REVIEW

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Role of ocular pigment epithelial cells in immune privilege

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Abstract

The ocular microenvironment is both immunosuppressive and anti-inflammatory in nature. Pigment epithelial (PE) cells isolated from the eye possess the ability to suppress the T cell receptor-dependent activation of T cells and the induction of regulatory T cells *in vitro*. This property is dependent on the cells' capacity to produce cell-surface and soluble inhibitory molecules, for example CD86 (B7-2), transforming growth factor (TGF)-β, thrombospondin-1, programmed cell death 1 ligand 1 (PD-L1/B7-H1), and cytotoxic T lymphocyte-associated antigen 2α. Cultured ocular PE cells from the iris, ciliary body, and retina can individually suppress T-cell activation via mechanisms that partially overlap. Moreover, PE-derived regulatory T cells acquire functions that play a role in establishing immune regulation in the eye. Multiple strategies are employed within the eye to control immune-mediated inflammation. This phenomenon is known as immune privilege and is instrumental in helping to prevent extensive damage to bystander cells that would otherwise lead to blindness. This review focuses on the immunosuppressive property and role of ocular PE cells in immune privileged sites.

Key words: pigment epithelium, immune privilege, eye, suppression, T regulatory cells.

Abbreviations: CBPE – ciliary body pigment epithelium, CTLA-2α – cytotoxic T lymphocyte-associated antigen 2α, IPE – iris pigment epithelium, PD-L1 – programmed cell death 1 ligand 1, PE – pigment epithelium, Treg cells – T regulatory cells, TSP-1 – thrombospondin-1, RPE – retina pigment epithelium.

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IMMUNE PRIVILEGE IN THE EYE

Ocular immune privilege is an evolutionarily designed multifactorial mechanism that can prevent immunogenic inflammation from disrupting the visual axis and causing blindness (Niederkorn 2002; Streilein 2003; Streilein and Stein-Streilein 2000). To avoid these consequences of intraocular inflammation, the eye expresses an extensive array of mechanisms by which innate and adaptive immune effectors can be regulated, and even silenced (Streilein 2003). The mechanisms that have been revealed to date include an intraocular microenvironment (aqueous humor and vitreous fluids) that is rich in soluble immunomodulatory factors (Taylor et al. 1997; Taylor 1999; Taylor 2007), blood-tissue barriers that limit the ingress of blood-borne cells and molecules that are capable of mediating immunogenic inflammation, and the constitutive expression of CD95 ligand (CD95L/FasL) on ocular parenchymal cells, which triggers the apoptosis of effector T cells (Griffith et al. 1995; Griffith et al. 1996). These and other mechanisms help to explain why the eye has been shown experimentally to be an immune-privileged site (Stuart et al. 1997; Niederkorn and Wang 2005). Thus these mechanisms make it possible for the eye to accept foreign tissue grafts for extended, if not indefinite, intervals, whereas conventional body sites summarily reject such grafts.

OCULAR PIGMENT EPITHELIAL CELLS

A monolayer of pigment epithelium (PE) lines the iris (IPE), ciliary body (CBPE), and retina (RPE), all of

which contribute to the immune-privileged property of the eye. Neural crest-derived epithelial cells participate in the ocular immune privilege and many previous studies have defined the individual molecular mechanisms involved in this process (Sugita and Streilein 2003; Sugita et al. 2006a; Usui et al. 2008; Yoshida et al. 2000a; Yoshida et al. 2000b; Zamiri et al. 2007). The diverse but related PE of the iris, ciliary body, and retina possess distinct properties that are related to their disparate anatomic locations. Various laboratories have demonstrated that these PE cells display immunomodulatory features, which suggests that this layer of cells contributes to the immune privilege. It was reported several years ago that cultured PE cells isolated from the iris and ciliary body were able to secrete immunosuppressive factors *in vitro* (Yoshida et al. 2000a; Yoshida et al. 2000b). Freshly explanted RPE as well as immortalized cell lines derived from RPE have been found to secrete immunosuppressive factors (Sugita et al. 2006a; Zamiri et al. 2007) and to express surface molecules such as CD95L.

