CCL20 Signaling in the Tumor Microenvironment

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Abstract

CCL20, as a chemokine, plays an important role in rheumatoid arthritis, psoriasis, and other diseases by binding to its receptor CCR6. Recent 10 years' research has demonstrated that CCL20 also contributes to the progression of many cancers, such as liver cancer, colon cancer, breast cancer, pancreatic cancer, and gastric cancer. This article reviews and discusses the previous studies on CCL20 roles in cancers from the aspects of its specific effects on various cancers, its remodeling on tumor microenvironment (TME), its synergistic effects with other cytokines in tumor microenvironment, and the specific mechanisms of CCL20 signal activation, illustrating CCL20 signaling in TME from multiple directions.

Keywords

CCL20 · Tumor microenvironment (TME) · CCR6 · NF-κB · Chemokine · Cytokine · Cancer · Dendritic cells (DCs) · Regulatory T cells (Tregs) · T helper 17 cells (Th17 cells)

6.1 Introduction

The growth process of tumor is regulated not only by its own internal signals but also by many external factors. These external regulatory factors come from the tumor microenvironment (TME) in which cancer cells are located [1–5]. More and more studies have shown that tumor growth is not an independent development process, but a complex regulatory process influenced the tumor microenvironment. These regulatory processes further affect the initiation of cancer, tumor growth, metastasis, drug resistance, recurrence of cancer, and so on. Tumor microenvironment is often a kind of tissue environment which has been reconstructed by tumor cells. That is to say, it often promotes the progress of cancer. What is more interesting is that some immune cells with normal functions gradually weaken or even lose their antitumor ability after they infiltrate into the tumor tissues, which further proves the reprogramming ability of tumor cells to the microenvironment [6–11]. Therefore, if the microenvironmental factors can be taken into account in studying the mechanism of cancer

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development, more useful and feasible anticancer strategies may be discovered. Recent findings suggest that in the course of anticancer treatment (such as chemotherapy and radiotherapy), some measures targeting the altered TME can be taken to improve the therapeutic effect of tumors. Recurrence of cancer is a process in which a small number of residual cancer cells recover their proliferative ability and lead to the growth of tumor again under the support of specific environment after treatment. Why can't the body's own immune system recognize and clean up the remaining cancer cells? If the normal tissue environment (such as normal antitumor immune function) can be effectively restored in the lesion site, the re-proliferation of cancer cells may be inhibited.

However, targeting the tumor microenvironment is not very easy. Tumor microenvironment is highly heterogeneous [12–15]. Firstly, the components of tumor microenvironment are complex, including tumor cells, fibroblasts, T cells, B cells, NK cells, macrophages, DC cells, pericytes, endothelial cells, mesenchymal stem cells, adipocytes, red blood cells, and other components, such as the exosomes and cytokines produced by these cells and extracellular matrix. Moreover, some cells are in different states induced by different environments. Tumor-associated macrophages (TAM) can be further classified into type I, type II, and other types due to their different differentiation, and the effects of different subtypes of macrophages on cancer are diverse [16–20]. These various cells in the microenvironment can regulate each other, thus forming a complex network related to cancer progression. Secondly, tumors occurring in various organs and tissues differ greatly because of their specific physiological environments. For example, chronic inflammation may exist before cancer initiation such as colon cancer, stomach cancer, and liver cancer, but rarely in glioma and breast cancer. Thirdly, the composition of tumor microenvironment is also different during the distinct stages of cancer development. The infiltration of multiple immune cells may be different between early- and late-stage tumors. It is possible that as tumors progress, the types and numbers of cells recruited and infiltrated into the microenvironment become more complex, and treatment becomes more difficult. In addition, after cancer cells are stimulated differently (e.g., with different therapeutic drugs), they may become resistant to treatment. And drugs can also lead to changes in the microenvironment, and the ultimate result may be to further enhance the resistance of cancer cells to drugs. In the treatment of cancer patients, the tumor microenvironment is not constant, but a dynamic process. All in all, the above factors may affect the complexity of tumor microenvironment and lead to its high heterogeneity.

Cytokines, produced by stromal cells or cancer cells, are an indispensable factor in tumor microenvironment formation [21–26]. Because cytokines can be secreted outside the cell, and can reach to a distant location, even as the circulatory system spreads, its influence range is extensive through the mode of autocrine or paracrine, establishing plenty of connections between tumor cells, or tumor cell and stromal cells [27–30]. Cytokines can transfer stimuli from the environment to cancer cells and promote their tolerance to environmental stress. In turn, cancer cells can create favorable conditions by secreting specific cytokines to act on a variety of microenvironmental stromal cells expressing the corresponding receptors. If we call cytokines in microenvironment as messengers, then they play the role of transmitting different signals in the environment. Tumor cells and stromal cells in the environment are the recipients of this information. For example, many studies have shown that IL-6, IL-8, TGF-beta, and other factors are closely related to the malignancy of multiple cancers. Chemokine, as the subfamily of cytokines, can recruit specific cell types, mainly those related to immune function. The presence of chemokines provides a vital condition for the infiltration of immune cells in tumor microenvironment [31–33]. Therefore, chemokines are very important for the formation and remodeling of tumor microenvironment, and also have a great impact on cancer progression. More importantly, chemokines not only have the

ability of recruiting specific cells, but also have the function of signal transduction (ligand-receptor binding). In other words, through chemokines, cancer cells can not only recruit specific cells, but also transmit "friendly" signals to these cells, further reprogramming the microenvironment to be conducive to their survival.

CCL20 is a member of chemokine family. It has antimicrobial activity and is related to arthritis, psoriasis, and other diseases in pathology [34–37]. Recent studies have shown that high levels of CCL20 are associated with malignancies of various cancers. Importantly, CCL20 can recruit immune cells such as DC cells and Treg cells, which further links CCL20 with tumor microenvironment. This chapter will review and discuss the regulation of CCL20 on various cancers, the remodeling of tumor microenvironment mediated by CCL20, the synergistic regulation of CCL20 and other factors on microenvironment, and the activation and transmission of CCL20 signaling in tumor microenvironment.

