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REVIEW

The role of CX3CL1 in fetal-maternal interaction during human gestation

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ABSTRACT

Embryo implantation and subsequent placentation require a fine balanced fetal-maternal cross-talk of hormones, cytokines and chemokines. Amongst the group of chemokines, CX3CL1 (also known as fractalkine) has recently attracted attention in the field of reproductive research. It exists both as membrane-bound and soluble isoforms. On the basis of current experimental evidence, fractalkine is suggested to regulate adhesion and migration processes in fetal-maternal interaction at different stages of human pregnancy. Expressed by uterine glandular epithelial cells, predominantly during the mid-secretory phase of the menstrual cycle, fractalkine appears to prime the blastocyst for forthcoming implantation. After implantation, fractalkine is suggested to regulate invasion of extravillous trophoblasts by altering their expression profile of adhesion molecules. With onset of perfusion of the intervillous space at the end of first trimester, fractalkine present at the apical microvillous plasma membrane of the syncytiotrophoblast may mediate close interaction of placental villi with circulating maternal blood cells.

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Introduction

Embryo implantation into the maternal decidua and subsequent placentation are mandatory steps for successful human pregnancy. These essential steps require a well-orchestrated interaction between fetal and maternal tissues and comprise a fine balanced cross-talk of hormones, cytokines and chemokines. Chemokines represent a special heterogeneous family of 8-15 kDa low molecular mass cytokines that promote migration of leukocytes and thereby mediate inflammation and modulate immune responses.[1,2] Moreover, chemokines play important key roles in several physiologic and pathologic aspects of human reproduction, including menstruation, ovulation, implantation, cervical ripening, preterm labor, and endometriosis.[3] According to the number and spacing of the first two cysteine residues in a conserved cysteine structural motif, chemokines are classified into four subclasses.[4] These four subclasses are referred to as C, CC, CXC, and CX3C, where C is a cysteine and X any amino-acid residue. A unique member of the CX3C subclass is CX3CL1 (also referred as fractalkine), which is encoded on chromosome 16, and derives from non-haemopoietic cells.[5,6] Fractalkine is synthesized as transmembrane molecule, but can be shed by a disintegrin and metalloprotease (ADAM)10 and ADAM17 into a soluble isoform.[7-9] Depending on whether it is cleaved or not, fractalkine mediates different steps of leukocyte recruitment. Full length fractalkine represents a 373 amino acid transmembrane molecule, comprising an extracellular N-terminal domain (residues 1-76), a mucin-like stalk (77-317), a transmembrane α-helix (318-336) and a short cytoplasmic tail (337-373).[10,11] While the soluble form has chemoattractive activity, the membrane-bound form promotes flow resistant adhesion of leukocytes to endothelial or epithelial cells via its corresponding G protein-coupled, 7-transmembrane receptor CX3CR1, which is expressed on natural killer (NK) cells, CD3+ T-cells and a majority of CD14+ monocytes.[5,12]

Fractalkine and its receptor CX_3CR1 are expressed in several reproductive tissues, including ovaries, Fallopian tubes, uterus and testis.[5,13,14] Mice lacking fractalkine are fertile and do not show any developmental defects, which most likely excludes a fundamental functional role of the chemokine/receptor duo in reproduction at least in mice.[15,16] This is not surprising given the redundancy between chemokines and their receptors. However, accumulating evidence suggests that dysregulation of fractalkine expression is associated with a number of

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pregnancy complications. In pregnancies complicated by diabetes mellitus, upregulated placental fractalkine was suggested to contribute to increased placental villous microvessel density.[17] Moreover, increased release of soluble fractalkine was detected in perfusion fluids of perfused placental cotyledons in response to lipopolysaccharide and hypoxia,[18] indicating upregulation of fractalkine in the placental endothelium under pro-inflammatory conditions. In line with this assumption, increased fractalkine expression was shown in human amnionic epithelial cells in pregnancies complicated by chorioamnionitis.[19] Recently, increased placental fractalkine expression and a trend towards elevated levels of circulating soluble fractalkine was shown in patients with severe early-onset preeclampsia.[20,21]

This review will focus on putative roles of fractalkine in several aspects of fetal-maternal interaction at different stages of human pregnancy.

