Editorial

Ocular Immunology

Ocular Immunology is a growing field in the last years. For a long time the eye was regarded as a "protuberance" of the brain, but now many special characteristics different from the brain and other regions of the body have been identified. The inner eye is "immune privileged", which prevents spontaneous assaults from the immune system and rather induces immune tolerance than defense. The external surfaces of the eye have to deal with the environment, which includes harmless antigens as well as pathogens.

Those pathogens that can cause tremendous problems to the surface (cornea) as well as in the inner eye are herpes viruses, which commit a life-long relationship with their host. Herpes keratitis and HSV uveitis are sight-threatening diseases, which are caused by the viruses themselves and, on the other side, by the host's own immune system. The characteristics of the infection by various herpes viruses as well as the immune reaction of the host is extensively reviewed by G.M.G.M Verjans and A. Heiligenhaus (Herpes Simplex Virus-induced ocular diseases – Detrimental interactions between virus and host) in this issue.

Herpes keratitis can blur the corneal stroma to an extent that needs corneal transplantation. The normally clear cornea allows the light to pass through and reach the retina for photoperception, and enables us to directly observe the intraocular tissues and inflammatory events. The cornea is a part of the anterior chamber-associated immune privilege, which confers long-term acceptance of corneal grafts under non-inflamed conditions. The latter is, however, abolished after herpes infection. J.Y. Niederkorn describes in his review "Cornea: Window to ocular immunology" how and why the cornea is involved in the immune privilege and what happens when the immune privilege breaks down. In addition to the capabilities of the cornea to protect itself against infection and contribute to the immune privilege of the anterior chamber, the author also covers the immune principles of dry eye disease.

The immune privilege of the eye has been a topic of intensive research in the past decades, for it protects the delicate intraocular tissues from irreversible damage by the immune system. Not only the anterior chamber, but also the retina is concerned about its integrity and is thus provided with mechanisms to downregulate potentially deteriorating immune responses, as described by J. Stein-Streilein and K. Lucas in their article "A current understanding of ocular immune privilege". Each eye takes care of the other, that is, the generation of regulatory T cells that confer tolerance will also protect the contralateral eye from deleterious immune responses. On the other hand, this group has recently show that loss of ACAID in one eye leads to loss of protection in the contralateral eye as well, an effect that could be attributed to neuropeptide mediators.

S.W. McPherson and his colleagues N.D. Heuss, U. Lehmann and D.S. Gregerson focus on the "Generation of regulatory T cells to antigen expressed in the retina", and they describe that regulatory T cells specific for sequestered retinal antigens can be generated from mature, peripheral T cells. Their transgenic mouse model enabled the authors to dissect the generation of regulatory T cells by ectopic expression of antigen in the thymus from the generation of Tregs by antigen expressed exclusively in the retina. These cells are able to protect from experimental autoimmune disease directed against the retina.

Despite of the necessity for preventing the eye from immune assault, it is sometimes essential for the immune system to be active within the eye, especially when pathogens have invaded. This will lead to a breakdown of the blood-ocular barriers and the tolerance that is usually established by ACAID. Innate as well as adaptive immune responses can result in sight-threatening conditions. In their article "Intraocular immune reactions during uveitis" J. Curnow, G. Wallace, A. Denniston and P. Murray focus on human disease. They cover the different immune reactions in autoimmunity and autoinflammation, the role of genetic factors such as HLA-associations, cytokines and chemokines that are related to different types of uveitis, and finally dwell on the mechanisms underlying the current therapies.

The normal healthy eye is not completely devoid of components of the immune system. In their article "Emerging role of complement in ocular diseases", N.S. Bora, P. Jha, V. Lyzogubov and P.S. Bora deal with experimental animal models as well as with human diseases, and describe constitutive, low-level complement activation in the eye. This complement activation is delicately regulated by the expression of complement inhibitory factors that protect intraocular tissue. On one hand proteins of the complement system protect the eye from invading pathogens, but on the other hand activation of the complement system can cause severe inflammation and might play a role in uveitis, which was underestimated for a long time. One of the major problems in ophthalmology, age-related macular degeneration, was recently found to be highly associated with mutations of the complement inhibitory factor H as well as other variants of complement factors. Together with findings in glaucoma and diabetic retinopathy this underlines the importance of components of the innate immune system in various diseases that had not even been regarded as immune-mediated.

The comparison of human disease and animal models is also a topic of the manuscript by C. Deeg, G. Wildner and S. Thurau in their article "Uveitis in horses, rats and men: What do we learn from our pets?" Here the authors introduce uveitis in horses, which is the only species with spontaneous and experimentally inducible uveitis (EAU). In their manuscript, the authors compare autoantigen specificities, T cell and autoantibody responses in uveitis of rats, mice, horses and humans. Differences in the proteome of healthy eyes and eyes affected by equine recurrent uveitis give a hint of the reaction of the affected tissue during inflammation. Equine uveitis is a highly valuable model, not only because of the direct comparison of spontaneous and experimental disease, but in contrast to humans and rodents they provide large specimens for investigation and thus helped to identify a new potential autoantigen. Different experimental models are correlated with different clinical types of human

uveitis, and finally, a new translational therapy of oral tolerance induction with a mimicry peptide of retinal S-Ag, developed in rat EAU and transferred to uveitis patients, is described.

The last article in this series about "Intraocular inflammation and systemic immune-mediated diseases" by J.R. Smith and J.T. Rosenbaum concentrates on human uveitis and tries to elucidate the fact that uveitis is rarely an isolated ocular inflammation, but associated with various systemic diseases. Different systemic diseases, like HLA-B27-associated ankylosing spondylitis, juvenile idiopathic arthritis, sarcoidosis, multiple sclerosis, Vogt-Koyanagi-Harada disease or Behçet´s disease are all featuring different types of intraocular inflammation with respect to course of uveitis, anatomical localization and type of inflammation. Little is known about the immune mechanisms behind these different diseases. The authors mainly focus on HLA-associations, gene array analyses to define differences in the gene expression between healthy donors and uveitis patients and potential autoantigens, which have been confirmed in animal models.

This hot topic issue provides an overview of the immunology of the eye, of protective as well as deleterious immune reactions, it includes spontaneous and experimentally induced diseases, and compares human diseases with animal models. The unique features of ocular immunology, including the mechanisms of the ocular immune privilege, are emphasized, but also the also numerous similarities with other, especially autoimmune diseases, are considered.

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