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Chemokines & Their Receptors in Non-Small Cell Lung Cancer Detection

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1. Introduction

One of the most commonly diagnosed cancers is non-small cell lung cancer (NSCLC), which is the leading cause of lung cancer related deaths throughout the world [1,2]. NSCLC is an aggressive tumor having poor surveillance. Patients with NSCLC have only 15% or less five year survival rate [3]. Many genetic abnormalities involved in the pathogenesis of NSCLC e.g. mutation in the *p53* gene a tumor suppressor gene.

Chemokines; a superfamily of cytokines, low molecular weight (8-10kDa) proteins, are chemo-attractants for leukocytes and chemokines contains more than 40 ligands and 20 receptors [4,5]. Chemokines can be grouped into four sub families on the basis of the first two of four conserved cysteine residues, functional activity and receptor binding properties and are abbreviated as C, CC, CXC and CX3C.

C chemokines or γ chemokines contains only two cysteines residues; one cysteine present at amino terminal and second present downstream, present in thymus and are chemoattractant for T cell precursors.

CC chemokines are also called as ß-chemokines, have two adjacent cysteines at their N-terminal. These proteins induce the migration of immune cells, mainly dendritic cells, natural killer cells and monocytes.

CXC chemokines or α-chemokines are those in which single amino acid separates two adjacent cysteines present at N- terminal, thus have an "X" in their name. These are divided into two groups, ELR positive and ELR-negative.

In CX3C chemokines or d-chemokines, two cysteines are separated by three amino acids. It acts in an autocrine manner i.e. secreted and act on the same cell.

Chemokines have an important role in pro-inflammatory as well as non-inflammatory cell homing [6]. Chemokines cause the migration of leukocytes to inflammatory sites and also play role in the hematopoietic stem cells regulation, angiogenesis and the extracellular matrix. This super-family also plays additional role in diverse fields including development, immunology and cancer.

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Chemokines also play an important role in the neoplastic transformation of a cell, encourage angiogenesis, tumor colonial expansion and changes in EMC and also mediate organ specific metastasis during carcinogenesis [7;8]. Tumor metastatic potential can be determined by the tumor microenvironment and target organs [9;10].

Chemokine receptors are G protein coupled receptors and numerous cells show the expression of these receptors including leukocytes, endothelial cells, stromal cells, epithelial cells and tumor cells [10-12]. These receptors have vital roles in malignant tumor and cardiovascular diseases, also play role in allergic reactions, tissue damage and microbial infections [13;14]. Chemokine receptors are classified into four subfamilies on the basis of four subfamilies of chemokines they bind, CXCR, CCR, CX3CR and XCR.

Chemokine receptors play major role in tumor metastasis [14-16]. At each step of metastasis these receptors potentially facilitate tumor dissemination. In order to estimate the clinical significance of these receptors few clinical studies have been done. But there is no comprehensive study regarding all the chemokine receptors in NSCLC [17-19].

2. Expression of CXCL8 in NSCLC

In cancers having angiogenic phenotypes like NSCLC, CXCL8 is a very effective and powerful angiogenic factor. Its receptors are CXCR1 and CXCR2 [20].Tumor angiogenesis, metastasis and poor survival rate is related to high level of CXCL8 [21-23].

CXCL8 directly promotes proliferation of endothelial cell, chemo taxis and tubular morphogenesis [24-26]. CXCL8 was identified in a gene expression of patients that were predictive of poor prognosis with stage 1 lung cancer [7;27].

Two of the six cell lines of NSCLC expressed high levels of CXCL8, these cell lines are A549 and H441, while the other cell lines expressed low levels of CXCL8. Earlier studies assumed that only cancer cells produce CXCL8. However stromal cells secrete high level of CXCL8 and also increase tumor cells in tumor and stromal cells co-culture. Mechanism of this induction is still undefined. In several in-vitro models, cell to cell contact is involved in the induction of CXCL8 [20]. Role of CXCL8 in lung cancer is not obvious. CXCL8 receptors are present on lung cancerous cells but their effect on tumor angiogenesis and proliferation is still uncertain.

