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AGE RELATED MACULAR DEGENERATION-A REVIEW ON ITS PATHOPHYSIOLOGY AND MANAGEMENT

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ABSTRACT

Age-related macular degeneration (AMD) is the leading cause of legal blindness in the industrialized world. AMD is characterized by accumulation of extracellular deposits, namely drusen, along with progressive degeneration of photoreceptors and adjacent tissues. AMD is a multifactorial disease encompassing a complex interplay between ageing, environmental risk factors and genetic susceptibility. Chronic inflammation, lipid deposition, oxidative stress and impaired extracellular matrix maintenance are strongly implicated in AMD pathogenesis. However, the exact interactions of pathophysiological events that culminate in drusen formation and the associated degeneration processes remain to be elucidated. Despite tremendous advances in clinical care and in unravelling pathophysiological mechanisms, the unmet medical need related to AMD remains substantial. Although there have been major breakthroughs in the treatment of exudative AMD, no efficacious treatment is yet available to prevent progressive irreversible photoreceptor degeneration, which leads to central vision loss. Compelling progress in high-resolution retinal imaging has enabled refined phenotyping of AMD in vivo. These insights, in combination with clinicopathological and genetic correlations, have underscored the heterogeneity of AMD. Hence, our current understanding promotes the view that AMD represents a disease spectrum comprising distinct phenotypes with different mechanisms of pathogenesis. Hence, tailoring therapeutics to specific phenotypes and stages may, in the future, be the key to preventing irreversible vision loss.

KEYWORDS: Age-related macular degeneration (AMD), Pathophysiology, Management, Anti-VEGF therapy.

INTRODUCTION

Age-related macular degeneration (AMD) is the world's leading cause of blindness among the elderly.[1] Globally, AMD ranks third as a cause of blindness after cataract and glaucoma. Most of the affected individuals live in developed countries. In general, advanced AMD is rare before the age of 55, and more common in persons of 75 years and older. The prevalence of neovascular AMD and geographic atrophy appears to vary in different ethnic and racial groups throughout the world. The prevalence of advanced AMD increases with each decade after the age of 50 with the highest prevalence occurring after the age of 80. Approximately 11 million people have AMD, a prevalence that is similar to that of all invasive cancers combined, and more than double of that of Alzheimer's disease.[2]

AMD is a degenerative disorder affecting the macula, often associated with visual impairment in the older age group (above 50 years of age). Since AMD adversely affects activities of daily living, rendering it more difficult to read, write and drive, many affected individuals lose their independence in their retirement years. AMD is classified into two forms, a non-neovascular or "dry" form and a neovascular or "wet" form. In the wet form, rapid, severe vision loss can occur due to the development of new blood vessels from the choroid into the subretinal space, within Bruch's membrane, or in the subretinal pigmented epithelial (RPE) space that can leak fluid, hemorrhage, and with time, develop fibrosis around these neovascular tufts. In dry AMD, vision loss is typically gradual. Dry AMD is defined clinically by the presence of at least intermediate-size yellow sub-RPE deposits called drusen (63 µm or larger in diameter), RPE pigmentary abnormalities, and subretinal deposits called reticular pseudodrusen.[3] These pigmentary abnormalities are the clinical manifestation of RPE degeneration, which can ultimately culminate in death of the RPE and of the overlying photoreceptors. Multiple medium-sized drusen, large-sized drusen, RPE pigmentary changes, and AMD duration are independent risk factors for developing late AMD.[3] In late, dry AMD or geographic atrophy (GA), patches of RPE cell loss become confluent. When GA involves the fovea, vision loss is severe.

While successful treatment using anti-vascular endothelial cell growth factor treatment is available for wet AMD[4], no effective prevention or treatment is available for dry AMD. The Age-related Eye Disease Study (AREDS) trials demonstrated that antioxidant micronutrient supplements given to intermediate AMD patients modestly reduced the risk of developing advanced disease, and in particular, wet AMD.[5,6] A number of other approaches for treating GA have failed in human trials (e.g., visual cycle inhibitors, sustained release of neurotrophic factors, NT501, Neurotech, and complement pathway inhibitors, eculizumab, Soliris).[7,8,9]

