Transient receptor potential ion channel family has come on to the front stage in the eye research field

In recent years, biomedical researchers and clinicians have been working more closely together to identify novel drug treatment strategies to selectively inhibit growth factor expression levels such as epidermal growth factor, transforming growth factor β, and vascular endothelial growth factor (VEGF). The efforts targeting VEGF are a proven great success. This outcome stems from developing anti-VEGF (anti-VEGF) antibodies which inhibit the VEGF-induced neovascularization, which in turn, slows down the growth of malignant tumors. In the ophthalmic field, blocking VEGF access to their cognate receptors is an established gold standard treatment of age-related macular degeneration (AMD) and other neovascular ocular diseases.

One of the other successful outcomes of searching for novel drug targets started with the reported cloning in 1997 of the mammalian homologs of the Drosophila transient receptor potential (TRP) channel. Subsequently, it was discovered that other members of the TRP channel superfamily serve as thermo-sensitive transducers. This superfamily is composed of 27 different mammalian channel subtypes divided into seven different subfamilies. TRPV1 is the archetype channel of this TRP superfamily. It is also referred to as the capsacin receptor because capsacin is a selective agonist of this nonselective ion channel. Many of these TRP channels are activated by environmental stresses and ultimately induce responses, which contribute to the maintenance of tissue homeostasis. The external stimuli of the different TRP members are polymodal. They include specific ligands, alteration of pH, osmotic stress, and biomechanical stresses. TRP channel activation leads to transient rises in intracellular calcium levels which trigger the activation of linked signal pathway cascades that stimulate responses that affect the tissue homeostasis.

Recent reports describe important roles played by TRP ion channels in inducing the pathophysiology of ocular disorders. They are critical to modulating functions of both nerve and non-nerve cells. There is accumulating evidence that controlling TRP channel activity is a potential therapeutic option for improving the treatment of a number of ocular diseases in animal models. These studies suggest that it will be worthwhile to determine if they can be translated to treating and even curing a number of different human diseases in future.

Cornea

Normal vision is critically dependent on the maintenance of corneal transparency, a regular curvature, and a smooth optical surface. These properties depend on the preservation of its structural integrity and functional activity of its three component tissue layers: epithelium, stroma, and endothelium. Severe corneal injury can induce critical inflammation followed by permanent scarring both of which drastically reduce the visual performance. A number of different TRP channel subtypes are expressed in the different resident corneal cell types and also on corneal...
sensory nerve endings. Their activation by noxious environmental stresses induces a host of different cellular responses. For example, epithelial cells sense and respond to either an increase or a decrease in the osmolarity of the tear fluid which may be involved in the pathobiology of dry eye disease. Moreover, some of the family TRP members modulate both inflammation and wound healing responses to tissue damage. For example, inhibition of a specific TRP channel subtype or its gene ablation suppresses excess inflammation neovascularization and fibrosis in a disease model in mice. These findings strongly suggest that TRP member subtypes could be drug targets for treating ocular surface disorders resulting from inflammatory fibrosis.

TRP channel family members are also known to have important roles in supporting sensory nerve functions. For example, the trigeminal nerve sensory function is critical for the maintenance of the tissue integrity of the cornea. Damage to this nerve impairs wound healing of the corneal epithelium. Among the TRP family members, trigeminal nerve TRPV4 function is reportedly critical to the maintenance of limbal epithelial stem cell turnover during epithelial repair in a mouse cornea. Its involvement in this process suggests that selective TRPV4 activation might be viable treatment to hasten epithelial wound healing in neurotrophic keratopathy.

**Lens**

Lens epithelial cells express TRP channel subtypes. Moreover, it is well known that TRPV1 activation induces increases in lens epithelial cell proliferation. Injury-induced TRP channel activation of remnant lens and capsular epithelial cells increases their proliferation and epithelial–mesenchymal transition (EMT) following cataract surgery. These responses to injury are the main causes of lens implant opacification. Promotion of the EMT transition results in the upregulation of contractile proteins and secretion of excess extracellular matrix components by the myofibroblasts, which also contributes to obstruction of normal vision. On the other hand, in the lungs, countering disease-induced TRPV4 activation suppresses the EMT-related tissue fibrosis. This result points to the possibility that blocking lens epithelial capsular TRPV4 activation before performing cataract surgery could be a treatment option to prevent remnant epithelial cells from undergoing EMT and inducing fibrosis. This possibility warrants testing since it could prevent the postcapsular lens opacification.

