ABSTRACT

Background: Age-related macular degeneration (AMD) is a major cause of vision loss. Its prevalence has increased over the past decade. This increase is partly due to the scarcity of preventive and therapeutic interventions for this disorder, except when it is in its advanced neovascular form. Discovery of effective treatments for AMD is complicated by the multifactorial pathology of the disorder. Thus, it is difficult to determine which potential disease mechanism to target in order to achieve the greatest clinical benefit.

Hypothesis: Over a decade ago, it was hypothesized that many of the pathologies observed in AMD stem from retinal pigment epithelial (RPE) cell senescence. This provided a potentially key mechanistic target. Supporting this hypothesis, many of the agents that were in development or clinical use for AMD at that time influenced RPE cell senescence, although they were not utilized for this specific effect. The present article re-evaluates this hypothesis by exploring the logical prediction that if RPE cell senescence is a key contributor to AMD, then inhibition of RPE cell senescence is important in the treatment of AMD. If this hypothesis holds true, the inhibition or reversal of RPE cell senescence or its effects should be a common characteristic of new treatments for AMD.

Conclusions: Over the past decade, many agents have been investigated for the treatment of AMD. Although a few were designed to address cell senescence, the majority targeted other potential pathological mechanisms. In support of our original hypothesis, we now present evidence that many of the newer agents investigated for the treatment of AMD, even those that were not meant to reduce cell senescence or its effects, have this function as part of their activity profiles. Further experimental studies or clinical trials exploring the safety and efficacy of inhibiting RPE cell senescence or reversing its effects are needed to pave the way for improved AMD treatment.

KEYWORDS

age-related macular degeneration, retinal pigment epithelium, cell senescence, VEGF, vascular endothelial growth factor, dry AMD, exudative AMD, wet macular degeneration, geographic atrophy, macular degeneration
INTRODUCTION

Currently, the worldwide incidence and progression rate of age-related macular degeneration (AMD) are approximately 2% and 6%, respectively [1]. AMD treatments have had variable success rates over the past decade. Fortunately, the prevalence of blindness due to AMD decreased between 2010 and 2020 [2, 3]. However, the prevalence of moderate-to-severe vision impairment due to AMD increased during the same period [2, 3]. The increase in vision impairment reflects the limited development of effective treatments for most forms of the disorder, particularly the early stages (Figure 1A, B), whereas the decrease in blindness largely reflects the growing use of new drugs to treat the neovascular stage of AMD (Figure 1C, D) [2, 3].

In fact, only three of the clinical stages of AMD have approved or accepted treatments [4-9]. One stage is advanced neovascular AMD, which can be treated using several available medications, including vascular endothelial growth factor (VEGF) inhibitors, and other treatments are under development [4-8, 10-12]. Another is advanced AMD with geographic atrophy (GA), for which a new drug has been approved [13]. Lastly, a dietary supplement with antioxidant vitamins, carotenoids, and zinc can decrease the risk of progression from intermediate to advanced AMD by approximately 30% [14, 15].

Cell senescence was first described by Hayflick and Moorhead in 1961 as the loss of replicative capacity in cell cultures that have undergone a large number of subcultivations [16]. The trigger for this phenomenon was discovered to be a critical level of telomere shortening after many cell divisions due to the end-replication problem [17]. Many additional triggers for cell senescence were subsequently identified, including genomic damage, aberrant oncogenic signaling, mitochondrial dysfunction, disrupted nicotinamide adenine dinucleotide metabolism, hyperglycemia, and oxidative stress [16, 18]. Oxidative stress may be a particularly important driver of senescence in tissues that produce high levels of reactive oxidative species, such as the retina [19-21].

Although the phenotypic changes that occur in cell senescence may differ somewhat based on cell type, triggering mechanism, and the cellular environment, some features are nearly ubiquitous and have been used as markers for senescence [16, 18]. These features include decreased cell replication, increased levels of the cyclin-dependent kinase inhibitors p16 and p21, adoption of a pro-inflammatory secretory profile called the senescence-associated secretory phenotype (SASP), adoption of an enlarged and flattened morphology, and the presence of lysosomal dysfunction. Lysosomal dysfunction, often measured as an increase in senescence-associated beta-galactosidase activity (SABG), is a standard indicator of cell senescence [16, 22].

