Austin Journal of Genetics and Genomic Research

Austin Publishing Group

Open Access Full Text Article

Review Article

Age Related Macular Degeneration: a Complex Pathology

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Received: June 20, 2014; **Accepted:** July 22, 2014; **Published:** July 23, 2014

Abstract

Age-Related Macular Degeneration (AMD) is the leading cause of severe irreversible central vision loss and blindness in individuals of over 65 years of age in the developed countries. There are two types of AMD, the "dry" and "wet" forms. Both genetic and non-genetic (environmental) factors are considered for the onset of AMD. The etiology and pathogenesis of AMD are not well understood and remain a major challenge to understand. This review discusses recent advancement in genetics and genomics, and the molecular pathways involved in AMD pathogenesis.

Keywords: Age-Related Macular Degeneration; Choroidal Neovascularization; Polypoidal Choroidal Vasculopathy; HTRA1; Complement Factor H; Inflammation; Autophagy

Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness worldwide. At present, 8·7% of the worldwide population has AMD and by 2010 around 196 million expected to have AMD which is further increasing to 288 million in 2040 [1]. There are two types of AMD, the "dry" and "wet" forms. Wet AMD includes classic and occult choroidal neovascularization (CNV) and polypoidal choroidal vasculopathy (PCV). The chronic form "Dry AMD" typically develops first and is characterized by the deposition of acellular, polymorphous debris between the retinal pigment epithelium (RPE) and Bruch's membrane (BM) called "drusen". The excessive "drusen" deposition may lead to damage of the RPE, degeneration of collagen or elastin in BM, the outer retina and the choroid vasculature, This may lead to wet form of AMD where abnormal vessels grow within the sub-RPE space or grow out in to the retina by rupturing the RPE, this form occurs at the late stage. Therefore, dry AMD is considered a precursor for the wet AMD. Caucasian AMD patients predominantly exhibit late stage geographic atrophy of dry "AMD" while Asian AMD patients frequently have CNV or PCV forms of "wet AMD" with few or no drusen. Wet AMD represents only 10 to 15% of the overall prevalence of AMD but is responsible for more than 80% of cases of legal blindness [2]. Overall, AMD is a progressive, polygenic and multi factorial disease with a poorly understood etiology. Numerous studies have suggested the involvement of advanced age, race, heredity, and a history of smoking and alcohol drinking, oxidative stress, inflammation and immune response [3,4], which makes AMD pathology extremely complex.

AMD Genetics

Over the years, the involvement of genetics in the development of AMD has been very well studied and established. Genome-Wide Association Studies (GWAS) have revealed more than 30 risk loci (e.g. 1q25-31, 9p13, 9p24, 10q26, 15q21, and 17q25) and have implicated several candidate genes—*CFH*, *C3*, *C2-CFB*, *CFI*, *HTRA1*/ *ARMS2*, *CETP*, *TIMP3*, *LIPC*, *VEGFA*, *COL10A1*, *TNFRSF10A*, and *APOE* with AMD [5-7]. Among them, chromosome loci 1q32 and 10q26 are major candidate regions associated with the susceptibility of AMD [5,8-17] including PCV [18-20]. The genetic variants in complement factor H at chromosome loci 1q32 and additional complement-related genes firmly established a link between the complement cascade and AMD biology, which have been implicated in mediating drusen formation [21]. *CFH* Y402H is a major AMD susceptibility variant in Caucasians and has been shown that heterozygote alleles conferred a 4.6-fold where-as homozygote alleles have a 7.4-fold increased risk, as compared with the homozygous non-risk genotype [14]. On the other hand, chromosome loci 10q26 is more complex due to the strong linkage disequilibrium (LD) across this region comprising of three genes: pleckstrin homology domain containing family A member 1 (*PLEKHA1*), age-related maculopathy susceptibility 2 (*ARMS2*) and high-temperature requirement A serine peptidase 1 (*HTRA1*) [8,14-17]. Because of strong LD, statistical genetic analysis alone is incapable of distinguishing the effect of an individual gene in this locus and has yielded widely conflicting results [15,17,22-28]. As a result, the functional involvement of *HTRA1*, *ARMS2* or *PLEKHA1* in AMD remains uncertain, despite strong genetic evidence. So far, rs10490924, indel polymorphisms of *ARMS2,* and rs11200638 of *HTRA1* promoter region are most significantly AMD associated haplotypes at this locus [29]. The *HTRA1* gene encodes an evolutionarily conserved multifunctional serine protease that is ubiquitously expressed in mammalian tissues but *ARMS2* is only expressed in certain primates with unknown function. The subcellular localization of ARMS2 is controversial and studies suggesting that it present in mitochondria, extracellular matrix, or as a non coding RNA [16,17,27]. An increased level of *HTRA1* is suggested to play a potential role in the pathogenesis of AMD [15,23-25]. Therefore, we studied the functional involvement of *HTRA1* by transgenically expressing human *HTRA1* in mouse RPE and showed that increased HTRA1 induced characteristic features of PCV, including branching networks of choroidal vessels (BVN) and polypoidal lesions (polyps). Ultrastructural study revealed degeneration of both the elastic lamina and tunica media of choroidal vessels, as well as the degradation of the elastic lamina of Bruch's membrane in *hHTRA1*$^{+}$ mice. Another group also reported the degradation of EL in BM when over expressing mouse HTRA1 in RPE [30]. The phenotypes of *hHTRA1*$^{+}$ mouse we generated share remarkable similarities to the

