Review Article

Involvement of transient receptor potential channels in ocular diseases: a narrative review

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Background and Objective: Transient receptor potential (TRP) channels are a superfamily of functionally diverse and widely expressed cation channels which exhibit complex regulatory patterns and sensitivity to multiple environmental factors. The involvement of these ion channels is critical in various physiological functions and pathophysiological conditions. In recent decades, a growing number of studies have identified the essential role that TRP channels play in many ocular diseases. In this study, we performed a narrative review of research on the expression and function of TRP channels in various eye diseases.

Methods: PubMed, Google Scholar, and Web of Science were searched for all relevant original papers and reviews published from database inception to January 31, 2022. Searches were conducted using the related keywords 'transient receptor potential channels', 'TRPs', 'Ca^{2+} signaling', 'iron channel', 'TRPV4', 'TRPM1', 'retina', 'optic nerve', 'cornea', 'retinal ganglion cells', 'ON-bipolar', 'TRPs and retina', 'TRP channel and retinal ganglion cells', 'TRPs and cornea', 'diabetes', 'glaucoma', 'dry eye disease', 'cataract', 'retinopathy of prematurity', 'retinoblastoma', and 'congenital stationary night blindness'.

Key Content and Findings: In this narrative review, we summarize the history of TRP channels and introduce the TRP channel-related literature in eye disease. Next, we discuss the molecular mechanisms of TRP channels in various eye diseases and suggest future research directions.

Conclusions: The relevant studies indicate that TRP channels play vital roles in various eye diseases. However, considerable work is needed to more fully understand the functional and mechanistic aspects of how TRP channels contribute to the pathophysiology of eye disease, especially in the context of animal models and patients. Further investigations will aid in the development of future drugs targeting TRP channels for eye diseases.

Keywords: Ca^{2+} signaling; diabetic retinopathy (DR); eye disease; transient receptor potential channels (TRP channels)

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Introduction

Transient receptor potential (TRP) channels were first discovered in *Drosophila* phototransduction (1). Over the past 30 years, research has demonstrated the importance of these sensory transducer molecules in numerous biological and pathophysiological processes. Belonging to a large and diverse family of nonselective cation channels, TRP channels are considered to be polymodal signal integrators that respond to various mechanical forces and chemical stimuli. The mammalian genome encodes approximately 20 TRP channels (2,3). Based on primary amino acid sequence homology, the TRP superfamily can be subdivided into seven main subfamilies: TRPC (canonical; seven members), TRPV (vanilloid; six members), TRPM (melastatin; eight members), TRPA (ankyrin; one member), TRPN (*Drosophila* no mechanoreceptor potential C, NOMPC-like; one member), TRPP (polycystin; three members), and TRPML (mucolipin; three members) (4). All TRP channels comprise six transmembrane domains (TMs), a pore-forming loop, and cytosolic amino (N) and carboxy (C) termini. They can assemble as tetramers present and activated on the membranes of intracellular organelles in a large variety of organ systems, in both vertebrates and invertebrates (5). Arguably, TRP channels can act as coincidence detectors by directly controlling the flux of Ca^{2+} across the plasma membrane. Ca^{2+} concentration induced by TRP channels affects other ion channels that are sensitive to Ca^{2+}, such as voltage-gated Ca^{2+} channels and Ca^{2+}-activated K^+ channels, and that translate changes in cytosolic Ca^{2+} into cation flux and electrical activity (6-9).

TRP channels regulate a plethora of cellular processes related to photo-, chemo-, thermo-, and mechanosensation and ion homeostasis. Research has revealed that TRP channelopathies lie at the origin of diverse pathological states, including central nervous system dysfunction, cancer, asthma, cardiac hypertrophy, lower urinary tract disorders (LUTd), diabetes mellitus (DM), obesity, and pain (10-17). Several recent studies have advanced our understanding of the role of TRP channels in ocular diseases (*Table 1*). A few key functional themes and promising preclinical data highlighting the potential of small molecules targeting TRPA1, TRPM8 (for dry eye), TRPV4 (for diabetic macular edema), and TRPV1 (for glaucoma) have also begun to emerge. Nevertheless, the function and biological relevance of TRP channels in ocular diseases have remained largely unexplored. Understanding how TRP channels respond to angiogenesis and nerve injury is of direct clinical relevance to patients with diseases that affect visual function, and these channels may become valuable alternatives for the pharmacological treatment of ocular diseases. In this study, we summarize recent insights into the roles of TRP channels in eye tissue. In particular, we discuss what is known about the physiological roles of these channels in vasculature and neural networks. We also reflect on how the recent interest in TRP channels is deeply rooted in biology's longstanding concern with the evolution of chronic eye diseases. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-6145/rc).

Methods

Relevant articles published in English from database inception up to November 2021 were retrieved from PubMed, Google Scholar, and Web of Science. The cited references in published articles were also searched. The search method was a systematic search of the databases using Boolean operators (e.g., AND, OR) and combinations of the following search terms: 'transient receptor potential channels', 'TRPs', 'Ca^{2+} signaling', 'iron channel', 'TRPV4', 'TRPM1', 'retina', 'optic nerve', 'cornea', 'retinal ganglion cells', 'ON-bipolar', 'TRPs and retina', 'TRP channel and retinal ganglion cells', 'TRPs and cornea', 'diabetes', 'glaucoma', 'dry eye disease', 'cataract', 'retinopathy of prematurity', 'retinoblastoma', and 'congenital stationary night blindness'. The final reference list was generated based on the relevance and originality of articles concerning the topics covered in this review. The detailed search strategy is listed in *Table 2*.

The expression of TRP channels in ocular tissues and the pathophysiological roles of TRP channels in ocular disease

Mammalian TRP channels are expressed in several ocular tissues. Serving as sensors, they respond to a wide range of chemical and biophysical intracellular and extracellular stimuli and, in turn, permit cation entry. The influx of Ca^{2+} through TRP channels enables individual cells to sense changes in their local environment, alters enzymatic activities, and provides a pivotal way to impact cellular behavior. Given the unique importance of $[Ca^{2+}]_i$ in all cell types, it is unsurprising that dysfunctions in TRP channels

Table 1 TRP channel involvement in eye disease

Disease	TRP	Tissue/cell type	Experiment	Effects
Dry eye	TRPA1 (18)	Mouse cornea	*In vivo*	Lacrimal functional unit produced Fos-like immunoreactivity at the ventrolateral pole of trigeminal interpolaris/caudalis transition region in a TRPA1-dependent manner
		Trigeminal ganglia		
	TRPV1 (19-21)	Mouse/rat cornea	*In vivo/in vitro*	Corneal cold nociception; promoted tear film instability
		Trigeminal ganglia		
		Human cornea	Phase I/II clinical trials	
	TRPM8 (22-24)	Mouse/rat cornea	*In vivo/in vitro*	Increased the production of tears under non-noxious cooling stimuli; modulated cold-pain sensation
		Trigeminal ganglia		
Allergic conjunctivitis	TRPA1 (25,26)	Mouse blood	*In vivo*	Interacted with histamine receptor H1
		Conjunctival		
		Cervical lymph nodes		
	TRPV1 (26)	Mouse conjunctiva	*In vivo*	Regulated histamine-dependent ocular itch signaling
	TRPM8 (27)	HConEpiC	*In vivo*	Interacted with TRPV1; suppressed TRPV1-induced IL-6 release
Cataracts	TRPM8 (28-30)	Mouse lens/eye	*In vivo/in vitro*	TRPM3 deficiency impaired lens growth and eye development
		Head/blood		TRPM3 dysfunction resulted in progressive lens degeneration
		Human blood		
		HEK293T		
Glaucoma	TRPV1 (31-33)	Mouse retina/brain	*In vivo/in vitro*	Responded to disease-relevant stressors by enhancing activity necessary for axonal signaling
		Optic nerve		Contributed to RGC apoptosis and increased $[Ca^{2+}]_i$ with exposure to hydrostatic pressure
		Rat retina		
		RGCs		
	TRPA1 (34)	Mouse retina/DRGs	*In vivo*	Mediated the oxidative stress burden and inflammation
		Human retina		
Diabetic retinopathy	TRPA1 (35)	Chick retina	*In vivo*	Contributed to cell death under ischemic condition in early stages
	TRPV4 (36-38)	Mouse retina	*In vivo/in vitro*	Increased microvascular endothelial permeability
		RPEs		Endothelial dysfunction; aggravated water diffusion and BRB breakdown in the retina
		Bovine RMECs		
	TRPC1/3/4/5/6 (39,40)	Mouse retina	*In vivo/in vitro*	Mediated endothelial function in a VEGF-dependent manner under HG
		HRECs		Regulated glyoxalase 1 enzyme activity