6.2 CCL20 Signaling

Chemokines are a class of inducible secretory proteins with a molecular weight of 8–10 kDa produced by a variety of cells and participate in the activation, chemotaxis, and migration of white blood cells, and play an important role in inflammation and immune response. Chemokines also have a positive impact on angiogenesis, hematopoiesis, and organogenesis. According to the arrangement of conservative cysteine at N-terminal, chemokines can be divided into four subfamilies, C, CC, CXC, and CX3C. CCL20, belonging to the CC subfamily of chemokines, also known as macrophage inflammatory protein 3 alpha (MIP3α), Liver and Activation Regulated Chemokine (LARC), and Exodus-1, was first discovered and characterized in hepatocytes [38]. CCL20 gene contains four exons and three introns. Due to the alternative splicing between the first intron and the second exon, two kinds of mRNA encoding CCL20 are produced. After translation and signal peptide removing, CCL20 contained only 70/69 amino acid residues. Since the initial discovery of CCL20 (a small ~8 kDa protein) in the early 1990s, it was gradually demonstrated that CCL20 is primarily expressed in the liver, colon, prostate, cervix, and skin. CCL20 is related with rheumatoid arthritis and human immunodeficiency virus infection and also linked to malignancies such as hepatocellular, colorectal, and breast cancers.

The binding receptors of chemokine are G protein-coupled receptors (GPCR) with seven transmembrane regions, mainly expressed in endothelial cells, immune cells, and some tumor cells. Unlike many other cytokines, CCl20 only binds CCR6 [39–41]. Under non-pathological conditions, the expression level of CCR6 was low in most tissues, but highest in intestinal mucosa, lung mucosa, and lymphoid tissue [42, 43]. At the cellular level, CCR6 was mainly expressed in B cells, memory and effector T cells, Th17, Tregs, and immature DCs [44–48].The basic expression of CCR6 on immune cells induces cells homing to ligand secretion sites [35, 49–51]. CCR6 was significantly upregulated in inflammatory bowel disease, rheumatoid arthritis, and other pathological autoimmune diseases [36, 52–54]. Interestingly, some studies have shown that CCR6 is highly expressed in cancer cells than in normal tissues and is associated with malignancy, making it a potential prognostic biomarker and therapeutic target. The expression of CCR6 in colon cancer cells was higher than that in normal adjacent tissues, and was related to lymph node status and distant metastasis. CCR6 expression was higher in colon cancer cells of node-positive cases, and highest in cases with metastasis [55]. In gastric cancer tissues, CCR6 was upregulated compared with that in adjacent noncancerous gastric tissues. High CCR6 expression was determined in 56.5% (210/372) of the samples, which was significantly correlated with recurrence and poor overall survival of gastric cancer [56].

CCL20 functions through binding to its receptor CCR6, and their high expression in some tumors further demonstrates the vital role of CCL20 signaling in the development of cancer.

6.3 Roles of CCL20 in Multiple Cancers

There is growing evidence that CCL20 is associated with a variety of cancers, including hepatocellular cancer, breast cancer, colorectal cancer, pancreatic cancer, gastric cancer, lung cancer, etc.

6.3.1 Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma (HCC) is primary liver cancer with high mortality, and it is the most common malignant tumor in the world. HCC is the main histological subtype of liver cancer, accounting for 90% of primary liver cancer. Heredity, epigenetic changes, chronic hepatitis B, hepatitis C virus infection, aflatoxin exposure, smoking, obesity, and diabetes are the main risk factors for HCC. The poor prognosis of HCC is due to the high recurrence and metastasis rate. Although there have been some new technologies and methods in the diagnosis and treatment of HCC in recent decades, the 5-year overall survival of patients is very low, still at 3–5%.

Chemokines and their receptors play a complex role in the progression of HCC. At present, chemokines and their receptors, such as CXCL12-CXCR4 axis, CX3CL1-CX3CR1 axis, and CCL20-CCR6 axis, have attracted extensive attention [57]. A large number of studies have shown that these signal axes are closely related to hepatocellular carcinoma. Ding et al. revealed the prognostic significance of CCL20 in patients with hepatocellular carcinoma after curative resection [58]. They found that CCL20 expression evaluated by immunohistochemistry in tumors was associated with tumor size, tumor number, vascular invasion, tumor differentiation, and recurrence. The recurrence-free survival rate and overall survival rate of patients with high expression of CCL20 were lower than those with low expression of CCL20. Multivariate analysis showed that CCL20 expression was an independent predictor of tumor recurrence, recurrence-free survival, and overall survival [58].These results suggested that CCL20 expression was associated with tumor recurrence and survival of HCC patients. Through determining secreted CCL20 levels in serum of two HCC cohort patients ($n = 95$, $n = 85$, respectively) and observing the mRNA expression of CCL20 and CCR6 in 41 paired HCC tumor and adjacent non-tumor tissues, researchers showed that pretherapy serum CCL20 was elevated in HCC patients and CCR6 expression was increased in HCC tissues, of which both were closely associated with tumor metastasis and disease poor prognosis [59]. Moreover, in HCC tissues, CCL20 expression was positively correlated with CCR6. Importantly, the neutralization of CCL20 activity could reduce the incidence of tumors and inhibit tumor outgrowth and distal metastasis. After blocking CCL20 activity, tumor angiogenesis was significantly inhibited [59]. This further suggests that CCL20 may be a new target for the treatment of HCC.

6.3.2 Breast Cancer

Breast cancer is an important factor threatening women's health, and it is the most common type of cancers in women. Breast cancer can be classified into different molecular subtypes, namely luminal A, luminal B, HER2+, and basal-like, according to the expression of specific genes in cancer cells, i.e., estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and nucleoprotein antigen (ki67). Patients of some receptor-positive subtypes, such as luminal A, luminal B, and HER2+ subtypes, are commonly treated with strategies such as surgery, chemotherapy, radiotherapy, endocrine therapy, and targeted therapy. Breast cancer without expression of the three receptors ($ER^-PR^-HER2^-$), also known as triple-negative breast cancer (TNBC) and predominantly identified as basal-like subtype, is the most malignant subtype of breast cancer, prone to recurrence, metastasis, and drug resistance.

Many cytokines play a specific role in the occurrence and development of breast cancer. Some may promote the progress of breast cancer by regulating the proliferation and invasion of

cancer cells, others affect the growth of breast cancer by regulating the self-renewal of breast cancer stem cells (BCSC), and some cytokines regulate the cancer process by regulating the microenvironment of breast cancer.

