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# Interleukin 8 and the male genital tract

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ABSTRACT

Interleukin 8 (IL-8) is a pro-inflammatory CXC chemokine involved in inflammatory reactions. IL-8 exerts its function in concert with other cytokines and chemokines causing chemoattraction of leukocytes to the inflammatory sites, recruitment and activation of neutrophils to phagocytosis and bacterial clearance. Furthermore, IL-8 is characterized by chemoattractant activity on basophils and T cells, and by a potent pro-angiogenic action. IL-8 is crucially involved in several inflammatory diseases. In particular, it has been suggested that IL8 might play a key role in male genital tract (MGT) infection/inflammation. In fact, IL-8 seems crucially involved in benign prostatic hyperplasia-related inflammation. In addition, among different cytokines and chemokines, seminal plasma IL-8 (sIL-8) appears to be the most reliable and predictive surrogate marker of prostatitis. Furthermore, evidence is emerging on sIL-8 involvement in inflammation not only of the prostate, but also of other organs of the MGT, in particular seminal vesicles and epididymis, but not the testis, and in male accessory gland infection (MAGI). Accordingly, an association between sIL-8 levels and color-Doppler ultrasound characteristics of the MGT suggestive of inflammation has been recently reported. sIL-8 is strongly related to leukocytospermia, and although the relationship between sIL-8 levels and sperm parameters has not been completely clarified, a tight inverse correlation with ejaculate volume has been demonstrated, suggesting an association with distal MGT sub-obstruction, corroborated by the correlation with ejaculatory duct and seminal vesicle abnormalities. Finally, recent studies have focused on the role of IL-8 in cancer biology, in particular in prostate cancer, thus increasing the interest in this pro-inflammatory chemokine.



## 1. Introduction

Interleukin-8 (IL-8), also known as CXCL8, is a pro-inflammatory CXC chemokine. Chemokines constitute a large family of small cytokines with four conserved cysteines linked by disulfide bonds. The two subfamilies CXC and CC chemokines are distinguished according to the position of the first two cysteines, which are separated by one amino acid in CXC or are adjacent in CC chemokines (Baggiolini et al., 1997). In humans, the genes of the CXC chemokines are clustered on chromosome 4, and those of the CC chemokines on chromosome 17 (Baggiolini et al., 1997). Transcription of the IL-8 gene encodes for a protein of 99 amino acids that is subsequently processed to yield a signaling competent protein of either 77 amino acids in non-immune cells or 72 amino acids in monocytes and macrophages (Waugh and Wilson, 2008). Expression of IL-8 is primarily regulated by activating proteins and/or nuclear factor-κB-mediated transcriptional activity, although additional hormone-responsive elements and NF-IL-6 consensus sites have been characterized on the IL-8 gene promoter. Accordingly, expression of IL-8 has been shown to be regulated by a number of different stimuli including inflammatory signals (e.g., tumor necrosis factor α, IL-1β), chemical and environmental stress (e.g., exposure

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to chemotherapeutic agents and hypoxia), and steroid hormones (e.g., androgens, estrogens, and dexamethasone) (see Brat et al., 2005; Waugh and Wilson, 2008).

Interleukin 8 (IL-8) and platelet factor 4 (PF4) are the first CXC chemokines for which the three-dimensional structure was determined. Their monomeric structures are very similar and comprise an NH2-terminal loop, three antiparallel β strands connected by loops, and a COOH-terminal helix. IL-8 forms globular dimers in a solution consisting of a six-stranded antiparallel β sheet (made up of the three β strands of each subunit) and two antiparallel helices lying across the β sheet (Clore et al., 1990; Baldwin et al., 1991; Clore and Gronenborn, 1995). Because most chemokines dimerize in solution, the dimer is generally assumed to be the biologically relevant form until proof is provided that IL-8 can function as a monomer (Rajarathnam et al., 1994). Although the biological activities are observed at nanomolar concentrations, the dissociation constants are mostly found within the micromolar range (Burrows et al., 1994; Clark-Lewis et al., 1995). Data obtained by size exclusion high performance liquid chromatography (HPLC), analytical ultracentrifugation, chemical cross-linking, and titration microcalorimetry support the conclusion that IL-8, at physiological concentrations, occurs predominantly as a monomer (Burrows et al., 1994).

