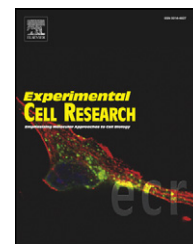


available at www.sciencedirect.comwww.elsevier.com/locate/yexcr

Review

Chemokines in cancer related inflammation

Paola Allavena^a, Giovanni Germano^a, Federica Marchesi^a, Alberto Mantovani^{a,b,*}

^aDepartment of Immunology and Inflammation, IRCCS Humanitas Clinical Institute, Via Manzoni 56, 20089, Rozzano, Milan, Italy

^bDepartment of Translational Medicine, University of Milan, Italy

ARTICLE INFORMATION

Article Chronology:

Received 6 October 2010

Revised version received

29 November 2010

Accepted 29 November 2010

Available online 4 December 2010

Keywords:

Chemokines

Receptors

Cancer

Inflammation

Macrophages

ABSTRACT

Chemokines are key players of the cancer-related inflammation. Chemokine ligands and receptors are downstream of genetic events that cause neoplastic transformation and are abundantly expressed in chronic inflammatory conditions which predispose to cancer. Components of the chemokine system affect multiple pathways of tumor progression including: leukocyte recruitment, neo-angiogenesis, tumor cell proliferation and survival, invasion and metastasis. Evidence in pre-clinical and clinical settings suggests that the chemokine system represents a valuable target for the development of innovative therapeutic strategies

© 2010 Elsevier Inc. All rights reserved.

Contents

Introduction	665
Chemokines as targets of genetic lesions causing cancer.	665
Chemokine regulation of leukocyte attraction within tumors	665
Direct and indirect chemokine effects on tumor cells	667
Angiogenesis and matrix remodeling	667
Tumor cell survival and proliferation	667
Tumor cell invasion and migration to distant organs	667
Therapeutic perspectives	669
Concluding remarks	669
Acknowledgments	669
References	669

* Corresponding author.

E-mail address: alberto.mantovani@humanitasresearch.it (A. Mantovani).

Introduction

Epidemiological and experimental studies have provided clear evidence that unresolved pathogen infections and chronic inflammation are a prerequisite for carcinogenesis in certain types of cancer; on the other hand, also tumors unrelated to inflammatory cues are characterized by the presence of reactive leukocytes and expression of a large number of inflammatory mediators (e.g. cytokines, chemokines, enzymes). Chemokines and their receptors are major players of this cancer-related inflammation (CRI) [1–4]. Over the last decade it has been established that CRI affects many aspects of malignancy and in particular endorses tumor cell survival, proliferation and distant spread [3,5,6]. Since their discovery more than 20 years ago, the chemokine system has been linked to cancer biology. The early connection was the identification of the Monocyte Chemotactic Protein-1, later termed CCL2, in culture supernatants of tumor cell lines [7,8].

A variety of chemokines have been detected in neoplastic tissues as products of either tumor cells or stromal elements. Chemokines regulate the directional movement of immune and other cells, and this tissue trafficking is of great importance both in physiology (e.g. embryogenesis) and pathology (e.g. resistance to infections, chronic inflammatory diseases, cancer). Our understanding of the chemokine role in tumor biology now ranges from their ability to recruit blood leukocytes within tumors, to direct effects on cancer cell survival, metastasis and regulation of angiogenesis.

Chemokines as targets of genetic lesions causing cancer

The connection between inflammation and cancer can be schematically viewed as consisting of an intrinsic pathway, driven by genetic alterations that cause neoplasia (e.g. oncogenes), that trigger the inflammatory cascade, and an extrinsic pathway, driven by leukocytes and mediators that establish inflammatory conditions that increase cancer risk.

In the last few years, a number of studies demonstrated that chemokines and their receptors are direct targets of the activation of several oncogenes. For example, components of the RAS-RAF signalling pathway induce the activation of the transcription factor NF- κ B and the production of several inflammatory chemokines (e.g. CXCL8) [9,10]. The tyrosine kinase RET, a prototypic transforming oncogene in human papillary carcinoma of the thyroid, activates in normal primary human thyrocytes an inflammatory programme, where chemokines are the most abundant category in addition to other cytokines and reactive mediators [11]. Expressed chemokines include CCL2, CCL20, angiogenic CXC ligands, CXCL12 and its receptor CXCR4. Recently, we reported that the oncogenic fusion transcript FUS-CHOP, characteristic of the human myxoid liposarcoma, trans-activates the chemokines CCL2, CCL5 and CXCL8 [12]. The transcription factor Myc, which is overexpressed in many human tumors, in addition to promoting cell autonomous proliferation, instructs remodelling of the extracellular microenvironment with inflammatory cells and mediators (e.g. IL-1) playing key roles. The myc activated genetic programme includes several CC chemokines which recruit mast cells. Mast cells have long been known to drive angiogenesis

by sustaining new vessel formation and tumor growth [13]. Other examples are mutation of p53 in tumor cells, able to trans-activate CXCL1 [14] and of Notch1 in T cell-acute lymphocytic leukemia, up-regulating CCR7 expression [15].

The human herpes virus 8 (HHV8) represents an example of how oncogenic viruses may exploit the chemokine system to drive tumor progression. HHV8 is the etiologic agent of Kaposi sarcoma and of hematological malignancies in humans; its genome encodes the constitutively active viral G-protein coupled receptor (vGPCR) which recognizes both ELR– and ELR+ CXC chemokines. vGPCR acts as a transforming receptor in vitro and causes vascular lesions in transgenic mice, thus behaving as an oncogene [16]. Another example is the chemokine receptor US28 encoded by Cytomegalovirus; transgenic mice in which US28 expression was targeted to intestinal epithelial cells developed intestinal adenoma and carcinoma [17].

The chemokine system is modulated also by inactivation of tumour-suppressor genes. Examples are the von Hippel-Lindau tumour suppressor (VHL) that targets the transcription factor HIF1 α which trans-activates CXCR4 [18]. Furthermore, loss of TGF- β signalling results in increased secretion of CXCL1, CXCL5 and CCL20 in human breast cancer [19].

In other conditions, transcription factors controlling the induction of chemokines are deregulated in tumor cells. In melanoma, constitutive activation of NF- κ B is responsible for CXCL1 production [20,21] and in acute myelogenous leukemia high levels of the transcription factor MEF2C induce over-expression of CCL2, CCL3 and CCL4 [22]. CXCR4 and CCR5 can also be trans-activated by the Insulin-like Growth Factor-1 or via its receptor [23,24]. TNF- α signalling up-regulates functional CXCR4 in ovarian cancer cells and favours peritoneal dissemination [25].

A further demonstration of the importance of chemokines in cancer biology comes from a recent study on the chemokine receptor D6, a promiscuous decoy receptor that scavenges several inflammatory CC chemokines. Genetic ablation of D6 in mice results in increased carcinogenesis and tumor burden in a model of colitis-associated cancer (CAC) [26].

Thus, causative genetic lesions involved in the pathogenesis of human tumors (oncogenes, mutations) share the capacity to up-regulate chemokines thereby amplifying the inflammatory cascade.

Chemokine regulation of leukocyte attraction within tumors

Chemokines have been historically associated to leukocyte recruitment in tumors [7,8,27]. Major attractants of monocytic precursors are the CC-chemokines [27–29]. In a variety of human cancers, CCL2 and CCL5 levels are correlated with high numbers of intra-tumor myeloid cells [7,30,31]. Further differentiating in mature tumor-associated macrophages (TAM) in the local micro-environment (Fig. 1), these cells are key inflammatory components of the cancer stroma, able to affect different aspects of the neoplastic tissue [32,33].