Table 1 (*continued*)

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Disease	TRP	Tissue/cell type	Experiment	Effects
ROP	TRPV1/4 (41)	Mouse retina	*In vivo/in vitro*	TRPV1 and TRPV4 formed a functional heteromeric channel to deliver pro-angiogenics in a VEGF-independent manner
		Bovine RMECs		
	TRPC5 (42)	Mouse retina	*In vivo/in vitro*	Triggered angiogenic activities in response to the ischemic condition by regulating Ca^{2+} entry
		HEK293		
CSNB	TRPM1 (35,43-46)	Mouse retina/eye	*In vivo/in vitro*	TRPM1 mutations were a major cause of autosomal recessive CSNB
		Horse retina/skin		TRPM1 was gated by the mGluR6 signaling cascade
		Human blood	Clinical trial	
Retinoblastoma	TRPV1	RB tumor tissue	*In vivo*	Interacted with cannabinoid receptor 1 in etoposide-sensitive RB cells
	TRPA1	WERI-Rb1		
	TRPM8 (47)			
	TRPM7 (48)	RB cells derived from patients	*In vivo*	Formed a heterooligomeric complex with other TRPM members to regulate RB cell viability through increasing intracellular Ca^{2+} influx

BRB, blood-retinal barrier; CSNB, congenital stationary night blindness; DRG, dorsal root ganglion; HEK293T, human embryonic kidney cells; HG, high glucose; HRECs, human retina vascular endothelial cells; HConEpiC, human conjunctival epithelial cells; IL-6, interleukin 6; mGluR6, metabotropic glutamate receptor; RB, retinoblastoma; RGCs, retinal ganglion cells; RMECs, retinal microvascular endothelial cells; ROP, retinopathy of prematurity; RPEs, retinal pigment epithelial cells; TRP, transient receptor potential; VEGF, vascular endothelial growth factor.

Table 2 Summary of the search strategy

Items	Specification
Dates on which the search was performed	From August 17, 2021, to April 5, 2022
Databases and other sources searched	PubMed, Google Scholar, and Web of Science
Search terms used	'transient receptor potential channels', 'TRPs', 'Ca^{2+} signaling', 'iron channel', 'TRPV4', 'TRPM1', 'retina', 'optic nerve', 'cornea', 'retinal ganglion cells', 'ON-bipolar', 'TRPs and retina', 'TRP channel and retinal ganglion cells', 'TRPs and cornea', 'diabetes', 'glaucoma', 'dry eye disease', 'cataract', 'retinopathy of prematurity', 'retinoblastoma', 'congenital stationary night blindness'
Timeframe	From July 1954 to November 2021
Inclusion and exclusion criteria	All study types were included; language was restricted to English
Selection process	TJ Yang and Y Yu conducted the study selection together. They selected literature based on criteria including correlation with subjects, time of publication, and experimental design

are causal to, or at least involved in, pathological processes in several diseases. Our knowledge of diseases that involve TRP channel dysfunction has increased impressively during the last 10 years, which underscores their importance in human biology. However, exploration of the function of TRP channels in ocular disease is only in its infancy. Recent work has demonstrated that TRP channels contribute to a variety of eye diseases, including dry eye disease (DED),

cataracts, glaucoma, diabetic retinopathy (DR), and congenital stationary night blindness (CSNB).

TRP channels in the cornea and DED

The cornea is an avascular connective tissue that acts as the eye's primary infectious and structural barrier. The cornea must have a perfectly defined shape and optical clarity, and in humans, consists of five recognized layers: two cellular layers (a stratified epithelium and a single-cell layered endothelium), two interface layers (Bowman's membrane and Descemet's membrane), and the collagenous stroma. In most mammals, the cornea contains a wide variety of ion channels and pumps to detect noxious stimuli, such as TRP channels.

The epithelial surface is the anterior-most structure of the cornea; it functions as a semi-permeable, highly electrically-resistant membrane which protects the underlying stroma from pathogenic invasion. The first TRP channel subtype to be identified in human corneal epithelial cells (HCECs) was TRPC4 (49). Functional expression of TRPV1–4 has been detected in the epithelial layer (50,51). Studies have also shown that TRPV1, TRPV3, TRPA1, and TRPM8 are expressed in corneal nerve fibers (46,52-55). In recent years, corneal innervation has become an increasingly important topic, and we have gained critical insights into how TRP channels can be generated and regulated, and how they function, in sufficient detail.

The TRPV family is best known for several well-characterized thermosensitive channels. One of the most important and well-understood representative subsets of the family is TRPV1 (56,57), which is expressed on the nasociliary branch of the ophthalmic division trigeminal sensory axons terminating in the corneal epithelial layer (58,59). This cation channel can be activated by noxious heat (>43 ℃), protons (extracellular pH <6), animal toxins (centipede, tarantula), resiniferatoxin, and capsaicin (60-63).

Initially known as the capsaicin receptor, TRPV1 was later recognized as a unique molecule entity and formally named transient receptor potential vanilloid 1 (64). Knockout (KO) mice for TRPV1 represent an important approach to understanding the functions of this receptor in normal physiology and disease. In a seminal work that examined vanilloid sensitivity in cultured dorsal root ganglion (DRG) neurons from wild-type (WT) and $TRPV1^{-/-}$ mice, both capsaicin and resiniferatoxin (a thermogenesis and pain-related molecule) were reported to evoke rapid, robust calcium inward currents of around 20% WT neurons; however, significantly reduced responses were observed in TRPV1 KO mice (65). These observations demonstrate that disruption of TRPV1 expression in mice eliminates responses to noxious stimuli. In an alkali burn model study, the incidence and degree of corneal haze and opacification in the burned cornea were more severe in WT mice than in $TRPV1^{-/-}$ mice at 1, 2, 5, 10, and 20 days. Findings from real-time quantitative reverse transcription-polymerase chain reaction (qRT-PCR) showed that a lack of TRPV1 significantly suppressed the mRNA levels of myeloperoxidase (MPO, polymorphonuclear marker) and F4/80 (macrophage marker) staining in the burned cornea at each time point (66). The study therefore demonstrated that TRPV1 is essential for mediating the inflammatory process *in vivo* and that it is involved in regulating corneal thermal-mechanical acute pain and tissue injury.

An increasing amount of evidence suggests that corneal epithelial cells release a variety of neurotrophic cytokines, including nerve growth factor (NGF), neurotrophin-3 (NT3), and glial cell-derived neurotrophic factor (GDNF), to maintain neurite extension and survival (67-69). One study used qRT-PCR to measure the TRPA1 mRNA expression profile in developing sensory nerves from the ophthalmic division of the trigeminal ganglion (OTG) in the embryonic chicken cornea. Results showed a progressive increase in TRPA1 mRNA from embryonic days 6 to 12. Treatment with NT3 produced a 100-fold increase in TRPA1 mRNA, while the responses to NGF and GDNF were slight (58). These results support the hypothesis that NT3 regulates TRPA1 expression. However, future work is needed to determine the mechanism between NT3 and TRPA1 regulation.

Research has demonstrated that TRPA1 is temperature sensitive and is activated by painful cold (<17 ℃) (70,71). However, at present, cold-induced activation of TRPA1 in ocular nociception remains contentious. Li *et al.* (19), for example, argued that the ocular responses of TRPA1 KO mice to cold were not significantly different from those of WT mice. Research has also shown that TRPM8 is widely expressed in corneal afferent fibers (72). This thermosensitive TRP channel is activated by moderate cold and cooling agents such as menthol and icilin (73,74). Parra *et al.* (22) recorded cold and menthol-evoked nerve terminal impulse (NTI) activity in the corneas of $TRPM8^{-/-}$ mice. In WT mice, ongoing activity was detected in only scarce nerve endings, and the firing frequency was extremely low. In contrast, no NTI activity could be evoked in $TRPM8^{-/-}$ corneas with 50 μM menthol at 34 ℃ or during cooling.

