Interleukin 8, the first chemokine to be characterized, was discovered in 1987. IL-8, known as a pro-inflammatory chemokine, induces accumulation of neutrophils along the vascular wall. The release of this cytokine is triggered by special inflammatory signals from different types of cells. This diversity indicates multiple functionality of this cytokine. IL-8 has a key role in the defense mechanism through the effects on neutrophil activity, but continued and prolonged presence of IL-8 in circulation in response to inflammatory conditions may cause variable degrees of tissue injuries. Like most of the peptide hormones or mediators, IL-8 transmits its signals through proper cell surface heptahelica receptors. In addition, IL-8 stimulates the mitogen-activating protein kinase (MAPK) and tyrosine phosphorylation of cellular proteins. Blocking of IL-8 actions could be considered for therapeutic purposes. The primary receptor-binding domain of all chemokines are near terminal NH2, and its antagonists can be obtained by truncation or substitutions in this region. Chemokines or chemotactic cytokines are structurally small (7–14 kDa) protein molecules regulating various types of cells trafficking through interactions with 7-transmembrane, G protein coupled receptors. To date, about 50 chemokines have been identified in humans. Based on the arrangement of N-terminal cysteine residues, chemokines can be divided into two major subfamilies, CC and CXC, depending on whether the first two cysteine residues are next to each other (CC) or have an amino acid linking them (CXC). Two small groups, CX3C chemokines and C chemokines, also have been identified. The CX3C formula (fractalkine) has 4–6 cysteines and is the only membrane-bound chemokine with a mucin-like stalk, and the C chemokine (lymphotactin), unlike the typical chemokine structure, lacks the first and third cysteines in its formula. Ocular effects of IL-8 differ based on the source of the secretion and site of the action. Anti-IL-8 targeted immunotherapy has been introduced as an important treatment modality, provided that IL-8 signal blocking takes place in desired areas and tissues. 

Keywords: angiogenesis, chemokine, cytokine, interleukine-8, ocular inflammation
receptor-dependent manner, for instance, CXCL8/IL8 as a pro-angiogenic chemokine, interacting with the CXCR2 receptor and interferon-inducible protein related to IL-8 (CXCL10/IP10) as an anti-angiogenic (i.e., angiostatic) chemokine, interacting with the CXCR3 receptor. Some chemokines also regulate angiogenesis in a receptor-independent manner such as bFGF and VEGF. To the best of our knowledge there are no ophthalmic-related IL-8 review articles in the medical literature. Therefore, the purpose of this review is to clarify the complexity and the functional diversity of IL-8 in ocular inflammatory disorders.

**MATERIALS AND METHODS**

The data sources were a literature review using PubMed, Medline, and ISI databases (from 1990 to 2011). Search items included interleukin-8 (IL-8), CXCL8, chemokines, cytokines, alone or in combination with the, serum, aqueous, vitreous, eye, ocular, ocular tissues, ophthalmic, and review. More than 19,000 articles related to IL-8 are present in the pub Med, Medline, and ISI databases, in which more than 850 articles relating to the eye, ocular, and ophthalmic items were recognized and were considered as the general basic data framework. About 385 papers were more relevant to the eyes and were used as the ocular data bank; finally, 131 full text articles were selected and used in this review. Selected language was in English. Human beings and animals as in vitro and in vivo studies were included to review the mechanisms of action and clinical effects of IL-8 focused on ocular manifestations of this cytokine in human ocular diseases.

