Review Article

Understanding the immunology of the ocular surface and its relevance to clinical practice

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The immunology of the ocular surface has an important role in maintaining homeostasis and in the etiopathogenesis of a number of diseases when dysregulated. This can result in damage to the cornea and ocular surface and loss of clarity and vision. As the entire ocular surface is linked via its epithelium, vascular supply, and innervation, changes across one aspect have tangible effects on the other. Immune cells residing on the ocular surface and those that traffic across the ocular surface interact with the structural tissues to release molecular factors and result in tissue response and disease. Studies in animal models and *in vitro* experiments along with *in vivo* studies on the human ocular surface have given newer insights with closer representation of actual health and disease. Some of the diseases which have been found to have a strong immunological basis include dry eye disease (DED) and Sjogren's syndrome, keratoconus, corneal graft rejection, autoimmune conditions such as peripheral ulcerative keratitis, and Stevens–Johnson syndrome. The ocular surface immunology has unique patterns and signatures across different diseases. These give us an opportunity to understand the diseases better find newer targets for therapy and an opportunity to reduce visual morbidity. Clinically, we envisage a shift from steroids and broad action immunomodulators toward target specific drugs making personalized medicine and customized therapy the way forward.

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The ocular surface is a unique environment with a constant interplay between anatomical, physiological, and immunological features.[1] Immune cells from both the innate (neutrophils, monocytes, macrophages, dendritic cells, and natural killer cells) and adaptive (T and B lymphocytes) immune systems are present on the ocular surface. The first line of defense in the body is usually the innate immune system. On the cornea and ocular surface, it comprises epithelial cells, fibroblasts, antigen-presenting cells (Langerhans's cells, dendritic cells), neutrophils, macrophages, and natural killer (NK) cells.[2] It is not antigen-specific unlike the adaptive immune system, which acts as a second line of defense, demonstrates immunologic memory, and reacts more rapidly on subsequent exposure to the same stimulus. Immune cells are found on the ocular surface, loosely attached to the surface epithelium and within the corneal and conjunctival epithelium and stroma.[3] They actively pass across the ocular surface, to and from draining lymph nodes, and also extravasated from the vessels.[4] The lacrimal gland contributes to this as well as its interstitial spaces contain different immune cells including B and T cells, dendritic cells (DCs), and macrophages among others.[3]

Immune cells in ocular surface homeostasis

The ocular surface has a number of similarities to other mucosal surfaces across the body including the gastrointestinal and respiratory tracts. However, maintaining the optical clarity of the cornea is extremely important and the balance in a normal immune system is directed toward this aim. If there is an exaggerated immune response, it can damage the cornea and ocular surface, and cause loss of transparency of the cornea and thereby affect the vision.[1,5] In a normal eye, there are mechanisms for regulating the immune response and immune cell migration across the ocular surface. This regulation and relative restraint is termed immune privilege and is important in preventing excessive inflammatory response, which can be destructive to the cornea's unique structure.[6] However, this immune privilege can be disturbed in conditions with high inflammation and any condition, which disrupts the innate and adaptive immune response.[7] The balance between the immune cells resident to the ocular surface, those passing through (trafficking cells), and the structural cells help maintain tissue homeostasis on the ocular surface. An alteration in this balance can result in a variety of pathologies.[8,9] A unique feature of the ocular surface, unlike other mucosal surfaces of the body, is that it is in direct contact with the external environment and stressors such as desiccation, infection, and trauma which can result in a dysregulated immune system and pathology.[10] In response to environmental stressors, structural cells release inflammatory molecules activating the immune system.[11] Pro-inflammatory factors such as cytokines and matrix metalloproteinases (MMPs), are then released by the

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activated immune system resulting in loss of homeostasis.[12] The inflammatory and biochemical profile on the ocular surface is of great importance in the proportion, type and activation of immune cells. Tear cytokines and other molecular factors are produced by structural cells and immune cells and play a crucial role in ocular surface homeostasis and pathology.[13,14]

