Chemokines as mediators of angiogenesis
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Summary
Chemokines were originally described as cytokines that mediate leukocyte recruitment to sites of inflammation. Members of a subgroup of chemokines, the CXC family, also play a critical role in both physiologic and pathologic angiogenesis, including in the context of chronic inflammation, fibrosis, and malignancy. A unique feature of this family of cytokines is that, on the basis of their structure and receptor binding, individual ligands display either angiogenic or angiostatic biological activity in the regulation of angiogenesis. In this review, we summarize the key literature in this growing field.

Keywords
Chemokine, chemokine receptor, angiogenesis, cancer

Introduction
Chemokines are a superfamily of homologous 8–10 kDa heparin-binding proteins, originally described for their role in mediating leukocyte recruitment to sites of inflammation. A subgroup of chemokines, the CXC family, plays a critical role in angiogenesis, in both physiologic and pathologic contexts, including chronic inflammation, fibrosis, and malignancy.

Structurally, the defining feature of the CXC chemokine family is four conserved cysteine amino acid residues near the amino-terminus, the first two of which are separated by a non-conserved amino acid, thus constituting the Cys-X-Cys or ‘CXC’ motif. This family is further subdivided on the basis of the presence or absence of another three amino acid sequence, glutamic acid-leucine-arginine (the ‘ELR’ motif), immediately proximal to the CXC sequence. Unique amongst the mediators of angiogenesis, this structural motif determines the function of specific ligands: the ELR containing CXC chemokines, originally discovered for their potent neutrophil chemoattractant properties, promote angiogenesis, while the non-ELR ligands, which attract mononuclear leukocytes, inhibit angiogenesis (Table 1; references [1, 2]).

CXCR2: The major angiogenic chemokine receptor
The human ELR+CXC chemokine ligands signal via one of two receptors, CXCR1 and CXCR2, whereas there is no mouse equivalent for CXCR1, and all murine ELR+CXC chemokines signal via CXCR2. Several lines of data indicate that the angiogenic properties of ELR+CXC chemokines are only mediated via CXCR2 in the human, as well as the murine system: First, while only CXCL8 and CXCL6 specifically bind to CXCR1, all human ELR+CXC chemokines mediate angiogenesis. Second, while both CXCR1 and CXCR2 are detected in endothelial cells (3–5), only the expression of CXCR2 is necessary for endothelial cell chemotaxis (3, 4). In addition, the response of human endothelial cells to CXCL8 can be blocked by immunoneutralization of CXCR2 or inhibitors of its intracellular signalling pathways (6).

The in-vivo role of CXCR2 in mediating ELR+CXC chemokine-induced angiogenesis has been examined in models of corneal neovascularization (3) and wound repair (7). In the corneal system, both CXCR2-deficient hosts and immunoneutralization of CXCR2 inhibited corneal vascularization in response to ELR+CXC chemokine ligands (3). In the wound healing model, full-thickness excisional wounds demonstrated delayed healing which was associated with impaired angiogenesis in CXCR2-deficient mice (7).

CXCR3: The major chemokine receptor inhibiting angiogenesis
The receptor for non-ELR CXC chemokines that mediate angiostasis is CXCR3 (8–12). Endothelial cells express CXCR3 (13), and CXCR3 ligands inhibit microvascular human endothelial cell migration and proliferation in response to a variety of an...
CXCR4: A role in angiogenesis?

The CXCL12-CXCR4 ligand-receptor pair has been implicated in migration of cancer cells to induce metastases (19) and also in promoting angiogenesis (5, 20–22), but distinguishing between the contributions of these mechanisms in the context of disease has been difficult. Expression of CXCR4 has been documented in multiple tumour lines and primary cancer cells, whereas the ligand, CXCL12, is essentially absent from the tumours (19, 23, 24). Absence of CXCL12 from tumours could hypothetically be explained by the tumour cells “out-competing” endothelial cells for available ligand. In animal models bearing breast or non-small cell lung cancers (NSCLC), immunoneutralization of CXCL12 or CXCR4 did not affect the size or angiogenesis of the primary tumour but attenuated tumour metastases (19, 23), suggesting that, at least in these systems, the CXCL12-CXCR4 axis mediates metastases independent of angiogenesis. In contrast, similar depletion of classical angiogenic factors and their receptors results in measurable reduction of angiogenesis, and a consequent reduction in both primary tumour size and metastases (1, 25–27).