Figure 1. Fundus photographs (A and C) taken using an Optos Daytona™ camera (Optos, Inc., Marlborough, MA) and macular optical coherence tomography (OCT) images (B and D) (Heidelberg Spectralis HRA+OCT; Heidelberg Engineering Inc., Franklin, MA) in a patient with intermediate age-related macular degeneration (AMD) (A and B) that later converted to advanced, wet AMD (C and D). In intermediate AMD, drusen appeared as light dots on the fundus photograph (A) and as elevations of the retinal pigment epithelial cell layer (white layer above the lower red line) in the OCT image (B). In advanced AMD (C and D), a choroidal neovascular membrane (D, red arrow) can be seen. Lines and arrows have been added to the OCT images for illustrative purposes.
Another characteristic of senescent cells is their persistence in the tissues in which they occur. This durability appears to be achieved through the inhibition of apoptotic processes that normally operate to eliminate compromised cells [23, 24]. Given their altered morphological and functional characteristics, senescent cells within a tissue can negatively impact tissue function [16, 18, 24]. Furthermore, the chronic release of pro-inflammatory mediators by these cells can damage or kill adjacent non-senescent cells [16, 18, 24].

AMD is closely associated with dysfunction of the retinal pigment epithelial (RPE) cell layer [25-27]. For example, the loss of pigment uniformity observed early in the disorder is partially due to pigmentary changes in the RPE cells [26-28]. In addition, the drusen that occurs in AMD contains material from the photoreceptor outer segments, indicating improper processing by RPE cells [26-29]. Changes in RPE function are also linked to the other advanced form, neovascular AMD (nAMD), in which choroidal blood vessels enter the retina, causing severe structural damage and significant vision impairment [26]. The growth of these vessels into the retina is supported by VEGF and requires a breach of the choroidal-retinal barrier [11, 26, 30]. Since RPE cells participate in both VEGF production and maintenance of the choroidal-retinal barrier, their dysfunction is implicated in the development of neovascularization [11, 26, 30, 31].

Cell senescence is thought to contribute to the pathologies of several age-related disorders, including Alzheimer disease, cardiovascular disease, diabetes, frailty, multiple sclerosis, Parkinson disease, and pulmonary fibrosis [16, 18, 24, 34-39]. The contribution of cell senescence to age-related pathology is supported by the demonstration that senolytic agents, which eliminate senescent cells from tissues, can improve health and function in aging humans and animal models of age-related human disorders [16, 18, 37, 38]. Since the late 1990s, several investigators have suggested that RPE cell senescence plays a role in the pathology of AMD [33, 40-43].

**HYPOTHESIS**

Over a decade ago, senescence of RPE cells was hypothesized as a key contributor to AMD pathology [33]. Three arguments were made in support of this hypothesis. First, the changes in cell physiology that accompany senescence are consistent with pathological changes seen in AMD [33]. Second, there are significant parallels between AMD risk factors and causes of cell senescence [33]. Third, many of the clinical and experimental treatments for AMD known at that time were able to reduce RPE cell senescence or its effects [33].

The present article re-evaluates this hypothesis by exploring the logical prediction that if RPE cell senescence is a key contributor to AMD, then inhibition of RPE cell senescence is important in the treatment of AMD. If this hypothesis holds true, the inhibition or reversal of RPE cell senescence or its effects should be a common characteristic of new treatments for AMD.

**EVALUATION OF THE HYPOTHESIS**

To evaluate the prediction that the inhibition of RPE cell senescence is important for the treatment of AMD, the actions of a group of agents that have been discovered and, in some cases, developed for treating AMD are presented below. These agents were generally introduced over the past decade. The influence of these substances on cellular senescence is also discussed.

**Metformin**

In recent years, four separate retrospective studies found a significant decrease in the incidence of AMD in patients using metformin to treat diabetes and other metabolic disorders [44-47]. Two other studies did not observe this association; however, this may have been due to the study designs, as one used a short dosing duration for metformin [48], and the other included some patients younger than those in which AMD normally occurs [49]. Based on these data, metformin is currently undergoing phase 2 clinical trials for GA [50].