**INTERLEUKIN-8 STRUCTURE, RECEPTORS, AND SIGNALING**

IL-8 is the most recognized CXC chemokine. The molecular structure of IL-8 has been determined by X-ray crystallography and nuclear magnetic resonance spectroscopy. The three-dimensional structure of IL-8 forms a homo-dimer in vitro at high concentrations. Each monomer helix comprises an N-terminal loop, three β-strand loops, and a C-terminal. The monomer strand has full action on neutrophils and its three-dimensional form acts like the subunits of the IL-8 dimers. Beta-1 and β2 regions of the loop are potentially involved in receptor recognition and residue mutations (Figure 1). The N-terminal ELR motif preceding the first cysteine has a major role in binding and activation of the cytokine. Transmitted signals across the cellular membranes induce structural changes and expose the epitopes on the intracellular loops and C-terminal at the end of the receptor. These epitopes facilitate the coupling with the functional heterotrimeric G proteins. At least 18 human chemokine receptors have been identified to date. There are some limited overlaps in binding of CXC chemokines to their receptors (i.e., CXCRs): some receptors bind to more than one chemokine and some chemokines bind to more than one receptor. These receptors have been found to be located on leukocytes, endothelial cells, epithelium, neurons, astrocytes, and microglia in the brain, as well as on a variety of tumor cells. Chemokine receptors are classified similarly according to which group of chemokines they bind and are classified as CXCR1–CXCR6, CCR1–CCR11, CX3CR1, and XCR1. CXCL8 bind to CXCR1 with more affinity than CXCR2 (Figure 2). Another chemokine receptor, that is located on red blood cells (and to a lesser extent on endothelial and epithelial cells) is a 40- to 45-kDa glycosylated protein expressed as Duffy antigen receptor for cytokines (DARC). It is possible that this receptor participates in chemokine transport (Figure 2).

**INTERLEUKIN-8 SUPER FAMILY**

Because of the potent pro-inflammatory properties of IL-8, this chemokine is tightly regulated, and its expression is low or undetectable in normal tissues. IL-8 is a small, soluble peptide with an 8- to 10-kDa molecular weight. The chemokine family has been divided into

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four major groups, CXC, CC, C, and CX3C, with individual classification based on the number and location of conserved cysteines within the N-terminal amino acid sequence.1

Interleukin-8 is the prototype of the CXC group. The other members include growth-regulated oncogene (GRO) α, β, and γ (CXCL1–3), platelet factor 4 (PF4; CXCL4), epithelial-cell-derived neutrophil-activating protein (ENA78; CXCL5), granulocyte chemotactic protein-2 (GCP-2; CXCL6), neutrophil-activating protein-2 (NAP-2; CXCL7), monokine induced by interferon (Mig; CXCL9), interferon-inducible protein 10 (IP-10; CXCL10), interferon-inducible T-cell α chemoattractant (I-TAC; CXCL11), stromal-cell-derived factor-1 (SDF-1; CXCL12), BCA-1 (CXCL13), and BRAK (CXCL14). Human genes for CXC group are clustered on chromosome 4 between 4q12 and 4q21. About 252 interleukin-8 proteins and homologues have been recognized, which are shared among humans, birds, and fishes. The sequences can be organized into five major known clusters. IL-8 belongs to the second cluster in which two subclusters for mammalian and avian have been considered9 (Figure 2). IL-8 and related chemokines bind to receptors belonging to the large family of G-protein-coupled receptors. Some of them cause cell migration, such as neutrophils and eosinophils, and some are implicated in angiogenic activities. More than 40 subfamilies of these ligands are known that share poor sequence similarity and display receptor specificity. Small fold of the ligand could display remarkable receptor specificity. Beta-1 and β2 loops of the fold are potentially involved in receptor recognition and could be potential sites for mutations.9

**SOURCES AND INTERACTION**

Among the first chemokines discovered, IL-8 was identified as a chemoattractant factor secreted by activated monocytes and macrophages that promotes the directional migration of neutrophils, basophils, and T lymphocytes. Human mast cells, macrophages, and neutrophils in response to proper stimuli secrete several cytokines, including IL-8. IL-8 is expressed

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**FIGURE 2** Cluster and subclusters of CXC and CC chemokines (left sided) and their ligands and corresponding receptors (right sided). Clusters 1, 2, and 3 (Megacluster A) include members of CXCL1 to CXCL8, CXCL10, CXCL12, and CXCL15. Clusters 4 and 5 (Megacluster B) include mainly CC subfamily members and few CX3C subfamily members. Reprinted from IOS Press BV, 8(3-4), Kanagarajadurai K, Sowdhamini R, Sequence and structural analyses of interleukin-8-like chemokine superfamily, 307-30, Copyright (2008), with permission from IOS Press.
by vascular endothelial cells, smooth muscle cells, and macrophages and is a potent chemoattractant for circulating monocytes and T cells. It has been also shown to contribute in smooth muscle cell proliferation and migration.\(^24\) Despite the fact that IL-8 has been thought to act predominantly on neutrophils, it induced firm adhesion of rolling monocytes to endothelial monolayers expressing E-selectin.\(^25\)

