Eye-associated lymphoid tissue (EALT) and its relationship to sicca syndrome

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3. Eye-associated lymphoid tissue (EALT) and its relationship to sicca syndrome

3.1. Overview of the dry eye

3.1.1. Definition and forms

The dry eye syndrome (also known as keratoconjunctivitis sicca or sicca syndrome) is a relatively frequent change in the normal homeostasis of the ocular surface and represents a complex disorder of the functional anatomy and immunology of the ocular surface [1] and leads to the development of changes in the ocular surface, mostly in the freely lying interpalpebral region and to the development of symptoms. According to the original definition from the US National Eye Institute (NEI) [2], this is caused either by quantitative changes (usually a decrease in the amount of tears but occasionally also a transient increase via a reflex mechanism [3]) or by qualitative changes (e.g. deficiency of the lipid phase) of the tear film [1, 4-7]. This definition was subsequently extended to include the importance of hyperosmolarity of the tear film [8-11] and the presence usually of subclinical but occasionally also severe clinical inflammatory phenomena [12-17]. In advanced stages, it may be difficult to differentiate between the tear deficit and the evaporative dry eye [18, 19]. The development of dry eye is also influenced, for example, by systemic diseases, gender, age, hormonal disturbances [20, 21], psychogenic factors [22-24] and environmental factors such as dry air [25-27] or working in front of a computer screen [28-30].

3.1.2. Symptoms and investigations

The symptoms of dry eye are, at least if the condition is not very severe, often uncharacteristic and, depending on the underlying disorder, in some cases also dependent on the time of day. They are manifested as a feeling of dryness and irritation of the ocular surface or a diffuse feeling of tired eyes [31], fluctuating vision [32] and often intolerance to contact lenses [33-37]. The clinical parameters of the amount of tears (Schirmer's test) and tear film stability (tear film break-up time) are typically altered [4, 5, 19, 38-40]. Through complex analysis of different parameters, subtypes can be differentiated from each other, which may be important for therapy [41]. During the course of the disease, mechanical and inflammatory changes in the conjunctiva, lid margin and especially the cornea can occur.

3.1.3. Epidemiology

Dry eye is one of the most common disorders of the ocular surface, and, depending on the age-group, gender and severity, approximately 10-30% of the population suffer from it [42-46]. More females suffer from it than males, and the incidence increases with increasing age and is also affected by ethnic factors. Although dry eye is occasionally mistaken to be a subjective complaint, it is nevertheless a disorder that should be taken seriously the investigation and therapy of which belong in the hands of the ophthalmologist [7].

3.1.4. Effect of the mucosal immune system on dry eye

In later stages of dry eye, inflammatory changes can occur which are progressive the longer they are present and then can no longer be satisfactorily treated with conventional therapy using artificial tears. The reason for this is an initially subclinical and then clinical inflammatory process which is influenced through deregulation of the mucosal immune system of the ocular surface, thus above all of the conjunctiva locally.

If this protective mucosal immune system is deregulated by various factors that play a role in dry eye, there is an excessive reaction which is characterised by loss of normal immune tolerance and then becomes directed against non-pathogenic environmental antigens or even components of the eye tissue itself (autoimmune reaction). These processes are accompanied by an immunologically modulated inflammatory reaction and, in severe cases, can required topical immunosuppressant therapy.

The way in which the mucosal immune system of the ocular surface works and disorders of its function in dry eye will be discussed in this chapter.

3.2. Anatomy of the ocular surface and mucosal immune system

3.2.1. Structure of the ocular surface and tear film

With the exception of the cornea, the surface of the eye is made of conjunctiva, whose surface area is much larger than that of the cornea. Both consist of an epithelial surface which is physiologically moist and thus represents a mucosa [47].

In order to be able to fulfil its main tasks of moistening the ocular surface and stabilising the tear film, which serve to ensure the integrity and transparency of the cornea for fulfilling its optical function [48], the conjunctiva also has a moist surface. This is ultimately very similar to the conditions in other mucous membranes of the body with the difference that, because of the necessary optical function, at least in the precorneal interpalpebral region, the surface fluid layer (tear fluid) of the ocular surface must be spread out to give a very thin, homogeneous layer, the tear film [49]; this is achieved by blinking. Beneath the epithelial layer of the conjunctiva is loose connective tissue (lamina propria), which typically contains immune cells (☞ Figure 3.1), which, together with soluble factors in the tissue and tear film, principally serve to protect against the increased risk of colonisation of moist surfaces by micro-organisms [50].