As shown in Fig. 1, cultured ocular PE cells from the retina, ciliary body, and iris suppress T-cell proliferation of effector T cells *in vitro*. In the presence of 1×10^4 PE cells, anti-CD3-stimulated T-cell proliferation was not fully suppressed, whereas activated T cells were significantly suppressed by 2×10^4 PE cells (around 80% inhibition, Fig. 1). The immunosuppressive properties of these ocular PE cells are summarized in Table 1. Cultured RPE cells suppress T-cell activation by both cell contact and via the secretion of immunosuppressive factors (Ishida et al. 2003; Sugita and Streilein 2003; Sugita et al. 2006a; Sugita et al. 2009). In addition, cultured RPE cells convert both CD4 and CD8 T cells into T regulatory cells *in vitro* (Sugita et al. 2008). On the other hand, cultured IPE cells can suppress T-cell activation by cell contact only, which indicates that IPE cells do not secrete soluble factors (Sugita and Streilein 2003; Sugita et al. 2004). Interestingly, IPE cells are able to induce CD8 Treg cells, but not CD4, *in vitro* (Sugita et al. 2006b). In addition to the soluble immunosuppressive factors that cultured CBPE cells secrete, a cell contact inhibitory mechanism is also probably involved (Sugita and Streilein 2003). However, CBPE cells are not able to convert T cells into Treg cells *in vitro* (Sugita et al. 2006b).

As shown in Table 1, transforming growth factor (TGF)-β is a common denominator in the various suppressive mechanisms elicited by these PE cells. When these cells were examined by a mouse microarray analysis using RNA (Futagami et al. 2007), many immunosuppressive factors were detected, including thrombospondin (TSP)-1, which converts latent TGF-β into active forms non-enzymatically in eyes that exhibit high levels of expression. Among the neuropeptides that are rich in aqueous humor (Taylor 1999; Taylor 2007), calcitonin gene-related peptide was detected in all PE cells. This is in contrast to Fas ligand (FasL, CD95L), α--melanocyte-stimulating hormone, and vasoactive intestinal peptide, which were not detected in all PE cells. Among the eye-related complement regulators, only CD59a exhibited high levels of expression. Thus the previous data provide solid proof that the PE contributes to the ocular immune privilege.

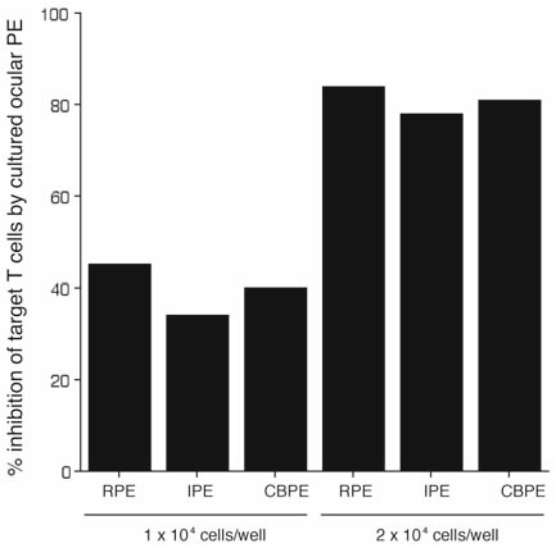

Fig. 1. Capacity of cultured ocular pigment epithelial cells RPE, IPE, and CBPE to suppress T-cell activation *in vitro*. PE cells cultured from retina, iris, and ciliary body of C57BL/6 mice served as substrates for T-cell activation. Purified pan--T cells in the presence of anti-mouse CD3 antibody (1.0 μg/ml) were co-cultured with RPE, IPE, or CBPE (1×10^4 or 2×10^4/well in 96-well culture plates) for 72 h. T-cell activation was assessed for proliferation by [^{3}H]-thymidine incorporation. The Y-axis indicates the percentage inhibition of target pan-T cells by the cultured ocular PE cells.