The role of fractalkine in blastocyst attachment and implantation

In human, the first step of blastocyst implantation – the so-called apposition – takes place around day 6 to 7 post-coitus (p.c.). At this stage, the implanting blastocyst is composed of approximately 250 cells, most of which comprise the outer wall surrounding the blastocyst cavity and the inner cell mass.[22] This outer wall consists of mononucleated trophoblast cells (also referred to as trophectoderm cells). Implantation is initiated by attachment of the apical plasma membranes of the trophoblasts to the apical plasma membranes of the uterine epithelium. This process has been discussed as paradoxic phenomenon, since apical plasma membranes of epithelia are described as normally nonadhesive.[22] Nevertheless, adhesiveness of the trophectoderm cells of the blastocyst and the apical plasma membrane of the uterine epithelium is assured for a short phase described as the implantation window. At that time, uterine epithelial cells become highly secretory and release numerous regulatory molecules into the uterine lumen, where they can affect the blastocyst even prior to attachment.[23] Fractalkine may be part of the molecular cocktail released by uterine epithelial cells. This assumption is based on immunohistochemical analysis of human endometrium, showing fractalkine maximally expressed in the luminal and glandular uterine epithelium during the mid-secretory phase of the menstrual cycle.[13] These data suggest that released uterine fractalkine, as part of a secreted chemokine cocktail, may prime the blastocyst for attachment through activation of various chemokine receptors that have been detected in human blastocysts.[24]

However, whether or not the fractalkine/CX_3CR1 interaction directly mediates attachment of the blastocyst is not known. Since appropriate human specimens are rare and usually poorly preserved, current knowledge on molecular and micro-anatomical processes taking place in the human implantation window are very limited. However, there are considerable differences between mammalian species in the type of implantation and placentation.[25] Nevertheless, our understanding of the earliest stages of implantation is mainly based on animal models, most of which have the initial steps of apposition and attachment, although the step of invasion is not a feature of implantation in all species. For example, in sheep, elongation of the trophoblast on day 11, is followed by immobilization of the embryo in the uterine lumen at day 14, and induction of implantation at day 15.[26] However, there is no invasion: instead there is fusion of trophectodermal and endometrial epithelial cells to form specialized trinucleate cells.[27] Gene expression analysis of ewe conceptuses at the stages of elongation, immobilization and implantation showed increasing fractalkine levels during elongation with peak expression on day 14, suggesting specific upregulation at the time when the first contacts between trophoblast and uterus are established.[28] Fractalkine-mediated attachment of the conceptus to the uterine epithelium implies epithelial expression of the receptor CX_3CR1, but this was not examined in this study. Compared with ruminants, human embryos have three phases of implantation, including apposition, adhesion and invasion. During apposition an active cytokine and growth factor dialogue is established between the blastocyst and the decidua. This dialogue induces upregulation of adhesive molecules on the surface of both and enables adhesion. In human, while fractalkine is produced by endometrial epithelium, CX_3CR1 expression was detected only in the uterine glandular epithelium whereas luminal epithelial cells were consistently negative for CX_3CR1 expression at all stages of the cycle.[13] CX_3CR1 was also present on invasive trophoblast cells, although trophectoderm was not available for analysis. It is therefore still not known whether there is direct involvement of the fractalkine/CX_3CR1 axis in blastocyst attachment. However, available data certainly suggests involvement of fractalkine in the process of trophoblast invasion.

