Gene Therapy for Oxidative Damage to the Retina and Optic Nerve

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Reactive Oxygen Species (ROS) have been implicated in the pathogenesis of several eye diseases including diabetic retinopathy and age related macular degeneration (AMD). We have been using Adeno-associated virus to transfer genes that might be therapeutic for some of these conditions. One of the hereditary diseases affecting vision is Leber Hereditary Optic Neuropathy (LHON), which is caused by mutations in mitochondrial DNA. We have created a mouse model of LHON by constructing a nuclear version of the mutant mitochondrial gene ND4 coupled to an import sequence for mitochondrial proteins. When delivered to the retinal ganglion cells, this gene leads to hallmarks of the human disease: death of retinal ganglion cells, thinning and demyelination of the optic nerve, invasion of inflammatory cells. When eyes treated with the mutant gene are also treated with the gene for manganese superoxide dismutase, this damage was severely reduced. Reactive oxygen species are also implicated in the acquired disease, age related macular degeneration. It has been suspected that oxidative damage to the retinal pigment epithelium initiates an inflammatory process resulting in the breakdown of Bruch's membrane separating the retina from the choriocapillaris, which provides nutrients to the back of the eye. We asked if ROS also play a role late in the process-once Bruch's membrane has already been breached. For this, we used laser induced injury to Bruch's membrane and measured choroidal neovascularization—the spread of blood vessels from the choroid into the retina. AAV-mediated delivery of a small hairpin RNA targeting a subunit of NADPH oxidase, an enzyme that generated superoxide radicals, reduced or eliminated choroidal neovascularization in this mouse model. We conclude that ROS mediated signaling stimulates pathogenic neovascularization in the "wet" form of AMD, and that this pathway can be blocked by gene therapy.