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Animal models of age related macular degeneration

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Abstract

Age related macular degeneration (AMD) is the leading cause of vision loss of those over the age of 65 in the industrialized world. The prevalence and need to develop effective treatments for AMD has lead to the development of multiple animal models. AMD is a complex and heterogeneous disease that involves the interaction of both genetic and environmental factors with the unique anatomy of the human macula. Models in mice, rats, rabbits, pigs and non-human primates have recreated many of the histological features of AMD and provided much insight into the underlying pathological mechanisms of this disease. In spite of the large number of models developed, no one model yet recapitulates all of the features of human AMD. However, these models have helped reveal the roles of chronic oxidative damage, inflammation and immune dysregulation, and lipid metabolism in the development of AMD. Models for induced choroidal neovascularization have served as the backbone for testing new therapies. This article will review the diversity of animal models that exist for AMD as well as their strengths and limitations.

1. Introduction

Age related macular degeneration (AMD) is the leading cause of blindness in the industrialized world of adults older than 65 years (Klein et al., 2002). AMD is a heterogeneous disease, which first manifests in the macula with the appearance of pigmentary changes and subretinal deposits called drusen. AMD can progress to a “dry”, non-neovascular form leading to geographic atrophy of the retinal pigment epithelium (RPE), choriocapillaris, and photoreceptors, or to a more rapid “wet”, neovascular form, which occurs when new blood vessels invade from the choroid and penetrate Bruch's membrane resulting in vascular leakage, hemorrhage, and scarring. Dry AMD is much more common than wet, but choroidal neovascularization (CNV) in wet AMD accounts for the majority of the vision loss (Bressler et al., 1988).

Accurate animal models of a disease can assist greatly in the development of new therapies. The ideal model of AMD would be inexpensive, recapitulate the histological and functional changes, but evolve in a rapid time course to allow more efficient studies. As shown in Table 1, numerous models mimic several of the important pathological features seen in AMD, but none recreated all of its characteristics. Developing a model that mimics both the early and late features of AMD has been challenging due to several obstacles. First, AMD is a complex process involving both genetic and environmental factors. Rather than being caused by a single genetic defect, numerous genetic polymorphisms have been implicated in contributing increased risk for AMD. Oxidative stress, inflammation, and lipid and carbohydrate metabolism have all been implicated in the pathology of AMD. Second,

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anatomical differences between the species used for AMD models and the human retina have lent further complexity to the task.

Models of AMD have been created in mice, rats, rabbits, pigs, and non-human primates. Rodent models offer the advantages of low cost, disease progression on a relatively quick time scale, and the ability to perform genetic manipulation. However, one distinct disadvantage of mice and rats is the lack of an anatomical macula. On the other end of the spectrum, non-human primates offer the closest anatomy to humans, but are quite difficult to manipulate genetically, costly to maintain, and have a slow time course of disease progression. In spite of these limitations, numerous animal models for AMD have been created and have revealed many important aspects about the underlying pathology of the disease. This review attempts to provide a comprehensive and updated report on animal models of AMD by building on several other reviews previously published on the subject (Edwards and Malek, 2007; Grossniklaus et al., 2010; Marmorstein and Marmorstein, 2007; Rakoczy et al., 2006; Ramkumar et al., 2010; Zeiss, 2010).

2. Rodent models of dry macular degeneration

To evaluate a given animal model, it is important to determine which features need to be present to consider it a good model. Some of the histological features that have been reported from the eyes of patients with AMD include thickening of Bruch's membrane (BM), sub-RPE basal laminar deposits and basal linear deposits (i.e. drusen), changes in the RPE including loss of the basal infoldings, atrophy, and hyperplasia, accumulation of immune cells such as macrophages or microglia, deposition of activated complement proteins, photoreceptor atrophy, retinal or choroidal neovascularization and fibrosis (Green, 1999; Green and Enger, 1993; Sarks, 1976). Additionally, accumulation of lipofuscin in RPE cells with increased levels of A2E and corresponding increases in autofluorescence have been demonstrated in AMD patients (Sparrow et al., 2003). Functional changes include decreased signals on electroretinograms (ERGs) reflecting photoreceptor atrophy (Gerth, 2009). This paper will review many animal models with the features of human AMD, but it is important to realize that most of these are laboratory creations and may not be an etiological representation of human disease.

2.1. Complement factor pathway

The discovery of components of the complement cascade in drusen from the eyes of patients with AMD suggested an important role for inflammation in this disease (Johnson et al., 2000; Mullins et al., 2000). Further work demonstrated that polymorphisms in the gene for complement factor H (*CFH*) are associated with an increased risk of AMD (Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005; Klein et al., 2005; Thakkinstian et al., 2006; Zareparsi et al., 2005). The Y402H polymorphism in *CFH* increases the risk of AMD five to sevenfold, and at least 50% of AMD cases are associated with this polymorphism, making it the single largest genetic risk factor (ibid). Polymorphisms in other complement factors (such as Factor B, C2, C3) have also been associated with conferring protection or susceptibility to the development and progression of AMD (Gold et al., 2006; Maller et al., 2007; Montes et al., 2009; Reynolds et al., 2009; Yates et al., 2007). Recent work has begun to link together the models of oxidative damage to those with defects in the innate immune system. For example, the Y402H polymorphism in complement factor H results in a reduced ability of this protein to bind to malondialdehyde, a product of lipid peroxidation which is present in AMD (Weismann et al., 2011). Such loss of binding would impair the ability of CFH to down regulate complement activation in surfaces coated by proteins adducted with malondialdehyde. In the last several years, a number of animal models have emerged to examine the role of complement in the development of AMD.

2.1.1. Cfh$^{-/-}$ mice—Complement factor H (CFH) plays an important regulatory role in the alternative pathway by preventing the binding of C3b with factor B and blocking the formation of C3 convertase (Pickering and Cook, 2008). Lack of CFH function leads to dysregulation of the alternative pathway resulting in low systemic levels of C3, deposition of C3 in glomerular basement membranes, and ultimately membranoproliferative glomerulonephritis (MPGN) Type II (Pickering and Cook, 2008). Interestingly, these patients develop macular drusen similar to those seen in AMD (Duvall-Young et al., 1989a, b). Mice genetically engineered to lack complement factor H also develop MPGN and retinal abnormalities reminiscent of AMD (Coffey et al., 2007; Pickering et al., 2002). At two years of age, these animals demonstrated decreased visual acuity as measured by water maze, reduction in rod-driven ERG a- and b-wave responses, increased subretinal autofluorescence, complement deposition in the retina, and disorganization of photoreceptor outer segments. One feature of these animals, which was not typical compared to other models of AMD, was thinning of the Bruch's membrane. The authors hypothesized that unregulated C3 activation may lead to an increase in phagocytic activity thereby resulting in decreased thickness.

2.1.2. Transgenic CFH Y402H mice—To further elucidate the mechanisms by which *CFH* mutations contribute to AMD, transgenic mouse lines expressing the Y402H polymorphism under control of the human *ApoE* promoter were constructed (Ufret-Vincenty et al., 2010). The ApoE gene codes for apolipoprotein E, which is important in forming lipoproteins for lipid transport. At one year of age, these animals demonstrated a larger number of drusen-like deposits than seen in wild-type mice or *Cfh*$^{-/-}$ mice. Immunohistochemistry revealed increased numbers of microglial and macrophages in the subretinal space and electron microscopy showed thickening of Bruch's membrane and basement membrane deposition of C3d. Compared to the *Cfh*$^{-/-}$ mice, transgenic *CFH Y402H* mice did not show photoreceptor atrophy. This could be due to the younger age at which these mice were studied (one year versus two years) or may be secondary to the presence of some functional activity of CFH protein that prevented a more severe dysregulation of the alternative pathway. With the recent studies by Weismann et al. (2011) demonstrating the loss of *CFH Y402H* to bind malondialdehyde, it will be quite intriguing to study the effects of lipid peroxidation products in *CFH Y402H* mice.

2.1.3. Transgenic mice overexpressing C3—Complement factor C3 plays a pivotal role in the activation of complement by integrating signals from the three distinct complement-activating pathways. Cleavage of C3 to C3a and C3b can activate further downstream components including C5a and lead to the formation of the membrane attack complex, which is composed of C5b through C9. Since C3 plays such a central role in regulating the cascade, it is reasonable to expect that overexpression of this protein might lead to accelerated activation of complement and the development of retina pathology. Mice transfected with a C3-expressing adenovirus regulated under the CMV promoter expressed C3 at higher levels than normal (Cashman et al., 2011). Near the areas of injected virus, these animals showed several features of AMD including proliferation and migration of endothelial cells within the retina, disruption of the RPE with migration of pigmented cells into the retina, complement deposition, and atrophy of the photoreceptor outer segments. In AMD, new vessels typically appear in the form of choroidal neovascularization, but some patients can develop new vessels in the retina in a process known as retinal angiomatous proliferation (RAP). The migration of endothelial cells in the retina could be analogous to the development of RAP. However, compared to animals injected with a GFP vector, the C3-overexpressing animals demonstrated increased incidence of retinal detachments, a feature not consistent with AMD. This change as well as evidence that the adenovirus itself could contribute to the pathological features might be limitations of this model.

2.1.4. C3a and C5a receptor$^{-/-}$ mice—Both complement components C3 and C5 have been found in drusen (Johnson et al., 2000; Mullins et al., 2000). Aside from their activities in opsonization and formation the membrane attack complex, these proteins can also elicit additional biological responses through activation of their endogenous receptors. Mice lacking the receptors for C3a or C5a exhibit smaller lesions in the laser-induced CNV model (described below), decreased levels of VEGF expression, and impaired leukocyte recruitment (Nozaki et al., 2006a). This evidence suggests that activation of the C3a and C5a receptors plays a role in the development of CNV in AMD.

