

## Chemokines and hepatocellular carcinoma

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### INTRODUCTION

Chemokines in humans are a family of small proteins of 45-50 kb which contain a structural homologous conservative family of cysteine residues. Chemokines are classified into four families, namely CXC, CC, CX3C and C according to the presence of four cysteine residues in conserved locations. CXC are subdivided into two categories, those with a specific amino acid sequence (or motif) of glutamic acid-leucine-arginine (or ELR for short) immediately before the first cysteine of the CXC motif (ELR-positive), and those without an ELR motif (ELR-negative). CXC and its cognate receptor are combined and activated. The receptors are mainly found in neutrophils, lymphocytes, endothelial cells and epithelial cells. Typical chemokine proteins begin with a signal peptide of approximately 20 amino acids that is cleaved from the mature portion of the molecule during its secretion from the cell. All chemokines share a typical 3-dimensional structure which is stabilized by two disulfide bonds joining the first to the third, and the second to the fourth cysteine residues. CC receptors are mainly distributed in dendritic cells, lymphocytes, macrophages, eosinophilic leukocytes, and natural killer cells, but they do not activate neutrophils. Currently, more than 50 kinds of chemokines have been found with only 20 kinds of chemokine receptors, therefore, in this system a considerable number of useless receptors (receptor, R)/ligand (ligand, L) interact with each other.

Chemokines play a central role in many biological events, such as embryonic development, wound healing, angiogenesis, Th1/Th2 development, leukocyte homeostasis, lymphatic organ development, inflammatory diseases, and tumors. Previous studies suggest that

### Abstract

Chemokines play a paramount role in tumor progression. In hepatocellular carcinoma (HCC) progression, chemokines and their receptors play an intricate role. Currently, chemokines and their receptors such as the CXCL12-CXCR4 axis, CX3CL1-CX3CR1 axis and the CCL20-CCR6 axis have received much research attention. Although a large number of studies show that these axes are strongly associated with HCC, the exact mechanism by which these axes promote the growth and progression of HCC remains unknown. In this paper, several chemokines and their receptor interactions in HCC progression, growth and metastasis and immune response to HCC are reviewed.

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chemokines are soluble molecules, and are involved in inflammatory response by regulating the transfer of white blood cells. Chemokines are now considered to play a critical and complicated role in a variety of cells such as tumor cells. Chronic inflammation is a long-term and low-grade injury caused by chemical factors, bacteria, and viruses, and there is a strong association between chronic inflammatory conditions in a particular organ and cancer specific to that organ such as colon cancer and ulcerative colitis, colorectal cancer and inflammatory bowel disease, pancreatic cancer and chronic pancreatitis, esophageal adenocarcinoma and Barrett's esophagus, liver cancer and hepatitis<sup>[1-3]</sup>. The most striking evidence of the direct regulation of tumors and tumor growth by chemokines is the over-expression of GRO (CXCL1, growth-related oncogene),  $\alpha$ ,  $\beta$ ,  $\gamma$  in human melanoma cells, and its tumorigenicity in nude mice from *in vitro* research<sup>[4,5]</sup>. Recent studies have been focused on the roles of chemokines and their corresponding receptors in the growth and progression of tumors. The chemokines and their receptors involved in these processes are known as axes. At present, a large number of studies have demonstrated that the CXCL12-CXCR4 axis may be related to distant organ metastasis of tumors while the CCL21-CCR7 axis may be associated with lymph node metastasis.

Many studies have been conducted on chemokines and their receptors in hepatocellular carcinoma (HCC). However, various axes may not play the same role in HCC as they do in other tumors. Currently, chemokines and their receptors such as the CXCL12-CXCR4 axis and the CCL20-CCR6 axis have received much research attention. This paper will analyze the relationship between chemokines and their receptors in HCC.