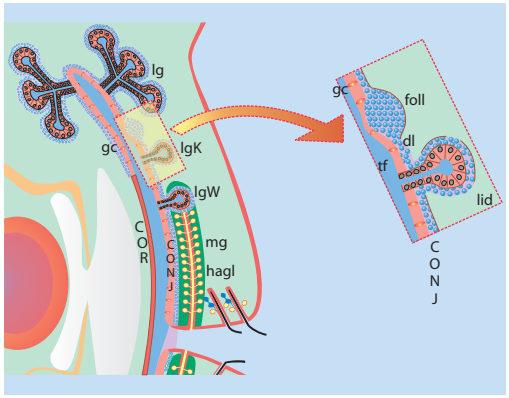


Figure 3.1: Ocular surface and attached glands with the cells of the mucosal immune system. The mucosa of the cornea (COR) and conjunctiva (CONJ) form a sac into which flow the aqueous secretion of the lacrimal gland (lg) and accessory lacrimal glands of Krause (lgK) and Wolfring (lgW). Hair-associated glands (hagl) of Zeiss and Moll are found on the eye lashes. The secretion of the numerous goblet cells (gc) in the conjunctiva forms the main part of the mucin phase. The lipid phase is formed from the oil of the meibomian glands (mg) in the tarsal plates of the eye lids which is released onto the posterior lid margin. With the exception of the cornea, the entire mucosa of the ocular surface contains cells of the mucosal immune system as a diffuse layer (dl) and solitary follicles (foll), as can be seen in the magnification of a labelled region of the lid with tear fluid (tf) and an accessory lacrimal gland; schematic diagram.

In the region of the palpebral fissure and especially on the surface of the cornea, the tear fluid is spread to form a thin layer, which ensures high optical quality. Accordingly, inhomogeneities of the tear film, as occurs with excessive tear production under the influence of emotion (crying), for example, or in the dry eye, are associated with fluctuating and reduced vision.

As was already known from early studies [51], this precorneal tear film [49] is formed of 3 chemically different layers, the two lower layers of which are probably mixed to a certain degree (☞ Figure 3.2). The layer thickness of the entire tear film as well as its individual layers has not yet been satisfactorily elucidated [49, 52].

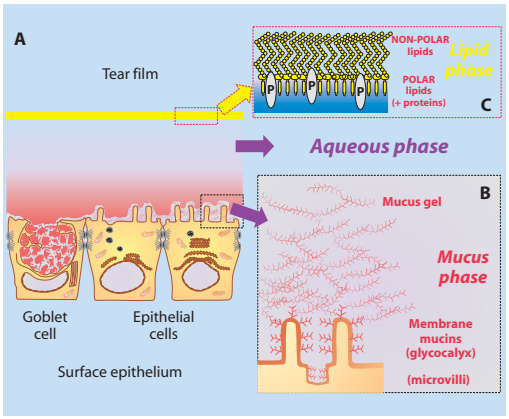


Figure 3.2: Tear film. The tear film basically consists of 3 phases, which approximately form layers (**A**). The mucin layer (**B**) consists of the cell-containing glycocalyx of the epithelial surface on which the soluble mucins from the goblet cells are deposited. These mix with the overlying aqueous phase, which is covered by a thin superficial lipid layer (**C**). The lipid layer consists of a lower layer of polar lipid and presumably proteins, which mediate adherence with the aqueous phase, as well as an outer layer of non-polar lipids (based on [1], with the kind permission of Springer Medizin Verlag).

The tear film is principally produced by aqueous secretion from the lacrimal gland in the orbit and accessory lacrimal glands in the lid connective tissue (☞ Figure 3.1). The aqueous layer contains an as yet unknown number of active substances, mostly proteins, which are formed by the lacrimal glands themselves, the surface epithelium or by a transudate from the blood serum [38, 39, 53-58]. These proteins, acting as growth factors or hormones for example, regulate the maturation and integrity of the ocular surface, and, as rheological factors, stabilise the structure of the tear film or have a protective function in the context of immune defence.

The adherence of the aqueous tear phase to the epithelium of the ocular surface is achieved by a mucin layer consisting of membrane mucins (glycocalyx) in the cell membrane of the conventional epithelial cells of the cornea and conjunctiva [59] and allowing moistening of the epithelium [60]. A further and presumably greater mucin proportion consists of soluble mucins, which are formed by the goblet cells of the conjunctiva [61]. They are deposited on the glycocalyx and are mixed with the aqueous phase. This mucin layer is adhesive and associated within it are also numerous soluble factors for immune defence (e.g. antimicrobial peptides (AMP) and specific secretory IgA). Pathogens and microbial antigens as well as environmental particles and cell debris are thus bound and rendered harmless [62]. Regular blinking allows the soluble mucin layer to be renewed, assembled together and removed from the ocular surface by the efferent tear ducts or as a strand of mucus in the medial palpebral angle [63].