The overall survival and metastasis-free survival of breast cancer patients with high CCL20 expression were decreased. Intraperitoneal injection of anti-CCL20 antibody can inhibit bone metastasis of osteolytic breast cancer cells in mice. CCL20 treatment significantly promoted cell invasion and MMP-2/9 secretion in basal-like TNBC cells, further confirming the role of CCL20 in bone metastasis of breast cancer [60]. Other studies have shown that overexpression of CCL20 promotes the proliferation and invasiveness of triple-negative breast cancer cells and accelerates the growth of tumors in xenograft models [61]. Moreover, CCL20 promotes the self-renewal of breast cancer stem cells and enhances the expansion ability of cancer stem cell population, suggesting that CCL20 may regulate the growth of breast cancer by affecting cancer stem cells. Interestingly, CCL20 can also enhance the chemotherapeutic resistance of breast cancer cells. It activates the NF-kappa B pathway through PKC and p38 MAPK, promotes the expression of ABCB1, the protein responsible for drug efflux, and then enables taxanes to be continuously pumped out of cells, thereby enhancing the drug resistance of cancer cells. In addition, paclitaxel chemotherapeutic drugs can significantly induce the production of CCL20, which also explains why cancer cells appear to be resistant to taxanes in the treatment of breast cancer: drugs induce the production of CCL20, and CCL20 promotes chemotherapeutic resistance [61]. Therefore, targeting CCL20 or the downstream pathway (such as NF-kappa B) activated by CCL20 can significantly improve the therapeutic effect of breast cancer patients, especially triple-negative breast cancer.

Communication between tumor cells and surrounding cells is helpful to drive the development of tumors. Chemokine CCL20 in breast cancer microenvironment regulates the physiology of healthy breast epithelial cells in areas adjacent to the tumor. Breast cells of primary cultures of mammary cells taken from normal peritumoral areas expressed CCR6 [62]. CCR6 activates various signal kinases that participates in the proliferation and migration of breast cells induced by CCL20. Moreover, different concentrations of CCL20 may have different effects on breast epithelial cells. CCL20 (10 ng/ml) induces cell migration while 15–25 ng/ml CCL20 promotes cell proliferation [62]. In mechanism, CCL20 may promote cell invasion by PKC-alpha that activated Src, which may also lead to activation of downstream Akt, JNK, and NF-kB pathways [62]. Furthermore, CCL20 modulated the epithelial-mesenchymal transition (EMT) of primarily cultured healthy breast epithelial cells in areas adjacent to the tumor through downregulating E-cadherin and ZO-1 and upregulating N-cadherin, vimentin, and Snail expressions [63].

6.4 Tumor Microenvironment Alteration Mediated by CCL20 Signaling

Infiltration of specific type of cells is one of the most important aspects of CCL20 impacts on the tumor microenvironment. After being recruited into the tumor niche, these particular cells may undergo diverse alterations of themselves when challenged with the specific stimulus from tumor cells, in turn they will reprogram the tumor microenvironment to benefit cancer cell survival, leading to poorer prognosis of patients in the majority of cases. The following is the representative of recruited cell type via CCL20 signaling reported in recent studies.

6.4.1 Dendritic Cells (DCs)

DCs are the central cells in the development of antitumor immune response, but the number and function of these cells will change in microenvironment of various cancers. CCL20 functions in the recruitment of inflammatory cells by binding to CCR6 expressed on DCs which are critically linked to initiation of immunity to antigens and recruited to certain sites through CCL20-CCR6

interaction [64]. In colon cancer, the binding of lipopolysaccharide (LPS) to TLR4 activated ERK and NF-kappa B signals in colon cancer cells and promoted the production of CCL20. The chemoattractant ability to immature DCs of colon cancer cells after treatment with LPS was increased significantly. If CCL20 was neutralized, this recruitment effect was significantly weakened, indicating that CCL20 mediated the recruitment of immature DCs by LPS-treated colon cancer cells [65]. In addition, plasmacytoid DCs (PDCs) from patients with melanoma expressed higher CCR6 levels than those from controls, and can migrate to CCL20 sites. CCR6-expressing PDCs were present in melanoma primary lesions, and CCL20 was also produced in melanoma tumors, indicating that PDCs may contribute to the diagnosis of melanoma, and CCL20 may be involved in the recruitment of PDCs from blood to tumors [66].The infiltration of DC cells mediated by CCL20 signaling into the microenvironment of colon cancer and melanoma reprogrammed the tumor microenvironment, influenced the characteristics of cancer cells, and ultimately affected the survival and prognosis of cancer patients.

6.4.2 Regulatory T Cells (Tregs)

Regulatory T cells (Tregs) are a subset of T cells that control autoimmune response. Dysfunction or abnormal expression of Tregs are closely correlated with the occurrence of autoimmune diseases [67–69]. Tregs are very common in cancer tissues and can inhibit effective antitumor immune response. However, the reasons for the increase in infiltrated Tregs in tumors and its impact on cancer progression are not well demonstrated. High expression of CCR6 on circulating Tregs and their directional migration to CCL20 accounted for the selective recruitment of tumor-infiltrating Tregs though CCL20-CCR6 axis, which was also confirmed by the correlation of expression and distribution between intratumoral CCL20 and tumor-infiltrating Tregs [70]. The number of Tregs infiltrated into tumors was associated with cirrhosis background and tumor differentiation, and was an independent prognostic factor for disease-free survival and overall survival [70]. Increasement of Tregs infiltration indicated poor prognosis in patients with hepatocellular carcinoma.

More interestingly, CCL20 signal influencing Tregs infiltration in the tumor microenvironment may originate from stromal macrophages besides tumor cells. In colorectal cancer (CRC), Tregs significantly infiltrated into tumors, and expressed CCR6 [71]. In the in vivo and in vitro experiments, colon cancer cells (CMT93) and macrophages can produce a large number of CCL20. In the colon cancer graft model, injecting recombinant mouse CCL20 protein into the tumor site could significantly promote tumor progression and increase Tregs recruitment [71]. In addition, conditional macrophage deletion can significantly reduce CCL20 level, suppress Tregs recruitment, and then inhibit the growth of colorectal cancer [71]. CCl20 signaling from tumor cells or stromal macrophages mediates Tregs infiltration into tumor microenvironment through binding to CCR6 expressed in Tregs, which leads to cancer progression and poor prognosis in HCC and CRC patients.

6.4.3 T Helper 17 Cells (Th17 Cells)

Th17 cells are a subset of T cells secreting interleukin 17 (IL-17), which plays an important role in autoimmune diseases and body defense response. Th17 cells can produce and secrete IL-17, IL-17F, IL-6, tumor necrosis factor α (TNF-α), etc. These cytokines can motivate, recruit, and activate neutrophils collectively, thus effectively mediating inflammation in tissues. The main physiological roles of Th17 cells are to promote host defense against infectious agents, including certain bacteria, fungi, viruses, and protozoa and to maintain barrier immunity at mucosal surfaces, such as the gut and lungs, as well as in the skin [72–75]. Th17 cells are associated with the development of multiple cancers and the prognosis of patients, such as colorectal

cancer, bladder carcinoma, breast cancer, and cervical cancer [76–80].