Treatment of monocytes with IL-2 increased IL-8 mRNA expression, but IFN-\(\gamma\)-gamma, which is also a potent monocyte activator, not only failed to induce IL-8 expression but inhibited the stimulation of IL-8 by IL-2.\(^26\) Lipopolysaccharides, IL-1\(\beta\), and TNF-\(\alpha\) are able to increase IL-8 production, in contrast to, IL-10 is a potent inhibitor of IL-8 synthesis and appears to play an antagonism role for IL-8.\(^27\) IL-17, a cytokine represents an early event in the development of the inflammatory reaction. IL-17 selectively increased the secretion of an array of angiogenic CXC chemokines, including CXCL1, CXCL5, CXCL6, and CXCL8, and its ability to recruit neutrophils may also explain its pro-angiogenic activity.\(^28\)

**IL-8 BIOLOGY**

The biological activity of chemokines is made possible by binding to specific cell surface receptors. IL-8, like most chemokine receptors, has high affinity for multiple ligands.\(^24\) Interleukin-8 is synthesized primarily as a 99 amino acid peptide. IL-8 mature formula contains 72 amino acids that are actively secreted as a result of types of cellular stimuli. Transcription of the IL-8 gene encodes for a protein of 99 amino acids that is either cleaved to 77 amino acids in nonimmune cells or 72 amino acids in immune cells of monocytes and macrophages.\(^29\) Most of the chemokines are first biologically inactive signal propeptides with 90 amino acids. They gradually cleave to the bioactive formulas during the secretion process from the cells. Biological activities of chemokines initiate after binding to specific cell surface receptors. Most chemokine receptors have high affinity for multiple ligands.\(^24\) Signal sequence cleavage and N-terminal proteolysis entails biologically relevant residues with 72 and 77 amino acids that are active IL-8 isoforms.\(^19\)

The 72 amino acid molecule secreted by immune cells of monocytes and macrophages, whereas the 77 amino acid variant secretes by nonimmune cells. The monomer molecule of IL-8 contains an NH2-terminal loop, three antiparallel beta strands connected by loops, and a C-terminal alpha helix (Figure 1). While IL-8 readily forms dimers in solution, the monomer is believed to be the biologically relevant and active form of this chemokine.\(^8,30\) Expression of IL-8 can be enhanced by IL-1, TNF-\(\alpha\), IL-6, interferon-\(\gamma\), lipopolysaccharide, phytohemagglutinin, phorbol myristate acetate, reactive oxygen species, and other cellular stressors.\(^31\)

Potent inhibitors of IL-8 production include dexamethasone, IL-4, and IL-10.\(^32\) The biological activities of CXC chemokines, such as IL-8, are in part dependent on their sequence of ELR amino acid motif (Glu–Leu–Arg). These three specific amino acids play crucial role in binding of IL-8 to these receptors. IL-8 is relatively resistant to temperature, proteolysis, and acidic environments. These biochemical natures make IL-8 an ideal molecule for acute inflammation sites, where it must stand firm in these destructive conditions. IL-8 molecule is produced in early inflammatory phase and remains active for a long period of time, even up to weeks at the site of inflammation. This is in contrast to most of the other inflammatory cytokines, which disappear from the site of inflammation after a few hours in vivo.\(^33,34\)

IL-8 gene expression is highly sensitive to oxidants, and anti-oxidants.\(^31\) Two cell surface G-protein-coupled receptors of CXCR1 and CXCR2 have been discovered to mediate biological activities of IL-8. These receptors have considerable structural similarity with nearly identical biological activities.\(^35,36\) It has been demonstrated that CXCR2 has high affinity for all CXC chemokines that attract neutrophils, including IL-8, while CXCR1 has high affinity only for IL-8.\(^37\) This biological preference in receptors may refer N-terminal four residues that are absent in the truncated form.\(^38\)

