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Chapter 15

Lipoproteins and Apolipoproteins of the Ageing Eye

Edward Loane

Additional information is available at the end of the chapter

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1. Introduction

In this chapter, we outline the structure of the retina and the aetiopathogenesis of the major age-related eye disease: age-related macular degeneration (AMD). We then discuss the role that lipoproteins and apolipoproteins play in the ageing eye and in the development of AMD.

2. The macula and retina

The macula is the central part of the retina, the neurosensory portion of the eye, and it is responsible for detailed central and colour vision due to its high concentration of cone photoreceptors. Anatomically, the macula is centred on the foveola, and has a ganglion cell layer of more than one cell in thickness. The macula has a diameter of approximately 5.5 mm. The macula is characterised by a yellowish colour (hence the term *macula lutea*, which is Latin for 'yellow spot'), attributable to the presence of macular pigment (MP).[1] The concentration of MP peaks at the centre of the macula, where the appearance of the 'yellow spot' may be clearly evident on clinical examination or fundus photography [Figure 1]. MP is optically undetectable outside the macula.[2] Within the layer structure of the retina, the highest concentration of MP is seen in the receptor axon layer and the inner plexiform layer.[1]

The retina consists of a neurosensory portion comprised of nine individual layers, and an external retinal pigment epithelium (RPE). The RPE plays an important physiological role in the maintenance of neurosensory retinal health, through functions including Vitamin A metabolism, phagocytosis of photoreceptor outer segments, maintenance of the outer blood-retina barrier, heat exchange, and the active transport of substances in and out of the RPE.[3] The blood supply of the retina is derived from the inner retinal vasculature and the outer choriocapillaris. Non-pathological changes that occur in the RPE with age include an

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increase in cellular pleomorphism and a decrease in cell number, with migration of peripheral RPE cells towards the macula, reduced melanin composition, and an accumulation of the age-pigment lipofuscin.[4;5] These changes may lead to a reduction in the metabolic activity of the RPE, with subsequent apoptosis, which pre-dates pathological change.[5;6] The RPE is separated from the choriocapillaris by Bruch's membrane (BrM). BrM is a semipermeable filtration barrier, comprised of five individual layers.[7;8] Disruption of BrM may result in alteration of its filtration properties, impacting on the function of the RPE and the neurosensory retina.[9] Changes that occur in BrM with age include an increase in its overall thickness, with a reconfiguration of associated lipids and proteins and the accumulation of debris.[10;11] When this debris accumulates between BrM and the RPE, it is referred to as a basal laminar deposit (BlamD) and is not specifically pathological in nature.[12] However, when deposits accumulate within the inner collagenous layer of BrM, they are referred to as basal linear deposits (BlinDs) and are a histopathological hallmark of AMD.[13] These deposits (BlamDs and BlinDs) contain a wide range of constituents including collagen, inflammatory proteins and lipoproteins. When sufficient debris accumulates in BlinDs, they are visible clinically as drusen.[14;15]

3. Age-related macular degeneration

Age-related macular degeneration (AMD) is the leading cause of blindness in people over 50 years of age in the developed world, and it results in loss of central and colour vision if not treated, or if not amenable to treatment.[16-18] The loss of central vision impacts greatly on the individual, as their ability to perform simple daily tasks, such as reading, watching television, driving and recognizing people's faces becomes increasingly difficult. Thus, their quality of life and their ability to lead an independent life diminish significantly as the disease progresses. The peripheral retina is not affected in individuals with AMD, regardless of stage, such that, in the absence of other ocular pathology, peripheral (navigational) vision remains unchanged.

It is currently estimated that late AMD affects 513,000 people in the United Kingdom (2.4% of those over the age of 50), and that this number will increase to 679,000 by the year 2020.[19] Prevalence data from the United States in 2004 estimated that more than 1.75 million individuals were affected by the disease, with this latter figure expected to rise to almost 3 million by the year 2020.[20] The prevalence of this condition is likely to increase dramatically in the future, as a result of increasing life-expectancy and the resultant increasing senescence of society.[21] Data from the National Eye Institute in the United States in 2004 indicated that the prevalence of advanced AMD in people over 40 years of age was 1.47%, rising to 15% in white females aged over 80 years. Beyond its impact on the individual sufferer,[22] the predicted increase in longevity (Figure 2), coupled with the predicted growth in world population (Figure 3) will significantly increase the socio-economic burden that AMD places on countries and their health-care systems.[23-26]

