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REVIEW

Microvascular contributions to age-related macular degeneration (AMD): from mechanisms of choriocapillaris aging to novel interventions

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Abstract Aging of the microcirculatory network plays a central role in the pathogenesis of a wide range of age-related diseases, from heart failure to Alzheimer's disease. In the eye, changes in the choroid and choroidal microcirculation (choriocapillaris) also occur with age, and these changes can play a critical role in the pathogenesis of age-related macular degeneration (AMD). In order to develop novel treatments for amelioration of choriocapillaris aging and prevention of AMD, it is essential to understand the cellular and functional changes that occur in the choroid and choriocapillaris during aging. In this review, recent advances in in vivo analysis of choroidal structure and function in AMD patients and patients at risk for AMD are discussed. The pathophysiological roles of fundamental cellular and molecular mechanisms of aging including oxidative

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stress, mitochondrial dysfunction, and impaired resistance to molecular stressors in the choriocapillaris are also considered in terms of their contribution to the pathogenesis of AMD. The pathogenic roles of cardiovascular risk factors that exacerbate microvascular aging processes, such as smoking, hypertension, and obesity as they relate to AMD and choroid and choriocapillaris changes in patients with these cardiovascular risk factors, are also discussed. Finally, future directions and opportunities to develop novel interventions to prevent/delay AMD by targeting fundamental cellular and molecular aging processes are presented.

Keywords Retina · SD-OCT · OCTA · Choroidal thickness · Cardiovascular risk factors · Smoking · Hypertension

Introduction

The retina is one of the most metabolically active tissues in the body with an extremely high associated oxygen demand (Anderson 1968). It is thus not surprising that virtually all blinding retinal diseases, including diabetic retinopathy, age-related macular degeneration (AMD), and glaucoma, have a significant vascular component. Oxygen is supplied to the retina through two vascular beds, the retinal vasculature which penetrates the inner retina and the denser choroidal vascular network residing behind the retinal pigment epithelium (RPE) and Bruch's membrane (BrM). Overall, ~ 60% of oxygen supply and ~ 75% of nutrient supply to the retina come from the choroid (Alder et al. 1983; Anderson 1968; Yu and Cringle 2001). However, in-depth analysis of the role of the choroidal circulation, and particularly the choriocapillaris, in the development of ocular diseases has historically been hampered by difficulties in imaging and analyzing the choroidal microcirculation. This is especially galling for diseases such as AMD where late-stage disease and severe vision loss are clearly associated with profound choroidal pathologies. However, recently, powerful in vivo imaging modalities for analyzing changes in choriocapillaris perfusion and blood flow have become more widespread. Coupled with increasing support for the hypothesis that localized choroidal dysfunction and abnormal hemodynamics is a significant disease mechanism for AMD (Gelfand and Ambati 2016), these technological advancements have ushered in a new age of research enthusiasm evaluating the role of the choroidal microcirculation in healthy, aged, and diseased vision. Here, we discuss the current understanding of how the choriocapillaris changes during normal aging and during the development of AMD, and how the choroid and choriocapillaris are affected by cellular and molecular mechanisms of aging and systemic vascular disease.

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The choroid

Choroidal structure

The choriocapillaris is the innermost layer of the choroid, residing adjacent to BrM and the RPE. It is composed of fairly large diameter (20–50 μm; Fryczkowski 1994) fenestrated capillaries which interconnect to form a characteristic network with a planar geometry (Fig. 1). In the human eye, the choriocapillaris structure is not uniform. In the central retina, the choriocapillaris exhibits a honeycomb or cobblestone-like appearance which transitions toward a more longitudinally arranged array of tubular capillaries separated by intercapillary pillars in the peripheral/equatorial region. This choriocapillaris meshwork is supplied by feeding arterioles/venules found in the middle Sattler's layer which are then connected to arteries and veins in the outer Haller's layer. Choroidal blood flow is regulated by autonomic innervation (Hashitani et al. 1998; Koss and Gherezghiher 1993; Lutjen-Drecoll 2006), but also has some capacity to autoregulate, particularly in cases where intraocular pressure is changed (Akahori et al. 2017; Kiel and Shepherd 1992; Polska et al. 2007; Riva et al. 1997).

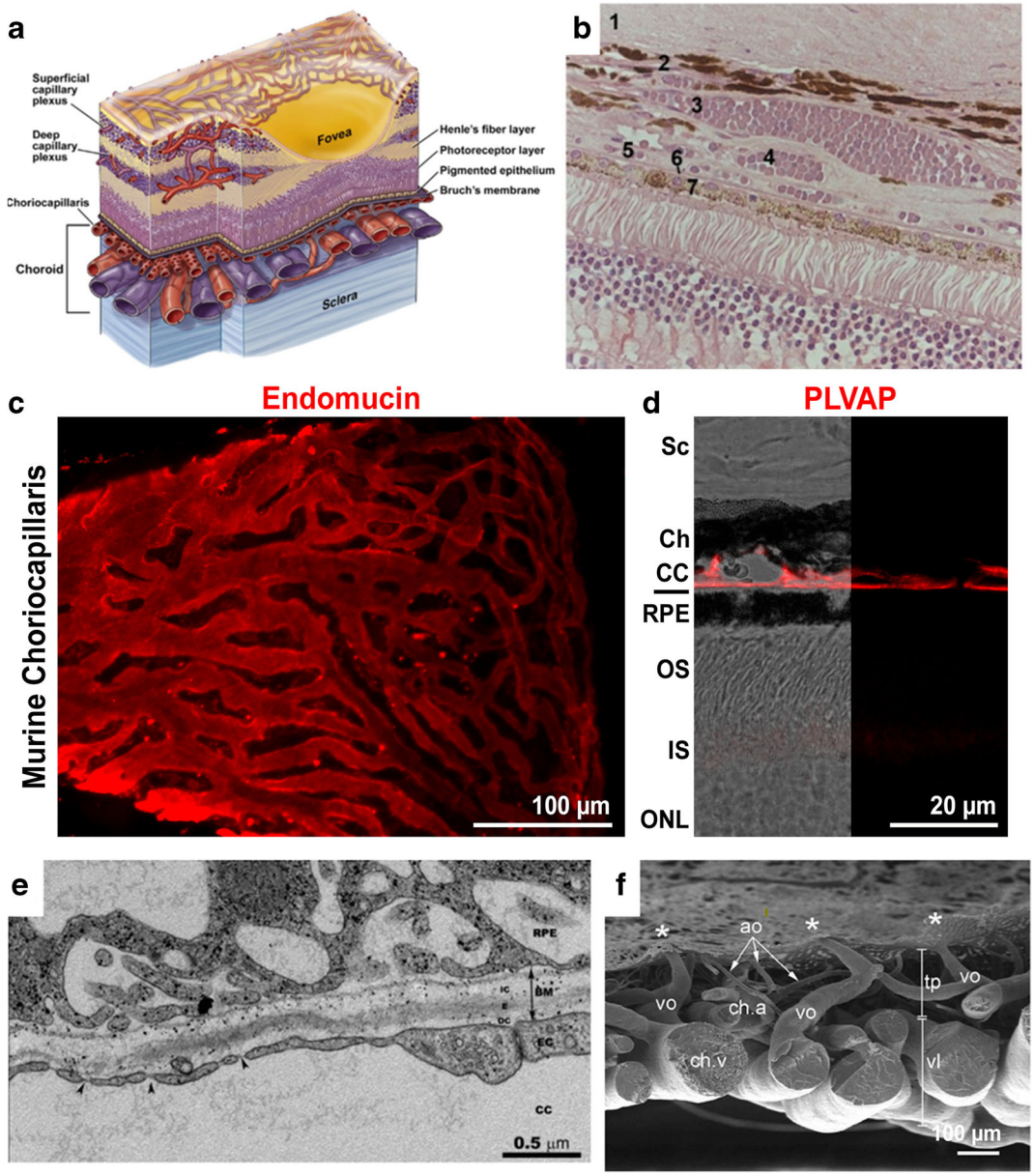
Studying the choroid and choroidal blood flow

The choroid is one of the few microvascular beds that can be optically imaged and has the potential to provide insights into ocular and systemic vascular disorders. Advances in imaging technology have significantly improved our understanding of the role of choroidal failure in the pathogenesis of age-related macular degeneration

(Pemp and Schmetterer 2008). Measurement of choroidal thickness is important in the diagnosis, follow-up, and monitoring of response to treatment of a number of eye diseases (Lavinsky and Lavinsky 2016). However, the assessment of choroidal thickness and structural changes has been very challenging with conventional imaging modalities, such as ultrasonography, due to its limited resolution and repeatability (Coleman and Lizzi 1979). Indocyanine green angiography (ICGA) provides visualization of the choroid, but the technique requires intravenous administration of a dye, and extraction of quantitative blood flow data using this method has proven difficult (van Stokkum et al. 1995).

High-resolution, cross-sectional imaging of the choroid became possible after the development of optical coherence tomography (OCT) (Rahman et al. 2011). In spectral domain OCT (SD-OCT), depth information is encoded as different frequencies of the interference spectrum. With recent advances, including enhanced depth imaging, the outer limit of the choroid can be reliably identified (Spaide et al. 2008). Swept source OCT (SS-OCT) uses a frequency swept laser with a light source that enables the measurement of interference at different optical frequencies or wavelengths sequentially over time (Lavinsky and Lavinsky 2016). Recently, optical coherence tomography angiography (OCTA) has attracted much interest and has proven to be a valuable tool to evaluate the pattern of the choriocapillaris without the need for dye injection. In contrast to conventional dye-based angiography, OCTA uses motion contrast technology by detecting the movement of red blood cells in consecutive scans. As OCT angiograms are simultaneously co-registered with the corresponding cross-sectional OCT B-scans, OCTA provides both structural and blood flow information of the retina and the choroid (Spaide et al. 2018). However, current OCTA is not sufficiently advanced to provide information regarding the blood flow speeds in the choriocapillaris, nor does it illustrate leakage (Borrelli et al. 2018; Leitgeb et al. 2014). In the absence of direct measurements of individual vessels, this approach has been used to assess the choroidal vascularity index, which is the ratio of the lumenal area to the total choroidal area (Koh et al. 2017b; Tan et al. 2016). Choroidal vascularity index can indirectly measure choroidal vascularity, thus overcoming the limitation of using choroidal thickness alone. Another recent approach has been to assess choriocapillary flow voids/deficits, localized areas of decreased choriocapillaris perfusion, using SS-OCTA. This analytical approach has high repeatability and can be used to track localized changes in the choroid in both normal and diseased eyes (Zhang et al. 2018a; Zheng et al. 2019). OCTA has also been combined with adaptive optics (AO-OCTA) to directly image individual vessels in the choriocapillaris, enabling direct measurements of capillary diameter, capillary density, choriocapillaris depth, etc. (Kurokawa et al. 2017). This approach represents a significant advancement and will permit much more cell biological and anatomical analysis in the future.

There is increasing interest in the quantification of choroidal blood flow (CBF) with optical techniques. Color Doppler imaging enables qualitative and quantitative assessment of the ophthalmic artery and its branches, including the posterior ciliary arteries supplying the choroid, but it cannot obtain information on volumetric blood flow (Stalmans et al. 2011). Using laser Doppler flowmetry, choroidal hemodynamic measurements (velocity, volume, and flux) are limited to the subfoveal area, because of the lack of retinal vessels in this region (Riva et al. 2010). However, because the density of photoreceptors is so much greater in the fovea, choroidal blood flow in this area is likely to be different from blood flow elsewhere in the choroid, making it difficult to generalize results obtained with this method (Straubhaar et al. 2000). A third optical method is laser speckle flowgraphy (LSFG) which can produce two-dimensional images of blood flow with high spatial and temporal resolution (Sugiyama et al. 2010). This technique has been used to study optic nerve head blood flow, but when retinal areas are measured, the signal contains proportions from both retinal and choroidal circulations. Recently, a technique was introduced to extract blood flow information from retinal vessels, separating the signal arising from the larger vessels from background mean blur rate (MBR) originating from the surrounding microvasculature (Calzetti et al. 2018). The development of these novel imaging tools has led to extremely rapid advancements in our understanding of the role of the choroid/choriocapillaris in aging/AMD and overall expansion of this area of research.



Changes in the choroid with systemic AMD risk factors

There are a variety of systemic risk factors for AMD, and here we evaluate what is known about their effects on the choroid.

Age

With age, choroidal thickness drops dramatically (Gattoussi et al. 2019; Wakatsuki et al. 2015), a change accompanied by decreased choroidal blood flow (Grunwald et al. 1998a). The choriocapillaris and the large vessel layer of the choroid both show age-related thinning as measured by SS-OCT (Wakatsuki et al. 2015) and reduced choriocapillary vascular density (Fig. 2). Choriocapillaris flow deficits also increased with increasing age in nondiseased eyes (Zheng et al. 2019), findings that are recapitulated histologically. Nondiseased aged eyes can exhibit loss of up to 27% of the choriocapillaris, characterized by loss of capillaries and reduction in choriocapillary endothelial cell

Fig. 1 Choriocapillaris anatomy. **a** Tridimensional diagram of the retinal and choroidal vasculature. The branches from the central retinal circulation divide into two distinct capillary plexi within the ganglion cell layer (the superficial capillary plexus and the deep capillary plexus). These two vascular plexi end as the ganglion cell and inner nuclear layer disappear in the foveal slope. The choroid contains a dense vascular network terminating with the fenestrated choriocapillaris adjacent to Bruch's membrane (drawing by Dave Schumick, adapted with permission from Kur et al. 2012). **b** Histological section (hematoxylin/eosin staining) of choroidal vascular layers. 1: Sclera; 2: suprachoroid; 3: large-sized vessel layer (Haller's layer); 4: medium-sized vessel layer (Sattler's layer); 5: choriocapillaris; 6: Bruch's membrane; 7: retinal pigment epithelium (modified with permission from Ramírez et al. 2012). **c** Representative section from an adult mouse choroidal flatmount in which the choriocapillaris has been labeled with the endothelial marker endomucin (red). The choriocapillaris is formed from interconnected, wide capillaries. Scale bar 100 μm. **d** Representative retinal/choroidal cross-section from an adult mouse in which plasmalemmal vesicle–associated protein (PLVAP-red) is used to label the fenestrated capillaries in the choriocapillaris. Sc, sclera; Ch, choroid; CC, choriocapillaris; –, Bruch's membrane; RPE, retinal pigment epithelium; OS, outer segment; IS, inner segment; ONL, outer nuclear layer. Scale bar 20 μm. **e** Electron micrograph of Bruch's membrane (BM) and choriocapillaris (CC). Bruch's membrane is composed of several layers: the basal membrane of the retinal pigment epithelium (RPE), the inner collagenous layer (IC), the elastic layer (E), the outer collagenous layer (OC), and the basal membrane of the choriocapillary endothelium. Endothelial cells (EC) of the choriocapillaris present fenestrations (arrowhead) (adapted with permission from Ramírez et al. 2012). **f** Scanning electron microscope image of the vascular cast of the horse choriocapillaris. In this cross-section of the choroidal vasculature, note the choroidal arteries (ch.a) and choroidal veins (ch.v) in the vascular laminar (vl), arterioles (ao), and venules (vo) penetrating the tapetum (tp), and the choriocapillaris (asterisks). Note the feeding arterioles and draining venules inserting into the outer surface of the choriocapillaris. Bar = 100 μm (adapted with permission from Ninomiya and Inomata 2014)

fenestrations (Biesemeier et al. 2014). Critically, this choriocapillaris degeneration can precede RPE/photoreceptor damage. These age-related changes are most pronounced in the central macular regions (Zheng et al. 2019), and choriodal subfoveal thickness has been shown to decrease by ~3 μm per year (Chirco et al. 2017; Wakatsuki et al. 2015).

In contrast to the choroid, BrM becomes thicker and loses its distinct layers with age. For example, measurements taken from nondiseased eyes in the sixth decade of life show that BrM is thicker and more hyalinized than in the second decade (Gupta et al. 2017; Ramrattan et al. 1994). BrM continues to thicken through the ninth and tenth decades and becomes increasingly undulated (Gupta et al. 2017). Several studies have shown that drusen (both in normal aging and in AMD) exhibit clear spatial associations with the choriocapillaris (Friedman et al. 1963; Lengyel et al. 2004; Lutty et al. 1999). In studies from human donor eyes with no diagnosed eye disease spanning a 50-year age range, 90% of drusen were found to accumulate above the intercapillary pillars, rather than above the lumen of the capillaries (Lengyel et al. 2004). In addition, in healthy eyes (both young and aged), autofluorescent drusen are found on the intercapillary pillars between the tubular capillaries in the peripheral choroid and in the empty cobblestone spaces in the area where the choriocapillaris is transitioning to the honeycomb morphology, i.e., not directly beneath the choroidal endothelial cells (Lengyel et al. 2004). Intercapillary pillars also become increasingly hyalinized starting at the macula in the sixth decade and spreading to the peripheral retina by the ninth and tenth decades (Gupta et al. 2017).

Smoking

Following age, smoking is the largest environmental risk factor for AMD (Evans 2001; Nita and Grzybowski 2017) and for progression of early AMD to both geographic atrophy (dry AMD) and neovascular AMD (Bonyadi et al. 2017; Chakravarthy et al. 2007; Keenan et al. 2018; Klein et al. 2004; Saunier et al. 2018). However, the direct role of smoking on choroidal health (i.e., in healthy eyes prior to AMD onset) has been controversial. In multiple case–control studies comparing long-term smokers with nonsmokers, no significant difference in choroidal thickness was observed between healthy smokers and nonsmokers in the central or peripheral retina (Kantarci et al. 2016; Sizmaz et al. 2013; Ulas et al. 2014). However, choroidal thickness, choroidal blood flow, and choriocapillary perfusion are acutely reduced following smoking (Ayhan et al. 2017; Ulas et al. 2014), a finding in some cases more pronounced in chronic smokers (Sizmaz et al. 2013; Tamaki et al. 2000). In addition, many more recent studies have shown a modest but significant negative correlation between smoking and in choroidal thickness (Gattoussi et al. 2019; Moschos et al. 2016; Sigler et al. 2014; Tamaki et al. 2000). Using SD-OCT, choroidal vascularity index was shown to be significantly decreased in smokers in a dose-dependent manner, although there were no detectable changes in subfoveal choroidal thickness, suggesting that choroidal thickness may not be as sensitive a measure of choroidal function as other approaches (Wei et al. 2019). However, many

of these studies have small populations and not all report as many details as might be desired (e.g., time of day, which is important for diurnal variations in choroidal thickness). In contrast, the larger ALIENOR (Antioxydants, Lipides Essentiels, Nutrition et maladies OculaiRes) study (Delcourt et al. 2010), a prospective French study evaluating nutrition and age-related eye diseases, recently published their findings on choroidal thickness. The ALIENOR study conducted SD-OCT coupled with enhanced depth imaging of the choroid in 271 participants with and without eye disease and found heavy smoking was associated with choroidal thinning (Gattoussi et al. 2019) after controlling for age, sex, and other potential confounding factors. Interestingly, in this population, overall choroidal thickness was not associated with AMD (Gattoussi et al. 2019). Detailed analysis of changes in the choriocapillaris in response to smoking is sparse, but some studies can be gleaned from work using animal models. In an aged high-fat diet mouse model, smoking led to increased sub-RPE deposits, as well as abnormalities in the choriocapillaris including increased cellular infiltration, increased thickening and decreased fenestration in the choriocapillary endothelial cells, and penetration of endothelial cells into BrM. These findings were similar to those observed in groups fed hydroquinone (an oxidant in tar derived from cigarette smoke) and the positive control blue light group consistent with the idea that oxidative stress from cigarette smoking leads to detrimental changes in the choriocapillaris (Espinosa-Heidmann et al. 2006). Combined, these studies suggest that heavy smoking is a risk factor for choroidal thinning and choriocapillary defects.