Citation: Kumar S and Fu Y. Age Related Macular Degeneration: a Complex Pathology. Austin J Genet Genomic Res. 2014;1(1): 5.

well established clinical features of human PCV (e.g. BVN, polyps, late geographic hyper fluorescence, pigment epithelium detachment, and hyper fluorescent plaque) [31-33]. The *hHTRA1*$^{+}$ mouse is the first PCV model and no other animal models exist with these features. The strengths and limitations of available AMD animal models are comprehensively reviewed by Pennesi ME [34]. HTRA1 is clearly important in maintaining the vasculature by inhibiting the signaling of TGFb family members [35,36]. Loss-of-function mutations in HTRA1 were linked to familial ischemic cerebral small-vessel disease [37,38]. In the eye, knockout of HTRA1 leads to reduced blood vessels in mouse retina [39]. However, several studies demonstrated that AMD associated variants at 10q26 locus are not correlated with the expression level of *HTRA1* in AMD-affected eyes [26, 27,40-42]. Recently, it is shown that AMD linked synonymous SNPs within exon 1 of *HTRA1* makes it conformationally defective. This conformationally defective HTRA1 is more susceptible to proteolysis and has a reduced binding capacity to IGF-1, which supports cellular division and growth therefore may compromise photoreceptors and choriocapillaris survival [43]. Currently, all three possibilities (up-regulation, down-regulation or no change) in HTRA1 levels with AMD-associated variants are being investigated. HTRA1 is the leading candidate for the 10q26 genetic risk. However, more studies are necessary to establish a firm link.

Inflammation and AMD

In recent years, numerous clinical-genetic studies documented the crucial role of inflammation and immune-mediated processes (e.g. complement activation) in the pathogenesis of AMD. The ectopic levels of complement components C3a and C5a, C5 and C5b-9 terminal complement complex [44-46], complement factor H (CFH) [13, 47], membrane cofactor protein (MCP) [48], and C-reactive protein (CRP) [49] are observed in AMD patients and clearly indicating that complement activation is crucial in AMD pathogenesis. In fact, the hallmark of AMD, "drusen", contains large amount of components involved in the complement pathway [44,50-57]. In addition, it's been shown that Membrane Attacking Complex (MAC) formation is increased in the photoreceptors that may trigger the apoptotic processes inducing retinal degeneration [50-53,57-58]. The deposition of esterified/unesterified cholesterol (7kCh) and glycation/lipoxidation end products (AGEs/ALEs) has been identified in the retina, BM and in RPE/choroid of human AMD donor eyes [59-61], suggesting that lipid metabolism pathways also have a crucial role in AMD pathogenesis via inflammation. The accumulation of macrophages in the AMD tissues suggest an important role for macrophages in AMD pathogenesis [62-65], which is well supported in AMD animal model studies [66-70]. However, macrophage populations are heterogeneous and can be both protective and destructive to local tissues. Based on macrophage functions, surface markers, and cytokine/chemokine profiles they are characterized as classically activated macrophages (M1), which are generally pro-inflammatory. On the other hand, alternatively, activated macrophages (M2), facilitate tissue repair and neovascularization. Both types of macrophages have been characterized in only a limited number of AMD tissues samples [62,63]. The precise roles and impacts of macrophages in AMD are unclear and debated in the AMD field. It is important that more histochemical studies shall be performed to elucidate those factors that alter macrophage polarity and mediate angiogenesis. These factors may have the potential of aiding in new anti-inflammatory therapies for AMD. Recent studies suggest NLRP3 inflammasome may play a critical role in AMD [71]. NLRP3 is an intracellular pattern-recognition receptor, which responds to a wide variety of danger signals. The exact mechanism by which NLRP3 inflammasomes become activated has remained unclear. During the past decade, the major breakthrough is the development of anti-VEGF therapy for wet AMD. VEGF-A induces proliferation, sprouting and tube formation of endothelial cells and plays a major role in CNV. In addition to VEGF, aberrant levels of interleukins IL-6, IL-8 and IL-10 are also found in - CNV patients.