It was previously believed that no immune cells were present in the central cornea.[15,16] However, it has now been demonstrated from murine animal studies that antigen-presenting cells such as dendritic cells (DCs) are present in an immature form in the peripheral and anterior cornea even in normal conditions.[17,18] They have an important role in innate and adaptive immunity on the ocular surface.[19] Under normal conditions, DCs are major histocompatibility complex (MHC) class II negative. They mature in response to inflammation or pathogens on the ocular surface, become MHC class II-positive, and spread across the cornea.[15,19] They modulate B and T lymphocyte activity of the adaptive immunological response.[20] Both T-cell-dependent and independent mechanisms can perpetuate an immune-mediated response. This is relevant to the varied presentations of the same disease and individual responses to therapy observed in the clinic.[5]

The interplay between cells, inflammatory molecules, and corneal nerves is crucial to the disease prognosis and outcome. Alterations in these interactions and homeostasis have been involved in the pathogenesis of various diseases such as dry eye disease,[21] Sjogren's syndrome,[22] keratoconus,[23] Stevens–Johnson syndrome, graft rejection,[24] peripheral ulcerative keratitis (PUK), and ocular cicatricial pemphigoid.[25]

This immune response is associated with the altered presence of immune cell subtypes such as neutrophils, macrophages, and T-cells in the diseased ocular surface. Understanding this altered immune cell profile and the associated secretory factors is vital as they may serve as therapeutic targets in various diseases.[2] We face various clinical conundrums in managing these conditions, including the mismatch between symptoms and signs, overlapping features that make accurate diagnosis difficult, and varied natural progression of diseases and responses to therapy. The challenges enumerated can make it difficult to treat these conditions, delay diagnosis and treatment, and result in permanent visual impairment with significant deterioration of their quality of life.

Techniques used to study the immune cell and molecular profile on the ocular surface include tear molecular profile by ELISA-based techniques, corneal nerve morphology using *in vivo* confocal microscopy, and study of immune cells collected by impression cytology and ocular surface wash.[26] Tear molecular factors along with immune cells on the ocular surface can be a sensitive way of diagnosing or prognosticating a disease. However, many of the tests available are laboratory-based, time and labor-intensive, and difficult to incorporate into clinical practice. Given the potential role of targeted therapy in the future, the ability to evaluate and monitor these factors will be invaluable. Patient stratification using point-of-care diagnostic biomarker analysis with techniques such as the microfluidic cartridge-based multiplex ELISA system (Bio-M Pathfinder, NovoMol-Dx, India, a customized version of the Ella™ Automated ELISA system, Bio-Techne® Corporation, Minnesota, USA) can help monitor, treat and prognosticate disease.[27] Looking at the immune cells and molecular profile in conjunction with clinical features can help link the various factors, which play a role in disease pathophysiology such as trying to solve a jigsaw puzzle of the clinical picture in different diseases.

The knowledge available about the immune regulation on the ocular surface is obtained from animal studies, *in vitro* experiments, and directly off the ocular surface using tools such as the ocular surface immune wash and impression cytology. These studies have systematically investigated a wide range of immune cells and proteins in the context of disease stage and sequelae. Broadening our knowledge of these ocular surface diseases allows us to find new tools to better stratify and monitor patients for surgery and topical therapy.

Ocular surface profile of immune cells across various disease states

Dry eye disease (DED) is a growing public health problem affecting millions worldwide.[28] It can be of aqueous deficiency and evaporative types but often have a mixed picture. In addition, there is variability in patient symptomatology which may or may not correlate with signs of DED.[29] Suboptimal response to therapy also underlines the importance of understanding the immunopathology involved. Inflammation of the ocular surface is one of the key factors related to etiopathogenesis.[21,30] These inflammatory mediators are produced by the ocular surface tissue and immune cells in response to hyperosmotic stress and other triggers.[11,31] Different immune cells have been shown to be associated with DED including dendritic cells, T cells, and neutrophils.[32,33] Animal studies and *in vitro* experiments have shown alterations in dendritic cells (DCs), neutrophils, and T cells on the ocular surface in DED.[10,34] Immunophenotyping of ocular surface wash samples also showed a statistically significant increased proportion of neutrophils, macrophages, double-positive T cells, and NKT cells in patients with DED, along with a decrease in the proportion of NK cells in those with surface staining.[26] This suggests a possible protective association of NK cells on the ocular surface in DED. Aqueous deficient DED (ADED) eyes had a significant relative increase in CD4 T cells suggesting a possible CD4 T cell-specific role in ADED. Inflammatory factors such as IL-1β, IL-2, IL-4, IL-6, IL-9, IL-12, IL-17A, IFNγ, TNFα, CCL2, CCL4, CXCL8, MMP9, FGF, VEGF-A, sICAM1, sTNFRI, IL-1RA, NGF, and substance P were reported to be increased in DED.[35] Clinical improvement in response to the treatment of dry eye correlates well with improvement in the ocular surface immune milieu and inflammatory status. Post intense pulse light therapy, decreasing proportions of NK cells, NKT cells, and T cells were observed in ocular surface wash samples, along with a decrease in inflammatory mediators such as MMP 9 and an increase in TGFβ levels.[36] These findings clearly show the variation in immune cell profile with phenotypes of disease and therapy suggesting that the structural cells of the cornea may be interacting with the surveillant immune cells at a molecular level, a link to the etiopathogenesis of diseases.