Hypertension

Previous meta-analysis and several individual studies suggest hypertension is a moderate risk factor for AMD (reviewed in Chakravarthy et al. 2010; Evans 2001). For example, in the large Age-Related Eye Disease trial (AREDS), patients with intermediate AMD (characterized by large drusen or extensive intermediate drusen) or with neovascular AMD were more likely than controls to be hypertensive (Age-Related Eye Disease Study Research 2000). However, not all

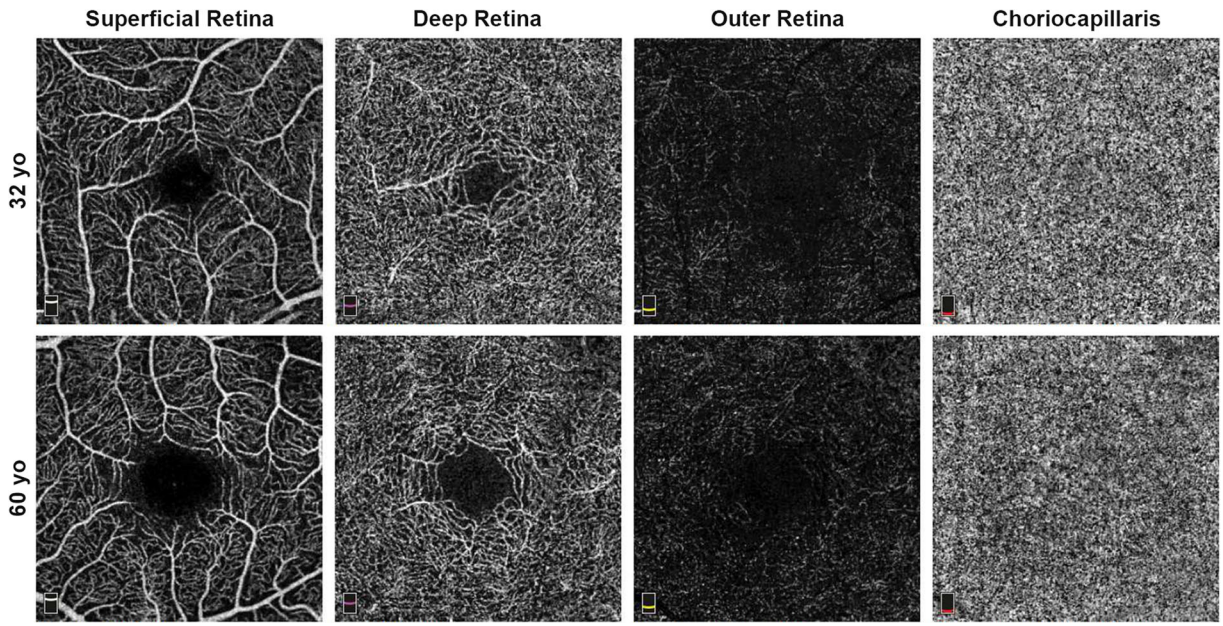


Fig. 2 Aging leads to a decline in choriocapillaris vascularity. Example of retinal and choroidal circulation imaged with the Optovue AngioVue OCTA system in healthy subjects (32 years, top row) and (60 years, bottom row). Images are captured from the superficial retina (ILM–IPL), deep retina (IPL–OPL), outer retina (OPL–BrM), and choriocapillaris (BrM–BrM + 30 μm). Although there is no conspicuous change in superficial, deep, and outer retinal vascular density, choriocapillary vascularity is substantially decreased in the aged subject. At the level of the choriocapillaris, granular bright areas (choriocapillaris flow) alternate with small dark regions that indicate choriocapillaris flow reduction. ILM, inner limiting membrane; IPL, inner plexiform layer; OPL, outer plexiform layer; BrM, Brunch's membrane

studies have identified an association between hypertension and AMD. Changes in the choroid with hypertension have likewise been inconsistent. Severe hypertension can result in hypertensive retinopathy which can rarely manifest as hypertensive choroidopathy. Hypertensive choroidopathy is characterized by increased areas of choriocapillaris nonperfusion as well as exudative changes in the retina and presentation of Elschnig spots (characteristic black spots surrounded by yellow halos) (Rezkallah et al. 2019; Saito et al. 2018; Sato and Takeuchi 2018; Verstappen et al. 2019). However, this severe retinopathy is not an aging-associated disease and can occur in young people or in cases of pregnancy-induced hypertension. Frequently, the associated choroidal perfusion defects resolve after hypertension is controlled (Saito et al. 2018).

When considering the effects of chronic primary hypertension on the choroid, some studies, including the recently published Gutenberg Health Study, have found that elevated systolic blood pressure was negatively associated with choroidal thickness (Akay et al. 2016; Icel et al. 2018; Schuster et al. 2019; Usui et al. 2012). More recent evaluation of choriocapillary flow voids using OCTA has reported that hypertension is a predictor of increasing choriocapillary flow void area (Spaide 2016). However, other studies have found no association between hypertension and choroidal thinning (Gok et al. 2015; Polak et al. 2003). This finding was supported by a recent OCTA study of choriocapillaris perfusion in patients with well-controlled vs. poorly controlled hypertension. Patients with well-controlled hypertension (and lower systolic blood pressure) had small increases in choriocapillary flow voids compared to patients with poorly controlled hypertension (and higher systolic blood pressure) (Chua et al. 2019). Similarly, in a population of normotensive patients, increasing blood pressure was associated with increased choroidal perfusion (Polak et al. 2003). In the context of age and the development of choroidal pathologies, it is not clear whether increased choroidal perfusion is protective (by preventing ischemia) or detrimental (by promoting oxidative stress). The larger ALIENOR study reported no associations between choroidal changes and hypertension and found no consistent association between anti-hypertensive medication use and subfoveal choroidal thickness (Gattoussi et al. 2019). Assessing choroidal changes due to hypertension in patients is further complicated by widespread anti-hypertensive use, making it challenging to directly assess the effects of chronic hypertension on the choroid.

Some information may be gleaned from animal studies. Choriocapillaris rarefaction and thickening of choroidal arteries have been reported in young (~ 6 months) spontaneously hypertensive rats (Tomassoni et al. 2002). In aged hypertensive rats, narrowing of choroidal artery lumen, choriocapillary engorgement, smooth muscle cell engorgement, and basement membrane thickening have been observed (Bhutto and Amemiya 2002). These animals also exhibit reduced choroidal blood flow which is not responsive to acetylcholine (which induces vasodilation in normal rats via induction of NO) (Granstam et al. 1998). Recent studies also show that spontaneously hypertensive rats exhibit significant thinning of the choriocapillaris endothelial glycocalyx, the intravascular protective layer of glycolipids, glycoproteins, proteoglycans, and glycosaminoglycans that play an important role in vascular homeostasis (Kumase et al. 2010). These results suggest that hypertension does affect the morphology and function of the choroid, but to what degree this manifests clinically remains an open question.

Diabetes

Diabetic microangiopathy shares common pathogenic pathways with AMD, but the contribution of diabetes to early and late AMD is inconsistent in studies (Chen et al. 2014). Hyperglycemia, dyslipidemia, and chronic inflammation are possible common pathophysiologic mechanisms of both conditions (Zhang et al. 2011). In a longitudinal study over 10 years, individuals with diabetic retinopathy, including both the nonproliferative and proliferative forms, were at higher risk for neovascular AMD when compared to diabetic patients without diabetic retinopathy or normal controls (Hahn et al. 2013). Vascular endothelial growth factor (VEGF) is a key proangiogenic growth factor which plays an important role in both diabetic retinopathy and AMD, and anti-VEGF treatments are useful for both (Ho et al. 2012).

Several choroidal alterations in diabetic patients have been described in the literature. Previous histopathologic studies showed vascular abnormalities in the choroid, including microaneurysms, obstruction of the choriocapillaris, vascular remodeling with increased vascular tortuosity, and choroidal neovascularization in patients with diabetes (Cao et al. 1998). Studies in

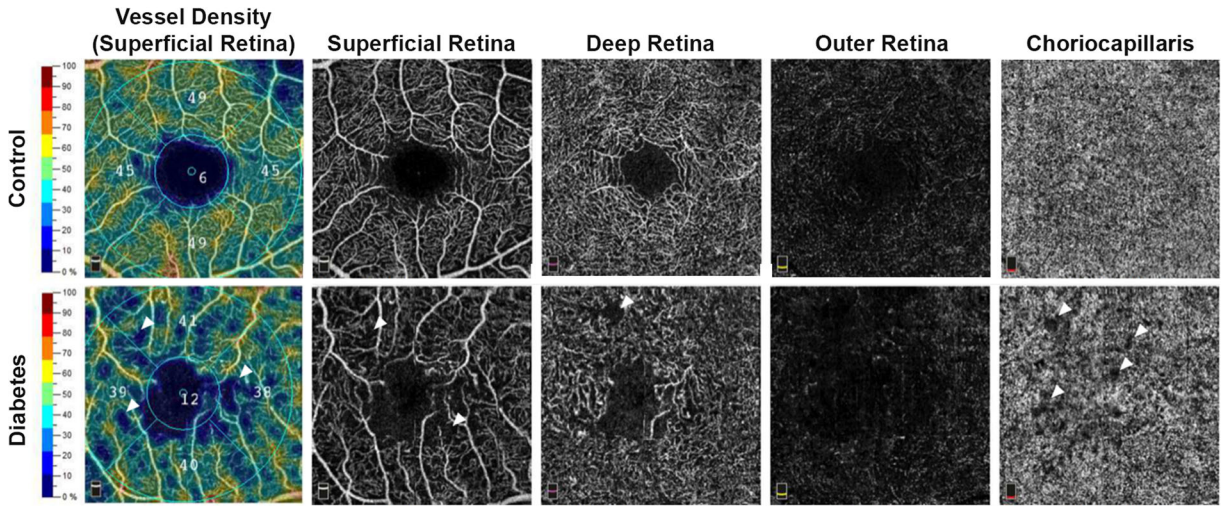


Fig. 3 Diabetes impairs choriocapillaris blood flow. Example of retinal and choroidal blood flow in a healthy subject (60 years, top row) and in a diabetic patient (61 years, bottom row) imaged with the Optovue AngioVue OCTA system. Images are captured from the superficial retina (ILM–IPL), deep retina (IPL–OPL), outer retina (OPL–BrM), and choriocapillaris (BrM–BrM + 30 μm). Characteristic features of impaired microcirculation due to diabetic retinopathy such as decrease in blood flow in the superficial and deep layers as well as irregular choriocapillary blood flow is seen compared to the healthy eye. The white arrowheads demonstrate the capillary dropout areas. ILM, inner limiting membrane; IPL, inner plexiform layer; OPL, outer plexiform layer; BrM, Bruch's membrane

diabetic eyes using fluorescein angiography, ICGA, and newer imaging modalities have shown several choroidal filling abnormalities, including reduction in choroidal flow density and choriocapillary dropout (Fig. 3). These changes are well correlated with the severity of diabetic retinopathy, HbA1c levels, and poor diabetes control (Shiragami et al. 2002; Yang et al. 2019). Doppler flowmetry revealed progressive reduction of choroidal

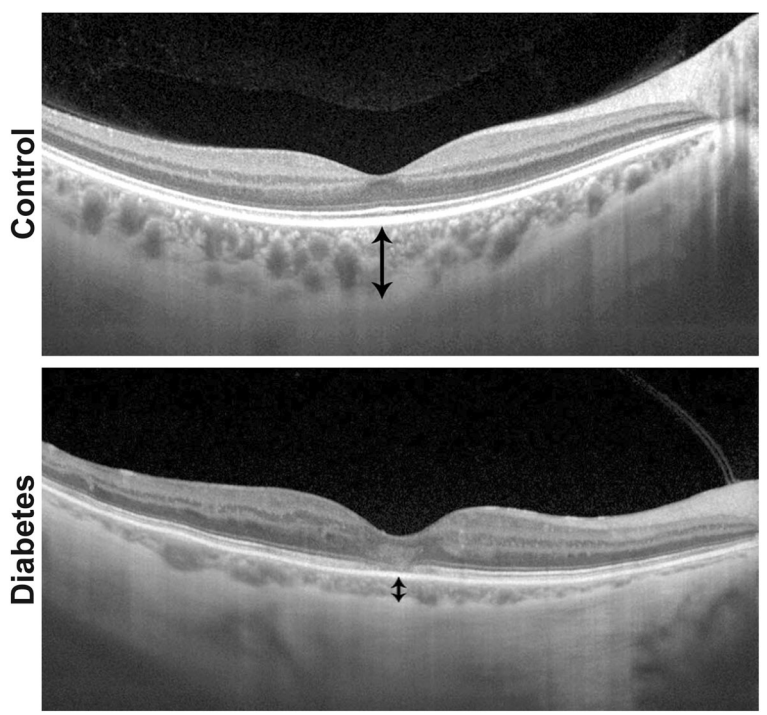


Fig. 4 Aging and diabetes promote choroidal thinning. Example of choroidal thinning due to age and background diabetic retinopathy. Examples are from a 30-year-old healthy subject (top) and a 77-year-old patient with diabetes (bottom) imaged with the Topcon swept-source OCT. The black double-headed arrows indicate choroidal thickness measurements

blood flow and volume in patients with diabetes, even in eyes with clinically undetected diabetic retinopathy (Nagaoka et al. 2004), suggesting choroidal pathologies are an important component of the disease. Recently, there has been a focus on choroidal thickness; however, the pattern of diabetic choroidopathy-related changes in choroidal thickness is still not well understood. Several investigators have reported that choroidal thickness was significantly reduced in mild or moderate nonproliferative diabetic retinopathy compared to non-diabetic control eyes (Querques et al. 2012; Shen et al. 2017; Vujosevic et al. 2012) with examples shown in Fig. 4. In contrast, other studies showed that as diabetic retinopathy worsened to the proliferative form, choroidal thickness increased (Kim et al. 2013; Regatieri et al. 2012). According to Kim et al. (2018), a reduction in the choroidal vascular index was evident in type-2 diabetic patients, regardless of diabetic retinopathy stage.

Metabolic risk factors

Obesity is considered a risk factor for AMD, though in common with other risk factors, not all studies report an association. A recent meta-analysis encompassing seven prospective cohort studies and 31,151 subjects found that obese subjects (assessed using body mass index (BMI)) had significantly increased risk of developing late AMD but not early AMD (Zhang et al. 2016) compared to nonobese controls. Other studies have suggested that abdominal obesity (assessed by waist/hip ratio) also correlates with development of AMD, and may have stronger relationship than that between BMI and AMD (Klein et al. 2001; Peeters et al. 2008; Seddon et al. 2003). There are only a few studies evaluating the relationship between obesity and choroidal health, and though several have reported vascular changes, results are inconsistent. For example, Ersan et al. (2016) reported that obese children had significantly reduced macular and subfoveal choroidal thickness (as measured by SD-OCT coupled with enhanced depth imaging), compared to nonobese children, and a second group found reduced temporal choroidal thickness in obese children (Topcu-Yilmaz et al. 2018). However, other studies have found the opposite, reporting increased choroidal thickness in obese children compared to controls (using a similar imaging approach) (Bulus et al. 2017). Significantly thinner choroidal thickness was also reported in morbidly obese adults compared to nonobese controls (Dogan et al. 2016; Oner and Karadag 2018).

In the ALIENOR study, lipid-lowering treatment is positively correlated with choroidal thickness, while

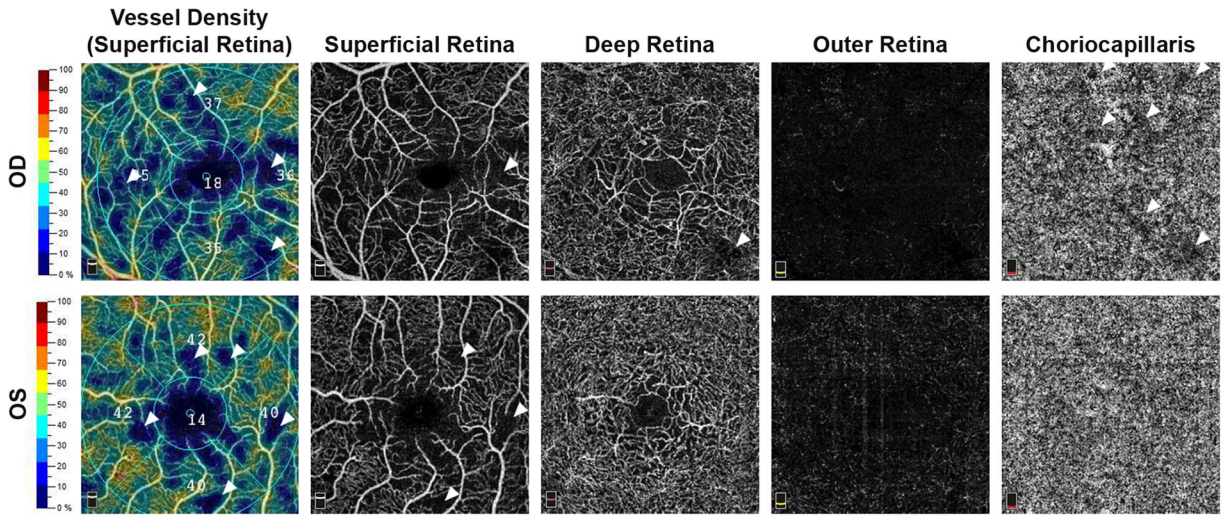


Fig. 5 Systemic atherosclerosis associates with choriocapillaris impairments. Shown is an example of retinal and choroidal circulation in a 59-year-old patient with symptomatic bilateral carotid arterial occlusion imaged with the Optovue AngioVue OCTA system. Images are from the right eye (top row, OD) and left eye (bottom row, OS), and retinal and choroidal blood flow are predominantly impaired in the right eye. The white arrowheads demonstrate areas of capillary dropout in the retina and choroid. Images are captured from the superficial retina (ILM–IPL), deep retina (IPL–OPL), outer retina (OPL–BrM), and choriocapillaris (BrM–BrM + 30 μm). ILM, inner limiting membrane; IPL, inner plexiform layer; OPL, outer plexiform layer; BrM, Bruch's membrane

elevated blood glucose is negatively associated with choroidal thickness (Gattoussi et al. 2019). However, no correlation between overall cholesterol levels and choroidal thickness was found. Coronary artery disease has been identified as a risk factor for AMD, and choroidal thickness is also reduced in patients with coronary artery disease (Ahmad et al. 2017; Thomas et al. 2015). A recently published case study found that a patient with a history of an ischemic stroke, multiple ischemic attacks, and vascular cognitive impairment had decreased subfoveal choroidal thickness in both eyes (Chang et al. 2019), and the large Gutenberg Health Study found cardiac dysfunction to be significantly associated with choroidal thinning (Schuster et al. 2019). Similarly, a study including 158 patients with coronary heart disease and controls found a significant negative correlation between choriocapillary density and Gensini score (a measure of arterial stenosis) (Wang et al. 2019), suggesting that the same pathological processes that contribute to coronary artery disease also promote choriocapillary defects. To illustrate this concept, a representative OCTA image from a patient with severe carotid atherosclerosis exhibiting choriocapillary dropout is shown in Fig. 5.

Changes in the choroid during AMD

Having discussed how many of the environmental risk factors for AMD can lead to choroidal changes even in nondiseased eyes, we turn now to alterations in the choroid during AMD. It is estimated that 196 million individuals worldwide are affected by AMD which is predicted to increase to 288 million by 2040 (Wong et al. 2014), and AMD is the leading cause of vision loss in the elderly (Bourne et al. 2013). Although classification systems have varied over time, currently AMD is classified according to five stages: stage 1 is no disease, stage 2 represents changes associated with normal aging including small drusen (< 65 μm) without RPE changes, stage 3 is early AMD and is characterized by the presence of medium-sized drusen (65–125 μm) and no RPE changes, stage 4 is intermediate AMD and is characterized by medium or large drusen and pigmentary changes, while stage 5 is defined by eyes with either geographic atrophy or neovascular AMD (Ferris 3rd et al. 2013). The biggest risk factor for development of AMD is age, but several other environmental risk factors have been identified (in addition to genetic risk factors), including the cardiovascular risk factors discussed above such as smoking, obesity, and history of cardiovascular disease (Chakravarthy et al. 2010; Hogg et al. 2008). Although research on the choroid and the role of the choroidal blood supply in AMD has recently been rapidly expanding, the idea that aberrations in choroidal blood flow can contribute to AMD dates to the beginning of the twentieth century (Possek 1905). Over the years, this idea has been refined (Friedman 1997) based on new data and was recently updated to reflect the current state of knowledge (Gelfand and Ambati 2016). This revised hemodynamic theory of AMD posits that highly localized changes in choroidal perfusion lead to alterations in shear stress, heat dissipation, endothelial cell remodeling, and immune cell transport and can lead to hypoxia and changes in transport of nutrients/waste with the RPE and serve directly as cues to promote choroidal remodeling and subsequent changes in the outer retina (Gelfand and Ambati 2016). Critically, this theory provides a framework tying different types of localized cellular and physiological changes in the choroid to the later development of either geographic atrophy or neovascular AMD. For an in-depth discussion of this topic, the reader is referred to Gelfand and Ambati (2016). There is a vast literature on the multiple mechanisms and pathogenesis of AMD; here, we limit our focus to changes in the choroid during the AMD process.

