World Journal of Hepatology

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DOI: 10.4254/wjh.v7.i10.1390

World J Hepatol 2015 June 8; 7(10): 1390-1402
ISSN 1948-5182 (online)

REVIEW

Chemokines and their receptors play important roles in the development of hepatocellular carcinoma

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Author contributions: All the authors contributed to this paper.
Supported by National Science Foundation of China, No. 31471147.
Conflict-of-interest: The authors certify that there is no actual or potential conflict of interest and publication copyright in relation to this article.

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Received: August 28, 2014
Peer-review started: August 28, 2014
First decision: October 14, 2014
Revised: March 17, 2015
Accepted: April 1, 2015
Article in press: April 7, 2015
Published online: June 8, 2015

Abstract

The chemokine system consists of four different subclasses with over 50 chemokines and 19 receptors. Their functions in the immune system have been well elucidated and research during the last decades unveils their new roles in hepatocellular carcinoma (HCC). The chemokines and their receptors in the microenvironment influence the development of HCC by several aspects including: inflammation, effects on immune cells, angiogenesis, and direct effects on HCC cells. Regarding these aspects, pre-clinical research by targeting the chemokine system has yielded promising data, and these findings bring us new clues in the chemokine-based therapies for HCC.

Key words: Chemokines; Hepatocellular carcinoma; Immune cells; Chemokine receptors; Inflammation; Angiogenesis; Tumor behaviors; Treatments

Core tip: The chemokine system not only serves as the core components in orchestrating the normal immune response but also plays a key role in the microenvironment of hepatocellular carcinoma (HCC). Therefore, the thorough understanding of its role is indispensible for devising effective treatments. During the progress of HCC, the chemokine system boosts aberrant inflammation and angiogenesis through simultaneously affecting different kinds of immune cells and influencing the migration, invasion, growth and survival of tumor cells. Targeting the chemokine system has elicited powerful anti-tumor effects and this indicates an encouraging treatment option in HCC.

Liang CM, Chen L, Hu H, Ma HY, Gao LL, Qin J, Zhong CP. Chemokines and their receptors play important roles in the development of hepatocellular carcinoma. *World J Hepatol* 2015; 7(10): 1390-1402 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i10/1390.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i10.1390

INTRODUCTION

The chemokines are a family of small chemotactic molecules about 8-14 kDa which have been well

described during the past decades. There are now over 50 chemokines and 19 chemokine receptors, and these chemokines can be divided into four subclasses: CX_3C, CXC, CC and (X)C according to the arrangement of the N-terminal two cysteine residues. Corresponding to the four subclasses of chemokines, the chemokine receptors are also subdivided into four families [CX_3CR, CXCR, CCR and (X)CR] which are typical G-protein coupled receptors with seven trans-membrane domains[1,2].

The chemokine system is initially found to be critical for immune cells. They orchestrate the migration and localization of immune cells in both lymph organs and other tissues, exerting the "chemotactic effects" which are necessary for the normal immune response *in vivo*[3]. In addition to chemotactic effects, chemokines can also directly influence the differentiation, survival and functions of immune cells, among which include CCR4, CCR7 and CCR8[4-8]. These observations suggest the chemokine system is not merely the guide signs for the immune cells; instead, they are pleiotropic small molecules with various functions.

The original interest of chemokines in tumor is torched by the observation of immune cells infiltration in tumor tissues. Several groups have speculated that some molecules might be responsible for attracting these immune cells[9]. Although the full spectrum of these molecules is still on the way, some of these important molecules turn out to be chemokines. Since the first chemokine monocyte chemotactic protein 1/CCL2 was detected in the culture media of several different tumor cell lines in 1980s[10,11], more and more chemokines and chemokine receptors have been identified in tumors, including the hepatocellular carcinoma (HCC).

Various studies on the chemokine system have greatly broadened our understanding of its role in HCC, and there are 23 chemokines and 15 chemokine receptors reported in HCC (Table 1). On the one hand, the chemokine system in HCC exerts pleiotropic effects on immune cells and other stroma cells in the microenvironment, and brings both anti- and pro-tumor effects; on the other hand, the HCC cells themselves express chemokine receptors, which allow the chemokines to directly modulate the behaviors of tumor cells including the migration, invasion, growth and survival (Table 2). Data from clinical studies again emphasize the importance of chemokine system in HCC, closely correlating with prognosis. In this review, we will summarize the key roles of the chemokine system in HCC.

THE SIGNIFICANCE OF CHEMOKINES AND CHEMOKINE RECEPTORS

Chemokines in HCC tissues are derived from different sources, including tumor cells, and non-tumor cells such as hepatic stellate cells, T cells, macrophages, neutrophils, *etc*. Similarly, the chemokine receptors that are involved in the progression of HCC are either expressed on tumor cells or non-tumor cells. This complicated network reflects the mutual interaction between HCC cells and other cells in the microenvironment (Figure 1).