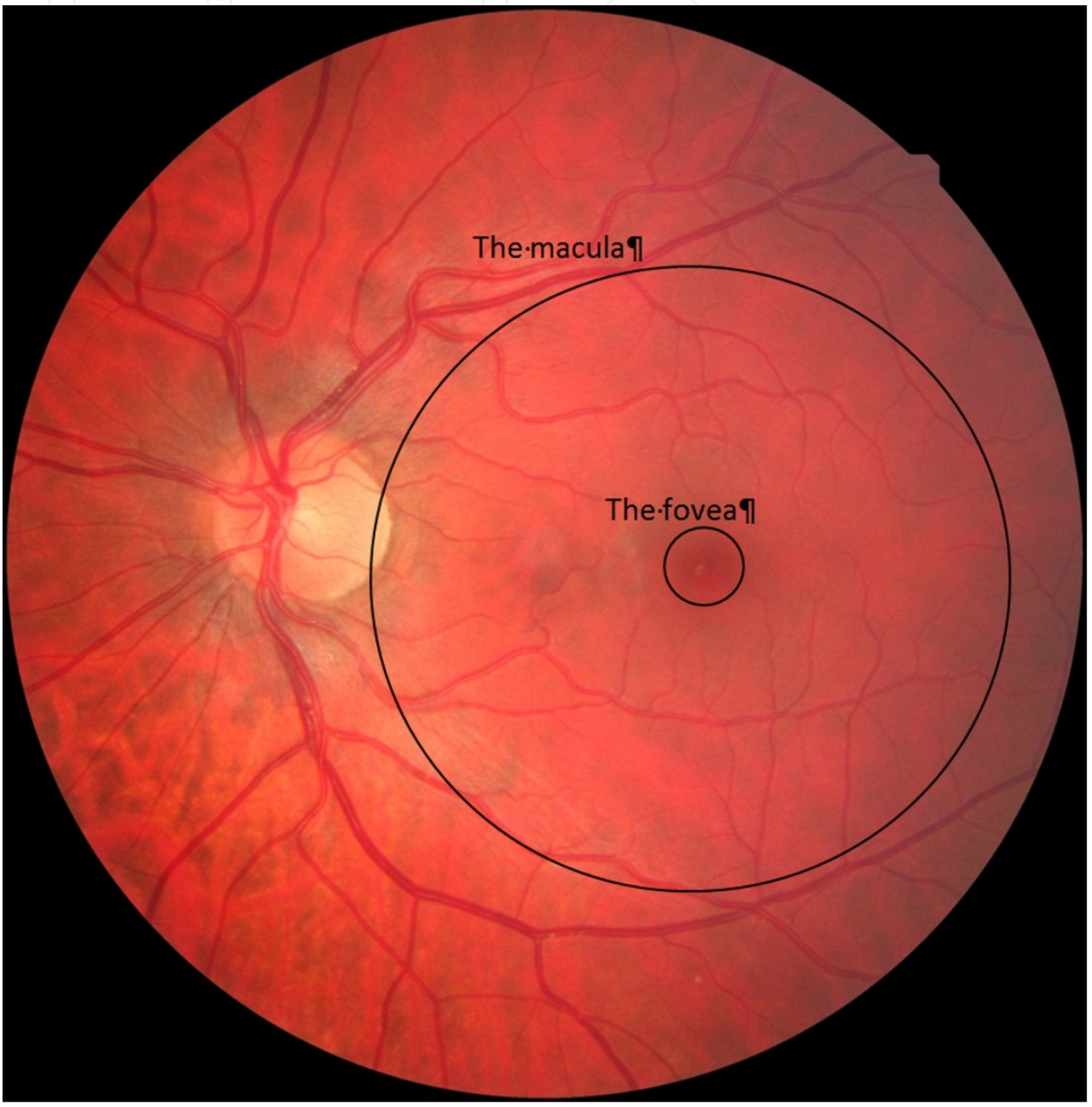

Figure 1. Colour fundus photograph showing the macula, surrounding the fovea, which is centred on the foveola (not marked, but evident as the 'yellow spot') of a left eye.

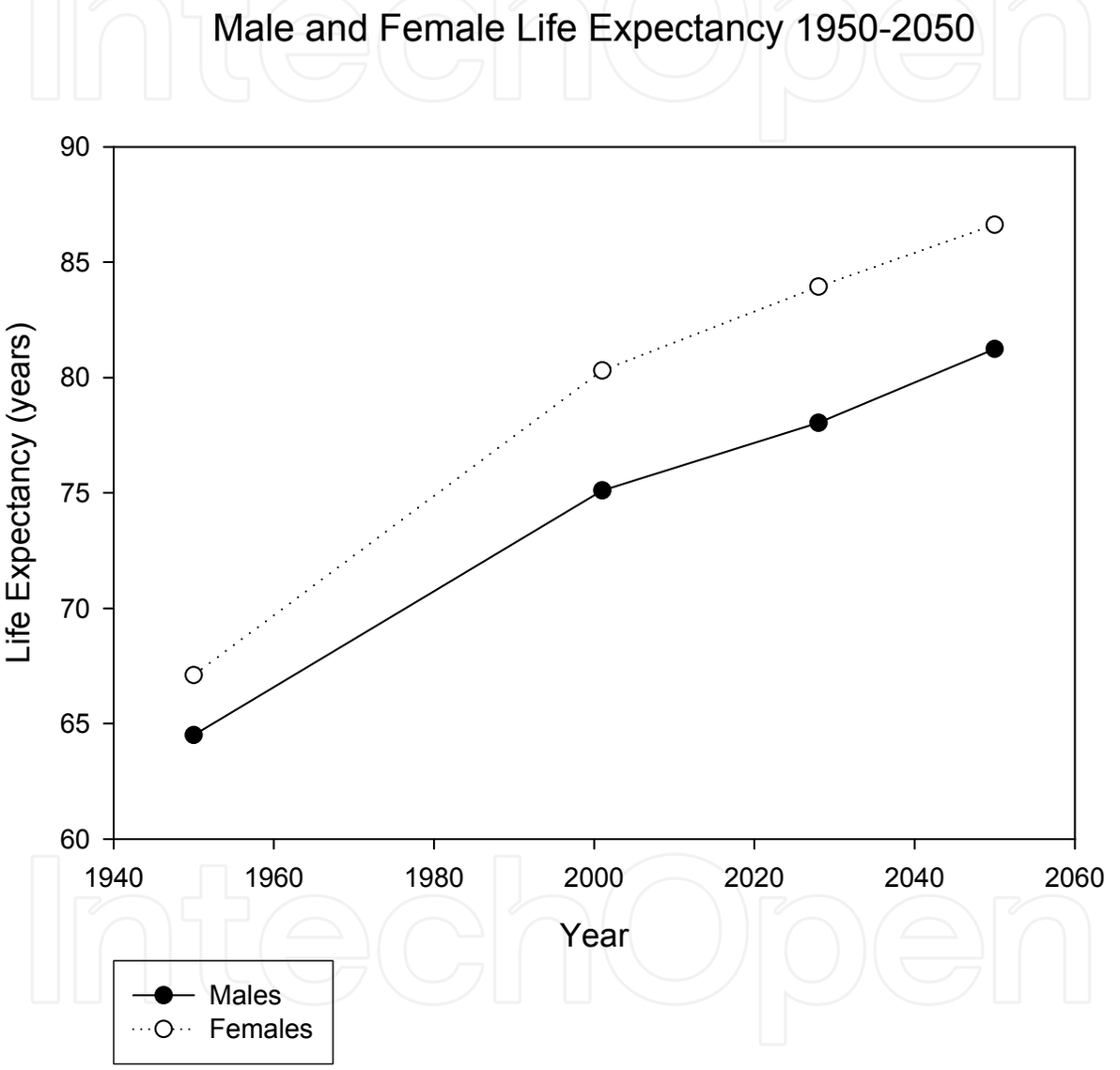

Figure 2. Male and female life expectancy 1950-2050.
* Figures from 1950 and 2001: Irish Department of Health and Children data;
Projected figures for 2028 and 2050: USA data.

