Influence of the Eye-associated Lymphoid Tissue (EALT) on Inflammatory Ocular Surface Disease

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ABSTRACT **Certain similarities exist in the pathophysiological processes and clinical features of advanced stages of various inflammatory ocular surface diseases, suggesting that common pathways contribute to these diseases. In this article, common pathways are analyzed with a focus on the role of the physiological resident mucosal immune system of the ocular surface, termed eye-associated lymphoid tissue (EALT). This is physiologically protective but if it is deregulated it can mediate an inflammatory immune answer. Common events in inflammatory ocular surface disease lead to a vicious circle of immune-modulated inflammation, with degenerative remodeling and loss of function.**

KEY WORDS **Eye-associated lymphoid tissue (EALT), inflammation, mucosal immune system, mucosa-associated lymphoid tissue (MALT)**

I. INTRODUCTION

Inflammatory processes contribute to various forms of ocular surface disease as subclinical or clinically overt inflammation. In recent years, it has been learned that inflammation is regulated by the immune system, and it involves a T-cell mediated process that produces an immune-modulated inflammation. Inflammation is an important pathogenetic factor in diseases that are known for involvement of lymphocytic infiltration, such as Sjogren syndrome, chronic ocular allergy, or corneal transplant rejection. Furthermore, also in dry eye syndrome due to a primary tear deficiency, inflammatory processes represent an important and underestimated component of the disease. All the ocular surface diseases with an inflammatory component have a chronic, self-perpetuating and deteriorating course that can eventually result in degenerative tissue remodeling and loss of function.

The pathophysiological processes and clinical findings in advanced stages of various inflammatory ocular surface diseases have certain similarities and, thus, appear to be based on certain common pathways that contribute to the self-perpetuating character of this disease type. In this review, common pathways are analyzed, with a focus on the role of the physiological resident mucosal immune system of the ocular surface (EALT). These pathways involve the alteration of the cytokine milieu, the mode of antigen presentation, the up-regulation of adhesion molecules with recruitment of leukocytes, and the activation of matrix metalloproteinases.

II. LYMPHOID CELLS ARE A NORMAL COMPONENT OF THE HUMAN OCULAR SURFACE

Lymphoid cells in the tissues of the ocular surface (i.e., the contiguous mucosal surface of the cornea, conjunctiva, lacrimal glands, and lacrimal drainage system) have long been recognized.[1,2] Their functional significance, however, was not recognized, and the understanding of these cells was complicated by the historic misconception that lymphoid cells were simply part of a group of leukocytes that were termed "inflammatory cells." The use of this term continued even after lymphoid cells were regularly observed in normal conjunctival tissue[3] and were acknowledged as a normal component of, for example, the lacrimal gland.[4,5]

Several studies over recent decades have provided convincing evidence that lymphoid cells (mainly lymphocytes and plasma cells) are a normal and noninflammatory component of the ocular surface; this topic has been reviewed.[6] In the light of advances in mucosal immunology in other parts of the body, it was recognized that, in fact, the entire

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Abbreviations are printed in **boldface** where they first appear with their definitions.

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ARTICLE OUTLINE

ocular surface contains a mucosa-associated lymphoid tissue (**MALT**, Figure 1), which had previously been known in the intestine as gut-associated lymphoid tissue (**GALT**) or in the airways as bronchus-associated lymphoid tissue (**BALT**).

The mucosal immune system has the task of immune protection of the moist mucosal inner and outer surfaces of the body. Components of the mucosal immune system also form a continuous MALT[7] from the gland-associated lymphoid tissue of the lacrimal gland over the conjunctiva-associated lymphoid tissue (**CALT**)[8] and along the lacrimal drainage-associated lymphoid tissue (**LDALT**),[9] including the nasolacrimal duct.[10] Together, these form an eye-associated lymphoid tissue (**EALT**)[11] that joins GALT and BALT as a new component of the mucosal immune system of the body. It is connected to the other tissues of the immune system by the regulated migration of lymphoid cells (recirculation) in the body via specialized vessels.[12]

Therefore, lymphoid cells are resident at the normal ocular surface. They are physiologically non-inflammatory, they are continuously involved in the maintenance of mucosal immune regulation, and they do not need to immigrate in order to interact in local immunological processes.[11] This is an important difference from the previous perception that lymphoid cells immigrate as "inflammatory cells" into a primarily lymphocyte-free normal ocular surface as a secondary or tertiary event in inflammatory disease processes.