The role of fractalkine in trophoblast invasion

Trophoblast invasion is a key event during implantation and placentation, which is not only responsible for further invasion of the blastocyst itself but also for anchorage of the developing placenta and remodelling of uteroplacental arteries to adapt to

pregnancy.[22] During very early stages of implantation, trophoblasts of the implanting embryonic pole of the blastocyst show increased proliferation which results in a double-layered trophoblast. By fusion of neighbouring mononucleated trophoblasts of the outer layer directly facing the decidua, the so-called syncytiotrophoblast is formed: this is the trophoblast type responsible for enzymatic cleavage of the extracellular matrix of the developing decidua, enabling progression of trophoblast invasion until day 14 p.c.[22] Thereafter, proliferating and migrating cytotrophoblasts reach the trophoblastic shell via syncytiotrophoblast trabeculae and finally penetrate the decidual stroma. Thus, very early invasion processes are driven by the syncytiotrophoblast, whereas from day 15 p.c. mononucleated cytotrophoblasts – so-called extravillous trophoblasts (EVT) – invade the uterine tissue as far as to the inner third of the myometrium. In this context it should be noted that the vast majority of studies on trophoblast invasion, describe advanced implantation processes using mononucleated trophoblast cell lines. However, expression analyses and functional studies suggest a functional role of the fractalkine/CX_3CR1 axis in stimulating the migratory and invasive behaviour of extravillous trophoblasts.

Noteworthy, expression patterns of fractalkine and CX_3CR1 seem to vary between different types of trophoblasts. While fractalkine expression has been detected in primary term trophoblasts and several trophoblast cell lines such as JEG-3, AC1M-32 and AC1M-88 as well as differentiated BeWo,[29-31] CX_3CR1 is differentially expressed throughout different types of trophoblasts. Immunohistochemistry of first-trimester human implantation sites detected CX_3CR1 in endovascular EVT, which invade uteroplacental vessels. In contrast, no CX_3CR1 expression was detected in interstitial EVT, which migrate through the decidual stroma, but do not invade blood vessels.[30] Differential CX_3CR1 expression was also shown for trophoblast cell lines. While Jeg-3 and AC1M-88 express the receptor, both undifferentiated and differentiated BeWo cells lack CX_3CR1 expression.[29,30] Thus, fractalkine may function on well-defined

