Special Issue: Inflammation in Ophthalmology

Brief Review

Inflammation in Ophthalmology

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Inflammation is necessary to combat bacterial and/or viral infections. Physiological inflammation is tightly controlled from the onset of inflammation to the end. However, when inflammation is sustained and becomes chronic, it harms rather than provides benefits. This situation occurs in the eye too. So, chronic inflammation is now considered to be the important cause of various eye disorders. The definition of inflammation is the presence of fever, pain, infection and swelling. Recent findings show the silent-type of inflammation (low-grade inflammation) without the classical signs is also causing the various ocular diseases such as diabetic retinopathy or dry eye. It is similar to the observation that silent inflammation causes vascular aging and sclerosis, resulting in cardiac arrest or brain infarction. In this small review of "Inflammation in Ophthalmology," we cover the classical inflammation as well as the importance of mild inflammation.

The first review is on the role of low-grade inflammation in diabetic retinopathy by Noda and Ishida at Hokkaido University. They have been studying the low-grade inflammation in the eye for a long period of time, showing the clear relationship between the inflammation and ocular diseases. This concept of low-grade inflammation is particularly important for the treatment and/or prevention of the diseases, because suppression of inflammation can be the therapeutic target in the very early phase of the disorders. There are many new and old strategies for the control of low-grade inflammation, including nutritional factors such as carotenoids or polyphenols, exercise, calorie restriction and drugs such as renin-angiotensin (RAS) blockers. Systemic RAS is well known to be the system that maintains blood pressure and the aberrant chronic activation causes high blood pressure. Previously, Dr. Ishida and Dr. Noda's group have found the local RAS system in the retina and this system can cause inflammation in the eye. Thus, the suppression of the RAS system may be the interesting intervention of inflammation. In diabetic retinopathy, abnormal neovascularization is of course the major cause of the problem, but we can learn the importance of low-grade inflammation in the development of the retinopathy.

The second topic is dry eye, which is covered by Ogawa from Keio University. The definition of dry eye was proposed by the International Dry Eye Workshop sponsored by the Tear Film and Ocular Surface Society in 2007 as "Dry eye is a multifactorial disease of the tears and ocular surface

that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface."[1] The readers may be surprised that inflammation is involved even in the definition of the disease, but chronic inflammation has been shown to be the major risk factor in dry eye. Actually the only available dry eye therapy in the USA is cyclosporine eye drops which suppresses T cells. Dr. Ogawa is the world wide leader in the dry eye associated GVHD in which inflammation is largely involved. Her last 20 years of research revealed that the fibrosis followed by chronic inflammation in the lacrimal gland is the major cause of lacrimal dysfunction. Very interestingly her group has found the local renin-angiotensin system in the lacrimal gland just as Dr. Ishida's group has found in the retina. Suppression of fibrosis by the RAS control in lacrimal gland is really the breakthrough in the control of severe GVHD-associated dry eye syndrome.

The third topic is genetic susceptibility for Stevens-Johnson syndrome/toxic epidermal necrolysis with mucosal involvements by Ueta et al in Kyoto Prefectural University. Stevens-Johnson syndrome/toxic epidermal necrolysis is the major cause of drug-related side effects and the etiology is unknown. Dr. Ueta's group has been performing extensive research on the genetic factors and found several key molecules which are involved in innate immunology. Although the research is still in the early phase, it may be able to find the real mechanism of Stevens-Johnson syndrome/toxic epidermal necrolysis in the near future.

Th17 is involved deeply in autoimmune disorders. Takeda, Ishibashi and Sonoda at Kyushu University and Yamaguchi University described "Regulation of Th1 and Th17 cell differentiation in uveitis." Uveitis is the most typical inflammatory disorder of the eye and various therapeutic approaches were executed. Immunosuppressants such as cyclosporine and steroids are the major treatment options, but the more specific intervention is awaited. The regulation of TH1, Th2, and TH17 differentiation is the very important aspect for chronic uveitis and the details are discussed in this review.

Dr. Usui of Tokyo Medical University wrote the involvement of non-T cells in infectious uveitis. T cell is of course the major player in the immune reaction, but the recent advance of disease understating has shed light to the importance of non-T cells in the infectious uveitis. Tokyo Medical College has a long history of research activity in infectious and non-infectious uveitis lead by Dr. Masahiko Usui, the father of the author and Dr. Goto the current chairman of the department. This review provides the unexpected importance of non-T cell involvement in this disease.

Finally Dr. Hori at Nippon Medical School covers the interesting aspects of ocular immunology, immune privilege. Readers may be aware that the eye is a unique organ that has the system to suppress inflammation, similar to testis. If the inflammation is strong, it may be able to kill the bacteria or viruses, it damages the sensitive retinal structure as well as the transparency of lens or cornea. The permanent damage to the retina or opacity of the lens and cornea deteriorates the function of the eye, so it is beneficial to keep the mild inflammatory reaction when the event happens. This suppressed inflammation system is called "immune privilege" which may be achieved by the high concentration of IL-10 in the eye, strong blood retinal barrier, covered by FASL expressing epithelium, and upregulation of TGF-β in aqueous humor. It is well known that 50% of corneal transplants can survive without HLA matching and the use of steroid, possibly due to the immune privilege of the eye. This unique system first was described by Dr. Weinlen at Harvard University where Dr. Hori has studied and continued the research after coming back to Japan. Her review "Immune privilege as new therapeutic strategies for success of transplantation" provides us with the most recent understanding of the system and the possibility of unique activation as a therapeutic purpose.

It is my great pleasure to have this opportunity to serve as guest editor of this special issue of "Inflammation in Ophthalmology." Inflammation as well as silent inflammation are the important aspects of etiology of various eye disorders and I hope readers will enjoy the contents.

Reference

1) The Definition and Classification of Dry Eye Disease: Report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). The Ocular Surface. 2007; 5: 75-92.