

# CXC Motif Chemokine Receptor 2: Glimpses into the Molecular Pathogenesis of Placenta Accreta Spectrum Disorder

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## CXC Motif Chemokine Receptor 2: Glimpses into the Molecular Pathogenesis of Placenta Accreta Spectrum Disorder

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### Abstract

Investigation into the mechanism underlying excessive trophoblast invasion yields further strategies and insights for the diagnosis and treatment of placenta accreta spectrum disorder (PASD). We conducted a comprehensive literature review to analyze the relationship between CXCR2 expression and PASD, as well as the possibility of CXCR2 being used as a therapeutic and diagnostic biomarker for PASD. Chemokines are well-known mediators in the immune system, particularly for cell recruitment, angiogenesis, and tumor infiltration. CXCR2 is an important component of the immune system, particularly in neutrophils. One of the CXCR2 ligands, IL-8, has also been found to be expressed in the decidua and trophoblasts of humans and to promote autocrine or paracrine trophoblast migration and invasion. The potential role of CXCR2 in trophoblast invasion in PASD provides researchers with a glimpse into the molecular pathogenesis of PASD.

Key words: biomarker; CXCR2; placenta accreta

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## CXC Motif Chemokine Receptor 2: Sekilas tentang Patogenesis Molekuler Gangguan Spektrum Plasenta Akreta

### Abstrak

Investigasi mekanisme invasi berlebihan trofoblas pada gangguan Spektrum Plasenta Akreta (SPA) akan memberikan lebih banyak strategi dan ide untuk diagnosis dan pengobatan. Kami melakukan tinjauan literatur yang komprehensif untuk menganalisis hubungan antara ekspresi CXCR2 dan SPA serta potensi CXCR2 sebagai penanda terapeutik dan diagnostik untuk SPA. Kemokin berperan sebagai mediator dalam sistem imun karena perannya dalam perekrutan sel, angiogenesis, dan infiltrasi tumor. CXCR2 mempengaruhi sistem imun, terutama pada neutrofil. Salah satu ligan CXCR2, IL-8, juga telah ditemukan diekspresikan dalam desidua dan trofoblas manusia serta untuk mempromosikan migrasi dan invasi trofoblas autokrin atau parakrin. Peran CXCR2 dalam invasi trofoblas pada SPA memungkinkan para peneliti untuk melihat sekilas patogenesis molekuler SPA.

**Kata kunci:** penanda; CXCR2; plasenta akreta

## Introduction

Placenta accreta spectrum disorder (PASD) is defined as excessive infiltration of the myometrium into the chorionic villi, which can cause significant bleeding during and after childbirth, making it one of the most common causes of maternal death and emergency hysterectomy. Currently, research into the pathophysiology of PASD focuses mainly on myometrial scarring, decidua loss or altered function, and aberrant angiogenesis at the invasive site. However, these factors can only explain PASD to a limited extent. The chemical mechanism that causes PASD over-penetration is unknown.<sup>1</sup>

The CXC motif chemokine receptor 2 (CXCR2) sequence has been a hotspot for studying the development of many cancers. CXCR2 regulates tumor cell adherence, colonization, angiogenesis, proliferation, and metastasis. Given the biological behavior of trophoblasts, which is similar to that of cancer cells, it can be inferred that CXCR2 and its ligands can also be involved in the pathogenesis of PASD, i.e., trophoblast differentiation, proliferation, and invasion.<sup>2</sup> The role of CXCR2 in the pathogenesis of PASD has not been thoroughly investigated. This article provides an extensive literature review to assess the association between CXCR2 expression and PASD.

## Review

Placenta Accreta Spectrum Disorder (PASD) is a condition characterized by the failure of the placenta to detach spontaneously after childbirth, making it impossible to remove it forcefully without risking significant, potentially lethal postpartum bleeding. PASD is becoming more common worldwide. This is most likely due to an increase in cesarean deliveries, which has been widely studied as a significant risk factor for PASD. Because it is linked to maternal morbidity and mortality,

PASD is one of the most severe pregnancy diseases. Prenatal diagnosis of PASD and early intervention by an experienced interdisciplinary team can increase maternal and neonatal outcomes.<sup>3</sup>