Changes in the choroid in early and intermediate AMD

Multiple groups have reported that in some cases of early AMD, choriocapillary endothelial cell loss precedes RPE degeneration (Biesemeier et al. 2014; Seddon et al. 2016), and several other studies have shown that choriocapillary vascular density is decreased in eyes with early AMD (Lee et al. 2018a). Choriocapillary density is also inversely related to endothelial cell loss, which leads to an increased number of "ghost vessels" (vessels with endothelial dropout) in early AMD (Farazdaghi and Ebrahimi 2019; Mullins et al. 2011). Interestingly, choriocapillaris vascular density has also been inversely correlated with drusen density, suggesting that proper choroidal microcirculation may be essential for preventing drusen formation (Mullins et al. 2011). This idea is supported by findings that drusen and complement proteins both accumulate

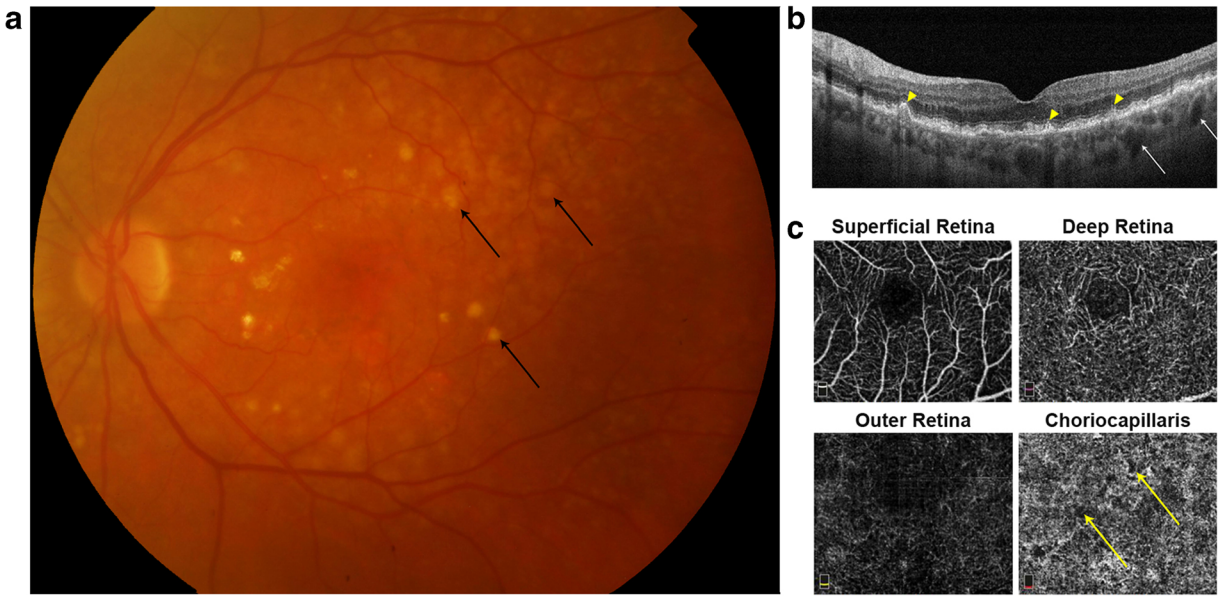


Fig. 6 Choriocapillaris impairment in intermediate AMD. Shown is an eye from a 72-year-old patient with intermediate dry AMD. Large drusen (black arrows) are seen as yellow spots on a fundus photo (**a**) and as solid elevations from Bruch's membrane (yellow arrowheads, **b**) by OCT. White arrows in **b** highlight large choroidal vessels. **c** OCTA shows preserved retinal microcirculation, but substantial irregularity in choriocapillary blood flow (yellow arrows). Images are captured from the superficial retina (ILM–IPL), deep retina (IPL–OPL), outer retina (OPL–BrM), and choriocapillaris (BrM–BrM + 30 μm). ILM, inner limiting membrane; IPL, inner plexiform layer; OPL, outer plexiform layer; BrM, Bruch's membrane

over intercapillary pillars in early AMD eyes (Fett et al. 2012; Seth et al. 2008) (similar to normal aging, see above). Figure 6 shows an example AMD eye with drusen and irregularities in choriocapillary blood flow.

There are also immune changes in early AMD. Mast cells are increased throughout the choroid in early AMD compared to age-matched controls, and their prevalence correlates with choriocapillaris loss in human donor

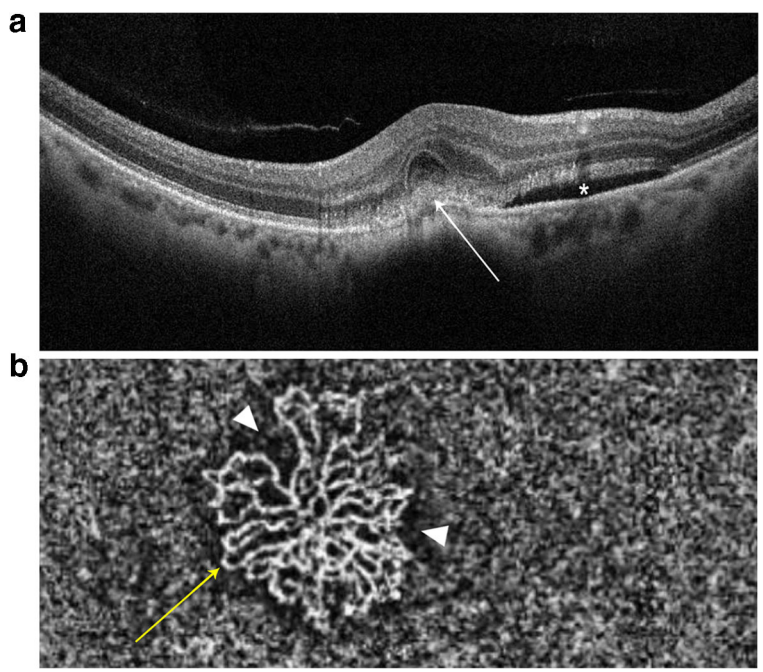


Fig. 7 Choroidal neovascularization (CNV). Example of an active CNV lesion imaged with the Optovue AngioVue OCTA system. On SD-OCT, subretinal CNV (white arrow) and the surrounding fluid (asterisk) can be seen (**a**). The superficial and deep retinal plexuses as well as the outer retina and the choriocapillaris are depicted. **b** The presence of a densely packed CNV net composed of loops and peripheral anastomoses (yellow arrow) and surrounded by a hypointense halo (white arrowheads) can be seen in the choriocapillary layer

eyes (Bhutto et al. 2016). In addition, complement factor H (CFH), normally a protective component of the complement pathway found in BrM, the choriocapillaris, and intercapillary pillars, is reduced in early AMD as well as in geographic atrophy (Bhutto et al. 2011). Other cellular changes in the choroid have also been described and may contribute to choriocapillaris dropout. Choriocapillary endothelial cells are highly polarized, with thin cytoplasm and fenestrated membranes toward the RPE and thicker cytoplasm and nuclei on the choroidal side. However, this polarity is frequently lost in AMD eyes, a finding thought to contribute to reduced perfusion and RPE hypoxia (Biesemeier et al. 2014; Campos and Abu-Asab 2017).

There are also functional changes in the choroid in early AMD. These include prolonged choroidal filling (as measured by the appearance of hypofluorescent regions during fluorescein angiography or ICGA). In eyes diagnosed with early AMD, 36% exhibited a prolonged choroidal filling phenotype (Pauleikhoff et al. 1999). This vascular phenotype was significantly associated with areas of RPE atrophy (Pauleikhoff et al. 1999). In addition, laser Doppler flow studies have found that drusen accumulation is inversely correlated with choroidal blood volume and choroidal blood flow in early AMD eyes (Berenberg et al. 2012). More recent work has demonstrated increased presence of choriocapillary flow voids (areas of decreased choriocapillaris perfusion) in intermediate AMD eyes compared to healthy age-matched controls using SD-OCT angiography (Vujosevic et al. 2019). Degeneration and functional deficits in the choriocapillaris with resulting outer retinal hypoxia have been hypothesized to be driving factors in the development of AMD.

Changes in the choroid in late AMD

Intermediate and large drusen have been identified as a significant risk factor for late forms of AMD. A recent study using OCTA reported that choriocapillaris flow impairment predicts the development and enlargement of drusen (Nassisi et al. 2019). In exudative or neovascular AMD, the most pronounced vascular pathology is choroidal neovascularization in which vision loss is associated with formation of new vessels penetrating into the retina and originating in the choriocapillaris (Fig. 7 shows a representative example). The region of choroidal neovascularization is often surrounded by localized regions of choriocapillaris nonperfusion, often termed a “dark halo” (white arrowheads, Fig. 7), both in eyes with exudative choroidal neovascularization (CNV) and in eyes

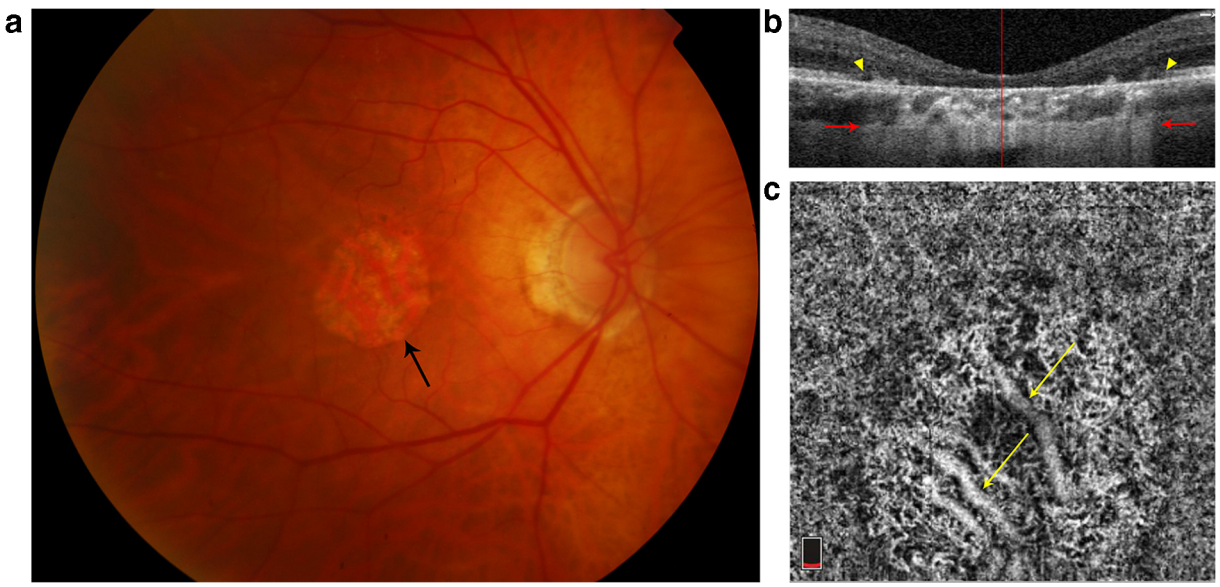


Fig. 8 Choriocapillaris impairment in geographic atrophy. Shown are examples from an eye with geographic atrophy. The atrophic area (black arrow, **a**) on the fundus corresponds with the area marked by red arrows in the OCT image (**b**), and with the region shown in the OCTA image (**c**). In the atrophic region, there is discontinuity of the RPE (yellow arrowheads, **b**). **c** As a result of the atrophy, this area exhibits increased deep OCT signal (red arrows) compared to the adjacent areas where the RPE is intact. **c** OCTA shows choriocapillaris flow impairment and displacement of large choroidal vessels under the regions of GA (yellow arrows)

with subclinical neovascularization (Jia et al. 2014; Moult et al. 2014; Treister et al. 2018), and histological reports have shown areas of choriocapillaris atrophy in neovascular AMD eyes (Lutty et al. 1999; McLeod et al. 2009). One hypothesis is that ischemia in areas of choriocapillary flow reductions/flow voids dictates the location in which neovascular lesions develop. Choroidal thickness measurements in neovascular AMD have been inconsistent; some groups report eyes with choroidal neovascularization have thinner choroids than age-matched healthy controls (Chung et al. 2011), while the development of active or recurrent exudative neovascular AMD has also been associated with increased subfoveal choroidal thickness (Bouteleux et al. 2019; Invernizzi et al. 2018). This increased choroidal thickness has been shown to be accompanied by an increase in the choroidal vascularity index (Invernizzi et al. 2018), suggesting the change may be due to neovascularization within the choroid rather than edematous thickening. Several studies have demonstrated that OCTA can accurately identify choroidal neovascularization (de Carlo et al. 2015; Jia et al. 2014, 2015), offering a clear depiction of the CNV net (Fig. 7b), which is visible since the OCTA image is not obscured by dye leakage. OCTA may also be useful in the screening of eyes at risk for CNV as it detects CNV by the presence of an abnormal vascular pattern above Bruch's membrane.

Geographic atrophy, also known as advanced dry AMD, also exhibits severe choroidal pathologies. These can include almost complete degeneration of the choriocapillaris and RPE, decreased total choroidal blood flow, and choroidal thinning, which may be more pronounced in eyes with unilateral geographic atrophy (where the other eye has neovascular AMD) (Adhi et al. 2014; Biesemeier et al. 2014; Ciulla et al. 1999; Grebe et al. 2019; Grunwald et al. 1998b; McLeod et al. 2002, 2009; Pilotto et al. 2019; Sohn et al. 2019), and an example is given in Fig. 8. Recent ultrastructural analysis of human donor eyes has demonstrated that loss of choriocapillary endothelial cells in cases of geographic atrophy is preceded by defects in cellular mechanisms by which the endothelial cells promote nuclear transport, including decreased presence of endothelial cell fenestrations in atrophic areas and increased area of caveolae (Grebe et al. 2019). In addition, the fenestrations that are present in geographic atrophy eyes exhibited size abnormalities and often defective diaphragms. Interestingly, many AMD eyes also exhibited abnormal distribution of choriocapillary pericytes. Normally, pericytes are present in the choriocapillaris, but only on the scleral side of the capillaries (Grebe et al. 2019). However, in some AMD eyes, venules fully covered by pericytes penetrated into the choriocapillaris layer, while in other cases, pericytes were found between choriocapillaris endothelial cells and BrM, or appeared dysfunctional and dying (Grebe et al. 2019).

Again, functional changes in the choroid accompany these structural changes. Defects in choroidal blood flow first observed in intermediate/early AMD worsen with increasing severity of AMD, particularly in eyes that develop neovascular AMD (Grunwald et al. 2005; Metelitsina et al. 2008). Similarly, choriocapillary flow voids also increase with advancing AMD. Recent studies analyze the prevalence of choriocapillary flow voids in eyes with geographic atrophy. Eyes with geographic atrophy had significantly higher choriocapillary flow deficits compared to either age-matched healthy control eyes or eyes with neovascular AMD in peripheral macular regions (Alagorie et al. 2019). Increases in choriocapillary flow voids throughout the eye were also positively correlated with increases in geographic atrophy enlargement rate (Thulliez et al. 2019), consistent with the idea that choriocapillaris defects contribute to the progression of geographic atrophy.

Effect of treatments for neovascular AMD on the choroid

There are currently no effective therapies for the treatment of geographic atrophy. However, since VEGF promotes choroidal neovascularization and angiogenesis in AMD (Atienzar-Aroca et al. 2016; Jiang et al. 2017; Sun et al. 2017), anti-VEGF therapy, such as ranibizumab and aflibercept, has become a mainstay of treatment for neovascular AMD. These treatments have substantial, long-term benefits in terms of preserving vision and promoting vessel regression (see examples in Fig. 9) (Bhisitkul et al. 2016; Brown et al. 2006; Rofagha et al. 2013). However, because the premise of these treatments is blocking angiogenesis/vessel remodeling, there has been some concern that anti-VEGF treatments may exacerbate atrophy of the choriocapillaris and, therefore, worsen the subsequent retinal/macular atrophy. Early studies indirectly suggested this was the case. Development of geographic atrophy (which is often associated with choriocapillaris loss) was significantly associated with the number of

ranibizumab treatments given (Lois et al. 2013) and was detected significantly more often in patients receiving anti-VEGF therapies on a continuous rather than discontinuous treatment regimen (Chakravarthy et al. 2013; Grunwald et al. 2014). There has also been significant controversy about whether different anti-VEGF

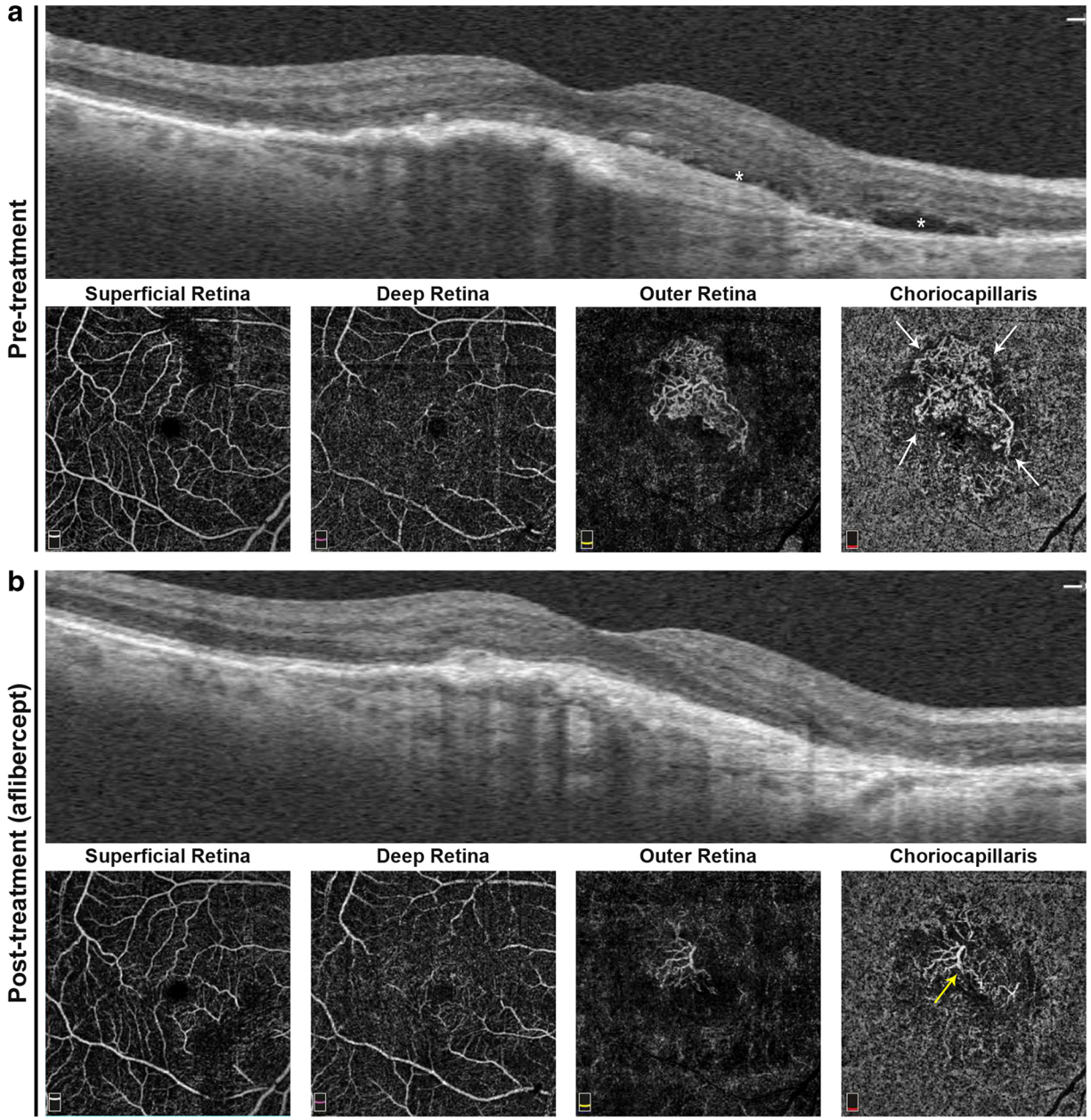


Fig. 9 CNV regression after 6 months of anti-VEGF treatment. Shown is an example of monitoring the response to intravitreal anti-VEGF treatment of exudative AMD in an 87-year-old patient using the Optovue AngioVue OCTA system. SD-OCT and OCTA images depict the status of the CNV before treatment (**a**) demonstrating the presence of subretinal fluid (asterisks) as well as anastomoses and loops branching in capillaries building up a peripheral arcade (white arrows). **b** After 6 months of treatment (four aflibercept injections), subretinal fluid disappeared, and a marked regression of the peripheral anastomoses can be seen and only the central, larger vessels are visible (yellow arrow). Bottom images in each panel are captured from the superficial retina (ILM–IPL), deep retina (IPL–OPL), outer retina (OPL–BrM), and choriocapillaris (BrM–BrM + 30 μm). ILM, inner limiting membrane; IPL, inner plexiform layer; OPL, outer plexiform layer; BrM, Bruch's membrane

therapies have differing effects on the development of geographic atrophy (Chakravarthy et al. 2013; Comparison of Age-related Macular Degeneration Treatments Trials Research et al. 2012; Grunwald et al. 2014, 2015; Lois et al. 2013). One difficulty is that anti-VEGF treatments are now standard care, so controlled studies evaluating the progression of choriocapillaris defects in untreated vs. treated eyes are challenging to perform. It is therefore difficult to assess whether changes in macular atrophy are due to disease progression or the anti-VEGF therapy. Data from the SEVEN-UP study (a 7-year follow-up for patients who were enrolled in original trials for the anti-VEGF drug ranibizumab/Lucentis) tried to evaluate this by comparing development of geographic atrophy in fellow eyes, i.e., the contralateral eye that was not enrolled in the original study and therefore was precluded from receiving anti-VEGF treatments for the first 2 years. Fellow eyes included in the analysis were those that had been diagnosed with CNV at either the baseline, 2-year follow-up, or 7-year follow-up (all enrolled study eyes had CNV at the time of initial treatment). This study found that ranibizumab-treated study eyes were significantly less likely to develop macular atrophy compared to untreated fellow eyes that also had CNV (79% of eyes, $n = 22$ vs. 100% of eyes, $n = 12$) (Bhisitkul et al. 2016).