Experimental evidence indicates that TAM express several characteristics of M2-polarized macrophages [34], and display pro-tumoral functions, including promotion of tumor cell and blood vessel proliferation, matrix remodelling and immune suppression. The important role of TAM in cancer is supported

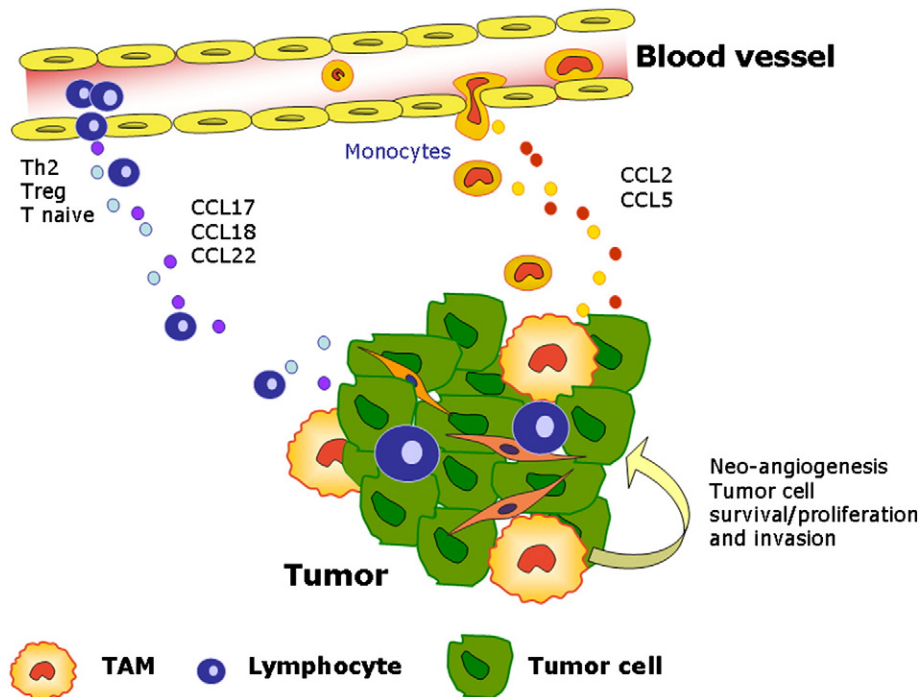


Fig. 1 – Tumor-derived chemokines attract blood leukocytes ultimately having a pro-tumoral role. Chemokines secreted by tumor and stromal cells (e.g. CCL2 and CCL5) regulate the recruitment of circulating monocytes. Differentiated Tumor-Associated Macrophages (TAM) promote tumor progression by up-regulating neo-angiogenesis, matrix remodeling, cancer cell survival, proliferation and invasion of surrounding tissues. By producing the chemokines CCL17, CCL18 and CCL22, which attract lymphocytes devoid of cytotoxic functions and suppressing anti-tumor adaptive immune responses, TAM contribute to tumor immune evasion.

by clinical studies that found—in most tumors—a correlation between the high macrophage content and poor patient prognosis [35]. In turn, genetic studies in mice have shown decreased rates of tumor growth and metastasis to be associated with decreased TAM number [36]. Thus cancer cells produce chemokines to attract blood monocytes to their own advantage.

A major pro-tumoral function of TAM in established tumors, is the suppression of adaptive anti-tumor immune responses. TAM are characterized by an IL-12^{low} IL-10^{high} phenotype, high production of prostaglandins, TGF β and indoleamine dioxigenase (IDO) metabolites [34]. In addition, TAM themselves are potent producers of chemokines. Indeed, part of the immune suppressive activity of TAM is exerted indirectly by their release of chemokines such as CCL17 and CCL22 that preferentially attract T cell subsets devoid of cytotoxic functions (Th2 and Treg cells) (Fig. 1)[30,37]. Further, TAM from ovarian cancer are major producers of CCL18, a chemokine recruiting naïve T cells [38]. Attraction of naïve T cells in a tissue dominated by M2 macrophages and immune suppressive mediators will induce T cell anergy.

Another example of how chemokines can boost neoplastic progression by shaping the leukocyte infiltrate of human tumors, is offered by the oncogenic virus HHV8. Besides the oncogenic vGPCR, the genome of HHV8 encodes three CC chemokines (vMIP-I, II and III) that attract Th2 lymphocytes and Treg cells, devoid of anti-viral activity [30,37,39,40]. These viral inflammatory chemokines represent a strategy to subvert potential effective anti-viral and anti-tumor immunity.

Tumor immune escape by the loss of homeostatic chemokine expression has been reported recently. Human keratinocyte-

derived tumors may evade T-cell immunity by down-regulating the expression of CCL27. Neutralization of CCL27 in mice leads to decreased immune cell recruitment to tumor masses and significant increase of primary tumor growth in vivo [41].

Finally, there is evidence that CC and CXC chemokines are involved also in the attraction of Myeloid Derived Suppressor Cells (MDSC) in tumors [29]. MDSC are a heterogeneous population of immature cells with suppressive function, which includes myeloid-related and mononuclear phagocyte-related elements [42,43].

The other major leukocyte subset present in the neoplastic stroma is constituted by Tumor-Infiltrating Lymphocytes (TIL). Chemokines can also regulate the recruitment and trafficking of cells of the adaptive immunity to sites of tumor and secondary lymphoid organs.

Earlier studies demonstrated that transplantable tumor cells transduced with chemokine genes grew slower in vivo and could elicit anti-tumor immunity. This was the case for CCL5, CXCL9, CX3CL1, CCL16 and other [30,37,44,45]. In some experiments, the anti-tumor effect could be credited to the recruitment of T cells at the tumor site. In diverse human tumors, especially in colorectal cancer, an abundance of TIL is a strong prognostic factor and active research is focusing on the chemokines responsible for their recruitment [46,47]. TIL have been reported to express the CXCR3 receptor; the corresponding ligands CXCL9 and CXCL10 can elicit anti-tumoral responses which correlated with increased infiltration of CD4 and CD8 lymphocytes [48]. In gastric and colorectal carcinoma [49,50] significant levels of CXCL9 and CXCL10 are produced by stromal cells, and are correlated with CXCR3-positive

TIL. Murine tumors engineered with CXCL9 or CXCL10 [51,52], and intra-tumor injection of CXCL9 [48] further demonstrated the ability of these chemokines to recruit T as well as NK cells and to elicit antitumoral responses.

A peculiar chemokine is CXCL16 which contributes to TIL attraction in tumor stroma. In human glioma, colorectal, breast and renal cancer, tumors with high CXCL16 expression had slower progression and showed infiltration of CD4 and CD8 lymphocytes [53–57]. On the contrary in prostate cancer CXCL16 expression has been correlated with poor prognosis [58]. Interestingly, it has been reported that ionizing radiation therapy markedly enhanced CXCL16 secretion by mouse and human breast cancer cells, which recruited CXCR6+ effector cells [55].

An original experimental approach to enhance recruitment of anti-tumor effectors of the adaptive immunity is the forced expression of homeostatic chemokines which guide T cells to secondary lymphoid organs. Transfection of LIGHT, a member of the TNF superfamily, in the tumor environment induced CCL21 expression and subsequent infiltration of naive T cells which are primed locally and acquire cytotoxic functions [59]. Further, in mouse cancer models, intra-tumoral injection of CCL21 or stable transfection of antigen presenting cells lead to potent antitumor responses [60–62].

Direct and indirect chemokine effects on tumor cells

Angiogenesis and matrix remodeling

The last decade has witnessed a much broader involvement of chemokine functions in tumor biology. One of the first recognized mechanism of chemokine functions different from cell chemotaxis was their effect on angiogenesis. As detailed elsewhere in this issue, chemokines have important implications in the regulation of the angiogenic switch in tumors, either directly (through receptors expressed on endothelial cells) or indirectly, by recruiting leukocytes that provide angiogenic factors [63]. Endothelial cells express CXCR4 and its triggering by CXCL12 induces endothelial cell migration and proliferation; moreover CXCR4 acts synergistically with VEGF to enhance neo-angiogenesis in human ovarian cancers [64]. CXCL12 promotes tumor angiogenesis also by the local recruiting of circulating or bone marrow-derived endothelial precursors [65]. Both CXCR4 and CXCL12 are targets of the hypoxia transcription factor HIF-1 α ; during tumor-induced hypoxia both molecules are up-regulated in tumor cells, TAM and vessels and participate in the building of vascular network that is essential for tumor progression [18,66].

In the complexity of the chemokine system, other ligands-identified by the lack of the tripeptide ELR-are characterized as powerful antagonistic mediators of angiogenesis. The CXC chemokines (CXCL9, CXCL10 and CXCL11) inhibit endothelial cell proliferation [67] and suppress tumor angiogenesis in diverse tumors [68–70]. Therefore, the balance of angiogenic ELR+ vs. angiostatic non-ELR chemokines produced in the tumor microenvironment may determine the development of angiogenesis within a tumor tissue and the consequent clinical outcome.

Inflammatory chemokines are also potent activators of matrix-metalloproteases (MMPs), enzymes that digest the extracellular matrix. TAM in tumor stroma produce MMPs and other proteolytic enzymes that affect matrix degradation. The incessant stroma

remodelling which characterizes solid tumors has two major effects: the release of active growth factors and the promotion of tumor cell invasion. Chemokines have been shown to induce gene expression and functional activation of various MMPs, in particular MMP-9 [71]. In a model of primary pancreatic carcinogenesis it has been shown that neutrophil-derived MMP-9 is essential for the angiogenic switch, by rendering VEGF available [72].

Tumor cell survival and proliferation

Since the discovery that tumor cells express chemokine receptors and may functionally respond to ligands, much research focused on the identification of direct chemokine effects on neoplastic cells. Earlier studies already pointed out that some tumor cell lines were able to migrate in response to CXCL8, and that antibodies against CXCR2 inhibited melanoma cell growth in vitro [20]. In the last decade several studies have provided evidence that tumor cells express a wide panel of chemokine receptors. [30,37]. In general, receptor engagement enhances cancer cell resistance to apoptotic stimuli and proliferation through the activation of the MAP/Erk and PI3K pathways (Fig. 2) [30,73].