The thin outer lipid layer of the tear film [64] is mainly formed by the meibomian glands [65, 66], although the epithelia of the ocular surface can probably also synthesise lipids to a certain extent [67], and has the main task of reducing evaporation of the aqueous phase [68-72]. If it is reduced in amount or quality, there is a evaporative tear deficiency due to increased evaporation of the aqueous phase with a decrease in tear film stability and consequently a shortened tear film break-up time (BUT), surface defects and symptoms of dry eye. Disorders of the lipid phase as a result of altered function of the meibomian glands are termed meibomian gland dysfunction (MGD) [73-80] and have been recognised as the most frequent cofactor [74, 81] and probably the most important trigger of dry eye. MGD is the most frequent form of posterior blepharitis and should be differentiated from the inflammatory anterior blepharitis as a syndrome in its own right [82]. If present for a long period of time, as a result of being diagnosed and treated too late, then besides abnormalities of the tear film, MGD may also lead to progressive degenerative destruction of the meibomian gland tissue with secondary decreased lipid secretion [73, 83-86].

3.2.2. Mucosal immune system of the ocular surface

The conjunctiva is subjected to very different environmental influences. Besides physical and chemical harmful substances and particles, colonisation by micro-organisms that may be pathogenic to a variable degree is also possible [87-89]. Although the conjunctiva is very directly exposed to the outside world compared with other mucous membranes of the body, it is usually astonishingly resistant to infections as a result of the protective mucosal immune system.

3.2.2.1. Components of the mucosal immune system

Soluble immune factors in the tear film and mucosal tissue

Part of the mucosal immune system consists of a chemical defence system of soluble proteins found in the tissue and also in the tear film (☞ Figure 3.3) and produced by epithelial cells and immune cells. Non-specific antimicrobial peptides and proteins (AMP) that are active enzymatically or in other ways, e.g. lysozyme and lactoferrin, but also substances that have only been described in recent years, such as defensins, TFF etc, are produced in the lacrimal gland but also in the conjunctiva itself and in the efferent tear ducts [90-93]. AMP non-specifically recognise microbes, e.g. on the basis of their cell surface that differs from body cells. Furthermore, specific immunoglobulins, especially IgA, produced by plasma cells, contribute to protection against antigens, especially those of microbes, which have previously come into contact with the immune system. For a long time, it was thought that only IgA from the lacrimal gland [94, 95] brought about passive protection of the epithelia of the ocular surface. In the meantime, however, it has been shown that the entire mucosa of the conjunctiva [96] and the efferent tear ducts [97] also actively produce IgA, which contributes to immune defence in the tissue and tear film [98]. Furthermore, there are numerous soluble messengers and active factors (cytokines and chemokines) that functionally link cells [99].

Cellular mucosal immune system of the ocular surface

In addition to the soluble factors of immune defence, there is also a cellular immune system in the mucosa of the entire ocular surface in the narrower sense and in the mucosal adnexae (lacrimal gland and efferent tear ducts). This is involved in direct action against antigens but is also a key producer of the soluble immune factors. The cellular mucosal immune system consists of lymphocytes and accessory leucocytes (e.g. dendritic cells, macrophages, neutrophils granulocytes, mast cells). They are associated with each other and with the stromal cells of the connective tissue (fibrocytes) as well as with the surface epithelium through soluble immunomodulators. Cytokines regulate the activity status of the cells and mediate, e.g. inflammatory stimuli to surrounding cells, while chemokines additionally have a chemotactic effect, hence regulate the migration of cells, for example, to the site of an inflammatory stimulus. All cell types of the mucosa thus work together and ensure effective immune defence.

