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Ocular Immune Privilege in the Year 2010: Ocular Immune Privilege and Uveitis

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Abstract

The phrase “immune privilege” was coined by Peter Medawar to describe the absence of an immune response to allografts placed into the anterior chamber of the eye or brain. We now understand that immune privilege is more than a passive microenvironment with a distinctive anatomical structure that holds back immunity. The ocular microenvironment actively engages the immune system with immunosuppressive biochemical mechanisms. The unique characteristics of ocular immune privilege appear designed to protect the eye from damage while preserving foveal vision, thus providing the host with a definite survival advantage. However, the protection is not always sufficient and the eye becomes susceptible to uveitis. Uveitis is an intraocular inflammatory disorder that encompasses a wide range of underlying etiologies. It may be idiopathic or associated with systemic disease or infection. Understanding the biochemistry of immune privilege has the potential to identify its weaknesses that allow for immunity to break through.

Keywords

adaptive immunity; autoimmunity; immune privilege; innate immunity; uveitis

In 1948 Medawar described the prolonged survival of skin allografts within the anterior chamber of the rabbit eye.[1] He observed that the grafts survived as along as new vessels did not grow into the transplanted tissue. Thus, he defined the concept of immune tolerance as “immunologic ignorance”— namely, the lack of sensitization of the host because of the absence of direct lymphatic drainage and the presence of a blood–ocular barrier. He reasoned that the transplanted tissue was afforded immune privilege through a passive mechanism of immunologic ignorance. In 1977 Kaplan and Streilein showed that the immune system of the host was not ignorant of alloantigens placed into the anterior chamber, rather an aberrant immune response developed.[2] The placement of alloantigen into the anterior chamber induced an effector immune response characterized by the induction of antigen-specific suppressor cells, specifically, the induction of antigen-specific efferent suppressor CD8 T cells and afferent suppressor CD4 T cells, now called T_{reg} (T regulatory) cells.[3]

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Concomitant with the induction of T_{reg} cells was the production of non-complement-fixing antibodies.[4] The term anterior chamber-associated immune deviation (ACAID) was used to describe this novel response since placement of the same alloantigens into other organs (e.g., skin) induced a potent delayed-type hypersensitivity response. The induction of ACAID required that the spleen be intact for at least 4 days after inoculation of the antigen into the anterior chamber, and that the eye containing the antigen not be removed before 2 days.[5] The induction of T regulatory cells is a complex process mediated by F4/80 macrophages that present the inoculated antigen to a cluster of B cells, NKT cells, and CD4 and CD8 T cells in the spleen.[6–8]

Induction of ACAID is also dependent on an intact sympathetic nervous system through a strong link in mice between the sympathetic nervous system and the generation of suppressor T cells that mediate ACAID.[9,10] Sympathetic denervation of the eye itself does not cause or promote spontaneous uveitis. In the denervated eyes there is a significant drop in TGF-β concentration in the aqueous humor; however, the levels of TGF-β remain well above the levels needed for TGF-β-mediated immunosuppression.[10] Since the methods used to denervate affect more than just the eye, it is uncertain if a lack of sympathetic innervation is directly or indirectly mediating a loss in the ACAID response. In addition, as we discuss below, cultured iris, ciliary body, and retinal pigment epithelial cells in culture with an obvious absence of sympathetic innervation continue to effectively mediate immunosuppression. The induction of ACAID demonstrates that the regulation of immunity to intraocular antigens is more than anatomical isolation of the ocular microenvironment.