PE CELLS FROM RETINA

The ocular pigment epithelia of the retina have been identified as important participants in helping to create and maintain immune tolerance (Streilein 2003). The RPE layer has a primary vision-related function that serves as a "light sink", thereby quenching any unfocused light that might otherwise enter the eye and compete with focused images that pass through the visual axis to the retina (Camacho-Hubner and Beermann 2001). RPE also has secondary functions that are related in part to the region of the eye in which they are located; for example, the RPE provides nutritive and biochemical support for the proper functioning of the rod and cone photoreceptor cells of the retina (Rothermel and Layer 2001). Cultured RPE cells from the posterior segment of the eye have been demonstrated to suppress T-cell activation *in vitro*. It has been proposed that the immunoregulatory property of RPE is related to the intraocular suppression of immunogenic inflammation (Wenkel and Streilein 2000; Zamiri et al. 2007).

Table 1. Summary of immunosuppressive properties of the ocular pigment epithelial cells RPE, IPE, and CBPE

Ocular PE cells	Use of cell contact	Secretion of soluble factors	Induction of Treg cells	Candidate molecules	Representative reference
RPE	(+)	(++)	(+) (CD4 and CD8)	TGF-β	Sugita et al. 2006a
				TSP-1	Futagami et al. 2007
				PD-L1/B7-H1	Sugita et al. 2009
				Galectin-1	Ishida et al. 2003
				PEDF	Zamiri et al. 2006
				CTLA-2α	Sugita et al. 2008
IPE	(++)	(–)	(+) (CD8)	TGF-β	Sugita et al. 2006b
				TSP-1	Futagami et al. 2007
				CD86 (B7-2)	Sugita and Streilein 2003
CBPE	(+)	(+)	(–)	TGF-β	Sugita et al. 2006a
				TSP-1	Futagami et al. 2007

TSP-1 – thrombospondin-1, PEDF – pigment epithelial-derived factor, CTLA-2α – cytotoxic T-lymphocyte antigen-2α.

We previously demonstrated that primary RPE cells suppress T-cell activation by both cell contact and via the secretion of immunosuppressive factor(s) (Sugita and Streilein 2003; Ishida et al. 2003; Sugita et al. 2006a; Sugita et al. 2009). We also reported that cultured RPE cells established from normal mice and humans can significantly suppress the activation of T cells by secreting TGF-β (Sugita et al. 2006a). Moreover, both human and murine RPE cells constitutively express programmed cell death 1 ligand 1 (PD-L1/B7-H1) costimulatory molecules and RPE profoundly suppresses bystander programmed cell death (PD)-1$^+$ T cells (Usui et al. 2008; Sugita et al. 2009). Interferon-γ significantly up-regulates these molecules, with the PD-L1/PD-1 interactions able to suppress T-cell proliferation and cytokine production via activated T cells (Dong et al. 1999; Freeman et al. 2000). Thus RPE cells produce immunosuppressive molecules on their surface and secrete immunoregulatory soluble factors into the supernatants of the culture medium.

