Review Articles

New cytokine: stromal derived factor-1

K. Jaszczyñska-Nowinka[1], A. Markowska[2]

[1]Department of Gynaecological Oncology; [2]Perinathology and Gynaecology Department, Poznan University of Medical Sciences, Poznan (Poland)

Summary

Cytokines are proteins which regulate and control the basic functions of cells, including proliferation, differentiation and migration by auto- and paracrine communication. Chemokines are a family of proinflammatory chemotactic cytokines. Chemokines play a significant role in many physiological and pathological processes. Chemokines usually join many receptors, and the same receptors can join many different chemokines. SDF-1 works by its receptor CXCR4. The SDF-1+CXCR4 complex plays a significant role in the creation of metastases of neoplasms and as a response to cytostatic treatment. Identification of this complex may be a useful prognostic factor in the therapy of many types of carcinoma. The ability to block CXCR4 indicates the existence of new targets in breast or ovarian carcinoma treatment as well as in cases of cervical adenocarcinoma.

Key words: Chemokines; Stromal derived factor (SDF-1); CXCR4; Complex SDF-1-CXCR4.

Introduction

Cytokines are proteins which regulate and control the basic functions of cells, including proliferation, differentiation and migration by auto- and paracrine communication. Among many divisions of cytokines specific proinflammatory, proangiogenic, haemopoietic and inhibitor cytokines may be indicated, however many of them perform a set of parallel functions.

Chemokines are a family of proinflammatory chemotactic cytokines. Their name derives from the ability to draw chemotaxis into the vicinity of sensitive cells. They are CHEMO-toxic cyto-KINES. The former names of these proteins are: SIS cytokines family, SIG cytokines family, SCY cytokines family. SDF-1 is a small cytokine of the chemokine family, officially called CHEMOKINE (C-X-C motif) ligand 12 or CXCL 12.

Chemokine classification

The classification of proteins which belong to the chemokine family is based on their characteristic structural features, not on their ability to attract cells. All chemokines are small, with a molecular mass varying from 8 to 15 kDa. They are secreted by leucocytes and stromal cell lines, such as endothelial cells, macrophages, mesenchymal fibroblasts and epithelial cells as a response to inflammation [1].

They are within 20-50% identical and differ in gene and amino acid sequence. Amino acids are essential in the creation of three-dimensional folding, which in the case of chemokines takes the shape of a "Greek key". Chemokines consist of four cysteines combined with disulphide bonds (the first with the third, the second with the fourth). The first two cysteines in a chemokine are situated together near the N-end, the third in the middle and the fourth at the C-end. Depending on the configuration of the first two cysteine chemokines are divided into four groups:

– CC chemokines (β chemokines) which contain four, or in some cases six cysteines. CC chemokines are responsible for the migration of monocytes, NK cells and dendritic cells,

– CXC chemokines (α chemokines), where N-end cysteines are separated with an "X" amino acid. About 17 different CXC chemokines have been discovered, e.g., they are present in the mammary gland.

– C chemokines (γ chemokines), contrary to other groups, contain only one cysteine. In this group two chemokines have been described: XCL-1 and XCL-2 which attract T-cell precursors to the thymus.

– CX3C chemokines possess three amino acids between two cysteines. The only discovered chemokine of this group is called fractalkine (CX3CL1) [2, 3].

Functions of chemokines

Chemokines play a significant role in many physiological and pathological processes such as: cell migration, angiogenesis promotion, bacterial and viral infections, autoimmunological diseases, and also in pathogenesis of many neoplasms, i.e., breast or ovarian carcinoma [4-6].

Chemokine receptors and their classification

Chemokines work through their receptors. Chemokine receptors are "helical" receptors from seven transmembrane domains. Signal transmission is performed via cytoplasmic G-proteins in destination cells. Up to now 19 different receptors have been described.