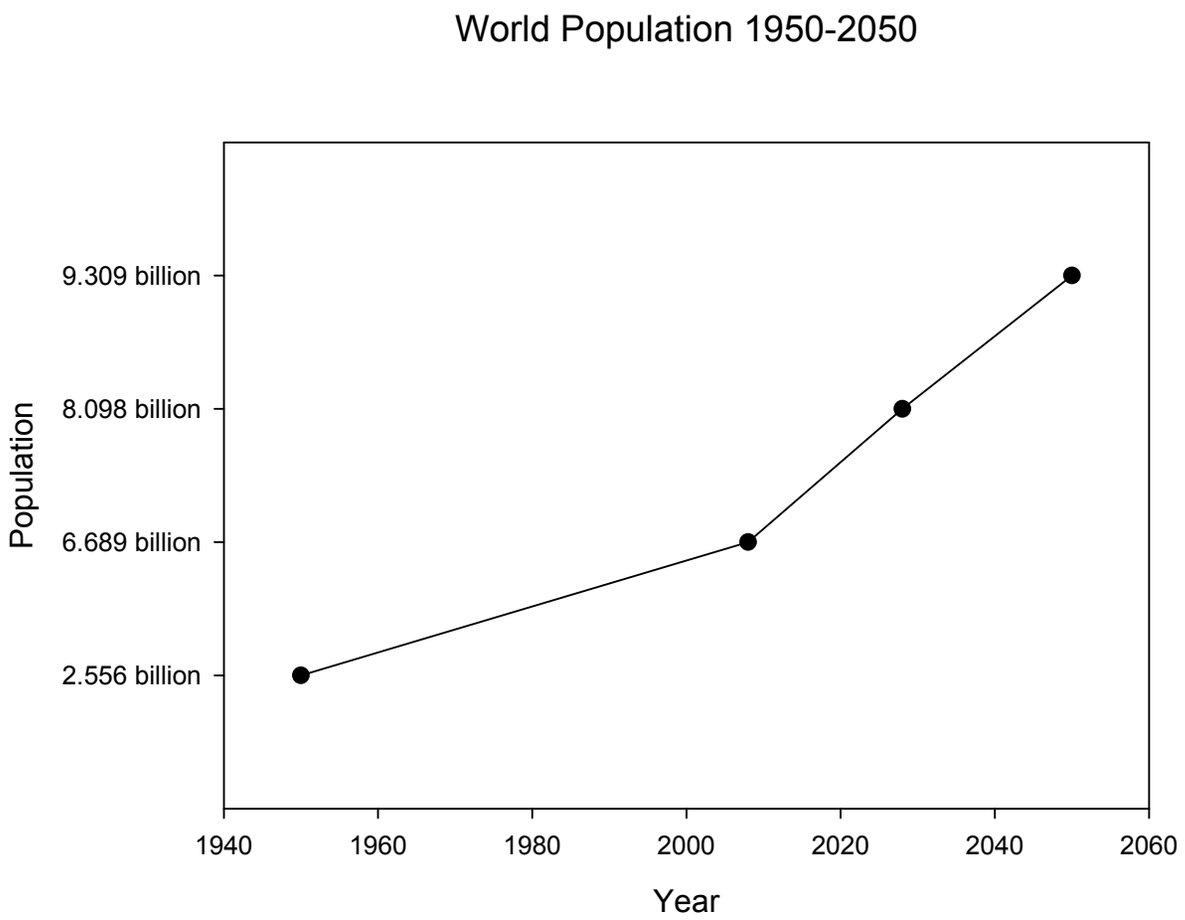

Figure 3. World population 1950-2050 (predicted).

4. Classification of AMD

In 1995, the International Age-Related Maculopathy Epidemiological Study Group clarified the definition and core grading system used to detect and define AMD.[27] This was done to homogenize the systems used to identify and classify this disease in all future clinical and epidemiological studies. This current classification system defines AMD primarily on the basis of morphological changes, without reference to visual acuity.

AMD is defined as a disorder of the macular area, most often clinically apparent after 50 years of age, and characterised by any of the following findings, which are not patently due to another disorder:

1. Soft drusen ≥ 63 μm in diameter. Drusen are whitish-yellow spots that lie external to the neurosensory retina or the RPE (Figure 4). Drusen may be soft and confluent, soft distinct, or soft indistinct. Hard drusen do not, of themselves, characterize AMD.
2. Hyperpigmentation in the outer retina or choroid associated with drusen.
3. Hypopigmentation of the RPE, most often more sharply demarcated than drusen, without any visible choroidal vessels associated with drusen.

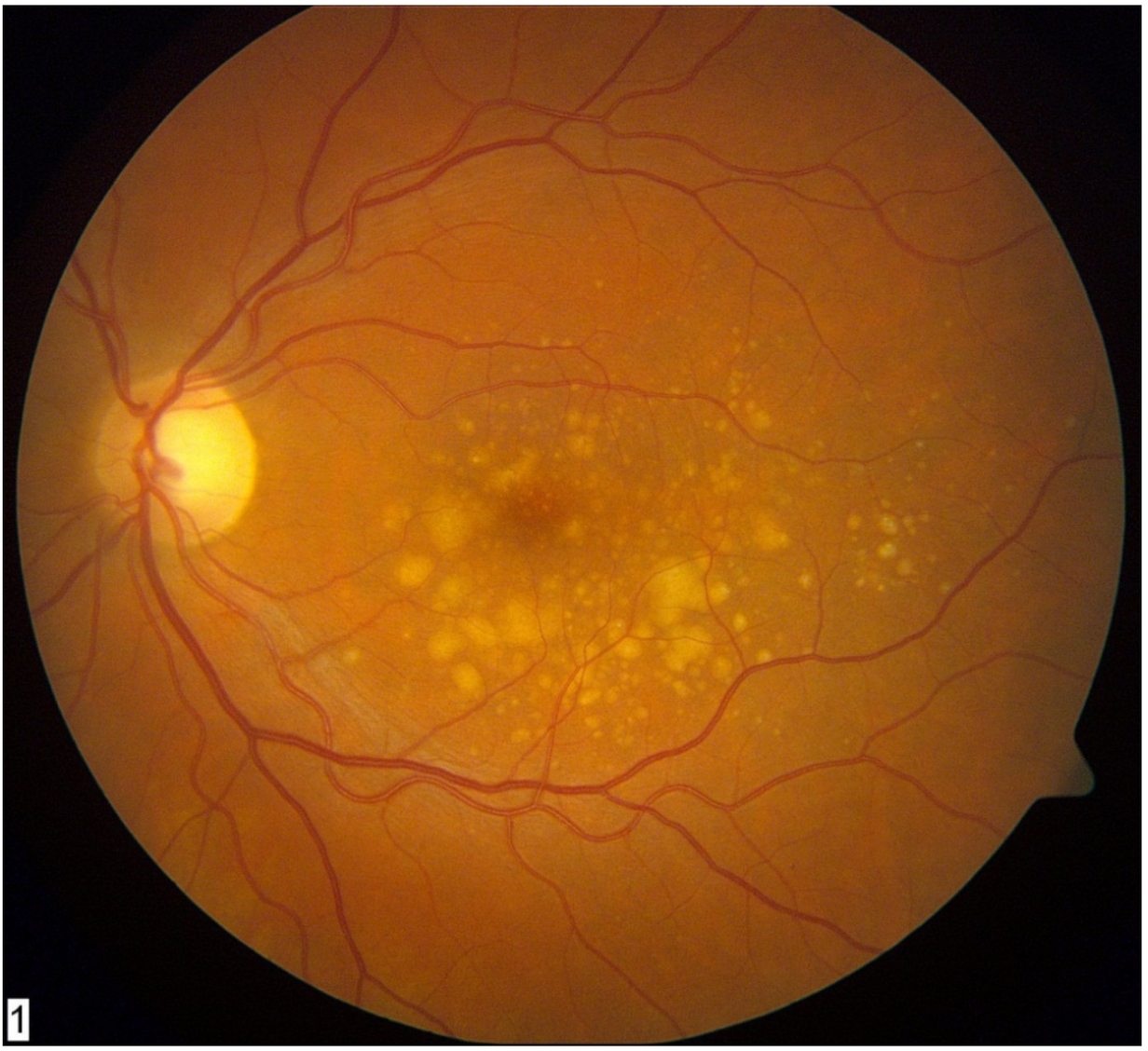

Figure 4. Macular soft drusen of a left eye.

These age-related pathological changes, which are associated with progressive accumulation of debris under the retina, predispose to the late stage of AMD.[28;29] Late AMD is classified as either geographic atrophy (atrophic AMD) or neovascular AMD (choroidal neovascularisation, also referred to as 'exudative AMD' or 'disciform AMD').

Geographic atrophy (GA) is characterised by the following, which is not patently due to another disorder:

1. Any sharply delineated area of hypopigmentation, or depigmentation, or apparent absence of the RPE, in which the choroidal vasculature is more visible than in the surrounding area. The area of atrophy must be ≥ 175 μm in diameter (Figure 5).