The lack of preventive measures and treatment for dry AMD underscores the importance of gaining a better understanding of its pathobiology. Prior research has implicated strong roles for inflammation, and complement in particular, mitochondrial dysfunction, oxidative stress, lipid abnormalities, and cell death in dry AMD pathobiology, but their precise mechanisms are unclear. Furthermore, the relative magnitude and temporal contributions of these factors remain elusive. Due to the multifactorial etiology, effective management of dry AMD may require multiple targets that differ for prevention and therapy of early, intermediate, and late-stage disease. These targets will likely result from the elucidation of the mechanistic pathways that are critically involved at each disease stage. The National Advisory Eye Council established a working group to evaluate the current knowledge on dry AMD pathobiology and propose future research directions that would expedite the development of new treatments and the purpose of this perspective is to report on the findings from this working group. The intention is to raise awareness of the impact of AMD on public health, review the current understanding of the pathobiology of this disease, offer future research directions that focus on unbiased systems approaches, encourage the continued efforts of dedicated vision scientists who focus on dry AMD, and encourage the broader scientific community to join in a collaborative effort to develop therapies for this complex and debilitating disease.

PATHOPHYSIOLOGY

The macula is the central area of the retina, 6 mm in diameter, which contains more than one layer of ganglion cell nuclei. The central macula or fovea, 0.8 mm in diameter, is cone-dominated while the surrounding parafovea is rod-dominated. In the normal aging parafovea, the retinal pigment epithelium (RPE) become enlarged and often multinucleated.[10] In early, dry AMD, parafoveal rods die before either the RPE or cones.[11] With advancing dry AMD, the RPE degenerates with severe changes in cell shape, often becoming multilayered, and dissociated from Bruch's membrane with migration into the retina or below Bruch's membrane.[12] These changes suggest that RPE dysfunction has a central role in the development of photoreceptor loss in dry AMD.

Coincident with RPE changes, Bruch's membrane develops basal deposits or accumulations of heterogeneous debris. With aging, the inner Bruch's membrane accumulates apolipoprotein B100-containing lipoproteins[13], which stimulate inflammatory infiltration, accumulation of cellular debris, and the formation of basal deposits. Basal laminar deposits accumulate between the RPE and its basement membrane, and are associated with dry AMD when they become thick and composed of heterogeneous debris. Basal linear deposits, which form within Bruch's membrane's inner collagenous layer, are specific to dry AMD. Nodular-shaped basal linear deposits and focal basal laminar deposits accumulations are visualized as soft drusen on clinical exam.

The choriocapillaris is the sinusoidal capillary network of the choroidal circulation that is adjacent to Bruch's membrane. Choriocapillaris endothelium has fenestrations that enable the bidirectional movement of fluid and macromolecules with the RPE and outer retina. Early dry AMD is characterized by loss of the choriocapillaris, which provides oxygen and nutrients for RPE and photoreceptor survival. Choriocapillaris loss precedes RPE atrophy and correlates with drusen size and density, thus implicating choriocapillaris dysfunction in RPE survival and drusenogenesis.[14] Finally, reticular pseudodrusen are extracellular deposits that accumulate in the subretinal space. While initially overlooked, improved imaging has shown that reticular pseudodrusen are part of a continuum of pathology that is referred to as subretinal drusenoid deposits (SDDs). The presence and progression of SDD can predict disease advancement to GA.[15]

1. OXIDATIVE STRESS

Photoreceptors and the RPE have high metabolic activity that results in reactive oxygen species (ROS) generation. The high metabolic demand requires a high oxygen partial pressure of 70–90 mmHg[16], and the unique, photo-oxidative stress from light exposure make the macula a high oxidative stress microenvironment. In addition, several lifestyle choices such as cigarette smoking, and high fat or high glycemic index diets, add to the oxidative stress burden, and are associated with AMD risk.[17,18,19] The AREDS trials showed that, among patients with intermediate AMD, antioxidants lower the risk of developing advanced AMD. Finally, genetic variants in oxidative stress-related genes, including MTND2*LHON-4917G, NADH subunits, SOD2, and PPARGC1A, are associated with AMD risk.[20,21,22]