While the ACAID response can be seen only when induced under laboratory conditions, the healthy ocular microenvironment is constitutively rich with immunosuppressive molecules that influence the immune response. The aqueous humor in the anterior chamber contains the neuropeptides α-MSH, VIP, somatostatin, the cytokine TGF-β_2, and molecules such as indoleamine, as well as cell surface expression of FasL to suppress the activation of Th1 cells.[11–16] In addition, cultured pigment epithelial cells of the iris, ciliary body, and retina through contact (PD-L1, CTLA-2α) and soluble factors can suppress Th1 cell activation, and possibly induce T_{reg} cell functionality.[17–21] These various soluble factors and cell surface expressed molecules, as well as others, suppress the recruitment of neutrophils and macrophages into the anterior chamber, the activation of the inflammatory cascade in macrophages, and the activation of NKT-cells.[22–24] Other soluble proteins, such as thrombospondin, also contribute to ocular immune privilege through the local activation of TGF-β.[25] Which of these factors are important for the ocular microenvironment to prevent or suppress uveitis remains to be seen; however, the abundance of immunosuppressive molecules produced by the cells of the ocular microenvironment strongly indicates that there is a robust blockade to the induction of inflammation.

More recently, the interaction of innate and adaptive immunity in the generation of a host immune response, including the T_{reg} cell response, has been recognized. A major component of innate immunity is the complement cascade, which consists of over 30 fluid phase and cell membrane proteins.[26] Since inadvertent activation of complement can result in a destructive, pro-inflammatory immune response, complement-regulatory proteins (CRPs) serve to regulate the complement cascade in an efficient manner. There is constant activation of the complement cascade within the anterior chamber of the eye.[27] The complement activation products iC3b and membrane attack complex (MAC) are present in the normal eye, as well as both membrane-bound and soluble CRPs. Thus, the complement system is continuously active at a low level in the normal eye, presumably as a protective mechanism, but is very finely regulated by the presence of CRPs. It was observed that iC3b induces the secretion of TGF-β_2 and interleukin-10 by antigen-presenting cells (APC) while downregulating IL-12.[28] The injection of neutralizing monoclonal antibodies to CRPs

results in the development of a severe anterior uveitis, with increased formation of iC3b and MAC. Thus, demonstrating the importance of regulation by CRPs to both maintain ocular immune privilege and protect ocular cells from destruction by products released during intraocular inflammation. Complement is only one component of innate immunity important in the ocular immune response. Most recently, the role of toll-like ligands in the breach of ocular immune privilege has been identified. More details soon will undoubtedly indicate the important role such molecules play in control of the autoimmune response to organ-specific antigens, such as ocular-specific antigens.[29]

Antigen-specific T cells treated in vitro with aqueous humor will demonstrate a change in profile from IFN-γ-producing T cells to TGF-β-producing T cells.[30] A similar effect is observed when antigen activation of such T cells occurs in the presence of α-MSH and TGF-β_2.[31] These T cells no longer function as delay-type hypersensitivity effector T cells, but as T_{reg} cells. Additionally, effector T cells entering the eye may undergo apoptosis upon contact with cells in the ocular microenvironment that express FasL.[16] The effect of aqueous humor on APC function has also been studied in detail, including the effect of TGF-β_2, α-MSH, and CGRP (calcitonin gene-related peptide) on the inflammatory activity of macrophages.[32,33] α-MSH-treated APC cannot activate Th1 cells, and they suppress IFN-γ production by Th1 cells. All these mostly in vitro assays for immunosuppression have demonstrated that the intact ocular microenvironment has a wide range of immunomodulating mechanisms to regulate immunity and suppress inflammation to protect vision.

Uveitis is a general term for intraocular inflammatory disorders that involve the uveal tract and encompasses a wide range of underlying etiology. It may be idiopathic, associated with systemic disease, or result from a variety of infectious agents. Uveitis is responsible for over 2.8% of blindness in the United States. Each year, 17.6% of active uveitis patients experience a transient or permanent loss of vision with 12.5% developing glaucoma.[34] An incidence rate of uveitis of 17/100,000 person-years and a prevalence ratio of 204/100,000 over a 10-year period has been reported.[35] However, recent reports suggest a higher disease rate for an older population, particularly women, with a higher incidence of chronic disease.[36] Recurrence rates after an initial episode of uveitis in Great Britain showed that 11.3% of patients had at least one recurrence within 5 years, with 2.5% experiencing a second recurrence during this period.[37]