In recent studies we investigated how T cells cultured *in vitro* in the presence of RPE cells are able to acquire the capacity to regulate other T cells in secondary cultures. CD4$^+$ T cells acquire T regulatory activity when exposed to RPE cells and this conversion occurs in the presence of a novel inhibitory factor, cytotoxic T lymphocyte antigen (CTLA)-2α (Sugita et al. 2008). While transcripts for CTLA-1, -2, and -3 are present in various cytotoxic T lymphocytes, they are absent or expressed at much lower levels in non-cytotoxic T lymphocytes (Brunet et al. 1986). CTLA-4 is mainly expressed in activated lymphocytes (Brunet et al. 1987), with the CTLA-2α and -2β transcripts restricted to either T cells, where they are induced upon activation, or to mast cells (Kurata et al. 2003). The open reading frames of both cDNA transcripts encode proteins that are homologous to cysteine proteinase precursors. CTLA-2α, which functions as a cysteine proteinase inhibitor, promotes the RPE-dependent formation of regulatory T cells. Cultured RPE cells can also constitutively express CTLA-2α, while CD4$^+$ T cells exposed to RPE cells are able to up-regulate the expression of CD25 and Foxp3. In addition, recombinant CTLA-2α can induce CD4$^+$CD25$^+$Foxp3$^+$ regulatory T cells both *in vitro* and *in vivo*. These regulatory T cells produce high levels of immunosuppressive cytokines, including active TGF-β. CTLA-2α controls cathepsin L activity in cultured RPE cells, and CTLA-2α via RPE can promote TGF-β activity. As seen in Fig. 2, these results demonstrate that regulatory T cells, which are generated in response to the co-culturing of CTLA-2α with RPE cells, can acquire full regulatory functions for peripheral immune tolerance. Therefore, these previous results suggest that the CTLA-2α-TGF-β pathway plays a critical role in the regulatory T-cell generation in the eye.

PE CELLS FROM THE IRIS

We previously demonstrated that iris PE cells differ from ciliary body PE and RPE cells in that they primarily suppress T-cell activation *in vitro* by a cell-to-cell contact-dependent mechanism (Sugita and Streilein 2003; Ishida et al. 2003; Sugita et al. 2004; Sugita et al. 2006c). When IPE cells are co-cultured with T cells stimulated with anti-mouse CD3 (1st signal), the activated T cells will then bind to the IPE cells via a cell-to-cell contact mechanism. Previous experimental evidence collected in our laboratories demonstrated that CD86 (B7-2) acted as a second signal that was uniquely and constitutively expressed on the surface of the IPE cells. The IPE cells then caused a contact-dependent inhibition of the T cells via an interaction between CD86 and the CTLA-4 (Sugita and Streilein 2003). Interestingly, the T cells themselves were found to participate in the global suppression caused by the IPE cells and, in addition, the novel expression of CD86 on the subpopulation of the IPE-exposed T cells was essential for maximal suppression to occur (Sugita et al. 2004). When a subpopulation of CD8$^+$ T cells encounter CD86$^+$ IPE, these cells are able to efficiently up-regulate CTLA-4 as well as CD86 provided that the cells simultaneously receive a signal via the TCR (anti-CD3). The subset of T cells that are preferentially targeted for activation by CD86$^+$ IPE