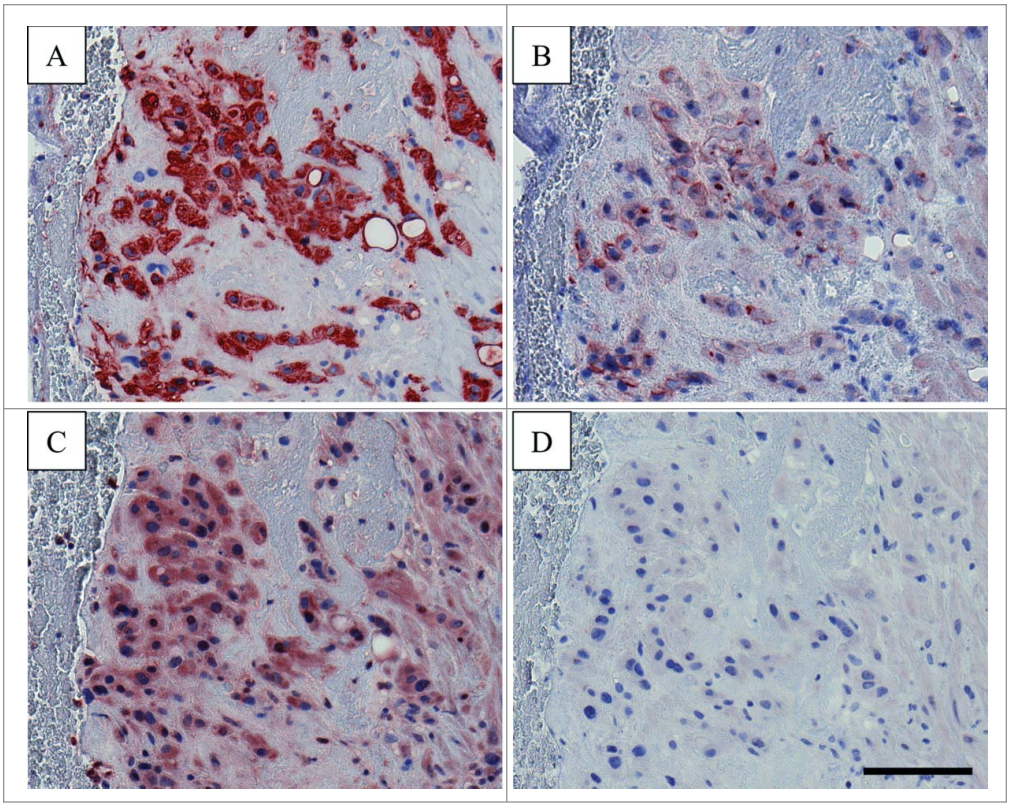

Figure 1. Immunohistochemical staining for fractalkine and CX_3CR1 in human postpartum decidua. Serial postpartum decidua sections (5 μm) obtained from human hysterectomy were stained for (A) extravillous trophoblast marker HLA-G (using clone 4H84, BD Pharmingen, 0.25 μg/ml working concentration), (B) fractalkine (using monoclonal anti-human CX3CL1/fractalkine antibody, clone 81513, R&D Systems, 1 μg/ml), (C) CX_3CR1 (using polyclonal anti-CX3CR1 antibody C8354, Sigma-Aldrich, 2 μg/ml) and (D) Negative Control for Rabbit IgG Ab-1 (Neomarkers, Thermo Scientific, 2 μg/ml). Staining was performed using the UltraVision Large Volume Detection System HRP Polymer Kit (Thermo Fisher Scientific) as previously described.[21,29,38] Invading extravillous trophoblasts were positive for fractalkine and CX_3CR1. Scale bar represents 100 μm.

