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Chapter

An Overview of Age-Related Macular Degeneration: Clinical, Pre-Clinical Animal Models and Bidirectional Translation

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Abstract

Age-related macular degeneration (AMD) is a multifactorial disease that results from a complex and unknown interplay among environmental, genetic, and epidemiologic factors. Risk factors include aging, family history, obesity, hypercholesterolemia, and hypertension, along with cigarette smoking, which is the most influential modifiable risk factor. Single nucleotide polymorphisms (SNPs) in numerous genes such as complement factor H (*CFH*) pose some of the known genetic risks. The pathophysiology in AMD is incompletely understood, but is known to involve oxidative stress, inflammation, dysregulated antioxidants, lipid metabolism, and angiogenesis. Animal models have been integral in expanding our knowledge of AMD pathology. AMD is classified as non-exudative or exudative. Because there is no perfect animal model that recapitulates all aspects of the human disease, rodents, rabbits, and non-human primates offer different advantages and disadvantages to serve as models for various aspects of the disease. Scientific advances have also allowed for the creation of polygenic pre-clinical models that may better represent the complexity of AMD, which will likely expand our knowledge of disease mechanisms and serve as platforms for testing new therapeutics. There have been, and there continues to be, many drugs in the pipeline to treat both exudative and non-exudative AMD. However, Food and Drug Administration (FDA)-approved therapies for exudative AMD that mainly target angiogenic growth factors are the only therapeutics currently being used in the clinics. There remains no FDA-approved therapy for the non-exudative form of this disease. This chapter contains a basic overview and classification of AMD and multiple animal models of AMD are highlighted. We include an overview of both current FDA-approved treatments and those in development. Lastly, we conclude with a summary of the important role of pre-clinical studies in the development of therapeutics for this highly prevalent disease.

Keywords: age-related macular degeneration, pre-clinical models, animal models, rodents, non-human primates, geographic atrophy, neovascularization, anti-VEGF complement, retina

1. Introduction

Age-related macular degeneration (AMD) is a multifactorial disease that results from interplay among genetic, environmental, and epidemiologic factors. It is the leading cause of irreversible blindness in people over 60 years of age, with numbers projected to increase over time. Animal models have been integral for understanding pathophysiology of and to develop treatments for AMD. This chapter reviews the basics of AMD including pathophysiology and classification. We then highlight specific examples of animal models and the insight they provide. We discuss both current FDA-approved treatments and those in development. Lastly, we conclude with a summary of the important role of pre-clinical studies in the development of therapeutics for AMD.

1.1 Basics of AMD

The retina plays an integral role in vision by converting light to an electrical stimulus, which is ultimately processed as an image in the occipital lobe of the visual cortex. The macula, located in the posterior pole of the retina, contains the highest concentration of cone photoreceptors across the retina and is responsible for central, high-resolution, and color vision [1]. AMD is a multifactorial disease of the elderly that progressively affects vision through pathological changes to the retinal pigment epithelium (RPE) and loss of photoreceptors in the macula [2]. AMD is classified as non-exudative or exudative. Non-exudative AMD is defined by the presence of drusen — aggregates of lipid, protein, and immune complexes — underneath the RPE with subsequent thickening of Bruch's membrane [3, 4]. AMD is responsible for about 8.7% of blindness and remains as a leading cause of blindness in people over 60 years of age in the developed world [5, 6]. The disease burden will increase as the population ages with longer life expectancies. The global estimate of AMD cases was 196 million in 2020 and is expected to be 288 million by 2040 [6].

Although age is the most impactful risk factor, others include obesity, hypercholesterolemia, hypertension, lighter iris colors, lack of exercise, cigarette smoking, Western diet, elevated C-reactive protein, and family history [7–10]. Cigarette smoking is the most influential modifiable risk factor [11].

In addition to the above risk factors, genetics plays an important role in this multifactorial disease. The International Age-Related Macular Degeneration Genomics Consortium conducted a genome-wide association study of 43,566 subjects that revealed 52 genetic variants of AMD shared between 34 loci. Some of these include genes encoding for collagen type IV (*COL4A3*), matrix metalloproteinases (*MMP9, MMP19*), ATP binding cassette (*ABCA1*) involved in cholesterol transport, paired immunoglobin like type 2 receptor beta (*PILRB*) involved in immune regulation, vascular endothelial growth factor A (*VEGFA*) involved in angiogenesis, and various components of the complement cascade including complement factor H (*CFH*), complement factor I (*CFI*), and complement factors 3 and 9 (*C3*, *C9*) [12]. Among the 34 AMD loci, burden testing of rare (frequency < 0.1%) variants identified 4 protein-altering genes — *CFH, CFI*, tissue inhibitor of metalloproteinases 3 (*TIMP3*), and solute carrier family 16 member 8 (*SLC16A8*) — that contribute to AMD pathology [12]. For example, a knockout mutation in *SLC16A8* resulted in defective lactate transport with consequent acidification along with dysfunction of the retina and photoreceptors [12]. Discovering susceptible AMD loci helps expand knowledge of factors underlying the pathophysiology of this multifactorial disease, along with plausible therapeutic targets.

1.2 Pathophysiology of AMD in humans

Although incompletely understood, AMD is a complex disease that results from a mix of genetic predisposition, environmental factors, and age. There are many models that attempt to explain the pathophysiology of AMD, the underlying disease mechanisms of which are multifaceted and not mutually exclusive. These can be categorized as oxidative stress, inflammation, dysregulated antioxidants, lipid metabolism, and angiogenesis [13]. This chapter highlights the multifactorial etiology of RPE damage and dysfunction, a key event in AMD pathogenesis and briefly touches on other aspects of AMD pathophysiology [3].

A properly functioning RPE is important for retinal homeostasis because of the multiple roles it plays including: transportation of nutrients from the choroidal vasculature; absorption of stray photons of light; phagocytosis of photoreceptor outer segments; metabolism of fatty acids; formation of the blood-retinal barrier; regulation of subretinal water transport; and regeneration of visual pigments during the visual transduction cascade [14]. Some retinal changes that are characteristic of AMD include dysfunction of the RPE, sub-RPE deposition of lipids and proteins, neovascularization of the choroid or retina, and disciform scar formation [13]. Most people develop asymptomatic extracellular lipid deposition underneath the RPE. However, as these lesions enlarge they can cause dysfunction of the RPE [15]. Although an exact stepwise development of disease is not clear, early AMD is defined by the appearance of drusen under the RPE with thickening of Bruch's membrane (BrM). Consequently, this impairs the ability of the RPE to efflux fluids across BrM and to deliver nutrients such as glucose, vitamin A (all-*trans* retinal), and docosahexenoic acid (DHA), causing stress on the RPE and photoreceptors [15]. The impaired transport across BrM may exacerbate formation of drusen, thus causing a vicious cycle of pathology.