2. LIPIDS

Because lipids can occupy more than 40% of drusen volume[23], and polymorphisms in several lipid-related genes, including LIPC, CETP, ABCA1, and APOE, are associated with AMD risk[24,25,26,27], lipids play a critical role in drusenogenesis. The RPE accumulates cholesterol either from phagocytosis of photoreceptor outer

segments or from the ingestion of lipoproteins from the circulation. The RPE recycles cholesterol back to the photoreceptor or eliminates it through reverse cholesterol transport by effluxing cholesterol to Apo AI-I to form a high-density lipoprotein (HDL).[28] With lipoproteinemia, lipoprotein ingestion is excessive, and the RPE becomes cholesterol-overloaded. Should the reverse cholesterol transport fail, the RPE will secrete apoB100 lipoproteins into Bruch's membrane.[29] With aging, Bruch's membrane accumulates advanced glycation end products, which induces lipoprotein lipase, causing the retention and oxidation of lipoproteins.[30,31] Hydroxyapatite surrounds the oxidized lipoproteins, which get coated with lipids and inflammatory proteins to promote drusen growth.[32] Since cones contain more cholesterol than rods, drusen tend to accumulate in the cone-rich fovea.[33] Photoreceptors and the RPE have an active bidirectional cholesterol transport where HDLs accumulate cholesterol released into the subretinal space and cycles cholesterol between the RPE and photoreceptors. With RPE dysfunction, cholesterol-laden HDLs accumulate in the subretinal space, triggering inflammation, and the accumulation of complement factors, vitronectin, and immune cells.[34,35,36]

3. INFLAMMATION AND INNATE IMMUNITY

Altered immune responses that lead to destructive neuroinflammation are thought to contribute to the dry AMD phenotype. Para inflammation is a low-grade cytoprotective adaptation to local stress that is intermediate between immune-mediated homeostasis and chronic inflammation that maintains cellular and tissue function. Loss of Para inflammation control contributes to dry AMD by invoking a chronic, heightened immune response that causes tissue destruction. The hallmarks of immune activation include drusen formation, subretinal and choroidal recruitment of microglia/macrophages, mast cell activation, and RPE immune activation.[37,38,39] This immune activation may involve close interplay between intracellular complement regulation and NLRP3 assembly in either immune cells or the RPE, although a recent study argues against NLRP3 inflammasome activation in the RPE.[40] At present, it is unclear at what point such immune activation converts from being protective to pathologic.[41,42]

4. COMPLEMENT SYSTEM

Genetic studies have identified complement pathway gene variants with AMD risk, which strongly implicates the complement pathway in driving AMD progression. However, the assumption that these variants induce excessive complement activation that leads to tissue injury remains unvalidated. CFH acts as both a cofactor during Factor I-mediated C3b cleavage and as a decay accelerating agent against the alternative pathway C3-convertase. The 402H variant increases complement activity. However, it is unclear whether this increased activity induces elements of the dry AMD phenotype because CFH 402H also has impaired interaction with C-reactive protein, malondialdehyde, and heparan sulfate proteoglycans that can increase inflammation and lipoprotein accumulation.[43,44,45]

5. MITOCHONDRIAL DYSFUNCTION

While age-associated mitochondrial dysfunction reduces cytoprotective pathway function, mitochondrial impairment severe enough to cause tissue damage will herald disease. In dry AMD, RPE mitochondrial mass is reduced, mitochondria are morphologically abnormal, and mitochondrial DNA (mtDNA) damage increases with disease severity.[46,47] In early and dry AMD, before a patient loses vision, mtDNA damage in genes involved in electron transport complex I, II, IV, and V in the RPE accumulates more in the macula than in the periphery, and occurs in the RPE prior to the neurosensory retina.[48,49] With mitochondrial loss and injury, the RPE has reduced baseline oxygen consumption and reserve capacity, and elevated ROS, making them poorly responsive to stress.[50] This change results in decreased ATP production, compromised calcium- and ROS-mediated signaling, and altered nucleotide metabolism, amino acid, lipid, and heme biosynthesis, which subsequently impair essential cytoprotective or specialized functions.[51] In addition, mitochondrial damage can activate apoptosis, leading to RPE degeneration and death, two key features of AMD.

6. CELL DEATH

Photoreceptor cell death is the basis for permanent visual decline in dry AMD. Therefore, identifying the mechanisms involved in photoreceptor death is critical for developing new treatments to prevent permanent visual loss. Photoreceptor cell death is principally caused by apoptosis and necrosis.[52] Preventing photoreceptor cell death by specifically blocking apoptosis has been unsuccessful when inhibiting caspase because photoreceptor death is also caused by receptor-interacting protein kinase (RIPK)-mediated necrosis.[53] Likewise, when RIPK is inhibited, photoreceptor loss is unaffected. In contrast, inhibiting both RIPK and caspases impairs both necrosis and apoptosis and rescues photoreceptors.[53] The mechanisms for RPE cell death may differ from those of photoreceptors. Double stranded RNA (dsRNA), a component of drusen, is a ligand for Toll-like Receptor-3, which mediates the innate immune response and cell death. After injecting dsRNA into the eye, photoreceptors die by apoptosis and RPE cells die by necrosis.[54] Since cell death pathways are redundant and complementary, combination therapies that block both apoptosis and necrosis may be effective for dry AMD.

