Challenges for Atrophic Age-Related Macular Degeneration Research

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Age-related macular degeneration (AMD) is an idiopathic retinal degenerative disease that predominates in the elderly in the Western world as a cause of irreversible and profound vision loss [1,2]. AMD occurs in two major forms: atrophic (dry) AMD and exudative (wet) AMD that are both part of the same disease process and share similar risk factors. The atrophic AMD is characterized by RPE atrophy and subjacent photoreceptor degeneration and accounts for approximately 80~90% of AMD cases while the exudative AMD is characterized by choroidal neovascularization (CNV) and retinal hemorrhage [3]. Photodynamic therapy, surgery, and anti-VEGF therapy are currently available treatments for AMD patients with CNV. However, no therapy is available yet for maintaining or improving vision associated with atrophic AMD since developing pharmacological approaches to prevent onset or progression of atrophic AMD faces significant hurdles including lack of understandings of the disease mechanisms, the paucity of experimental models for testing potential drugs, and established endpoints for clinical trials.

Disease Biology of Atrophic AMD

AMD is an ageing-related syndrome caused by multiple factors including environmental, nutritional, and behavioral [4,5]. Although the vision loss results from damage of photoreceptor cells that convert the light entering the eye into electrical and molecular signals being transmitted to the brain for visual processing in the central retina, the initial pathogenesis of AMD has been attributed to the degeneration of retinal pigment epithelial (RPE) cells [6,7]. The eye with its intense exposure to light, enrich in unsaturated fatty acids, robust metabolic activity and high oxygen tension in the macular region is particularly susceptible to oxidative damage by accumulation of reactive oxygen species. Oxidative damage to RPE cells [8,9] and chronic RPE cell inflammatory responses [10,11] are experimentally associated with AMD etiology. The specific genetic and biochemical mechanisms responsible for RPE degeneration in AMD have not been determined.

Recently, a single-nucleotide polymorphism at position 402 from tyrosine to histidine (the Y402H mutation) in complement factor H (CFH), an inhibitor of the complement alternative pathway, conveys a significant risk of developing AMD [12]. The functional consequence of Y402H mutation reduces the ability of CFH to control the inflammation, thereby leading to AMD. Malondialdehyde (MDA), a common decomposition product of free radical-initiated lipid peroxidation, reacts with cellular proteins to form MDA-protein adducts that induce inflammatory responses. CFH peptides constitute the majority of highly-specific MDA-binding proteins, blocking inflammatory reactions in RPE cells and macrophages. The Y402H CFH showed a markedly reduced ability to bind MDA compared with normal CFH [13]. Whether CFH interacts with other oxidized lipid-protein adducts such as carboxyethylpyrrole-adducts in a similar way to the MDA–CFH paradigm, remains to be addressed.

Animal Models for Atrophic AMD

Accordingly, oxidative stress or inflammatory animal models have been developed to investigate the pathogenic roles of oxidative stress and inflammation and to test therapeutic compounds in ameliorating the pathology. Deletion of the superoxide dismutase gene, the product of which is responsible for scavenging superoxide, results in mice that develop many of the hallmark features of AMD including drusen, RPE atrophy and lesions [14,15]. Mice challenged with the oxidized adduct of mouse serum albumin with carboxyethyl pyrole, an oxidation fragment of docosahexaenoic acid, produce antigen-specific antibodies, develop subretinal deposition of macrophages and complement components, drusen under the RPE, and lesions mimicking atrophic AMD [16]. Manifestation of AMD-like phenotypes can be facilitated by knocking out more than one risk genes such as the chemokine (C-C motif) ligand 2 and CX3C chemokine receptor 1 [17,18] or combined genetic deficiency with environmental risk factor [19].

AMD is a multi-factor disease; however, the available animal models only evaluate the contributions of one or at most two risk factors. Moreover, the appearance of many of the AMD-like features occurs over a protracted period, thereby requiring a prolonged treatment regimen to evaluate potential drug candidates, which limits the utility of these AMD animal models. Efforts to accelerate the manifestation of the measurable AMD-like features of animal models are ongoing by crossing various transgenic and knockout mice and/or adding additional environmental risk factors.

Clinic Endpoints for Atrophic AMD Trials

The widely accepted endpoints for clinical trials designed to study the efficacy of treatments for retinal diseases are visual acuity, contrast sensitivity, and macular light flash recovery time. Among them, visual acuity is regarded as the gold standard for evaluating the effectiveness of a new treatment for AMD. However, the natural history of vision loss due to atrophic AMD is slow and patients with atrophic AMD even in the advanced stages can still maintain good visual acuity until the disease has progressed to involve the central fovea. It will take years to see an appreciated difference in visual acuity outcomes. Thus, there is growing consensus that clinical evaluation of atrophic AMD treatment requires establishment of new performance-based endpoint measurements.

It is undefined what the best clinical trial endpoint is for demonstrating efficacy in a short period of time for new emerging treatment for atrophic AMD. However, several alternative endpoints are undergoing development that might show a positive outcome without waiting years to see visual acuity benefit. These alternative endpoints include shortening dark adaptation time and reducing the drusen

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burden in the macula. Dark adaptation is significantly impacted in AMD long before any apparent loss of visual acuity and prolongation of dark adaptation is well related to the AMD severity. Drusen formation, in particular soft drusen, in the macular region is an early biomarker of AMD and might be another parameter measuring the progression of atrophic AMD. Complete assessment of drusen morphology including shape, area, and volume can be done by spectral domain optical coherence tomography. Thus, measuring dark adaptation, or the number and size of drusen are two of the workable ways to monitor the drug efficacy for the treatment of atrophic AMD. These strategies are currently being tested in clinical trials.

Perspectives

The progressive nature of atrophic AMD and the extensive cell damage in affected individuals at the time of diagnosis suggest that the future of atrophic AMD therapeutics is in the prevention of progression of the disease. A disease preventive drug needs fulfill two crucial requirements: target a key mechanism responsible for the disease initiation and/or progression and have minimal side effects for extended periods. Clinically, antioxidant supplements can modestly delay the progression of atrophic AMD from an intermediate stage to the advanced stages for some of the AMD patients in the Age-related Eye Disease Study (AREDS) [20]. At 5 years, people at risk of developing advanced AMD in the second eye lowered this risk by about 25% when treated according to the AREDS recommendations [20]. These results from AREDS indicate that intervention of atrophic AMD progression can be achieved by pharmacological agents. Therefore, identifying cellular targets that control the key biological processes in etiology of atrophic AMD will provide novel mechanisms for discovering agents that can modify those biological processes. Advancing atrophic AMD research will certainly come from with the concurrent development of efficient AMD animal models that could mimic the disease processes in atrophic AMD patients. The progress in understanding disease biology, availability of better AMD animal models, and establishment of clinical endpoints could one day be exploited to design novel therapies that target a specific enzyme in atrophic AMD etiology, rather than depending on a non-specific and often inefficient, broad anti-oxidant approach in the fight against atrophic AMD.

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