The same study also found that the basal tear fluid volume of TRPM8$^{-/-}$ mice was significantly lower than that of their WT counterparts. These findings suggest that the cold responsiveness of TRPM8 may allow it to serve as a 'humidity detector' to regulate basal tearing. Although the detailed mechanism underlying corneal ulcers and chronic ocular pain is associated with different conditions, these findings demonstrate the functional significance of TRP channels in the cornea and their potential clinical relevance.

Dry eye disease is a chronic multifactorial syndrome characterized by a loss of tear film homeostasis and ocular surface inflammation. Patients with DED experience typical ocular symptoms of dryness, irritation, debris sensation, blurred or fluctuating vision, and ocular fatigue, and are often accompanied with burning, tenderness, and aching. The disease is among the most common ocular conditions that lead patients to seek eye care, with estimates of the presence of DED in the global adult population ranging from 5% to 50% (75). Ocular surface (cornea, conjunctiva, lacrimal and meibomian glands) abnormalities may prevent basal tear secretion and can accompany or affect DED. Recent studies have identified several TRP channels associated with DED, thus providing a putative pathogenetic mechanism of ocular surface disease.

Approximately three TRP channels (TRPM8, TRPV1, and TRPA1) are expressed on the cornea. Corneal cold thermoreceptors number approximately half of all corneal sensors, which play a major role in detecting ocular dryness and maintaining tear homeostasis (76). Functioning as master regulators, TRPM8 channels exert the electrical activity of corneal cold receptors to maintain basal tearing and spontaneous blinking. One study identified the critical role of TRPM8 channels in ocular surface sensitization in response to moderate, non-noxious cooling stimuli. Under cool corneal temperatures and topical menthol application, cold-evoked NTI activity, evaluated by electrophysiological recording, was largely absent in TRPM8$^{-/-}$ mice compared to WT mice. The study also revealed that under basal thermal conditions (18–34 ℃), the tearing flow values of TRPM8$^{-/-}$ mice were significantly decreased. These findings suggested that TRPM8 in corneal cold receptors contributes to maintaining the basal tear secretion at normal corneal temperatures (22). Two prospective pilot studies indicated that topical application of the TRPM8 agonist cryosim-3 in patients with dry eye could stimulate basal tear secretion and relieve neuropathic pain, suggesting that this TRPM8 agonist could be a promising treatment for irritation and pain related to DED (23,77). Fakih *et al.* (78) confirmed that TRPM8 is implicated in corneal inflammation in a severe mice model of DED via extraorbital lacrimal gland and Harderian gland excision. However, although their study showed that TRPM8 blockage diminished inflammation in the cornea and the trigeminal ganglion, it did not directly test the influences of the TRPM8 antagonist M8-B on tear production, and further exploration is needed. Of note, TRPM8 is required for ocular cold nociception, and it is a promising drug target for dry eye management because it regulates basal tearing and maintains the ocular surface wetness. However, TRPM8 is not the only channel responsive to DED.

Animal models of DED typically use corneal fluorescein staining to evaluate the expression, distribution, and changes of TRPs in ophthalmic nerve bundles, fibers, or the corneal epithelium. In a study using mice with genetically marked TRPM8 loci (*TRPM8*$^{EGFPf/+}$ mice), whole-mount immunohistochemistry of nerve fibers showed that approximately half of corneal TRPM8-positive neurons expressed TRPV1 (19). This overlap between TRPM8 and TRPV1 in cornea-projecting sensory neurons suggests that TRPV1 is also necessary and sufficient for cold nociception in the cornea. The authors demonstrated that capsaicin-sensitive TRPM8-positive neurons (identified by calcium imaging) displayed increased amplitude of calcium responses to cold. In contrast, pharmacological blockade of TRPV1 significantly suppressed depolarization and neuronal firing upon subsequent cold treatments. In a surgical dry eye mouse model established in the same study, the percentage of TRPM8^{+} cold-sensing neurons did not change; however, TRPV1 was significantly upregulated in TRPM8^{+} cold-sensing neurons in mice with dry eye compared with sham-operated mice. This observation further corroborates the finding of another study that TRPV1 protein levels were increased in anterior eye samples and trigeminal ganglia from rats with dry eye, while values for the TRPM8 protein were similar between the sham group and dry eye group (20). Furthermore, the upregulation of TRPV1 in TRPM8^{+} neurons led to severe cold allodynia, as shown by significant reflex blinking; however, this could be effectively attenuated by genetic TRPV1 deletion or selective TRPV1 antagonist treatment (19). Although TRPV1 has long been believed to serve as the primary heat and capsaicin sensor in the skin and cornea of mammals (79,80), the above results further support the indispensable role of TRPV1 in enhancing the neuronal excitability of TRPM8^{+} neurons to cold and generating cold allodynia in the cornea. Also, TRPV1$^{-/-}$ mice were found to lack the eye-closing response

to cold stimulation entirely, which suggests that TRPV1 is a more promising drug target than TRPM8 is for pain management in DED. Some researchers consider TRPV1 to be the primary DED facilitator. However, experiments have proposed that TRPV1 is the primary osmoreceptor of the organum vasculosum lamina terminalis (OVLT) neurons and arginine-vasopressin-releasing neurons (AVP, an antidiuretic hormone) (81,82). In TRPV1$^{-/-}$ mice, osmosensory transduction of supraoptic nucleus neurons is abolished, evidencing a role of TRPV1 in osmotic control (81). Transduction channels that are TRPV1 dependent may be a potential mechanism of ocular osmoregulation. Benitez-Del-Castillo *et al.* (21) developed a small interfering oligonucleotide RNA (siRNA) compound targeting TRPV1 and evaluated its efficacy and safety for DED treatment in one phase I and two phase II clinical trials. The data demonstrated that topical TRPV1 siRNA could extend tear break-up time and prevent tear hyperosmolarity, with an improvement in the ocular surface disease index score. These results showed that TRPV1 has a function in tear film instability. Although additional studies are required to define the mechanisms responsible for the hyperosmolarity, corneal damage, and inflammation in DED, TRPV1 may act as a candidate transducer in sensing osmotic stimuli during corneal drying.

Involvement of TRPA1 in DED has been reported in rats (18). In an extraorbital lacrimal gland excision model of murine tear-deficient DED, the TRPA1 agonist mustard oil (0.02–0.2%) caused dose-related increases in eyeblink and forelimb eye-wipe nocifensive behavior. In a recent study, Fakih *et al.* (83) demonstrated that TRPA1 channels are present in mouse corneas, with higher TRPA1 mRNA levels being observed in mice with DED. This finding might lead to a better understanding of the important correlation between TRPA1 and DED. Nonetheless, more studies are needed to verify the specific effects of TRPA1 in DED.

TRP channels in the conjunctiva and conjunctivitis

The conjunctiva is a transparent mucous membrane. It is a continuous barrier that provides immunological defense and sustains the equilibrium of the tear film. In human conjunctival epithelial cells (HCjECs) and normal human conjunctiva tissues, studies using qRT-PCR experiments and immunohistochemistry have detected TRPV1, TRPV2, and TRPV4 expression (84,85). These findings have been further confirmed by qRT-PCR and western blot analysis of the immortalized HCjEC line (86). An immunocytochemistry study also showed TRPM8 protein localization in both the endoplasmic reticulum compartment and the plasma membrane of HCjECs (27).

The thyronamine 3-iodothyronamine (T_1AM) has been found to be a novel putative thyroid hormone derivative that can exert remarkable hypothermia (87,88). Khajavi *et al.*'s novel theory (27) described the interactions between T_1AM and TRPM8. Treatment of HCjECs with T_1AM increased the fluorescence ratio (f340 nm/f380 nm), a relative index of changes in intracellular free Ca^{2+} concentration ($[Ca^{2+}]_i$), within minutes. After administration of N-(4-tertiarybutylphenyl)-4-(3-chloropyridin-2-yl)-tetrahydropyrazine-1(2H)-carbox-amide (BCTC, TRPM8 blocker) for 20 minutes, the T_1AM-induced Ca^{2+} rise was abolished, indicating that T_1AM can act as a potent activator of TRPM8. However, the biosynthetic and deiodinase pathway of T_1AM should also be taken into account, and the role of this endogenous amine in regulating TRP channels remains to be established.