2.2. Chemokines

Chemotactic cytokines, or chemokines, are a diverse set of small molecular weight proteins that mediate the migration of leukocytes (Graves and Jiang, 1995). Chemokines can be pro-inflammatory or homeostatic and are divided into four families: CXC, CX3C, CC, and C depending on their conserved cysteine residues (Murphy et al., 2000; Zlotnik and Yoshie, 2000). The receptors for chemokines are G-protein coupled receptors that can mediate diverse second messenger signaling resulting in the recruitment of inflammatory cells to a target. In AMD, there is activation of macrophages and microglia resulting in the migration of both into the subretinal space, which is normally devoid of these cells (Combadiere et al., 2007; Gupta et al., 2003; van der Schaft et al., 1993; Xu et al., 2009). The CCL2/CCR2 and CX3CL1/CX3CR1 ligand/receptor pairs in particular have been implicated in the pathogenesis of AMD both through the occurrence of at-risk SNPs as well as by pathology in animal models (Raoul et al., 2010). The T280 M allele of *Cx3cr1* gene has been shown to be associated with AMD in several patient populations (Chan et al., 2005; Combadiere et al., 2007; Tuo et al., 2004; Yang et al., 2010). Knockout mice for these ligand/receptor pairs have created models with many features of AMD.

2.2.1. Ccl2$^{-/-}$ and Ccr2$^{-/-}$ mice—The CCL2/CCR2 signaling axis is known to play an important role in macrophage mobilization. Ccl2, also known as monocyte chemoattractant protein 1 (MCP-1), mediates the binding of monocytes to blood vessels for subsequent tissue extravasation (Kuziel et al., 1997; Lu et al., 1998). RPE cells under oxidative stress can upregulate Ccl2 (Higgins et al., 2003). Interestingly, mice lacking either the CC-motif ligand (*Ccl2*$^{-/-}$) or receptor (*Ccr2*$^{-/-}$) have been found to have changes suggestive of AMD. After nine months of age, these animals demonstrate subretinal drusen-like accumulations, thickening of Bruch's membrane, an increase in autofluorescence and lipofuscin granules, photoreceptor malfunction, and the occurrence of CNV (Ambati et al., 2003). These findings led to the hypothesis that dysfunctional phagocytic clearance might play a key role in AMD. However, screening of the *Ccl2* and *Ccr2* loci have yet to reveal any at risk alleles associated with the development of AMD (Despriet et al., 2008). Additional studies from *Ccl2*$^{-/-}$ mice have challenged the interpretation of some of the initial retinal findings (Luhmann et al., 2009). The drusen-like subretinal deposits initially observed were demonstrated to be accumulations of swollen macrophages. Luhmann et al. found no difference between thickening of Bruch's membrane, RPE and photoreceptor atrophy, and ERG amplitudes compared to age matched wild-type animals. Additionally, they did not observe development of CNV in any *Ccl2*$^{-/-}$ mice and found these animals to be less susceptible to laser induced CNV. Thus, the exact contribution of the CCL2/CCR2 pathway to AMD pathogenesis remains to be clarified.

2.2.2. Cx3cr1$^{-/-}$ mice—The ligand, CX3CL1, is heavily expressed on retinal endothelial cells as well as Muller and ganglion cells, while its receptor, CX3CL1, has only been found in microglial cells in the retina (Cardona et al., 2006; Combadiere et al., 2007; Silverman et al., 2003). Studies of two independently generated *Cx3cr1* deficient mice (Combadiere et al., 2003; Jung et al., 2000) have revealed changes consistent with AMD (Combadiere et al.,

2007). At 12 months of age, *Cx3cr1*$^{-/-}$ mice demonstrated drusen-like deposits that were not apparent in age matched wild-type mice. Similar to the deposits in *Ccl2*$^{-/-}$ mice, these deposits were composed of accumulations of subretinal microglia, however these cells were lipid laden. At 18 months of age, *Cx3cr1*$^{-/-}$ mice showed significant retinal thinning (40%) compared to wild-types. Additionally, laser induced CNV in *Cx3cr1*$^{-/-}$ mice lead to twice the area of neovascularization as in control animals. Lack of CX3CL1 function on retinal microglia may have led to deficiencies in egress of these cells from the retina leading to the formation of subretinal deposits.

2.2.3. Ccl2$^{-/-}$ Cx3cr1$^{-/-}$ double knockout mice—Ccl2$^{-/-}$ and *Cx3cr1*$^{-/-}$ single knockout mice exhibit many features of AMD, but do not manifest these changes until older ages (16 and 18 months, respectively) and the phenotype is not fully penetrant. To determine if loss of both CCL2 and CX3CR1 might have a synergistic effect, *Ccl2*$^{-/-}$ and *Cx3cr1*$^{-/-}$ double knockout mice were generated (Tuo et al., 2007). Combination *Ccl2*$^{-/-}$ *Cx3cr1*$^{-/-}$ mice developed retinal changes as early as 6 weeks providing a more convenient model to study than the single knockout animals. By 9 weeks of age, all *Ccl2*$^{-/-}$ *Cx3cr1*$^{-/-}$ mice demonstrated subretinal drusen, which enlarged with age. Immunostaining revealed increased complement in Bruch's membrane, RPE, and choroidal capillaries (Ross et al., 2008). Knockout mice had focal thickening of Bruch's membrane, increased levels of A2E, infiltration of microglial, and photoreceptor atrophy. In older animals, areas of atrophy and chorioretinal scars were observed. In about 15% of eyes, CNV was observed with the earliest occurrence at 12 weeks. Double knockout mice fed a diet high in omega-3 fatty acids had a smaller number of retinal lesions than animals fed a deficient diet (Chan et al., 2008). This correlates with clinical evidence that high dietary intake of fish or omega-3 fatty acids decrease the likelihood of developing AMD (SanGiovanni and Chew, 2005; SanGiovanni et al., 2007). All of these findings seem to indicate that *Ccl2*$^{-/-}$ *Cx3cr1*$^{-/-}$ mice are a useful model for AMD. However, Raoul and coworkers have questioned the validity of the severe findings in the *Ccl2*$^{-/-}$ *Cx3cr1*$^{-/-}$ mice developed by Tuo et al., because their independently developed lines of *Ccl2*$^{-/-}$ *Cx3cr1*$^{-/-}$ double knockout mice do not exhibit severe features and are not phenotypically different from *Ccl2*$^{-/-}$ or *Cx3cr1*$^{-/-}$ single knockout mice (Raoul et al., 2010). They suggest that selective breeding of animals with the worst drusen may have inadvertently selected for AMD factors independent of CCL2 or CXCR1. Furthermore, recent studies reveal that these mouse lines are contaminated with mutations in CRB1, which confound interpretation of the phenotypes (Matapalli et al. 2012).

2.3. Oxidative damage models

There are several lines of evidence to suggest that oxidative damage might play a role in the development of AMD. The retina is particularly susceptible to oxidative damage due its high metabolic demand, high concentration of oxidizable polyunsaturated fatty acids, and the presence of photosensitive molecules such as rhodopsin or lipofuscin that can produce reactive oxygen intermediates when exposed to light (Cai et al., 2000). Epidemiological studies have suggested that oxidative damage, such as from smoking or sunlight contribute to the risk of AMD (Cruickshanks et al., 1997; Vingerling et al., 1996; Wenzel et al., 2005). Individuals with AMD have significantly higher levels of lipid peroxidation products compared to controls (Nowak et al., 2003). Finally, dietary supplements that include anti-oxidants have been shown to reduce the risk of progression from dry to wet AMD (Group, 2001). Animal models that lack intrinsic anti-oxidant mechanisms or those where additional oxidative stress is applied demonstrate many of the features of AMD.

2.3.1. Immunization with carboxyethylpyrrole adducted proteins—The oxidation of docosahexaenoic acid (DHA), one of the most prevalent fatty acids in the retina, can lead to the formation of carboxyethylpyrrole (CEP) adducted proteins. These modified proteins

are found in drusen and are more prevalent in the RPE/Bruch's membrane of patients with AMD (Crabb et al., 2002; Hollyfield et al., 2003). Additionally, compared to age-match donor eyes from patients without AMD, those with AMD demonstrate higher plasma levels of CEP-adducted proteins as well as demonstrate antibodies to these conjugated proteins (Gu et al., 2003). To test the hypothesis that oxidative damage leading to formation of CEP adducted proteins could be the initiating event in AMD, Hollyfield et al. created a mouse model whereby animals were immunized with CEP-adducted mouse serum albumin (Hollyfield et al., 2008, 2010). Animals were divided in two groups: a short-term group received a strong immunological challenge over three months, while the long-term group was inoculated with a weaker challenge over one year. Both groups developed antibodies to CEP-adducted albumin. At 3 months, the short-term group exhibited deposition of complement component C3d in Bruch's membrane, sub-RPE deposits, RPE swelling and lysis, invasion of macrophages, and pyknosis of overlying photoreceptors. Long-term animals demonstrated a 3 to 5-fold thickening of Bruch's membrane. Furthermore, the severity of pathology correlated with the levels of CEP-specific antibodies. No neovascularization was observed in either the short-term or long-term groups of mice demonstrating the usefulness of this model for dry AMD, but not wet AMD. One advantage of this model is that genetic manipulation or extreme lighting conditions were not needed to induce the phenotype. It will be interesting to see how animals that have been genetically altered to carry human polymorphisms related to AMD, such as *Cfh Y402H* mice, respond to immunization with CEP-adducted proteins.

