

Association between preeclampsia and the CXC chemokine family (Review)

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Abstract. Preeclampsia is a major cause of maternal and perinatal mortality and morbidity, characterized by gestational hypertension, proteinuria, systemic endothelial cell activation and an exaggerated inflammatory response. The precise cause of preeclampsia is not currently known; however, it is widely accepted that the pathogenesis of preeclampsia involves inadequate trophoblast invasion, leading to generalized endothelial dysfunction and an exaggerated inflammatory response. Chemokines are a superfamily of structurally similar proteins that mediate cell recruitment, angiogenesis, immunity and stem cell trafficking. CXC chemokines are a family of cytokines, unique in their ability to behave in a disparate manner in the regulation of angiogenesis. The CXC chemokine family further divides into two subfamilies; CXC ELR+, which promotes angiogenesis, and CXC ELR-, which inhibits angiogenesis. Furthermore, CXC chemokines are involved in the pathogenesis of various conditions, including malignant tumors, wound repair, chronic inflammation, atherosclerosis and potentially preeclampsia.

Contents

1. Pathogenesis and etiology of preeclampsia
2. Features of CXC chemokines and their receptors
3. Regulation of CXC chemokines in angiogenesis
4. CXC chemokines and preeclampsia

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1. Pathogenesis and etiology of preeclampsia

Preeclampsia is characterized by gestational hypertension, proteinuria, systemic endothelial cell activation and an exaggerated inflammatory response (1). The cause of preeclampsia is currently unknown; however, it is widely accepted that the pathogenesis is associated with inadequate trophoblast invasion, resulting in endothelial dysfunction and an exaggerated inflammatory response (2). Preeclampsia may develop spontaneously in the placenta and the only known treatment is the removal of the placenta (3).

Following implantation, the trophoblast differentiates into two subtypes, the cytotrophoblast and syncytiotrophoblast. Cytotrophoblasts may further differentiate along two pathways; the extravillous (invasive) and villous (syncytial) pathways. The extravillous cytotrophoblast invades the decidua basalis and penetrates the uterine wall, disrupting the endothelium and tunica media of the spiral arteries. This disruption transforms the spiral artery from a low-flow, high-resistance vessel into a high-flow, low-resistance vessel, resulting in an increase in the uteroplacental perfusion that is required to sustain the fetus (2,4,5). Subsequently, the villous cytotrophoblast remains at the basal membrane and is covered by the syncytiotrophoblast, forming a syncytium (2).

The invasive capability of the trophoblast is hypothesized to function similarly to that of malignant cells, but in a strictly controlled manner (6). The pathogenesis of preeclampsia may involve the disruption of this regulatory process. In cases of preeclampsia, inadequate trophoblast invasion, leading to insufficient spiral artery remodeling, is hypothesized to result in hypoxia-reperfusion injury and the generation of oxidative stress in the placenta. Oxidative stress stimulates the release of materials from the syncytium that may activate the maternal endothelium. These materials, which include anti-angiogenic and pro-apoptotic factors, stimulate the placenta to release vasoactive factors. These factors produce an exaggerated inflammatory response and endothelial cell dysfunction by altering the circulating levels of a number of factors, including angiogenic factors, pro-inflammatory cytokines and other immunological factors (7). Thus, a positive feedback loop is established.

An imbalance of angiogenic and anti-angiogenic factors is considered to be key in the pathogenesis of preeclampsia (8), and a number of factors have been associated with this

Table I. CXC chemokines and their receptors.

Systematic nomenclature	Old nomenclature	ELR motif	Receptor
Angiogenic			
CXCL1	GRO- α	ELR ⁺	CXCR2
CXCL2	GRO- β	ELR ⁺	CXCR2
CXCL3	GRO- γ	ELR ⁺	CXCR2
CXCL5	ENA-78	ELR ⁺	CXCR2
CXCL6	GCP-2	ELR ⁺	CXCR2, CXCR1
CXCL7	NAP-2	ELR ⁺	CXCR2
CXCL8	IL-8	ELR ⁺	CXCR2, CXCR1
CXCL12	SDF-1	ELR ⁻	CXCR4, CXCR7
Angiostatic			
CXCL4	PF-4	ELR ⁻	CXCR3
CXCL9	Mig	ELR ⁻	CXCR3
CXCL10	IP-10	ELR ⁻	CXCR3
CXCL11	I-TAC	ELR ⁻	CXCR3, CXCR7
CXCL14	BRAX	ELR ⁻	CXCR4

