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Review

Genomic aspects of age-related macular degeneration

Kuniko Horie-Inoue [a,*], Satoshi Inoue [a,b]

[a] Division of Gene Regulation and Signal Transduction, Research Center for Genomic Medicine, Saitama Medical University, Saitama, Japan
[b] Department of Anti-Aging Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

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ABSTRACT

Age-related macular degeneration (AMD) is a major late-onset posterior eye disease that causes central vision to deteriorate among elderly populations. The predominant lesion of AMD is the macula, at the interface between the outer retina and the inner choroid. Recent advances in genetics have revealed that inflammatory and angiogenic pathways play critical roles in the pathophysiology of AMD. Genome-wide association studies have identified *ARMS2/HTRA1* and *CFH* as major AMD susceptibility genes. Genetic studies for AMD will contribute to the prevention of central vision loss, the development of new treatment, and the maintenance of quality of vision for productive aging.

Contents

1. Introduction

Age-related macular degeneration (AMD) is a common eye disease that leads to the deterioration of the central vision in elderly people, particularly in those over 60 years of age. This disease causes damage to the macula, which is a small spot near the center of the retina (2 mm in diameter). When the structure of eyeball is likened to that of a traditional camera, the retina corresponds to a film and the subretinal pigment-rich tissue, the choroid, corresponds to a camera obscura. The macula would be considered as a special film with intense light sensitivity, as it is the particular region of the retina due to the high density of cone photoreceptors

* Corresponding author. Address: Division of Gene Regulation and Signal Transduction, Research Center for Genomic Medicine, Saitama Medical University, 1371-1 Yamane, Hidaka City, Saitama 350-1231, Japan. Fax: +81 42 982 4541.
E-mail address: khorie07@saitama-med.ac.jp (K. Horie-Inoue).

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that are responsible for the sharpness of the central vision and color vision.

AMD is one of the most frequent diseases for acquired vision loss and blindness in developed countries. Because of the exponential growth of the aging population, the prevalence of AMD is increasing. A meta-analysis by the Eye Diseases Prevalence Research Group estimated that the overall prevalence of AMD in the population of the United States 40 years and older in 2000 was estimated to be 1.5%, with 1.75 million individuals affected by the disease [1]. AMD is far more prevalent among whites than among blacks [1,2]. A recent meta-analysis of 3 large population-based cohort studies within the Three Continent AMD Consortium, using data for 6,953 participants from the Beaver Dam Eye Study (BDES) in the United States, Blue Mountains Eye Study (BMES) in Australia, and Rotterdam Study (RS) in the Netherlands, the average 5-year incidences of early AMD were 8.1%, 15.1%, and 13.0% in the BDES, BMES, and RS, respectively [3]. The average 5-year incidences of late AMD were 1.2%, 1.7%, and 1.7% in the BDES, BMES, and RS, respectively. A meta-analysis in Asians aged 40–79 years showed that age-specific prevalence of late AMD in Asians was similar to that in Europeans, whereas early AMD was less common in Asians (6.8%) than in Europeans (8.8%) [4]. Based on a recent systemic review and meta-analysis, 8.7% of the worldwide population has AMD, and the projected number of people with the disease will be ~196 million in 2020, increasing to ~288 million in 2040 [5].

From genomic aspects, AMD has been paid a particular attention by researchers involved in human genetics as well as those involved in ophthalmology. Disease-susceptible genes including such as complement pathway, proteases, and lipid metabolism have been successfully identified genetic analyses including genome-wide association studies (GWASs) [6]. As elucidated by these studies, it is now assumed that both genetic and nongenetic factors coordinately contribute to the development and progression of AMD. Here we overview the genomic aspects of AMD that have been extensively studied since the beginning of this century. We also discuss the non-genetic factors that modify the effects of genetic factors on the pathophysiology of AMD.

