



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

Tian-Jing Yang<sup>1,2^</sup>, Yang Yu<sup>1,2</sup>, Jing-Yi Yang<sup>3</sup>, Jin-Jing Li<sup>4,5</sup>, Jun-Ya Zhu<sup>1,2</sup>, João Alexandre Cardoso Vieira<sup>6</sup>, Qin Jiang<sup>2</sup>

<sup>1</sup>The Fourth School of Clinical Medicine, Nanjing Medical University, Nanjing, China; <sup>2</sup>The Affiliated Eye Hospital of Nanjing Medical University, Nanjing, China; <sup>3</sup>Key Laboratory of Special Function Materials and Structure Design, Ministry of Education, Lanzhou University, Lanzhou, China; <sup>4</sup>The First School of Clinical Medicine, Nanjing Medical University, Nanjing, China; <sup>5</sup>Department of Ophthalmology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; <sup>6</sup>Faculty of Pharmacy, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

*Contributions:* (I) Conception and design: TJ Yang, JY Yang; (II) Administrative support: Q Jiang; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Qin Jiang. The Affiliated Eye Hospital of Nanjing Medical University, Nanjing 210029, China. Email: jqin710@vip.sina.com.

**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<sup>2+</sup> signaling’, ‘ion 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<sup>2+</sup> signaling; diabetic retinopathy (DR); eye disease; transient receptor potential channels (TRP channels)

Submitted Nov 03, 2021. Accepted for publication May 23, 2022.

doi: 10.21037/atm-21-6145

**View this article at:** <https://dx.doi.org/10.21037/atm-21-6145>

<sup>^</sup> ORCID: 0000-0002-9191-5219.

## 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  $\text{Ca}^{2+}$  across the plasma membrane.  $\text{Ca}^{2+}$  concentration induced by TRP channels affects other ion channels that are sensitive to  $\text{Ca}^{2+}$ , such as voltage-gated  $\text{Ca}^{2+}$  channels and  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  channels, and that translate changes in cytosolic  $\text{Ca}^{2+}$  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.amegroupp.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', ' $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  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  $[\text{Ca}^{2+}]_i$  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	<i>In vivo</i>	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	<i>In vivo/in vitro</i>	Corneal cold nociception; promoted tear film instability	
		Trigeminal ganglia			
		Human cornea	Phase I/II clinical trials		
		TRPM8 (22-24)	Mouse/rat cornea	<i>In vivo/in vitro</i>	Increased the production of tears under non-noxious cooling stimuli; modulated cold-pain sensation
		Trigeminal ganglia			
Allergic conjunctivitis	TRPA1 (25,26)	Mouse blood	<i>In vivo</i>	Interacted with histamine receptor H1	
		Conjunctival			
		Cervical lymph nodes			
		TRPV1 (26)	Mouse conjunctiva	<i>In vivo</i>	Regulated histamine-dependent ocular itch signaling
	TRPM8 (27)	HConEpiC	<i>In vivo</i>	Interacted with TRPV1; suppressed TRPV1-induced IL-6 release	
Cataracts	TRPM8 (28-30)	Mouse lens/eye	<i>In vivo/in vitro</i>	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	<i>In vivo/in vitro</i>	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	<i>In vivo</i>	Mediated the oxidative stress burden and inflammation
	Human retina				
Diabetic retinopathy	TRPA1 (35)	Chick retina	<i>In vivo</i>	Contributed to cell death under ischemic condition in early stages	
		TRPV4 (36-38)	Mouse retina	<i>In vivo/in vitro</i>	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	<i>In vivo/in vitro</i>	Mediated endothelial function in a VEGF-dependent manner under HG
	HRECs			Regulated glyoxalase 1 enzyme activity	

Table 1 (continued)

Table 1 (continued)

Disease	TRP	Tissue/cell type	Experiment	Effects
ROP	TRPV1/4 (41)	Mouse retina	<i>In vivo/in vitro</i>	TRPV1 and TRPV4 formed a functional heteromeric channel to deliver pro-angiogenics in a VEGF-independent manner
		Bovine RMECs		
	TRPC5 (42)	Mouse retina	<i>In vivo/in vitro</i>	Triggered angiogenic activities in response to the ischemic condition by regulating Ca <sup>2+</sup> entry
		HEK293		
CSNB	TRPM1 (35,43-46)	Mouse retina/eye	<i>In vivo/in vitro</i>	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	<i>In vivo</i>	Interacted with cannabinoid receptor 1 in etoposide-sensitive RB cells
	TRPA1	WERI-Rb1		
	TRPM8 (47)			
	TRPM7 (48)	RB cells derived from patients		

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 <sup>2+</sup> signaling', 'ion 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 °C), 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<sup>-/-</sup> 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<sup>-/-</sup> 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 °C) (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<sup>-/-</sup> 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<sup>-/-</sup> corneas with 50 µM menthol at 34 °C or during cooling.



The same study also found that the basal tear fluid volume of TRPM8<sup>-/-</sup> 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<sup>-/-</sup> mice compared to WT mice. The study also revealed that under basal thermal conditions (18–34 °C), the tearing flow values of TRPM8<sup>-/-</sup> 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). Fakhri *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<sup>EGFP/+</sup> 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<sup>+</sup> cold-sensing neurons did not change; however, TRPV1 was significantly upregulated in TRPM8<sup>+</sup> 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<sup>+</sup> 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<sup>+</sup> neurons to cold and generating cold allodynia in the cornea. Also, TRPV1<sup>-/-</sup> 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<sup>-/-</sup> 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, Fakhri *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<sub>1</sub>AM) 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<sub>1</sub>AM and TRPM8. Treatment of HCjECs with T<sub>1</sub>AM increased the fluorescence ratio (f340 nm/f380 nm), a relative index of changes in intracellular free Ca<sup>2+</sup> concentration ([Ca<sup>2+</sup>]<sub>i</sub>), 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<sub>1</sub>AM-induced Ca<sup>2+</sup> rise was abolished, indicating that T<sub>1</sub>AM can act as a potent activator of TRPM8. However, the biosynthetic and deiodinase pathway of T<sub>1</sub>AM 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<sup>2+</sup> to be released from the endoplasmic reticulum. Depletion of intracellular Ca<sup>2+</sup> stores activates store-operated Ca<sup>2+</sup> entry (SOCE) and allows extracellular Ca<sup>2+</sup> influx. In an allergic reaction, the increase in Ca<sup>2+</sup> 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<sup>2+</sup> to lens clarity, hydration, and crystallin degradation and aggregation has long been recognized (103). New information is emerging on the regulation of Ca<sup>2+</sup> 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<sup>2+</sup>/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  $\text{Ca}^{2+}$  through the cell membrane. Intracellular free calcium ( $[\text{Ca}^{2+}]_i$ ) is mainly mediated by nonselective cation channels, which serve as a major  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  is well documented to be a major contributor in almost all types of cataracts, and elevated levels of  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  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  $\mu\text{M}$ ) of TRP inhibitor completely blocked  $[\text{Ca}^{2+}]_i$  recovery in optic nerve astrocytes, oligodendrocytes, and optic nerve explants. In contrast, SOCE was found to be essential for glial  $\text{Ca}^{2+}$  signaling in this typical white-matter tract, which indicated that replenishment of intracellular  $\text{Ca}^{2+}$  stores was entirely dependent on  $[\text{Ca}^{2+}]_i$  from the extracellular milieu via SOCE. Moreover, TRPV1 and TRPV4 were found in the optic nerve head, which supports the idea that  $\text{Ca}^{2+}$  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<sup>-/-</sup> 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<sup>2+</sup>, 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<sup>-/-</sup> 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<sup>-/-</sup> 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. Immunocytochemistry 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 lamina 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<sup>2+</sup> 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  $\alpha$ -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<sup>-/-</sup> mice had similar retinal thickness to the nondiabetic TRPV4<sup>-/-</sup> 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  $\text{Ca}^{2+}$  entry contributed to the cell stretch of RGCs. Further, sustained exposure to TRPV4 activators (4 $\alpha$ -PDD and GSK1016790A) led to an excessive rise in cytosolic  $\text{Ca}^{2+}$  levels, which may activate  $\text{Ca}^{2+}$ -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<sup>-/-</sup> 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  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  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<sup>-/-</sup> mice showed delayed vascular revascularization in a hindlimb ischemia model, and riluzole treatment contributed to ischemic tissue recovery by triggering TRPC5-mediated Ca<sup>2+</sup> 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, TRPM1 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.