CC chemokines

While most of the literature on chemokine regulation of angiogenesis has centered on the role of the CXC family, several members of the CC chemokine family, including CCL11, CCL16 and CCL21 have also been implicated in angiogenesis (28–30). The best studied CC chemokine ligand implicated in angiogenesis, however, is CCL2: endothelial cells express the CCL2 receptor, CCR2, and demonstrate chemotaxis and tube formation in response to CCL2 in vitro (31, 32). In vivo, CCL2-mediated angiogenesis has been demonstrated in corneal implantation, chick chorioallantoic membrane, Matrigel plug, and sponge implantation models (33–35), and appears to be independent of its induction of leukocyte recruitment (34). The chemotaxis of endothelial cells by CCL2 is dependent on CCL2-induced over-expression of membrane type 1-metalloproteinase on endothelial cell surfaces (31) and is mediated via the ERK cascade and the transcription factor Ets-1 (36).

Virally encoded chemokine receptors

Human herpes virus-8 (HHV-8, also known as Kaposi sarcoma herpes virus, KSHV), is the cause of human Kaposi’s sarcoma and body-cavity lymphoma, and encodes a seven-transmembrane G-protein coupled receptor that is homologous to CXCR2 (37, 38). This receptor is constitutively signal-coupled, but its signal-coupling can be further augmented when bound to ELR+ chemokine ligands, CXCL8 or CXCL1 (39–41). The relevance of this receptor to pathogenesis of Kaposi’s sarcoma was established using transgenic mice expressing KSHV-GPCR, which spontaneously develop angioproliferative KS-like lesions (42, 43). In further support of this contention is the finding that a point mutation of CXCR2, but not CXCR1, results in constitutive signalling of the receptor and cellular transformation of transfected cells in a similar manner as KSHV-GPCR (37). Furthermore, the persistent activation of CXCR2 by specific CXC chemokine ligands can lead to a similar cellular transformation...
as seen with either the point mutation of CXCR2 or KSHV-GPCR (37).

Another virally encoded chemokine receptor, US28, is expressed by human cytomegalovirus and also induces a pro-angiogenic phenotype (44). US28 expressing cells promote tumourigenesis and angiogenesis in mice (44). This is mediated through the expression of VEGF, indicating important interactions between chemokines/chemokine receptors and VEGF in promoting tumour growth. Furthermore these findings indicate potential mechanisms for viral involvement in the tumourigenesis and angiogenesis.

**Duffy antigen**

The red blood cell Duffy antigen receptor for chemokines (DARC) is a promiscuous but non-signalling chemokine receptor (45). Within the ELR+ CXC chemokines, DARC binds the angiogenic ELR+ CXC chemokines CXCL1, CXCL5 and CXCL8. Transgenic expression of the Duffy antigen on mouse endothelial cells resulted in impaired angiogenic response of the animals to ELR+ CXC chemokines in vivo (46). Conversely, in a mouse model of spontaneous prostate cancer, animals on a DARC-deficient background developed larger and more aggressive tumours (47). This was associated with increased intra-tumour levels of angiogenic ELR+ CXC chemokines and blood vessel density, supporting the hypothesis that red blood cell expression of DARC sequesters angiogenic chemokines thereby inhibiting tumour growth.

To assess its therapeutic potential, DARC was stably transfected and over-expressed in a human NSCLC tumour cell line. This did not affect the growth characteristics of the tumour in vitro, but when implanted into animals, DARC-expressing tumours had greater necrosis and decreased tumour cellularity, associated with a marked decrease in tumour-associated vascularity and a reduction in metastatic potential (45). Similar findings have also been reported using breast cancer cell lines (48). In summary, DARC appears to act as a decoy receptor that inhibits angiogenesis by sequestering ELR+ CXC chemokines.