Conjunctivitis, or inflammation of the conjunctiva, is a common ocular ailment that typically presents as widening of the conjunctival vessels and cellular infiltration leading to hyperemia and edema of the conjunctiva. The typical signs of conjunctivitis are a red eye and discharge. Conjunctivitis can be classified based on infectious and noninfectious causes. Infectious conjunctivitis has diverse causes, with 20–70% of all cases being caused by viruses (89-91). The etiologies of noninfectious conjunctivitis include allergy, toxicity, mechanical trauma, immune response, and the neoplastic process (92). Although several TRP channels appear to be linked to conjunctivitis, little is known about how these channels contribute to the development of the condition. To date, only two channels, TRPV1 and TRPA1, have been reported to mediate conjunctivitis; both are proposed to play an important role in allergic conjunctivitis (AC) (25,26).

AC is mainly caused by immunoglobulin E (IgE) and mast cells (MCs), which trigger the type I hypersensitivity response, resulting in MC degranulation and the release of a cascade of histamine, leukotrienes, neutral proteases, proteoglycans, and other inflammatory mediators (93,94). These molecules, especially histamine, contribute to symptoms such as tearing, redness, conjunctival edema, and itching, which characterize the early-phase response in AC. In the late-phase reaction, increased expression of the high-affinity receptor for IgE (FcεRI) on dendritic cells in the conjunctiva and the limbus aids in the maturation and differentiation of T-lymphocytes into effector T cells

(Th1 or Th2 lymphocytes). Th2 cells are the primary contributors to MC growth, eosinophil accumulation, and mucus hyperproduction, which lead to chronic inflammation of the ocular surface and severe forms of ocular allergic disorders (95,96). MC IgE-FcεRI signaling activation also results in the phosphorylation of enzymes, including mitogen-activated protein kinase, protein kinase C (PKC), and phospholipase C, which causes Ca^{2+} to be released from the endoplasmic reticulum. Depletion of intracellular Ca^{2+} stores activates store-operated Ca^{2+} entry (SOCE) and allows extracellular Ca^{2+} influx. In an allergic reaction, the increase in Ca^{2+} permeation activates TRPA1 and TRPV1, and opened TRPV1 and TRPA1 channels, in turn, induce infiltration by inflammatory cells and a rise in Th2 cytokine levels (97).

Studies have found that TRPV1 is the downstream transduction channel of the histamine H1 receptor in sensory neurons that are sensitive to capsaicin (98). The TRPV1 channel contributes to chronic allergic inflammation in animals, such as that seen in irritable bowel syndrome and asthma (99-101). In Kwon *et al.*'s study, topical treatment with a TRPV1 antagonist in the AC murine model significantly reduced blinking and tearing. Cell counts also showed sparse MCs and eosinophil infiltration, with decreasing levels of interleukin (IL)-4 and IL-13 in ipsilateral cervical lymph nodes quantified by enzyme-linked immunosorbent assay; in contrast, no significant change was found in the TRPA1 antagonist treatment group (25). These results indicated that TRPV1 antagonist treatment could potentially be widely used to alleviate ocular discomfort associated with AC. It should be noted that TRPA1 antagonist treatment is involved in the regulation of blinking but has no effect on tearing or inflammatory cell infiltration. Unlike TRPA1, TRPV1 might mediate itch-scratching behavior in AC by attenuating associated inflammation.

Itching is the cardinal feature of AC. Data indicate that this symptom results from a series of different pathological mechanisms, which may overlap or crossover. The ovalbumin-induced AC mouse model is insufficient for analyzing the function of TRPs in AC because of the complexity of neuropathic pain and itch. Huang *et al.* (26) applied the genetic channel deletion technique to analyze TRPV1 and TRPA1 function in AC. Examination of the itch responses after histamine treatment suggested that TRPV1 KO mice showed fewer wiping bouts than did WT and TRPA1 KO mice, while no difference was found between WT and TRPA1 KO mice. Loss of TRPV1 was found to inhibit the conduction of the histamine-associated itch pathway, which confirmed the earlier conclusion that TRPV1 is one of the downstream transduction channels of the histamine receptor. The same researchers also demonstrated that TRPA1 might represent a histamine-independent itch pathway contributing to bradykinin excitatory effects (26). They evaluated the anti-hyperalgesic effect of TRPV1 antagonist alone or complexed with TRPA1 antagonist in their ovalbumin-induced AC model established in TRPA1 KO and TRPV1 KO mice, showing that targeting both TRPA1 and TRPV1 may achieve a better therapeutic outcome for ocular itch.

Current pharmacologic measures for AC include antihistamines, membrane-stabilizing agents, MC stabilizers, vasoconstrictors, nonsteroidal anti-inflammatory drugs, and topical corticosteroids (102). Ocular itch management relies heavily on antihistamines and immunosuppressive drugs, but these often have limited efficacy. Among the TRP channels, TRPV1 and TRPA1 appear to offer alternative analgesic approaches to suppress or regulate the immune response triggered by allergens.

TRP channels in the lens and ciliary body, and cataracts

The lens is a transparent tissue that fine-tunes the passage of light onto the retina. The critical importance of Ca^{2+} to lens clarity, hydration, and crystallin degradation and aggregation has long been recognized (103). New information is emerging on the regulation of Ca^{2+} levels in the lens by mechanisms that rely on TRP channels. The presence of TRPV1, TRPV4, and TRPM3 has been found in the lenses of various species, including humans (28,85,104,105).

Nakazawa *et al.* (104) confirmed that TRPV1 and TRPV4 are expressed in all regions of the mouse lens (the epithelium, outer cortex, inner cortex, and inner core). They reported that TRPV1 and TRPV4 might act as mechanosensors that transduce hydrostatic pressure changes into dynamic signaling to regulate lens ion transport activity and cellular osmosis. Mechanical stimuli, such as hyposmotic shock, can activate TRPV4 channels, which trigger hemichannel-mediated ATP release from the lens and regulate the transport function in the lens. Also, TRPV1 is involved in hyperosmotic lens shrinkage and modulates the overall lens volume by activating Ca^{2+}/PKC-dependent ERK1/2 signaling. Previous research has shown that TRPV4 activation can lead to ATP release, but the biological mechanism has yet to be identified at the molecular level (105). One very recent study indicated that

germline knockdown of TRPM3 impaired lens growth, while TRPM3 dysfunction resulted in progressive anterior pyramid-like cataracts and microphthalmia (29). These findings underline the need to better define the function of TRP channels in the lens.

The ciliary body, the anterior continuation of choroid, and the retina are composed of smooth muscle cells. The ciliary epithelium mediates the production and secretion of aqueous humor, and visual accommodation. The contractile state of the ciliary muscle requires a sustained influx of Ca^{2+} through the cell membrane. Intracellular free calcium ($[Ca^{2+}]_i$) is mainly mediated by nonselective cation channels, which serve as a major Ca^{2+} entry pathway in various smooth muscles. Takai *et al.* (106) detected the existence of TRPC1, TRPC3, TRPC4, and TRPC6 mRNAs in the bovine ciliary body through reverse transcription-polymerase chain reaction (RT-PCR) experiments, which indicated that TRPCs are a possible alternative pathway for Ca^{2+} entry. However, there is limited information on the functional and biological relevance of TRP channels in the ciliary body, and these results need further confirmation.

Cataracts, or lens clouding, is the leading cause of reversible vision loss worldwide. Among the more than 2.2 billion cases of near or distance vision impairment globally, recent figures estimate that 94 million people are affected by cataracts (107). Cataractogenesis is a multifactorial process closely associated with lens chronological aging, presbyopia, oxidative stress, calcium imbalance, hydration, and crystallin modifications (108-111). Due to its avascularity, the lens primarily relies on its circulation system to maintain its transparency and homeostasis. Unregulated Ca^{2+} is well documented to be a major contributor in almost all types of cataracts, and elevated levels of Ca^{2+} range from 0.1 to 64 mM (110,112-114). However, reports regarding the association of TRP channels with cataracts are scarce. Bennett *et al.* (28) detected abundant levels of TRPM3 reference transcripts in postmortem human lens analysis by RT-PCR. Among them, TRPM3 transcript variant-9 was predicted to be associated with isoleucine-to-methionine change, with deleterious effects on protein function that led to lens opacity. Zhou *et al.* (29) confirmed this finding in homozygous *Trpm3*-M/M mutant mice, which developed severe, progressive, anterior pyramid-like cataracts. Emerging evidence suggests that the *Pax6* gene, a master transcription regulator of eye development in vertebrates, upregulates *Trpm3* and miR-204 during eye development in mice (30,115,116). Further insights on the TRPM3 mutation in cataracts, especially congenital cataracts, await discovery.

