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Review:

Chemokines and their receptors in lung cancer progression and metastasis*

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Abstract: Lung cancer is the leading cause of cancer-related mortality around the world. Despite advancements in diagnosis, surgical techniques, and neoadjuvant chemoradiotherapy over the last decade, the mortality rate is still high and the 5-year survival is a dismal 15%. Fortunately, early detection by low-dose computed tomography (LDCT) scans has reduced mortality by 20%; yet, overall, 5-year-survival remains low at less than 20%. Therefore, in order to ameliorate this situation, a thorough understanding of the underlying molecular mechanisms is urgently needed. Chemokines and their receptors, crucial microenvironmental factors, play important roles in lung tumor genesis, progression, and metastasis, and exploring the mechanisms of this might bring new insights into early diagnosis and precisely targeted treatment. Consequently, this review will mainly focus on recent advancements on the axes of chemokines and their receptors of lung cancer.

Key words: Lung cancer, Chemokines, Tumor progression, Metastasis
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1 Introduction

Lung cancer is the leading cause of cancer-related mortality in both genders worldwide. In China, with its serious air pollution and high tobacco consumption, the incidence and mortality of lung cancer have increased rapidly in recent years. It has been reported that approximately 500 000 patients were diagnosed and 430 000 died from lung cancer in 2005, and the number of deaths is anticipated to be more than one million by 2025 (Yang *et al*., 2005a; 2005b; Dong *et al*., 2010). Histologically, lung cancer has been classified into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC); the former, originating from respiratory epithelial cells, accounts for 80% of cases with subtypes of adenocarcinoma, squamous cell carcinoma, and large cell carcinoma in order of incidence rate; the latter, from cells with differentiation in neuroendocrine along the bronchial tree, accounts for the remaining 20% (Goldstraw *et al*., 2007; Groome *et al*., 2007; Sutherland and Berns, 2010).

Despite advances in diagnosis, staging, surgical techniques, and neoadjuvant chemoradiotherapy over the last decade, the mortality rate of lung cancer is still high and 5-year survival is only 15% (Siegel *et al*., 2012a; 2012b). As a result of a lack of early specific signs and symptoms, most of these patients are diagnosed at advanced stages where surgery is no longer feasible. Fortunately, early detection with a lung cancer screening program using low-dose

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computed tomography (LDCT) scans has recently brought bright prospects, and the mortality rate has reduced by 20% (National Lung Screening Trial Research, 2011). Nevertheless, overall, 5-year-survival remains low, at less than 20% (Keith and Miller, 2013). Therefore, early detection is only the first step; personalized precise treatments following detection, based on molecular mechanisms, are also crucial; these treatments either fight tumor cells directly or modify the tumor microenvironment indirectly (Burger and Gribben, 2014). Chemokines seem to be central in this microenvironment by promoting leukocyte infiltration and tumorogenesis (Mukaida and Baba, 2012).

Chemokines, a superfamily of inducible, secreted, heparin-binding proteins, are structurally homologous and are involved in tumor growth and metastasis (Keeley *et al*., 2011). The receptors, a superfamily of seven transmembrane spanning proteins coupled to G-protein-coupled-receptors (GPCRs), are classified into four major groups based on the pattern of cysteine residues: CXC, CC, C, and CX3C, where C stands for cysteine and X for non-cysteine amino acids (Zlotnik and Yoshie, 2000). Functionally speaking, chemokines are grouped into inflammatory and homeostatic; the former are induced by inflammation while the latter are constitutively expressed and involved in homeostatic immune regulation (Sarvaiya *et al*., 2013). Their binding leads to conformational changes and the following activation of signaling pathways, which play an important role in both normal inflammatory reactions if the expression is regular and abnormal reactions if aberrant, leading to constitutive activation of oncogenes, inactivation of tumor suppressor genes, or altered expression of transcription factors. This consequently results in tumor angiogenesis, growth, epithelial mesenchymal transition (EMT), and further metastasis (Richmond, 2002; Sparmann and Bar-Sagi, 2004; Mantovani *et al*., 2010).