**Chemokine-mediated inhibition of angiogenesis via undefined receptors**

CXCL4, a component of the platelet α-granule, was the first chemokine described to inhibit neovascularization (49). In addition to signalling via CXCR3B, discussed earlier, CXCL4 has been postulated to mediate inhibition of angiogenesis by either interaction with cell surface glycosaminoglycans or via direct interaction with proangiogenic mediators and their receptors (50). CXCL4 is reported to prevent activation of the extracellular signal-regulated kinase by bFGF, and to inhibit down-regulation of the cyclin-dependent kinase inhibitor p21 (51, 52). Furthermore, CXCL4 function is not abrogated in heparan sulfate-deficient cells, and CXCL4 mutants or peptides lacking heparin-affinity are capable of inhibiting angiogenesis (50, 53, 54), suggesting that interaction with cell surface glycosaminoglycans is not essential for these effects. Other studies have reported that the inhibitory effect of CXCL4 is mediated through complex formation with bFGF or CXCL8 (53, 55). Finally, CXCL4 also exists as a non-allelic gene variant, CXCL4L1, which differs from CXCL4 in its signalling region, subcellular localization, and regulation of secretion (56–58). CXCL4L1 has been found to be a more potent inhibitor of angiogenesis both in vitro and in vivo models of angiogenesis (59), but the mechanism by which this variant mediates these effects is yet to be defined.

CXCL14, another ELR-negative CXC chemokine, is another recently identified inhibitor of angiogenesis. CXCL14 was first identified by differential display of normal oral epithelial cells and head and neck squamous cell carcinoma when it was noted to be down-regulated in tumour specimens (60–62), but its mechanism of action, including its receptor, remain to be identified. CXCL14 was found to inhibit microvascular endothelial cell chemotaxis to CXCL8, bFGF, and VEGF in vitro and attenuate angiogenesis to these agonists in vivo (63). In the context of the prostate, CXCL14 expression did not differ between normal tissue and hypertrophic tissue but it correlated with Gleason score in prostate cancer, and inhibited tumour growth when transfected into prostate cancer cells implanted into animals (64). The above studies support the notion that the loss or inadequate expression of CXCL14 is associated with the transformation of normal epithelial cells to cancer and the promotion of a pro-angiogenic microenvironment suitable for tumour growth. The receptor that mediates the actions of CXCL14 remains to be determined.

**Chemokine-induced angiogenesis in inflammatory and fibroproliferative disorders**

Angiogenesis is a demonstrable histopathologic feature of many chronic inflammatory and fibroproliferative disorders, and disproportionate expression of angiogenic CXC chemokines can be demonstrated in many such illnesses; examples include rheumatoid arthritis synovium (65), and psoriatic dermal plaques (66).

Increasing evidence points to a role for inflammation and fibroproliferation in the pathogenesis of atherosclerosis (67–69). Angiogenesis has also been demonstrated within atherosclerotic plaques, and may contribute to the pathogenesis of plaque formation (70–72). The angiogenic ELR+ CXC chemokine, CXCL8, is over-expressed in human coronary artery plaque samples, as compared to control samples from internal mammary arteries without atherosclerosis, where it co-localized with factor VIII-related antigen expression on endothelial cells in the coronary atherectomy specimens, and is the major mediator of net angiogenic activity of the plaque in the rat cornea micro-pocket assay (73). A large number of chemokines are induced in the context of myocardial ischaemia and heart failure (74, 75), but the specific contribution of these mediators to angiogenesis has not been clearly established. CCL2, in particular, was critically involved in infarct-associated inflammation and subsequent healing in a mouse model of myocardial infarction, but its absence did not influence angiogenesis (76). CCL2 has, however, been implicated in ischaemia-induced arteriogenesis in a murine hind-limb ischaemia model (77), and may therefore be relevant in similar collateralization in the context of chronically ischaemic myocardium.
Angiogenesis is also a major mechanism in the pathogenesis of a number of lung diseases. The human lung is supplied by both the pulmonary and the bronchial circulation. Neovascularization and development of anastomoses between these circuits control pulmonary vascular resistance, necessary to maintaining blood flow to the metabolically active lung tissue in the context of injury and repair (78–81). Compensatory neovascularization of up to 30% of the original pulmonary blood flow can occur in the bronchial circulation in all mammals in response to marked increases in pulmonary vascular resistance (81), and the mouse systemic circulation can supply 15% of the pulmonary flow within days after pulmonary artery ligation, a process that is associated with up-regulation of ELR+ CXC chemokines but not VEGF (82, 83).

