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REVIEW

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ABSTRACT

Chemokine network is central to the innate and adaptive immunity and entails a variety of proteins and membrane receptors that control physiological processes such as wound healing, angiogenesis, embryo growth and development. During early pregnancy, the chemokine network coordinates not only the recruitment of different leukocyte populations to generate the maternal-placental interface, but also constitutes an additional checkpoint for tissue homeostasis maintenance. The normal switch from a pro-inflammatory to an anti-inflammatory predominant microenvironment characteristic of the post-implantation stage requires redundant immune tolerance circuits triggered by key master regulators. In this review we will focus on the recruitment and conditioning of maternal immune cells to the uterus at the early implantation period with special interest on high plasticity macrophages and dendritic cells and their ability to induce regulatory T cells. We will also point to putative immunomodulatory polypeptides involved in immune homeostasis maintenance at the maternal-placental interface.

Introduction

Pregnancy implies a modulation of the maternal immune response associated with a variety of cellular processes to ensure trophoblast growth and invasion, uterine quiescence, vascularization and tissue remodeling at the maternal-placental interface. The induction and maintenance of tolerance is provided by maternal immune cells differentially activated and selectively recruited to the uterus at different stages. A highly coordinated chemokine network underlies not only different leukocyte subset recruitment but also orchestrates unique mechanisms of immunomodulation.[1-5] Trophoblast cells have a central role in the control of maternal immune homeostasis through modulating uterine NK cell activity, decidual macrophage polarization to an alternative profile, tolerogenic dendritic cell (DC) differentiation and induction of regulatory T cells (Tregs).[6-8]

Following the inflammatory period characteristic of implantation, an anti-inflammatory and immune tolerant microenvironment is induced to sustain immune homeostasis and successful pregnancy. Many redundant mechanisms trigger immune tolerance through key master immune regulators of different nature, such as cytokines, hormones, lectins and immune polypeptides, all of them displaying pivotal immunotolerance mechanisms.

In this review we will focus on the recruitment and conditioning of main subsets of immune-maternal cells at the early implantation period with special interest on macrophages and dendritic cells due to their immunological plasticity and ability to induce regulatory T cells. We will discuss the chemokine network involved in their recruitment toward the maternal-placental interface; and whether chemokines among other locally synthesized immune polypeptides contribute to maintain the homeostasis in the pregnant uterus.

Chemokines and other chemoattractants at early pregnancy

Chemokines are central to innate and adaptive immunity and they control physiological processes such as wound healing and angiogenesis, as well as embryo growth and development.[9,10] During early pregnancy, the chemokine network coordinates not only the

recruitment of different leukocyte populations to generate the maternal-placental interface but it also constitutes an additional checkpoint for tissue homeostasis maintenance, even in the presence of threats and infection.[11-13]

Basically, these chemo-attractant cytokines and their receptors are classified according to their structure or expression. The first classification is based on the cystein-conserved positions: CXC, CC, CX3C and C groups of the α, β, γ and δ-chemokines.[14,15] The second one, correspond to inflammatory or induced upon T-cell activation, and constitutive chemokines that fulfill housekeeping functions and/or participate in constitutive leukocyte trafficking.[9,15,16]

The chemokine receptors are named according to the chemokine structure (CXCR for CXC or CCR for CC chemokines) and belong to the super-family of G protein coupled receptors. The switch from receptors for constitutive chemokines to receptors for inflammatory chemokines changes the migratory properties of leukocyte populations.[17-19]

This system is highly promiscuous since a single chemokine can interact with multiple receptors.[10] In fact, chemokine receptors signaling could be regulated by several adaptors that mediate the internalization and signal transduction by forming a dynamic bond with spatial and temporal plasticity (chemosynapse).[20-22]

Interestingly, non-signaling-chemokine receptors (decoy receptors) were described which do not elicit conventional signaling responses, but display inflammatory and immunomodulatory effects. Until now, 3 decoy receptors were described, chemokine decoy receptor (D6), Duffy antigen receptor for chemokines (DARC) and chemocentryx decoy receptor (CCX CKR). The expression of decoy receptors is mainly restricted to placental cells and endothelial cells of lymphatic afferent vessels in skin, gut and lung.[23,24]

Among other factors of protein nature synthesized at the maternal-placental interface that have proved chemotaxis properties associated to their immunomodulatory role TGF-β1, hCG, vasoactive intestinal peptide or Galectin 1 are suitable examples.