**IL-8 EXPRESSION AND RECEPTORS IN VIVO**

Once the IL-8 molecule is internalized by the endothelial cells, it is transported through the cellular plasma vesicles and released onto the luminal surfaces from the tips of membrane protrusions either directly from the Golgi apparatus or following storage in Weibel-Palade bodies.\(^39\) In vivo, IL-8 provokes a massive neutrophil accumulation at the injection site. Five molecules structurally similar to IL-8 of neutrophil-activating cytokines have been identified. IL-8 and the related cytokines are thought to be the main cause of local neutrophil accumulation following infection, inflammation, ischemia, or trauma.\(^40\) IL-8 and its homologues are potent signals for leukocyte migration and cell adhesion, but deletion of the IL-8 receptor homologue had minimal effect on cell rolling or arrest of in vivo video imaging.\(^41\) Predominantly, the proangiogenic activity of IL-8 seems to occur following binding to CXCR2, but CXCR1 appears to contribute as well through independent, small-GTPase activity.\(^19\) Immunohistochemical methods, Western blotting, and real-time PCR examinations of normal human and rabbit retinas revealed a positive immuno-reactivity for CXCL8, CXCR1, and CXCR2 in virtually all cultured glial cells and in the human Müller cell line and distinct expression of CXCR1 and CXCR2 in several neuronal cell types.\(^42\)
ROLE OF IL-8 AND IL-8RS IN OCULAR ANGIOGENESIS

In the CXC chemokine family, angiogenic activity refers to the presence or absence of a sequence of amino acids (Glu–Leu–Arg) in their molecular structure known as the ELR motif, which is located immediately before the first N-terminal cysteine residue. These three sequences of amino acids are important in ligand/receptor interactions and biological activation of neutrophils. The ELR-positive α-chemokines, CXCL8 (IL-8), CXCL7 (NAP-2), CXCL1 (MCSA/GRO-α), and CXCL5 (ENA-78) promote angiogenesis, whereas interferon-inducible α-chemokines that lack the ELR motif, such as CXCL4 (PF4), CXCL10 (IP-10), CXCL9 (MIG), and platelet factor 4 (PF4), are potent inhibitors of both CXC (ELR) chemokine, and basic fibroblast growth factor (bFGF)-induced angiogenesis CXCR2 binds to all of the ELF+ CXCs involved in angiogenesis, including IL-8, but CXCR1 binds with high affinity only to IL-8 and GCP-2; therefore, CXCR2 is a more suitable candidate for mediating the proangiogenic effects of IL-8. Clinically important angiogenic factors other than IL-8, include vascular endothelial growth factor, angiogenin, IL-6, MCP-1, and TGF-β1. Some of the proinflammatory cytokines, such as IL-1β, induce the synthesis of IL-8 in human mast cells via the leukotriene B4 receptor, thus contributing to angiogenesis. Neutrophils make up an essential part of the innate immune system, and are involved both in the initial responses to pathogens, and in orchestrating later immune responses. Neutrophils recognize pathogens through recently discovered pattern-recognition receptors. The Nod-like receptors (nucleotide-binding domain leucine-rich) activation resulted in interleukin-1β secretion and facilitated neutrophil migration and interleukin-8 secretion. Generally, IL-8 has at least four distinct proangiogenic properties, each of which is manifested through an endothelial cell response: (1) enhancement of endothelial cell proliferation by stimulation of both endothelial proliferation and capillary tube formation, both of which can be blocked by monoclonal antibodies to IL-8; (2) chemotaxis via directional migration of neutrophils, basophils, and T lymphocytes; (3) survival by ability to inhibit the apoptosis of endothelial cells; and (4) protease activation by stimulation of endothelial cell mRNA to increase expression of matrix metalloproteinases (MMPs) MMP-2, 9 and gelatinase activity.

In Vitro Eye Studies

In ocular surface, corneal epithelial cells play an important role in neutrophil chemotaxis, through the secretion of IL-8 in the early stages of corneal herpetic keratitis. IL-8 may play a role in the development of subepithelial infiltrates in adenovirus keratitis. The expression of IL-8 and monocyte chemotactic protein-1 (MCP-1) were unregulated after mitomycin C (MMC) exposure of corneal fibroblasts in a time- and dose-dependent manner. Human corneal endothelial and stromal cells produce IL-8, known as the neutrophil and lymphocyte chemokine, especially in response to stimulation by IL-1β or TNF-α. Staphylococcus aureus colonization in atopic keratoconjunctivitis upregulates TNF-α and IL-8 release in a dose-dependent manner. In intraocular tissues, thrombin extravasation at the sites of blood-retina barrier breakdown induced retinal pigment epithelial cells (RPE) secretion of IL-8 and MCP-1. This is enhanced in RPE cell/magnet co-cultures, and inhibited by anti-TNF-α antibody.

