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Review

Can innate and autoimmune reactivity forecast early and advance stages of age-related macular degeneration?

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ABSTRACT

Age-related macular degeneration (AMD) is a major cause of central vision loss in persons over 55 years of age in developed countries. AMD is a complex disease in which genetic, environmental and inflammatory factors influence its onset and progression. Elevation in serum anti-retinal autoantibodies, plasma and local activation of complement proteins of the alternative pathway, and increase in secretion of proinflammatory cytokines have been seen over the course of disease. Genetic studies of AMD patients confirmed that genetic variants affecting the alternative complement pathway have a major influence on AMD risk. Because the heterogeneity of this disease, there is no sufficient strategy to identify the disease onset and progression sole based eye examination, thus identification of reliable serological biomarkers for diagnosis, prognosis and response to treatment by sampling patient's blood is necessary. This review provides an outline of the current knowledge on possible serological (autoantibodies, complement factors, cytokines, chemokines) and related genetic biomarkers relevant to the pathology of AMD, and discusses their application for prediction of disease activity and prognosis in AMD.

Contents

1. Incidence and etiology

In modern medicine biomarkers are important tools helping in diagnosis, drug discovery, and clinical care of any disease, in particular, complex degenerative diseases such as age-related macular degeneration (AMD) [1]. AMD is a major cause of legal blindness in persons over 55 years of age in developed countries [2]. It is estimated that 6 to 10 million Americans are blind from AMD and new cases are diagnosed in the U.S. each year [3]. It has been reported that annual incidence of advanced stage AMD (neovascular AMD and geographic atrophy) in Caucasian Americans was 293,000 new cases per year (3.5 per 1000 persons) and was 38% higher in women compared to men [4].

Macular degeneration is characterized by the disruption of the macula, the central part of retina responsible for high acuity vision [5]. AMD is a complex disease in which genetic as well as environmental risk factors, such as cigarette smoking, diet, and lifetime light exposure influence its progression [6]. The thickening of the Bruch's membrane and

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accumulation of debris (drusen) on the retinal pigment epithelium/Bruch's membrane are the ocular signs of AMD (Fig. 1) [7–9]. It starts with small numbers of drusen and then larger numbers, in effect leading to end-stage AMD and loss of central vision [10,11]. Although the initial drusen deposits are not associated with macular blindness, those individuals with drusen are considered at risk for developing more advanced forms of AMD and loss of vision [12]. End-stage AMD occurs in one of two forms: geographic atrophy or choroidal neovascularization. Approximately 90% of patients with AMD have the non-neovascular "dry" form characterized by atrophy of the retinal pigment epithelium (RPE), and loss of photoreceptor cells in the macula [2,12].

Choroidal neovascularization, the "wet form" of AMD is characterized by the development of new blood vessels, originating in the choroid, that break through Bruch's membrane and the RPE and invade the subretinal space or sub-RPE space [12]. These new blood vessels leak blood into the retina, causing distortion of vision and in consequence loss of central vision. Also, these blood vessels can hemorrhage in the compartment between the foveal photoreceptors and RPE, leading to immediate blindness [13]. The neovascular form affects about 10% of persons with the disease [12]. AMD stages were recently defined by the Age-Related Eye Disease Study (AREDS) classification scheme, which was based on results, obtained from examining retinal and fundus color photographs and is shown in Table 1 [11].

Pathology of AMD involves the disruption of many physiological pathways, but chronic inflammation is thought to play a major role in AMD progression (Fig. 2) [14]. Low-grade inflammation is mediated by many factors and stimulated by a complement system of an alternative pathway, which starts within Bruch's membrane, and then leads to early and advanced, exudative AMD forms [15–17]. It is important to point out that the low-grade inflammatory process exists also in the aging retina under physiologic conditions, however, persistent inflammation may trigger early and then advanced forms of the disease [18,19]. Yet, most individuals do not progress to end stage AMD. Even if inflammatory activities are a cause of early AMD, it is not known whether therapeutic interventions that reduce systemic inflammation will reduce the incidence of early AMD [20]. As a result, there is no adequate strategy to identify the disease stage based only on the risk factors.

In recent years, biomarkers have become major indicators of personalized medicine, in particular, molecular biomarkers that provide minimally invasive objective procedures that help in diagnosis, prognosis and response to treatment [21,22]. The aim of this review is to provide an overview of the current knowledge on possible serological and genetic biomarkers in relation to different stages of AMD, and discuss their application for prediction of disease activity and prognosis in AMD.

