REVIEW ARTICLE

The role of proteases and inflammatory molecules in triggering neovascular age-related macular degeneration: basic science to clinical relevance

SIVARAMAN A. BALASUBRAMANIAN, KAAVYA KRISHNA KUMAR, and PAUL N. BAIRD

VICTORIA, AUSTRALIA

Age-related macular degeneration (AMD) causes severe vision impairment in aged individuals. The health impact and cost of the disease will dramatically increase over the years, with the increase in the aging population. Currently, antivascular endothelial growth factor agents are routinely used for managing late-stage AMD, and recent data have shown that up to 15%–33% of patients do not respond to this treatment. Henceforth, there is a need to develop better treatment options. One avenue is to investigate the role proteases and inflammatory molecules might have in regulating and being regulated by vascular endothelial growth factor. Moreover, emerging data indicate that proteases and inflammatory molecules might be critical in the development and progression of AMD. This article reviews recent literature that investigates proteases and inflammatory molecules involved in the development of AMD. Gaining insights into the proteolytic and inflammatory pathways associated with the pathophysiology of AMD could enable the development of additional or alternative drug strategies for the treatment of AMD. (Translational Research 2014;164:179–192)

Abbreviations: AMD = age-related macular degeneration; RPE = retinal pigment epithelium; nvAMD = neovascular age-related macular degeneration; VEGF = vascular endothelial growth factor; HtrA1 = heat temperature required factor A; IL = interleukin; TNF = tumour necrosis factor; MMP = matrix metalloproteinase

INTRODUCTION

Age-related macular degeneration (AMD) is a progressive, debilitating eye disease affecting the macula or the central area of the retina. It is the leading cause of irreversible vision loss in people aged 50 years or older in the developed world.[1,2] Because of the rapidly growing aging population, the number of individuals visually impaired from AMD is expected to increase substantially in the future years.[3]

The diagnosis of AMD is based on its diverse clinical presentation.[4] Drusen is considered to be the hallmark clinical sign of early AMD (Fig 1, *A*), and these are focal extracellular deposits of proteins and lipids between the retinal pigment epithelium (RPE) and Bruch's membrane (BrM) of the retina.[4] Most people with early stages of AMD do not complain of vision impairment, but as the disease progresses to later stages, there is distortion of central vision. Late-stage AMD includes

From the Centre for Eye Research Australia, The Royal Victorian Eye and Ear Hospital, University of Melbourne, Melbourne, Victoria, Australia; Walter and Eliza Hall Institute, Parkville, Victoria, Australia; Department of Medical Biology, University of Melbourne, Parkville, Victoria, Australia.

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Reprint requests: Sivaraman A. Balasubramanian, 32 Gisborne Street, East Melbourne, Victoria 3002, Australia; e-mail: siva.bala@unimelb.edu.au.

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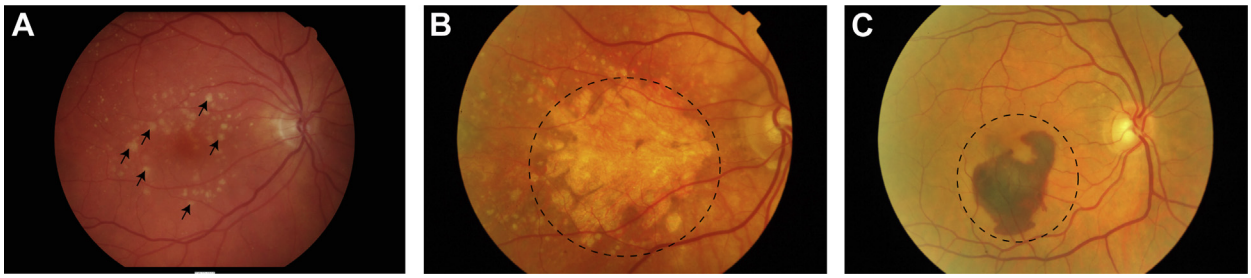