III. EYE-ASSOCIATED LYMPHOID TISSUE (EALT) MAINTAINS THE PHYSIOLOGICAL IMMUNE PROTECTION OF THE OCULAR SURFACE.

The ocular surface is equipped with a complete mucosal immune system, consisting in part of organized lymphoid follicles in CALT and LDALT, which provide the

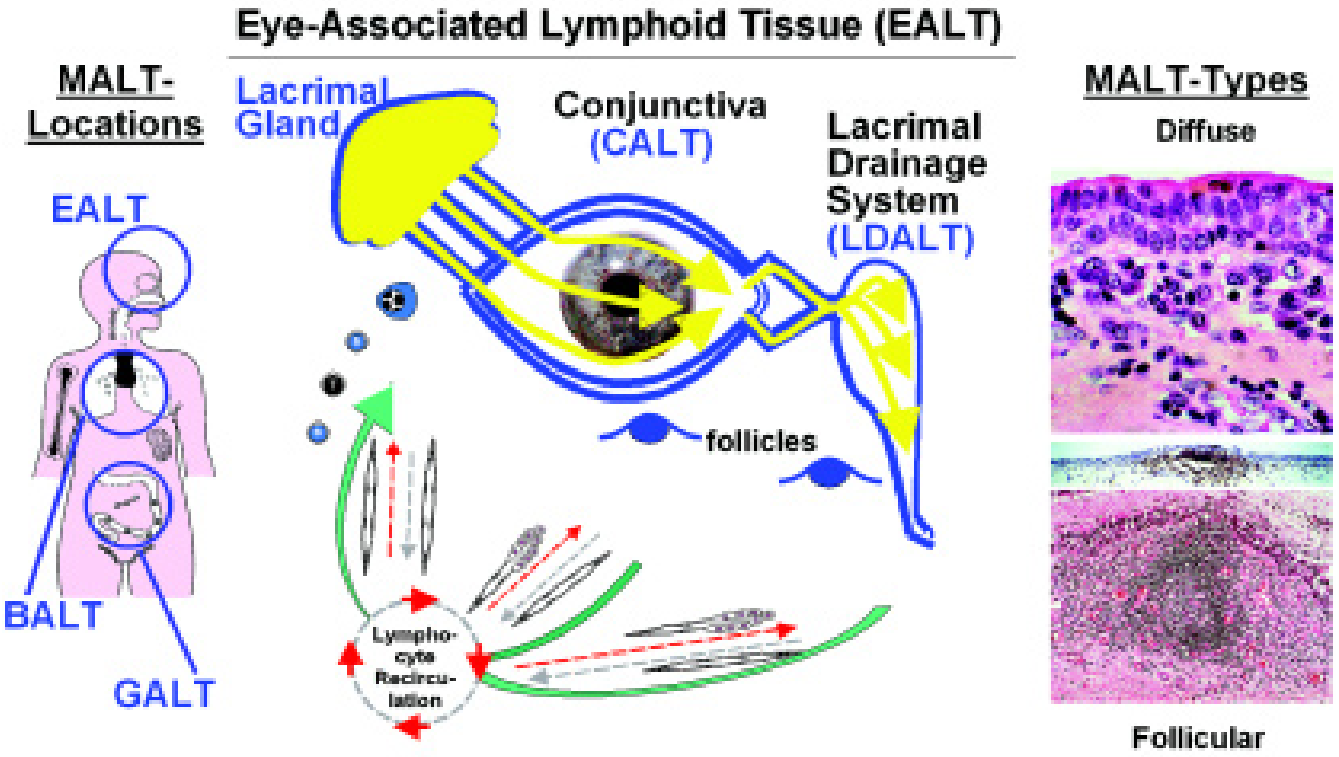

Figure 1. Eye-associated lymphoid tissue (EALT). EALT is a part of the mucosa-associated lymphoid tissue (MALT) together with, e.g., the gut- and bronchus-associated lymphoid tissue (GALT and BALT). It is continuous at the ocular surface and its mucosal adnexa from the lacrimal gland via the conjunctiva-associated lymphoid tissue (CALT) along the lacrimal drainage-associated lymphoid tissue (LDALT). These organs are also linked by the flow of tears and the recirculation of lymphoid cells via specialized vessels. MALT is composed of two conformations, the diffusely interspersed lymphoid effector cells and the follicular organized cells that represent the afferent arm of the immune system for antigen uptake and presentation and for the generation of lymphoid effector cells.