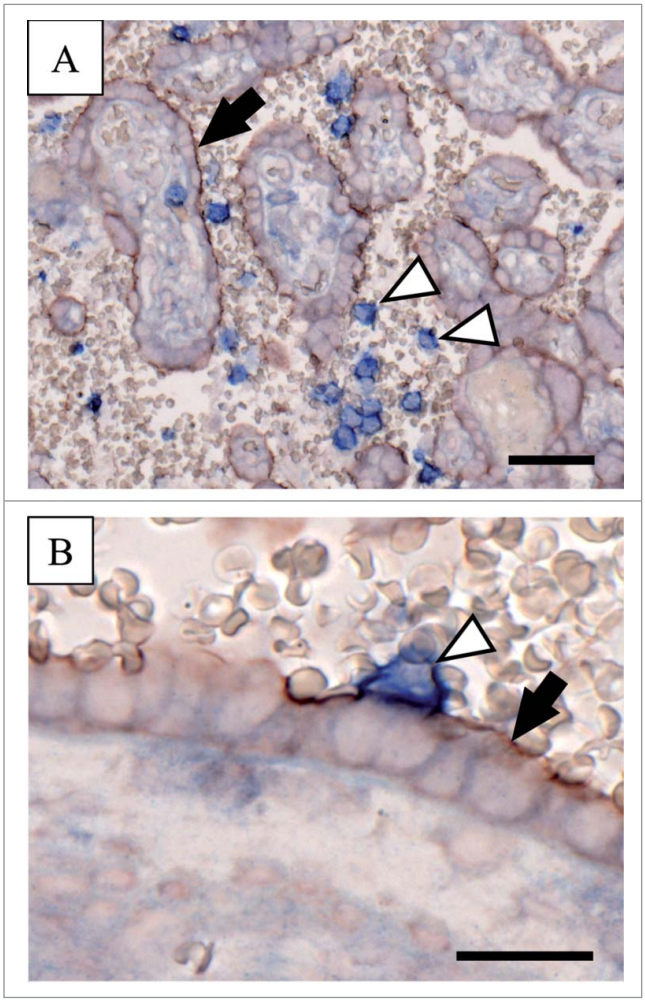

Figure 2. Immunohistochemical double staining for fractalkine and CX_3CR1 in human term placenta. Human term placenta sections (5 μm) were stained with the MultiVision Polymer Detection System (Thermo Scientific), using monoclonal anti-human CX3CL1/fractalkine antibody (clone 81513, R&D Systems, 1 μg/ml) and polyclonal anti-CX3CR1 antibody (C8354, Sigma-Aldrich, 0.5 μg/ml) as previously described.[21,29,38] (A) Immunohistochemical double staining of human term placenta localized fractalkine at the apical microvillous plasma membrane of the syncytiotrophoblast (red staining; arrow), whereas CX_3CR1 was detected on circulating maternal blood cells (blue staining; arrowheads) in the intervillous space. (B) Tight contact of the fractalkine positive syncytiotrophoblast (arrow) and a CX_3CR1 expressing maternal blood cell (arrowhead) was occasionally observed and suggest fractalkine/CX_3CR1-mediated fetal-maternal interaction. Scale bars in Aand Brepresent 50 μm and 20 μm, respectively.

subpopulations of invading trophoblasts, depending on their CX_3CR1 expression profile. Accordingly, AC1M-88 trophoblasts, abundantly expressing CX_3CR1, show enhanced migration in response to recombinant fractalkine.[30] Besides uterine glandular epithelial cells, also decidualized stromal cells, uterine natural killer cells and macrophages in decidualized zones were shown to express fractalkine,[13] which may act on invading trophoblasts in a paracrine manner. This assumption is substantiated by experiments using specific neutralizing antibodies to fractalkine, which significantly attenuated migration of AC1M-88 trophoblasts in response to conditioned culture medium from primary endometrial epithelial cells.[30] Since some trophoblast cell lines show both fractalkine and CX_3CR1 expression, it is tempting to speculate on autocrine functions of the chemokine/receptor duo, as shown for granulosa cells in preovulatory follicles,[32] fibroblast-like synoviocytes,[33] and rat aortic smooth muscle cells.[34] Indeed, our preliminary immunohistochemistry showed both fractalkine and CX_3CR1 expression in invading extravillous trophoblasts in postpartum decidua sections from a human hysterectomy (Fig. 1).

Recently, a regulatory role of fractalkine on trophoblast adhesion has been suggested and may explain observed effects in migration studies. Treatment of AC1M-88 trophoblasts with recombinant fractalkine significantly increased adhesion to fibronectin. This increased adhesion properties of fractalkine treated trophoblasts are based on altered gene expression of adhesion molecules and extracellular matrix components, as shown by oligo-array and qPCR analysis.[31] Importantly, another chemokine (CCL14, also known as HCC-1), examined in the same study, also stimulating adhesion, but regulated different adhesion and extracellular matrix components.

The role of fractalkine in the perfused intervillous space

Due to endovascular trophoblast plugs within the lumen of invaded spiral arteries, perfusion of the intervillous space with maternal blood is not established prior to the end of the first trimester.[35,36] In this period only a combination of maternal blood plasma and secretory products of uterine glands, passes the endovascular trophoblast plugs as an ultrafiltrate and circulates through the intervillous space. This way, nutrients, growth factors and cytokines are provided to, but maternal blood cells are kept away from developing placental villi in first trimester.[37] Thus, although fractalkine is present at the apical microvillous plasma membrane of the syncytiotrophoblast in human first trimester placental villi,[38] direct interaction between the syncytiotrophoblast and maternal CX_3CR1 expressing cells can be excluded at this stage of pregnancy. However, soluble fractalkine from placental villi and eroded uterine glands, which are connected with the intervillous space by the enlarging syncytiotrophoblast from approximately day 17 post-conception throughout the first trimester,[39,40] may be continuously released into the intervillous space, i.e. maternal plasma,

