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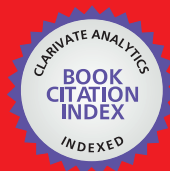
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Transient Receptor Potential (TRP) Channels in the Eye

Zan Pan¹, José E. Capó-Aponte^{2,3} and Peter S. Reinach³

¹Margaret Dyson Vision Institute,
Weill Cornell Medical College, New York, NY,

²Visual Sciences Branch,

U.S. Army Aeromedical Research Laboratory, Fort Rucker, AL,

³Department of Biological Science, State University of New York,
College of Optometry, New York, NY,

USA

1. Introduction

The first member of transient receptor potential (TRP) channel superfamily was discovered in photoreceptors of *Drosophila* over 30 years ago.¹ Since then this protein superfamily has been extensively characterized based on exponential increases in the number of publications related to TRP channels. With 28 TRP homologous genes identified in mammals, TRP channels have been detected in both neural and non-neural tissues.

In humans, 27 different TRP genes are classified into two groups and six different subfamilies based on their amino acid homology and phenotypes associated with mutant genes. The genes of TRP channel in Group 1 and Group 2 are only distantly related. The Group 1 of TRP genes are comprised of TRPC (canonical), TRPM (melastatin), TRPV (vanilloid) channel subfamilies, with TRPA (ankyrin) being more recently assigned to this group.² Such categorization is based on their resemblance to the amino acid sequence of the *Drosophila* TRP channel. The nomenclature of TRP channel genes in Group 2 is based on the human phenotypes generated by the mutation of the founding genes of each subfamily, including polycystic kinase disease (PKD) and mucopolipidosis type IV (MCOLN, mucolipin). Their encoded proteins have also been referred to as TRPP (polycystin) and TRPML (mucolipin), respectively (Figure 1).

The TRP superfamily is evolutionally conserved from nematodes to mammals.³ The common features of TRP channels are six putative transmembrane spanning domains and a cation-permeable pore formed by a short hydrophobic region between transmembrane domains 5 and 6. They are configured as homo- or hetero-tetramers to form non-selective cation channels (Figure 2). Their permeability ratios to $\text{Ca}^{2+}/\text{Na}^{+}$ vary significantly among individual members. TRPV5 and TRPV6 channels exhibit a $\text{Ca}^{2+}/\text{Na}^{+}$ permeability ratio of greater than 100, indicating high Ca^{2+} selectivity.⁴ In contrast, TRPM4 and TRPM5 channels are impermeable to Ca^{2+} but are selective for monovalent cations (Na^{+} , K^{+}).^{5, 6} Such intra-family variability is unique to the TRP channel superfamily whereas most other ion channel families have little difference in ionic permeability within a family.⁷