Animal Eye Studies

Cornea and Ocular Surface Effects
IL-8 plays a bifunctional role in corneal inflammations by both neovascularization and wound healing. Overexpression of IL-8 in the corneal tissues induced by adenoviral stimulation causes the formation of some types of corneal ulcers. In the cornea IL-8 increase collagen degradation by stimulation of polymorphonuclear neutrophils (PMNs) but TNF-α promoted collagen degradation by keratocytes. IL-8, produced by keratocytes and neutrophils, may be involved in the development of diffuse lamellar keratitis (DLK) after laser in situ keratomileusis in the rabbit cornea. Some of the cytokines and mediators have angiogenic activity such as IL-8, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and their receptors. This activation mediated by TNF-α and inhibited by the administration of anti-IL-8, anti-VEGF, and anti-bFGF antibodies and nuclear factor kappa B (NF-kappaB) in the rabbit cornea.

Uveal Effects
Intraocular injections of IL-1, IL-6, IL-8, TNF, and GM-CSF have been shown to induce inflammation in experimental animals. IL-1α initiates the inflammatory cascade containing IL-8, which acts more specifically on a smaller population of leukocytes in induced rat uveitis. Intravitreal injection of an anti-IL-8 antibody (WS-4) in endotoxin-induced uveitis in rabbit eye caused a decrease in the clinical and histologic grade of inflammation.

Vitreo-retinal Effects
Angiogenesis by the same mechanism has been proved in the mouse retina. Animal studies have showed IL-8 mediated angiogenesis inhibited by the mechanisms of decreased intravascular volume and dynamic forces and the direct effects of diabetes on cell growth or
angiogenesis but these mechanisms have little effects on VEGF. Anterior-chamber-associated immune deviation (ACAID) may be due to the intraocular effects of some cytokines, including IL-8. Common complications of ocular inflammation, such as glaucoma, keratic precipitates, retinal (macular) edema, and neovascularization, may be mediated by these cytokines.

**Human Eye Studies**

**Normal Human Tear IL-8 Values**

Undiluted basal and reflex tear fluid IL-8 levels are 731.4 ± 116.2 and 276.1 ± 47.5 pg/mL. IL-8 levels in reflex tears were significantly lower than those in basal tears. The amount of some tear cytokines changed during daytime based on a diurnal rhythm with a specific pattern and this may influence on the symptoms of ocular surface diseases during the course of a day. IL-8 tear levels remain low throughout the day.

**Ocular Surface and Corneal Effects**

Among levels of 15 cytokines and chemokines measured by multiplex bead analysis, IL-6, IL-8/CXCL8, and epidermal growth factor (EGF) levels correlated with pain and with clinical parameters measuring tear stability, tear production, or ocular surface integrity. Tear fluid levels of IL-6 and IL-8 increased following penetrating keratoplasty, acute bacterial conjunctivitis, or corneal foreign body. This may be used as an indicator of various inflammatory reactions in the early postoperative period. Mechanical stimulation of the corneal surface by rubbing or rigid contact lenses leads to increased tear levels of epidermal growth factor and IL-8. In a patient with Stevens-Johnson syndrome (SJS), tear IL-8 levels and ocular inflammation decreased more rapidly in the eye with cultivated limbal stem cell transplantation (LSCT) in contrast with conventional LSCT in the next eye. More severe corneal scarring and opacification were noted in the eyes with conventional LSCT 4 years later. Tear IL-6 and IL-8 levels increased in parallel with the severity and stages of the diseases in patients with conjunctivochalasis, especially when punctal occlusion and delayed fluorescein clearance test are also present.

Conjunctival epithelial cells in response to stimulation by gram-positive *Staphylococcus aureus* activate the innate immune response by IL-8 gene expression and secretion. IL-8 and, to some extent, IL-6 and VEGF are expressed by pterygium epithelium. This expression is enhanced by exposure to ultraviolet (UV) radiation and causes abnormal blood vessel formation, cellular proliferation, tissue invasion, and inflammation. In severe allergic eye diseases the levels of IL-8 in the extracellular spaces of conjunctival epithelium increased significantly in correlation with the percentages of neutrophils and eosinophils.