Hence, TGF-β1 reversibly regulates chemotaxis of DCs via regulation of chemokine receptor expression.[25] The treatment of immature DCs with TGF-β1 resulted in increased expression of several chemokines associated with a chemotactic migratory response; whereas it induced down-regulation of CCR1, CCR3, CCR5, CCR6 and CXCR-4 on mature DCs, and chemotaxis to their respective ligands.[25] Another example is hCG, a very first hormone produced by trophoblast cells, that acts as a chemoattractant and selectively recruits Tregs at the human fetal–maternal interface.[26]

The vasoactive intestinal peptide (VIP) is a pleiotropic peptide targeting multiple cell types at the maternal interface with suppressant/tolerant activity. It binds to G protein coupled receptors VPAC1 and VPAC2 with potent immunomodulatory and trophic effects on adult and embryonic tissues.[27-37] At the maternal-placental interface, VIP localize in first and third trimester placenta in the syncytium and extravillous cytotrophoblast cells.[38] VIP dose-dependently stimulated hCG production from human primary cultured trophoblast cells as well as choriocarcinoma cell line JEG-3.[39,40]

Finally, Galectin-1 is a lectin with a central immunoregulatory role in the post-implantation period.[41] Gal1 is mainly evolutionarily conserved and expressed in invasive extravillous trophoblast cells of human first trimester and term placenta. It is regulated by progesterone and pro-inflammatory cytokines thus limiting T cell viability, dampening the secretion of Th1-type cytokines and favoring the expansion of CD4+CD25+FoxP3+ Treg cells.[42] In fact, mice lacking Gal1 (Lgals1−/−) showed higher rates of fetal loss and the administration of recombinant Gal1 prevents fetal loss and restores tolerance in vivo.[8]

Physiology of the chemokine network: Relevance to their role in pregnancy

The classical physiologic function associated with chemokine is the recruitment of immune cells in inflammation or homeostatic conditions, depending on the synthesis and release of different sets of chemokines.[43] In this way, chemokines direct the trafficking of immune cells through the circulation in blood, lymph vessels and tissues. Particularly, they mediate the generation of the maternal-placental interface through the interaction between decidual stromal cells, trophoblast cells and the selective recruitment of maternal and fetal leukocytes.

Trophoblast cells actively recruit immune cells through chemokine production and can also condition their functional profile. Mei-Rong Du et al. have investigated differential expression patterns of chemokines and their receptors and they determined that primary trophoblasts express CXCR4 and CXCR6.[14] In fact, trophoblasts secrete high levels of CXCL12, CXCL16 and CCL24 (Fig. 1 and Table 1).

Regarding the decidual stromal cells, CCR2, CCR5 and CCR10 are highly expressed as well CCL2 and CCL13 (the ligands of CCR2), and CCL28 (the ligand of CCR10).[14] Liang Ren et al. explored the role of CXCR4-mediated signal transduction on primary cultured decidual stromal cells.[44] The decidualization process increases CXCR4 in response to CXCL12 secreted by human first-trimester trophoblast cells, and this increase could be

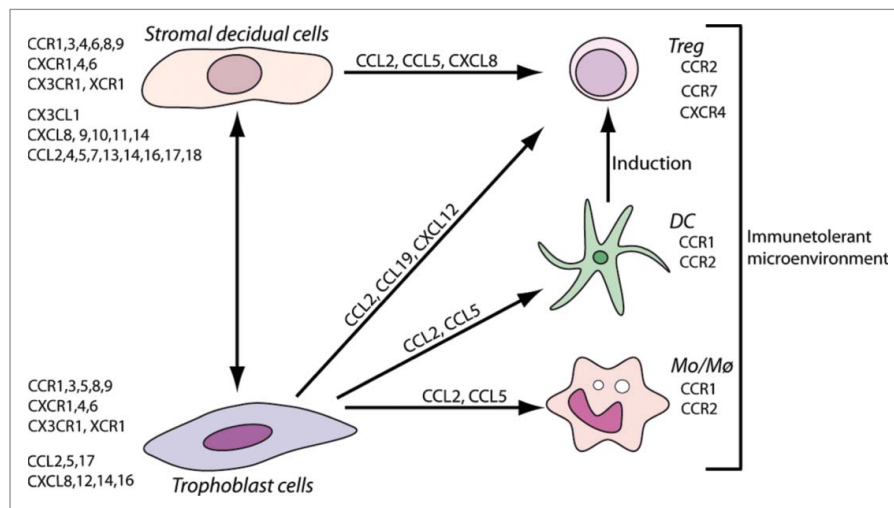**Figure 1.** Chemokines, as multifunctional molecules, contributes to the generation of the maternal-placental interface through the interaction between: decidual stromal cells, trophoblast cells and the selective recruitment of maternal and fetal leukocytes.