Although several animal models of uveitis have been developed, the most studied model of intraocular inflammation is experimental autoimmune uveoretinitis (EAU). Most frequently, EAU has been induced in inbred rodents with various retinal proteins —e.g., retinal soluble antigen (retinal S antigen), interphoto-receptor retinoid binding protein (IRBP), rhodopsin, or phosducin.[38–40] Although the severity of the EAU can be altered by the dose of retinal protein used for sensitization, as well as the accompanying adjuvant, the inflammation produced is primarily confined to the posterior segment of the eye. Most recently, the pathogenic antigen in acute anterior uveitis in rodents has been purified to homogeneity.[41] This uveitic antigen is a 22-kDa fragment of the bovine type I collagen α-2 chain. This immunogen was different from type I collagen in other organs because of the carbohydrates bound to the molecule. Thus, local ocular disease involving collagen could occur without manifestations of systemic disease—e.g., articular joints.

Although human acute anterior uveitis has been historically characterized as a collagen disease,[34] this is the first time that collagen has been identified as the target autoantigen in uveitis. There are spontaneous models of uveitis in mice where central tolerance has been altered.[42,43] These models suggest that an inability for central tolerance to clonally delete ocular-autoantigen-specific T cells or select for T_{reg} cells promotes expansion of ocular-

autoantigen-specific effector T cells that target the retina. All together the methods of inducing experimental autoimmune uveitis require expansion of ocular-autoantigen-specific effector T cells though either adjuvant-mediated immunization or knocking out central tolerance. These expanded effector T cells find their way into the eye, and must either overwhelm, override, or take advantage of a change in the local ocular immunosuppressive mechanisms.

When autoimmune intraocular inflammation (i.e., EAU) occurs there has been an obvious breach of the immunosuppressive ocular microenvironment. Study of the changes that occur in EAU have revealed that before the onset of the detection of intraocular inflammation, the aqueous humor has lost its immunosuppressive properties and pro-inflammatory cytokines have appeared.[44] These pro-inflammatory cytokines were found in the aqueous humor up to the peak of the disease, although the immunosuppressive properties of the aqueous humor were reestablished before the height of intraocular inflammation. As expected, the ocular microenvironment no longer supported ACAID at the onset of inflammation and did not recover its ability to promote ACAID until after the disease started to resolve. These observations confirmed that the some aspects of the normal immunosuppressive microenvironment of the eye were abrogated during an acute inflammatory response. However, this loss of immunosuppression was short-lived and resulted in the return of immune privilege with the control of intraocular inflammation.

There are in the post-EAU spleens ocular autoantigenspecific T_{reg} cells.[45] The T_{reg} cells are not present in enucleated mice that are immunized for EAU and nor are these T_{reg} cells present in mice that have the melanocortin 5 receptor knocked-out (MC5r), a receptor for α-MSH.[45,46] These T_{reg} cells are $CD25^+CD4^+$ inducible T_{reg} cells that can suppress EAU following adoptive transfer into mice immunized to induce EAU. Unlike ACAID, the regulatory activity cannot be transferred with the post-EAU $CD8^+$ T cells; but, similar to ACAID, a post-EAU spleen APC is needed to reactivate the $CD25^+CD4^+$ T_{reg} cells. Whether this natural induction of tolerance works through similar or different mechanisms as ACAID is to be determined. Mice with the MC5r knocked out are no more susceptible to EAU than wild-type mice; however, the knockout mice have no resistance to induction of a second episode of EAU.[46] This suggests that it is the factors within the ocular microenvironment that reimpose immunosuppression in the initial episode of EAU, and the by-product of this suppression is the induction of tolerogenic T cells. It would appear that the effector or regulatory function of these T cells is dependent on very subtle microenvironmental interactions.