**Uveal Effects**

Serum levels of IL-8 and IL-6 were significantly elevated in patients with active uveitis and were decreased during remission. IL-8 levels were higher in patients with anterior and acute uveitis, while IL-6 is higher in chronic uveitis. There is association between the disease activity and increased reflex tears levels of IL-8 induced by soft contact lens wearing in Behçet syndrome. IL-8 plays a role in the progression of intraocular inflammation, and lens-induced endophthalmitis in Behçet disease and granulocytes are thought to be a possible source of IL-8 in these patients. In the aqueous humor from patients with active uveitis, IL-8, levels are significantly increased. HLA-B27-associated uveitis had the highest IL-8 levels. In Behçet disease with hypopyon, the mean levels of IL-8 were significantly higher than in patients without hypopyon. IL-8 participates in the inflammatory processes in the eye by attracting and degranulating neutrophils. It is suggested that these processes contribute to the pathogenesis of tissue destruction in uveitis. Lipopolysaccharide-induced uveitis causes IL-8-mediated neutrophil infiltration and MCP-1-mediated mononuclear cell infiltration and protein leakage.

**Vitreous and Retinal Effects**

IL-8 levels in the vitreous may play a role in the pathogenesis of proliferative vitreoretinopathy (PVR). Vitreous gel levels of IL-8 were significantly increased in patients with active proliferative diabetic retinopathy (PDR). Vitreous gel levels of IL-6, IL-8, and nitric oxide (NO) increased significantly following retinal laser photoagulation. Diabetic individuals showed significant elevation of IL-8, VEGF, and angiogenin in the vitreous but not in serum samples compared to control subjects. NF-kappaB protein overlapped with angiogenic factor of IL-8 in formation of epiretinal membranes (ERMs) after PDR and PVR. Mechanical stress to RPE cells, such as exposure to magnetic force, induces the RPE cells to express MCP-1 and IL-8, the two inflammatory cytokines that may be involved in the early stage of primary retinal detachment. Retinal pericytes, glial cells, ganglion cells, and ciliary epithelium release VEGF and/or IL-8 in response to hypoxia and cause endothelial cell proliferation and neovascularization. Serum levels of IL-8 increased during the acute phase of nonarteritic anterior ischemic optic neuropathy (NAION), but decreased during the follow-up period; these changes are in accordance with other acute vascular thromboses. Serum levels of IL-8 and IL-6 and aqueous humor levels of IL-8 are higher immediately following acute retinal artery occlusion. Aqueous humor levels of IL-6, IL-8, VEGF, and MCP-1 are significantly higher in clinically significant macular edema (CSME). The pro-inflammatory homozygous gene for IL-8 is an important risk factor for age-related macular degeneration (ARMD). Higher vitreous IL-8
levels at vitrectomy surgery, significantly increased risk of recurrent vitreous hemorrhage, this association may be explained by the role of IL-8 in angiogenesis.94

**Orbital Effects**

In thyroid-associated opthalmopathy, progression of inflammation refers to the types of fibroblasts and amount of IL-8 production in these cells.95 In orbital inflammations, orbital fibroblasts in response to cytokines, such as IL-1β, TNF-α, lipopolysaccharides (LPS), and IFN-γ stimulation, produced dose-dependent IL-8 and MCP-1.96

**IL-8-TARGETTED IMMUNOTHERAPY**

Pretreatment of human monocyte-derived macrophages with methylprednisolone, dexamethasone, and hydrocortisone potentiate the phagocytosis of apoptotic neutrophils, and this effect is blocked by the glucocorticoid receptor antagonist. Methyl prednisolone enhancement effects did not trigger the release of the chemokines IL-8 and monocyte chemoattractant protein-1. This property of glucocorticoids aims to the resolution of inflammatory diseases.97 Only a limited amount of data is available concerning the therapeutic potential of IL-8. Anti-IL-8 monoclonal antibody medications may effectively improve multiple human diseases.98 IL-8 cytokine expression in numerous xenograft and orthotopic in vivo models correlates with the angiogenesis, tumorigenicity, and metastasis of tumors. Therefore, suppressing the effects of IL-8 signaling may be a beneficial therapeutic intervention in targeting the tumor microenvironment.29

The ability of some members of CC chemokines, such as IL-1β, TNF-α, lipopolysaccharides (LPS), and IFN-γ, to recruit immune cells is pivotal to the success in the treatment of several ocular surface inflammatory disease.102 It is reported that IL-8 and MCP-1 play major roles in the progression of recurrent vitreous hemorrhage, this association may be explained by the role of IL-8 in angiogenesis.94

**DISCUSSION AND CONCLUSION**

IL-8 is one of the most important inflammatory cytokines and has been noticed in many scattered research articles. Despite more than 30 years from discovery of IL-8 and the presence of many wide-ranging published articles about this cytokine, there are very few specific review articles concerning the body organs and especially no review article focused on the ocular effect of the IL-8. This review introduces the ocular effects of this cytokine as an accessible collection.