### Acknowledgments

The authors thank the reviewers for their time and comments when editing this article.

*Funding:* None.

### Footnote

*Reporting Checklist:* The authors have completed the Narrative Review reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-21-6145/rc>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-21-6145/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

### References

1. Minke B, Wu C, Pak WL. Induction of photoreceptor voltage noise in the dark in *Drosophila* mutant. *Nature* 1975;258:84-7.
2. Wu LJ, Sweet TB, Clapham DE. International Union

- of Basic and Clinical Pharmacology. LXXVI. Current progress in the mammalian TRP ion channel family. *Pharmacol Rev* 2010;62:381-404.
3. Gees M, Owsianik G, Nilius B, et al. TRP channels. *Compr Physiol* 2012;2:563-608.
  4. Tomilin V, Mamenko M, Zaika O, et al. Role of renal TRP channels in physiology and pathology. *Semin Immunopathol* 2016;38:371-83.
  5. Kaneko Y, Szallasi A. Transient receptor potential (TRP) channels: a clinical perspective. *Br J Pharmacol* 2014;171:2474-507.
  6. Clapham DE. TRP channels as cellular sensors. *Nature* 2003;426:517-24.
  7. Vangeel L, Voets T. Transient Receptor Potential Channels and Calcium Signaling. *Cold Spring Harb Perspect Biol* 2019;11:a035048.
  8. Wang M, Tang YB, Ma MM, et al. TRPC3 channel confers cerebrovascular remodelling during hypertension via transactivation of EGF receptor signalling. *Cardiovasc Res* 2016;109:34-43.
  9. Grayson TH, Murphy TV, Sandow SL. Transient receptor potential canonical type 3 channels: Interactions, role and relevance - A vascular focus. *Pharmacol Ther* 2017;174:79-96.
  10. Vennekens R, Mesuere M, Philippaert K. TRPM5 in the battle against diabetes and obesity. *Acta Physiol (Oxf)* 2018.
  11. Philippaert K, Pironet A, Mesuere M, et al. Steviol glycosides enhance pancreatic beta-cell function and taste sensation by potentiation of TRPM5 channel activity. *Nat Commun* 2017;8:14733.
  12. Atala A. Re: Intravesical TRPV4 blockade reduces repeated variate stress-induced bladder dysfunction by increasing bladder capacity and decreasing voiding frequency in male rats. *J Urol* 2015;193:1060-1.
  13. Quiding H, Jonzon B, Svensson O, et al. TRPV1 antagonistic analgesic effect: a randomized study of AZD1386 in pain after third molar extraction. *Pain* 2013;154:808-12.
  14. Prevarskaya N, Skryma R, Shuba Y. Calcium in tumour metastasis: new roles for known actors. *Nat Rev Cancer* 2011;11:609-18.
  15. Park HW, Kim JY, Choi SK, et al. Serine-threonine kinase with-no-lysine 4 (WNK4) controls blood pressure via transient receptor potential canonical 3 (TRPC3) in the vasculature. *Proc Natl Acad Sci U S A* 2011;108:10750-5.
  16. Colsoul B, Nilius B, Vennekens R. On the putative role of transient receptor potential cation channels in asthma. *Clin Exp Allergy* 2009;39:1456-66.
  17. Michlig S, Merlini JM, Beaumont M, et al. Effects of TRP channel agonist ingestion on metabolism and autonomic nervous system in a randomized clinical trial of healthy subjects. *Sci Rep* 2016;6:20795.
  18. Katagiri A, Thompson R, Rahman M, et al. Evidence for TRPA1 involvement in central neural mechanisms in a rat model of dry eye. *Neuroscience* 2015;290:204-13.
  19. Li F, Yang W, Jiang H, et al. TRPV1 activity and substance P release are required for corneal cold nociception. *Nat Commun* 2019;10:5678.
  20. Bereiter DA, Rahman M, Thompson R, et al. TRPV1 and TRPM8 Channels and Nocifensive Behavior in a Rat Model for Dry Eye. *Invest Ophthalmol Vis Sci* 2018;59:3739-46.
  21. Benitez-Del-Castillo JM, Moreno-Montañés J, Jiménez-Alfaro I, et al. Safety and Efficacy Clinical Trials for SYL1001, a Novel Short Interfering RNA for the Treatment of Dry Eye Disease. *Invest Ophthalmol Vis Sci* 2016;57:6447-54.
  22. Parra A, Madrid R, Echevarria D, et al. Ocular surface wetness is regulated by TRPM8-dependent cold thermoreceptors of the cornea. *Nat Med* 2010;16:1396-9.
  23. Yang JM, Li F, Liu Q, et al. A novel TRPM8 agonist relieves dry eye discomfort. *BMC Ophthalmol* 2017;17:101.
  24. Bellone RR, Brooks SA, Sandmeyer L, et al. Differential gene expression of TRPM1, the potential cause of congenital stationary night blindness and coat spotting patterns (LP) in the Appaloosa horse (*Equus caballus*). *Genetics* 2008;179:1861-70.
  25. Kwon JY, Lee HS, Joo CK. TRPV1 Antagonist Suppresses Allergic Conjunctivitis in a Murine Model. *Ocul Immunol Inflamm* 2018;26:440-8.
  26. Huang CC, Kim YS, Olson WP, et al. A histamine-independent itch pathway is required for allergic ocular itch. *J Allergy Clin Immunol* 2016;137:1267-1270.e6.
  27. Khajavi N, Reinach PS, Slavi N, et al. Thyronamine induces TRPM8 channel activation in human conjunctival epithelial cells. *Cell Signal* 2015;27:315-25.
  28. Bennett TM, Mackay DS, Siegfried CJ, et al. Mutation of the melastatin-related cation channel, TRPM3, underlies inherited cataract and glaucoma. *PLoS One* 2014;9:e104000.
  29. Zhou Y, Bennett TM, Shiels A. Mutation of the TRPM3 cation channel underlies progressive cataract development and lens calcification associated with pro-fibrotic and immune cell responses. *FASEB J* 2021;35:e21288.
  30. Aryal S, Viet J, Weatherbee BAT, et al. The cataract-linked



