AGE-RELATED MACULAR DEGENERATION: A NEW VIEWPOINT

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1. ABSTRACT

Age-related macular degeneration (AMD) is a major cause of blindness in the United States. AMD can be categorized into an atrophic (dry) form and a neovascular (wet, exudative) form. The atrophic form involves alterations of pigment distribution, loss of RPE cells and photoreceptors and diminished retinal function due to an overall atrophy of the cells. The neovascular AMD involves proliferation of abnormal choroidal vessels, which penetrate the Bruch's membrane and RPE layer into the subretinal space, thereby forming extensive clots and/or scars. Both environmental and genetic factors are suspected to play a role in AMD. Despite extensive genetic screening of candidate genes only two associations have been identified with AMD (Adenosine triphosphate (ATP)-binding cassette rim (ABCR) protein and apolipoprotein E gene-ApoE). The ABCR protein is retinal specific and accounts for only 3% of AMD cases. ApoE is not specific to the retina, and has been more intriguingly associated with Alzheimer's, another disease of age. The most consistent major risk factor in AMD is age. Our studies on the ACE gene show an association of protection with an Alu element insert, which might be affecting the level of the ACE gene. The ApoE 4 allele and the ACE Alu+/+ genotype have both been shown to be a risk for Alzheimer's and protective for AMD. Given these recent genetic associations, we should examine possible common pathways in diseases of age and their interaction with human genetic polymorphisms.

2. AGE-RELATED MACULAR DEGENERATION: CLINICAL DESCRIPTION

The most common cause of decreased best corrected vision over 65 years of age in the United States and Western Europe is the retinal disorder known as age-related macular degeneration (AMD) (51,60). Approximately 23% of the individuals between 65-74 have some degree of AMD. This increases to 35-40% between the ages of 75-84 years (51). In the United States an estimated 10 million patients have decreased vision due to AMD. With the increasing age of the population, it is predicted that 21 million individuals are at risk.

AMD is a significant health problem in the United States because 1) we do not understanding the etiology of the disease; 2) we can not prevent the onset of the disease (besides addressing risk factors such as stop smoking, use UV protection, use antioxidant vitamin supplements); 3) we have only limited techniques to treat the advanced forms; and 4) the advanced cases of AMD have profound visual loss.

The earliest changes found in AMD consist of scattered macular or perimacular drusen (lipoproteinaceous deposits within the inner Bruch’s membrane) (1,32,77). In general, drusen by themselves usually have a minimal effect on the visual acuity. However, their presence can alter the Bruch’s membrane upon which the retinal pigment epithelial (RPE) cells are situated (78). This is suspected to play a role in the degeneration of the RPE cells that occurs. Another feature of early AMD is sites of hyperpigmentation (proliferation of RPE cells) within the macular region.

2.1. Atrophic (dry) AMD

In AMD, the atrophy can occur in small, focal regions or larger, more extensive areas (> 175 µm) that are known as geographic atrophy. The atrophy can involve the RPE cells, the overlying photoreceptors and in some cases the underlying choroid (76,81,95,97). For patients older than 75 years of age, there is a prevalence rate of 3.5% for
geographic atrophy (45,48,103). This increases to approximately 20-35% of patients older than 90 years of age (37). Advanced geographic atrophy accounts for approximately 20% of the patients with vision < 20/200 (96,98,100). It affects both eyes in 48%-65% of patients and the progression rate is often similar (100). There are many more patients with moderate atrophy that have some degree of involvement but still retain functional vision because often the fovea is not involved. In general, atrophy in the fovea can lead to loss of “central, reading” vision. If the atrophic area is outside of the foveal region, then the patient might have a scotoma but retain “central, reading” vision.

2.2. Neovascular (wet, exudative) AMD

The most devastating form of AMD is the neovascular form (26,62). Fortunately it occurs in only 13-15% of AMD patients. The onset of neovascular AMD occurs because of the formation of an abnormal choroidal neovascular network beneath the neural retina. This leads to accumulation of subretinal fluid and blood leading to loss of visual acuity. Eventually there is total loss of functional retina in the involved region, as a large, disciform scar involving the choroid and retina forms.

