We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

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

Nadeem Sheikh*, Tasleem Akhtar and Nyla Riaz

Department of Zoology, University of the Punjab, Q-A campus, Lahore, Pakistan

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 β -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 δ -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.

* Corresponding Author

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 metastases²⁸. 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 observed³².

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 sites³³. 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 TRIBUTE 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.

8. Acknowledgements

The authors are thankful to the Vice Chancellor of the University of the Punjab, Lahore, Pakistan for providing the financial assistance to meet the publication expenses.

9. References

- [1] Bhattacharjee A, Richards WG, Staunton J et al. Classification of human lung carcinomas by mRNA expression profiling reveals distinct adenocarcinoma subclasses. *Proc.Natl.Acad.Sci.U.S.A* 2001;98:13790-13795.
- [2] Jemal A, Siegel R, Ward E et al. Cancer statistics, 2007. *CA Cancer J.Clin.* 2007;57:43-66.
- [3] Mulshine JL, Sullivan DC. Clinical practice. Lung cancer screening. *N.Engl.J.Med.* 2005;352:2714-2720.
- [4] Ohri CM, Shikotra A, Green RH, Waller DA, Bradding P. Chemokine receptor expression in tumour islets and stroma in non-small cell lung cancer. *BMC.Cancer* 2010;10:172.
- [5] Rossi D, Zlotnik A. The biology of chemokines and their receptors. *Annu.Rev.Immunol.* 2000;18:217-242.
- [6] Slettenaar VI, Wilson JL. The chemokine network: a target in cancer biology? *Adv.Drug Deliv.Rev.* 2006;58:962-974.
- [7] Baird AM, Gray SG, O'Byrne KJ. Epigenetics underpinning the regulation of the CXC (ELR+) chemokines in non-small cell lung cancer. *PLoS.One.* 2011;6:e14593.
- [8] Lazennec G, Richmond A. Chemokines and chemokine receptors: new insights into cancer-related inflammation. *Trends Mol.Med.* 2010;16:133-144.
- [9] Balkwill F. Cancer and the chemokine network. *Nat.Rev.Cancer* 2004;4:540-550.
- [10] Reckamp KL, Figlin RA, Burdick MD et al. CXCR4 expression on circulating pan-cytokeratin positive cells is associated with survival in patients with advanced non-small cell lung cancer. *BMC.Cancer* 2009;9:213.

- [11] Kakinuma T, Hwang ST. Chemokines, chemokine receptors, and cancer metastasis. *J.Leukoc.Biol.* 2006;79:639-651.
- [12] Zlotnik A, Yoshie O. Chemokines: a new classification system and their role in immunity. *Immunity.* 2000;12:121-127.
- [13] Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002;420:860-867.
- [14] Iwakiri S, Mino N, Takahashi T et al. Higher expression of chemokine receptor CXCR7 is linked to early and metastatic recurrence in pathological stage I nonsmall cell lung cancer. *Cancer* 2009;115:2580-2593.
- [15] Rollins BJ. Chemokines. *Blood* 1997;90:909-928.
- [16] Taub DD. Chemokine-leukocyte interactions. The voodoo that they do so well. *Cytokine Growth Factor Rev.* 1996;7:355-376.
- [17] Spano JP, Andre F, Morat L et al. Chemokine receptor CXCR4 and early-stage non-small cell lung cancer: pattern of expression and correlation with outcome. *Ann.Oncol.* 2004;15:613-617.
- [18] Su L, Zhang J, Xu H et al. Differential expression of CXCR4 is associated with the metastatic potential of human non-small cell lung cancer cells. *Clin.Cancer Res.* 2005;11:8273-8280.
- [19] Takanami I. Overexpression of CCR7 mRNA in nonsmall cell lung cancer: correlation with lymph node metastasis. *Int.J.Cancer* 2003;105:186-189.
- [20] Zhu YM, Webster SJ, Flower D, Woll PJ. Interleukin-8/CXCL8 is a growth factor for human lung cancer cells. *Br.J.Cancer* 2004;91:1970-1976.
- [21] Chen JJ, Yao PL, Yuan A et al. Up-regulation of tumor interleukin-8 expression by infiltrating macrophages: its correlation with tumor angiogenesis and patient survival in non-small cell lung cancer. *Clin.Cancer Res.* 2003;9:729-737.
- [22] Masuya D, Huang C, Liu D et al. The intratumoral expression of vascular endothelial growth factor and interleukin-8 associated with angiogenesis in nonsmall cell lung carcinoma patients. *Cancer* 2001;92:2628-2638.
- [23] Yuan A, Yang PC, Yu CJ et al. Interleukin-8 messenger ribonucleic acid expression correlates with tumor progression, tumor angiogenesis, patient survival, and timing of relapse in non-small-cell lung cancer. *Am.J.Respir.Crit Care Med.* 2000;162:1957-1963.
- [24] Anderson IC, Mari SE, Broderick RJ, Mari BP, Shipp MA. The angiogenic factor interleukin 8 is induced in non-small cell lung cancer/pulmonary fibroblast cocultures. *Cancer Res.* 2000;60:269-272.
- [25] Koch AE, Polverini PJ, Kunkel SL et al. Interleukin-8 as a macrophage-derived mediator of angiogenesis. *Science* 1992;258:1798-1801.
- [26] Kumar R, Yoneda J, Bucana CD, Fidler IJ. Regulation of distinct steps of angiogenesis by different angiogenic molecules. *Int.J.Oncol.* 1998;12:749-757.
- [27] Seike M, Yanaihara N, Bowman ED et al. Use of a cytokine gene expression signature in lung adenocarcinoma and the surrounding tissue as a prognostic classifier. *J.Natl.Cancer Inst.* 2007;99:1257-1269.
- [28] Arenberg DA, Keane MP, DiGiovine B et al. Epithelial-neutrophil activating peptide (ENA-78) is an important angiogenic factor in non-small cell lung cancer. *J.Clin.Invest* 1998;102:465-472.