Most tumors express CXCR4 at levels higher than the normal corresponding tissues [30,74]; other investigated receptors are for instance: CCR6 and CX3CR1 in colorectal and pancreatic cancer [75,76], CXCR6 in prostate cancer [77], CXCR2 in melanoma [78], and esophageal cancer cells [77], CCR7 in squamous cell carcinoma of the head and neck [79] and CCR10 in melanoma [80]. In ovarian cancer cells, the small CXCR4 antagonist CTCE-9908 caused cells death via a mechanism that was not apoptotic but involved damage of DNA checkpoint proteins and cell cycle arrest [81].

Interestingly, it has been reported that chemokines and growth factors can influence each other in some tumors. Estrogens increase the expression of CXCL12; activation of the CXCR4/CXCL12 signalling pathway, in turn, promotes estrogen receptor transcriptional activity [82]. In human glioblastoma cells, activation of the formyl-peptide chemotactic receptor (a non-chemokine receptor) resulted in the phosphorylation of Epidermal Growth Factor Receptor. Silencing of both receptors abolished tumor formation in nude mice [83].

Cellular senescence can have a dual function in cancer progression, by favoring clearance of DNA damaged cells and in opposite direction by favoring progression of neighboring cells via secreted factors [84–86]. Chemokines - and CXCL8 in particular - have been associated with the phenomenon of cellular senescence [87,88]. CXCR2 and its ligands are secreted during senescence in a NFkB and p53-dependent way and reinforce senescence [87,89]. It is envisaged that in malignancy CXCR2 dysregulation or p53 mutation disable this chemokine dependent control pathway, unleashing the pro-tumorigenic inflammatory paracrine functions of chemokines.

Tumor cell invasion and migration to distant organs

There is now ample evidence that chemokines can serve as cues for the secondary localization of tumor cells (Fig. 2). The most frequently over-expressed chemokine receptor on tumor cells is CXCR4. In general, CXCR4 is associated with tumor progression and metastasis [30,37]. In a seminal paper, Muller and colleagues [90] demonstrated the expression of CXCR4 and its involvement in metastasis in a model of breast cancer. Leukemic cells expressing

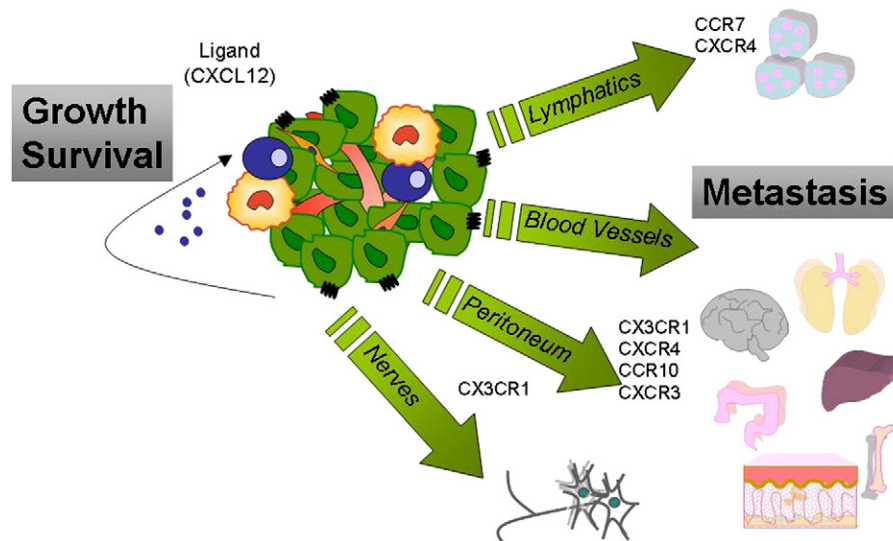


Fig. 2 – Direct effects of chemokines on tumor cells. Cancer cells secrete chemokine ligands (e.g. CXCL12) which act in a paracrine fashion on receptor-positive tumor cells (e.g. CXCR4) to sustain their resistance to apoptotic stimuli and active proliferation. Chemokine receptors also guide tumor cell dissemination to distant organs.

CXCR4 home to bone marrow and access to niches where stromal cells secrete CXCL12 [73]. In glioblastoma, several CXC receptors have been reported, with CXCR4 being the most frequent and being associated with aggressive disease and poor patient survival [91–93].

CXCR4 is the principal chemokine receptor identified on cancer stem cells (CSC). CXCR4+ CSC have been isolated from glioblastoma [91] and pancreas [94]. In this latter case, a distinct subpopulation of CD133+/CXCR4+ CSC was identified at the invasive front of the tumor and determined the metastatic phenotype of individual tumors [94]. We recently reported that progenitor cells derived from human glioblastoma are expressing also the CX3CR1 receptor [95].

Other CXC-receptors have been implicated in the malignant dissemination to distant organs. For instance, CXCR1, CXCR2 and CXCR3 in malignant melanoma [96,97]; CXCR3 in B-cell chronic lymphocytic leukemia cells [98]; CXCR5 in liver metastasis of colorectal carcinoma [99]. The CX3CR1 receptor is implicated in the perineural invasion frequently occurring in pancreatic adenocarcinoma [76] and in metastasis to bone of prostatic tumors [100].

Secondary lymphoid organs are a primary site of metastasis; in several tumors (e.g. breast, melanoma, gastric, non-small cell lung cancer, head and neck tumors, colorectal carcinoma), CCR7 is up-regulated and mediates tumor cell dissemination to lymph nodes [101–106]. In a recent study, brain infiltration by T-cell leukemic blasts was mediated by CCR7 [15]. Members of the CCR family are also used by tumor cells to spread to specific tissues such as the skin, the gut and the liver. CCR6 plays a role in organ selective liver metastasis of colorectal cancer [107,108]. The skin-homing receptors CCR4 and CCR10 were found expressed together with CCR3 in cutaneous lymphoma [109–111]. CCR9 was associated with intestinal melanoma metastasis [112], and CCR10 with spread to LN [113]. CCR5 is expressed by Hodgkin lymphoma [114], in prostate cancer [115] and by mammary tumors [116].

Overall, the above studies have indicated a strong involvement of the chemokine system in metastasis dissemination. This was

more precisely demonstrated in vivo with mouse tumor models where receptor-transduced tumor cells indeed metastasized more than parental cells [25,117]. But how tissue specific is this phenomenon? Dissemination to bone marrow involves mainly CXCR4, however not all CXCR4-expressing tumors spread to bones; most tumors disseminate to LN but only few have been reported to express CCR7. Another crucial matter is the chemokine gradient. Tumor tissues usually express higher levels of chemokines compared to surrounding tissues, fluids and blood. Based on our knowledge of CXCL12 retaining hematopoietic precursor cells in the BM, chemokines at tumor site should retain neoplastic cells, rather than encourage distant dissemination. It is however possible that in certain tumor areas a differential expression of ligands and receptors occurs, for example due to protein degradation or changes in oxygen tension (e.g. CXCR4 and CXCL12).

Another important aspect in the generation of a chemical gradient is the chemokine production by non-tumoral adjacent cells (e.g. endothelial cells and fibroblasts, as well as macrophages). Cancer-associated fibroblasts (CAF) have been extensively studied in more recent years and found to be a source of CCL2, CCL5 and CXC-chemokines; indeed there is a bidirectional cross-talk between tumor cells and CAF [118,119]. A positive correlation has been reported between stromal expression of CXCL12 and high tumor proliferative index [120] and, in another study, with proliferation of CD44+ CD24– breast cancer stem cells [83]. A notable example was provided in breast cancer, where tumor cells induced CCL5 secretion in newly recruited mesenchymal cells; stromal-derived CCL5 then interacted with CCR5-positive tumor cells enhancing their growth in vivo and metastatic ability [116].

No matter how complex the system, receptor signalling in tumor cells is likely to grant a pro-motile phenotype with activation of adhesive molecules and cytoskeleton rearrangement. Conceivably, chemokines expressed locally in primary tumors may be more important to set tumor cells in motion rather than guide them at distant sites.

Therapeutic perspectives

The evidence that cells and mediators of the inflammatory response are implicated in malignant progression opens the way for the identification of novel anti-tumor treatments and approaches for cancer prevention. Chemokines and their receptors are considered important potential targets of the CRI. Chemokine production is triggered by inflammatory cytokines (e.g. TNF); antagonists of TNF are now an available treatment and their clinical use is being experimented in cancer patients and may have an impact also on the chemokine system [121].

Targeting of CCL2 has been actively pursued because of its crucial role in regulating macrophage accrual within tumors and effects on angiogenesis. Antibodies against CCL2 have been investigated in experimental mouse models and a strong case for anti-CCL2 therapy has been made for prostate cancer [122]. Clinical trials with anti-CCL2 mAb are now being evaluated in human prostate and ovarian cancer patients.