There is controversy as to whether the atrophic and neovascular forms of AMD are a spectrum of the same disease or represent different disease processes. Certainly, they are not necessarily a continuum. For example, many patients with mild atrophic AMD do not go on to develop the neovascular form. Studies have reported that patients with bilateral geographic atrophy have a low rate of developing neovascularization (95,99). Alternatively, many patients with the neovascular form have minimal atrophic changes. In other respects, these 2 forms behave very differently. The atrophic AMD progresses slowly and functional vision can be maintained for a long period of time. In contrast, the onset of the neovascular AMD is rapid and the loss of vision is often very severe.

The treatments for atrophic AMD and neovascular AMD are also different. Since the atrophic AMD involves cell death of the RPE and photoreceptors, the options to re-establish viable functional retina are very limited. Transplantation of RPE cell and/or photoreceptors into the atrophic regions have been attempted with little success (2,3). In contrast, the neovascular AMD involves proliferation of networks of abnormal blood vessels, which can be targeted and destroyed by various methods. Laser treatments for neovascular AMD can stabilize the progression of the disease and often improve the vision. There are numerous ongoing clinical trials to evaluate treatments for neovascular AMD. These include laser photocoagulation of the neovascular net, photodynamic therapy combining laser and light sensitive dyes (PDT), transpupillary thermal treatment (TTT) and radiation.

3. AGE-RELATED MACULAR DEGENERATION: EPIDEMIOLOGY STUDIES AND RISK FACTORS

Over the past decade there have been a number of excellent epidemiology studies regarding AMD (49-52,59-61,64,87,88,104). While it is still not clear if hypertension, history of cardiovascular disease, and serum cholesterol are risk factors for AMD, most studies agree that the smoking, aging and family history are consistent risk factors (59,60,87). The Beaver Dam Eye Study also reported a 7 fold increased incidence of late AMD in females compared to males (51). Verifications that AMD has genetic components are provided by twin studies (19,47), familial aggregation studies (25,40) and population-based segregation analyses. Numerous investigations looking for specific genetic mutations have been performed (see Tables 1 & 2). It is very likely that AMD is a spectrum of diseases and more than a single etiology will be found.

4. RETINAL BIOLOGY, STRUCTURE AND FUNCTION:

While there are excellent reviews of AMD (13,14,16,28,69,79,80,93), understanding the retinal structure and biology can help us formulate questions and possible mechanisms for the disease process. The neurosensory retina, retinal pigment epithelium (RPE), Bruch’s membrane and choroid are located between the vitreous and the sclera (Figure 1). The neurosensory retina is composed of approximately 8 layers of glial, neural and vascular components. The outer nuclear layer (ONL) is composed of nuclei from the photoreceptor rod and cone cells. The outer segments of these cells contain visual pigments (opsins and rhodopsin) that are responsible for visual excitation. The inner nuclear layer, with its amacrine cells, bipolar cells, horizontal cells, ganglion cells and Mueller cells, is mainly responsible for the synaptic contacts to transmit the impulses from the photoreceptor cells to the optic nerve and ultimately to the visual cortex. Adjacent to the neurosensory retina is the retinal pigment epithelium (RPE) composed of a monolayer of cuboidal cells whose apical processes interface with the photoreceptor outer segments and the basal cell surface contacts Bruch’s membrane. The functions of the RPE cells include phagocytosis of the shed photoreceptor disks (106), absorption of light by the melanin granules (82), recycling of the vitamin A for the retina, and transport of growth factor/cytokines/metabolites to the retina (102). Bruch’s membrane is a specialized basement membrane of the RPE cells. The choroid is a network of vessels adjacent to Bruch’s membrane. It consists of the inner large fenestrated choriocapillaris and the outer plexiform network of larger vessels. The perfusion rate in the choroid is extremely high and the choroidal venous oxygen content is only 2-3% less that arterial blood. Drusen, the lipoproteinaceous deposits that are characteristic for AMD, are located between the basal cell surface of the RPE layer and Bruch's membrane (31,32).