Another condition shown to have an underlying inflammatory etiopathogenesis is keratoconus (KC). Keratoconus is an ectatic corneal disease that can result in significant visual impairment.[23] Serum from keratoconus patients showed expression of Toll-like receptors in neutrophils and monocytes was higher along with high molecular factors associated with inflammation such as IL-1β, IL-6, TNF-α, MMP-9.[23] Tear fluid and corneal tissue in KC are shown to have elevated inflammatory mediators important for ECM

remodeling.[37] Immunophenotyping of ocular surface wash samples in KC eyes showed a significant increase in the proportions of total and increased cytokine-producing natural killer (NK) cells along with gamma delta T cells compared to controls. This change seemed to increase with the worsening severity of KC. NK cells proportions were directly related to perforins and granzymes and inversely to neutrophils.[38]

Immune cell interaction also plays an important role in corneal graft survival or rejection. Although corneal transplants are the most successful solid organ transplants, various donor and host factors can lead to graft rejection or failure.[39] Early classic clinical features of corneal graft rejection such as the Khodadoust line, which consists of inflammatory infiltrates on the endothelium or epithelial rejection line of lymphocytes, plasma cells, and neutrophils, demonstrate the importance of immune pathology in this condition.[40] However, clinical signs can be subtle in the early stages and may be missed until the graft rejection progresses to severe corneal edema and loss of optical clarity, which may be irreversible. The immune basis for graft rejection has been studied in animal experiments but direct knowledge from the human ocular surface is limited resulting in lacunae in our understanding. Corneal graft rejection is primarily a T cell-driven pathology (mainly CD4 T cells). Antigen-presenting cells on the ocular surface also play an important role in the pathogenesis.[41,42] Langerhans' cells (LCs) are located in the paracentral cornea in immature form. Cytokines such as IL-1 and TNF-α help in the maturation of the LCs, which then activate the host T cells.[41,42] Macrophages also have a significant role in graft rejection pathogenesis. They can perform phagocytosis and secrete inflammatory cytokines in addition to expressing low levels of MHC class II antigens. Cytokines and chemokines released along with adhesion molecules are an important link in the rejection pathway and control the severity of the allograft response.

Stevens–Johnson syndrome (SJS) is an idiosyncratic reaction of the condition of the skin and mucous membranes due to a type IV delayed hypersensitivity reaction to systemic medications or viral infections.[43] Even though acute stage mortality is a challenge, morbidity due to ocular sequelae which can affect 43–90%, is difficult to manage in chronic severe stages.[44] Various molecular factors including interleukin (IL)-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), perforin/granzyme B, and Fas/Fas ligand have been associated with different stages of SJS.[45,46] Immunophenotyping of ocular surface immune cells in eyes with chronic sequelae of SJS showed a significant increase in activated neutrophils, unlike the T cell-driven picture in the acute stage. Other immune cell alterations include a significant decrease in the proportions of NK T cells coupled with no change in the NK cell proportions. Increased perforin, granzyme, and TNF-α on the ocular surface were noted.[47] Interestingly, changes in molecular and immune cells showed an association with particular clinical features or stages. TNF-α was increased in eyes with significant mucocutaneous junction involvement, hyperemia, ocular surface staining, neovascularization, and conjunctivalization. A higher proportion of IL-8 levels was observed in eyes with conjunctivalization and loss of palisades of Vogt (POV).[47] Thus, the different stages and clinical phenotypes showed varied proportions of immune cells and molecular factor alteration.

