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Review

Profiles, Distribution, and Functions of Gamma Delta T Cells in Ocular Surface Homeostasis and Diseases

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Abstract

The ocular surface microenvironment, containing the cornea, conjunctiva, and lacrimal gland, constitutes the mucosal frontline of the eye and houses a myriad of immune cells. As a part of unconventional T cells, gamma delta ($\gamma\delta$) T cells differ in the development and functions from canonical alpha beta ($\alpha\beta$) T cells. They are predominantly situated in mucosal sites throughout the body, including ocular surface tissues. Recent research has elucidated that $\gamma\delta$ T cells serve as the primary interleukin-17A (IL-17A) source in the conjunctiva. They play a pivotal role in preserving ocular surface homeostasis and exhibit both protective and pathogenic roles in ocular surface diseases. This review delves into the general profiles of $\gamma\delta$ T cells, their distribution in ocular surface tissues, and consolidates current insights into their functions in different conditions including dry eye disease, infectious keratitis, corneal wound healing, anterior chamber-associated immune deviation, allergic conjunctival disease, and diabetic ocular surface disease. The aim is to provide a systemic perspective on $\gamma\delta$ T cells in the ocular surface microenvironment and outline potential directions for future studies.

Keywords: $\gamma\delta$ T cells; ocular surface; distribution; functions; homeostasis

1. Introduction

The ocular surface, the mucosal system of the eye, serves as a crucial barrier against environmental pathogens and plays a vital role in vision. The core ocular surface consists of the cornea, limbus, and conjunctiva, according to the anatomical and histological structure [1]. In 2017, the ocular surface microenvironment (OSM) was put forward by Zhang *et al.* [2] to better understand the delicate and complex system, including the cornea, conjunctiva, meibomian glands, lacrimal glands, as well as other components such as immune cells, microbiome, nerve innervation, etc. The mucosa-localized immune cells are critical to ocular surface homeostasis in terms of immune tolerance and host protection.

Gamma delta ($\gamma\delta$) T cells are an important component of unconventional T cells which recognize non-peptide antigens without the help of classical MHC molecules, with the rest including mucosal-associated invariant T (MAIT) cells and natural killer T (NKT) cells [3]. In both humans and mice, $\gamma\delta$ T cells make up only 1–5% of the T cells in the blood, lymph nodes, and spleen. However, $\gamma\delta$ T cells are rich in epithelial and mucosal tissues such as the skin epidermis, gastrointestinal tract, and reproductive tracts, with a proportion of 10–70% of T cells [4]. In our previous study, $\gamma\delta$ T cells make up 27.45% and 18.90% of T cells in murine conjunctiva and lacrimal gland, respectively [5]. $\gamma\delta$ T cells are pivotal in maintaining mucosal barrier integrity, facilitating epithelial repair, and contributing to resistance against pathogens [6]. On the other hand, $\gamma\delta$ T cells, in particular interleukin-17A (IL-17A)-producing $\gamma\delta$ T cells, may induce or exacerbate tissue inflammation including psoriasis, atopic dermatitis, and uveitis [7–9]. $\gamma\delta$ T cells can even play both protective and pathogenic roles in the same disease, such as in age-related macular degeneration (AMD) [10–13]. In this review, we delve into the world of $\gamma\delta$ T cells, addressing their roles in maintaining ocular surface homeostasis, and their contributions to ocular diseases.

2. General Information of $\gamma\delta$ T Cells

2.1 Definition and Nomenclature

$\gamma\delta$ T cells, a distinct subset of T lymphocytes, were first discovered in the 1980s [14] and were suggested to coexist for 400–500 million years of vertebrate evolution alongside $\alpha\beta$ T cells and B cells [15]. They differ from the more common alpha beta ($\alpha\beta$) T cells structurally by their T-cell receptor (TCR), which is composed of γ and δ chains rather than α and β chains. This discovery opened up new avenues for understanding their roles in immunity.

Unlike $\alpha\beta$ TCR, $\gamma\delta$ TCR–mediated recognition is major histocompatibility complex (MHC) unrestricted, and $\gamma\delta$ TCR ligands include diverse molecules, such as H2-T10 and H2-T22 (which are non-peptide-binding MHC class Ib molecules), lipids presented by CD1, metabolites presented

Table 1. Nomenclature systems for $\gamma\delta$ T cells.

Human	Mouse	
	Garman-Donerty-Raulet system	Heilig-Tonegawa system
Vδ1 (major subset)	Vγ1.1	Vγ1
Vδ2 (major subset)	Vγ1.2	Vγ2
Vδ3	Vγ1.3	Vγ3
Vδ4-δ8 (detected in lymphoma patients)	Vγ2	Vγ4
	Vγ3 (DETC)	Vγ5 (DETC)
	Vγ4	Vγ6
	Vγ5 (intestinal IEL)	Vγ7 (intestinal IEL)

DETC, dendritic epidermal $\gamma\delta$ T cell; IEL, intraepithelial lymphocyte.

by MHC-related protein 1 (MR1) [16–18]. Apart from $\gamma\delta$ TCR, $\gamma\delta$ T cells can be activated by innate receptors such as NKG2D to sense stress ligands [19]. That makes $\gamma\delta$ T cells able to participate in both innate and adaptive immunity [20].

Human $\gamma\delta$ T cell subsets are distinguished by Vδ chains, while mouse $\gamma\delta$ T cell subsets are classified by different Vγ chains. There are two different γ-chain nomenclatures for mouse $\gamma\delta$ T cells: the Garman-Donerty-Raulet system and the Heilig-Tonegawa system, which is informative for selecting antibodies [21,22]. Nomenclature by Heilig and Tonegawa is used in the rest of this review. Nomenclature systems for human and mouse $\gamma\delta$ T cells are listed in Table 1.

2.2 Development

In mice, $\gamma\delta$ T cell development originates from a common CD4-CD8- progenitors in the fetal thymus and then goes through the somatic rearrangement of T-cell receptor (TCR) genes to develop into a Vγ-characteristic subset [23]. At embryonic day 15, these cells express a monoclonal TCR called Vγ5Vδ1 in the Skint1-dependent manner and consistently migrate to the epidermis of the skin and then are called dendritic epidermal $\gamma\delta$ T cell (DETC) [24]. Shortly thereafter, Vγ6+ and Vγ4+ $\gamma\delta$ T cells emerge and disperse to various peripheral sites, including the tongue, lungs, dermis, uterus, testis, peritoneal cavity, adipose tissue, and lymph nodes [25]. Subsequent Vγ7+ $\gamma\delta$ T cells are shaped by enterocytes-derived butyrophilin-like 1 (Btnl1) and colonize the intestine, where they are called IELs [26]. In the postnatal period, polyclonal CD27+Vγ1+ and CD27+Vγ4+ $\gamma\delta$ T cells develop and distribute mainly in the liver and lymph nodes, where they exhibit adaptive-like responses when activated [25]. However, the development of Vγ2+ and Vγ3+ $\gamma\delta$ T cells remains unsolved yet.

Meanwhile, mouse $\gamma\delta$ T cells can commit to two subsets during thymic development, producing interferon-γ (IFN-γ) and IL-17A, respectively. Subpopulations that secrete IFN-γ are CD27 positive and mainly include the Vγ5+ DETC, Vγ7+ $\gamma\delta$ T, and Vγ1+ $\gamma\delta$ T cells. IL-17A-producing $\gamma\delta$ T cells lack CD27 expression and include Vγ6+ $\gamma\delta$ T and the Vγ4+ $\gamma\delta$ T cells [23].

3. The Distribution of $\gamma\delta$ T Cells in Ocular Surface

3.1 Cornea

The cornea is a crucial barrier to the eyeball and serves as the primary refractive medium. The corneal epithelium anchors the tear film, providing a smooth optical interface and a comfortable sensation. The cornea is characterized by immune privilege due to three main aspects [27–29]. Firstly, the central cornea is absent of blood vessels and lymphatics, which restricts the migration of immune cells. Secondly, corneal cells do not express MHC II or MHC Ia, preventing the presentation of specific antigens to CD4+ T or CD8+ T cells and thus inhibiting the activation of effector T cells. In addition, corneal epithelial cells, stromal cells, and endothelial cells express various negative immune regulatory transmembrane molecules and secreted proteins, such as pigment epithelium-derived factor [30]. Thirdly, regulatory T cells (Tregs) mediate anterior chamber-associated immune deviation (ACAID), leading to compromised inflammation in the cornea [31,32].

With the advancement of *in vivo* confocal microscopy (IVCM), it is now convenient to observe Langerhans cells (LCs) in the corneal sub-basal epithelium and stroma in the clinic. Basic research has confirmed the presence of various immune cells in the cornea, including LCs, conventional dendritic cells (cDCs), plasmacytoid DCs, macrophages, pre-monocytes, neutrophils, mast cells (MCs), and group 2 innate lymphoid cells (ILC2) [33–37]. The quantity of immune cells resident in the limbal region which is rich in blood supply, is about 16-fold that in the central cornea [5]. Recently, Dou *et al*. [38] carried out a study using single-cell RNA transcriptional profiling on the human limbus and found that myeloid cells (*CD68*, 48.16%) represented the largest proportion of limbus immune cells, followed by T cells (*CD3E*, 37.41%). However, T cells only made up 6.80% of the murine peripheral corneal immune cells in our study by flow cytometry [5].

