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## PATHWAY-BASED THERAPIES FOR AGE-RELATED MACULAR DEGENERATION

### An Integrated Survey of Emerging Treatment Alternatives

MARCO A. ZARBIN, MD, PhD,\* PHILIP J. ROSENFELD, MD, PhD†

**Purpose:** To review treatments under development for age-related macular degeneration (AMD) in the context of current knowledge of AMD pathogenesis.

**Methods:** Review of the scientific literature published in English.

**Results:** Steps in AMD pathogenesis that appear to be good targets for drug development include 1) oxidative damage; 2) lipofuscin accumulation; 3) chronic inflammation; 4) mutations in the complement pathway; and 5) noncomplement mutations that influence chronic inflammation and/or oxidative damage (e.g., mitochondria and extracellular matrix structure). Steps in neovascularization that can be targeted for drug development and combination therapy include 1) angiogenic factor production; 2) factor release; 3) binding of factors to extracellular receptors (and activation of intracellular signaling after receptor binding); 4) endothelial cell activation (and basement membrane degradation); 5) endothelial cell proliferation; 6) directed endothelial cell migration; 7) extracellular matrix remodeling; 8) tube formation; and 9) vascular stabilization.

**Conclusion:** The era of pathway-based therapy for the early and late stages of AMD has begun. At each step in the pathway, a new treatment could be developed, but complete inhibition of disease progression will likely require a combination of the various treatments. Combination therapy will likely supplant monotherapy as the treatment of choice because the clinical benefits (visual acuity and frequency of treatment) will likely be superior to monotherapy in preventing the late-stage complications of AMD.

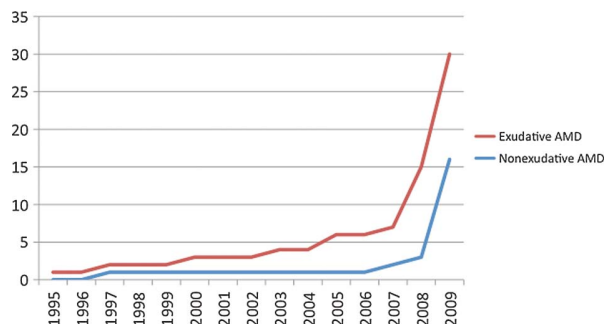
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A large number of treatments for exudative and nonexudative age-related macular degeneration (AMD) are in preclinical development or in early-stage clinical trials (Figure 1). In this review, six observations relevant to the pathogenesis of AMD will be described. Emerging and established AMD treatments will then be reviewed within the context of these pathogenic schemes. This information should be especially useful for the rational development of combination therapies.

#### Pathogenesis of Age-Related Macular Degeneration

Detailed consideration of the pathogenesis of AMD is beyond the scope of this perspective, but it has been discussed extensively elsewhere.<sup>1,2</sup> Six concepts will be considered briefly.

First, biochemical studies and histological studies of AMD have implicated oxidative damage as a possible cause of this disease. Eyes with geographic atrophy



**Fig. 1.** Rate of AMD treatment growth. The number of treatments for AMD in preclinical testing, early clinical testing, or clinical practice has undergone exponential growth during the past 5 years.

(GA) exhibit DNA strand breaks and lipoperoxidation.<sup>3</sup> Antioxidant changes in the retinal pigment epithelium (RPE) of AMD eyes indicate that the RPE cells are under oxidative stress (e.g., increased levels of heme oxygenase-1 and heme oxygenase-2 and Cu-Zn superoxide dismutase).<sup>4</sup> Advanced glycation end products occur in soft drusen, basal laminar and basal linear deposits, and the cytoplasm of RPE cells associated with choroidal neovascularization (CNV).<sup>5,6</sup> Carboxymethyl lysine is present in drusen and CNV<sup>5,7</sup> as are carboxyethyl pyrrole protein adducts.<sup>5</sup> Additionally, Fe<sup>2+</sup>—which is an essential element for enzymes involved in the phototransduction cascade, outer segment disk membrane synthesis, and conversion of all-*trans*-retinyl ester to 11-*cis*-retinol in RPE—also catalyzes the conversion of hydrogen peroxide to hydroxyl radicals and is known to accumulate in Bruch's membrane in AMD eyes.<sup>8,9</sup> Epidemiologic studies indicate that one of the main risk factors for AMD is smoking, which is known to cause oxidative damage. One interpretation of the Age-Related Eye