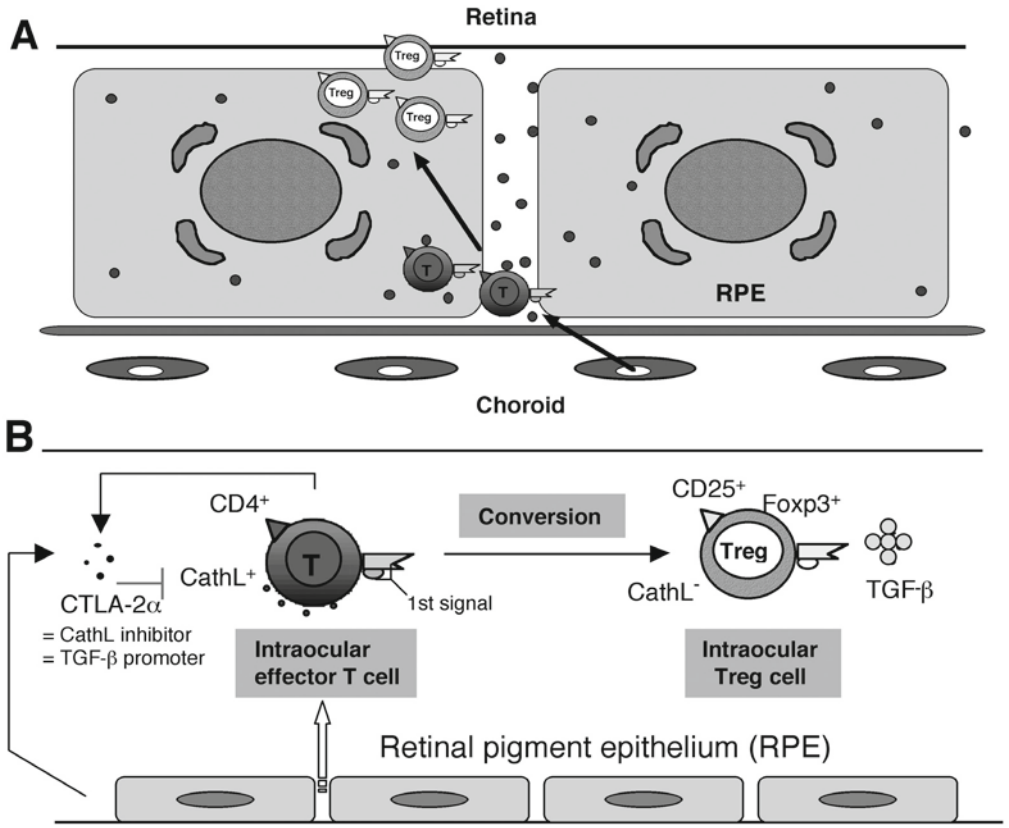

Fig. 2. Summary of the process for Treg conversion by eye-derived CTLA-2α. (**A**) Intraocular migratory T cells that escape from choroid vessels into the stroma must pass through the RPE layer to penetrate into the retinal space. T cells are functionally converted to Treg cells during the traffic of migratory T cells through the pigment epithelium from the retina (RPE). (**B**) In the subretinal space that includes the RPE layer, the secretion of CTLA-2α by the RPE converts intraocular effector T cells into Treg cells that acquire regulatory functions, as the CTLA-2α by T cells and RPE cells inhibits cathepsin L (CathL) activities. The Treg cells express high levels of CD25 and Foxp3 in addition to producing active TGF-β. Thus RPE-derived $CD4^+$ Treg cells play an important role in the immune tolerance in the eye. The small black circles indicate CTLA-2α secreted by RPE cells.

cells express CD8, CTLA-4, and CD86, and when interactions between the T and PE cells occur, there is generation of enhanced amounts of active TGF-β. Recently we showed that both IPE and IPE-exposed T cells were able to produce enhanced amounts of active TGF-β, and when suppressing T-cell activation they predominantly used the membrane-bound TGF-β (Sugita et al. 2006c). This evidence indicates that the function of the surface interactions between B7 (by IPE) and CTLA-4 (by the responder target T cells) is to direct the delivery of the membrane-associated TGF-β to the appropriate target T cells. In order to suppress the activation of bystander T cells *in vitro*, primary cultured IPE exclusively uses cell-to-cell contact.

PE CELLS FROM THE CILIARY BODY

Inhibition of T-cell proliferation is mediated by either an IPE cell contact-dependent mechanism or by soluble factors from CBPE and RPE cells established from the posterior segment of the eye (Sugita and Streilein 2003; Sugita et al. 2006c). CBPE cells established from normal C57BL/6 mice are able to significantly suppress T-cell activation *in vitro* as well as in the IPE and RPE cells (Sugita and Streilein 2003; Sugita et al. 2007a). CBPE cell division is much greater than that seen in other PE cells, such as IPE and RPE. In addition, the morphology of the primary cultured CBPE in 5-day-old cultures demonstrated confluence from a very early phase (Sugita et al. 2007a). Mouse microarray analysis showed that the expression of candidate genes in CBPE was similar to that seen in other PE cells (Sugita et al. 2007a); for example, TGF-β1-3, TGF-β receptor (TGF-βR) I-III, and TSP-1 exhibited high levels of expression on the PE cells. These results suggest that the CBPE cells might also have an inhibitory function within the immune-privileged site.