In cervical cancer, there was obvious aggregation of Th17 cells in the tumor tissue, and this kind of Th17 cells were an activated phenotype, accompanied by a significant increase in CCR6 expression [81]. The expression level of CCL20 in tumor tissue was significantly higher than that in normal control tissue, and there was a positive correlation between CCL20 and Th17 cells. In addition, CCL20 can effectively chemoattract Th17 cells in in vitro migration experiments [81]. In cervical squamous cell carcinoma, level of CCAAT/enhancer-binding protein beta (C/EBPbeta) in cervical fibroblast was increased after the stimuli of IL-6 produced by cervical cancer cells [80]. Subsequently, the instructed fibroblast produced high level of CCL20 which attracted CD4/IL-17/CCR6-positive cells in a CCL20/CCR6-dependent manner. This study demonstrated a novel mechanism through which cervical cancer cells reprogram the tumor microenvironment with the recruitment of Th17 cells via interplay between cancer cell and cervical fibroblast [80]. And the signaling axis IL-6/C/EBPbeta/CCL20 may be considered as the novel targets for new strategies for cervical squamous cancer treatment.

6.5 Synergistic Tumor Regulation of CCL20 with Other Cytokines in Tumor Microenvironment

There exists the cytokine network in tumor microenvironment to collectively regulate tumor progression [25, 82–85]. During the process that CCL20 functions in tumor microenvironment, other cytokines such as CXCL8 and IL-6 may participate in the modulation. Analysis based on 213 colorectal cancer patients who underwent surgery identified CCL20 and CXCL8 as the prognostic factors of CRC patients [86]. More interestingly, CCL20 and CXCL8 could collaboratively induce epithelial-mesenchymal transition (EMT) in CRC cells but CCL20 or CXCL8 alone could not. EMT was required to maintain cell migration and invasion of colorectal cancer. In addition, concomitant expression of CCL20 and CXCL8 was negatively correlated with E-cadherin expression in CRC tissues, confirming the synergistic role of the two in mediating EMT in CRC cells. Liver metastases more likely occurred in patients with coexpression of CCL20 and CXCL8. Besides, high expression of both CCL20 and CXCL8 predicted the poorest overall survival and disease-free survival of CRC patients, making the two designated as the independent high-risk factor for CRC [86]. However, this study did not clearly demonstrate the interaction manner between CCL20 and CXCL8 mechanistically.

6.6 Input and Output of CCL20 Signaling

The factors that can activate CCL20 signaling are diverse, and vary in different cancers. This may be due to differences in the characteristics of different types of cancer, such as the microenvironment in which they live. If we call these molecules that activate CCL20 pathways as input signals, then the downstream pathway activated by CCL20 is the output signal of CCL20 (Table 6.1). Unlike input, the output of CCL20 signaling is relatively fixed, and most studies have shown that CCL20 can activate the NF-κB pathway to promote different cancer progression (Table 6.1). It is worth mentioning that, a study revealed that the positive-feedback loop between CCL20 and NF-κB contributed to the promotion of taxane resistance in triple-negative breast cancer [61], indicating NF-κB as both input and output of CCL20 signaling (Fig. 6.1).

6.7 Conclusions and Perspectives

Although CCL20 receptor is only CCR6, its effects in TME are diverse due to the following reasons: firstly, as a cytokine, it acts in a

Table 6.1 Inputs (factors that promote CCL20 signaling) and outputs (pathways that CCL20 activates) of CCL20 signaling

	Molecules/ factors	Cancer type	Description	Ref.
Input	HCV	HCC	HCV induced CCL20 protein expression and secretion in hepatoma cells.	[87]
	NNK	Lung cancer	Tobacco carcinogen nicotine-derived nitrosaminoketone (NNK) induces production of chemokine CCL20 to promote lung cancer.	[88]
	CD105	Oral cancer	CCL20 expression participated in CD105-elicited cell motility in oral cancer cells.	[89]
	CXCR4	Prostate cancer	CXCR4 upregulates CCL20 mRNA and protein expression in prostate cancer cells.	[90]
	C/EBPβ	Cervical Cancer	Cervical cancer cells instructed primary cervical fibroblasts to produce high levels of CCL20 through C/EBPβ pathway.	[80]
	ENO1	Head and neck cancer	ENO1-mediated cell transformation partly via CCL20 upregulation.	[91]
	HuR	Breast cancer	HuR regulates CCL20 production by directly binding to the 3′-UTR of CCL20 mRNA and stabilizing it.	[60]
	lncRNA u50535	Colorectal cancer (CRC)	LncRNA-u50535 promotes CRC growth and metastasis via activation of CCL20 signaling.	[92]
	NF-κB	PDAC	CCL20 represents the strongest TRAIL inducible direct RelA target gene in PDAC cells.	[93]
	NF-κB	Ovarian cancer	The CCL20 promoter activity was regulated by NF-κB dependent pathways.	[94]
	NF-κB	TNBC	CCL20 production in breast cancer cells could be abolished by inhibition of p65 NF-κB.	[61]
	RBPJK	Breast cancer.	Silencing of RBPJK in MDA-MB-231 cells significantly decreased CCL20 mRNA while protein levels were not significantly altered.	[95]
	RANK/ RANKL	Endometrial cancer	CCL20 was dramatically enhanced in RANKL-treated RANK over-expressed EC cells.	[96]
	STAT3	HCC	Tumor cells transfected with STAT3 siRNA presented significantly lower CCL20 expression than tumor cells transfected with control siRNA.	[97]
	TLR4	Colon cancer	TLR4 ligation by LPS significantly promotes CT-26 colon cancer cells to produce chemokine CCL20 via activation of TLR4 signaling pathways.	[65]
Output	NF-κB	Thyroid cancer	CCL20/CCR6 interaction induced the activation of NF-κB, and stimulated the expression and secretion of MMP-3.	[98]
	AwKT, NF-κB	GCTB	CCL20 recruited mononuclear cells and induced osteoclastogenesis by overactivating the AKT and NF-κB signaling pathways.	[99]
	PKC/ p38-NF-κB	TNBC	CCL20 activated the axis of PKC/p38-NF-κB-ABCB1 in TNBC to promote taxane resistance.	[61]
	ABCB1	Ovarian cancer	CCL20 activated NF-κB signal pathway to promote ABCB1 expression.	[100]
	CrkL	Gastric cancer	CCL20 activated the expression of p-CrkL in MGC803 cells in a dose-dependent manner.	[101]
	p38	Laryngeal cancer	P38 was activated significantly when the cells were treated with CCL20 at 100 ng/ml.	[102]
	ERK1/2, PI3K	Lung cancer	CCL20 promoted lung cancer cells migration and proliferation in an autocrine manner via activation of ERK1/2-MAPK and PI3K pathways.	[103]