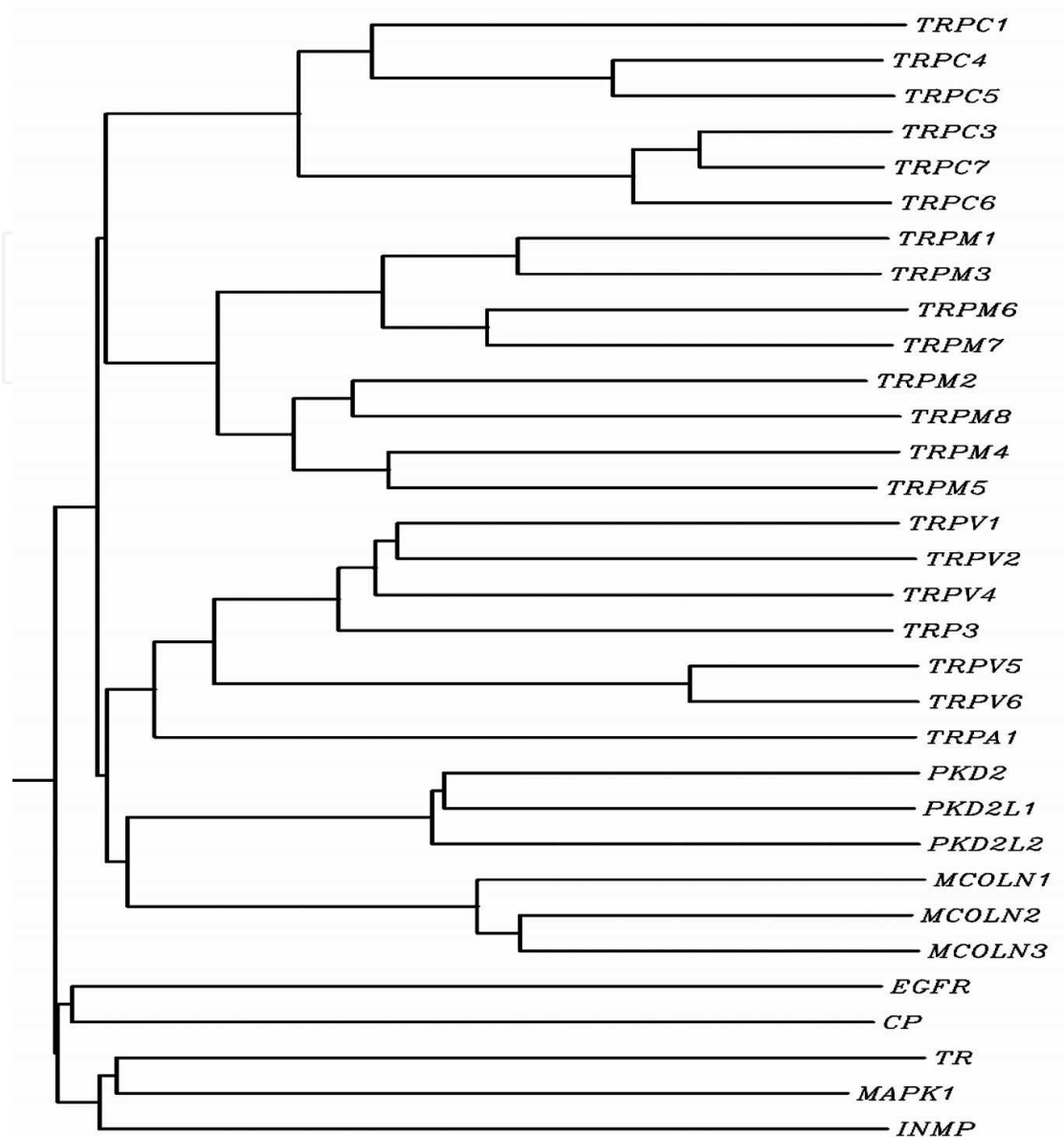


Fig. 1. Human TRP channel superfamily dendrogram. Random proteins bound to the plasma membrane (i.e., EGF receptor, EGFR), endoplasmic reticulum (i.e., calreticulin precursor, CP), mitochondria (thioredoxin reductase, TR), cytosolic protein (i.e., mitogen-activated protein kinase 1, MAPK1) and nuclear membrane (i.e., inner nuclear membrane protein, INMP) are shown to illustrate that PKD and MCOLN are evolutionarily related to TRP channels or are the results of convergent evolution. The dendrogram shows that PKD and MCOLN belong to the TRP channel superfamily, since random genes extend from branches distinct from the TRP channel superfamily.⁸

TRP channel subfamilies in Group 1 share substantial sequence homology in the transmembrane domain 6. What divides each subfamily is differences in their intracellular domains. TRPC, TRPV and TRPA channels contain ankyrin repeats near the intracellular N-terminal domain, whereas the TRPC and TRPM channels subfamilies possess proline-rich 'TRP domain' in the region of the C-terminal near the putative transmembrane segment. TRPM6 and TRPM7 channels have a protein kinase domain in the C-terminal.

The TRPC subfamily consists of seven genes (TRPC1-7) in mammals, but TRPC2 channel is a pseudogene in humans. TRPC channels are widely expressed in multiple systems. TRPC4, TRPC5, TRPC6 and TRPC7 channels are identified in the various ocular tissues of mammals.⁹⁻¹² The TRPM channel subfamily comprises eight genes (TRPM 1-8), of which three encode channel-like proteins and five non-channel proteins. TRPM1 channels are expressed in retinas and TRPM8 channels in corneas.^{13, 14} The TRPV channels subfamily contains six members (TRPV1-6). TRPV1, TRPV2, TRPV3 and TRPV4 channels are expressed in the cornea whereas TRPV1, TRPV2, TRPV5 and TRPV6 channels are expressed in the retina.¹⁵⁻²⁰ The TRPA channel subfamily has only one member, TRPA1.