Of all the chemokines and their receptors in HCC, the CXC subclass accounts for the largest group. Among them, the CXCL12-CXCR4/CXCR7 axis is the most documented, and abnormal expression of either CXCL12 or CXCR4/CXCR7 is correlated with clinicopathological characteristics[12-15]. CXCL8 is a potent pro-inflammation chemokine widely studied in other tumors and it is also elevated in serum from HCC patients and represents a risk factor for survival[16]. The CXCL9/CXCL10-CXCR3 axis also shows important influences on prognosis of HCC patients[17-19]. The increase of CXCL1, CXCL2 and their common receptor CXCR2 indicates the increased risk for HCC[20,21]. The possible roles of CXCL5 and CXCL14 are unveiled too in HCC patients[22,23].

The CC subclass constitutes another major part of chemokines in HCC. Expression levels and genetic polymorphisms of CCL2 and CCR2 affect the prognosis of HCC patients[17,24,25]. The CCL5-CCR5 axis is closely correlated with liver chronic inflammation induced by different pathogens and finally participates in the development of HCC[26,27]; meanwhile, CCL3 and CCL4, the other two ligands of CCR5, show a definitive role in accelerating the course HCC[28,29]. The CCL20-CCR6 axis is a prognostic factor for HCC patients and this relates its role to recruiting regulatory T cells (Tregs)[30-32]. The other CC chemokines and receptors have also been found correlated with the clinicopathological parameters of HCC, including CCL15[33], CCL17[34], CCL22[35], CCL27[36], CCR7[37] and CCR9[38]. The CX3C subclass contains only one single member CX_3CL1 and this CX_3CL1-CX_3CR1 axis participates in HCC[39,40].

INFLAMMATION

Cancer related inflammation is the hallmark of HCC, especially for hepatitis B virus (HBV)/HCV-associated HCC, and the chemokine system has dual roles in the inflammation of HCC. On the one hand, chemokines themselves can be induced by different inflammatory cytokines such as interleukin-1 (IL-1) and IL-6, and exist as mediators for inflammation by recruiting different immune cells (details will be discussed in EFFECTS ON IMMUNE CELLS); on the other hand, chemokines can trigger the secretion of various other inflammatory cytokines from tumor cells and non-tumor cells in the microenvironment of HCC. Both of the two facets are indispensible in the inflammation of HCC.

CXCL8 is a well-defined pro-inflammatory chemokine. It is produced by HCC cells through activation of several different pathways including JNK, nuclear factor-kappa B (NF-κB), and PI3K-AKT pathways[41,42], and the elevated CXCL8 in turn induces multiple inflammatory cytokines and recruits various immune cells, all of which promotes the development of the inflammation microenvironment in HCC[43].