2.3.2. Ceruloplasmin/hephaestin$^{-/-}$ mice—Iron is a potent generator of oxidative stress and its levels increase in the body, including the retina, with aging (Dunaief, 2006). Ceruloplasmin is a ferroxidase that is thought to mediate iron export from cells.

Humans with ceruloplasminemia, who lack functional ceruloplasmin, develop drusen and retinal pigmentary changes later in life (Miyajima et al., 1987; Morita et al., 1995; Yamaguchi et al., 1998). Mice lacking ceruloplasmin, demonstrate at most mild retinal changes, likely because a second ferroxidase, hephaestin, can compensate for the loss (Harris et al., 1999; Patel et al., 2002; Vulpe et al., 1999). To analyze the potential contribution of iron overload to AMD pathology, mice lacking both *ceruloplasmin* and *hephaestin* were created (Hahn et al., 2004). After 6–9 months, these animals displayed focal areas of RPE hypertrophy and hypopigmentation in the midperipheral retina, subretinal deposits, photoreceptor atrophy, and subretinal neovascularization. Studies from mice older than 12 months demonstrated infiltration of macrophages, focal areas of hyperautofluorescence, and complement deposition (Hadziahmetovic et al., 2008). One limitation of this model is that most double knockout animals die young from a movement related disorder. This limits the ability to study long terms effects in senescent mice. Recently, treatment with an iron chelator, deferiprone, has been shown to decrease iron levels in these double knockout mice and ameliorate retinal degeneration (Hadziahmetovic et al., 2011).

2.3.3. Sod1$^{-/-}$ mice—Super oxide dismutase (SOD) is a powerful anti-oxidant that is expressed in three forms. SOD1, which has the highest expression in retina, localizes primarily to the cytosol, while SOD2 and SOD3 localize to the mitochondria and extracellular space, respectively (Behndig et al., 1998). Prior to 7 months of age, retinas from *Sod1*$^{-/-}$ mice were indistinguishable from age matched wild-type animals (Imamura et al., 2006). After 7 months of age, knockout animals displayed yellowish drusen-like deposits between the RPE and Bruch's membrane. These deposits stained for several biomarkers of drusen including: vitronectin, carboxymethyl lysine, and tissue inhibitor metalloproteinase 3 (TIMP3) (Crabb et al., 2002; Imamura et al., 2006). There was evidence of oxidative damage to the RPE and thickening of Bruch's membrane and light exposure in these animals

hastened the appearance of drusen in a dose dependent manner. About 10% of *Sod1*$^{-/-}$ mice demonstrated evidence of CNV by fundus examination or histology. Senescent *Sod1*$^{-/-}$ mice demonstrated evidence of necrotic death of cells in the INL and reduced ERGs (Hashizume et al., 2008).

2.3.4. Sod2$^{-/-}$ and Sod2 knockdown mice—Polymorphisms in the *Sod2* gene have been associated with increased risk of the development of AMD (Kimura et al., 2000). Unfortunately, *Sod2*$^{-/-}$ mice die soon after birth from a dilated cardiomyopathy, limiting their use as a model for AMD (Li et al., 1995). Retinal histology from some of the few animals that survived to 3 weeks demonstrated thinning primarily of the inner retina and evidence of mitochondrial dysfunction (Sandbach et al., 2001). To study, the effects of Sod2 on retinal function, Justilien and coworkers developed a mouse model in which the retina and RPE were transfected by an adenovirus to expresses a ribozyme that degrades Sod2 (Justilien et al., 2007). These mice demonstrated increased markers of oxidative damage including nitrated and carboxyethylpyrrole-modified proteins. Histology showed thickening of Bruch's membrane, degeneration of the RPE, increased autofluorescence, elevation of A2E levels and atrophy of the photoreceptors. However, the development of CNV was not observed in this model.

2.3.5. Cigarette smoke/hydroquinone$^{+/-}$ high fat diet$^{+/-}$ blue light—Cigarette smoke contains over 4000 potentially harmful substances including many pro-oxidants such as nitric oxide, carbon monoxide, and hydroquinone (Smith and Hansch, 2000). Smoking is the most significant preventable risk factor for AMD (Evans, 2001; Klein et al., 2008; Seddon et al., 1996; Smith et al., 2001; Thornton et al., 2005). The role of cigarette smoke to induce or worsen AMD has been studied in several animal models as well as the additive risk of oxidation from blue light and high fat diets. Espinosa-Heidmann and colleagues studied exposing mice to combinations of high fat diets, blue light, and whole cigarette smoke versus oral hydroquinone (Cousins et al., 2002; Espinosa-Heidmann et al., 2006). They found that animals stressed with blue light and on a high fat diet developed thickening of Bruch's membrane and significantly increased basal laminar deposits. Mice exposed to cigarette smoke or hydroquinone in their diet developed similar changes to Bruch's membrane and had increased basal laminar deposits. Some animals showed invasion of the choriocapillaris into Bruch's membrane reminiscent of early AMD. Wild-type mice treated with hydroquinone in their drinking water develop decreased expression of Ccl-2 in the RPE and choroid and demonstrated altered ratios of pro-angiogenic VEGF versus anti-angiogenic PEDF (Pons and Marin-Castano, 2011). These studies suggest that hydroquinone can further the risk of CNV by altering the balance of these angiogenic factors. However, Weikel et al., 2011 found that hydroquinone exposure did not enhance age-related retinal phenotypes of mice fed high glycemic index diets. The exact relationship between hydroquinone and the development of AMD requires further study.

2.3.6. The OXYS rat—The OXY rats are an inbred strain of Wistar rats that were selected for susceptibility or resistance to the early development of cataracts when placed on a cataractogenic diet rich in galactose (Salganik et al., 1994b). The susceptible line (OXYS) demonstrates high levels of hydroxyl radical generation and lipid peroxidation resulting in mitochondrial oxidative damage and a senescence accelerated model. These animals exhibit multiple signs of premature aging including the development of cataracts, emphysema, scoliosis, tumors, and myocardiopathy (Kolosova et al., 2003; Marsili et al., 2004; Salganik et al., 1994a,b). OXYS rats first demonstrated fundoscopic changes at 1.5 months of age with the appearance of atrophic areas in the RPE and choriocapillaris (Markovets et al., 2011). Older rats developed thickening of Bruch's membrane, drusen and RPE detachments. By 12 months, some animals demonstrated photoreceptor atrophy, decreased ERGs,

destruction of the choriocapillaris with fibrosis and in some cases hemorrhagic detachment of the retina due to neovascularization (Markovets et al., 2011; Neroev et al., 2008; Salganik et al., 1994a).

2.4. Lipid/glucose metabolism

Lipid metabolism and more recently glucose metabolism have long been suspected to play a role in the development of AMD. Parallels have been drawn between the deposition of cholesterol and lipids in atherosclerotic plaques and the material that accumulates in Bruch's membrane. There has been disagreement as to how strongly cardiovascular disease and AMD are related with some studies demonstrating a positive relationship (Klein et al., 2003; van Leeuwen et al., 2003) and others not (Hyman et al., 2000; Tomany et al., 2004). Deciphering the exact relationship between dietary fat and cholesterol intake and the development of AMD has been complex. Lipids and cholesterol are known to accumulate within Bruch's membrane with advancing age and are thought to interfere with the transport of metabolites between the RPE and the choriocapillaris (Curcio et al., 2001; Pauleikhoff et al., 1990; Sheraidah et al., 1993; Sunness et al., 1988, 1985). The deposition of lipids and cholesterol may also contribute to the formation of basal laminar and basal linear deposits. Additionally, increased consumption of cholesterol, monounsaturated, polyunsaturated, and saturated fats have been linked to the development of AMD (Mares-Perlman et al., 1995; Seddon et al., 2003). Genetic polymorphisms in apolipoproteins, which mediate lipid transport have also been implicated in the risk of AMD (Klaver et al., 1998; Simonelli et al., 2001). As will be detailed below, a number of animal models have been created to explore the relationship between lipid metabolism and AMD.

2.4.1. Aging mice$^{+/-}$ high fat diet$^{+/-}$ light treatment—To study the relationship of lipid metabolism in the development of basal laminar deposits beneath the RPE, Cousins and coworkers analyzed young (2 months) and old (16 months) C57BL/6 mice fed normal and high fat diets (Cousins et al., 2002). They found only older mice fed high fat diets developed basal laminar deposits. Additional exposure to blue-green light and estrogen depletion increased the number and severity of deposits (Cousins et al., 2002, 2003). Dithmar and colleagues performed a similar study where they analyzed five groups of animals: 2-month-old mice on a normal diet, and 8-month-old mice on a normal or high fat diet, with or without phototoxic treatment (Dithmar et al., 2001). They found thickening of Bruch's membrane in 8-month-old mice on both normal and high fat diets. 8-month-old mice on high fat diets that also received laser treatment demonstrated the development of basal linear deposits.

2.4.2. High glycemic index diet—Consumption of low glycemic index (GI) diets has been associated with a decreased risk for the onset and progression of AMD (Chiu et al., 2006; Chiu et al., 2011, 2007a,b; Chiu and Taylor, 2011). Advanced glycation end products (AGEs) have been found as a component of drusen. Uchiki and coworkers sought to determine if a diet with an elevated glycemic index could lead to the development of AMD-like lesions in an animal model (Uchiki et al., 2011). Senescent animals on a low GI diet showed fewer and smaller basal laminar deposits and more preservation of RPE basal infoldings compared to those on a high glycemic diet. Additionally, low GI diet animals had lower levels of AGEs in the retina. Animals on the high GI diet demonstrated increased AGEs in the RPE and Bruch's membrane correlating with previous studies that have shown these byproducts to be present in human drusen (Crabb et al., 2002). The incidence and severity of retinal changes progressed as the animals aged with 23.5-month-old animals showing more thickening of Bruch's membrane, more basal laminar deposits, disorganization of RPE basal infolding, and increased photoreceptor atrophy compared to 17-month-old mice (Weikel et al., 2011).