The most frequently expressed chemokine receptor, CXCR4, has been targeted by a number of small antagonists such the bicyclam AMD3100 and peptide analogues. In pre-clinical settings, CXCR4 antagonists significantly reduced the size of primary tumors and had anti-metastatic effects in mouse models of melanoma, osteosarcoma, breast and prostate tumors [123–127].

AMD3100 was unexpectedly found to mobilize CD34+ stem cells from the bone marrow [128]. This compound is currently in clinical use for the mobilization of normal hematopoietic stem cells. Further, mobilization of malignant cells from the bone marrow niche appears to enhance their sensitivity to chemotherapy in multiple myeloma and acute myeloid leukemia [129].

The pro-angiogenic chemokine CXCL8 can be successfully inhibited by specific antibodies. These reagents have shown to inhibit angiogenesis and reduce tumor growth in nude mice [130,131]. Humanized anti-CXCL8 mAb are now available for therapeutic purposes.

Finally, novel chemotherapeutic agents are being studied for their impact on cancer-related inflammation. The registered anti-tumor agent of marine origin Trabectedin, in addition to a strong anti-proliferative effect on cancer cells, is able to down-modulate the production of a wide set of tumor-related chemokine, among which CCL2 and CXCL8 [12,132]. This anti-inflammatory effect of Trabectedin, not shared by conventional anti-tumor agents, combined with its action on tumor cells, may represent an ideal therapeutic tool in inflammation-related tumors.

Concluding remarks

Chemokines are key determinants of leukocyte recruitment in tumors, a paradigm of the cancer-related inflammation. This family is a particularly complex network, with a high number of ligands and receptors, redundant activities and diverse functions relevant for cancer biology. Yet, experimental in vitro and in vivo studies have provided unequivocal evidence of the importance of selected chemokines in specific tumors. Their additional contribution to angiogenesis and direct effects on tumor cell survival lead to the development of new drugs specifically targeting this system. Twenty-five years after their association with TAM

infiltration, chemokines are prime targets for pharmacological intervention. Chemokine inhibition in tumor pre-clinical models (e.g. CCL2 in prostate cancer) has shown significant antitumor activity. These results paved the way to testing anti-chemokine strategies in the clinic.

Acknowledgments

This work was supported by Italian Association for Cancer Research (AIRC) Italy: the FP6 European Programme ATTACK; The FP7 European People Programme ATTRACT; the Italian Ministry of Health, University and Research (Project Oncology 2006 and Alleanza contro il Cancro).

REFERENCES

- [1] B.J. Rollins, Inflammatory chemokines in cancer growth and progression, *Eur. J. Cancer* 42 (2006) 760–767.
- [2] G. Lazenec, A. Richmond, Chemokines and chemokine receptors: new insights into cancer-related inflammation, *Trends Mol. Med.* 16 (2010) 133–144.
- [3] A. Mantovani, P. Allavena, A. Sica, F. Balkwill, Cancer-related inflammation, *Nature* 454 (2008) 436–444.
- [4] A. Mantovani, B. Savino, M. Locati, L. Zammataro, P. Allavena, R. Bonecchi, The chemokine system in cancer biology and therapy, *Cytokine Growth Factor Rev.* 21 (2010) 27–39.
- [5] M. Karin, Nuclear factor- κ B in cancer development and progression, *Nature* 441 (2006) 431–436.
- [6] D.G. DeNardo, M. Johansson, L.M. Coussens, Immune cells as mediators of solid tumor metastasis, *Cancer Metastasis Rev.* 27 (2008) 11–18.
- [7] B. Bottazzi, N. Polentarutti, R. Acero, A. Balsari, D. Boraschi, P. Ghezzi, M. Salmona, A. Mantovani, Regulation of the macrophage content of neoplasms by chemoattractants, *Science* 220 (1983) 210–212.
- [8] C.O. Zachariae, A.O. Anderson, H.L. Thompson, E. Appella, A. Mantovani, J.J. Oppenheim, K. Matsushima, Properties of monocyte chemoattractant and activating factor (MCAF) purified from a human fibrosarcoma cell line, *J. Exp. Med.* 171 (1990) 2177–2182.
- [9] A. Sparmann, D. Bar-Sagi, Ras-induced interleukin-8 expression plays a critical role in tumor growth and angiogenesis, *Cancer Cell* 6 (2004) 447–458.
- [10] H. Sumimoto, F. Imabayashi, T. Iwata, Y. Kawakami, The BRAF-MAPK signaling pathway is essential for cancer-immune evasion in human melanoma cells, *J. Exp. Med.* 203 (2006) 1651–1656.
- [11] M.G. Borrello, L. Alberti, A. Fischer, D. Degl'innocenti, C. Ferrario, M. Gariboldi, F. Marchesi, P. Allavena, A. Greco, P. Collini, S. Pilotti, G. Cassinelli, P. Bressan, L. Fugazzola, A. Mantovani, M.A. Pierotti, Induction of a proinflammatory program in normal human thyrocytes by the RET/PTC1 oncogene, *Proc. Natl Acad. Sci. USA* 102 (2005) 14825–14830.
- [12] G. Germano, R. Frapolli, M. Simone, M. Tavecchio, E. Erba, S. Pesce, F. Pasqualini, F. Grosso, R. Sanfilippo, P.G. Casali, A. Gronchi, E. Viridis, E. Tarantino, S. Pilotti, A. Greco, M. Nebuloni, C.M. Galmarini, J.C. Tercero, A. Mantovani, M. D'Incalci, P. Allavena, Antitumor and anti-inflammatory effects of trabectedin on human myxoid liposarcoma cells, *Cancer Res.* 70 (2010) 2235–2244.
- [13] L. Soucek, E.R. Lawlor, D. Soto, K. Shchorr, L.B. Swigart, G.I. Evan, Mast cells are required for angiogenesis and macroscopic expansion of Myc-induced pancreatic islet tumors, *Nat. Med.* 13 (2007) 1211–1218.