Although the animal models of uveitis have significantly advanced our understanding of the molecular mechanisms of ocular immune privilege, there are still many unanswered questions. Unlike the animal models, which allow for a continuous analysis of the kinetics of uveitis, being able to characterize uveitis in humans has been limited to discrete times usually when ocular surgery is needed. Furthermore, the uveitis induced in the rodent models is of a known imposed etiology, whereas in humans there is the potential for multiple causes of uveitis. This has filled the literature with unclear and sometimes contradictory characterizations of the ocular microenvironment in human uveitis.[47–57] What is clear is that during uveitis in humans there is a significant intraocular expression of pro-inflammatory cytokines, chemokines, and activated complement similar to what is seen in the animal models of EAU.[47,58] However, we still do not know what mechanisms of ocular immune privilege are most important in the loss of intraocular immunosuppression, and in the recurrence of autoimmune uveitis. Furthermore, we do not know what characteristics of ocular immune privilege can be restored by reintroducing immunomodulating neuropeptides or soluble surface molecules, or inhibiting complement activation, and whether they are sufficient to protect the eye. Also, does effective treatment to prevent recurrence of uveitis

need to both reestablish immune privilege in the ocular microenvironment and reestablish systemic immune tolerance to ocular autoantigens? The similarity between the animal models of autoimmune uveitis and human endogenous uveitis suggest that there must be at least two parts to the induction of autoimmune uveitis. There is the expansion of effector T cells caused by a failure of central tolerance or peripheral immunity to clonally delete and suppress ocular-autoantigenspecific effector T cells, and there is an inhibition of one or more mechanisms of ocular immune privilege. Whether these occur simultaneously or in sequence, or one causes the other is to be determined.

There are in the eye endogenous mechanisms to minimize the collateral damage of inflammation caused by autoimmunity or by infection to preserve the clarity of the visual axis, and the integrity of the fovea. The eye, as well as the central nervous system, has evolutionarily developed novel immune privilege microenvironments to suppress the destruction of cells critical to the survival and normal function of these organs. Our ability to rapidly reestablish an immunosuppressive microenvironment within the eye following intraocular inflammation will be of significant benefit in preserving vision.

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REFERENCES

[1]. Medawar P. Immunity to homologous grafted skin, III: the fate of skin homografts transplanted to the brain to subcutaneous tissue, and to the anterior chamber of the eye. Br J Exp Pathol. 1948; 29:58–69. [PubMed: 18865105]

[2]. Kaplan HJ, Streilein JW. Immune response to immunization via the anterior chamber of the eye, I: F1 lymphocyte induced-immune deviation. J Immunol. 1977; 118:809–814. [PubMed: 321682]

[3]. Streilein JW. Ocular immune privilege: the eye takes a dim but practical view of immunity and inflammation. J Leukoc Biol. 2003; 74:179–185. [PubMed: 12885934]

[4]. Wilbanks GA, Streilein JW. Distinctive humoral immune responses following anterior chamber and intravenous administration of soluble antigen: evidence for active suppression of IgG2-secreting B lymphocytes. Immunology. 1990; 71:566–572. [PubMed: 2149124]

[5]. Kaplan HJ, Streilein JE. Immune response to immunization via the anterior chamber of the eye, I: F1 lymphocyte induced-immune deviation. J Immunol. 1977; 118:809–814. [PubMed: 321682]

[6]. Lin HH, Faunce DE, Stacey M, et al. The macrophage F4/80 receptor is required for the induction of antigen-specific efferent regulatory T cells in peripheral tolerance. J Exp Med. 2005; 201:1615–1625. [PubMed: 15883173]

[7]. Sonoda KH, Stein-Streilein J. Ocular immune privilege and CD1d-reactive natural killer T cells. Cornea. 2002; 21:S33–S38. [PubMed: 11995808]

[8]. D'Orazio TJ, Niederkorn JY. Splenic B cells are required for tolerogenic antigen presentation in the induction of anterior chamber-associated immune deviation (ACAID). Immunology. 1998; 95:47–55. [PubMed: 9767456]

[9]. Li X, Taylor S, Zegarelli B, Shen S, O'Rourke J, Cone RE. The induction of splenic suppressor T cells through an immune-privileged site requires an intact sympathetic nervous system. J Neuroimmunol. 2004; 153:40–49. [PubMed: 15265662]