Although none of these reports directly assessed choroidal changes, several more recent studies have tried to evaluate this. In a small case study of 11 AMD eyes, anti-VEGF treatment reduced not only the CNV area but also reduced the dark halo area of choroidal nonperfusion surrounding the CNV (Rispoli et al. 2018). Acute evaluation 1–2 weeks after anti-VEGF treatment showed a statistically significant reduction in choroidal blood velocity in a small population of neovascular AMD (Mottet et al. 2018) eyes and reduction in choriocapillaris endothelial cell fenestrations in a primate model (Peters et al. 2007), but it is not clear whether these acute changes result in any longer-term defects. Hikichi et al. performed long-term follow-up (mean follow-up from baseline to end of study was 14 months) in 124 patients with a history of long-term anti-VEGF treatment (mean treatment time at the time of enrollment was 68 months). They reported a statistically significant decrease in the density of the choriocapillaris during the follow-up period, which was not seen in healthy age-matched controls (Hikichi and Agarie 2019). Similarly, decreased choroidal thickness was measured in neovascular AMD eyes treated with aflibercept or ranibizumab (Adhi et al. 2014; Inan et al. 2019; Sariyeva Ismayilov et al. 2019; Ting et al. 2016; Yamazaki et al. 2012). Animal studies support the hypothesis that blocking VEGF may lead to choroidal

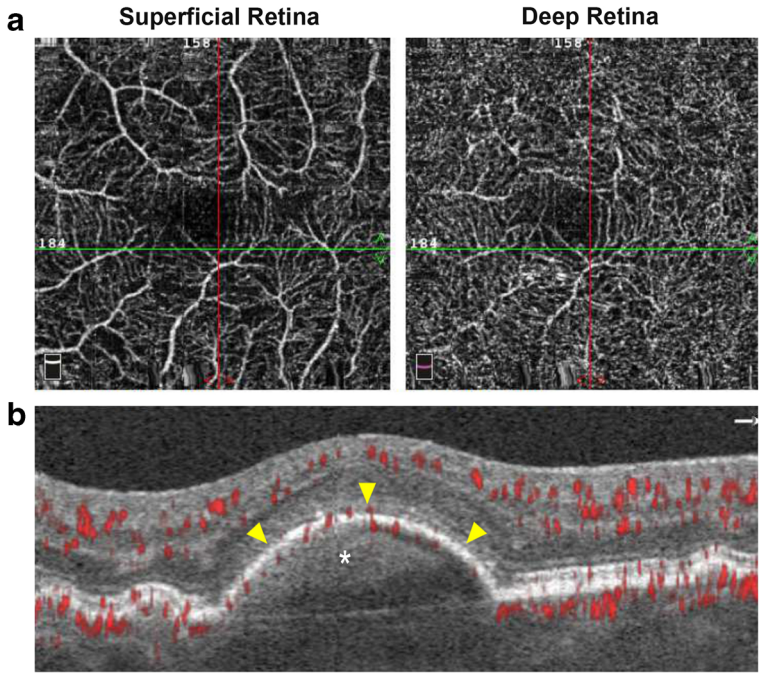


Fig. 10 Polypoidal choroidal vasculopathy. Shown is an example of an eye with polypoidal choroidal vasculopathy. **a** The superficial and deep retinal capillary vascular density remains high, despite high serous retinal pigment epithelial (RPE) detachment (yellow arrowheads) and sub-RPE lesion (asterisk) (**b**). Hyperflow sub-RPE signal (red overlay) can be seen on cross-sectional OCTA. Images in **a** are captured from the superficial retina (ILM–IPL) and deep retina (IPL–OPL). ILM, inner limiting membrane; IPL, inner plexiform layer; OPL, outer plexiform layer

toxicity. In the tetracycline-inducible RPE-specific Vegfa knockout mouse, Vegfa knockout in the adult animal led to choriocapillaris loss as soon as 3 days after Cre induction (Kurihara et al. 2012). Unfortunately, because untreated neovascular AMD eyes cannot be ethically included, it remains difficult to tell whether reductions in choriocapillaris hemodynamic parameters/structure are due to the activity of the anti-VEGF treatment in counteracting the role of endogenous VEGF in the choriocapillaris, due to the progression of the neovascular AMD and choroidal neovascularization, or may be secondary to RPE degeneration.

However, in light of potential concerns about choriocapillaris side effects with current therapies, a variety of novel targets are currently under exploration for the treatment of neovascular AMD. One exciting new target still undergoing preclinical evaluation is Tie2. The angiopoietin–Tie2 system is essential for vascular regulation and homeostasis, and stabilizing Tie2 by delivering angiopoietin 1 can suppress neovascularization, edema, and leakage in a mouse model of CNV (Lee et al. 2014). More recent work has shown that in addition to these beneficial effects in suppression of CNV and its side effects, a Tie2-activating antibody also promotes regeneration of the choriocapillaris in animal models of CNV (Kim et al. 2019), suggesting this may be an exciting therapeutic target for multiple forms of choroidal disease where choriocapillaris involvement occurs.

Changes in the choroid in polypoidal choroidal vasculopathy

Polypoidal choroidal vasculopathy (PCV) is a disease of the choroidal vasculature characterized by serosanguineous detachments of the pigmented epithelium and accumulation of subretinal fluid (Yannuzzi et al. 1990). The name reflects the appearance of a network of branching choroidal vessels with terminal, polyp-like aneurysmal dilations. Evidence supports that symptomatic patients with PCV can have complete regression without severe vision loss with anti-VEGF treatment (Koh et al. 2012, 2013, 2017a). Due to a superior visualization of polyps and branching vascular network, ICGA has long been the gold standard for the diagnosis of PCV. Recent studies have shown that OCTA is comparable to ICGA for the detection of the PCV (see example in Fig. 10). Cross-sectional OCTA scans proved to be more sensitive than en face OCTA in visualizing flow signal in polyps (Inoue et al. 2015). However, the lumen often appears devoid of flow signals that can be explained due to the turbulent flow or the slow flow within the polyp. According to previous reports, the rate of polyp detection by OCTA varied between 17 and 85% (Cheung et al. 2017; Srour et al. 2016). As a result, although a combination of OCT and OCTA can be used to detect PCV with high sensitivity and specificity, ICGA remains the gold standard imaging technique in the diagnosis of PCV (Cheung et al. 2019).

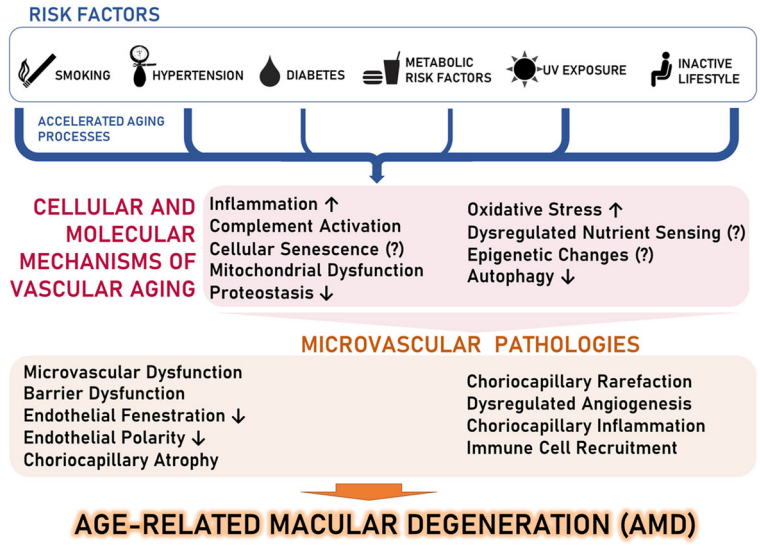


Fig. 11 Mechanisms of microvascular aging contributing to the pathogenesis of age-related macular degeneration (AMD). Scheme depicting the links among shared cellular and molecular mechanisms of aging, microvascular aging phenotypes, and pathogenesis of AMD. Known risk factors of AMD that exacerbate microvascular aging processes are indicated

Cellular mechanisms of vascular aging in the choroid and AMD

Choroidal defects clearly contribute to AMD pathologies; however, cellular mechanisms underlying these microvascular changes remain to be fully elucidated. The field of geroscience has identified a series of common cellular and molecular mechanisms of aging that also play key roles in age-related vascular changes. These factors are also logical candidates to contribute to the development of all the age-related choroidal pathologies, including microvascular contributions to AMD. Common vascular aging mechanisms include oxidative stress, inflammation, impaired proteostasis, mitochondrial dysfunction/DNA damage, deregulated nutrient sensing, and cellular senescence, among others (Ungvari et al. 2018). Many of these factors have been at least partially studied in the context of AMD (Fig. 11), but the majority of studies largely focus on the RPE with less evaluation of the choroid. Here, we highlight what is known about the role of common cellular aging mechanisms in the choroid during aging and the pathogenesis of AMD.

Oxidative stress in the aging/AMD choroid

Increased cellular and mitochondrial oxidative stress is a characteristic feature of microvascular aging (Csiszar et al. 2014, 2019; Fulop et al. 2018; Kiss et al. 2019; Springo et al. 2015; Tarantini et al. 2017, 2018b, 2019; Ungvari et al. 2018). Oxidative stress is also widely recognized to be a key pathogenic stimulus in the development of both neovascular AMD and geographic atrophy (Datta et al. 2017; Ding et al. 2009). The macula is a high oxidative stress environment and several cardiovascular risk factors (e.g., hypertension, diabetes, obesity, smoking) that promote AMD also accelerate microvascular aging by exacerbating oxidative stress in vascular cells (Addabbo et al. 2009; Bailey-Downs et al. 2013; Csipo et al. 2018; Csiszar et al. 2008b, 2009b; Dikalov and Ungvari 2013; Mattison et al. 2014; Orosz et al. 2007; Springo et al. 2015; Tarantini et al. 2018a; Toth et al. 2015; Tucsek et al. 2014a, 2014b, 2014c, 2017; Ungvari et al. 2004, 2011c, 2017b; Valcarcel-Ares et al. 2018). In addition, many of the genetic variants that increase risk for AMD do so by altering oxidative stress–associated genes. As a result, there has been persistent interest in nutritional approaches to combat oxidative stress in AMD, including supplementation with antioxidant vitamins and dietary polyphenols (Age-Related Eye Disease Study 2 Research 2013; Age-Related Eye Disease Study Research 2001; Gorusupudi et al. 2017; Ivanescu et al. 2015; Kanavi et al. 2014; Pandian et al. 2017; Pawlowska et al. 2019; Zhuang et al. 2011).

In cultured choroidal endothelial cells, oxidative stress induced by both hypoxia and chemical mediators can increase VEGF production (Balaiya et al. 2012; Eichler et al. 2008), and suppressing oxidative stress with the antioxidant dietary polyphenol resveratrol suppresses VEGF secretion (Balaiya et al. 2013). Pretreatment with resveratrol also suppresses VEGF upregulation and choroidal neovascularization in the laser-induced choroidal neovascularization mouse model in a manner dependent on AMPK signaling in the RPE and choroid (Nagai et al. 2014). Other models have also suggested that oxidative stress plays a role in choroidal neovascularization. For example, injection of inhibitors of the small GTPase Rap1 in a laser-induced choroidal neovascularization model suppressed the production of reactive oxygen species (ROS), expression of NADPH oxidase, and development of neovascular lesions (Li et al. 2018).

Several oxidative stress models also exhibit characteristics of both dry AMD/geographic atrophy and choroidal neovascularization. The enhanced oxidative stress OXYS rat model exhibits several different aging pathologies including a dry AMD-like retinopathy characterized by defects in the retina and RPE as well as reduction in the choroidal microcirculation, blood cell stasis, and choriocapillaris atrophy (Markovets et al. 2011; Telegina et al. 2015; Zhdankina et al. 2008). The superoxide dismutase 1 (SOD1) knockout mouse also develops AMD disease features, including choroidal neovascularization (Imamura et al. 2006).

One of the key homeostatic mechanisms cells utilize to combat oxidative stress is the Nrf2 antioxidant pathway. Dysregulation of this pathway and thus cellular maladaptation to molecular stressors occurs during aging and is thought to contribute to various vascular pathologies (Ungvari et al. 2011a, 2011b). However, while Nrf2 activation is considered largely protective, it can also have proangiogenic effects (Valcarcel-Ares et al. 2012). While these effects could be beneficial in the case of choriocapillary degeneration during geographic atrophy, suppressing angiogenesis is typically

the desired outcome in choroidal neovascularization. Several studies have demonstrated that Nrf2 is an essential component of the antioxidant response in the RPE. Overall, Nrf2 activity is modestly reduced in the retina/RPE of aged mice compared to young controls (Bonilha et al. 2017). In addition, Nrf2 knockout animals develop an age-related AMD-like retinopathy characterized by RPE loss, basal deposits, BrM thickening, and infrequent choroidal neovascularization (Zhao et al. 2011). Nrf2 knockout mice also exhibited age-related decreases in choriocapillary endothelial cell fenestrations and thickening of choriocapillary endothelial cells suggesting the choroid is affected by the elimination of Nrf2. A few studies have evaluated the role of Nrf2 in laser-induced choroidal neovascularization and other angiogenic retinal models with mixed results. For example, treatment with nonsteroidal anti-inflammatories in a murine laser-induced choroidal neovascularization model suppressed VEGF levels, reduced the size of the neovascular lesion, and increased nuclear Nrf2 and one of its antioxidant target genes HO-1 (Yoshinaga et al. 2011). Similarly, administration of the Nrf2 activator RS9 modestly suppressed neovascular leakage in a primate model of choroidal neovascularization (Nakamura et al. 2019). DMBT (6,6′-bis(2,3-dimethoxybenzoyl)-α,α-D-trehalose), which has been used to suppress tumor angiogenesis by inhibiting breast cancer cell production of VEGF, also suppressed laser-induced choroidal neovascularization and VEGF production. However, corresponding in vitro studies showed that DMBT treatment decreased Nrf2/HO-1 protein levels in hypoxic ARPE-19 cells (Chen et al. 2018). The question of whether choroidal Nrf2 plays a role in the AMD process remains unanswered. In a study evaluating control and AMD human donor eyes, mRNA expression of Nrf2 in the RPE/choroid varied widely and was not significantly different between the two groups. HO-1 in the RPE/choroid was significantly upregulated in AMD eyes, while both Nrf2 and HO-1 were significantly downregulated in AMD retinas (Aberami et al. 2019).

Combined, this body of literature indicates clearly that oxidative stress can lead to choroidal defects and AMD is associated with oxidative stress, but further research is needed to clearly understand the role of oxidative stress in the choroidal vasculature during AMD.

Complement activation and inflammation in the aging/AMD choroid

The "inflammaging" hypothesis predicts that chronic, low-grade inflammation is a critical factor contributing to the genesis of many microvascular aging phenotypes (Csiszar et al. 2003; Minor et al. 2011; Tucsek et al. 2014a, 2014c; Ungvari et al. 2007b, 2018; Valcarcel-Ares et al. 2018). Inflammatory processes are also likely to play critical roles both in age-related changes in the choroid and the pathogenesis of AMD. Importantly, cardiovascular risk factors that promote AMD, including hypertension, diabetes, obesity, and smoking, are known to exacerbate microvascular inflammation.

Since the 2005 identification of high-risk AMD alleles in the complement factor H gene (CFH, an inhibitor of the alternative complement pathway) (Edwards et al. 2005; Hageman et al. 2005; Haines et al. 2005; Klein et al. 2005), a large amount of AMD research has focused on complement pathways. The alternative complement pathway is the primary pathway involved in AMD, and in the intervening years, risk alleles in many additional alternative pathway genes have been identified. This extensive topic is ably reviewed elsewhere (Datta et al. 2017; McHarg et al. 2015; Whitmore et al. 2015); here, we focus on what is known about complement and changes in the choroid during AMD. The alternative complement pathway has low levels of constitutive activity and is tightly regulated by both tissue-resident and bloodborne complement components (such as CFH) to avoid unnecessary signal amplification and downstream consequences such as formation of the membrane attack complex (MAC) and inflammation/recruitment of other immune cells. Complement components are found in AMD drusen (Johnson et al. 2000; Mullins et al. 2000), as well as in the choriocapillaris (Mullins et al. 2014). MAC complex accumulation is frequently observed in the choriocapillaris in an age-associated manner, is higher in AMD patients than controls, and is higher in patients with high-risk CFH alleles (Mullins et al. 2014; Seth et al. 2008). Consistent with this increase in active complement in AMD/aging, CFH is reduced during early and late AMD. CFH is important for the normal choroid. For example, choroidal thinning is more pronounced in patients with high-risk CFH alleles (Mullins et al. 2014). Within the choriocapillaris, MAC complexes frequently accumulate over intercapillary pillars, consistent with abnormal clearance of material in those spaces. This

choriocapillaris accumulation of MAC during aging was specific to the choroid, not occurring in other tissues including the cerebellum, cerebral cortex, heart, or many other organs, perhaps highlighting why AMD targets the eye (Chirco et al. 2016a). One contributor to increased choroidal MAC complexes during AMD is likely to be reduced CFH (produced by the RPE and in the blood), possibly due to reductions in some glycosaminoglycan (GAGs) CFH binding partners in Bruch's membrane and the nearby extracellular matrix (ECM) (Keenan et al. 2014).

In vitro studies using choroidal endothelial cells showed that accumulation of MAC can lead to cell death and increased secretion of VEGF (Zeng et al. 2016), providing support for the idea that complement-mediated injury may promote both angiogenesis/choroidal neovascularization and choriocapillary atrophy. VEGF has been shown to be important for local RPE production of CFH in both cultured human RPE and animal models. In adult mice, genetic or pharmacological ablation of *Vegfa* leads to reduction of CFH and CD59 along with increased complement activation as soon as 3 days after treatment (Keir et al. 2017). This anti-VEGF treatment led to activation of choriocapillary endothelial cells (as measured by levels of PAI-1, P-selectin, and Lox), in a complement-dependent manner. Similarly, complement factor C5a treatment in an organ culture model led to increased choriocapillary endothelial cell expression of the inflammatory leukocyte recruitment adhesion molecule ICAM-1 (Skeie et al. 2010). Similarly, in aging and AMD eyes, choroidal expression of CD34, a cellular glycoprotein thought to suppress leukocyte–endothelial cell adhesion in the choroid, is reduced (Sohn et al. 2014). Together, these findings suggest there may be increased leukocyte trafficking during AMD.

Other inflammatory mediators are also thought to contribute to choroidal defects in AMD. The pentraxin C-reactive protein (CRP) is an acute phase protein upregulated quickly in the liver/circulation after the onset of inflammation and can have pro- and anti-inflammatory activities depending on whether it remains pentameric or dissociates into monomers. Elevated serum CRP is associated with AMD risk and progression (Seddon et al. 2004, 2005). Like CFH, CRP also accumulates in the choriocapillaris during AMD, and the primary form that accumulates is the pro-inflammatory monomeric form (Bhutto et al. 2011; Chirco et al. 2016b). Elevation of CRP, combined with reductions in CFH, contributes to an inflammatory environment in the AMD choroid. For example, choroidal endothelial cells treated with mCRP exhibit increased migration, and choroidal organ cultures treated with mCRP upregulate inflammatory mediators/cytokines including ICAM-1 (Chirco et al. 2016b). Other pentraxins may also play a role in regulating choroidal health in oxidative stress and inflammation. For example, pentraxin 3 works to suppress inflammation; in its absence, IL-1B and the NLRP3 inflammasome are upregulated, and macrophages accumulate in the choroid (Wang et al. 2016).

Inflammation and innate immunity clearly play an essential role in AMD, which is often interrelated with the role of oxidative stress. Future studies will continue to shed light on this complex age-related process in the choroid.

Mitochondrial dysfunction, DNA damage, and genome instability in the aging/AMD choroid

There is increasing evidence that mitochondrial dysfunction plays a critical role in microvascular aging processes (Addabbo et al. 2009; Csiszar et al. 2007, 2008a, 2009a, 2012, 2014; Labinskyy et al. 2009; Springo et al. 2015; Tarantini et al. 2019; Tarantini et al. 2018b; Ungvari et al. 2007a, 2007b, 2008, 2009). Mitochondrial dysfunction and accumulation of widely varying DNA damage, characterized by somatic DNA mutations, copy number variations, and aneuploidies, is a contributing factor in cellular aging, often as a consequence of oxidative stress. Evidence suggests that endothelial cells are particularly susceptible to DNA damage, and that in the aging vasculature, accumulation of DNA damage can lead to replicative senescence (Ungvari et al. 2018). Accumulation of both nuclear DNA (nDNA) and mitochondrial DNA (mtDNA) damage occurs in the aging eye and is worsened in AMD (Barreau et al. 1996; Lin et al. 2011). mtDNA damage correlates with AMD stage and is worse in macular RPE than peripheral RPE (Lin et al. 2011). One contributor to this increased damage may be the decreased DNA damage repair capacity seen in aged and AMD eyes (Lin et al. 2011), a hypothesis supported by genetic association studies suggesting that polymorphisms in some of the DNA repair genes may increase risk for AMD (Blasiak et al. 2012; Synowiec et al. 2012). Mitochondrial damage also occurs in AMD, and changes in RPE mitochondrial structure are common in AMD

eyes (Feher et al. 2006). This mitochondrial damage/mtDNA damage is thought to be a significant contributor to RPE death in AMD, and various studies have evaluated the accumulation of DNA damage in the RPE (and ways to control it) (Tokarz et al. 2016; Wang et al. 2009a). However, little evaluation has been done on DNA damage or mitochondrial changes in the choroid, apart from the observation that aging leads to choroidal nDNA and mtDNA damage (Wang et al. 2008), and this remains an area where further study is indicated.