Moreover, the RPE is susceptible to oxidative stress from high oxygen utilization, prolonged exposure to visible light, lipid oxidation by photoreceptors and drusen, and cigarette smoking [4, 13]. During phototransduction, visual pigments called opsins use the chromophore 11-*cis* retinal to absorb photons of light. Upon absorption, the 11-*cis* configuration becomes all-*trans*, the initiating step for phototransduction. To convert the all-*trans* back to 11-*cis*, it must proceed through the retinoid cycle whereby the RPE re-isomerizes the molecule back to its 11-*cis* conformation. A byproduct of this cycle is A2E, which accumulates in lipofuscin — particularly in the macula — and reacts with oxygen to form free radicals. This may partly explain why the macula is preferentially affected in AMD [15]. Lipofuscin also accumulates in aging eyes which may exacerbate oxidative stress by forming free radicals and inhibiting the RPE's function of degrading organelles [4, 13]. In short, there are many etiologies of oxidative stress and the literature supports that it is an important part of AMD pathophysiology [13].

Identification of SNPs in several complement factor components sheds light on its role in AMD pathogenesis. The complement system is beneficial for its role in innate immunity and encouraging phagocytosis and removal of unwanted cellular material; however, dysregulation of this system can cause damage and inflammation in surrounding tissue [4]. Similarly, inflammation is a cascade of events that is beneficial in the short term in response to foreign and damaged material, yet chronic inflammation can be harmful and may contribute to the development of AMD [16]. There are many genetic variants of complement genes associated with AMD and one example is the Y402H polymorphism in the *CFH* gene. CFH normally regulates the alternate complement pathway by interfering with C3b and factor B interaction and inhibiting the formation of C3 convertase [17]. However, the

Y402H polymorphism prevents CFH from binding to BrM or to malondialdehyde, a byproduct of lipid peroxidation, ultimately causing unregulated complement activation and chronic inflammation [4, 13, 17].

Antioxidants scavenge reactive oxygen species (ROS) thereby attenuating oxidative stress. Nuclear factor erythyroid 2-related factor 2 (NRF2) is a transcription factor that upregulates antioxidants when signaled by oxidative stress. Studies of *Nrf2*$^{-/-}$ mice showed retinal damage and changes such as thickened BrM, sub-RPE deposits, and complement activation. Thus, antioxidants may protect against AMD, and in contrast, the loss of antioxidants, as shown in the *Nrf2*$^{-/-}$ mice, may exacerbate AMD progression [13].

In humans, the inner and outer retina are supplied by the retinal artery and choroidal circulation, respectively. The choroidal circulation is located beneath BrM, which acts as a physical barrier. Drusen accumulation may disrupt this barrier and when conditions favor angiogenesis, permeable blood vessels lacking endothelial tight junctions and pericytes can develop between the retina and choroidal blood vessels. These vessels can grow into the central retina, a process called choroidal neovascularization (CNV) as seen in exudative AMD [15, 18, 19]. Neovascularization may also originate from the retina in a process called retinal angiomatous proliferation (RAP) [17]. Vascular endothelial growth factor (VEGF) plays a major role in angiogenesis. There is sufficient evidence that points to the role of VEGF in exudative AMD pathogenesis, given the higher VEGF levels in AMD patients and the successful decrease in neovascularization with anti-VEGF agents [13]. Pigment epithelium-derived growth factor (PEDF) is an antiangiogenic molecule whose expression is reduced in eyes with AMD. This imbalance between angiogenic VEGF and antiangiogenic PEDF suggests that homeostasis of vascular factors is disrupted in exudative AMD [15]. In summary, AMD is a multifaceted disease with genetic and environmental risk factors that likely progresses due to a combination of oxidative stress and inflammation, combined with dysregulated antioxidants, lipid metabolism, and increased angiogenesis.

1.3 Classification of AMD

Disease classification can elucidate pathophysiological processes, prognosis, and guide in clinical decision-making. Drusen, the hallmark lesion of AMD, is visible by fundoscopy and can be classified by their size and border characteristics [15]. Specifically, drusen can be small (< 63 mm), intermediate (63–124 mm), or large (>124 mm). They can also be stratified as hard (well demarcated), soft (poorly demarcated), or confluent (contiguous) [20, 21]. Higher number and larger size of drusen portends greater likelihood of progression in AMD. Moreover, compared to hard drusen, soft drusen tend to be located in the macula and increase risk of progression [21].

AMD is categorized as non-exudative or exudative. There are many ways to stratify AMD, but this chapter uses the classification of the Age-Related Eye Disease Study (AREDS) as follows: no AMD (no or few small drusen), early AMD (multiple small drusen, few intermediate drusen, or mild RPE abnormalities), intermediate AMD (numerous intermediate drusen, at least one large drusen, or geographic atrophy without center foveal involvement), and advanced AMD (geographic atrophy with center foveal involvement or neovascular maculopathy) [22].

Each stage has defining characteristics. The advanced non-exudative form of AMD is known as geographic atrophy (GA) and is defined by slow progressive atrophy of the photoreceptors, RPE, and the choriocapillaris that form sharply demarcated lesions [23]. Advanced exudative AMD represents 10–15% of all AMD and is characterized by growth of choroidal blood vessels through BrM and into the

retina, consequently causing intraretinal or subretinal leakage, hemorrhage, and RPE detachment. These changes can cause acute vision loss [15, 18, 24]. Follow-up data from the AREDS found that progression to advanced AMD is associated with the following retinal risk factors: increased baseline drusen severity, the presence of a large drusen within 1 disc diameter of the fovea, the presence of bilateral medium drusen, the presence of advanced AMD in the fellow eye, and the simultaneous presence of AMD RPE abnormalities and large drusen [25].

2. Preclinical models of AMD

Animal models have been generated by multiple laboratories by reconstructing specific features of AMD. These models have become integral for providing insight into the pathophysiology of this disease, as well as to develop proof-of-principle studies to support the advancement of new therapies [26]. In general, an optimal animal model is inexpensive and mimics the features of the human disease in a timely manner to allow for efficient studies [17]. In studies focused on AMD, these changes include a thickened BrM, sub-RPE deposits, RPE atrophy and hyperplasia, accumulation of immune cells or complement, photoreceptor atrophy, CNV, and fibrosis [17]. However, when trying to recapitulate AMD, animal models can be challenging because AMD is a complex disease with multiple polymorphisms able to be influenced by environmental and epidemiologic factors [15]. Furthermore, there are inherent differences in the eyes of animals and humans, such that no single model perfectly captures all features of AMD. Although space limits inclusion of all animal models, this review highlights the weaknesses and strengths of specific animal models and how they have been useful for understanding aspects of AMD development, progression, and treatment.