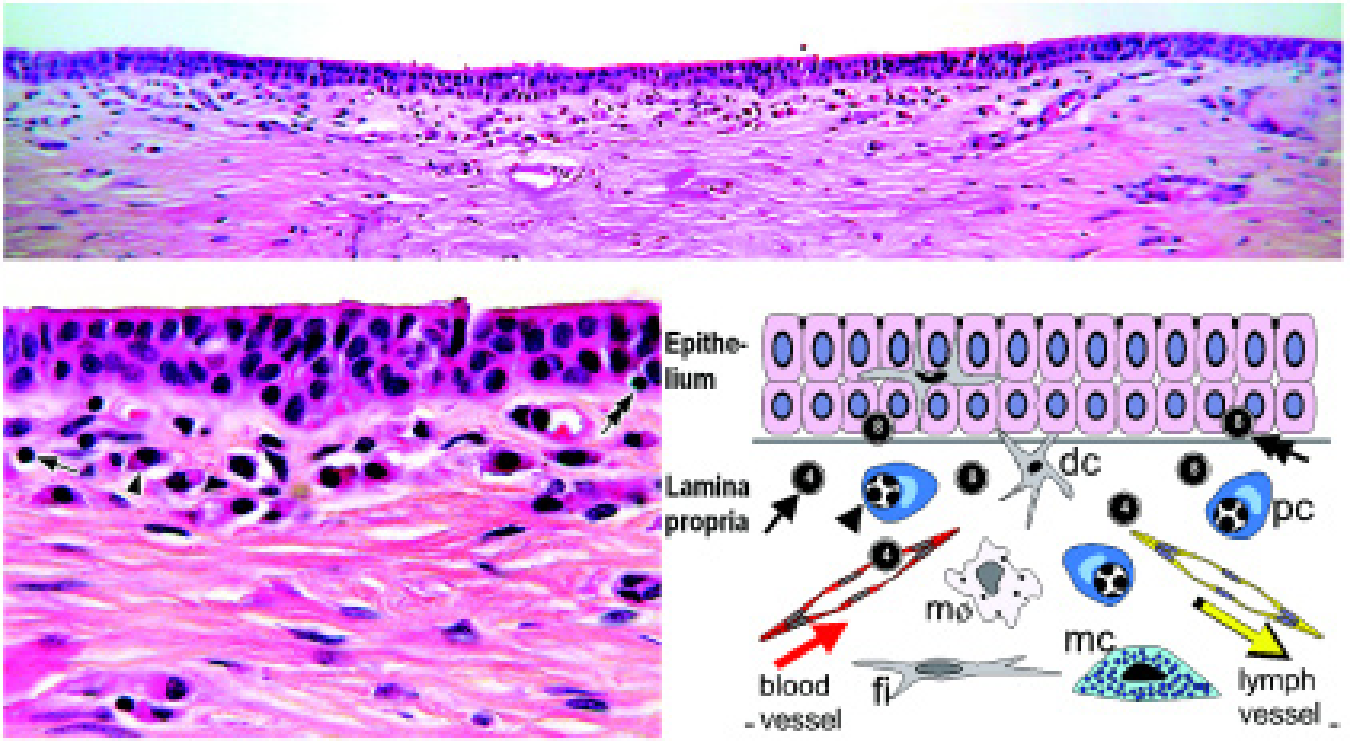

Figure 2. Diffuse lymphoid tissue. The diffuse type of conjunctival lymphoid tissue is universally present at the normal human ocular surface, but it is not easily seen in overview because it consists of a usually narrow layer of diffusely interspersed cells in the lamina propria together with small vessels and of intraepithelial lymphocytes. Closer examination shows that they have all the typical characteristics of diffuse lymphoid tissue, as found in other mucosal lymphoid organs. This concerns the predomination of CD8+ vs. CD4+ lymphocytes in the epithelium and their roughly equal distribution in the lamina propria, as well as the presence of IgA+ plasma cells (pc), dendritic cells (dc), macrophages (mø), mast cells (mc) and stromal fibrocytes (fi). Lymphoid cells are, therefore, continuously present at the normal human ocular surface and are intimately involved in the physiological homeostasis and immune regulation without the necessity to immigrate prior to any kind of action as previously believed.

uptake and presentation of antigens to lymphocytes and their eventual proliferation and differentiation into effector cells. An additional diffuse lymphoid tissue,[13] consisting of the diffusely interspersed generated lymphoid effector cells, is present throughout all the ocular tissues (Figure 2). The ocular tissues are connected by the regulated migration of lymphoid cells via numerous small vessels, including specialized high endothelial venules.[14] The interspersed lymphoid cells show all the characteristics of a regular diffuse lymphoid tissue. They consist mainly of lymphocytes, which are present as a thin layer of lamina propria lymphocytes in the connective tissue and as intraepithelial lymphocytes (**IEL**) in the basal layers of the epithelium and of plasma cells in the lamina propria. The lymphoid cells are supplemented by other bone marrow-derived cells, such as dendritic cells, macrophages, and mast cells, and can interact with the stromal fibrocytes and vascular endothelial cells (Figure 2). The subtypes and distribution of lymphocytes at the human ocular surface resemble those observed in other organs of the mucosal immune system.[15-17]

Analysis of the topographical distribution of EALT in the conjunctiva shows that it matches the position of the cornea and is in direct contact with the corneal surface,