effectively abolished by CXCL12 or CXCR4 neutralizing antibody.[45] This chemokine/chemokine receptor pair contributes to additional reproductive biology processes, such as uterine NK cell recruitment, placentation, implantation and embryogenesis.[46-51]

Despite CXCR4 is expressed by trophoblast and decidual stromal cells, the CXCL12/CXCR4 ligand/receptor pair might present various effects on different cells via different signaling pathways. It was proposed that CXCL12 produced by trophoblast cells has a cascade pathway which promotes cytotrophoblast proliferation and invasion, while it enhances MMP activity in decidual stromal cells, cooperating in the formation of the maternal–fetal immune milieu. This is a suitable example to show the relevance of the cell type involved on the multiple effects displayed by the same chemokine-chemokine receptor axis.

Another interesting point is that decidual endometrial cells could regulate the access to the fetal-maternal interface. Nancy et al. demonstrated that decreased chemoattraction of T cells to the decidua occurs in order to support a tolerogenic response.[52] They demonstrated that the epigenetic silencing associated with methylation of T cell-attracting inflammatory chemokines genes through repressive histone marks in decidual stromal cells impaired the accumulation of maternal effector T cells within the decidua.[52] This new insight suggests an active role of the decidua controlling the migration of maternal T cells toward the implantation site. In this sense, trophoblast cells secrete cytokines that regulate the function and differentiation of decidual immune cells and also might induce epigenetic changes in stromal decidual cells modulating their capacity to produce chemokines responsible for T cell recruitment. Under pathologic conditions, for example following recognition of pathogen associated molecular patterns (PAMPs) expressed on bacteria, virus, parasite or fungi, this balance could be broken and the same stromal decidual cells might be involved in the local recruitment and activation of effector T cells, generating a threat for pregnancy.[50-53]

Since chemokines are multifunctional molecules, they also contribute to 3 crucial processes to sustain embryo implantation: angiogenesis, wound healing and embryogenesis.

Regarding the chemokines' angiogenic properties, the CXC family can be further subdivided by the presence or absence of the ELR motif, a Glu-Leu-Arg conserved sequence at the NH2 terminus. The presence of the ELR motif in CXCL1-3 and CXCL5-8, which bind to CXCR1 and CXCR2, allows angiogenic effects.[56] Also the CXCL12-CXCR4 axis displays angiogenic properties during embryogenesis.[57,58]

Pointing to the wound healing process, chemokines play an integral part in directing wound closure and healing.[59-61] Epithelial cells express chemokine ligands and receptors involved in several steps in the reconstitution of the epithelial barrier as cell migration, extracellular matrix deposition, cellular adhesion and proliferation.[62-64] CXCL12, CXCL1, and CXCL8, guide these steps of re-epithelialization in the skin however their relevance at the maternal-placental interface is unclear.[64,65]

Differential migration and activation profile of maternal monocytes/macrophages

Monocytes/macrophages at the maternal-placental interface coordinate opposite demands. On one hand, they produce suppressor cytokines and wound healing mediators that provide immune tolerance signals to dampen pro-inflammatory signals and to suppress the response to allogeneic fetal antigens; on the other, macrophages can

Table 1. Expression of most relevant chemokines and chemokine receptors on different subpopulations involved in the generation of the maternal-fetal interfase.