- RNA-binding protein Celf1 post-transcriptionally controls the spatiotemporal expression of the key homeodomain transcription factors Pax6 and Prox1 in lens development. *Hum Genet* 2020;139:1541-54.
31. Ward NJ, Ho KW, Lambert WS, et al. Absence of transient receptor potential vanilloid-1 accelerates stress-induced axonopathy in the optic projection. *J Neurosci* 2014;34:3161-70.
  32. Nucci C, Gasperi V, Tartaglione R, et al. Involvement of the endocannabinoid system in retinal damage after high intraocular pressure-induced ischemia in rats. *Invest Ophthalmol Vis Sci* 2007;48:2997-3004.
  33. Sappington RM, Sidorova T, Ward NJ, et al. Activation of transient receptor potential vanilloid-1 (TRPV1) influences how retinal ganglion cell neurons respond to pressure-related stress. *Channels (Austin)* 2015;9:102-13.
  34. Souza Monteiro de Araújo D, De Logu F, Adembri C, et al. TRPA1 mediates damage of the retina induced by ischemia and reperfusion in mice. *Cell Death Dis* 2020;11:633.
  35. Araújo DSM, Miya-Coreixas VS, Pandolfo P, et al. Cannabinoid receptors and TRPA1 on neuroprotection in a model of retinal ischemia. *Exp Eye Res* 2017;154:116-25.
  36. Monaghan K, McNaughten J, McGahon MK, et al. Hyperglycemia and Diabetes Downregulate the Functional Expression of TRPV4 Channels in Retinal Microvascular Endothelium. *PLoS One* 2015;10:e0128359.
  37. Phuong TTT, Redmon SN, Yarishkin O, et al. Calcium influx through TRPV4 channels modulates the adherens contacts between retinal microvascular endothelial cells. *J Physiol* 2017;595:6869-85.
  38. Orduña Ríos M, Noguez Imm R, Hernández Godínez NM, et al. TRPV4 inhibition prevents increased water diffusion and blood-retina barrier breakdown in the retina of streptozotocin-induced diabetic mice. *PLoS One* 2019;14:e0212158.
  39. Lang HB, Xie RX, Huang ML, et al. The Effect and Mechanism of TRPC1, 3, and 6 on the Proliferation, Migration, and Lumen Formation of Retinal Vascular Endothelial Cells Induced by High Glucose. *Ophthalmic Res* 2020;63:284-94.
  40. Sachdeva R, Schlotterer A, Schumacher D, et al. TRPC proteins contribute to development of diabetic retinopathy and regulate glyoxalase 1 activity and methylglyoxal accumulation. *Mol Metab* 2018;9:156-67.
  41. O'Leary C, McGahon MK, Ashraf S, et al. Involvement of TRPV1 and TRPV4 Channels in Retinal Angiogenesis. *Invest Ophthalmol Vis Sci* 2019;60:3297-309.
  42. Zhu Y, Gao M, Zhou T, et al. The TRPC5 channel regulates angiogenesis and promotes recovery from ischemic injury in mice. *J Biol Chem* 2019;294:28-37.
  43. van Genderen MM, Bijveld MM, Claassen YB, et al. Mutations in TRPM1 are a common cause of complete congenital stationary night blindness. *Am J Hum Genet* 2009;85:730-6.
  44. Koike C, Obara T, Uriu Y, et al. TRPM1 is a component of the retinal ON bipolar cell transduction channel in the mGluR6 cascade. *Proc Natl Acad Sci U S A* 2010;107:332-7.
  45. Oronowicz J, Reinhard J, Reinach PS, et al. Ascorbate-induced oxidative stress mediates TRP channel activation and cytotoxicity in human etoposide-sensitive and -resistant retinoblastoma cells. *Lab Invest* 2021;101:70-88.
  46. Alcalde I, Íñigo-Portugués A, González-González O, et al. Morphological and functional changes in TRPM8-expressing corneal cold thermoreceptor neurons during aging and their impact on tearing in mice. *J Comp Neurol* 2018;526:1859-74.
  47. Mergler S, Cheng Y, Skosyrski S, et al. Altered calcium regulation by thermosensitive transient receptor potential channels in etoposide-resistant WERI-Rb1 retinoblastoma cells. *Exp Eye Res* 2012;94:157-73.
  48. Hanano T, Hara Y, Shi J, et al. Involvement of TRPM7 in cell growth as a spontaneously activated Ca<sup>2+</sup> entry pathway in human retinoblastoma cells. *J Pharmacol Sci* 2004;95:403-19.
  49. Yang H, Mergler S, Sun X, et al. TRPC4 knockdown suppresses epidermal growth factor-induced store-operated channel activation and growth in human corneal epithelial cells. *J Biol Chem* 2005;280:32230-7.
  50. Lapajne L, Lakk M, Yarishkin O, et al. Polymodal Sensory Transduction in Mouse Corneal Epithelial Cells. *Invest Ophthalmol Vis Sci* 2020;61:2.
  51. Ryskamp DA, Frye AM, Phuong TT, et al. TRPV4 regulates calcium homeostasis, cytoskeletal remodeling, conventional outflow and intraocular pressure in the mammalian eye. *Sci Rep* 2016;6:30583.
  52. Eguchi H, Hiura A, Nakagawa H, et al. Corneal Nerve Fiber Structure, Its Role in Corneal Function, and Its Changes in Corneal Diseases. *Biomed Res Int* 2017;2017:3242649.
  53. El Andaloussi-Lilja J, Lundqvist J, Forsby A. TRPV1 expression and activity during retinoic acid-induced neuronal differentiation. *Neurochem Int* 2009;55:768-74.
  54. Quallo T, Vastani N, Horridge E, et al. TRPM8 is a neuronal osmosensor that regulates eye blinking in mice.