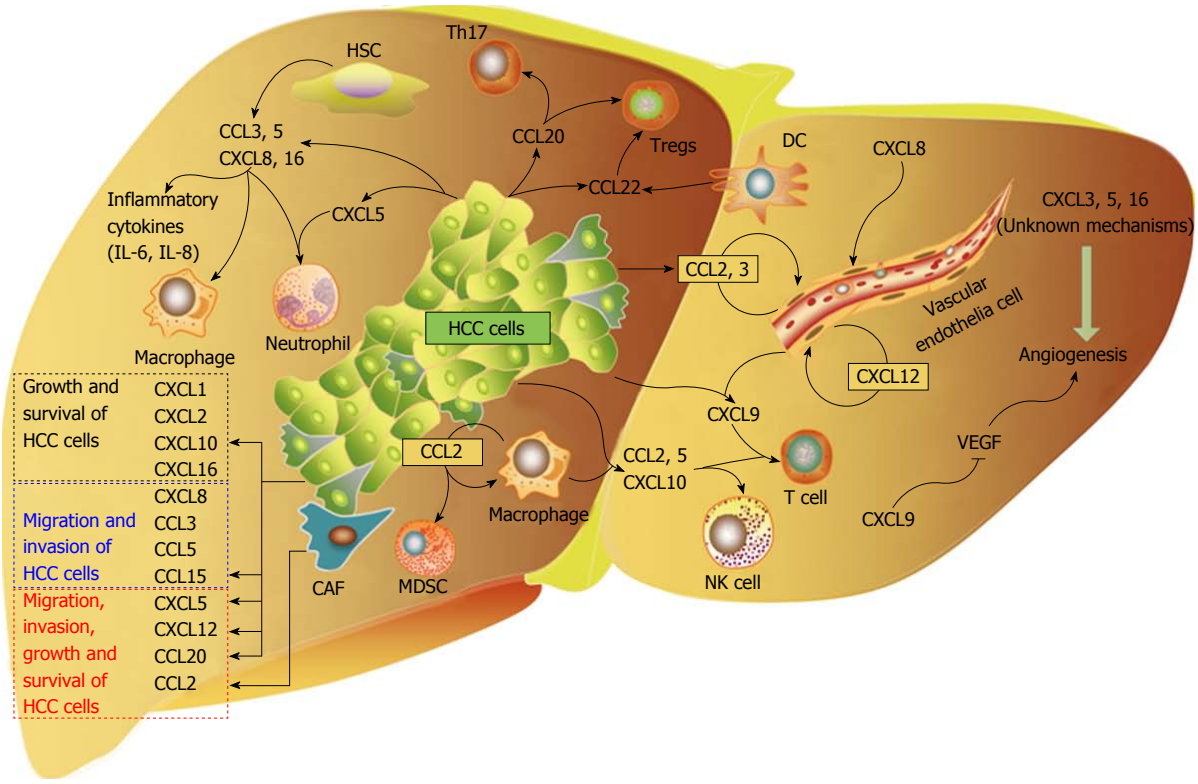

Figure 1 The complicated chemokine network in the microenvironment of hepatocellular carcinoma. The chemokine system exerts pleiotropic effects in the microenvironment of hepatocellular carcinoma (HCC). Chemokines derived from either tumor cells or non-tumor cells induce potent inflammation response, along with increased levels of cytokines and infiltration of immune cells; the potent chemotactic effects of chemokines also lead to recruitment of various immune cells into the tumor sites, exerting both anti- and pro-tumor effects. Several other chemokines such as CXCL9 and CXCL12 manifest a key role in angiogenesis of HCC *via* different mechanisms. As the HCC cells intrinsically express chemokine receptors, they are directly influenced by chemokines too, which affect the behaviors of tumor cells such as the migration, invasion, growth and survival. Both the paracrine and autocrine mechanisms constitute this mutual complex network that is indispensible in HCC. Refer to the text for abbreviations. HSC: Hepatic stellate cell; IL: Interleukin; NK: Natural killer; CAF: Cancer-associated fibroblast; MDSC: Myeloid derived suppressor cells; Tregs: Regulatory T cells; DCs: Dendritic cells; VEGF: Vascular endothelial growth factor.

CCR5 mediated inflammation is also important in the development of HCC. CCL3, one ligand for CCR5, is remarkably increased in different HCC cell lines when stimulated with IL-1α or IL-1β, which consequently attracts large amount of macrophages and neutrophils into the inflammation sites[44]. The hepatic stellate cells are capable of producing a group of inflammatory cytokines including IL-6 and transforming growth factor alpha (TGF-β); blocking the CCR5 signals with maraviroc, a CCR5 antagonist, effectively abrogates the intracellular signal transduction and inhibits the progression of HCC *in vivo*[45]. Likewise, in the CCR5-knockout mice (Mdr2:CCR5 DKO), the oval cells, which are the putative liver progenitor cells that proliferate and differentiate in response to liver damage[46,47], show decreased levels of insulin-like growth factor-binding protein 1, secreted phosphoprotein 1, CD24, keratin 19, and epithelial cell adhesion molecule, concomitant with reduced risk of HCC[48]. Besides, activation of the CXCR6 signal in HCC cells results in increased expression of IL-6 and IL-8, while disturbing the CXCL16-CXCR6 axis can potently abrogate this effect[49].

During the infection of HCV, CXCL10 and CXCL11 play a key role in the HCV-related inflammation. Either interferon (IFN)-α or IFN-γ stimulation results in a significant increase of CXCL11, and IFN-γ shows potent synergy with TNF-α in promoting the expression of CXCL11 *in vitro*[50]. Resembling this phenomenon, TLR3 and RIG-1 also potentiate the induction of CXCL10 in the course of HCV infection in hepatocytes, and IFN-α/IFN-β and IFN-γ boost this induction synergistically[51].

EFFECTS ON IMMUNE CELLS

The liver is a very special organ containing huge amount of immune cells in normal physiological state, and these immune cells consist of T cells, natural killer cells (NK cells), Kupffer cells, macrophages, neutrophils, *etc*. Therefore, it is considered to be a lymph organ[52,53]. During the development of HCC, the numbers and ratios of different immune cells have changed specifically, which exerts profound influences in the course of HCC, either promoting or inhibiting the tumor progression[54].

Regarding this issue, the first question is how these immune cells abnormally aggregate in HCC tumor tissues or peri-tumor tissues. The chemokines in the microenvironment have surely played a critical role[55]. In a CCR2-knockout mice model, intraportal injected colon cancer cells exhibit obvious delayed growth in liver; the reduced accumulation of macrophages and

Table 1 Chemokines and chemokine receptors in hepatocellular carcinoma

Chemokines	Other names	Chemokine receptors	Subclass	Ref.
CXCL1	GROα	CXCR2	CXC	[20,21,83]
CXCL2	GROβ	CXCR2	CXC	[21,83]
CXCL5	ENA78	CXCR2	CXC	[21,22]
CXCL8	IL-8	CXCR1, CXCR2	CXC	[16,17,21]
CXCL9	MIG	CXCR3	CXC	[17,18,70]
CXCL10	IP-10	CXCR3	CXC	[17,29,51,70]
CXCL11	I-TAC	CXCR3, CXCR7	CXC	[14,50]
CXCL12	SDF-1	CXCR4, CXCR7	CXC	[12,13,15,86,89,92]
CXCL14	BRAK	Unknown	CXC	[23]
CXCL16	SR-PSOX	CXCR6	CXC	[49,106]
CCL2	MCP-1	CCR2	CC	[17,56,81,116]
CCL3	MIP-1α	CCR1, CCR5	CC	[27,28,81,122]
CCL4	MIP-1β	CCR5	CC	[29,48]
CCL5	RANTES	CCR1, CCR3, CCR5	CC	[27,29,100]
CCL15	HCC-2, leukotactin-1	CCR1, CCR3	CC	[33,100]
CCL17	TARC	CCR4	CC	[34,66]
CCL19	ELC, MIP-3β	CCR7	CC	[37,117-119]
CCL20	MIP-3α	CCR6	CC	[30-32]
CCL21	SLC	CCR7	CC	[37,117-119]
CCL22	MDC	CCR4	CC	[35,66]
CCL26	Eotaxin-3	CCR3, CX3CR1	CC	[110]
CCL27	CTACK, ILC	CCR10	CC	[36]
CX3CL1	Fractalkine	CX3CR1	CX3C	[39,40]