$\gamma\delta$ T cells in corneal epithelium were initially reported by Li *et al*. [39] in 2007 through immunofluorescence staining. But it could go back to 2001 when mice lacking $\gamma\delta$ T cells failed to develop ACAID and suffered high corneal allograft rejection [40], suggesting that $\gamma\delta$ T cells contributed

to maintaining corneal immune privilege [41]. Li *et al*. [42] reported that $\gamma\delta$ T cells were rich in murine limbal epithelium and stroma (about 27 and 17 per field, respectively), and decreased to 0 at the central cornea. Moreover, Fitzpatrick *et al*. [43] found that $\gamma\delta$ T cells in the cornea were Vγ5 negative but expressed CCR6 so that they could be recruited by the chemokine CCL20. Contact lens wear of mice could induce the infiltration of $\gamma\delta$ T cells in the cornea [44], but no difference in $\gamma\delta$ T cell infiltration was observed in conjunctival impression cytology of contact lens wear patients [45]. However, the subtypes of $\gamma\delta$ T cells and their effectors need further investigation.

3.2 Conjunctiva

Conjunctival tissues contribute to most areas of the ocular surface and are abundant in immune cells at homeostasis. Conjunctiva-associated lymphoid tissue (CALT) is the immune cell-pooled structure in the conjunctiva and consists of conjunctival lymphoid follicles and scattered lymphoid tissues, which are mainly distributed in the substantia propria and to a lesser extent in the epithelial layer [37,46]. In previous studies of human conjunctival biopsies, immune cells colonized in the human conjunctiva were mainly distributed in the bulbar conjunctival region [47].

In mice, as Yoon *et al*. [48] suggested, the ratios of $\gamma\delta$ T cells to CD4+ or CD8+ cells were about 1/4–1/3 in the conjunctival epithelium at 4 weeks old, and the ratio in conjunctiva stroma even decreased to 1/20. As the mice grew to 16 weeks old, the density of $\gamma\delta$ T cells in conjunctival epithelium and stroma increased compared with 4 weeks old, but the density of CD4+ or CD8+ cells remained stable or mildly decreased. This study used immunohistochemistry staining which requires manual counting of multiple slices, therefore it did not show the total number of T cell subsets. In our recent study mapping resident immune cells in 6-8 weeks old murine conjunctiva by flow cytometry, T cells consisted of CD4$^+$ T cells (36.41%), $\gamma\delta$ T cells (25.64%), CD8$^+$ T cells (19.49%) and unconventional T cells (18.46%) [5]. Single-cell RNA transcriptional profiling of 6–8 weeks old murine conjunctiva in another study performed by Alam *et al*. [49] showed that the percentage of $\gamma\delta$ T cells (3.19%) in CD45+ immune cells was even close to the sum (3.96%) of CD4+ T and CD8+ T cells. Meanwhile, $\gamma\delta$ T cells were reported to make up 4.27% of CD45+ immune cells in conjunctival brush cytology of mild dry eye patients and 33.89% of lymphocytes in healthy individuals [50,51]. The detailed compositions of $\gamma\delta$ T cells in the cornea and conjunctiva in ocular surface homeostasis and diseases are listed in **Supplementary Table 1**.

Among $\gamma\delta$ T cells in wild-type C57BL/6 murine conjunctiva, only 2.00% to 3.66% were IFN-γ-producing $\gamma\delta$ T ($\gamma\delta$ T1) cells. IL-17A-producing $\gamma\delta$ T ($\gamma\delta$ T17) cells took up a wide range of 36.70% to 88.00% in several different reports [5,50,52]. That suggests the local environment including microbes in the animal house, perhaps poses significant effects on IL-17A secretion in $\gamma\delta$ T cells and was partly supported by the expansion of $\gamma\delta$ T17 cells driven by the commensal *Corynebacterium mastitidis* (*C. mast*) in the conjunctiva [52]. Leger *et al*. [52] noted that about half of $\gamma\delta$ T17 cells were Vγ4+ $\gamma\delta$ T cells in the conjunctiva, which was similar to their counterpart in dermal cells [7]. Type 3 immune cells, whose significant marker is IL-17A, include Th17 cells, $\gamma\delta$ T17 cells, type 3 innate lymphoid cells (ILC3), and IL-17A$^+$ unconventional T cells [53]. Type 3 immune cells protect against extracellular pathogens [52] and play important roles in ocular surface autoimmune diseases [54]. $\gamma\delta$ T17 cells accounted for 48.02% of type 3 immune cells that are IL-17A positive in the conjunctiva, which was much more than ILC3 (18.82%) and Th17 cells (4.00%), suggesting that $\gamma\delta$ T17 cells could play essential physiological roles in the ocular surface, such as tissue repair and wound healing, in reference to their skin and gut counterparts [25]. Our previous study showed that 2.00% $\gamma\delta$ T cells in murine conjunctiva expressed IL-22, however, 31.5% of $\gamma\delta$ T cells were reported to be IL-22 positive in human conjunctiva [55].

3.3 Lacrimal Gland

As an exocrine gland, the lacrimal gland plays a dominant role in the lacrimal functional unit and contributes to the majority of aqueous tear film [56,57]. Plenty of immune cells are present in the lacrimal gland, including macrophages, DCs, and lymphocytes [37]. Plasma cells, abundantly present in the interstitium of the lacrimal gland, synthesize and secrete IgA, which is released into tears to resist microbial invasion of the ocular surface and promote ocular surface immune homeostasis [58]. T and B cells in the lacrimal gland were first identified by immunochemistry staining in 1988 and were resident in the intraepithelial tissues but not the substantia propria [58,59].

Recent studies based on single-cell RNA transcriptional profiling by Mauduit *et al*. [60] showed that immune cells comprised about 20.0% of total cells in the murine lacrimal gland, including plasma cells (*Jchain*), macrophages (*Gsn*), B cells (*Cd79a*) and T cells (*Cd3g*), consistent with prior studies based on immunohistochemistry staining or flow cytometry. In another study, only T cells were detected by single-cell RNA transcriptional profiling of the human lacrimal gland [61], suggesting that immune cells in the lacrimal gland should be sorted for further sequencing if necessary. In a more detailed study of the murine lacrimal gland, Rattner *et al*. [62] classified immune cells into 16 subsets, including but not limited to CD4+ T cells, CD8+ T cells, B cells, NK cells, macrophages, DC, plasmacytoid DCs, proliferating monocytes, and CSF2/GM-CSF+ ILCs. These studies provided more information about the immune cells of the lacrimal gland. However, $\gamma\delta$ T cells were not reported in the above sequencing data.

In 2000, $\gamma\delta$ T cells were reported to make up 25.0% of T cells in the murine lacrimal gland [63]. In our recent study, the immune cell landscape of the murine lacrimal gland was updated by flow cytometry [5]. Our results showed that T cells (22.40% of total immune cells) exceeded B cells (1.25%) greatly. Besides CD4+ T and CD8+ T cells, $\gamma\delta$ T cells made up 18.90% of T cells in the lacrimal gland. Furthermore, $\gamma\delta$ T17 cells made up 42.80% of $\gamma\delta$ T cells, much more than $\gamma\delta$ T1 cells (1.65%), IL-4+ $\gamma\delta$ T cells (1.19%), and IL-22+ $\gamma\delta$ T cells (0.55%). Moreover, $\gamma\delta$ T17 cells were the main source of IL-17A and accounted for 75.85% of type 3 T cells, followed by unconventional T cells (18.85%), Th17 cells (3.03%), and Tc17 cells (2.07%). This study also found ILCs in the murine lacrimal gland for the first time.

4. The Functions of Gamma Delta T Cells in Ocular Surface Diseases

4.1 Dry Eye Disease

Dry eye disease (DED) is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles [64]. Increasing evidence indicated that DED is a mucosa-localized, autoimmune-mediated, non-infectious inflammatory disease [65]. IL-17A is one of the most important pro-inflammatory factors in the pathogenesis of DED. In 2022, Li *et al.* [50] identified $\gamma\delta$ T cells as the predominantly IL-17A-expressing population in mice conjunctiva, supporting the pro-inflammatory role of $\gamma\delta$ T cells in DED.

T helper (Th) 17 cells rather than $\gamma\delta$ T cells were thought to be the main source of IL-17A in the ocular surface at the beginning of IL-17A-related research. In 2009, Chauhan *et al.* [66] were the first to confirm that the level of *Il17a* mRNA in the draining lymph nodes (submandibular and cervical lymph nodes) and conjunctiva of DED mice was significantly increased, and the flow cytometry results showed that the number of IL-17A+CD4+ cells in the draining lymph nodes of DED mice was much higher than that of control. However, they did not examine the proportion of CD4+ cells in conjunctival IL-17A+ cells. Chauhan *et al.* [66] attributed the biological effects of IL-17A solely to T helper (Th) 17 cells, and most studies on the effects of IL-17A in DED have since tied the biological effects of IL-17A to Th17 cells. In the same year, de Paiva *et al.* [67] using immunofluorescent staining found that IL-17A+ cells were only present in the cornea and conjunctiva of DED mice, but not in the control. However, they did not investigate whether these IL-17A+ cells were CD4+. As Chauhan *et al.* [68] later commented on de Paiva *et al.*'s study [67] and other studies since then [69,70], Th17 cells mainly present in the draining lymph nodes of mice under non-DED conditions and need to migrate to the ocular surface to exert their pro-inflammatory effects. However, the ELISPOT results of de Paiva *et al.* [67] showed that the number of IL-17A+ cells in the cornea and the conjunctiva increased significantly on the 5th day under desiccating stress, but not until the 10th day in draining lymph nodes, suggesting the existence of cells colonizing the cornea and conjunctiva that can produce IL-17A under desiccating stress.