To date, the most studied chemokine axis in lung cancer is CXCL12/CXCR4, which has been proved to be related to greater invasiveness and higher potential for metastasis (Burger *et al*., 2011; Saintigny and Burger, 2012), and many new drugs targeting this axis are under development (Peled *et al*., 2012). It is the case that other chemokine axes have also been investigated. Therefore, it is necessary to review the role of chemokines and their receptors in lung cancer (Table 1), particularly the most common histological type, NSCLC, in progression and metastasis, which might provide insights into the molecular mechanisms of lung tumorigenesis and progression, and consequently assist early diagnoses and targeted treatments.

2 CXCL12/CXCR4

CXCR4, the most frequently overexpressed and thoroughly studied chemokine receptor in malignancies, is present in many different types of human cancers, including lung cancer (Balkwill, 2004; Burger and Kipps, 2006), the expression of which is upregulated in hypoxia, as might be encountered in a tumor microenvironment (Schioppa *et al*., 2003; Phillips *et al*., 2005). The corresponding ligand, CXCL12, is constitutively expressed in tissues that are targets of metastases (Burger and Kipps, 2006).

In lung cancer, the CXCL12/CXCR4 axis plays a crucial role in migration and metastasis. NSCLC cells expressing CXCR4 were noticed to migrate to tissues or organs with a high level of CXCL12, such as lymph nodes, contralateral lung, liver, brain, and bone marrow (Phillips *et al*., 2003; Belperio *et al*., 2004; Su *et al*., 2005; Wagner *et al*., 2009), even if the primary tumor was resected, just as Wang *et al*. (2014) found that a high expression level of CXCR4 correlated with brain-specific metastasis following complete resection of NSCLC. In addition, the axis can promote cell proliferation, tumor growth, and angiogenesis (Phillips *et al*., 2003; Wald *et al*., 2011), and CXCR4 also appears to have an effect on the biology of cancer stem cells, which possess high self-renewal capacities, potential recapitulation of tumors in ectopic settings, and drug-resistant properties in NSCLC (Eramo *et al*., 2008; Wald *et al*., 2011). NSCLC cells expressing CXCR4 are strong candidates for those stem cells that maintain their property of self-renewal through a CXCR4-mediated signal transducer and activator of transcription 3 (STAT3) pathway (Jung *et al*., 2013). In addition, CXCR4 might act to the transcriptional factor 5T4 downstream in EMT and consequently in migration (Damelin *et al*., 2011). Hence, high expression of CXCL12/CXCR4 is correlated with poor prognosis in NSCLC (Suzuki *et al*., 2008), and a substantial body

Table 1 Summary of chemokines/receptors related to lung tumor progression and metastasis

Chemokine/Receptor	Pro-tumor	Anti-tumor	Reference
CXCL12/CXCR4 (co-expression: Nrf2/EGFR/uPAR)	√		Phillips *et al*., 2003; Belperio *et al*., 2004; Su *et al*., 2005; Eramo *et al*., 2008; Wagner *et al*., 2009; Damelin *et al*., 2011; Montuori *et al*., 2011; Wald *et al*., 2011; Almasi *et al*., 2013; Jung *et al*., 2013; Hu *et al*., 2014; Li and Tai, 2014; Wang *et al*., 2014
Ub/CXCR4 (extracellular Ub)	√		Majetschak, 2011; Yan *et al*., 2013
CXCL1/5/8/CXCR2	√	√	Luppi *et al*., 2007; Maxwell *et al*., 2007; **Acosta *et al*., 2008**; Sun *et al*., 2008; Yanagawa *et al*., 2009; Saintigny *et al*., 2013
CCL2/CCR2	√	√	Li and Tai, 2013; 2014; **Zhang X.W. *et al*., 2013**; Chen *et al*., 2015;
CCL19/21/CCR7	√	√	Muller *et al*., 2001; **Hillinger *et al*., 2003**; Cabioglu *et al*., 2007; **Cao *et al*., 2007**; **Itakura *et al*., 2013**; **Sharma *et al*., 2013**; Zhang Q. *et al*., 2013
CCL25/CCR9	√		Gupta *et al*., 2014
CCL4/CCR5	√		Lee *et al*., 2012; Mango *et al*., 2014
Atypical chemokine receptors (DARC/D6/CCX-CKR)		√	**Addison *et al*., 2004**; **Wu *et al*., 2013**

Nrf2: NF-E2-related factor 2; EGFR: epidermal growth factor receptor; uPAR: urokinase plasminogen activator receptor; Ub: ubiquitin; DARC: Duffy antigen receptor for chemokines; CCX-CKR: ChemocentryX chemokine receptor. References in bold: chemokines/receptors with anti-tumor effect

of literature supports the fact that interruption of this ligand-receptor interaction can inhibit cancer cell migration and metastasis (Burger and Kipps, 2006; Sun *et al*., 2010; Xie *et al*., 2014).