- [14] W. Yan, X. Chen, Identification of GRO1 as a critical determinant for mutant p53 gain of function, *J. Biol. Chem.* 284 (2009) 12178–12187.
- [15] S. Buonamici, T. Trimarchi, M.G. Ruocco, L. Reavie, S. Cathelin, B.G. Mar, A. Klinakis, Y. Lukyanov, J.C. Tseng, F. Sen, E. Gehrie, M. Li, E. Newcomb, J. Zavadil, D. Meruelo, M. Lipp, S. Ibrahim, A. Efstratiadis, D. Zagzag, J.S. Bromberg, M.L. Dustin, I. Aifantis, CCR7 signalling as an essential regulator of CNS infiltration in T-cell leukaemia, *Nature* 459 (2009) 1000–1004.
- [16] M.G. Grisotto, A. Garin, A.P. Martin, K.K. Jensen, P. Chan, S.C. Sealfon, S.A. Lira, The human herpesvirus 8 chemokine receptor vGPCR triggers autonomous proliferation of endothelial cells, *J. Clin. Invest.* 116 (2006) 1264–1273.
- [17] G. Bongers, D. Maussang, L.R. Muniz, V.M. Noriega, A. Fraile-Ramos, N. Barker, F. Marchesi, N. Thirunarayanan, H.F. Vischer, L. Qin, L. Mayer, N. Harpaz, R. Leurs, G.C. Furtado, H. Clevers, D. Tortorella, M.J. Smit, S.A. Lira, The cytomegalovirus-encoded chemokine receptor US28 promotes intestinal neoplasia in transgenic mice, *J. Clin. Invest.* 120 (2010) 3969–3978.
- [18] T. Schioppa, B. Uranchimeg, A. Saccani, S.K. Biswas, A. Doni, A. Rapisarda, S. Bernasconi, S. Saccani, M. Nebuloni, L. Vago, A. Mantovani, G. Melillo, A. Sica, Regulation of the chemokine receptor CXCR4 by hypoxia, *J. Exp. Med.* 198 (2003) 1391–1402.
- [19] B. Bierie, C.H. Chung, J.S. Parker, D.G. Stover, N. Cheng, A. Chytil, M. Aakre, Y. Shyr, H.L. Moses, Abrogation of TGF-beta signaling enhances chemokine production and correlates with prognosis in human breast cancer, *J. Clin. Invest.* 119 (2009) 1571–1582.
- [20] A. Richmond, NF-kappa B, chemokine gene transcription and tumour growth, *Nat. Rev. Immunol.* 2 (2002) 664–674.
- [21] Y.M. Thu, A. Richmond, NF-kappaB inducing kinase: a key regulator in the immune system and in cancer, *Cytokine Growth Factor Rev.* 21 (2010) 213–226.
- [22] M. Schwieger, A. Schuler, M. Forster, A. Engelmann, M.A. Arnold, R. Delwel, P.J. Valk, J. Lohler, R.K. Slany, E.N. Olson, C. Stocking, Homing and invasiveness of MLL/ENL leukemic cells is regulated by MEF2C, *Blood* 114 (2009) 2476–2488.
- [23] C. Akekawatchai, J.D. Holland, M. Kochetkova, J.C. Wallace, S.R. McColl, Transactivation of CXCR4 by the insulin-like growth factor-1 receptor (IGF-1R) in human MDA-MB-231 breast cancer epithelial cells, *J. Biol. Chem.* 280 (2005) 39701–39708.
- [24] E. Mira, R.A. Lacalle, M.A. Gonzalez, C. Gomez-Mouton, J.L. Abad, A. Bernad, A.C. Martinez, S. Manes, A role for chemokine receptor transactivation in growth factor signaling, *EMBO Rep.* 2 (2001) 151–156.
- [25] H. Kulbe, T. Hagemann, P.W. Szlosarek, F.R. Balkwill, J.L. Wilson, The inflammatory cytokine tumor necrosis factor-alpha regulates chemokine receptor expression on ovarian cancer cells, *Cancer Res.* 65 (2005) 10355–10362.
- [26] S. Vetrano, E.M. Borroni, A. Sarukhan, B. Savino, R. Bonecchi, C. Correale, V. Arena, M. Fantini, M. Roncalli, A. Malesci, A. Mantovani, M. Locati, S. Danese, The lymphatic system controls intestinal inflammation and inflammation-associated colon cancer through the chemokine decoy receptor D6, *Gut* 59 (2010) 197–206.
- [27] A. Mantovani, The chemokine system: redundancy for robust outputs, *Immunol. Today* 20 (1999) 254–257.
- [28] I. Conti, B.J. Rollins, CCL2 (monocyte chemoattractant protein-1) and cancer, *Semin. Cancer Biol.* 14 (2004) 149–154.
- [29] Y. Sawanobori, S. Ueha, M. Kurachi, T. Shimaoka, J.E. Talmadge, J. Abe, Y. Shono, M. Kitabatake, K. Kakimi, N. Mukaida, K. Matsushima, Chemokine-mediated rapid turnover of myeloid-derived suppressor cells in tumor-bearing mice, *Blood* 111 (2008) 5457–5466.
- [30] F. Balkwill, Cancer and the chemokine network, *Nat. Rev. Cancer* 4 (2004) 540–550.
- [31] G. Soria, A. Ben-Baruch, The inflammatory chemokines CCL2 and CCL5 in breast cancer, *Cancer Lett.* 267 (2008) 271–285.
- [32] J.W. Pollard, Tumour-educated macrophages promote tumour progression and metastasis, *Nat. Rev. Cancer* 4 (2004) 71–78.
- [33] G. Solinas, G. Germano, A. Mantovani, P. Allavena, Tumor-associated macrophages (TAM) as major players of the cancer-related inflammation, *J. Leukoc. Biol.* 86 (2009) 1065–1073.
- [34] A. Mantovani, S. Sozzani, M. Locati, P. Allavena, A. Sica, Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes, *Trends Immunol.* 23 (2002) 549–555.
- [35] L. Bingle, N.J. Brown, C.E. Lewis, The role of tumour-associated macrophages in tumour progression: implications for new anticancer therapies, *J. Pathol.* 196 (2002) 254–265.
- [36] J. Condeelis, J.W. Pollard, Macrophages: obligate partners for tumor cell migration, invasion, and metastasis, *Cell* 124 (2006) 263–266.
- [37] A. Mantovani, B. Savino, M. Locati, L. Zammataro, P. Allavena, R. Bonecchi, The chemokine system in cancer biology and therapy, *Cytokine Growth Factor Rev.* 21 (2010) 27–39.
- [38] E. Schutyser, S. Struyf, P. Proost, G. Opdenakker, G. Laureys, B. Verhasselt, L. Peperstraete, I. Van de Putte, A. Saccani, P. Allavena, A. Mantovani, J. Van Damme, Identification of biologically active chemokine isoforms from ascitic fluid and elevated levels of CCL18/pulmonary and activation-regulated chemokine in ovarian carcinoma, *J. Biol. Chem.* 277 (2002) 24584–24593.
- [39] S. Sozzani, W. Luini, G. Bianchi, P. Allavena, T.N. Wells, M. Napolitano, G. Bernardini, A. Vecchi, D. D'Ambrosio, D. Mazzeo, F. Sinigaglia, A. Santoni, E. Maggi, S. Romagnani, A. Mantovani, The viral chemokine macrophage inflammatory protein-II is a selective Th2 chemoattractant, *Blood* 92 (1998) 4036–4039.
- [40] J.T. Stine, C. Wood, M. Hill, A. Epp, C.J. Raport, V.L. Schweickart, Y. Endo, T. Sasaki, G. Simmons, C. Boshoff, P. Clapham, Y. Chang, P. Moore, P.W. Gray, D. Chantry, KSHV-encoded CC chemokine vMIP-III is a CCR4 agonist, stimulates angiogenesis, and selectively chemoattracts TH2 cells, *Blood* 95 (2000) 1151–1157.
- [41] A. Pivarcsi, A. Muller, A. Hippe, J. Rieker, A. van Lierop, M. Steinhoff, S. Seeliger, R. Kubitzka, U. Pippirs, S. Meller, P.A. Gerber, R. Liersch, E. Buenemann, E. Sonkoly, U. Wiesner, T.K. Hoffmann, L. Schneider, R. Piekorz, E. Enderlein, J. Reifemberger, U.P. Rohr, R. Haas, P. Boukamp, I. Haase, B. Nurnberg, T. Ruzicka, A. Zlotnik, B. Homey, Tumor immune escape by the loss of homeostatic chemokine expression, *Proc. Natl Acad. Sci. USA* 104 (2007) 19055–19060.
- [42] A. Sica, V. Bronte, Altered macrophage differentiation and immune dysfunction in tumor development, *J. Clin. Invest.* 117 (2007) 1155–1166.
- [43] D.I. Gabrilovich, S. Nagaraj, Myeloid-derived suppressor cells as regulators of the immune system, *Nat. Rev. Immunol.* 9 (2009) 162–174.
- [44] P.A. Ruffini, P. Morandi, N. Cabioglu, K. Altundag, M. Cristofanilli, Manipulating the chemokine-chemokine receptor network to treat cancer, *Cancer* 109 (2007) 2392–2404.
- [45] J.J. Mule, M. Custer, B. Averbook, J.C. Yang, J.S. Weber, D.V. Goeddel, S.A. Rosenberg, T.J. Schall, RANTES secretion by gene-modified tumor cells results in loss of tumorigenicity in vivo: role of immune cell subpopulations, *Hum. Gene Ther.* 7 (1996) 1545–1553.
- [46] J. Galon, A. Costes, F. Sanchez-Cabo, A. Kirilovsky, B. Mlecnik, C. Lagorce-Pages, M. Tosolini, M. Camus, A. Berger, P. Wind, F. Zinzindohoue, P. Bruneval, P.H. Cugnenc, Z. Trajanoski, W.H. Fridman, F. Pages, Type, density, and location of immune cells within human colorectal tumors predict clinical outcome, *Science* 313 (2006) 1960–1964.
- [47] L. Laghi, P. Bianchi, E. Miranda, E. Balladore, V. Pacetti, F. Grizzi, P. Allavena, V. Torri, A. Repici, A. Santoro, A. Mantovani, M. Roncalli, A. Malesci, CD3+ cells at the invasive margin of deeply invading (pT3-T4) colorectal cancer and risk of post-surgical