7. GENETICS AND GENOMICS

Genetic approaches have contributed enormously to our understanding of AMD pathobiology. The association of APOE variants with AMD was the first indication that a specific gene affected disease risk.[55,56] The advent of high-throughput technologies and agnostic genome-wide searches using family-based linkage and genome-wide association study (GWAS) approaches facilitated the

identification of genes on chromosomes 1 (CFH)[57,58,59,60] and 10 (ARMS2/HTRA1).[61,62,63,64] These discoveries are remarkable because they are among the few genetic associations for a common disease that increase the odds of disease by more than 2.5 among heterozygotes and 7.5 among homozygotes.[62] The association with CFH prompted focused investigation of complement system genes which uncovered associations with *C3*, BF/C2, and CFI.[65,66,67,68]

RISK FACTORS

Risk factors for AMD may be broadly classified into 2 types:

A. **Environmental factors:** smoking, sunlight exposure, and nutritional factors including micronutrients, dietary fish intake, and alcohol consumption.

B. Personal factors

1) Sociodemographic - Age, sex, race/ ethnicity, heredity, and socioeconomic status.

2) Ocular - Iris color, macular pigment optical density, cataract and its surgery, refractive error, and cup/ disc ratio)

3) Systemic factors – cardiovascular disease and its risk factors, reproductive and related factors, dermal elastotic degeneration, and antioxidant enzymes.

CLASSIFICATION

1. DRY AGE-RELATED MACULAR DEGENERATION

Drusen are one of the earliest signs in AMD. Clinically, typical drusen appear as focal, whitish yellow excrescences deep to the retina. Typical drusen deposits are located beneath the retinal pigment epithelium and Bruch's membrane and vary widely in number, shape size, and distribution. Most drusen are 20-100 µm and are characterized as hard or soft.

Hard drusen, which appear as round, discrete yellow-white spots are commonly identified in many populations. They are not age-related and do not carry an increased risk for the development of neovascularization.[69] In contrast, soft drusen are ill defined, with non-discrete borders, measuring 63 µm or greater. Different studies and trials have indicated that large, soft, confluent drusen are age-related and associated with a higher risk for the development of advanced AMD with neovascularization.[70]

If the foveal center is spared, good visual acuity may be preserved, although reading vision may remain poor because of a constricted central visual field.[71]

2. WET AGE-RELATED MACULAR DEGENERATION

Wet AMD is characterized by the presence of neovascularization within the macula.

Choroidal neovascularization (CNV) is an ingrowth of new vessels from the choriocapillaris through a break in the outer aspect of Bruch's membrane into the sub-pigment epithelial space.

The clinical manifestations of neovascular AMD can include the following: subretinal fluid, intraretinal fluid, retinal, subretinal, or sub-RPE hemorrhage, lipid exudates, gray or yellow-green discoloration or plaque-like membrane, RPE detachment, RPE tear.

In the end-stage of the disease, the neovascularization results in a fibrovascular or atrophic macular scar (*disciform scar*), and subsequent permanent damage to the central vision.[71]

MANAGEMENT

The appropriate treatment for AMD depends on the stage of the disease. In all stages, the elimination of risk factors is clearly advisable; above all, smoking cessation. Multiple prospective population-based studies have shown that smokers have a higher risk of progression of AMD than non-smokers, even after AMD has been diagnosed.[72] Early detection of AMD may thus help motivate the patient to change lifestyle habits that promote the progression of the disease.