It took more than ten years for the role of $\gamma\delta$ T cells in DED to receive attention. In 2012, Zhang *et al.* [71], using flow cytometry and immunohistochemical staining measured the distribution of intraepithelial lymphocytes in the ocular surface for the first time, revealing that $\gamma\delta$ T cells accounted for the highest proportion of conjunctival CD103+ intraepithelial lymphocytes (43%), while CD4+ cells accounted for only 0.75%. The flow cytometry results showed that the number of $\gamma\delta$ T cells in the ocular surface increased significantly under desiccating stress. However, Zhang *et al.* [71] still focused on the pathogenic role of Th17 cells in DED. The retinoid X receptor α (RXRα) plays a central role in the regulation of many intracellular receptor signaling pathways and is expressed by a variety of immune cells. In 2022, Alam *et al.* [72] found that IL-17A+ $\gamma\delta$ T cells were involved in the DED-like signs caused by a loss of function RXRα mutation. In the same year, Li *et al.* [50] finally confirmed that $\gamma\delta$ T cells accounted for 59.5% of IL-17A+ cells in the conjunctiva of DED mice, while CD4+ T cells, including Th17 cells, accounted for only 17.14%. Li *et al.* [50] further discovered that the proportion of Vγ4 subset cells in IL-17A+ cells was 56.5% in DED mouse conjunctiva and was significantly greater than in the control, indicating that Vγ4 subset cells were the main source of IL-17A in the ocular surface under DED. They also showed that C57BL/6 *TCRδ-/-* mice had less ocular surface damage under desiccating stress than C57BL/6 wild-type mice. The research of Li *et al.* [50] indicated that conjunctival resident $\gamma\delta$ T cells are the predominant source of IL-17A and promote the severity of DED at least in the early stage of DED onset.

The role of IL-17A in the pathogenesis of DED and other ocular surface diseases has been well described, including corneal barrier disruption, epithelial keratinization, neovascularization and lymphangiogenesis, and recruiting the CD4+T cells. Matrix metalloproteinases (MMPs) are the primary effector molecules for corneal and conjunctival epithelial damage in DED, especially MMP-3 and MMP-9 [73,74]. MMPs cause proteolytic disruption of epithelial tight junctions that maintain corneal barrier function. IL-17A has been recognized to upregulate MMPs expression levels of epithelial cells and fibroblasts in other diseases [75,76]. In DED model mice and in vitro cultured human corneal epithelial cells, de Paiva *et al.* [67] confirmed that exogenous IL-17A significantly up-regulated the mRNA expression levels of corneal epithelial cells *Mmp3* and *Mmp9*, while the use of anti-IL-17A antibody to neutralize IL-17A significantly down-regulated the expression levels of *Mmp3* and *Mmp9* mRNA in corneal epithelial

cells, and alleviated the corneal epithelial barrier disruption caused by desiccating stress. Corneal and conjunctival epithelial keratinization and the resulting goblet cell apoptosis are important features of DED. IL-17A has been shown to activate cornified envelope precursor genes such as *Sprr2g* and *Sprr2h* in psoriasis, resulting in abnormal keratinization of the skin [77,78]. Alam *et al*. [72] found IL-17A-induced activation of *Sprr2g* and *Sprr2h* in RXRα inactivating mutant DED mice, suggesting that IL-17A is also involved in corneal and conjunctival epithelial keratinization in DED. IL-17A can directly act on corneal epithelial cells to promote VEGF-D secretion. The VEGF-D binds to vascular endothelial growth factor receptor 3 (VEGFR3) on the surface of lymphatic endothelial cells to cause lymphangiogenesis [79]. IL-17A can also indirectly act on corneal epithelial cells through IL-1β to mediate the secretion of VEGF-A and VEGF-C to cause neovascularization [79–81]. IL-17A promotes the secretion of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α by corneal and conjunctival epithelial cells [82,83]. IL-6 induces the development of Th17 cells from naïve T cells [84]. IL-1, TNF-α, and IL-17A further promote the synthesis and secretion of CCL20 by corneal epithelial cells and stromal cells [85]. CCL20 acts on the CCR6 on the surface of CD4+ T cells in draining lymph nodes and then exerts a strong chemotactic effect. CD4+T cells continue to secrete a variety of pro-inflammatory factors including IL-17A after reaching the ocular surface, starting the vicious cycle of DED [85]. The pathogenesis of Sjögren's syndrome (SS) DED and non-SS DED is quite different, but multiple studies have shown that IL-17A is also involved in SS DED [86–90]. However, studies on the pathogenic role of IL-17A in SS DED are limited to the cytokine perspective, and there are no studies to clarify whether $\gamma\delta$ T cells are the main source of IL-17A in SS DED.

IL-17A is not the only cytokine associated with $\gamma\delta$ T cells that exerts biological effects in DED. Li *et al*. [50] showed that 3.66% of $\gamma\delta$ T cells secrete IFN-γ in the ocular surface of DED mice. IFN-γ plays a complex role in DED, including maturation of antigen-presenting cells [71,91,92], activation and recruitment of CD4+ T cells [91], thereby promoting epithelial keratinization [93,94], and goblet apoptosis [95]. There are no studies on whether IFN-γ+ $\gamma\delta$ T cells play an irreplaceable role in DED or simply serve as an auxiliary source of IFN-γ.

In addition, there is an intriguing research topic that $\gamma\delta$ T cells may have a migration mechanism from the conjunctival epithelium to the cornea or conjunctival lamina propria (stroma) under desiccating stress. The immunohistochemistry staining in the study of Zhang *et al*. [71] showed that the number of $\gamma\delta$ T cells in the conjunctival epithelium decreased significantly under desiccating stress, but the flow cytometry results of corneal and conjunctival full-thickness cells showed that $\gamma\delta$ cells increased significantly under desiccating stress. IL-17A-producing $\gamma\delta$ T cells have also been found to infiltrate the cornea under the chemotaxis of ICAM-1 and CCL20 secreted by injured corneal epithelial cells following corneal epithelial trauma [39,42,80,96,97].

Compared with the more thoroughly studied $\gamma\delta$ T cell effector cytokines, there are few studies on the upstream regulatory cells and cytokines of $\gamma\delta$ T cells. NK cells are an important source of IFN-γ in the early DED. Zhang *et al*. [71] found that the mRNA levels of *Il6*, *Il23*, and *Ifn*γ in NK/NKT cells increased significantly after 1 day of desiccating stress, while the mRNA levels of *Il17a* in non-NK/NKT cells increased significantly. Furthermore, the elimination of NK/NKT cells significantly reduced the mRNA levels of *Il17a* in the ocular surface under desiccating stress. Alam *et al*. [72] showed that 9-cis retinoic acid (RA) could directly inhibit the secretion of IL-17A by $\gamma\delta$ T cells, and could also act on the RXRα of monocytes to inhibit the AP-1 pathway, thereby inhibiting the secretion of IL-23, IL-1α, IL-1β, TNF-α and other $\gamma\delta$ T-promoting cytokines, indirectly inhibiting the production of IL-17A by $\gamma\delta$ T cells. How $\gamma\delta$ T cells perceive desiccating stress is an issue that needs further research. Alam *et al*. [72] proposed that $\gamma\delta$ T cells can be activated by a variety of PAMPs in a non-antigen-specific manner and conceivably by desiccating stress which activates the same signaling pathways as microbial products. The mechanism by which $\gamma\delta$ T cells are involved in the pathogenesis of DED is summarized in Fig. 1.

4.2 Infectious Keratitis

Infectious keratitis (IK) can be caused by various pathogens, including bacteria, fungi, viruses, and parasites, among which bacteria and fungi are the most common pathogens leading to corneal infections. Major risk factors for keratitis include trauma, ocular surface diseases, eyelid disorders, the use of contact lenses, and post-eye surgery [98]. Typical symptoms and signs of IK encompass decreased visual acuity, corneal ulcers, and stromal immune cell infiltration [99]. A notable characteristic of IK is the presence of associated pain during the acute phase [100]. It is crucial to note that IK may trigger a series of complications such as corneal perforation and scarring, thereby increasing the complexity of treatment.

Substantial evidence indicates that $\gamma\delta$ T cells can enhance the inflammatory capacity of neutrophils in IK, not only by mediating their activation [101,102] but also by inducing effective survival signals to protect neutrophils from apoptosis (Fig. 2) [103,104].

4.2.1 Bacterial Keratitis

Bacterial keratitis (BK) is characterized by painful epithelial defects accompanied by inflammation and ulcers in the corneal stroma. Infected eyes often appear red due to widespread conjunctivitis, and in severe cases, there may be involvement of the episclera and sclera. Localized corneal opacification and thinning are common, along with anterior uveitis, fibrous exudate, or hypopyon in some cases [105].

