Cytokines and Chemokines in Uveitis – Is there a Correlation with Clinical Phenotype?

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Uveitis is a general term for intraocular inflammation and includes a large number of clinical phenotypes. As a group of disorders, it is responsible for 10% of all registered blind patients under the age of 65 years. Immune-mediated uveitis may be associated with a systemic disease or may be localized to the eye. The pro-inflammatory cytokines interleukin (IL)-1 β , IL-2, IL-6, interferon- γ and tumor necrosis factor- α have all been detected within the ocular fluids or tissues in the inflamed eye together with others, such as IL-4, IL-5, IL-10 and transforming growth factor- β . The chemokines IL-8, monocyte chemoattractant protein-1, macrophage inflammatory protein (MIP)-1 α , MIP-1 β and fractalkine are also thought to be involved in the associated inflammatory response. There have been a number of studies in recent years investigating cytokine profiles in different forms of uveitis with a view to determining what cytokines are important in the inflamed eye. This review attempts to present the current state of knowledge from *in vitro* and *in vivo* research on the inflammatory cytokines in intraocular inflammatory diseases.

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Uveitis is an umbrella term for intraocular inflammation of a variety of types and etiologies. It is most commonly classified anatomically as anterior, intermediate, posterior or diffuse (panuveitis) depending on which segment of the eye is affected. There are numerous causes including systemic autoimmune disorders and infection. Immune-mediated systemic diseases that are associated with uveitis include Behçet's disease (BD), sarcoidosis and Vogt-Koyanagi-Harada (VKH) disease. Infectious causes include toxoplasmosis and syphilis. Those in which infection has been suggested to play a role include ankylosing spondylitis, Reiter's disease and Fuchs' heterochromic cyclitis (FHC). Acute inflammation can have major deleterious effects on the eye which can lead to visual loss. Some sequelae, such as cataract, are treatable but others including glaucoma and retinal vascular ischemia may cause irreversible visual loss. When corticosteroids or other drugs are given for a systemic inflammatory disorder, side effects such as cataracts may also occur.

Experimental autoimmune uveitis provides an established animal model of posterior segment immune-mediated, non-infectious inflammatory disorders which affect the retina and choroid

depending on the strain and the mode of induction. Experimental autoimmune uveitis is an immune-mediated response against soluble retinal antigens, including S-antigen and interphotoreceptor retinoid-binding protein, which are situated, for the most part, within or surrounding photoreceptor segments.¹⁻³ Experimental autoimmune uveitis disease induction is characterized by polarization of early T-helper (Th)0 or Th2-like responses towards Th1, whereas resistance to disease is associated with regulatory cells as well as polarization towards a Th2 pathway.⁴ Th2 cells are also capable of inducing ocular inflammation, but only in immunodeficient mice, and they are profoundly inferior to Th1 cells in their immunopathogenic capacity.⁵

Experimental autoimmune anterior uveitis is a well-established model of acute anterior uveitis which parallels the human disease clinically and pathologically.⁶ It can be induced in Lewis rats with bovine melanin associated antigen from the iris and ciliary body with the resultant inflammation confined solely to the anterior chamber.⁷ Previous work in experimental autoimmune anterior uveitis has revealed similar Th1-like predominance and has defined the importance of chemokines in the pathogenesis of acute anterior uveitis.^{8,9}

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Since the last major reviews of cytokines in uveitis,¹⁰⁻¹² the advent of bead-based multi-detection assays has made possible the measurement and correlation of multiple cytokine analytes from a single, small, aqueous humor sample.^{13,14} Combined with work in experimental uveitis and genotyping for cytokine polymorphisms, these bead-based assays have allowed new insights into the interplay of cytokines and chemokines within individual uveitis entities and their relative contributions to the disease process.

Cytokines in Experimental Uveitis

For experimental autoimmune uveitis, peripheral activation of T cells is required which is completely independent of the eye. Therefore, anything affecting priming of Th1 cells will likely affect experimental autoimmune uveitis. Indeed, a pivotal role for antigen-specific CD4⁺ Th1 cells and pro-inflammatory cytokine-mediated disease has been demonstrated in both rat and mouse experimental autoimmune uveitis with nude rats, devoid of T cells, unable to develop experimental autoimmune uveitis.¹⁵ Interferon (IFN)- γ is also considered to be a major effector cytokine in the pathogenesis of autoimmunity.¹⁶ IFN- γ helps to mediate delayed-type hypersensitivity responses via upregulation of HLA-DR activation of a variety of cells, including dendritic cells and macrophages which, in turn, generate tumor necrosis factor (TNF)- α and further facilitate Th1 cell development.¹⁷ In rat models, inoculation with recombinant IFN- γ has led to the detection of major histocompatibility complex (MHC) class II antigen upregulation on a variety of ocular cells in the anterior segment, including iris and ciliary epithelium, as well as posteriorly with expression on the retinal pigment epithelial cells.¹⁸ This IFN- γ -mediated MHC class II upregulation is thought to be important in the pathogenesis of organ-specific autoimmune disease.¹⁹ Concentrations of IFN- γ have been found to predominate in experimental autoimmune uveitis at peak inflammation in Lewis rats, and as such, susceptibility to experimental autoimmune uveitis in Lewis rats is thought to be connected with a Th1-dominant response involving IFN- γ .^{20,21} A slight peak in IFN- γ mRNA expression in the iris and ciliary body, again corresponding with maximal inflammation, has also been observed in experimental autoimmune anterior uveitis.¹¹

Interleukin (IL)-12, produced by macrophages and dendritic cells, has been reported to be a dominant factor in the development of Th1 cells.²² IL-12-deficient mice have shown resistance to induction of experimental autoimmune uveitis, but following IL-12 administration to cells from these mice, the cells are induced to produce large amounts of IFN- γ and can adoptively transfer experimental autoimmune uveitis to naïve recipients.²³ In addition, anti-IL-12 monoclonal antibodies (mAb) administered prior to immunization prevented experimental autoimmune uveitis induction in mice.²⁴ Furthermore, experimental autoimmune uveitis-susceptible mice show a greater amount of IL-12 receptor expression on Th1 cells correlating with IFN- γ expression.²⁵ Excessive IL-12 administered during the course of disease, however,

ameliorated experimental autoimmune uveitis consistent with its known apoptotic effects on T cells, possibly via a self-regulatory negative feedback loop.^{26,27}