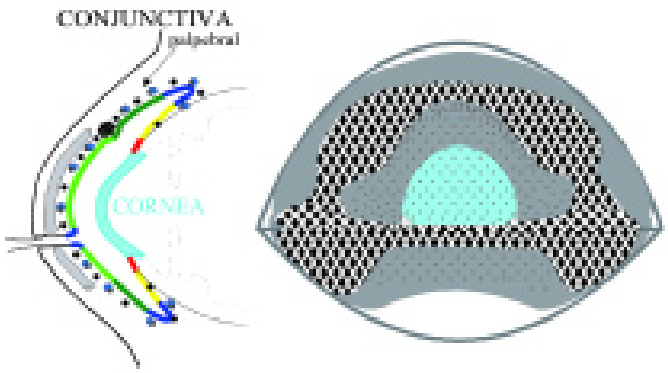

Figure 3. The topography of ocular surface lymphoid tissue is congruent with the position of the cornea. The cells of the conjunctival lymphoid tissue are present in the whole conjunctiva (left, eye in cross section) but show a predominant expression in the tarso-orbital zones of upper and lower palpebral conjunctiva. This is true for the diffuse and follicular types of lymphoid tissue and also for the cells associated with the conjunctival crypts indicated here by hatched lines and open dots in right-hand diagram. If the location of the lymphoid tissue is projected onto the bulbar surface (right, ocular surface of closed eye in frontal view), it nicely correlates with the position of the cornea that does not contain lymphoid cells itself and, hence, depends on the immune protection provided by the conjunctival immune system. The mucosal immune system of the conjunctiva is, therefore, relevant for corneal health and disease.

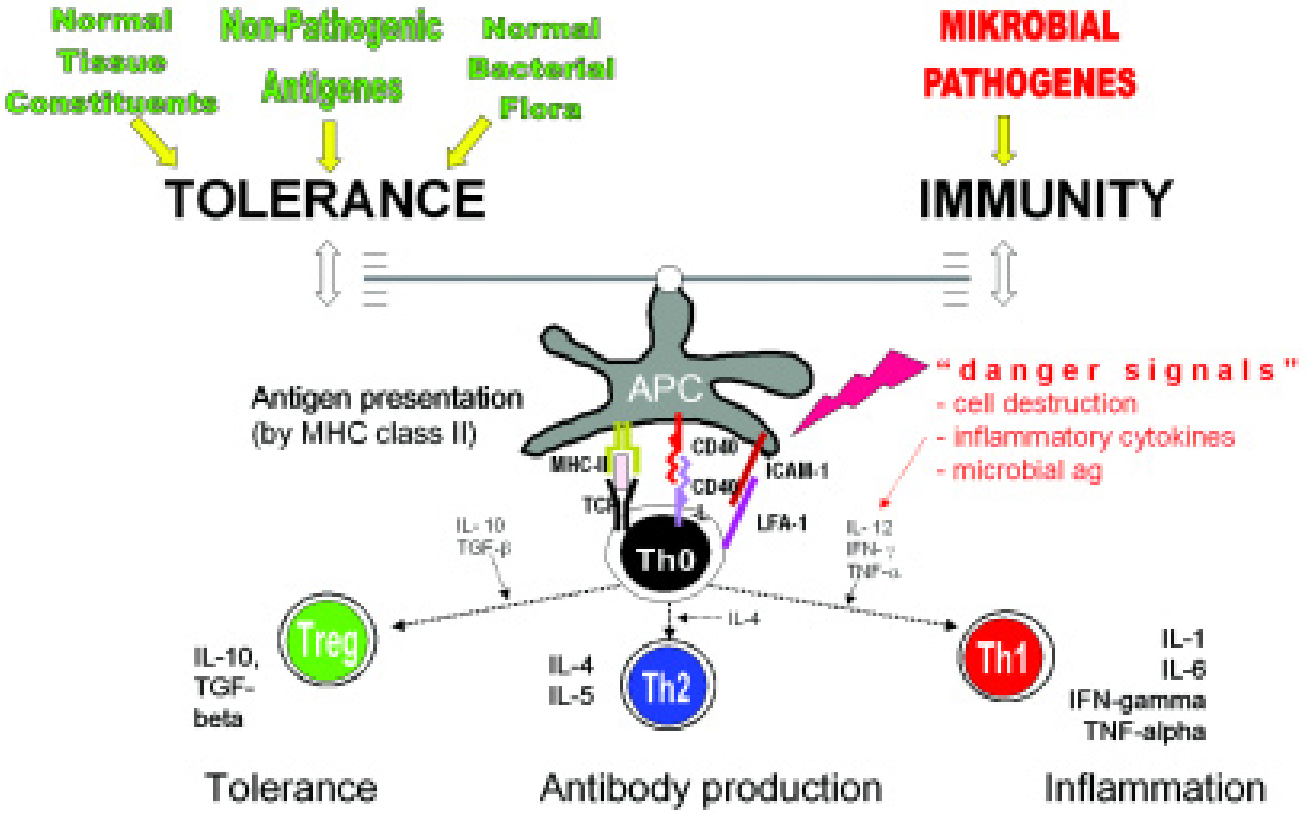

Figure 4. The physiological function of the ocular mucosal immune system is protective and anti-inflammatory. The ocular mucosal immune system maintains the delicate balance between the tolerance to ubiquitous nonpathogenic antigens and adverse immune reactions e.g., against pathogenic microorganisms, which involve inflammatory reactions and, hence, endanger ocular surface integrity. This balance is mediated by the mode of antigen presentation maintained by antigen-presenting cells (APC) and results in the generation of different subtypes of effector T-cells. Physiologically, EALT favors immune tolerance by regulatory T-cells (Treg) and the production of protective anti-inflammatory IgA antibodies stimulated by Th2 cells. Disturbance of the physiological condition by the presence of "danger signals," however, can lead to an inflammatory Th1 response and includes the risk of a deregulation of mucosal immunity.