CXCR1 is a major receptor of CXCL8 which allows or influence the mitogenic activity of it in NSCLC. Thus, targeting mitogenic and angiogenic activity of CXCL8 may help to control tissue invasion and metastasis of NSCLC [20]. Circulating human CXCL8 can be a valuable, clinically applicable tumor protein marker owed to its affirmative correlation by means of numerous physiologic variables related by lung cancer progression.

3. Expression of CXCL5 & CXCL12 in NSCLC

CXCL5 is an important mediator of angiogenesis in NSCLC. In different experimental studies, it is observed that angiogenesis in NSCLC is directly correlated to higher level of CXCL5 [28].

Surgical specimens of NSCLC show a direct link between tumor angiogenesis and CXCL5. In SCID mice, CXCL5 expression was directly related to tumor proliferation and metastasis.

Reduction of CXCL5 expression, reduce tumor proliferation and metastases [28].This was also suggested by recent studies that the presence of CXCL5 in NSCLC have higher degree of correlation with both tumor proliferation and patient prognosis [21;29].

CXCL12 with CXCR4 had also been involved in stimulating angiogenesis of NSCLC [30;31]. However, recent experimental studies of NSCLC make it clear that CXCR4 is expressed on cancerous cells and does not stimulate tumor angiogenesis in an in vivo culture. In this experimental study, with reduction of CXCL12 level, no significant change in primary tumor size and tumor angiogenesis was observed [32].

However, there is an obvious reduction of metastasis of these tumors into *in vitro* culture, indicating that the CXCL12/CXCR4 promotes metastasis and proliferation of the tumor cells. A reason for this noticeable difference of these *in vivo* studies from other *in vitro* studies of angiogenesis mediated by CXCL12/CXCR4 is that CXCR4 expressing tumor cells can "outcompete" tumor-associated endothelial cells for CXCL12. Therefore, there is a very great difference in the function of CXCL12 against the other factors associated with angiogenesis, such that metastasis is promoted by CXCL5, CXCL8, and vascular endothelial growth factors.

CXCL5 & CXCL12 receptors over expression in tumor tissues possibly will suggest the development of diagnostic agents and therapy targeted at chemokine receptor–over expressing tumors. In this regard only some exhaustive clinical studies have been undertaken to assess the clinical importance of these receptors status but no comprehensive study has been known in NSCLC.

4. Expression of CXCR1& CXCR2

There are two cell surface receptors which bind to CXCL8, known as CXCR1 and CXCR2; these receptors have similar structure but different binding sites [33]. CXCR1 binds only with one CXC chemokine, CXCL8, while CXCR2 binds to numerous CXC chemokines. These receptors are present on different cell types including leukocytes, keratinocytes, endothelial cells [34;35] and various tumor cells including NSCLC[36;37].

When functions of CXCL8 and importance of its receptors, CXCR1 and CXCR2 were observed in different cancer cell lines, it was found that an increased level of CXCL8 mediated cell invasion and migration is directly correlated with increased expression of CXCR1 &CXCR2. By using different neutralizing antibodies, it was observed that CXCR1 was not involved in cell migration and invasion, only CXCR2 was involved, while both receptors are involved in angiogenesis. Thus making strategies against CXCL8 signaling pathways promises a better therapy of cancer. It is demonstrated by several studies that CXCR2 is responsible for CXCL8 mediated angiogenesis in NSCLC and human micro vascular endothelial cells [24;38;39].

CXCR1 is an important receptor which promotes the function of CXCL8. Thus targeting expression of CXCR1 & production of CXCL8 may ultimately help to develop strategies against lung cancer proliferation, invasion and metastasis.

5. Expression of CXCR4

CXCR4 is receptor for chemokine CXCL12. In NSCLC, tumor cells at stage 1 show expression of CXCR4, present in the nucleus and cytoplasm of these tumor cells. Several

studies on tumor cells show that CXCR4 positive nuclear staining is related with improve survival rate. The 5 year overall survival rate was 93% for the patients having strong nuclear staining 52% for those having weak nuclear staining [10].

CXCL12 and its receptor CXCR4 promote metastasis of different tumors having angiogenic phenotype including NSCLC [17;32;40-42].CXCR4 may transform a benign tumor to malignant phenotype [17;43].