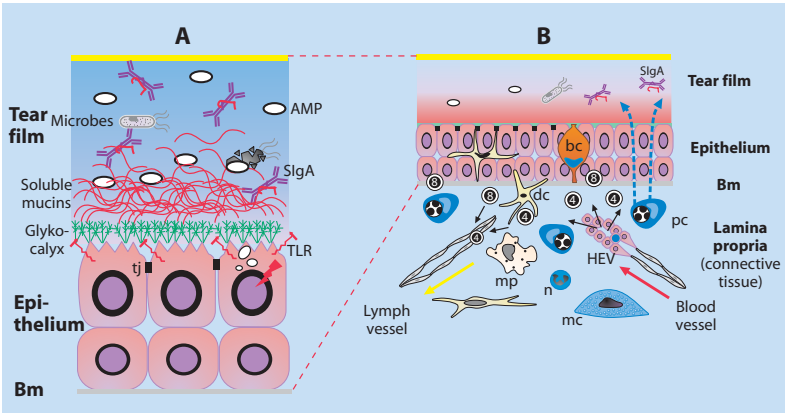


Figure 3.3: Diffuse mucosal immune system of the ocular surface.
(**A**) The mucosal immune system consists of soluble factors (e.g. non-specific antimicrobial peptides (AMP) and specific secretory IgA antibodies (SIgA), which both to some extent bind to the soluble mucins, and cell receptors for microbial antigens (e.g. toll-like receptors, TLR). The cellular component (**B**) consists of lymphocytes (CD4 or CD8 positive T-helper cells) and plasma cells (pc) and of accessory leucocytes (e.g. dendritic cells, dc; macrophages, mp; neutrophilic granulocytes, n; mast cells, mc), which are distributed over the entire mucosal surface as a diffuse cell layer. Individual lymphocytes are also found between the basal epithelial cells. The leucocytes interact with the stromal cells (fibrocytes, fi) and with the epithelial cells as well as the vessels. Normal flat endothelial and specific high endothelial (HEV) blood vessels aid the migration while lymph vessels aid the removal of cells.

Lymphocytes have long been known to be present in the conjunctiva [100-103]. However, the question as to whether there is a functionally active lymphoid tissue here was for a long time insufficiently studied. One problem was that the principles of mucosal immunology had been inadequately investigated and thus lymphocytes like other leucocytes were in general mistaken for inflammatory cells [103]. A further problem was that plasma cells, although accepted as being a normal physiological component in the lacrimal glands, were nonetheless considered as pathological in the functionally and spatially neighbouring tissue of the conjunctiva [104-106]. Furthermore, the studies were undertaken mostly on small tissue samples from clinical biopsies, in some cases from pathologically altered tissue, and were difficult to exactly localise, and thus led to incorrect conclusions being drawn as to the distribution of immune cells. It was subsequently shown that so-called mucosa-specific lymphocytes are present in the conjunctiva [107] and efferent tear ducts [97] and that there is a typical pattern of lymphocytes and other leucocytes in the conjunctiva [107, 108].

Diffuse and organised lymphoid tissue is associated with each other through the migration of lymphatic cells

Besides the cells diffusely distributed in the tissue, accumulations of lymphocytes forming organised lymph follicles also occur. Organised lymph follicles consisting of B lymphocytes and the surrounding T-cell zones have the function of taking up antigens from the lumen, that is, from the tear film, and then specifically forming effector cells which, as plasma cells, are indirectly active against antigens via the produced immunoglobulins and, as T lymphocytes, are directly active against antigens and represent essential components of immune defence. Lymph follicles as well as the diffuse lymphoid tissue are most marked in the tarso-orbital conjunctiva. They can be found in only approximately two thirds of elderly adults, with approximately 10 follicles per eye [96]. In contrast, they are much more common in children and can always be found in children before puberty [101]. Lymph follicles are found with a similar frequency in the efferent tear ducts [97, 109].

The diffuse and follicular lymphoid tissue is associated with each other through the regulated migration of lymphatic cells in vessels (☞ Figure 3.4). Thus, after the recognition of antigens at a site, effector cells can be activated against them, and made to differentiate and multiply. From there, the effector cells can then be distributed in the body and in the diffuse lymphoid tissues of the ocular surface and other organs through removal via efferent lymph vessels and subsequent re-entry into the circulation (recirculation of lymphatic cells) [110, 111]. With regard to function, it has been demonstrated, for example, that B cells in follicles of the conjunctiva become plasma cell precursors through antigen exposure [112] and that after the topical administration of retinal S antigens protective tolerance occurs [113, 114].

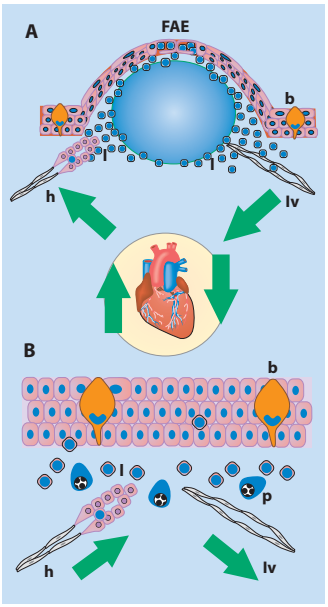


Figure 3.4: Functional cooperation between follicular and diffuse lymphoid tissue.
Mucosa-associated lymphoid tissue is found organised as follicles (**A**) with follicle-associated epithelium (FAE) without goblet cells (b) and as a diffuse form (**B**) with plasma cells (p), lymphocytes (l) and other leucocytes (☞ Figure 3.3). Antigens are transported from the lumen into the tissue via specialised M cells in the FAE and antigen-specific lymphocytes are subsequently activated to effector cells against these antigens. Lymphocytes (l) can migrate into the tissue via venules with high endothelium (h) and leave it again via lymph vessels (lv) in order to recirculate in the body. In this way, effector cells can be distributed in the peripheral immune organs of the body (schematic diagram) (based on [110], with the kind permission of Kaden Verlag).

