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Review article

Role of genetic factors in the pathogenesis of exudative age-related macular degeneration

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ABSTRACT

Exudative age-related macular degeneration (AMD) is one of the leading causes of irreversible blindness worldwide. Many recent genetic association studies on large case–control cohorts have helped in drawing an outline of the pathogenesis of AMD. The majority of the associations observed in oxidative stress and lipid peroxidation (*complement factor H or CFH*), complement (*CFH, C3, complement factor I, C2, complement factor B*), and neovascularization (*vascular endothelial growth factor A, high-temperature requirement factor A1*) genes have been replicated in diverse populations worldwide. In this review, we have provided an overview on the genetic factors in the pathogenesis of AMD, and highlight their underlying molecular genetic mechanisms. Further comprehensive research is needed to verify this outline, to explore the treatment target, and to develop the effective primary and secondary prevention of AMD.

1. Introduction

1.1. Age-related macular degeneration

Age-related macular degeneration (AMD) is the leading cause of visual impairment in elderly individuals and is the most common cause of blindness in Western countries.[1,2] Advanced AMD has two major subtypes, namely, geographic atrophy (also called advanced "dry" AMD) and choroidal neovascularization (CNV; also called exudative AMD or "wet" AMD). Exudative AMD affects 10–15% of patients with AMD and rapidly progresses to blindness if left untreated.[3]

1.2. Hypothesis of AMD pathogenesis

In the early stages of AMD, the abnormal oxidative stress in retinal pigment epithelium (RPE) triggers the dysfunction or changes in the composition or permeability of Bruch's membrane, leading to the formation of drusen. Drusen are small, yellowish extracellular deposits of cellular debris, protein, lipid, carbohydrate, complement components, and anaphylatoxins. Local inflammatory and immune-mediated events play an important role in the development of drusen.[4–8] In turn, the inflammation becomes chronic and increasingly amplified over decades as the outer macula becomes even more hypoxic. The complement system may play a central role in chronic inflammation. The inflammation triggers the production of vascular endothelial growth factor (VEGF), which was identified to play a major role in CNV in 1996.[9,10] A previous study demonstrated that VEGF plays a role in the progression of CNV and enhancement of vascular permeability, both of which result in loss of vision.[11] It stimulates dissociation of tight junction components, promotes vascular permeability, and endothelial cell growth.[12,13] In the late stages of AMD, there is excessive recruitment of scar tissue that leads to irreversible destruction of photoreceptors (Fig. 1).

2. Role of genetic factors in the pathogenesis of AMD

Recent large-sample genome-wide association studies (GWASs) confirmed previously reported AMD-associated genes, including *complement factor H (CFH)*,[14] *high-temperature requirement factor A1 (HTRA1)*,[14] *age-related maculopathy susceptibility protein 2 (ARMS2)*,[14] *C3*,[14,15] *VEGFA*,[14] etc. In this paper, the role of these genes in the pathogenesis of AMD is reviewed.

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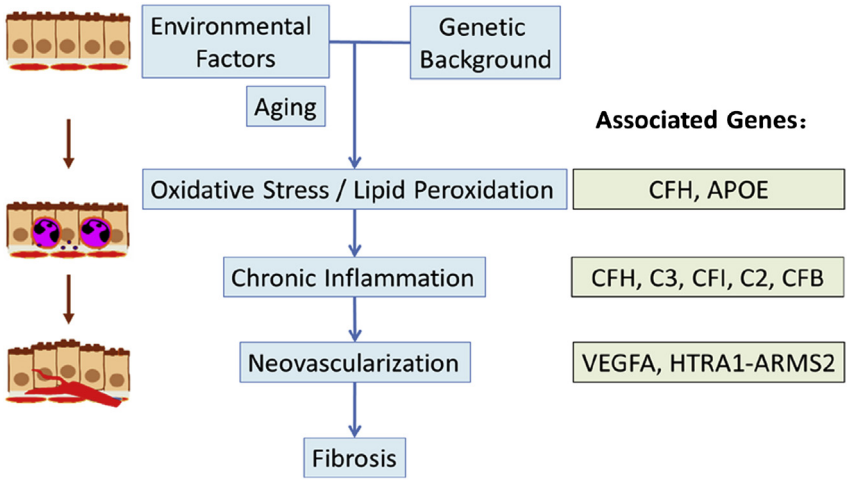

Fig. 1. Hypothesis of age-related macular degeneration pathogenesis. APOE = apolipoprotein E; ARMS2 = age-related maculopathy susceptibility protein 2; CFB = complement factor B; *CFH* = complement factor H; CFI = complement factor I; HTRA1 = high-temperature requirement factor A1; VEGFA = vascular endothelial growth factor A.