Several theories have been presented to explain the pathogenesis of PASD. When placental implantation occurs in the uterus wall area with endometrial loss, e.g., at the site of uterine scars, implantation defects at the interface between the endometrium and myometrium can cause decidualization failure, allowing aberrantly deep trophoblast infiltration. Destruction of the decidua, such as by a previous cesarean section, can result in loss of intrinsic regulation throughout the depth of the myometrium and uncontrolled invasion of trophoblasts. The degree of damage to the myometrium directly determines the degree of penetration of villous tissue into the myometrium. Patients who have undergone manual placenta removal, uterine curettage, or endometritis are at greater risk of having an abnormally attached placenta, i.e., placenta accreta.<sup>3</sup>

Chemokines have a well-established function as mediators in the immune system and in the recruitment of cells, angiogenesis, and the trafficking of stem cells. Chemokines are a superfamily of four subfamilies: C, CC, CXC, and CX3C. CXC chemokines have recently been confirmed by a growing number of researchers to play a role in the development of PASD. The inclusion or exclusion of the Glu-Leu-Arg<sup>+</sup> (ELR<sup>+</sup>) sequence further divides the CXC chemokine subfamily into two distinct subgroups. CXC chemokines with ELR<sup>+</sup> sequence induce neovascularization as they bind to CXCR2 receptors. Conversely, CXC chemokines that do not consist of the ELR<sup>+</sup> sequence exhibit antiangiogenic properties by suppressing angiogenesis induced by ELR<sup>+</sup>CXC chemokines.<sup>4</sup>

Prior research has documented that trophoblast cells in PASD demonstrate

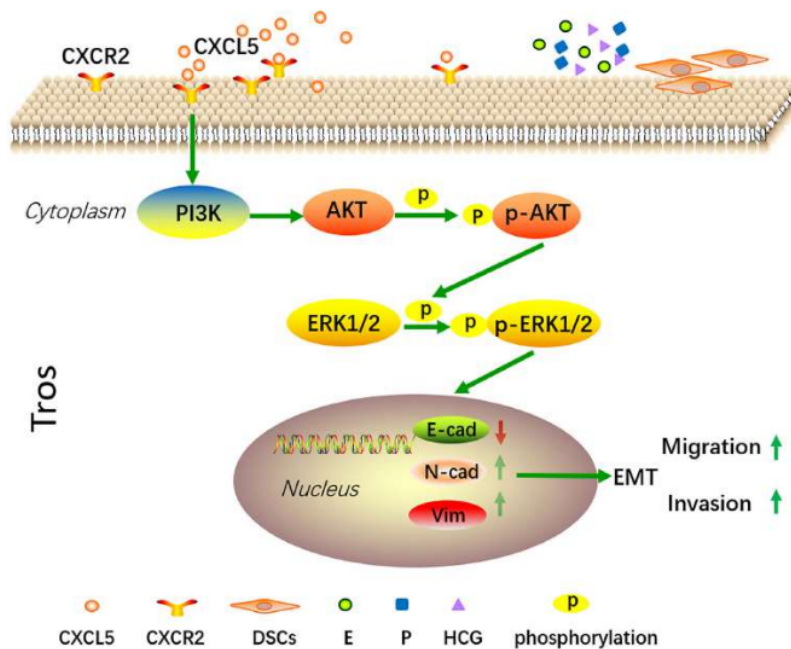
elevated expression of the C-X-C motif ligand (CXCL)-12 along with CXCR4/CXCR7. The expression levels of CXCL12, CXCR4, and CXCR7 proteins are directly influenced by the extent of trophoblast infiltration. Therefore, it can be inferred that CXCL12-CXCR4/CXCR7 plays an essential role in the pathogenesis of PASD. Changes in oxygen concentration affect trophoblast cell proliferation, differentiation, and infiltration, whereas hypoxia may promote CXCL12 secretion and subsequently stimulate trophoblast cell migration and infiltration. Therefore, some researchers have suggested that local hypoxia causes the placenta to aberrantly attach to the lower part of the uterus or uterine scars in patients with PASD. Long et al. reported an association between CXCL12-CXCR4/CXCR7 and trophoblast cell perinfiltration in PASD.<sup>1</sup>

CXCR2 is a receptor for ELR+ CXC chemokines, including CXCL13 and CXCL58. A recent study has shown a connection between CXCR2 and the migration and infiltration of tumors in several types of cancers, such as lung, rectal, ovarian, prostate, esophageal, and stomach cancers.<sup>2</sup> CXCR2 inhibitors have been shown to slow the development of tumors. According to immunohistochemistry, CXCR2 is also expressed in maternal and fetal interface villous and deciduous cells, according to immunohistochemistry.<sup>5</sup> However, because CXCR2 is only one of the ELR+ CXC chemokine receptors, its involvement in regulating trophoblast infiltration activity is unknown.<sup>4</sup>