Dysregulated nutrient-sensing pathways and impaired proteostasis in the aging/AMD choroid

It has become clear that cellular energy–sensing pathways such as mTOR (mechanical/mammalian target of rapamycin) (An et al. 2017, 2018; Lee et al. 2017, 2018b; Nacarelli et al. 2018; Urfer et al. 2017)), AMP-kinase, and sirtuins regulate cellular aging at a central level. These metabolic regulators control cellular responses to changes in nutrient availability, anabolic processes (including synthesis of cellular macromolecules), and catabolic processes (such as autophagy) (Ungvari et al. 2018). Within the vasculature, regulation of these nutrient-sensing pathways has been shown to play a role in vascular oxidative stress, endothelial cell senescence, vascular smooth muscle cell phenotypic switching, and arterial stiffness, among other outcomes (Ha et al. 2015; Lesniewski et al. 2017; Wang et al. 2009b). Pathologically, these changes play a role in regulating vascular damage in Alzheimer's and atherosclerosis disease models (Fry et al. 2016; Lin et al. 2013). Only a few studies have explored the role of these pathways in age- and AMD-associated choroidal changes. The AMD-like pathologies in the OXYS rat model are thought to be associated with the mTOR pathway, with enhanced autophagy, and with mitochondrial dysfunction (Kolosova et al. 2012; Kozhevnikova et al. 2013; Muraleva et al. 2014). However, while neuronal and RPE deficits associated with retinopathy in OXYS rats were improved with rapamycin (the canonical mTOR inhibitor), choroidal/vascular defects were not (Kolosova et al. 2012).

The histone deacetylase sensitive sirtuin 1 can upregulate angiogenic growth factors (such as VEGF) in a hypoxia-dependent manner. Given the role that hypoxia may play in inducing choroidal neovascularization in wet AMD, this pathway is a relevant one to examine in the aged/AMD eye. In the aged mouse, sirtuin 1 and one of its regulators Mir34 have been shown to be upregulated in the retina and RPE, but the choroid has not been clearly evaluated (Smit-McBride et al. 2014). In vitro, cultured choroidal endothelial cells exposed to hypoxia respond by modestly upregulating Sirt1 expression (in addition to VEGF) (Balaiya et al. 2012).

The process of preserving the functional cellular protein pool, termed proteostasis, is essential for normal cell functioning. To maintain proteostasis, damaged proteins and organelles are degraded, typically by the ubiquitin–proteasome system and by autophagy. Evidence suggests that impairments in proteostasis/autophagy may contribute to vascular aging; for example, proteasome activity is decreased in atherosclerotic plaques in the elderly and the hearts of aging rats (Bulteau et al. 2002; Marfella et al. 2008), as well as AMD (Mitter et al. 2014; Viiri et al. 2013). Consequences of impaired proteostasis and autophagy are particularly important in the RPE and can include accumulation of protein aggregates and damaged proteins, accumulation of lipofuscin, accumulation of advanced glycation end products (AGEs), and defective digestion of phagocytosed photoreceptor outer segments. Altered proteostasis in the RPE, for example by impairing regulation by collagen XVIII, is also thought to contribute to RPE degeneration in aged mice (Kivinen et al. 2016). In the low-dose D-galactose model, which exhibits an accelerated aging phenotype due to accumulation of AGEs, choriocapillary fenestrations are lost (Ida et al. 2004), suggesting accumulation of AGEs may contribute to the cellular defects seen in the aging choriocapillaris. In animal models, AGEs and AGE-associated proteins have also been shown to promote VEGF secretion from the RPE and promote choroidal neovascularization (Sun et al. 2017). Consistent with this idea, blocking autophagy can suppress hypoxia-induced tube formation/cell migration in cultured choroidal endothelial cells (Li et al. 2016). However, it is not clear whether impaired proteostasis or autophagy contributes to choriocapillary/choroidal defects in aging and AMD, and if so how central regulatory pathways such as mTor/sirtuins contribute.

Cellular senescence

Increasing evidence suggest that the cellular stress response pathway, termed "cellular senescence,"

contributes significantly to aging processes, including the genesis of vascular aging phenotypes (Campisi 2013; Chinta et al. 2014, 2018; Fulop et al. 2018; Tchkonia et al. 2013; Ungvari et al. 2017a). Cellular senescence can be a consequence of oxidative stress and other cellular dysregulation. Senescence is a key age-related mechanism that occurs in many vascular/microvascular aging pathologies including cerebromicrovascular dysfunction-associated cognitive decline, vasomotor dysfunction, atherosclerosis, and heart failure (Roos et al. 2016; Rossman et al. 2017; Ungvari et al. 2017a; Uryga and Bennett 2016). As is frequently the case, significantly more research has evaluated the RPE than the choroid. It has been hypothesized that RPE senescence may contribute to AMD by reducing the regenerative capacity of the RPE and thus promoting RPE cell loss (Blasiak et al. 2017), and several studies using accelerated senescence models have documented RPE defects/degeneration (Majji et al. 2000; Markovets et al. 2011). In addition, many studies have shown that cultured ARPE-19 cells undergo senescence induced by oxidative stress (Arend et al. 2015; Aryan et al. 2016; Marazita et al. 2016; Supanji et al. 2013), but it remains to be seen whether RPE cells become senescent in either AMD eyes or animal models of AMD, and much less is known about senescence in the choroid.

There is some evidence that cellular senescence may contribute to choroidal changes during aging and to the development of age-related pathologies. For example, choriocapillary atrophy is a characteristic of the animal models with accelerated senescence such as the senescence-associated mouse line (SAM P(8)) (Majji et al. 2000) and the OXYS rat (Markovets et al. 2011; Telegina et al. 2015; Zhdankina et al. 2008). In vitro models have shown that inducing replicative cell senescence in cultured choroidal endothelial cells increases both cell stiffness and sensitivity to membrane attack complex (MAC)-mediated lysis (Cabrera et al. 2016). Perivascular MAC deposition on the choriocapillaris consequent to complement activation in the choroid/RPE is a common feature in AMD (Chirco et al. 2016a), and it has been hypothesized that choriocapillary atrophy/dropout in AMD may occur due to senescence-associated increases in MAC-mediated cell lysis. However, it remains to be seen to what extent cellular senescence occurs in the aging/AMD choroid.

Epigenetic changes

Epigenetic changes including alterations in DNA methylation, histone modifications, and microRNA regulation have been hypothesized to contribute to aging processes, including age-related changes in the vasculature and vascular pathologies, such as atherosclerosis (Connelly et al. 2013; Nanoudis et al. 2017; Nguyen et al. 2016; Paz et al. 2019; Zhang et al. 2018b). This is an active field of research and much remains to be explored regarding the contributions of epigenetic changes to vascular aging. Virtually nothing is known about epigenetic changes in the choroid during aging and AMD, so this remains a potentially highly promising area for further exploration.

Concluding perspectives

The high prevalence of AMD has meant that human studies on disease progression abound, with far more publications than could ever be cited in a single review. However, interpreting this vast literature can be complicated. The vast majority of studies have fairly small sample sizes; do not report the same outcome variables; do not have the same controls, inclusion, and exclusion criteria; and often do not report all relevant details. As a result, findings are often contradictory and inconsistent. However, these studies, especially when combined with larger studies such as AREDS and the ALIENOR, provide clear evidence that the choroid and, in particular, the choriocapillaris play a critical role in the pathogenesis of AMD.

It is likewise clear that many cellular mechanisms of aging and vascular aging contribute to the development of AMD, particularly factors such as oxidative stress and inflammation/innate immunity, providing a common foundation for understanding of multiple age-related diseases. However, in other cases, the role of cellular aging factors in AMD is less well understood. In addition, the RPE has been the primary focus of many mechanistic studies, making it difficult to understand microvascular contributions to the disease processes. From some standpoints, this may not matter; the RPE and the choroid work very closely together both physiologically and pathologically, and defects affecting one frequently affect the other, particularly in AMD. However, as more support for a vascular/microvascular theory of AMD becomes available, including evidence that choriocapillary

defects/degeneration precede RPE loss, it becomes increasingly evident that a thorough understanding of the cellular and molecular changes in the choroid will be essential to develop novel therapeutic interventions.

Luckily, the recent advancements in choroid/choriocapillaris imaging technology coupled with growing appreciation of the importance of the choroid mean that the field is advancing extremely quickly. As an example, PubMed hits for "choriocapillaris" nearly doubled from 2015 to 2016 (57 vs. 103, respectively) then nearly doubled again by 2018 (to 193). More importantly, the newer imaging technologies permit more detailed, refined analysis of choroidal structure and physiology, allowing significantly more information to be gleaned than in the past. One limitation is that these imaging advancements have not yet been widely adapted for use in small animal models, so mechanistic studies evaluating cellular/molecular pathways have thus far been largely limited to analysis of post-mortem tissues. However, in common with other imaging modalities, development of small animal approaches for advanced choroidal imaging is likely to occur in the future. Combined, the prevalence of AMD, the widely appreciated role of the choroidal blood supply in disease pathology, and dramatic advancements in tools mean that we will likely see substantial progress in our understanding of the role of the choriocapillaris in aging and AMD in the near future. Recent studies provide proof-of-concept that cerebrovascular aging phenotypes are potentially reversible (Kiss et al. 2019; Lin et al. 2013; Tarantini et al. 2018b, 2019; Van Skike et al. 2018). We propose that by targeting shared mechanisms of microvascular aging, age-related impairments in the choriocapillaris can also be potentially reversed and thereby novel therapies for prevention of AMD can be developed.

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References

Aberami S, Nikhalashree S, Bharathselvi M, Biswas J, Sulochana KN, Coral K (2019) Elemental concentrations in choroid-RPE and retina of human eyes with age-related macular degeneration. Exp Eye Res 186:107718. https://doi.org/10.1016/j.exer.2019.107718

Addabbo F et al (2009) The Krebs cycle and mitochondrial mass are early victims of endothelial dysfunction: proteomic approach. Am J Pathol 174:34–43. https://doi.org/10.2353/ajpath.2009.080650

Adhi M, Lau M, Liang MC, Waheed NK, Duker JS (2014) Analysis of the thickness and vascular layers of the choroid in eyes with geographic atrophy using spectral-domain optical coherence tomography. Retina 34:306–312. https://doi.org/10.1097/IAE.0b013e3182993e09

Age-Related Eye Disease Study 2 Research G (2013) Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA 309:2005–2015. https://doi.org/10.1001/jama.2013.4997

Age-Related Eye Disease Study Research G (2000) Risk factors associated with age-related macular degeneration. A case-control study in the age-related eye disease study: Age-Related Eye Disease Study Report Number 3. Ophthalmology 107:2224–2232

Age-Related Eye Disease Study Research G (2001) A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 119:1417–1436. https://doi.org/10.1001/archopht.119.10.1417

Ahmad M, Kaszubski PA, Cobbs L, Reynolds H, Smith RT (2017) Choroidal thickness in patients with coronary artery disease. PLoS One 12:e0175691. https://doi.org/10.1371/journal.pone.0175691

Akahori T, Iwase T, Yamamoto K, Ra E, Terasaki H (2017) Changes in choroidal blood flow and morphology in response to increase in intraocular pressure. Invest Ophthalmol Vis Sci 58:5076–5085. https://doi.org/10.1167/iovs.17-21745

Akay F, Gundogan FC, Yolcu U, Toyran S, Uzun S (2016) Choroidal thickness in systemic arterial hypertension. Eur J Ophthalmol 26:152–157. https://doi.org/10.5301/ejo.5000675

Alagorie AR, Verma A, Nassisi M, Sadda SR (2019) Quantitative assessment of choriocapillaris flow deficits in eyes with advanced age-related macular degeneration versus healthy eyes. Am J Ophthalmol. https://doi.org/10.1016/j.ajo.2019.04.037

Alder VA, Cringle SJ, Constable IJ (1983) The retinal oxygen profile in cats. Invest Ophthalmol Vis Sci 24:30–36

An JY et al (2017) Rapamycin treatment attenuates age-associated periodontitis in mice. Geroscience. https://doi.org/10.1007/s11357-017-9994-6

An JY, Darveau R, Kaeberlein M (2018) Oral health in geroscience: animal models and the aging oral cavity. Geroscience 40:1–10. https://doi.org/10.1007/s11357-017-0004-9

Anderson B Jr (1968) Ocular effects of changes in oxygen and carbon dioxide tension. Trans Am Ophthalmol Soc 66:423–474

Arend N, Wertheimer C, Laubichler P, Wolf A, Kampik A, Kernt M (2015) Idebenone prevents oxidative stress, cell death and senescence of retinal pigment epithelium cells by stabilizing BAX/Bcl-2 ratio. Ophthalmologica 234:73–82. https://doi.org/10.1159/000381726

Aryan N, Betts-Obregon BS, Perry G, Tsin AT (2016) Oxidative Stress Induces Senescence in Cultured RPE. Cells Open Neurol J 10:83–87. https://doi.org/10.2174/1874205X01610010083

Atienzar-Aroca S et al (2016) Oxidative stress in retinal pigment epithelium cells increases exosome secretion and promotes angiogenesis in endothelial cells. J Cell Mol Med 20:1457–1466. https://doi.org/10.1111/jcmm.12834

Ayhan Z, Kaya M, Ozturk T, Karti O, Hakan Oner F (2017) Evaluation of macular perfusion in healthy smokers by using optical coherence tomography angiography. Ophthalmic Surg Lasers Imaging Retina 48:617–622. https://doi.org/10.3928/23258160-20170802-03

Bailey-Downs LC et al (2013) Aging exacerbates obesity-induced oxidative stress and inflammation in perivascular adipose tissue in mice: a paracrine mechanism contributing to vascular redox dysregulation and inflammation. J Gerontol A Biol Sci Med Sci 68:780–792. https://doi.org/10.1093/gerona/gls238

Balaiya S, Khetpal V, Chalam KV (2012) Hypoxia initiates sirtuin1-mediated vascular endothelial growth factor activation in choroidal endothelial cells through hypoxia inducible factor-2alpha. Mol Vis 18:114–120

Balaiya S, Murthy RK, Chalam KV (2013) Resveratrol inhibits proliferation of hypoxic choroidal vascular endothelial cells. Mol Vis 19:2385–2392

Barreau E, Brossas JY, Courtois Y, Treton JA (1996) Accumulation of mitochondrial DNA deletions in human retina during aging. Invest Ophthalmol Vis Sci 37:384–391

Berenberg TL et al (2012) The association between drusen extent and foveolar choroidal blood flow in age-related macular degeneration. Retina 32:25–31. https://doi.org/10.1097/IAE.0b013e3182150483

Bhisitkul RB, Desai SJ, Boyer DS, Sadda SR, Zhang K (2016) Fellow eye comparisons for 7-year outcomes in ranibizumab-treated AMD subjects from ANCHOR, MARINA, and HORIZON (SEVEN-UP Study). Ophthalmology 123:1269–1277. https://doi.org/10.1016/j.ophtha.2016.01.033

Bhutto IA, Amemiya T (2002) Choroidal vasculature changes in spontaneously hypertensive rats—transmission electron microscopy and scanning electron microscopy with casts. Ophthalmic Res 34:54–62. https://doi.org/10.1159/000048329

Bhutto IA, Baba T, Merges C, Juriasinghani V, McLeod DS, Lutty GA (2011) C-reactive protein and complement factor H in aged human eyes and eyes with age-related macular degeneration. Br J Ophthalmol 95:1323–1330. https://doi.org/10.1136/bjo.2010.199216

Bhutto IA, McLeod DS, Jing T, Sunness JS, Seddon JM, Lutty GA (2016) Increased choroidal mast cells and their degranulation in age-related macular degeneration. Br J Ophthalmol 100:720–726. https://doi.org/10.1136/bjophthalmol-2015-308290

Biesemeier A, Taubitz T, Julien S, Yoeruek E, Schraermeyer U (2014) Choriocapillaris breakdown precedes retinal degeneration in age-related macular degeneration. Neurobiol Aging 35:2562–2573. https://doi.org/10.1016/j.neurobiolaging.2014.05.003

Blasiak J, Synowiec E, Salminen A, Kaarniranta K (2012) Genetic variability in DNA repair proteins in age-related macular degeneration. Int J Mol Sci 13:13378–13397. https://doi.org/10.3390/ijms131013378

Blasiak J, Piechota M, Pawlowska E, Szatkowska M, Sikora E, Kaarniranta K (2017) Cellular senescence in age-related macular degeneration: can autophagy and DNA damage response play a role? Oxidative Med Cell Longev 2017:5293258. https://doi.org/10.1155/2017/5293258

Bonilha VL et al (2017) Absence of DJ-1 causes age-related retinal abnormalities in association with increased oxidative stress. Free Radic Biol Med 104:226–237. https://doi.org/10.1016/j.freeradbiomed.2017.01.018

Bonyadi MHJ, Yaseri M, Bonyadi M, Soheilian M, Nikkhah H (2017) Association of combined cigarette smoking and ARMS2/LOC387715 A69S polymorphisms with age-related macular degeneration: a meta-analysis. Ophthalmic Genet 38:308–313. https://doi.org/10.1080/13816810.2016.1237664

Borrelli E, Sarraf D, Freund KB, Sadda SR (2018) OCT angiography and evaluation of the choroid and choroidal vascular disorders. Prog Retin Eye Res 67:30–55. https://doi.org/10.1016/j.preteyeres.2018.07.002

Bourne RR et al (2013) Causes of vision loss worldwide, 1990-2010: a systematic analysis. Lancet Glob Health 1:e339–e349. https://doi.org/10.1016/S2214-109X(13)70113-X

Bouteleux V et al (2019) Increased choroidal thickness: a new feature to monitor age-related macular degeneration recurrence. Graefes Arch Clin Exp Ophthalmol 257:699–707. https://doi.org/10.1007/s00417-018-04216-8

Brown DM et al (2006) Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 355:1432–1444. https://doi.org/10.1056/NEJMoa062655

Bulteau AL, Szweda LI, Friguet B (2002) Age-dependent declines in proteasome activity in the heart. Arch Biochem Biophys 397:298–304. https://doi.org/10.1006/abbi.2001.2663

Bulus AD, Can ME, Baytaroglu A, Can GD, Cakmak HB, Andiran N (2017) Choroidal thickness in childhood obesity. Ophthalmic Surg Lasers Imaging Retina 48:10–17. https://doi.org/10.3928/23258160-20161219-02

Cabrera AP, Bhaskaran A, Xu J, Yang X, Scott HA, Mohideen U, Ghosh K (2016) Senescence increases choroidal endothelial stiffness and susceptibility to complement injury: implications for choriocapillaris loss in AMD. Invest Ophthalmol Vis Sci 57:5910–5918. https://doi.org/10.1167/iovs.16-19727

Calzetti G et al (2018) Assessment of choroidal blood flow using laser speckle flowgraphy. Br J Ophthalmol 102:1679–1683. https://doi.org/10.1136/bjophthalmol-2017-311750

Campisi J (2013) Aging, cellular senescence, and cancer. Annu Rev Physiol 75:685–705. https://doi.org/10.1146/annurev-physiol-030212-183653

Campos MM, Abu-Asab MS (2017) Loss of endothelial planar cell polarity and cellular clearance mechanisms in age-related macular degeneration. Ultrastruct Pathol 41:312–319. https://doi.org/10.1080/01913123.2017.1348418

Cao J, McLeod S, Merges CA, Lutty GA (1998) Choriocapillaris degeneration and related pathologic changes in human diabetic eyes. Arch Ophthalmol 116:589–597

Chakravarthy U et al (2007) Cigarette smoking and age-related macular degeneration in the EUREYE study. Ophthalmology

114:1157–1163. https://doi.org/10.1016/j.ophtha.2006.09.022

Chakravarthy U et al (2010) Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. BMC Ophthalmol 10:31. https://doi.org/10.1186/1471-2415-10-31

Chakravarthy U et al (2013) Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet 382:1258–1267. https://doi.org/10.1016/S0140-6736(13)61501-9

Chang LY, Acosta ML, Black J (2019) Choroidal thinning and ocular electrophysiology in a case of vascular cognitive impairment after stroke. Clin Exp Optom 102:184–187. https://doi.org/10.1111/cxo.12831

Chen X et al (2014) Diabetes mellitus and risk of age-related macular degeneration: a systematic review and meta-analysis. PLoS One 9:e108196. https://doi.org/10.1371/journal.pone.0108196

Chen S, Zhou Y, Zhou L, Guan Y, Zhang Y, Han X (2018) Anti-neovascularization effects of DMBT in age-related macular degeneration by inhibition of VEGF secretion through ROS-dependent signaling pathway. Mol Cell Biochem 448:225–235. https://doi.org/10.1007/s11010-018-3328-6

