Dyslipidemia in retinal metabolic disorders

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Abstract

The light-sensitive photoreceptors in the retina are extremely metabolically demanding and have the highest density of mitochondria of any cell in the body. Both physiological and pathological retinal vascular growth and regression are controlled by photoreceptor energy demands. It is critical to understand the energy demands of photoreceptors and fuel sources supplying them to understand neurovascular diseases. Retinas are very rich in lipids, which are continuously recycled as lipid-rich photoreceptor outer segments are shed and reformed and dietary intake of lipids modulates retinal lipid composition. Lipids (as well as glucose) are fuel substrates for photoreceptor mitochondria. Dyslipidemia contributes to the development and progression of retinal dysfunction in many eye diseases. Here, we review photoreceptor energy demands with a focus on lipid metabolism in retinal neurovascular disorders.

Keywords dyslipidemia; FGF21; photoreceptor; retinal metabolism; β-oxidation

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See the Glossary for abbreviations used in this article.

Photoreceptor biology and retinal lipid use

Energy demands of the retina

Vertebrate retinas are light-sensitive neural tissues. Rod and cone photoreceptors of the retina utilize photosensitive pigments to convert photons into electrical impulses (phototransduction; Arshavsky et al, 2002). The retina uses more energy in the dark than in light to maintain the “dark current”. In the light, there is an ongoing outward potassium (K+) current through non-gated K+-selective channels, which induces sodium (Na+) ion channel closure and hyperpolarization of photoreceptors. In the light, glutamate release is suppressed and neurons are excited, leading to phototransduction.

By contrast, in the dark, perpetually open (Na+) channels allow a steady flow of ions into the cell, thereby resulting in cellular depolarization (dark current) and glutamate release, which inhibits photoreceptor excitation (Stryer, 1991). More than half of photoreceptor energy (adenosine triphosphate, ATP) is used by Na+/K+ ATPase ion pumps to maintain intracellular ion levels (Hagins et al., 1970; Okawa et al., 2008).

The replacement of shed photoreceptor outer segments is also energy intensive (Du et al., 2015; Ng et al., 2015). Photoreceptors maintain a consistent outer segment length by balancing disk shedding and assembly (Young, 1967; Young & Bok, 1969; LaVail, 1976). Continuous shedding of “used” outer segments containing lipids damaged by light and oxidation is critical for the maintenance of normal retinal function (Fliesler & Anderson, 1983) perhaps as a fuel source scavenged by retinal pigment epithelium (RPE). Other lipid fuel sources may be serum lipids processed by Müller glial cells, and lipids synthesized at a high rate in the inner segments (Wang et al., 2005; Kevany & Palczewski, 2010; Casson et al., 2013). The details of lipid processing in the retina are not fully defined; however, some lipids are used as fuel/energy sources while the others, which cannot be synthesized, are recycled (Chen & Anderson, 1993; Mukherjee et al., 2007).

Fuel sources for the retina to make ATP

ATP, used to transfer energy, is generated via two metabolic pathways: glycolysis in the cytoplasm and oxidative phosphorylation (OXPHOS) in mitochondria. Glycolysis converts one glucose to two pyruvates (yielding 2 ATP). In the presence of oxygen, pyruvate is further converted to acetyl-CoA, which enters the Krebs cycle...
Limited.

The catabolic process that breaks down fatty acid molecules to generate acetyl-CoA, which in mitochondria enters the citric acid cycle for energy (ATP) production. β-oxidation occurs in the peroxisomes and mitochondria but in peroxisomes no ATP is produced.

Glycolysis
The process of breaking down glucose into pyruvic acid for energy production.

Neovascularization
Uncontrolled blood vessel growth in the eye. New vessels are often fragile and leaky, causing blindness in the late stage of neovascular retinal diseases.

Oxidative phosphorylation
The process to form ATP through the transfer of electrons from NADH or FADH2 to oxygen by a series of electron carriers in the mitochondrial membrane.

Photoreceptors
A retinal neuronal cell that is capable of visual phototransduction, converting light signals to electric signals. They possess the highest density of mitochondria in the body.

Retinal pigment epithelium
The pigmented cell layer provides nutrients and clears wastes for photoreceptors.