2.1 Introduction to rodent models

Rodents have been the "go-to" model for retinal disease for decades. There are many advantages to the rodent model. Economically, rodents are small animals that require little space and resources, are easy to breed and handle, have short gestation times while producing many offspring, and have short life spans. Diseases can also progress relatively quickly allowing for efficient studies [17, 27]. Mouse, rat, and human genomes have been sequenced, and each were found to have around 30,000 genes, 95% of which are shared among all three species. Further, advances in molecular genetic techniques allow for ease of genetic manipulation [27]. Anatomically, mice have key retinal structures — RPE, BrM, and choriocapillaris — that are affected in human AMD [15]. The economic, genetic, and anatomic benefits of rodents make them invaluable animal models for studying human disease and testing treatments. Clinicians and scientists alike have been working to recapitulate the human AMD phenotype in mice by taking what is known about the human condition and applying it to mice. This may come in the form of genetic manipulation to induce SNPs in known AMD-associated genes or applying risk factors for AMD to mice such as exposure to cigarette smoke or inducing obesity. Several of these manipulations will be discussed below.

It is important to highlight that there are some structural differences in the retinas of humans and rodents. Unlike humans, rodents do not have a macula, defined anatomically as having at least two layers of ganglion cells with a mixture of rod and cone cells [26]. Rodents also lack an area of the retina with high density of cones similar to the fovea. Moreover, interpretation of findings from early murine AMD models was confounded by a spontaneous point mutation in Crumbs homolog 1

(*Crb1*) that segregated in a sub-strain of the C57B/6 J mouse from the Jackson Laboratories. The *Crb1* mutation affects photoreceptor health and development, but is not relevant in human AMD pathogenesis [28]. This mutation is now screened for prior to use of mouse strains originated from the C57B/6 J mouse strain. Although rodents are not the perfect animal model, they have shed light on many aspects of AMD, of which numerous examples are highlighted in this review.

2.2 Rodent models of oxidative stress

The retina is susceptible to oxidative stress due to its high metabolic demand, lipid oxidation by photoreceptors, and the presence of molecules that form ROS mentioned in section 1.2. Below we present several mouse models that mimic AMD pathology induced by the lack of antioxidants or the addition of oxidative stress.

2.2.1 Superoxide dismutase knockout ($Sod^{-/-}$) mice

There are two isoforms of SOD, the primary antioxidant enzyme in the retina that catalyzes the breakdown of potentially harmful ROS [28]. After 7 months of age, knockout mice lacking SOD1 ($Sod1^{-/-}$) develop sub-RPE deposits that share similar composition to drusen found in human AMD. Other pathology in these mice include thickened BrM, RPE atrophy, and CNV in about 10% of mice [17]. This model, however, is also a model of amyotrophic lateral sclerosis resulting in extra-retinal phenotypes which can complicate the use of this mouse strain [29]. Similarly, mouse models transduced with an adenovirus-mediated ribozyme delivery system to inactivate SOD2 showed signs of oxidative damage like $Sod1^{-/-}$ models, with the caveat that SOD2 null mice did not show signs of CNV. Therefore, SOD2 depletion is not a good model for exudative AMD but may be useful for studying non-exudative AMD [17, 28].

2.2.2 Mice immunized with carboxyethylpyrrole (CEP)-adducted proteins

Oxidized DHA forms CEP-adducted proteins that are present in drusen at higher concentrations in AMD eyes compared to eyes without AMD. In studies performed to test the effects of adding oxidative stress, two groups of mice — 3-month-old mice given a strong inoculation (short-term) and 1-year-old mice given a weaker inoculation (long-term) — were immunized with CEP-adducted proteins. The short-term group developed complement deposition in BrM, sub-RPE deposits, RPE lysis, and the presence of macrophages. The long-term group developed a thickening of BrM [17]. However, neither group developed CNV, making this a potential model for non-exudative AMD. A benefit of this model is that there is no genetic manipulation of the mice, so this model can be combined with other genetically modified models, a condition that may be beneficial for a multifaceted disease such as AMD [17].

2.2.3 Nuclear factor erythroid 2-related factor 2 knockout ($Nrf2^{-/-}$) mice

NRF2 is a transcription factor that encodes for detoxifying and antioxidant enzymes such as SOD. $Nrf2^{-/-}$ mice developed hard drusen-like deposits at 8–11 months of age and larger soft drusen-like deposits at 11–18 months of age similar to changes in early AMD. At 11–17 months of age, 18% of the mice developed CNV. Other changes include RPE atrophy and hyperpigmentation with increased autofluorescence, thickened BrM and choriocapillaris endothelium, photoreceptor atrophy, and increased levels of complement and vitronectin by 12 months of

age. This model is a promising model for both non-exudative and exudative AMD because it has characteristics of both conditions [26].

2.2.4 Ceruloplasmin/hephaestin double knockout (DKO) mice

Iron can be a source of oxidative stress and its transport is mediated by ceruloplasmin, transferrin, and hephaestin [15, 17]. Humans lacking ceruloplasmin can develop AMD in middle age. Ceruloplasmin/hephaestin DKO mice by 6–9 months of age developed focal RPE hypertrophy, increased lipofuscin, photoreceptor atrophy, and subretinal deposits and neovascularization [15, 17]. Retinal changes peak by about 12 months of age, showing signs of oxidative damage and complement deposition [15]. Studying the retinal changes in older mice of this DKO strain is limited, however, due to a movement-related premature death caused by the DKO of ceruloplasmin/hephaestin [17]. Hadziahmetovic *et al.* showed that oral iron chelator deferiprone given to ceruloplasmin/hephaestin DKO mice decreases iron levels and can mitigate retinal degeneration [30]. These findings suggest that iron may play a role in AMD pathology.

2.2.5 Cigarette smoke/hydroquinone exposure in mice

Cigarette smoke contains many toxins and oxidants, the most abundant of which is hydroquinone (HQ). C57BL/6 J mice at 16 months of age were fed a high-fat diet (HFD) for 4.5 months causing the mice to develop sub-RPE deposits when exposed to oxidative stress. The mice were then divided into two groups to examine the additive effects of cigarette smoke and HQ on a HFD. The mice were exposed to a combination of HFD with blue light (positive control), cigarette smoke, or oral HQ. Espinosa-Heidmann *et al.* found that mice fed a HFD yet had no oxidative stress exposure showed normal retinal morphology, while mice exposed to oxidative stress through blue light, cigarette smoke, or oral HQ demonstrated retinal changes similar to early AMD, such as sub-RPE deposits and BrM thickening [31]. Furthermore, mice treated with HQ in their drinking water were found to have more proangiogenic VEGF compared to anti-angiogenic PEDF. The imbalance of angiogenic factors from HQ may contribute to CNV [17]. These findings may partly explain why cigarette smoking is an influential risk factor in AMD.