- Nat Commun 2015;6:7150.
55. Rivera B, Campos M, Orio P, et al. Negative Modulation of TRPM8 Channel Function by Protein Kinase C in Trigeminal Cold Thermoreceptor Neurons. *Int J Mol Sci* 2020;21:4420.
  56. Caterina MJ, Julius D. The vanilloid receptor: a molecular gateway to the pain pathway. *Annu Rev Neurosci* 2001;24:487-517.
  57. Julius D, Basbaum AI. Molecular mechanisms of nociception. *Nature* 2001;413:203-10.
  58. Canner JP, Linsenmayer TF, Kubilus JK. Developmental regulation of trigeminal TRPA1 by the cornea. *Invest Ophthalmol Vis Sci* 2014;56:29-36.
  59. Alamri A, Bron R, Brock JA, et al. Transient receptor potential cation channel subfamily V member 1 expressing corneal sensory neurons can be subdivided into at least three subpopulations. *Front Neuroanat* 2015;9:71.
  60. Caterina MJ, Schumacher MA, Tominaga M, et al. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature* 1997;389:816-24.
  61. Yang S, Yang F, Wei N, et al. A pain-inducing centipede toxin targets the heat activation machinery of nociceptor TRPV1. *Nat Commun* 2015;6:8297.
  62. Bohlen CJ, Priel A, Zhou S, et al. A bivalent tarantula toxin activates the capsaicin receptor, TRPV1, by targeting the outer pore domain. *Cell* 2010;141:834-45.
  63. Jara-Oseguera A, Huffer KE, Swartz KJ. The ion selectivity filter is not an activation gate in TRPV1-3 channels. *eLife* 2019;8:e51212..
  64. Montell C, Birnbaumer L, Flockerzi V, et al. A unified nomenclature for the superfamily of TRP cation channels. *Mol Cell* 2002;9:229-31.
  65. Caterina MJ, Leffler A, Malmberg AB, et al. Impaired nociception and pain sensation in mice lacking the capsaicin receptor. *Science* 2000;288:306-13.
  66. Okada Y, Reinach PS, Shirai K, et al. TRPV1 involvement in inflammatory tissue fibrosis in mice. *Am J Pathol* 2011;178:2654-64.
  67. Kolli S, Bojic S, Ghareeb AE, et al. The Role of Nerve Growth Factor in Maintaining Proliferative Capacity, Colony-Forming Efficiency, and the Limbal Stem Cell Phenotype. *Stem Cells* 2019;37:139-49.
  68. Chaudhary S, Namavari A, Yco L, et al. Neurotrophins and nerve regeneration-associated genes are expressed in the cornea after lamellar flap surgery. *Cornea* 2012;31:1460-7.
  69. Nidegawa-Saitoh Y, Sumioka T, Okada Y, et al. Impaired healing of cornea incision injury in a TRPV1-deficient mouse. *Cell Tissue Res* 2018;374:329-38.
  70. Fajardo O, Meseguer V, Belmonte C, et al. TRPA1 channels mediate cold temperature sensing in mammalian vagal sensory neurons: pharmacological and genetic evidence. *J Neurosci* 2008;28:7863-75.
  71. Broad LM, Mogg AJ, Beattie RE, et al. TRP channels as emerging targets for pain therapeutics. *Expert Opin Ther Targets* 2009;13:69-81.
  72. Scheeterson LC, Pazevic AA, Yang R, et al. TRPV1, TRPA1, and TRPM8 are expressed in axon terminals in the cornea: TRPV1 axons contain CGRP and secretogranin II; TRPA1 axons contain secretogranin 3. *Mol Vis* 2020;26:576-87.
  73. Madrid R, Pertusa M. Intimacies and physiological role of the polymodal cold-sensitive ion channel TRPM8. *Curr Top Membr* 2014;74:293-324.
  74. McKemy DD, Neuhauser WM, Julius D. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. *Nature* 2002;416:52-8.
  75. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. *Ocul Surf* 2017;15:276-83.
  76. Belmonte C, Gallar J. Cold thermoreceptors, unexpected players in tear production and ocular dryness sensations. *Invest Ophthalmol Vis Sci* 2011;52:3888-92.
  77. Yoon HJ, Kim J, Yang JM, et al. Topical TRPM8 Agonist for Relieving Neuropathic Ocular Pain in Patients with Dry Eye: A Pilot Study. *J Clin Med* 2021;10:250.
  78. Fakh D, Baudouin C, Réaux-Le Goazigo A, et al. TRPM8: A Therapeutic Target for Neuroinflammatory Symptoms Induced by Severe Dry Eye Disease. *Int J Mol Sci* 2020;21:8756.
  79. Gava NR, Bannon AW, Surapaneni S, et al. The vanilloid receptor TRPV1 is tonically activated in vivo and involved in body temperature regulation. *J Neurosci* 2007;27:3366-74.
  80. González-González O, Bech F, Gallar J, et al. Functional Properties of Sensory Nerve Terminals of the Mouse Cornea. *Invest Ophthalmol Vis Sci* 2017;58:404-15.
  81. Ciura S, Bourque CW. Transient receptor potential vanilloid 1 is required for intrinsic osmoreception in organum vasculosum lamina terminalis neurons and for normal thirst responses to systemic hyperosmolality. *J Neurosci* 2006;26:9069-75.
  82. Sharif Naeini R, Witty MF, Séguéla P, et al. An N-terminal variant of Trpv1 channel is required for osmosensory transduction. *Nat Neurosci* 2006;9:93-8.
  83. Fakh D, Guerrero-Moreno A, Baudouin C, et al.