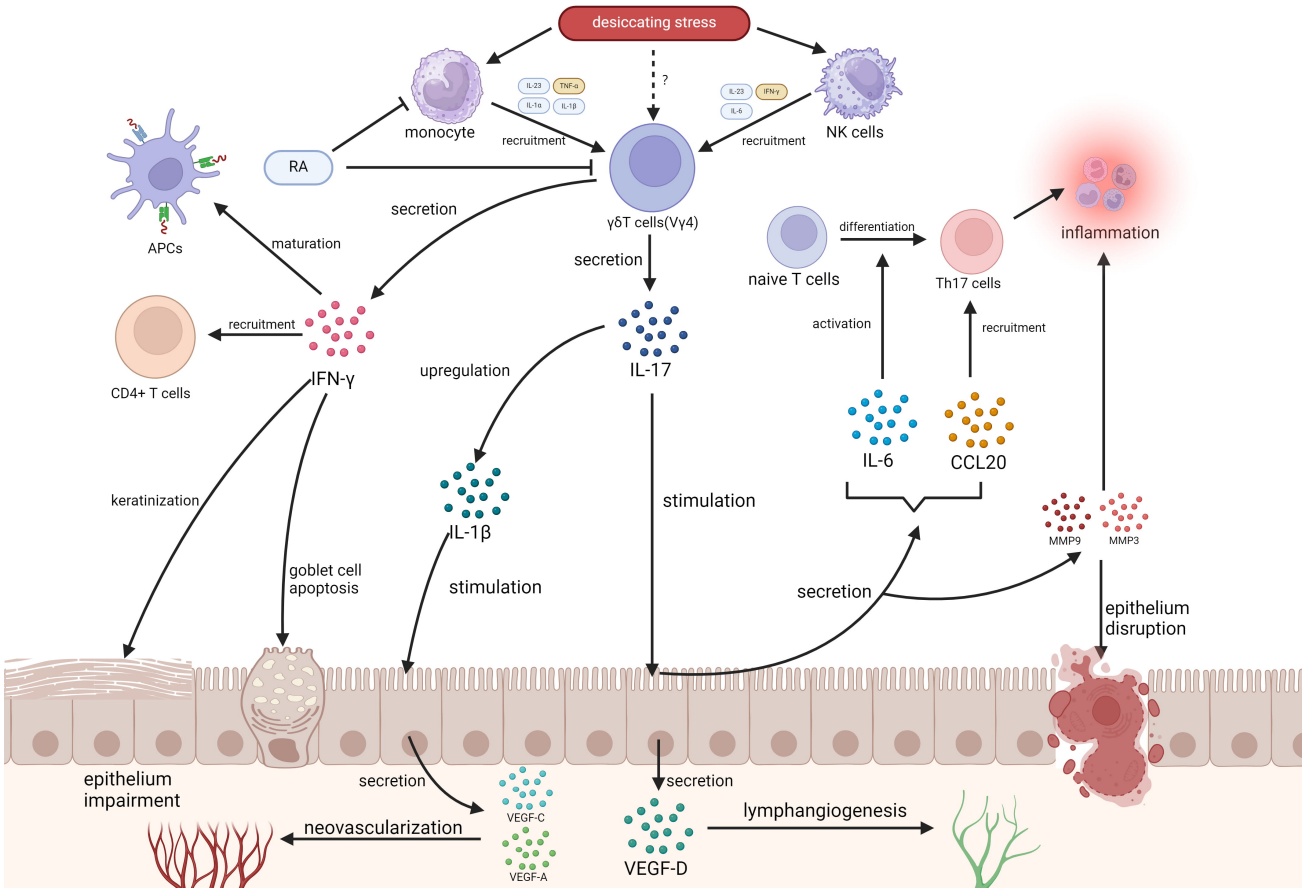

Fig. 1. Gamma delta T cells play a pathogenic role in dry eye disease. Desiccating stress activates and recruits gamma delta ($\gamma\delta$) T cells by monocytes and natural killer (NK) cells. A pathway where desiccating stress directly stimulates $\gamma\delta$ T cells is possible. 9-cis retinoic acid (RA) directly inhibits the $\gamma\delta$ T cells and also acts on monocytes to indirectly inhibit the $\gamma\delta$ T cells. $\gamma\delta$ T cells contribute to dry eye disease (DED) pathogenesis through the secretion of IL-17 and IFN-γ. IL-17A upregulates MMP3 and MMP9 expression of corneal epithelial cells, mediating corneal epithelial barrier disruption. IL-17A activates cornified envelope precursor genes *Sprr2g* and *Sprr2h* resulting in corneal and conjunctival epithelial keratinization. IL-17A directly acts on corneal epithelial cells to promote VEGF-D secretion. The VEGF-D binds to VEGFR3 on the surface of lymphatic endothelial cells to cause lymphangiogenesis. IL-17A also indirectly acts on corneal epithelial cells through IL-1β to mediate the secretion of VEGF-A and VEGF-C to cause neovascularization. IL-17A promotes the secretion of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α by corneal and conjunctival epithelial cells. IL-6 induces the development of Th17 cells from naïve T cells. IL-1, TNF-α, and IL-17A further promote the synthesis and secretion of CCL20 by corneal epithelial cells and stromal cells. CCL20 acts on the CD4+ T cells in draining lymph nodes and then exerts a strong chemotactic effect. CD4+T cells continue to secrete a variety of pro-inflammatory factors including IL-17A after reaching the ocular surface, promoting ocular surface inflammation. IFN-γ plays a complex role in DED, including the maturation of antigen-presenting cells (APCs), activation and recruitment of CD4+ T cells, thereby promoting epithelial keratinization and goblet apoptosis (Created with BioRender.com). TNF-α, tumor necrosis factor-α; IL-17, interleukin-17; IFN-γ, interferon-γ; VEGFR3, vascular endothelial growth factor receptor 3; MMP, matrix metalloproteinase; Th17, T helper 17; CCL20, C-C motif chemokine ligand 20.

The staple pathogenic bacteria in BK are *Pseudomonas. aeruginosa* (*P. aeruginosa*) and *Staphylococcus. aureus* (*S. aureus*). *P. aeruginosa* can induce perforation in the corneal epithelial cell membrane. This is achieved through the secretion of various proteases (elastases A and B, and alkaline protease [106]) and the injection of toxin factors via the Type III Secretion System (T3SS) actively secreting exotoxins, including ExoU, ExoS, ExoT, and ExoY, which promote tissue destruction, manipulate host cell signaling pathways, and disrupt the host immune response [107]. *S. aureus* exerts its pathogenic effects by releasing α-toxin, γ-hemolysin (γHLs) [108], and panton-valentine leukocidin (PVL) [109], which contribute to cell barrier disruption and immune response suppression.

Hazlett *et al.* [110] reveal that dendritic cells accumulate in the center of the cornea after *P. aeruginosa* infection and promote macrophage recruitment, whereas macrophages can recruit polymorphonuclear neu-