NNK nitrosaminoketone, *PDAC* pancreatic ductal adenocarcinoma, *TNBC* triple-negative breast cancer, *EC* endometrial cancer, *LPS* lipopolysaccharide, *GCTB* giant cell tumor of bone

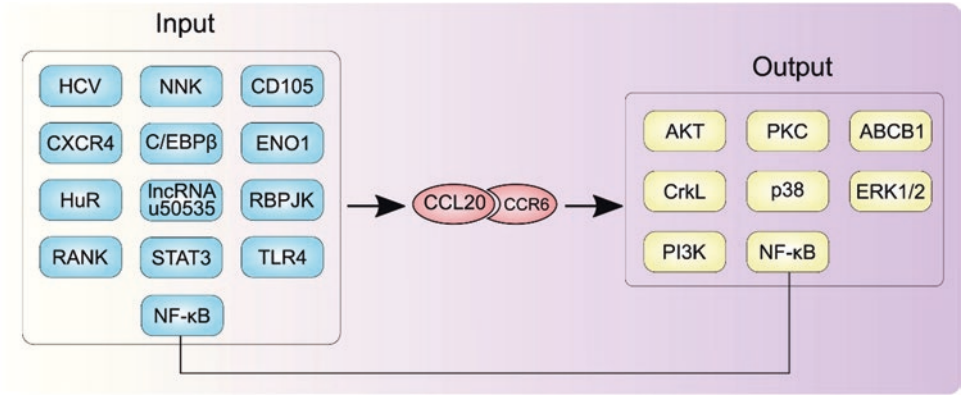

Fig. 6.1 Illustration of input and output of CCL20 signaling. It is the abridged general view of CCL20 signaling. Inputs originated from cancer cells or stromal cells in the tumor microenvironment or even from tumor matrix are the factors that activate CCL20 signaling. Outputs are the pathways that active CCL20 enhances. Noticeably and interestingly, NF-κB was proved to be both input and output of CCL20 signaling

variety of ways, including autocrine, paracrine, and endocrine; secondly, the input signals that can activate CCL20 in microenvironment are diverse, which makes it more complicated of CCL20 activation in tumor niche. In addition, by binding to CCR6, CCL20 recruits different types of cells to infiltrate into TME, which further complicates the signaling network in the microenvironment. These reasons, but not limited to them, make CCL20 regulate the malignant progression of multiple cancers.

However, so far, there are still some problems to be solved or worth exploring. Does CCL20 have potential clinical value as a target for cancer treatment? This requires more in vivo and even clinical experiments to illustrate. What is the importance of CCL20 signal in tumor microenvironment? Will its deletion cause great changes in tumor microenvironment and subsequent effects on tumor growth and even cancer treatment efficacy? CCL20-knockout mice model may be helpful to this problem. In addition, changes in the metabolic pattern of cancer cells cannot be ignored in the process of cancer development, so does CCL20 signal also have an impact on it? Therefore, more experiments and efforts are needed to bring us closer to the true face of CCL20 in tumor microenvironment.

References

1. Bussard KM, Mutkus L, Stumpf K, Gomez-Manzano C, Marini FC (2016) Tumor-associated stromal cells as key contributors to the tumor microenvironment. Breast Cancer Res 18(1):84
2. Chen F, Zhuang X, Lin L, Yu P, Wang Y, Shi Y et al (2015) New horizons in tumor microenvironment biology: challenges and opportunities. BMC Med 13:45
3. Goubran HA, Kotb RR, Stakiw J, Emara ME, Burnouf T (2014) Regulation of tumor growth and metastasis: the role of tumor microenvironment. Cancer Growth Metastasis 7:9–18
4. Munn DH, Bronte V (2016) Immune suppressive mechanisms in the tumor microenvironment. Curr Opin Immunol 39:1–6
5. Wang M, Zhao J, Zhang L, Wei F, Lian Y, Wu Y et al (2017) Role of tumor microenvironment in tumorigenesis. J Cancer 8(5):761–773
6. Beatty GL, Gladney WL (2015) Immune escape mechanisms as a guide for cancer immunotherapy. Clin Cancer Res 21(4):687–692
7. Binnewies M, Roberts EW, Kersten K, Chan V, Fearon DF, Merad M et al (2018) Understanding the tumor immune microenvironment (TIME) for effective therapy. Nat Med 24(5):541–550
8. Joyce JA, Fearon DT (2015) T cell exclusion, immune privilege, and the tumor microenvironment. Science 348(6230):74–80
9. Powell DR, Huttenlocher A (2016) Neutrophils in the tumor microenvironment. Trends Immunol 37(1):41–52
10. Ribas A (2015) Adaptive immune resistance: how cancer protects from immune attack. Cancer Discov 5(9):915–919