GRO: Growth regulated oncogene; ENA78: Epithelial neutrophil-activating protein 78; IL-8: Interleukin 8; MIG: Monokine induced by IFN-γ; IP-10: IFN-γ-induced protein 10; I-TAC: IFN-inducible T cell alpha chemoattractant; SDF-1: Stromal cell-derived factor 1; BRAK: Breast and kidney expressed chemokine; SR-PSOX: Scavenger receptor that binds phosphatidylserine and oxidized lipoprotein; MCP-1: Monocyte chemotactic protein 1; MIP-1α: Macrophage inflammatory protein-1α; HCC: Hepatocellular carcinoma; TARC: Thymus activation-regulated chemokine; ELC: Epstein-Barr virus-induced molecule 1 ligand CC chemokine; SLC: Secondary lymphoid tissue chemokine; MDC: Macrophage-derived chemokine; CTACK: Cutaneous T-cell-attracting chemokine; ILC: Interleukin-11 receptor α-locus chemokine; IFN: Interferon.

hepatic stellate cells, relying on the CCL2-CCR2 signal for effective migration to the liver, accounts for this inhibitory effects[56]. Besides, the HCC cells secrete high levels of CCL2 upon up-regulation of Forkhead box Q1, and conduct a direct chemotactic effect on macrophages, which again deteriorates the progression of HCC[57]. In addition to macrophages, the CCL2-CCR2 signal also recruits myeloid derived suppressor cells (MDSCs) into tumor tissues, and maintains the immunosuppression in the microenvironment. The HCC cell line H22 produces CCL2 constitutionally and induces the migration of MDSCs significantly *in vitro*[58]. Following experiments *in vivo* confirm this observation that the increased expression of CCL2 in tumor tissues correlates with the accumulation of MDSCs in different HCC models, either DEN-induced HCC or subcutaneously implanted HCC model[59]. However, the roles of CCL2 might be both harmful and beneficial, as suggested by the finding that the reduction of intratumoral CCL2, due to nitration by reactive nitrogen species, inhibits the infiltration of tumor specific T cells and traps these T cells in the peri-tumor stroma, contributing to the immune suppression in tumor tissues[60]. Indeed in the human HCC tissues, the CCL2 produced by both tumor cells and immune cells also correlates significantly with intratumoral $CD4^+$ Th1 cells, $CD8^+$ cells and NK cells, indicating a chemotactic role for these cells that favor an anti-tumor repertoire[61]. Therefore, the thorough understanding of CCL2 in HCC needs further experiments taking into account both the models and tumor stages.

Regulatory T cells (Tregs) are key modulators in tumor-induced immune suppression and the aggregation of Tregs in HCC inevitably influences the progression of HCC[62]. Different chemokines have been found to attract Tregs into the HCC tissues. In patients infected by HCV, intrahepatic levels of CCL17 and CCL22 are significantly up-regulated, correlating with the increased number of Tregs; the *in vitro* system identifies that dendritic cells (DCs) derived CCL17 and CCL22 leads to the enhanced aggregation of Tregs[63]. Interestingly, in HBV-positive HCC, CCL22 also recruits Tregs into tumor tissues *via* the TGF-β-miR-34a-CCL22 axis[64]. The CCL20-CCR6 axis is another chemokine signal that recruits Tregs into the tumor tissues. The CCL20 is highly expressed in tumor tissues and correlates with the increased number of Tregs, and the migration experiments also confirm the direct chemotactic effects of CCL20 on Tregs[31]. In concordance with these observation, our recent results also indicate a key role of chemokine system in Tregs from peripheral blood of HCC from the perspective of microRNAs[65]. However, the highly expressed CCL20