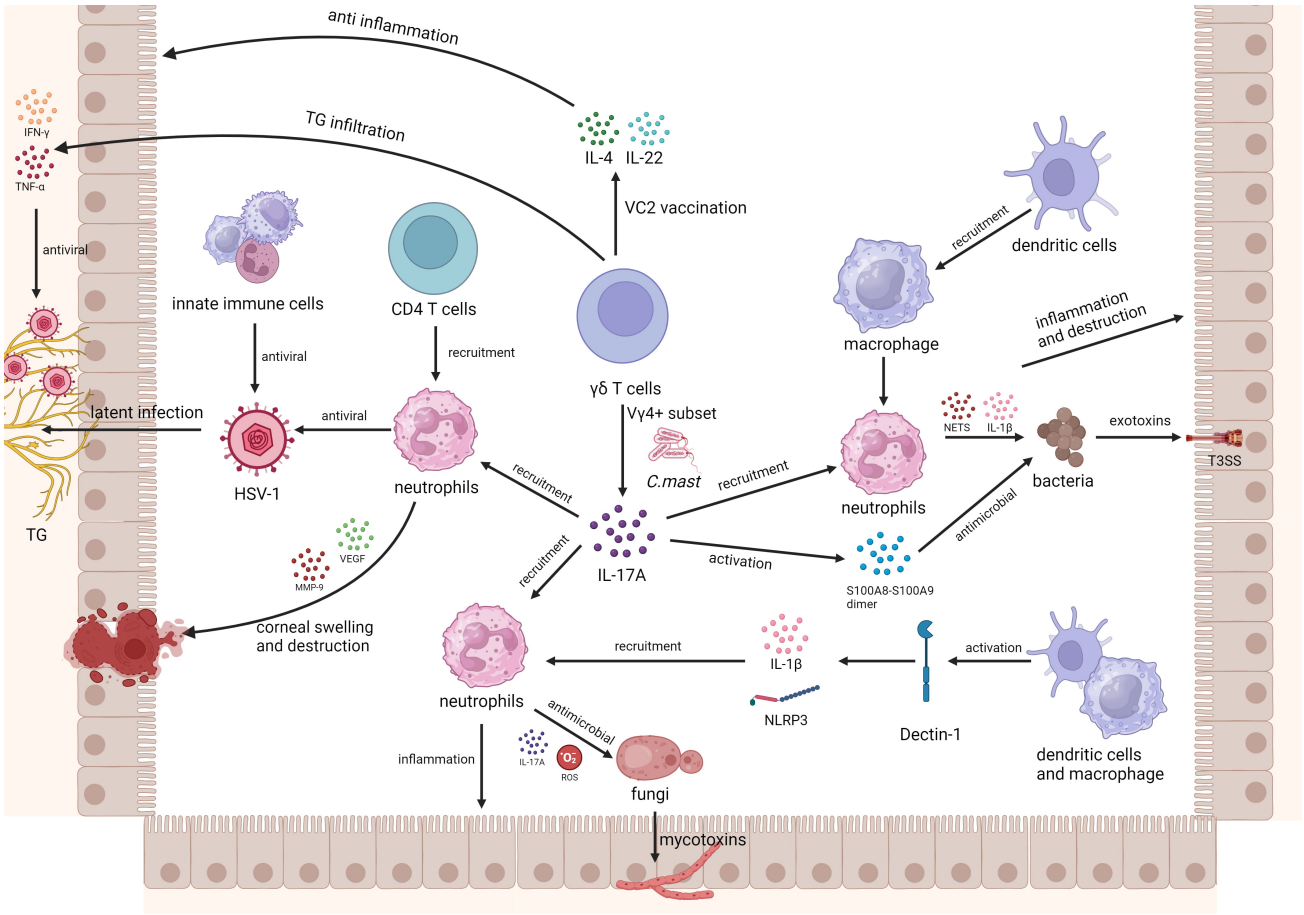

Fig. 2. The mechanism by which gamma delta T cells are involved in infectious keratitis. The production of IL-17A induced by the commensal colony *Corynebacterium mastitidis* (*C. mast*), which recruits neutrophils to mediate the antipathogen response as well as inflammation, is an important mechanism for gamma delta ($\gamma\delta$) T cells in infectious keratitis (IK). In bacterial keratitis (BK), in addition to antimicrobial IL-β as well as NETS released by neutrophils, IL-17A also directly stimulates the release of peptides S100A8-S100A9, resulting in bacteria clearance. In viral keratitis (VK), $\gamma\delta$ T cells can migrate to the trigeminal ganglion (TG) and clear latent HSV-1 from the TG by releasing IFN-γ and TNF-α. On the other hand, $\gamma\delta$ T cells can release IL-4 and IL-22 to alleviate epithelium damage caused by inflammation. In fungal keratitis (FK), $\gamma\delta$ T upregulates antifungal molecules such as reactive oxygen species (ROS) by mediating neutrophil recruitment, contributing to antifungal response as well as inflammation (Created with BioRender.com). NETS, neutrophils extracellular traps; HSV-1, herpes simplex virus type 1; NLRP3, NLR family pyrin domain containing 3; S100A8, S100 calcium-binding protein A8; T3SS, type III secretion system; VC2, HSV-1 live-attenuated vaccine strain.

trophils (PMNs) and upregulate the secretion of IL-1β, and macrophage-inflammatory protein 1 and 2 [111]. In BK, neutrophil infiltration primarily exerts corneal inflammation, which promotes not only antibacterial effects but also epithelial destruction. Minns *et al.* [112] discovered that *P. aeruginosa* in corneal infections can stimulate neutrophils to release neutrophil extracellular traps (NETs) and IL-1β, thereby mitigating the severity of corneal lesions.

Leclercq *et al.* [113] found that on the surface of the skin, the Vγ3 $\gamma\delta$ T subset can respond to Gram-negative bacteria directly via lipopolysaccharide (LPS)-mediated stimulation, promoting the secretion of macrophage colony-stimulating factor (GM-CSF) and IL-2. Leger *et al.* [52] discovered that on the surface of the cornea, $\gamma\delta$ T cells were activated by a commensal community of *C. mast* and alleviated the *P. aeruginosa* IK by secreting IL-17A, which induced antimicrobial peptides such as S100A8 and S100A9. Zaidi *et al.* [114] showed that topical neutralization of IL-17A decreased neutrophil infiltration and pathology on the surface of *P. aeruginosa*-infected corneas, but without affecting bacterial clearance. These results indicate that $\gamma\delta$ T cells play an antimicrobial role and contribute to corneal inflammation in *Pseudomonas* keratitis.

4.2.2 Viral Keratitis

The ACSIKS study reveals that viral keratitis was the most common cause of IK in China (46%), attributed mainly to herpes simplex keratitis (HSK) (24%) and herpes zoster keratitis (HZK) (17%) [115]. Herpes simplex virus-

1 (HSV-1) is the main causative pathogen of viral keratitis, which is an enveloped double-stranded DNA virus belonging to the herpesvirus family responsible for corneal infection [116].

Primary ocular HSV-1 infection is less common and usually presents as conjunctivitis, which may involve inflammation of the eyelids (blepharoconjunctivitis), marked by inflammatory vesicles and ulcers, and may include dendritic lesions of the corneal epithelium [117]. In general, HSV-1 ocular infections are due to reactivation following the establishment of latent infection in the trigeminal ganglion (TG). Clinical signs of HSK include corneal clouding, edema, and neovascularization [116]. Recurrent episodes are also an important feature of HSK, which can lead to irreversible corneal scarring and blindness.

At the primary stage of HSK, innate immune cells, which consist of neutrophils, plasmacytoid DCs, NK cells, and macrophages [118,119] secret various immune-regulatory mediators such as IFN-γ and IL-2, which induce corneal inflammation and neovascularization [120]. In the late clinical stages, CD4+ T cells are considered the staple coordinators of HSK lesions, appearing in the cornea around 6-7 days post-infection and facilitating the second wave of neutrophil infiltration [121]. Lepisto *et al.* [122] demonstrated that mice lacking CD4+ T cells were unable to develop symptoms of HSK. Meanwhile, Chen *et al.* [123] showed that CD4+ T cells are necessary for neutrophil recruitment. Neutrophils are the main infiltrating cell population, accounting for 80–90% [124], which promote neovascularization and inflammation via secreting factors such as MMP-9 and VEGF, resulting in corneal swelling and destruction [125].

The antiviral and inflammatory effects of $\gamma\delta$ T cells in viral keratitis were validated in several experiments. Kodukula *et al.* [126] discovered that during HSV-1 replication in the cornea, macrophages and $\gamma\delta$ T cells infiltrated the TG and expressed TNF-α, IFN-γ, inducible nitric oxide synthase (iNOS) enzymes, and IL-12, inhibiting HSV-1 proliferation. Suryawanshi *et al.* [127] revealed that, upon HSV infection of the cornea, the first wave of IL-17A reaches the climax around the second day post-infection, and the second wave steadily rises from day 7, reaching a peak around day 21, coinciding with the appearance of prominent clinical symptoms. Additionally, the research indicates $\gamma\delta$ T cells are the primary producers of early IL-17A during the early phase of HSV infection. Like the study of Leger *et al.* [52], IL-17 also stimulates the recruitment of neutrophils in HSK, which both favor viral clearance and contribute to inflammation and tissue damage. The follow-up experiments of Suryawanshi *et al.* [127] showed that either neutralization of IL-17 or deletion of the IL-17R can result in the attenuation of HSK symptoms.

However, a comparative experiment by Nabi *et al.* [128] reveals that, ocular stimulation in VC2 (HSV-1 live-attenuated vaccine strain)-immunized mice induced a unique mucosal response, resulting in $\gamma\delta$ T cell infiltration, which upregulates the secretion of IL-4, IL-22 and suppresses neutrophil infiltration. The result indicated that $\gamma\delta$ T cells on the cornea correlate positively with corneal protection but inversely with tissue damage. However, infiltrating $\gamma\delta$ T cells do not exhibit HSV-1-specific memory and have no impact on virus count in TG, suggesting that $\gamma\delta$ T cells merely play an inhibitory role in regulating inflammatory responses [128].

4.2.3 Fungal Keratitis

Fungal keratitis (FK) can occur in both immunocompetent and immunocompromised hosts [129]. Yeasts such as *Candida spp.* and filamentous fungi including *Fusarium spp.*, *Aspergillus spp.*, and dematiaceous fungi are common pathogens in FK [130]. The feathery rim observed in the early stages of infiltration is the most characteristic clinical feature of FK [131]; other features include surface elevation, endothelial plaques, dry texture, and satellite-shaped lesions [132].

Fungal-expressed adhesins enable fungi to evade host defenses by binding to mannose glycoproteins with up-regulated expression in damaged epithelium [133], followed by invasion into deeper layers of corneal tissue and morphological changes (formation of barriers to antifungal drugs, etc.) [134]. Fungi secrete a wide range of mycotoxins as well as proteases (serine proteases, cysteine proteases, fungal collagenases, etc.), which play a pathogenic role in corneal epithelial disruption and corneal clouding [135].

Macrophages and DCs express the C-type cell lectin (Dectin-1), which activates the Syk-CARD9-NF$\kappa\beta$ intracellular signaling pathway by binding to β-glucan on the surface of sporocysts, resulting in the release of IL-1β and activation of NLRP3 inflammasome. It consequently leads to the recruitment of neutrophils [136]. Neutrophils are the main infiltrating cells of FK, accounting for 95% of the cellular infiltration and limiting fungal growth through the production of reactive oxygen species (ROS) [137], IL-17 [138], and chitinase [139].

