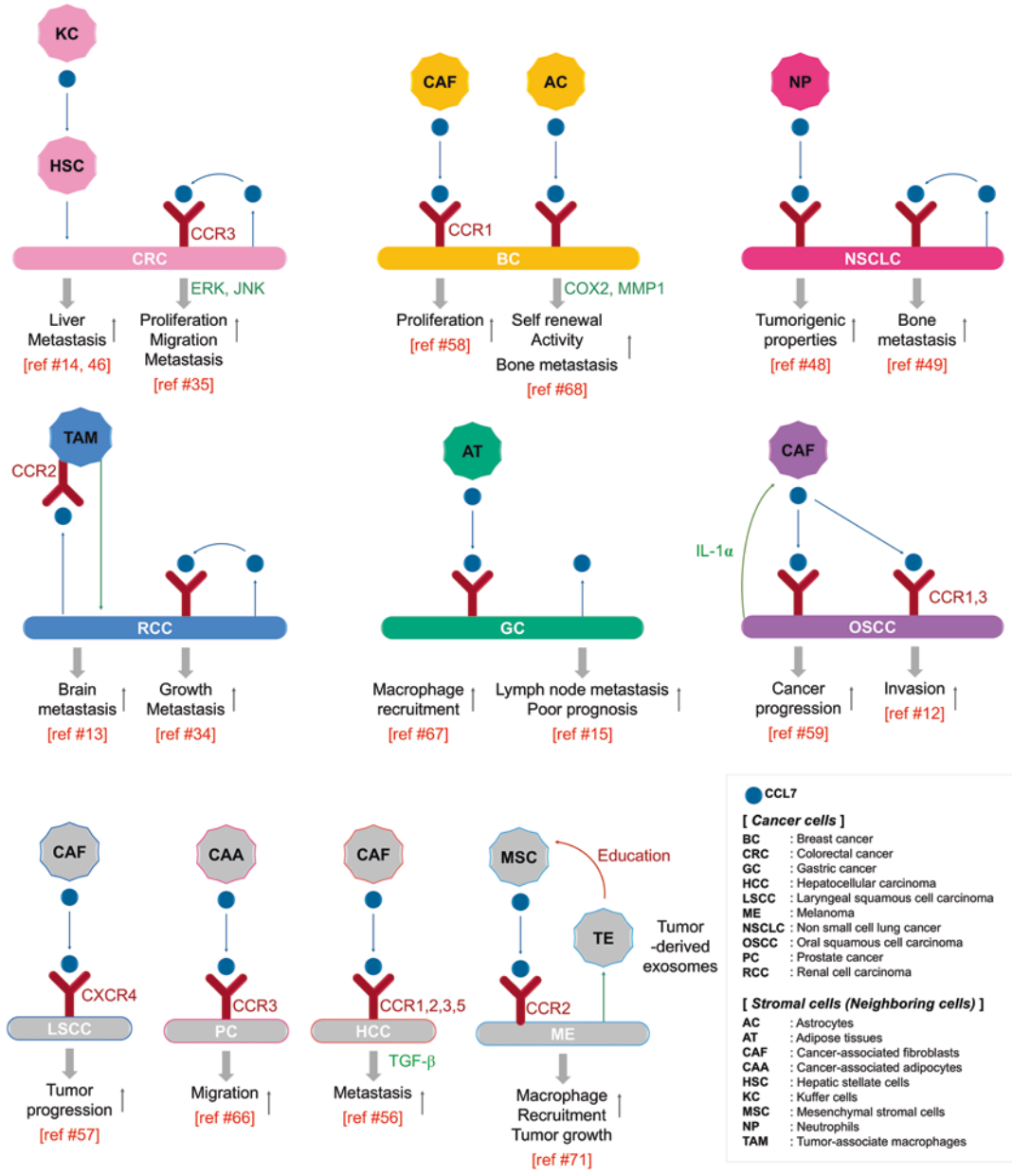

Fig. 4.1 The role of CCL7 signaling in tumor microenvironment

tissue [74]. CCL7-transduced melanoma cells also show strongly inhibited tumor growth in mice [75]. Such tumor regression is partly mediated via recruited CD4, CD8 T cells, and NK cells [75]. Another parvovirus-mediated CCL7 overexpression model of PDAC study has shown that CCL7 can activate and recruit NK cells and monocytes to enhance antitumor responses [76]. In addition to controlling tumor growth, CCL7 also impedes tumor metastasis in a mouse colon cancer model [77]. In brief, parvovirus-mediated transduction of CCL7 to cancer cells can reduce tumor progression through activated immune cell infiltration. In other words, CCL7 might be a strong activator of immune surveillance via recruiting immune cells to the TME.

4.3 Immunotherapy Landscape and Future Direction

As described earlier, the role of CCL7 in the tumor microenvironment has been consistently investigated over the last three decades since it was first identified in osteosarcoma cell (MG-63) supernatant [9]. Because CCL7 is derived from various normal cells [39, 78] as well as tumor microenvironmental cells, its physiological roles in the living body are profoundly complicated. Since CCL7 can bind to multiple seven-transmembrane receptors in normal physiology and plays a crucial role, anti-CCL7 antibody or such ligand targeting may inhibit other signaling pathways that are crucial for sustaining normal homeostasis. Therefore, rather than targeting chemokine itself, targeting chemokine receptors is an ideal immunotherapeutic strategy. Many preclinical models and clinical trials have been performed to validate their roles in actual patient's survival. In fact, anti-CCR4 monoclonal antibody and CXCR4 antagonist are already in the stage of clinical practice for various tumors [79–81]. Regarding CCL7 receptors, CCR1, CCR2, CCR3, and CCR5 have been investigated in preclinical studies. Clinical trials on CCR1, CCR2, and CCR5 in multiple myeloma, colorectal cancer, pancreatic cancer, and breast cancer have also been performed [82–86]. Although the role of CCR3 as a receptor for CCL7 has been revealed in many cancer types, clinical trials on CCR3 have not been reported yet. Because inhibiting chemokine receptor shows potential clinical value itself or when it is combined with immune checkpoint inhibitors, studies on chemokine receptor such as CCR3 might give encouraging results. Therefore, strategies targeting CCL7 receptors might be useful in the future to overcome poor survival outcomes of patients.

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