Besides the above, some co-expression proteins and receptors can produce synergistic effects. Nrf2, a key transcriptional factor, regulates antioxidant response to accumulated oxidative reaction with tumor growth (Bauer *et al*., 2013). Its abnormal expression, together with CXCR4, was noticed to contribute to large tumor size, poor differentiation, an advanced TNM stage, lymph node metastasis, and distant metastasis in NSCLC (Hu *et al*., 2014). However, the mechanism underlying this needs to be elaborated. Concomitant overexpression of EGFR and CXCR4 is associated with a worse prognosis in NSCLC, and EGFR can enhance the expression of CXCR4 in NSCLC cells through the PI-3K pathway (Al Zobair *et al*., 2013). Urokinase plasminogen activator receptor (uPAR), a glycoprotein of the Ly-6 family, takes effect in tumorigenesis (Ploug and Ellis, 1994; Dass *et al*., 2008). In human malignancies, uPAR overexpression is associated with an increased propensity for cancer progression and metastasis (Mazar, 2008), and intact uPAR and its cleaved forms are testified to be associated with poor prognosis in NSCLC and SCLC (Almasi *et al*., 2013). uPAR could interfere in CXCR4 activity and regulate the adhesive and migratory ability of CXCR4-expressing cells (Montuori *et al*., 2011). Co-expression of uPAR and CXCR4 promotes tumor growth and metastasis in SCLC (Li and Tai, 2014). Therefore, the role of the CXCL12/CXCR4 axis in lung tumor progression and metastasis can be enhanced when these proteins are aberrantly co-expressed. Targeting these proteins together with the CXCL12/CXCR4 axis would hamper lung cancer progression.

3 Ubiquitin/CXCR4

Ubiquitin (Ub), a post-translational protein modifier inside the cell, was detected in increased concentrations during various disease processes (Majetschak, 2011). Extracellular Ub, a recently identified new ligand for CXCR4, was found to act as an anti-inflammatory immune modulator in hematopoietic cells, and to induce suppressive and apoptotic effects on these cells (Saini *et al*., 2010; Majetschak, 2011). Recent studies on the potential role of extracellular Ub in non-hematological cells found that it had anti-apoptotic effects via activation of the PI3K

pathway and was related to cell migration in epithelial cells. To date, only a few investigations have been carried out on the Ub-CXCR4 axis, which showed that it played an important part in acute lung infection-enhanced lung tumor metastasis (Majetschak, 2011; Yan *et al*., 2013). Nevertheless, the effect on human lung tumors with or without acute inflammation setting of the axis should be further investigated and the mechanism should be elucidated in the future.

4 CXCL1/CXCR2

CXCL1, also called growth-related oncogene protein-α (GRO-α) or melanoma growth stimulatory activity factor (MGSA), is a polypeptide initially isolated from Hs294 human melanoma cells, and belongs to the Glu-Leu-Arg (ELR+) chemokine family that is primarily chemotactic for endothelial cells and neutrophils. These chemokines are potent promoters of angiogenesis by recruiting neutrophils to synthesize and store angiogenic molecules like vascular endothelial growth factors (VEGFs) (Scapini *et al*., 2004), which can induce CXCL1 release via JNK and PI-3K-dependent pathways in human lung carcinoma epithelial cells (Lo *et al*., 2013). CXCL1 was also found to play a pivotal role in thrombin-induced angiogenesis (Caunt *et al*., 2006).

