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Review

## Chemokines in the corpus luteum: Implications of leukocyte chemotaxis

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### Abstract

Chemokines are small molecular weight peptides responsible for adhesion, activation, and recruitment of leukocytes into tissues. Leukocytes are thought to influence follicular atresia, ovulation, and luteal function. Many studies in recent years have focused attention on the characterization of leukocyte populations within the ovary, the importance of leukocyte-ovarian cell interactions, and more recently, the mechanisms of ovarian leukocyte recruitment. Information about the role of chemokines and leukocyte trafficking (chemotaxis) during ovarian function is important to understanding paracrine-autocrine relationships shared between reproductive and immune systems. Recent advances regarding chemokine expression and leukocyte accumulation within the ovulatory follicle and the corpus luteum are the subject of this mini-review.

### Introduction

Leukocyte recruitment and activation within the ovary are thought to play important roles in follicular atresia, ovulation, and luteal function [1-6]. Consequently, many studies concerning ovarian function within the past several years have focused on characterizing leukocyte populations within the ovary, understanding further the importance of leukocyte-ovarian cell interactions, and more recently, discerning the mechanisms of ovarian leukocyte recruitment. The existence of specific subsets of leukocytes (e.g., monocytes-macrophages, T-lymphocytes, eosinophils, etc.) and their fluctuation in number within the ovary during select stages of ovarian function are currently well-documented [7-15]. Leukocytes and their secretory products are thought to influence ovarian function by acting as local mediators of follicular atresia, ovulation, and luteolysis [16-20]. The observation that leukocytes accumulate only within certain structures of the ovary, suggests that these cells migrate from the bloodstream in response to specific, unidirectional chem-

oattractant cues. The discovery and characterization of an ever-expanding family of molecules specialized to attract leukocytes, called chemokines, has led to a renewed interest among reproductive biologists concerning the importance of leukocyte trafficking within the ovary. This mini-review focuses primarily on recent advances relative to chemokine expression and leukocyte recruitment during the periovulatory period, luteinization, and during regression of the corpus luteum.

### Classification of chemokines

Chemokines are small molecular weight peptides responsible for adhesion, activation, and chemotaxis of leukocytes [21]. Chemokines are structurally related, possessing a pattern of conserved cysteine residues near the amino-terminal domain. It is the position of these cysteine residues that is the basis for the classification of chemokines into four families (see Table 1). The -CXC-, or alpha chemokine family, has one amino acid (X) separating two of four conserved cysteine residues. A well-characterized