Autophagy and AMD

Recently, autophagy has caught the attention of AMD researchers. Autophagy plays a critical role in removing misfolded or aggregated proteins, clearing damaged organelles, such as mitochondria, endoplasmic reticulum and peroxisomes [72]. It also eliminates intracellular pathogens to keep post-mitotic cells healthy and functional [73]. The autophagy processes are highly active in the RPE layer because RPE cells are subject to oxidative stress, high oxygen tension, lifelong light illumination, and are involve in daily phagocytosis of photoreceptor outer segments. As we read in the previous section, the physiological balance between various interlinked pathways (eg vascular growth factor pathways, lipid pathways and oxidative stress pathways) has been perturbed in AMD which may impair the autophagy process. Some exosome and autophagy markers have been detected in drusen [74]. Inflammation and local hypoxia are the hallmarks of autophagy and are present in the aging choriocapillaris, RPE cells, and neural retina [75]. It is well known that oxidative stress leads to mitochondrial DNA damage, increases ROS generation and reduces the metabolic capacity. The increased mitochondrial stress and dysfunctional autophagy in the RPE cells of AMD patients also support the involvement of autophagy in the pathology of AMD [76,77]. The association between the variant of *CST3,* (encoding cystatin C), an inhibitor of lysosomal cysteine proteases, and AMD has been established. Also, increased serum levels of cystatin C found in AMD patients are correlated with the risk of development of advanced AMD [78,79]. In addition, *in-vitro* studies on lysosome function on RPE cells also provided insights on the disruption of lysosomal functions and possible role of lysosomes in the development of AMD [79-82]. Vascular dysfunctions also result in oxidative stress, that is, overproduction of ROS, which induces further changes in the retinal and choroidal vasculature. Such changes can also be evoked by hypoxia, since it stimulates synthesis and release of hypoxia-inducible factor-1 (HIF-1) and vascular endothelial growth factor (VEGF) that contribute to neovascularization (NV). Recent reports suggest that dysfunctional autophagy activates inflammasomes probably through the dysregulation of mitochondrial homeostasis [83,84]. To date, there is no consensus as to whether autophagy inhibitors or activators would be beneficial in AMD therapy.

Treatment

There is no cure for AMD. Nevertheless, AMD treatment may prevent severe vision loss or slow the progression of the disease considerably, for example, anti-angiogenic drugs (anti-VEGF) and photodynamic therapy with verteporfin (PDT-V) are very