In the meantime, studies [115-117] of complete human tissue from donated bodies and from animal tissues using various investigation techniques have shown that there is a regular mucosal immune system both in the conjunctiva [96] and in the efferent tear ducts [97]. In accordance with the nomenclature for the mucosal immune system [118], this tissue is termed "**c**onjunctiva-**a**ssociated **l**ymphoid **t**issue" (CALT) in the conjunctiva [96] and "**l**acrimal **d**rainage-**a**ssociated **l**ymphoid **t**issue" (LDALT) [97] in the efferent tear ducts. CALT and LDALT belong within the context of the mucosal immune system of the body which is termed "**m**ucosa-**a**ssociated **l**ymphoid **t**issue" (MALT) and is found in other organs as well, such as the intestine, airways or urogenital tract.

3.2.2.2. The mucosal immune system of the ocular surface forms coherent eye-associated lymphoid tissue

Further studies showed that the lymphoid tissue of the lacrimal gland, conjunctiva and efferent tear ducts is linked via various mechanisms (☞ Figure 3.5).

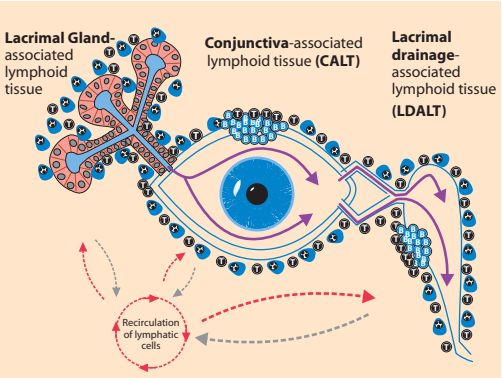


Figure 3.5: Composition of the eye-associated lymphoid tissue (EALT).
The mucosal immune system of the continuous mucosal surface of the conjunctiva (CALT), efferent tear ducts (LDALT) and gland-associated lymphoid tissue of the lacrimal gland together form the eye-associated lymphoid tissue (EALT) as a functional unit. The individual parts are linked externally through the continuity of the tissue, via the flow of tears (continuous line), and via the recirculation of lymphatic cells (broken lines) via specialised vessels (based on [47], with the kind permission of Karger Verlag).

1. CALT and LDALT are anatomically continuous with each other and, via the excretory tear ducts [97], are also linked to the gland-associated lymphoid tissue of the lacrimal gland [96, 119]. As a result, the actual surface of the eye and its mucosal adnexa form a continuous mucosal surface.

2. CALT and LDALT contain specific vessels, including high endothelial venules (HEV) [120, 121], which possess specific molecules (homing receptors) [122] on the endothelial surface for the mediation of regulated and presumably organ-specific migration of lymphocytes from the blood vessels into the lymphoid tissue [111]. Similar homing receptors are also found on conventional flat endothelial vessels in the lacrimal gland. An exchange of the protective effector cells that have been generated, e.g. T lymphocytes and plasma cells, is therefore possible.

3. The mucosal surfaces from the lacrimal gland through the conjunctiva to the efferent tear ducts are linked by the flow of tears and consequently share protective factors but possibly also pathogenic factors which reach the ocular surface through the open palpebral fissure in the region of the conjunctiva and cornea.

These results have led to the concept that the lymphoid tissue of the actual ocular surface together with its mucosal adnexa form the **e**ye-**a**ssociated **l**ymphoid **t**issue (EALT) [97, 119, 123, 124]. EALT covers the lymphoid tissue of the lacrimal gland, the conjunctiva (CALT) and efferent tear ducts (LDALT). EALT is a newly discovered part of the body's immune system and belongs with the other parts of the body's mucosal immune system that have been discovered so far, e.g. gut-associated lymphoid tissue in the intestine (GALT) and bronchus-associated lymphoid tissue (BALT) in the airways. The recognition that the ocular surface has a regular mucosal immune system with typical characteristics has facilitated understanding of the normal homeostasis on the ocular surface, its immune defence mechanisms as well as the occurrence of possible immune-modulated inflammatory disorders, e.g. in very common diseases such as dry eye or eye allergy [1, 16, 17, 125-128].

3.3. Influence of the mucosal immune system on dry eye

Recent studies of the dry eye have revealed inflammatory changes which, when present for a long period of time, are self-intensifying and can then no longer be satisfactorily treated with conventional therapy using artificial tears. The reason for this is an initially subclinical and then clinical inflammatory process which is caused by deregulation of the mucosal immune system of the ocular surface, that is, above all, a local deregulation of the CALT of the conjunctiva.