Considerable evidence suggests that cell senescence plays a role in the pathology of type 2 diabetes [38, 51-58]. Senescence produces cellular changes that can impair the functioning of tissues in which the senescent cells reside, as discussed above. Cell senescence appears to be associated with decreased insulin release by the pancreas, adipose tissue dysfunction, and insulin resistance [51-58]. Moreover, the removal of senescent cells reduces diabetic pathology [38].

Although different classes of antidiabetic drugs target diverse physiological mechanisms underlying diabetes, a remarkable number, including biguanides, gliflozins, sulfonylureas, and thiazolidinediones, can also reduce cell
An update on RPE cell senescence as a key contributor to AMD

Given the potential involvement of senescence in type 2 diabetes, the ability of antidiabetic medications to reduce cell senescence has been suggested to play a role in their therapeutic efficacies [38, 51-58]. We recently found that metformin inhibits senescence in RPE cells exposed to oxidative stress, as measured by reduced p21 levels and decreased SABG staining [70]. Thus, the ability of metformin to reduce AMD incidence may be at least partly due to its ability to reduce RPE cell senescence [71, 72].

**Brimonidine**

Brimonidine tartrate, delivered through a biodegradable intravitreal implant, reduces the rate of lesion growth in patients with GA [4, 73]. Brimonidine is an alpha-2 adrenergic receptor agonist used to treat glaucoma and has neuroprotective effects in several models of ocular injury [74]. Part of this protective activity may be mediated by increased levels of fibroblast growth factor [74], a peptide that reduces senescence in several cell types, although its effects on RPE cell senescence have not been reported [74-76]. Thus, the anti-GA effect of brimonidine may be indirect, at least partly, due to reduction in cell senescence.

**Complement pathway inhibitors**

Complement pathway activation has been implicated in the pathology of AMD, and certain polymorphisms that decrease the activity of complement factor H, a negative regulator of the complement pathway, are genetic risk factors for AMD [33, 77]. Several agents that inhibit the complement pathway have been explored for treatment of AMD [4-7]. One such drug, pegcetacoplan (Syfovre™, a C3 inhibitor), was recently approved by the FDA for treatment of GA [13]. Others that are still in, or have been in, clinical trials include APC-1905 (anti-C5 aptamer), eculizumab (anti-C5 monoclonal antibody [mAb]), lampalizumab (anti-CFD mAb), LGF316 (anti-C5 antibody), and avacincaptad pegol (Zimura™, a C3 inhibitor) [4-7].

The complement pathway may be activated in AMD by the materials present in drusen, which are themselves linked to RPE cell senescence [33, 77]. Alternatively, the presence of apoptotic or necrotic cells may lead to pathway activation [77]. Although senescent RPE cells are resistant to apoptosis [23, 24], they may cause the death of surrounding cells by releasing immunomodulators [16, 18, 24]. Thus, while not directly inhibiting RPE cell senescence, complement pathway inhibitors may act in part by reducing its effects.

**Senolytic agents such as UBX1325**

If senescent cells within a tissue produce pathological effects, then removal of the cells or their influence should alleviate these effects. Senolytic agents selectively clear senescent cells from tissues [23, 78]. Senolytics generally counteract the resistance of senescent cells to apoptosis [23, 78]. Two senolytic agents used to evaluate the contribution of cell senescence to AMD are Nutlin-3a and UBX1325 [79-81]. Nutlin-3a antagonizes the mouse double minute 2 protein, which blocks the action of the proapoptotic tumor suppressor p53 [82]. UBX1325 is an inhibitor of Bcl-xL, a pro-survival member of the BCL-2 family of proteins that regulates commitment to apoptosis [83].

The effects of Nutlin-3a have been examined in animal models of three clinical stages of AMD: early-to-intermediate, GA, and nAMD [80, 81]. In each case, Nutlin-3a decreased the number of senescent RPE cells, as well as the signs of AMD. Furthermore, Nutlin-3a increased visual function under each condition, as assessed using electroretinography. Bhisitkul et al. demonstrated that a single intravitreal injection of UBX1325 improved visual function in patients with nAMD for at least 12 weeks [79]. The effectiveness of senolytic compounds in AMD is consistent with a role of RPE cell senescence in the disorder.