TRP channels in the optic nerve and trabecular meshwork (TM), and glaucoma

The optic nerve, an integral part of the central nervous system, contains approximately 1 million axons that originate from multiple retinal ganglion cell (RGC) subtypes (117). These axons project to the brain, transmitting visual signals and ultimately relaying image-forming information onto the cortex.

Previous studies have shown that most TRP subfamilies (TRPC, TRPM, TRPV, TRPA, and TRPP) are expressed in the optic nerve head of mice (118). An analysis using qRT-PCR indicated the rank order of TRP-channel subtype expression to be TRPM3 >>> TRPM7 > TRPC1 > TRPV2 > TRPC3 ≥ TRPM6, with little evidence of developmental regulation between the postnatal and adult optic neuronal array (119). Through calcium signaling, TRP channels mediate various neuronal responses to physiologic and pathogenic stimuli. However, past studies examining TRP channel functions in neuronal circuits have mainly explored the roles of Ca^{2+} signals originating from intracellular stores. These studies assume that the main mechanism is SOCE in astrocytes and oligodendrocytes, which is important for axon-myelin maintenance and integrity (120). The primary channel for SOCE is TRPM3, which is also the most highly expressed TRP channel in the optic nerve. Papanikolaou *et al.* (119) illustrated that a high concentration (50 μM) of TRP inhibitor completely blocked $[Ca^{2+}]_i$ recovery in optic nerve astrocytes, oligodendrocytes, and optic nerve explants. In contrast, SOCE was found to be essential for glial Ca^{2+} signaling in this typical white-matter tract, which indicated that replenishment of intracellular Ca^{2+} stores was entirely dependent on $[Ca^{2+}]_i$ from the extracellular milieu via SOCE. Moreover, TRPV1 and TRPV4 were found in the optic nerve head, which supports the idea that Ca^{2+} handling could be relevant to optic nerve function (118,121).

The TM is a complex three-dimensional porous tissue located at the iridocorneal angle. The TM and the adjacent Schlemm's canal play a key role in regulating the outflow of aqueous humor and controlling intraocular pressure (IOP). The cells in the TM are excitable and display contractile properties (122,123). Expression of TRPC1 and TRPC4 has been discovered in bovine TM cells and has been found to behave as the SOCE pathway (124).

A growing body of evidence confirms the presence of TRPV4 in cultured human TM cells, primary human TM cells, and mouse and human TM tissues (51,125). There was a significant decrease in TRPV4-induced calcium flux in human TM cells treated with hydrostatic pressure. Lowe syndrome, or oculocerebrorenal syndrome, is a rare X-linked recessive disorder that causes bilateral congenital cataracts and glaucoma. The *OCRL1* gene is mutated in Lowe syndrome; this mutation leads to abnormal intracellular trafficking to the primary cilium, which is a single hair-like membrane structure found in almost every cell type (126,127). Coimmunoprecipitation assays showed that TRPV4 interacts with the *OCRL1* gene, with both localizing within the primary cilium of human TM cells. Further, siRNA *OCRL1* knockdown in human TM cells was found to significantly reduce the Ca^{2+} influx in the presence of TRPV4 agonist (125). Therefore, OCRL is required for TRPV4-mediated calcium signaling, and TRPV4 trafficking to the primary cilium is important in human TM cells. Importantly, in mice with TM-specific TRPV4 channel KO, Patel *et al.* observed a significant increase in IOP (128). The same study found that TRPV4 activation could enhance nitric oxide release via endothelial nitric oxide synthase signaling, thus revealing a novel mechanism to suppress IOP elevation. Another study also showed that pharmacological activation of TRPV4 channels in mouse eyes improved the aqueous humor outflow facility and reduced IOP (51), supporting the finding that TRPV4 channels have a crucial role in IOP regulation.

Glaucoma is a panoply of chronic progressive optic neuropathy characterized by progressive degeneration of the optic nerve and retinal nerve fiber layer, with loss of RGCs and their axons, and is accompanied by visual field damage. It affects more than 76 million people worldwide and has become the most common cause of irreversible blindness globally (129-132). In approximately 10% of cases, glaucoma results in bilateral blindness, but in 10% to 50% of cases, the individual is unaware of their condition, because the disease often remains asymptomatic early in its course (133,134).

Glaucoma is a complex, multifactorial disorder, the underlying pathological mechanism of which is still under investigation. Elevated IOP is usually considered to be the main reason for enhanced apoptosis and loss of RGCs in glaucoma. Reducing IOP is currently the only method to treat glaucoma approved by the United States Food and Drug Administration (135). However, therapeutic IOP control is insufficient to ensure the visual function and prognosis of patients with glaucoma, because some patients with relatively normal eye pressure still exhibit damage to RGCs and the optic nerve. Evidence suggests that neurotrophin signaling, oxidative stress, protein misfolding, mitochondrial damage, and hypoxic and ischemic phenomena may all contribute to glaucoma-related cell death.

In mice and in humans, TRPA1 is widely expressed throughout the retinal layers (34). In an ischemia and reperfusion (I/R) mouse model and the ischemic event exposed-chick retina, pharmacological blockade of TRPA1 was found to reduce retinal cell death and attenuate the reductions in retinal thickness and the total number of RGCs (35). Thus, the inhibition of a TRPA1-dependent pathway may be a noninvasive therapeutic approach to limit glaucoma-related retinal damage.

Studies have revealed that TRPC6 participates in glaucoma retinopathy. In normal rat retinas, TRPC6 was found by Wang *et al.* to mainly be localized in the RGC layer. In the same study, TRPC6 expression was further elevated in the retinal I/R model at 12 and 24 hours after reperfusion. Progressive RGC loss was also observed after I/R, and this effect was inhibited by pretreatment with SKF96365 (a TRPC channel antagonist) (136). However, since SKF96365 lacks specificity, additional contributions from other Ca^{2+} entry channels cannot be ruled out; therefore, the results of Wang *et al.*'s study were not strong enough to determine the early neuroprotective effects of this TRPC6 antagonist on RGCs. The same research team found specific alterations of *TRPC6* gene expression in the peripheral blood samples from patients with primary open-angle glaucoma. The gene expression pattern was also correlated with IOP and the cup-to-disc ratio (137). In chronic glaucoma, optic disc cupping may stretch RGC axons (138); consequently, TRPCs, which are stress and mechanosensitive cation channels, can be activated. Although Wang *et al.*'s work supported the finding that TRPC6 may serve as a biomarker for glaucoma, it did not evaluate RGC layer thickness. Further assessment of the role of TRPC6 during RGC loss in clinical trials is needed to confirm the results found in the I/R animal model. Thus, further research is still required to analyze the effect of TRPC6 in the process of glaucoma.

Optic nerve degeneration in glaucoma involves early stress to RGC axons caused by sensitivity to IOP. Voltage-gated sodium channel (NaV) subunits normally function in initiating and propagating action potentials, especially Nav1.6 and 1.2. Studies of glaucoma progression in mice

using microbead-induced IOP elevation suggest that NaVs are expressed in the RGC soma and axons as part of an early adaptive role in the condition (139,140). Early axon dysfunction after IOP elevation often precedes outright morphologic degeneration. Over 2 weeks of IOP elevation in mice, McGrady *et al.* found that Nav1.6 increased in RGC axons. In this context, excitability included increased depolarization of the resting membrane potential, which reduced the threshold for excitation. In their experimental glaucoma mouse model, genetic deletion of TRPV1 was found to increase NaV1.6 in RGC axons (141). However, that result cannot exclude the possibility that additional voltage-dependent mechanisms can enhance excitability, since the Nav1.2 subunit is also located in RGC axons. Ward *et al.* (31) established a glaucoma rodent model using anterior chamber polystyrene microbead occlusion in rats and TRPV1$^{-/-}$ mice to test the role of TRPV1 in RGC damage evoked by 4 to 5 weeks of IOP elevation. Data showed that KO or pharmacological inhibition of TRPV1 accelerated RGC degeneration, which presented as an accumulated loss of RGC axonal terminals, a thinner retinal nerve fiber layer, attenuated axon density, and overt hypertrophy of astrocytes. Accordingly, IOP elevation may provide a preconditioning stimulus early in glaucoma to slow RGC axonal degeneration. However, further studies are needed to assess whether this mechanism is protective or ultimately deleterious to survival.