In AMD, the region that is most often effected is the macula. The macula (5mm) can be subdivided into a central foveola (0.35 mm), a fovea (1.5 mm), and the perifoveal region (from the fovea to the vascular arcades (Figure 2). The fovea avascular zone (0.25 to 0.6 mm) is an area beneath the foveola and fovea that does not contain any capillaries. Within the human retina, there are two types of photoreceptor cells, the rods (120 million) and cones (6 million). As you move from the central foveola to
Figure 1. Diagram showing cross section of the layers of the retina.

Figure 2. Geometric view of the macular region shows the foveola (a), fovea (b), parafoveal area (c) and perifoveal regions (d).

the more peripheral perifoveal region, the rod/cone densities change. The foveola is entirely made up of cones, which dramatically decrease in number in the more peripheral retina. There are three types of cones found in humans, each having a different visual pigment (opsins), red, green or blue. The foveola only contains red and green cones. The peripheral retina outside the vascular arcades has few cones and is mainly rods, with rhodopsin as the visual pigment.

Structurally, the cones are different than the rods (Figure 1). The rod outer segments are made up of free-floating disks that are separate from the plasma membrane as opposed to simply the folding of the outer cell membranes found in cone cells (Figure 1). Functionally the cones provide fine detail, color and the vision that provides to us the ability to see small objects (20/20 vision). The rods provide night vision but give us vision to see only large objects (20/200 visual acuity). For that reason, patients with AMD that have lost the macular region, are unable to read of see fine print be still retain their peripheral vision and can see large objects.

4.1. Biochemical and Metabolic Activities of the Retina

The biology of light reception and transmission from the eye to the brain is an intricate process involving many interacting layers of the retina. The retina and the choroid complex are one of the most metabolically active sites in the body. The photoactivation of the rhodopsin and opsin molecules, for example, elicit chemical and electrical impulses that are ultimately transmitted to the visual cortex in the brain. The well-studied rhodopsin molecule is a trans-membrane protein with 7 helices spanning the disk membrane of the rod photoreceptor cell.
Age-related macular degeneration

Table 1. Genetic risks of Age-related macular degeneration

<table>
<thead>
<tr>
<th>Gene/polymorphism</th>
<th>Mutation</th>
<th>Case</th>
<th>Risk</th>
<th>Methodology</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCR</td>
<td>Single nucleotide polymorphism (SNP)</td>
<td>Associated with dry AMD; gene product found in rod disks</td>
<td>Increased risk with G1961E, D2177N</td>
<td>PCR/RFLP</td>
<td>4</td>
</tr>
<tr>
<td>ApoE</td>
<td>SNP</td>
<td>Non-retinal specific gene</td>
<td>Increased risk with epsilon 2 protection with epsilon 4 ?allele</td>
<td>PCR/RFLP</td>
<td>6,90</td>
</tr>
<tr>
<td>ACE</td>
<td>Alu Polymorphism</td>
<td>Associated with dry AMD non-retinal specific gene</td>
<td>Protection with ACE Alu&lt;sup&gt;+&lt;/sup&gt;</td>
<td>PCR</td>
<td>34</td>
</tr>
</tbody>
</table>

Table 2. Candidate genes that have been screen and being found to be negative for an association with AMD

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Associated diseases</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripherin/RDS</td>
<td>6p21.2 centomere</td>
<td>Pattern dystrophy; Adult vitelliform dystrophy; Digenic retinitis pigmentosa</td>
<td>24,43,84,93</td>
</tr>
<tr>
<td>TIMP-3</td>
<td>22q12.1-q13.2</td>
<td>Sorsby's fundus dystrophy</td>
<td>17,93</td>
</tr>
<tr>
<td>VMD2</td>
<td>11p12-q13</td>
<td>Best's disease (dominant)</td>
<td>56</td>
</tr>
<tr>
<td>EFEMP1</td>
<td>2p16-21</td>
<td>Malattia Leventinese</td>
<td>92,93</td>
</tr>
<tr>
<td>ELOVLA4</td>
<td>6q16</td>
<td>Stargardt-like dominant macular dystrophy</td>
<td>93</td>
</tr>
<tr>
<td>IMPG2</td>
<td>3q12.2-12.3</td>
<td></td>
<td>54</td>
</tr>
</tbody>
</table>