2.4.3. ApoE$^{-/-}$ mice—Mice lacking *ApoE* develop very high levels of circulating cholesterol (Plump et al., 1992; Zhang et al., 1992). Histological examination of these animals at 8 months of age, revealed thickening of Bruch's membrane and the presence of electrolucent particles and membrane-bounded material (Dithmar et al., 2000).

2.4.4. APOEe2/e4 transgenic mice—To emulate and study the various APOE alleles seen in humans, transgenic animals were made where the native mouse ApoE was replaced by the various human APOE alleles (i.e. e 2, e 3, e 4) (Malek et al., 2005, 2006; Sullivan et al., 1997). When placed on a high fat diet, APOE e 2 and APOε4 mice over 16 months of age, showed thickening of Bruch's membrane, vacuolization of the RPE, and RPE pigmentary changes. These changes were worse in the APOEe4 mice than in the APOEe2 mice. APOEe4 mice additionally demonstrated areas of CNV and photoreceptor atrophy. Transgenic APOEe4 mice fed high fat cholesterol enriched diets have also been shown to accumulate amyloid β (Aβ), a component of human drusen (Mullins et al., 2000). Systemic administration of antibodies to Aβ40 and Aβ42 provide visual protection in these animals suggesting a role for Aβ in the pathogenesis of AMD (Ding et al., 2011). In humans, the APOEe4 allele is correlated with relative protection from the development of AMD compared with the APOEe2, while in the mice the opposite appears to be true (Baird et al., 2004; Klaver et al., 1998; Schmidt et al., 2002; Souied et al., 1998). It is unclear why this discrepancy exists between species.

2.4.5. APO*E3-Leiden transgenic mice—APO*E3-Leiden is a dysfunctional form of APO-E3 that was first discovered in a Dutch family with hyperlipoproteinemia and early onset atherosclerosis (Havekes et al., 1986). Mice constructed to express this mutant protein develop basal laminar drusen, which are worsened when the mice are placed on a high fat diet (Kliffen et al., 2000; van den Maagdenberg et al., 1993).

2.4.6. APOB100 transgenic mice + high fat diet—Apolipoprotein B100 (APOB100) is the major apolipoprotein in low-density lipoprotein (LDL) cholesterol. Lipoprotein particles in Bruch's membrane have been shown to contain APOB100. To study how APOB100 might contribute to the formation of lipoproteinacious deposits in AMD, several groups have examined mice that express the human form of APOB100. Young APOB100 mice when fed a high fat diet and exposed to oxidative blue-green light developed basal laminar deposits (Espinosa-Heidmann et al., 2004). At older ages, APOB100 mice fed a normal diet demonstrated increased thickness of Bruch's membrane, loss of the basal infoldings of the RPE, and development of basal laminar deposits (Fujihara et al., 2009; Sallo et al., 2009). When these animals were additionally fed high fat diets, basal linear deposits were observed.

2.4.7. Ldl receptor$^{-/-}$ mice + high fat diet—*Ldl receptor*$^{-/-}$ mice are not able to import cholesterol, resulting in high increased plasma cholesterol levels and membrane translucent particles in Bruch's membrane (Rudolf et al., 2004, 2005). Feeding these animals high fat diets leads to further thickening of Bruch's membrane and was correlated with increased expression of the pro-angiogenic factor VEGF in the RPE and the outer retina.

2.4.8. Vldl receptor$^{-/-}$ mice—Mouse homozygous for mutations in the gene encoding the very low-density lipoprotein (VLDL) receptor do not develop dyslipidemia, but have been shown to develop retinal neovascularization starting at 2 weeks of age (Frykman et al., 1995; Heckenlively et al., 2003; Tiebel et al., 1999). These vessels grow towards the subretinal space and between 1 and 2 months can form choroidal anastomosis or cause retinal hemorrhages. Further examination of this model revealed the development of CNV, elevated levels of VEGF, and dysregulation of the Wnt pathway (Chen et al., 2007). These

findings suggest that the VLDL receptor functions as a negative regulator of CNV (Chen et al., 2007). Thus, modulation of the VLDL receptor may offer a new pathway for treatment in AMD.

2.4.9. CD36$^{-/-}$ mice—Polymorphisms in CD36 have been shown to be protective in AMD (Kondo et al., 2009). CD36 is a scavenger receptor for oxidized low density lipoproteins (OxLDL) and is expressed in the apical and basolateral membrane of the RPE (Gordiyenko et al., 2004; Hayes et al., 1989; Ryeom et al., 1996). Mice deficient for *CD36* accumulate subretinal OxLDL even when fed a regular diet (Picard et al., 2010). These animals demonstrate thickening of Bruch's membrane, which is worsened when these animals were crossed with *ApoE*$^{-/-}$ mice to create *ApoE*$^{-/-}$.

Cd36$^{-/-}$ double knockout mice. Interestingly, treatment of *ApoE*$^{-/-}$ mice with a ligand of the CD36 receptor, EP80317, decreases thickness of Bruch's membrane and prevents photoreceptor atrophy (Picard et al., 2010).

CD36$^{-/-}$ mice have also been reported to develop age dependent choroidal involution thought to be secondary to down regulation of COX2, an upstream activator of VEGF (Houssier et al., 2008).

2.4.10. Mcd/mcd mice (transgenic mutant cathepsin D)—Cathepsin D is an aspartic protease that is highly expressed in the RPE and plays an important role in processing photoreceptor outer segments (Bosch et al., 1993; Regan et al., 1980). Cathepsin D is secreted as a proenzyme, which requires further post translational processing for activity (Davies, 1990). The accumulation of inactive forms of procathepsin D have been linked to RPE dysfunction (Rakoczy et al., 1996). To study the effects of inactive cathepsin accumulation on photoreceptors, transgenic mice with a mutant form of cathepsin (*mcd*) have been created (Zhang et al., 2002). Mice homozygous for the transgene (*mcd/mcd*) demonstrate areas of RPE atrophy starting at 9 months of age (Rakoczy et al., 2002). Mice between 10 and 18 months of age develop areas of RPE hypertrophy, photoreceptor atrophy and reduced ERGs. Notably, these animals develop small yellowish spots in the fundus, which on histology resemble basal laminar and basal linear spots. Autofluoresent imaging reveals hyperautofluoresent areas resembling accumulation lipofuscin. The *mcd/2/mcd2* mouse, which expresses a mutant form of procathepsin D, but has higher levels of inactive proteins, demonstrates similar findings as the mcd1/mcd1 mice, but they manifest earlier at 3 months of age (Zhang et al., 2005).

2.5. Other rodent models of AMD

2.5.1. Senescence accelerated mice—The senescence accelerated mouse (SAM) model is comprised of mice originally derived from AKR/J mice that have been selectively bred for advanced aging (Takeda et al., 1994). The original progenitor lines were subsequently expanded to nine senescence prone lines (SAMP) and four senescence resistant lines (SAMR). The phenotypic characteristics vary from line to line, but animals from the SAMP lines collectively demonstrate early onset development of senile amyloidosis, osteoporosis, degenerative joint disease, cataracts, hearing impairment and brain atrophy with deficits in learning and memory (Takeda et al., 1997, 1994). SAMP1 mice have been shown to exhibit thickening of Bruch's membrane and RPE changes including swelling of basal infoldings and accumulation of lipofuscin granules (Ogata et al., 1992; Takada et al., 1993, 1994). At 10 months, SAMP8 mice also demonstrate thickening of Bruch's membrane, deposition of sub-RPE basal laminar deposits, basal linear-like deposits, and small areas of intra-Bruch's membrane neovascularization (Majji et al., 2000).

2.5.2. Single gene mutations causing macular dystrophies—A number of animal models of inherited macular dystrophies caused by single genetic mutations have been constructed and used to as models of AMD. These include the *Timp3*$^{-/-}$ mice (model for Sorsby Fundus Dystrophy) (Weber et al., 2002), the *Abcr*$^{-/-}$ mice (model for autosomal recessive Stargardt disease) (Mata et al., 2000; Weng et al., 1999), the *ELOVL4* transgenic mouse (model for autosomal dominant Stargardt disease) (Karan et al., 2005), and fibulin-3 transgenic mice (model for human EFEMP1 mutations) (Marmorstein et al., 2007). These models will not be covered in this review and the reader is referred to several excellent reviews on these animals (Edwards and Malek, 2007; Rakoczy et al., 2006; Ramkumar et al., 2010; Zeiss, 2010).

3. Non-human primate models of dry AMD

3.1. Nonhuman primate retinal anatomy

Nonhuman primates are the only animals with a retinal structure closely resembling that found in humans, most notably the presence of a macula. In the center of the macula, the central fovea has multiple features designed to optimize spatial resolution. These include a predominance of cone photoreceptors, their unique morphology and high packing density, as well as displacement of other retinal cell types to create the foveal pit and allow an unobstructed path of light to the cone photoreceptors. In addition, blood vessels are absent from the inner retina and a central capillary-free zone. The macula is also characterized by the presence of the yellow macular pigment (hence the full name “macula lutea” meaning yellow spot), which consists of the plant pigments lutein and zeaxanthin. The macula is exposed to high levels of focused light, has an unusually high metabolic rate and oxygen tension, and has only the underlying choroidal circulation to provide oxygen and nutrients and to remove waste products. All of these features may contribute to the macula's special vulnerability to age-related disease in human and nonhuman primates. Furthermore, several nonhuman primate species develop the early to intermediate stages of AMD.