Neovascular AMD is characterised by any of the following, which are not patently due to another disorder:

1. RPE detachment(s), which may be associated with neurosensory retinal detachment.
2. Subretinal or sub-RPE neovascularisation.
3. Epiretinal, intraretinal, subretinal, or sub-RPE glial tissue or fibrin-like deposits.
4. Subretinal haemorrhage (Figure 6).
5. Hard exudates (lipids) within the macular area, related to any of the above, in the absence of other retinal vascular disease.

Rarely, neovascular AMD may develop in an area of GA. If this happens, the affected eye is re-classified as having neovascular AMD.

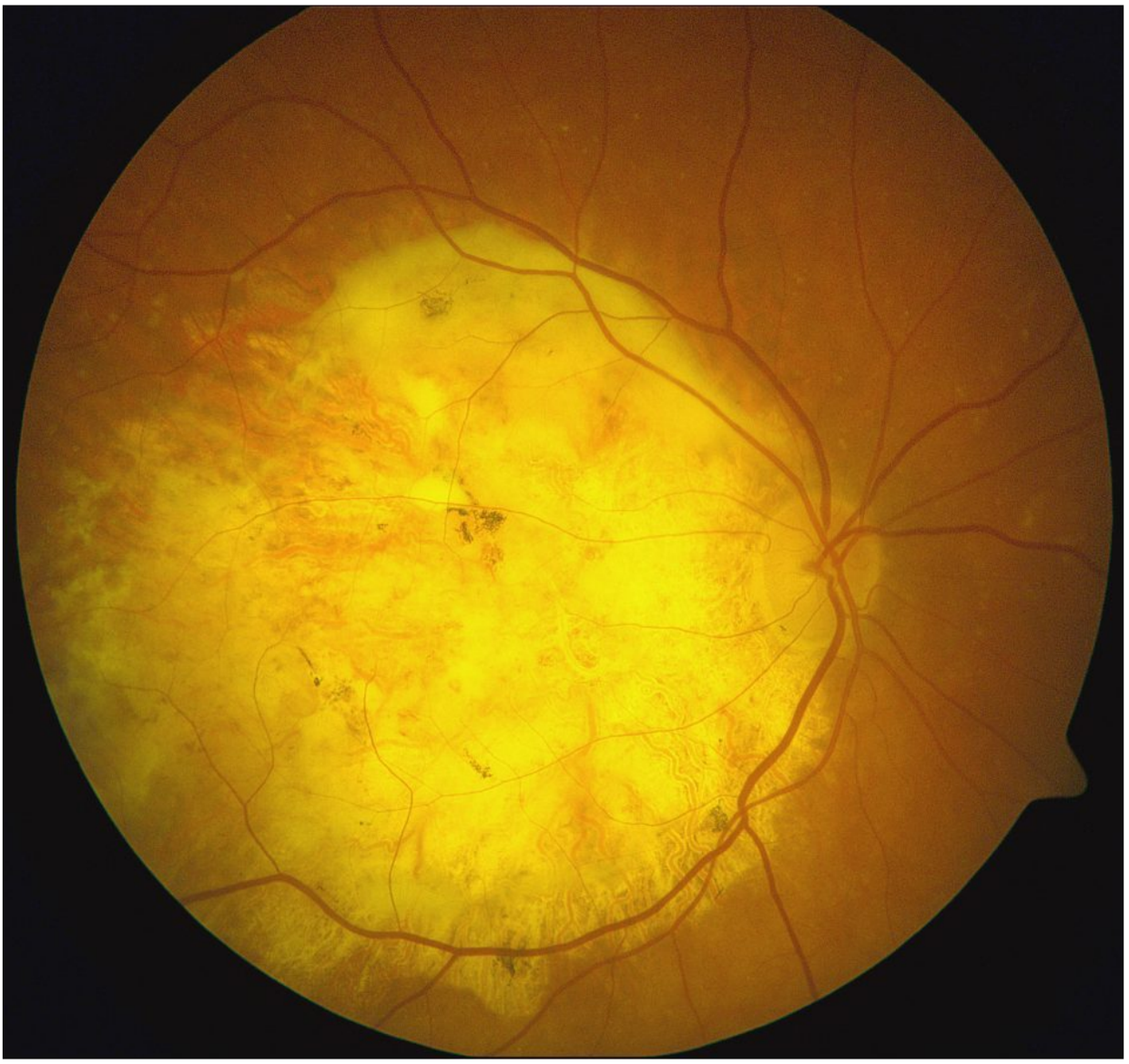

Figure 5. Geographic atrophy, affecting the entire macula of a right eye.