- [29] White ES, Flaherty KR, Carskadon S et al. Macrophage migration inhibitory factor and CXC chemokine expression in non-small cell lung cancer: role in angiogenesis and prognosis. *Clin.Cancer Res.* 2003;9:853-860.
- [30] Bachelder RE, Wendt MA, Mercurio AM. Vascular endothelial growth factor promotes breast carcinoma invasion in an autocrine manner by regulating the chemokine receptor CXCR4. *Cancer Res.* 2002;62:7203-7206.
- [31] Salcedo R, Wasserman K, Young HA et al. Vascular endothelial growth factor and basic fibroblast growth factor induce expression of CXCR4 on human endothelial cells: In vivo neovascularization induced by stromal-derived factor-1alpha. *Am.J.Pathol.* 1999;154:1125-1135.
- [32] Phillips RJ, Burdick MD, Lutz M et al. The stromal derived factor-1/CXCL12-CXC chemokine receptor 4 biological axis in non-small cell lung cancer metastases. *Am.J.Respir.Crit Care Med.* 2003;167:1676-1686.
- [33] Cerretti DP, Kozlosky CJ, Vanden Bos T et al. Molecular characterization of receptors for human interleukin-8, GRO/melanoma growth-stimulatory activity and neutrophil activating peptide-2. *Mol.Immunol.* 1993;30:359-367.
- [34] Cataisson C, Ohman R, Patel G et al. Inducible cutaneous inflammation reveals a protumorigenic role for keratinocyte CXCR2 in skin carcinogenesis. *Cancer Res.* 2009;69:319-328.
- [35] Richardson RM, Marjoram RJ, Barak LS, Snyderman R. Role of the cytoplasmic tails of CXCR1 and CXCR2 in mediating leukocyte migration, activation, and regulation. *J.Immunol.* 2003;170:2904-2911.
- [36] Norgauer J, Metzner B, Schraufstatter I. Expression and growth-promoting function of the IL-8 receptor beta in human melanoma cells. *J.Immunol.* 1996;156:1132-1137.
- [37] Varney ML, Li A, Dave BJ et al. Expression of CXCR1 and CXCR2 receptors in malignant melanoma with different metastatic potential and their role in interleukin-8 (CXCL-8)-mediated modulation of metastatic phenotype. *Clin.Exp.Metastasis* 2003;20:723-731.
- [38] Heidemann J, Ogawa H, Dwinell MB et al. Angiogenic effects of interleukin 8 (CXCL8) in human intestinal microvascular endothelial cells are mediated by CXCR2. *J.Biol.Chem.* 2003;278:8508-8515.
- [39] Salcedo R, Resau JH, Halverson D et al. Differential expression and responsiveness of chemokine receptors (CXCR1-3) by human microvascular endothelial cells and umbilical vein endothelial cells. *FASEB J.* 2000;14:2055-2064.
- [40] Burger JA, Kipps TJ. CXCR4: a key receptor in the crosstalk between tumor cells and their microenvironment. *Blood* 2006;107:1761-1767.
- [41] Muller A, Homey B, Soto H et al. Involvement of chemokine receptors in breast cancer metastasis. *Nature* 2001;410:50-56.
- [42] Phillips RJ, Mestas J, Gharaee-Kermani M et al. Epidermal Growth Factor and Hypoxia-induced Expression of CXC Chemokine Receptor 4 on Non-small Cell Lung Cancer Cells Is Regulated by the Phosphatidylinositol 3-Kinase/PTEN/AKT/Mammalian Target of Rapamycin Signaling Pathway and Activation of Hypoxia Inducible Factor-1+|. *Journal of Biological Chemistry* 2005;280:22473-22481.
- [43] Holland JD, Kochetkova M, Akekawatchai C et al. Differential functional activation of chemokine receptor CXCR4 is mediated by G proteins in breast cancer cells. *Cancer Res.* 2006;66:4117-4124.