2.3 Rodents models of inflammation

Inflammation is associated with AMD onset and progression with complement being a major component. Inflammatory components found in drusen further support inflammation taking a role in AMD pathogenesis [15]. Below are a few example models of inflammation and the complement pathway.

2.3.1 Complement factor H knockout ($Cfh^{-/-}$) mice

CFH is a regulatory protein that prevents C3b from binding to complement factor B and ultimately prevents the formation of C3 convertase. Loss of regulation of this pathway causes deposition of C3 in the kidneys and ultimately membranoproliferative glomerulonephritis (MPGN) Type II. These patients also develop drusen similar to those in AMD [17]. $Cfh^{-/-}$ mice also developed MPGN and retinal changes such as increased retinal autofluorescence, complement deposition, and disorganization of photoreceptor outer segments (POS). However, these mice also showed thinning of BrM, which is atypical of AMD, possibly from increased phagocytic activity mediated by complement [17].

2.3.2 Transgenic CFH Y402H mice

The CFH Y402H polymorphism causes chronic inflammation by disrupting the binding of CFH to C-reactive protein and heparan sulfate [26]. At one year of age, transgenic mice with this polymorphism were found to have more drusen-like deposits compared to wild-type or *Cfh*$^{-/-}$ mice [17]. The CFH Y402H mice also exhibited thickening of BrM and increased accumulation of immune cells and complement in the subretinal space and basement membrane, respectively. Unlike *Cfh*$^{-/-}$ mice, CFH Y402H mice did not show photoreceptor atrophy possibly because the mice studied were younger by one year of age or from retaining partial functionality of CFH [17].

2.3.3 Transgenic mice overexpressing C3

Implied by the regulation of C3b through CFH, C3 plays an important activating role in complement pathways. Transgenic mice transduced using adenovirus expressing C3 have higher levels of C3 and a pathology similar to AMD including loss of photoreceptor outer segments and RPE, along with the accumulation of complement. Another finding in these mice was the migration and proliferation of endothelial cells in the retina which may correspond to RAP documented in patients with exudative AMD. However, this model is limited because these mice also exhibit retinal detachments, which are not seen in AMD. It is possible that the injected adenovirus may contribute to some of the unexpected retinal changes [17].

2.3.4 Cluster of differentiation 46 (*Cd46*$^{-/-}$) mice

Like CFH regulating C3b, CD46 is a regulatory cofactor that aids in inactivating C3b and C4b. *Cd46*$^{-/-}$ mice at 12 months of age exhibit increased complement in the RPE with hypertrophic and vacuolated RPE. These findings along with increased autofluorescence, lipofuscin, and autophagosomes of the RPE suggest degeneration of this retinal layer. Other findings in these mice include sub-RPE deposits with thickening of BrM, decreased choriocapillary lumen and fenestrations, and decreased number of nuclei in the outer nuclear layer of the retina. In this model there were low levels of VEGF and no signs of neovascularization, positioning this mouse as a model to the study of non-exudative AMD [26].

2.3.5 Inflammasome mice

Inflammasomes are multiprotein complexes that respond to pathogen-associated molecular patterns or other cellular stresses. Inflammasome activation leads to secretion of proinflammatory substances such as caspase-1, interleukin-1β (IL-1β), and interleukin-18 (IL-18). The NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome has been implicated in many inflammatory conditions such as gout, autoimmune diseases, atherosclerosis, and AMD [32]. Eyes with GA have lower levels of Double-Stranded RNA-Specific Endoribonuclease (DICER1), a micro-RNA, which leads to increased levels of Arthrobacter luteus (Alu) RNA. Alu RNA activates the NLRP3 inflammasome leading to increased levels of myeloid differentiation primary response 88 (MYD88) and IL-18 and ultimately causing RPE atrophy [26]. However, in *Myd88*$^{-/-}$ mice and *Il18r1*$^{-/-}$ mice, Alu RNA did not cause RPE degeneration [33]. These findings suggest that inflammasome activation may have a role in AMD pathogenesis and present potential targets for future therapies.

2.4 Polygenic rodent models

As discussed, AMD is a multifactorial disease resulting from a mixture of multiple genetic and environmental factors. Because monogenic animal models do not represent the complexity of human AMD, combining multiple SNPs with nongenetic factors to create a polygenic animal model may prove beneficial for studying AMD pathogenesis as well as providing platforms on which to test new therapeutics that are being developed in laboratories across the world. Mice make excellent candidates for polygenic models of AMD due to the relative ease of manipulating their genomes and simplicity of affecting their environment [17, 34].

2.4.1 Peroxisome proliferator-activated receptor gamma coactivator – 1 alpha (Pgc1α)/Nrf2 DKO mice

As stated previously, NRF2 is a transcription factor that regulates the expression of detoxifying and antioxidant enzymes. PGC-1α regulates angiogenesis and oxidative stress, among other functions. Single *Nrf2*$^{-/-}$ mice present signs of AMD, such as degenerated RPE and photoreceptor outer segment atrophy. When fed a HFD, *Nrf 2*$^{-/-}$ mice exhibited exacerbated signs of AMD such as RPE hyper/hypopigmentation. On a similar HFD, *Pgc-1α*$^{+/-}$ mice also develop increased lipofuscin accumulation, another indication of AMD [26].

PGC-1α/*Nrf2* DKO mice exhibit AMD signs and dysfunctional photoreceptors by 12 months of age. Autophagy and oxidative damage were greater in the DKO compared to single knockout mice [26]. This polygenic model may better represent the multifactorial nature of AMD. Environmental factors such as cigarette smoke or HFD exposure have not yet been tested in this model, which may be useful for future studies.

2.4.2 Systems genetics and the BXD family of mice

In recent years, the use of systems genetics to uncover genes underlying the pathological mechanisms of retinal diseases has become an invaluable tool in the study of multiple human diseases. Specifically, applying this approach to the BXD family of mice has elucidated novel genes associated with ocular hypertension and optic nerve necrosis in glaucoma [35, 36]. As a brief background, the BXD family of mice were generated by breeding the standard C57B/6 J mouse with the DBA/2 J strain from the Jackson Labs. Offspring were then inbred for 20 or more generations to allow for a homologous recombination-induced variety of genetic backgrounds [37]. Currently, studies are underway to use the BXD family of mice to generate a more accurate model of AMD in the mouse. This is being done by delving into the genomes of each strain of BXD mouse to find different combinations of haplotypes in AMD-associated genes which contain SNPs similar to those found in humans, or that result in an altered protein function as observed in humans. Currently, multiple strains have shown promise for not just AMD, but other retinal diseases as well.