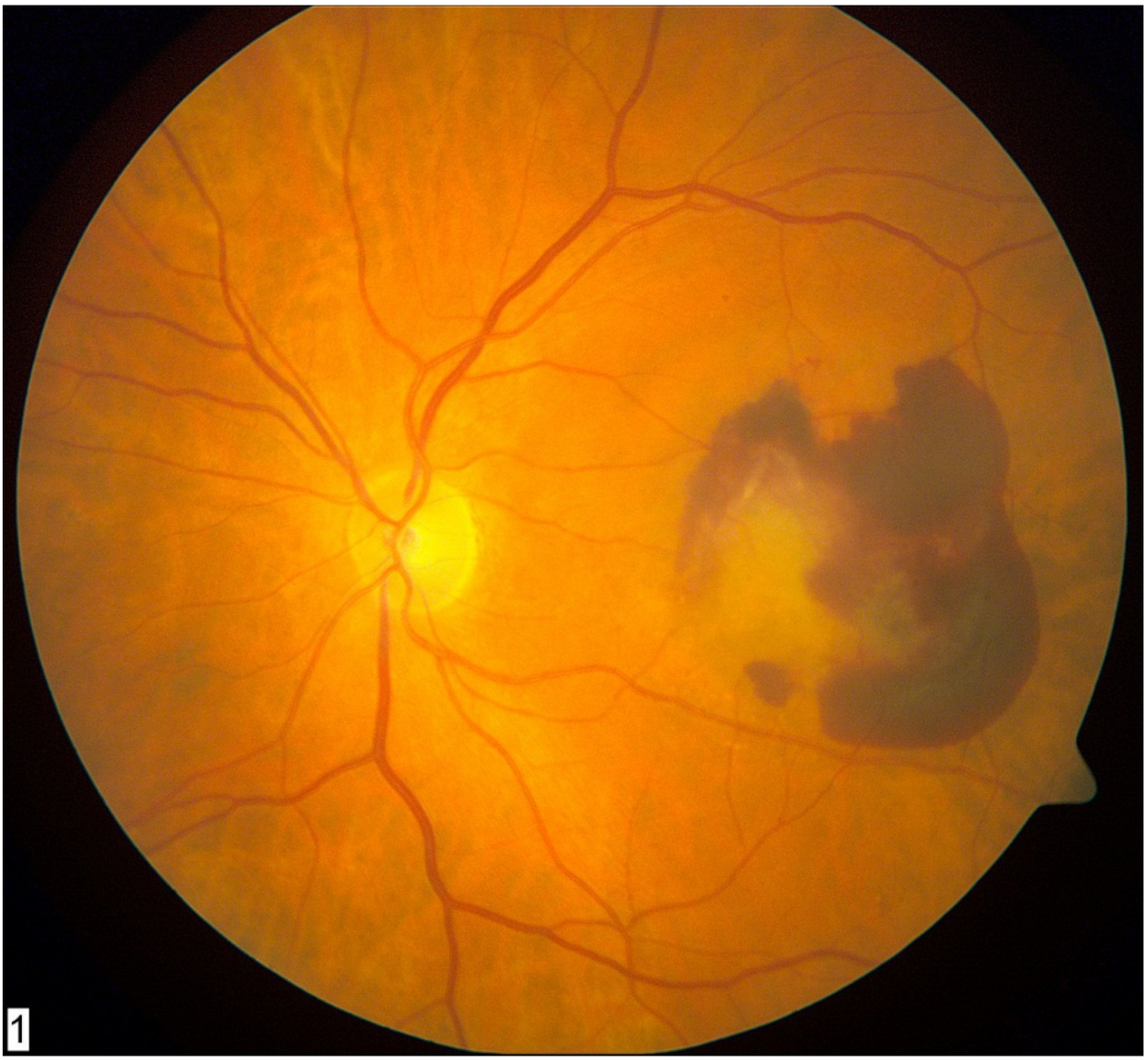

Figure 6. Neovascular AMD, showing sub-retinal haemorrhage in a left eye.

5. Pathogenesis of AMD

AMD has a multi-factorial pathogenesis.[30;31] Therefore, the development of AMD is dependent on a complex interaction between an individual's genetic composition (genotype) and lifestyle (or environmental) factors. This interaction is complex and incompletely understood; however, certain factors have been well established as representing risk for this condition, whereas others are known as putative risk factors, according to our current understanding of this disease. The well-established risk factors for the development of AMD are: increasing age, a positive family history of AMD (including specific genotypes), and tobacco smoking.[30;32;33] Therefore, tobacco smoking is the only proven environmental/lifestyle risk factor for this disease.[34;35] Putative risk factors include: obesity,[36;37] hypertension,[38] light iris colour,[39] cumulative sunlight exposure,[40] and a diet low in anti-oxidant fruits and vegetables,[41] particularly those

containing the hydroxy-carotenoids: lutein and zeaxanthin.[42] Although the pathogenesis of AMD remains incompletely understood, there is a growing consensus that one or more of the following processes contribute to this condition: inflammation; oxidative stress; cumulative blue light damage; RPE cell and BrM dysfunction; reduced foveolar choroidal circulation.

6. Macular pigment

Macular pigment (MP) is composed of the hydroxy-carotenoids lutein (L), zeaxanthin (Z), and *meso*-zeaxanthin (*meso*-Z). L and Z are of dietary origin and are not synthesized *de novo* in humans, whereas *meso*-Z is not found in a conventional western diet, but is understood to be primarily formed in the retina following conversion from L.[43;44] Interestingly, it has been shown that L is the dominant carotenoid in the diet,[45] whereas Z/*meso*-Z have been shown to be the dominant carotenoids at the central macula.[46;47] MP is found in highest concentration at the central macula, where it functions as a powerful antioxidant and acts as a filter of actinic short wavelength blue light, thus limiting (photo-)oxidative damage to retinal cells.[48] These properties of MP are believed to be the mechanism whereby it may protect against the development, and/or progression, of AMD.

Although MP is entirely of dietary origin, it is also subject to heritability, as reported in 2005 by Liew *et al.* in a classic twin study.[49] In that study of 76 monozygotic and 74 dizygotic female twin pairs, they estimated that heritability accounted for between 67% and 85% of an individual's MP level. However, to date a direct significant association between MP levels and the major risk genes for AMD has not been shown.[50]

MP can be measured *in vivo* by non-invasive psychophysical means, resulting in an MP optical density measurement.[51;52]

7. Lipoproteins

Circulating lipoproteins consist of a complex of triglycerides, phospholipids and cholesterol, and one or more specific proteins, referred to as apolipoproteins. The association of lipoproteins with high affinity receptors on cell surfaces regulates lipid metabolism and transport in the body.[53] Lipoproteins are classified into the following six groups: chylomicrons; chylomicron remnants; very low density lipoproteins (VLDL); intermediate density lipoproteins (IDL); low density lipoproteins (LDL); high density lipoproteins (HDL).[53]

Chylomicrons are synthesised by the intestine and deliver dietary triglycerides to muscle and adipose tissue, and dietary cholesterol to the liver. Lipoprotein lipase, located at capillary endothelial cell surfaces, hydrolyses the triglyceride core of the chylomicron, thus liberating fatty acids and glycerol, which are used as energy sources by various cells, or are taken up by adipocytes and stored as triglycerides. Chylomicron remnants, which are rich in cholesterol, result from chylomicron metabolism, and are rapidly cleared by the liver.[53]

Subsequently, the liver synthesises a second class of triglyceride-rich lipoprotein, referred to as VLDL, which, upon secretion, functions as a transporter of lipids and cholesterol. In the bloodstream, VLDL undergoes progressive removal of triglycerides from its core by lipoprotein lipase, in a similar way to chylomicrons. The VLDL particles thus become increasingly smaller, leading to the formation of IDL, and LDL. LDL are the final metabolic products of VLDL and are responsible for most of the cholesterol transport in serum.[53]

HDL are the smallest lipoproteins, arising from several sources including the intestine and liver. HDL are involved in a process known as 'reverse cholesterol transport', whereby HDL acquire cholesterol from cells and deliver it to the liver.[53] This is a particularly important mechanism in humans, as the quantities of cholesterol transported out of the gut and liver far exceed the quantities converted to steroid hormones, or those lost through the skin in sebum. Thus, unless the requirement for cell membrane repair or synthesis is high, excess cholesterol must be returned to the liver for excretion.[54]

8. Association of carotenoids with plasma lipoproteins

The majority of plasma carotenoids are transported on LDL, with 55% of total carotenoids associated with this lipoprotein, whereas HDL is associated with 33%, and VLDL is associated with 10-19%, of the total carotenoids.[55] However, in the case of the hydroxy-carotenoids, L and Z, some studies have reported that they are relatively equally distributed between LDL and HDL molecules, but other studies have reported that HDL is the preferential carrier of the MP carotenoids in plasma.[56;57]

MP is inversely related to percentage body fat.[58] Interestingly, Viroonudomphol *et al.* have demonstrated lower levels of HDL in overweight and obese subjects, consistent with the possibility that a relative lack of HDL may impair transport and/or retinal capture of the carotenoids.[59] Furthermore, Seddon and co-workers have demonstrated a significantly increased risk of AMD in association with obesity.[33] These findings have prompted the suggestion that an individual's lipoprotein, and apolipoprotein, profile may influence the transport and delivery of these carotenoids to the retina, with a consequential impact on MP.