TNF- α is synthesized by monocytes, macrophages, neutrophils, mast cells, natural killer (NK) cells and T cells.²⁸ During the inflammatory process, it orchestrates the initiation of further leukocytic infiltration via adhesion molecule upregulation, dendritic cell maturation and survival, macrophage activation, and driving Th1 T cell responses within tissues in experimental autoimmune uveitis.²⁹ Increased TNF- α expression in inflammatory cell infiltrates has been seen in experimental autoimmune uveitis near peak inflammation as well.²⁰ Increased TNF- α mRNA has also been detected in the iris and ciliary body at the peak of the disease in experimental autoimmune anterior uveitis.¹¹ Administration of TNF- α at the time of experimental autoimmune uveitis induction has been demonstrated to increase the susceptibility to experimental autoimmune uveitis in mice and worsen its course, possibly through an increase in blood-retinal barrier permeability.^{30,31} Conversely, the neutralization of TNF- α activity with a p55 TNF receptor fusion protein after the induction of experimental autoimmune uveitis delays its onset and attenuates tissue damage.³² TNF- α is also thought to facilitate on-going T cell effector responses, possibly through the activation of anti-apoptotic pathways dependent on TNF-induced nuclear factor (NF) κ B activation.³³

IL-2 is produced mainly by activated T lymphocytes and can activate T cells and NK cells. It has been detected in experimental autoimmune uveitis at concentrations approaching those of IFN- γ near maximal inflammation.²⁰ Increasing signaling positivity for IL-2 mRNA has also been demonstrated to correlate with increasing disease severity in experimental autoimmune uveitis.^{34,35} IL-2 has also been shown to induce anterior uveitis in a rabbit model after intravitreal injection.³⁶ Administration of IL-2 receptor mAb in efferent-stage experimental autoimmune uveitis in the Lewis rat has also achieved partial experimental autoimmune uveitis suppression.³⁷ Oral tolerance in a murine model with human recombinant IL-2 has been documented to protect against experimental autoimmune uveitis, possibly through the induction of IL-4 and transforming growth factor (TGF)- β .³⁸

IL-1 β , along with IL-1 α , makes up the pleiotropic cytokine IL-1.³⁹ Each has its own receptor, but receptor usage is not highly restricted. Thus, IL-1 α and IL-1 β have broadly similar effects on cells. In Lewis rats, IL-1 α injected intravitreally has been demonstrated to induce intraocular inflammation in agreement with the concept of IL-1, initiating a cascade of inflammatory mediators.⁴⁰ IL-1 β is also a pro-inflammatory cytokine and is derived predominantly from activated macrophages but also from B cells and vascular endothelial cells. IL-1 β injected intravitreally into Lewis rats is also associated with a breakdown in the blood-retinal barrier and induces an inflammatory response characterized by an infiltrate of polymorphonuclear and mononuclear cells.^{31,41}

the majority of which migrated through retinal endothelial cells with a smaller contribution from the ciliary body.⁴¹ A further study has shown that vascular endothelial growth factor and TNF- α , as well as IL-1 β , may contribute to the breakdown of the blood-retinal barrier in experimental autoimmune uveitis as well as in patients with uveitis, possibly through opening of tight junctions and increased vesicular transport within the endothelial cells.⁴² Conversely, IL-1 β blockers have been shown to inhibit experimental uveitis.⁴³

IL-6 is a macrophage-derived cytokine, also thought to be produced by endothelial and ocular parenchymal cells.⁴⁴ It is a pleiotropic cytokine that is able to function in a pro- and anti-inflammatory manner. Macrophage activation and the differentiation of B cells to plasma cells are other known key effector roles for IL-6. Readily induced by TNF- α , IFN- γ and IL-1, IL-6 has been shown to stimulate production of acute phase proteins, such as fibrinogen and C-reactive protein.⁴³ Evidence exists to suggest that IL-6 is involved in the direct induction of IL-2 receptor expression, differentiation and proliferation of T cells.⁴⁵ It is even thought to be more active in this respect than both IL-1 and TNF- α .⁴⁶ Increased levels of IL-6 have been detected in the aqueous humor in a murine model of experimental autoimmune uveitis with serial sampling demonstrating an increased local production at disease onset followed by a decrease as the inflammation mounted.⁴⁷ Its pleiotropic properties may, however, allow for negative feedback that inhibits the production of IL-1 and TNF- α , just as its decrease may allow for the recovery of TGF- β 2 function.^{47,48}

TGF- β describes a group of pleiotropic cytokine isoforms that includes TGF- β 1, - β 2 and - β 3. All are structurally and functionally similar having effects on many cell types including macrophages, T cells and B cells. For T cells, TGF- β inhibits T cell proliferation and suppresses cytotoxic T cells.⁴⁹ In the eye, TGF- β is present at high levels in the aqueous humor and is thought to be implicated in the maintenance of immune privilege through the inhibition of antigen-driven T cell activation and proliferation.⁵⁰ TGF- β 2 levels have been found to be increased in experimental autoimmune uveitis and are thought to be antagonized by IL-6, such that TGF- β 2 suppresses inflammation once IL-6 levels fall.⁴⁴ TGF- β 2, in conjunction with α -melanocyte-stimulating hormone, has been demonstrated to generate ocular autoantigen-specific T regulatory cells which produce TGF- β 1 and are able to reduce the incidence and severity of experimental autoimmune uveitis.⁵¹ Further characterization with anti-TGF- β 2 antibodies has delineated TGF- β 2 as an important immunosuppressive cytokine for CD8⁺ T regulatory cells in their ability to delay the onset of experimental autoimmune uveitis in rats and reduce its incidence and severity.³⁶