Cones versus rods in energy consumption and production
Cones are more metabolically active than rods (Nikonov et al., 2006; Okawa et al., 2008). In darkness, cones and rods have comparable ATP expenditures, and similar dark currents. However, in the light, rod responses are suppressed, thereby reducing total retinal energy consumption by >75%. But cones do not saturate in bright light so the energy demand remains high. Even when cones are maximally bleached, they still have a baseline need that is more than 50% of the dark current (Nikonov et al., 2006).

It is essential to coordinately control the synaptic terminal ATP production and Ca2+ concentration to regulate transient exocytosis and ensure recovery for the next action potential (Johnson et al., 2007). Cones increase ATP production by increasing the number of mitochondria (about twofold more than rods) and mitochondrial cristae surface membrane area (about threefold more than rods; Perkins et al., 2003). Cones lower Ca2+ levels during light adaption and increase their response kinetics by utilizing a low affinity/high turnover Na+-Ca2+ exchanger, while rods use high affinity/low turnover plasma membrane Ca2+ ATPase (Johnson et al., 2007). The knowledge of fuel use in cones and rods is still limited. Loss of hexokinase 2 (a key aerobic glycolysis enzyme) in rods inhibits rod function but not rod survival, while cone hexokinase 2 loss does not affect photoreceptor function (Petit et al., 2018), suggesting that aerobic glycolysis is not necessary for photoreceptor survival, but is a metabolic choice to maintain neuronal function.

Peroxisome fatty acid β-oxidation
Fatty acid degradation, through β-oxidation, takes place in both mitochondria and peroxisomes in mammals. Peroxosomal degradation breaks down long-chain fatty acids (producing no ATP), into shorter chain fatty acids that can be used by mitochondria for further oxidation to acetyl-CoA, which enters the Krebs cycle to produce ATP (Fig 1; Poirier et al., 2006; Schrader et al., 2015).

Very long-chain monocarboxylic (≥22 carbons) and long-chain dicarboxylic fatty acids are oxidized only in peroxisomes (Poirier et al., 2006). In addition, polyunsaturated fatty acids are also oxidized faster in peroxisomes than in mitochondria (Hiltunen et al., 1986). Long-chain fatty acids (13–21 carbons) must first be conjugated to either coenzyme A (peroxisomes) or carnitine (mitochondria) outside the organelle and then imported into organelles by ABC class D transporters (peroxisomes) or carnitine-acylcarnitine translocases (mitochondria). Fatty acids are subsequently degraded by β-oxidation, which involves four enzymes and leads to the release of acetyl-CoA, FADH2, and NADH (Fig 1). Acetyl-CoA enters the Krebs cycle where it is oxidized into CO2 and H2O, and generates additional FADH2 and NADH. FADH2 and NADH from β-oxidation and the Krebs cycle are then used for ATP production by the mitochondrial electron transport chain.

Retinal lipid composition
A rod photoreceptor has three functional domains: (i) synaptic terminal, (ii) inner segment, and (iii) outer segment (Fig 2A). One retinal lipid source comes from shed photoreceptor outer segments. Rod outer segments consist of stacks of photosensitive disks, which contain proteins (predominantly photosensitive...
lipids contain an abundance of long-chain polyunsaturated fatty acid "tails", which can be cleaved to provide fatty acids. Retinal phospholipids (90% pigments) and lipids (Fliesler & Anderson, 1983), predominantly phospholipids (90–95% of total lipids) and cholesterols (4–6%) (Daemen, 1973).

Phospholipids consist of a phosphate “head” with fatty acid “tails”, which can be cleaved to provide fatty acids. Retinal phospholipids contain an abundance of long-chain polyunsaturated fatty acid (LCPUFA, ~45% of total phospholipids), saturated fatty acid (SFA, ~37% of total phospholipids), and monounsaturated fatty acid (MUFA, ~10% of total phospholipids; Schneebelen et al, 2009). While fatty acid composition analysis in the human retina is limited, the retina of a healthy senior is composed of 16.7% ω-6 LCPUFA, 16.6% ω-3 LCPUFA, 42.4% SFA, and 19.2% MUFA (Acar et al, 2012).