**Sirolimus (rapamycin)**

In a recent pilot study in patients with refractory nAMD, sirolimus was significantly more effective than anti-VEGF treatment in reducing retinal pathology [84]. Sirolimus is a senomorphic agent, in that it suppresses the effects of senescent cells on the surrounding normal cells, whereas senolytics eliminate the cells [23, 78]. Sirolimus reduces the SASP, and thereby, its damaging effects [85, 86]. The senomorphic effects of sirolimus extend to RPE cells [87, 88].

One component of the SASP is increased secretion of interleukin-6 (IL-6). This phenomenon occurs in many cell types, including RPE cells [89-92]. Increased IL-6 levels have been linked to AMD; elevated IL-6 levels were found in the serum of patients with GA or nAMD as well as in the eyes of patients with nAMD [91, 93-95]. In addition, systemic IL-6 levels are correlated with the progression of AMD [93, 96]. At least a fraction of the IL-6 expressed in the retina originates from RPE cells [97]. Increased IL-6 levels are thought to promote AMD via pro-inflammatory activity [93, 94, 96]. Sirolimus decreases this effect by reducing the SASP [85, 86].
Risuteganib

Integrins are a family of cell adhesion receptors. They exist as heterodimers composed of one of 18 alpha subunits combined with one of eight beta subunits [98]. In addition to facilitating attachment to the extracellular matrix, integrins have signaling activities that regulate complex cellular processes, including adhesion, migration, proliferation, and survival [99]. Certain functions of integrins, such as increasing inflammation and responsiveness to oxidative stress, originally suggested a role of integrin inhibitors in treating AMD [100]. The integrin inhibitor risuteganib (Luminate™) was recently reported in a phase 2 clinical study to significantly improve visual acuity in patients with intermediate-stage AMD [100]. This efficacy profile is different from that of the Age Related Eye Disease Study Research Group (AREDS) dietary supplements, which decrease the odds of progression from intermediate to advanced AMD but do not improve visual acuity [101].

Integrin signaling is partly mediated by integrin-linked kinase (ILK) [102]. In rat kidney cells, an elevation in ILK level occurs with cell aging and is correlated with markers of cell senescence, including increased SABG activity and reduced proliferative capacity [103]. In cardiac fibroblasts from young rats, ILK overexpression produces several signs of cell senescence, including increased cell size, reduced proliferative capacity, elevated p21 levels, and increased SABG activity. Conversely, in cardiac fibroblasts from older rats, ILK knockdown prevents these senescence-associated changes [104]. In mouse renal cells, oxidative stress, an inducer of cell senescence, increases ILK expression and activity, as well as p16 levels and SABG activity. Ectopic expression of ILK, even in the absence of oxidative stress, increases p16 levels. Conversely, ILK downregulation prevents the elevation of p16 levels caused by oxidative stress [105].

Integrin interacts with ILK through the cytoplasmic domains of β1 and β3 subunits [106]. In rat kidney cells, aging increases the association of integrin β1 with ILK [103]. Risuteganib inhibits the activity of two integrin heterodimers that contain the β1 or β3 subunits (α5β1, αVβ3) [100]. The reduction in ILK activity resulting from this inhibition is expected to decrease senescence in RPE cells, as in other cells [104]. Thus, reduced RPE senescence may contribute to the efficacy of risuteganib in treating dry AMD.

AKST4290

The C-C motif chemokine receptor 3 (CCR3) antagonist, AKST4290, improved best-corrected visual acuity in a small trial involving patients with newly diagnosed nAMD [107]. This effect was attributed to inhibition of the stimulatory effect of CCR3 receptor activation on angiogenesis [107, 108]. Interestingly, one of the natural ligands of CCR3, eotaxin-1, is associated with several aging disorders, although its direct effect on cell senescence has not yet been reported [109]. However, another CCR3 antagonist (CCR3A) reportedly inhibits senescence in periodontal cells [110]. If the anti-senescence effects of CCR3 antagonists extend to RPE cells, this may contribute to the anti-AMD activity of AKST4290.

VEGF inhibitors

Drugs that inhibit VEGF or lower the levels of VEGF signaling are quite effective in treating nAMD [111]. Over the past ten years, many new agents and technologies in this class have been introduced [7, 8, 12]. The most common pathology of nAMD is extension of choroidal blood vessels into the retina [25, 26, 111]. This vessel growth is thought to be caused by increased VEGF levels [111]. In support of this idea, elevated VEGF levels were found in the intraocular compartments of patients with AMD compared to those of age-matched controls [112, 113].