Cheung CMG et al (2017) Characterization and differentiation of polypoidal choroidal vasculopathy using swept source optical coherence tomography angiography. Retina 37:1464–1474. https://doi.org/10.1097/IAE.0000000000001391

Cheung CMG et al (2019) Improved detection and diagnosis of polypoidal choroidal vasculopathy using a combination of optical coherence tomography and optical coherence tomography angiography. Retina 39:1655–1663. https://doi.org/10.1097/IAE.0000000000002228

Chinta SJ, Woods G, Rane A, Demaria M, Campisi J, Andersen JK (2014) Cellular senescence and the aging brain. Exp Gerontol. https://doi.org/10.1016/j.exger.2014.09.018

Chinta SJ et al (2018) Cellular senescence is induced by the environmental neurotoxin paraquat and contributes to neuropathology linked to Parkinson's disease. Cell Rep 22:930–940. https://doi.org/10.1016/j.celrep.2017.12.092

Chirco KR, Tucker BA, Stone EM, Mullins RF (2016a) Selective accumulation of the complement membrane attack complex in aging choriocapillaris. Exp Eye Res 146:393–397. https://doi.org/10.1016/j.exer.2015.09.003

Chirco KR et al (2016b) Monomeric C-reactive protein and inflammation in age-related macular degeneration. J Pathol 240:173–183. https://doi.org/10.1002/path.4766

Chirco KR, Sohn EH, Stone EM, Tucker BA, Mullins RF (2017) Structural and molecular changes in the aging choroid: implications for age-related macular degeneration. Eye (Lond) 31:10–25. https://doi.org/10.1038/eye.2016.216

Chua J et al (2019) Impact of systemic vascular risk factors on the choriocapillaris using optical coherence tomography angiography in patients with systemic hypertension. Sci Rep 9:5819. https://doi.org/10.1038/s41598-019-41917-4

Chung SE, Kang SW, Lee JH, Kim YT (2011) Choroidal thickness in polypoidal choroidal vasculopathy and exudative age-related macular degeneration. Ophthalmology 118:840–845. https://doi.org/10.1016/j.ophtha.2010.09.012

Ciulla TA et al (1999) Color Doppler imaging discloses reduced ocular blood flow velocities in nonexudative age-related macular degeneration. Am J Ophthalmol 128:75–80

Coleman DJ, Lizzi FL (1979) In vivo choroidal thickness measurement. Am J Ophthalmol 88:369–375

Comparison of Age-related Macular Degeneration Treatments Trials Research G et al (2012) Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 119:1388–1398. https://doi.org/10.1016/j.ophtha.2012.03.053

Connelly JJ et al (2013) Epigenetic regulation of COL15A1 in smooth muscle cell replicative aging and atherosclerosis. Hum Mol Genet 22:5107–5120. https://doi.org/10.1093/hmg/ddt365

Csipo T et al (2018) Short-term weight loss reverses obesity-induced microvascular endothelial dysfunction. Geroscience. https://doi.org/10.1007/s11357-018-0028-9

Csiszar A, Ungvari Z, Koller A, Edwards JG, Kaley G (2003) Aging-induced proinflammatory shift in cytokine expression profile in rat coronary arteries. FASEB J 17:1183–1185

Csiszar A et al (2007) Vascular superoxide and hydrogen peroxide production and oxidative stress resistance in two closely related rodent species with disparate longevity. Aging Cell 6:783–797

Csiszar A et al (2008a) Endothelial function and vascular oxidative stress in long-lived GH/IGF-deficient Ames dwarf mice. Am J Physiol Heart Circ Physiol 295:H1882–H1894. https://doi.org/10.1152/ajpheart.412.2008

Csiszar A et al (2008b) Vasoprotective effects of resveratrol and SIRT1: attenuation of cigarette smoke-induced oxidative stress and proinflammatory phenotypic alterations. Am J Physiol Heart Circ Physiol 294:H2721–H2735

Csiszar A et al (2009a) Resveratrol induces mitochondrial biogenesis in endothelial cells. Am J Physiol Heart Circ Physiol. https://doi.org/10.1152/ajpheart.00368.2009

Csiszar A, Podlutsky A, Wolin MS, Losonczy G, Pacher P, Ungvari Z (2009b) Oxidative stress and accelerated vascular aging: implications for cigarette smoking. Front Biosci 14:3128–3144

Csiszar A, Sosnowska D, Wang M, Lakatta EG, Sonntag WE, Ungvari Z (2012) Age-associated proinflammatory secretory phenotype in vascular smooth muscle cells from the non-human primate Macaca mulatta: reversal by resveratrol treatment. J Gerontol A Biol Sci Med Sci 67:811-820 doi: https://doi.org/10.1093/gerona/glr228 glr228 [pii]

Csiszar A et al (2014) Caloric restriction confers persistent anti-oxidative, pro-angiogenic, and anti-inflammatory effects and promotes anti-aging miRNA expression profile in cerebromicrovascular endothelial cells of aged rats. Am J Physiol Heart Circ Physiol 307:H292–H306. https://doi.org/10.1152/ajpheart.00307.2014

Csiszar A et al (2019) Role of endothelial NAD+ deficiency in age-related vascular dysfunction. Am J Physiol Heart Circ Physiol:in press. https://doi.org/10.1152/ajpheart.00039.2019

Datta S, Cano M, Ebrahimi K, Wang L, Handa JT (2017) The impact of oxidative stress and inflammation on RPE degeneration in non-neovascular AMD. Prog Retin Eye Res 60:201–218. https://doi.org/10.1016/j.preteyeres.2017.03.002

de Carlo TE et al (2015) Spectral-domain optical coherence tomography angiography of choroidal neovascularization.

Ophthalmology 122:1228–1238. https://doi.org/10.1016/j.ophtha.2015.01.029
Delcourt C et al (2010) Nutrition and age-related eye diseases: the Alienor (Antioxydants, Lipides Essentiels, Nutrition et maladies OculaiRes) Study. J Nutr Health Aging 14:854–861
Dikalov SI, Ungvari Z (2013) Role of mitochondrial oxidative stress in hypertension. Am J Physiol Heart Circ Physiol 305: H1417–H1427. https://doi.org/10.1152/ajpheart.00089.2013
Ding X, Patel M, Chan CC (2009) Molecular pathology of age-related macular degeneration. Prog Retin Eye Res 28:1–18. https://doi.org/10.1016/j.preteyeres.2008.10.001
Dogan B, Kazim Erol M, Dogan U, Habibi M, Bulbuller N, Turgut Coban D, Bulut M (2016) The retinal nerve fiber layer, choroidal thickness, and central macular thickness in morbid obesity: an evaluation using spectral-domain optical coherence tomography. Eur Rev Med Pharmacol Sci 20:886–891
Edwards AO, Ritter R 3rd, Abel KJ, Manning A, Panhuysen C, Farrer LA (2005) Complement factor H polymorphism and age-related macular degeneration. Science 308:421–424. https://doi.org/10.1126/science.1110189
Eichler W, Reiche A, Yafai Y, Lange J, Wiedemann P (2008) Growth-related effects of oxidant-induced stress on cultured RPE and choroidal endothelial cells. Exp Eye Res 87:342–348. https://doi.org/10.1016/j.exer.2008.06.017
Ersan I et al (2016) Noninvasive assessment of the retina and the choroid using enhanced-depth imaging optical coherence tomography shows microvascular impairments in childhood obesity. J AAPOS 20:58–62. https://doi.org/10.1016/j.jaapos.2015.10.006
Espinosa-Heidmann DG, Suner IJ, Catanuto P, Hernandez EP, Marin-Castano ME, Cousins SW (2006) Cigarette smoke-related oxidants and the development of sub-RPE deposits in an experimental animal model of dry AMD. Invest Ophthalmol Vis Sci 47:729–737. https://doi.org/10.1167/iovs.05-0719
Evans JR (2001) Risk factors for age-related macular degeneration. Prog Retin Eye Res 20:227–253
Farazdaghi MK, Ebrahimi KB (2019) Role of the choroid in age-related macular degeneration: a current review. J Ophthalmic Vis Res 14:78–87. https://doi.org/10.4103/jovr.jovr_125_18
Feher J, Kovacs I, Artico M, Cavallotti C, Papale A, Balacco Gabrieli C (2006) Mitochondrial alterations of retinal pigment epithelium in age-related macular degeneration. Neurobiol Aging 27:983–993. https://doi.org/10.1016/j.neurobiolaging.2005.05.012
Ferris FL 3rd et al (2013) Clinical classification of age-related macular degeneration. Ophthalmology 120:844–851. https://doi.org/10.1016/j.ophtha.2012.10.036
Fett AL, Hermann MM, Muether PS, Kirchhof B, Fauser S (2012) Immunohistochemical localization of complement regulatory proteins in the human retina. Histol Histopathol 27:357–364. https://doi.org/10.14670/HH-27.357
Friedman E (1997) A hemodynamic model of the pathogenesis of age-related macular degeneration. Am J Ophthalmol 124: 677–682. https://doi.org/10.1016/s0002-9394(14)70906-7
Friedman E, Smith TR, Kuwabara T (1963) Senile choroidal vascular patterns and drusen. Arch Ophthalmol 69:220–230
Fry JL et al (2016) Vascular smooth muscle sirtuin-1 protects against diet-induced aortic stiffness. Hypertension 68:775–784. https://doi.org/10.1161/HYPERTENSIONAHA.116.07622
Fryczkowski AW (1994) Anatomical and functional choroidal lobuli. Int Ophthalmol 18:131–141
Fulop GA et al (2018) Nrf2 deficiency in aged mice exacerbates cellular senescence promoting cerebrovascular inflammation. Geroscience 40:513–521. https://doi.org/10.1007/s11357-018-0047-6
Gattoussi S et al (2019) Choroidal thickness, vascular factors, and age-related macular degeneration: the ALIENOR Study. Retina 39:34–43. https://doi.org/10.1097/IAE.0000000000002237
Gelfand BD, Ambati J (2016) A revised hemodynamic theory of age-related macular degeneration. Trends Mol Med 22:656–670. https://doi.org/10.1016/j.molmed.2016.06.009
Gok M, Karabas VL, Emre E, Aksar AT, Aslan MS, Ural D (2015) Evaluation of choroidal thickness via enhanced depth-imaging optical coherence tomography in patients with systemic hypertension. Indian J Ophthalmol 63:239–243. https://doi.org/10.4103/0301-4738.156928
Gorusupudi A, Nelson K, Bernstein PS (2017) The Age-Related Eye Disease 2 Study: micronutrients in the treatment of macular degeneration. Adv Nutr 8:40–53. https://doi.org/10.3945/an.116.013177
Granstam E, Granstam SO, Fellstrom B, Lind L (1998) Endothelium-dependent vasodilation in the uvea of hypertensive and normotensive rats. Curr Eye Res 17:189–196
Grebe R, Mughal I, Bryden W, McLeod S, Edwards M, Hageman GS, Lutty G (2019) Ultrastructural analysis of submacular choriocapillaris and its transport systems in AMD and aged control eyes. Exp Eye Res 181:252–262. https://doi.org/10.1016/j.exer.2019.02.018
Grunwald JE, Hariprasad SM, DuPont J (1998a) Effect of aging on foveolar choroidal circulation. Arch Ophthalmol 116: 150–154
Grunwald JE et al (1998b) Foveolar choroidal blood flow in age-related macular degeneration. Invest Ophthalmol Vis Sci 39: 385–390
Grunwald JE, Metelitsina TI, Dupont JC, Ying GS, Maguire MG (2005) Reduced foveolar choroidal blood flow in eyes with increasing AMD severity. Invest Ophthalmol Vis Sci 46: 1033–1038. https://doi.org/10.1167/iovs.04-1050
Grunwald JE et al (2014) Risk of geographic atrophy in the comparison of age-related macular degeneration treatments trials. Ophthalmology 121:150–161. https://doi.org/10.1016/j.ophtha.2013.08.015
Grunwald JE, Pistilli M, Ying GS, Maguire MG, Daniel E, Martin DF, Comparison of Age-related Macular Degeneration Treatments Trials Research G (2015) Growth of geographic atrophy in the comparison of age-related macular degeneration treatments trials. Ophthalmology 122:809-816 doi: https://doi.org/10.1016/j.ophtha.2014.11.007
Gupta T, Saini N, Arora J, Sahni D (2017) Age-related changes in the chorioretinal junction: an immunohistochemical study. J Histochem Cytochem 65:567–577. https://doi.org/10.1369/0022155417726507
Ha JM et al (2015) Platelet-derived growth factor regulates vascular smooth muscle phenotype via mammalian target of rapamycin complex 1. Biochem Biophys Res Commun 464:57–62. https://doi.org/10.1016/j.bbrc.2015.05.097
Hageman GS et al (2005) A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad

Sci U S A 102:7227–7232. https://doi.org/10.1073/pnas.0501536102

Hahn P, Acquah K, Cousins SW, Lee PP, Sloan FA (2013) Ten-year incidence of age-related macular degeneration according to diabetic retinopathy classification among Medicare beneficiaries. Retina 33:911–919. https://doi.org/10.1097/IAE.0b013e3182831248

Haines JL et al (2005) Complement factor H variant increases the risk of age-related macular degeneration. Science 308:419–421. https://doi.org/10.1126/science.1110359

Hashitani H, Windle A, Suzuki H (1998) Neuroeffector transmission in arterioles of the guinea-pig choroid. J Physiol 510(Pt 1):209–223

Hikichi T, Agarie M (2019) Reduced vessel density of the choriocapillaris during anti-vascular endothelial growth factor therapy for neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci 60:1088–1095. https://doi.org/10.1167/iovs.18-24522

Ho AC, Scott IU, Kim SJ, Brown GC, Brown MM, Ip MS, Recchia FM (2012) Anti-vascular endothelial growth factor pharmacotherapy for diabetic macular edema: a report by the American Academy of Ophthalmology. Ophthalmology 119:2179–2188. https://doi.org/10.1016/j.ophtha.2012.07.058

Hogg RE et al (2008) Cardiovascular disease and hypertension are strong risk factors for choroidal neovascularization. Ophthalmology 115(1046-1052):e1042. https://doi.org/10.1016/j.ophtha.2007.07.031

Icel E, Imamoglu HI, Turk A, Icel A, Akyol N (2018) A comparison of the effects of perindopril arginine and amlodipine on choroidal thickness in patients with primary hypertension. Turk J Med Sci 48:1247–1254. https://doi.org/10.3906/sag-1803-171

Ida H, Ishibashi K, Reiser K, Hjelmeland LM, Handa JT (2004) Ultrastructural aging of the RPE-Bruch's membrane-choriocapillaris complex in the D-galactose-treated mouse. Invest Ophthalmol Vis Sci 45:2348–2354. https://doi.org/10.1167/iovs.03-1337

Imamura Y et al (2006) Drusen, choroidal neovascularization, and retinal pigment epithelium dysfunction in SOD1-deficient mice: a model of age-related macular degeneration. Proc Natl Acad Sci U S A 103:11282–11287. https://doi.org/10.1073/pnas.0602131103

Inan S, Baysal Z, Inan UU (2019) Long-term changes in submacular choroidal thickness after intravitreal ranibizumab therapy for neovascular age-related macular degeneration: 14-mo follow-up. Curr Eye Res:1–8. https://doi.org/10.1080/02713683.2019.1600195

Inoue M, Balaratnasingam C, Freund KB (2015) Optical coherence tomography angiography of polypoidal choroidal vasculopathy and polypoidal choroidal neovascularization. Retina 35:2265–2274. https://doi.org/10.1097/IAE.0000000000000777

Invernizzi A et al (2018) Choroidal structural changes correlate with neovascular activity in neovascular age related macular degeneration. Invest Ophthalmol Vis Sci 59:3836–3841. https://doi.org/10.1167/iovs.18-23960

Ivanescu AA et al (2015) Modifying choroidal neovascularization development with a nutritional supplement in mice. Nutrients 7:5423–5442. https://doi.org/10.3390/nu7075229

Jia Y et al (2014) Quantitative optical coherence tomography angiography of choroidal neovascularization in age-related macular degeneration. Ophthalmology 121:1435–1444. https://doi.org/10.1016/j.ophtha.2014.01.034

Jia Y et al (2015) Quantitative optical coherence tomography angiography of vascular abnormalities in the living human eye. Proc Natl Acad Sci U S A 112:E2395–E2402. https://doi.org/10.1073/pnas.1500185112

Jiang H et al (2017) Serine racemase deficiency attenuates choroidal neovascularization and reduces nitric oxide and VEGF levels by retinal pigment epithelial cells. J Neurochem 143:375–388. https://doi.org/10.1111/jnc.14214

Johnson LV, Ozaki S, Staples MK, Erickson PA, Anderson DH (2000) A potential role for immune complex pathogenesis in drusen formation. Exp Eye Res 70:441–449. https://doi.org/10.1006/exer.1999.0798

Kanavi MR et al (2014) The sustained delivery of resveratrol or a defined grape powder inhibits new blood vessel formation in a mouse model of choroidal neovascularization. Molecules 19:17578–17603. https://doi.org/10.3390/molecules191117578

Kantarci FA, Tatar MG, Colak HN, Uslu H, Yildirim A, Goker H, Gurler B (2016) A pilot study of choroidal thickness in long-term smokers. Retina 36:986–991. https://doi.org/10.1097/IAE.0000000000000815

Keenan TD et al (2014) Age-dependent changes in heparan sulfate in human Bruch's membrane: implications for age-related macular degeneration. Invest Ophthalmol Vis Sci 55:5370–5379. https://doi.org/10.1167/iovs.14-14126

Keenan TD et al (2018) Progression of geographic atrophy in age-related macular degeneration: AREDS2 report number 16. Ophthalmology 125:1913–1928. https://doi.org/10.1016/j.ophtha.2018.05.028

Keir LS et al (2017) VEGF regulates local inhibitory complement proteins in the eye and kidney. J Clin Invest 127:199–214. https://doi.org/10.1172/JCI86418

Kiel JW, Shepherd AP (1992) Autoregulation of choroidal blood flow in the rabbit. Invest Ophthalmol Vis Sci 33:2399–2410

Kim JT, Lee DH, Joe SG, Kim JG, Yoon YH (2013) Changes in choroidal thickness in relation to the severity of retinopathy and macular edema in type 2 diabetic patients. Invest Ophthalmol Vis Sci 54:3378–3384. https://doi.org/10.1167/iovs.12-11503

Kim M, Ha MJ, Choi SY, Park YH (2018) Choroidal vascularity index in type-2 diabetes analyzed by swept-source optical coherence tomography. Sci Rep 8. https://doi.org/10.1038/s41598-017-18511-7

Kim J et al (2019) Tie2 activation promotes choriocapillary regeneration for alleviating neovascular age-related macular degeneration. Sci Adv 5:eaau6732. https://doi.org/10.1126/sciadv.aau6732

Kiss T et al. (2019) Nicotinamide mononucleotide (NMN) treatment attenuates oxidative stress and rescues angiogenic capacity in aged cerebromicrovascular endothelial cells: a potential mechanism for prevention of vascular cognitive impairment. GeroScience:in press

Kivinen N et al (2016) Absence of collagen XVIII in mice causes age-related insufficiency in retinal pigment epithelium proteostasis. Biogerontology 17:749–761. https://doi.org/10.1007/s10522-016-9647-7

Klein BE, Klein R, Lee KE, Jensen SC (2001) Measures of obesity and age-related eye diseases. Ophthalmic Epidemiol 8:251–262

Klein R, Peto T, Bird A, Vannewkirk MR (2004) The epidemiology of age-related macular degeneration. Am J Ophthalmol 137:486–495. https://doi.org/10.1016/j.ajo.2003.11.069

Klein RJ et al (2005) Complement factor H polymorphism in age-related macular degeneration. Science 308:385–389. https://doi.org/10.1126/science.1109557

Koh A et al (2012) EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy. Retina 32:1453–1464. https://doi.org/10.1097/IAE.0b013e31824f91e8

Koh AH et al (2013) Polypoidal choroidal vasculopathy: evidence-based guidelines for clinical diagnosis and treatment. Retina 33:686–716. https://doi.org/10.1097/IAE.0b013e3182852446

Koh A et al (2017a) Efficacy and safety of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: a randomized clinical trial. JAMA Ophthalmol 135:1206–1213. https://doi.org/10.1001/jamaophthalmol.2017.4030

Koh LHL, Agrawal R, Khandelwal N, Sai Charan L, Chhablani J (2017b) Choroidal vascular changes in age-related macular degeneration. Acta Ophthalmol 95:e597–e601. https://doi.org/10.1111/aos.13399

Kolosova NG, Muraleva NA, Zhdankina AA, Stefanova NA, Fursova AZ, Blagosklonny MV (2012) Prevention of age-related macular degeneration-like retinopathy by rapamycin in rats. Am J Pathol 181:472–477. https://doi.org/10.1016/j.ajpath.2012.04.018

Koss MC, Gherezghiher T (1993) Adrenoceptor subtypes involved in neurally evoked sympathetic vasoconstriction in the anterior choroid of cats. Exp Eye Res 57:441–447. https://doi.org/10.1006/exer.1993.1146