During postnatal development, rod lipid composition transitions from rich in saturated fatty acids to rich in unsaturated fatty acids (Scott et al, 1988). The increasing unsaturated lipid portion of the maturing retina is biased for selective accretion of docosahexaenoic acid (DHA) while arachidonic acid (AA) levels are reduced (Alessandri & Goustard-Langelier, 2001). Docosahexaenoic acid accounts for approximately 35% of total phospholipid FA in the retina and 50% in rod outer segments (Stinson et al, 1991), while AA accounts for approximately 8–10% of total phospholipid fatty acid in rod outer segments.

Transcriptional control of retinal cell functions

The retina contains more than 10 different cell types that contribute uniquely to phototransduction (Fig 2B), requiring a highly individualized gene expression pattern. The emergence of single-cell transcriptomics (scRNAseq) provides insight into the metabolism of individual cells within the retina, which is likely to lead to a greater understanding of the cellular metabolic influences on neovascularization. scRNAseq examines the combinatorial expression of genes, which leads to the clustering of retinal cells according to their gene expression patterns (Fig 3A; Macosko et al, 2015). The scRNAseq approach is very efficient in discovering new retinal cell subtypes (Shekhar et al, 2016; Rheaume et al, 2018). Beside identity markers associated with specialized functions (like phototransduction in photoreceptors; Fig 3B), different retinal cells regulate specific metabolic genes at the transcriptional level to perform certain functions. However, caution is required when analyzing transcriptomic data from rod photoreceptors, as this cell type has low basal gene expression. The scRNAseq approach is very efficient in discovering new retinal cell subtypes (Shekhar et al, 2016; Rheaume et al, 2018). Beside identity markers associated with specialized functions (like phototransduction in photoreceptors; Fig 3B), different retinal cells regulate specific metabolic genes at the transcriptional level to perform certain functions. However, caution is required when analyzing transcriptomic data from rod photoreceptors, as this cell type has low basal gene expression (Macosko et al, 2015), which is correlated with a uniquely closed chromatin architecture compared to cones (Hughes et al, 2017). Moreover, rods are very sensitive to single-cell dissociation since the end part of rod outer segments is buried in the RPE and may be separated from the main cell body during retinal digestion. Single-nucleus RNAseq may therefore be more suitable to assess the rod transcriptome in situ (Habib et al, 2017).

Dyslipidemia in neurovascular retinopathies

Metabolic dysfunction and dyslipidemia produce deleterious effects on the eye (Folz & Trobe, 1991; Chang & Wu, 2013; Yonekawa et al, 2015). Dyslipidemia is characterized by an abnormal circulating lipid profile including triglycerides, cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), or polyunsaturated fatty acids. In premature infants, high triglycerides are associated with increased severity of retinopathy of prematurity (ROP; Sinclair...
Total amount of lipids in stacks of rod photosensitive discs contains 90–95% phospholipids and 4–6% cholesterol.

Daemen, 1973

Percentage of FAs in total amount of retinal phospholipids:
- 45% LCPUFA
- 37% SFA
- 10% MUFA

Schnebelen et al, 2009

Percentage of FAs in retina of a healthy senior:
- 16.7% ω-6 LCPUFA
- 16.6% ω-3 LCPUFA
- 42.4% SFA
- 19.2% MUFA

Acar et al, 2012

Figure 2.
The α-6 LCPUFA, arachidonic acid, level is also significantly lower in severe ROP in premature infants at postmenstrual age of 32 weeks (Lofqvist et al., 2018). Although the results from many studies exploring the associations between diabetic retinopathy (DR) and lipid abnormality are inconsistent, one study found that high circulating LDL cholesterol levels are a significant risk factor for diabetic macular edema and retinal hard exudates (Chang & Wu, 2013). In advanced age-related macular degeneration (AMD), high HDL cholesterol levels are implicated in the disease pathogenesis in European and Asian populations (Cougnard-Gregoire et al., 2014; Fan et al., 2017). A recent European Eye Epidemiology consortium study found that HDL is associated with an increased risk of AMD and drusen development, while triglycerides are associated with a decreased risk of AMD and drusen development. Variants in lipid genes and their association with cholesterol levels are unclear. The cholesterol ester transfer protein risk variant (rs17231506) for AMD was associated with increased HDL cholesterol levels, but lipase C risk variants (rs2043085, rs2070895) were negatively linked with HDL cholesterol levels (Colijn et al., 2019). In retinitis pigmentosa (RP) versus control patients, decreased plasma α-3 and α-6 LCPUFA are found (Converse et al., 1983; Holman et al., 1994).
Dietary modulation of the lipid supply can positively influence diseases with pathological neovascularization such as ROP, AMD, and DR in patients and in animal models of retinopathy (Gong et al., 2017). Photoreceptor energy demands drive vessel growth (Sapienza, 2012; Joyal et al., 2016, 2018; Fu et al., 2018), while photoreceptor-derived oxidative stress and inflammation lead to retinal vascular damage or regression (Kern & Berkowitz, 2015; Sun et al., 2017). Retinal disorders such as ROP, DR, AMD, RP, and Zellweger spectrum disorder (ZSSD) are associated with disturbances in photoreceptor activity, which may further affect the blood supply and induce pathological vascular remodeling during disease progression.