- metastasis: a longitudinal study, *Lancet Oncol.* 10 (2009) 877–884.
- [48] J. Pan, M.D. Burdick, J.A. Belperio, Y.Y. Xue, C. Gerard, S. Sharma, S.M. Dubinett, R.M. Strieter, CXCR3/CXCR3 ligand biological axis impairs RENCA tumor growth by a mechanism of immunoangiostasis, *J. Immunol.* 176 (2006) 1456–1464.
- [49] H. Ohtani, Z. Jin, S. Takegawa, T. Nakayama, O. Yoshie, Abundant expression of CXCL9 (MIG) by stromal cells that include dendritic cells and accumulation of CXCR3+ T cells in lymphocyte-rich gastric carcinoma, *J. Pathol.* 217 (2009) 21–31.
- [50] H. Musha, H. Ohtani, T. Mizoi, M. Kinouchi, T. Nakayama, K. Shiiba, K. Miyagawa, H. Nagura, O. Yoshie, I. Sasaki, Selective infiltration of CCR5(+)CXCR3(+) T lymphocytes in human colorectal carcinoma, *Int. J. Cancer* 116 (2005) 949–956.
- [51] A. Saudemont, N. Jouy, D. Hetuin, B. Quesnel, NK cells that are activated by CXCL10 can kill dormant tumor cells that resist CTL-mediated lysis and can express B7-H1 that stimulates T cells, *Blood* 105 (2005) 2428–2435.
- [52] M. Wendel, I.E. Galani, E. Suri-Payer, A. Cerwenka, Natural killer cell accumulation in tumors is dependent on IFN-gamma and CXCR3 ligands, *Cancer Res.* 68 (2008) 8437–8445.
- [53] A. Ludwig, A. Schulte, C. Schnack, C. Hundhausen, K. Reiss, N. Brodway, J. Held-Feindt, R. Mentlein, Enhanced expression and shedding of the transmembrane chemokine CXCL16 by reactive astrocytes and glioma cells, *J. Neurochem.* 93 (2005) 1293–1303.
- [54] J. Meijer, J. Ogink, B. Kreike, D. Nuyten, K.E. de Visser, E. Roos, The chemokine receptor CXCR6 and its ligand CXCL16 are expressed in carcinomas and inhibit proliferation, *Cancer Res.* 68 (2008) 4701–4708.
- [55] S. Matsumura, B. Wang, N. Kawashima, S. Braunstein, M. Badura, T.O. Cameron, J.S. Babb, R.J. Schneider, S.C. Formenti, M.L. Dustin, S. Demaria, Radiation-induced CXCL16 release by breast cancer cells attracts effector T cells, *J. Immunol.* 181 (2008) 3099–3107.
- [56] P. Gutwein, A. Schramme, N. Sinke, M.S. Abdel-Bakky, B. Voss, N. Obermuller, K. Doberstein, M. Koziolok, F. Fritzsche, M. Johannsen, K. Jung, H. Schaidler, P. Altevogt, A. Ludwig, J. Pfeilschifter, G. Kristiansen, Tumoural CXCL16 expression is a novel prognostic marker of longer survival times in renal cell cancer patients, *Eur. J. Cancer* 45 (2009) 478–489.
- [57] S. Hojo, K. Koizumi, K. Tsuneyama, Y. Arita, Z. Cui, K. Shinohara, T. Minami, I. Hashimoto, T. Nakayama, H. Sakurai, Y. Takano, O. Yoshie, K. Tsukada, I. Saiki, High-level expression of chemokine CXCL16 by tumor cells correlates with a good prognosis and increased tumor-infiltrating lymphocytes in colorectal cancer, *Cancer Res.* 67 (2007) 4725–4731.
- [58] M. Darash-Yahana, J.W. Gillespie, S.M. Hewitt, Y.Y. Chen, S. Maeda, I. Stein, S.P. Singh, R.B. Bedolla, A. Peled, D.A. Troyer, E. Pikarsky, M. Karin, J.M. Farber, The chemokine CXCL16 and its receptor, CXCR6, as markers and promoters of inflammation-associated cancers, *PLoS ONE* 4 (2009) e6695.
- [59] P. Yu, Y. Lee, W. Liu, R.K. Chin, J. Wang, Y. Wang, A. Schietinger, M. Philip, H. Schreiber, Y.X. Fu, Priming of naive T cells inside tumors leads to eradication of established tumors, *Nat. Immunol.* 5 (2004) 141–149.
- [60] S. Sharma, M. Stolina, J. Luo, R.M. Strieter, M. Burdick, L.X. Zhu, R.K. Batra, S.M. Dubinett, Secondary lymphoid tissue chemokine mediates T cell-dependent antitumor responses in vivo, *J. Immunol.* 164 (2000) 4558–4563.
- [61] L. Novak, O. Igoucheva, S. Cho, V. Alexeev, Characterization of the CCL21-mediated melanoma-specific immune responses and in situ melanoma eradication, *Mol. Cancer Ther.* 6 (2007) 1755–1764.
- [62] N. Yousefieh, S.M. Hahto, A.L. Stephens, R.P. Ciavarra, Regulated expression of CCL21 in the prostate tumor microenvironment inhibits tumor growth and metastasis in an orthotopic model of prostate cancer, *Cancer Microenviron.* 2 (2009) 59–67.
- [63] R.M. Strieter, M.D. Burdick, J. Mestas, B. Gomperts, M.P. Keane, J.A. Belperio, Cancer CXC chemokine networks and tumour angiogenesis, *Eur. J. Cancer* 42 (2006) 768–778.
- [64] I. Kryczek, A. Lange, P. Motttram, X. Alvarez, P. Cheng, M. Hogan, L. Moons, S. Wei, L. Zou, V. Machelon, D. Emilie, M. Terrasa, A. Lackner, T.J. Curiel, P. Carmeliet, W. Zou, CXCL12 and vascular endothelial growth factor synergistically induce neoangiogenesis in human ovarian cancers, *Cancer Res.* 65 (2005) 465–472.
- [65] A. Orimo, P.B. Gupta, D.C. Sgroi, F. Arenzana-Seisdedos, T. Delaunay, R. Naeem, V.J. Carey, A.L. Richardson, R.A. Weinberg, Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion, *Cell* 121 (2005) 335–348.
- [66] C. Cursiefen, L. Chen, L.P. Borges, D. Jackson, J. Cao, C. Radziejewski, P.A. D'Amore, M.R. Dana, S.J. Wiegand, J.W. Streilein, VEGF-A stimulates lymphangiogenesis and hemangiogenesis in inflammatory neovascularization via macrophage recruitment, *J. Clin. Invest.* 113 (2004) 1040–1050.
- [67] P. Romagnani, F. Annunziato, L. Lasagni, E. Lazzeri, C. Beltrame, M. Francalanci, M. Uguccioni, G. Galli, L. Cosmi, L. Maurenzig, M. Baggolini, E. Maggi, S. Romagnani, M. Serio, Cell cycle-dependent expression of CXC chemokine receptor 3 by endothelial cells mediates angiostatic activity, *J. Clin. Invest.* 107 (2001) 53–63.
- [68] R.M. Strieter, J.A. Belperio, M.D. Burdick, S. Sharma, S.M. Dubinett, M.P. Keane, CXC chemokines: angiogenesis, immunoangiostasis, and metastases in lung cancer, *Ann. NY Acad. Sci.* 1028 (2004) 351–360.
- [69] E. Naschberger, R.S. Croner, S. Merkel, A. Dimmler, P. Tripal, K.U. Amann, E. Kremmer, W.M. Brueckl, T. Papadopoulos, C. Hohenadl, W. Hohenberger, M. Sturzl, Angiostatic immune reaction in colorectal carcinoma: Impact on survival and perspectives for antiangiogenic therapy, *Int. J. Cancer* 123 (2008) 2120–2129.
- [70] E. Sato, J. Fujimoto, H. Toyoki, H. Sakaguchi, S.M. Alam, I. Jahan, T. Tamaya, Expression of IP-10 related to angiogenesis in uterine cervical cancers, *Br. J. Cancer* 96 (2007) 1735–1739.
- [71] E. Giraud, M. Inoue, D. Hanahan, An amino-bisphosphonate targets MMP-9-expressing macrophages and angiogenesis to impair cervical carcinogenesis, *J. Clin. Invest.* 114 (2004) 623–633.
- [72] H. Nozawa, C. Chiu, D. Hanahan, Infiltrating neutrophils mediate the initial angiogenic switch in a mouse model of multistage carcinogenesis, *Proc. Natl Acad. Sci. USA* 103 (2006) 12493–12498.
- [73] J.A. Burger, T.J. Kipps, CXCR4: a key receptor in the crosstalk between tumor cells and their microenvironment, *Blood* 107 (2006) 1761–1767.
- [74] M. Darash-Yahana, E. Pikarsky, R. Abramovitch, E. Zeira, B. Pal, R. Karplus, K. Beider, S. Avniel, S. Kasem, E. Galun, A. Peled, Role of high expression levels of CXCR4 in tumor growth, vascularization, and metastasis, *FASEB J.* 18 (2004) 1240–1242.
- [75] P. Ghadjar, S.E. Coupland, I.K. Na, M. Noutsias, A. Letsch, A. Stroux, S. Bauer, H.J. Buhr, E. Thiel, C. Scheibenbogen, U. Keilholz, Chemokine receptor CCR6 expression level and liver metastases in colorectal cancer, *J. Clin. Oncol.* 24 (2006) 1910–1916.
- [76] F. Marchesi, L. Piemonti, G. Fedele, A. Destro, M. Roncalli, L. Albarello, C. Doglioni, A. Anselmo, A. Doni, P. Bianchi, L. Laghi, A. Malesci, L. Cervo, M. Malosio, M. Reni, A. Zerbi, V. Di Carlo, A. Mantovani, P. Allavena, The chemokine receptor CX3CR1 is involved in the neural tropism and malignant behavior of pancreatic ductal adenocarcinoma, *Cancer Res.* 68 (2008) 9060–9069.
- [77] B. Wang, D.T. Hendricks, F. Wamunyokoli, M.I. Parker, A growth-related oncogene/CXC chemokine receptor 2 autocrine loop contributes to cellular proliferation in esophageal cancer, *Cancer Res.* 66 (2006) 3071–3077.