CXCR2, a member of GPCRs, is the receptor of ELR+ CXC chemokines such as CXCL1, CXCL2, CXCL3, CXCL5, and CXCL7 (PPBP). CXCL6 and CXCL8 (interleukin-8 (IL-8)) are shared ligands of CXCR1 and CXCR2. Alveolar epithelial cells transformed by oncogenic KRAS were reported to express high levels of CXCR2 ligands, which recruited inflammatory and endothelial cells and promoted progression of premalignant alveolar lesions to lung adenocarcinoma (Wislez *et al*., 2006), and biopsy specimens of NSCLC had also been found to express high concentrations of CXCR2 ligands (CXCL1, CXCL5, and CXCL8) and type-2 cytokines (IL-4, IL-5, IL-10, and IL-13) (Arenberg *et al*., 1998). NSCLC cell lines and lung adenocarcinomas expressing CXCR2 were noticed to be associated with smoking, CXCL5 expression and poor prognosis by promoting invasion and metastasis (Saintigny *et al*., 2013). In addition, IL-17 was reported to augment secretion of an array of angiogenic CXC chemokines, including CXCL1, CXCL5, CXCL6, and CXCL8 by three different NSCLC cell lines (Numasaki *et al*., 2005), and activation of the IL-8/CXCR2 axis, followed by neutrophils recruitments and eutrophil elastase release, was found to promote lung tumorigenesis in the inflammation settings (Gong *et al*., 2013).

The role of CXCR2 in tumor cells is debatable. Some studies have shown that it could promote cell proliferation, migration, and invasion (Luppi *et al*., 2007; Sun *et al*., 2008; Yanagawa *et al*., 2009) and also assist cancer cells in evading stress-induced apoptosis (Maxwell *et al*., 2007), suggesting that it is a poor prognostic factor, while others have reported recently that depletion of CXCR2 could not only delay replicative senescence but also impair the senescence response to oncogenic signals, suggesting its role in tumor suppression (Acosta *et al*., 2008). Hence, more studies should be conducted to testify the exact role of this axis hereafter.

5 CCL2/CCR2

CCL2, also known as monocyte chemoattractant protein-1 (MCP-1), interacts with its receptor CCR2 and then takes effect not only on mediation of monocytes recruitment during inflammation and immunological reaction, but also on tumor progression and metastasis (Kudo-Saito *et al*., 2013). Investigations from human lung adenocarcinoma cells showed that the expression of MCP-1/CCL2 was induced by activation of protease-activated receptor 2 (PAR2) through matrix metalloproteinase-1 (MMP-1) release which was mediated by the thromboxane A2 receptor (Li and Tai, 2014), and activation of the latter receptor could increase the expression of MCP-1/CCL2 and recruit macrophages, thereby promoting lung cancer invasion (Li and Tai, 2013). In addition, it has been recently reported that the CCL2/CCR2 axis could activate STAT3-Twist signaling corporately and subsequently enhance EMT induced by IL-6 (Chen *et al*., 2015), thus leading to lung cancer metastasis. Nevertheless, a study of 134 NSCLC surgical specimens revealed that MCP-1/CCL2 was detected much more than CCR2 with no positive correlation, and overexpression of MCP-1/CCL2 was a good independent prognostic factor for NSCLC patients

(Zhang X.W. *et al*., 2013). Therefore, more studies are warranted to testify the real role of this axis in human lung cancers.

6 CCL19/21/CCR7

CCR7, another member of GPCRs, has two ligands, CCL19 and CCL21, is preferentially expressed on naive T cells and mature dendritic cells (DCs), and binds to its ligands in promotion of migration, invasion, and chemotaxis of some cells, including T cells, B cells, natural killer (NK) cells, mature DCs, and some tumor cells (Ding *et al*., 2003; Iijima *et al*., 2005).

Overexpression of CCR7 was demonstrated to closely correlate with invasion and metastasis of NSCLC in most investigations (Muller *et al*., 2001; Cabioglu *et al*., 2007), and the underlying mechanism might be up-regulation of heparanase via specificity protein-1 (Sp1) to promote invasion (Zhang Q. *et al*., 2013). However, other studies found that CCL19 had an antitumor effect with corroboration of its promoting interferon (IFN)-γ-dependent antitumor responses in a lung cancer model (Hillinger *et al*., 2003; Cao *et al*., 2007); and high CCR7 expression was strongly related to CrkL and c-ABL kinase mRNA expression and could improve postoperative prognosis of lung adenocarcinoma patients (Itakura *et al*., 2013). In addition, a phase-1 clinical trial of immunotherapy found that DCs expressing CCR7 receptor ligand CCL21 administrated into lung tumors could enhance immunity and subsequently make the tumor shrink (Sharma *et al*., 2013). Consequently, this chemokine axis is like a double-edged sword acting for both good and bad according to the particular microenvironment during lung cancer progression and metastasis.