particularly when the eye is closed (Figure 3). This topography, the fact that the cornea itself does not contain its own lymphoid cells, and the fact that during night-time in the closed-eye situation, the corneal integrity is protected by massive influx of leukocytes and their mediators[18] strongly suggests that EALT has an important role in the protection of corneal health and integrity.[6]

The task of the ocular surface lymphocytes is, contrary to previous assumptions, not to generate inflammation but, rather the reverse, to protect the ocular surface against inflammatory processes that may lead to tissue destruction. The generation and modulation of the mucosal immune response is regulated through the mode of antigen presentation[19] by so-called professional antigen-presenting cells (mainly by dendritic cells, including Langerhans cells)[20] and is executed by the different populations of effector T-helper-cells that result from this priming process (Figure 4).

IV. THE MODE OF ANTIGEN PRESENTATION REGULATES THE FUNCTION OF LYMPHOID CELLS

The physiological mode of EALT is the immunological nonresponsiveness (tolerance) or the production of IgA antibodies (Figure 4). Tolerance is directed against the multitude of nonpathogenic environmental antigens that have access to the ocular surface and it is generated by regulatory T-cells (Treg)[21] via the production of immunosuppressive cytokines, such as interleukin (**IL**)-10 and transforming growth factor (**TGF**)-β. Tolerance must, of course, also be maintained against the body's own tissue antigens.[22] If they were regarded as foreign by the immune system, autoimmune disease would occur, as seen when components of intercellular adherence junctions become auto-antigens, as occurs in ocular pemphigoid.

Another frequent and usually immuno-protective mucosal mechanism is regulated by T-helper cells type 2 (**Th2**) via their cytokines IL-4 and Il-5. It consists of the secretion of antibodies by mucosal plasma cells, because these produce mainly the anti-inflammatory IgA isotype.[23] When other immunoglobulin isotypes, e.g., IgE, are produced, however, they may result in allergic disease. The presence of pathogenic microbial antigens usually makes it necessary to mount an inflammatory cellular response induced by Th1 lymphocytes, because the risk of infection may be more critical for the health and integrity of the individual than the potential tissue destruction that occurs during its elimination.