Kozhevnikova OS, Korbolina EE, Stefanova NA, Muraleva NA, Orlov YL, Kolosova NG (2013) Association of AMD-like retinopathy development with an Alzheimer's disease metabolic pathway in OXYS rats. Biogerontology 14:753–762. https://doi.org/10.1007/s10522-013-9439-2

Kumase F, Morizane Y, Mohri S, Takasu I, Ohtsuka A, Ohtsuki H (2010) Glycocalyx degradation in retinal and choroidal capillary endothelium in rats with diabetes and hypertension. Acta Med Okayama 64:277–283. https://doi.org/10.18926/AMO/40502

Kur J, Newman EA, Chan-Ling T (2012) Cellular and physiological mechanisms underlying blood flow regulation in the retina and choroid in health and disease. Prog Retin Eye Res 31:377–406. https://doi.org/10.1016/j.preteyeres.2012.04.004

Kurihara T, Westenskow PD, Bravo S, Aguilar E, Friedlander M (2012) Targeted deletion of Vegfa in adult mice induces vision loss. J Clin Invest 122:4213–4217. https://doi.org/10.1172/JCI65157

Kurokawa K, Liu Z, Miller DT (2017) Adaptive optics optical coherence tomography angiography for morphometric analysis of choriocapillaris [Invited]. Biomed Opt Express 8:1803–1822. https://doi.org/10.1364/BOE.8.001803

Labinskyy N et al (2009) Longevity is associated with increased vascular resistance to high glucose-induced oxidative stress and inflammatory gene expression in Peromyscus leucopus. Am J Physiol Heart Circ Physiol 296:H946–H956. https://doi.org/10.1152/ajpheart.00693.2008

Lavinsky F, Lavinsky D (2016) Novel perspectives on swept-source optical coherence tomography. Int J Retina Vitreous 2:25. https://doi.org/10.1186/s40942-016-0050-y

Lee J et al (2014) Angiopoietin-1 suppresses choroidal neovascularization and vascular leakage. Invest Ophthalmol Vis Sci 55:2191–2199. https://doi.org/10.1167/iovs.14-13897

Lee MB et al (2017) A system to identify inhibitors of mTOR signaling using high-resolution growth analysis in Saccharomyces cerevisiae. Geroscience. https://doi.org/10.1007/s11357-017-9988-4

Lee B, Ahn J, Yun C, Kim SW, Oh J (2018a) Variation of retinal and choroidal vasculatures in patients with age-related macular degeneration. Invest Ophthalmol Vis Sci 59:5246–5255. https://doi.org/10.1167/iovs.17-23600

Lee HJ et al (2018b) Hydrogen sulfide ameliorates aging-associated changes in the kidney. Geroscience 40:163–176. https://doi.org/10.1007/s11357-018-0018-y

Leitgeb RA, Werkmeister RM, Blatter C, Schmetterer L (2014) Doppler optical coherence tomography. Prog Retin Eye Res 41:26–43. https://doi.org/10.1016/j.preteyeres.2014.03.004

Lengyel I, Tufail A, Hosaini HA, Luthert P, Bird AC, Jeffery G (2004) Association of drusen deposition with choroidal intercapillary pillars in the aging human eye. Invest Ophthalmol Vis Sci 45:2886–2892. https://doi.org/10.1167/iovs.03-1083

Lesniewski LA et al (2017) Dietary rapamycin supplementation reverses age-related vascular dysfunction and oxidative stress, while modulating nutrient-sensing, cell cycle, and senescence pathways. Aging Cell 16:17–26. https://doi.org/10.1111/acel.12524

Li R, Du J, Chang Y (2016) Role of autophagy in hypoxia-induced angiogenesis of RF/6A cells in vitro. Curr Eye Res 41:1566–1570. https://doi.org/10.3109/02713683.2016.1145234

Li J, Zhang R, Wang C, Wang X, Xu M, Ma J, Shang Q (2018) Activation of the small GTPase Rap1 inhibits choroidal neovascularization by regulating cell junctions and ROS generation in rats. Curr Eye Res 43:934–940. https://doi.org/10.1080/02713683.2018.1454477

Lin H et al (2011) Mitochondrial DNA damage and repair in RPE associated with aging and age-related macular degeneration. Invest Ophthalmol Vis Sci 52:3521–3529. https://doi.org/10.1167/iovs.10-6163

Lin AL et al (2013) Chronic rapamycin restores brain vascular integrity and function through NO synthase activation and improves memory in symptomatic mice modeling Alzheimer's disease. J Cereb Blood Flow Metab 33:1412–1421. https://doi.org/10.1038/jcbfm.2013.82

Lois N, McBain V, Abdelkader E, Scott NW, Kumari R (2013) Retinal pigment epithelial atrophy in patients with exudative age-related macular degeneration undergoing anti-vascular endothelial growth factor therapy. Retina 33:13–22. https://doi.org/10.1097/IAE.0b013e3182657fff

Lutjen-Drecoll E (2006) Choroidal innervation in primate eyes. Exp Eye Res 82:357–361. https://doi.org/10.1016/j.exer.2005.09.015

Lutty G, Grunwald J, Majji AB, Uyama M, Yoneya S (1999) Changes in choriocapillaris and retinal pigment epithelium in age-related macular degeneration. Mol Vis 5:35

Majji AB, Cao J, Chang KY, Hayashi A, Aggarwal S, Grebe RR, De Juan E, Jr. (2000) Age-related retinal pigment epithelium and Bruch's membrane degeneration in senescence-accelerated mouse. Invest Ophthalmol Vis Sci 41:3936–3942

Marazita MC, Dugour A, Marquioni-Ramella MD, Figueroa JM, Suburo AM (2016) Oxidative stress-induced premature senescence dysregulates VEGF and CFH expression in retinal pigment epithelial cells: implications for age-related macular degeneration. Redox Biol 7:78–87. https://doi.org/10.1016/j.redox.2015.11.011

Marfella R et al (2008) Effects of ubiquitin-proteasome system deregulation on the vascular senescence and atherosclerosis process in elderly patients. J Gerontol A Biol Sci Med Sci 63:200–203. https://doi.org/10.1093/gerona/63.2.200

Markovets AM, Saprunova VB, Zhdankina AA, Fursova A, Bakeeva LE, Kolosova NG (2011) Alterations of retinal pigment epithelium cause AMD-like retinopathy in senescence-accelerated OXYS rats. Aging (Albany NY) 3:44–54. https://doi.org/10.18632/aging.100243

Mattison JA et al (2014) Resveratrol prevents high fat/sucrose diet-induced central arterial wall inflammation and stiffening in nonhuman primates. Cell Metab 20:183–190. https://doi.org/10.1016/j.cmet.2014.04.018

McHarg S, Clark SJ, Day AJ, Bishop PN (2015) Age-related macular degeneration and the role of the complement system. Mol Immunol 67:43–50. https://doi.org/10.1016/j.molimm.2015.02.032

McLeod DS, Taomoto M, Otsuji T, Green WR, Sunness JS, Lutty GA (2002) Quantifying changes in RPE and choroidal vasculature in eyes with age-related macular degeneration. Invest Ophthalmol Vis Sci 43:1986–1993

McLeod DS, Grebe R, Bhutto I, Merges C, Baba T, Lutty GA (2009) Relationship between RPE and choriocapillaris in age-related macular degeneration. Invest Ophthalmol Vis Sci 50:4982–4991. https://doi.org/10.1167/iovs.09-3639

Metelitsina TI, Grunwald JE, DuPont JC, Ying GS, Brucker AJ, Dunaief JL (2008) Foveolar choroidal circulation and choroidal neovascularization in age-related macular degeneration. Invest Ophthalmol Vis Sci 49:358–363. https://doi.org/10.1167/iovs.07-0526

Minor RK et al (2011) SRT1720 improves survival and healthspan of obese mice. Sci Rep 1:70. https://doi.org/10.1038/srep00070

Mitter SK et al (2014) Dysregulated autophagy in the RPE is associated with increased susceptibility to oxidative stress and AMD. Autophagy 10:1989–2005. https://doi.org/10.4161/auto.36184

Moschos MM, Nitoda E, Laios K, Ladas DS, Chatziralli IP (2016) The impact of chronic tobacco smoking on retinal and choroidal thickness in Greek population. Oxidative Med Cell Longev 2016:2905789. https://doi.org/10.1155/2016/2905789

Mottet B et al (2018) Choroidal blood flow after the first intravitreal ranibizumab injection in neovascular age-related macular degeneration patients. Acta Ophthalmol 96:e783–e788. https://doi.org/10.1111/aos.13763

Moult E et al (2014) Ultrahigh-speed swept-source OCT angiography in exudative AMD. Ophthalmic Surg Lasers Imaging Retina 45:496–505. https://doi.org/10.3928/23258160-20141118-03

Mullins RF, Russell SR, Anderson DH, Hageman GS (2000) Drusen associated with aging and age-related macular degeneration contain proteins common to extracellular deposits associated with atherosclerosis, elastosis, amyloidosis, and dense deposit disease. FASEB J 14:835–846

Mullins RF, Johnson MN, Faidley EA, Skeie JM, Huang J (2011) Choriocapillaris vascular dropout related to density of drusen in human eyes with early age-related macular degeneration. Invest Ophthalmol Vis Sci 52:1606–1612. https://doi.org/10.1167/iovs.10-6476

Mullins RF et al (2014) The membrane attack complex in aging human choriocapillaris: relationship to macular degeneration and choroidal thinning. Am J Pathol 184:3142–3153. https://doi.org/10.1016/j.ajpath.2014.07.017

Muraleva NA, Kozhevnikova OS, Zhdankina AA, Stefanova NA, Karamysheva TV, Fursova AZ, Kolosova NG (2014) The mitochondria-targeted antioxidant SkQ1 restores alphaB-crystallin expression and protects against AMD-like retinopathy in OXYS rats. Cell Cycle 13:3499–3505. https://doi.org/10.4161/15384101.2014.958393

Nacarelli T, Azar A, Altinok O, Orynbayeva Z, Sell C (2018) Rapamycin increases oxidative metabolism and enhances metabolic flexibility in human cardiac fibroblasts. Geroscience. https://doi.org/10.1007/s11357-018-0030-2

Nagai N, Kubota S, Tsubota K, Ozawa Y (2014) Resveratrol prevents the development of choroidal neovascularization by modulating AMP-activated protein kinase in macrophages and other cell types. J Nutr Biochem 25:1218–1225. https://doi.org/10.1016/j.jnutbio.2014.05.015

Nagaoka T et al (2004) Alteration of choroidal circulation in the foveal region in patients with type 2 diabetes. Br J Ophthalmol 88:1060–1063. https://doi.org/10.1136/bjo.2003.035345

Nakamura S et al (2019) Nrf2 activator RS9 suppresses pathological ocular angiogenesis and hyperpermeability. Invest Ophthalmol Vis Sci 60:1943–1952. https://doi.org/10.1167/iovs.18-25745

Nanoudis S, Pikilidou M, Yavropoulou M, Zebekakis P (2017) The role of microRNAs in arterial stiffness and arterial calcification. An update and review of the literature. Front Genet 8:209. https://doi.org/10.3389/fgene.2017.00209

Nassisi M, Tepelus T, Nittala MG, Sadda SR (2019) Choriocapillaris flow impairment predicts the development and enlargement of drusen. Graefes Arch Clin Exp Ophthalmol. https://doi.org/10.1007/s00417-019-04403-1

Nguyen A, Leblond F, Mamarbachi M, Geoffroy S, Thorin E (2016) Age-dependent demethylation of Sod2 promoter in the mouse femoral artery. Oxidative Med Cell Longev 2016:8627384. https://doi.org/10.1155/2016/8627384

Ninomiya H, Inomata T (2014) Functional microvascular anatomy of the horse eye: a scanning electron microscopic study of corrosion casts. Open Journal of Veterinary Medicine 04:91–101

Nita M, Grzybowski A (2017) Smoking and eye pathologies. a systemic review. Part II. Retina diseases, uveitis, optic neuropathies, thyroid-associated orbitopathy. Curr Pharm Des 23:639–654. https://doi.org/10.2174/1381612823666170111095723

Oner RI, Karadag AS (2018) Evaluation of choroidal perfusion changes in obese patients: ocular effects of insulin resistance.

Arq Bras Oftalmol 81:461–465. https://doi.org/10.5935/0004-2749.20180088

Orosz Z et al (2007) Cigarette smoke-induced proinflammatory alterations in the endothelial phenotype: role of NAD(P)H oxidase activation. Am J Physiol 292:H130–H139

Pandian S, Jeevanesan V, Ponnusamy C, Natesan S (2017) RES-loaded pegylated CS NPs: for efficient ocular delivery. IET Nanobiotechnol 11:32–39. https://doi.org/10.1049/iet-nbt.2016.0069

Pauleikhoff D, Spital G, Radermacher M, Brumm GA, Lommatzsch A, Bird AC (1999) A fluorescein and indocyanine green angiographic study of choriocapillaris in age-related macular disease. Arch Ophthalmol 117:1353–1358

Pawlowska E, Szczepanska J, Koskela A, Kaarniranta K, Blasiak J (2019) Dietary polyphenols in age-related macular degeneration: protection against oxidative stress and beyond. Oxidative Med Cell Longev 2019:9682318. https://doi.org/10.1155/2019/9682318

Paz AA et al (2019) Premature vascular aging in guinea pigs affected by fetal growth restriction. Int J Mol Sci:20. https://doi.org/10.3390/ijms20143474

Peeters A, Magliano DJ, Stevens J, Duncan BB, Klein R, Wong TY (2008) Changes in abdominal obesity and age-related macular degeneration: the Atherosclerosis Risk in Communities Study. Arch Ophthalmol 126:1554–1560. https://doi.org/10.1001/archopht.126.11.1554

Pemp B, Schmetterer L (2008) Ocular blood flow in diabetes and age-related macular degeneration. Can J Ophthalmol 43:295–301. https://doi.org/10.3129/i08-049

Peters S et al (2007) Ultrastructural findings in the primate eye after intravitreal injection of bevacizumab. Am J Ophthalmol 143:995–1002. https://doi.org/10.1016/j.ajo.2007.03.007

Pilotto E, Midena E, Longhin E, Parrozzani R, Frisina R, Frizziero L (2019) Muller cells and choriocapillaris in the pathogenesis of geographic atrophy secondary to age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. https://doi.org/10.1007/s00417-019-04289-z

Polak K et al (2003) Choroidal blood flow and arterial blood pressure. Eye (Lond) 17:84–88. https://doi.org/10.1038/sj.eye.6700246

Polska E, Simader C, Weigert G, Doelemeyer A, Kolodjaschna J, Scharmann O, Schmetterer L (2007) Regulation of choroidal blood flow during combined changes in intraocular pressure and arterial blood pressure. Invest Ophthalmol Vis Sci 48:3768–3774. https://doi.org/10.1167/iovs.07-0307

Possek E (1905) Ueber senile. Maculaveränderung bei Arteriosklerose Ophthalmologica 13(suppl 1):771–779. https://doi.org/10.1159/000290375

Querques G et al (2012) Enhanced depth imaging optical coherence tomography in type 2 diabetes. Invest Ophthalmol Vis Sci 53:6017–6024. https://doi.org/10.1167/iovs.12-9692

Rahman W, Chen FK, Yeoh J, Patel P, Tufail A, Da Cruz L (2011) Repeatability of manual subfoveal choroidal thickness measurements in healthy subjects using the technique of enhanced depth imaging optical coherence tomography. Invest Ophthalmol Vis Sci 52:2267–2271. https://doi.org/10.1167/iovs.10-6024

Ramírez JM, Salazar JJ, de Hoz R, Rojas B, Gallego BI, Ramírez AI, Triviño A (2012) Choroidal vessel wall: hypercholesterolaemia-induced dysfunction and potential role of statins. In: Sugi H (ed) Current basic and pathological approaches to the function of muscle cells and tissues—from molecules to humans. Intech, Rijeka, Croatia, p 255

Ramrattan RS, van der Schaft TL, Mooy CM, de Bruijn WC, Mulder PG, de Jong PT (1994) Morphometric analysis of Bruch's membrane, the choriocapillaris, and the choroid in aging. Invest Ophthalmol Vis Sci 35:2857–2864

Regatieri CV, Branchini L, Carmody J, Fujimoto JG, Duker JS (2012) Choroidal thickness in patients with diabetic retinopathy analyzed by spectral-domain optical coherence tomography. Retina 32:563–568. https://doi.org/10.1097/IAE.0b013e31822f5678

Rezkallah A, Kodjikian L, Abukhashabah A, Denis P, Mathis T (2019) Hypertensive choroidopathy: multimodal imaging and the contribution of wide-field swept-source OCT-angiography. Am J Ophthalmol Case Rep 13:131–135. https://doi.org/10.1016/j.ajoc.2019.01.001

Rispoli M, Savastano MC, Lumbroso B (2018) Quantitative vascular density changes in choriocapillaris around CNV after anti-VEGF treatment: dark halo. Ophthalmic Surg Lasers Imaging Retina 49:918–924. https://doi.org/10.3928/23258160-20181203-02

Riva CE, Titze P, Hero M, Petrig BL (1997) Effect of acute decreases of perfusion pressure on choroidal blood flow in humans. Invest Ophthalmol Vis Sci 38:1752–1760

Riva CE, Geiser M, Petrig BL (2010) Ocular blood flow assessment using continuous laser Doppler flowmetry. Acta Ophthalmol 88:622–629. https://doi.org/10.1111/j.1755-3768.2009.01621.x

Rofagha S, Bhisitkul RB, Boyer DS, Sadda SR, Zhang K, Group S-US (2013) Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). Ophthalmology 120:2292–2299. https://doi.org/10.1016/j.ophtha.2013.03.046

Roos CM et al (2016) Chronic senolytic treatment alleviates established vasomotor dysfunction in aged or atherosclerotic mice. Aging Cell 15:973–977. https://doi.org/10.1111/acel.12458

Rossman MJ et al (2017) Endothelial cell senescence with aging in healthy humans: prevention by habitual exercise and relation to vascular endothelial function. Am J Physiol Heart Circ Physiol 313:H890–H895. https://doi.org/10.1152/ajpheart.00416.2017

Saito M, Ishibazawa A, Kinouchi R, Yoshida A (2018) Reperfusion of the choriocapillaris observed using optical coherence tomography angiography in hypertensive choroidopathy. Int Ophthalmol 38:2205–2210. https://doi.org/10.1007/s10792-017-0705-1

Sariyeva Ismayilov A, Esen E, Sizmaz S, Demircan AN (2019) Aflibercept therapy in eyes with neovascular age-related macular degeneration and its effect on choroidal thickness. Clin Exp Optom. https://doi.org/10.1111/cxo.12877

Sato T, Takeuchi M (2018) Pregnancy-induced hypertension-related chorioretinitis resembling uveal effusion syndrome: a case report. Medicine (Baltimore) 97:e11572. https://doi.org/10.1097/MD.0000000000011572

Saunier V et al (2018) Incidence of and risk factors associated with age-related macular degeneration: four-year follow-up from the ALIENOR study. JAMA Ophthalmol 136:473–481. https://doi.org/10.1001/jamaophthalmol.2018.0504

Schuster AK et al (2019) Choroidal thickness is associated with cardiovascular risk factors and cardiac health: the Gutenberg

Health Study. Clin Res Cardiol. https://doi.org/10.1007/s00392-019-01498-8

Seddon JM, Cote J, Davis N, Rosner B (2003) Progression of age-related macular degeneration: association with body mass index, waist circumference, and waist-hip ratio. Arch Ophthalmol 121:785–792. https://doi.org/10.1001/archopht.121.6.785

Seddon JM, Gensler G, Milton RC, Klein ML, Rifai N (2004) Association between C-reactive protein and age-related macular degeneration. JAMA 291:704–710. https://doi.org/10.1001/jama.291.6.704

Seddon JM, George S, Rosner B, Rifai N (2005) Progression of age-related macular degeneration: prospective assessment of C-reactive protein, interleukin 6, and other cardiovascular biomarkers. Arch Ophthalmol 123:774–782. https://doi.org/10.1001/archopht.123.6.774

Seddon JM et al (2016) Histopathological insights into choroidal vascular loss in clinically documented cases of age-related macular degeneration. JAMA Ophthalmol 134:1272–1280. https://doi.org/10.1001/jamaophthalmol.2016.3519

Seth A, Cui J, To E, Kwee M, Matsubara J (2008) Complement-associated deposits in the human retina. Invest Ophthalmol Vis Sci 49:743–750. https://doi.org/10.1167/iovs.07-1072

Shen ZJ, Yang XF, Xu J, She CY, Wei WW, Zhu WL, Liu NP (2017) Association of choroidal thickness with early stages of diabetic retinopathy in type 2 diabetes. Int J Ophthalmol 10:613–618. https://doi.org/10.18240/ijo.2017.04.18

Shiragami C, Shiraga F, Matsuo T, Tsuchida Y, Ohtsuki H (2002) Risk factors for diabetic choroidopathy in patients with diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol 240:436–442. https://doi.org/10.1007/s00417-002-0451-5

Sigler EJ, Randolph JC, Calzada JI, Charles S (2014) Smoking and choroidal thickness in patients over 65 with early-atrophic age-related macular degeneration and normals. Eye (Lond) 28:838–846. https://doi.org/10.1038/eye.2014.100