Chemokine receptors contain about 350 amino acids. They may be divided into four groups depending on the kind of chemokine they join. CXCR joins CXC

Revised manuscript accepted for publication May 23, 2008

chemokine, CCR joins CC chemokine and CX3CR1 joins CX3C chemokine; finally receptor XCR1 blocks XCL1 and XCL2 chemokines.

Binding chemokines to receptors linked to the G-protein at the destination cell leads to a sequence of events of signal transfer including creation of 1,4,5- inositol triphosphate, protein kinase dependant on cyclic adenosine monophosphate (cAMP), phosphatidylinositol-3 kinase (PI3K) activation, protein kinase phosphorylation B (AKT), and extracellular signal regulated kinase phosphorylation (ERK) which all are components of focal adhesion and protein kinase C activation. Chemokine receptor activation may cause cell growth, adhesion, and directional migration [7].

CXCR4 receptor

Chemokines usually join many receptors, and the same receptors can join many different chemokines. A described exception of this general rule is CXCR4 receptor. CXCR4 joins only SDF1, and is its only receptor [3, 8]. This phenomenon suggests that SDF-1 and CXCR4 play a unique biological role [9].

CXCR4 receptor is encoded by a highly conservative gene of two exons separated with a sequence of intron [10]. CXCR4 expresses widely on leucocytes, neutrophils, neurons, glia and endothelial cells, peripheral skeleton muscles, and myocardium, as well as on cancer cells, including breast, ovary, prostate, urinary bladder and pancreas carcinoma as well as multiple myeloma [4, 11-15].

CXCR4 receptor activity of a physiological and cancer cell is modulated by different factors: the receptor's expression level on the surface of the cell or the number of sulphate bonds in the N-end pathway. Other factors are expression and biological accessibility of SDF-1 in the tissues, positive modulation of the CXCR4 bond in the lipid part of the membrane by cells connected with inflammation and tissue remodelling and negative modulation caused by polyenic antibiotics. The same situation is also caused by a split of the N-end pathway to the cells and SDF1 in the intercellular space via serine protease and metalloproteinase MPPs. All these factors may modulate CXCR4 response of normal and cancer cells to SDF1 concentration and influence their transformation or metastases [9].

SDF-1 as the only ligand of CXCR4 receptor

The only ligand of CXCR4 receptor is the SDF-1 chemokine of α chemokine family [13, 16, 17]. SDF-1 is encoded by the SDF-1 gene situated on 10q11.1 chromosome [12, 15].

As a result of splicing of the same pre-mRNA, SDF-1 takes the shape of two isoforms: SDF-1α and SDF-1β, which differ in amino acid content and function (89,93). Currently SDF-1α is better known [13, 14, 16].

SDF-1 is a factor of chemotaxis of T lymphocytes, monocytes and neutrophils [18]. Its expression has been found in the pancreas, spleen, ovary, small intestine, brain, colon, lymph nodes and placenta [13, 14, 16].

SDF-1 secretion increases during tissue injury (cardiac infraction, extremities ischaemia, toxic liver injury, heavy bleeding, exposure to radiation, and tissue injury caused by chemotherapy) [9].

SDF-1 + CXCR4 complex and its function in the organism

SDF-1 works by its receptor CXCR4. SDF-1 and CXCR4 interaction may lead to resistance to apoptose via stimulation of AKT-PKB (protein kinase B) or to activation of apoptose (via the MAPK pathway – miogen activated protein kinase). The result depends on the balance of pro- and antiapoptose signals transferred through different pathways, which is essential in regular and pathologic cell cycles connected with the evolution of cancer [3, 14]. The function of SDF-1 + the CXCR4 complex is regulated by various biological mechanisms.