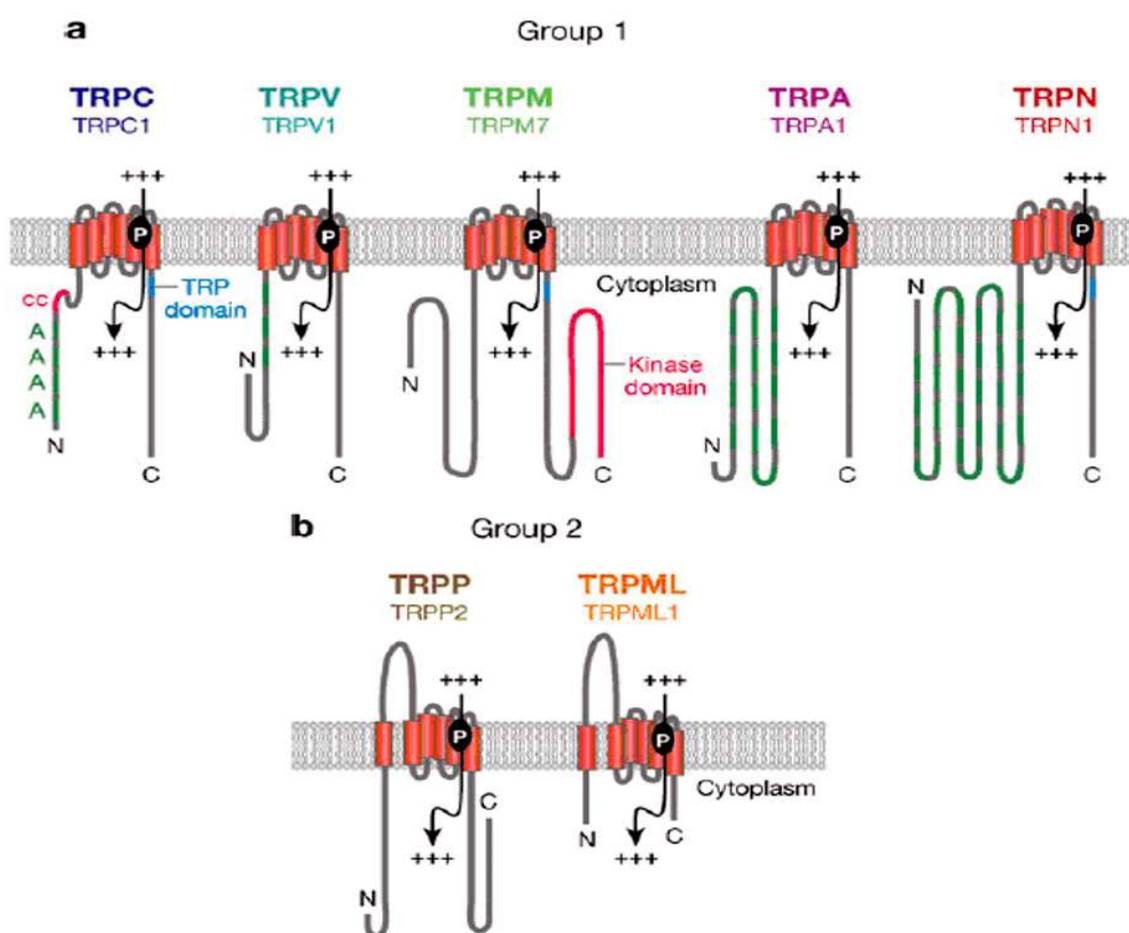


Fig. 2. Domain structure of the TRP channel superfamily. There are five TRP channel subfamilies in Group 1 (TRPN, no mechanoreceptor potential C channels are expressed in mammals) (a) and two TRP channel subfamilies in Group 2 (b). All subfamilies contain a six-transmembrane domain unit with a cation-permeable pore between domains 5 and 6. Four of such units are assembled as a homo- or hetero-tetramer to form a TRP channel. Domain indications: ankyrin repeats (A), coiled-coil domain (cc), protein kinase domain (TRPM6 and TRPM7 channels only), cation-permeable pore (P), transmembrane (TM) domain, cation-permeable (+++), TRP channels domain (TRPC and TRPM channels only), large extracellular loop between transmembrane domains 1 and 2 (TRPP and TRPML channels only). Adapted with permission from Venkatachalam and Montell.²¹