- [44] Burns JM, Summers BC, Wang Y et al. A novel chemokine receptor for SDF-1 and I-TAC involved in cell survival, cell adhesion, and tumor development. *J.Exp.Med.* 2006;203:2201-2213.
- [45] Choi SH, Mendrola JM, Lemmon MA. EGF-independent activation of cell-surface EGF receptors harboring mutations found in gefitinib-sensitive lung cancer. *Oncogene* 2007;26:1567-1576.
- [46] Wang J, Shiozawa Y, Wang J et al. The role of CXCR7/RDC1 as a chemokine receptor for CXCL12/SDF-1 in prostate cancer. *J.Biol.Chem.* 2008;283:4283-4294.
- [47] Brightling CE, Kaur D, Berger P et al. Differential expression of CCR3 and CXCR3 by human lung and bone marrow-derived mast cells: implications for tissue mast cell migration. *J.Leukoc.Biol.* 2005;77:759-766.
- [48] Newton P, O'Boyle G, Jenkins Y, Ali S, Kirby JA. T cell extravasation: demonstration of synergy between activation of CXCR3 and the T cell receptor. *Mol.Immunol.* 2009;47:485-492.
- [49] Wendel M, Galani IE, Suri-Payer E, Cerwenka A. Natural killer cell accumulation in tumors is dependent on IFN-gamma and CXCR3 ligands. *Cancer Res.* 2008;68:8437-8445.
- [50] Villegas FR, Coca S, Villarrubia VG et al. Prognostic significance of tumor infiltrating natural killer cells subset CD57 in patients with squamous cell lung cancer. *Lung Cancer* 2002;35:23-28.
- [51] Welsh TJ, Green RH, Richardson D et al. Macrophage and mast-cell invasion of tumor cell islets confers a marked survival advantage in non-small-cell lung cancer. *J.Clin.Oncol.* 2005;23:8959-8967.
- [52] Matsuda A, Fukuda S, Matsumoto K, Saito H. Th1/Th2 cytokines reciprocally regulate in vitro pulmonary angiogenesis via CXC chemokine synthesis. *Am.J.Respir.Cell Mol.Biol.* 2008;38:168-175.

IntechOpen

Cancer Management

Edited by Dr. Doaa Hashad

ISBN 978-953-51-0650-0

Hard cover, 94 pages

Publisher InTech

Published online 13, June, 2012

Published in print edition June, 2012

Cancer remains a major clinical challenge as a cause of death due to its frequent poor prognosis and limited treatment options in many cases. Cancer management book addresses various cancer management related topics including new approaches for early cancer detection and novel anti-cancer therapeutic strategies. This book is a collection of studies and reviews written by experts from different parts of the world to present the most up-to-date knowledge on cancer management.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Nadeem Sheikh, Tasleem Akhtar and Nyla Riaz (2012). Chemokines & Their Receptors in Non-Small Cell Lung Cancer Detection, Cancer Management, Dr. Doaa Hashad (Ed.), ISBN: 978-953-51-0650-0, InTech, Available from: <http://www.intechopen.com/books/cancer-management/expressions-of-cxc-chemokines-and-their-receptors-in-non-small-cell-lung-cancer>

INTeCH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen