Molecular Immunology 61 (2014) 118–125

Contents lists available at ScienceDirect

Molecular Immunology

journal homepage: www.elsevier.com/locate/molimm

Genetic variants in the complement system predisposing to age-related macular degeneration: A review☆

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ARTICLE INFO

Article history:
Received 17 May 2014
Received in revised form 20 June 2014
Accepted 23 June 2014
Available online 15 July 2014

Keywords:
Age-related macular degeneration
Complement system
Alternative pathway
Genetic variants

ABSTRACT

Age-related macular degeneration (AMD) is a major cause of visual impairment in the western world. It is characterized by the presence of lipoproteinaceous deposits (drusen) in the inner layers of the retina. Immunohistochemistry studies identified deposition of complement proteins in the drusen as well as in the choroid. In the last decade, genetic studies have linked both common and rare variants in genes of the complement system to increased risk of development of AMD. Here, we review the variants described to date and discuss the functional implications of dysregulation of the alternative pathway of complement in AMD.

1. Introduction

Age-related macular degeneration (AMD) is the leading cause of vision loss in the developed world with approximately 50 million sufferers worldwide. Its prevalence is continuing to rise due to the increasing numbers of older individuals in the population (Lim et al., 2012; Sobrin and Seddon, 2014). AMD is a slowly progressive, degenerative ophthalmologic disease, which normally occurs during or after the sixth decade of life. In populations of European ancestry, the prevalence of advanced AMD ranges from 1.4% at 70 years of age to 20% at 90 years of age (Rudnicka et al., 2012). The disease manifests itself with the loss of photoreceptor cells (the rod and cone cells) in the central region of the retina at the back of the eye (called the macula) (Fig. 1). This leads to a loss of central vision, leaving patients dependent on the acuity of their peripheral vision.

Not only does the disease cause emotional hardship, it also imposes a large socioeconomic burden on healthcare services, patients and their caregivers. AMD affects reading and driving, greatly reducing the ability of patients to contribute to work-related activities. AMD is likely a syndrome with multiple environmental and genetic factors playing a role. While diet and environmental factors (i.e. smoking) are associated with the risk of AMD, it has become increasingly evident that AMD risk is driven by genetic factors as well (Cipriani et al., 2012; Fritsche et al., 2013; Sobrin and Seddon, 2014).

A number of genetic alterations are associated with increased risk of developing AMD and many reside in genes encoding the complement cascade (Klein et al., 2005; Maller et al., 2006; Hughes et al., 2006; Maller et al., 2007; Fritsche et al., 2010; Sofat et al., 2012). These variants span the allelic spectrum of disease from common variants that impart relatively low risk of disease to rare variants with nearly complete penetrance. This, together with the identification of a number of inflammatory mediators in drusen, the hallmark lesion of AMD, has led to the hypothesis that an inflammatory response, driven by an inadequately regulated complement cascade, significantly contributes to the progression of AMD (Anderson et al., 2010; Ambati et al., 2013).

☆ This article belongs to SI: XXV ICW Rio 2014.