Retinopathy of prematurity
Retinopathy of prematurity is a leading cause of blindness in children worldwide (Hellstrom et al., 2013). After preterm birth, the immature retinal vasculature growth is suppressed, secondary to oxygen supplementation, loss of growth factors provided in utero, and metabolic dysregulation. As the neural retina slowly matures, metabolic demand increases, particularly in photoreceptors. The relatively avascular retina becomes hypoxic and deprived of nutrients, driving vascular growth factor expression and subsequent neovascularization. The onset of neovascular ROP at ~32 weeks postmenstrual age coincides with the rapid development and increased metabolic demand of rods (Fulton et al., 1999; Hansen et al., 2017). This observation is supported by rodent studies. In mice, hyperglycemia (a key risk factor for ROP) triggers photoreceptor metabolic alterations and delays retinal vascular development (Fu et al., 2018). In rats, early photoreceptor dysfunction also predicts subsequent neovascularization (Akula et al., 2010).

In premature infants, there is a ~44% decrease in DHA after preterm birth, and serum DHA levels remain low for at least 4 weeks (Lapillonne & Jensen, 2009; Martin et al., 2011). Severe ROP is reduced in premature infants (GA < 32 weeks) receiving ω-3 LCPUFA versus parenteral soybean and olive oil supplementation (Pawlik et al., 2014). There is also an association between low serum levels of ω-6 LCPUFA (AA) and later development of ROP (Lofqvist et al., 2018). In mice, dietary ω-3 versus ω-6 LCPUFA suppresses retinal neovascularization (Connor et al., 2007; Fu et al., 2017b). Further studies on the impact of DHA and AA and other lipids on photoreceptor function and metabolism are needed.

Diabetic retinopathy
In addition to ROP, DR is also associated with abnormal energy metabolism. DR, a significant complication of diabetes, starts with vascular loss (non-proliferative DR), followed by neovascularization (proliferative DR). In DR, abnormalities in retinal neural responses occur early before vascular abnormalities are seen, suggesting that neuronal metabolic demands drive vessel growth (De Benedetto et al., 2014; Pescosolido et al., 2015). Mitochondrial dysfunction is accompanied by oxidative stress (Barot et al., 2011), which induces a wide range of microvascular abnormalities throughout the course of DR (Kowluru & Mishra, 2015). In diabetic mice, photoreceptors with their high density of mitochondria contribute to the majority of induced retinal oxidative stress and inflammation, which is associated with retinal vessel loss in DR (Du et al., 2013; Liu et al., 2016; Tonade et al., 2016).