TRPP and TRPML channel subfamilies belong to Group 2. They contain limited sequence homology to TRP channels in Group 1, although such resemblance to classical TRP channels is still larger than those of random genes (e.g., EGFR, INMP) (Figure 1). TRPP channel proteins share 25 percent amino acid sequence homology to TRPC3 and TRPC6 channels over a region including transmembrane domains 4 and 5 and the hydrophobic pore loop between domains 5 and 6. TRPML channel proteins consist of three small proteins compared with other TRP channel proteins. Homology of their amino acid sequence with TRPC channels proteins is restricted to the region spanning transmembrane domains 4 to 6 (amino acids 331 to 521). TRP channels in Group 2 have a unique large extracellular loop between their first and second transmembrane domains. They are named as TRP channels based on the six transmembrane domains that they contain and function as cation-permeable channels.

The activation mechanisms of TRP channels are unique in that there are a diverse host of stimuli that can activate TRP channels and exhibit sharp differences in stimulatory modes even within each TRP channel subfamily. TRP channels were initially recognized as sensory mechanisms to a variety of stimuli, ranging from light, temperature, osmotic pressure, smell, taste, mechanical stress and acidity. There is also increasing awareness of their roles in mediating wound healing, inflammation, apoptosis and excretion. These channels are sensitive to intracellular and extracellular messengers, as well as declines in the calcium content of intracellular calcium stores (ICS).

Their activation following conformation changes modulates $\text{Ca}^{2+}/\text{Na}^{+}$ cell permeability ratios, which is dependent on TRP channel subunit composition. Transient increases in intracellular calcium concentration trigger intracellular activation of mediators including: 1) phospholipase C (PLC) by coupled GTP-binding protein, leading to stimulation of store-operated Ca^{2+} channels; 2) transactivation of EGF tyrosine receptors through MMP-mediated HB-EGF shedding.^{4, 10, 16} The physiological significance of TRP channel expression is indicated by the finding that TRP channel mutations are linked to human diseases.²²

There is compelling evidence that the TRP channel superfamily plays a critical role in ocular homeostasis and pathogenesis. Functional importances of TRP isotypes expressed in different ocular tissues are multi-faceted. Their activation is essential for retaining corneal deturgescence and clarity, mediating aqueous humor outflow through trabecular meshwork and ciliary body as well as inducing light sensation in retina. Mutation of TRP channels is associated with ocular pathological phenotypes either due to loss of its homeostatic role or over-activation of its function. The realization of the importance of TRP channel has prompted much research effort to investigate novel strategies for regulating TRP channels function in a number of ocular diseases.

2. Roles of TRP channels in corneal sensation and wound healing

Continuous renewal of corneal epithelial layer is essential to maintain corneal transparency. The intact epithelium not only offers a smooth and clear optical surface, but also provides corneal barrier function. This property protects the underlying stroma from swelling and pathogenic invasion. Should such protection become compromised by ocular surface diseases, outcomes can range from mild symptoms, such as irritation, photophobia, to severe consequences including corneal opacity, ulceration and even perforation. TRP

channel functions have been indicated to associate with maintaining corneal sensation and integrity. Corneas express ample collection of TRP channel isotypes in various mammals. There are TRPC1, TRPC3, TRPC4, TRPC6 and TRPC7 as well as TRPV1–4 channels in the corneal epithelium, TRPV1–4 in the corneal endothelium, TRPV1, TRPA1, and TRPM8 in the corneal nerves.^{10, 15-17, 23, 24, 25-27} These channels are involved in corneal regenerative, protective and sensory mechanisms.