IL-4 is a multifunctional cytokine that can be secreted by several cell types, but the most important producers of IL-4 in T cell-mediated disease are CD4⁺ Th2 cells activated by

antigen recognition through the T-cell receptor. Among the effector functions of IL-4 are induction of IgE production by B cells⁵² and direct differentiation of naïve CD4⁺ T cells into a Th2 population, thereby favoring the growth of cells which produce IL-4 and IL-5 while inhibiting the production of IFN- γ .⁵³ IL-4 is also involved in the inhibition of TNF- α and IL-1 production by activated monocytes,⁵⁴ and in macrophages, it has been demonstrated to suppress IL-6 through the inhibition of NF κ B activity.⁵⁵ It also acts as a growth factor for both B cells and Th2 cells.^{56,57} In experimental autoimmune uveitis, the addition of IL-4 has been reported to block the production of IFN- γ , while anti-IL-4 mAb therapy has been shown to lead to enhanced IFN- γ production. In experimental models of uveitis, both IL-4 and IL-10 are thought to be important cytokines for the immunosuppressive effects of CD4⁺ T regulatory cells.⁵⁸ The production of both IL-4 and IL-10 has been documented to correlate with a recession of disease, suggesting their possible importance in the spontaneous termination of experimental autoimmune uveitis. Furthermore, although IL-4 appears to be able to prevent differentiation of the primed precursor into the uveitogenic Th1 effector cell, once the mature effector is generated, only IL-10 is effective in suppressing its function.⁵⁹

IL-5 is a cytokine produced by activated Th2 cells and mast cells, which in humans selectively stimulates differentiation, proliferation and functional activation of the eosinophil lineage. Therefore, its role in uveitis has only been minimally investigated in experimental models. The use of anti-IL-12 mAb in the protection against experimental autoimmune uveitis has, however, been associated with an increase in IL-5, as well as IL-4 mRNA. This was thought to be reflective of the generation of antagonistic Th2 cells which were then able to confer a complete resistance to experimental autoimmune uveitis on further challenge with the same antigen.²⁴ Its production has also been shown to be increased in response to a uveitogenic antigen in experimental autoimmune uveitis-resistant mice and in concert with IL-4, as well as IL-10, in a polarized Th2 manner.⁶⁰ Its role in human disease remains unclear.

IL-10 is an essential anti-inflammatory multifunctional cytokine produced primarily from T cells and activated macrophages. It was first recognized for its ability to inhibit activation and effector function of T cells, monocytes and macrophages. In addition to its limiting activity on inflammation, IL-10 regulates growth and/or differentiation of B cells, NK cells, Th and cytotoxic T cells, mast cells, granulocytes, dendritic cells, keratinocytes and endothelial cells. IL-10 plays a key role in the differentiation and function of T regulatory cells which figure prominently in control of immune responses and tolerance *in vivo*.⁶¹ T regulatory cells, themselves, produce IL-10, as well as TGF- β .⁶² In this scenario, IL-10 is thought to act as a positive autocrine factor for the development of T regulatory cells.⁶³ IL-10 also strongly inhibits cytokine production and proliferation of CD4⁺ T cells and T cell clones via its downregulatory effects

on APC function.^{64,65} In addition to depressing APC function, IL-10 affects dendritic cell maturation, thereby providing a potential bimodal feedback inhibition of Th1 and Th2 responses.^{61,66} It has been proposed that the higher expression of the IL-10 gene in some rat strains may confer a greater resistance to experimental autoimmune uveitis.⁶⁷ Furthermore IL-10 mRNA expression has been shown to coincide with downregulation of IFN- γ and TNF- α coinciding with the resolution of experimental autoimmune uveitis.⁶⁸ More recently, the local administration of an adeno-associated viral vector expressing IL-10 significantly decreased experimental autoimmune uveitis disease severity.⁶⁹ It is not clear how IL-10 acts as a suppressor for IFN- γ production in T cells, but in macrophages, it has been demonstrated that IL-10 reduces the stability of mRNA for IL-6.⁵⁵

Chemokines in Experimental Uveitis

Chemokines are a family of small, secreted polypeptides that are known to be produced during an inflammatory reaction and can be produced by endothelial cells in response to cytokines, such as TNF- α and IL-1. They play a major role in the control of leukocyte adhesion, chemotaxis and activation.⁷⁰ These chemotactic cytokines include the inflammatory chemokines (CC and CXC) as well as the immune chemokines (C and CXC3) and are, therefore, thought to play a major role in inducing/regulating inflammation and various immune responses. A number of ocular chemokines have now been discovered that contribute to the recruitment of inflammatory cells into the eye in uveitis. Levels of mRNA for monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 (MIP-1), and interferon- γ -inducible protein-10 have been found to increase prior to the onset of experimental autoimmune anterior uveitis, suggesting that they might have a role in the initial recruitment of inflammatory cells.⁷¹ The level of regulated-upon-activation, normal T cell mRNA (RANTES) has also been documented to increase at the onset of experimental autoimmune anterior uveitis implicating it as an amplification factor.⁷¹

IL-8 activates and attracts neutrophils after secretion by lipopolysaccharide-stimulated monocytes.⁷² *In vivo*, IL-8 is also produced by many other cells, both immune and non-immune. IL-8 and its homologues are potent signals for leukocyte migration but not for rolling or arrest.^{73,74} Increased IL-8 has also been documented in experimental autoimmune anterior uveitis but without mRNA expression on T cells for its receptors, CXCR1 and CXCR2. A feedback mechanism is implied whereby neutrophils are, therefore, less responsive to IL-8 with resultant inhibition of their recruitment in the iris and ciliary body.^{75,76} An NF- κ B inhibitor targeting the transcription of MCP-1, RANTES and IL-8 ameliorated disease in experimental autoimmune anterior uveitis induced in Lewis rats, thereby illustrating their potential contribution to experimental autoimmune anterior uveitis and possibly acute anterior uveitis.⁷¹

Recently, the dual-adhesion molecule-chemokine, fractalkine (CX3C), was found to be expressed in a variety of ocular tissues and cells. It is thought to play an important role in regulating leukocyte efflux in inflammatory eye diseases, such as anterior uveitis and retinochoroiditis.⁷⁷ Fractalkine upregulation prior to disease onset in experimental autoimmune uveitis has also been demonstrated.⁷⁸ As yet, only the chemokines IL-8, MIP-1 β and MCP-1 have been investigated in the aqueous humor in patients with acute anterior uveitis,^{13,79} and CCL2 (MCP-1), CCL5 (RANTES), CCL11 (Eotaxin), TGF- β 2 and CXCL12 (SDF-1) have been investigated in patients with anterior uveitis.¹³