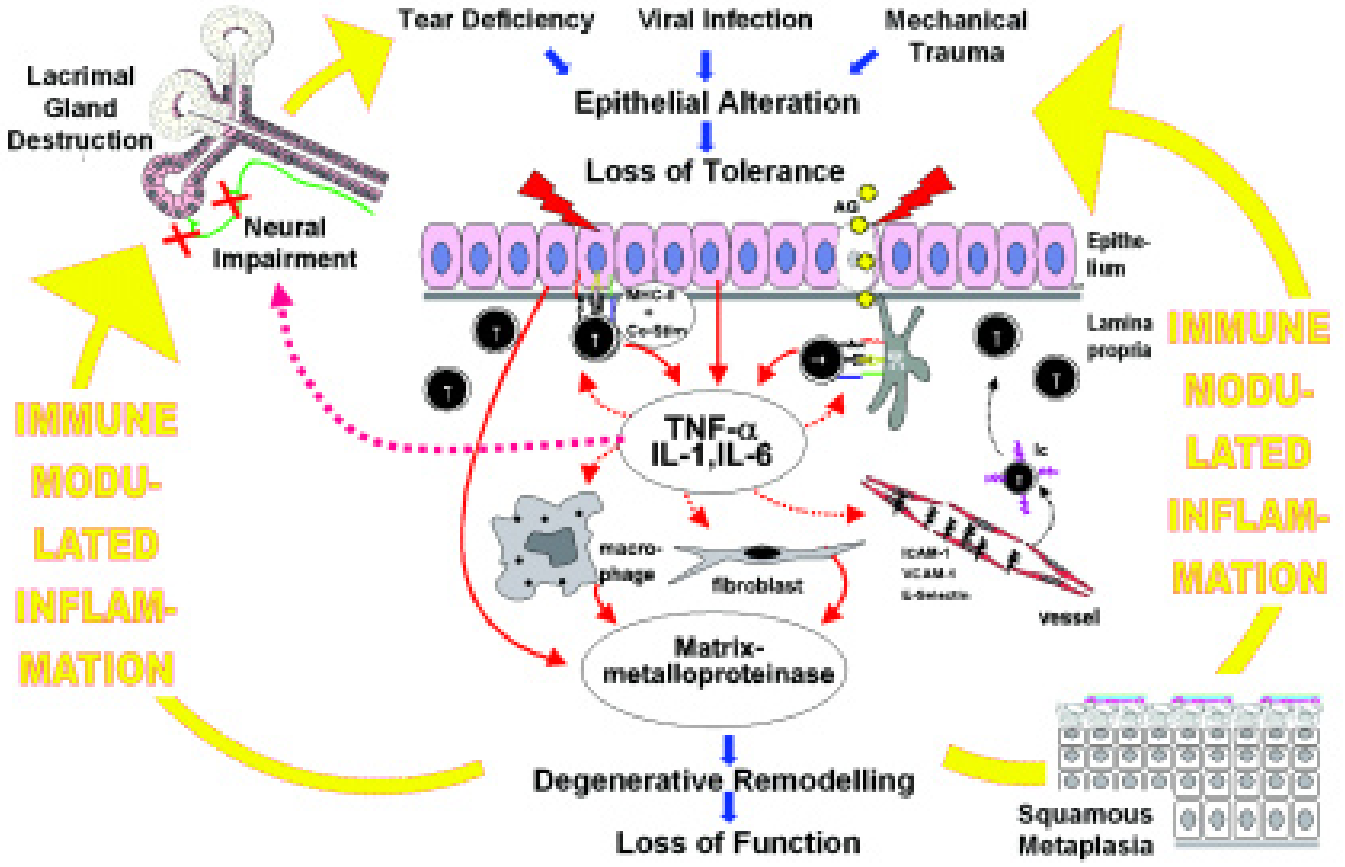

Figure 5. Inflammatory ocular surface disease includes a deregulation of the mucosal immune system by initial stimuli, such as infection, mechanical trauma, or tear deficiency, which are present, for example, in dry eye syndrome. A deregulation and loss of physiological mucosal tolerance leads to skewed antigen presentation to the resident lamina propria lymphocytes (T) and to the increase of inflammatory cytokines, which induce a T cell-mediated inflammatory process. Together with the release of destructive matrix metalloproteinases resulting in a degenerative remodeling and loss of function of the ocular tissues, this can lead to a self-perpetuating cycle of immune-modulated inflammation and ocular surface destruction, as is found in advanced stages of various types of inflammatory ocular surface disease.

V. TISSUE WOUNDING AND ALTERATION OF THE CYTOKINE MILIEU CAN DEREGULATE ANTIGEN PRESENTATION AND PHYSIOLOGICAL LYMPHOCYTE FUNCTION

Not only microbial antigens, but also other "danger signals,"[24] such as tissue destruction or a change of the cytokine milieu involving an increase of inflammatory cytokines, can skew the normal mode of antigen presentation in the direction of an inflammatory response and can, hence, deregulate the physiologically protective mucosal immune system. Both mechanical destruction and an elevation of inflammatory cytokines occur, for instance, in dry eye disease. Mechanical destruction in dry eye disease results from wounding of the epithelium due to the shear forces of lid movement over the dry surface.[25] Inflammatory cytokines are produced by the altered epithelial cells and, conceivably, accumulate in dry eye conditions that include reduced tear clearance; they also occur in ocular allergy.[26]

The increased presence of "danger signals," such as inflammatory cytokines and the activation of cells, alter the mode of antigen presentation toward the generation of inflammatory immune response. This does not apply only to professional antigen-presenting cells. In chronic conjunctivitis and dry eye, an expression of the antigen-presenting molecule MHC-class-2 and costimulatory signals, such as the adhesion molecule ICAM-1 and CD40, are observed on epithelial cells,[27,28] and they may, thus, acquire the potential of presentation of self-antigens, as shown for the lacrimal gland epithelial cells.[29] The resulting inflammatory T-cells are themselves important sources of inflammatory cytokines. This represents a vicious cycle of increasing lymphocyte activation and contributes to a further accumulation of inflammatory cytokines in the tissue and tear film, causing a continuing alteration of the normal cytokine milieu (Figure 5).

VI. UNCONTROLLED ACTIVATION OF MATRIX METALLOPROTEINASES CAN SUPPORT A DEGENERATIVE REMODELLING OF THE OCULAR TISSUES AND A LOSS OF FUNCTION

Inflammatory cytokines do not only act on antigen presenting cells, but they also influence a number of other cell types at the ocular surface. One effect appears to be an inhibition of neural signaling, which results, via a blockade of the lacrimo-functional unit,[30] in a decrease of tear

production by the lacrimal gland. Another important local effect is the up-regulation of adhesion molecules, like ICAM-1, VCAM-1, or E-Selectin, on vascular endothelial cells.[31] This results in a recruitment of leucocytes, including additional lymphocytes that contribute to the disease,[32] from the vascular compartment into the ocular tissues. Furthermore, other cells, such as stromal macrophages, fibrocytes, granulocytes, and the surface epithelium, are stimulated by inflammatory cytokines to produce tissue proteases (matrix metalloproteinases [**MMP**s], mainly MMP9)[33] that degrade the connective tissue structure and epithelial basement membrane. Elevated levels of activated MMPs are observed in various inflammatory ocular surface diseases, such as tear-deficient dry eye,[34] Sjogren syndrome,[35] corneal disease,[36,37] conjunctivochalasis,[38] and ocular allergy.[39]

Apart from connective tissue destruction, the presence of inflammatory cytokines also has a deleterious effect on the differentiation of the ocular epithelia; they appear to induce an increased proliferation of epithelial cells that remain in an immature state, probably due to a decreased level of differentiating factors like EGF from the lacrimal gland in dry eye conditions.[40,41] This explains the development of squamous metaplasia, which is observed as a uniform reaction in several different types of inflammatory ocular surface disease. Similar events are described in inflammatory bowel disease of the intestine,[42] which highlights the fact that the described sequence of events in immune-modulated ocular surface inflammation appears to be a general characteristic of inflammatory mucosal disease.