2. Pathology and etiology

AMD is pathologically derived from the interface between the retina and the choroid in the macular region. The chorioretinal interface consists of the retinal pigment epithelium (RPE) in the outer layers of the retina and Bruch's membrane, the inner extracellular matrix layer of the choroid. A debris-like extracellular deposit, designated as drusen, often accumulates between the RPE and Bruch's membrane with aging. In the RPE, intracellular lysosomal lipofuscin, which is a nondegradable debris that composed of a mixture of different fluorophores, often aggregates with age [7]. The term lipofuscin was originated from the Greek "lipo" (for fat) and Latin "fuscus" (for dark) [8]. Although the nature of lipofuscin fluorophores has not been fully characterized, autofluorescent compounds derived mainly from vitamin A have been identified in RPE cells as byproducts of the visual cycle. One of the vitamin A-derived fluorophores is N-retinyl-N-retinylidene ethanolamine (A2E), which has the structure of a Schiff base that is generated by reactions between retinaldehyde (all-*trans*-retinal) and phosphatidylethanolamine, both are components of photoreceptor outer segment membranes [9,10]. Lipofuscin has been shown to mediate light-induced damage via radial oxygen species (ROS) and to be toxic to RPE cells [11–14]. A2E might also enhance the effects of moderate mitochondrial defects, impairing oxidative phosphorylation-dependent energy production and phagocytosis of the photoreceptor outer segment in aging RPE cells [15]. Similar to AMD, analogous lipofuscin-like proteins also interact with mitochondrial dysfunction in other neurodegenerative diseases, such as amyloid beta in Alzheimer's disease, parkin in Parkinson's disease, and superoxide dismutase (SOD) 1 in amyotrophic lateral sclerosis, and Huntingtin in Huntington's disease [16]. It has been speculated that lipofuscin in RPE and drusen on Bruch's membrane might interact with each other, although their precise relationship remains to be studied. Confluent drusen at the chorioretinal interface could activate the complement cascade and induce retinal inflammation, leading to the pathogenesis of early AMD. These age-related changes at Bruch's membrane may also be involved in the pathogenesis of other retinal diseases including retinitis pigmentosa and Stargardt disease [17,18]. Overall, the inflammation at the chorioretinal interface is likely a primary event for the onset of AMD, although aging itself is the major risk factor for the disease.

Impaired secretion of proteins by the RPE from both apical and basolateral sides will contribute to the pathogenesis of AMD, as recently reviewed by Dr. Paraoan and her colleagues [19]. In particular, cystatin C, a cysteine proteinase inhibitor, is one of the most abundantly expressed and basolaterally secreted proteins in the RPE [20,21]. Reduced secretion of cystatin C in brain may contribute to the development of Alzheimer's disease [22]. A homozygous genotype for mutant variant B of cystatin C has been shown to correlate with an increased risk of developing exudative AMD, with a relatively early onset [23].

In advanced stages of AMD, the disease can be roughly categorized into following 2 phenotypes: "atrophic AMD"/"dry AMD", with the presence of drusen and thinning of the macula because of RPE cell atrophy, or "neovascular AMD"/"exudative AMD"/"wet AMD", with choroidal neovascularization (CNV) that is new blood vessels underneath the retina (Fig. 1). In wet AMD, at least 3 subtypes are sub-categorized: typical AMD (tAMD), polypoidal choroidal vasculopathy (PCV), and retinal angiomatous proliferation (RAP). PCV was first defined by Dr. Yannuzzi in 1982, with a phenotype of subretinal vascular lesions associated with serous and hemorrhagic detachments of the RPE [24,25]. PCV was initially considered a distinct abnormality of the choroidal vasculature found in the peripapillary area. Currently PCV is considered a subtype involved in wet AMD [26]. The prevelance of PCV in Asians is higher than that in Caucasians. For example, PCV is observed in 48% of Japanese patients whereas in 9% French patients [27]. RAP is usually described as "deep retinal vascular anomalous complex" and "retinal–choroidal anastomosis" [28]. According to a classification by Dr. Gass and its modification by Dr. Freund, 3 types of posterior chorioretinal neovascularization are defined in terms of its anatomical relationship to RPE layer: type 1 neovascularization as fibrovascular tissue posterior to RPE, type 2 neovascularization as fibrovascular complex that lies anterior to the RPE, and type 3 as intraretinal neovascularization, putatively occurred in RAP lesions [29,30].

In the pathogenesis of AMD, macrophages play a critical role in inflammatory lesions. Both bone marrow-derived immigrant macrophages and local microglia-derived macrophages from the inner retina are involved in the phagocytosis of apoptotic photoreceptors and the clearance of cell debris [31]. Although the specific roles of macrophages at different disease stages remain controversial, both pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages may be involved in the development and progression of AMD. Recent studies have revealed that macrophages recruited under the retina at the initial stage of AMD exhibit a pro-inflammatory M1 phenotype [32–34]. T cells may also be involved in the pathology, as shown by a study of carboxyethylpyrrole-immunized mice, which exhibit AMD-like pathology [33]. Human histopathological studies suggest that M2 macrophages are likely activated in later AMD stages rather than in early stages

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