Cytokines and Chemokines in Patients with Uveitis

Idiopathic Uveitis

Generally, the most common form of anterior, intermediate, posterior and panuveitis in Western countries is idiopathic.^{80,81} It is unknown as to whether the immune processes occurring intraocularly in idiopathic uveitis are the same as those in which a systemic immune disease is also present. This is because, where there is an associated systemic disease, the ocular inflammatory activity does not necessarily parallel systemic inflammation.⁸² It has been suggested, however, that in some cases of idiopathic uveitis in which there is no detectable systemic disease, there is still concurrent abnormal systemic immune activation.⁸³

Various pro-inflammatory cytokines have been investigated in patients with uveitis (table 1), including IL-1 β which has been detected in the vitreous aspirates of patients with idiopathic panuveitis and may act as a local amplification signal in pathological processes associated with chronic eye inflammation.⁸⁴ IL-2 has been demonstrated in the choroid and aqueous humor of patients with idiopathic uveitis, and serum levels have also been found to positively correlate with the aqueous humor levels.^{85,86} In one study, there was a significant increase in IL-2 receptor- α chain expression specifically on CD4⁺ T cells in the peripheral blood analysis of 52 patients with idiopathic posterior uveitis.⁸⁷ Similarly, a selective increase in aqueous humor CD4⁺ T cells has since been reported. This supported the hypothesis that CD4⁺ T cells are involved in more aggressive forms of disease, because inflammation in idiopathic uveitis is often clinically more severe than in uveitis associated with a systemic disease.⁸² Adult patients with idiopathic uveitis have also been shown to have elevated aqueous humor and serum levels of TNF- α ⁸⁸ and IFN- γ , as well as IL-2.⁸⁶ Elevated serum TNF- α levels seem to be positively correlated with recurrent episodes of uveitis of idiopathic origin.⁸⁸ Significantly increased levels of IFN- γ have also been detected in the aqueous humor of patients with chronic idiopathic anterior uveitis,⁸⁹ in the aqueous humor from patients with intermediate idiopathic uveitis in association with a significantly increased CD4⁺ population as compared to FHC,⁹⁰ in vitreous humor-derived T cell lines from patients with idiopathic intermediate uveitis,⁹¹ and in the choroid of patients with idiopathic uveitis.⁸⁵ Raised MHC class I and II

Table 1. Cytokines in ocular fluids or cells (aqueous humor, vitreous) in uveitis.

Cytokine	Aqueous humor	Vitreous
IL-1	↑ Sarcoid [9] ^{*95}	↑ Idiopathic [2/5] ⁸⁴
IL-2	↑ Idiopathic [7] ⁸⁶ ↑ BD [3] ⁸⁶ ↓ BD [4] ¹³ ↑ AS [5] ⁸⁶ ↑ FHC [1] ⁸⁶ ↓ FHC [5] ¹³	↑ Idiopathic [10] ^{*91}
IL-6	↑ Idiopathic [7], ¹¹² [23], ¹³ [5] ⁸⁴ ↑ BD [3], ¹¹³ [4], ¹³ [3] ¹¹⁸ ↑ Sarcoid [1], ^{*95} [8] ¹¹⁸ ↑ VKH [2], ^{*95} [2] ^{†151} ↑ AS [5] ¹¹³ ↑ FHC [2], ¹¹³ [9/11] ¹¹⁸	↑ Idiopathic [5], ⁸⁴ [11/19] ⁹² ↑ BD [3] ¹¹⁸ ↑ Sarcoid [8] ¹¹⁸ ↑ FHC [9/11] ¹¹⁸
IFN-γ	↑ Idiopathic [23] ¹³ [7] ⁸⁶ Idiopathic < FHC [18], ⁹⁰ [10] ⁹⁰ ↑ BD [3] ⁸⁶ ↑ VKH [1] ^{*95} ↑ AS [5] ⁸⁶ ↑ FHC [1] ⁸⁶	ND
TNF-α	↑ Idiopathic [7] ⁸⁸ ↑ BD [3] ⁸³ ↑ AS [5] ⁸³ ↑ FHC [2] ⁸³	ND
IL-10	↓ Idiopathic [8] ⁸² ↑ FHC [4] ⁹⁰	↓ Idiopathic [4] ^{*91}
TGF-β	↓ Idiopathic [23] ¹³ ↑ BD [4] ¹³	ND

↑/↓ change as compared to equivalent control fluid unless otherwise specified.

[x] Number of patients.

* From T cell clones.

† From 2 melanoma-specific cytotoxic T lymphocyte populations.

ND Not done.

expression in iris biopsies was additionally noted in one study in conjunction with raised aqueous humor IFN-γ in idiopathic anterior uveitis.⁸⁹ Multiplex analysis has recently enabled the detection of significant increases in IL-6, IL-8, MCP-1, as well as IFN-γ, in the aqueous humor of patients with idiopathic uveitis, as compared to non-inflammatory control aqueous humor. The levels of each of these four cytokines/chemokines also correlated positively with each other.¹³ TGF-β₂ has been detected in patients with idiopathic uveitis at significantly lower levels than in control groups.^{13,92} Inversely, a significantly reduced TGF-β was found to negatively correlate with IL-6,¹³ which is consistent with experimental work,⁴⁴ and also with IL-8.¹³ IL-6 has been detected in vitreous, as well as aqueous humor aspirates of patients with idiopathic uveitis.⁸⁴ More specifically, vitreous increases in IL-6 have been detected in patients with active intermediate and posterior uveitis,⁹³ reflective of on-going

inflammation during disease. Its role in the pathogenesis and/or propagation of uveitis has been proposed,⁹³ but selective therapies that target the regulation of IL-6, such as an anti-IL-6 mAb, need to be demonstrated to reduce disease activity. Furthermore, in patients with recent onset uveitis, apoptotic lymphocytes have been found to be absent in their aqueous humor. It is, therefore, proposed that combinations of IL-6 and IL-6 receptors are highly effective inhibitors of T cell apoptosis mediated by uveitis aqueous humor.⁹⁴ In addition to being found in the aqueous humor of patients with anterior uveitis, increased serum IL-8 levels have been associated with increased disease activity in idiopathic intermediate uveitis.^{79,95}