11. Scharping NE, Menk AV, Moreci RS, Whetstone RD, Dadey RE, Watkins SC et al (2016) The tumor microenvironment represses T cell mitochondrial biogenesis to drive intratumoral T cell metabolic insufficiency and dysfunction. Immunity 45(2):374–388
12. Heindl A, Nawaz S, Yuan Y (2015) Mapping spatial heterogeneity in the tumor microenvironment: a new era for digital pathology. Lab Invest 95(4):377–384
13. Jimenez-Sanchez A, Memon D, Pourpe S, Veeraraghavan H, Li Y, Vargas HA et al (2017) Heterogeneous tumor-immune microenvironments among differentially growing metastases in an ovarian cancer patient. Cell 170(5):927–38.e20
14. McGranahan N, Swanton C (2017) Clonal heterogeneity and tumor evolution: past, present, and the future. Cell 168(4):613–628
15. Rucki AA, Foley K, Zhang P, Xiao Q, Kleponis J, Wu AA et al (2017) Heterogeneous stromal signaling within the tumor microenvironment controls the metastasis of pancreatic cancer. Cancer Res 77(1):41–52
16. Kurahara H, Shinchi H, Mataki Y, Maemura K, Noma H, Kubo F et al (2011) Significance of M2-polarized tumor-associated macrophage in pancreatic cancer. J Surg Res 167(2):e211–e219
17. Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P (2017) Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol 14(7):399–416
18. Quatromoni JG, Eruslanov E (2012) Tumor-associated macrophages: function, phenotype, and link to prognosis in human lung cancer. Am J Transl Res 4(4):376–389
19. Szebeni GJ, Vizler C, Kitajka K, Puskas LG (2017) Inflammation and cancer: extra- and intracellular determinants of tumor-associated macrophages as tumor promoters. Mediators Inflamm 2017:9294018
20. Yang L, Zhang Y (2017) Tumor-associated macrophages: from basic research to clinical application. J Hematol Oncol 10(1):58
21. Cui G, Yuan A, Sun Z, Zheng W, Pang Z (2018) IL-1beta/IL-6 network in the tumor microenvironment of human colorectal cancer. Pathol Res Pract 214(7):986–992
22. Dougan M, Ingram JR, Jeong HJ, Mosaheb MM, Bruck PT, Ali L et al (2018) Targeting cytokine therapy to the pancreatic tumor microenvironment using PD-L1-specific VHHs. Cancer Immunol Res 6(4):389–401
23. Fisher DT, Appenheimer MM, Evans SS (2014) The two faces of IL-6 in the tumor microenvironment. Semin Immunol 26(1):38–47
24. Galdiero MR, Marone G, Mantovani A (2018) Cancer inflammation and cytokines. Cold Spring Harb Perspect Biol 10(8):a028662
25. Korkaya H, Liu S, Wicha MS (2011) Breast cancer stem cells, cytokine networks, and the tumor microenvironment. J Clin Invest 121(10):3804–3809
26. Landskron G, De la Fuente M, Thuwajit P, Thuwajit C, Hermoso MA (2014) Chronic inflammation and cytokines in the tumor microenvironment. J Immunol Res 2014:149185
27. Liotti F, Collina F, Pone E, La Sala L, Franco R, Prevete N et al (2017) Interleukin-8, but not the related chemokine CXCL1, sustains an autocrine circuit necessary for the properties and functions of thyroid cancer stem cells. Stem Cells 35(1):135–146
28. Long X, Ye Y, Zhang L, Liu P, Yu W, Wei F et al (2016) IL-8, a novel messenger to cross-link inflammation and tumor EMT via autocrine and paracrine pathways (Review). Int J Oncol 48(1):5–12
29. Santander AM, Lopez-Ocejo O, Casas O, Agostini T, Sanchez L, Lamas-Basulto E et al (2015) Paracrine interactions between adipocytes and tumor cells recruit and modify macrophages to the mammary tumor microenvironment: the role of obesity and inflammation in breast adipose tissue. Cancers (Basel) 7(1):143–178
30. Wang Y, Chen J, Yang L, Li J, Wu W, Huang M et al (2019) Tumor-contacted neutrophils promote metastasis by a CD90-TIMP-1 juxtacrine-paracrine loop. Clin Cancer Res 25(6):1957–1969
31. Boyle ST, Faulkner JW, McColl SR, Kochetkova M (2015) The chemokine receptor CCR6 facilitates the onset of mammary neoplasia in the MMTV-PyMT mouse model via recruitment of tumor-promoting macrophages. Mol Cancer 14:115
32. Kitamura T, Pollard JW (2015) Therapeutic potential of chemokine signal inhibition for metastatic breast cancer. Pharmacol Res 100:266–270
33. Nagarsheth N, Wicha MS, Zou W (2017) Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy. Nat Rev Immunol 17(9):559–572
34. Armas-Gonzalez E, Dominguez-Luis MJ, Diaz-Martin A, Arce-Franco M, Castro-Hernandez J, Danelon G et al (2018) Role of CXCL13 and CCL20 in the recruitment of B cells to inflammatory foci in chronic arthritis. Arthritis Res Ther 20(1):114
35. Kim TG, Jee H, Fuentes-Duculan J, Wu WH, Byamba D, Kim DS et al (2014) Dermal clusters of mature dendritic cells and T cells are associated with the CCL20/CCR6 chemokine system in chronic psoriasis. J Invest Dermatol 134(5):1462–1465
36. Lee AY, Korner H (2014) CCR6 and CCL20: emerging players in the pathogenesis of rheumatoid arthritis. Immunol Cell Biol 92(4):354–358
37. Liu Y, Lagowski JP, Gao S, Raymond JH, White CR, Kulesz-Martin MF (2010) Regulation of the psoriatic chemokine CCL20 by E3 ligases Trim32 and Piasy in keratinocytes. J Invest Dermatol 130(5):1384–1390