Fig 1. Fundus photographs of the various clinical presentations of age-related macular degeneration. **A,** Drusen (indicated by arrows): yellow to yellowish white deposits found in the deeper layers of the retina. **B,** Geographic atrophy (dotted circle): sharply demarcated areas of depigmentation with enhanced visualization of deep choroidal vessels. **C,** Neovascular age-related macular degeneration (dotted circle): neovascularization leading to retinal hemorrhage. *Photo courtesy: The Royal Victorian Eye and Ear Hospital, Melbourne, Australia.*

geographic atrophy (dry AMD) and wet or neovascular AMD (nvAMD). In geographic atrophy there is damage to the RPE (Fig 1, *B*), and nvAMD is characterized by the presence of choroidal neovascular (CNV) membranes (Fig 1, *C*). Geographic atrophy can be a risk factor or precursor for nvAMD,[5] and this review focuses on nvAMD. New blood vessels grow and leak under the RPE during nvAMD, causing severe central vision loss or blindness.[4] Although nvAMD only accounts for approximately 10%–20% of the overall incidence of AMD, this subtype is responsible for 90% of cases of severe vision loss (20/200 or worse).[6,7]

Various imaging instruments, such as color fundus photography, fluorescein angiography, and ocular coherence tomography, are available today to diagnose, assess the severity, monitor the progression based on structural changes of the macula, and guide the treatment and retreatment of AMD. Despite a growing interest in AMD, the options for treatment remain limited. Oral intake of a cocktail of antioxidant vitamins together with lifestyle changes, such as losing weight and cessation of smoking, is advised for managing early-stage AMD.[8] Application of a low-energy nanosecond laser has been developed recently to slow the progression of early AMD, but long-term results are still being awaited to establish its efficacy.[9] The late stage, or nvAMD, routinely is managed by the use of antivascular endothelial growth factor (anti-VEGF) agents.

VEGF is an endothelial cell-specific mitogen that stimulates angiogenesis, leading to nvAMD.[10] The anti-VEGF agents are administered by intravitreal injections on more than one occasion and provide better visual outcome compared with the other treatment option, that is, photodynamic therapy.[11] Commercially available anti-VEGF agents include pegaptanib sodium (Macugen; OSI-Eyetech and Pfizer, San Dimas, CA), bevacizumab (Avastin; Genentech, South San Francisco, CA), and ranibizumab (Lucentis; Genentech, South San Francisco, CA). Although these drugs are effective in the treatment of nvAMD, it has been reported that approximately 15%–33% of patients with nvAMD are "nonresponders" despite undergoing treatment with anti-VEGF agents and a further 30%–40% of patients will experience no improvement in vision and no change in lesion size (termed as stable or subresponders).[12-14]

According to Krebs et al,[15] patients were categorized as nonresponders if 2 of the 3 following parameters were present: decreased best-corrected visual acuity, increased lesion size, and the absence of a decrease in central retinal thickness. Therefore, there is a pressing need to develop novel therapeutics, which entails understanding the disease process: its etiology, prognosis, and risk factors. Recently approved drug aflibercept (Eylea; Regeneron and Bayer, Tarrytown, NY) was reported to be effective in treating patients with nvAMD who did not respond to other anti-VEGF therapies. Future follow-up studies are required to confirm its efficiency.[16]

AMD is a complex multifactorial disease involving genetic, environmental, metabolic, and functional factors.[17] Known nonmodifiable risk factors for AMD include Caucasian race, elderly age, and genetic predisposition, whereas the most consistent modifiable risk factor for AMD is smoking.[18] A plethora of other modifiable risk factors, including alcohol consumption, hypertension, obesity, cumulative sunlight exposure, and cardiovascular disease, also have been associated with AMD.[18-21] These risk factors have been linked to increased oxidative stress and hypoxia,[22] inflammation, and the immune system in both triggering and subsequent progression of AMD.[23,24] Increased oxidative stress results in escalated proteolysis of the cellular component of RPE cells, primarily by proteases.[25] The loss and breakdown of RPE cells augment expression of the inflammatory system, which in turn enhances the expression of VEGF, leading to the development and progression of AMD (Fig 2).[25-27] Proteases and inflammatory markers have been observed in a number of ocular pathologies such as diabetic retinopathy,[28]