More than 100 years ago, the treatment of glaucoma was among the most advanced of ophthalmology disciplines, encompassing both specific medical therapy (pilocarpine) and surgical therapy (filtration). At that time, there were no specific treatments for retinal or corneal disease, and primitive techniques, such as couching, were being used for cataract surgery. A century later, however, the understanding of glaucoma and therapy for the disease seems to lag behind those in almost all other ophthalmology disciplines.

Open-angle glaucoma is, in general, a disease of two tissues: the trabecular meshwork/Schlemm’s canal conventional outflow system, which is responsible for intraocular pressure elevation, and the ganglion cells/axons/optic nerve complex, which is responsible for the visual loss in glaucoma. Yet, there are no truly effective therapies for either of these two diseased tissues. For example, prostaglandins target primarily the uveoscleral outflow pathway, and β-blockers decrease inflow, acting at the ciliary body. Although pilocarpine and similar “miotic” drugs can increase outflow, their effects are primarily on the ciliary muscle, increasing tension in the trabecular meshwork.

That is, there is no direct intrinsic effect on the conventional outflow pathway tissue. Although epinephrine-like compounds can increase conventional outflow facility, its multiple effects on intraocular pressure are complex, and there are many nonresponder patients. Such compounds are no longer used to treat glaucoma. Rho kinase inhibitors are under study as novel drugs that target the conventional outflow pathway.

A fundamental tenet of medicine is to identify diseased tissues and target them for specific therapy. Unfortunately, in almost all forms of open-angle glaucoma, the true pathogenic mechanism in either tissue is not understood, and therefore no true disease targets for drugs have been identified.

To make matters worse, early glaucoma is not detectable. Further, although intraocular pressure is a very accurate measurement at one time point, a patient’s integrated mean intraocular pressure (the equivalent of glycated hemoglobin in diabetes) between patient visits is unknown. Finally, despite multiple methods and new technologies, progression of early glaucoma is not detectable with certainty.

Primary open-angle glaucoma (POAG) is a diagnosis of exclusion, rendered when a physician looks into the eyes of a patient with typically somewhat symmetrical bilateral disease and observes no specific abnormalities (e.g., no pigment accumulation or exfoliation). Most likely, there are also multiple subtypes of POAG, each with its own genetic and environmental components. After all, it usually takes decades to develop POAG, yet no subcategories have been established for what are likely multiple subtypes.

Taking all these factors into account, a new paradigm shift is needed in therapy for glaucoma, from one of palliation to one of prevention and restoration. New advances in detection and treatment as outlined in the subsequent sections have the potential to bring about this shift.

References

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