Choroidal neovascularization requires not only the growth of new choroidal blood vessels but also their penetration through the boundary between the choroid and retina, which is formed by Bruch’s membrane and the RPE layer. The importance of this breach is highlighted by the finding that artificial breaks in Bruch’s membrane and the RPE layer are themselves sufficient to produce choroidal neovascularization in animal models of nAMD [114-116]. In addition to supporting blood vessel growth, VEGF decreases the trans-epithelial electrical resistance (TEER) of RPE layers in vitro, which is a sign of reduced integrity in the RPE layer [117]. Thus, VEGF inhibitors may also prevent choroidal neovascularization by maintaining the barrier between the choroid and retina.

The elevation in VEGF levels that stimulates the growth of new choroidal blood vessels in AMD may be a result of RPE cell senescence. Several studies have demonstrated that RPE cell senescence increases with aging in situ and that RPE cells of aged donors have increased VEGF expression compared with those of younger donors [118]. In addition, primary RPE cells with oxidative stress-induced senescence show increased expression of VEGF [119]. As an increase in VEGF levels is also observed in several other types of senescent human cells, it may be among the sequelae of cell senescence [120, 121].
A weakened choroid-RPE barrier, which permits the entry of choroidal blood vessels into the retina, may also be caused by RPE cell senescence. We found that the reduction in TEER caused by VEGF is greater in RPE layers formed by cells approaching senescence [122]. This suggests that the integrity of RPE layers containing senescent cells may be more easily disrupted by VEGF. Thus, although VEGF inhibitors do not directly influence RPE cell senescence, their reduction in VEGF signaling would inhibit many effects of senescence on the retina.

**The AREDS-2 nutritional supplement**

A nutritional supplement cocktail containing beta-carotene, vitamins C and E, and zinc, developed by AREDS, reduces the progression of AMD from intermediate to advanced stages by approximately 30% [101]. The potential for this decrease to be mediated by a reduction in RPE cell senescence was discussed in a previous article [33]. Beta-carotene, vitamins C and E, and zinc all have antioxidant activity and could prevent RPE cell senescence by reducing oxidative stress, an inducer of cell senescence [123]. In addition, zinc can increase telomerase activity, thereby decreasing telomere shortening, another inducer of cell senescence [124].

A new version of this nutritional supplement, called AREDS2, has been developed [15]. This new formulation was based on a large study examining the effect of several changes to the original AREDS formulation, including the addition of macular pigments (lutein and zeaxanthin) and omega-3 fatty acids (docosahexaenoic acid and eicosapentaenoic acid) [15]. These additions, individually and in combination, did not improve the efficacy of the original formulation. At first glance, this seems unsupportive of the importance of anti-senescence activity in treating AMD because both omega-3 fatty acids and macular pigments have antioxidant effects that can protect against senescence, and omega-3 fatty acids can activate telomerase [33, 125, 126]. However, because the constituents of the original AREDS formulation already have high concentrations of both antioxidant and telomerase-activating agents, adding other constituents with the same activities may not produce a noticeable change in efficacy [33].

**RPE cell senescence as a key contributor to AMD**

Designating RPE cell senescence as a “key contributor” to AMD [33] implies that many of the pathological processes that occur in AMD are rooted in RPE cell senescence. One pillar of support for the original hypothesis was that many of the effective agents against AMD, at that time, had the potential to reduce RPE cell senescence. In the past ten years, several new agents have been discovered and investigated, and in some cases, have been clinically developed for the treatment of AMD [4-9]. Based on the original hypothesis, it seems logical that many of these newer anti-AMD agents would also exhibit anti-senescence activity. The present review of the most significant of these agents seems to support this prediction (Table 1).

Perhaps the most direct indication of the importance of inhibiting RPE senescence in the treatment of AMD comes from the experimental and clinical effectiveness of senolytic and senomorphic agents [79-81]. The senolytic agent Nutlin-3a was effective against many stages of AMD in animal models and eliminated senescent RPE cells in vivo [79-81]. The senolytic compound UBX1325 was active against nAMD in a phase 2 clinical trial [79-81], and the senomorphic agent sirolimus was also active against nAMD in a clinical trial [84]. For these compounds, a reduction in the impact of senescent cells is the primarily known element of their activity profiles.