**Table 1: Summary of Select Chemokines**

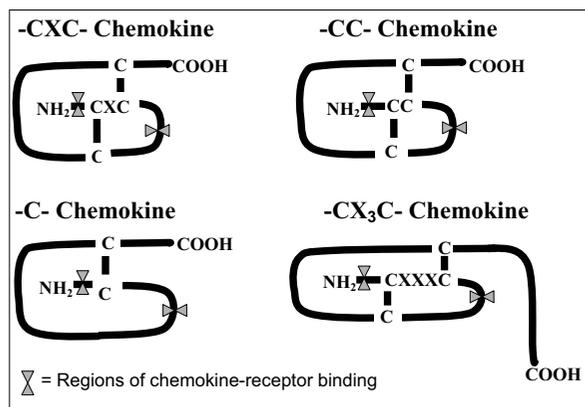
<b>-CXC-Chemokines</b>			
<b>Chemokine</b>	<b>Source</b>	<b>Primary Target</b>	<b>Receptor</b>
BCA-1	lymphoid tissue	B-lymphocytes	CXCR5
ENA-78	epithelial cells	neutrophils	CXCR2
GCP-2	granulocytes	neutrophils	CXCR1
GRO- $\alpha\beta\gamma$	endothelial cells, fibroblasts, monocytes, macrophages	neutrophils	CXCR2
IL-8	macrophages, endothelial cells	neutrophils, basophils, T-lymphocytes, epithelial cells, macrophages	CXCR1, R2
IP-10	monocytes	T-lymphocytes, TIL, endothelial cells, NK cells	CXCR3
MIG	monocytes, macrophages	T-lymphocytes, TIL	CXCR3
SDF-1 $\alpha$ , 1 $\beta$	stromal cells	hematopoietic cells	CXCR4
<b>-CC-Chemokines</b>			
<b>Chemokine</b>	<b>Source</b>	<b>Primary Target</b>	<b>Receptor</b>
Eotaxin	monocytes	eosinophils	CCR3
Exodus-1	neutrophils, peripheral blood lymphocytes	T-lymphocytes, NK cells	CCR6
MCP-1	endothelial cells, monocytes, macrophages, fibroblasts	monocytes, basophils NK cells, T-lymphocytes	CCR2, R4, R10
MCP-2	monocytes, macrophages	monocytes, basophils, eosinophils, NK cells, T-lymphocytes	CCR1, R2, R3 R10
MCP-3	monocytes, macrophages	monocytes, basophils, eosinophils, NK cells, T-lymphocytes, dendritic cells	CCR1, R2 R3, R10
MCP-4	endothelial cells, monocytes, macrophages	monocytes, T-lymphocytes, eosinophils	CCR3
MIP-1 $\alpha$	monocytes, T-lymphocytes, neutrophils	monocytes, T-lymphocytes, NK cells, basophils, eosinophils, dendritic cells	CCR1, R4,
MIP-1 $\beta$	monocytes, neutrophils	monocytes, T-cells, NKs, dendritic cells	CCR5
MIP-5	monocytes	monocytes, eosinophils, basophils	CCR1, R3
RANTES	T-lymphocytes	T-lymphocytes, NK cells, basophils, eosinophils, dendritic cells	CCR1, R3, R4, R5, R10
TARC	monocytes, thymus tissue	T-lymphocytes	CCR4
<b>-C-Chemokine</b>			
<b>Chemokine</b>	<b>Source</b>	<b>Primary Target</b>	<b>Receptor</b>
Lymphotactin	T-lymphocytes, NK cells	T-lymphocytes, B-lymphocytes, neutrophils, NK cells	XCRI
<b>-CX3C-Chemokine</b>			
<b>Chemokine</b>	<b>Source</b>	<b>Primary Target</b>	<b>Receptor</b>
Fractalkine	macrophages, dendritic cells, epithelial cells	NK cells	CX3CRI

BCA = B-cell Attracting Chemokine; ENA = Epithelial-cell-derived Neutrophil-Activating protein; GCP = Granulocyte Chemotactic Peptide; GRO = Growth-Related Oncogene; IL = Interleukin; IP = Interferon-gamma-inducible Protein; MCP = Monocyte Chemoattractant Protein; MIG = Monokine induced by Interferon-Gamma; MIP = Macrophage Inflammatory Protein; NAP = Neutrophil-Activating Protein; NK = Natural Killer cells; RANTES = Regulated upon Activation, Normal T-cell Expressed and Secreted; SDF = Stromal-Derived Factor; TARC = Thymus- and Activation-Regulated Chemokine; TIL = Tumor-Infiltrating Lymphocytes.

chemokine of this family is interleukin-8 (IL-8), which is often expressed by endothelial cells to attract neutrophils. Conversely, the -CC-, or beta family of chemokines has two adjacent cysteine residues. A representative chemokine of this family is monocyte chemoattractant protein-1

(MCP-1), a potent chemotactic molecule that elicits monocyte and T-lymphocyte recruitment [22].

Two relatively new chemokine families have been identified, the -C- family and -CX<sub>3</sub>C-family. Lymphotactin, a member of the -C-chemokine family, has only one



**Figure 1**  
Schematic representation of the four chemokine families. Chemokine families are structurally related peptides possessing a pattern of conserved cysteine residues near the amino-terminal (-NH<sub>2</sub>) domain. The position of the cysteine residues is the basis for the classification into four families. The -CXC-, or alpha chemokine family, has one amino acid (X) separating two of four conserved cysteine residues. The -CC-, or beta family of chemokines has two adjacent cysteine residues. The -C-chemokine, lymphotactin, has only one conserved cysteine residue. The -CX<sub>3</sub>C-chemokine, fractalkine, has three amino acids separating two of four cysteines. Regions of chemokine-receptor interaction are also depicted.

conserved cysteine residue and predominantly attracts lymphocytes. The -CX<sub>3</sub>C-chemokine, fractalkine, has three amino acids separating two of four cysteines and attracts natural killer cells. Interestingly, fractalkine is a membrane-bound protein that may be cleaved, leaving a functional adhesion molecule and releasing the soluble chemokine [23].