- Capsazepine decreases corneal pain syndrome in severe dry eye disease. *J Neuroinflammation* 2021;18:111.
84. Mergler S, Garreis F, Sahlmüller M, et al. Calcium regulation by thermo- and osmosensing transient receptor potential vanilloid channels (TRPVs) in human conjunctival epithelial cells. *Histochem Cell Biol* 2012;137:743-61.
  85. Martínez-García MC, Martínez T, Pañeda C, et al. Differential expression and localization of transient receptor potential vanilloid 1 in rabbit and human eyes. *Histol Histopathol* 2013;28:1507-16.
  86. Garreis F, Schröder A, Reinach PS, et al. Upregulation of Transient Receptor Potential Vanilloid Type-1 Channel Activity and Ca<sup>2+</sup> Influx Dysfunction in Human Pterygial Cells. *Invest Ophthalmol Vis Sci* 2016;57:2564-77.
  87. Scanlan TS, Suchland KL, Hart ME, et al. 3-Iodothyronamine is an endogenous and rapid-acting derivative of thyroid hormone. *Nat Med* 2004;10:638-42.
  88. Rutigliano G, Bandini L, Sestito S, et al. 3-Iodothyronamine and Derivatives: New Allies Against Metabolic Syndrome? *Int J Mol Sci* 2020;21:2005.
  89. Kuo IC, Gower EW. Cost Savings From a Policy to Diagnose and Prevent Transmission of Adenoviral Conjunctivitis in Employees of a Large Academic Medical Center. *JAMA Ophthalmol* 2021;139:518-24.
  90. Li J, Lu X, Jiang B, et al. Adenovirus-associated acute conjunctivitis in Beijing, China, 2011-2013. *BMC Infect Dis* 2018;18:135.
  91. O'Brien TP, Jeng BH, McDonald M, et al. Acute conjunctivitis: truth and misconceptions. *Curr Med Res Opin* 2009;25:1953-61.
  92. Varu DM, Rhee MK, Akpek EK, et al. Conjunctivitis Preferred Practice Pattern®. *Ophthalmology* 2019;126:P94-P169.
  93. Fukuda K, Ohbayashi M, Morohoshi K, et al. Critical role of IgE-dependent mast cell activation in a murine model of allergic conjunctivitis. *J Allergy Clin Immunol* 2009;124:827-33.e2.
  94. Ding Y, Li C, Zhang Y, et al. Quercetin as a Lyn kinase inhibitor inhibits IgE-mediated allergic conjunctivitis. *Food Chem Toxicol* 2020;135:110924.
  95. Irkec MT, Bozkurt B. Molecular immunology of allergic conjunctivitis. *Curr Opin Allergy Clin Immunol* 2012;12:534-9.
  96. Grimbaldston MA, Chen CC, Piliponsky AM, et al. Mast cell-deficient W-sash c-kit mutant Kit W-sh/W-sh mice as a model for investigating mast cell biology in vivo. *Am J Pathol* 2005;167:835-48.
  97. Wilson SR, Gerhold KA, Bifolck-Fisher A, et al. TRPA1 is required for histamine-independent, Mas-related G protein-coupled receptor-mediated itch. *Nat Neurosci* 2011;14:595-602.
  98. Scheurer ME, Amirian ES, Davlin SL, et al. Effects of antihistamine and anti-inflammatory medication use on risk of specific glioma histologies. *Int J Cancer* 2011;129:2290-6.
  99. Wouters MM, Balemans D, Van Wanrooy S, et al. Histamine Receptor H1-Mediated Sensitization of TRPV1 Mediates Visceral Hypersensitivity and Symptoms in Patients With Irritable Bowel Syndrome. *Gastroenterology* 2016;150:875-87.e9.
  100. Choi JY, Lee HY, Hur J, et al. TRPV1 Blocking Alleviates Airway Inflammation and Remodeling in a Chronic Asthma Murine Model. *Allergy Asthma Immunol Res* 2018;10:216-24.
  101. Lieu TM, Myers AC, Meeker S, et al. TRPV1 induction in airway vagal low-threshold mechanosensory neurons by allergen challenge and neurotrophic factors. *Am J Physiol Lung Cell Mol Physiol* 2012;302:L941-8.
  102. Sánchez-Hernández MC, Montero J, Rondon C, et al. Consensus document on allergic conjunctivitis (DECA). *J Investig Allergol Clin Immunol* 2015;25:94-106.
  103. Duncan G, Wormstone IM. Calcium cell signalling and cataract: role of the endoplasmic reticulum. *Eye (Lond)* 1999;13 ( Pt 3b):480-3.
  104. Nakazawa Y, Donaldson PJ, Petrova RS. Verification and spatial mapping of TRPV1 and TRPV4 expression in the embryonic and adult mouse lens. *Exp Eye Res* 2019;186:107707.
  105. Shahidullah M, Mandal A, Delamere NA. TRPV4 in porcine lens epithelium regulates hemichannel-mediated ATP release and Na-K-ATPase activity. *Am J Physiol Cell Physiol* 2012;302:C1751-61.
  106. Takai Y, Sugawara R, Ohinata H, et al. Two types of non-selective cation channel opened by muscarinic stimulation with carbachol in bovine ciliary muscle cells. *J Physiol* 2004;559:899-922.
  107. GBD 2019 Blindness and Vision Impairment Collaborators; Vision Loss Expert Group of the Global Burden of Disease Study. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. *Lancet Glob Health* 2021;9:e144-60.
  108. Chiu CJ, Taylor A. Nutritional antioxidants and age-related cataract and maculopathy. *Exp Eye Res*

- 2007;84:229-45.
109. Brennan LA, Kantorow M. Mitochondrial function and redox control in the aging eye: role of MsrA and other repair systems in cataract and macular degenerations. *Exp Eye Res* 2009;88:195-203.
  110. Periyasamy P, Shinohara T. Age-related cataracts: Role of unfolded protein response, Ca<sup>2+</sup> mobilization, epigenetic DNA modifications, and loss of Nrf2/Keap1 dependent cytoprotection. *Prog Retin Eye Res* 2017;60:1-19.
  111. Baynes JW, Thorpe SR. Role of oxidative stress in diabetic complications: a new perspective on an old paradigm. *Diabetes* 1999;48:1-9.
  112. Rhodes JD, Sanderson J. The mechanisms of calcium homeostasis and signalling in the lens. *Exp Eye Res* 2009;88:226-34.
  113. Rasi V, Costantini S, Moramarco A, et al. Inorganic element concentrations in cataractous human lenses. *Ann Ophthalmol* 1992;24:459-64.
  114. Tang D, Borchman D, Yappert MC, et al. Influence of age, diabetes, and cataract on calcium, lipid-calcium, and protein-calcium relationships in human lenses. *Invest Ophthalmol Vis Sci* 2003;44:2059-66.
  115. Shiels A. TRPM3\_miR-204: a complex locus for eye development and disease. *Hum Genomics* 2020;14:7.
  116. Xie Q, Ung D, Khafizov K, et al. Gene regulation by PAX6: structural-functional correlations of missense mutants and transcriptional control of Trpm3/miR-204. *Mol Vis* 2014;20:270-82.
  117. Quigley HA, Addicks EM, Green WR. Optic nerve damage in human glaucoma. III. Quantitative correlation of nerve fiber loss and visual field defect in glaucoma, ischemic neuropathy, papilledema, and toxic neuropathy. *Arch Ophthalmol* 1982;100:135-46.
  118. Choi HJ, Sun D, Jakobs TC. Astrocytes in the optic nerve head express putative mechanosensitive channels. *Mol Vis* 2015;21:749-66.
  119. Papanikolaou M, Lewis A, Butt AM. Store-operated calcium entry is essential for glial calcium signalling in CNS white matter. *Brain Struct Funct* 2017;222:2993-3005.
  120. Luo L, Song S, Ezenwukwa CC, et al. Ion channels and transporters in microglial function in physiology and brain diseases. *Neurochem Int* 2021;142:104925.
  121. Ryskamp DA, Witkovsky P, Barabas P, et al. The polymodal ion channel transient receptor potential vanilloid 4 modulates calcium flux, spiking rate, and apoptosis of mouse retinal ganglion cells. *J Neurosci* 2011;31:7089-101.
  122. Coroneo MT, Korbmacher C, Flügel C, et al. Electrical and morphological evidence for heterogeneous populations of cultured bovine trabecular meshwork cells. *Exp Eye Res* 1991;52:375-88.
  123. Kageyama M, Fujita M, Shirasawa E. Endothelin-1 mediated Ca<sup>2+</sup> influx does not occur through L-type voltage-dependent Ca<sup>2+</sup> channels in cultured bovine trabecular meshwork cells. *J Ocul Pharmacol Ther* 1996;12:433-40.
  124. Abad E, Lorente G, Gavara N, et al. Activation of store-operated Ca(2+) channels in trabecular meshwork cells. *Invest Ophthalmol Vis Sci* 2008;49:677-86.
  125. Luo N, Conwell MD, Chen X, et al. Primary cilia signaling mediates intraocular pressure sensation. *Proc Natl Acad Sci U S A* 2014;111:12871-6.
  126. Madhivanan K, Ramadesikan S, Aguilar RC. Role of Ocr1 in primary cilia assembly. *Int Rev Cell Mol Biol* 2015;317:331-47.
  127. Luo N, West CC, Murga-Zamalloa CA, et al. OCRL localizes to the primary cilium: a new role for cilia in Lowe syndrome. *Hum Mol Genet* 2012;21:3333-44.
  128. Patel PD, Chen YL, Kasetti RB, et al. Impaired TRPV4-eNOS signaling in trabecular meshwork elevates intraocular pressure in glaucoma. *Proc Natl Acad Sci U S A* 2021;118:e2022461118.
  129. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology* 2014;121:2081-90.
  130. Stevens GA, White RA, Flaxman SR, et al. Global prevalence of vision impairment and blindness: magnitude and temporal trends, 1990-2010. *Ophthalmology* 2013;120:2377-84.
  131. Jonas JB, Aung T, Bourne RR, et al. Glaucoma. *Lancet* 2017;390:2183-93.
  132. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA* 2014;311:1901-11.
  133. Budenz DL, Barton K, Whiteside-de Vos J, et al. Prevalence of glaucoma in an urban West African population: the Tema Eye Survey. *JAMA Ophthalmol* 2013;131:651-8.
  134. Rotchford AP, Kirwan JF, Muller MA, et al. Temba glaucoma study: a population-based cross-sectional survey in urban South Africa. *Ophthalmology* 2003;110:376-82.
  135. Bucolo C, Salomone S, Drago F, et al. Pharmacological management of ocular hypertension: current approaches and future prospective. *Curr Opin Pharmacol* 2013;13:50-5.

