Progress in the Genetics of Retinal Disease

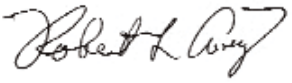
Despite remarkable advances in the treatment of neovascular age-related macular degeneration (AMD), which have been made possible by the widespread use of antivascular endothelial growth factor (VEGF) agents, we have limited treatment options to offer patients with nonexudative AMD or other forms of retinal degeneration. Fortunately, great strides are being made in the understanding, characterization, and now treatment of retinal diseases with a genetic cause. Therefore, in this edition we focus on the genetics of retinal diseases.

Rando Allikmets, PhD, provides us with an overview of the role of genetics in the development of AMD, and in particular how this relates to complement factor H. Stephen H. Tsang, MD, PhD, and colleagues review the retinal dystrophies and the genes that are presumed to cause them. Albert M. Maguire, MD, updates his and his colleagues' work using gene therapy to treat Leber congenital amaurosis (LCA), a group of devastating inherited eye diseases causing profound visual loss in childhood often progressing to complete blindness in early adulthood. This seminal work, along with that of James Bainbridge, PhD, FRCOphth, and colleagues, was recently published in the *New England Journal of Medicine*. Each group injected subretinal adeno-associated virus vector containing replacement gene therapy into three human patients with LCA2—a type of LCA caused by a specific mutation in a gene that encodes a protein necessary for retinal pigment epithelial cell function. All three of Dr. Maguire's patients demonstrated objective signs of improvement in the pupillary response to light, as well as subjective increases in visual acuity and visual field testing. Although none of Dr. Bainbridge's three patients demonstrated improvement in visual acuity, one showed improvement in microperimetry. All six patients seemed to tolerate the gene therapy well, with no adverse events directly related to the adeno-associated viral vector itself. One patient, however, developed a macular hole, which could have been related to the surgical procedure.

EARLY DATA ARE PROMISING

These studies are of tremendous importance, not only because they address the needs of patients with this rare disease, but because they also represent the first demonstrations of successful in vivo gene therapy in humans. The eye is ideally suited for this type of therapy given its relative isolation from the rest of the body and our ability to observe and measure responses in a noninvasive fashion. Furthermore, the increased wealth of knowledge about the genetic basis of so many retinal diseases opens the door for the potential treatment of many other patients. One caveat: Although LCA is ideally suited to this therapy given that the affected cells typically survive, the cells do not function normally, even in late stages of the disease. Therefore, it is probably easier to rescue these cells by providing the deficient gene than it would be to attempt to utilize this therapy in other diseases that manifest themselves via cell loss. Furthermore, these results are preliminary, and are from only a few patients. Encouragingly, in the animal model of LCA2, the effects of a single gene therapy treatment have been shown to last at least 7 years. Obviously further follow-up in humans is necessary, but these preliminary data are quite exciting and will hopefully herald the beginning of new therapeutic options for the treatment of numerous retinal diseases.

One final note: please look for the Eyetube logo in the *Table of Contents* in this issue. The Eyetube logo indicates that there is video associated with the article on www.eyetube.net, an ophthalmic video resource provided by the publishers of *Retina Today*, Bryn Mawr Communications. ■



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