Several functions for IL-8 have been suggested in different cell types and tissues, including neutrophil recruitment, cell adhesion, homing of neutrophils and lymphocytes, tumor growth, angiogenesis, neuronal protection, and even brain development.21 PMN are the primary effectors cells in acute inflammatory responses. Appropriate interactions of these cells with macrophages in injured, stressed, or infected tissues are required for the successful performance of the routine tissue response. Any deviation from these fundamental programs as a major problem may lead to many ocular diseases. Counter-regulatory signals are critical for controlled activation of immune responses in the cornea, uvea, and/or retina. The role of these circuits may provide insight to maintain a pre-inflammatory state, namely homeostasis, rather than limiting therapeutic options to palliative inhibition of pro-inflammatory circuits.108

Monocyte infiltration is a prominent feature of inflammatory ocular disorders such as uveitis, ARM and epiretinal membranes,109–111 Interleukin (IL) 8 and monocyte chemoattractant protein (MCP) 1 play major roles in pro-inflammatory human retinal pigment epithelial (HRPE) -derived leukocyte chemotactic activity.112 IL-8 is suppresses neovascular activity.105 Recent data showed that not only are antiangiogenic molecules inhibitors of angiogenesis, they are also efficient at reversing some levels of immunosuppression. This link may lead to the emergence of a new class of antiangiogenic and immunosuppressive medications.88 Most of the antiangiogenic molecules affect not only VEGF signaling pathways but also alternative pathways such as IL-12.106

IL-10 seems to be the most suppressive cytokine on secretion of IL-8 and MCP-1 by RPE cells, suggesting potential therapeutic effects of IL-10 on the ocular inflammatory and proliferative diseases.105 Thalidomide as an immunomodulatory, anti-inflammatory, and antiangiogenic medication acts by decreasing circulating CD4+ T cells and stimulating CD8+ T cells. Thalidomide also inhibits proliferation of stimulated T cells and leukocyte chemotaxis. Thalidomide inhibits TNF-α, IL-5, IL-6, IL-8, and IL-12 and increases IL-2, IL-10, and IFN-γ production. Moreover, thalidomide plays an important role in inhibition of VEGF and FGF-2 mediated angiogenesis.107
and MCP-1. Hypoxia or oxidative stress caused rapid lial cells resulted in the increased expression of IL-8 interactions between monocytes and vascular endothelial cells resulted in the increased expression of IL-8 and MCP-1. Hypoxia or oxidative stress caused rapid upregulation of IL-6 and IL-8 mRNA expression. Better understanding of such basic mechanisms may help to improve methods for treatment of the ocular inflammatory disorders. Th2 cytokines such as IL-4, -10, and -13 are able to downregulate the pro-inflammatory cytokine release by stimulated monocytes. These cytokines, thus, may have an immunoregulatory role in clinical and experimental ocular inflammation.

In vitro and in vivo eye studies all support the angiogenic and inflammatory effects of IL-8. Angiogenesis in most of the cases is harmful for the ocular tissues. In humans, the most frequent type of angiogenic activity on ocular surface is pterygium. During active process of ocular cicatricial pemphigoid, tear angiogenic molecules of IL-8 and matrix metalloproteinase-9 (MMP-9), in particular, were elevated, but decreased after systemic immunomodulatory therapy. IL-8, which is smaller than the other chemokines and shows powerful attractive chemotactic properties on T cells and neutrophil polynuclear cells, dramatically increased in the tears of dry eye patients.

Corneal angiogenesis are encountered in many frequent pathologic disorders, such as penetrating keratoplasty or corneal foreign body and in rare conditions such as SJ and sulfur mustard (SM) intoxicated patients. Intraocular angiogenesis may be encountered in vitreous and retina (diabetic retinopathy) and orbital tissues. Pro-angiogenic cytokines such as IL-8 are more highly represented than anti-angiogenic cytokines such as IL-4 and IL-12 in the tears of diabetic patients with retinopathy.