3.2. Age-related maculopathy in rhesus and cynomolgus macaques

Monkeys rarely show spontaneous development of either the wet or dry form of advanced AMD. However, many studies have documented the signs of early to intermediate AMD, including drusen and pigmentary changes, in older rhesus macaque monkeys (*Macaca mulatta*) (Bellhorn et al., 1981; Dawson et al., 1989; El-Mofty et al., 1980; Francis et al., 2008; Hope et al., 1992; Jonas et al., 2003; Monaco and Wormington, 1990; Nicolas et al., 1996; Olin et al., 1995; Stafford et al., 1984; Ulshafer et al., 1987); see Fig. 1. The prevalence of drusen in these reports ranges from 6% in populations that included young and middle-aged adults (Bellhorn et al., 1981; Stafford et al., 1984) to 50% or more in older animals. A particularly high prevalence was found in a free-ranging colony established in the 1938 on the Caribbean island of Cayo Santiago (Dawson et al., 1989; El-Mofty et al., 1980; Hope et al., 1992). A similar late-onset drusen syndrome was found in another macaque species, the cynomolgus macaque (*Macaca fascicularis*) (Umeda et al., 2005a).

The structural similarity to human drusen has been confirmed by histopathology in both species (Gouras et al., 2008a,b, 2010; Ishibashi et al., 1986; Olin et al., 1995; Ulshafer et al., 1987; Umeda et al., 2005b). Electron microscopy of affected monkey retinas provided evidence for several steps in drusen formation, including budding and disconnection of segments of basal epithelial cytoplasm and thickened basal lamina, and for the consistent presence of macrophages in Bruch's membrane near drusen and in the segments of disconnected cytoplasm (Gouras et al., 2008b). In some cases RPE cells overlying drusen were atrophic. In cynomolgus macaques, drusen were shown by immunohistochemistry and by proteomic analysis of isolated drusen to contain many of the compounds present in

human drusen, including apolipoprotein E, amyloid P component, complement component C5, the terminal C5b-9 complement complex, vitronectin, membrane cofactor protein, annexins, crystallins and immunoglobulins (Umeda et al., 2005b).

In some cases, ophthalmoscopic spots appearing as drusen were found to correspond not with sub-RPE deposits but with RPE cells filled with vacuoles and lipid droplets, a pattern termed lipoidal degeneration (Anderson et al., 2006; Feeney-Burns et al., 1981; Fine and Kwapien, 1978; Umeda et al., 2005b). Feeney-Burns et al. (1981) found that these degenerating RPE cells generally corresponded to punctate fluorescein angiographic window defects, while patches of RPE cells with high lipofuscin and low melanin content corresponded to areas of more diffuse hyperfluorescence.

Genetic factors have been implicated in age-related monkey macular disease. In the Cayo Santiago colony, certain matri-lines were found to have a particularly high prevalence of macular disease (Dawson et al., 1989). More recently, two of the major genes involved in human AMD were found to be linked to maculopathy in rhesus monkeys. Specifically, one polymorphism in *ARMS2 (LOC387715)* and one in the *HTRA1* promoter region were significantly associated with the presence of drusen (Francis et al., 2008). In functional analyses, the disease-associated *HTRA1* polymorphism resulted in a 2-fold increase in gene expression, supporting a role in pathogenesis. Among several primate species, orthologous exons for the human *ARMS2* gene were present only in Old World monkeys and apes. Furthermore, the predicted gene was transcribed in rhesus and human retinas. Associations with polymorphisms in these two genes were confirmed in a second population, although significant association with drusen was found for a different *HTRA1* variant (Singh et al., 2009). These findings represent the first case of genetic factors for a prevalent, complex disease that are shared between humans and macaques, and they support the assumption that pathogenetic mechanisms are also shared.

Monkeys and humans also appear to share key nutritional risk factors. Rhesus monkeys fed diets throughout life that lack the macular pigment carotenoids lutein and zeaxanthin have no macular pigment, show angiographic window defects, (Malinow et al., 1980) and develop drusen at younger ages than those fed standard laboratory diets (Neuringer et al., 2010). In middle age (14–16 years), some of those receiving diets lacking both carotenoids and omega-3 fatty acids develop patches of RPE atrophy as seen ophthalmoscopically (Neuringer et al., 2010), which represent the first documented nonhuman primate cases of more advanced macular disease. Thus, the major limitation of the rhesus model of AMD, that monkeys fail to develop the most advanced forms of the disease, may be due in part to their intake of standard laboratory diets that are extremely low in fat and rich in protective nutrients.

3.3. Early onset drusen in Japanese and cynomolgus macaques

In a large pedigree of cynomolgus macaques (*M. fascicularis*), a group of Japanese investigators identified an early-onset macular degeneration syndrome (Nicolas et al., 1996; Suzuki et al., 2003; Umeda et al., 2005b). Widespread drusen are present in both the macula and periphery starting at 1–2 years of age and show a dominant inheritance pattern, thus closely resembling a cluster of human diseases called dominant drusen that include Malattia Leventinese and Doyne's Honeycomb Dystrophy. Drusen from these animals have been confirmed by histopathology to closely resemble human drusen and, like rhesus drusen, have been shown by immunohistochemistry and proteomic analysis to contain markers of human drusen, including apolipoprotein E, amyloid P component, complement component C5, the terminal C5b-9 complement complex, vitronectin, membrane cofactor protein, annexins, crystallins and immunoglobulins (Umeda et al., 2005b). The pedigree was screened for mutations in 13 genes that are known to underlie early macular degeneration

syndromes in humans, and all were excluded (Umeda et al., 2005a). A similar syndrome has been identified in the Japanese macaque (*M. fuscata*) (Neuringer et al., 2010) (Fig. 2). The dominant inheritance and early onset of this disease could facilitate production of animals for preclinical therapy development.

4. Rodent models of wet macular degeneration

CNV is the hallmark lesion of exudative AMD and is a significant cause of severe vision loss in the elderly population (Klein et al., 1995). Before the era of anti-vascular endothelial growth factor (VEGF) therapy, treatment options for CNV were limited, consisting mainly of ablative modalities (1991; 1999). In the following decades, animal models served to elucidate some of the molecular mechanisms involved in the pathogenesis of CNV while providing reproducible, short time-course models for identifying and testing novel treatments. As a result, anti-VEGF therapy has dramatically altered the prognosis for patients afflicted with exudative AMD and shifted the therapeutic paradigm to increasingly targeted pharmacotherapy (Martin et al., 2011).

Despite the recent improvements in treatments for CNV, the exact underlying pathogenesis of CNV remains elusive; similarly, current animal models of CNV are limited in their ability to recapitulate the complex chain of events leading to the development of CNV in patients with AMD. Ideally, an animal model of exudative AMD would not only include the neovascular component of the disease, but also the underlying senescent degeneration of the macula that predisposes to the growth of new blood vessels from the choroid. The majority of present models rely on either laser or direct mechanical injury to the RPE/Bruch's membrane complex, or alteration of the RPE and surrounding environment by external interventions (such as exogenous compounds injected in the subretinal space) or internally (such as genetic knock-out models).

4.1. Laser induced CNV

While the laser trauma model was first developed in non-human primates by Ryan more than three decades ago (Ryan, 1979b) rodent adaptations of the model are perhaps the most employed. In the laser trauma model, high-powered, focused laser energy is used to induce a break in Bruch's membrane. In 1989 Dobi et al. first described the model in rats using a 647 nm krypton laser (100 μm, 50–160 mW, 0.1 s) (Dobi et al., 1989). Their initial observations regarding the power necessary to reliably produce CNV remain salient: burns that were insufficient to create a break in Bruch's membrane (60 mW) did not result in CNV; burns that were too powerful (130 mW and higher) resulted in extensive choroidal hemorrhage and eventual avascular scarring without CNV; burns that created a white spot with central bubble formation, with or without associated hemorrhage, were found to reliably induce breaks in Bruch's membrane and produce CNV (120 mW in their study) (Dobi et al., 1989). In 1998 the first mouse model was produced by Tobe et al. also using a krypton laser (50 μm, 350–400 mW, 0.05 s) to make three burns in the posterior pole, with CNV formation in 87% of burns at 2 weeks (Tobe et al., 1998). The authors noted a higher rate of CNV formation in burns with bubble formation. Variations using diode, Nd:YAG, or argon lasers have also been commonly employed (Campos et al., 2006; Giani et al., 2011; Olson et al., 2007).

Numerous methods of analyzing the experimental CNV have been described. Fluorescein angiography may be used to visualize leakage from membranes, though leakage is difficult to quantify and mature CNV complexes may not leak, possibly due to surrounding RPE cells (Tobe et al., 1998). Histology is adept at identifying CNV, particularly when aided by immunohistochemical stains such as alkaline phosphatase, or antibodies to CD31 or CD102, among others (Campa et al., 2008; Semkova et al., 2003). However, it is labor intensive,

difficult to quantify, and limited by the technical difficulty required to achieve adequate sampling. Sclera-choroid-RPE flatmounts may be created and combined with fluoresceinated high molecular weight dextran angiography to allow computer assisted, quantitative imaging (Edelman and Castro, 2000). It has been questioned whether the vascular tissue imaged in this technique is choroidal in origin, (Semkova et al., 2003) and further, non-perfused vessels are unlikely to be imaged (Campos et al., 2006). Fluorescent labeling of individual cell populations of RPE-choroid flatmounts followed by 3D reconstruction and volume analysis using confocal microscopy may provide more robust quantification of CNV membrane development (Campos et al., 2006). With the recent development of hand-held spectral-domain optical coherence tomography, advanced in vivo imaging modalities with sophisticated post-acquisition processing algorithms may represent the future method of choice to study CNV membrane formation after laser injury (Giani et al., 2011).