Chemokines activate G protein-mediated signal transduction cascades by signaling through seven-transmembrane receptors [24,25]. Chemokine receptor families are generally categorized according to their corresponding ligand family (i.e., CXCR, CCR, XCR and CX<sub>3</sub>CR receptors correspond with -CXC-, -CC-, -C-, and -CX<sub>3</sub>C-chemokines, respectively; see Table 1). Although chemokine-receptor interactions are specific within families, many chemokines bind to more than one type of receptor, and most receptors bind several different chemokines (see Table 1). Thus, leukocytes may exhibit varying patterns of chemokine receptors. For example, neutrophils express receptors from the CXCR family, while T-lymphocytes express receptors from both CXCR and CCR families (Table 1).

Moreover, resting T-lymphocytes express only a couple of chemokine receptors, whereas activated T-lymphocytes display many. All chemokines have two key regions within their structure that are necessary for interaction with their corresponding receptors (Figure 1). The first is a loop within the peptide backbone stretching between the second and third cysteine residues. This loop region initiates binding to the receptor, allowing then for proper presentation of the second key region, a domain within the amino-terminus (Figure 1). Together, these regions of the chemokine molecule trigger receptor activation [24].

### Chemokines of the periovarian period

Leukocyte chemoattractant activity within the ovary was discovered initially in follicular fluid of ovulatory follicles [26-29]. Murdoch and McCormick [3,30] reported that periovarian follicles secrete low molecular weight factors, 15–16 amino acids in length, capable of stimulating leukocyte migration in vitro. Of particular interest in these studies was the finding that subsets of leukocytes migrated in a temporal manner. That is, neutrophils and eosinophils were attracted to conditioned medium from follicular tissue obtained 24 and 36 hours after the LH surge; whereas monocytes migrated only in response to tissues from the 36-hour time point (approximately 12 hours after the occurrence of ovulation). Basophils and lymphocytes did not exhibit chemotaxis. A similar pattern of neutrophilic and/or eosinophilic chemotaxis at ovulation, followed by monocyte-macrophage chemotaxis during luteinization, occurs in other mammalian species, including humans [8,10,31-34]. Neutrophilic chemokines, interleukin-8 (IL-8) and growth related oncogene (GRO), and eosinophilic chemokines, eotaxin and RANTES (regulated upon activation, normal T-cell expressed and secreted) are all expressed by ovulatory follicles [35-44]. Similarly, monocyte chemoattractant protein-1 (MCP-1), a chemokine specific for monocytes and T-lymphocytes, is expressed during ovulation and the formation of the corpus luteum [42,45]. Collectively, these observations are consistent with the concept that specific leukocyte subsets are recruited to play a role in the process of ovulation and luteinization.

At present, there is limited information available about the hormonal regulation and temporal expression of chemokines during the periovarian period. Chemokines from all four families are transcribed within follicles of rats following treatment with eCG and hCG [42]. However, this gonadotropin effect on chemokine expression is possibly due to the actions of hCG alone. Ushigoe and co-workers [41] determined that GRO expression in the rat ovary is stimulated by hCG, but not eCG. Similar findings of hCG-stimulated, chemokine expression have been reported in follicles of human and rabbit ovaries [35,37,39,45]. Neutrophilic chemokine expression occurs

initially within the thecal layer of the follicle, and then progresses to the granulosa-lutein layer as ovulation becomes imminent [35,37,39,45]. Chemokine expression within follicles probably results from an indirect effect of hCG. Gonadotropins induce the expression of interleukin-1 $\beta$  (IL-1 $\beta$ ) and tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) in preovulatory follicles [46]. Chemokine expression by thecal and granulosa-lutein cells in culture is stimulated directly by IL-1 $\beta$  and TNF $\alpha$  [35,37,39,45]. Hence, gonadotropin-stimulated chemokine expression within follicles is likely mediated by IL-1 $\beta$  and TNF $\alpha$  effects. Similar actions of gonadotropins and cytokines would be expected to establish the recruitment of eosinophils and monocytes as described in other species [3,13,33,34,43-45], but the regulatory aspects have not been fully elucidated. Importantly, neutrophilic and eosinophilic chemotaxis into the follicle occurs prior to extravasation of red blood cells and vascular damage [47]. As a consequence of recruitment and activation, neutrophils and eosinophils release proteolytic enzymes, cytokines, and other mediators that may be involved in aspects of ovulation and luteinization. Monocytes most likely engage in similar activities, including the possible expression of IL-8 to attract additional neutrophils [35,45].