CXCR2 appears to play an essential role in tumor infiltration and migration between tumor types, according to growing data in recent years. Targeting CXCR2 can inhibit tumor growth and invasion in several investigations. Surprisingly, tumor cells and human trophoblasts have the same infiltration potential and molecular mechanism.<sup>2</sup> The studies that demonstrate the connection

between CXCR2 and trophoblasts are summarized in Table 1. The mechanism by which CXCR2 expression promotes trophoblast migration and invasion is shown in Figure 1. However, this intrusive process is strictly regulated and controlled. Early in the first and second trimesters, extravillous trophoblasts (EVT) infiltrate the maternal decidua and blood vessels, but no further invasion occurs, and the endothelium is replaced. Epithelial Stroma Translocation is a physiological cellular program that aids this process. Extravillous trophoblasts have been observed to remain very invasive in placenta accreta due to EMT, which can cause myometrial infiltration.<sup>2</sup> Based on extensive studies reporting the role of CXCR2 in cell infiltration in cancer pathogenesis, CXCR2 may induce trophoblast infiltration and, therefore, be involved in the development of PASD.

An increasing number of studies have assessed the association between CXCR2 and trophoblast diseases.<sup>7</sup> Studies assessing the relationship between CXCR2 and placental disease reported that CXCR2 inhibitors suppress Akt pathway expression, similar to matrix metalloproteinases (MMP) in the trophoblast. Proteolysis of extracellular matrix (ECM) molecules is required for cell infiltration. MMPs are zinc-dependent endopeptidases. It plays a role in the breakdown of the ECM and is thus involved in cell migration and infiltration. In particular, MMP-9 have been found to be crucial in human trophoblast invasion. CXCR2 inhibition has also been shown to lower MMP-2 and MMP-9 expression. Several signaling pathways play crucial roles in cell proliferation and invasion. CXCR2 can regulate the trophoblast biological activity of HTR8/SVneo and TEV1 cells through Akt signaling rather than through extracellular signal-regulated kinase (ERK)1/2 signaling. The Akt pathway has been associated with trophoblast infiltration by regulating



**Figure 1** CXCL5 promotes trophoblast migration, invasion, and EMT via the PI3K/AKT/ERK1/2 signalling pathway, as shown in the diagram. Trophoblast cells express CXCR2, the CXCL5 receptor. Exogenous CXCL5, in combination with CXCR2, induces EMT by activating the PI3K/AKT/ERK1/2 signalling cascade, increasing trophoblast cell invasiveness and migration. Downregulation of CXCL5, on the other hand, results in an inadequate invasion. In addition, E, P, HCG, and DSCs have a contribution in controlling the expression of CXCL5 and CXCR2 in trophoblast cells at the maternal-fetal interface throughout pregnancy. PI3K: phosphoinositide 3-kinases; Akt: Protein kinase B; ERK: extracellular signal-regulated kinase; EMT: epithelial-to-mesenchymal transition; CXCL: CXC motif chemokine ligand; CXCR: CXC motif chemokine receptor; DSCs: decidual stromal cells; E: estrogen; P: progesterone; HCG: human chorionic gonadotropin.<sup>6</sup>

MMP-9 production in recent research, but another study showed MMP-2 secretion in trophoblast.<sup>8</sup>

Another study reported a role of CXCR2 chemokines in recurrent spontaneous abortion. This is almost the opposite of PASD. In relapsed spontaneous abortion, trophoblast infiltration is less, whereas trophoblast in PASD is highly invasive. CXCL5 is a chemokine that was first discovered in neutrophils and belongs to the CXC chemokine subfamily. It is one of

the CXCR2 chemokines. CXCL5 has been shown in several studies to facilitate cancer cell infiltration and metastasis by inducing the EMT pathway. Regarding their ability to infiltrate, migrate, and proliferate, trophoblast cells and cancer cells share remarkable behavioral similarity. The effect of effect on trophoblast infiltration has not been studied. CXCR2 is expressed in human chorionic villi, according to previous research. Interlukin (IL)-8, a CXCR2 ligand, was also discovered to be expressed in human decidua

and trophoblasts and to enhance autocrine or paracrine trophoblast migration and invasion. Similar results were found for CXCL3.<sup>6</sup>