## CXCL12-CXCR4 AXIS IN HCC

The CXCL12-CXCR4 axis is considered to be an important factor in the regulation of angiogenesis which is essential for growth and progression of HCC. Using immunohistochemistry, Li *et al*<sup>[6]</sup> found a much higher expression of the CXCL12-CXCR4 axis in HCC specimens than in adjacent, cirrhosis, liver adenocarcinoma, and normal liver tissues. The findings of the study by Sutton *et al*<sup>[7]</sup> indicated that the CXCL12-CXCR4 axis in HCC cell lines promoted the growth, invasion and metastasis of these cell lines. Liu *et al*<sup>[8]</sup> suggested that CXCR4 and CXCL12 may play an important role in the metastasis of HCC by promoting the migration of tumor cells. In addition, some researchers found that fucoidan exhibited antitumor activity toward Huh7 cells through the down-regulation of CXCL12 expression<sup>[9]</sup>. Data from recent research strongly suggests that CXCL12-CXCR4 stimulates the proliferation of oval cells, and HCC occurrence correlates with the abnormal differentiation of these cells<sup>[10]</sup>. All these studies reveal a strong association between CXCL12-CXCR4 and the incidence of HCC development, however, the exact mechanism remains unknown. Chu *et al*<sup>[11]</sup> conducted studies on HCC cell lines which suggested that the CXCL12-

CXCR4 system mediates active MMP-9 and MMP-2 secretion, which facilitates the consequent metastasis of those cells. Schimanski *et al*<sup>[12]</sup> found that in patients with HCC, the expression of CXCR4 significantly correlated with the progression of local tumor, distant dissemination of lymphatic metastasis, as well as a decreased 3-year-survival rate. Strong expression of CXCR4 was significantly associated with HCC progression. They also found that loss of p53 function did not impact on CXCR4 expression, which indicated that CXCR4 influences HCC progression through other channels. However, Schimanski's work did not suggest which channel may be involved.

Some researchers have shed doubt on whether CXCL12-CXCR4 promotes the growth and progression of HCC. Using immunohistochemistry and RT-PCR, Shibuta *et al*<sup>[13]</sup> detected the down-regulation of CXCL12/CXCR4 expression in HCC and also found that CXCR4 expression correlated with the cell cycle when studying HCC cell lines. Nahon<sup>[14]</sup> conducted a retrospective analysis on 120 HCV-infected HCC patients, and suggested a lack of association between CXCL12/CXCR4, death and HCC recurrence. New research shows that SDF-1-3'A (CXCL12) gene polymorphisms are considered to be relevant factors in HCC occurrence and development which have little to do with CXCR4<sup>[15]</sup>. Different findings from previous studies can be attributed to the various research methods and statistical methods adopted. These studies need to be improved. For example, in Nahon's study, results could be achieved if the sample size was increased. In addition, most of the HCC studies did not include different forms of hepatitis (HBV and HCV) as a variable.

Therefore, even though most of the research data show that the CXCL12-CXCR4 axis is important in HCC, its specific role is still unknown and some evidence to the contrary can not be explained. Further study and discussion are needed to clarify these issues.

## CCL20-CCR6 AXIS IN HCC

There is currently an increasing interest in the CCL20-CCR6 axis in HCC. Fujii *et al*<sup>[16]</sup> found in *in vitro* experiments that the CCL20-CCR6 axis may promote the growth of the hepatoma cell line Huh7 through phosphorylation of mitogen-activated protein kinase (MAPK).

Rubie *et al*<sup>[17]</sup> also studied CCL19, CCL20, CCL21, CXCL12 and the expression of their receptors in HCC, and found that all chemokines were found to be expressed in normal liver and HCC tissues, yet CCL20 was the only chemokine which showed significant up-regulation in HCC tissues. The only chemokine receptor to show significant up-regulation in HCC tissues was CCR6. Clinicopathological analysis revealed a strong association between the levels of expression and the degrees of differentiation. That is, with high differentiation, the expression was low. Therefore, the authors proposed that the CCL20-CCR6 axis plays an important role in the growth and progression of HCC, namely a distinct increase in CCL20 expression rates in HCC tis-

sues of grade III tumors in comparison to grade II tumors. In addition, high expression of CCL20 is often accompanied by high expression of CCR6. Therefore, the authors suggested that CCL20-CCR6 may be involved in the formation and development of HCC.