ELR⁺, Glu-Leu-Arg motif positive; ELR⁻, Glu-Leu-Arg motif negative.

process. Amongst these factors, the vascular endothelial growth factor (VEGF) system has been studied extensively (8). Previous studies have indicated that plasma levels of VEGF and placental growth factor (PLGF) are significantly reduced in female patients with preeclampsia (8,9). In addition, the expression levels of soluble fms-like tyrosine kinase-1, a circulating anti-angiogenic protein that acts as an antagonist by binding VEGF and PLGF, appear to increase in patients with preeclampsia prior to the onset of the disease (8,10). A number of angiogenic factors, such as soluble Tie-2 and epidermal growth factor, exhibit reduced expression levels in patients with preeclampsia. By contrast, anti-angiogenic factors, including endostatin, transforming growth factor- β and soluble endoglin are elevated in patients with preeclampsia (8,10).

2. Features of CXC chemokines and their receptors

Chemokines are a superfamily of structurally-associated proteins that were initially identified as mediators of cell recruitment. In particular, chemokines aid the movement of pro-inflammatory cells to the sites of inflammation by binding to a subset of seven-transmembrane G protein-coupled receptors (11). Furthermore, chemokines are recognized as key mediators of angiogenesis, immunity and stem cell trafficking and are involved in the pathogenesis of various conditions, including malignant tumors, wound repair, chronic inflammation, fibro-proliferative disorders, myocardial ischemia, atherosclerosis and possibly preeclampsia (12). The chemokine family is divided into four subfamilies, CXC, CC, CX3C and C, according to the number and spacing of the first two conserved cysteine residues at the N-terminal end of the protein (11).

CXC chemokines are characterized by the presence of four conserved cysteine amino acid residues at the amino terminus

of the protein, in which the first two conserved cysteine residues are separated by a single nonconserved residue. CXC chemokines are unique in their ability to behave in a disparate manner in the regulation of angiogenesis (13). Typically, the CXC family is further divided into two subgroups depending on the presence of a Glu-Leu-Arg sequence (ELR motif) preceding the first conserved cysteine residue. In general, CXC chemokines such as CXCL1, 2, 3, 5, 6, 7 and 8, that contain the ELR motif (ELR⁺), are potent inducers of angiogenesis (14,15). By contrast, CXC chemokines that lack the ELR motif (ELR⁻), such as CXCL4, 9, 10, 11 and 12, are potent anti-angiogenic factors that may inhibit the neovascularization induced by ELR⁺ CXC chemokines (14,16). Furthermore, ELR⁻ CXC chemokines have been demonstrated to inhibit the neovascularization induced by classical angiogenic factors, such as basic fibroblast growth factor (bFGF) and VEGF (14). However, CXCL12 is an exception, as it does not contain an ELR motif but induces angiogenesis by interacting with its receptor CXCR4 (17), as displayed in Table I.

Only CXCL6 and CXCL8 bind specifically to CXCR1 (13,18). By contrast, CXCR2 binds to all angiogenic CXC chemokines with high affinity, with the exception of CXCL12 (19,20). CXCR3 has been demonstrated to bind to the ELR⁻ CXC chemokines CXCL4, 9, 10 and 11 (21); however, it is unknown whether CXCR3 is the putative receptor for the ELR⁻ chemokine-mediated inhibition of angiogenesis. CXCR4 is able to bind to CXCL12 and CXCL14 (22,23). As presented in Table I, CXCR7 has been identified as a further receptor for CXCL12 and CXCL11 (24).

3. Regulation of CXC chemokines in angiogenesis

In general, the expression of ELR⁺ CXC chemokines induces angiogenesis in the absence of preceding inflammation via

CXCR2 and has been linked to diseases that are associated with neovascularization (13). For example, elevated expression levels of CXCL1, 2 and 3 have been observed in patients with melanoma (25). Yoneda *et al* (26) demonstrated that CXCL8, bFGF and VEGF are expressed in five human ovarian carcinoma cell lines. Notably, the expression levels of CXCL8 correlated directly with the rate of tumor cell survival, whereas the VEGF expression levels correlated only with the production of ascites. No correlations were identified between bFGF and tumor neovascularization or survival rate (26).

CXCL5 and CXCL8 are key angiogenic factors in non-small cell lung cancer (NSCLC) (27). The rates of tumor growth and spontaneous metastasis are markedly reduced in animals with NSCLC in the absence of CXCL5 (28). Furthermore, a previous study indicated an association between tissue levels of CXCL5 in surgical specimens of NSCLC and the extent of capillary density. This finding was consistent with tumor angiogenesis and its associated clinical outcomes, which include mortality (29). A severe combined immunodeficiency (SCID) mouse model with depleted expression levels of CXCL8 exhibited a significant reduction in tumor size, tumor-induced angiogenesis and metastasis (30).