In humans, IL-4 has only been detected in low levels and at levels not significantly different from controls in the aqueous humor and serum of patients with idiopathic uveitis.⁸⁶ It has

also been found to be produced at low levels by T cells derived from the vitreous humor of patients with uveitis.⁹¹ A recent study also showed that there were no significant differences in aqueous humor IL-4 levels between anterior uveitis, panuveitis and control groups, but that IL-5 was significantly not detected in the panuveitis groups with idiopathic uveitis as compared to controls and those with idiopathic anterior uveitis.¹⁴ A decrease in aqueous humor IL-10 has been demonstrated in conjunction with an increase in activated CD4⁺ T cells in anterior uveitis, which could partially explain why in acute anterior uveitis, the inflammation is more severe.⁸² Another study, however, showed that levels of IL-10 were found to be not significantly different from controls in patients with anterior uveitis and those with panuveitis.¹³

Studies determining whether polymorphisms in genes are critical to the inflammatory process are few in idiopathic uveitis, but TNF- α , lymphotoxin- α , TNFR1 and TNFR2 gene polymorphisms in patients with idiopathic anterior uveitis have been recently investigated, and a significant increase in the TNF-857T allele has been found. This polymorphism may be linked to an alteration in the binding of a repressor in the promoter region of the TNF gene.⁹⁶ Additional analysis of the 874T allele of the IFN- γ gene, which reflects a constitutively higher production of IFN- γ , has shown that it is more prevalent in patients with idiopathic intermediate uveitis as compared to controls.⁹⁷ A significant association between IL-10-1082 AA homozygosity and poor visual outcome has also been shown.⁹⁷ Combined IFN- γ 874TA or TT genotype along with the IL-10-1082AA genotype has been shown to be prevalent in up to 75% of patients with idiopathic intermediate uveitis with poor visual outcomes.⁹⁷

Behçet's Disease

Behçet's disease (BD) is a systemic vasculitis of unknown origin that affects veins and arteries of all sizes, producing recurrent mucocutaneous lesions and frequent ocular involvement. This is characterized by severe uveitis often with hypopyon and ischemic

retinal vasculitis (figure 1). Musculoskeletal, neurological and gastrointestinal manifestations are also seen.⁹⁸ It presents more commonly in males 20 to 30 years of age, and the prevalence is highest in Turkey, the Middle East, Japan and Korea.⁹⁸

BD has been associated with the HLA-B51 phenotype, but the strength of this association varies worldwide. Thus, the diagnosis is currently clinically based.⁹⁸ HLA-B51 has been associated with neutrophil hyperfunction, as evidenced by increased superoxide production in affected individuals.⁹⁹ HLA-B5101, in particular, and HLA-B5102, to a lesser degree, have been associated with ocular BD, as has the extended haplotype, B51-DR5-DQW3.^{100,101} Some cases have been associated with the MHC class I chain-related molecule A gene located near the B51 gene.¹⁰² Heat shock proteins (HSP) are elevated in BD and have been found to upregulate the expression of the MHC class I chain-related molecule A locus. The human HSP60 has been capable of inducing uveitis in rats,¹⁰³ in Japanese patients with BD,¹⁰⁴ and in Turkish patients with BD¹⁰⁵ with increased T cell proliferation to HSP antigens detected in association with increased mRNA for IL-8, TNF- α and TNF- β .¹⁰⁴ Gamma- δ T cells, which are activated by HSP, have been found to be elevated in ocular BD.¹⁰⁶ They are also responsive to viral or bacterial phosphoantigens¹⁰⁷ and superantigens¹⁰⁸ that are produced by infectious organisms such as streptococci,¹⁰⁹ which are implicated in the pathogenesis of BD. The TNF promoter allele TNF-1031C has been recently reported to be associated with BD susceptibility in Caucasoid patients,¹¹⁰ and the co-expression of the TNF- β *2 allele with HLA-B*51 has also been found to contribute to the severity of ocular disease.¹¹¹ More recently, it has been shown that susceptibility to BD has also been documented to be significantly increased in patients carrying the IL-1 β +3953T allele and TT genotype, which correlate with increased IL-1 β secretion *in vitro*.¹¹²

IL-1 β levels appear to be not significantly different from controls in the aqueous humor of BD-associated uveitis in a

Figure 1. Uveitis in Behçet's disease. (A) Red eye with white fluid level in anterior chamber (hypopyon). (B) Area of retinal vascular ischemia and inflammation causing retinitis (white) and hemorrhage (red).

Figure 2. Uveitis in sarcoidosis. (A) Multifocal choroiditis (as shown by the pigmented scars). (B) Right optic nerve is swollen with a granuloma as compared to the left nerve which is normal.

recent study of five samples, but it is not clear whether these patients were on treatment at the time of sampling.¹³ Significantly raised IL-2, IL-6, IFN- γ and TNF- α levels have, however, been found in the aqueous humor and serum of patients with uveitis and BD.^{86,88,113} Elevated serum levels of IL-2 receptors,¹¹⁴ IL-6, IL-8, TNF- α ,¹¹⁵ IFN- γ ¹¹⁶ and MIP-1 α ¹¹⁷ have also been found by others, while IL-6 has also been detected in vitreous humor aspirates.⁸⁴ Aqueous humor IL-8 detected with the multicytokine assay was significantly increased in comparison with controls.¹³ Furthermore, significant positive correlations appear to exist between elevated serum TNF- α levels and recurrent episodes of uveitis associated with BD.⁸⁸ It is difficult, however, to determine whether these cytokine abnormalities detected in the serum are related to the uveitis associated with BD or, in fact, reflect ongoing systemic disease.