TRPC4 channels protein is localized in plasma membranes of cultured human corneal epithelial cells (HCEC) and mediate epidermal growth factor (EGF)-promoted epithelial proliferation. They are activated by EGF-induced depletion of ICS content in the endoplasmic reticulum. This depletion occurs as a consequence of stimulation of PLC activity which results in increases in inositol 1,4,5-trisphosphate (IP₃) formation. This response leads to declines in ICS content and activation of TRPC4 store operated channel (SOC) function. Its activation induces intracellular Ca²⁺ influx leading to stimulation of downstream signalling cascades. They include the mitogen activated protein kinase (MAPK) cascade composed of ERK, JNK and p38 cassettes as well as protein kinase A (PKA), protein kinase C (PKC), JAK/STAT and PI3-K/AKT/GSK-3. All of their activations contribute to the control of increases in cell survival and proliferation elicited by EGF. The importance of TRPC4 channels activation to mediate EGF-induced mitogenic responses is indicated by the finding that knockdown of its gene expression in HCEC eliminated the mitogenic response to EGF.¹⁰

TRPV1 channel expression was first identified on the ophthalmic branch of the trigeminal nerve. More recently, the functional expression of this channel was also identified in the corneal epithelial and endothelial layers. A hallmark of its activity is that the vanilloid compounds (such as capsaicin isolated from hot chilli pepper), hyperosmolarity, acidity (pH below 6) and high temperatures (above 43°C) stimulate TRPV1 channels. In the mouse corneal epithelium, severe chemical injury to corneal epithelium induces TRPV1 channel activation leading to dysregulated inflammation, scarring and loss of corneal transparency. On the other hand, its activation stimulates in HCEC proliferation and migration through EGF receptor (EGFR) transactivation.²⁸ The involvement of TRPV1 channel activation in inducing these diverse responses is indicated by the finding that in homozygous TRPV1 knockout mice the wound healing response to an alkali burn does not result in losses of corneal transparency. Similarly, TRPV1 channel activation in some types of dry eye disease resulting from exposure to hyperosmolar tears may account for chronic inflammation since TRPV1 channels activation caused by exposure to a hyperosmolar challenge induced large increases in a host of proinflammatory cytokines (e.g., IL-6, IL-8, TNF α and IL-1 β) and chemoattractants (e.g., MCP-1) in HCEC. On the other hand, pre-exposure to a selective TRPV1 channel antagonist obviated all of these responses, suggesting that TRPV1 channels are potential drug target for the treatment of dry eye syndrome because suppression of its activation may reduce ocular surface inflammation.^{16, 23}

In contrast with TRPV1, its cohort, TRPV4 channel reacts to a different spectrum of stresses. Unlike TRPV1, which is thought to only be activated by a hyperosmolar stress, TRPV4 channels may instead be an osmosensor for a hypoosmolar challenge.¹⁷ Such a stress is encountered by the cornea during exposure to fresh water (e.g., swimming, bathing, use of some eye drops). This hypotonic exposure results initially in corneal epithelial swelling due to obligatory water influx in order to reach equilibration between the cell interior and

surface tears. However, excessive swelling can lead to cell lysis. To counter the initial swelling, corneal epithelial cells mediate regulatory volume decrease (RVD) behavior by stimulating volume-sensitive potassium and chloride channels as well as potassium-chloride co-transporter (KCC) activity to restore isotonic cell volume through osmotically coupled net fluid efflux.

TRPV1–4 channel isoforms also serve as thermosensors over defined temperature ranges in the corneal epithelium. In addition, TRPV3 channel activation, either by temperatures above 33°C or by its selective agonist, carvacrol, not only contributes to thermosensation, but also accelerates epithelial wound recovery by enhancing cell survival, proliferation and migration.^{15, 29} TRPV1–3 and TRPC4 channels are also expressed in corneal endothelial cells.^{9, 30} TRPV1–3 channels are sensitive to temperatures from 25 to 40°C, similar to their epithelial counterparts.

TRP channels play an important role in mediating corneal sensations. The cornea has the highest sensory nerve density of any tissue in the body. The corneal sensory nerves originate from the ophthalmic branch of the trigeminal ganglion and are responsible for eliciting nociception to thermal, chemical and mechanical stimuli.³¹ TRPV1 channels colocalize with substance P (SP) and calcitonin-gene-related peptide (CGRP) in the ophthalmic branch of the trigeminal nerve indicating their role in eliciting nociceptive perception. This realization makes TRPV1 channel tenable as a potential drug target for treating neurotrophic keratopathy.^{31, 32} Additionally, the TRPM8 channel contributes to corneal cold sensation and basal tear secretion required to maintain corneal surface hydration.^{14, 33}

Taken together, these studies on the corneal epithelial, endothelial cells and corneal nerves indicate that functional expression of TRP channels are essential for maintaining corneal transparency and eliciting adaptive responses to stresses. This indicates the importance of further studies on TRP channel regulation since such insight may lead to novel strategies for treating corneal diseases and better management of ocular surface inflammatory pain.

