Role of Mitochondrial Dysfunction in Dry Age-Related Macular Degeneration

The site of intracellular metabolism may be a relevant drug target in dry AMD.

BY SCOTT W. COUSINS, MD

Age-related macular degeneration (AMD) accounts for 54% of all blindness in Americans of European ancestry, as well as 5% of all blindness globally.[1] It affects 30% of people over the age of 65 and is the most common cause of blindness in the elderly.[2] The prevalence of AMD was estimated to be 6.5% in the 2005-2008 National Health and Nutrition Examination Survey.[3] AMD costs the United States more than $51 billion a year in medical expenses and lost worker productivity,[4] as reflected by research data associated with disability in instrumental activities of daily living.[5] The incidence of AMD in this country is expected to grow from 11 million today to approximately 22 million by 2050.[6]

AMD is a progressive degenerative disorder of the macula in which central vision becomes impaired.[7] There are two subtypes of AMD: early and late. Early AMD is characterized by moderate to severe lipid-rich, sub–retinal pigment epithelium (RPE) deposits (ie, drusen) and pigment abnormalities. Late-stage AMD is often subdivided into geographic atrophy (degenerative loss of the photoreceptors, RPE, and choriocapillaris) and neovascular AMD (subretinal invasion of pathologic new vessels).

The drusen and geographic atrophy stages of AMD are collectively termed dry AMD, and this entity presents a considerable challenge for the vision community because the etiology has not been clearly resolved.[8] The pathogenesis of dry AMD is multifactorial, and it includes aging,[3,9] genetic abnormalities,[10] systemic health,[9,11] environmental risk factors (including cigarette smoking),[12] and mitochondrial dysfunction.[13,14] Currently, no treatment is available for dry AMD, nor, more important, is there any known treatment that causes the regression of drusen or prevents their progression to geographic atrophy.

A NEW PARADIGM FOR DRY AMD PATHOGENESIS

Mitochondrial Dysfunction Induced by Environmental Toxicants

Multiple paradigms have been proposed for the pathogenesis of early AMD or, more broadly, dry AMD, including genetic susceptibility interacting with environmental

At a Glance

- Mitochondrial dysfunction induced by environmental toxicants may be an important risk factor in the etiology of dry age-related macular degeneration (AMD).
- In laboratory models, a novel mitochondrial protective compound targeting mitochondria in the retinal pigment epithelium appears to prevent dysfunction that might be a causative factor in AMD.

and systemic health factors. We propose that mitochondrial dysfunction induced by environmental toxicants is a fundamental risk factor for, and a hypothesis for, the etiology of dry AMD.

Role of Mitochondria in Health and Disease

Mitochondria are intracellular organelles necessary for cell function and survival—including the cells of the RPE. They are crucial for the synthesis of adenosine triphosphate (ATP), the major form of cellular energy. Understanding of the role that mitochondria play in health, disease, and aging has advanced considerably since mitochondrial dysfunction was first described by Luft et al.[15] Major structures of mitochondria include the inner and outer mitochondrial membranes, cristae, and electron transport chain (ETC).[16] Cardiolipin (CL), a unique phospholipid exclusive to mitochondria and present only in the inner membrane of mitochondria (IMM), acts as a linchpin to hold together the respiratory protein complex subunits (complexes I, II, III, and IV) of the ETC that are essential to achieve optimal functioning of numerous enzymes involved in mitochondrial energy metabolism.[17]

However, CL is susceptible to peroxidation, leading to loss of its biophysical properties that support the ETC. Abnormal function of the ETC drives mitochondrial dysfunction, defined as loss of ATP synthesis, coupled with pathologic production of reactive oxygen species (ROS), especially superoxide, and loss of transmembrane potential of the IMM.

Dry AMD and Mitochondrial Damage

Mitochondrial dysfunction has been implicated in the etiology of dry AMD. Mitochondria are located along the basal RPE near drusen. Mitochondrial dysmorphology observed in RPE in eyes with AMD is consistent with severe dysfunction, and mitochondrial DNA from these eyes demonstrate increased oxidative damage. Finally, a genetic disease with mitochondrial DNA mutation, maternally-inherited diabetes and deafness (MIDD), is associated with an AMD-like maculopathy.[14]

A novel mitochondrial protective compound, MTP-131 (Ocuvia, Stealth BioTherapeutics), is a topical ophthalmologic investigational drug under development to treat both common and rare eye disorders, including retinal diseases and inherited mitochondrial optic neuropathies. It works by targeting the IMM, electrostatically and transiently interacting with CL, including its various forms (eg, peroxidized CL), and restoring biophysical properties (healthy ATP and ROS levels) and function of the ETC,[18] thereby modifying ophthalmologic disease progression.