- [78] S. Singh, K.C. Nannuru, A. Sadanandam, M.L. Varney, R.K. Singh, CXCR1 and CXCR2 enhances human melanoma tumorigenesis, growth and invasion, *Br. J. Cancer* 100 (2009) 1638–1646.
- [79] J. Wang, R.R. Seethala, Q. Zhang, W. Gooding, C. van Waes, H. Hasegawa, R.L. Ferris, Autocrine and paracrine chemokine receptor 7 activation in head and neck cancer: implications for therapy, *J. Natl Cancer Inst.* 100 (2008) 502–512.
- [80] T. Murakami, A.R. Cardones, S.E. Finkelstein, N.P. Restifo, B.A. Klauenberg, F.O. Nestle, S.S. Castillo, P.A. Dennis, S.T. Hwang, Immune evasion by murine melanoma mediated through CC chemokine receptor-10, *J. Exp. Med.* 198 (2003) 1337–1347.
- [81] J. Kwong, H. Kulbe, D. Wong, P. Chakravarty, F. Balkwill, An antagonist of the chemokine receptor CXCR4 induces mitotic catastrophe in ovarian cancer cells, *Mol. Cancer Ther.* 8 (2009) 1893–1905.
- [82] K. Saueve, J. Lepage, M. Sanchez, N. Heveker, A. Tremblay, Positive feedback activation of estrogen receptors by the CXCL12–CXCR4 pathway, *Cancer Res.* 69 (2009) 5793–5800.
- [83] J. Huang, J. Hu, X. Bian, K. Chen, W. Gong, N.M. Dunlop, O.M. Howard, J.M. Wang, Transactivation of the epidermal growth factor receptor by formylpeptide receptor exacerbates the malignant behavior of human glioblastoma cells, *Cancer Res.* 67 (2007) 5906–5913.
- [84] W.J. Mooi, D.S. Peeper, Oncogene-induced cell senescence—halting on the road to cancer, *N. Engl. J. Med.* 355 (2006) 1037–1046.
- [85] F. d'Adda di Fagagna, Living on a break: cellular senescence as a DNA-damage response, *Nat. Rev. Cancer* 8 (2008) 512–522.
- [86] J.P. Coppe, C.K. Patil, F. Rodier, Y. Sun, D.P. Munoz, J. Goldstein, P.S. Nelson, P.Y. Desprez, J. Campisi, Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor, *PLoS Biol.* 6 (2008) 2853–2868.
- [87] J.C. Acosta, A. O'Loughlen, A. Banito, M.V. Guijarro, A. Augert, S. Raguz, M. Fumagalli, M. Da Costa, C. Brown, N. Popov, Y. Takatsu, J. Melamed, F. d'Adda di Fagagna, D. Bernard, E. Hernando, J. Gil, Chemokine signaling via the CXCR2 receptor reinforces senescence, *Cell* 133 (2008) 1006–1018.
- [88] A.V. Orjalo, D. Bhaumik, B.K. Gengler, G.K. Scott, J. Campisi, Cell surface-bound IL-1 α is an upstream regulator of the senescence-associated IL-6/IL-8 cytokine network, *Proc. Natl Acad. Sci. USA* 106 (2009) 17031–17036.
- [89] T. Kuilman, C. Michaloglou, L.C. Vredevelde, S. Douma, R. van Doorn, C.J. Desmet, L.A. Aarden, W.J. Mooi, D.S. Peeper, Oncogene-induced senescence relayed by an interleukin-dependent inflammatory network, *Cell* 133 (2008) 1019–1031.
- [90] A. Muller, B. Homey, H. Soto, N. Ge, D. Catron, M.E. Buchanan, T. McClanahan, E. Murphy, W. Yuan, S.N. Wagner, J.L. Barrera, A. Mohar, E. Verastegui, A. Zlotnik, Involvement of chemokine receptors in breast cancer metastasis, *Nature* 410 (2001) 50–56.
- [91] M. Ehteshami, K.Y. Mapara, C.B. Stevenson, R.C. Thompson, CXCR4 mediates the proliferation of glioblastoma progenitor cells, *Cancer Lett.* 274 (2009) 305–312.
- [92] A. Bajetto, F. Barbieri, A. Dorcarratto, S. Barbero, A. Daga, C. Porcile, J.L. Ravetti, G. Zona, R. Spaziante, G. Corte, G. Schettini, T. Florio, Expression of CXC chemokine receptors 1–5 and their ligands in human glioma tissues: role of CXCR4 and SDF1 in glioma cell proliferation and migration, *Neurochem. Int.* 49 (2006) 423–432.
- [93] Y. Zhou, P.H. Larsen, C. Hao, V.W. Yong, CXCR4 is a major chemokine receptor on glioma cells and mediates their survival, *J. Biol. Chem.* 277 (2002) 49481–49487.
- [94] P.C. Hermann, S.L. Huber, T. Herrler, A. Aicher, J.W. Ellwart, M. Guba, C.J. Bruns, C. Heeschen, Distinct populations of cancer stem cells determine tumor growth and metastatic activity in human pancreatic cancer, *Cell Stem Cell* 1 (2007) 313–323.
- [95] M. Erreni, G. Solinas, P. Brescia, D. Osti, F. Zunino, P. Colombo, A. Destro, M. Roncalli, A. Montovani, R. Draghi, D. Levi, Y.B.R. Rodriguez, P. Gaetani, G. Pelecci, P. Allavena, Human glioblastoma tumours and neural cancer stem cells express the chemokine CX3CL1 and its receptor CX3CR1, *Eur. J. Cancer.* 46 (2010) 3383–3392.
- [96] M.L. Varney, S.L. Johansson, R.K. Singh, Distinct expression of CXCL8 and its receptors CXCR1 and CXCR2 and their association with vessel density and aggressiveness in malignant melanoma, *Am. J. Clin. Pathol.* 125 (2006) 209–216.
- [97] X. Ma, K. Norsworthy, N. Kundu, W.H. Rodgers, P.A. Gimotty, O. Goloubeva, M. Lipsky, Y. Li, D. Holt, A. Fulton, CXCR3 expression is associated with poor survival in breast cancer and promotes metastasis in a murine model, *Mol. Cancer Ther.* 8 (2009) 490–498.
- [98] D. Jones, R.J. Benjamin, A. Shahsafaei, D.M. Dorfman, The chemokine receptor CXCR3 is expressed in a subset of B-cell lymphomas and is a marker of B-cell chronic lymphocytic leukemia, *Blood* 95 (2000) 627–632.
- [99] J. Meijer, I.S. Zeelenberg, B. Sipos, E. Roos, The CXCR5 chemokine receptor is expressed by carcinoma cells and promotes growth of colon carcinoma in the liver, *Cancer Res.* 66 (2006) 9576–9582.
- [100] S.A. Shulby, N.G. Dolloff, M.E. Stearns, O. Meucci, A. Fatatis, CX3CR1–fractalkine expression regulates cellular mechanisms involved in adhesion, migration, and survival of human prostate cancer cells, *Cancer Res.* 64 (2004) 4693–4698.
- [101] Y. Ding, Y. Shimada, M. Maeda, A. Kawabe, J. Kaganai, I. Komoto, Y. Hashimoto, M. Miyake, H. Hashida, M. Imamura, Association of CC chemokine receptor 7 with lymph node metastasis of esophageal squamous cell carcinoma, *Clin. Cancer Res.* 9 (2003) 3406–3412.
- [102] K. Gunther, J. Leier, G. Henning, A. Dimmler, R. Weissbach, W. Hohenberger, R. Forster, Prediction of lymph node metastasis in colorectal carcinoma by expression of chemokine receptor CCR7, *Int. J. Cancer* 116 (2005) 726–733.
- [103] K. Mashino, N. Sadanaga, H. Yamaguchi, F. Tanaka, M. Ohta, K. Shibuta, H. Inoue, M. Mori, Expression of chemokine receptor CCR7 is associated with lymph node metastasis of gastric carcinoma, *Cancer Res.* 62 (2002) 2937–2941.
- [104] I. Takanami, Overexpression of CCR7 mRNA in nonsmall cell lung cancer: correlation with lymph node metastasis, *Int. J. Cancer* 105 (2003) 186–189.
- [105] H. Takeuchi, A. Fujimoto, M. Tanaka, T. Yamano, E. Hsueh, D.S. Hoon, CCL21 chemokine regulates chemokine receptor CCR7 bearing malignant melanoma cells, *Clin. Cancer Res.* 10 (2004) 2351–2358.
- [106] H.E. Wiley, E.B. Gonzalez, W. Maki, M.T. Wu, S.T. Hwang, Expression of CC chemokine receptor-7 and regional lymph node metastasis of B16 murine melanoma, *J. Natl Cancer Inst.* 93 (2001) 1638–1643.
- [107] P. Ghadjar, C. Loddenkemper, S.E. Coupland, A. Stroux, M. Noutsias, E. Thiel, F. Christoph, K. Miller, C. Scheibenbogen, U. Keilholz, Chemokine receptor CCR6 expression level and aggressiveness of prostate cancer, *J. Cancer Res. Clin. Oncol.* 134 (2008) 1181–1189.
- [108] P. Ghadjar, C. Rubie, D.M. Aebbersold, U. Keilholz, The chemokine CCL20 and its receptor CCR6 in human malignancy with focus on colorectal cancer, *Int. J. Cancer* 125 (2009) 741–745.
- [109] H. Harasawa, Y. Yamada, K. Hieshima, Z. Jin, T. Nakayama, O. Yoshie, K. Shimizu, H. Hasegawa, T. Hayashi, Y. Imaizumi, S. Ikeda, H. Soda, H. Soda, S. Atogami, Y. Takasaki, K. Tsukasaki, M. Tomonaga, K. Murata, K. Sugahara, K. Tsuruda, S. Kamihira, Survey of chemokine receptor expression reveals frequent co-expression of skin-homing CCR4 and CCR10 in adult T-cell leukemia/lymphoma, *Leuk. Lymphoma* 47 (2006) 2163–2173.
- [110] T. Ishida, A. Utsunomiya, S. Iida, H. Inagaki, Y. Takatsuka, S. Kusumoto, G. Takeuchi, S. Shimizu, M. Ito, H. Komatsu, A. Wakita, T. Eimoto, K. Matsushima, R. Ueda, Clinical significance of CCR4 expression in adult T-cell leukemia/lymphoma: its close association with skin involvement and unfavorable outcome, *Clin. Cancer Res.* 9 (2003) 3625–3634.