3. Roles of TRP channels in glaucoma

Some members of the TRPC and TRPV channel subfamilies are expressed in trabecular meshwork, ciliary muscle and retinal ganglion cells.^{34, 35} Their roles have been associated with regulating intraocular pressure through modulation of aqueous humor flows and ganglion cell survival. The trabecular meshwork contains contractile elements whose tension modulation changes fluid drainage rate from the anterior chamber into the Canal of Schlemm. The contractile state of trabecular meshwork is governed by tension imparted from the ciliary muscle and possibly trabecular meshwork itself.^{35, 36} The trabecular meshwork and the ciliary muscle act as functional antagonists. Such opposition is evident since ciliary muscle contraction leads to relaxation of the trabecular meshwork with subsequent increases in fluid outflow whereas trabecular meshwork contraction has the opposite effect.³⁵ Malfunction of trabecular meshwork and ciliary muscle contractility often leads to ocular hypertension and glaucoma.³⁷ Their contractile states are modulated by changes in intracellular Ca²⁺ concentration and Ca²⁺ channel activity. Specifically, increases in cytoplasmic Ca²⁺ resulting from the stimulation of TRP channels enhance contractility. Other types of Ca²⁺ channels that regulate intracellular Ca²⁺ concentration include L-type voltage-gated Ca²⁺ channels, receptor operated Ca²⁺ channels and store-operated calcium

entry (SOCE) pathways. In bovine trabecular meshwork cells, TRPC1 and TRPC4 channels are implicated in the formation of heteromeric SOCE channels which contribute to rises in cytoplasmic Ca^{2+} store and therefore trabecular meshwork contractility during exposure to bradykinin or endothelin-1.⁴

Similarly TRPC1, TRPC3, TRPC4 and TRPC6 channels are also present in ciliary muscle cells. The ciliary muscle is densely innervated by parasympathetic nerves that stimulate muscle contraction through acetylcholine-mediated muscarinic receptor stimulation on neighboring muscle cells. Such activation leads to a surge in intracellular Ca^{2+} concentration resulting in membrane voltage depolarization via receptor-operated non-selective cation channels. TRPC1, TRPC3, TRPC4 and TRPV6 channels are considered as potential candidates for such channels as they are co-localized with muscarinic receptor type 3 in ciliary muscle fibres.^{38,39}

Modulation of TRPC channel activity in turn alters aqueous humor outflow and therefore intraocular pressure through changes in trabecular meshwork contractility. The dual localization of TRPC channels on ciliary muscles and trabecular meshwork cells suggests that strategies targeted towards their selective modulation may prove to be advantageous in providing better control of intraocular pressure in patients with ocular hypertension or glaucoma. Such an outcome is possible once there is definitive identification of the TRP channels subtypes on each of these tissues. At this point, it may be possible to maximize fluid outflow rates by selectively decreasing trabecular meshwork resistance through a decrease in its contractile state. Accordingly, additional studies are needed to map the TRP channels subtypes and characterize their mechanisms of regulation in the ciliary muscle and trabecular meshwork.