2.5 Rabbit models

Although rodents are the most studied, the larger eye size of rabbits make them advantageous for certain pharmacological and pathological studies. While rabbits are more expensive than rodents, they are less expensive than non-human primates (NHP). Rabbits are also relatively easy to handle and breed. Furthermore, the size of the rabbits allow for easy administration of subretinal injections and vectors for

gene therapy [38]. Rabbits possess a visual streak where rods and cones are dense, but they do not have a macula which, like mice, can present a caveat for direct translation to human AMD [38, 39].

Promoting a wet AMD phenotype using conventional methods of inducing CNV in rodents and primates, such as laser-induced damage of BrM and injection of proangiogenic factors, have not worked for rabbit models; however, Qui *et al*. created an exudative AMD model in rabbits by injecting Matrigel, a membrane matrix mixture that includes growth factors like basic fibroblast growth factor and endothelial growth factor. Growth factors from the Matrigel are slowly released for up to 9 weeks, with subsequent production of CNV lesions and BrM disruption that are reminiscent of AMD. This shows promise of a way to test new therapies for exudative AMD on an inexpensive and reproducible model with similar pathological features of AMD [39].

2.6 Non-human primate models

Although primates and humans have the most similar anatomy, primates are disadvantageous as models because they are difficult to genetically manipulate, expensive, and their disease course is relatively long [17]. Furthermore, they are difficult to handle and breed [38]. Historically, there were limitations to exudative AMD models, however new techniques have generated some exudative AMD models, discussed below.

Because AMD affects the cone dense macula, a major limitation of animal models such as rodents, canines, and felines is the lack of a macula [40]. NHPs are the only pre-clinical animals that have a macula and a similar organization of photoreceptors within the macula like humans [17, 41]. Another advantage of NHP models is their shared similarity in organization of the visual pathway. The macula only receives nutrients and removes waste from the choroidal circulation. Furthermore, since the macula is responsible for high acuity central vision, copious amounts of light are focused on the macula subjecting it to high levels of ROS. These details may explain why the macula is affected in AMD in both humans and NHP [17].

Genetic risk factors are also suspected in NHPs with AMD. Polymorphisms in age-related maculopathy susceptibility 2 (*ARMS2*) and high-temperature requirement factor A1 (*HTRA1*) were linked to significantly higher rates of drusen formation in both humans and rhesus monkeys. These findings suggest shared genetic risk factors and can further infer that humans and rhesus monkeys have commonality in pathophysiology [17].

Another shared risk factor between humans and NHPs is diet. Rhesus monkeys with a diet without lutein or zeaxanthin formed drusen earlier than monkeys fed a standard diet. In another study, monkeys without carotenoids and omega-3 fatty acids developed some RPE atrophy [17]. In fact, the AREDS2 study found that human subjects in the bottom quartile of nutrition benefited the most from vitamin supplementation [42].

2.6.1 Primate models for early onset drusen

Some NHP species such as rhesus macaque monkeys spontaneously develop drusen and early to intermediate AMD. The amount of drusen increased with age [43]. Drusen analyzed in these monkeys were found by immunohistochemical analysis to have similar location and composition as human drusen, sharing compounds such as apolipoprotein E, amyloid P component, complement components, immunoglobulins, vitronectin, membrane cofactor protein, annexins, and crystallins [17, 28].

Interestingly, a group of cynomolgus macaques and Japanese macaques were found to have early-onset drusen in the macula and periphery at around 1–2 years of age. The drusen in these groups of monkeys were also similar in composition to human drusen. This syndrome exhibited a dominant inheritance which along with early onset drusen may serve as a useful animal model for future studies [17].

2.6.2 Primate models for neovascularization

NHP models do not spontaneously develop advanced forms of AMD. Laser induced NHP models of exudative AMD only provide vascular leakage for about 2–3 weeks. However, Patel *et al*. created a NHP model for chronic neovascularization by intravitreal (IVT) injection of DL-alpha-aminoadipic acid, a selective glial cytotoxin, in African green monkeys. In this model, neovascularization progressed for 8–10 weeks after injection and maintained leakage for over 90 weeks. Importantly, anti-VEGF injections decreased leakage at 2–4 weeks, then neovascularization resumed at 4–8 weeks, and repeat anti-VEGF injections at 90 weeks decreased neovascular lesions. These findings are important because this may serve as a good model for testing short and extended-release therapeutics for exudative AMD in model eyes that resemble human eyes [19].

3. FDA-approved treatments for AMD

3.1 Vitamin supplementation for AMD

Lifestyle modifications are thought to delay progression of AMD. The American Academy of Ophthalmology recommends smoking cessation, an antioxidant-rich diet with healthy unsaturated fats or omega-3 supplements, management of other medical conditions, routine exercise, and regular eye examinations for all AMD patients [44]. Additionally, antioxidant vitamins and minerals have been demonstrated to slow progression to advanced AMD according to the AREDS [45]. The original formulation consisted of: 500 mg vitamin C, 400 international units (IU) vitamin E, 15 mg beta carotene, 80 mg of zinc (zinc oxide), and 2 mg of copper (cupric oxide) [45]. Copper was added to the formulation as zinc supplementation can cause copper-deficiency anemia. Smoking cessation is specifically recommended because the high dose of beta-carotene supplementation is subject to a small increased risk of lung cancer [46]. The subsequent AREDS 2 investigation evaluated adding lutein + zeaxanthin and DHA + eicosapentaenoic acid [EPA], or lutein + zeaxanthin + DHA + EPA to the original AREDS preparation. It also explored removal of beta carotene and decreased the original dose of zinc. It adapted the formula to include: 10 mg of lutein and 2 mg of zeaxanthin, 350 mg DHA and 650 mg EPA, no beta-carotene, and 25 mg zinc [47]. They found that lutein + zeaxanthin or DHA/EPA did not further halt the progression of AMD; however, removal of beta-carotene from the lutein + zeaxanthin formulation proved to be protective against AMD and better for patients due to the decreased risk of lung cancer in patients using the beta carotene poor formulation. Additionally, the decreased quantity of zinc was deemed less protective than the higher doses administered in AREDS. In short, AREDS 2 concluded administration of 500 mg vitamin C, 400 IU vitamin E, 10 mg of lutein and 2 mg of zeaxanthin, 80 mg of zinc (zinc oxide), and 2 mg of copper (cupric oxide), without beta carotene was beneficial in decreasing the progression to advanced AMD in patients with intermediate and advanced AMD in at least once eye [47].