In a SCID mouse model of human prostate cancer, various prostate cancer cell lines were demonstrated to exhibit different ELR⁺ CXC chemokine ligands. Depletion of CXCL1, but not CXCL8, inhibited tumor angiogenesis in DU145 prostate cancer cells, whereas the depletion of CXCL8, but not CXCL1, inhibited angiogenesis in PC-3 tumor cells (31). As CXCL1 and CXCL8 share the same receptor, the results of the study notably indicated the role of CXCR2 in angiogenesis. A number of previous studies have indicated that tumor-induced angiogenesis is inhibited by blocking the CXCR2 receptor (13,32). A previous study by Addison *et al* (13), which used a corneal micropocket angiogenesis assay in CXCR2^{+/+} and CXCR2^{-/-} mice, indicated that ELR⁺ CXC chemokine-mediated angiogenesis can be inhibited in the CXCR2 knockout mice, and in the presence of CXCR2-neutralizing antibodies (13). Furthermore, the overexpression of ELR⁺ CXC chemokines has been associated with increased angiogenesis in psoriatic tissue, and in patients with idiopathic pulmonary fibrosis (13).

CXCR3 exists in three forms; CXCR3A, 3B and 3-alt, which are produced by the alternative mRNA splicing of a single gene product. CXCR3A is primarily responsible for the recruitment of leukocytes and its expression is markedly induced by interleukin (IL)-2 (33). CXCR3B is the primary angiostatic variant of CXCR3 and is expressed by endothelial cells (34). CXCR3-alt, has been observed to possess a higher binding affinity for CXCL11 compared with CXCL9 and CXCL10; however, its function in the progression of angiogenesis remains unclear (35).

Human CXCL4, 9, 10 and 11 mediate angiostasis by interacting with the CXCR3B receptor (36). Interferon (IFN)-induced chemokines, including CXCL9, 10 and 11, are potent inhibitors of angiogenesis and respond to the angiogenic ELR⁺ CXC chemokines, VEGF and bFGF (37). IFN- α , - β and - γ each stimulate the expression of CXCL10, while CXCL9 and CXCL11 are induced by IFN- γ alone (37,38). Furthermore, IL-12 and IL-18 inhibit angiogenesis via the induction of IFN- γ , which in turn induces the production of CXCL9, 10 and 11 (39). A prior study, which employed fluo-

rescein isothiocyanate-labeled CXCL4, indicated that CXCL4 binds selectively to areas of the endothelium exhibiting active angiogenesis (40). CXCL4, a potent inhibitor of endothelial cell chemotaxis and proliferation, has been indicated to inhibit the angiogenic effects of VEGF and bFGF (41).

The expression levels of CXCL10 and CXCL9 are higher in tumors that exhibit spontaneous regression and have been directly associated with impaired angiogenesis (42). The depletion of the expression levels of CXCL10 in squamous cell carcinoma specimens of NSCLC resulted in augmented angiogenic activity (43).

Continuous intratumor injections of recombinant human CXCL10 (100 ng, every other day) into the primary tumor of a SCID mouse model of NSCLC resulted in reduced angiogenesis, delayed metastasis and improved survival rates (44).

The CXCL12-CXCR4 axis is currently one of most frequently studied chemokine pathways. CXCL12-CXCR4 has been associated with >20 different types of human cancer, including melanoma, as well as ovarian, prostate and breast cancer (45). In addition, CXCR4 overexpression appears to induce the metastatic dissemination of breast cancer cells to the lungs and lymph nodes (46). It has been hypothesized that hypoxic conditions in solid tumors may induce the expression of CXCR4 via hypoxia inducible factor-1 α . Furthermore, tumor cells are able to produce VEGF, which may in turn induce CXCR4 expression in the tumor cell itself and/or in the tumor-associated endothelial cells that facilitate tumor angiogenesis and metastasis (47). CXCR7 is a recently identified receptor for CXCL12 and may to serve a critical function in cancer progression. A prior study indicated that CXCR7 interacts with CXCL11, which is a member of the ELR⁻ CXC chemokine subfamily (48). In an animal model of lung cancer, blockage of CXCR7 by its antagonist CCX754 was observed to inhibit tumor growth, suggesting that CXCR7 possesses protumorigenic properties (49). Tumor endothelial cells (TECs) from renal cell carcinoma tissue were used in a previous study that hypothesized that the upregulation of CXCR7 in TECs is a result of tumor microenvironment factors, such as the levels of VEGF (50). Prior studies have indicated that CXCL14 is an inhibitor of the CXCL12-CXCR4 signaling axis, and is downregulated by DNA methylation in prostate (51) and lung cancer (52).