If this system is deregulated by various factors that also play a role in dry eye, there is an excessive reaction characterised by loss of the normal immune tolerance and which is then directed against non-pathogenic environmental antigens or even components of the tissue of the eye itself (autoimmune reaction). These processes are accompanied by an immunologically modulated inflammatory reaction and in severe cases can require immunosuppressant therapy.

3.3.1. The normal function of EALT is protective

The normal function of the mucosal immune system of the ocular surface (EALT) is to bring about immune tolerance to the very large number of non-pathogenic antigens that constantly reach the mucosa of the conjunctiva and cornea through the open palpebral fissure. Since these antigens are foreign to the body but are not pathogenic, it is necessary to avoid an immune response involving inflammatory mechanisms in order to prevent the associated destruction of the sensitive structure of the ocular surface, especially the sensitive structure of the cornea that is important for optical function. That this lack of a response is a desired and necessary measure can be seen, for example, when, in the presence of an eye allergy, unnecessary and excessive inflammatory responses are triggered to what are in fact harmless antigens such as flower pollen or house dust and which lead to considerable symptoms and damage to the ocular surface.

Furthermore, it is important that the normal tissue components do not trigger an immune response. Failure of this protective function is manifested in autoimmune reactions, as occur in pemphigoid, for example, where as a result of a defect in immune tolerance autoantibodies are produced against the structures responsible for the attachment (hemidesmosomes) of epithelial cells to the basement membrane beneath them.

Since on the other hand a very large number of dangerous pathogens can reach the ocular surface, it is of course necessary nevertheless to keep the mucosal immune system constantly in a state of readiness. The balance between immune tolerance and protection against pathogens through "curative" inflammation is therefore the main function of the mucosal immune system (☞ Figure 3.6). This balance is regulated by the method of the presentation of antigens.

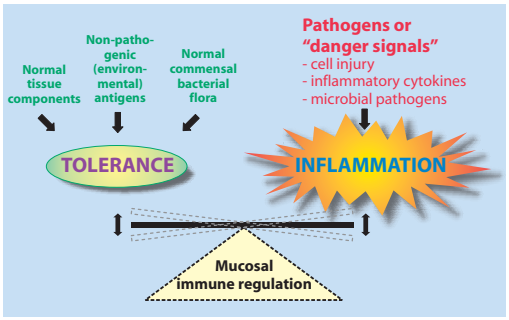


Figure 3.6: Balance of the mucosal immune system between tolerance and immunity.
The balance between immune tolerance to non-pathogenic antigens and auto-antigens of the tissue itself and the triggering of usually inflammatory defensive responses to dangerous pathogens is the most important function of the mucosal immune system. The focus is on maintaining immune tolerance with the avoidance of unnecessary inflammatory reactions that can damage the tissue.

3.3.2. Deregulation of the mucosal immune system through chronic surface irritation in dry eye can lead to the loss of immune tolerance

In dry eye, there are various forms of chronic irritation of, and injury to, the epithelium of the ocular surface [129, 130]. These involve, for example, chronic mechanical irritation [131], chemical irritation due to hyperosmolarity [132] or injuries to the epithelial surface (☞ Figure 3.7). As a result of this, there is activation of the epithelial cells. These react with various changes which are not compatible with normal immunological homeostasis and breach the physiological immune tolerance. Con-

sequently, there is an excessive reaction on the part of the mucosal immune system of the ocular surface (EALT), which initiates inflammatory tissue changes [17].

Through activation in the context of these disturbances, the epithelial cells acquire the ability to synthesise pro-inflammatory cytokines (e.g. interferon gamma, IFN-γ; interleukins 1, 6, 8, 17; tumour necrosis factor alpha, TNF-α) [133, 134], which are released as messengers into the tissue and tear film and activate further cells in the vicinity. Furthermore, they acquire on their cell surface a molecule for antigen presentation (MHC-II) as well as molecules for co-stimulation (e.g. intercellular adhesion molecule 1, ICAM-1; CD40; CD40L) [135, 136], which act as danger signals that influence the presentation of antigens and bring about effective, typically inflammatory activation of lymphocytes [137] of the local mucosal immune system [125]. The epithelial cells consequently acquire the property of abnormal presentation of antigens.