The influence of ovarian steroids on chemokine expression during the periovulatory period is controversial. In two recent studies it was determined that estradiol and progesterone do not affect chemokine (IL-8 & GRO) expression in ovarian tissue [40,41]. These results are in contrast to work by Arici and co-workers [35], who concluded that progesterone suppresses both basal and IL-1 $\alpha$ -stimulated IL-8 expression in cultures of ovarian stromal and granulosa-lutein cells. Considering that many of the chemokines are regulated through the common pathway of NF-kappa B activation [48], it is plausible that ovarian steroids influence chemokine expression through transcriptional regulation. Further work is needed to define the temporal and hormonal regulation of chemokine expression during the periovulatory period, especially the effects of cytokines and ovarian steroids. Moreover, there have been no studies to our knowledge that have investigated whether or not steroidogenic cells of the ovary respond to chemokines directly, or for that matter, possess chemokine receptors. In contrast, there is evidence that Leydig cells of the testis express the -CXC-chemokine, interferon-gamma-inducible protein 10 (IP-10), and that IP-10 inhibits basal and hCG-induced testosterone production [49].

Chemokine expression within the ovulatory follicle could have important physiological implications. Diminished ovulation rates have been reported in animals depleted of neutrophils [39,50]; whereas the addition of peripheral blood leukocytes to in vitro-perfused rat ovaries increases

the number of LH-induced ovulations [6]. In other studies, ovulation rate is unaffected by depletion of leukocytes [51,52], but development and function of the corpus luteum is impaired [53-55]. Thus, whether chemokines, leukocyte chemotaxis, and leukocytes are indispensable to ovulation remains controversial, but these factors may contribute to aspects of luteinization and the early development of the corpus luteum.

The influence of chemokines on luteinization has not been studied extensively, but may be related to promoting neovascularization, similar to the effects of vascular endothelial growth factor (VEGF) [56-58]. Several -CXC-chemokines, including IL-8 and GRO, have potent angiogenic properties distinct from their ability to attract leukocytes and promote inflammation [59]. Of the -CC-chemokines, MCP-1 has been characterized as a potent angiogenic molecule in corneal angiogenesis and collateral vessel formation [60,61], but initial evidence indicates that MCP-1 does not promote vascularization of the corpus luteum [61]. In addition to the potential angiogenic effects of chemokines, eosinophils have been recently implicated as a source of VEGF in the developing corpus luteum [54]. Thus, the combined actions of chemokines and leukocytes might encourage neovascularization during luteal development.

The consequences of genetic deletion of chemokines or of similar chemotactic molecules during the folliculo-luteal transition have been examined directly in only a few studies [55,62-64]. Experiments with genetic knock-out mice have not resolved whether or not the absence of a single chemokine impairs ovulation and luteal function [55,62-64]. The inherent redundancy of chemokine expression in tissues might be a confounding issue in these studies. Multiple chemokines are often expressed in response to a single stimulus (e.g., the induction of IL-8, GRO, and MCP-1 in follicles by hCG), and might provide for overlapping influences. Such redundant pathways serve to optimize error-free information transmission. However, within this redundancy are elements of specificity, including the hormonal microenvironment (e.g., chemokine concentration) and the temporal pattern and cellular source(s) of chemokine/receptor expression. An emerging view of chemokine action is that distinct networks of cells interact through production of specific chemokines and/or the expression of a highly unique pattern of chemokine receptors [21]. Thus, future work determining the role and physiological implications of chemokines during ovulation and luteinization should consider these emerging concepts.

### **Chemokines of the regressing corpus luteum**

The accumulation of leukocytes, particularly monocytes-macrophages, within the regressing corpus luteum is well-

documented, but only recently have investigators considered that this accumulation might result from chemokine expression. Monocyte chemoattractant protein-1 (MCP-1), a potent and monocyte-specific peptide, was the first identified and is currently the most studied chemokine involved in the process of luteal regression. Hosang and co-workers determined that porcine luteal tissue contains mRNA for MCP-1 and -2 [65,66]. This initial discovery was followed quickly by studies documenting that MCP-1 expression occurs prior to and during luteal regression [67], is induced by luteolytic hormones [68-70], and is accompanied by an accumulation of monocytes-macrophages within the corpus luteum [67]. Similar increases in MCP-1 expression and monocyte-macrophage accumulation during luteal regression have been observed in a variety of mammalian species [15,71,72] such that increased MCP-1 expression is now viewed as an indicator of the luteolytic process [19,20,73,74].