A few factors that increase CXCR4 cell response to SDF-1 concentration have been indentified. These include anaphylatoxin C3a, hylauronic acid and phosphoric sphingosine [19, 20]. Moreover some molecules have been found: fibronectin, fibrinogen, thrombine, soluble uPAR (receptor of urokinase type plasminogen activator), and V-CAM-1 (vascular cell adhesion molecule-1), which enhances response to low concentration of SDF-1 [21]. These observations emphasize the idea that SDF-1 +CXCR4 complex can be modulated by the many abovementioned molecules connected to tissue damage or inflammation (anaphylatoxin C3a, Arg C3a, fibronectin, hylauronic acid), coagulation (fibrinogen, uPAR, thrombine) or cell activation (s-VCAM-1, s-ICAM-1) [21, 22]. Molecular research has proven that SDF-1 concentration is dependant on the presence of cholesterol in the cell membrane. Such medicines like polyenic antibiotics, i.e., amphotericin B and nystatin, which disturb the lipid part of the membrane via usage of cellular cholesterol, may have a negative influence on cancer cell vulnerability to statins. Anti-carcinoma properties of statin compounds have been proven. They block synthesis of intracellular cholesterol, which can be explained by a decrease in the amount of membrane cholesterol which results in a reduction in the structure of the lipid part of the cell membrane. However, this requires further research.

SDF-1 + CXCR4 interaction at destination cells causes an increase in transfer via the receptor from lymphopoietic cells to lymphopoietic organs and their accumulation in inflammed tissues. Described interaction also provokes progenitor cells to migrate during organogenesis and the regeneration of tissues and organs. The SDF-1 +CXCR4 complex influences developmental defects in the heart, brain and large vessels [14, 23].

SDF-1+CXCR4 is responsible for various signal transmission mechanisms which influence growth promotion, apoptose blocking, angiogenesis induction, and cellular invasion activation. It causes metastases of CXCR4+ cells to organs which present SDF-1 expression (bones, lymph nodes, lungs, liver) working through the SDF-1 influence on migration of cancer cells, chemotaxis and adhesion [24]. It was proven that this process plays a sig-

nificant role in driving breast cancer cells to the lungs and metastasis development [4].

Binding SDF-1 with CXCR4 receptor leads to an increase in integrins in neoplasmatic cells and their increased adhesion to stromal cells and molecules of the extracellular matrix, which leads to a higher resistance of neoplasms to chemotherapy [24-26].

In recent years it has been proven that the SDF-1+CXCR4 complex plays a key role in the metastases of at least 23 types of cancers including the breast, ovary, prostatic carcinoma, small cell lung carcinoma and cervical adenocarcinoma [12, 25-29].

Experiments have shown that SDF-1 levels correlate with lymph node invasion and survival of patients who suffered from breast carcinoma. SDF-1+CXCR4 complex stimulates proliferation of breast and ovary carcinoma via paracrine communication as efficiently as oestradiol.

It has also been established that specific monoclonal antibodies versus CXCR4 block metastases of breast carcinoma to the lungs and lymph nodes and impair blood vessel permeability, angiogenesis, and cell migration. For example anti-HER-2 antibodies (trastuzumab-herceptin) in breast carcinoma cause a CXCR4 down-regulation effect [30].

Conclusions

The SDF-1+CXCR4 complex plays a significant role in the creation of metastases of neoplasms and as a response to cytostatic treatment. Identification of this complex may be a useful prognostic factor in the therapy of many types of carcinoma. The ability to block CXCR4 indicates the existence of new targets in breast or ovarian carcinoma treatment as well as in cases of cervical adenocarcinoma. During the last five years we have faced a chemokine revolution in carcinoma treatment.

Blocking or stimulating SDF-1+CXCR4 takes place throughout the body even if it promotes carcinoma dissemination. It may cause undetermined complications, because as yet the full immunological response and delivery of progenitor cells to peripheral regenerative tissue is not known.

Scientists and oncologists realize the key role of chemokine at every stage of neoplasmatic transformation and progression.

Complex dependence between chemokines and their function in neoplasms will soon be translated into vital advantages for patients [30].

There is no doubt that soon a new compound will be created, which will be more effective, without side-effects, and which will have the ability to control metastases of neoplasmatic CXCR4+ cells and will enhance progenitor cell mobilization to be used in tissue regeneration.

References

[1] Luster A.D.: "Chemokines-chemotactic cytokines that mediate inflammation". *N. Engl. J. Med.*, 1998, *338,* 436.