[10]. Vega JL, Keino H, Masli S. Surgical denervation of ocular sympathetic afferents decreases local transforming growth factor-beta and abolishes immune privilege. Am J Pathol. 2009; 175:1218–1225. [PubMed: 19700755]

[11]. Taylor AW, Streilein JW, Cousins SW. Identification of alpha-melanocyte stimulating hormone as a potential immunosuppressive factor in aqueous humor. Curr Eye Res. 1992; 11:1199–1206. [PubMed: 1490338]

[12]. Taylor AW, Streilein JW, Cousins SW. Immunoreactive vasoactive intestinal peptide contributes to the immunosuppressive activity of normal aqueous humor. J Immunol. 1994; 153:1080–1086. [PubMed: 8027541]

[13]. Taylor AW, Yee DG, Streilein JW. Suppression of nitric oxide generated by inflammatory macrophages by calcitonin gene-related peptide in aqueous humor. Invest Ophthalmol Vis Sci. 1998; 39:1372–1378. [PubMed: 9660485]

[14]. Taylor AW, Yee DG. Somatostatin is an immunosuppressive factor in aqueous humor. Invest Ophthalmol Vis Sci. 2003; 44:2644–2649. [PubMed: 12766068]

[15]. Ryu YH, Kim JC. Expression of indoleamine 2,3- dioxygenase in human corneal cells as a local immunosuppressive factor. Invest Ophthalmol Vis Sci. 2007; 48:4148–4152. [PubMed: 17724200]

[16]. Griffith TS, Brunner T, Fletcher SM, Green DR, Ferguson TA. Fas ligand-induced apoptosis as a mechanism of immune privilege. Science. 1995; 270:1189–1192. [PubMed: 7502042]

[17]. Usui Y, Okunuki Y, Hattori T, et al. Functional expression of B7H1 on retinal pigment epithelial cells. Exp Eye Res. 2008; 86:52–59. [PubMed: 17981268]

[18]. Sugita S, Usui Y, Horie S, et al. T-cell suppression by programmed cell death ligand 1 on retinal pigment epithelium during inflammatory conditions. Invest Ophthalmol Vis Sci. 2009; 50:2862–2870. [PubMed: 19182257]

[19]. Sugita S, Horie S, Nakamura O, et al. Acquisition of T regulatory function in cathepsin L-inhibited T cells by eye-derived CTLA-2alpha during inflammatory conditions. J Immunol. 2009; 183:5013–5022. [PubMed: 19801522]

[20]. Sugita S, Horie S, Nakamura O, et al. Retinal pigment epithelium-derived CTLA-2alpha induces TGFbeta-producing T regulatory cells. J Immunol. 2008; 181:7525–7536. [PubMed: 19017942]

[21]. Horie S, Sugita S, Futagami Y, et al. Human iris pigment epithelium suppresses activation of bystander T cells via TGFbeta-TGFbeta receptor interaction. Exp Eye Res. 2009; 88:1033–1042. [PubMed: 19450450]

[22]. Catania A, Rajora N, Capsoni F, Minonzio F, Star RA, Lipton JM. The neuropeptide alpha-MSH has specific receptors on neutrophils and reduces chemotaxis in vitro. Peptides. 1996; 17:675–679. [PubMed: 8804079]

[23]. Masli S, Turpie B, Hecker KH, Streilein JW. Expression of thrombospondin in TGFbeta-treated APCs and its relevance to their immune deviation-promoting properties. J Immunol. 2002; 168:2264–2273. [PubMed: 11859114]

[24]. Apte RS, Sinha D, Mayhew E, Wistow GJ, Niederkorn JY. Cutting edge: role of macrophage migration inhibitory factor in inhibiting NK cell activity and preserving immune privilege. J Immunol. 1998; 160:5693–5696. [PubMed: 9637476]

[25]. Zamiri P, Masli S, Kitaichi N, Taylor AW, Streilein JW. Thrombospondin plays a vital role in the immune privilege of the eye. Invest Ophthalmol Vis Sci. 2005; 46:908–919. [PubMed: 15728547]

[26]. Atkinson JP, Farries T. Separation of self from non-self in the complement system. Immunol Today. 1987; 8:212–215.