6. Expression of CXCR7

It was previously thought that CXCL12 has only one surface receptor, CXCR4, but Burns and colleagues [14;44] characterized that another receptor CXCR7 binds CXCL12. CXCR7 together with CXCR3 also has another ligand CXCL11. CXCR7 presents on many cell lines including cancer cell lines, fetal liver cells and activated endothelial cells. It facilitates angiogenesis and the blockage of CXCR7 inhibits tumor growth in mouse models.

Patients with EGFR gene mutations show high level of CXCR7 expression. Choi and colleagues reported that mutations in one EGFR domain, tyrosine kinase are responsible for phosphorylation of EGFR, tyrosine independent mutations and caused constant activation of EGFR [14;45].

Molecular analysis of tumor of patients that took part in the TRIBUT or IDEAL/INTAC experimental study revealed that patients with improve prognosis had an EGRF mutated tumor. This is one of the explanations that CXCR7 is an independent disease free prognostic factor [14].

Wang and colleagues by using qualitative mRNA characterized that increasing tumor grade show increased expression of CXCR7 in prostate cancer. Fluorescence activated cell sorting analysis also indicated higher CXCR7 expression [46].

In conclusion higher expression of CXCR7 is linked with tumor metastasis and poor survival of patients with P-stage1 NSCLC. As the elevated CXCR7 expression is directly correlated with increased EGFR gene mutations, therefore the expression of CXCR7 is not the only one factor for overall survival. We can also say that in future, studies of CXCR7 possibly will lead on the road to the development of diagnostic agents and targeted therapy for patients with p-stage I NSCLC.

7. Expression of receptors in tumor islets

Survival of NSCLC patients is directly related to CXCR2, CXCR3 and CXCR4 expression in tumor stroma. Expression of CXCR3 and CCR1 is also positively correlated to increase in number of mast cells and islet macrophages. The chemokine receptor CCR1 is present on macrophages and involved in the migration of macrophages into tumor islets. CCR1 is a receptor of CCL3 protein. TNF-α production and release is stimulated by CCL1 and has cytotoxic potential in tumor islets. Natural killer cells, T lymphocytes and mast cells show the expression of CXCR3; there is no evidence of expression of CXCR3 on macrophages [4;47-49]. These immune cells are linked with increase survival in NSCLC and together with macrophages involved tumor killing [4;19;50;51].

The tumors enriched for cells expressing CXCR3, having large quantities of one or all of the CXCR3 binding chemokines including CXCL9, CXCL10 and CXCL11. Host anti tumor

immune response is mediated by expression of CXCR3 on various immune cells in mouse model. CXCR3 binding chemokines are secreted by a variety of inflammatory and structural cells and act as indicating markers for Th1 immunological [4;52].

In NSCLC, CCL5 produced by tumor epithelial cells and involved in determination of the nature and intensity of the immune response. While CXCR2 is not expressed in epithelial cells of the tumor islets, but is expressed on inflammatory cells. Expression of CXCR2 is directly correlated with increased survival. So it is suggested that neoplastic transformation is promoted by reduction of CXCR2 expression on epithelial cells in NSCLC. It is also suggested that expression of CXCR2 on inflammatory cells used to limit tumor proliferation. There is dichotomy in function of CXCR2 in NSCLC. In the stroma, it acts as an angiogenic factor and helps in tumor proliferation, but on the other side by the recruitment of the inflammatory cells to tumor islet, it limits tumor growth. Thus targeting CXCR2 has unpredictable effects depending on the relative balance between these two different functions [4].

Conclusively, this information can be considered to target the chemokines and chemokine receptors to establish the therapeutic strategies and to confine the tumor microenvironment to minimize the possibility of metastasis.

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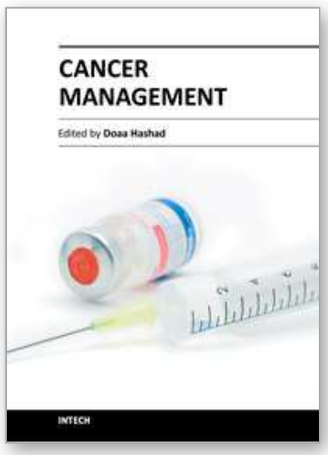

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