Idiopathic pulmonary fibrosis (IPF) is a chronic and often fatal pulmonary fibroproliferative lung disease characterized by on-going and dysregulated tissue repair. Neovascularization was first recognized in the IPF lung in postmortem studies, as extensive anastomoses between pulmonary and bronchial circulations (84), and was subsequently identified in animal models of bleomycin-induced pulmonary fibrosis (85). Indeed the lung tissue and bronchoalveolar lavage fluid (BALF) from patients with IPF is strongly angiogenic, as determined in the rat corneal micro-pocket model, and this angiogenic activity is entirely attributable to over-expression of the angiogenic ELR+ CXC chemokine, CXCL8, as compared to angiostatic non-ELR CXC chemokine, CXCL10, in the lung (86). In the mouse model of bleomycin-induced pulmonary fibrosis, the expression and biological activity of angiogenic ELR+ CXC chemokine, MIP-2 (CXCL2/3) contributed to pulmonary fibrosis and angiogenic activity, while CXCL10 had the reverse effect (87, 88). Moreover, depletion of endogenous CXCL2/3 or administration of exogenous CXCL10 resulted in marked attenuation of pulmonary fibrosis that was entirely attributable to a reduction in angiogenesis in the lung (87, 88). Finally, administration of exogenous CXCL11 in this model also resulted in reduced lung fibrosis, as measured by lung collagen deposition, and this effect was abrogated with concomitant blockade of CXCR3 (89).

Bronchiolitis obliterans syndrome (BOS) is a pulmonary fibroproliferative disorder centered around small airways, and constitutes the single most important cause of long-term organ dysfunction and death in lung transplant recipients (90). Human lung samples from patients with BOS demonstrate aberrant blood vessel formation, and both lung samples and BALF have elevated ELR+ CXC chemokine ligand levels and pronounced angiogenic activity in the corneal micro-pocket model that is inhibited by neutralizing CXCR2 (91). A mouse model of heterotopic tracheal allograft transplantation into MHC-mismatched recipients also demonstrated these properties, which were dependent on CXCR2 and CXCR2 ligands, but were independent of neutrophil presence (91).

Acute respiratory distress syndrome (ARDS) is a common and severe manifestation of acute lung injury, and progresses to a fibroproliferative phase after several days, which is associated with marked angiogenesis related to ELR+ CXC chemokines (92): BALF from patients with ARDS has elevated levels of angiogenic chemokines and reduced levels of angiostatic chemokines, as compared to control ventilated patients without ARDS, and this was associated with BALF angiogenic activity and BALF pro-collagen I and pro-collagen III levels (92). In contrast, while BALF levels of VEGF were elevated in ARDS patients, VEGF did not appear to be a predominant factor in contributing to the overall angiogenic activity (92). Taken together, these findings support the notion that angiogenesis is critical to promote fibroplasia and deposition of ECM associated with chronic fibroproliferation, and that angiogenic and angiotostatic factors, such as CXC chemokines play an important role in the pathogenesis of this process. On this basis, they represent potential therapeutic targets for the treatment of chronic inflammatory/fibroproliferative disorders associated with aberrant angiogenesis.