The rodent laser trauma model is appealing for its lower cost, ability to efficiently generate high numbers of CNV lesions for statistical analysis, and its short time course. Similar to the CNV that occurs in human ocular disease, laser-induced CNV follows predictable stages of development: early membrane formation, establishment of a mature fibrovascular network, and involution (Miller et al., 1990a). The time course of CNV development after laser is similar in mice and rats, with the early phase occurring over the first week, and mature membranes developing by 10 to 14 days in most studies (Edelman and Castro, 2000; Tobe et al., 1998). It is not clear at what point involutional changes begin, some investigators have found a slight increase in neovascular area during the first 30 days while others have found involutional changes beginning at 5 days post laser (Edelman and Castro, 2000; Giani et al., 2011). The primary drawback of the rodent laser trauma model is its inability to recapitulate the complex sequence of events that leads to CNV in AMD. It is a model of acute injury and inflammation, rather than a result of long standing senescent degeneration and chronic inflammation. Anatomic discrepancies exist as well, since the laser coagulation causes significant damage to the overlying neural retina to a greater degree than is typical of human AMD. It is unknown to what extent this may alter the local environment surrounding the experimental CNV.

Either through direct pathologic study of cell types and their mediators of angiogenesis, or through the use of transgenic models, the rodent laser trauma model has contributed greatly towards our present understanding of the pathogenesis of CNV. Numerous components of the angiogenic cascade have been studied in murine laser models, including secreted factors such as fibroblast growth factor 2 (FGF-2), (Ogata et al., 1996; Yamada et al., 2000) Ang-2, (Oshima et al., 2004) VEGF, (Shen et al., 1998; Wada et al., 1999; Yi et al., 1997) nitric oxide, (Ando et al., 2002) and matrix metalloproteinases (Berglin et al., 2003; Lambert et al., 2002). Intracellular kinase signaling of growth factors has also been studied, (Seo et al., 1999; Zhu et al., 2009) as have the various cell types involved in CNV formation, including macrophages, (Sakurai et al., 2003; Yi et al., 1997) endothelial cells, (Dobi et al., 1989) fibroblasts, (Ogata et al., 1996) and RPE (Zhang et al., 2011). Laser induced CNV in rodents has also been used to evaluate the role of the complement cascade in experimental CNV (Bora et al., 2006; Lyzogubov et al., 2010).

In addition to improving our understanding of the pathogenesis of CNV at a molecular level, the laser trauma model has supported early work in novel treatments of CNV, and helped to establish proof of concept for pharmacotherapy of CNV. In 1999, Seo and colleagues demonstrated a dramatic reduction in laser-induced CNV in a rodent model with an orally administered protein kinase inhibitor, and in doing so, anticipated the era of pharmacologic therapy of CNV (Seo et al., 1999). Since that time, pharmacologic inhibition of laser CNV has been an active area of research. Intravitreal injections of steroid preparations, (Ciulla et

al., 2001) various anti-angiogenic and anti-inflammatory compounds, (Kim and Toma, 2010; Lima e Silva et al., 2005; Olson et al., 2009; Zou et al., 2006) antibodies (Olson et al., 2007; Rennel et al., 2011; Xie et al., 2009) and sustained release preparations have all been studied (Fu et al., 2007; Pan et al., 2011). Inhibition of VEGF beyond binding antibodies and other molecules has also been explored, including small-interfering RNA mediated techniques (Reich et al., 2003) and receptor blockade (Huang et al., 2011; Takahashi et al., 2006). The most recent anti-VEGF treatment to gain FDA approval for use in patients with AMD, aflibercept ophthalmic solution, has also been studied in the rodent laser model (Saishin et al., 2003). Gene therapy (Balaggan et al., 2006; Lai et al., 2001; Mori et al., 2002) initially evaluated in rodent laser models has recently resulted in investigation in human trials and shows great promise for adjuvant therapy to anti-VEGF modalities. Despite these promising results, it remains critical to maintain strict standards in the evaluation of toxicity and safety when transitioning successful compounds from the rodent laser trauma model to human studies, as illustrated by recent experience with infliximab (Giganti et al., 2010; Olson et al., 2007; Theodossiadis et al., 2009). Furthermore, it is currently unclear whether rodent models are a logical choice for the study of humanized antibodies as a recent investigation in rats found no significant inhibition of CNV formation with intravitreal bevacizumab or ranibizumab, a result attributed to species difference (Lu and Adelman, 2009b).

4.2. Subretinal injection induced CNV

Injection of material between the neural retina and RPE holds promise as an additional mechanism of producing experimental CNV. In this approach, angiogenic substances can be placed in near proximity to the choroidal vasculature, and perturbation of the RPE during injection, when combined with angiogenic signals, appears to be sufficient insult to allow invasion of the subretinal space by CNV (Oshima et al., 2004).

4.2.1. Subretinal matrigel injection—Matrigel is a mixture of extracellular matrix proteins secreted from Engelbreth-Holm Swarm mouse sarcoma cells, primarily containing laminin, collagen IV, entactin/nidogen, perlecan, certain matrix metalloproteinases, and various growth factors, including FGF-2 (Kleinman and Martin, 2005). The mixture is a liquid at 4 °C and solidifies at 24–37 °C, such as when in injected in vivo; in this solid form is thought to allow slow release of angiogenic factors and recruit host cells (Qiu et al., 2006). Its utility in angiogenesis research was demonstrated in early experiments, which became known as the matrigel plug assay (Passaniti et al., 1992). CNV was induced in *ccl2*-deficient mice and wild type mice by subretinal injection of matrigel in the peripheral mouse fundus. Also observed were RPE and photoreceptor degeneration, RPE migration, and various degrees of CNV (Shen et al., 2006). A similar model in the rabbit eye, using subretinal injection of matrigel alone or matrigel with VEGF, achieved CNV in 100% of the lesions (Qiu et al., 2006). Further studies on matrigel in rodents demonstrated the necessary relationship between the RPE and Bruch's membrane to prevent CNV. In a model in which matrigel is injected between the RPE and neurosensory retina, RPE cells migrate across the deposit in order to reestablish contact with photoreceptors, creating a sub-RPE deposit; new vessels from the choroid are then allowed to penetrate Bruch's membrane, resulting in CNV (Zhao et al., 2007). Subsequently, the model was further evaluated in the context of VEGF inhibition with VEGF Trap, demonstrating not only inhibition of CNV in treated rats, but also profiling the cellular constituents of the neovascular response and highlighting similarities with human exudative AMD lesions (Cao et al., 2010). In light of its ability to mirror the subretinal deposit component of exudative AMD and its more lasting capacity to promote angiogenesis—either through sustained elution of angiogenic factors or recruitment of host cells—subretinal matrigel is an appealing model (Cao et al., 2010; Qiu et al., 2006).

4.2.2. Subretinal VEGF gene therapy—The central role of VEGF in ocular angiogenesis has been well established; (Miller et al., 1994a) the RPE is recognized as a principle secretor of VEGF and dysfunction of this system has been suggested to play a critical role in the pathogenesis of CNV (Blaauwgeers et al., 1999). As such, numerous groups have sought to create animal models of CNV by inducing overexpression of VEGF in the RPE. In 2000, Baffi et al. and Spilsbury et al. each described models of CNV in rats given subretinal injections of adenovirus vectors expressing VEGF (Baffi et al., 2000; Spilsbury et al., 2000). Both groups found robust evidence of CNV, as measured by angiography and histology, at 4 weeks following injection despite the reportedly transient infection seen in adenoviral models; in Spilsbury's study, organized neovascular complexes were still seen at 80 days when evaluated by histology. In 2003, Wang's group demonstrated a 95% rate of CNV formation in rats given subretinal injections of adeno-associated virus vectors expressing VEGF, with duration of membrane complexes as late as 20 months post injection (Wang et al., 2003).

The importance of the subretinal injection in these models is elucidated by transgenic mice. In rho/VEGF mice, which display increased VEGF expression by photoreceptors, florid neovascularization arising from the retinal circulation occurs without CNV (Ohno-Matsui et al., 2002). When VEGF expression is induced in the RPE, such as in VMD2/VEGF mice with a tetracycline-inducible promoter system, either no CNV occurs, (Oshima et al., 2004) or intrachoroidal neovascularization is seen without penetration of Bruch's membrane (Schwesinger et al., 2001). However, with additional insult to RPE integrity such as subretinal injection of a gutless adenovirus vector, pronounced CNV develops (Oshima et al., 2004). Moreover, Schmack and colleagues found that subretinal injection of RPE cells produced CNV, which they attributed to VEGF production by the injected cells coupled with mechanical disturbance of the RPE during the injection (Schmack et al., 2009). Notably, they also found CNV, albeit to a lesser degree, in eyes undergoing a subretinal injection of control substance.