136. Wang X, Teng L, Li A, et al. TRPC6 channel protects retinal ganglion cells in a rat model of retinal ischemia/reperfusion-induced cell death. *Invest Ophthalmol Vis Sci* 2010;51:5751-8.
137. Chen S, Fan Q, Gao X, et al. Increased expression of the transient receptor potential cation channel 6 gene in patients with primary open-angle glaucoma. *Clin Exp Ophthalmol* 2013;41:753-60.
138. Sigal IA, Flanagan JG, Tertinegg I, et al. Finite element modeling of optic nerve head biomechanics. *Invest Ophthalmol Vis Sci* 2004;45:4378-87.
139. Risner ML, Pasini S, Cooper ML, et al. Axogenic mechanism enhances retinal ganglion cell excitability during early progression in glaucoma. *Proc Natl Acad Sci U S A* 2018;115:E2393-402.
140. Risner ML, McGrady NR, Pasini S, et al. Elevated ocular pressure reduces voltage-gated sodium channel NaV1.2 protein expression in retinal ganglion cell axons. *Exp Eye Res* 2020;190:107873.
141. McGrady NR, Risner ML, Vest V, et al. TRPV1 Tunes Optic Nerve Axon Excitability in Glaucoma. *Front Physiol* 2020;11:249.
142. Maione S, Cristino L, Migliozi AL, et al. TRPV1 channels control synaptic plasticity in the developing superior colliculus. *J Physiol* 2009;587:2521-35.
143. Sappington RM, Sidorova T, Long DJ, et al. TRPV1: contribution to retinal ganglion cell apoptosis and increased intracellular Ca<sup>2+</sup> with exposure to hydrostatic pressure. *Invest Ophthalmol Vis Sci* 2009;50:717-28.
144. Leonelli M, Martins DO, Britto LR. Retinal cell death induced by TRPV1 activation involves NMDA signaling and upregulation of nitric oxide synthases. *Cell Mol Neurobiol* 2013;33:379-92.
145. Weitlauf C, Ward NJ, Lambert WS, et al. Short-term increases in transient receptor potential vanilloid-1 mediate stress-induced enhancement of neuronal excitation. *J Neurosci* 2014;34:15369-81.
146. Ryskamp DA, Redmon S, Jo AO, et al. TRPV1 and Endocannabinoids: Emerging Molecular Signals that Modulate Mammalian Vision. *Cells* 2014;3:914-38.
147. Liang Z, Freed MA. The ON pathway rectifies the OFF pathway of the mammalian retina. *J Neurosci* 2010;30:5533-43.
148. Chalupa LM, Günhan E. Development of On and Off retinal pathways and retinogeniculate projections. *Prog Retin Eye Res* 2004;23:31-51.
149. Risner ML, McGrady NR, Boal AM, et al. TRPV1 Supports Axogenic Enhanced Excitability in Response to Neurodegenerative Stress. *Front Cell Neurosci* 2020;14:603419.
150. Taylor L, Arnér K, Ghosh F. Specific inhibition of TRPV4 enhances retinal ganglion cell survival in adult porcine retinal explants. *Exp Eye Res* 2017;154:10-21.
151. Li Q, Cheng Y, Zhang S, et al. TRPV4-induced Müller cell gliosis and TNF- $\alpha$  elevation-mediated retinal ganglion cell apoptosis in glaucomatous rats via JAK2/STAT3/NF- $\kappa$ B pathway. *J Neuroinflammation* 2021;18:271.
152. Jo AO, Ryskamp DA, Phuong TT, et al. TRPV4 and AQP4 Channels Synergistically Regulate Cell Volume and Calcium Homeostasis in Retinal Müller Glia. *J Neurosci* 2015;35:13525-37.
153. Gao F, Yang Z, Jacoby RA, et al. The expression and function of TRPV4 channels in primate retinal ganglion cells and bipolar cells. *Cell Death Dis* 2019;10:364.
154. Sánchez-Ramos C, Guerrero MC, Bonnín-Arias C, et al. Expression of TRPV4 in the zebrafish retina during development. *Microsc Res Tech* 2012;75:743-8.
155. Masland RH, Raviola E. Confronting complexity: strategies for understanding the microcircuitry of the retina. *Annu Rev Neurosci* 2000;23:249-84.
156. Gilliam JC, Wensel TG. TRP channel gene expression in the mouse retina. *Vision Res* 2011;51:2440-52.
157. Lakk M, Young D, Baumann JM, et al. Polymodal TRPV1 and TRPV4 Sensors Colocalize but Do Not Functionally Interact in a Subpopulation of Mouse Retinal Ganglion Cells. *Front Cell Neurosci* 2018;12:353.
158. Hsu CC, Chien KH, Yarmishyn AA, et al. Modulation of osmotic stress-induced TRPV1 expression rescues human iPSC-derived retinal ganglion cells through PKA. *Stem Cell Res Ther* 2019;10:284.
159. Reinach PS, Chen W, Mergler S. Polymodal roles of transient receptor potential channels in the control of ocular function. *Eye Vis (Lond)* 2015;2:5.
160. Ayoub GS, Copenhagen DR. Application of a fluorometric method to measure glutamate release from single retinal photoreceptors. *J Neurosci Methods* 1991;37:7-14.
161. Euler T, Haverkamp S, Schubert T, et al. Retinal bipolar cells: elementary building blocks of vision. *Nat Rev Neurosci* 2014;15:507-19.
162. Morigiwa K, Vardi N. Differential expression of ionotropic glutamate receptor subunits in the outer retina. *J Comp Neurol* 1999;405:173-84.
163. Nomura A, Shigemoto R, Nakamura Y, et al. Developmentally regulated postsynaptic localization of a metabotropic glutamate receptor in rat rod bipolar cells. *Cell* 1994;77:361-9.