He *et al.* [140] revealed that in the cornea of mice with *Fusarium solani* keratitis, a significant increase in $\gamma\delta$ T cells was observed 36 h after infection, and a significant decrease in IL-17A was observed after neutralization of $\gamma\delta$ T cells with antibodies. This is similar to the experimental results of Leger *et al.* [52] where $\gamma\delta$ T cells recruited in the commensal *C. mast* can secrete IL-17A. Additionally, the tear fluid of mice that received corneal *C. mast* colonization had a greater ability to clear *Candida albicans* and *Candida mastocytophilus*.

However, Taylor *et al.* [138] showed that it was the neutrophil subpopulation with Th17 cells that produced IL-17A as well as provided optimal protective immunity in *Aspergillus* and *Fusarium*-infected corneas. Further studies by He *et al.* [140] illustrated that in the corneas of FK mice in the $\gamma\delta$ T-neutralized group, the counts of neutrophil infil-

tration as well as the duration of infiltration were the same as in the FK control group, and the mycelial volume was smaller than that of the control FK group at 48 h and 72 h post-infection, predicting that $\gamma\delta$ T cells not only do not play a predominant role in chemotaxis to centroblasts but even limit the clearance of FK in some cases.

4.3 Corneal Trauma and Contact-Lens Related Corneal Injury

$\gamma\delta$ T cells play a pro-inflammatory role in corneal trauma, but this inflammation is beneficial for corneal wound healing (Fig. 3). From 2007 to 2011, Li *et al.* [39,42,80] and Byeseda *et al.* [96] carried out a series of work using corneal trauma C57BL/6 mice as a model and elucidated the role of $\gamma\delta$ T cells in corneal wound healing. IL-17A+ $\gamma\delta$ T cells (Vγ6+ $\gamma\delta$ T and the Vγ4+ $\gamma\delta$ T cells) play a primary role in promoting corneal wound healing. These cells express receptors such as CD11a/CD18 (LFA-1), CCR6, etc. First, damaged corneal epithelial cells secrete ICAM-1 (ligand of LFA-1) and CCL20 (ligand of CCR6), and $\gamma\delta$ T cells migrate to the trauma area under chemotaxis by ICAM-1 and CCL20 [96]. $\gamma\delta$ T cells then secrete IL-22 and IL-17A. IL-22 has been shown to promote keratinocyte proliferation and wound healing in some epithelial tissues [141,142]. IL-22 acts on corneal epithelial cells, directly promoting corneal epithelial cell proliferation and wound healing [42], and on the other hand, promoting corneal epithelial cells to produce chemokines such as CXCL1 to recruit neutrophils and platelets to the wound area. Neutrophils and platelets promote wound repair and corneal nerve regeneration through mechanisms such as VEGF-A and growth factors [42,80]. IL-17A acts on lymphatic vessels endothelial cells and jointly recruits neutrophils and platelets with IL-22 [39].

Compared with mechanical corneal trauma alone, corneal injury caused by contact lens (CL) is more complex, involving mechanical damage, hypoxia stimulus, toxic substances, and altered commensal microorganisms [143]. The research on the role of $\gamma\delta$ T cells in CL-related corneal injury is still in a preliminary stage, but several studies suggested that IL-17A+$\gamma\delta$ T cells play a crucial role in CL-related corneal injury.

The CLs with different mechanical properties and oxygen permeability have different effects on the ocular surface inflammation mediated by IL-17A+ $\gamma\delta$ T cells. The results of Chao *et al.* [144] and Muhafiz *et al.* [145] showed that the tear IL-17A level was the lowest in patients using daily disposable hydrogel CL, while the tear IL-17A level was the highest in patients using reusable silicone hydrogel CL, and the tear IL-17A level increased with the time course of CL use regardless of the type of CL used. In addition to the CL itself, the multipurpose solution for CL also causes IL-17A+ $\gamma\delta$ T cells-mediated ocular surface inflammation. Kalsow *et al.* [146] showed that multipurpose solution for CL may increase IL-17A levels in CL-wearing patients' tears and the increase of IL-17A in tears depends on the choice of different multipurpose solution. The ocular surface inflammation mediated by IL-17A+ $\gamma\delta$ T cells is also associated with subjective discomfort symptoms caused by CL. Gad *et al.* [147] found that people experiencing CL discomfort had higher tear IL-17A levels than people who did not. Downie *et al.* [148] explored the therapeutic effects of topical corticosteroid and omega-3 supplements on inflammation associated with CL discomfort, and the results showed topical corticosteroids and Omega-3 supplementation reduced tear levels of IL-17A with a concomitant reduction of CL discomfort.

The specific immune mechanism by which IL-17A+ $\gamma\delta$ T cells are involved in CL-related corneal injury began to be studied in 2023. Datta *et al.* [44,149] proposed that IL-17A+ $\gamma\delta$ T cells infiltrate the cornea and recruit neutrophils in CL-related corneal injury and also identified the key receptors in this process in two consecutive studies. They considered corneal inflammation caused by CL wearing to be "para-inflammation", which was described as a response to tissue stress that resided between the homeostatic state and classical "symptomatic" inflammation. Firstly, they found that corneal infiltration of IL-17A+ $\gamma\delta$ T cells and subsequent neutrophil corneal infiltration mediated by IL-17A+ $\gamma\delta$ T cells were closely related to CL-induced corneal parainflammation in CL-wearing C57BL/6 mice. Further, they identified that TRPA1 and TRPV1 ion channels of corneal sensory nerves were required for not only CL-induced corneal infiltration of $\gamma\delta$ T cells and neutrophils but also for maintaining baseline levels of resident corneal $\gamma\delta$ T cells. It can be seen that the corneal infiltration of IL-17A+ $\gamma\delta$ T cells and neutrophils induced by CL shares similarities with the corneal wound healing mechanism revealed by Li *et al.* [42], which may act as a reference for future research on CL-induced corneal injury.

In conclusion, it has been elucidated that $\gamma\delta$ T cells promote corneal wound healing but the mechanism of the action of $\gamma\delta$ T cells in CL-related corneal injury needs further research. Whether the immune mechanisms of traumatic factors such as mechanical damage, hypoxia stimulus, toxic substances, and altered commensal microorganisms are different requires exploration. The role of IFN-γ-producing $\gamma\delta$ T cells in corneal trauma and wound healing is also worth exploring. The research on CL-related corneal injury can refer to the pathway found in previous studies on non-CL-related corneal trauma.

4.4 Anterior Chamber-Associated Immune Deviation

ACAID is a form of systemic tolerance to alloantigen placed in the anterior chamber of the eye and is one of the most crucial molecular mechanisms contributing to the immune privilege in the cornea [27]. ACAID can manifest as an Ag-specific down-regulation of systemic delayed-type hypersensitivity (DTH) after introducing the Ags into the anterior chamber. Several studies have shown that $\gamma\delta$ T cells play an integral role in ACAID.