Table 2 Pleiotropic functions of chemokines in hepatocellular carcinoma

Categories	Chemokines	Chemokine origins	Receptors participated	Functions
Inflammation	CXCL8	HCC cells	Not clarified	Increasing inflammatory cytokines
	CXCL16	HCC cells	CXCR6	(IL-6, IL-8, *etc*.) and recruiting leukocytes
	CCL3	HCC cells and HSC	CCR3	(macrophages, neutrophils, *etc*.)
	CCL5	HCC cells and HSC	CCR5	
Influences on immune cells	CXCL5	HCC cells	Not clarified	Chemotaxis of neutrophils
	CXCL9	HCC cells and endothelial cells	CXCR3	Chemotaxis of T cells
	CXCL10	HCC cells, macrophages and TILs	CXCR3	Chemotaxis of T cells and NK cells
	CXCL16	HCC cells	CXCR6	Chemotaxis of neutrophils
	CCL2	HCC cells, macrophages and TILs	CCR2	Chemotaxis of HSC, macrophages, MDSC, and T cells
	CCL5	HCC cells, macrophages and TILs	CCR5	Chemotaxis of T cells and NK cells
	CCL20	HCC cells	CCR6	Chemotaxis of Th17 cells and Tregs
	CCL22	HCC cells and DCs	CCR4	Chemotaxis of Tregs
Angiogenesis	CXCL3, CXCL5	HCC cells	Not clarified	Promoting angiogenesis *via* mechanisms not clarified
	CXCL8	CSCs	Not clarified	Promoting endothelial cell tube formation
	CXCL9	Not clarified	CXCR3	Inhibiting angiogenesis by abrogation of VEGF effects
	CXCL12	Endothelia cells	CXCR4, CXCR7	Enhancing angiogenesis through VEGF
	CXCL16	HCC cells	CXCR6	Promoting angiogenesis via mechanisms not clarified
	CCL2	HCC cells and endothelial cells	CCR2	Enhancing the proliferation of endothelial cells
	CCL3	HCC cells and endothelial cells	CCR1, CCR5	Enhancing the proliferation of endothelial cells
Direct effects on HCC cells	CXCL1, CXCL2, CXCL16	Not clarified	Not clarified	Enhancing the growth of HCC cells
	CXCL5	HCC cells	Not clarified	Enhancing the migration, invasion, and growth of HCC cells
	CXCL8	Not clarified	CXCR2	Enhancing the migration of HCC cells
	CXCL10	hepatocytes	Not clarified	Enhancing the survival of hepatocytes
	CXCL12	HCC cells, HSC	CXCR4, CXCR7	Enhancing the migration, invasion, growth and survival of HCC cells
	CCL2	WAT, CAF	CCR2	Enhancing the migration, invasion, and growth of HCC cells
	CCL3, CCL5	Not clarified	CCR1	Enhancing the migration and invasion of HCC cells
	CCL15	HCC cells	Not clarified	
	CCL20	HCC cells	CCR6	Enhancing the migration, invasion, and growth of HCC cells

HSC: Hepatic stellate cells; TILs: Tumor-infiltrating leucocytes; MDSC: Myeloid derived suppressor cells; Tregs: Regulatory T cells; DCs: Dendritic cells; VEGF: Vascular endothelial growth factor; CSCs: Cancer stem cells; WAT: White adipose tissue; CAF: Cancer-associated fibroblast; HCC: Hepatocellular carcinoma.

is also an important signal for Th17 cells infiltration into HCC[66]. Because Tregs and Th17 cells are two representative T cells with relatively opposite functions in most immune milieu, it is worth elucidating how the two subpopulations work in the same HCC micro-environment.

The CXCL16-CXCR6 and CXCL5-CXCR2 axes have a major effect on neutrophils in HCC. HCC cell lines and tumor tissues contain high levels of CXCL16 and CXCR6, and the latter correlates with increased neutrophils in tumor tissues and with a worsen prognosis of HCC patients[49]. It should be noted that the evidence for direct chemotaxis of neutrophils towards CXCL16 is still lacking, and it is not clear what and how this axis affects neutrophils. In contrast, CXCL5 shows an obvious chemotactic effect on neutrophils *in vitro*, and the level of CXCL5 in HCC tissues significantly associates with the increased neutrophils in the tumor tissues and promotes the progression of tumor[22]. CXCR3 and CCR5 are reported to facilitate different T cells traffic to the HCC, either inhibiting or promoting the progression of HCC. CXCL9 and CXCL10, the ligands for CXCR3, are produced by HCC cells and show potent attraction of $CD4^+$ and $CD8^+$ T cells[17,67]; CCL5 produced by tumor tissues has closely correlated with infiltration of CCR5 positive T cells and macrophages[48,61].

Although macrophages can be efficiently recruited into the tumor sites in HCC *via* CCL2/CCR2 and CCR5[48,56,57], their functions tightly rely on their phenotypes. Upon activation by stimuli such as antigens and cytokines,

macrophages undergo different polarization into either M1 or M2 or M2-like phenotype. M1 phenotype (classical activation, stimulated by TLR ligands and IFN-γ) shows potent anti-tumor functions *via* production of large amount of proinflammatory cytokines, while M2 and M2-like phenotype (alternative activation, stimulated IL-4/IL-13) promote tumor progression *via* tissue remodeling and immunoregulation[68,69]. Therefore, it is worth exploring exactly which phenotypes dominate in the microenvironment and its roles in the progress of HCC.

The abundant chemokines in the HCC milieu contribute greatly to the aberrant infiltration of immune cells; in the meantime, some chemokine receptors on these immune cells also alter significantly, which synergistically contributes to the abnormal migration. To gain a better understanding of the chemokine system in immune cells, these alterations of chemokine receptors should not be neglected.