Peripheral ulcerative keratitis (PUK) is a condition that can have both infective and autoimmune etiologies with crescentric thinning of the peripheral part of the cornea.[48] The exact etiopathogenesis is only partly understood. The presence of complement factors and immunoglobulins near the limbus and vascular conjunctiva could be the reason for the involvement of this specific part of the cornea. Both cell-mediated immunity and humoral immunity are involved in the disease pathogenesis with immune complex deposition and hypersensitivity to antigens being proposed as theories.[49] Stromal keratocytes are activated by cytokines produced by immune cells and this triggers a cycle of inflammation. This in turn releases more cytokines and inflammatory factors such as neutrophil calgranulin C and metalloproteinases resulting in stromal thinning.

Ocular graft-versus-host disease (oGVHD) can occur after a hematopoietic stem cell transplant. It results in tissue inflammation and can present with varying severity of ocular surface damage.[50] Patients can present with what appears to be pseudomembranous conjunctivitis, corneal epithelial sloughing, severe dry eye, and filamentary keratitis to conjunctival cicatrization. GVHD occurs due to the activation of T cells from the donor by antigen-presenting cells (APCs) from the recipient, resulting in effector T cell tissue damage. Molecular factors such as IL-6, TNF-α, IL-8, ICAM1, IL-12p70, VEGF, IFNγ, and MMP-9 have been found to be involved in the pathogenesis. Neutrophils have also been shown to play a role

Table 1: A list of increased proportion of immune cells and increased levels of molecular factors on the ocular surface in different ocular surface conditions

Ocular Surface Condition	Immunological factors
Dry Eye Disease	Increased proportions – Neutrophils, DCs, Macrophages, T cells, Neutrophils-NK cells ratio Increased levels – IL-1β, IL-2, IL-4, IL-6, IL-9, IL-12, IL-17A, IFNγ, TNFα, CCL2, CCL4, CCL4, CXCL8, MMP9, FGF, VEGF-A, sICAM1, sTNFRI, IL-1RA, NGF, Substance P
Keratoconus	Increased proportions – NK cells, Activated neutrophils Increased levels – IL-1β, IL-6, IL-17A, IFNγ, TNFα, EPO, IgE, MMP2, MMP9
Ocular Stevens-Johnson Syndrome	Increased proportions – Total & activated Neutrophils, Neutrophils-NK cells ratio, Neutrophils-T cells ratio Increased levels – IL-6, IL-18, IFNα, β, γ, HGF, LIF, Perforins, Granzyme, sTNFRI, MMP9/TIMP1
Peripheral Ulcerative Keratitis	Increased proportions – Neutrophils, Mast cells, Eosinophils, T cells, Plasma/B cells Increased levels – Complement, Ig, MMP1, MMP2, MMP8, MMP9, IL-1β, IL-6, TNFα, Neutrophil calgranulin C
Ocular Graft Versus Host Disease	Increased proportions – Neutrophils, APCs - T cells interaction Increased levels – IL-6, IL-8, IL-12p70, TNFα, IFNγ, MMP9, ICAM1, VEGF-A, and Neutrophil extracellular traps (NETs)
Corneal Transplant rejection	Increased proportions – Neutrophils, DCs, Macrophages, NK cells, T cells, B cells Increased levels – IL-6, IL-18, IFNα, β, γ, HGF, LIF, Perforins, Granzyme, sTNFRI, MMP9/TIMP1