There is clear evidence of neurovascular cross talk in DR. In patients with both proliferative DR and progressive photoreceptor degeneration (RP), spontaneous neovascular regression occurs when photoreceptor loss from RP becomes clinically evident (Lahdenranta et al., 2001). As there is higher retinal energy consumption in darkness versus light, illuminating the retina with 507-nm light during sleep might reduce the risk of DR progression (Sivaprasad & Arden, 2016). In fact, exposure to a 505-nm light during sleep leads to the regression of macular edema and improved visual function in early DR patients (Arden et al., 2011). However, a recent multi-year phase 3 clinical trial (CLEOPATRA) of wearing a light mask at night in DR patients failed to support the hypothesis that decreasing energy needs for photoreceptor “dark current” would inhibit diabetic macular edema (Sivaprasad et al., 2018). Dyslipidemia is associated with more retinal abnormalities and faster progression of DR (Sacks et al., 2014; Hammer & Busik, 2017). Increasing dietary PUFA versus saturated FA is associated with a reduced incidence and severity of DR (Sasaki et al., 2015). A Mediterranean diet with olive oil or nut supplements showed an additional 48% decrease in incidence of DR in type 2 diabetes when the diet also included ≥ 500 mg/day DHA plus eicosapentaenoic acids, or at least 2 weekly servings of oily fish (Sala-Vila et al., 2016). In murine models of early DR, fish oil and a ω-3 LCPUFA-enriched diet preserve retinal neuronal function (Yee et al., 2010; Sapihea et al., 2012). Linoleic acid- versus saturated-fat-rich diets inhibit progression of diabetic microangiopathy (Houtsmuller et al., 1980). Not all lipids appear to affect DR. The absence of acid sphingomyelinase (ASM) in ASM−/− mice or inhibition of ASM activity by DHA inhibited the diabetes-induced degeneration of retinal capillaries (Opreanu et al., 2011). Studies show no association between total cholesterol or high-density lipoprotein and incidence of DR or macular edema in long-term type 1 diabetes (Klein et al., 2015). Taken together, these findings suggest a link between some aspects of dyslipidemia and DR progression. As such, dietary modulation of specific lipids may help prevent or treat DR.

Age-related macular degeneration
The human macula, critical for central vision, consists of a small cone-dominated fovea surrounded by a rod-dominated parafovea. AMD particularly affects the macula and is the leading cause of legal blindness in the elderly. Clinically, AMD is classified as either dry or wet (neovascular) based on the absence or presence of pathologic blood vessels invading into the photoreceptor layer (Ambati & Fowler, 2012). Current treatments mainly target neovascular AMD; no drugs are approved by the U.S. Food and Drug Administration for dry AMD.

Mitochondrial morphological changes and dysfunction occur in degenerating macular cones and likely contribute to AMD progression (Barron et al., 2001; Litts et al., 2015). Mitochondrial abnormalities can cause overproduction of superoxide radicals, primarily in the electron transport chain (Fig 4; Selivanov et al., 2011). Oxidative stress causes damage to cell structures, lipids, proteins, and DNA, and particularly affects metabolically active neuronal cells, like photoreceptors. Photoreceptor loss is seen in AMD donor eyes (Curcio et al., 1996). In aging and in early AMD, there is a prominent decline in rod-mediated ERG sensitivity (Jackson et al., 2002). Additionally, cone dysfunction can predict early AMD and is a reliable measure of AMD progression (Hogg & Chakravarthy, 2006).
As well as mitochondrial dysfunction, dyslipidemia is also implicated in dry AMD pathogenesis (Gong et al., 2017). The most established clinical hallmark of dry AMD is the formation of subretinal drusen, extracellular deposits rich in lipid and protein (Hageman et al., 2001). Although the exact mechanism of drusen formation is unclear, Bruch’s membrane, found between the choriocapillaris and RPE, thickens due to accumulation of oxidized lipids, lipid-related molecules, and inflammatory debris preceding drusen formation. This slows down nutrient and waste transportation between RPE cells and choroidal vessels, leading to malfunction of RPE cells (Sarks et al., 2007; Curcio, 2018a,b).

Epidemiologic studies link increased HDL levels with AMD across different populations (Fan et al., 2017; Colijn et al., 2019). Genome-wide association studies also identify several HDL cholesterol genes associated with AMD susceptibility, including genes encoding ATP-binding cassette transporter A1 (ABCA1), cholesteryl ester transfer protein (CETP), apolipoprotein E (APOE), hepatic lipase C (LIPC), and lipoprotein lipase precursor (LPL) (Chen et al., 2010; Neale et al., 2010; Fritsche et al., 2013, 2016). Impaired ABCA1-mediated cholesterol efflux in mouse RPE cells or subretinal macrophages induces lipid accumulation and retinal degeneration (Lyssenko et al., 2018; Storti et al., 2019). ApoE is important for the transport of lipids across cell membranes and is highly expressed by RPE cells. ApoE-null mice exhibit raised serum triglycerides and cholesterol. Thickened Bruch’s membrane, and accumulation of lipid deposits in the basal RPE and Bruch’s membrane are seen in ApoE-null and genetically engineered ApoE-mutated mice (Malek et al., 2005; Edwards & Malek, 2007). However, how CETP, LIPC, and LPL link to AMD pathogenesis is still unclear.