2.1. Role of genetic factors in oxidative stress/lipid peroxidation stage

Increased oxidative stress has been implicated in the pathogenesis of AMD.[16,17] Owing to oxidative stress, proteins, lipids, and DNA can be damaged. When phospholipids in cell membranes undergo lipid peroxidation, malondialdehyde (MDA) and other reactive decomposition products are generated.[18] Previous studies have reported that oxidative stress and lipid peroxidation-related genes—*CFH* and *apolipoprotein E (APOE)*—are associated with AMD.

2.1.1. CFH protects from oxidative stress

The *CFH* is one of the first genes reported to be associated with AMD.[19] Individuals with a *CFH* variant that substitutes a tyrosine for a histidine at position 402 have an increased likelihood of developing AMD by 4.6-folds if the variation is present on one allele and by 7.4-folds if it is present on both alleles.[19] Further *CFH* studies found that the *CFH* haplotype significantly increased the risk for AMD with odds ratios (ORs) between 2.45 and 5.57 and that a common variant likely explains approximately 43% of AMD in older adults.[20–25]

Recent research found that *CFH* is an innate defense protein against oxidative stress.[17] Results from animal models lacking immunoglobulins showed that over 55% of peptides that bind to MDA could be attributed to *CFH*. Mapping of the binding site for MDA on *CFH* showed that it crossed the amino acid position 402, highlighted in the original genetic association studies and, most importantly, the H402 variant of *CFH* showed reduced MDA binding by up to 23% in the plasma of heterozygotes and up to 52% in homozygotes. Normal *CFH* then appears to protect against inflammation by inhibiting the complement pathway; however, once mutated, the *CFH*'s ability to control the inflammation associated with AMD appears to be lost. Functioning *CFH* is able to suppress the inflammatory response by mopping up the MDA adducts.[17]

2.1.2. APOE suppresses lipid peroxidation

APOE is a lipid transport protein that acts as a ligand for the low-density lipoprotein (LDL) receptor, which is involved in the maintenance and repair of neuronal cell membranes. Variation at two single-nucleotide polymorphisms (SNPs) within the coding sequence of the *APOE* gene, rs429358 and rs7412, results in different isoforms reported to attenuate binding affinity to the LDL receptor. Three allelic variants derived from these SNPs commonly referred to as ε2, ε3, and ε4 are differentiated based on cysteine (Cys) and arginine (Arg) residue interchanges at positions 112 (rs429358) and 158 (rs7412) in the amino acid. APOε2 has a much reduced binding affinity leading to lower total cholesterol levels with respect to APOε3 and APOε4, which reveal a higher binding affinity with higher total cholesterol levels.[26] The *APOE* has been found to be associated with AMD. A pooled analysis of 15 studies demonstrated the associations between late AMD and APOε4 (OR = 0.72 per haplotype) and APOε2 (OR = 1.83 for homozygote carriers).[27]

APOE plays an important role in suppressing the oxidative stress and lipid peroxidation. *APOE* binds directly to 4-hydroxynonenal and has a protective effect against lipid peroxidation.[28] A recent study found that lipid peroxidation is caused by a reduction of antioxidant activity with aging in *APOE* knockout mice.[29]

2.1.3. Role of genetic factors in chronic inflammation

Oxidatively modified proteins are known to induce inflammatory responses and are recognized by innate immunity.[30,31] The oxidation-specific epitopes are recognized as danger signals by innate immune receptors.[32] Following a series of independent research papers in late 2005 suggesting a link between the body's immune system and AMD, further investigations established the alternative complement system as a potentially critical player that may help scientists to join the dots between drusen, a fatty tissue characteristic of the disease, and the symptomatic degeneration of the macula. Understanding the links between the genetic susceptibility data and the clinical symptoms should provide a framework for a deeper understanding of AMD pathogenesis and consequently contribute to identifying new therapeutic targets to slow or halt vision loss associated with the disease.

2.1.4. CFH

We have previously discussed that *CFH* protects from oxidative stress. Moreover, *CFH* plays an important role in the regulation of the alternative pathway. *CFH* binds *C3b*, and accelerates the decay of the alternative C3 convertase (*C3bBb*). It also acts as a cofactor for the inactivation of *C3b* by *complement factor I (CFI)*.[33,34] CFH binds to cell surfaces to regulate amplification of the alternative complement pathway resulting from spontaneous *C3b* deposition, which occurs on any surface in contact with blood.[33,34]

2.1.5. Complement C3

Complement C3 is the most abundant component of the complement pathway. Variations in the *C3* gene are associated with AMD. A