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Chapter

Introductory Chapter: Macular Degeneration: Mechanisms of Action

Giuseppe Lo Giudice

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1. Introduction

Macular degeneration refers as a progressive condition in which patients are suffering of a disease that is a leading cause of blindness in the elderly worldwide. In particular age-related macular degeneration (AMD) is characterized by two forms, wet and dry, that are classified on the presence or absence of new blood vessels (CNV) [1]. However, there is emerging evidence that significantly overlap which exists in the underlying pathogenetic mechanisms of these clinical conditions. Clarification of the overlapping process that lead to wet and dry diseases will be crucial for the future development in the prevention and treatment of AMD.

By definition, early AMD is characterized by confluent regions of drusen, which are multicomponent, heterogeneous aggregates that lie both external and internal to the retinal pigment epithelium (RPE) cells [2–3]. They are located primarily at the macular region of the retina with relative sparing of the surrounding peripheral retina.

A slow growth of drusen occurs over years or decades with RPE cell death and synaptic dysfunction during the advanced stage of AMD, with the development of advanced AMD (CNV or geographic atrophy (GA)) [4]. All we know about pathogenetic mechanism underlying AMD is that it has the RPE as the fulcrum of AMD pathogenesis. However, whereas, the stepwise development of certain maladies is relatively well-defined, no such hallmarks of disease progression have been identified in AMD.

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2. The RPE: at the core of AMD disease

The RPE is the fulcrum of AMD pathogenesis. In general, in spite of interindividual heterogeneity, RPE dysfunction and atrophy precedes the final stages of AMD [5–6]. The RPE cells integrate numerous stimuli to regulate its own health, while also receiving and broadcasting signals to and from the retinal microenvironment. There are several human AMD samples displaying significant interindividual variation in RPE transcript expression, which supports the concept that heterogenic stress responses underlie a categorical AMD phenotype. The effect of specific AMD-associated stresses and AMD in retinal molecular composition have been cataloged by mean genome-wide stress-response transcriptome and proteome assays on whole-genome RPE gene. Such studies reveal common protective and deleterious RPE gene responses that could clarify the key molecular basis of the disease. One of the most important evidences involved in the AMD pathology is the crosstalk of RPE with immune and vascular system. Indeed there are numerous overlapping proangiogenic mechanisms that underlie AMD, many of which involve

the intersection of immune and vascular system. Whether this immunovascular axis modulates RPE cell is not clear. However in the presence of the AMD pathogenesis, the critical event from which there is not return is RPE dysfunction and damage, although perturbations in other tissues (e.g., choroid, Bruch's membrane, and photoreceptors) are important burdens [7–9].

3. RPE vascular response in neovascular AMD

Response to complement and oxidative stress represent the two major pathways by which the RPE secretes VEGF-A [10–12]. Oxidative stress is the oxidation of cellular macromolecules and complement system, if left unregulated, can directly damage host tissue and recruit immune cells to the vicinity of active complement activation. Also these stresses may act inducing complement-induced RPE secretion of VEGF-A and other vasculogenic molecules in response to oxidative stress and activated complement [13]. However, it is important to emphasize as RPE not be only source of proangiogenic factors, the latter ones could originate from various immune cells or other cell types but RPE is a central player in CNV developing by two important step: (1) the potential for multiple distinct stresses to converge to produce a common (proangiogenic) effect and (2) the diversity of response molecules produced by the RPE that could drive angiogenesis.

4. RPE and immune response in neovascular AMD

There are multiple pathways by which the RPE can regulate the retinal immune-landscape, which in turn can regulate neovascularization in AMD:

1. Macrophages. The macrophages might be the hallmark of CNV [14]. Whether macrophages are critical for CNV development is not clear. The most macrophage activity in CNV development seems to be linked to complex local macrophage-polarizing factors. The role of a complex local regulation of macrophage vascular-modifying activity might be related to the vascular modeling during neovascular process. Among the many factors that control macrophage chemotaxis, VEGF-A has a well-defined role in recruitment of proangiogenic macrophages. However, there are still several questions, the answer to which has important therapeutic implications; whether suppression of VEGF-A dramatically increased the number of retinal macrophages within human neovascular membranes also increasing the activity of proangiogenic macrophages by inflammatory cell recruitment and leukocyte-endothelial adhesion, can this finding does explain the tachyphylaxis that occurs with multiple anti-VEGF-A treatments? Microenvironmental influences in CNV remains an area of needed research [15–16].