164. de la Villa P, Kurahashi T, Kaneko A. L-glutamate-induced responses and cGMP-activated channels in three subtypes of retinal bipolar cells dissociated from the cat. *J Neurosci* 1995;15:3571-82.
165. Masu M, Iwakabe H, Tagawa Y, et al. Specific deficit of the ON response in visual transmission by targeted disruption of the mGluR6 gene. *Cell* 1995;80:757-65.
166. Euler T, Schneider H, Wässle H. Glutamate responses of bipolar cells in a slice preparation of the rat retina. *J Neurosci* 1996;16:2934-44.
167. Dhingra A, Lyubarsky A, Jiang M, et al. The light response of ON bipolar neurons requires G[alpha]o. *J Neurosci* 2000;20:9053-8.
168. Nawy S, Jahr CE. Suppression by glutamate of cGMP-activated conductance in retinal bipolar cells. *Nature* 1990;346:269-71.
169. Morgans CW, Zhang J, Jeffrey BG, et al. TRPM1 is required for the depolarizing light response in retinal ON-bipolar cells. *Proc Natl Acad Sci U S A* 2009;106:19174-8.
170. Morgans CW, Brown RL, Duvoisin RM. TRPM1: the endpoint of the mGluR6 signal transduction cascade in retinal ON-bipolar cells. *Bioessays* 2010;32:609-14.
171. Koike C, Numata T, Ueda H, et al. TRPM1: a vertebrate TRP channel responsible for retinal ON bipolar function. *Cell Calcium* 2010;48:95-101.
172. Snellman J, Kaur T, Shen Y, et al. Regulation of ON bipolar cell activity. *Prog Retin Eye Res* 2008;27:450-63.
173. Da Silva N, Herron CE, Stevens K, et al. Metabotropic receptor-activated calcium increases and store-operated calcium influx in mouse Müller cells. *Invest Ophthalmol Vis Sci* 2008;49:3065-73.
174. Brown RL, Xiong WH, Peters JH, et al. TRPM3 expression in mouse retina. *PLoS One* 2015;10:e0117615.
175. Leonelli M, Martins DO, Kihara AH, et al. Ontogenetic expression of the vanilloid receptors TRPV1 and TRPV2 in the rat retina. *Int J Dev Neurosci* 2009;27:709-18.
176. Ho KW, Lambert WS, Calkins DJ. Activation of the TRPV1 cation channel contributes to stress-induced astrocyte migration. *Glia* 2014;62:1435-51.
177. Zhao PY, Gan G, Peng S, et al. TRP Channels Localize to Subdomains of the Apical Plasma Membrane in Human Fetal Retinal Pigment Epithelium. *Invest Ophthalmol Vis Sci* 2015;56:1916-23.
178. Arredondo Zamarripa D, Noguez Imm R, Bautista Cortés AM, et al. Dual contribution of TRPV4 antagonism in the regulatory effect of vasoinhibins on blood-retinal barrier permeability: diabetic milieu makes a difference. *Sci Rep* 2017;7:13094.
179. Cordeiro S, Seyler S, Stindl J, et al. Heat-sensitive TRPV channels in retinal pigment epithelial cells: regulation of VEGF-A secretion. *Invest Ophthalmol Vis Sci* 2010;51:6001-8.
180. Kennedy BG, Torabi AJ, Kurzawa R, et al. Expression of transient receptor potential vanilloid channels TRPV5 and TRPV6 in retinal pigment epithelium. *Mol Vis* 2010;16:665-75.
181. McKay AJ, Gunn LH, Nugawela MD, et al. Associations between attainment of incentivized primary care indicators and incident sight-threatening diabetic retinopathy in England: A population-based historical cohort study. *Diabetes Obes Metab* 2021;23:1322-30.
182. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet* 2010;376:124-36.
183. Saaddine JB, Honeycutt AA, Narayan KM, et al. Projection of diabetic retinopathy and other major eye diseases among people with diabetes mellitus: United States, 2005-2050. *Arch Ophthalmol* 2008;126:1740-7.
184. Spencer BG, Estevez JJ, Liu E, et al. Pericytes, inflammation, and diabetic retinopathy. *Inflammopharmacology* 2020;28:697-709.
185. Hammes HP, Lin J, Wagner P, et al. Angiopoietin-2 causes pericyte dropout in the normal retina: evidence for involvement in diabetic retinopathy. *Diabetes* 2004;53:1104-10.
186. Hammes HP. Diabetic retinopathy: hyperglycaemia, oxidative stress and beyond. *Diabetologia* 2018;61:29-38.
187. Wong TY, Cheung CM, Larsen M, et al. Diabetic retinopathy. *Nat Rev Dis Primers* 2016;2:16012.
188. RübSam A, Parikh S, Fort PE. Role of Inflammation in Diabetic Retinopathy. *Int J Mol Sci* 2018;19:942.
189. Bearse MA Jr, Han Y, Schneck ME, et al. Local multifocal oscillatory potential abnormalities in diabetes and early diabetic retinopathy. *Invest Ophthalmol Vis Sci* 2004;45:3259-65.
190. Greenstein VC, Shapiro A, Zaidi Q, et al. Psychophysical evidence for post-receptor sensitivity loss in diabetics. *Invest Ophthalmol Vis Sci* 1992;33:2781-90.
191. Parisi V, Uccioli L. Visual electrophysiological responses in persons with type 1 diabetes. *Diabetes Metab Res Rev* 2001;17:12-8.
192. Altmann C, Schmidt MHH. The Role of Microglia in Diabetic Retinopathy: Inflammation, Microvasculature Defects and Neurodegeneration. *Int J Mol Sci* 2018;19:110.
193. Kern TS, Barber AJ. Retinal ganglion cells in diabetes. *J Physiol* 2008;586:4401-8.