1. ANTI-VEGF MONOTHERAPY

Dry AMD

No effective treatment is yet available for the atrophic late form of AMD. All of the clinical trials carried out to date have yielded negative results, including recent ones that have focused on modulators of the complement system.[73] The same reasons are generally cited for these failures as for the failure of treatment for other degenerative diseases of the central nervous system: in particular, that the treatment has presumably been initiated too late in the course of a disease cascade that has already reached a point of no return. At a certain stage in the disease process, neural tissue; in this case, the retinal photoreceptors have been irreversibly lost; nor has any way yet been found to prevent the further loss of photoreceptors at the periphery of the already atrophic regions of the macula. Clinical research into the atrophic late form of AMD now centers on gaining a better understanding of the pathogenesis of disease progression, so that future interventions can be directed at the most promising targets and applied with optimal timing.

Wet AMD

At the beginning of this article, the aging of the population was cited as a likely reason for the increasing prevalence of AMD. As a logical consequence of this, one would expect to have seen a marked increase in the number of cases of blindness or severe visual impairment over the past few years; yet statistics from Germany and other countries[74] reveal a stagnation, or even a decrease, in the rates of blindness and severe visual impairment, even though the prevalence of AMD has measurably risen. This is presumably largely due to the introduction,

in 2005, of an effective treatment for the most aggressive form of AMD, the exudative late form.[75] In 2006, after the publication of two successful phase 3 clinical trials, the journal Science listed anti-VEGF therapy for exudative macular degeneration as one of the top ten scientific breakthroughs of the year. In this form of treatment, an anti-VEGF drug is injected directly in the vitreous body of the eye (intravitreal administration). Four such drugs are now available, one of them off-label (bevacizumab, in use since 2005) and three that have been approved for use in Europe: ranibizumab (approved 2007), aflibercept (approved 2012), and brolucizumab (approved 2020).

Anti-VEGF therapy is ineffective, however, in the early, intermediate, and atrophic late stages of AMD. It is thus very important that the subtype of AMD present in each individual eye be properly diagnosed, so that timely treatment can be initiated in those who have exudative late AMD—if at all possible, before the disease has led to irreversible visual loss.

2. COMBINATION THERAPY

Photodynamic therapy

Combination treatments using ranibizumab or bevacizumab and PDT have yielded visual outcomes that are comparable to those given by ranibizumab alone, while the number of treatments required to maintain a dry macula is reduced slightly.[76]

Photodynamic therapy + anti-VEGF + dexamethasone

Trials of triple therapy are under way to investigate the treatment of exudative AMD using PDT to eradicate the existing CNV, steroid to limit the inflammatory response and reduce further upregulation of VEGF, and anti-VEGF to prevent any further angiogenesis.[77]

3. OTHER TREATMENT OPTIONS

Stem cell therapy

It has been proposed to both restore retinal function and protect viable tissue from degeneration. Subretinal transplantation of human embryonic stem cell–derived RPE cells (MA09-hRPE) has been performed in two patients. One patient had GA due to AMD.[78] Patients were systemically immunosuppressed during the trial, and no safety concerns arose during the observation period. Further clinical investigations in AMD are planned.

Brimonidine

It is a highly selective α_2-adrenergic agonist that has gained attention for its role in reducing intraocular pressure in the treatment of glaucoma. More recent experimental and animal models suggest brimonidine protects retinal ganglion cells, bipolar cells, and photoreceptors from degeneration after a number of types of insults, including retinal ischemia and retinal phototoxicity.[79] The neuroprotective effects of brimonidine are likely multifactorial. Proposed mechanisms include upregulation of trophic factors such as brain-derived neurotrophic factor in retinal ganglion cells and of intrinsic cell survival signaling pathways and antiapoptotic genes.[80]

CONCLUSION

Age-related macular degeneration negatively affects visual acuity in the elderly population. Although there is no single preventive method, alteration of modifiable risk factors can effectively impede the development of AMD. Both genetic and environmental risk factors are influential in the occurrence of AMD. Several major gene loci have been demonstrated as profoundly affecting the development of AMD. Modification of environmental risk factors, such as smoking and diet can play a preventive role in the progression of AMD. Recent progress in early diagnosis of the disease has facilitated early and efficient intervention. The visual activity has been found to remain stable in more than 70% of treated eyes, while just under 20% actually improve in visual acuity markedly after the initial treatments. Anti-VEGF therapy is the best available treatment for AMD. However, the current regime is being refined through research on optimal monotherapy and combination strategies. There is ongoing, exciting research looking at immunomodulation and targeting various inhibition sites in the angiogenesis pathway, which may be the future of AMD treatment. Further studies are required to gain more clarification of specific pathophysiology mechanisms that will allow us to develop novel preventive and therapeutic pathways in the future.

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