A growing bank of studies state that different glaucoma-relevant stressors, such as ischemic insult, oxidative stress by-products, and pressure, can activate TRPV1 and other channels, thus increasing intracellular Ca^{2+}, and contribute to RGC damage or modulate RGC survival indirectly *via* signaling pathways (32,142-144). A study that used qRT-PCR measurements showed that enhanced TRPV1 expression was transient under pressure both *in vivo* and *in vitro* (145). Primarily, TRPV1 is located in the large cell bodies of RGCs in the ganglion cell and inner plexiform layers of rat and mouse retinas (146). There are two general types of RGCs in mammalian retinas: ON-RGCs, which respond to light increments, and OFF-type RGCs, which are excited by decrements of light. Both ON- and OFF-RGCs have transient and sustained subtypes based on whether they respond to light that is offset with a transient or sustained burst of spikes (147,148). At 15 to 30 days after IOP elevation, OFF-transient RGCs show a progressive reduction in their dendritic arbor size and complexity, and enhanced RGC excitability (139,145). One study reported that, with short-term IOP elevation, TRPV1 decreased excitability for ON-sustained RGCs but increased it for OFF-sustained RGCs (149). Results demonstrated that ON-sustained RGCs in TRPV1$^{-/-}$ retinas exhibited sustained but robust light-evoked activity, as shown by the increased mean and peak firing rates compared to WT retinas. Regarding OFF-sustained RGCs, TRPV1 deletion produced a less robust response to light offset, and blocking NaV channels abolished the differences in light response between WT and TRPV1$^{-/-}$ RGCs (149). These results suggest that TRPV1 activity involves multiple voltage-sensitive mechanisms that control the excitability of RGCs. Except for physiological criteria, TRPV1 has morphological influences on how RGCs respond to pressure-related stress, which are shown by shorter dendrite length, reduced dendritic branch points, and RGC body loss with TRPV1 deletion *in vivo* or with capsaicin treatment *in vitro* (33,143). Thus, a future area of research interest is whether the TRPV1 channel contributes to retinal osmoregulation and intrinsic responsiveness to pathological conditions, such as IOP and mechanical trauma.

Another channel through which ganglion cell apoptosis may be mediated is TRPV4. Immunochemistry has shown that a substantial amount of TRPV4 is localized in RGCs and the plexiform layers in the rat and porcine retinas (150,151). In many species, TRPV4 has been observed in RGC dendrites, somas and axon bundles in the retina, the optic nerve head, and the laminar region of the optic nerve (121,150,152-154). Activation of TRPV4 increases the spontaneous firing rate and excitability of RGCs, which causes membrane depolarization and Ca^{2+} influx, and sustained activation of these channels leads to RGC death (121). Inhibition of TRPV4 channels within the retina has been reported to improve the survival of RGCs (150). Also, intraocular injection of TRPV4 antagonists has been found to lower IOP in glaucomatous mouse eyes and to protect retinal neurons from IOP-induced cell death by mediating the JAK2/STAT3/NF-κB signaling pathway (151). These findings indicate that inhibition of TRPV4 could be used as a potential treatment for glaucoma.

Together, the TRPV1 and TRPV4 channels may be involved in several aspects of glaucoma, such as the direct response of ganglion cells to increased IOP and astrocyte activation. Although existing reports support the idea that TRPV4 is a promising molecular target of glaucoma, pharmacological modulators of TRPV4 for treating pressure-induced retinal disorders have yet to be tested in clinical trials. We still need to better elucidate the normal

roles of TRPV1/4 in interactions between different types of channels and effective channel modification capable of reducing IOP.

TRP channels in the retina and retinal disease

Retinas contain a large diversity of distinct cell types, each of which responds to endogenous stimuli, sets the intracellular ion concentrations, and carries out specific functions (155). Several studies have demonstrated that TRP channels are important in the mammalian retina. In one study, RT-PCR confirmed that mRNAs of 28 TRP channel genes were present in the mouse retina, of which 16 were weakly expressed, with TRPC6 and TRPC7 mRNAs being detected at very low levels (156).

Visual processing of information begins with synaptic input driven by the rod and cone photoreceptors. Downstream of these outer photoreceptors are numerous RGC types that convey visual information from the retina to the brain. In the mouse retina, TRPV4 antibodies labeled somata, axons, and dendrites of RGCs (157). Ryskamp *et al.* reported that TRPV4 could directly mediate the osmotransduction and mechanotransduction of RGCs, and sustained exposure to TRPV4 agonists prompted RGC apoptosis or cell death pathways (121). Various other TRPs have also been detected in RGCs, including TRPC1/3/4, TRPM3, TRPML1, TRPP2, and TRPV2. In particular, TRPV1 was recently implicated in mediating $[Ca^{2+}]_i$ increases and hydrostatic pressure-induced autophagy and apoptosis in human induced pluripotent stem cell-derived RGCs (158,159).

Retinal bipolar cells serve as the only neural link between photoreceptors and ganglion cell retinal output. Photoreceptors release only one neurotransmitter: glutamate. In response to light, all photoreceptors hyperpolarize and release less glutamate (160). More than ten distinct types of bipolar cells have been described in mammals, and these morphologically and functionally fall into two separate major groups: OFF- and ON-bipolar cells (161). Anatomical differences between bipolar cells and different glutamate receptors (GluRs) expressed on their dendrites generate the functional diversity of bipolar cells. OFF-bipolar cells express ionotropic AMPA/kainate receptors (iGluRs), while ON-bipolar cells express metabotropic GluR (mGluR6), an ON-bipolar cell-specific glutamate receptor (162,163). In response to glutamate reduction at the onset of light, OFF-bipolar cells hyperpolarize, whereas ON-bipolar cells, by virtue of sign-inverting synapses, depolarize. Unlike iGluRs, mGluR6 does not form ion channels; it is negatively coupled to a cation-permeable channel to mediate visual transduction (164-166). The transduction cation channel of retinal ON-bipolar cells was once hypothesized to be a cyclic guanosine monophosphate (cGMP)-gated channel (167,168); however, research ultimately identified TRPM1 as the ON-bipolar-cell ion channel downstream of the mGluR6 transduction pathway (44,169-171). Studies suggest that glutamate binds to the mGluR6 receptor and activates a heterotrimeric G-protein, Go (composed of $G\alpha_o$, $G\beta_3$, and $G\gamma_{13}$), and keeps TRPM1 channels mostly closed in darkness. Light decreases mGluR6 activation and allows the channels to open, depolarizing the cell and inverting the photoreceptor signal (169-172). Müller cells are the only cell type that spans all retinal layers and exert multiple functions, such as controlling the ionic balance in the extracellular space, monitoring retinal homeostasis, and aiding trophic factors. Studies have reported that the sentinels for osmotic signals are partly mediated by TRP channels, and various TRP channels have been detected in Müller cells (85,173). In the mouse retina, TRPM3 antiserum was found to be punctuated and distributed throughout the plexiform and ganglion cell layers and to be distributed at a lower density throughout the inner nuclear layer and outer plexiform layer (174). Da Silva *et al.* (173) reported that the mRNA and protein of TRPC1 and TRPC6 were present in mouse Müller cells, and also found TRPV4 staining of Müller cells in mouse retinal vertical sections.

Müller cells and astrocytes are the principal glia of the mammalian retina. Astrocytes are almost exclusively confined to the innermost retinal layers and are mainly localized in the nerve fiber and ganglion cell layers. Astrocytes envelop and support the axons of RGCs by connecting them to retinal blood vessels; they are also essential for the functionality of the blood-retina barrier (BRB). In Leonelli *et al.*'s study using rat retinas, TRPV1 was found in astrocytes (175). In a later study, this channel was found to play a role in mediating astrocyte migration in response to mechanical injury (176). The same study also concluded that TRPV1 contributes to astrocyte migration by rearranging the cytoskeleton, because TRPV1 antagonist reduced α-tubulin intensity, decreased cell size, and caused retraction and fragmentation of microfilaments in astrocytes in a scratch wound assay. However, other factors could also mediate astrocyte migration in the wound milieu. Increases in intracellular Ca^{2+} might result from other TRP channels or ion channels, such as TRPM7, which can be activated

in response to shear stress. Reactive astrocytes have been observed in neurodegenerative diseases, such as glaucoma. Understanding the molecular mechanisms of TRPV1 that lead to reactive gliosis and astrocyte migration requires *in vivo* or clinical studies.