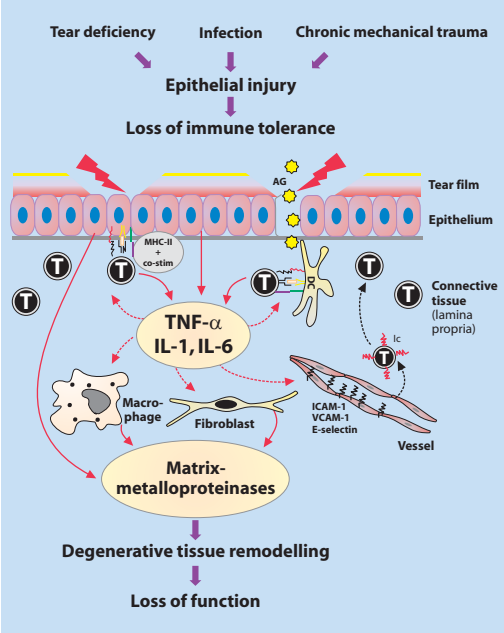


Figure 3.7: Mechanism of inflammatory deregulation.
Deficiency of tears in dry eye, chronic mechanical irritation or infections lead to injuries to, and defects of, the surface epithelium and, through epithelial activation, can lead to the loss of immune tolerance. There is the formation of an inflammatory cytokine milieu (e.g. with the inflammatory cytokines TNFα, IL-1, IL-6 etc.) as the central mechanism. As a result of cytokine stimulation, not just the professional antigen-presenting dendritic cells (DC) can be activated but also the epithelial cells acquire the property of antigen presentation through synthesis of the antigen presentation molecule MHC class II (MHC II) on their surface. This can result in the abnormal presentation of non-pathogenic and also endogenous antigens in an inflammatory context by epithelial cells and dendritic cells (DC). Furthermore, there is the formation and activation of matrix metalloproteinases by the cells of the epithelium as well as by leucocytes and stromal cells in the loose connective tissue (lamina propria) of the conjunctiva. Matrix metalloproteinases destroy the tissue and make an essential contribution to degenerative tissue remodelling and loss of function. Inflammatory cytokines also activate the endothelial cells of the vessels with the synthesis of adhesion molecules, which favour the further migration of leucocytes into the tissue and thus promote the spread of inflammation.

Injuries to the epithelium allow uncontrolled entry of external luminal antigens, and cell destruction also brings about the release of internal cell com-

ponents (autoantigens) with the risk of the generation of autoimmune reactions to the tissue components that make up the surface of the eye. In fact, animal models of dry eye have shown that there are autoreactive T cells [137]. In this inflammatory context, the presentation of antigen leads to the preferential production of T helper (Th) lymphocytes of the inflammatory subtypes Th-1 and Th-17 [137, 138], which synthesise further inflammatory cytokines and thus contribute to increasing the inflammatory micromilieu in the tissue and tear film. In the case of an eye allergy, B cells directed against non-pathogenic antigens from the environment that have entered the tissue are activated and then synthesise the well-known IgE antibodies.

In an inflammatory milieu, macrophages and fibrocytes of the connective tissue and also the epithelial cells synthesise increased amounts of enzymes (such as matrix metalloproteinases, MMP) [130], which break up the connective tissue, as would be necessary for an actual protective inflammatory response with effective destruction of microbes but in the case of chronic inflammatory deregulation in dry eye leads to degenerative tissue changes (☞ Figure 3.8). Inhibition of MMPs can prevent this in part [139].

An inflammatory milieu in the tissue also results in activation of endothelial cells of the small vessels in the loose connective tissue (lamina propria) of the mucosa, and the synthesis of adhesion molecules is stimulated (e.g. intercellular adhesion molecule 1, ICAM-1; vascular cell adhesion molecule 1, VCAM-1; E selectin) [135]. These allow increased binding and massive migration of further leucocytes from the vessel lumen into the tissue and can thus intensify the inflammatory response and lead to the histological picture of inflammation [140].

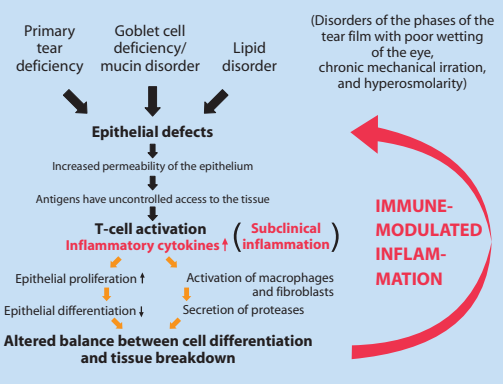
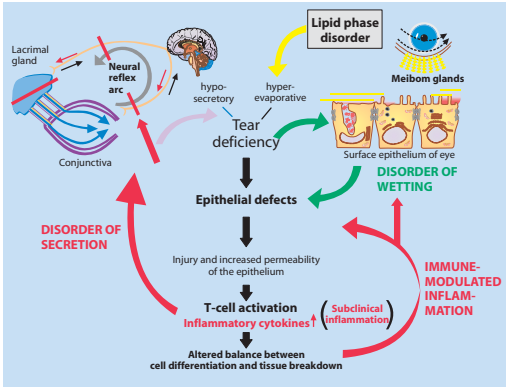


Figure 3.8: Various disorders of the tear film in dry eye trigger chronic inflammation with degenerative tissue changes.
The described mechanisms (☞ Figure 3.7) initially lead to subclinical inflammation. This maintains an abnormal balance between cell differentiation and tissue breakdown and subsequently leads to further degeneration of the epithelium. This represents a self-intensifying mechanism of immune-modulated inflammation which, in a vicious circle, can lead to progression of dry eye (based on [1], with the kind permission of Springer Medizin Verlag).