Chronic intraocular hypertension is a risk factor which in some cases can induce glaucoma due to damage to retinal ganglion cells. Such damage can result from either increased hydrostatic pressure, declines in retrograde neurotrophin flow, ischemic or oxidative stress. Irreversible loss of retinal ganglion cells leads to gradual and often insidious vision impairment and possible blindness. Elevated intraocular pressures can activate TRP channels in retinal ganglion cells. TRP channel sensitivity to hydrostatic pressure has been described in the bladder, lungs and skin.⁴⁰⁻⁴² Sappington et al. showed *in vitro* that exposure of retinal ganglion cells to elevated hydrostatic pressure induced transient rises of intracellular Ca^{2+} accumulation due to TRPV1 channel activation. This effect promoted apoptosis of retinal ganglion cells whereas suppression of TRPV1 channel activation protected retinal ganglion cells from pressure-induced death.³⁴ Recently, similar stresses were identified to stimulate TRPV4 channel and induce apoptosis in retinal ganglion cells.⁴³ The increased levels of cytoplasmic Ca^{2+} are the underlying mechanism leading to retinal ganglion cells apoptosis.⁴⁴ Ca^{2+} -dependent calcineurin and calpain are a phosphatase and a protease, respectively, that trigger apoptosis signalling. Both of them induce cytochrome c release from mitochondria and trigger pro-apoptotic signalling. In contrast, the TRPV1 channel in the retinal microglia appears to have a retinoprotective effect. Retina microglia cells are essential to neuronal homeostasis and provide innate immunity for retina to defend against pathogenic infiltration. Exposure of microglia to chronic stress is associated with various neurodegenerative diseases, including retinal dystrophies. TRPV1 channel activation in the cultured retinal microglia cells by hydrostatic pressure induces increases in IL-6 and TNF- α release through transient rises in intracellular Ca^{2+} levels. Rises in IL-6 suppress pro-apoptotic signalling pathways and cell

death.⁴⁵ Therefore, provided strategies can be devised to selectively induce increases in microglial TRPV1 channels expression, TRPV1 channels may be a potential drug target in managing pressure-induced retinal ganglion cell loss in glaucoma.

4. Possible roles of TRP channels in cataract development

Maintenance of intracellular Ca^{2+} levels is imperative to crystalline lens clarity.⁴⁶ Lenses with cortical cataracts have intracellular Ca^{2+} levels that are above those in the physiological range.⁴⁷ Accordingly, a better understanding of the mechanisms mediating control of lens intracellular Ca^{2+} levels is pertinent for identifying economical and novel drug strategies to preserve lens transparency or slow cataract progression.

As previously described, store-operated calcium entry (SOCE) channels are composed of TRP subunits and are heterogeneously expressed in the lens epithelial cells. Epithelial cells in the lens equatorial region have higher SOCE expression than that in the central anterior region. This difference is attributable to the fact that the size of the intracellular calcium storage is larger in the equatorial than the central anterior epithelial cells.⁴⁸ The higher intracellular Ca^{2+} load in the equatorial epithelium is required for its more rapid proliferative rate than other parts of the lens epithelium. However, the equatorial epithelium is more susceptible to damage that can induce cortical cataracts since the development of such cataracts is associated with Ca^{2+} overload in the lens epithelial cells. The identity of the TRP channels isoforms constituting SOCE channels is elusive since drugs that modulate SOCE channels activity have poor selectivity for each of the different TRP subunits in the TRPV and TRPC channel subfamilies. For example, the inhibitory effects of lanthanum are used as a criterion to distinguish between SOCE and TRPC channel involvement in the development of cataract. At lower concentrations (i.e., in the nanomolar range), lanthanum inhibits SOCE channels, whereas at higher concentrations it blocks TRPC-containing channels.^{49, 50} However, this approach is problematic because a cut-off between lanthanum concentration ranges having the inhibitory effect on either SOCE or TRPC channel is poorly defined. Another complication is that, in the micromolar range, Ca^{2+} influx is potentiated through TRPC4- and TRPC5-containing pathways. Nevertheless, the current understanding is that SOCE channels are the major pathway for Ca^{2+} influx in the lens. Better insight into the specific involvement of TRP channels dysfunction in cataractogenesis will be clarified once either more selective Ca^{2+} channel modulators become available or genetic approaches are employed to selectively modulate levels of TRP channel isoform expression.

5. Roles of TRP channels in retinopathy

TRP channels are abundantly expressed in the entire retinal layer including the retinal pigment epithelium (RPE), photoreceptors, retinal ganglion cells, Müller cells, and microglia. Initially, TRP channel-mediated phototransduction was identified in *Drosophila* and 13 of the known 28 homologues of the mutant insect channels were next identified in the mammalian retina.⁵¹ For example, the TRPC channels in mammals are most closely related to the *Drosophila* TRP channels. The difference is that in mammals the six TRPC subfamily genes (i.e., *trpc* 1, 3–7) encode seven proteins (TRPC1–7 channels), since TRPC2 is a pseudogene.