Existing reports show that retinal pigment epithelial (RPE) cells express TRPA1, TRPC1/4, TRPM1/3/4/7/8, and TRPV1–6 (177-180). However, the presence of mRNA and immunofluorescence does not guarantee the functional importance of TRP channels. Kennedy *et al.* (180) identified that TRPV5 and TRPV6 contribute to regulating the calcium composition changes in the subretinal space that accompany light/dark transitions, indicating these two most calcium-selective TRPV channels are needed for the RPE layer to sustain retinal health. Research has also found that TRPV4 is distributed throughout the retina and that its functional expression maintains the integrity of retinal capillaries, while intravitreal administration of TRPV4 activators in rats increases the permeability of capillaries, leading to circulatory collapse (178). Although the exact physiologic role of each TRP channel in the retina is not yet known, further examination may show that they are involved in the pathogenesis of microaneurysms, hemorrhages, and retinal edema, which is a novel concept.

Diabetic retinopathy

DR is one of the most common microvascular complications of DM. Approximately one-third of the world's diabetic population has DR (181). Among the global working-age (20 to 65 years old) population, DR remains the leading cause of preventable vision loss (182,183). The main structural change accounting for DR is BRB breakdown, which starts with the loss of pericytes and endothelial cells, and includes neurodegeneration and neuropathy (184). Disruption of the retinal neurovascular unit leads to increased vasopermeability, vascular tortuosity, areas of retinal nonperfusion, and pathologic intraocular proliferation of retinal vessels that triggers a reduction in retinal thickness and irreversible retinal damage (185,186).

DR is a multifactorial disease characterized by dysregulation in the reactive metabolites and high glucose. Dyslipidemia, angiogenic, inflammatory, oxidative stress, and extracellular matrix pathways are implicated in the pathogenesis of DR (187,188). The initial vascular phenotype of DR is BRB dysfunction triggered by chronic hyperglycemia, which contributes to macular edema (which is the major cause of visual loss in type 2 DM), hemorrhages, exudates, and capillary microaneurysms (182). The BRB comprises an outer barrier (RPE cells) and an inner barrier (retinal capillary endothelial cells and their intercellular junctions). In the retina, TRPV4 is expressed in RGCs, Müller cells, astrocytes, endothelial cells, and RPE cells, and it has shown some efficacy in regulating BRB permeability in RPE cells and retinal microvascular endothelial cells (RMECs) (36,177,178). *In vitro* treatment with a TRPV4-selective agonist (GSK1016790A/GSK101) was found to induce a massive influx of Ca^{2+} and increase the barrier permeability of human RMEC monolayers (37). In a study using rat RMECs, diabetes and hyperglycemia-mimicking conditions were associated with TRPV4 downregulation (36). *In vivo* studies have shown that TRPV4-selective antagonists (RN-1734 and GSK2193874) can mitigate BRB breakdown in streptozotocin-induced diabetic mice and rats. These results indicate that TRPV4 plays a strong role in Ca^{2+} homeostasis and barrier function in retinal capillaries, suggesting that it may function as a polymodal sensor of physical-chemical stimuli that dynamically modulates the inner BRB permeability. More recently, Orduña Ríos *et al.* (38) quantified retinal water mobility and retinal thickness using diffusion-weighted magnetic resonance imaging to evaluate the potential roles of TRPV4 in diabetic macular edema. Their study observed that diabetic WT mice had thinner retinas than did their nondiabetic counterparts. In contrast, diabetic TRPV4$^{-/-}$ mice had similar retinal thickness to the nondiabetic TRPV4$^{-/-}$ and WT groups. Further, the apparent diffusion coefficient (ADC) values showed restricted water diffusion in TRPV4 KO mice. These findings suggest that TRPV4 channel inhibition prevents and reverts retinal edema. Also, TRPV4 may contribute to retinal structural stability and is necessary for BRB breakdown and increased retinal water diffusion under sugar-dense conditions. Thus, TRPV4 channels may hold potential as a significant therapeutic target for controlling BRB breakdown in diabetic macular edema.

DR manifests as structural alterations in retinal blood vessels and impaired perivascular neuronal function. It is understood to result from the dysfunction of the retinal neurovascular unit, a special mechanism that couples neuronal computations with blood flow. DR is invariably responsible for neuronal defects, and neuro-retinal function is weakened even before microangiopathic lesions occur (189-192). The two hallmarks of neuronal dysfunction are neural apoptosis and reactive gliosis. In DR, RGCs and amacrine cells are the first detected neurons to undergo apoptosis; consequently, there is a reduction in the thickness

of the inner retinal layers and the nerve fiber layer, which can be detected by optical coherence tomography (193,194). The expression of TRPV1, TRPV4, and TRPM3 can be found in RGCs and Müller cells (157,195-197). Ryskamp *et al.* (121) showed that TRPV4-mediated Ca^{2+} entry contributed to the cell stretch of RGCs. Further, sustained exposure to TRPV4 activators (4α-PDD and GSK1016790A) led to an excessive rise in cytosolic Ca^{2+} levels, which may activate Ca^{2+}-dependent proapoptotic signaling pathways in a time- and dose-dependent manner. Therefore, antagonizing excessive TRPV4 activation may alleviate osmotic pressure-induced RGC apoptosis. The TRPV4 mechanism involved in RGC protection represents a neuroprotective molecular target for neuronal dysfunction in DR. Moreover, endothelial cells have an essential role in the hemodynamic response of DR. A recent study showed that TRPC1, TRPC3, and TRPC6 channels are critically involved in maintaining the normal function of cultured human retinal vascular endothelial cells (39). *In vitro*, the protective phenotype in DR was observed in TRPC1/4/5/6$^{-/-}$ compound KO mice, which showed a TRPC blocker compound to be highly promising for the treatment of DR (40). However, the specific effect of each TRPC channel mentioned needs to be identified to precisely understand the causative role of TRPCs in DR.

Pericytes, the spatially isolated mural cells on capillaries, play a vital role in stabilizing and remodeling microvessels in the retina under pathological conditions. Awry signals, oxidative stress, increased leukocyte adhesion, and advanced glycation end products can disturb pericyte-endothelial interactions, resulting in BRB breakdown. Pericytes represent the first and last vascular elements of the retinal neurovascular unit in controlling the blood flow of the retinal microvasculature (185,198). Pericyte loss has been implicated in three well-defined aspects of vascular remodeling: pericyte differentiation, cell adhesion, and key factors involved in ion transport. Jiang *et al.* (199) first demonstrated the role of the TRPM2 ion channel and autophagy in the pathological process of pericyte injury. However, at present, the cause of pericyte apoptosis in DR is poorly understood. Jiang *et al.*'s study raises interesting questions regarding the interrelationships between pericyte-specific TRPM2 channels and other neurovascular components in the pathological process of neurovascular injury.

Retinopathy of prematurity (ROP)

ROP is a vasoproliferative disorder of the developing retinal vasculature in premature infants. Improved technologies and modern neonatal care have increased the survival rate of extremely low gestational age neonates (<1,250 grams, <28 weeks gestation). The incidence of ROP has increased over recent decades, and it is a leading cause of severe visual impairment and blindness in childhood, especially in some developing countries (200). In ROP, there are two postnatal phases: vaso-obliteration (phase 1) and vasoproliferation (phase 2). Phase 1 involves delayed physiologic retinal vascular development beginning at preterm birth with the transition from the intrauterine to extrauterine environment. Exposure to supplemental oxygen suppresses retinal growth factors, which halts vascular development and causes many newly developed blood vessels to regress. In phase 2, the poorly perfused retina becomes hypoxic, resulting in abnormal retinal neovascularization. Abnormal retinal neovessels can ultimately cause retinal hemorrhages, retinal folds, dilated and tortuous posterior retinal blood vessels, "Plus" disease, and even retinal detachment (201,202).

It is virtually impossible to study the cellular and molecular mechanisms within the human preterm retina that cause the biological features of severe ROP. Accordingly, animal models have been developed to test heterotypic cell interactions and signaling events in this disease. Due to the relatively low cost of mice and the advanced understanding of mouse genetics compared to other species, the oxygen-induced ischemic retinopathy (OIR) mouse model is the most widely used. This model has unquestionably aided in furthering the understanding of the pathophysiology of ROP and assessing the effects of potential treatments.