The initial research finds that CCR6 is reduced significantly in $CD4^+$ and $CD8^+$ T cells from peripheral blood in HCC patients, indicating a possible role in the recruitment of lymphocytes from peripheral blood to HCC[70]; however, following studies in delineated T cell subpopulation find that CCR6 expression is not altered significantly on Th17 cells from either tumor tissues or peripheral blood[66]. In contrast, the expression of CCR6 is significantly higher on IL-17-producing $CD8^+$ T cells (Tc17 cells, derived from HCC tissues) and Tregs (derived from peripheral blood), suggesting a role of CCR6 facilitating Tc17 cells and Tregs infiltration into tumor tissues[31,71]. The origins of immune cells might affect the expression pattern of CCR6[72], but this need more evidence. Similarly, the expression of CCR5 is reduced significantly in $CD4^+$ and $CD8^+$ T cells from peripheral blood in HCC patients[70], but increased on intrahepatic $CD4^+$ and $CD8^+$ T cells, NKT cells, NK cells, and B cells in chronic HCV infection[73]. The detailed comparison of expression levels of CCR5 on $CD4^+$ and $CD8^+$ T cells from different sources yields interesting results: T cells from both tumor infiltrating leukocytes and non-tumor liver-infiltrating lymphocytes show increased levels of CCR5 compared with those from peripheral blood lymphocytes[72]. The expression of other chemokine receptors (CCR2, CCR4, CXCR3, CXCR4 and CXCR6) also exhibits certain alterations on T cells, neutrophils, NK cells, NK T cells[34,35,66,71-74].

ANGIOGENESIS

HCC is the typical tumor with hypervascular behaviors and different anti-angiogenic treatments have been utilizing in clinical practices[75,76]. In addition to the traditional angiogenic factors including vascular endothelial growth factor (VEGF) and angiopoietins, the chemokine system is also involved in this process during the development of HCC.

The CXCL12-CXCR4/CXCR7 axis exhibits a direct pro-angiogenic effect in HCC. The initial findings in the rat model demonstrate that AMD3100 (a specific CXCR4 antagonist) simultaneously decreases the size and number of blood vessels *in vivo*[77]. In support of this result, experiments *in vitro* detect large amount of VEGF produced by the HCC cell line SMCC7721 in the presence of CXCL12; the elevated CXCL12 is responsible for tube formation of endothelial cells *in vitro* and *in vivo*[14]. Importantly, cancer stem cells or tumor-initiating cells (TICs) also utilize chemokines to facilitate the angiogenesis. Previous studies have identified CD133 as a marker of TICs in HCC; the $CD133^+$ cells only account for 1.3%-13.6% of the cells in human primary HCC, whereas they have great potentials to self-renew and differentiate, and constitute the indispensible core for HCC cells[78,79]. The sorted $CD133^+$ TICs secrete high levels of CXCL8, and this chemokine consequently promotes the growth and capillary tube formation of HUVECs *in vitro*; blocking the CXCL8 signal by neutralizing antibodies or RNA interfering in HUEVCs leads to reduction of their ability to proliferate and form capillary tubes *in vitro,* and animal experiments validate the angiogenic functions of CXCL8 *in vivo*[80].

CCL2 and CCL3, which are significantly up-regulated in endothelial cells from HCC tissues, also enhance the proliferation of endothelial cells strikingly[81]; further studies facilitated by the CCR1-knockout mice demonstrate that CCR1, the putative receptor for CCL3, directly induces the growth of endothelial cells in HCC[82]. In the CCR2-knockout mice, the reduced microvessel density is correlated with decreased number of macrophages and hepatic stellate cells which are important components during the angiogenesis[56].

Utilizing a different mechanism, CXCL3, CXCL5, CXCL8, and CXCL16 are found to recruit neutrophils into the HCC tissues, and the neutrophils have a well-defined pro-angiogenic role in hepatocarcinogenesis; disrupting these signals either by antibodies or virus-mediated silencing yields potent anti-angiogenic effects[49,83].

Not all chemokines induce angiogenesis in the context of HCC. For example, in the CXCR3-knockout mice, the microvessels in the liver are much higher than the wild type counterpart; in contrast, stimulation of chemical carcinogen carbon tetrachloride leads to the increased levels of the ligand CXCL9 that efficiently ameliorates the angiogenesis in the liver[84].

DIRECT EFFECTS ON BEHAVIORS OF HCC CELLS

As the scenarios in the immune system[1,85], chemokines not only exert chemotaxis effects on HCC cells but also directly influence the properties of tumor cells. Now it is well demonstrated that chemokines directly affect the migration, invasion, growth and survival of tumor cells, which plays a critical role in the development of HCC.

Among the chemokines and receptors, the CXCL12-CXCR4 axis is of great importance. The first study of CXCR4 in HCC demonstrates that in the presence of