OCULAR PE CELLS INDUCE REGULATORY T CELLS

Murine T cells were converted into regulatory T cells by *in vitro* exposure to pigment epithelia cells that had been harvested from the iris or retina of uninflamed nor-

mal eye (Futagami et al. 2007; Sugita et al. 2006b; Sugita et al. 2006c; Sugita et al. 2007b; Sugita et al. 2008; Yoshida et al. 2000b). The ocular PE-induced Treg cells suppress the activation of bystander target T cells by anti-CD3 Abs when added to secondary cultures containing the target T cells plus the Treg cells. The ability of IPE to convert T cells into Tregs depends solely upon cell-to-cell contact (Sugita et al. 2006b; Sugita et al. 2007b). These PE-induced Treg cells inhibit in an antigen-nonspecific manner (unpublished observation). The contact-dependent process by which IPE converted $CD8^+$ T cells into Treg cells resembled that reported in a previous study that used $CD8^+$ T cells and gut epithelium (Li et al. 1995). That study showed that an antigen-nonspecific interaction between CD8 on the T cells and gp180 on the intestinal epithelial cells was required. Our research group previously found that it was an antigen-nonspecific interaction between CTLA-4 on T cells and B7 co-stimulatory molecules on the IPE cells that was required (Sugita et al. 2006c). Li et al. reported that $p56^{lck}$-dependent T-cell activation, which presumably occurred via the TCR, is important when intestinal epithelial cells induce $CD8^+$ Treg cells. However, with regard to the induction of $CD8^+$ Treg cells, TGF-β appears to be irrelevant.

On the other hand, RPE cells can convert both $CD4^+$ T cells (as opposed to $CD8^+$) into Treg cells via soluble factor(s). Interestingly, the analogous interaction between $CD4^+$ T cells and retinal PE does not involve CTLA-4 and CD86. Instead, RPE, but not IPE or CBPE, cells can produce CTLA-2α, which is a cathepsin L inhibitor. This novel molecule plays a role in the induction of Treg by RPE cells (Sugita et al. 2008). In several recent studies we also found that there is a second pathway that resembles regulatory co-stimulation in that there is a required signaling through a TGF-βR on the T cells (Futagami et al. 2007; Sugita et al. 2006c; Sugita et al. 2008). While we are aware that T cells stimulated via CTLA-4 can begin to synthesize and secrete TGF-β (Nakamura et al. 2001; Chen et al. 1998), we found that the IPE-induced Treg cells were not able to suppress bystander T-cell activation if the latter were obtained from dominant negative TGF-βR II donors (Lucas et al. 2000). In addition, we also demonstrated that CTLA-2α, which is only produced by cultured RPE cells, is able to convert latent forms of TGF-β into active forms and that intraocular TGF-β can up-regulate the production of RPE-CTLA-2α (Sugita et al. 2008). These previously published studies indicate that members of the CTLA family, such as CTLA-2 and CTLA-4, may require a TGF-β signal in order to be able to acquire their regulatory function. However, perhaps more important is the finding that the PE-induced Treg cells can produce TGF-β (Fig. 2). In fact, not only are ocular PE cells the major source of the TGF-β constitutively found within ocular fluids (Granstein et al. 1990; Pasquale et al. 1993), but the PE-induced Treg cells are also the major source of the significant amounts of TGF-β that are present in the ocular fluids during inflammatory conditions (Ohta et al. 2000).

CONCLUDING REMARKS

Overall, these findings demonstrate that ocular PE contributes to the immune tolerance in the eye. Thus the immune privilege in the eye is created by the pigment-containing epithelial layer that lines the posterior surfaces of the iris, ciliary body, and neural retina. We are now investigating whether it is possible for human ocular PE-dependent human regulatory T cells to expand *in vitro* and whether these expanded T cells can acquire a suppressive function. The present data, however, indicate that the *in vitro* manipulated Treg cells have potential use in therapeutic applications in patients with ocular inflammatory disorders such as uveitis.