38. Osuala KO, Sloane BF (2014) Many roles of CCL20: emphasis on breast cancer. Postdoc J 2(3):7–16
39. Nandi B, Pai C, Huang Q, Prabhala RH, Munshi NC, Gold JS (2014) CCR6, the sole receptor for the chemokine CCL20, promotes spontaneous intestinal tumorigenesis. PLoS One 9(5):e97566
40. Frick VO, Rubie C, Keilholz U, Ghadjar P (2016) Chemokine/chemokine receptor pair CCL20/CCR6 in human colorectal malignancy: an overview. World J Gastroenterol 22(2):833–841
41. Schutyser E, Struyf S, Van Damme J (2003) The CC chemokine CCL20 and its receptor CCR6. Cytokine Growth Factor Rev 14(5):409–426
42. Williams IR (2006) CCR6 and CCL20: partners in intestinal immunity and lymphorganogenesis. Ann N Y Acad Sci 1072:52–61
43. Acosta-Rodriguez EV, Rivino L, Geginat J, Jarrossay D, Gattorno M, Lanzavecchia A et al (2007) Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells. Nat Immunol 8(6):639–646
44. Lyu M, Li Y, Hao Y, Lyu C, Huang Y, Sun B et al (2019) CCR6 defines a subset of activated memory T cells of Th17 potential in immune thrombocytopenia. Clin Exp Immunol 195(3):345–357
45. Lee AYS, Korner H (2019) The CCR6-CCL20 axis in humoral immunity and T-B cell immunobiology. Immunobiology 224(3):449–454
46. Godefroy E, Alameddine J, Montassier E, Mathe J, Desfrancois-Noel J, Marec N et al (2018) Expression of CCR6 and CXCR6 by gut-derived CD4(+)/CD8alpha(+) T-regulatory cells, which are decreased in blood samples from patients with inflammatory bowel diseases. Gastroenterology 155(4):1205–1217
47. Skovdahl HK, Damas JK, Granlund AVB, Ostvik AE, Doseth B, Bruland T et al (2018) C-C Motif ligand 20 (CCL20) and C-C motif chemokine receptor 6 (CCR6) in human peripheral blood mononuclear cells: dysregulated in ulcerative colitis and a potential role for CCL20 in IL-1beta release. Int J Mol Sci 19(10):E3257
48. Luo K, Zavala F, Gordy J, Zhang H, Markham RB (2017) Extended protection capabilities of an immature dendritic-cell targeting malaria sporozoite vaccine. Vaccine 35(18):2358–2364
49. Campbell JJ, Ebsworth K, Ertl LS, McMahon JP, Newland D, Wang Y et al (2017) IL-17-Secreting gammadelta T cells are completely dependent upon CCR6 for homing to inflamed skin. J Immunol 199(9):3129–3136
50. Cochez PM, Michiels C, Hendrickx E, Dauguet N, Warnier G, Renauld JC et al (2017) Ccr6 is dispensable for the development of skin lesions induced by imiquimod despite its effect on epidermal homing of IL-22-producing cells. J Invest Dermatol 137(5):1094–1103
51. Planas D, Zhang Y, Monteiro P, Goulet JP, Gosselin A, Grandvaux N et al (2017) HIV-1 selectively targets gut-homing CCR6+CD4+ T cells via mTOR-dependent mechanisms. JCI Insight 2(15):93230
52. Ranasinghe R, Eri R (2018) CCR6–CCL20-Mediated immunologic pathways in inflammatory bowel disease. Gastrointestinal Disorders 1(1):15–29
53. Skovdahl HK, Granlund A, Ostvik AE, Bruland T, Bakke I, Torp SH et al (2015) Expression of CCL20 and its corresponding receptor CCR6 is enhanced in active inflammatory bowel disease, and TLR3 mediates CCL20 expression in colonic epithelial cells. PLoS One 10(11):e0141710
54. Paulissen SM, van Hamburg JP, Dankers W, Lubberts E (2015) The role and modulation of CCR6+ Th17 cell populations in rheumatoid arthritis. Cytokine 74(1):43–53
55. Kapur N, Mir H, Clark Iii CE, Krishnamurti U, Beech DJ, Lillard JW et al (2016) CCR6 expression in colon cancer is associated with advanced disease and supports epithelial-to-mesenchymal transition. Br J Cancer 114(12):1343–1351
56. Zhang XG, Song BT, Liu FJ, Sun D, Wang KX, Qu H (2016) CCR6 overexpression predicted advanced biological behaviors and poor prognosis in patients with gastric cancer. Clin Transl Oncol 18(7):700–707
57. Huang F, Geng XP (2010) Chemokines and hepatocellular carcinoma. World J Gastroenterol 16(15):1832–1836
58. Ding X, Wang K, Wang H, Zhang G, Liu Y, Yang Q et al (2012) High expression of CCL20 is associated with poor prognosis in patients with hepatocellular carcinoma after curative resection. J Gastrointest Surg 16(4):828–836
59. He H, Wu J, Zang M, Wang W, Chang X, Chen X et al (2017) CCR6(+) B lymphocytes responding to tumor cell-derived CCL20 support hepatocellular carcinoma progression via enhancing angiogenesis. Am J Cancer Res 7(5):1151–1163
60. Lee SK, Park KK, Kim HJ, Park J, Son SH, Kim KR et al (2017) Human antigen R-regulated CCL20 contributes to osteolytic breast cancer bone metastasis. Sci Rep 7(1):9610
61. Chen W, Qin Y, Wang D, Zhou L, Liu Y, Chen S et al (2018) CCL20 triggered by chemotherapy hinders the therapeutic efficacy of breast cancer. PLoS Biol 16(7):e2005869
62. Marsigliante S, Vetrugno C, Muscella A (2013) CCL20 induces migration and proliferation on breast epithelial cells. J Cell Physiol 228(9):1873–1883
63. Marsigliante S, Vetrugno C, Muscella A (2016) Paracrine CCL20 loop induces epithelial-mesenchymal transition in breast epithelial cells. Mol Carcinog 55(7):1175–1186
64. Hong GH, Kwon HS, Moon KA, Park SY, Park S, Lee KY et al (2016) Clusterin modulates allergic airway inflammation by attenuating CCL20-mediated dendritic cell recruitment. J Immunol 196(5):2021–2030
65. Wang L, Liu Q, Sun Q, Zhang C, Chen T, Cao X (2008) TLR4 signaling in cancer cells promotes chemoattraction of immature dendritic cells via autocrine CCL20. Biochem Biophys Res Commun 366(3):852–856