Endothelial Ca^{2+} signals are critical in angiogenesis and arterial remodeling. Activation of receptors (such as bradykinin and acetylcholine receptors), the release of various vasoactive factors (including nitric oxide and insulin-like growth factor-1), and mechanical stimulation (such as pulsatile stretch and laminar shear stress) all induce neovessel formation through an increase in the intracellular Ca^{2+} concentration (203-205). Endothelial TRP channels have long been known to be a part of intracellular signaling pathways associated with endothelial cell proliferation, migration, adhesion, tubulogenesis, and permeability (206-208). Functional expression of TRPV1 and TRPV4 has been confirmed in RMECs (41). Further, pharmacologic inhibition of TRPV1 and TRPV4 has been found to impair endothelial cell capillary sprouting and tube formation. In an OIR mouse model established by O'Leary *et al.*, vitreous injection of TRPV1 and TRPV4 inhibitors

significantly inhibited pathologic retinal angiogenesis and effectively attenuated avascular areas in phase 2, increasing physiological angiogenesis (41). Blockade of TRPV1 and TRPV4 channels likely help to stimulate physiological revascularization of the ischemic retina. Recent work further explored the role of the TRPV4 channel in an OIR mouse model deficient in TRPV4 (209). Contrary to the above results, in mice with OIR, a higher number of neovascular tufts were observed throughout the superficial, intermediate, and deep retinal vascular layers in TRPV4 KO mice compared to their WT counterparts, which showed fewer and less pronounced abnormal vascular growths. The retinas of the TRPV4 KO mice also showed that TRPV4 deletion did not alter developmental physiological angiogenesis (209). Unlike genetic deletion, TRPV4 knockdown or reduction in endothelial cells has been shown to increase cell proliferation and migration, which are two remarkable events in angiogenesis (210,211). Ultimately, these inconsistent statements may be attributable to differences in TRP expression levels in mouse retinas.

A relatively early study showed that genetic deletion of TRPC5 with selective siRNA negatively affects hypoxia-induced capillary sprouting and endothelial cell tube formation. Consistently, genetic knockdown of TRPC5 was found to inhibit hypoxia-induced retinal neovascularization. Further, TRPC5$^{-/-}$ mice showed delayed vascular revascularization in a hindlimb ischemia model, and riluzole treatment contributed to ischemic tissue recovery by triggering TRPC5-mediated Ca^{2+} influx in vascular endothelial cells. These findings indicate that TRPC5 may be a new target for the clinical treatment of ischemia-related diseases (42).

Congenital stationary night blindness

CSNB is a clinically and genetically heterogeneous group of retinal disorders. It is generally considered to be a non-progressive or minimally progressive disease characterized by night blindness, moderately reduced visual acuity, myopia, nystagmus, strabismus, and photophobia. The predominant cause of CSNB is defective signal transmission from rod photoreceptors to adjacent ON-bipolar cells (169,212). Because of this transmission defect, electroretinograms (ERGs) show a near-normal a-wave and a reduced or absent b-wave. This ERG pattern is known as a negative ERG. Based on the pattern in ERG responses, CSNB can be divided into two subtypes: the complete form and the incomplete form (213). Further, CSNB can be X-linked, autosomal recessive, or autosomal dominant, and is caused by mutations in genes encoding proteins involved in phototransduction, photoreceptor to bipolar cell signaling cascades, and retinoid recycling (43,214,215). Over the last decade, the development of high-throughput technologies and gene expression analysis have allowed in-depth examination of the genome underlying this disorder. Corresponding mutations in at least 17 identified human genes, such as *CACNA1F*, *CABP4*, *CACNA2D4*, *GRM6* (the gene that encodes mGluR6), *GPR179*, *LRIT3*, *TRPM1*, and *NYX*, are associated with CSNB (216).

In the murine retina, TRPM1 is selectively and strongly expressed in the inner nuclear layer, especially in ON-bipolar cells (217,218). Bellone *et al.* (24) gave an important clue about the involvement of TRPM1 in CSNB. In the Appaloosa horse, the leopard complex (*LP*) is thought to be responsible for determining the Appaloosa coat-spotting pattern. Homozygosity for *LP* (*LP/LP*) is directly associated with CSNB in Appaloosa horses. Also, *LP/LP* horses have an absent b-wave and a depolarizing a-wave in dark-adapted ERG (219). Bellone *et al.* mapped the *LP* locus to a 6-cM region containing five candidate genes on ECA1, namely *TRPM1*, *OCA2*, *TJP1*, *MTMR10*, and *OTUD7A*. A PCR assay showed that the *TRPM1* transcript is downregulated in the retinal samples of CSNB horses, suggesting that TRPM1 might function in ON-bipolar cells. Further, studies reported that TRPM1-null mutant mice completely lost photoresponse in ON-bipolar cells, and identified an apparent role for TRPM1 in visual transduction (44,169); these results rendered TRPM1 a good candidate to be mutated in patients with CSNB, which was later confirmed (220). The TRPM1 mutation in patients with CSNB was first identified by autozygosity mapping in a consanguineous family with South Asian ethnicity using single-nucleotide polymorphism arrays (221). Since then, TPRM1 mutations have been reported worldwide as a major cause of autosomal recessive CSNB, especially in individuals with European ancestry. To our knowledge, 73 nonsense, missense, frameshift, splice site, and deletion mutations have been identified in TRPM1, of which 67 show different CSNB phenotypes. Some mutations cause TRPM1 dysfunction, while some, such as missense mutations, result in mislocalization of TRPM1. Collectively, the above studies contribute to an evolving understanding of the diverse group of TRP channels in human disease and provide new insights into the mechanisms of the retinal circuitry.

Retinoblastoma (RB)

RB is the most common aggressive neoplasm of the eye in infancy and childhood but is still an uncommon pediatric cancer, representing only 2.5% to 4% of all childhood malignancies (222,223). It appears as one or several yellowish-white retinal masses which can be isolated or coalesced, unilateral or bilateral. RB presents at a very young age, with the mean age at diagnosis being 27 months for unilateral RB and 15 months for bilateral cases (222,224,225). Despite its rarity, RB was the first tumor to draw attention to the genetic testing and screening of cancer, and has served as a cornerstone of oncology in terms of tumor diagnosis, classification, and treatment. The *RB1* gene was the first described tumor-suppressor gene located in chromosome 13q14. Heritable RB is initiated by mutations of the *RB1* gene, most of which are caused by nonsense or frameshift mutations within exons 2–25, resulting in the absence of *RB1* or loss of *RB1* function.

The expression and role of TRPs in RB remain largely unknown. A previous study showed that TRPV1, TRPM8, and TRPA1 were expressed in human RB tumor tissue and the human RB cell line WERI-Rb1. Further, PCR results showed that TRPV1 was consistently overexpressed in WERI-Rb1 and RB tumor tissue. In paraffin sections of the eye of a patient with RB, TRPV1 immunoreactivity was evident in the membrane of the RB cells. The researchers concluded that the cytostatic agent resistance of RB may be associated with TRPV1-mediated Ca^{2+} inward current (47). This study provides an intriguing insight into RB development and responses to treatment. A previous study also proposed that TRPs play an important role in the proliferation of human RB cells through their effects on cellular metabolism and protein translation (48). The authors concluded that TRPs, such as TRPM7, can be prognostic factors for RB progression. More recently, Oronowicz *et al.* (45) reported that dysfunctional regulation of intracellular calcium levels could disrupt RB tumorigenesis. Therefore, designing drugs to target TRP channels may be a viable approach to inhibiting RB cell viability and survival and increasing the efficacy of chemotherapeutic treatment for patients with RB.

Conclusions

Strong *in vitro* and *in vivo* data collected in the last two decades indicate that TRP channels regulate fundamental cellular processes. A plethora of studies has demonstrated the involvement of TRP channels in various eye diseases, and immense progress has been made in the understanding of TRP channels. However, considerable work is needed to more fully understand the functional and mechanistic aspects of the contribution of these channels to the pathophysiology of eye diseases, especially in the context of animal models or patients. Collectively, these channels hold tremendous potential that has yet to be uncovered in the hopes of achieving major clinical breakthroughs in eye disease.

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