Disease Study (AREDS) (<http://clinicaltrials.gov/ct2/show/NCT00000145?term=Age-Related+Eye+Disease+Study+%28AREDS%29&rank=3>) results is that antioxidant supplementation reduces the risk of visual loss associated with AMD among properly selected patients, especially for patients with the *CFHTT* genotype.<sup>10</sup>

Second, excessive accumulation of lipofuscin in the RPE may play an important role in the pathogenesis AMD.<sup>11</sup> In RPE cells, the main source of lipofuscin is probably the undegradable components of phagocytized outer segments.<sup>12</sup> In vertebrate photoreceptors, light causes isomerization of visual pigment chromophore, 11-*cis*-retinylidene, to all-*trans*-retinylidene, followed by release of all-*trans*-retinal from the opsin binding pocket and its reduction to all-*trans*-retinol (Figure 2).<sup>13</sup> ABCA4, an adenosine triphosphate-binding cassette transporter present in the outer segment of rods and cones, transports *N*-retinylidene-phosphatidylethanolamine from the outer segment disks to the photoreceptor cytoplasm.<sup>14,15</sup> Retinol dehydrogenase 8 (in outer segments) and retinal dehydrogenase 12 (in inner segments) reduces all-*trans*-retinal to all-*trans*-retinol.<sup>16,17</sup> Vitamin A (all-*trans*-retinol) diffuses to RPE where it is esterified by lecithin/retinol acyltransferase (LRAT) to all-*trans*-retinyl esters and is stored in retinosomes.<sup>18,19</sup> All-*trans*-retinyl esters are isomerized to 11-*cis*-retinol in a reaction involving RPE-65.<sup>20–22</sup> Next, 11-*cis*-retinol is oxidized to 11-*cis*-retinal,<sup>23,24</sup> which then diffuses across the extracellular space to photoreceptors and recombines with rod-and-cone opsin proteins to regenerate visual pigments. Within the outer segment disks, ethanolamine can combine with two retinaldehyde molecules to form *N*-retinylidene-*N*-retinylethanolamine (A2E); A2E is a major fluorophore in lipofuscin found in the RPE.<sup>25</sup>

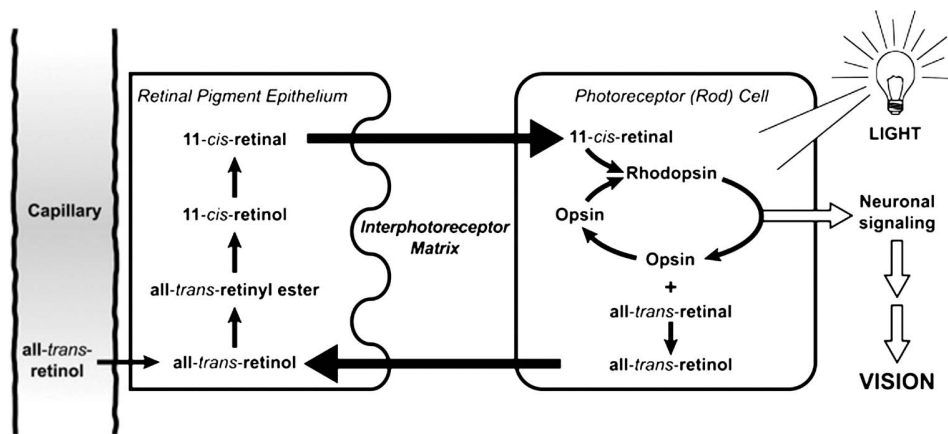
Third, AMD is associated with chronic inflammation in the region of the RPE, Bruch's membrane, and choroid.<sup>26</sup> Several lines of evidence demonstrate this fact. Drusen, for example, contain many components of the activated complement cascade.<sup>27–29</sup> Anatomical studies demonstrate the presence of inflammatory cells in Bruch membrane.<sup>30</sup> Bioactive fragments of C3 (C3a) and C5 (C5a) are present in the drusen of AMD eyes and induce vascular endothelial growth factor (VEGF) expression in RPE cells.<sup>31</sup> The latter findings may explain why confluent soft drusen are a risk factor for CNVs in AMD eyes. The presence of proinflammatory molecules in drusen constitutes a stimulus for chronic inflammation in the RPE–Bruch membrane–choriocapillary complex that may result in some features of late AMD. One interpretation of the AREDS is that zinc, one of the main therapeutic ingredients of this treatment, also affects the complement system, which in turn may slow