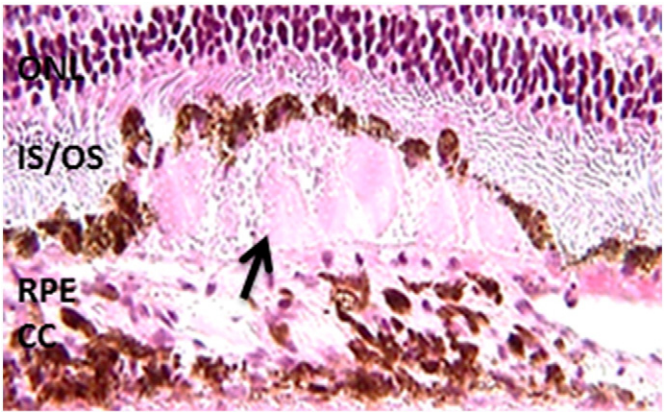

Fig. 1. Retina with subretinal debris (drusen) present beneath multiple layers of retinal pigment epithelium (RPE) cells (arrow). ONL - outer nuclear layer, IS/OS – inner segments/outer segments of photoreceptor cells; CC – choriocapillaris.

Table 1
AMD clinical classification.

Classification of AMD	Definition[a]
No apparent aging changes	No drusen and no AMD pigmentary abnormalities
Normal aging changes	Only drupelets (small drusen ≤63 μm) and no AMD pigmentary abnormalities[b]
Early AMD	Medium drusen >63 μm and ≤125 μm and no AMD pigmentary abnormalities[b]
Intermediate AMD	Large drusen >125 μm and/or any AMD pigmentary abnormalities[b]
Late AMD	Neovascular AMD and/or any geographic atrophy

AMD - age-related macular degeneration.
[a] Lesions assessed within 2 disc diameters of fovea in either eye.
[b] AMD pigmentary abnormalities = any definite hyper- or hypopigmentary abnormalities associated with medium or large drusen but not associated with known disease entities.

2. AMD and serological biomarkers

Serological biomarkers such as autoantibodies (AAbs), complement proteins and cytokines/chemokines can be measured in the blood, using minimally invasive methods. In the study of AMD, there are reports of the relationship between serum C-reactive protein (CRP), complement proteins, tumor necrosis factor-α receptor 2, interleukin-6, and soluble vascular cell adhesion molecule-1 independent of age, smoking status, and other factors [23]. Also, serum anti-retinal AAbs were detected at a much higher incidence in individuals with early AMD than in persons without AMD, suggesting their diagnostic value [24–26]. Below, we discuss the association of inflammatory mediators, autoantibodies, and complement proteins in early and advance AMD. In investigating markers associated with disease, one should establish whether a given biomarker shows an increased or decreased presence in disease as compared to healthy individuals.

2.1. Inflammatory mediators in AMD: cytokines and chemokines

Inflammation has been proposed as a central mechanism in the pathogenesis of AMD [7,27]. The presence of hematopoietic cells in the macular choroid and the analysis of drusen from human retinal lesions clearly proved the presence of inflammatory mediators and innate immune cells, such as macrophages and microglia that strongly supported their role in disease [20,28]. At all stages of AMD, macrophages are one of the main inflammatory cell types that are correlated with choroidal neovascularization (CNV), drusen, geographic atrophy, and ruptures of the Bruch's membrane [29,30]. Moreover, T cells and M1 macrophages can be activated by oxidative damage in AMD pathogenesis [31]. The RPE cells are also an important source of cytokines in the posterior segment of the eye [32,33]. When activated, they can produce

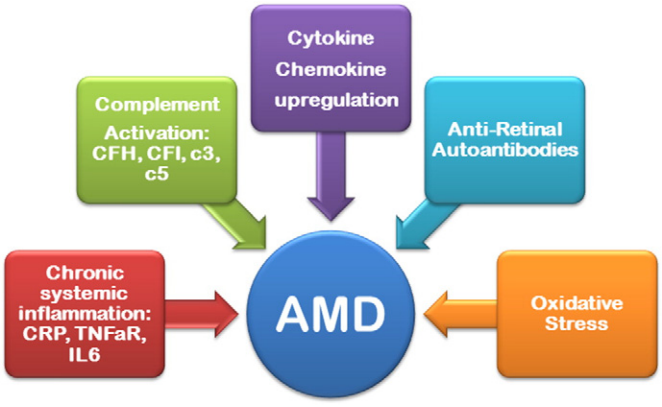

Fig. 2. A diagram showing potential factors influencing early AMD.