4. CXC chemokines and preeclampsia

The role of CXC chemokines in the process of carcinogenesis has been increasingly investigated. As trophoblasts possess similar invasive properties to malignant cells, the association between CXC chemokines and trophoblast invasion has been studied extensively.

CXCL10 is expressed in vascular endothelial and vascular smooth muscle cells in the placenta and extravillous trophoblast-induced CXCL10 expression contributes to a reshaping of the spiral arteries by altering the motility and differentiation status of vascular smooth muscle cells in blood vessels (53). CXCL6 has been observed to restrict human trophoblast cell migration and invasion *in vitro* by suppressing matrix metalloproteinase (MMP)-2 activity in the first trimester of pregnancy (29). By contrast, CXCL8 stimulates trophoblast cell migration and invasion by increasing the expression levels of MMP-2 and -9 (30).

CXCL14 proteins appear to be expressed selectively during early but not late pregnancy. Furthermore, CXCL14 appears to be expressed markedly in villous cytotrophoblasts, moderately in decidual stromal cells (DSCs) and weakly in syncytiotrophoblasts and extravillous trophoblasts (54). In an *in vitro* study, the expression of CXCL14 appeared to significantly inhibit primary and secondary trophoblast attachment and outgrowth and correlated with a stage-dependent downregulation of MMP-2 and/or -9 activity in a paracrine or autocrine manner (55).

Analysis of the CXCL12-CXCR4 axis indicated that anti-CXCL12 and -CXCR4 neutralizing antibodies may inhibit the increase of CD82 expression in decidua induced by the trophoblast supernatant (56). In addition, pretreatment with CXCR4-neutralizing antibody has been observed to significantly reduce trophoblast invasiveness. Furthermore, trophoblast-derived CXCL12 has been demonstrated to increase cell invasiveness in an autocrine manner and to mitigate trophoblast invasiveness by promoting CD82 expression in DSCs in a paracrine manner (56). This process maintains the physiological balance of human trophoblast invasiveness via the interaction between trophoblasts and DSCs (56).

Female patients undergoing a healthy pregnancy exhibit a significantly higher median serum concentration of CXCL10 (median, 116.1 pg/ml; range, 40.7-1,314.3 pg/ml) compared with non-pregnant females (median, 90.3 pg/ml; range, 49.2-214.7 pg/ml; $P < 0.05$). Furthermore, female patients with preeclampsia exhibit a higher median serum concentration of CXCL10 (median, 156.4 pg/ml; range, 47.4-645.9 pg/ml) compared with healthy pregnant females (median, 116.1 pg/ml; range, 40.7-1,314.3 pg/ml; $P < 0.05$) (57).

In a previous study, the plasma levels of CXCL10 were increased in patients with preeclampsia, and the plasma levels of CXCL11 were elevated significantly in early-onset preeclampsia patients compared with control patients ($P < 0.05$) (58).

Maternal serum levels of CXCL12 are increased in patients with preeclampsia compared with normal control patients ($2,000 \pm 402$ vs. $1,484 \pm 261$ pg/ml; $P = 0.01$). In a previous study by Schanz *et al* (59), syncytiotrophoblast staining of placental tissue revealed significantly increased levels of CXCL12 in the preeclampsia group. They hypothesized that the syncytiotrophoblast contributed to the preeclampsia-associated increase in CXCL12 levels in maternal blood.

In our previous study, plasma CXCL3 levels were observed to be elevated in patients with preeclampsia (60). The placental expression levels of CXCL3, which is stained in syncytiotrophoblasts and vascular endothelium, were reduced in cases of severe preeclampsia. Furthermore, exogenous CXCL3 was able to promote the proliferation and invasion profile of HTR-8/SVneo cells *in vitro*.

Thus far, the majority of studies have examined the serum or placental expression levels of CXC chemokines and their receptors in patients with preeclampsia. However, the mechanism underlying the effects of CXC chemokines on trophoblast invasiveness remains unclear. Therefore, future studies should investigate the association between CXC chemokines and preeclampsia, which may result in the development of novel therapeutic applications.

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