3.2 Past therapeutics for AMD

Past therapies for AMD include photodynamic therapy, photocoagulation, low vision rehabilitation, and radiation therapy [44, 46]. First introduced in the 1990's, photodynamic therapy (PDT) involved injecting verteporfin (Visudyne) into an arm vein. The injected medication collects in pathologic neovascular membranes in the central macula. The verteporfin is light activated by using a 690 nm laser over the affected area, causing the formation of ROS. Unfortunately, new models of the PDT laser are no longer available for sale in the United States, although a single model is available in Europe. PDT has become obsolete for AMD treatment with the rise of anti-VEGF therapeutics, although it is still used for other retinal conditions [46]. A second method, photocoagulation treatment, uses a laser to accomplish the same goal. This may also require retreatment; however, the laser can produce scarring, which can cause blind spots. For this reason, it is no longer used to treat pathology within the macula. Moreover, increased damage to the macula lowers the success rate of treatment.

Studies in the 1980s examined the use of photocoagulative therapies in minimizing the progression of disease due to CNV lesions. These assessed laser therapy of the extrafoveal, juxtafoveal, and subfoveal neovascular membranes [46]. It was determined that laser therapy of extrafoveal or juxtafoveal sites was more effective than subfoveal sites. Subfoveal photocoagulation was associated with increased risk of vision loss [46]. However, with increased anti-VEGF therapies, the use of photocoagulation is also declining [46]. A third treatment is low vision rehabilitation, which is used as supplemental therapy to accommodate the central vision changes that may ensue from AMD. This can include implementation of reading glasses, magnifiers, additional lighting, among others [44]. New advances in wearable technology use individualized deficit mapping and artificial intelligence to assist users in navigating their environment and common activities of daily living. The fourth form, radiotherapy, has been used to inhibit neovascularization, but the effectiveness of this method is unclear [46].

3.3 Current therapeutics for AMD

Although there is no current treatment to delay the onset of non-exudative AMD, once the disease progresses to the exudative form, there are treatments to delay its progression, preserve remaining vision, and sometimes recover lost vision [44]. Most of these therapies target the neovascularization and associated fluid leakage and hemorrhage. These drugs inhibit VEGF, the main proangiogenic factor that contributes to neovascularization. Current treatments include bevacizumab (Avastin, Genetech), ranibizumab (Lucentis, Genentech), aflibercept (Eylea, Regeneron Pharmaceuticals), and brolucizumab (Beovu, Novartis).

Pegaptanib (Macugen, Pfizer) was the first anti-VEGF therapy approved by the FDA in 2004 and is an oligonucleic aptamer specifically targeting VEGF-165. Ranibizumab is a monoclonal antibody fragment to all VEGF-A that was approved by the FDA in 2006 based on the results of the phase III MARINA and ANCHOR trials [48, 49]. Aflibercept is a receptor-antibody fusion protein of VEGF receptors 1 and 2 fused to the Fc portion of IgG1 that blocks VEGF-A and B. Aflibercept was approved by the FDA in 2011 based on the VIEW-1 and 2 phase III trials [18, 46]. Brolucizumab is a single-chain antibody fragment approved by the FDA in October 2019 based on the phase III HAWK and HARRIER trials [46, 50]. Ranibizumab, aflibercept, and brolucizumab were created specifically for the treatment of exudative AMD, while bevacizumab was approved for colon cancer and is used off-label.

Bevacizumab is considerably less expensive at an average of $50 per treatment versus $1,800 or $2,000 for the other three available treatments and has been shown to be equally efficacious in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) studies [51].

In any of the treatment trials that are evaluating the efficacy of the anti-VEGF family of therapies, patients are monitored for exudation and treatment response using optical coherence tomography after intravitreal injection [45]. Frequency of injections varies, but most patients require multiple doses and repeat treatments. Brolucizumab is groundbreaking as it is the first anti-VEFG therapy that has demonstrated similar efficacy from a single injection, 4 times a year [46]. Unfortunately, adoption of Brolucizumab has been limited by intraocular inflammation, vasculitis, and vascular occlusion causing visual decline that was seen in 4.6% of trial participants [52]. Potential adverse effects of anti-VEGF therapies include conjunctival hemorrhage, vitreous hemorrhage, increased intraocular pressure, cataract progression, and, rarely, retinal detachment, infection, and intraocular inflammation [44].

4. Potential therapeutics for AMD

There are many studies that have evaluated potential therapies for non-exudative and exudative AMD. Along with vitamin supplementation, there are three main classes of therapies being investigated: antibody, gene, and cell-based therapies.

Aside from the successful anti-VEGF therapies, antibodies targeting the complement pathway show some promise. Because activation of the alternative complement pathway contributes to AMD pathology, antibodies targeting components of this pathway, such as C3 and C5, may attenuate inflammation and damage to the retina by reducing complement mediated cell lysis [53, 54].

Gene therapy involves introducing genetic material, typically a viral vector, into tissues of interest to replace the blueprint of a protein product. The most used viral vectors are adeno-associated viral vectors due to their lower immunogenicity and extended duration of gene expression [54].

Another way to treat AMD is through cellular therapy which works by replacing a protein product, like gene therapy; however, instead of replacing the genetic code, the cells that produce the protein of interest are replaced or supplemented. Cellular therapy allows for the replacement of dead or diseased tissue with healthy tissue. For AMD, this typically involves replacement of the RPE. Replacement of neural retinal tissue is challenging as it relies on the re-establishment of neural connections. In contrast, the RPE does not have neural connections, but serves to maintain healthy photoreceptors by providing nutrients and removing waste products. For these reasons, the RPE is currently the primary target of cell-based therapy for AMD [54]. Another promising cellular therapy for exudative AMD is replacement of the choroidal endothelial layer as this may prevent neovascularization [55]. However, there are many challenges associated with the delivery of cell-based therapy such as immune rejection, high rates of tumor formation, and differentiation into unintended cell types. Previous studies have shown the dangers of using stem cell therapy in the treatment of AMD citing complications like IVT fibrosis and tractional retinal detachment [56]. Furthermore, the timing of RPE transplant is critical to its success. It must be performed early enough so that the underlying retinal cells can still be salvaged; however, performing the therapy too early runs the risk of complications from prepathological intervention [54].

4.1 Failed therapeutics for non-exudative AMD

Lampalizumab, a fragment antigen binding portion of a humanized monoclonal antibody that selectively binds and inhibits complement factor D [57], showed success early on as it passed both Phase I and II clinical trials. Unfortunately, it failed to show superior effects to sham treatment in treating non-exudative AMD with GA in Phase III trials [58]. Eculizumab is another antibody, which targets complement component C5. It was investigated in the COMPLETE trial to assess the progression of GA in patients with non-exudative AMD. While it demonstrated safety, it did not prove to be efficacious in slowing the rate of GA progression [59]. Much like eculizumab, LFG316, another C5 inhibitor, failed to progress past Phase II when it did not show success in stunting the growth of GA [60].