Uchida *et al.*<sup>[18]</sup> observed the formation of pseudopodia in HCC cell lines with high expression of CCR6, which was not observed in cells low in CCR6. The incidence of intrahepatic metastasis was higher in patients with increased expression of CCR6 than in patients with low expression of CCR6. Disease-free survival was significantly poorer in the high CCR6 expression group than in the low CCR6 expression group. The author concluded that CCR6 might be associated with the intrahepatic metastasis of HCC and may be used as a prognostic factor after hepatic resection for HCC.

In addition, researchers have studied the differences in RNA and protein expression of the chemokines CXCL12, CCL19, CCL20, CCL21 and their receptors in primary liver cancer and colon cancer metastasis; even though they have a high expression of CCL20 and CXCR4, the expression in colon cancer liver metastasis was significantly higher than that in primary liver cancer, thus CXCR4 is important in differentiating primary and secondary liver tumors, while CCL20 and its receptor CCR6 may promote tumor growth in addition to their role in identifying primary and secondary liver tumors<sup>[19]</sup>.

Although a large number of studies show that the CCL20-CCR6 axis is strongly associated with HCC, the exact mechanism by which the CCL20-CCR6 axis promotes the growth and progression of HCC remains unknown.

## FRACTALKINE-CX3CR1 AXIS IN HCC

Fractalkine (CX3CL1) and its receptor CX3CR1 are expressed in DC, NK cells, CD8+ T cells, and macrophages. Although studies have shown that fractalkine can regulate the host immune response, the relationships between the fractalkine-CX3CR1 axis, tumor biochemistry and HCC are unclear. According to recent studies, the fractalkine-CX3CR1 axis is critical in the diagnosis of HCC, because it can not only regulate the immune response, but can also regulate the cell cycle of HCC<sup>[20]</sup>. Relevant experiments indicate that fractalkine can enhance the anti-tumor effect of the immune system against HCC in mice. Tang *et al.*<sup>[21]</sup> observed that CX3CL1 could elicit tumor-specific cytotoxic T cells and an increased production of IL-2 and IFN- $\gamma$  capable of inhibiting tumor growth. Matsubara *et al.*<sup>[20]</sup> found that HCC patients with an high expression of fractalkine and its receptor CX3CR1 have a low rate of recurrence of intrahepatic metastasis or extrahepatic metastasis, which suggest that the expression of fractalkine and its receptor CX3CR1 may be related to the prognosis of HCC patients, and may be involved in tumor immunity by killing tumor cells.

However, some researchers have proposed that there is a lack of association between the CX3CL1-CX3CR1 axis and HCC, as studies have demonstrated that CX3CR1

is not a risk factor for HCC<sup>[22]</sup>. These researchers believe that tumor-derived chemokines have dual roles. Leukocyte aggregation following a signal of increasing chemokine concentration may not only be beneficial to the host, but also contribute to tumor growth. The roles virus-related chemokines play in tumors may be multiple, therefore the specific role of CX3CR1 in the formation of chronic hepatitis and liver disease needs to be elaborated.

In addition, the up-regulated expression of CX3CL1-CX3CR1 in ischemia-reperfusion injury suggests that CX3CL1-CX3CR1 is crucial in reperfusion injury<sup>[23]</sup>.