Cell population	Chemokines expressed	Chemokine receptors expressed
Decidual stromal cells	CCL2, CCL3, CCL4, CCL7, CCL14, CCL16, CCL17, CCL28, CXCL1, CXCL9, CXCL10, CXCL11, CXCL14, CX3CL1	CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR8, CCR9, CCR10, CXCR1, CXCR3, CXCR4, CXCR5, CX3CR1
Trophoblast cells	CCL2, CCL5, CCL17, CCL24, CXCL8, CXCL12, CXCL14, CXCL16	CCR1, CCR3, CCR4, CCR5, CCR6, CCR8, CCR9, CCR10, CXCR1, CXCR4, CXCR6, CXCR7, CX3CR1, XCR1
Dendritic cells	CCL2, CCL4, CCL5, CCL7, CCL20, CCL21	CCR1, CCR2, CCR3, CCR5, CCR6, CCR7
Macrophages	CCL2, CCL3, CCL5, CXCL16	CCR1, CCR2, CCR5, CXCR6
Tregs	CCL2, CCL4, CCL17, CCL19, CCL20, CCL22, CXCL12	CCR2, CCR4, CCR5, CCR6, CCR7, CXCR4

be activated into the classic inflammatory profile in response to ascending and blood-borne pathogens.[66]

Several evidences point that macrophage responses are determined by the kind of stimulus and the specific micro-environmental conditions in which cells were differentiated prior to their activation.[67,68] Analysis of microarray gene expression indicates that macrophages isolated from decidua during the first trimester, display an alternative activation profile, also know as M2 phenotype, with upregulation of CCL18, DC-SIGN, mannose receptor C type-1, fibronectin 1 and insulin-like growth factor-1.[69]

When we explored maternal CD14+ cell profile, isolated from fertile women, after interaction with first trimester trophoblast cell line Swan-71, we observed the induction of an alternative activated phenotype based on an increased expression of CD16, a marker associated with a regulatory monocyte profile, and also the expression of CD39, a surface enzyme that was proposed as self-limiting for macrophage pro-inflammatory activation based on its rapid catabolism of endogenous ATP into adenosine.[67,70] At the same time, macrophages did not modulate the expression of the co-stimulatory molecule CD80. Their phenotypic profile was accompanied by changes in CD14+ cell functional profile with increased IL-10 synthesis but not of pro-inflammatory cytokine production as IL-12, IL-1β and TNFα.[71] Also decidual macrophages secrete high level of CCL2 that recruit additional macrophages into the decidua potentiating this loop.[11]

An interesting point is that under bacterial or viral PAMP stimulation, trophoblast cells restrain early monocyte migration depending on the type of PAMP stimulus.[71] For example, they restrict monocytes migration toward trophoblast cells in the presence of bacterial PAMP (LPS or PGN) with a decrease in the expression of CCR1, CCR5, CCL5 and CXCL8 on the CD14+ cells, while in the presence of a viral PAMP (poly[I:C]), this decrease was not observed.[71]

On the other hand, the modulation of chemoattractant signals upon trophoblast-monocyte interaction is bidirectional: not only monocytes modulate chemokines and their receptor expression in the context of the maternal-placental interaction, but also trophoblasts modulate them after culture with monocytes in the presence of PAMPs stimuli.[71] Therefore, trophoblast cells are able to attract and condition monocytes to produce and secrete a particular set of cytokines and chemokines, supporting their growth and survival. At the earliest phases of an infection, the selective modulation of chemokines and their receptor expression by trophoblast cells would represent one of the first steps to control leukocyte trafficking to avoid potential tissue damage.

In addition, trophoblast cells secrete multiple target molecules as VIP with the ability to induce a regulatory/suppressant activation profile in macrophages.[33,72,73] In human and murine macrophages, VIP increases IL-10 synthesis and reduces IL-12, TNF-α and inducible nitric oxide synthase activity through both VPACs. In an in vitro model, we could observed that trophoblast cell conditioned media increased CD14+ cell migration and the effect was further induced when trophoblast cells were pretreated with VIP, due to VIP increases CCL2, CCL3, CCL5 and CXCL$^-$8 mRNA expression in trophoblast cells.[74]

Differential migration and activation profile of dendritic cells

Conventional DC are specialized antigen presenting cells with a critical role in the generation of the maternal-fetal interface.[75-78] In fact, during implantation, the depletion of uterine DC (uDC) results in a severe impairment of the implantation process, leading to embryo resorption in allogeneic or syngeneic pregnancies.[79] Consistent with these observations, using a transgenic mouse model that allows conditional ablation of uDC, Plaks and colleagues observed an impaired proliferation and differentiation of the decidua, even in the absence of embryos. These changes are associated with disrupted angiogenesis characterized by reduced vascular expansion and attenuated maturation, associated to sFlt1 (FMS-like tyrosine kinase 1) and TGF-β1 modulation.[80]