In uveitis associated with BD, only minimal concentrations of IL-4 have been detected in the aqueous humor^{86,118} and vitreous humor,¹¹⁸ which do not significantly differ from controls. IL-5 and IL-10 detection by multiplex analysis has revealed the aqueous humor levels in uveitis associated with four patients with BD to be not significantly different from that of controls.¹³ Aqueous and vitreous humor levels of IL-10

were also reported as unchanged from controls in four patients with BD-associated uveitis.¹¹⁸ Significant reductions of TGF- β have, however, been detected as compared to controls. As in idiopathic uveitis, these reductions in TGF- β again inversely correlated with IL-6 and IL-8.¹³

Sarcoidosis

Sarcoidosis is a common granulomatous inflammatory disorder of unknown cause that typically affects the respiratory system but can also involve the skin, eyes, neurological system, and liver. Studies have put the incidence of sarcoidosis at 6 to 10 per 100,000^{119,120} with an increased incidence among Swedes and Afro-Americans.¹²¹

Although numerous HLA associations in sarcoidosis have been reported, and the results are not clear cut,¹²² the HLA region is strongly implicated in its pathogenesis.¹²³ As the lung is a common site of involvement in this disease, the phenotypic profile of T cells from bronchoalveolar lavage has shown an increased CD4⁺/CD8⁺ ratio, which may aid in its diagnosis.¹²⁴ Raised bronchoalveolar lavage levels of IFN- γ , TNF- α ,¹²⁵ IL-12,¹²⁶ IL-6 and IL-8¹²⁷ have all been detected, while only a few cells positive for IL-4 have been observed, suggesting a polarization towards a Th1 cytokine profile.¹²⁵ With successful corticosteroid treatment, the balance between Th1 and Th2 has been restored.¹²⁸ Different polymorphisms of cytotoxic T-lymphocyte antigen 4 which affect T cell activation and cytokine secretion have, however, been associated with different end organ manifestations in sarcoidosis including those with ocular sarcoidosis predominance.¹²⁹ Although a polymorphism has been found in the TNFA2 allele to be significantly associated with Lofgren's syndrome, the acute pulmonary form of the disease with frequent spontaneous remission, the suggestion that the gene for TNF- α was etiologically associated with sarcoidosis has been largely discounted and explained by linkage disequilibrium.¹³⁰ Polymorphisms have also been identified for the cytokines IL-1¹³¹ and the CC chemokine receptors, CCR2¹³² and CCR3.¹³³ HSP70 has been detected in the eyes of Lewis rats in experimental autoimmune uveitis,¹³⁴ and circulating antibodies to inducible HSP70 have also been found in patients with uveitis associated with sarcoidosis as well as BD.¹³⁵ HSPs from various infectious pathogens may induce disease through molecular mimicry, and as such, $\gamma\delta$ T cells that are reactive against HSPs have been associated with sarcoidosis.¹³⁶ Inhaled antigens have been studied, and evidence has been found for the presence of airborne typical and atypical mycobacteria.¹³⁷ Only histological examination of affected tissue, however, can confirm clinical diagnosis.¹³⁸

Intraocular sarcoidosis can present as acute or chronic uveitis, and typical signs include acute anterior uveitis, chronic anterior uveitis, intermediate uveitis, multifocal choroiditis, retinal vasculitis and optic disc swelling¹³⁹ (figure 2). In those patients who present with classic ocular signs without evidence of disease in other organ systems, there are neither predictors for which patients will go on to develop systemic

Figure 3. Uveitis in Vogt-Koyanagi-Harada (VKH) disease. (A) Swollen pink optic nerve with white granulomas in the choroid. (B) Total serous retinal detachment. Retina is gray instead of pink.

sarcoidosis nor pathognomonic ocular signs to diagnose sarcoidosis. Up to 45% lose vision from the consequences of ocular sarcoidosis.¹⁴⁰

Aqueous humor cytokine studies of patients with sarcoidosis uveitis are few. Nine T cell clones derived from the aqueous humor of a patient with sarcoidosis in one study were shown to produce large amounts of IL-1 α , IL-6 and IL-8 but not TNF- α .¹⁴¹ Analysis of aqueous and vitreous humor samples of eight patients with sarcoidosis has also documented significantly increased levels of IL-6 but unchanged levels of IFN- γ and IL-2 as compared to controls.⁵⁹

No significant differences in the levels of IL-4 have been found as compared to controls in the aqueous humor^{86,118} and vitreous humor¹¹⁸ of patients with sarcoidosis. The expression of TNF- α on peripheral blood CD4⁺ lymphocytes has been documented to be significantly increased in patients with presumed sarcoid intermediate uveitis.¹⁴² High IL-2:IL-5 and IFN- γ :IL-5 ratios were also found in the peripheral blood lymphocyte culture supernatants further illustrating the polarization of the systemic immune response towards Th1 in this type of uveitis.¹⁴² Further cytokine profiling and genotyping studies with greater numbers of patients are required in order to more fully understand the possible differences in cytokine patterns associated with the different polymorphisms present in patients with sarcoidosis and ocular disease.

Vogt-Koyanagi-Harada Disease

Vogt-Koyanagi-Harada disease (VKH) is a chronic, bilateral panuveitis associated with aseptic meningitis, vitiligo, alopecia and poliosis.¹⁴³ VKH is one of the most common causes of uveitis in Japan, and women are more affected than men. It typically has a prodromal neurological and auditory phase, characterized by headache, fever, hyperacusis,

dysacusis and tinnitus followed by severe panuveitis several days later.¹⁰⁸ The exact cause of this condition remains unknown, but cell-mediated autoimmunity directed against a melanocyte antigen, which may be a member of the tyrosinase family of proteins, appears to be the common mechanism.¹⁴⁴ VKH is associated with HLA-DR1 and HLA-DR4,¹⁴⁵ highly related to HLA-DRB1*0405 in people of Japanese and Asian heritage.^{146,147} In experimental models, tyrosinase family proteins have been documented to induce an autoimmune disease that strongly resembles VKH.¹⁴⁸ Furthermore, T cell clones specific to the tyrosinase family of proteins have been isolated from patients with VKH, and some of these clones have shown proliferative responses to peptides that match the motif of the strong binding site for HLA-DRB1*0405.¹⁴⁹