[27]. Sohn JH, Kaplan HJ, Suk HJ, Bora PS, Bora NS. Chronic low level complement activation within the eye is controlled by intraocular complement regulatory proteins. Invest Ophthalmol Vis Sci. 2000; 41(11):3492–3502. [PubMed: 11006244]

[28]. Sohn JH, Bora PS, Suk HJ, Molina H, Kaplan HJ, Bora NS. Tolerance is dependent on complement C3 fragment iC3b binding to antigen-presenting cells. Nat Med. 2003; 9:206–212. [PubMed: 12514742]

[29]. Jiang G, Ke Y, Sun D, Wang Y, Kaplan HJ, Shao. Regulatory role of TLR ligands on the activation of autoreactive T cells by retinal astrocytes. Invest Ophthalmol Vis Sci. 2009; 50(10): 4769–4776. [PubMed: 19443727]

[30]. Taylor AW, Alard P, Yee DG, Streilein JW. Aqueous humor induces transforming growth factor-beta (TGF-beta)-producing regulatory T cells. Curr Eye Res. 1997; 16:900–908. [PubMed: 9288451]

[31]. Nishida T, Taylor AW. Specific aqueous humor factors induce activation of regulatory T cells. Invest Ophthalmol Vis Sci. 1999; 40:2268–2274. [PubMed: 10476792]

[32]. Streilein JW, Masli S, Takeuchi M, Kezuka T. The eye's view of antigen presentation. Hum Immunol. 2002; 63:435–443. [PubMed: 12039518]

[33]. Taylor AW, Streilein JW, Cousins SW. Alpha-melanocyte-stimulating hormone suppresses antigen-stimulated T cell production of gamma-interferon. Neuroimmunomodulation. 1994; 1:188–194. [PubMed: 7489333]

[34]. Nussenblatt RB. The natural history of uveitis. Int Ophthalmol. 1990; 14:303–308. [PubMed: 2249907]

[35]. Darrell RW, Wagener HP, Kurland LT. Epidemiology of uveitis: incidence and prevalence in a small urban community. Arch Ophthalmol. 1962; 68:502–514. [PubMed: 13883604]

[36]. Gritz DC, Wong IG. Incidence and prevalence of uveitis in Northern California: the Northern California Epidemiology of Uveitis Study. Ophthalmology. 2004; 111:491–500. [PubMed: 15019324]

[37]. Knox EG, Mayho A, Cant W, Truelove P. Iridocyclitis: incidence, distribution and health service usage. Community Med. 1980; 2:97–101. [PubMed: 7190479]

[38]. Wacker WB, Donoso LA, Kalsow CM, Yankeelov JA Jr, Organisciack DT. Experimental allergic uveitis: isolation, characterization and localization of a soluble uveitopathogenic antigen from the bovine retina. J Immunol. 1977; 119:1949–1958. [PubMed: 334977]

[39]. Gery I, Wiggert B, Redmond RM, et al. Uveoretinitis and pinealitis induced by immunization with interphotoreceptor retinoid-binding protein. Invest Ophthalmol Vis Sci. 1986; 27:1296–1300. [PubMed: 3488297]

[40]. Schalkin JJ, Winkens HJ, Van Vugt AH, Bovee-Geurts PHM, deGrip WJ, Broekhuyse RM. Rhodopsin-induced experimental autoimmune uveoretinitis: dose-dependent clinico-pathological features. Exp Eye Res. 1988; 47:135–145. [PubMed: 2970396]

[41]. Bora NS, Sohn JH, Kang SG, et al. Type I collagen is the autoantigen in experimental autoimmune anterior uveitis. J Immunol. 2004; 172:7086–7094. [PubMed: 15153531]

[42]. Ichikawa T, Taguchi O, Takahashi T, et al. Spontaneous development of autoimmune uveoretinitis in nude mice following reconstitution with embryonic rat thymus. Clin Exp Immunol. 1991; 86:112–117. [PubMed: 1914224]