where it can interfere with maternal CX_3CR1 expressing cells by an endocrine route. Besides endocrine actions, autocrine/paracrine signalling by syncytiotrophoblast derived soluble fractalkine may be considered, since weak CX_3CR1 staining has been detected in the villous trophoblast layer of human first trimester placenta.[30] CX_3CR1 expression in the villous trophoblast compartment declines until it is completely absent at term,[17,41] probably excluding autocrine effects with progressing pregnancy.

At the end of the first trimester of human pregnancy, dissolution of endovascular trophoblast plugs enables onset of maternal blood flow into the intervillous space and gives rise to direct physical interaction between maternal circulating blood cells and the placental syncytiotrophoblast.[37,42] This is regulated by cytokines, chemokines and adherence molecules. Amongst the panel of adhesion molecules, membrane-bound fractalkine has recently been suggested as another candidate enabling stable interaction between CX_3CR1 expressing maternal leukocytes and the syncytiotrophoblast. This assumption is based on adhesion assays, showing impaired adherence of the monocyte cell line THP-1 to villous trophoblasts after pre-incubation of THP-1 with human recombinant fractalkine and silencing of CX_3CR1 expression.[29] Our preliminary immunohistochemical double staining of term placenta for fractalkine and CX_3CR1 substantiates previous cell culture findings by occasionally showing tight contact of CX_3CR1 expressing maternal blood cells and the syncytiotrophoblast (Fig. 2). Since adhesion of circulating maternal leukocytes to syncytiotrophoblast does not seem to be a prevalent event in healthy pregnancy, potential mechanisms preventing exaggerated binding of CX_3CR1 expressing cells to the syncytiotrophoblast may exist. In this context, specific glycans, (like sialyl Lewis X and Lewis a) on glycosylated proteins such as human chorionic gonadotropin (hCG), have recently been suggested to prevent maternal leukocyte adhesion to trophoblast.[43] However, the small proportion of circulating maternal leukocytes, which finally adhere to the syncytiotrophoblast may fulfil physiological functions. This has been suggested for adhering monocytes, which may be involved in trophoblast renewal.[44] In this process, membrane-bound fractalkine could mediate detection and elimination of aged trophoblast areas by adhering monocytes. Beside this highly speculative hypothesis, another attractive hypothesis has recently been proposed, suggesting a bidirectional monocyte-trophoblast interaction, enabling trophoblasts to attract and prime monocytes to release a particular set of cytokines supporting their growth and survival.[45]

In contrast to healthy pregnancy, fractalkine-mediated adhesion of circulating maternal leukocytes to the syncytiotrophoblast may be affected under inflammatory conditions in pregnancy pathologies, such as gestational diabetes mellitus (GDM) or preeclampsia. Indeed, placental fractalkine expression is upregulated in severe early onset preeclampsia, and recent data from human