High plasma levels of high-density lipoprotein cholesterol are associated with an increased risk for advanced AMD (Fan et al., 2017). A 42% decreased incidence of AMD is associated with high plasma ω-3 LCPUFA levels in a large cohort study of US female health professionals (Christen et al., 2011). A 30% decrease in central geographic atrophy development and a 50% decrease in neovascular AMD development are found in participants with high versus low ω-3 LCPUFA intake in the Age-Related Eye Disease Study (AREDS) (Sangiovanni et al., 2009). There was no further reduced risk of progression to advanced AMD in participants with ω-3 LCPUFA supplementation in the AREDS2 study; however, the participants had a much higher baseline level of circulating ω-3 LCPUFA in comparison with those in the first AREDS (Souied et al., 2015). It also may be that other fats in fish (alone or in combination with DHA) are required to suppress AMD progression. In a Japanese population with a high baseline intake of fish oil, there was no significant association between serum ω-3 LCPUFA levels and AMD progression (Kabasawa et al., 2011). Dietary ω-3 LCPUFA inhibits neovascularization in a laser-induced wet AMD mouse model and in mice lacking the very low-density lipoprotein receptor (VLDLR) (Fu et al., 2017b). The lack of VLDLR promotes the development of neovascularization originating from the superficial retinal vasculature similar to some neovascularization seen in AMD. The lack of VLDLR leads to intracellular lipid and glucose insufficiency which drives neovascularization, including retinal angiomatous proliferation and choroidal neovascularization (Joyal et al., 2016). Therefore, both clinical and experimental investigations support the concept that dyslipidemia may be associated with AMD progression.

Retinitis pigmentosa

Retinitis pigmentosa is also associated with abnormal energy metabolism. There are ~60 genes (to date), mostly expressed in rods, which are involved in RP retinal degenerations (Ali et al., 2017). In RP, the initial loss of rods results in night blindness and

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Figure 4. Schematics of electron transport chain (ETC).

The ETC passes electrons from NADH and FADH₂ to protein complexes (I to V) and mobile electron carriers coenzyme Q (CoQ) and cytochrome c (Cyt c). Oxygen (O₂) is the final electron recipient. The transfer of electrons generates energy to pump protons (H⁻) from the mitochondrial matrix into the intermembrane space. An electrochemical proton gradient is created across the inner mitochondrial membrane, allowing the protons to pass through complex V (ATP synthase) to generate adenosine triphosphate (ATP) from adenosine diphosphate (ADP). Complex I, NADH coenzyme Q reductase, complex II, succinate dehydrogenase, complex III, cytochrome bc₁, complex complex IV, cytochrome c oxidase. Complex I and complex III are the main sites for superoxide (ROS) formation.
loss of peripheral vision; central (cone) vision is initially preserved but eventually central vision is also lost, secondary to a bystander effect (Punzo et al., 2009; Ait-Ali et al., 2015). In mouse models of RP, 34.9% of gene expression changes following cone loss are associated with cellular metabolism (Punzo et al., 2009), suggesting that improving fuel sources (perhaps such as lipids for FA β-oxidation) may improve cone metabolism. Mathematical models predict that preventing a 1–2% decrease in nutrients can permanently halt cone death even when 90% have already died (Camacho et al., 2016). Therefore, improving nutrient availability is a reasonable general approach to increase cone survival in RP. In RP patients, reduced ocular blood flow is also described as possibly associated with a decreased neuronal demand for nutrient supply (Falsini et al., 2011). Further studies are needed to establish the link between retinal vascular changes at different stages of RP.

**Zellweger syndrome spectrum disorders**

Zellweger syndrome spectrum disorders (ZSSD), including Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease (Smith et al., 2016), are caused by defects in any of the peroxisomal PEX genes (Crane, 2014), resulting in peroxisomal lipid metabolic dysfunction. As peroxisomes break down long-chain fatty acids to shorter length chains that can be used in mitochondria, deficits in PEX genes often also result in mitochondrial dysfunction. In ZSSD, the central nervous system is severely affected (Vamecq et al., 2014), producing unique ocular deficits including pigmentary retinopathy and optic atrophy, corneal opacification, cataract, and glaucoma (Folz & Trobe, 1991). In addition, attenuated retinal vasculature and macular edema are reported in infantile Refsum disease (Pakzad-Vaezi & Maberley, 2014).