[43]. Anderson MS, Venanzi ES, Klein L, et al. Projection of an immunological self shadow within the thymus by the aire protein. Science. 2002; 298:1395–1401. [PubMed: 12376594]

[44]. Ohta K, Wiggert B, Yamagami S, Taylor AW, Streilein JW. Analysis of immunomodulatory activities of aqueous humor from eyes of mice with experimental autoimmune uveitis. J Immunol. 2000; 164:1185–1192. [PubMed: 10640729]

[45]. Kitaichi N, Namba K, Taylor AW. Inducible immune regulation following autoimmune disease in the immune privileged eye. J Leuk Biol. 2005; 77:496–502.

[46]. Taylor AW, Kitaichi N, Biros D. Melanocortin 5 receptor and ocular immunity. Cell Mol Biol. 2006; 52:53–59. [PubMed: 16914087]

[47]. Mondino BJ, Glovsky MM, Ghekiere L. Activated complement in inflamed aqueous humor. Invest Ophthalmol Vis Sci. 1985; 25:871–873. [PubMed: 6610667]

[48]. Sugita S, Takase H, Taguchi C, Mochizuki M. The role of soluble TNF receptors for TNF-alpha in uveitis. Invest Ophthalmol Vis Sci. 2007; 48:3246–3252. [PubMed: 17591895]

[49]. Banerjee S, Savant V, Scott RA, Curnow SJ, Wallace GR, Murray PI. Multiplex bead analysis of vitreous humor of patients with vitreoretinal disorders. Invest Ophthalmol Vis Sci. 2007; 48:2203–2207. [PubMed: 17460280]

[50]. Curnow SJ, Falciani F, Durrani OM, et al. Multiplex bead immunoassay analysis of aqueous humor reveals distinct cytokine profiles in uveitis. Invest Ophthalmol Vis Sci. 2005; 46:4251–4259. [PubMed: 16249505]

[51]. Perez VL, Papaliodis GN, Chu D, Anzaar F, Christen W, Foster CS. Elevated levels of interleukin 6 in the vitreous fluid of patients with pars planitis and posterior uveitis: the Massachusetts eye & ear experience and review of previous studies. Ocul Immunol Inflamm. 2004; 12:193–201. [PubMed: 15385196]

[52]. Murphy CC, Greiner K, Plskova J, et al. Neutralizing tumor necrosis factor activity leads to remission in patients with refractory noninfectious posterior uveitis. Arch Ophthalmol. 2004; 122:845–851. [PubMed: 15197059]

[53]. Kotake S, Kitaichi N, Ohno S. Macrophage migration inhibitory factor in uveitis. Int Ophthalmol Clin. 2002; 42:99–103. [PubMed: 12189621]

[54]. Sugita S, Taguchi C, Takase H, et al. Soluble Fas ligand and soluble Fas in ocular fluid of patients with uveitis. Br J Ophthalmol. 2000; 84:1130–1134. [PubMed: 11004098]

[55]. Ongkosuwito JV, Feron EJ, van Doornik CE, et al. Analysis of immunoregulatory cytokines in ocular fluid samples from patients with uveitis. Invest Ophthalmol Vis Sci. 1998; 39:2659–2665. [PubMed: 9856775]

[56]. de Boer JH, Limpens J, Orengo-Nania S, de Jong PT, La Heij E, Kijlstra A. Low mature TGF-beta 2 levels in aqueous humor during uveitis. Invest Ophthalmol Vis Sci. 1994; 35:3702–3710. [PubMed: 7522227]

[57]. Murray PI, Hoekzema R, van Haren MA, de Hon FD, Kijlstra A. Aqueous humor interleukin-6 levels in uveitis. Invest Ophthalmol Vis Sci. 1990; 31:917–920. [PubMed: 2335453]

[58]. Curnow SJ, Murray PI. Inflammatory mediators of uveitis: cytokines and chemokines. Curr Opin Ophthalmol. 2006; 17:532–537. [PubMed: 17065921]