Identifying the cellular sources and regulation of MCP-1 within the corpus luteum has been the focus of recent investigations. Endothelial cells of the corpus luteum are clearly a source of MCP-1 [15,61,71,75] and as expected, proinflammatory cytokines such as TNF $\alpha$  and interferon-gamma directly stimulate MCP-1 production [75]. However, progesterone and prostaglandin F $2\alpha$  (PGF) do not affect endothelial cell secretion of MCP-1 [75]. How then does PGF-induced luteal regression in the cow and ewe result in an increase in MCP-1 expression [70,76]? One possibility is that other cell types within the corpus luteum (e.g., T-lymphocytes, monocytes-macrophages, steroidogenic cells, fibroblasts) respond to PGF and secrete MCP-1. T-lymphocytes are a potential source of MCP-1 within the corpus luteum [77], but the responsiveness of T-lymphocytes to PGF has not been determined. Large steroidogenic luteal cells possess PGF receptors, but their capacity to synthesize MCP-1 is controversial [69,70,78]. Another possibility is that endothelial cells of the corpus luteum express MCP-1 in response to factors produced by other PGF-sensitive cells (e.g., steroidogenic cells, immune cells). In addition to cytokines, other factors that provoke MCP-1 expression include oxygen-derived free radicals, Fas-ligand [79,80], and metabolites of apoptosis. In a very recent study, the onset of luteal cell apoptosis was proposed to activate MCP-1 gene expression in adjacent, non-apoptotic cells of the corpus luteum [78]. Specifically, the process is thought to be Fas-ligand/Fas mediated, in which luteal cells undergoing Fas-ligand induced apoptosis stimulate MCP-1 expression in non-apoptotic cells: MCP-1 then attracts monocytes-macrophages to the corpora lutea containing apoptotic cells, and the apoptotic cells are selectively removed by phagocytosis. These concepts are intriguing, and are completely consistent with the recently hypothesized 'nurturing role' of immune cells in luteal regression (i.e., to diminish an

inflammatory condition resulting from dead and dying cells) proposed by Pate and Keyes [19]. Hence, future research should focus on the importance of cell-cell interactions during luteal regression, and the relationships among PGF, Fas, chemokines (especially MCP-1), and apoptosis within the corpus luteum.

Aside from MCP-1, there is very little information available about other chemokines expressed during luteal regression. Endothelial cells of the bovine corpus luteum express RANTES, and this expression is elevated in response to TNF $\alpha$  [81]. The ovine corpus luteum produces chemoattractant(s) for eosinophils following treatment of ewes with PGF [2], but a specific chemokine has not been identified. Eosinophils accumulate within the corpus luteum prior to functional and structural manifestations of regression [2], but are not considered essential to luteolysis despite their capacity to affect tissue structure and inflammatory events [51]. The equine corpus luteum also secretes chemoattractant(s) for leukocytes in late diestrus (before a decline in progesterone secretion), and throughout spontaneous and PGF-induced luteal regression [82]. Recent evidence of chemokine expression and leukocyte accumulation within the corpus luteum prior to regression in these and other studies [15,67,77] infers that chemokines might be a contributing cause rather than effect of luteolysis. Moreover, the observation that rescue of the corpus luteum during simulated early pregnancy is associated with a diminished accumulation of luteal macrophages [83] indicates that leukocyte-ovarian cell interactions may be of fundamental importance to a variety of reproductive states. Further examination of chemokine expression and leukocyte accumulation within the corpus luteum during luteal regression and during early pregnancy is warranted.

## Conclusion

The discovery and characterization of an ever-growing family of chemokines over the past two decades has prompted renewed interest in leukocyte trafficking during ovarian function. Chemokines are expressed within ovulatory follicles and within the corpus luteum, predominantly during luteal regression. Chemokine expression in these ovarian structures is regulated in part by hormones of reproductive function (e.g., gonadotropins, PGF) and immune response (e.g., TNF $\alpha$ , IL-1 $\beta$ ), and is associated with the accumulation of select subsets of leukocytes (e.g., neutrophils, eosinophils, monocytes). Future work should focus further on the physiological implications of chemokines and leukocytes in ovarian function, especially the role of these elements in ovulation, luteal regression, and other aspects of ovarian function that have not received as much attention (i.e., follicular atresia and maternal rescue of the corpus luteum). This will provide

important and new insight about relationships shared between reproductive and immune systems.

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