In *Drosophila* retinal photoreceptors, TRPC channels lead to photoexcitation. Light absorption converts rhodopsin to active metarhodopsin, which activates PLC. PLC hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP₂) to IP₃ and diacylglycerol (DAG). DAG can be degraded to release polyunsaturated fatty acids and protons. TRPC channel activation occurs as a consequence of phosphoinositide depletion and acidification resulting from PLC-induced PIP₂ hydrolysis and proton release associated with IP₃ formation.³⁴ TRPC channel activation by phosphoinositide metabolites suggests that these channels are part of the light-sensing mechanism for *Drosophila*, but their role in humans is still unclear.

TRP channel dysfunction has been implicated in mammalian retinopathy. Mutation of TRPM1 channels in ON bipolar cells has been linked to autosomal-recessive congenital stationary night blindness (CSNB), a heterogeneous group of retinal disorders characterized by non-progressive impaired night vision and variable decreased visual acuity.⁵² On the other hand, Wang et al. reported that TRPC6 channel activation has a neuroprotective effect on retinal ischemia-reperfusion (IR) injury in the rat.⁵³ Following IR, the expression of TRPC6 channels decreases in retinal ganglion cells. Activation of TRPC6 channels before IR reduces retinal ganglion cell losses whereas suppression of TRPC6 channels has an opposite effect. Such protection by TRPC6 channels of retinal ganglion cells is dependent on brain-derived neurotrophic factor (BDNF) signalling.

The RPE layer has essential roles in sustaining normal retinal function. It regulates the hydration and ionic composition of the subretinal space, as well as rod outer segment function. RPE also secretes cytokines that are essential for retinal health. TRPV5 and TRPV6 expressions were identified *in vitro* in the human RPE, implicating that these two most calcium-selective channels of the TRP channel superfamily contribute to the regulation of the subretinal space calcium composition accompanying light/dark transitions.¹⁹ TRPV2 channels were shown in another study to control RPE release of vascular endothelial growth factor (VEGF). Insulin-like growth factor-1 (IGF-1) is a TRPV2 channel activator that selectively induces the intracellular Ca²⁺ transients required for inducing VEGF release. Control of this response is needed to reduce retinal neovascularization, since wet age-related macular degeneration (AMD) is decreased or stabilized by treatment with anti-VEGF antibodies. These results suggest that reducing TRPV2 channels activity may provide another option for managing wet AMD.⁵⁴

6. Summary

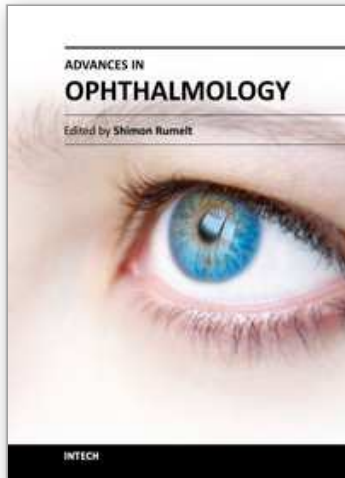
TRP channels are involved in ocular sensory and cellular functions. In mammals, TRP channel subunit proteins are encoded by 27 genes and are classified into two groups and six different subfamilies, based on differences in amino acid sequence homology. Group 1 and Group 2 of TRP channels are only remotely related, but share similar cation channel-forming structures of six transmembrane domains. Their cation selectivity and activation mechanisms are very diverse and depend on individual TRP channel. TRP channel activation induces a host of responses to variations in ambient temperature, pressure, osmolarity and pH. In addition, their activation by injury induces inflammation, neovascularization, pain and cell death, as well as wound healing. There is emerging interest in characterizing their roles in inducing ocular surface disease, glaucoma, cataracts and retinopathy. Such efforts could lead to the identification of novel drug targets for improving management of many ocular diseases.

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This book focuses on the different aspects of ophthalmology - the medical science of diagnosis and treatment of eye disorders. Ophthalmology is divided into various clinical subspecialties, such as cornea, cataract, glaucoma, uveitis, retina, neuro-ophthalmology, pediatric ophthalmology, oncology, pathology, and oculoplastics. This book incorporates new developments as well as future perspectives in ophthalmology and is a balanced product between covering a wide range of diseases and expedited publication. It is intended to be the appetizer for other books to follow. Ophthalmologists, researchers, specialists, trainees, and general practitioners with an interest in ophthalmology will find this book interesting and useful.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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