CXCL12 HCC cell lines show peri-nuclear translocation of CXCR4 and increase the invasion ability significantly[86], and the increased expression level of CXCR4 in HCC tissues also correlates with the tumor size, metastasis, and survival[86-88]. The binding of CXCL12 to CXCR4 on HCC cells triggers reorganization of cytoskeleton and activates matrix metalloproteinase-9 (MMP-9) and MMP-2, both of which give rise to increased migration and invasion[89-91]. In the cancerous ascitic fluid, CXCL12 is up to 8364 pg/mL, and this concentration effectively induces the migration of HCC cells[87]. During the epithelial-mesenchymal transition (EMT), the CXCL12-CXCR4 signal also plays an important role. On the one hand, in the TGF-β induced EMT system, CXCR4 is highly expressed and required for the enhanced migration and invasion of HCC cells, and further immunostaining in tumor tissues finds that CXCR4 concentrates at the tumor border and perivascular areas[92,93]; on the other hand, CXCL12 derived from hepatic stellate cells induces EMT of HCC cells *in vitro*, coinciding with the increased migration[94]. The findings that CXCR4 can be modulated by several other molecules in the microenvironment complicate its roles. TGF-β, osteopontin and astrocyte elevated gene-1 significantly up-regulate the expression of CXCR4 *via* NF-κB, PI3K-Akt and JNK pathways[91,93,95]. Glycosaminoglycans also compete with cellular heparan sulfate chains to bind CXCL12, which finally causes inhibition of CXCL12 mediated chemotaxis of HCC cells[96].

The other receptor for CXCL12, CXCR7, also has profound effects on the migration and invasion of HCC cells. Increased expression of CXCR7 is found in HCC tumor tissues and highly invasive cell lines; knockdown of its expression in different invasive cell lines results in reduced migration and invasion abilities both *in vitro* and *in vivo*, and this reduction are partially caused by decreased levels of MMP-2 and MMP-9[14,97]. However, in a large cohort of 408 HCC samples, up-regulation of CXCR7 in HCC tissues is confirmed specifically on endothelial cells, but neither human primary hepatocytes nor HCC cell lines. Furthermore, the expression level of CXCR7 on endothelial cells is regulated by hypoxia and low pH which is the typical microenvironment in HCC[15]. These controversial results need to be verified by more experiments in future.

The effects of the CXCL12-CXCR4 axis on proliferation and survival of HCC cells are examined in different cell lines. Because of the intrinsic heterogeneity of these cell lines, the data seem a little paradoxical. Therefore, when reach the conclusions, we should be more cautious. CXCL12 stimulates the proliferation of Huh7 cells[86], possibly through activation of JNK[89]; analysis of the cell cycle demonstrates that CXCL12 triggers the transition of Huh7 cells from G0 into cycle phase, and also drives those cells in G1 phase into S, G2-M phase[89]. In contrast, in other HCC cell lines such as HepG2, there exist no or subtle such effects. Although HepG2 cells express CXCR4, the binding of CXCL12 does not trigger the Ca^{2+} influx, phosphorylation or internalization of CXCR4, and finally fails to activate the following cascade signals[86,98]. Consequently, blocking this axis by other molecules, such as fucoidan, obviously prevents the growth of HCC cells induced by CXCL12[99]. In another HCC cell line FaO induced by TGF-β, CXCL12 efficiently activates extracellular signal-regulated protein kinases (ERK) pathway and enhances the survival in the absence of serum; however, the proliferation and cell cycle of FaO cells is not affected[93]. Recent data also suggest that CXCL12-CXCR7 axis, another ligation of CXCL12, has the same function on proliferation of HCC cells. Silencing CXCR7 by small interfering RNAs in HCCLM3, a highly invasive HCC cell line with abundant expression of CXCR7, decreases the growth of tumor cells both *in vitro* and *in vivo*[97].

The binding of CCL5 and CCL3 to HCC cells depends on CCR1 expression. After the ligation, CCL5 stimulates the tyrosine phosphorylation of focal adhesion kinase, activates PI3K, MAPK, and Rho kinase, leading to increased migration and invasion of HCC cells[100,101]; in contrast, knocking down the expression of CCR1 on HCC cells or disrupting the binding of CCL5 to CCR1 *via* monoclonal antibodies against SDC-1 or SDC-4 effectively abrogates this effect[101,102]. Once binding to the CCR1, CCL3 also induces the potent influx of Ca^{2+} in HCC cells and consequently stimulates the formation of various pseudopodia. These downstream effects directly enhance the migration of tumor cells[103]. Other recent reports also identify a direct effect of CXCL5, CXCL8, CCL15 and CCL20 on the migration and invasion of HCC cells[22,33,104,105], which sheds more light on this field.

CXCR2, along with its ligands CXCL1, CXCL2, and CXCL5, exhibits potent functions in promoting growth of HCC cells. CXCL5 efficiently promotes the proliferation of HCC cells by activating the PI3K-Akt and ERK1/2 pathways *via* the receptor CXCR2[22]. In another experiment *in vitro*, the addition of CXCL1, CXCL2 as well as CXCL16 significantly increases the proliferation of different HCC cell lines[106]. In addition, other chemokines belonging to the CXC family potently drive the growth and survival of hepatocytes under certain pathophysiological conditions such as toxic liver injury which increases the risk of HCC. CXCL10 is largely secreted by hepatocytes treated with CCL4 in the acute toxic liver injury model, and this increased chemokine efficiently rescues the injured hepatocytes from death in an autocrine manner[107].