A study evaluating the safety of transplanting subretinal RPE cells derived from human umbilical tissue showed complications associated with the method of delivery. This study reported high rates of retinal perforations and detachments [61].

A unique technique of delivering cell therapy to a tissue of interest is through encapsulated cell technology (ECT). A study utilizing this technology with the NT-501 ECT implant showed promising results. A capsule containing a mass of RPE cells engineered to produce and release ciliary neurotrophic factor (CNTF) was implanted into the eye. CNTF can diffuse across the capsule and act on retinal cells to induce differentiation and promote survival of retinal cells. The exact mechanism of CNTF remains to be elucidated [62]. Studies proved this method is safe, but visual acuity (VA) did not show significant improvement. There was, however, significant improvement in the thickness of the macular region, which has been shown to be associated with increased stabilization of VA regardless of baseline best corrected visual acuity (BCVA) [63, 64]. Despite a lack of significant improvement in VA in AMD patients, this technology has since been repurposed for use in macular telangiectasia type 2 and is effective at improving BCVA and slowing progression of retinal degeneration [65].

4.2 Therapeutics in development

4.2.1 Non-exudative AMD therapies in development

There is hope that an IVT formulation of Zimura, a C5 inhibiting RNA aptamer, will show more promising results than eculizumab and LFG316 [66]. A C3 inhibitor called APL-2 passed Phase II clinical trials in the FILLY study when it demonstrated the ability to impede progression of GA [67]. Two Phase III trials of this drug are underway with the Oaks and Derby trials (Apellis). These are multicenter, randomized, double blind, sham-controlled studies that are estimated to complete around December 2022 [68].

There are studies evaluating the utility of combination antibody therapy. This concept involves inhibition of two separate pathogenic mechanisms contributing to disease progression to elicit compounding effects. A Phase I trial evaluating the combination of LFG316 and CLG561, an inhibitor of complement regulator properdin, is underway for GA [69].

Bone marrow stem cells (BMSCs) have shown safety and efficacy in patients affected by non-exudative AMD. The Stem Cell Ophthalmology Treatment Study (SCOTS) trial showed improvement in BCVA and demonstrated both safety and tolerability [70]. The trial consisted of 32 eyes affected by non-exudative AMD that were treated with autologous BMSC transplant by a variety of methods. Over a one-year period, 63% of eyes showed improvement in VA while 34% maintained a

stable VA. There were no complications, and as these were autologous transplants, no immunosuppression was required.

Current gene therapy in development for non-exudative AMD works to target the complement pathway. Gene supplementation of CD59 inhibits formation of the membrane attack complex (MAC) and is being investigated with the drug AAVCAGsCD59 [71]. By preventing formation of the MAC, inhibition of complement-mediated cell lysis reduces retinal cell death, thus slowing progression of GA. Results from the recently finished Phase 1 clinical trials for AAVCAGsCD59 are being evaluated. Another promising drug, GT005, holds genetic information coding for complement factor I. It will be delivered using a recombinant, non-replicating adeno-associated viral vector. Phase I/IIa clinical trials are underway [72].

4.2.2 Exudative AMD therapies in development

The use of a port delivery system involves implanting a device into the eye that slowly releases drug over an extended period. With this device in place, the patient can have fewer office appointments and less injections. The Phase 2 Ladder study has already shown promise with this type of drug administration [73]. Bifunctional antibodies, antibodies that can bind two or more targets, are being investigated for use in exudative AMD. By targeting both the VEGF and the complement pathway it is hypothesized that patients may require fewer injections and/or show improved outcomes, similarly to the non-exudative AMD combined therapy. IBI302 is an antibody with domains for both VEGF and complement. It is undergoing dose escalation Phase I clinical trials [74]. Another drug being developed for exudative AMD is abicipar pegols, a designed ankyrin repeat protein that is part of the designed ankyrin repeat proteins (DARPin) class that inhibits all isoforms of VEGF-A. While it showed similar efficacy to ranibizumab, the FDA currently denied its approval because of reports of associated intraocular inflammation [75].

A Phase I clinical trial involving only two patients with severe exudative AMD and no control group showed successful implantation of fully differentiated human ESC-derived RPE cells that were grown on a synthetic basement membrane. VA at 12 months showed improvement in 29 and 21 letters. The patch of RPE cells appeared intact and healthy when visualized through biomicroscopy and optical coherence tomography (OCT) [76].

There are documented cases of successful autologous and allogenic transplants of induced pluripotent stem cells. However, the cost of these studies and unexpected genetic changes have been discouraging [78, 79]. Further endeavors in cell-based treatment of AMD are aimed at generating a layer of multipotent stem cells from RPE cells. Proliferation and differentiation of these stem cells may restore function to diseased retina [77].

Exudative AMD gene therapy mainly targets the VEGF pathway, but other areas of intervention include PEDF, angiostatin, and endostatin. Phase II clinical trials of rAAV.sFLT-1, which codes for a soluble, full length version of the VEGFR-1 protein, are currently underway [78]. A Phase I clinical trial evaluating safety and tolerability is currently underway for a recombinant, replication-deficient adeno-associated virus (AAV.7 m8-aflibercept) IVT injection gene therapy carrying an aflibercept coding sequence [79]. A Phase I clinical trial demonstrated safety for using an adeno-associated virus vector carrying genetic information for human PEDF (AdPEDF.11) [80]. Endostatin and angiostatin, are proteins that inhibits angiogenesis. A combination drug of endostatin and angiostatin (RetinoStat) demonstrated safety and tolerability [81]. There are many promising therapies in different stages of clinical trials for the treatment of AMD.

5. Bidirectional translation from humans to pre-clinical models and back again

In summary, the "virtuous cycle" of bidirectional translation allows the examination of the outcome of experimental modulation in normal and pathological phenotypic animal models to discover novel regulators with the potential to evade, delay, or overturn human disease [82]. This cycle demonstrates that breakthroughs in human and experimental models facilitate a recurring sequence of human observation, pre-clinical model experimentation, followed by verification in humans (**Figure 1**). Animal models are fundamental to this discipline, as they advance the progression of understanding of the genetic framework that produces the pathological condition of interest and is a potentially vital target for novel therapeutics. It is proven that this series of bidirectional translation efficiently drives the investigation of diagnosis, treatment, and prevention of congenital, progressive, and adult conditions alike [82].

