

THE TRABECULAR MESHWORK AND ROCK INHIBITORS

Reviewing the mechanisms behind one of the newest classes of glaucoma drugs.



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The majority of glaucoma medications control IOP by three main mechanisms: (1) increasing aqueous humor (AH) outflow via the trabecular meshwork (TM) pathway, (2) increasing AH outflow via the uveoscleral outflow pathway, or (3) decreasing the production of AH. The TM pathway is believed to be responsible for approximately 85% of aqueous outflow.¹ For the most common form of glaucoma, primary open-angle glaucoma (POAG), the pathology underlying increased IOP resides in the TM.² However, prior to the relatively recent development of Rho kinase (ROCK) inhibitors, few glaucoma drugs have targeted this important pathway. In fact, ROCK inhibitors such as netarsudil (Rhopressa, Aerie Pharmaceuticals) are the first to target the TM to increase aqueous outflow since the development of pilocarpine in the 1870s. A review of what is known about how current ROCK inhibitors work suggests possible therapeutic advances for the future.

THE TM PATHWAY

The TM consists of a cellular network surrounded by an extracellular matrix (ECM). AH outflow through the TM begins at the corneoscleral TM, flows to the juxtacanalicular TM, and passes into Schlemm canal before entering the episcleral venous system. ROCK inhibitors have multiple mechanisms of action when it comes to glaucoma management, including modulating the cells responsible for TM outflow resistance and targeting ECM-cell interaction. They may also decrease episcleral venous pressure, decrease reactive oxidative species formation, increase optic nerve head vasodilation, exhibit neuroprotective effects, and decrease fibrotic action.³⁻⁵

GTPASES

In order to understand ROCK inhibitors, one must first understand the mechanism behind GTPases,⁶ a large family of molecules to which the Rho proteins belong. The protein members of the GTPase family are involved in several complex cellular processes. A GTPase is *on* or *active* when bound to

GTP and *off* or *inactive* when bound to GDP. When bound to GTP, a GTPase can bind to an effector molecule, thereby transmitting a signal within the cell. The interaction with the effector leads to the hydrolyzation of the bound GTP to GDP, turning the GTPase off. The GTPase can then be reactivated by interaction with a guanine nucleotide exchange factor that promotes the replacement of the bound GDP with GTP. Due to their *on* and *off* forms, the GTPases are sometimes referred to as *molecular switches*.

Similarly, Rho is activated by the binding of GTP, causing its interaction with one of several dozen effector proteins, including the extensively studied ROCKs. Activation of GTP-bound Rho leads to the activation of ROCK, which, in turn, leads to downstream phosphorylation of various substrates, including myosin light chain phosphatase and LIM kinase.³ ROCK molecules are expressed in all cellular tissues, although the degree of expression may vary among tissues. The ROCK

AT A GLANCE

- For the most common form of glaucoma, primary open-angle glaucoma, the pathology underlying increased IOP resides in the trabecular meshwork.
- Rho kinase inhibitors such as netarsudil are the first to target the trabecular meshwork to increase aqueous outflow since the development of pilocarpine in the 1870s.
- Selective ROCK inhibitors are in development, and technologies to make drug delivery more precise and controlled are under investigation.

signaling pathway is involved in several cellular events, including cell adhesion, migration, differentiation, proliferation, and apoptosis.

ROCK AND THE TM

ROCK signaling has been identified as an important regulator of TM outflow. It is well known that the TM exhibits smooth muscle-like properties due to expression of both actin and myosin.^{7,8} ROCK has been shown to sensitize smooth muscle in a calcium-independent manner.⁹ Similarly, ROCK leads to contraction of the TM via phosphorylation of myosin light chain and LIM kinase/cofilin pathways, resulting in formation of actin stress fibers and increasing outflow resistance.^{4,10} ROCK inhibitors, on the other hand, decrease the density of actin stress fibers, causing TM cells to relax. Intercellular space subsequently increases and disrupts focal adhesions in the TM and the inner wall endothelial lining of Schlemm canal, thereby increasing AH outflow and decreasing IOP.

Investigators have shown that increasing ECM production leads to elevated IOP.¹¹ ROCK inhibitors have been shown to decrease ECM synthesis and possibly long-term ECM remodeling, thereby reducing IOP.³ Recent human studies using Schiotz tonography have shown that ROCK inhibitors reduced episcleral venous pressure, a finding that suggests these drugs also work on the distal outflow system of the TM pathway.¹² Additionally, ROCK signaling leads to an increase in reactive oxygen species in the TM, and ROCK inhibitors have been shown to suppress this mechanism by increasing the expression of catalase.¹³

ROCK inhibitors have been shown to increase blood flow to the optic nerve by vasodilation.¹⁴ They may therefore slow the progression of glaucomatous optic neuropathy not only by lowering IOP but also by working directly on optic nerve blood vessels. Additionally, ROCK inhibitors may have neuroprotective effects, as they have been shown to promote retinal ganglion cell survival and optic nerve axon regeneration after optic nerve damage in animal models.¹⁵

Another way these drugs may aid in treating glaucoma is as antifibrotic agents in glaucoma surgery. Experiments have shown a reduction in subconjunctival scarring after filtration surgery involving the topical application of ROCK inhibitors in rabbits.¹⁶ Further studies in humans are required to determine efficacy and optimal dosage.

CONCLUSION

Additional work is required to further elucidate how ROCK signaling is regulated and to understand the mechanisms behind ROCK dysregulation in glaucoma. Moving forward, one notable issue is the need for selective ROCK inhibitors. Considering ROCK inhibitors' extensive roles in cellular function, increasing the concentration of a nonspecific ROCK inhibitor could have undesirable side effects. For example, one drawback to ROCK inhibitors is that they induce conjunctival hyperemia. Extensive dilation of conjunctival microvasculature may

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decrease the effect of concomitantly administered topical drugs by rapidly increasing clearance to the systemic circulation.¹⁷

Selective ROCK inhibitors are in development,¹⁸ and technologies to make drug delivery more precise and controlled are under investigation.¹⁹ Further study of the multitude of biochemical systems taking place inside the eye is required to optimize glaucoma treatment. ■

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