Interleukin-8 is an 8-kDa non-glycosylated protein that plays a role as a proinflammatory cytokine and belongs to one of the CXC chemokine subfamilies. IL-8 is produced by epithelial and stromal cells in the endometrium as well as epithelial cells, stromal cells, natural killer (NK) cells, macrophages, and CD8+ T lymphocytes in the decidua. IL-8 is produced by several cell types, including fibroblasts, chondrocytes, keratinocytes, hepatocytes, endothelial cells, bronchial epithelial cells, mesangial cells, and white blood cells. IL-8 acts as a chemoattractant for neutrophils and a stimulant for neutrophil transendothelial migration. It also promotes angiogenesis and inhibits myeloid progenitor cell growth.<sup>9</sup> Elevated concentrations of IL-8 in both the bloodstream and the localized environment of the tumor may substantially enhance the growth of colon cancer cells, the formation of new blood vessels around the tumor, and the spread of cancer cells to the lungs and liver. In mice with CXCR2, tumor development was suppressed, with decreased tumor angiogenesis and enhanced tumor necrosis.<sup>10</sup>

It is an essential component of the immune system, particularly in neutrophils. This implies a potential correlation between CXCR2 and vitamin D levels. The active form of vitamin D, 25(OH)2D3, facilitates the production of IL-8. This indicates that vitamin D may enhance the responsiveness of neutrophils to invading pathogens by drawing a greater number of neutrophils to the site of infection. Vitamin D regulates the release of IL-8 in hyperinflammatory macrophages. IL-8 has a CXCR2 receptor and has been shown to enhance the synthesis of IL-8 and CXCR2 under certain circumstances, such as in the context of cancer. On the other hand, some studies have reported that IL-8

promotes the formation of new blood vessels and facilitates the migration and invasion of tumors by enhancing the growth of cancer cells and suppressing their programmed cell death. A previous study discovered a positive correlation between elevated IL-8 activity and increased CXCR2 expression.<sup>11</sup>

CXCR2 has a high affinity for CXCL8, or IL-8.<sup>12</sup> Interleukin-8 is a chemoattractant neutrophil and transendothelial migration stimulator of neutrophils and can induce angiogenesis. It has been reported that in the pathogenesis of PASD, there is an EMT process that is too aggressive and persistent due to the increased invasion capability of EVT. This may be explained by the increased ability of EVT to degrade the extracellular matrix by secreting proteolytic enzymes, namely MMP-2 and MMP-9, due to IL-8 stimulation. Increased MMP is also associated with abnormal maternal vascular remodeling in PASD.<sup>13</sup> It has been reported that CXCR2 inhibitors can suppress MMP-2 and MMP-9 expression through the protein kinase B (Akt) signaling pathway.<sup>8</sup> Thus, CXCR2 expression plays a role in increasing trophoblast invasion and vascular remodeling. In addition, CXCR2 is a critical receptor for neovascularization. The presence of CXCR2 in endothelial cells may stimulate their migration, infiltration, and survival, leading to angiogenesis.<sup>14</sup> A better understanding of the molecular basis of other placental disorders, such as preeclampsia, suggests that the inflammatory process is closely related to placental invasion. Several comparisons can be made between the microenvironment of PASD and the tumor. Both conditions require the cell's ability to fight the local immune system, activate invasion, and induce angiogenesis. Several biomarkers may lead researchers to the bright spots of PASD pathogenesis, including CXCR2.<sup>15</sup> Increased expression of CXCR2 has been reported to correlate with tumorigenesis, cancerous tissue angiogenesis, and metastasis

of some cancers, including ovarian cancer. According to a study conducted by Yang et al., ovarian cancer cells often express CXCR2 to stimulate tumor development by enhancing the formation of new blood vessels, inhibiting programmed cell death and disrupting the normal control of cell division.<sup>16</sup>

### Conclusion

CXCR2 plays an essential role in the immune system and may affect trophoblast infiltration through several pathways. These critical roles of CXCR2 in the pathogenesis of PASD establish the pathway as a promising diagnostic indicator and therapeutic target. It also allows researchers to get a glimpse into the molecular pathogenesis of PASD.

### Conflict of Interest

The authors declare no conflict of interest.

### Advice and Thanks

We express our gratitude to all the professors and colleagues from the Department of Obstetrics and Gynecology dr. Mohammad Hoesin General Hospital and Faculty of Medicine Universitas Sriwijaya, Palembang, South Sumatra, Indonesia, for their insightful discussions while writing this literature review

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