A recent study, designed to investigate the respective relationships between lipoprotein profile, MP optical density and serum concentrations of L and Z, was conducted in 302 healthy adult subjects.[60] This study found that there was a statistically significant inverse association between serum triglyceride concentration and MP optical density, and an inverse association between serum triglyceride concentration and serum L concentration in subjects with a positive family history of AMD. There have been no previous reports on the association between serum triglyceride concentration and either MP optical density or serum concentrations of L and/or Z. Elevated serum triglyceride concentration is an element of an undesirable lipoprotein profile and represents risk for cardiovascular disease.[61;62] Since there is an inverse association between serum triglyceride concentration and serum HDL concentration,[62] one could expect an inverse association between serum triglyceride concentration and serum L, since HDL appears to be the most important lipoprotein

involved in the transport of L in serum. This expected inverse association was observed in subjects with a positive family history of AMD. In this study sample there was a positive and significant association between serum HDL concentration (and serum cholesterol concentration) and serum L and Z concentrations. Of note, there was no significant association observed between MP optical density and either serum cholesterol concentration or serum HDL concentration. There was also no association between serum LDL concentration and MP optical density (or serum concentrations of its constituent carotenoids). These findings suggest that a desirable lipoprotein profile (higher serum HDL, lower serum LDL and lower serum triglyceride concentrations) is associated with greater serum L concentration. However, the impact of lipoprotein profile on the capture and/or stabilization of these carotenoids at the macula, where they comprise MP, is less clear from this data.

In this study, the lipoprotein particle-concentration of L and/or Z in serum was not directly measured, nor were lipoprotein subspecies measured, as performed by Goulinet *et al*.[57] In their study, they fractionated HDL and LDL subspecies on the basis of their hydrated density by gradient ultracentrifugation, and they found that serum L and Z (combined) were relatively equally distributed between HDL and LDL; but more importantly, they found that there was a progressive decrease in the concentration of these carotenoids with increasing density (and decreasing lipoprotein particle size) from light to dense LDL. They also found that the majority of macular carotenoid transport by LDL was accounted for by the most abundant subspecies, LDL3 (intermediate LDL) and LDL4 (dense LDL). This is highly relevant to the transport of L and Z in serum, as LDL3 and LDL4, despite being the most abundant subspecies of LDL in that study, had reduced particle-concentrations of these carotenoids compared to less dense LDL subspecies, making them more vulnerable to oxidation.[63] LDL is the primary component of total cholesterol,[62] and has previously been reported in various studies to transport between 22-44% of L and Z in serum.[55;57;64-66] Of note, it has been shown that there is no significant difference in the transport of L and Z by lipoproteins between subjects with and without AMD.[65]

The findings of Goulinet *et al* in relation to HDL were similar to that of LDL, in that there was a progressive and marked decrease in HDL particle concentration of L and Z, with maximal carotenoid concentration evident in the lightest, largest HDL subspecies (HDL2-1), and minimal concentration in the densest HDL. Certainly, the findings of Goulinet *et al* with respect to HDL, in concert with our findings, are consistent with the view that HDL plays an important role in the transport of L and Z in human serum, and are provocative given that AMD and cardiovascular disease share certain antecedants.[32;57;60;67-70] Furthermore, and again consistent with a shared pathogenesis between AMD and cardiovascular disease, the finding of an inverse association between serum triglyceride concentration and MP optical density (and between serum triglyceride concentration and serum L concentration) in subjects with a positive family history of AMD, is noteworthy.[60] Since AMD has been shown to be associated with low serum concentrations of L,[71] and given that risk factors for AMD are associated with a relative lack of MP,[31] our observations are yet another example of how AMD and cardiovascular disease share risk factors.[32;60-62;67-70]

In 2007, Connor *et al* reported on the role that HDL plays in the transport of L and Z in serum in a study involving WHAM chicks.[64] WHAM chickens have a recessive sex-linked mutation in the *ABCA1* transporter gene that results in very low circulating HDL concentration, with normal, or increased, concentrations of other plasma lipoproteins, particularly LDL. The analogous mutation in humans results in Tangier disease, which is characterized by a similar deficiency in circulating HDL concentration.[72] In their study, involving 24 WHAM chicks and 24 control chicks, Connor *et al* found that one-day old WHAM chicks had only 9% of the L concentration in plasma when compared with control chicks, and only 6% of the retinal concentration of controls (the corresponding concentrations of Z were 6% and 9%, respectively). Following a high-L diet for 28 days, there was a significant increase in the plasma and retinal concentrations of L in WHAM chicks and controls, but the increases were still greatly inferior in the WHAM chicks when compared with control chicks and, furthermore, still did not reach the concentrations observed in the one-day old control chicks. The observations of Connor *et al* suggest an important role for HDL in the transport of L and Z in serum and/or their incorporation into the retina, and are consistent with our findings.[60;64]

Interestingly, although all subjects in our study were healthy volunteers with no evidence of ocular pathology, it is notable that, on average, subjects with a positive family history of AMD had a higher serum concentration of L than subjects with a negative family history of AMD, yet MP optical density levels in both groups were comparable, as were serum concentrations of HDL.[60] As was shown in this study, and as has previously been documented,[73] serum concentrations of L and Z generally correlate positively with MP optical density. Therefore, it is plausible to suggest that in the subjects in this study with a positive family history of AMD, the delivery to, and/or uptake by, the retina of the macular carotenoids is defective when compared to subjects without such a family history.[60] Indeed, although MP optical density levels were comparable between subjects with and without a family history of AMD, subjects with a positive family history of this disease also had higher serum L concentrations. This is consistent with the observations of Nolan *et al*, where a relative lack of MP was seen in association with a positive family history of AMD in 828 healthy subjects, but where dietary and serum concentrations of L and Z were comparable for subjects with and without a family history of this condition, suggesting defective retinal capture of circulating L and/or Z in persons who are genetically predisposed to AMD.[31] Mechanisms governing the retinal capture and/or stabilization of L and/or Z may be subject to influence by HDL subspecies profile, by affecting receptor-mediated uptake of these carotenoids from serum. Indeed, apolipoprotein profile is probably a determinant of retinal uptake of the macular carotenoids from serum, reflected in our recently reported finding that individuals with at least one Apo ε4 allele exhibit significantly higher MP optical density than individuals without this protective allele, despite statistically comparable serum concentrations of L and Z.[74] Interestingly, the lack of an association between MP optical density and either serum cholesterol concentration or serum HDL concentration in our study would suggest that our observations are more likely due to impaired uptake and/or stabilization of circulating L and/or Z by the macula than

due to any impact the HDL subspecies profile may have on the transport of the macular carotenoids in serum.

Another recent study has shown somewhat conflicting evidence regarding the association between circulating lipoprotein levels and MP levels in serum and in the macula.[75] These differences may be attributable to differences in the methods used to measure serum lipoproteins, although it should be noted that this study also found a positive association between serum L and serum HDL levels, underscoring the importance of HDL as a transporter of L in serum. However, it should be emphasised that a notable paucity of data still remains regarding the mechanism(s) whereby L and Z accumulate in the liver, are repackaged into lipoproteins, and transported via the circulatory system to specific target tissues such as the retina.