3.3.3. The loss of immune tolerance leads to chronic progressive immune-modulated inflammation with destruction of the ocular surface

An inflammatory micromilieu leads to various vicious circles which, as self-intensifying mechanisms, favour destruction of the ocular surface and can lead to progressive inflammation of the ocular surface (☞ Figure 3.9) [1, 16, 17, 138] [125].



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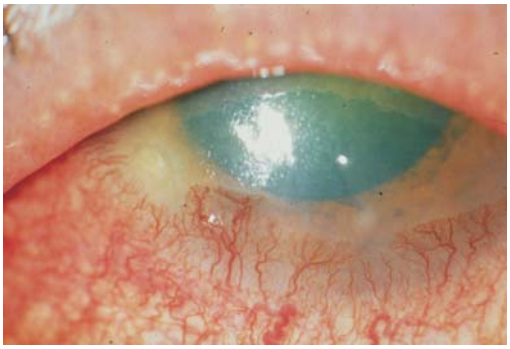

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Figure 3.9: Self-intensifying vicious circles of immune-modulated inflammation of the ocular surface can lead to severe forms of dry eye.
The immune-modulated disease of the ocular surface in severe inflammatory dry eye involves various self-intensifying immune-modulated vicious circles, such as degenerative remodelling of the ocular surface with destruction of the normal epithelial morphology, epithelial squamous metaplasia, a disorder of wetting of the surface and abnormal secretion from the lacrimal gland due to inflammation, with secondary tear deficiency. If there are insufficient compensatory factors or inadequate therapy, this can eventually result in the full-blown picture (b) of severely inflamed dry eye (diagram (a) based on [1] and photo (b) from [127] with the kind permission of Springer Medizin Verlag).

As a result of the influence of the inflammatory cytokine milieu, the epithelial cells are stimulated to increased proliferation, while their maturation is decreased, leading to the picture of epithelial squamous metaplasia with a reduction in goblet cells [141] and thus degenerative tissue remodelling through the matrix metalloproteinases is further increased. Since the surface mucins are also immature in these disturbances [143], the wetting abnormality of the epithelial surface is further intensified and the permeability of the epithelium is increased due to injury. In the context of the altered cell differentiation, there is also an increased rate of programmed cell death of epithelial cells (apoptosis), which is suggested as being an important pathological mechanism in dry eye [143]. Abnormalities of the peripheral hormone effect, especially a deficiency of the effect of androgen, which not only promotes gland function in various ways, but also has an anti-inflammatory effect on the glands and ocular surface [20, 76, 144], are a further negatively impacting factor. This is one of the reasons why, in general, the prevalence of dry eye is higher in women and in old age generally [44, 145].

There is also evidence that surface injuries in the presence of an inflammatory milieu lead to a disorder of innervation of the ocular surface, thereby inhibiting the generation and propagation of secretory impulses to the lacrimal glands, which presumably form a regulatory cycle (lacrimo-functional unit). This leads to secretory tear deficiency or exacerbates such a deficiency [146-148]. As a result of reduced tear production or increased evaporation in the relatively frequent dysfunction of the meibomian glands (MGD), the amount of tears on the ocular surface is decreased in dry eye and consequently their exchange (tear clearance) is reduced, resulting in increased accumulation of inflammatory substances in the relatively decreased tear fluid [149].

If these vicious circles are not stopped in good time and in a suitable manner, e.g. by improving the environmental conditions in the work place (air conditioning, air currents, working at computer screens with reduced frequency of blinking), by adequate replacement of the aqueous or lipid tear phase or by treatment of the relatively widespread dysfunction of the meibomian glands with physical measures (such as regular lid margin hygiene and application of moist heat [82]), severe immune-modulated inflammation of the ocular surface can arise as described above (☞ Figure 3.9). This can then often no longer be satisfactorily treated using conventional measures alone and, in selected cases, the temporary use of topical immunomodulatory therapy, e.g. with the lymphocyte activation inhibitors ciclosporin or tacrolimus (FK506), may be necessary [150].

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