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http://dx.doi.org/10.1016/j.molimm.2014.06.032
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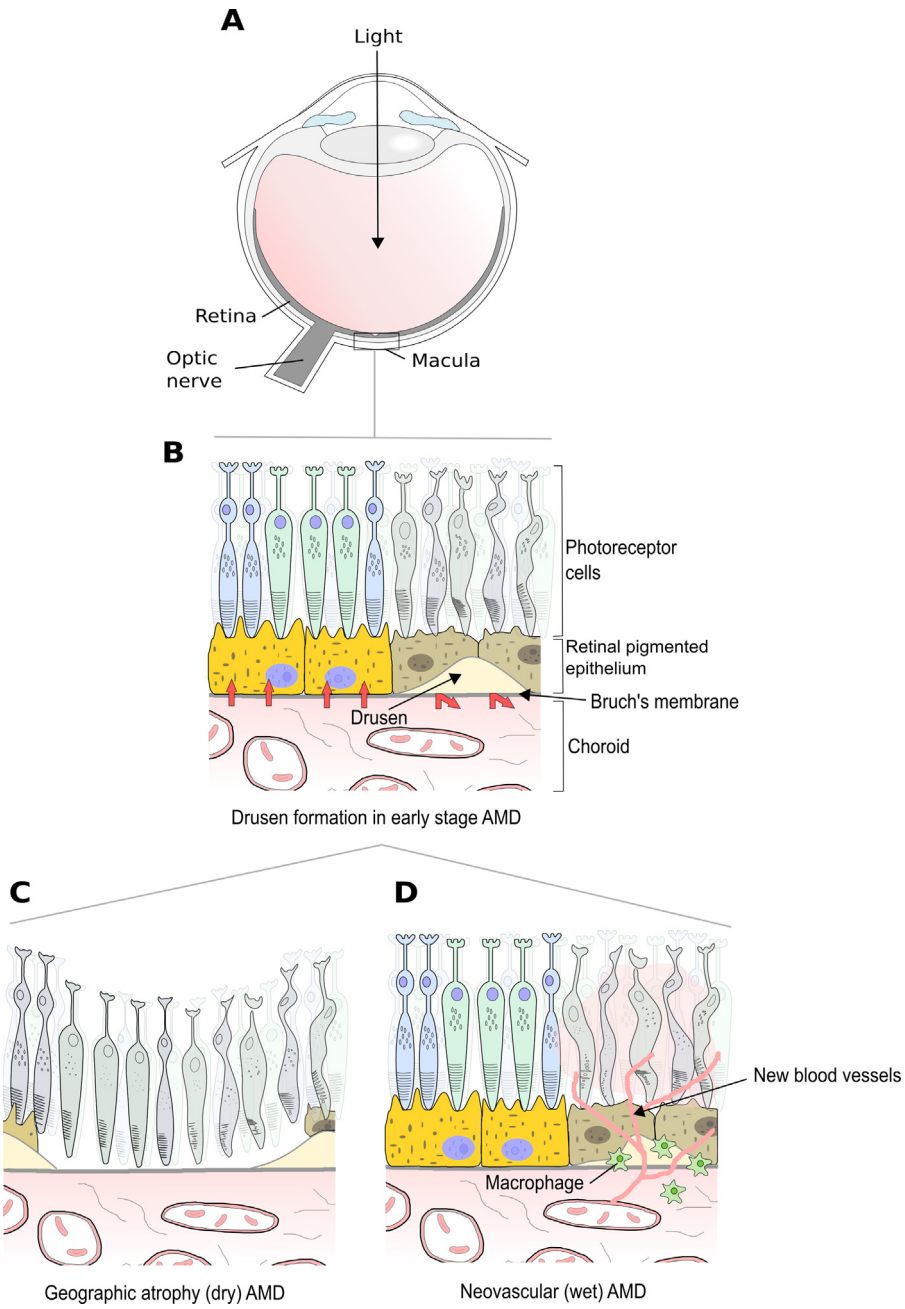

Fig. 1. A cross-section diagram of the human eye (A) indicating the location of the retina and macula. In early AMD (B) accumulation of subretinal drusen can block nutrient uptake and cause damage in the photoreceptor cell layer, eventually leading to geographic atrophy (or 'dry') AMD (C) with complete RPE cell loss and photoreceptor neurodegeneration. Neovascular or 'wet' AMD (D) is characterized by invasion of abnormal, leaky blood vessels and macrophages in the retina, leading to photoreceptor cell degeneration.

Drusen are extracellular deposits containing cellular debris, lipids and various protein components including a number from the innate immune system (Johnson et al., 2000; Mullins et al., 2000; Crabb et al., 2002; Anderson et al., 2010). These drusen form in the extracellular matrix that separates the photoreceptor cells and the supporting retinal pigment epithelium (RPE) from the choroid and the posterior eye's blood supply (Fig. 1). This disrupts the nutrient flow from the choroid to the RPE cells, leading to cell disruption and death, which subsequently affects the health of the adjacent photoreceptor cells. The consequences of drusen formation are also believed to contribute to excessive blood vessel growth from the choroid into the retina, bleeding, macrophage recruitment through the compromised Bruch's membrane, all of which leads to cell damage. The late-stage disease is commonly subdivided into two categories, neovascular ('wet') and atrophic ('dry') and albeit having different disease characteristics, both are usually preceded by formation of drusen and retinal pigment irregularities.

2. Common variants

2.1. Factor H and factor H related proteins

The implication that complement was somehow involved in AMD initiation and/or progression initially focused around the discovery of complement byproducts in drusen, including the main