Rhodopsin is coupled to the chromophore 11-cis-retinal through a Schiff base linked to the epsilon-amino group of lysine-296. Upon light excitation rhodopsin decomposes to the opsin protein and the all-trans-retinal (9,10). This occurs through several intermediates of rhodopsin with distinct spectral absorptions (44,53,57). One intermediate, metarhodopsin II, transmits the photosignal to a G protein, which subsequently triggers the hydrolyses of cGMP and subsequent inhibition of the sodium channels on the cell membrane leading to hyperpolarization of the cell (27,70). This leads to a cascade of events that amplify the signal along its way to the brain (55,71). Thus in the dark the rod cell is depolarized and sodium permeable in the outer segment is higher than in the light. The rod inner segment has an ATP-dependent Na<sup>+</sup>/K<sup>+</sup>-pump that pumps sodium out of the cell. An interesting regulator of the Na<sup>+</sup>/K<sup>+</sup>-pump is the renin-angiotensin system (12,38,39,67), which will become an important piece of information when considering the association of the ACE gene with AMD, described in the gene section of this review. Large quantities of energy are needed to drive the Na<sup>+</sup>/K<sup>+</sup>-ATPase pump located on the outer segments of the photoreceptor cells.

The machinery that transfers light signals received by the photoreceptor cells to cells of the neural retina include the rhodopsin in rods, the opsin in the cones, the sodium channels and Na<sup>+</sup>/K<sup>+</sup>-ATPases. The health and replenishing of these components is an important example of the interdependency of the retinal cell layers. This is best exemplified by the process, where the disks of the rods and cones are continuously sloughed at the distal ends and the material undergoes phagocytosis and processing by the RPE cells. The complete renewal rate for these disks is 9-13 days (106). Approximately every 10 days each photoreceptor completely renews its outer segments. The ratio of RPE to overlying photoreceptors can be as great as 1:200, meaning that one RPE cell can be digesting an equivalent of 10 rod outer segments per day. This requires tremendous metabolic stamina by the RPE layer. Another example of interdependency is the recycling of retinol between the RPE cells and photoreceptors. For example, after the rhodopsin is photolyzed it is converted to the all-trans-retinol, transported to the RPE where it is converted into the 11-cis-retinal form and transported back to the outer segment of the photoreceptor cell for recombination with opsin (9,18). A consequence of this interdependency between the retina and RPE is that damage to one layer will drastically affect the other layer.

5. GENE ASSOCIATIONS AND AMD

Three genes have so far been associated with AMD (Table 1). These include the ATP-binding cassette (ABC) rim protein (ABCR), the apolipoprotein E (APOE) and the angiotensin converting enzyme (ACE). Other candidate genes were screened and were found not to be associated with AMD (17,54,56,84,92,93) (Table 2). Below we mainly focus on the genes that were found to be associated with AMD.

5.1. The ABCR gene

The first gene identified with an association with AMD, the ABCR (5), is involved in energy-dependent transport of yet an unidentified molecule or ion. In fact, the ABCR gene, mutations of which were identified in Stargardt macular dystrophy (4) and a minority of AMD cases, is found at the edge of the rod disks (Figure 1). ABCR is an adenosine triphosphate (ATP)-binding cassette (ABC) membrane transport protein family. The ligand for ABCR has not been identified. Other transport proteins are found on the rod cell membrane and include sodium channels located on the outer segment of the plasma membrane and Na<sup>+</sup>/K<sup>+</sup>-ATPases on the inner segment (Figure 1).

Unlike the apoE and ACE, the ABCR is retina specific and has been localized to the disk membrane of retinal rod outer segments (Figure 1). Initially the ABCR gene was described only in the rods (4). Since Stargardt and AMD macular dystrophies involved extensive foveal cone degeneration, it was argued that the cone degeneration was the indirect result of rod degeneration in the perifoveal region. Later, however, ABCR was also localized in cone photoreceptors (63) and it can now be argued that the degeneration is due to mutations in the ABCR molecules found in the cones.
The APCR gene contains 51 exons, spans an estimated 150 kb and has been localized to chromosome 1p22.3-p22.2 between markers D1S3361 and D1S236 (7). APCR mutations (19 different mutations), the majority representing missense mutations in conserved amino acid positions, were first identified with Stargardt disease (a juvenile form of AMD) (6). The APCR was later found to also be associated with AMD. However, amid controversy over the initial reports an International APCR Screening Consortium was established to confirm whether APCR is a susceptibility locus for AMD (5). Over 2400 patients and control subjects were screened for the 2 most frequent AMD associated variants (G1961E, D2177N) in APCR. These sequence changes were found in 1 in 40 patients (3.4%) and in only 0.95% of control subjects. Although the risk of AMD was elevated approximately 3 fold in D2177N carriers and approximately 5 fold in G1961E carriers, they only represented about 3% of the total AMD cases.