## OTHER RELATED CHEMOKINES IN HCC

Recent studies have found that the combination of CCL5 with the CCR1 receptor can promote metastasis and invasion of the HCC cell line Huh7<sup>[24]</sup>. Furthermore, studies of the expression of CCL3 and its receptor CCR1 in liver cancer have shown a significantly higher level of expression in cancer tissues. Animal experiments also confirmed the essential contribution of CCL3 and CCR1 to the growth and progression of HCC<sup>[25]</sup>. Recent studies indicated that CCL3 induced by IL-1 combined with its effective receptor CCR1 may be involved in the growth and progression of HCC. The authors studied six chemokines in six types of HCC cell lines and found that all the hepatoma cell lines constitutively and exclusively expressed CCR1 mRNA and its protein on their cell surface, however, the expression of CCR1 was not detected in normal liver cells<sup>[26]</sup>. This research suggested a close relationship between the CCL3-CCR1 axis and HCC.

VCC-1 (VEGF correlated chemokine-1) is a newly discovered chemokine, and has a high expression in breast and colon cancer. Studies have demonstrated that it promotes tumor growth by increasing angiogenesis<sup>[27]</sup>. Our recent studies have shown (findings are not yet published) that the expression of VCC-1 in cancer tissues of HCC patients is much higher than that in paracancerous tissues and normal liver tissues. This expression is related to tumor size and tumor differentiation. The findings suggest that VCC-1 may be involved in the growth and progression of HCC, but whether it plays a role in HCC recurrence and metastasis remains unknown. In addition, it is not clear with which receptor VCC-1 interacts.

## CHEMOKINES AND THEIR RECEPTORS INVOLVED IN HCC TUMOR IMMUNITY

As mentioned above, not all chemokines promote tumor growth and metastasis. Fractalkine/CX3CL1 is believed to be able to inhibit tumor growth<sup>[21]</sup>. Hirano *et al.*<sup>[28]</sup> discovered that some chemokines induced by IFN- $\gamma$  such as Mig (CXCL9) and IP-10 (CXCL10) can promote the gathering of lymphocytes in HCC, and are essential in tumor immunity.

Despite lymphocyte infiltration in liver tumors, the tumor grows and spreads rapidly. Liu *et al.*<sup>[29]</sup> studied the expression of chemokines in HCC tissues and HCC cell lines, and found that IP-10 and Mig were expressed in

serum and tissues. The expression of IP-10 in cancer tissues was higher than that in paracancerous tissues. Auto-crine chemokines in HCC cell lines can lead to CXCR3-specific lymphocytes infiltration. However, if the liver cancer cell lines and normal lymphocytes are cultivated, the expression of CXCR3 in lymphocytes shows a distinct decrease. As a result, the combination of CXCR3 and IP-10 and metastasis of T cells to tumor cells are both reduced. *In vitro* experiments show weakening chemotactic effects of CD4+ and CD8+ T cells from liver cancer cells on IP-10, whereas the chemotactic effects of T-cells from normal tissues on IP-10 were enhanced. This study demonstrated the functional desensitization of the chemokine receptor CXCR3 in lymphocytes from HCC patients by CXCR3 ligands secreted by tumor cells. This may cause lymphocyte dysfunction and subsequently impaired immune defense against the tumor.

## CONCLUSION

In summary, the roles of chemokines in HCC are multiple, and range from promoting to inhibiting. But which role is dominant? HCC may be regulated by complicated chemokines and their receptors. Current studies show that in tumors such as lung cancer, colon cancer and prostate cancer, the CXCL12-CXCR4 axis may be related to tumor metastasis of distant organs and the CCL21-CCR7 axis may be associated with lymph node metastasis. However, further study is needed to clarify these associations in HCC. In addition, there are few reports on the expression of the CCL21-CCR7 axis in HCC although much research has been carried out on the relationship of this axis with lymph node metastasis in other tumors.

Researchers are expected to explore the possibility of chemokines and their receptors being target genes and to utilize their anti-tumor function when treating HCC. Recent studies have shown that co-expression of suicide genes and MCP-1 (monocyte chemotactic protein-1) in rat liver and colon cancer has a significant anti-tumor effect<sup>[50]</sup>. Gene therapy based on a variety of chemokine axes such as the CXCL12-CXCR4 axis is being studied. The desired effect can only be achieved by combining several chemokine axes rather than focusing on a single axis.

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