VII. COMMON EVENTS IN INFLAMMATORY OCULAR SURFACE DISEASE LEAD TO A VICIOUS CYCLE OF IMMUNE MODULATED INFLAMMATION

Taken together, immune-mediated inflammation of the ocular surface with degenerative remodeling of the tissue and a loss of function leads to decreased tear flow from the lacrimal gland, to squamous metaplasia with immature epithelium in the conjunctiva, and to an alteration of corneal epithelial integrity. All of this is sufficient to reinforce the initial causes of the disease, resulting in an increased likelihood of further epithelial defects, which, in another vicious cycle, enforce the deterioration of the micro-milieu at the ocular surface.

The disease state that results from these events may first be sub-clinical or mild and can be managed by symptomatic therapy, such as artificial tears, which decrease friction and/or dilute high concentrations of inflammatory cytokines. This may restore tissue integrity and interrupt the pathways before onset of immune-mediated inflammation. When the stimulus is strong enough or has continued long enough to initiate the self-perpetuating immune-modulated inflammation that can be mediated by deregulated resident lymphocytes of the mucosal immune system, it may be useful to introduce immuno-modulatory therapy. This therapy can either be generally immunosuppressive, e.g.,cortisone, or, preferably, it should interact specifically with the involved immune process that depends on the critical step of lymphocyte activation. Therefore, specific inhibitors of lymphocyte activation, such as cyclosporin A[43] or FK506, which have previously been successfully used in the pathophysiological similar inflammatory bowel disease, have recently been introduced in treatment of severe cases of human ocular surface disease.

REFERENCES

1. Kessing SV. A quantitative normal anatomical study. Acta Ophthalmol (Copenh) 1968;Suppl 95:1-133
2. Osterlind G. An investigation into the presence of lymphatic tissue in the human conjunctiva, and its biological and clinical importance. Acta Ophthalmol(Copenh) 1944;Suppl. 23:1-79
3. Allansmith MR, Greiner JV, Baird RS. Number of inflammatory cells in the normal conjunctiva. Am J Ophthalmol 1978;86:250-9
4. Franklin RM, Kenyon KR, Tomasi TB, Jr. Immunohistologic studies of human lacrimal gland: localization of immunoglobulins, secretory component and lactoferrin. J Immunol 1973;110:984-92
5. Wieczorek R, Jakobiec FA, Sacks EH, Knowles DM. The immunoarchitecture of the normal human lacrimal gland. Relevancy for understanding pathologic conditions. Ophthalmology 1988;95:100-9
6. Knop E, Knop N. The role of eye-associated lymphoid tissue in corneal immune protection. J Anat 2005;206:271-85
7. Knop E, Knop N. [Eye-associated lymphoid tissue (EALT) is continuously spread throughout the ocular surface from the lacrimal gland to the lacrimal drainage system]. Ophthalmologe 2003;100:929-42
8. Knop N, Knop E. Conjunctiva-associated lymphoid tissue in the human eye. Invest Ophthalmol Vis Sci 2000;41:1270-9
9. Knop E, Knop N. Lacrimal drainage associated lymphoid tissue (LDALT): A part of the human mucosal immune system. Invest Ophthalmol Vis Sci 2001;42:566-74
10. Paulsen FP, Paulsen JI, Thale AB, et al. Organized mucosa-associated lymphoid tissue in human naso-lacrimal ducts. Adv Exp Med Biol 2002;506:873-6
11. Knop E, Knop N. A functional unit for ocular surface immune defense formed by the lacrimal gland, conjunctiva and lacrimal drainage system. Adv Exp Med Biol 2002;506:835-44
12. Gowans JL. The recirculation of lymphocytes from blood to lymph in the rat. J Physiol 1959;146:54
13. Kraehenbuhl JP, Neutra MR. Molecular and cellular basis of immune protection of mucosal surfaces. Physiol Rev 1992;72:853-79
14. Knop E, Knop N. Lymphocyte homing in the mucosal immune system to the eye-associated lymphoid tissue (EALT), in Zierhut M, Sullivan DA, Stern ME, (eds). Immunology of the ocular surface and tearfilm. Amsterdam, Swets & Zeitlinger, 2004, pp 35-72
15. Dua HS, Gomes JA, Jindal VK, et al. Mucosa specific lymphocytes in the human conjunctiva, corneoscleral limbus and lacrimal gland. Curr Eye Res 1994;13:87-93