5.2 The APOE gene

The apolipoprotein E gene, APOE, is an important apoprotein of the chylomicron and binds to a specific receptor on liver and peripheral cells. Unlike the APCR gene, APOE is not retina specific, yet it has been localized in the retina and more intriguingly in drusen (46). The APOE gene has been localized to chromosome 19q13.2 (15). Many alleles of APOE have been identified, however, the major 3 alleles are the epsilon 2, epsilon 3, and epsilon 4 (73,105). The epsilon 2, epsilon 3, and epsilon 4 isoforms differ in amino acid sequence at 2 sites, residue 112 (called site A) and residue 158 (called site B). At site A, epsilon 2 and epsilon 3 have a cysteine and epsilon 4 has an arginine. At site B, epsilon 3, and epsilon 4 contain an arginine and epsilon 2 contains a cysteine. These APOE variants have functional effect on the protein by allowing differential binding to cell surface receptors. For example, it was shown that APOE epsilon 2, which contains cysteine at sites A and B, binds poorly with cell surface receptors, whereas epsilon 3 and epsilon 4, which contain at least one arginine, a charged amino acid, at either site A or site B, bind well. In genetic association studies the APOE- epsilon 4 variant was shown to have a statistically significant protective effect for AMD (46,83,90). The odds ratio (OR) associated with carrying an APOE- epsilon 4 allele was estimated as 0.43 (95% confidence interval: 0.21-0.88) and 0.34 (95% confidence interval: 0.17-0.68). Although the APOE epsilon 2 displayed an increased risk for AMD, it did not approach statistical significance. The APOE epsilon 4 association with AMD is intriguing, since it is known to be a strong risk factor for Alzheimer's disease (36,41,89), also a disease of old age.

5.3. The ACE gene

The angiotensin converting enzyme (ACE) is a dipeptidyl carboxypeptidase, which cleaves a dipeptide from the carboxy end of the decapeptide angiotensin I to yield the octapeptide angiotensin II (a hormone). Angiotensin II binds cell surface receptors, which transmit a signal by a guanine coupled second messenger system. ACE also deactivates bradykinin. Angiotensin II and bradykinin are potent vasoactive peptides, but also play a major role in cellular growth and differentiation of tissues.

The ACE gene is composed of 17 exons and has been localized to chromosome 17q23 (42). In the human population the levels of circulating serum ACE vary in different individuals (74). These levels are regulated in part by a polymorphism in a 300 base pair Alu element insertion in intron 16 (75). Homozygous individuals with the Alu"+" insert have approximately 50% lower circulating levels ACE compared to individuals that are Alu"-". PCR amplification has been used to distinguish the three genotypes for the ACE gene polymorphism: Alu"+", Alu"-", and Alu"−". It has been demonstrated that the Alu"−" genotype has been associated with insulin resistance (68,101), decreased renal function in patients with Type 2 diabetic nephropathy (23), and dementia (66).

In a recent study, we examined over 200 patients with AMD and found that the ACE Alu"+" genotype was protective against atrophic AMD (34). We have shown that the Alu"+" ACE polymorphism is associated with AMD, where the ACE Alu"+" genotype is found at higher frequencies in the normal than the atrophic AMD population (OR=4.5 p=0.004). We recently found that individuals also have dramatically differing ACE in the ocular tissue. The mechanism by which the Alu"+" insert would be protective from the atrophic changes of AMD is not clear at this time. It seems also interesting the genotypes in both ACE (Alu"+" and APOE (epsilon 4) that are protective for AMD are at risk for Alzheimer's disease.