Sizmaz S, Kucukerdonmez C, Pinarci EY, Karalezli A, Canan H, Yilmaz G (2013) The effect of smoking on choroidal thickness measured by optical coherence tomography. Br J Ophthalmol 97:601–604. https://doi.org/10.1136/bjophthalmol-2012-302393

Skeie JM, Fingert JH, Russell SR, Stone EM, Mullins RF (2010) Complement component C5a activates ICAM-1 expression on human choroidal endothelial cells. Invest Ophthalmol Vis Sci 51:5336–5342. https://doi.org/10.1167/iovs.10-5322

Smit-McBride Z, Forward KI, Nguyen AT, Bordbari MH, Oltjen SL, Hjelmeland LM (2014) Age-dependent increase in miRNA-34a expression in the posterior pole of the mouse eye. Mol Vis 20:1569–1578

Sohn EH, Flamme-Wiese MJ, Whitmore SS, Wang K, Tucker BA, Mullins RF (2014) Loss of CD34 expression in aging human choriocapillaris endothelial cells. PLoS One 9:e86538. https://doi.org/10.1371/journal.pone.0086538

Sohn EH et al (2019) Choriocapillaris degeneration in geographic atrophy. Am J Pathol. https://doi.org/10.1016/j.ajpath.2019.04.005

Spaide RF (2016) Choriocapillaris flow features follow a power law distribution: implications for characterization and mechanisms of disease progression. Am J Ophthalmol 170:58–67. https://doi.org/10.1016/j.ajo.2016.07.023

Spaide RF, Koizumi H, Pozzoni MC (2008) Enhanced depth imaging spectral-domain optical coherence tomography. Am J Ophthalmol 146:496–500. https://doi.org/10.1016/j.ajo.2008.05.032

Spaide RF, Fujimoto JG, Waheed NK, Sadda SR, Staurenghi G (2018) Optical coherence tomography angiography. Prog Retin Eye Res 64:1–55. https://doi.org/10.1016/j.preteyeres.2017.11.003

Springo Z et al (2015) Aging exacerbates pressure-induced mitochondrial oxidative stress in mouse cerebral arteries. J Gerontol A Biol Sci Med Sci 70:1355–1359. https://doi.org/10.1093/gerona/glu244

Srour M et al (2016) Optical coherence tomography angiography characteristics of polypoidal choroidal vasculopathy. Br J Ophthalmol 100:1489–1493. https://doi.org/10.1136/bjophthalmol-2015-307892

Stalmans I et al (2011) Use of colour Doppler imaging in ocular blood flow research. Acta Ophthalmol 89:e609–e630. https://doi.org/10.1111/j.1755-3768.2011.02178.x

Straubhaar M, Orgul S, Gugleta K, Schotzau A, Erb C, Flammer J (2000) Choroidal laser Doppler flowmetry in healthy subjects. Arch Ophthalmol 118:211–215

Sugiyama T, Araie M, Riva CE, Schmetterer L, Orgul S (2010) Use of laser speckle flowgraphy in ocular blood flow research. Acta Ophthalmol 88:723–729. https://doi.org/10.1111/j.1755-3768.2009.01586.x

Sun L, Huang T, Xu W, Sun J, Lv Y, Wang Y (2017) Advanced glycation end products promote VEGF expression and thus choroidal neovascularization via Cyr61-PI3K/AKT signaling pathway. Sci Rep 7:14925. https://doi.org/10.1038/s41598-017-14015-6

Supanji SM, Hasan MZ, Kawaichi M, Oka C (2013) HtrA1 is induced by oxidative stress and enhances cell senescence through p38 MAPK pathway. Exp Eye Res 112:79–92. https://doi.org/10.1016/j.exer.2013.04.013

Synowiec E, Blasiak J, Zaras M, Szaflik J, Szaflik JP (2012) Association between polymorphisms of the DNA base excision repair genes MUTYH and hOGG1 and age-related macular degeneration. Exp Eye Res 98:58–66. https://doi.org/10.1016/j.exer.2012.02.008

Tamaki Y, Araie M, Nagahara M, Tomita K, Matsubara M (2000) The acute effects of cigarette smoking on human optic nerve head and posterior fundus circulation in light smokers. Eye (Lond) 14(Pt 1):67–72. https://doi.org/10.1038/eye.2000.15

Tan KA, Laude A, Yip V, Loo E, Wong EP, Agrawal R (2016) Choroidal vascularity index—a novel optical coherence tomography parameter for disease monitoring in diabetes mellitus? Acta Ophthalmol 94:e612-e616 doi:https://doi.org/10.1111/aos.13044

Tarantini S et al (2017) Demonstration of impaired neurovascular coupling responses in TG2576 mouse model of Alzheimer's disease using functional laser speckle contrast imaging. Geroscience. https://doi.org/10.1007/s11357-017-9980-z

Tarantini S et al. (2018a) Nrf2 deficiency exacerbates obesity-induced oxidative stress, neurovascular dysfunction, blood brain barrier disruption, neuroinflammation, amyloidogenic gene expression and cognitive decline in mice, mimicking the aging phenotype. J Gerontol A Biol Sci Med Sci:in press

Tarantini S et al (2018b) Treatment with the mitochondrial-targeted antioxidant peptide SS-31 rescues neurovascular coupling responses and cerebrovascular endothelial function and improves cognition in aged mice. Aging Cell 17. https://doi.org/10.1111/acel.12731

Tarantini S et al (2019) Nicotinamide mononucleotide (NMN) supplementation rescues cerebromicrovascular endothelial function and neurovascular coupling responses and improves cognitive function in aged mice. Redox Biol 24:101192. https://doi.org/10.1016/j.redox.2019.101192

Tchkonia T, Zhu Y, van Deursen J, Campisi J, Kirkland JL (2013) Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. J Clin Invest 123:966–972. https://doi.org/10.1172/JCI64098

Telegina DV, Korbolina EE, Ershov NI, Kolosova NG, Kozhevnikova OS (2015) Identification of functional networks associated with cell death in the retina of OXYS rats during the development of retinopathy. Cell Cycle 14:3544–3556. https://doi.org/10.1080/15384101.2015.1080399

Thomas J, Mohammad S, Charnigo R, Baffi J, Abdel-Latif A, Ziada KM (2015) Age-related macular degeneration and coronary artery disease in a VA population. South Med J 108:502–506. https://doi.org/10.14423/SMJ.0000000000000329

Thulliez M et al (2019) Correlations between choriocapillaris flow deficits around geographic atrophy and enlargement rates based on swept-source OCT. Imaging Ophthalmol Retina 3:478–488. https://doi.org/10.1016/j.oret.2019.01.024

Ting DS et al (2016) Choroidal thickness changes in age-related macular degeneration and polypoidal choroidal vasculopathy: a 12-month prospective study. Am J Ophthalmol 164(128-136):e121. https://doi.org/10.1016/j.ajo.2015.12.024

Tokarz P, Piastowska-Ciesielska AW, Kaarniranta K, Blasiak J (2016) All-trans retinoic acid modulates DNA damage response and the expression of the VEGF-A and MKI67 genes in ARPE-19 cells subjected to oxidative stress. Int J Mol Sci 17. https://doi.org/10.3390/ijms17060898

Tomassoni D, Mancinelli G, Mignini F, Sabbatini M, Amenta F (2002) Quantitative image analysis of choroid and retinal vasculature in SHR: a model of cerebrovascular hypertensive changes? Clin Exp Hypertens 24:741–752

Topcu-Yilmaz P, Akyurek N, Erdogan E (2018) The effect of obesity and insulin resistance on macular choroidal thickness in a pediatric population as assessed by enhanced depth imaging optical coherence tomography. J Pediatr Endocrinol Metab 31:855–860. https://doi.org/10.1515/jpem-2018-0079

Toth P et al (2015) Aging exacerbates hypertension-induced cerebral microhemorrhages in mice: role of resveratrol treatment in vasoprotection. Aging Cell 14:400–408. https://doi.org/10.1111/acel.12315

Treister AD, Nesper PL, Fayed AE, Gill MK, Mirza RG, Fawzi AA (2018) Prevalence of subclinical CNV and choriocapillaris nonperfusion in fellow eyes of unilateral exudative AMD on OCT angiography. Transl Vis Sci Technol 7:19. https://doi.org/10.1167/tvst.7.5.19

Tucsek Z et al (2014a) Obesity in aging exacerbates blood brain barrier disruption, neuroinflammation and oxidative stress in the mouse hippocampus: effects on expression of genes involved in beta-amyloid generation and Alzheimer's disease. J Gerontol A Biol Sci Med Sci 69:1212–1226

Tucsek Z et al. (2014b) Obesity in aging exacerbates blood-brain barrier disruption, neuroinflammation, and oxidative stress in the mouse hippocampus: effects on expression of genes involved in beta-amyloid generation and Alzheimer's disease. J Gerontol A Biol Sci Med Sci 69:1212-1226 doi: https://doi.org/10.1093/gerona/glt177 glt177 [pii]

Tucsek Z et al (2014c) Aging exacerbates obesity-induced cerebromicrovascular rarefaction, neurovascular uncoupling, and cognitive decline in mice. J Gerontol A Biol Sci Med Sci 69:1339–1352. https://doi.org/10.1093/gerona/glu080

Tucsek Z et al (2017) Hypertension-induced synapse loss and impairment in synaptic plasticity in the mouse hippocampus mimics the aging phenotype: implications for the pathogenesis of vascular cognitive impairment. Geroscience. https://doi.org/10.1007/s11357-017-9981-y

Ulas F, Celik F, Dogan U, Celebi S (2014) Effect of smoking on choroidal thickness in healthy smokers. Curr Eye Res 39:504–511. https://doi.org/10.3109/02713683.2013.850099

Ungvari Z, Csiszar A, Kaminski PM, Wolin MS, Koller A (2004) Chronic high pressure-induced arterial oxidative stress: involvement of protein kinase C-dependent NAD(P)H oxidase and local renin-angiotensin system. Am J Pathol 165:219–226

Ungvari Z, Orosz Z, Labinskyy N, Rivera A, Xiangmin Z, Smith K, Csiszar A (2007a) Increased mitochondrial H2O2 production promotes endothelial NF-kappaB activation in aged rat arteries. Am J Physiol Heart Circ Physiol 293:H37–H47

Ungvari ZI, Orosz Z, Labinskyy N, Rivera A, Xiangmin Z, Smith KE, Csiszar A (2007b) Increased mitochondrial H2O2 production promotes endothelial NF-kB activation in aged rat arteries. Am J Physiol Heart Circ Physiol 293:H37–H47

Ungvari ZI, Labinskyy N, Gupte SA, Chander PN, Edwards JG, Csiszar A (2008) Dysregulation of mitochondrial biogenesis in vascular endothelial and smooth muscle cells of aged rats. Am J Physiol Heart Circ Physiol 294:H2121–H2128

Ungvari Z et al (2009) Resveratrol attenuates mitochondrial oxidative stress in coronary arterial endothelial cells. Am J Physiol Heart Circ Physiol 297:H1876–H1881. https://doi.org/10.1152/ajpheart.00375.2009

Ungvari Z et al (2011a) Age-associated vascular oxidative stress, Nrf2 dysfunction, and NF-{kappa}B activation in the nonhuman primate Macaca mulatta. J Gerontol A Biol Sci Med Sci 66:866–875. https://doi.org/10.1093/gerona/glr092

Ungvari Z et al (2011b) Vascular oxidative stress in aging: a homeostatic failure due to dysregulation of NRF2-mediated antioxidant response. Am J Physiol Heart Circ Physiol 301:H363–H372. https://doi.org/10.1152/ajpheart.01134.2010

Ungvari ZI et al (2011c) Adaptive induction of NF-E2-related factor-2-driven antioxidant genes in endothelial cells in response to hyperglycemia. Am J Physiol Heart Circ Physiol 300:H1133–H1140. https://doi.org/10.1152/ajpheart.00402.2010

Ungvari Z et al (2017a) Cerebromicrovascular dysfunction predicts cognitive decline and gait abnormalities in a mouse model of whole brain irradiation-induced accelerated brain senescence. Geroscience 39:33–42. https://doi.org/10.1007/s11357-017-9964-z

Ungvari Z, Tarantini S, Kirkpatrick AC, Csiszar A, Prodan CI (2017b) Cerebral microhemorrhages: mechanisms, consequences, and prevention. Am J Physiol Heart Circ Physiol 312:H1128–H1143. https://doi.org/10.1152/ajpheart.00780.2016

Ungvari Z, Tarantini S, Donato AJ, Galvan V, Csiszar A (2018) Mechanisms of vascular aging. Circ Res 123:849–867. https://doi.org/10.1161/CIRCRESAHA.118.311378

Urfer SR, Kaeberlein TL, Mailheau S, Bergman PJ, Creevy KE, Promislow DE, Kaeberlein M (2017) A randomized controlled trial to establish effects of short-term rapamycin treatment in 24 middle-aged companion dogs. Geroscience 39: 117–127. https://doi.org/10.1007/s11357-017-9972-z

Uryga AK, Bennett MR (2016) Ageing induced vascular smooth muscle cell senescence in atherosclerosis. J Physiol 594: 2115–2124. https://doi.org/10.1113/JP270923

Usui S, Ikuno Y, Akiba M, Maruko I, Sekiryu T, Nishida K, Iida T (2012) Circadian changes in subfoveal choroidal thickness and the relationship with circulatory factors in healthy subjects. Invest Ophthalmol Vis Sci 53:2300–2307. https://doi.org/10.1167/iovs.11-8383

Valcarcel-Ares MN et al. (2012) Disruption of Nrf2 signaling impairs angiogenic capacity of endothelial cells: implications for microvascular aging. J Gerontol A Biol Sci Med Sci 67: 821-829 doi:https://doi.org/10.1093/gerona/glr229 glr229 [pii]

Valcarcel-Ares MN et al (2018) Obesity in aging exacerbates neuroinflammation, dysregulating synaptic function-related genes and altering eicosanoid synthesis in the mouse hippocampus: potential role in impaired synaptic plasticity and cognitive decline. J Gerontol A Biol Sci Med Sci. https://doi.org/10.1093/gerona/gly127

Van Skike CE et al (2018) Inhibition of mTOR protects the blood-brain barrier in models of Alzheimer's disease and vascular cognitive impairment. Am J Physiol Heart Circ Physiol 314: H693–H703. https://doi.org/10.1152/ajpheart.00570.2017

van Stokkum IH, Lambrou GN, van den Berg TJ (1995) Hemodynamic parameter estimation from ocular fluorescein angiograms. Graefes Arch Clin Exp Ophthalmol 233:123–130

Verstappen M, Draganova D, Judice L, Makhoul D, Papadaki M, Caspers L, Willermain F (2019) Hypertensive choroidopathy revealing malignant hypertension in a young patient. Retina 39:e12–e13. https://doi.org/10.1097/IAE.0000000000002509

Viiri J et al (2013) Autophagy activation clears ELAVL1/HuR-mediated accumulation of SQSTM1/p62 during proteasomal inhibition in human retinal pigment epithelial cells. PLoS One 8:e69563. https://doi.org/10.1371/journal.pone.0069563

Vujosevic S, Martini F, Cavarzeran F, Pilotto E, Midena E (2012) Macular and peripapillary choroidal thickness in diabetic patients. Retina 32:1781–1790. https://doi.org/10.1097/IAE.0b013e31825db73d

Vujosevic S et al (2019) Quantitative choriocapillaris evaluation in intermediate age-related macular degeneration by swept-source optical coherence tomography angiography. Acta Ophthalmol. https://doi.org/10.1111/aos.14088

Wakatsuki Y, Shinojima A, Kawamura A, Yuzawa M (2015) Correlation of aging and segmental choroidal thickness measurement using swept source optical coherence tomography in healthy eyes. PLoS One 10:e0144156. https://doi.org/10.1371/journal.pone.0144156

Wang AL, Lukas TJ, Yuan M, Neufeld AH (2008) Increased mitochondrial DNA damage and down-regulation of DNA repair enzymes in aged rodent retinal pigment epithelium and choroid. Mol Vis 14:644–651

Wang AL, Lukas TJ, Yuan M, Du N, Handa JT, Neufeld AH (2009a) Changes in retinal pigment epithelium related to cigarette smoke: possible relevance to smoking as a risk factor for age-related macular degeneration. PLoS One 4: e5304. https://doi.org/10.1371/journal.pone.0005304

Wang CY et al (2009b) Obesity increases vascular senescence and susceptibility to ischemic injury through chronic activation of Akt and mTOR. Sci Signal 2:ra11. https://doi.org/10.1126/scisignal.2000143

Wang L et al (2016) Pentraxin 3 recruits complement factor H to protect against oxidative stress-induced complement and inflammasome overactivation. J Pathol 240:495–506. https://doi.org/10.1002/path.4811

Wang J, Jiang J, Zhang Y, Qian YW, Zhang JF, Wang ZL (2019) Retinal and choroidal vascular changes in coronary heart disease: an optical coherence tomography angiography study. Biomed Opt Express 10:1532–1544. https://doi.org/10.1364/BOE.10.001532

Wei X, Kumar S, Ding J, Khandelwal N, Agarwal M, Agrawal R (2019) Choroidal structural changes in smokers measured using choroidal vascularity index. Invest Ophthalmol Vis Sci 60:1316–1320. https://doi.org/10.1167/iovs.18-25764

Whitmore SS, Sohn EH, Chirco KR, Drack AV, Stone EM, Tucker BA, Mullins RF (2015) Complement activation and choriocapillaris loss in early AMD: implications for pathophysiology and therapy. Prog Retin Eye Res 45:1–29. https://doi.org/10.1016/j.preteyeres.2014.11.005

Wong WL, Su X, Li X, Cheung CM, Klein R, Cheng CY, Wong TY (2014) Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health 2: e106–e116. https://doi.org/10.1016/S2214-109X(13)70145-1

Yamazaki T, Koizumi H, Yamagishi T, Kinoshita S (2012) Subfoveal choroidal thickness after ranibizumab therapy for neovascular age-related macular degeneration: 12-month results. Ophthalmology 119:1621–1627. https://doi.org/10.1016/j.ophtha.2012.02.022

Yang J et al (2019) Optical coherence tomography angiography analysis of the choriocapillary layer in treatment-naive diabetic eyes. Graefes Arch Clin Exp Ophthalmol 257:1393–1399. https://doi.org/10.1007/s00417-019-04326-x

Yannuzzi LA, Sorenson J, Spaide RF, Lipson B (1990) Idiopathic polypoidal choroidal vasculopathy (IPCV). Retina 10:1–8

Yoshinaga N, Arimura N, Otsuka H, Kawahara K, Hashiguchi T, Maruyama I, Sakamoto T (2011) NSAIDs inhibit neovascularization of choroid through HO-1-dependent pathway. Lab Investig 91:1277–1290. https://doi.org/10.1038/labinvest.2011.101

Yu DY, Cringle SJ (2001) Oxygen distribution and consumption within the retina in vascularised and avascular retinas and in animal models of retinal disease. Prog Retin Eye Res 20:175–208

Zeng S et al (2016) Molecular response of chorioretinal endothelial cells to complement injury: implications for macular degeneration. J Pathol 238:446–456. https://doi.org/10.1002/path.4669

Zhang W, Liu H, Al-Shabrawey M, Caldwell RW, Caldwell RB (2011) Inflammation and diabetic retinal microvascular complications. J Cardiovasc Dis Res 2:96–103. https://doi.org/10.4103/0975-3583.83035

Zhang QY et al (2016) Overweight, obesity, and risk of age-related macular degeneration. Invest Ophthalmol Vis Sci 57:1276–1283. https://doi.org/10.1167/iovs.15-18637

Zhang Q et al (2018a) A novel strategy for quantifying choriocapillaris flow voids using swept-source OCT angiography. Invest Ophthalmol Vis Sci 59:203–211. https://doi.org/10.1167/iovs.17-22953

Zhang Y, Liao J, Zhang L, Li S, Wu Y, Shi L (2018b) BKCa channel activity and vascular contractility alterations with hypertension and aging via beta1 subunit promoter methylation in mesenteric arteries. Hypertens Res 41:96–103. https://doi.org/10.1038/hr.2017.96

Zhao Z, Chen Y, Wang J, Sternberg P, Freeman ML, Grossniklaus HE, Cai J (2011) Age-related retinopathy in NRF2-deficient mice. PLoS One 6:e19456. https://doi.org/10.1371/journal.pone.0019456

Zhdankina AA, Fursova A, Logvinov SV, Kolosova NG (2008) Clinical and morphological characteristics of chorioretinal degeneration in early aging OXYS rats. Bull Exp Biol Med 146:455–458

Zheng F et al (2019) Age-dependent changes in the macular choriocapillaris of normal eyes imaged with swept-source optical coherence tomography angiography. Am J Ophthalmol 200:110–122. https://doi.org/10.1016/j.ajo.2018.12.025

Zhuang P, Shen Y, Lin BQ, Zhang WY, Chiou GC (2011) Effect of quercetin on formation of choroidal neovascularization (CNV) in age-related macular degeneration(AMD). Eye Sci 26:23–29. https://doi.org/10.3969/j.issn.1000-4432.2011.01.006