4.2.3. Subretinal injection of macrophages, lipid hydroperoxide, and polyethylene glycol—Additional attempts to recreate the unique pathology of exudative AMD have been made by injecting other components or surrogate components of CNV lesions in the subretinal space. For example, macrophages are believed to be important cellular participants in CNV formation, secrete a variety of growth factors relative to angiogenesis and have been isolated from CNV membranes (Grossniklaus et al., 2002; Oh et al., 1999). Jo and colleagues attempted to recapitulate the fibrotic aspect of CNV by performing subretinal injection of macrophages on C57BL/6 or *Ccl2* knockout mice (Jo et al., 2011). They found that CNV co-existed with fibrosis in the experimental model, however it is worth noting that part of the experimental protocol included rupture of Bruch's membrane with a laser at the site of injection.

Lipid deposition in Bruch's membrane is a characteristic component of the pathogenesis of AMD (Wang et al., 2009) and oxidized lipids have been detected in aged Bruch's membrane (Spaide et al., 1999). Subretinal injection of one such oxidized lipid (13(*S*)-Hydroperoxy-9*Z*,11*E*-octadecadienoic acid (HpODE) led to CNV in a rabbit model (Tamai et al., 2002). Baba et al. extended subretinal injection of HpODE to a rat model, finding photoreceptor degeneration, lipid laden macrophages and RPE cells, and resultant CNV (Baba et al., 2010). While they made efforts to exclude animals in which a break in Bruch's membrane occurred during the subretinal injection, they postulated that HpODE induced RPE, endothelial, or infiltrating inflammatory cells to secrete proteases, compromising Bruch's membrane. Their observations also highlight the necessity of both a disturbance of Bruch's membrane and a continued stimulus for neovascularization.

The role of the complement cascade in the formation of CNV has been demonstrated in the laser trauma model (Bora et al., 2005). Drusen are known to contain components of the complement cascade, (Nozaki et al., 2006b) and the largest genetic risk factor known for AMD rests on complement factor H, a gene tied to regulation of the complement system (Haines et al., 2005). Lyzogubov et al. employed subretinal PEG-8 to create a new model of CNV (Lyzogubov et al., 2011). In this model, PEG-8 injection induced activation of the complement cascade and dose-dependent CNV production, which remained present at the last study time point of 42 days.

5. Rabbit and pig models of wet macular degeneration

While rodent models of wet AMD have proven indispensable, it is sometimes desirable to study pathology and particularly pharmacology in larger eyes. The rabbit eye is substantially larger than the rat eye and more akin in size to the human eye. However, it is unique in that the retina is supplied by a superior central ray of vessels and there is no distinct macula. The pig eye is, of the non-primate models, perhaps the most similar to the human, with an area of increased cone density arranged in a central horizontal band considered analogous to the human macula (Sanchez et al., 2011). Due to their anatomical qualities, numerous models of CNV have been developed in rabbit and pig eyes, some with considerable overlap with their rodent counterparts, some with entirely novel features.

5.1. Subretinal injection induced CNV

A number of subretinal injection strategies have also been employed in the rabbit. Subretinal matrigel and oxidized lipid have each been described with similar results to rodent models of the same (Qiu et al., 2006; Tamai et al., 2002). Likewise, subretinal injection of adenovirus vectors expressing VEGF have been shown to induce CNV related leakage in 83% of rabbits (Julien et al., 2008). Ni and colleagues performed one of the longest conducted experiments, following rabbits given subretinal injections of lipopolysaccharide and FGF-2 incorporated in heparin-Sepharose beads for as long as 3 years (Ni et al., 2005). They found CNV in 100% of eyes at 2 weeks with some lesions demonstrating clinical leakage to the end of the study period.

5.2. VEGF/bFGF eluting scleral pellets

The suprachoroidal space is another potential space for the delivery of angiogenic substances and gene therapy vectors (Peden et al., 2011). Zahn et al. used a scleral cut down and cyclodialysis spatula to access the suprachoroidal space in rabbits and implanted pellets impregnated with VEGF and FGF-2 or a control solution (Zahn et al., 2009a). In eyes treated with the growth factor releasing pellets, florid CNV and leakage developed at 2 weeks, while eyes with control pellets did not demonstrate any leakage on angiography. The study also demonstrated a dose-dependent reduction in CNV in eyes treated with a small-molecule inhibitor of integrin $\alpha 5\beta 1$. The exact mechanism by which angiogenic compounds originating in the suprachoroidal space result in changes in Bruch's membrane in relation to CNV formation remains to be described.

5.3. Surgical rupture of Bruch's membrane

The barrier role of Bruch's membrane has long been recognized. Traumatic mechanical rupture of this membrane, such as that occurring in choroidal rupture and chorioretinitis sclopetaria is known to cause CNV (Goldberg, 1976). Additionally, surgical repair of retinal detachment may result in CNV at sites of iatrogenic breaks in Bruch's membrane (Goldbaum et al., 1983; Wilson and Green, 1987). Initial studies of a surgical model of CNV were undertaken by Kiilgaard et al. in 2004, comparing xenon lamp and diode laser induced CNV with mechanical debridement of RPE cells and surgical perforation of Bruch's

membrane (Kiilgaard et al., 2005). The surgical technique was associated with a higher success rate of CNV induction, and histology results led the authors to conclude that the surgically induced CNV more accurately emulated human CNV. In comparison, the laser or xenon burns demonstrated substantial components of gliosis and neuroretinal damage and were significantly less efficient in producing CNV. Further study sought to refine the surgical technique and found that perforation of Bruch's membrane without prior RPE debridement resulted in the most reliable method of inducing CNV development (Lassota et al., 2007). This early research in the model was later complemented by angiographic and immunohistochemical evaluation showing persistently vascularized CNV at 42 days but with decreasing leakage (Lassota et al., 2008). Injection of bevacizumab in the porcine surgical model resulted in a significant reduction in endothelial cell presence in membranes and a trend towards decreased leakage on angiography but did not show any significant difference in CNV size (Lassota et al., 2010). While the surgical model has benefits of reduced neuroretinal damage, the technique is limited by higher cost and the necessity of a three port vitrectomy.

6. Non-human primate models of wet macular degeneration

6.1. Laser Induced CNV

As noted above, the use of laser injury to disrupt Bruch's membrane and induce CNV was first developed in a nonhuman primate, specifically the stumptailed macaque (*Macaca speciosa*) (Ryan, 1979a). It has since has been implemented in cynomolgus macaques (*M. fascicularis*), rhesus macaques (*Macaca mulatta*) and African green monkeys (*Chlorocebus sabaeus*) to investigate the pathogenesis of CNV (Miller et al., 1990b, 1994b), to document the strong selective vulnerability of the macular region to laser-induced CNV compared with more peripheral retina (Shen et al., 2004), and to test a variety of anti-angiogenic treatments. Most notably, the method was used to demonstrate the safety and efficacy of the treatment that is the current standard of care for neovascular AMD, the anti-VEGF antibody ranibizumab (Husain et al., 2005; Krzystolik et al., 2002). Rodent models proved to be inappropriate to test the effects of this humanized anti-VEGF antibody and showed no effect of treatment (Lu and Adelman, 2009a), presumably due to differences between the rodent and human forms of VEGF, whereas the studies in macaques showed strong evidence of safety and efficacy and helped to provide the basis for human clinical trials. A recent study in cynomolgus monkeys similarly demonstrated effectiveness of bevaciumab (Lichtlen et al., 2010). Other inhibitors of the neovascular process tested with this model include steroids (Ishibashi et al., 1985) and Ryan, 1985**), a phosphorothioate oligonucleotide targeting the VEGF gene (Shen et al., 2002), an inhibitor of the urokinase plasminogen activator system (Koh et al., 2006), and an integrin α5β1 inhibitor (Zahn et al., 2009b), and TNF-α inhibitors, including a topically-applied antibody fragment (Lichtlen et al., 2010). The model also has been used to demonstrate safety and efficacy of an adeno-associated virus (AAV) gene therapy delivering the *sFlt-1* gene, a soluble form of the Flt-1 VEGF receptor (Lai et al., 2005). Given the variable effectiveness of current anti-VEGF treatment, and the need for repeated monthly injections that are burdensome for many elderly patients and increase the cumulative risk of side effects, the need continues for a preclinical model that best predicts effectiveness in human patients.

Typical argon laser exposure parameters for the induction of CNV have included a 50 μm spot size, 100 ms duration and powers ranging from 300 to 700 mW but in some studies as high as 1500 mW. Photocoagulation is sometimes repeated to produce a break in Bruch's membrane and bubble formation. Outcome measures of efficacy include the extent of growth of laser-induced new vessels, the total area of blood vessel leakage and the percentage of laser lesions resulting in clinically significant (Grade III and IV) vessel leakage, as visualized by fluorescein angiography and in some cases confirmed by

histopathology. A limitation of the model is that not all eyes respond with new vessel formation. In some earlier studies, the incidence of CNV in eyes without experimental anti-CNV treatment was as low as 30% (Ryan, 1982; Shen et al., 2002). More recent studies have optimized laser parameters to produce Grade III lesions in approximately 70% of laser exposures and Grade IV lesions in 20–40% (Goody et al., 2011). A typical result is that 40% of laser lesions in control eyes result in vessel growth and Grade IV leakage, whereas this percentage is reduced to 15–30% in eyes receiving anti-angiogenic treatments (Zahn et al., 2009b). Group sizes of 8–10 monkeys are typically required to document significant effects, and in some studies smaller group sizes have generated inconclusive results (Tolentino et al., 2004a,b; Zahn et al., 2009b).