- [111] M. Kleinhan, A. Tun-Kyi, M. Gilliet, M.E. Kadin, R. Dummer, G. Burg, F.O. Nestle, Functional expression of the eotaxin receptor CCR3 in CD30+ cutaneous T-cell lymphoma, *Blood* 101 (2003) 1487–1493.
- [112] A. Letsch, U. Keilholz, D. Schadendorf, G. Assfalg, A.M. Asemisen, E. Thiel, C. Scheibenbogen, Functional CCR9 expression is associated with small intestinal metastasis, *J. Invest. Dermatol.* 122 (2004) 685–690.
- [113] O. Simonetti, G. Goteri, G. Lucarini, A. Filosa, T. Pieramici, C. Rubini, G. Biagini, A. Offidani, Potential role of CCL27 and CCR10 expression in melanoma progression and immune escape, *Eur. J. Cancer* 42 (2006) 1181–1187.
- [114] C. Buri, M. Korner, P. Scharli, D. Cefai, M. Uguccioni, C. Mueller, J.A. Laissue, L. Mazzucchelli, CC chemokines and the receptors CCR3 and CCR5 are differentially expressed in the nonneoplastic leukocytic infiltrates of Hodgkin disease, *Blood* 97 (2001) 1543–1548.
- [115] C. Murphy, M. McGurk, J. Pettigrew, A. Santinelli, R. Mazzucchelli, P.G. Johnston, R. Montironi, D.J. Waugh, Nonapical and cytoplasmic expression of interleukin-8, CXCR1, and CXCR2 correlates with cell proliferation and microvessel density in prostate cancer, *Clin. Cancer Res.* 11 (2005) 4117–4127.
- [116] A.E. Karnoub, A.B. Dash, A.P. Vo, A. Sullivan, M.W. Brooks, G.W. Bell, A.L. Richardson, K. Polyak, R. Tubo, R.A. Weinberg, Mesenchymal stem cells within tumour stroma promote breast cancer metastasis, *Nature* 449 (2007) 557–563.
- [117] A.R. Cardones, T. Murakami, S.T. Hwang, CXCR4 enhances adhesion of B16 tumor cells to endothelial cells in vitro and in vivo via beta(1) integrin, *Cancer Res.* 63 (2003) 6751–6757.
- [118] R. Kalluri, M. Zeisberg, Fibroblasts in cancer, *Nat. Rev. Cancer* 6 (2006) 392–401.
- [119] P. Mishra, D. Banerjee, A. Ben-Baruch, Chemokines at the crossroads of tumor-fibroblast interactions that promote malignancy, *J. Leukoc. Biol.* 89 (2011) 31–39.
- [120] H.H. Oliveira-Neto, E.T. Silva, C.R. Leles, E.F. Mendonca, C. Alencar Rde, T.A. Silva, A.C. Batista, Involvement of CXCL12 and CXCR4 in lymph node metastases and development of oral squamous cell carcinomas, *Tumour Biol.* 29 (2008) 262–271.
- [121] F. Balkwill, Tumour necrosis factor and cancer, *Nat. Rev. Cancer* 9 (2009) 361–371.
- [122] R.D. Loberg, C. Ying, M. Craig, L. Yan, L.A. Snyder, K.J. Pienta, CCL2 as an important mediator of prostate cancer growth in vivo through the regulation of macrophage infiltration, *Neoplasia* 9 (2007) 556–562.
- [123] M. Takenaga, H. Tamamura, K. Hiramatsu, N. Nakamura, Y. Yamaguchi, A. Kitagawa, S. Kawai, H. Nakashima, N. Fujii, R. Igarashi, A single treatment with microcapsules containing a CXCR4 antagonist suppresses pulmonary metastasis of murine melanoma, *Biochem. Biophys. Res. Commun.* 320 (2004) 226–232.
- [124] H. Tamamura, A. Hori, N. Kanzaki, K. Hiramatsu, M. Mizumoto, H. Nakashima, N. Yamamoto, A. Otaka, N. Fujii, T140 analogs as CXCR4 antagonists identified as anti-metastatic agents in the treatment of breast cancer, *FEBS Lett.* 550 (2003) 79–83.
- [125] S.Y. Kim, C.H. Lee, B.V. Midura, C. Yeung, A. Mendoza, S.H. Hong, L. Ren, D. Wong, W. Korz, A. Merzouk, H. Salari, H. Zhang, S.T. Hwang, C. Khanna, L.J. Helman, Inhibition of the CXCR4/CXCL12 chemokine pathway reduces the development of murine pulmonary metastases, *Clin. Exp. Metastasis* 25 (2008) 201–211.
- [126] S. Porvasnik, N. Sakamoto, S. Kusmartsev, E. Eruslanov, W.J. Kim, W. Cao, C. Urbanek, D. Wong, S. Goodison, C.J. Rosser, Effects of CXCR4 antagonist CTCE-9908 on prostate tumor growth, *Prostate* (2009).
- [127] M.M. Richert, K.S. Vaidya, C.N. Mills, D. Wong, W. Korz, D.R. Hurst, D.R. Welch, Inhibition of CXCR4 by CTCE-9908 inhibits breast cancer metastasis to lung and bone, *Oncol. Rep.* 21 (2009) 761–767.
- [128] W.C. Liles, H.E. Broxmeyer, E. Rodger, B. Wood, K. Hubel, S. Cooper, G. Hangoc, G.J. Bridger, G.W. Henson, G. Calandra, D.C. Dale, Mobilization of hematopoietic progenitor cells in healthy volunteers by AMD3100, a CXCR4 antagonist, *Blood* 102 (2003) 2728–2730.
- [129] E. De Clercq, The AMD3100 story: the path to the discovery of a stem cell mobilizer (Mozobil), *Biochem. Pharmacol.* 77 (2009) 1655–1664.
- [130] S. Huang, L. Mills, B. Mian, C. Tellez, M. McCarty, X.D. Yang, J.M. Gudas, M. Bar-Eli, Fully humanized neutralizing antibodies to interleukin-8 (ABX-IL8) inhibit angiogenesis, tumor growth, and metastasis of human melanoma, *Am. J. Pathol.* 161 (2002) 125–134.
- [131] B.M. Mian, C.P. Dinney, C.E. Bermejo, P. Sweeney, C. Tellez, X.D. Yang, J.M. Gudas, D.J. McConkey, M. Bar-Eli, Fully human anti-interleukin 8 antibody inhibits tumor growth in orthotopic bladder cancer xenografts via down-regulation of matrix metalloproteases and nuclear factor-kappaB, *Clin. Cancer Res.* 9 (2003) 3167–3175.
- [132] P. Allavena, M. Signorelli, M. Chieppa, E. Erba, G. Bianchi, F. Marchesi, C.O. Olimpico, C. Bonardi, A. Garbi, A. Lissoni, F. de Braud, J. Jimeno, M. D'Incalci, Anti-inflammatory properties of the novel antitumor agent yondelis (trabectedin): inhibition of macrophage differentiation and cytokine production, *Cancer Res.* 65 (2005) 2964–2971.