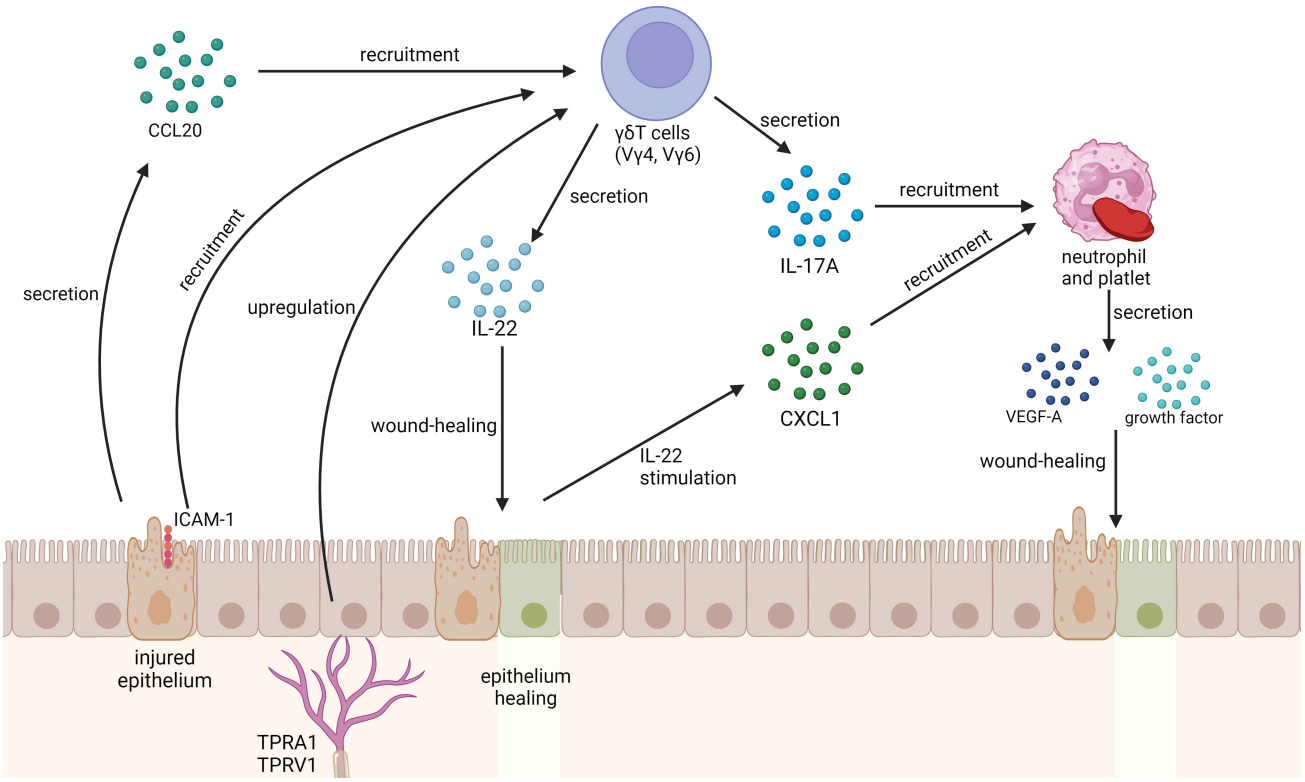

Fig. 3. The mechanism by which gamma delta T cells are involved in corneal trauma and wound healing. Damaged corneal epithelial cells secrete ICAM-1 and CCL20. Gamma delta ($\gamma\delta$) T cells migrate to the trauma area under chemotaxis by ICAM-1 and CCL20. $\gamma\delta$ T cells then secrete IL-22 and IL-17A. IL-22 acts on corneal epithelial cells, directly promoting corneal epithelial cell proliferation and wound healing, and on the other hand, promoting corneal epithelial cells to produce chemokines such as CXCL1 to recruit neutrophils and platelets to the wound area. Neutrophils and platelets promote wound repair and corneal nerve regeneration through mechanisms such as VEGF-A and growth factors. IL-17A acts on lymphatic vessels endothelial cells and jointly recruits neutrophils and platelets with IL-22. TRPA1 and TRPV1 ion channels of corneal sensory nerves are essential for contact lens-induced corneal infiltration of $\gamma\delta$ T cells and neutrophils and maintaining baseline levels of resident corneal $\gamma\delta$ T cells (Created with BioRender.com). ICAM-1, intercellular adhesion molecule 1; CXCL1, C-X-C motif chemokine ligand 1; TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid 1.

It is not the $\gamma\delta$ T cells in the ocular surface, but the $\gamma\delta$ T cells in the spleen and thymus that play a key role in ACAID. A series of studies from 2001 to 2006 showed the crucial role played by splenic $\gamma\delta$ T cells in ACAID. First, investigators found that ACAID cannot be induced in GL3 (a monoclonal antibody specific for a δ-chain determinant that is expressed by all murine $\gamma\delta$ T cells) -treated or TCR δ-chain knockout (KO) C57BL/6 mice [40,150]. Skelsey *et al.* [40] also found that mice treated with GL3 had a significantly higher incidence of corneal graft rejection than the untreated or normal hamster serum treated controls. Xu *et al.* [150] further discovered that the transfer of $\gamma\delta$ T cells from wild-type C57BL/6 to *TCRδ-/-* C57BL/6 mice reconstitutes ACAID. These studies confirmed that $\gamma\delta$ T cells play an indispensable role in ACAID.

Multiple studies have shown that $\gamma\delta$ T cells facilitate the generation of ACAID Tregs and further inhibit DTH. The reconstitution in *TCRδ-/-* C57BL/6 mice with $\gamma\delta$ T cells from MHC-I- or MHC-II-deficient donors restored ACAID successfully, indicating that $\gamma\delta$ T cells did not act as antigen-presenting cells (APCs) for the induction of ACAID [41]. Skelsey *et al.* [40] and Ashour *et al.* [41] demonstrated that ACAID immunized splenic cells eliminated of $\gamma\delta$ T cells could still suppress DTH, proving that $\gamma\delta$ T cells are not efferent end-stage Tregs in ACAID. The result that ACAID immunized splenic cells of *TCRδ-/-* C57BL/6 mice could not inhibit DTH indicated that $\gamma\delta$ T cells are needed for the generation of ACAID efferent end-stage Tregs [40]. Xu *et al.* [151] further demonstrated that CD8+ cytotoxic T-lymphocytes induced by priming with antigen in complete Freund's adjuvant (CFA) were not inhibited by ACAID in *TCRδ-/-* C57BL/6 mice while $\gamma\delta$+ spleen cells from wild-type C57BL/6 restored the inhibition by ACAID. They also found that the antigen-specific killing by the spleen effector cells was dramatically inhibited by the splenic $\gamma\delta$+ cells primed by ACAID *in vitro*. These studies demonstrated that $\gamma\delta$ T cells facilitate the generation of ACAID Tregs and further inhibit DTH.

However, the specific mechanism by which $\gamma\delta$ T cells exert their effects in ACAID has not been fully understood, possibly involving IL-10, IL-4, and IL-2. Ashour *et al.* [41] found that $\gamma\delta$ T cells from IL-10 KO donors can not restore ACAID in $\gamma\delta$ T cell KO mice and ACAID was restored in spleen cell cultures from $\gamma\delta$ T cell KO mice by adding recombinant mouse (rm) IL-10. Thus, Ashour *et al.* [41] proposed that $\gamma\delta$ T cells promote ACAID through their production of IL-10. However, their result cannot prove their conclusion solidly as IL-10 may induce the development of certain subsets of $\gamma\delta$ T cells and these $\gamma\delta$ T cells induce the secretion of IL-10 in other ACAID-related cells. Before Ashour *et al.* [41] proposed that $\gamma\delta$ T cells promote ACAID through their production of IL-10, Skelsey *et al.* [152] have found that CD4 KO spleen cultures reconstituted with CD4+ T cells from IL-10 KO mice were unable to generate ACAID suppressor cell activity and the ACAID suppressor cells generated in the presence of IL-10 suppressed DTH in an antigen-specific manner, from which they proposed that IL-10-producing CD4+ T cells are required for suppressor cell production in ACAID. The above two studies suggested that it is a potential research direction to elucidate the presence of the possible $\gamma\delta$ T cells-CD4+ T cell pathway in ACAID.

O'Brien *et al.* [153] conducted a series of studies based on the female C57BL/10 *TCRδ-/-* mice model of spontaneously developed autoimmune keratitis. O'Brien *et al.* [153] found that 70% to 80% of female C57BL/10 *TCRδ-/-* mice spontaneously developed autoimmune keratitis at 18 weeks. O'Brien *et al.* [153] further discovered that adoptive transfer of Vγ1+ cells from C57BL/10 wild-type donors reduced the incidence of keratitis in C57BL/10 *TCRδ-/-* females. Certain Vγ1+ cells are potent producers of IL-4 [154]. Thus, O'Brien *et al.* [153] proposed that autoimmune keratitis in female C57BL/10 *TCRδ-/-* mice may be caused by the insufficient efficacy of Vγ1 subset $\gamma\delta$ T cells in secreting IL-4 to inhibit $\alpha\beta$ T cells.

Huang *et al.* [155] identified that CD4+ Tregs were significantly reduced and the levels of the two molecules present in Tregs that are important for their functionality: IL-2Rlα (CD25) and IL-2Rβ (CD122) were also significantly reduced in the C57BL/10 *TCRδ-/-* mice than in the wild-type. There was a >2-fold decrease in both splenic CD4+ and CD8+ cells biased to produce IL-2 in C57BL/10 *TCRδ-/-* female mice. IL-2 is a cytokine critical for CD4+ Treg development, survival, and activation. To examine whether a reduction in IL-2 owing to the lack of $\gamma\delta$ T cells leads to Tregs reduction in C57BL/10 *TCRδ-/-* mice, they further examined IL-2 production by $\gamma\delta$ T cells isolated from the spleens and thymus, showing that splenic $\gamma\delta$ T cells produced much less IL-2 than did splenic $\alpha\beta$ T cells but thymic $\gamma\delta$ T cells produced IL-2 in amounts comparable to those produced by thymic $\gamma\delta$ TCR-negative thymocytes. If $\gamma\delta$ T cells provide a significant fraction of IL-2 necessary for the thymic development of CD4+ Tregs, the lack of this additional IL-2 source could diminish the levels of Tregs coming out of the thymus and reduce peripheral Tregs as well.

In conclusion, although $\gamma\delta$ T cells have been shown to mediate ACAID by promoting Tregs generation, the specific molecular mechanisms and cell-cell interactions involved have not yet been elucidated, and future high-quality studies are needed to advance our understanding.

4.5 Allergic Conjunctival Disease

Allergic conjunctival disease (ACD) is a conjunctival inflammatory disease associated with a type I allergy accompanied by some subjective and objective symptoms [156]. The Th2 response is one of the major drivers of the type I allergy in ACD [157,158]. Th2 cells secrete IL-4, IL-5, and IL-13. IL-4 and IL-13 induce isoform conversion of B cell isotype class switching, which promotes IgE production [159]. The binding of allergen-derived IgE to FcϵRI receptor highly expressed by mast cells promotes degranulation, which further releases histamine, heparin, and arachidonic acid (AA). AA is further metabolized to platelet-activating factors and leukotrienes and promotes the recruitment of neutrophils, eosinophils, and monocytes which can contribute to the inflammatory response and tissue damage [160]. IL-5 drives eosinophil differentiation [161], which exacerbates inflammation in ACD.