Uveitis is a feature of VKH and is an acute onset panuveitis characterized by multifocal choroiditis, serous retinal detachments and pink, swollen optic discs¹⁵⁰ (figure 3). The presence of uveitis usually leads to the diagnosis being considered and is a serious threat to vision, representing the major morbidity of the disease.⁹⁸ Cytokine studies on ocular fluids are scarce, but significantly increased levels of IL-6 have been found in the aqueous humor of VKH with the level of IL-6 in the aqueous humor correlating with the number of lymphocytes in the aqueous humor, reflecting the severity of the inflammatory response.¹⁵¹ T cell clones from the aqueous humor of two patients with VKH have been demonstrated to produce significantly larger amounts of IL-8, IFN- γ and IL-6.¹⁴¹ Levels of IL-1, however, were not significantly different from controls.¹⁴¹ Serum cytokine profiling of patients with VKH has shown a parallel increase in the expression of IFN- γ .¹⁵² Elevated serum levels of macrophage migration inhibitory factor in patients with VKH and uveitis have also been documented with high aqueous humor migration inhibitor factor detected at the onset of

Figure 4. Uveitis in ankylosing spondylitis. (A) Eye is red. (B) Shows magnified view with active inflammatory cells on the back of the cornea (keratic precipitates).

experimental autoimmune uveitis.¹⁵³ More recently, it has been shown that patients with VKH who are sensitized to melanocyte epitopes display a peptide-specific Th1 cytokine response with no IL-4 production in peripheral blood.¹⁵⁴ Levels of IL-5 in the serum of VKH patients also do not significantly differ from those of controls.¹⁵⁴

Ankylosing Spondylitis

Ankylosing spondylitis is a chronic inflammatory disease of the axial skeleton with variable involvement of peripheral joints and non-articular structures. It is the most common among a group of diseases known as the seronegative spondyloarthropathies. Extra-articular manifestations of ankylosing spondylitis besides uveitis include aortitis, heart block and fibrocystic pulmonary disease.¹⁵⁵

The association between HLA-B27 and ankylosing spondylitis is well known. The HLA-B27 molecule, when appropriately loaded with peptides of microbial or self-origin, presents them to CD8⁺ T cells. With disease in ankylosing spondylitis, molecular mimicry may underlie the pathogenesis such that antibodies directed against foreign antigens arising during an infection are cross-reactive with HLA-B27.¹⁵⁶ Abnormal forms of HLA-B27 may then present microbial or self-peptides to CD4⁺ T cells possibly involved in class I immune recognition and NK cells rather than CD8⁺ T cells.^{157,158} Peptides from HLA-B27 have sequence homology with peptides from enterobacteria¹⁵⁹ and Chlamydia¹⁶⁰ with the latter also documented to possibly reactivate autoreactive cytotoxic T cells with specificity for HLA-B27. TNF- α ,¹⁶¹ TGF- β ¹⁶² and IL-1¹⁶³ polymorphisms have also been confirmed as possible candidate genes for susceptibility to ankylosing spondylitis. A recent study of patients with HLA-B27-associated anterior uveitis identified an association between HLA-B27 and the alleles TNF-1031 and TNF-308,⁹⁶ strongly suggesting linkage disequilibrium between HLA-B27 and TNF-308. The TNF-308 allele has

previously been reported to be associated with a higher level of TNF- α production.¹⁶⁴ There also appears to be a trend between HLA-B27-positive patients with the TNFRSF1-201T and TNFRSF1-1135T alleles and a greater number of inflammation-related complications such as poor response to steroids, secondary cataract, cystoid edema and need for surgery.⁹⁶ A CCL2-251A>G polymorphism for increased MCP-1 synthesis was found in HLA-B27-positive patients with acute anterior uveitis but not the healthy HLA-B27-positive controls, suggesting that it may also play a role.¹⁶⁵

Uveitis associated with ankylosing spondylitis usually presents as an acute unilateral anterior type (figure 4) but can be bilateral.¹⁶⁶ Increased aqueous humor and serum IL-2 and IFN- γ have been demonstrated, however, in patients with ankylosing spondylitis uveitis.⁸⁶ Corresponding serum and aqueous humor elevations of TNF- α have also been detected in patients with ankylosing spondylitis and anterior uveitis.¹⁶⁷ A greater elevation of IL-6 in aqueous humor as compared to serum has been reported.¹¹³ Serum cytokine assays have revealed ankylosing spondylitis to be associated with increased TNF- α ,¹⁶⁸ as well as IL-6^{168,169} but not IL-1 β or IFN- γ .¹⁶⁸ A close correlation between serum IL-6 and disease activity and severity has also been demonstrated.¹⁶⁸

IL-4 has been detected at levels not significantly different from controls in the aqueous humor and serum from five patients with ankylosing spondylitis;¹⁶⁸ however, in another series of patients with ankylosing spondylitis, IL-4 has been noted in serum samples to be significantly decreased.¹⁶⁹ A possible linkage between increased IL-5 and an infectious causation with *Candida albicans* for HLA-B27 positive ankylosing spondylitis has also been proposed.^{14,170}

Fuch's Heterochromic Cyclitis

Fuch's heterochromic cyclitis (FHC) is a chronic, usually unilateral, anterior segment uveitis syndrome that is relatively

benign.¹⁷¹ It is usually painless with limited inflammation characterized by diffuse, scattered, small- and medium-sized keratic precipitates with anterior chamber flare, minimal anterior chamber cells, and iris atrophy that leads to heterochromia (figure 5).