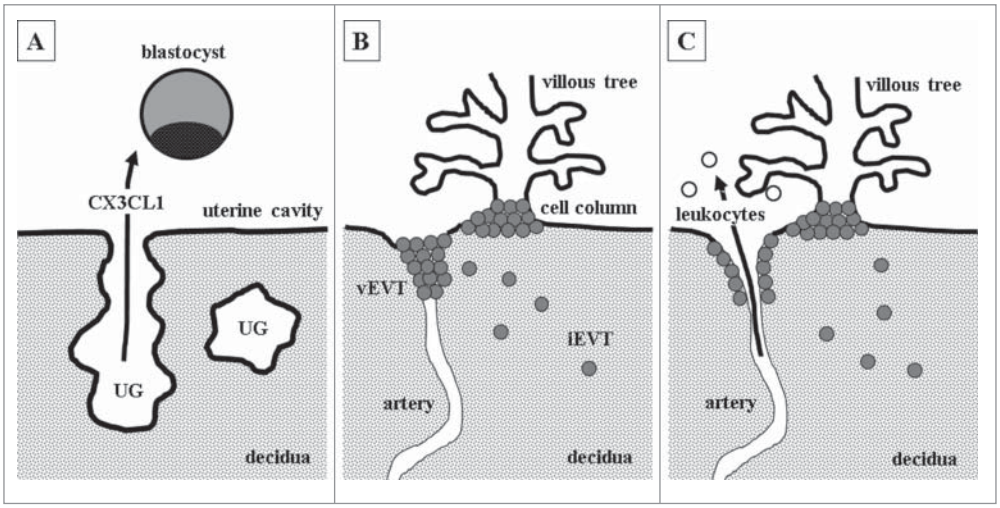

Figure 3. Potential roles of fractalkine at different stages of pregnancy. (A) Uterine glands (UG) secrete fractalkine (CX3CL1), which may prime the blastocyst for adhesion to the uterine epithelium and subsequent implantation. (B) After implantation, extravillous trophoblasts (EVT) detach from cell columns and start to invade as interstitial extravillous trophoblasts (iEVT) the decidua. Endovascular extravillous trophoblasts (vEVT) invade uteroplacental arteries and plug them. Fractalkine, either released by decidualized stromal cells, uterine natural killer cells, macrophages or EVT itself, may enhance invasion of vEVT in a paracrine and autocrine manner. (C) Dissolution of endovascular trophoblast plugs at the end of first trimester enables maternal blood flow into the intervillous space. Placental fractalkine, located on the surface of syncytiotrophoblast, mediates adhesion of maternal leukocytes to placental villi.

first trimester placental explant experiments showed increased expression and release of placental fractalkine in response to TNF-α.[21] Upregulated placental fractalkine may not only enhance leukocyte adhesion to the syncytiotrophoblast, but could also induce their activation, which has been suggested to contribute to the progression of preeclampsia.[46] Activation of leukocytes during their uteroplacental passage has been shown by increased adhesion molecules and complement related factors on neutrophils and monocytes in samples from uterine veins compared to samples from antecubital veins in patients with severe preeclampsia.[46] However, enhanced fractalkine-mediated leukocyte adhesion to the syncytiotrophoblast may also occur in other pregnancy pathologies, such as chronic intervillositis, which is associated with massive intervillous monocyte recruitment.[47] In this context, tightly adherent maternal mononuclear leukocytes have been proposed to facilitate transmission of cell-associated infectious pathogens across the placental barrier either by mediating direct infection of the trophoblast or by transmigration of infected cells into the villous stroma.[44,47] Finally, placental fractalkine may contribute to transplacental cancer transmission. Previous one-sided *ex vivo* placenta perfusion studies with fluorescence labeled T cell leukemia cell lines showed adhesion bridges formed between cells and the syncytiotrophoblast, enabling transmigration of cells through the villous trophoblast layer.[48]

Conclusion

Accumulating experimental evidence suggests fractalkine to be involved in the fetal-maternal cross-talk, regulating a number of critical steps required for successful pregnancy. Fractalkine as part of a molecule cocktail secreted by uterine glands may prime the blastocyst for implantation (Fig. 3A). After implantation, fractalkine may participate in regulating trophoblast invasion into the uterine wall to guarantee proper remodelling of uteroplacental arteries (Fig. 3B). With dissolution of endovascular trophoblast plugs and perfusion of the intervillous space at the end of first trimester, fractalkine may mediate interaction between circulating maternal blood cells and the syncytiotrophoblast (Fig. 3C). Thus, depending on the stage of pregnancy, fractalkine may mediate adhesion and migration processes of not only fetal but also maternal cells, at the fetal-maternal interface.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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