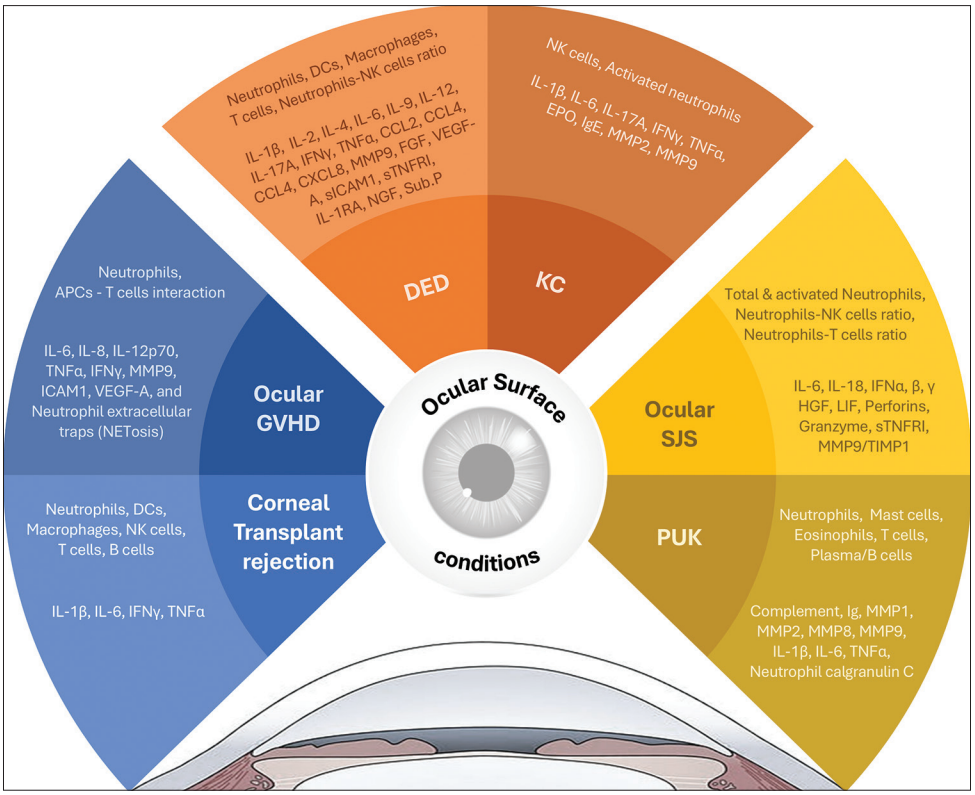

Figure 1: Schematic diagram depicting the altered immune cell proportions and molecular factors in various ocular surface conditions

in oGVHD immunopathogenesis, releasing nuclear chromatin complexes known as neutrophil extracellular traps (NETs).[51]

In addition to the conditions discussed here, there are a number of other ocular conditions which have an immunological basis for their etiology. In general, ocular surface conditions with immune-linked etiopathogenesis, are currently treated with topical or systemic steroid therapy and systemic immunomodulatory therapy as required. However, with our evolving knowledge of the immune profile associated with these conditions, we foresee a future where targeted therapies may be feasible, allowing for safer long-term therapies and avoiding steroid-associated complications such as glaucoma and cataracts. There are certain medications, which are available in clinics or under trial which are already in the form of targeted immunomodulation. For example, cyclosporine, lifitegrast, intravenous immunoglobulin (IVIg), and mast cell stabilizers as topical medications.

Cyclosporine A blocks T cell activation in addition to other immune cells and thereby the release of proinflammatory mediators. This decreases IFNγ expression, which has been linked to epithelial cell and goblet cell apoptosis, and thereby improves ocular surface health.[52] Lifitegrast is a relatively new drug, which is being used in the treatment of DED. It acts by inhibiting the activation and migration of T cells by competitively antagonizing the binding of LFA-1 to ICAM-1.[53] Topical IL-1 receptor antagonist is in trials and has shown good improvement in oGVHD and DED-related epitheliopathy.[54] Intravenous immunoglobulin (IVIg) has been shown to reduce autoimmune-mediated inflammation. Topical IVIg drop application for oGVHD DED is currently being investigated in phase 1/2 clinical trials.[55] Another simple example of targeted immunomodulation is in allergy management. Degranulation of mast cells results in the release of certain factors, which stimulate a hypersensitivity response. Mast cell stabilizers prevent the release of these chemical mediators by stabilizing the mast cells.[56]

Conclusion

The proportion of immune cells resident to and trafficking across the ocular surface is greatly influenced by interactions with the local milieu and systemic factors and has been found to have some unique patterns of proportions in different pathologies [Fig. 1/ Table 1]. A better understanding of interactions between immune cells, molecular factors, corneal nerves, and structural cells has provided important insight into the pathogenesis of disease. It paves the way for adopting targeted immunotherapy options from other fields of medicine for topical corneal applications, moving away from steroids and broad action immunomodulators for long-term therapy. Personalized medicine and patient-centric therapeutic modalities in ocular surface clinical practice hold great promise for the future.

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