7. Summary and conclusions

Developing new treatments for a complex disease, such as age related macular degeneration, remains challenging. Animal models of this disease have provided new insights into the underlying pathological mechanisms. Rodent models have offered the advantages of relative cost-effectiveness, accelerated time scale, and ease of genetic manipulation. Mouse models have been able to recreate many of the histological features of AMD such as the thickening of Bruch's membrane, the development of drusen-like subretinal deposits, and immune dysregulation resulting in complement activation and the accumulation of macrophages or microglia. Additionally, laser-induced CNV in rodents has served as the backbone for studying novel treatments for wet AMD. Together, these models have helped unlock the contributions of different pathological mechanisms such as genetic polymorphisms oxidative damage, lipid and carbohydrate metabolism, and complement dysregulation. Rodent models of AMD are still limited by the anatomical lack of a macula, which might explain whey none of these models has yet been able to capture the complexity of the evolution from early to late AMD. However, as the new insights into the genetic and environmental underpinnings of AMD emerge, there is no doubt that rodent models will remain on the front lines for modeling AMD.

Emerging models in non-human primates offer the hope of recreating some of the features of AMD not easily modeled in lower species as well as providing a platform for testing pre-clinical therapeutics. However, the development of primate models is not without many obstacles. Although, non-human primates offer the closest anatomy to humans, they are costly to maintain, have a slow time course for the development of disease, and are difficult to manipulate genetically. Currently their primary contribution is in the laser-induced CNV model of wet AMD, and in providing preclinical assessment of the safety of experimental treatments.

In spite of the challenges, the number of animal models for age related macular degeneration continues to grow. Increased understanding of the underlying pathological mechanisms will allow the creation models that more accurately recreate the histological and functional changes of the disease and serve as more optimal platforms for testing new therapies. The limitations of the current treatments for wet AMD, and the nearly complete lack of effective therapeutic options for dry AMD, drives a continuing need for such models.

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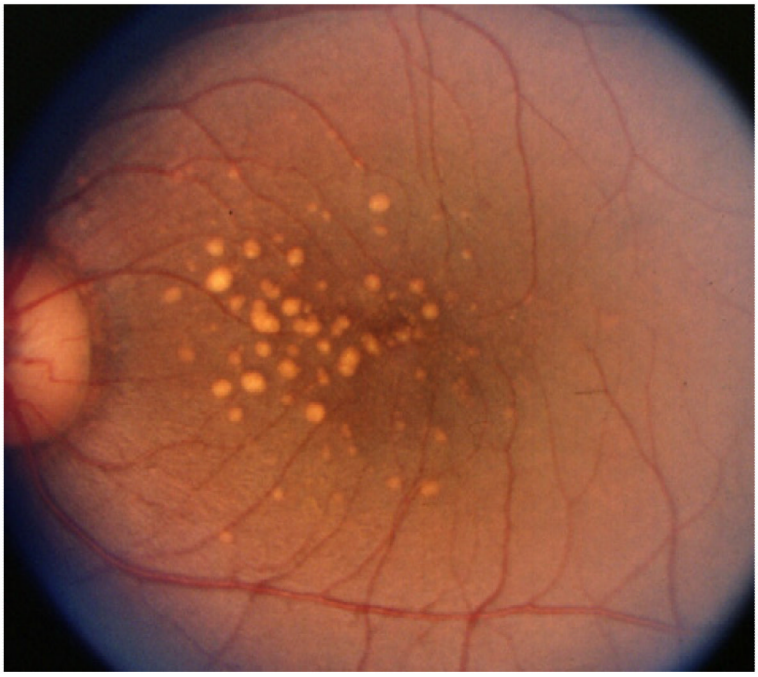

Fig. 1.
Macular drusen in a 25-year-old aged rhesus monkey.

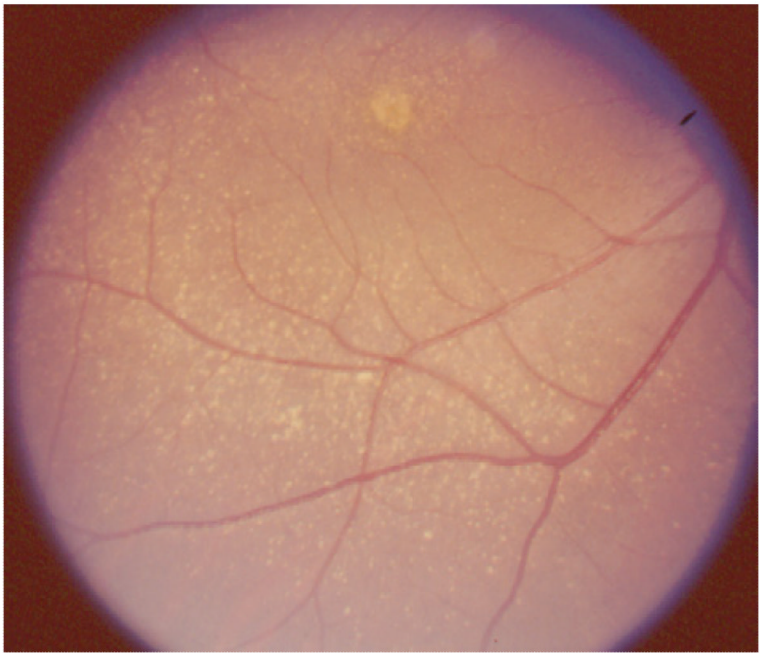

Fig. 2.
Panretinal drusen in a 15-year-old Japanese macaque.

Table 1

Complement Factor Pathway	Sub-RPE Deposits/Drusen	Thickened BM	RPE Hypoplasia/Atrophy	RPE Hyperplasia/Pigmentary Changes	Increased Autofluorescence	Increased Levels of A2E	Complement Deposition	Immune Cell Accumulation	Photoreceptor Atrophy	Reduced Electroretinograms	Choroidal Neovascularization	Retinal Neovascularization	Retinal Fibrosis	Reference	Comments
Cfh -/- mice					X		X		X	X				Coffey et al., 2007	
Transgenic Cfh Y402H mice	X	X					X	X						Ufret-Vincenty et al., 2010	
Transgenic C3 Overexpression mice			X	X			X		X			X		Cashman et al., 2011	
C3a and C5a receptor -/- mice														Nozaki et al., 2006	Reduced CNV, WBC migration after Laser injury
Chemokines															
Ccl2 -/- and Ccr2 -/- mice	X	X	X		X	X			X		X			Ambati et al. 2003	
Ccl2 -/- mice*	-	X	-		X			X	-	-	-			Luhmann et al. 2009	*results differ from Ambati et al. 2003
Cx3cr1 -/- mice		X					X	X	X		X*			Combadiere et al. 2007	*increased response to laser induced CNV
Ccl2/Cx3cr1 -/- mice	X	X	X			X	X		X		X		X	Tuo et al. 2007	
Oxidative Damage models															
Immunization with-CEP adducted MSA	X	X	X				X	X	X					Hollyfield et al., 2008	
Ceruloplasmin/hephaestin -/- mice			X	X	X		X	X				X		Hahn et al. 2004	
SOD1 knockout mice	X	X							X	X	X			Imamura et al. 2006	
SOD2 knockdown mice	X		X		X	X			X	X				Justilien et al. 2007	
NRF2 -/- mice	X	X	X	X	X		X			X	X			Zhao et al. 2007	
Cigarette smoke +/- high fat+/- blue light	X	X												Espinosa-Heidmann et al. 2006	
Hydroquinone in Ccl2 -/- mice														Pons et al. 2011	increased VEGF to PEDF ratio
OXYS Rat	X	X	X						X	X		X		Markovets et al. 2011	
Glucose/Lipid Metabolism															
Aging mice + high fat diet	X	X												Cousins et al. 2002	
High glycemic index diet	X	X							X					Uchiki et al. 2011, Weikel et al. 2011	
APOE -/- mice	X	X*												Dithmar et al. 2000	* Electrolucent densities in BM
APOEe2/e4 transgenic mice +/- high fat	X*	X*	X*	X*					X**		X**			Malek et al. 2005	* APOEe4 > APOEe2, when on high fat diet ** only in APOE4 mice
ApoE 3-Leiden transgenic mice +/- high fat		X	X											Kliffen et al. 2000	
Apo B100 transgenic mice + high fat	X	X												Fujihara et al 2009	
LDL receptor -/- mice + high fat	X	X*												Rudolf et al. 2005	* Electrolucent densities in BM
Vldlr -/- mice											X	X		Heckenlively 2003, Chen 2007	
CD36 -/- mice	X													Picard et al. 2010	
mcd/mcd mice (transgenic mutant cathepsin D)		X	X	X	X				X	X				Rakoczy et al. 2002	
Other															
Senesance accelerated mouse	X	X										X*		Takada et al. 1994	*Intrachoroidal NV
Induced CNV															
Matrigel induced CNV		(X)	X					X	X		X		X*	Shen et al. 2006; 2. Cao et al. 2010	*subretinal fibrosis
PEG-8 injection							X		X		X			Lyzogubov et al. 2011	
PEC-injected MCP mice								X			X		X*	Jo et al. 2011	*subretinal fibrosis
Rat Subretinal lipid hydroperoxide injection		(X)						X	X		X			Baba et al. 2010	
VEGF Transgenic mice											X*	X**		Multiple - see text	*intrachoroidal NV (VMD2/VEGF mice); CNV if subretinal injection **rho/VEGF mice
Naturally-occuring nonhuman primate models															
Rhesus monkey age-related drusen	X	X	X				X		X					Multiple - see text	
Cynomolgus monkey age-related drusen	X	X	X				X							Umeda et al., 2005 a	
Cynomolgus monkey early-onset drusen		X					X							Multiple - see text	
Japanese macaque early-onset drusen		X												Neuringer et al., 2010	