2. Microglia. Microglia are another immune cell type that might modulate human CNV pathogenesis. However, while macrophages accumulate in human CNV, it is not known whether microglia do. In the largest histopathologic characterization of microglia in AMD, which observed microglia at various stages of AMD pathology, there was a change in microglia morphology, but not in number AMD compared to nondiseased retinas. Interestingly, one-third of all infiltrating cells (immune and nonimmune cells) in experimental CNV are not classified, and immune cells besides macrophages and microglia could modify CNV. Future work could provide a comprehensive assessment of the composition of cellular infiltrate in CNV specimens. Full understanding of the

immunopathology of CNV will require an assessment of all potential vascular-modifying immune cells and their subsets, in health, disease, and following therapeutic intervention [17].

5. Dry AMD

Toxic accumulations, either within the RPE cell or at the RPE-Bruch membrane interface, are the molecular hallmarks of dry AMD [18]. Dry AMD may be considered as a form of a metabolic storage disease; two approaches to preventing their formation or removing them after formation are attempts to prevent RPE damage. AMD and other neurodegenerative disorders occur when a particular cell or group of cells die. In this scenario, AMD might share some pathogenetic mechanisms with several common neurodegenerative diseases of aging, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease in which mitochondrial defects, DNA mutations, impaired structural integrity, and defective mitochondrial function. Other toxins accumulate in AMD; an excessive amount of "lipofuscin," which is non-degradable debris that accumulates in the RPE with age, is associated with AMD. In the presence of light, lipofuscin forms ROS and is toxic to RPE cells [19–20].

6. Autophagy and damage control

Cells are equipped with machinery to discard toxic accumulations with a self-cleansing process called macroautophagy. Autophagy of the mitochondria and other cellular debris could rejuvenate cells by disposing defunct organelles, a concept which has been reviewed for AMD. Autophagy may also regulate RPE health by reducing cytotoxicity that is secondary to a primary insult. Future work should address several basic questions about this cell survival mechanism in AMD [21–23].

7. Environmental risk factors

Smoking of cigarette confers the greatest numerical risk for AMD with two to three times likely than nonsmokers to develop AMD (smoking cessation reduces the risk of developing AMD) [24]. Several nutritional deficiencies are associated with AMD risk. In a recent epidemiologic study, omega-3 fatty acid (FA) intake was associated with a lower risk of AMD [25]. The protective effect of statins on AMD is not well established and would require long-term prospective interventional studies to confirm its relevance to AMD pathogenesis.

8. Genetics

One prevailing approach in AMD research was the genome-wide association studies (GWAS) that have been used in attempt to predict risk of disease, understand pathogenesis, and identify potential therapeutic target [26]. GWAS have indeed identified several genetic loci, which harbor genetic variants known as single nucleotide polymorphisms (SNPs) that are associated with an increased risk of AMD. Factor H (CFH) represents the complement gene variant conferring the greatest quantitative statistical AMD risk. CFH inhibits a key activation step in complement activation, thereby reducing complement-induced host cell damage and inflammation [27]. The predictive power of AMD risk assessment can be

augmented greatly by considering genetic information from multiple loci in combination with epidemiologic and environmental risk factors. In contrast taking into consideration disease prevalence, the positive predictive value of genetic variation to assess AMD risk is inconclusive, even when multiple genetic loci are considered. Next-generation sequencing technologies combined with rigorous biological definition of mechanistic implications of the identified variants are likely to yield more valuable insights both into disease pathogenesis and rational development of novel diagnostics and therapeutics in the coming decade.

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Author details

Giuseppe Lo Giudice
San Paolo Ophthalmic Center, San Antonio Hospital, Padua, Italy

*Address all correspondence to: giuseppe.logiudice@aulss6.veneto.it

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