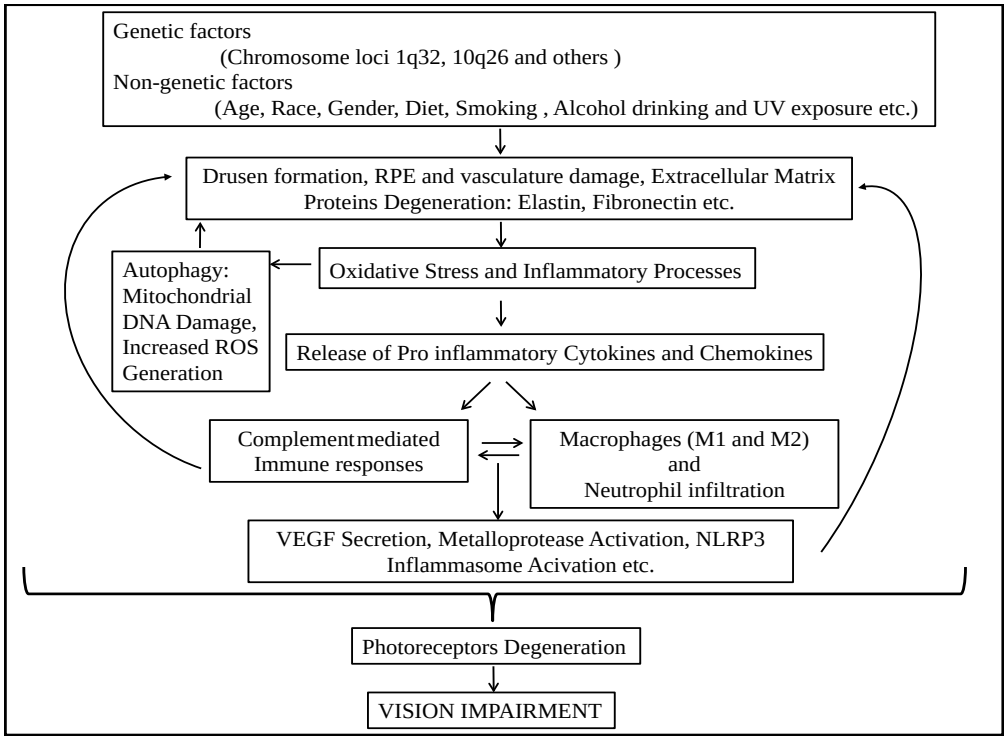

Figure1: A schematic representation on the risk factors and possible pathological mechanisms of AMD.

effective for wet AMD. However, the anti-VEGF therapy is not very effective in treating PCV compared with classic CNV (or type 2 neovascularization). Monoclonal antibodies Ranibizumab (Lucentis) and Bevacizumab (Avastin) are used to treat "wet form" of AMD by targeting all isoforms of VEGF-A. Currently, bevacizumab is the most widely used anti-VEGF agent throughout the world due to its significantly lower cost and similar efficacy compare to Lucentis. Another new promising drug is Aflibercept (known as VEGF-Trap) is a human recombinant fusion protein which consists of extracellular domains of VEGF receptor 1 and 2 (VEGFR-1 and -2) fused with the Fc portion of IgG1. It binds to VEGF-A, VEGF-B, and placental growth factor (PlGF). It has a higher affinity for VEGF compared to other anti-VEGFs, including bevacizumab and ranibizumab. For more detail we recommend reading the recent review from Hanout et al. 2013 [85]. Indeed, currently very little is available to prevent the progression to more serious stages for "dry" AMD's patients. Colloquially, quitting smoking and a healthy diet of dark green leafy vegetables and fruits supplemented by zinc and anti-oxidant vitamins (Vitamins E, C, and beta carotene) are recommended.

Conclusion

AMD is a genetically well-characterized disease with a high complexity. Despite several important findings in the last decade, we still do not have a clear picture of biological pathways that are actual culprits for AMD. Based on recent findings, the dysfunction and/or degenerative damages photoreceptors, RPE and BM of the macula, are initiated by "attacks" from drusen, aging, genetic and environmental risk factors. These primary factors create a para-inflammatory environment which may provoke the infiltration of macrophages, lymphocytes, neutrophils and various cytokines to the degenerated tissue sites in AMD patients and cause further damage and lead to "wet AMD" (Figure1). We have witnessed remarkable progress in identifying genetic risk factors for AMD. However, investigations of the underlying disease mechanisms by causal alleles are needed. It is also important to elucidate factors and/or signaling pathways that regulate inflammation, oxidative stress, and autophagy of this disease in order to develop effective preventive and treatment therapies.

Acknowledgement

This work was supported by NIH grant 1R01EY022901, P30 EY014800, the Career Development Award from Research to Prevent Blindness (RPB), C. M. Reeves & M. A. Reeves Foundation, E. Matilda Ziegler Foundation for the Blind, Knights Templar Eye Foundation, and an unrestricted grant to the Department of Ophthalmology at the University of Utah from RPB.

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Austin J Genet Genomic Res - Volume 1 Issue 1 - 2014
ISSN : 2471-030X | www.austinpublishinggroup.com

Citation: Kumar S and Fu Y. Age Related Macular Degeneration: a Complex Pathology. Austin J Genet Genomic Res. 2014;1(1): 5.