[2] Laing K.J., Secombes C.J.: "Chemokines". *Dev. Comp. Immunol.*, 2004, *28,* 443.

[3] Murphy P.M., Baggiolini M., Charo I.F., Hébert C.A., Horuk R., Matsushima K. *et al.*: "International union of pharmacology. XXII. Nomenclature for chemokine receptors". *Pharmacol. Rev.,* 2000, *52,* 145.

[4] Müller A., Homey B., Soto H., Ge N., Catron D., Buchanan M.E. *et al.*: "Involvement of chemokine receptors in breast cancer metastasis". *Nature,* 2001, *410,* 50.

[5] Plante M., Rubin S.C., Wong G.Y., Federici M.G., Finstad C.L., Gastl G.A. *et al.*: "Interleukin-6 level in serum and ascites as a prognostic factor in patients with epithelial ovarian cancer". *Cancer,* 1994, *73,* 1882.

[6] Porcile C., Bajetto A., Barbieri F., Barbero S., Bonavia R., Biglieri M. *et al.*: "Stromal cell-derived factor-1alpha (SDF-1alpha/CXCL12) stimulates ovarian cancer cell growth through the EGF receptor transactivation". *Exp. Cell. Res.,* 2005, *308,* 241.

[7] Ganju R.K., Brubaker S.A., Meyer J., Dutt P., Yang Y., Qin S. *et al.*: "The alpha-chemokine, stromal cell-derived factor-1alpha, binds to the transmembrane G-protein-coupled CXCR-4 receptor and activates multiple signal transduction pathways". *J. Biol. Chem.,* 1998, *273,* 23169.

[8] Richmond A.: "Nf-kappa B, chemokine gene transcription and tumour growth". *Nat. Rev. Immunol.,* 2002, *2,* 664.

[9] Kucia M., Reca R., Miekus K., Wanzeck J., Wojakowski W., Janowska-Wiecworek A. *et al.*: "Trafficking of normal stem cells and metastasis of cancer stem cells involve similar mechanisms: pivotal role of the SDF-1-CXCR4 axis". *Stem Cells.*, 2005, *23,* 879.

[10] Caruz A., Samson M., Alonso J.M., Alcani J., Baleux F., Virelizier J.L. *et al.*: "Genomic organization and promoter characterization of human CXCR4 gene". *FEBS Lett.,* 1998, *426,* 271.

[11] Baggiolini M.: "Chemokines and leukocyte traffic". *Nature,* 1998, *392,* 565.

[12] Balkwill F.: "Cancer and the chemokine network". *Nat. Rev. Cancer,* 2004, *4,* 540.

[13] Bleul C.C., Fuhlbrigge R.C., Casasnovas J.M., Aiuti A., Springer T.A.: "A highly efficacious lymphocyte chemoattractant, stromal cell-derived factor 1 (SDF-1)". *J. Exp. Med.,* 1996, *184,* 1101.

[14] Lee B.C., Lee T.H., Avraham S., Avraham H.K.: "Involvement of the chemokine receptor CXCR4 and its ligand stromal cell-derived factor 1alpha in breast cancer cell migration through human brain microvascular endothelial cells". *Mol. Cancer Res.*, 2004, *2,* 327.

[15] Volin M.V., Joseph L., Shockley M.S., Davies P.F.: "Chemokine receptor CXCR4 expression in endothelium". *Biochem. Biophys. Res. Commun.*, 1998, *242*, 46.

[16] Shirozu M., Nakano T., Inazawa J., Tashiro K., Tada H., Shinohara T. *et al.*: "Structure and chromosomal localization of the human stromal cell-derived factor 1 (SDF1) gene". *Genomics.,* 1995, *28,* 495.

[17] Vlahakis S.R., Villasis-Keever A., Gomez T., Vanegas M., Vlahakis N., Paya C.V. *et al.*: "G protein-coupled chemokine receptors induce both survival and apoptotic signaling pathways". *J. Immunol.*, 2002, *169*, 5546.