REFERENCES

Brunet JF, Denizot F, Luciani MF et al (1987) A new member of the immunoglobulin superfamily – CTLA-4. Nature 328:267–270

Brunet JF, Dosseto M, Denizot F et al (1986) The inducible cytotoxic T-lymphocyte-associated gene transcript CTLA-1 sequence and gene localization to mouse chromosome 14. Nature 322:268–271

Camacho-Hubner A, Beermann F (2001) Increased transgene expression by the mouse tyrosinase enhancer is restricted to neural crest-derived pigment cells. Genesis 29:180–187

Chen W, Jin W, Wahl SM (1998) Engagement of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) induces transforming growth factor beta (TGF-beta) production by murine $CD4^+$ T cells. J Exp Med 188:1849–1857

Dong H, Zhu G, Tamada K et al (1999) B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. Nat Med 5:1365–1369

Freeman GJ, Long AJ, Iwai Y et al (2000) Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 192:1027–1034

Futagami Y, Sugita S, Vega J et al (2007) Role of thrombospondin-1 in T cell response to ocular pigment epithelial cells. J Immunol 178:6994–7005

Granstein RD, Staszewski R, Knisely TL et al (1990) Aqueous humor contains transforming growth factor-beta and a small (less than 3500 daltons) inhibitor of thymocyte proliferation. J Immunol 144:3021–3027

Griffith TS, Brunner T, Fletcher SM et al (1995) Fas ligand-induced apoptosis as a mechanism of immune privilege. Science 270:1189–1192

Griffith TS, Yu X, Herndon JM et al (1996) CD95-induced apoptosis of lymphocytes in an immune privileged site induces immunological tolerance. Immunity 5:7–16

Ishida K, Panjwani N, Cao Z et al (2003) Participation of pigment epithelium in ocular immune privilege. 3. Epithelia cultured from iris, ciliary body, and retina suppress T-cell activation by partially non-overlapping mechanisms. Ocul Immunol Inflamm 11:91–105

Kurata M, Hirata M, Watabe S et al (2003) Expression, purification, and inhibitory activities of mouse cytotoxic T-lymphocyte antigen-2alpha. Protein Expr Purif 32:119–125

Li Y, Yio XY, Mayer L (1995) Human intestinal epithelial cell--induced $CD8^+$ T cell activation is mediated through CD8 and the activation of CD8-associated p56lck. J Exp Med 182:1079–1088

Lucas PJ, Kim SJ, Melby SJ et al (2000) Disruption of T cell homeostasis in mice expressing a T cell-specific dominant negative transforming growth factor beta II receptor. J Exp Med 191:1187–1196

Nakamura K, Kitani A, Strober W (2001) Cell contact-dependent immunosuppression by $CD4^+CD25^+$ regulatory T cells is mediated by cell surface-bound transforming growth factor beta. J Exp Med 194:629–644

Niederkorn JY (2002) Immune privilege in the anterior chamber of the eye. Crit Rev Immunol 22:13–46

Niederkorn JY, Wang S (2005): Immune privilege of the eye and fetus: parallel universes? Transplantation 80:1139–1144

Ohta K, Wiggert B, Yamagami S et al (2000) Analysis of immunomodulatory activities of aqueous humor from eyes of mice with experimental autoimmune uveitis. J Immunol 164:1185–1192

Pasquale LR, Dorman-Pease ME, Lutty GA et al (1993) Immunolocalization of TGF-beta 1, TGF-beta 2, and TGF--beta 3 in the anterior segment of the human eye. Invest Ophthalmol Vis Sci 34:23–30

Rothermel A, Layer PG (2001) Photoreceptor plasticity in reaggregates of embryonic chick retina: rods depend on proximal cones and on tissue organization. Eur J Neurosci 13:949–958

Streilein JW (2003) Ocular immune privilege: therapeutic opportunities from an experiment of nature. Nat Rev Immunol 3:879–889

Streilein JW, Stein-Streilein J (2000) Does innate immune privilege exist? J Leukoc Biol 67:479–487