194. Ng DS, Chiang PP, Tan G, et al. Retinal ganglion cell neuronal damage in diabetes and diabetic retinopathy. *Clin Exp Ophthalmol* 2016;44:243-50.
195. Lakk M, Yarishkin O, Baumann JM, et al. Cholesterol regulates polymodal sensory transduction in Müller glia. *Glia* 2017;65:2038-50.
196. Jo AO, Noel JM, Lakk M, et al. Mouse retinal ganglion cell signalling is dynamically modulated through parallel anterograde activation of cannabinoid and vanilloid pathways. *J Physiol* 2017;595:6499-516.
197. Webster CM, Tworig J, Caval-Holme F, et al. The Impact of Steroid Activation of TRPM3 on Spontaneous Activity in the Developing Retina. *eNeuro* 2020;7:ENEURO.
198. Ivanova E, Kovacs-Oller T, Sagdullaev BT. Vascular Pericyte Impairment and Connexin43 Gap Junction Deficit Contribute to Vasomotor Decline in Diabetic Retinopathy. *J Neurosci* 2017;37:7580-94.
199. Jiang Q, Gao Y, Wang C, et al. Nitration of TRPM2 as a Molecular Switch Induces Autophagy During Brain Pericyte Injury. *Antioxid Redox Signal* 2017;27:1297-316.
200. Hartnett ME, Penn JS. Mechanisms and management of retinopathy of prematurity. *N Engl J Med* 2012;367:2515-26.
201. ASHTON N. Pathological basis of retrolental fibroplasia. *Br J Ophthalmol* 1954;38:385-96.
202. Campochiaro PA. Molecular pathogenesis of retinal and choroidal vascular diseases. *Prog Retin Eye Res* 2015;49:67-81.
203. Moccia F. Endothelial Ca<sup>2+</sup> Signaling and the Resistance to Anticancer Treatments: Partners in Crime. *Int J Mol Sci* 2018;19:217.
204. Zhang DX, Gutterman DD. Transient receptor potential channel activation and endothelium-dependent dilation in the systemic circulation. *J Cardiovasc Pharmacol* 2011;57:133-9.
205. Yokota Y, Nakajima H, Wakayama Y, et al. Endothelial Ca<sup>2+</sup> oscillations reflect VEGFR signaling-regulated angiogenic capacity in vivo. *Elife* 2015;4:08817.
206. Moore TM, Brough GH, Babal P, et al. Store-operated calcium entry promotes shape change in pulmonary endothelial cells expressing Trp1. *Am J Physiol* 1998;275:L574-82.
207. Fantozzi I, Zhang S, Platoshyn O, et al. Hypoxia increases AP-1 binding activity by enhancing capacitative Ca<sup>2+</sup> entry in human pulmonary artery endothelial cells. *Am J Physiol Lung Cell Mol Physiol* 2003;285:L1233-45.
208. Cheng HW, James AF, Foster RR, et al. VEGF activates receptor-operated cation channels in human microvascular endothelial cells. *Arterioscler Thromb Vasc Biol* 2006;26:1768-76.
209. Cappelli HC, Guarino BD, Kanugula AK, et al. Transient receptor potential vanilloid 4 channel deletion regulates pathological but not developmental retinal angiogenesis. *J Cell Physiol* 2021;236:3770-9.
210. Adapala RK, Thoppil RJ, Ghosh K, et al. Activation of mechanosensitive ion channel TRPV4 normalizes tumor vasculature and improves cancer therapy. *Oncogene* 2016;35:314-22.
211. Thoppil RJ, Adapala RK, Cappelli HC, et al. TRPV4 channel activation selectively inhibits tumor endothelial cell proliferation. *Sci Rep* 2015;5:14257.
212. AlTalibishi A, Zelinger L, Zeitz C, et al. TRPM1 Mutations are the Most Common Cause of Autosomal Recessive Congenital Stationary Night Blindness (CSNB) in the Palestinian and Israeli Populations. *Sci Rep* 2019;9:12047.
213. Miyake Y, Yagasaki K, Horiguchi M, et al. Congenital stationary night blindness with negative electroretinogram. A new classification. *Arch Ophthalmol* 1986;104:1013-20.
214. Bech-Hansen NT, Naylor MJ, Maybaum TA, et al. Mutations in NYX, encoding the leucine-rich proteoglycan nycalopin, cause X-linked complete congenital stationary night blindness. *Nat Genet* 2000;26:319-23.
215. Scholl HP, Langrová H, Pusch CM, et al. Slow and fast rod ERG pathways in patients with X-linked complete stationary night blindness carrying mutations in the NYX gene. *Invest Ophthalmol Vis Sci* 2001;42:2728-36.
216. Zeitz C, Robson AG, Audo I. Congenital stationary night blindness: an analysis and update of genotype-phenotype correlations and pathogenic mechanisms. *Prog Retin Eye Res* 2015;45:58-110.
217. Koike C, Sanuki R, Miyata K, et al. The functional analysis of TRPM1 in retinal bipolar cells. *Neurosci Res* 2007;58:S41.
218. Kim DS, Ross SE, Trimarchi JM, et al. Identification of molecular markers of bipolar cells in the murine retina. *J Comp Neurol* 2008;507:1795-810.
219. Sandmeyer LS, Breaux CB, Archer S, et al. Clinical and electroretinographic characteristics of congenital stationary night blindness in the Appaloosa and the association with the leopard complex. *Vet Ophthalmol* 2007;10:368-75.
220. Nakamura M, Sanuki R, Yasuma TR, et al. TRPM1 mutations are associated with the complete form of congenital stationary night blindness. *Mol Vis* 2010;16:425-37.
221. Li Z, Sergouniotis PI, Michaelides M, et al. Recessive mutations of the gene TRPM1 abrogate ON bipolar cell

- function and cause complete congenital stationary night blindness in humans. *Am J Hum Genet* 2009;85:711-9.
222. Rodriguez-Galindo C, Orbach DB, VanderVeen D. Retinoblastoma. *Pediatr Clin North Am* 2015;62:201-23.
223. Balmer A, Zografos L, Munier F. Diagnosis and current management of retinoblastoma. *Oncogene* 2006;25:5341-9.

224. Mendoza PR, Grossniklaus HE. The Biology of Retinoblastoma. *Prog Mol Biol Transl Sci* 2015;134:503-16.
225. Dimaras H, Kimani K, Dimba EA, et al. Retinoblastoma. *Lancet* 2012;379:1436-46.

(English Language Editors: C. Mullens and J. Reynolds)

**Cite this article as:** Yang TJ, Yu Y, Yang JY, Li JJ, Zhu JY, Vieira JAC, Jiang Q. Involvement of transient receptor potential channels in ocular diseases: a narrative review. *Ann Transl Med* 2022;10(15):839. doi: 10.21037/atm-21-6145