7 CCL25/CCR9

The natural ligand of CCR9, CCL25, is a thymus-expressed chemokine, which has been found primarily in the involvement of immune homeostasis and then in human solid tumors such as colorectal, prostate, ovarian, and breast cancers with relation to tumor invasion and metastasis (Singh *et al*., 2004; Svensson and Agace, 2006; Johnson-Holiday *et al*., 2011; Singh *et al*., 2011; Chen *et al*., 2012). However, the study of the CCL25/CCR9 axis on lung cancer is limited; so far, only one study has found that its expression correlated with aggressiveness and mediated key steps of metastasis in clinical samples and cell lines of NSCLC, especially in adenocarcinomas compared with squamous cell carcinomas, due to differential expression of matrix metalloproteinases and tissue inhibitor of metalloproteinases under the influence of CCL25 (Gupta *et al*., 2014). Further and more studies are needed to explore the exact effect of the CCL25/CCR9 axis on lung cancer. If it does act as a pro-metastasis factor, targeting it would be of assistance in comprehensive tumor treatments.

8 CCL4/CCR5

CCL4, the ligand of CCR5, was found to enhance expression of stromal-derived factor-erythroid differentiation regulator 1 (ERDR1), which could promote cancer cell survival. CCR5 on pulmonary mesenchymal cells could promote experimental metastasis via the induction of ERDR1 (Mango *et al*., 2014), while deficiency of CCR5 suppressed tumor development by means of inactivation of nuclear factor-κB (NF-κB) and inhibition of monocyte chemoattractant protein-1 (MCP-1) in an urethane-induced lung tumor model (Lee *et al*., 2012). Accordingly, the CCL4/CCR5 axis seems to play a role in lung tumor progression and metastasis. Investigations of lung cancer patients should be conducted to test the effect in the future.

9 Atypical chemokine receptors

Atypical chemokine receptors including three members, the Duffy antigen receptor for chemokines (DARC), D6, and the ChemocentryX chemokine receptor (CCX-CKR), differ from other typical chemokine receptors, because they can efficiently internalize their cognate chemokine ligands without inducing a signaling cascade acting as chemokine scavengers.

In lung cancer, DARC-expressing A549 cells were observed to have a significant reduction in cellularity, increased levels of necrosis, lower microvessel

density, and decreased metastasis (Addison *et al*., 2004). D6 could inhibit human NSCLC growth by sequestration of some chemokines like CCL2, CCL4, and CCL5 (Wu *et al*., 2013).

It was reported that CCX-CKR acted as a negative regulator of growth and metastasis in breast cancer mainly by sequestration of homeostatic chemokines such as CCL19, CCL21, CCL25, and CXCL13, and subsequent inhibition of intratumoral neovascularity (Feng *et al*., 2009). However, studies on CCX-CKR expression status and its relation to tumor progression and invasion are lacking for lung cancer to date.

10 Conclusions

In conclusion, a group of chemokines and their receptors are aberrantly expressed during lung tumorigenesis, progression, and metastasis, leading to an unbalance of the tumor microenvironment. Overexpressed pro-tumor chemokines and receptors are correlated with poor prognosis, and thus diagnoses and treatments targeted at them could bring a bright future for lung cancer patients. Although normally expressed anti-tumor chemokines and their receptors may be correlated with better prognosis, further studies are needed to elucidate them for human lung cancers and translate this into clinical utilization.

Compliance with ethics guidelines

Zeng-hui CHENG, Yu-xin SHI, Min YUAN, Dan XIONG, Jiang-hua ZHENG, and Zhi-yong ZHANG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：趋化因子及其受体在肺癌侵袭与转移过程中的作用

概　要：本文对近年来与肺癌侵袭、转移相关的趋化因子轴及其可能的机制进行综述，为靶向治疗提供理论线索，并预测促癌趋化因子轴的激活与抑癌趋化因子轴的失活可能导致了肺癌的侵袭与转移。

关键词：肺癌；趋化因子；肿瘤进展；转移