16. Hingorani M, Metz D, Lightman SL. Characterisation of the normal conjunctival leukocyte population. Exp Eye Res 1997;64:905-12
17. Sacks EH, Wieczorek R, Jakobiec FA, Knowles DM. Lymphocytic subpopulations in the normal human conjunctiva. A monoclonal antibody study. Ophthalmology 1986;93:1276-83
18. Sack RA, Conradi L, Krumholz D, Beaton A, Sathe S, Morris C. Membrane array characterization of 80 chemokines, cytokines, and growth factors in open- and closed-eye tears: angionenin and other defense system constituents. Invest Ophthalmol Vis Sci 2005;46(4):1228-38.
19. Mougneau E, Hugues S, Glaichenhaus N. Antigen presentation by dendritic cells in vivo. J Exp Med 2002;196:1013-16
20. Dana MR. Corneal antigen-presenting cells: diversity, plasticity, and disguise. The Cogan Lecture. Invest Ophthalmol Vis Sci 2004;45:722-7
21. Annacker O, Pimenta-Araujo R, Burlen-Defranoux O, Bandeira A. On the ontogeny and physiology of regulatory T cells. Immunol Rev 2001;182:5-17
22. Steinman RM, Nussenzweig MC. Avoiding horror autotoxicus: the importance of dendritic cells in peripheral T cell tolerance. Proc Natl Acad Sci U S A 2002;99:351-8
23. Sullivan DA. Immunology of the lacrimal gland and tear film. Dev Ophthalmol 1999;30:39-53
24. Matzinger P. Tolerance, danger, and the extended family. Annu Rev Immuno 1994;12:991-1045
25. Pflugfelder SC. Tear fluid influence on the ocular surface. Adv Exp Med Biol 1998;438:611-7
26. McGill J. Conjunctival cytokines in ocular allergy. Clin Exp Allergy 2000;30:1355-7
27. Baudouin C, Haouat N, Brignole F, et a;. Immunopathological findings in conjunctival cells using immunofluorescence staining of impression cytology specimens.Br J Ophthalmol 1992;76:545-9
28. Brignole F, Pisella PJ, Goldschild M, et al. Flow cytometric analysis of inflammatory markers in conjunctival epithelial cells of patients with dry eyes. Invest Ophthalmol Vis Sci 2000;41:1356-63
29. Mircheff AK, Xie J, Qian L, Hamm-Alvarez SF. Diverse perturbations may alter the lacrimal acinar cell autoantigenic spectra. DNA Cell Biol 2002;21:435-42
30. Stern ME, Beuerman RW, Fox RI, et al. A unified theory of the role of the ocular surface in dry eye. Adv Exp Med Biol 1998;438:643-51
31. Gao J, Morgan G, Tieu D, et al. ICAM-1 expression predisposes ocular tissues to immune-based inflammation in dry eye patients and Sjogrens syndrome-like MRL/lpr mice. Exp Eye Res 2004;78:823-35
32. Stern ME, Gao J, Schwalb TA, et al. Conjunctival T-cell subpopulations in Sjogren's and non-Sjogren's patients with dry eye. Invest Ophthalmol Vis Sci 2002;43:2609-14
33. Sternlicht MD, Werb Z. How matrix metalloproteinases regulate cell behaviour. Annu Rev Cell Devel Biol 2001;17:463-516
34. Afonso AA, Sobrin L, Monroy DC, et al. Tear fluid gelatinase B activity correlates with IL-1alpha concentration and fluorescein clearance in ocular rosacea. Invest Ophthalmol Vis Sci 1999;40:2506-12
35. Konttinen YT, Halinen S, Hanemaaijer R, et al. Matrix metalloproteinase (MMP)-9 type IV collagenase/gelatinase implicated in the pathogenesis of Sjogren's syndrome. Matrix Biol 1998;17:335-47
36. Garrana RM, Zieske JD, Assouline M, Gipson IK. Matrix metalloproteinases in epithelia from human recurrent corneal erosion. Invest Ophthalmol Vis Sci 1999;40:1266-70
37. Smith VA, Rishmawi H, Hussein H, Easty DL. Tear film MMP accumulation and corneal disease. Br J Ophthalmol 2001;85:147-53
38. Meller D, Li DQ, Tseng SC. Regulation of collagenase, stromelysin, and gelatinase B in human conjunctival and conjunctivochalasis fibroblasts by interleukin-1beta and tumor necrosis factor-alpha. Invest Ophthalmol Vis Sci 2000;41:2922-9
39. Kumagai N, Yamamoto K, Fukuda K, et al. Active matrix metalloproteinases in the tear fluid of individuals with vernal keratoconjunctivitis. J Allergy Clin Immunol 2002;110:489-91
40. Jones DT, Monroy D, Ji Z, Pflugfelder SC. Alterations of ocular surface gene expression in Sjogren's syndrome. Adv Exp Med Biol 1998;438:533-6
41. Pflugfelder SC, Jones D, Ji Z, et al. Altered cytokine balance in the tear fluid and conjunctiva of patients with Sjogren's syndrome keratoconjunctivitis sicca. Curr Eye Res 1999;19:201-11
42. MacDonald TT, Bajaj-Elliott M, Pender SL. T cells orchestrate intestinal mucosal shape and integrity. Immunol Today 1999;20:505-10
43. Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group. Ophthalmology 2000;107:631-39