[18] Taub D.D., Oppenheim J.J.: "Chemokines, inflammation and the immune system". *Ther. Immunol.*, 1994, *1,* 229.

[19] Avigdor A., Goichberg P., Shivtiel S., Dar A., Peled A., Samira S. *et al.*: "CD44 and hyaluronic acid cooperate with SDF-1 in the trafficking of human CD34+ stem/progenitor cells to bone marrow". *Blood.*, 2004, *103,* 2981.

[20] Kimura T., Boehmler A.M., Seitz G., Kuçi S., Wiesner T., Brinkmann V. *et al.*: "The sphingosine 1-phosphate receptor agonist FTY720 supports CXCR4-dependent migration and bone marrow homing of human CD34+ progenitor cells". *Blood.*, 2004, *103,* 4478.

[21] Wysoczynski M., Reca R., Ratajczak J., Kucia M., Shirvaikar N., Honczarenko M. *et al.*: "Incorporation of CXCR4 into membrane lipid rafts primes homing-related responses of hematopoietic stem/progenitor cells to an SDF-1 gradient". *Blood.,* 2005, *105,* 40.

[22] Janowska-Wieczorek A., Majka M., Kijowski J., Baj-Krzyworzeka M., Reca R., Turner A.R. *et al.*: "Platelet-derived microparticles bind to hematopoietic stem/progenitor cells and enhance their engraftment". *Blood.,* 2001, *98,* 3143.

[23] Tachibana K., Hirota S., Iizasa H., Yoshida H., Kawabata K., Kataoka Y. *et al.*: "The chemokine receptor CXCR4 is essential for vascularization of the gastrointestinal tract". *Nature,* 1998, *393,* 591.
[24] Kucia M., Jankowski K., Reca R., Wysoczynski M., Bandura L., Allendorf D.J. *et al.*: "CXCR4-SDF-1 signalling, locomotion, chemotaxis and adhesion". *J. Mol. Histol.,* 2004, *35,* 233.
[25] Cooper C.R., Chay C.H., Gendernalik J.D., Lee H.L., Bhatia J., Taichman R.S. *et al.*: "Stromal factors involved in prostate carcinoma metastasis to bone". *Cancer,* 2003, *97,* 739.
[26] Hartmann T.N., Burger M., Burger J.A.: "The role of adhesion molecules and chemokine receptor CXCR4 (CD184) in small cell lung cancer". *J. Biol. Regul. Homeost. Agents.*, 2004, *18,* 126.
[27] Hall J.M., Korach K.S.: "Stromal cell-derived factor 1, a novel target of estrogen receptor action, mediates the mitogenic effects of estradiol in ovarian and breast cancer cells". *Mol. Endocrinol.,* 2003, *17*, 792.
[28] Kang H., Watkins G., Parr C., Douglas-Jones A., Mansel R.E., Jiang W.G. *et al.*: "Stromal cell derived factor-1: its influence on invasiveness and migration of breast cancer cells in vitro, and its association with prognosis and survival in human breast cancer". *Breast Cancer Res.*, 2005, *7*, R402.
[29] Yang Y.C., Lee Z.Y., Wu C.C., Chen T.C., Chang C.L., Chen C.P. *et al.*: "CXCR4 expression is associated with pelvic lymph node metastasis in cervical adenocarcinoma". *Int. J. Gynecol. Cancer*, 2007, *17,* 67.
[30] Arya M., Ahmed H., Silhi N., Williamson M., Patel H.R.: "Clinical importance and therapeutic implications of the pivotal CXCL12-CXCR4 (chemokine ligand-receptor) interaction in cancer cell migration". *Tumour Biol.*, 2007, *28,* 123.

Address reprint requests to:
K. JASZCZYŃSKA-NOWINKA, M.D.
Department of Gynaecological Oncology
Poznan University of Medical Sciences
ul. Ląkowa 1/2
61-878 Poznan (Poland)
e-mail: kjnowinka@onet.eu