**Glaucoma**

Impairment of the drainage of the aqueous fluid from the anterior chamber is the main cause of the open-angle glaucoma. Aqueous humor is secreted by the pigmented and nonpigmented interconnected coupled epithelial layers in the ciliary body. TRPV2 and TRPV4 are the most abundantly expressed TRP channel subtypes in the ciliary body. Signaling cascades activated by these two transient receptor potential channel (TRPV) subtypes is speculated to be involved in mediating control of aqueous humor production. On the other hand, mechanosensitive TRP channels including TRPV4 are reportedly potential targets for facilitating aqueous humor drainage through the trabecular meshwork. This possible because TRPV4-dependent cytoskeletal remodeling regulates the stiffness of trabecular meshwork and aqueous humor outflow. Moreover, mechanosensitive TRP channels expressed in trigeminal nerve endings on the inner walls of the ocular globe are reportedly involved in monitoring intraocular pressure.

**Retinal Angiogenesis and Macular Edema**

Currently, anti-VEGF agents followed by corticosteroids are the most important drug classes used to treat diabetic macular edema. Anti-VEGF agents attenuate neovascularization in patients with diabetes mellitus of premature retinopathy. Vascular endothelial cells also express TRP channel family subtypes. Although the roles of each subtype are still under investigation, experimental findings suggest that selective pharmacological blocking of the function of each subtype could be beneficial in the treatment of retinal diseases. This proposal is consistent with other studies showing that gene deletion or pharmacological blocking of the TRPV4/TRPA1 duplex suppresses the development of oxygen-induced angiogenic retinopathy in mice. Therefore, there is evidence that TRPV4/TRPA1 is potential targets for therapeutic intervention in vasoproliferative diseases of the retina.

TRPV4 is reportedly involved in maintaining the barrier function-related ultrastructure of matrix keratinocytes. Leakage of the blood plasma components based on losses in cell–cell junctional continuity in the vascular endothelium and also retinal hydro-mineral homeostasis imbalance causes diabetic macular edema. TRPV4 gene knockout or systemic pharmacological inhibition of TRPV4 function prevents the development of macular edema in diabetic animals. Overall, these reports show that selective blocking of different TRP ion channel subtypes is a promising alternative to treat diabetic retinopathy and other retinal angiogenic disorders.

**Neurodegenerative Disorders**

Many different TRP subtypes are expressed in the neural components of the central and peripheral nervous systems. TRPV4 has also been implicated in mediating neuronal degeneration in the retinal and other nervous
systems. This conclusion is supported by results showing that pharmacological inhibition of TRPV4 activation supports ganglion cell survival and suppresses gliosis in the retina and maintains the retinal laminar architecture. This indicates that TRPV4 signaling plays an important role in the pathophysiology underlying retinal degeneration in a disease model. Therefore, TRPV4 could be a relevant pharmaceutical target for the treatment of retinal degenerative disease.

**Choroidal Neovascularization**

Choroidal neovascularization (CNV) secondary to AMD accounts for most cases of AMD-related severe vision loss. Recent reports identified infiltrating activated macrophages as an important pathophysiological change inducing CNV development. This means that a network of numerous different growth factors/cytokines might underlie this disease process. Anti-VEGF agents are currently the therapeutic gold-standard. However, there are remaining numerous unexplored options related to modulating different TRP-linked signaling cascades, which modulate through cross talk other growth factors/cytokines receptor-linked signaling pathways.

As described above, TRP-linked pathway signaling is involved in inflammation control. Therefore, pharmacological inhibition of TRP channel receptor-linked signaling could be a viable option for suppressing CNV.

**Malignant Neoplasia**

Increases in the proliferation of neoplastic cells in a malignant tumor are modulated by a network of different growth factors. Neovascularization is also required for tumor expansion. Moreover, local invasion of cancer cells into both the surrounding tissue and the lumen of lymphatic and blood vessels is a critical determinant in tumor metastasis. Tumor cell metastasis is also dependent on the degree of EMT and their acquisition of migratory ability. Recently, there are reports supporting critical roles for TRP channel subtypes in inducing signaling activation that increases both tumor cell proliferation and EMT-related cell migration. Thus, it appears that changes in TRP channel activity appear to modulate responses that underlie tumor cell malignancy. This realization ought to promote studies that characterize the contribution of each TRP channel subtype in mediating through cross talk with growth factor and cytokine receptor control of tumor cell proliferation and migration. The insight gained may delineate novel treatment targets for suppressing this devastating disease.

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**Conflicts of interest**

The author declares that there are no conflicts of interests of this paper.

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