6. A NEW PERSPECTIVE ON AMD

There are basically 3 different major components to AMD; drusen, RPE atrophy and choroidal neovascularization. When each component is evaluated (Figure 3) it can be seen that the specific phenotype is also common to other diseases. For example, drusen can be found not only in AMD but also in RDS-associated pattern dystrophy (29), dominant drusen dystrophy (22) (Doyne's honeycomb dystrophy) and glomerulonephritis type II (65). Similarly, choroidal neovascularization is found in 13-15 % of AMD patients but is also found in ocular histoplasmosis syndrome (30), angiod streaks (91), ruptures in Bruch's membrane, myopic degeneration (72) and some retinal dystrophies. Although AMD and these other diseases share a common phenotype, the possibility exists that this is simply a convergent phenotype or a "final common pathway" that occurs as a result of a number of different insults (genetic, environmental, infectious, traumatic, etc). In some ways this would be analogous to the convergent evolution of the wings of bats and birds. Both have wings and can fly but they arrived at that point in evolution by different evolutionary pathways. Therefore, as it relates to eye disease, this would suggest that while the phenotypes of Stargardt disease and AMD are similar, the etiologies (mechanisms) may be different.

Scientists have identified defective genes and single nucleotide polymorphisms (SNP) associated with different retinal diseases, such as retinitis pigmentosa (20,35,43,58,94), Stargardt disease (11,85), pattern dystrophy (24), Best's disease (21) and Sorsby's fundus dystrophy, (see Table 2). These defective genes can change the structure/function of proteins (e.g. APCR), which
ultimately impacts biological and disease processes. However, in spite of extensive genetic screening of candidate genes (Table 2), to date no SNP or gene defect has been described, which accounts for the majority of AMD cases. The most consistent risk factor for AMD remains to be the age of the patient. At younger ages (< 50 years) the pre-AMD retina often appears completely normal and phenotypic changes of the AMD retina may not appear until 60 years of age or older. This suggests that for many decades the pre-AMD retina is clinically and functionally “normal”. A gene mutation or defect of an important functional protein would be unlikely to go “unnoticed” until the 5th or 6th decade of life. Based on this fact and the paucity of associative genes with AMD, another approach should be considered. That is to examine the possibility that AMD is associated with altered levels of gene expression and not an abnormality of protein structure or function due to a gene mutation.

We have previously advocated the concept, that phylogenetic differences due to the presence or absence of Alu DNA repeats, which affect the regulation of genes in the primates, could be a possible mechanism advancing speciation (33). An analogous concept can be hypothesized for disease processes in the human population, where by an Alu insertion/deletion or some other polymorphism, which regulates the level of gene expression could ultimately impact the severity or rate of progression of the disease.

Since the degree of gene expression is often altered with age, it may be that polymorphisms in the human population that further lead to a differential in gene expression between individuals ultimately contribute to disease. For example, individuals carrying the Alu<sup>+</sup> genotype in the ACE gene have lower levels of ACE in the blood (74). Is this polymorphism neutral in human biology or does it select for a disease process when opportunity presents itself? It has already been demonstrated that the Alu<sup>-</sup> genotype for the ACE gene is associated with decreased renal function and increased rate of mortality in post-renal transplant patients and type II diabetics (23).

The human population is polymorphic with respect to an Alu element insertion in the ACE gene, which controls the levels of the enzyme. We have shown that the Alu<sup>-</sup> genotype, which is associated with lower levels of circulating ACE, is found at a higher frequency in the normal population compared to AMD. Since AMD is a disease of age, we wonder how individuals carrying differing alleles of this polymorphism respond to aging, a
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development involving the senescence of cells as well as the depletion of energy reserves. During this process, machinery like the Na⁺/K⁺ ATPase, becomes less efficient (86). A similar decrease in the activity of this enzyme has been detected in diabetic rats. Interestingly, it could be reversed by decreasing ACE levels through Captopril administration (8,67). Based on these results, we wonder if the ACE polymorphisms, and the subsequent population variance in ACE levels, also regulate the efficiency of the neuronal and retinal Na⁺/K⁺ ATPase. This topic becomes relevant to general disease processes of age in light of the association of the ACE polymorphism to both Alzheimer's disease and AMD. Within this context, the association of the ACE Alu

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