66. Charles J, Di Domizio J, Salameire D, Bendriss-Vermare N, Aspord C, Muhammad R et al (2010) Characterization of circulating dendritic cells in melanoma: role of CCR6 in plasmacytoid dendritic cell recruitment to the tumor. J Invest Dermatol 130(6):1646–1656
67. Tanaka A, Sakaguchi S (2017) Regulatory T cells in cancer immunotherapy. Cell Res 27(1):109–118
68. Plitas G, Konopacki C, Wu K, Bos PD, Morrow M, Putintseva EV et al (2016) Regulatory T cells exhibit distinct features in human breast cancer. Immunity 45(5):1122–1134
69. Liu C, Workman CJ, Vignali DA (2016) Targeting regulatory T cells in tumors. FEBS J 283(14):2731–2748
70. Chen KJ, Lin SZ, Zhou L, Xie HY, Zhou WH, Taki-Eldin A et al (2011) Selective recruitment of regulatory T cell through CCR6-CCL20 in hepatocellular carcinoma fosters tumor progression and predicts poor prognosis. PLoS One 6(9):e24671
71. Liu J, Zhang N, Li Q, Zhang W, Ke F, Leng Q et al (2011) Tumor-associated macrophages recruit CCR6+ regulatory T cells and promote the development of colorectal cancer via enhancing CCL20 production in mice. PLoS One 6(4):e19495
72. Zou W, Restifo NP (2010) T(H)17 cells in tumour immunity and immunotherapy. Nat Rev Immunol 10(4):248–256
73. Miossec P, Korn T, Kuchroo VK (2009) Interleukin-17 and type 17 helper T cells. N Engl J Med 361(9):888–898
74. Halwani R, Al-Muhsen S, Hamid Q (2013) T helper 17 cells in airway diseases: from laboratory bench to bedside. Chest 143(2):494–501
75. Stockinger B, Omenetti S (2017) The dichotomous nature of T helper 17 cells. Nat Rev Immunol 17(9):535–544
76. Amicarella F, Muraro MG, Hirt C, Cremonesi E, Padovan E, Mele V et al (2017) Dual role of tumour-infiltrating T helper 17 cells in human colorectal cancer. Gut 66(4):692–704
77. Chang SH (2019) T helper 17 (Th17) cells and interleukin-17 (IL-17) in cancer. Arch Pharm Res 42(7):549–559
78. Chi LJ, Lu HT, Li GL, Wang XM, Su Y, Xu WH et al (2010) Involvement of T helper type 17 and regulatory T cell activity in tumour immunology of bladder carcinoma. Clin Exp Immunol 161(3):480–489
79. Wang J, Cai D, Ma B, Wu G, Wu J (2011) Skewing the balance of regulatory T-cells and T-helper 17 cells in breast cancer patients. J Int Med Res 39(3):691–701
80. Walch-Ruckheim B, Mavrova R, Henning M, Vicinus B, Kim YJ, Bohle RM et al (2015) Stromal fibroblasts induce CCL20 through IL6/C/EBPbeta to support the recruitment of Th17 cells during cervical cancer progression. Cancer Res 75(24):5248–5259
81. Yu Q, Lou XM, He Y (2015) Preferential recruitment of Th17 cells to cervical cancer via CCR6-CCL20 pathway. PLoS One 10(3):e0120855
82. Kulbe H, Chakravarty P, Leinster DA, Charles KA, Kwong J, Thompson RG et al (2012) A dynamic inflammatory cytokine network in the human ovarian cancer microenvironment. Cancer Res 72(1):66–75
83. Matsuo Y, Takeyama H, Guha S (2012) Cytokine network: new targeted therapy for pancreatic cancer. Curr Pharm Des 18(17):2416–2419
84. Lasry A, Zinger A, Ben-Neriah Y (2016) Inflammatory networks underlying colorectal cancer. Nat Immunol 17(3):230–240
85. Padoan A, Plebani M, Basso D (2019) Inflammation and pancreatic cancer: focus on metabolism, cytokines, and immunity. Int J Mol Sci 20(3):E676
86. Cheng XS, Li YF, Tan J, Sun B, Xiao YC, Fang XB et al (2014) CCL20 and CXCL8 synergize to promote progression and poor survival outcome in patients with colorectal cancer by collaborative induction of the epithelial-mesenchymal transition. Cancer Lett 348(1-2):77–87
87. Benkheil M, Van Haele M, Roskams T, Laporte M, Noppen S, Abbasi K et al (2018) CCL20, a direct-acting pro-angiogenic chemokine induced by hepatitis C virus (HCV): potential role in HCV-related liver cancer. Exp Cell Res 372(2):168–177
88. Wang GZ, Cheng X, Li XC, Liu YQ, Wang XQ, Shi X et al (2015) Tobacco smoke induces production of chemokine CCL20 to promote lung cancer. Cancer Lett 363(1):60–70
89. Chen CH, Chuang HC, Lin YT, Fang FM, Huang CC, Chen CM et al (2016) Circulating CD105 shows significant impact in patients of oral cancer and promotes malignancy of cancer cells via CCL20. Tumour Biol 37(2):1995–2005
90. Beider K, Abraham M, Begin M, Wald H, Weiss ID, Wald O et al (2009) Interaction between CXCR4 and CCL20 pathways regulates tumor growth. PLoS One 4(4):e5125
91. Tsai ST, Chien IH, Shen WH, Kuo YZ, Jin YT, Wong TY et al (2010) ENO1, a potential prognostic head and neck cancer marker, promotes transformation partly via chemokine CCL20 induction. Eur J Cancer 46(9):1712–1723
92. Yu X, Yuan Z, Yang Z, Chen D, Kim T, Cui Y et al (2018) The novel long noncoding RNA u50535 promotes colorectal cancer growth and metastasis by regulating CCL20. Cell Death Dis 9(7):751
93. Geismann C, Grohmann F, Dreher A, Hasler R, Rosenstiel P, Legler K et al (2017) Role of CCL20 mediated immune cell recruitment in NF-kappaB mediated TRAIL resistance of pancreatic cancer. Biochim Biophys Acta Mol Cell Res 1864(5):782–796
94. Ignacio RM, Kabir SM, Lee ES, Adunyah SE, Son DS (2016) NF-kappaB-mediated CCL20 reigns dominantly in CXCR2-driven ovarian cancer progression. PLoS One 11(10):e0164189
95. Kucukkose C, Yalcin OO (2019) Effects of Notch signalling on the expression of SEMA3C, HMGA2, CXCL14, CXCR7, and CCL20 in breast cancer. Turk J Biol 43(1):70–76

96. Liu Y, Wang J, Ni T, Wang L, Wang Y, Sun X (2016) CCL20 mediates RANK/RANKL-induced epithelial-mesenchymal transition in endometrial cancer cells. Oncotarget 7(18):25328–25339
97. Tan H, Wang S, Zhao L (2017) A tumour-promoting role of Th9 cells in hepatocellular carcinoma through CCL20 and STAT3 pathways. Clin Exp Pharmacol Physiol 44(2):213–221
98. Zeng W, Chang H, Ma M, Li Y (2014) CCL20/CCR6 promotes the invasion and migration of thyroid cancer cells via NF-kappa B signaling-induced MMP-3 production. Exp Mol Pathol 97(1):184–190
99. Zhao C, Wang D, Tang L, Zhang Z, Li S, Qian M et al (2018) Stromal cell-derived CCL20 promotes tumor progression and osteolysis in giant cell tumor of bone. Cell Physiol Biochem 51(5): 2472–2483
100. Su S, Sun X, Zhang Q, Zhang Z, Chen J (2019) CCL20 Promotes ovarian cancer chemotherapy resistance by regulating ABCB1 expression. Cell Struct Funct 44(1):21–28
101. Han G, Wu D, Yang Y, Li Z, Zhang J, Li C (2015) CrkL meditates CCL20/CCR6-induced EMT in gastric cancer. Cytokine 76(2):163–169
102. Lu E, Su J, Zhou Y, Zhang C, Wang Y (2017) CCL20/CCR6 promotes cell proliferation and metastasis in laryngeal cancer by activating p38 pathway. Biomed Pharmacother 85:486–492
103. Wang B, Shi L, Sun X, Wang L, Wang X, Chen C (2016) Production of CCL20 from lung cancer cells induces the cell migration and proliferation through PI3K pathway. J Cell Mol Med 20(5):920–929