The $\gamma\delta$ T cells were reported to drive Th2-mediated allergic response. Reyes *et al.* [162] revealed that after topical administration of short ragweed (SRW) pollen, compared with WT mice, *TCRδ-/-* mice showed alleviated lid edema, tearing, conjunctival vasodilatation, and conjunctival edema. Additionally, a significant decrease in IL-4, IL-5, and IL-13 levels, and eosinophilic infiltration was also observed. These results confirmed the promoting role of $\gamma\delta$ T cells in Th 2-mediated allergic response. Further research by Reyes *et al.* [162] showed that CD4+ T cells from pollen-sensitized *TCRδ-/-* mice induced attenuated allergic response after being adoptively transferred to WT naïve recipients than CD4+ T cells from pollen-sensitized WT mice. They also found that *TCRδ-/-* naïve recipients being transferred with CD4+ T cells from pollen-sensitized WT donors showed alleviated allergic response than WT naïve recipients. Reyes *et al.*'s results [162] indicated that $\gamma\delta$ T cells not only exaggerate the early onset of allergy (Th2 activation and generation of SRW pollen-specific Th2 cells) but also play a promoting role at the end-stage organ conjunctiva.

Several studies have shown that the $\gamma\delta$ T cell is one of the major subpopulations of IL-17-secreting cells in the conjunctiva. Chen *et al.* [163] discovered that in the conjunctiva of SRW-stimulated IL-27-signaling-deficient mice, compared with WT mice, the level of IL-17A was upregulated, accompanied by increased IL-4, IL-5, and IL-13, which indicated that $\gamma\delta$ T cells may exacerbate Th2 allergic responses via IL-17A.

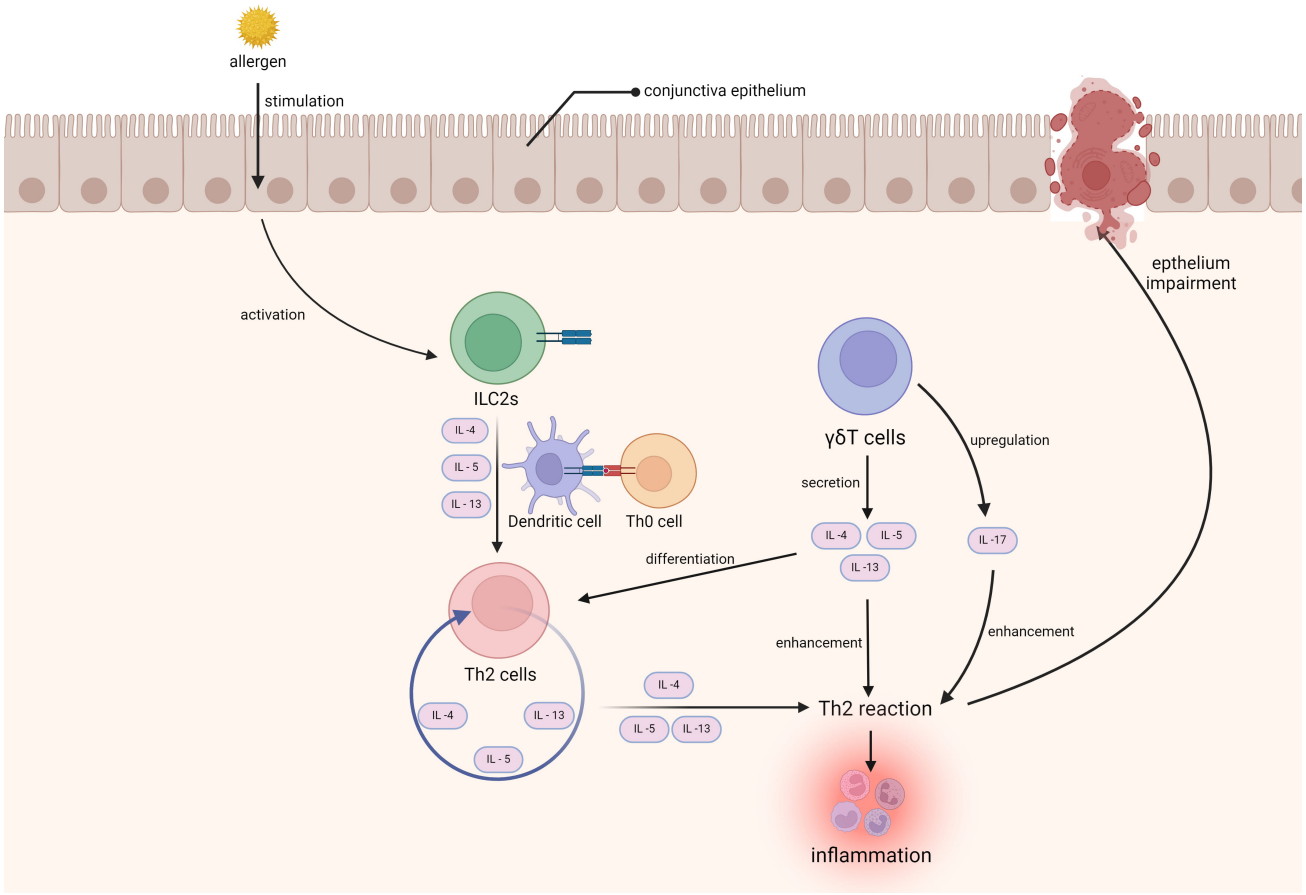

Fig. 4. The mechanism by which gamma delta T cells are involved in allergic conjunctival disease. Gamma delta ($\gamma\delta$) T cells exacerbate allergic conjunctival disease by upregulating cytokines such as IL-4, IL-5, IL-13, and IL-17. On the one hand, IL-4, IL-5, and IL-13 directly contribute to the T helper (Th) 2 response. On the other hand, they can promote the differentiation of Th2 cells, which can further upregulate the release of Th2 cytokines. The Th2 response leads to intense inflammation, which results in the injury of conjunctiva epithelium (Created with BioRender.com). ILC2s, type 2 innate lymphoid cells.

Conclusively, $\gamma\delta$ T cells can exacerbate allergic conjunctivitis via promoting a Th2-type response (Fig. 4). However, whether $\gamma\delta$ T cells upregulate Th2 response and cytokine secretion through IL-17A release or other mechanisms still requires further investigation. In addition, the interaction of $\gamma\delta$ T cells with other immune cells in mediating Th2-type responses deserves further exploration.

4.6 Diabetic Ocular Surface Disease

Diabetic mellitus (DM) patients with hyperglycemia for prolonged periods suffer from numerous complications affecting almost every organ system, including the ocular surface. Diabetic ocular surface diseases mainly include diabetic keratopathy (DK), which is characterized by delayed corneal epithelial wound healing, and diabetes-induced DED symptoms [164]. As mentioned above, $\gamma\delta$ T cells are closely involved in corneal epithelial wound healing and DED, which means that $\gamma\delta$ T cells may be involved in the pathogenesis of diabetic ocular surface disease. However, only one study suggested that $\gamma\delta$ T cells participate in the pathogenesis of diabetic ocular surface disease. Song *et al.* [165] found that corneal epithelium circadian rhythms were impaired in type 1 diabetic mice as the migration fluctuations of $\gamma\delta$ T cells toward the limbus were significantly elevated in type 1 diabetic mice compared with the controls. Additionally, insulin treatment restored the normal migration fluctuations of $\gamma\delta$ T cells.

The role of $\gamma\delta$ T cells in diabetic ocular surface disease is an interesting and promising topic. On the one hand, it is of great clinical significance to rapidly and effectively promote corneal epithelial wound healing and treat DK in diabetic patients, and $\gamma\delta$ T cells are a potential therapeutic target. On the other hand, the pathogenesis of diabetes-induced DED differs greatly from other types of DED, and studying the role of $\gamma\delta$ T cells in diabetes-associated DED helps broaden our understanding of the pathogenesis of DED.

5. Conclusions

Resident immune cells in the ocular surface act as guardians of the eye to ensure clear vision. $\gamma\delta$ T cells, as we reviewed, constitute over 20% of T cells in ocular surface

tissues including cornea, conjunctiva, and lacrimal gland, according to various studies. Although it is suggested that $\gamma\delta$ T cells become resident in mucosal sites including the ocular surface during the natal period, they are also found in adult lymph nodes and can be recruited by chemokines such as CCL20. Therefore, further studies are needed to determine whether $\gamma\delta$ T cells can migrate from lymph nodes and spleens to the ocular surface in adulthood.

$\gamma\delta$ T cells play a double-edged role in ocular surface homeostasis. $\gamma\delta$ T cells play a crucial role in maintaining ocular surface homeostasis by promoting ACAID and accelerating corneal wound healing. As pivotal defenders, $\gamma\delta$ T cells also safeguard the eye from various infections by activating neutrophils and increasing the secretion of antimicrobial peptides. However, $\gamma\delta$ T cells contribute to the majority of IL-17A in the conjunctiva, while secreting other pro-inflammatory cytokines including IFN-γ and Th2-response-promoting cytokines, causing further tissue damage in specific ocular surface diseases. This insight provides a new perspective on the pathogenesis and treatment of dry eye disease and allergic conjunctivitis, distinct from the pathogenic Th17 or Th2 cells. The functions of $\gamma\delta$ T cells in diabetic keratopathy remain obscure due to limited evidence. In summary, this review offers comprehensive information on $\gamma\delta$ T cells in ocular surface homeostasis and diseases, providing valuable clues for further original studies.

Author Contributions

HQ and BM conceived the study conception and design. ZS, HJ, YZ, and HD performed the literature review. ZS, HJ, and BM wrote the original manuscript. HJ and BM contributed to the table and figure preparation. HQ, YZ and HD revised the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.fbl2904146.

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