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Aging is not a disease: Distinguishing age-related macular degeneration from aging

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ABSTRACT

Age-related macular degeneration (AMD) is a disease of the outer retina, characterized most significantly by atrophy of photoreceptors and retinal pigment epithelium accompanied with or without choroidal neovascularization. Development of AMD has been recognized as contingent on environmental and genetic risk factors, the strongest being advanced age. In this review, we highlight pathogenic changes that destabilize ocular homeostasis and promote AMD development. With normal aging, photoreceptors are steadily lost, Bruch's membrane thickens, the choroid thins, and hard drusen may form in the periphery. In AMD, many of these changes are exacerbated in addition to the development of disease-specific factors such as soft macular drusen. Para-inflammation, which can be thought of as an intermediate between basal and robust levels of inflammation, develops within the retina in an attempt to maintain ocular homeostasis, reflected by increased expression of the anti-inflammatory cytokine IL-10 coupled with shifts in macrophage plasticity from the pro-inflammatory M1 to the anti-inflammatory M2 polarization. In AMD, imbalances in the M1 and M2 populations together with activation of retinal microglia are observed and potentially contribute to tissue degeneration. Nonetheless, the retina persists in a state of chronic inflammation and increased expression of certain cytokines and inflammasomes is observed. Since not everyone develops AMD, the vital question to ask is how the body establishes a balance between normal age-related changes and the pathological phenotypes in AMD.

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1. Introduction: aging, homeostasis, and age-related macular degeneration

Age-related macular degeneration (AMD) is a degenerative disease of the photoreceptors and retinal pigment epithelium (RPE) in the human macula. Early stages of the disease feature deposition of extracellular debris, known as drusen, from the basal side of the RPE into Bruch's membrane. From this point on, the disease may progress to one of two forms, known as geographic atrophy (GA) and neovascular AMD (nAMD). Patients with GA AMD exhibit areolar loss of the photoreceptors and RPE in the macula, whereas patients with choroidal neovascularization (CNV) experience breakthrough of choroidal neovascular vessels across Bruch's membrane, RPE, the neuroretinal layers and in some cases, deposition of exudates, and hemorrhaging (Coleman et al., 2008).

Late-stage AMD is a leading cause of central blindness in industrialized nations (Congdon et al., 2004; Pascolini et al., 2004) and as of 2010 is responsible for approximately 5% of all blindness globally (Pascolini and Mariotti, 2011). Additionally, it is projected that AMD will afflict 3 million Americans over the age of 50 by the year 2020 (Friedman et al., 2004). It is important to note that AMD is a multifactorial disease with no one single cause. Known risks factors for development of AMD are many (AREDS, 2000): age, smoking status (Cackett et al., 2011; Kabasawa et al., 2011; Seddon et al., 1996), obesity and dietary fat consumption (Seddon et al., 2003a, 2003b, 2006), and genetic polymorphisms, particularly the genes *CFH*, *C2*, *C3*, and *ARMS2/HRTA1* (Y. Chen et al., 2010). Additionally, much remains to be learned regarding the factors that lead to development of GA versus CNV. Only 10–15% of patients experience CNV and yet this form of the disease accounts for approximately 80% of all severe visual loss and blindness in AMD cases (Jager et al., 2008). As far as treatment strategies go, there has been success with intravitreal injection of anti-vascular endothelial growth factor (VEGF) to deter CNV, but there are no robust methods to treat patients suffering from GA AMD. In the latter cases, patients are encouraged to adopt lifestyle changes, including daily administration of the AREDS2 formulation (AREDS2, 2013).

The association of AMD with aging begs the same line of questioning geared towards all age-related disease. What is it about aging that makes individuals susceptible to diseases they never faced in their youth? Perhaps more poignantly, why is it that not all aging individuals experience age-related pathologies? In the case of AMD, what differentiates the anatomical, physiological, and biochemical changes common to every member of the elderly population from changes that cause disease and changes that do not? To these questions, we suggest that AMD be viewed as a disease very much to do with dysregulation and dysfunction of homeostatic processes that change as a function of age. These processes include imbalances that arise within the photoreceptor/RPE/choriocapillaris/choroid system (Bhutto and Lutty, 2012; Curcio et al., 2009) in addition to immunological and inflammatory imbalances resulting from the age-related increase in prevalence of the para-inflammatory state (Xu et al., 2009). Furthermore, we intend to distinguish some of the ways in which AMD can be viewed as a disease in which the aging process goes a few steps further than it should. The penultimate section frames these issues from a clinical/translational standpoint, exploring some of the ways in which this knowledge and the gaps in knowledge may be leveraged in order to treat patients suffering from AMD.

2. The aging paradigm

On the street, it is relatively simple to categorize individuals into one of a few subsets based on perceived biological age, including childhood, adulthood, and old age. Childhood, from infancy through adolescence, is very much a continuation of the developmental processes that begin during fertilization and terminate only when the body has reached maturity. It is from this point on that we call someone an adult, though there is no gold standard for distinguishing a 20-year-old from a 30-year-old, nor a 30-year-old from a 40-year-old. At least this does not hold true for everyone: there are the 30-year-olds who look 50 and 60-year-olds who look 40. However, we believe most people would agree that there is a high degree of variability when it comes to correlating biological age with chronological age using a purely observational method.

Further investigation into the philosophical nature of aging and how biological and chronological age are related led us to the work of noted Gerontologist Aubrey Nicholas Jasper De Grey. De Grey posits that biological aging stems from the body's need to undergo metabolism. Metabolism involves interactions between reactive chemical species, which lead to production of damaging toxins