Chemokines act via seven-transmembrane domain receptors (Baggiolini et al., 1994; Murphy, 1994). The biological effects of IL-8 are mediated through the binding to two cell-surface G protein-coupled receptors, CXCR1 and CXCR2 (Baggiolini et al., 1994; Baggiolini and Dahinden, 1994). These receptors share considerable structural similarity, suggesting that these genes arose through gene duplication. Signals are transmitted across the membrane through ligand-induced conformational changes, exposing epitopes on the intracellular loops and the carboxy-terminal tail of the receptor that promote coupling to functional heterotrimeric G proteins (Waugh and Wilson, 2008). Classically, the chemotactic response induced in response to CXC chemokines is attenuated in the presence of pertussis toxin, suggesting that Gα is the predominant G protein coupled to this family of receptors (Clore et al., 1990; Schall and Bacon, 1994). However, certain IL-8-promoted responses are insensitive to pertussis toxin, suggesting that these receptors might couple to and activate other as yet uncharacterized Gα proteins (Baldwin et al., 1991). This promiscuity of G protein coupling may be dictated by differential cell-specific expression of the Gα proteins that influences the affinity-based equilibrium established between the receptors and the intracellular pool of G proteins. Furthermore, the diversity of signaling pathways activated by CXCR1 and CXCR2 can also be understood on the basis of the increasingly recognized importance of the Gβγ subunits in signaling to primary effectors, in addition to the discovery that G protein-coupled receptors can signal through additional non-G protein dependent pathways (Waugh and Wilson, 2008).

CXCR1 and CXCR2 are expressed on neutrophils. They share 77% identical amino acids, and their genes are co-localized on chromosome 2q35. CXCR1 and CXCR2 exhibit a markedly distinct ligand binding pharmacology. CXCR1 receptors are activated only in response to the binding of IL-8 and granulocyte chemotactic protein-2. Conversely, CXCR2 is activated by multiple CXC chemokines, including growth-related oncogenes (GROα, β, and γ), neutrophil-activating peptide, and granulocyte chemotactic protein-2 (Baggiolini et al., 1994, 1997; Brat et al., 2005).

IL-8 receptors are also found on monocytes, basophils, and eosinophils, but the responses of these cells to IL-8 are much weaker than those of neutrophils (Baggiolini et al., 1994). In T lymphocytes, expression of both IL-8 receptors was revealed by RT-PCR, but not by Northern blotting (Moser et al., 1993; Xu et al., 1995), suggesting that their expression might be low. Using monoclonal antibodies and fluorescence activated cell sorter (FACS) analysis, it was observed that CXCR1 and CXCR2 are present on all neutrophils and monocytes, but only on a small percentage of lymphocytes. They are found in low percentages of NK and CD8+ T cells, and are absent in CD4+ T cells or B cells (Chuntharapai et al., 1994; Qin et al., 1996).

Pro-inflammatory cytokines display pleiotropic effects acting synergistically, additively or antagonistically on the function of the target cell. IL-8 facilitates the development of inflammatory reactions by acting in concert with IL-1 to cause chemoattraction of leukocytes to the site of inflammation, activation of neutrophils to phagocytosis and bacterial clearance (Feldmann and Saklatvala, 2001; Jedrzejczak et al., 2005; Fraczek and Kurpisz, 2007). IL-8 is secreted by several cell types, including monocytes, activated T lymphocytes, neutrophils, eosinophils, fibroblasts, synovial cells, adipocytes, endothelial cells, epithelial cells and keratinocytes (Steiner et al., 2002). Its primary role in the recruitment of neutrophils into inflammatory sites and their activation (Kobayashi, 2008) is accompanied by a chemoattractant activity on basophils and T cells, and by a potent pro-angiogenic action (Baggiolini et al., 1994).

## 2. Role of IL-8 in inflammatory diseases

Interleukin 8 is crucially involved in different inflammatory diseases, including psoriasis (Numerof and Asadullah, 2006), rheumatoid arthritis (Paradowska et al., 2007), inflammatory lung (Pease and Sabroe, 2002) and bowel diseases (MacDermott, 2007), gastritis (Naito et al., 2005) and atherosclerosis (Braunersreuther et al., 2007).

Psoriasis is a T cell-mediated disease with a strong cytokine component. Type 1 cytokine pattern predominates in psoriasis, and IL-8 has been described as being involved in the pathophysiology of the disease, together with a pro-inflammatory cytokine network (e.g., TNFα, IL-1, IL-12, IL-18, IL-23) (Numerof and Asadullah, 2006).

In rheumatoid arthritis, Paradowska et al. (2007) reported that IL-17 is the main cytokine involved in joint and cartilage inflammation, exerting synergistic effects with TNFα and IL-1. The authors also described that IL-17 binds to a specific receptor expressed on epithelial, endothelial, and fibroblastic stromal cells, triggering a biochemical cascade that results in the secretion of different cytokines, including IL-8, involved in the inflammatory response and in the progression of the autoimmune disease (Paradowska et al., 2007).

The role of IL-8 in the pathogenesis of many inflammatory lung diseases, including acute respiratory distress