After implantation, the immunoregulatory properties of uDC are more evident and constitute a unique and complex system of cells able to commit between tolerogenic and immunogenic responses. The uDC comprise about 1–2% of the immune cells in the decidua and are

scattered through both the decidua basalis (in which trophoblast cells are infiltrated) and the decidua parietalis. Kammerer et al. described the presence of subpopulations of DC in decidual tissue during the early phase of human pregnancy which seem to participate in the protection of the allogeneic fetus in a mouse pregnancy model.[81-83]

Using *in vitro* models we could oberve that those DC differentiated from CD14+ cells from fertile women and co-cultured with trophoblast cells prevented the up-regulation of CD83 expression, a maturation marker after a challenged with LPS.[84] In fact, they did not modulate the expression of CD86, CD40 and HLA-DR suggesting that DCs remained in a semi-mature state.[84] The modulation of phenotipic markers also was accompanied by an increase in the production of IL-10 and a reduction in the IL-12p70 and TNF-α production.[84]

From a functional point of view, those DC pre-cultured with trophoblast cells and challenged with LPS, suppressed the allogeneic response and were able to induce Tregs.

Finally, trophoblast cells appeared to be responsible of recruiting DC, as evidenced by a significant increase in the frequency of DC that migrated toward conditioned media from Swan-71 cells.[84]

Taking together all these data suggest that the 'education' that trophoblast cells impose to DCs might induce an alternative activation pattern and, in the present *in vitro* model, they acquired a functional profile compatible with a suppressor-tolerogenic profile.

Induction and migration of maternal tregs cells

The initial pro-inflammatory response characteristic of implantation is actively modulated to a predominant anti-inflammatory and tolerogenic profile at early gestation, and Treg cells are essential for this immune switch. The polarizing microenvironment will determine the chemokine receptor profile on Treg cells and therefore might direct them to appropriate tissue sites to regulate the immune response. Naturally, the induced Treg cells (iTregs) upregulate the expression of chemokine receptors that are also expressed by effector T cells favoring the co localization with effector T cells and then displaying their suppressive functions.[9]

Recently, Teles et al. have demonstrated using 2-photon imaging that Foxp3+ cells accumulated in the mouse uterus during the receptive phase of the estrus cycle. In vivo depletion of Tregs using Foxp3.DTR-based models prior to pairing, impaired implantation inducing a hostile microenvironment associated with the recruitment of effector T cells, uterine inflammation and fibrosis. In fact, CCR7 interfered with accumulation of Tregs in the

uterus and implantation indicating that homing of Tregs to the uterus was mediated by CCR7.[82]

Endometrial stromal cells under the decidualization program differentiate into epithelioid decidual cells and secrete diverse mediators, contributing to the generation of a local immune response supporting the nidation of a semiallogenic fetus.[83,84]

Using an *in vitro* model of decidualization with a human endometrial stromal cell line (HESC) stimulated with P4 and LPS simulating the inflammatory response during implantation, we observed that P4 increased VIP intracellular production in a concentration dependent manner.[71] LPS increased CCL2, CCL5 and CXCL8 expression evaluated by RTqPCR in HESC cells and VIP by itself did not have a significant effect on cytokine production by HESCs; however, the combination of LPS and VIP further enhanced LPS-induced CCL5 expression.[71] Getting insight into the VIP effects on this mechanism, we observed that VIP antagonist prevented the increase of CCL5 expression mediated by P4 and LPS, suggesting that CCL5 induction involved a VIP-mediated pathway.[71]

Since CCL5 contributes to the induction and the recruitment of Tregs we determined if HESC cells have the ability to attract iTregs.[16] Previously, we developed an *in vitro* differentiation model of iTregs from naïve CD45RA+CCR7+ obtained from peripheral blood mononuclear cells isolated from fertile women and we performed migration assays using a multi-chamber system. The condition media (CM) from HESC cells increased the frequency of Foxp3+ cells and VIP antagonist prevented the recruitment of iTregs. Moreover, addition of anti-RANTES neutralizing Ab to the CM from HESC treated with P4 and LPS also was able to prevent iTregs migration suggesting that CCL5 participates in the specific recruitment of iTregs toward HESC cells.[71]