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**Fig. 2.** The visual cycle. Reproduced with permission from <http://lpi.oregonstate.edu/infocenter/vitamins/vitaminA/visualcycle.html>. Courtesy of Jane Higdon, Linus Pauling Institute, Oregon State University, copyright 2010.

disease progression. Zinc inhibits C3 convertase activity,<sup>32</sup> and levels of C3a des Arg, which is a cleavage product of C3a and reflects complement activation, are higher in patients with AMD (including patients with early as well as late AMD) versus controls.<sup>33</sup> We are not aware of published data demonstrating that zinc supplements lower C3a des Arg levels in AMD patients.

Fourth, drusen, GA, and CNV are associated with mutations in components of the complement pathway, which is part of the innate immune system (Figure 3). Protective and risk-enhancing mutations in components of the complement pathways have been reported and include the following loci: complement factor H (CFH), complement component 2 (C2), factor B (CFB), complement component 3 (C3), and factor I (CFI).<sup>27,35–47</sup>

Fifth, oxidative damage can compromise regulation of the complement system by RPE cells. Thurman and Holers<sup>48</sup> noted that the alternative complement pathway is continuously activated in the fluid phase, and tissue surfaces require continuous complement inhibition to prevent spontaneous autologous cell injury. Sohn et al<sup>49</sup> demonstrated that the complement system is continuously activated in the eye. Thurman et al<sup>50</sup> showed that oxidative stress reduces the regulation of complement on the surface of ARPE-19 cells (i.e., reduces surface expression of the complement inhibitors, decay accelerating factor [CD55] and CD59) and impairs complement regulation at the cell surface by factor H. Sublytic activation of the complement cascade also causes VEGF release from the cells, which compromises RPE barrier function. Similarly, oxidative stress can reduce the ability of interferon-gamma to increase CFH expression in RPE cells.<sup>51</sup> In vitro evidence indicates that products of the photooxidation of A2E in RPE cells can serve as a trigger for the complement system.<sup>52</sup> Thus, the relative abundance of lipofuscin in the submacular RPE may predispose the macula to chronic inflammation and

AMD, particularly in patients who cannot control complement activation because of inherited abnormalities in the complement system. Hollyfield et al<sup>53</sup> have described an animal model that links oxidative damage and complement activation to AMD.

Sixth, some AMD-risk enhancing mutations not directly involving the complement pathway are also linked to inflammation or oxidative damage.<sup>54–59</sup>

A proposed pathogenesis (Figure 4) of AMD suggests the possibility of therapeutic intervention at different points in the natural history of the disease with antioxidants, visual cycle inhibitors, antiinflammatory agents, antiangiogenic agents, and neuroprotective agents.

## Treatment

### Antioxidants

The AREDS did not show a statistically significant benefit of the AREDS formulation for either the development of new GA or the involvement of the fovea in eyes with preexisting atrophy.<sup>60</sup> In part, this result may be because of the paucity of GA patients in the study. AREDS II (<http://clinicaltrials.gov/ct2/show/NCT00345176?term=Age-Related+Eye+Disease+Study+%28AREDS%29&rank=1>) is a randomized, multicenter, clinical trial to assess 1) the role of lutein (10 mg)/zeaxanthin (2 mg) and omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid [DHA]/eicosapentaenoic acid [EPA]) in prevention of development of GA or CNV; and 2) the possible deletion of beta-carotene and lowering the daily zinc oxide dose to 25 mg. A Phase 3 clinical trial is underway. A recently terminated Phase 2 clinical study, known as the OMEGA Study (Othera, Pharmaceuticals Inc., Conshohocken, PA) (<http://clinicaltrials.gov/ct2/show/NCT00485394?term=OMEGA+Study&rank=1>), investigated an eyedrop with a prodrug, known as OT 551

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