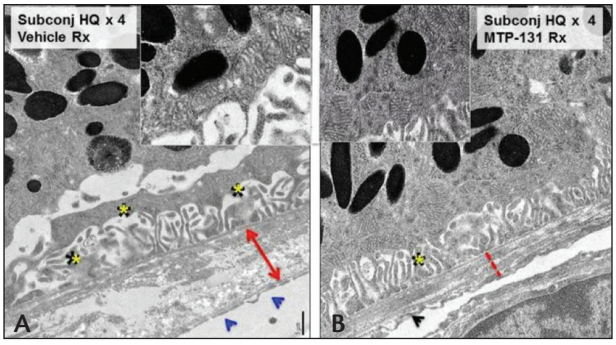

Figure 1. MTP-131 prevented HQ-induced deposits in an acute mouse model. Note: subconjuctival is abbreviated as subconj in the image.

DRY AMD AND CIGARETTE SMOKE–RELATED TOXICANTS

Cigarette smoking is the most important environmental risk factor for dry AMD onset and progression,[19-23] although other factors associated with Western lifestyle also play a role. Our laboratory identified a major chemical toxicant in tobacco tar, hydroquinone (HQ), as a potential biochemical cause of RPE cellular injury inducing drusen and geographic atrophy.[24] HQ is on the US Environmental Protection Agency's list of dangerous environmental toxicants.[25] In addition to cigarette tar, HQ is present in industrial pollution, engine exhaust, and food stored in plastic containers (due to HQ used in plastics).[21,26] Acute exposure to high doses of HQ causes seizures and death; however, less well-known are the health effects of chronic exposure to low levels of HQ.

Preclinical and Animal Models of Dry AMD and HQ-Induced Mitochondrial Dysfunction

Our research has shown that RPE mitochondria are a major target of HQ in the eye, and that HQ exposure induces acute and chronic mitochondrial dysfunction resulting in biochemical and cellular changes consistent with dry AMD. In vitro exposure of cultured RPE to HQ induces mitochondrial dysfunction, which in turn triggers cellular injury pathways consistent with AMD biochemistry. Further, aged mice fed HQ develop AMD-like sub-RPE deposits.[24,27] Finally, repeated subconjunctival injection of HQ in young mice over a 2-week period produces sub-RPE deposit formation and mitochondrial dysfunction with biochemical changes similar to those observed in cell culture.

MTP-131 Prevents Dry AMD Phenotype Associated with HQ-Induced Mitochondrial Dysfunction

Our laboratory has performed preliminary testing of MTP-131 in cell culture and in a mouse model, and

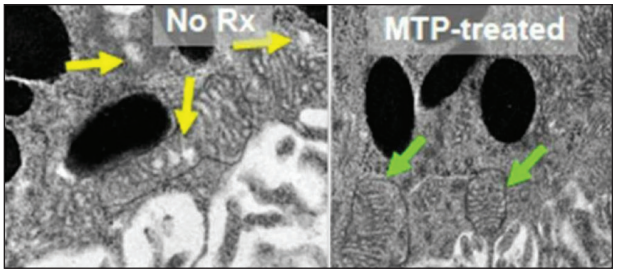

Figure 2. MTP-131 prevented mitochondrial vacuolization in mouse RPE after subconjunctival hydroquinone administration.

we have found that the investigational drug was highly effective in several experimental models. In cell culture, MTP-131 prevented HQ-induced mitochondrial dysfunction, activation of biochemical injury pathways, and cellular functions associated with deposits. Even more impressive, MTP-131 prevented HQ-induced mitochondrial dysfunction, biochemical injury pathways, and deposit formation in a mouse model.

As compared with HQ-exposed, vehicle-treated eyes (Figure 1A), the outer retinas of mice treated with daily MTP-131 (3 mg/kg subcutaneous, Figure 1B) before and during 2 weeks of HQ exposure had normal basal infoldings (yellow asterisk), minimal deposit formation, normal Bruch membrane thickness (red line), and endothelium with fenestrations (black arrowhead). Moreover, RPE mitochondrial morphology and ultrastructure, which shows irregular shape and typical vacuolization following repetitive subconjunctival HQ exposure, was normalized by treatment with MTP-131 (Figure 2). These mitochondrial ultrastructural differences between groups treated with vehicle and with MTP-131 are known to closely correlate with ATP and oxidative stress levels, mitochondrial respiration, and overall ETC function.[28]

HUMAN STUDY ONGOING

Jeffery Heier, MD, is leading a phase 1/2 open-label, dose-escalation clinical study of topical MTP-131 to better understand its safety and tolerability in patients with diabetic macular edema and dry AMD.[29] Our preliminary preclinical studies provide a rationale for advancing this therapy into later-stage clinical trials for early- or late-stage dry AMD. ■

Scott W. Cousins, MD, is the Robert Machemer Professor of Ophthalmology and a professor in immunology at Duke University Medical Center, Durham, North Carolina. Over the past 12 months, Dr. Cousins has been compensated as a consultant, investigator, and/or member of a Data Safety Monitoring Committee by Stealth BioTherapeutics Inc., Ophthotech, Heidelberg, SalutarisMD, Kala, Narrow River, Bausch + Lomb, Valeant, Pfizer, and PanOptica. Dr. Cousins may be reached at scott.cousins@duke.edu.

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