Various theories as to the etiology of FHC have been put forward, including adrenergic dysfunction with the iris hypopigmentation linked to denervation of iris stromal melanocytes, as in Horner's syndrome.^{172,173} Peripheral chorioretinal scars documented by FHC have been attributed to toxoplasmosis¹⁷⁴ as well as *Toxocara*,¹⁷⁵ but the incidence of toxoplasmosis is known to vary widely between populations, with the significance of retrospective reporting of chorioretinal scars questioned.¹⁷⁶ Herpes simplex virus has also been proposed to have a role,¹⁷⁷ but subsequent studies failed to detect herpes simplex virus genome or antibodies.¹⁷⁸ No significant positive HLA associations have been found, with monozygotic twin studies showing no concordance.¹⁷⁹

There are few studies profiling cytokines in the ocular fluids of patients with FHC. An increase in IL-2 in the aqueous humor and serum has been documented in one patient with FHC,⁸⁶ but the majority of patients with FHC have been documented as having levels of IL-2 in aqueous humor to be either significantly decreased or unchanged as compared to controls.^{13,118} Vitreous humor levels of IL-2 have also been documented to be not significantly different from controls.¹¹⁸ One study documented elevated TNF- α levels in two patients⁸⁸ but not significantly different from controls in five patients in another study.¹³ A number of patients have been shown to have aqueous humor IFN- γ levels not significantly different from controls,^{13,118} but in one study, levels were elevated in the aqueous humor and serum of one patient.⁸⁶ Furthermore, in a study comparing FHC with idiopathic intermediate aqueous humor specimens, significantly higher levels of IFN- γ were found in the FHC group. There were also larger numbers of aqueous humor specimens with a higher level of IL-10 in the FHC group, possibly downregulating cell-mediated immunity and inflammation, but this was not statistically significant. CD4⁺ T cells were found in significantly fewer numbers in the aqueous humor of the FHC group as compared to the idiopathic group, but CD8⁺ T cells were found at a significantly higher proportion.¹⁸⁰ Vitreous humor-derived T-cell lines from FHC patients have shown increased IFN- γ and IL-10 production with low levels of IL-2 and no IL-4 as compared to peripheral blood-derived T cell lines from the same patients.⁹⁰ Additionally, IL-10 was significantly increased and IL-2 significantly decreased in comparison with the vitreous humor-derived T-cell lines from patients with idiopathic intermediate uveitis, which may be consistent with the less aggressive clinical course seen with FHC. A significantly higher percentage of CD4⁺ T cells were also present in the T-cell lines derived from patients with idiopathic uveitis as compared to those with FHC.⁹¹ A positive correlation between IL-4 and IL-5 has also been demonstrated with IL-6 levels unchanged as compared to

Figure 5. Uveitis in Fuch's heterochromic cyclitis (FHC). Typical appearance of small white keratic precipitates all over back of cornea in a white eye.

controls but significantly decreased as compared to patients with idiopathic uveitis.^{13,14} In the aqueous humor of FHC uveitis patients, TGF- β 2 has been detected at significantly lower levels than control groups. A greater proportion of patients with FHC had detectable TGF- β 2 levels compared to those patients with different uveitis entities, although this was not statistically significant.⁹² Patients with FHC also have a non-significant trend towards raised levels of IL-8 and MCP-1 in the aqueous humor¹³ and raised levels of IL-8⁹⁵ in the serum as compared to patients with idiopathic uveitis. The relatively raised levels of TGF- β 2 combined with relatively decreased levels of IL-8 and MCP-1 as compared to idiopathic uveitis could correlate with the lower grade of inflammation associated with FHC.

Unlike other uveitic syndromes, FHC does not respond to corticosteroid therapy. It is suggested that since the beneficial effect of steroids in the control of disease activity may be due to their capacity to increase the spontaneous expression of IL-10, the already raised IL-10 level in aqueous humor precludes further beneficial steroid effects.⁹¹ The significantly decreased CD4⁺ T cell population in FHC could explain this steroid unresponsiveness as compared to idiopathic uveitis, as this T-cell subset is the predominant target of the corticosteroids.⁹¹ The clonal nature and predominance of CD8⁺ T cells in the aqueous humor of patients with FHC is suggestive of an antigen-driven process with a possible viral initiating factor,¹⁸⁰ and indeed the discovery of persistent rubella antibodies and DNA in FHC has suggested that rubella virus could be a causal factor.¹⁷⁸

Conclusion

Much remains to be elucidated with regards to the etiologies of the immune-mediated uveitides, but experimental models have contributed to the understanding that they are largely T cell-mediated. Despite discrepancies between some clinical studies with regards to exact delineation of which uveitis entities were steroid-treated, whether they were topically or

systemically steroid-treated, time-point of fluid collection during an immune response and sensitivity of the various cytokine detection techniques, some conclusions may be drawn. The pro-inflammatory cytokines IL-1 β , IL-2, IL-6, IFN- γ and TNF- α are all implicated in the pathogenesis of the various clinical subtypes of uveitis, with aqueous humor levels positively correlating with serum levels and disease severity. Relative contributions, however, do depend on different disease entities, and much remains to be delineated. IL-6, IFN- γ and TNF- α have been found to be increased in idiopathic uveitis, BD and ankylosing spondylitis. Ankylosing spondylitis, however, appears to be associated with a greater increase in TNF- α , while FHC appears to be associated with a relatively lower increase in IFN- γ . The chemokines IL-8, MCP-1, MIP-1 α , MIP-1 β and fractalkine are also thought to have a role in the recruitment of inflammatory cells in uveitis, with increased levels of IL-8 and MCP-1 being present in entities with greater clinical severity such as idiopathic uveitis, sarcoidosis and BD as compared to FHC. The low levels of IL-4 detected in the aqueous humor from patients with uveitis suggest that this cytokine may not play an important role in the etiology of uveitis in humans. Increased IL-5 levels have been detected in anterior uveitis associated with ankylosing spondylitis, as well as FHC, and may be commensurate with their possible infectious etiologies and less aggressive course, but the significance of this association remains to be proven. IL-5 has also been detected at low levels in anterior uveitis but appears to be absent in panuveitis where there is greater uveal tract involvement. Investigation into its possible therapeutic benefits would be of interest in panuveitis. IL-10 is important in the differentiation and function of T regulatory cells, which suppress Th1 immune responses in uveitis. IL-10 levels in aqueous humor appear to be decreased in uveitis but are raised following steroid administration and increase proportionately with IFN- γ in FHC. T cell cytokine profiling, along with genotyping for cytokine polymorphisms, has enabled a greater understanding of the immunopathogenic mechanisms involved with advances in multi-cytokine detection, enabling a more in-depth analysis of Th1 and Th2 immune responses *in vivo*. The resultant successful application of cytokine-specific immunotherapies, such as anti-TNF- α , has provided clinicians an expanded armamentarium with which to more specifically target and safely combat the different forms of uveitis.

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