Chemokine-induced angiogenesis in tumour models

Angiogenesis is an essential feature of development and progression of cancers, and represents an intriguing, if as yet elusive, therapeutic target (93). CXC chemokine-mediated angiogenesis has been shown to play a critical role in growth of many cancers, including bronchogenic carcinoma, breast cancer, gastrointestinal malignancies, prostate carcinoma, melanoma, renal cell carcinoma, ovarian cancer, glioblastoma, and head and neck cancer (94–100).

CXCL1, CXCL2, and CXCL3 have all been found to be highly expressed in human melanoma, and when transplanted into immortalized murine melanocytes that otherwise do not form tumours, they transformed the phenotype to one of anchorage-independent growth in vitro and the ability to form highly vascular tumours in vivo (101, 102). Furthermore, depletion of CXCL1, 2, or 3 in the hosts resulted in marked attenuation of tumour-associated angiogenesis and inhibition of tumour growth (101, 102).

Human pancreatic cancer cell lines also secrete the angiogenic chemokines CXCL1 and CXCL8 (103) with substantial heterogeneity in expression of these ligands between tumour lines (104). In comparing these lines using the corneal micro-pocket model, tumour-induced angiogenesis could be abrogated by blocking CXCR2 in one, but not another, cancer cell line (104), supporting the concept of redundancy of angiogenic ligands even within specific cancers. Similarly, in another gastrointestinal tract malignancy, colorectal cancer, PGE2 was found to induce in-vivo tumour growth by inducing expression of CXCL1 (105).

The progression of ovarian carcinoma is also dependent on successful angiogenesis. In one study of human ovarian carcinoma cell lines, in-vitro expression of CXCL8 by the lines correlated with tumour vascularity and tumour-induced mortality when implanted into the peritoneum of immunocompromised mice, whereas expression of VEGF correlated with ascites production only (106). In corroboration of this, another study found the angiogenic activity of ascites fluid from patients with ovarian cancer to correspond to its CXCL8 level (107).

CXCL8 also contributes to the angiogenic activity of NSCLC, and NSCLC cell lines that constitutively express CXCL8 display greater virulence and angiogenic activity in
mice (25, 108). In a model of human NSCLC in SCID mice, tumour-derived CXCL8 directly correlated with tumourigenesis, and CXCL8 depletion resulted in reduced tumour angiogenesis associated with reduced tumour size and metastatic potential (109). Similarly, CXCL5 also mediates NSCLC-associated angiogenesis (110): Both in surgical specimens and in the SCID mouse model, CXCL5 expression was directly correlated with tumour angiogenesis (110). Moreover, when NSCLC tumour-bearing animals were depleted of CXCL5, both tumour growth and spontaneous metastases were markedly attenuated, but in vivo and in-vitro proliferation of NSCLC cells was unaffected by the presence of CXCL5 (110). While a significant correlation of CXCL5 exists with tumour-derived angiogenesis, tumour growth, and metastases, CXCL5 depletion does not completely inhibit tumour growth (110), presumably reflecting a functional redundancy between angiogenic ligands. Overall, however, when all ELR+ CXC chemokines are evaluated in human NSCLC samples, it appears that their expression correlated with patient mortality (111, 112). As further evidence for this, in a lung cancer syngeneic tumour model system in CXCR2-deficient, as compared to wildtype mice, cancers in CXCR2-deficient mice demonstrated reduced growth, increased tumour-associated necrosis, inhibited tumour-associated angiogenesis and metastatic potential (113). In a different model, spontaneously developing lung adenocarcinomas in mice with somatic activation of the oncogene KRAS were found to produce ELR+ CXC chemokines, and neutralization of CXCR2 in these animals inhibited the development of pre-malignant lesions and apoptosis of endothelial cells within the lesions (114). These in-vitro and in-vivo studies establish that CXCR2 is an important receptor that mediates ELR+ CXC chemokine-dependent angiogenic activity.

In patients with prostate cancer, serum CXCL8 levels are elevated and correlate with disease stage independent of the ratio of free-to-total prostate specific antigen (PSA) (115, 116). In a model of implantation of human prostate cancer into SCID mice, different prostate cancer cell lines were found to use different ELR+ CXC chemokine ligands as angiogenic mediators, with depletion of CXCL1 and not CXCL8 inhibiting tumour growth and angiogenesis in some lines, and the converse in other lines (117). Thus, prostate cancer cell lines can utilize distinct CXC chemokines to mediate their tumourigenic potential.