At baseline, this methodology is possible due to advanced genetic and molecular technologies, as well as the Human Genome Project, which propelled the identification of complex traits and pathways causing disease. Those resources alone, however, do not account for the complex interplay between inherited and environmental factors. Animal models provide a degree of experimental control, not possible in humans, to explore just that [82]. Both phenotype-based (forward

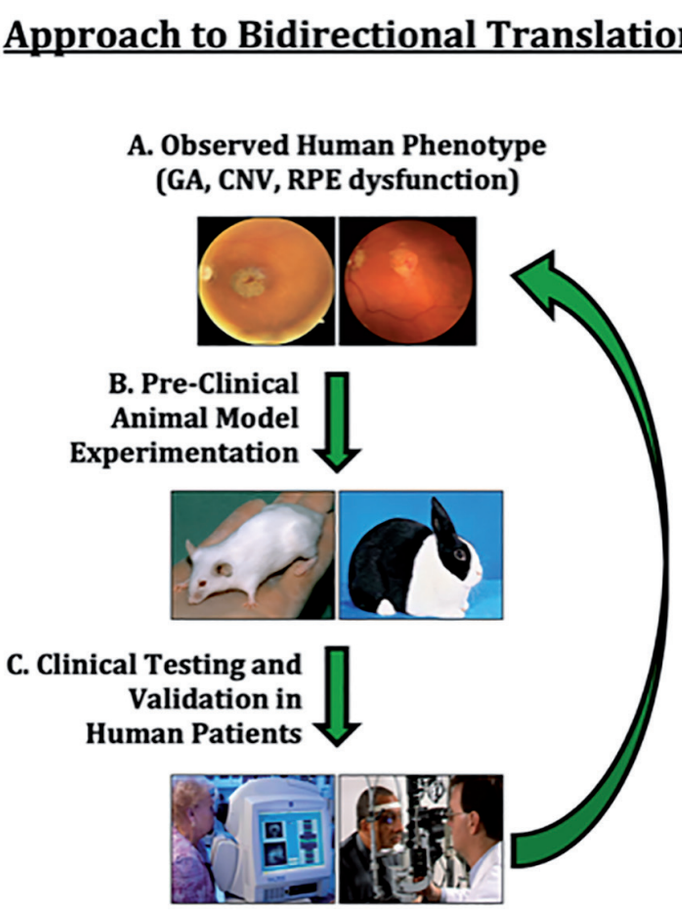


Figure 1.
Model of the "virtuous cycle" of bidirectional translation. (A) Bidirectional translation begins with the discovery of a human disease phenotype. (B) After observing a phenotype, animal models are generated to mimic the human condition as accurately as possible. This allows for a deeper understanding of the pathophysiology as well as a model on which to test therapeutics. (C) With the knowledge gained from animal models, treatments are carried back into human patients to test clinically the efficacy and tolerability of the therapeutics. The cycle then repeats allowing for a better understanding of both the disease itself and how to treat it more efficaciously.

genetics) and gene-based (reverse genetics) approaches permit linkage of genes and phenotypes in experimental animal models. Traditionally, genetic variants are accepted to relate in an additive fashion with functions that are stationary. Yet, there are many complexities in understanding these relationships, specifically in multigenic traits, with factors such as modifier genes, gene–gene interactions, gene–environment and gene-age interactions, and unconventional genetic complexities [82]. This is precisely where the beauty of animal models shines. They are the solution, the medium capable of exploring these intricacies. Puzzle pieces necessary to address gene–gene interactions, modifier genes, gene–environment interactions, and gene-age interactions can be tried and tested in pre-clinical models.

Although animal models cannot entirely replicate the human biological environment, they can reveal information that has been used to formulate hypotheses about the human manifestation of disease. This step has led to the discovery of genetic regulators and therapeutic modulators of disease, as part of the virtuous cycle of bidirectional translation. For example, the studies performed in mice undergoing oxidative stress (*Sod1*$^{-/-}$ and *Nrf2*$^{-/-}$ models) and the discovery that waste material from drusen contribute to RPE atrophy led to the development of treatments for lowering ROS and oxidative damage. Other studies demonstrated that loss of RPE cells and their functionality leads to an AMD-like phenotype, which then inspired the idea of RPE cell therapy [76]. Similarly, animal models (*Cfh*$^{-/-}$ mice) revealed the role of complement in AMD pathophysiology, which inspired the development of novel non-exudative AMD therapies that target complement such as Zimura and APL-2 [66, 67]. Finally, studies in which VEGF inhibition in animals led to the successful therapeutics (bevacizumab, ranibizumab, aflibercept, and brolucizumab) that are currently used to treat exudative AMD in humans [44]. In summary, observed phenotypes can be linked to specific genotypes (and vice versa) that can be corroborated between humans and pre-clinical models. This bidirectional translation and the virtual cycle using a cross-species approach has accelerated the discovery of novel disease-associated genes and the development of targeted therapies.

Nadeau and Auwerx recapitulate that the virtuous cycle pairs the trajectory of observations in humans with the potential of experimental animal models and confirmation in human cases. Human limitations are apparent, while animal models house the biological tools to foster disease onset and progression. They expose pathophysiology that illuminates related disease mechanisms in humans and are deemed vital for the prosperity of molecular, cellular, developmental, and physiological experimentation.

6. Conclusion

AMD is a complex, multifaceted disease that is becoming more prevalent in the aging population. Animal models provide insight into our current understanding of disease pathophysiology including an interplay of oxidative stress, inflammation, dysregulated antioxidants, lipid metabolism, and angiogenesis juxtaposed with genetic and environmental risk factors, the greatest of which are aging and cigarette smoking. Mice are the most used animal models and have provided information such as the roles of antioxidants and inflammation in AMD pathophysiology. Mice also provide excellent polygenic models which may better represent the complex pathology of AMD. Although other animal models, such as rabbits, have been helpful, NHP eyes are the most like human eyes making them an invaluable resource; however cost and ethical issues limit their widespread use.

After disease progresses to exudative AMD, there are several FDA-approved treatments such as bevacizumab, ranibizumab, aflibercept, and most recently brolucizumab that block members of the VEGF family of proteins. Through the AREDS 2 study, vitamin supplementation consisting of 500 mg vitamin C, 400 IU vitamin E, 10 mg of lutein and 2 mg of zeaxanthin, 80 mg of zinc (zinc oxide), and 2 mg of copper (cupric oxide) can slow the progression to advanced AMD. Although treatment options are currently limited, there are studies in various clinical phases evaluating potential therapies for both non-exudative and exudative AMD. Three main classes under investigation are antibodies, genes, and cell-based therapies. The virtuous cycle of bidirectional translation, along with the use of improved animal models, enhances our understanding of AMD pathophysiology and opens the doors to innovative treatment options.

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Conflicts of interest

The authors declare no conflict of interest.

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