Stuart PM, Griffith TS, Usui N et al (1997) CD95 ligand (FasL)-induced apoptosis is necessary for corneal allograft survival. J Clin Invest 99:396–402

Sugita S, Futagami Y, Horie S et al (2007a): Murine ciliary body pigment epithelial cells inhibit activation of T cells. Nippon Ganka Gakkai Zasshi 111:598–605

Sugita S, Futagami Y, Horie S et al (2007b): Transforming growth factor beta-producing Foxp3(+)CD8(+)CD25(+) T cells induced by iris pigment epithelial cells display regulatory phenotype and acquire regulatory functions. Exp Eye Res 85:626–636

Sugita S, Futagami Y, Smith SB et al (2006a): Retinal and ciliary body pigment epithelium suppress activation of T lymphocytes via transforming growth factor beta. Exp Eye Res 83:1459–1471

Sugita S, Horie S, Nakamura O et al (2008) Retinal pigment epithelium-derived cytotoxic T lymphocyte antigen-2α induces TGFβ-producing T regulatory cells. J Immunol 181:7525–7536

Sugita S, Keino H, Futagami Y et al (2006b) B7+ iris pigment epithelial cells convert T cells into CTLA-4+, B7-expressing CD8+ regulatory T cells. Invest Ophthalmol Vis Sci 47:5376–5384

Sugita S, Ng TF, Lucas PJ et al (2006c) B7+ iris pigment epithelium induce CD8+ T regulatory cells; both suppress CTLA-4+ T cells. J Immunol 176:118–127

Sugita S, Ng TF, Schwartzkopff J et al (2004) CTLA-4+CD8+ T cells that encounter B7-2+ iris pigment epithelial cells express their own B7-2 to achieve global suppression of T cell activation. J Immunol 172:4184–4194

Sugita S, Streilein JW (2003) Iris pigment epithelium expressing CD86 (B7-2) directly suppresses T cell activation in vitro via binding to cytotoxic T lymphocyte-associated antigen 4. J Exp Med 198:161–171

Sugita S, Usui Y, Horie S et al (2009) T cell suppression by programmed cell death 1 ligand 1 on retinal pigment epithelium during inflammatory conditions. Invest Ophthalmol Vis Sci 50:2862–2870

Taylor AW (1999) Ocular immunosuppressive microenvironment. Chem Immunol 73:72–89

Taylor AW (2007) Ocular immunosuppressive microenvironment. Chem Immunol Allergy 92:71–85

Taylor AW, Alard P, Yee DG et al (1997) Aqueous humor induces transforming growth factor-beta (TGF-beta)-producing regulatory T-cells. Curr Eye Res 16:900–908

Usui Y, Okunuki Y, Hattori T et al (2008) Functional expression of B7H1 on retinal pigment epithelial cells. Exp Eye Res 86:52–59

Wenkel H, Streilein JW (2000) Evidence that retinal pigment epithelium functions as an immune-privileged tissue. Invest Ophthalmol Vis Sci 41:3467–3473

Yoshida M, Kezuka T, Streilein JW (2000a) Participation of pigment epithelium of iris and ciliary body in ocular immune privilege. 2. Generation of TGF-beta-producing regulatory T cells. Invest Ophthalmol Vis Sci 41:3862–3870

Yoshida M, Takeuchi M, Streilein JW (2000b) Participation of pigment epithelium of iris and ciliary body in ocular immune privilege. 1. Inhibition of T-cell activation in vitro by direct cell-to-cell contact. Invest Ophthalmol Vis Sci 41:811–821

Zamiri P, Masli S, Streilein JW et al (2006) Pigment epithelial growth factor suppresses inflammation by modulating macrophage activation. Invest Ophthalmol Vis Sci 47:3912–3918

Zamiri P, Sugita S, Streilein JW (2007) Immunosuppressive properties of the pigmented epithelial cells and the subretinal space. Chem Immunol Allergy 92:86–93