Mitochondrial perturbation rapidly occurs following the loss of functional peroxisomes (Salpietro et al., 2015; Schrader et al., 2015). Very long-chain fatty acids (VLCFAs) accumulate in ZSSD; however, DHA (22:6ω3) is reduced in the plasma and brain (Poulos et al., 1986; Harding et al., 1999). Docosahexaenoic acid treatment maintains visual acuity and retinal function in patients with peroxisome biogenesis disorders (Noguer & Martinez, 2010). Over-accumulation of VLCFAs is also found in mouse models of peroxisomal biogenesis defects (Baes, 2000; Baes & Van Veldhoven, 2012). VLCFAs may affect membrane properties (Sassa & Kihara, 2014), and defects in the breakdown of VLCFAs may also cause substrate shortage for mitochondrial fatty acid β-oxidation.

**Pathways modifying metabolic lipid use**

Peroxisome proliferator-activated receptor-alpha (PPARα) and PPARγ are nuclear receptors involved in modulating lipid metabolic homeostasis. PPARα controls lipoprotein lipase expression and triglyceride metabolism, while PPARγ upregulates enzymes involved in steps of fatty acid metabolism like fatty acid entry into mitochondria and peroxisome (Gervois et al., 2000). Genetic deficiency of PPARα in mice leads to a decrease in lipid transporters and retinal degeneration (Pearsall et al., 2017). PPARγ is required for ω-3 LCPUFA-induced attenuation of mouse retinal neovascularization (Stahl et al., 2010). PPARγ coactivator-α (PGC-1α) regulates mitochondrial biogenesis and respiration (Alaynick, 2008). High-fat diet-exposed mice are more likely to develop AMD-like phenotypes with lack of PGC-1α (Zhang et al., 2018). PGC-1α activation increases RPE metabolism and protects against oxidative damage (Satish et al., 2018). Therefore, PPARα, PPARγ, and PGC-1α may modulate retinal lipid metabolism and therefore be pathways to manipulate in disease treatment.

Cyclooxygenases (COX), lipoxygenases (LOX), and cytochromes P450 (CYP)-mediated LCPUFA metabolism is important in regulating ocular inflammation, particularly through the LOX and CYP pathways (Gong et al., 2017). Inhibiting COX does not affect proliferative retinopathy (Sapieha et al., 2011). LOX ω-3 LCPUFA metabolites show anti-inflammatory and anti-angiogenic effects, while LOX ω-6 LCPUFA metabolites are pro-inflammatory and pro-angiogenic (Sapieha et al., 2011). However, both CYP2C8 ω-3 and ω-6 LCPUFA metabolites are pro-angiogenic and inhibition of CYP2C8 decreases ocular neovascularization (Shao et al., 2014; Gong et al., 2016a,b).

**Genetic association with retinopathies**

Understanding genetic susceptibility to ocular disorders may help understand disease mechanisms. In premature infants, gene mutations in vascular endothelial growth factor (VEGF) and insulin growth factor 1 (IGF1) are associated with advanced ROP (Holmstrom et al., 2007). The association of VEGF and IGF1 with ROP is further identified clinically and in animal models (Hellstrom et al., 2013). Genetics in DR has been widely explored. Mutations in metabolic genes such as aldose reductase, endothelial nitric oxide synthase (eNOS), receptor for advanced glycosylation end product (RAGE), adiponectin, peroxisome proliferator-activated receptor α and γ, and superoxide dismutase 2 (MnSOD), growth factors like VEGF, and erythropoietin (EPO), as well as inflammatory factors like complement factor H (CFH) and CFB, interleukin 6 and interleukin 10, have a positive association with DR (Hampton et al., 2015). Genome-wide association studies for diabetic macular edema identify a new associate single nucleotide polymorphism in rs1990145 on chromosome 2 (within the second intron of the mitochondrial ribosomal protein L19, MRPL19; Graham et al., 2018). The function of MRPL19 is unclear but other MRP genes including MRPL9 and MRPL23 are associated with retinitis pigmentosa (Kenmochi et al., 2001). Increasing evidence suggests a potential role of noncoding RNAs in regulating retinal inflammation during DR development (Gong & Su, 2017).