9. Apolipoproteins

Plasma lipoproteins include one or more protein constituents, known as apolipoproteins. Apolipoproteins have been classified into several subgroups, including apolipoprotein A (ApoA), apolipoprotein B (ApoB), apolipoprotein C (ApoC), and apolipoprotein E (ApoE). These subgroups are themselves further sub-classified, for example: ApoA-I, ApoA-II etc. Each lipoprotein class is associated with certain apolipoproteins, for example: chylomicrons and VLDL are associated with ApoB; chylomicrons, VLDL and HDL are associated with ApoE.[76] The primary role of apolipoproteins is the transport and redistribution of lipids amongst various tissues in the body. Specific apolipoproteins are recognised by cell surface receptors, and this facilitates the high affinity binding required for delivery to target tissues. Certain apolipoproteins also act as cofactors of enzymes involved in lipoprotein metabolic pathways, including those of lipoprotein lipase and lecithin-cholesterol acyl transferase (LCAT), which catalyse the formation of cholesterol esters. Another role of specific apolipoproteins is the maintenance of the structure of lipoproteins, by stabilizing their micellar structure, and by providing a hydrophilic surface in association with phospholipids.[53] The function of apolipoproteins has provoked interest in their possible role in a range of degenerative conditions. In particular, several investigators have suggested an association between ApoE and various diseases, including Alzheimer's disease, atherosclerosis and AMD.[77-80]

Abalain *et al.* investigated the association between AMD and serum levels of lipoproteins and lipoparticles.[78] They found that there was no difference in serum ApoA-I and ApoB levels between AMD patients and controls. However, they found that serum ApoE levels were higher, and that serum ApoC-III levels were lower, in AMD patients compared with controls. The higher level of serum ApoE in AMD patients is consistent with the findings of Boerwinkle and Utermann, who found that the Apo ε4 allele is associated with lower serum ApoE levels, and that the Apo ε2 allele is associated with higher serum levels of ApoE.[79] ApoC-III interferes with lipoprotein metabolism and, when associated with ApoB as a lipoparticle, it has been shown to be involved in atherogenesis.[80] Abalain *et al.* found no difference in the levels of this particular lipoparticle between AMD patients and

controls.[78] The evidence to date suggests that, of the apolipoproteins, ApoE has the strongest association with AMD.

10. Apolipoprotein E

ApoE is a structural component of plasma chylomicrons, VLDL, and a subclass of HDL. It is a 299 amino-acid protein, and is synthesised in a large number of tissues including the spleen, kidneys, lungs, adrenal glands, liver, brain and retinal Müller cells.[81] ApoE is polymorphic, with three common isoforms: E2, E3 and E4, which are coded for by three separate alleles: Apo ε2, Apo ε3 and Apo ε4. These alleles are differentiated on the basis of cysteine-arginine residue interchanges at sites 112 and 158 in the amino acid sequence.[82] As a result of this polymorphism, six common phenotypes exist: three homozygous phenotypes (ε3ε3, ε2ε2, ε4ε4) and three heterozygous phenotypes (ε2ε3, ε2ε4, ε3ε4). ApoE is crucial to many processes, including: cholesterol transport and metabolism; receptor-mediated uptake of specific lipoproteins; heparin binding; formation of cholesteryl-ester-rich particles; lipolytic processing of type IIIβ-VLDL; inhibition of mitogenic stimulation of lymphocytes; transport of lipids within the brain.[53]

ApoE is an important regulator of cholesterol metabolism because of its affinity for ApoE-specific receptors in the liver, and its affinity for LDL receptors in the liver and other peripheral tissues requiring cholesterol.[53] ApoE-specific receptors are present on the membranes of hepatic parenchymal cells, and have a high binding affinity for chylomicron remnants, IDL and a sub-class of HDL. ApoE also regulates the activity of several lipid-metabolising enzymes, including lipoprotein lipase, and LCAT.

ApoE is found in greatest concentrations in the liver. However, it is also the predominant apolipoprotein in the brain, and is responsible for lipid transport and cholesterol regulation within the central nervous system (CNS). ApoE is a major component of plasma and cerebrospinal fluid, and plays a fundamental role after CNS injury, where it appears to regulate the transport of cholesterol and phospholipids during the early and intermediate phases of the reinnervation process.[83;84]

ApoE polymorphisms result in differences in the metabolism of ApoE-containing lipoprotein particles.[85] For example, it is possible that certain ApoE polymorphisms affect their ability to interact with lipoprotein lipase in the conversion of VLDL to LDL.[86] Indeed, ApoE polymorphism influences plasma lipid levels both in sedentary states and in their response to exercise, and it is therefore believed to be related to risk for coronary artery disease. In general, carriers of the Apo ε4 allele have higher levels of total cholesterol and LDL-cholesterol than those with the Apo ε3 allele. ApoE polymorphism also appears to play a role in the responsiveness of blood lipids to dietary and lipid-lowering drug interventions. Thus, the ApoE gene-environmental interactions contribute to population variance in blood lipid-lipoprotein levels.[87]

ApoE receptors also play an important role in lipoprotein metabolism. The primary physiological role of ApoE is to facilitate the binding of lipoproteins to LDL receptors,

thereby regulating the uptake of cholesterol required by the cell. For instance, large amounts of lipids are released from degenerating cell membranes after nerve cell loss, thus stimulating astrocytes to synthesise ApoE, which binds these excess lipids and distributes them appropriately for reuse in cell membrane biosynthesis.[88] This observation prompted Klaver *et al.* to speculate that a high degree of ApoE biosynthesis is required to support the high rate of photoreceptor renewal at the macula.[88] Indeed, it has been demonstrated that mice which were fed a high-fat diet, or which were deficient in ApoE, exhibit an increase in the thickness of BrM, which is seen in association with ageing and with AMD.[89]

Ishida *et al.* identified the presence of ApoE and lipids at the inner aspect of the RPE, and proposed that both compounds may be secreted by the RPE.[90] The role of ApoE in reverse cholesterol transport prompted the authors to suggest that this apolipoprotein may also facilitate the efflux of lipids from the RPE into the adjacent BrM, and they proposed a possible pathway for RPE cell-secreted lipids to cross BrM, where partially digested or undigested photoreceptor outer segments are secreted across the basal surface in association with ApoE. Subsequent binding with HDL at BrM may then facilitate desorption of the lipid particles into the circulation.[90]

In the retina ApoE is synthesised in Müller cells and in the RPE, and the presence of ApoE has been demonstrated in drusen.[81;91;92] It has been suggested, therefore, that age and/or disease-related disruption of normal ApoE function may result in the accumulation of lipoproteins at the interface between the RPE and BrM, consistent with observations that lipid deposits in drusen are largely composed of cholesteryl esters and unsaturated fatty acids.

These findings are consistent with the view that ApoE plays an important physiological role in the maintenance of macular health, and that an impaired ApoE system may affect the functional integrity of BrM. Furthermore, there is a biologically plausible rationale whereby the ApoE profile might influence the transport, capture, and stabilization of key compounds, such as L and Z, at the macula.