CCL2 secreted by white adipose tissue induces lipid accumulation in both the primary hepatocytes and Huh7 cells, suggesting a direct role of CCL2 in the pathogenesis of liver steatosis[108]. In other studies, treating HCC cells with apigenin or co-culture them with cancer-associated fibroblasts significantly inhibits or promotes the proliferation of HCC cells, accompanied by the increase of CCR2/CCL2[109,110]. Nevertheless, direct evidence demonstrating the effects of CCL2-CCR2 axis on HCC cells is needed. In contrast, CCL20 has a definitive role and directly enhances the growth of HCC

cells through activating the p44/42 MAPK pathway[111].

THE CHEMOKINE SYSTEM AS THE COMBINATION TREATMENT TARGETS

HCC is among one of the most refractory tumors resistant to chemotherapies, and now there exist very few drugs available for systemic chemotherapies[112]. The important roles the chemokine system played pave new roads to solve this problem, albeit there are no chemokine-based therapies approved in clinical practices at present.

The roles of each single chemokine and the corresponding receptor in the development of HCC are well documented, and disruption of the signal axis indeed hinders the invasive behaviors of HCC; however, due to the complex of microenvironment in HCC, targeting the chemokines alone might not be enough for successful treatments. In contrast, many studies have already found that the chemokine-based combination therapies are promising.

The bicistronic recombinant adenovirus vector expressing HSV thymidine kinase, a suicide gene, and CCL2 on HCC cells has shown remarkable anti-tumor effects in different HCC models. The apoptosis of HCC cells and abundantly accumulated CCL2 synergistically elicits enhanced infiltration of M1 macrophages and NK cells, as well as elevated IL-12 and IL-18 in tumor tissues[113-115]. In the following work, an improved system with adenovirus vector expressing membrane-bound form of CCL2 manifests more powerful anti-tumor effects with increased intratumoral Mac-1^+ macrophages, $CD4^+$ and $CD8^+$ T cells[116].

Although the role of CCL21/CCL19-CCR7 axis in the development of HCC has not been clearly elucidated, the powerful chemotactic effects of this axis and the specific immune milieu in the liver prompt us to explore the therapeutic effects of the CCL21-CCR7 axis. Over-expression of CCL21 either in HCC cells or in DCs shows potent anti-tumor effects in HCC models. Within the tumors containing high level of CCL21, the number of $CD4^+$ and $CD8^+$ T cells and DCs significantly increases, along with elevated levels of IL-12 and IFN-γ and reduced microvessels[117,118]. To further enforce the anti-tumor effects, we devise the new treatment policy by combination of CCL21 and depleting the immunosuppressive Tregs. The combination therapy manifests better anti-tumor effects with increased intratumoral $CD4^+$ and $CD8^+$ T cells and decreased Tregs not only in the local tumor tissues but also in peripheral lymph organs; in addition, the profiles of cytokines and MMPs are also optimized in tumor tissues[119].

Combination therapies based on IL-12 treatment are very effective in different HCC models. CXCL10 is utilized and the co-transfer of IL-12 and CXCL10 yields a very powerful anti-tumor effect, in which the tumor specific cytotoxic lymphocytes and NK cells both play a key role[120]. With the same inspiration, combination of CXCL10/IL-12 expression vector with α-fetoprotein DNA vaccination also achieves better anti-tumor effects and significantly prolongs the survival of the model mice of HCC[121].

In addition, the traditional therapies of HCC can benefit from chemokine-based treatments. Radio-frequency ablation (RFA) is used to locally eradicate HCC, but the recurrence is relatively high. In the HCC mice model, RFA in combination with injection of CCL3 significantly enhances the number of $CD4^+$, $CD8^+$ T cells and $CD11c^+$ DCs in a CCR1-dependent manner, which finally leads to an obvious inhibition of tumor growth[122]. Cisplatin (cis-diamminedichloroplatinum) reduces the tumor burden by 52%, while the combination of cisplatin and G31P (the CXCL8 antagonist) remarkably enhances the suppression effects; meanwhile, the side effects of cispaltin are also released obviously[123].

CONCLUSION

During the carcinogenesis of HCC, the tumor itself needs pivotal mediators to efficiently modulate the microenvironment. These mediators should simultaneously fulfill the basics of tumor cells and steer or disable the functions of immune cells; the chemokines and their receptors are the ideal mediators. Firstly, the Morse code applied by immune cells for routine surveillance is the most effective way to patrol the body, but this code is unfortunately spied by the tumor cells, by which the tumor cells learn and gain effective invasion and dissemination. Secondly, the mechanisms and weapons gifted by the chemokine system, which are originally authorized to the normal immune cells, are excessively utilized by tumor cells in a pro-tumor way, such as modulating the cell cycle and survival, recruiting other immune cells, and secretion of MMPs, *etc*. Thirdly, the bidirectional influences between the tumor cells and the immune cells are bridged by the chemokine system, and this mutual interaction stabilizes the immunosuppression in the microenvironment of HCC. Taking advantages of the strength rooting in the chemokine system, the HCC cells achieve quick progression even when confronted with the host immune system.

Although we have not succeeded in managing HCC through targeting the chemokine system, the more we understand this system in the context of tumor, the more treatment options we will have. It is likely that the future translational research will give us more answers in verifying the therapeutic value of this complicated system in HCC.

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P- Reviewer: Fabris L, Solinas A **S- Editor**: Song XX
L- Editor: A **E- Editor**: Liu SQ

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