During the implantation period, CCL5 produced by human endometrium it has the potential to act in an autocrine manner by the differential expression of its receptors CCR1, CCR3, and CCR5.[85,86] CCL5 also is produced by human endometrial T-infiltrated lymphocytes, CD4+ and CD8+, which production increased in the presence of physiological P4 concentrations.[85]

At later pregnancy stages, the Foxp3+ cell subset suffer an expansion and using a Rag-1$^{-/-}$ model of cell transfer Tregs, Teles et al. demonstrated that natural Tregs (thymic origin), are needed for pregnancy establishment and induced Tregs (iTregs) contributes to the Treg pool in the periphery.[90]

Trophoblast cells not only contribute to iTreg cell differentiation, but also selectively recruit them. We demonstrated that Swan-71 cells secreted VIP and their co-culture with maternal PBMC significantly increased the

frequency of maternal CD4+CD25+FoxP3+ cells. This increase was prevented by an anti TGFβ Ab and VIP antagonist, suggesting that VIP could have an active role in the immunoregulatory through a mechanism involving TGFβ1.

Migration assays performed in transwell systems with conditioned media from first trimester trophoblast HTR-8 or Swan-71 cell lines doubled Foxp3+ cell recruitment compared to the positive control of human serum.[91,92] In fact, the frequency of Foxp3+ cells migrated toward trophoblast cells in the presence of a bacterial or viral stimulus increased and CCL4, CCL5, CXCL1 and CXCL8 secretion by trophoblast cells further recruited iTregs.[93]

Finally, Treg-trafficking is bidirectional. Mold et al. demonstrated that maternal alloantigens promote the development of tolerogenic fetal Treg cells in utero. Maternal cells migrate toward the fetal lymph nodes, inducing the development of fetal Tregs that suppress fetal anti-maternal immunity and persist at least until early adulthood.[94-96] Consistently, Tilburgs et al. presented evidence of a selective migration of fetus specific CD4+CD25bright Treg cells to decidua basalis and parietalis that suppress fetus specific and non specific responses.[97,98]

Finally, in the non-obese diabetic mice, VIP treatment of mice at gestational day 6,5 switches the Tregs/Th17 ratio leading to tolerance. VIP also reduces Th17/Th1 and Th1/Th2 ratios,[99] induces Foxp3+ regulatory T cells and, in the presence of TGF-β.[100]

Challenges for chemokine targeting

Approaches to targeting chemokine signaling require a careful analysis of the balance of chemokines and their receptors that belong to super family of GPCRs. One of available examples of attempts to block chemokine signaling through receptor inhibition is the AMD3100 (Plerixafor), which blocks localized CXCL12 signaling through CXCR4 stem cells in bone marrow allowing cells to enter the circulation.[101] This finding allowed AMD3100 to be proposed for autologous stem cell transplantation applied to patients with leukemia or multiple myeloma for short term.[102] Another novel approach involves the CCR5 inhibitor drugs. CCR5 is an HIV co-receptor and its inhibitor UK-427857 (Maraviroc) has been approved for patients resistant to conventional therapies.[103] Beyond the use of small molecule inhibitors, several neutralizing antibodies against chemokine receptors have been tested in early-phase clinical trials, including an antibody designed for blocking CCR2 activity in a variety of inflammatory diseases.[104,105]

Alternate strategies include the generation of inhibitors that antagonize chemokine ligands instead of receptor chemokines. Novel targeting of chemokine ligands involve the characterization of conserved sites present in all chemokines as the sulfotyrosine binding pocket.[106] This strategy gives potential versatility to targeting either individual chemokines or entire subgroups of ligands.[107]

Conclusion

The selective recruitment and activation of the different cell populations at the maternal-placental interface induce an immunological environment at the uterus and deciduas and represents a rich area of research for understanding the regulation of the immune system in order to a better understanding of pregnancies complications, cancer, infections or autoimmunity.

When the signaling of chemokines presents a dysregulation, the chemokine inhibition or the systemic blockade of chemokine receptor signaling as therapies might generate side effects; therefore the real challenge is to restore the physiologic gradient concentrations of chemokines.

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