In different diseases of anterior segment of the eye IL-8 plays special roles. A significantly increased IL-6 and IL-8 mRNA expression was found in the ciliary process and iris in eyes with early PEX syndrome. IL-6 and IL-8 mRNA expression levels were correlated in early stages of PEX syndrome, indicating a concerted expression of both cytokines in this condition. Significantly increased levels of IL-8 could be measured in aqueous samples of eyes with early stages of pseudo-exfoliation (PEX) syndrome (but not in late stages or in PEX glaucoma) as compared with control eyes with cataract. Patients with POAG displayed an increased IL-8 levels, however, the levels did not reach statistical significance. Patients with a history of inflammatory ocular disease displayed a significant increase of aqueous IL-8 compared with cataract controls. Aqueous levels of IL-8 were positively correlated both in patients with early stages of PEX syndrome and in patients with previous ocular inflammation. The latter showed further positive correlations between IL-8 and IL-1. Ciliary processes are the most potential sources for aqueous IL-6 and IL-8 (about 100 times higher than that of all other normal ocular tissues). Aqueous IL-8 levels highly increased following cataract surgery, whether done by local or general anesthesia. Aqueous humor levels of IL-8 concentration in primary open-angle glaucoma are significantly elevated. In patients with asymmetric glaucoma, the more severely affected eye had a significantly higher IL-8 concentration. This elevation is also correlated with the severity of visual field test abnormalities. Normal retina and optic nerve are of potential sources for aqueous humor IL-8 secretion. Significantly increased concentrations of VEGF, IL-6, and IL-8 were observed in aqueous humor samples of patients with CRVO. During therapy with bevacizumab, a decrease in aqueous VEGF levels was accompanied by a decrease in central retinal thickness (CRT) and improvement in visual acuity.

Interleukin-6 (IL-6), interleukin-8 (IL-8), and monocyte chemoattractant protein-1 (MCP-1) are significantly elevated in vitreoretinal diseases, including diabetic macular edema (DME), proliferative diabetic retinopathy (PDR), branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), and rhegmatogenous retinal detachment. In PDR patients, the elevation of VEGF was significantly correlated with the three factors—IL-6, IL-8, and MCP-1—while no significant correlation was observed with CRVO patients. These three major factors were strongly correlated with each other except for IL-8/MCP-1 in CRVO, indicating a common pathway involved in inflammation process in vitreoretinal diseases. VEGF may independently play a role in the pathologic process in PDR and CRVO. Presumably IL-6, IL-8, and MCP-1 in the vitreous cavity promote vascular permeability that causes DME. Retinal ischemia leads to an excessive production of VEGF that in turn causes further progression of DME to PDR. On the other hand, a substantial amount of VEGF can be initially produced by the sudden profound retinal ischemia, which in turn induces the major three factors afterward. The duration of DM was found to correlate with serum VEGF, IL-8, MCP-1, and EGF levels, but the progression of diabetic retinopathy (DR) was found to be significantly correlated with the median values of serum monocyte chemoattractant protein (MCP-1). In patients with DR, no correlation was found between macular thickness and serum cytokines of IL-6, IL-8, IL-10, and VEGF levels but only increased serum levels of VEGF and MCP-1 may act as a key regulator of DR and provide a potential tool for risk assessment in diabetic patients.

In this review we noticed that vitreoretinal effects of IL-8 have been recently taken into specific consideration by many investigators. This is due to the attractive and important subjects of ARMD, PVR, PDR, retinopathy of prematurity (ROP), retinal vascular accidents, and other causes of vitreoretinal angiogenesis or inflammatory disorders in this field. These broad-spectrum effects of IL-8 in ocular disease had encouraged the investigators to use
IL-8-targetted immunotherapy with anti-IL-8 cytokines such as IL-10 or medications. As in any immune-modulating therapeutic approach, there are several disadvantages regarding IL-8 blocking that need to be considered. IL-8 is an important mediator in numerous inflammatory treatments. In critical circumstances to avoid the dangers of such treatments.

In conclusion, IL-8 plays important roles in the ocular inflammation and inducing ocular angiogenesis in any parts of the eyes, such as the conjunctiva, cornea, iris, retina, and orbit. Anti-IL-8 targeted immunotherapy with specific immune products or medications and with specific techniques to act just at the inflammation sites has been introduced as new treatment modalities in IL-8 related ocular angiogenesis or inflammations. As with other vital organs, many of the inflammatory phenomena in the eyes are essential for health and vision survival. Thus, inhibition of inflammatory cytokines and chemokines such as IL-8 should be considered only in critical circumstances to avoid the dangers of such treatments.

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