Table 1. Agents with activity against AMD and their effects on cell senescence (see EVALUATION OF THE HYPOTHESIS)

<table>
<thead>
<tr>
<th>Drug or drug class</th>
<th>Reduction in cell senescence</th>
<th>Reduction in the effects of cell senescence</th>
<th>Activity demonstrated in RPE cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin [44-47, 50, 70-72]</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Brimonidine [4, 73-76]</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complement pathway inhibitors [4-7, 13]</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senolytics [79-81]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirolimus [23, 78, 84-88]</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risuteganib [100, 104]</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKST4290 [107, 108, 110]</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGF inhibitors [122]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AREDS nutritional supplement [123, 124]</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AMD, age-related macular degeneration; RPE, retinal pigment epithelium; Brimonidine, an alpha-2 adrenergic receptor agonist; Risuteganib, the integrin inhibitor; AKST4290, the C-C motif chemokine receptor 3 antagonist; VEGF, vascular endothelial growth factor; AREDS, age-related eye disease study research group. Note: The “✓” tick symbol indicates a reported drug action.
Circumstantial support for the hypothesis that inhibition of cell senescence is a key to the treatment of AMD comes from the sheer number of agents effective against AMD that also have anti-senescence effects, several of which have been reviewed in this article. Perhaps metformin currently has the highest profile [70-72]. Several studies have reported that patients receiving metformin have a reduced incidence of AMD [44-47]. Metformin is known to have anti-senescence activity, and this activity has been proposed to contribute to its antidiabetic effects [62, 65]. Recently, the anti-senescence activity of metformin was shown to extend to RPE cells [70].

Although the hypothesis that RPE cell senescence is a key contributor to AMD has not been disproven by an additional decade of research, it has not yet achieved ultimate validation, which will occur only when anti-senescence activity is correlated with anti-AMD activity. Although the realm of senolytic and senomorphic compounds is relatively new [23, 78], early clinical results may be the first step in this validation. However, many hurdles remain in developing a therapy for AMD based on the inhibition of RPE cell senescence or its effects. The most significant is that the hypothesis may be incorrect. However, the data presented in the current report, as well as those from an earlier study [33], do not appear to suggest this. Another hurdle is to inhibit RPE cell senescence with sufficient effectiveness and selectivity to produce a clinically safe and useful effect. To overcome this hurdle, additional research may be needed to gain a better understanding of cell senescence as it occurs in RPE cells, and how to prevent it. An additional obstacle is that cell senescence may be a trigger for AMD but not a sustaining factor. If so, inhibiting cell senescence may not be valuable in treating the disorder once it is established, but it may still have prophylactic use.

Nonetheless, the potential value of senescence-based therapies in treating AMD justifies overcoming the hurdles faced during their development. For example, if RPE cell senescence is foundational or contributes to many other pathological processes in AMD, then inhibitory agents may be effective against multiple stages of the disorder, as observed with the senolytic compound Nutlin-3a in animal models [82]. It would be particularly valuable to treat the mild and moderate stages of AMD, the incidences of which are increasing [2, 3]. In addition, agents that inhibit or delay cell senescence may be prophylactic against AMD [33], as appears to be the case for metformin [44-47]. Finally, as a corollary benefit, the successful treatment of AMD through a senescence-based approach may encourage the pursuit of anti-senescence treatments for other aging disorders.

CONCLUSIONS

The idea that the pathology of AMD involves RPE cell senescence was first proposed more than two decades ago. Over a decade ago, it was hypothesized that RPE cell senescence was, in fact, a key contributor to this pathology. Over the past decade, many agents have been investigated for the treatment of AMD. Although a few were designed to address cell senescence, the majority targeted other potential pathological mechanisms. In support of our original hypothesis, we now present evidence that many of the newer agents investigated for the treatment of AMD, even those that were not meant to reduce cell senescence or its effects, have this function as part of their activity profiles. Further experimental studies or clinical trials exploring the safety and efficacy of inhibiting RPE cell senescence or reversing its effects are needed to pave the way for improved AMD treatment.

ETHICAL DECLARATIONS

Ethical approval: Not required.
Conflict of interests: None

FUNDING

None.

ACKNOWLEDGMENTS

None.

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