11. Lipoproteins, apolipoproteins and the retina

As noted previously, the ageing retina features changes in the RPE and BrM, which include changes in the lipoprotein and apolipoprotein composition of both structures. These changes may progress to the disease state of AMD. In recent times, evidence accrued from light microscopy, ultrastructural studies, lipid histochemistry, isolated lipoprotein assays, and gene expression analysis had led to the identification of many of the constituents that deposit in the RPE and BrM with age and AMD.[93] One of the universal changes that occurs with age is the development of BlamDs between the RPE and BrM.[11;12] This process may progress to the development of a 'lipid wall', mainly composed of neutral lipid deposits, decreasing the permeability of BrM and hindering metabolic activity between the RPE and BrM, preceding pathological changes associated with AMD.[10;93;94] When these deposits accumulate within the inner collagenous layer of BrM, they are referred to as basal linear deposits (BlinDs) and are a histopathological hallmark of AMD, which, when sufficiently large, can be recognised clinically as drusen.[13-15;95]

Much of the debris that accumulates in BrM in the form of BlinDs is composed of lipoproteins and lipoprotein particles.[14] It has been found that almost 60% of the total cholesterol within these lipoproteins is esterified cholesterol.[96] Furthermore, the esterified cholesterol within BrM was enriched between 16 and 40-fold compared to plasma. If these extracellular lipid deposits had been derived from plasma, more than 90% of the phospholipid would be phosphatidylcholine, whereas in actual fact, these lipoproteins are comprised of less than 50% phosphatidylcholine.[96] Indeed, the composition of drusen, which are essentially large BlinDs, has been shown to include esterified and unesterified cholesterol, and multiple apolipoproteins, including apolipoproteins B, A-I, C-I, C-II, and E, appearing with frequencies ranging from 100% (ApoE) to approximately 60% (A-I).[88;91;97;98] Interestingly, ApoC-III, although abundant in plasma, is present in fewer drusen (16.6%) than ApoC-I (93.1%), which is not present in plasma in large quantities, indicating either a specific retention of plasma-derived apolipoproteins within drusen, or an intraocular source for these apolipoproteins.[93] It is now understood that the majority of lipoproteins in BrM have undergone intracellular processing within the RPE prior to secretion as neutral lipids, mainly esterified cholesterol.[99;100] The RPE origin has been definitively shown by two groups using metabolic labelling and immunoprecipitation in rat-derived and human-derived RPE cell lines that were shown to secrete full-length ApoB.[101;102] This evidence is further strengthened by the finding of microsomal triglyceride transfer protein within native human RPE, indicating that the RPE is capable of secreting lipoprotein particles.[102] The pattern of lipid deposition in BrM with age, in which debris appears firstly in the elastic layer and then fills in towards the RPE, is also consistent with this lipid being primarily of RPE origin.[103]

The hydrophobic nature of the age-related thickening of BrM has been implicated in the aetiopathogenesis of AMD. In the case of Apo E, it is noteworthy that ApoE4 presents a positive charge relative to both ApoE2 and ApoE3. ApoE4 possesses arginine at residue 112 of the amino acid sequence, whereas ApoE3 possesses cysteine at this position, and in the case of ApoE2, the most frequent variant has cysteine instead of the normally occurring arginine at residue 158. Thus, ApoE3 presents a neutral charge, and ApoE2 a negative charge, relative to ApoE4.[53] Souied *et al.* suggested that this difference in charges between the ApoE isoforms may also contribute to differences in the clearance of debris through BrM.[104]

It appears that Müller cells are the most prominent biosynthetic sources of ApoE in the neural retina, and RPE cells are the most prominent sources in the RPE/choroid.[91] However, it remains unclear whether the concentration of ApoE in the cytoplasm of some RPE cells, especially those in close proximity to drusen, is the result of biosynthesis or selective accumulation. It has been shown that, in both the central and peripheral nervous systems, ApoE expression by astrocytes is up-regulated in response to neuronal injury and neuro-degenerative disease.[84;105;106] Indeed, there is evidence for ApoE up-regulation by Müller cells in degenerating human retina, where increased ApoE immuno-reactivity is found in the sub-retinal space of detached retinas[107] and in the Müller cells of retinas affected by glaucoma or AMD.[108] Furthermore, the relatively high levels of ApoE mRNA detected in the retina, especially in the eyes of older donors and in an individual with

documented AMD, support the view that up-regulation by retinal glia may be responsible for the observed increase in ApoE expression.[91]

12. Apo ε4 allele status and AMD

ApoE gene status is believed to be a determinant of AMD risk.[88;104;109-111] The *ApoE* gene has three separate alleles: Apo ε2, Apo ε3 and Apo ε4, resulting in six common phenotypes: three homozygous (ε3ε3, ε2ε2, ε4ε4) and three heterozygous (ε2ε3, ε2ε4, ε3ε4) phenotypes. The ε4 allele has been found to be associated with a reduced risk of AMD, whereas the ε2 allele has been associated with an increased risk of developing this disease.[88;104;109-113]

Due to the lack of cysteine residues at positions 112 and 158, preventing the formation of disulphide bridges with ApoA-II or other peptide components, the Apo ε4 allele has an inability to form dimers. It has been suggested that this inability of the Apo ε4 allele to form dimers, when compared with the Apo ε2 and Apo ε3 alleles, favours easier transport of lipids through BrM because of the smaller sized lipid particles, thus protecting against a loss of permeability of BrM.[104]

In the same way, it is possible that the neurosensory retina and the RPE respond to conditions of high oxidative injury by up-regulation of ApoE synthesis and/or accumulation, with implications for selective capture and stabilisation of L and Z in the retina.[91] It has been demonstrated that there is selective binding of certain receptors within the CNS to HDL particles enriched with ApoE, and that there is a lack of binding of these receptors to HDL particles deficient in ApoE.[114] Should this selectivity of the uptake mechanism be dependent on the ApoE polymorphism of the transporting lipoproteins, and given that the Apo ε4 allele is putatively protective for AMD, it is tempting to hypothesise that retinal capture of L and Z may be related to apolipoprotein profile. In other words, the apolipoprotein composition as well as the lipoprotein profile, may play an important role in the transport and delivery of L and Z, and their subsequent accumulation and stabilisation within the retina.[115] Therefore, it is possible that the putative protective effect of the Apo ε4 allele against AMD is attributable, at least in part, to the role its phenotypic expression (ApoE4) plays in the transport and delivery of the macular carotenoids to the retina, and to their stabilisation within the retina. Furthermore, recent research has shown an association between possession of at least one Apo ε4 allele and higher levels of MP across the macula, which is consistent with the view that apolipoprotein profile influences the transport and/or retinal capture of the macular carotenoids.[74]

13. Conclusion

In conclusion, the role that lipoproteins and apolipoproteins play in the ageing eye and in the aetiopathogenesis of AMD is complex and, as yet, incompletely understood. Lipoproteins and apolipoproteins play an important role in the delivery of potentially protective nutrients from the digestive tract to the eye. The local ocular metabolic activity,

centred on the RPE and BrM, involves an exchange of nutrients from the choroidal circulatory system via BrM to the RPE and retina, with a reverse process whereby waste products are removed from the retina by the RPE through BrM in association with locally produced lipoproteins and apolipoproteins (particularly ApoB and ApoE). Unfortunately, over time it appears that these lipoproteins and apolipoproteins can accumulate between the RPE and BrM, and within BrM, leading to degradation in the metabolic efficiency between these two structures and the choroidal circulation. This deposition has been described as a 'lipid wall' and precedes the development of AMD.[93;94] Methods to detect and arrest or delay this process before it becomes clinically apparent and visually consequential to the patient have yet to be developed. Recent advances in our understanding of the lipoprotein and apolipoprotein molecular biology of the ageing and AMD-affected eye will help to direct future treatment strategies.[100]

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