Glioblastoma multiforme are highly aggressive brain tumours, associated with marked angiogenesis (118, 119). In a study of ING4, a candidate tumour suppressor gene, the gene was found to be down-regulated in human glioblastoma samples, and samples with lowest expression had greatest growth and angiogenesis when implanted into immunocompromised mice (118). The mechanism for this increased tumourigenicity was found to be CXCL8-dependent, as inhibition of CXCL8 in vivo markedly reduced their tumour growth and tumour-associated angiogenesis (118). These findings link a tumour suppressor gene to function and control of the expression of angiogenic ELR+ CXC chemokines in human tumours.

The observation that CXCR3 and its ligands both inhibit angiogenesis and mediate Th1-type cell mediated immunity via recruitment of CXCR3-expressing T cells (120–124) has led to the concept of “immunoangiostasis” in cancer (125, 126). As an example of this, intratumoural injection of a recombinant CC chemokine, CCL21, in tumours induced regression via spatial generation of intratumour IFN-γ, consequent CXCR3 ligands, and influx of CXCR3-expressing CD4, CD8, natural killer, and dendritic cells into both the tumour and the draining lymph nodes, in addition to a reduction in angiogenesis (127, 128). Furthermore, depletion studies demonstrated that CXCL9, CXCL10, and IFN-γ each attenuated the anti-tumour effects of CCL21 (128). These findings are similar to the previously reported study of IL-12-mediated regression of renal cell carcinoma in a murine model, where the anti-tumour effect of IL-12 was lost when CXCR3 ligands were depleted (129). More recently, the effectiveness of systemic IL-2 therapy in the mouse model of renal cell carcinoma was shown to be CXCR3-dependent, and resulted in up-regulation of CXCR3 on peripheral blood mononuclear cells but, surprisingly, down-regulation of CXCR3 ligands in the tumour (125). The effectiveness of this therapy was substantially enhanced when it was combined with over-expression of the CXCR3 ligand, CXCL9, in the tumour (125). Taken collectively, these findings support the notion that CXCR3 and its ligands contribute to anti-tumour defenses by two distinct and additive mechanisms, namely inhibition of angiogenesis and mediating direct anti-tumour immunity.

Therapeutic manipulation of chemokine-mediated angiogenesis

Chemokine-mediated angiogenesis and angiostasis have the potential to be utilized therapeutically, specially as adjunctive treatments in cancer and perhaps in fibroproliferative disorders. In this context, a neutralizing human anti-IL-8 mAb, shown to inhibit the effects of IL-8 in vitro and in preclinical models (130–132), had an acceptable safety profile in phase I trials but was abandoned when, in a phase II study of psoriasis, it did not meet its primary endpoint (133). Several compounds, currently in phase I and II trials, target the CXCR4-CXCL12 axis in various cancers (133), but as described above, this axis likely targets mechanisms other than angiogenesis. Interrupting the CCR2-CCL2 axis has the potential to interrupt angiogenesis but is likely to have a number of other complex effects, including inhibition of inflammatory leukocyte recruitment and augmenting Th-1 immunity; similarly targeting the CXCR3-ELR-CXC chemokine axis via systemic administration of IL-2 and intra-tumour administration of a ligand, as outlined above, may be effective in inhibiting angiogenesis and augmenting tumour rejection.

Conclusion

Although the function of chemokines was originally thought to be limited to recruitment of subpopulations of leukocytes, it has become clear that these cytokines display pleiotropic effects in other biological functions. These ligands appear to be important in the regulation of angiogenesis in inflammatory conditions, fibrosis, and malignancy. The findings summarized here support the notion that therapy directed at either inhibition of angiogenic or augmentation of angiostatic CC and CXC chemokines may be a novel approach in the treatment of a variety of such disorders.
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