Delayed rod-mediated dark adaption, the first functional biomarker for early AMD, is observed for both the age-related maculopathy susceptibility 2 (ARMS2) A69S variant and the CFH Y402H variant in AMD patients. In healthy participants with normal macular function, the ARMS2 A69S variant also was associated with delayed rod-mediated dark adaption (Mullins et al., 2019). In three population-based studies, the Rotterdam Study, the Beaver Dam Eye Study, and the Blue Mountains Eye Study, single nucleotide polymorphisms in the genes ARMS2, CFH, and complement factor H-related 5 (CFHR5) significantly increase the risk of late AMD (Buitendijk et al., 2013). In AMD patients with CFH and ARMS2 risk alleles, the treatment response to antioxidants is compromised (Awh et al., 2015). The CFH Y402H variant also seems to limit the effect of dietary DHA supplementation on CNV (Merle et al., 2015).
Potential therapeutic targets

Anti-vascular endothelial growth factor (VEGF) agents are the primary treatment for pathological retinal vessel growth in eye diseases (Kluftas & Chan, 2015; Bakri et al., 2019). However, anti-VEGF treatment is not always effective (Lux et al., 2007; Nigam et al., 2008) and may remain in systemic circulation up to a few months after a single intravitreal injection (Moorthy & Cheung, 2009; Ueta et al., 2009; Hapani et al., 2010; Bressler et al., 2012; Jalali et al., 2013; Avery et al., 2014). VEGF is an important growth factor to neurons and blood vessels. Therefore, inhibition of VEGF may affect normal neurovascular function.

Since photoreceptor metabolic needs drive neovascularization, improved retinal lipid metabolism might be another strategy to prevent or treat neurovascular retinal diseases. Increasing lipid β-oxidation by hormonal and transcriptional factor regulation, as well as dietary intervention, may protect retinal function and decrease the demand for neovessels. Targeting dysmetabolism-induced inflammatory responses may also suppress neovascularization.

**Fibroblast growth factor (FGF21), lipid metabolism, and autophagy**

Since modulation of retinal metabolism may help restore energy homeostasis to prevent signaling for blood vessel recruitment and therefore prevent neovascularization, the end cause of neurovascular diseases, it is important to assess potential interventions that increase glucose uptake or increase fatty acid oxidation to improve energy homeostasis. A novel candidate for improved lipid metabolism is FGF21. FGF21 is a key metabolic regulator of lipid and glucose use (Kharitonenkov & Larsen, 2011; Lin et al., 2012; Markan et al., 2014). In type 2 diabetes, FGF21 decreases body weight and improves the lipid profile (Gaich et al., 2013; Talukdar et al., 2016). In obese type 2 diabetic mice, FGF21 lowers plasma triglycerides by lipoprotein catabolism in adipose tissue and maintains adipocyte phospholipid homeostasis (Foltz et al., 2012; Schlein et al., 2016; Ye et al., 2016; Stanislaus et al., 2017). FGF21 also increases lipid use in response to amino acid starvation (De Sousa-Coelho et al., 2013). FGF21 functions through modulating the activities of PPAR and PGC-1α. FGF21 is crucial for PPARα agonists to ameliorate metabolic disorders in obese mice (Goto et al., 2017). FGF21 regulates PPARγ activity and controls body fat (Dutchak et al., 2012). FGF21 also induces PGC-1α to modulate glucose and fatty acid metabolism during starvation (Potthoff et al., 2009).

In diabetic mice with insulin deficiency, FGF21 enhances retinal antioxidant defense systems, reduces pro-inflammatory cytokines, restores disorganized cone photoreceptor segments, and improves retinal function (Fu et al., 2018). FGF21 also regulates adiponectin (APN) production and secretion, and APN is key in mediating FGF21 modulation of glucose and lipid metabolism in mice (Holland et al., 2013; Lin et al., 2013). FGF21, mediated by APN which is associated with a number of metabolic retinal disorders (Fu et al., 2016), inhibits ocular neovascularization in mice (Fu et al., 2017a). FGF21 also increases APN secretion to diminish accumulation of ceramides in obese animals (Holland et al., 2013). Ceramide contributes to the development of DR and thus, modulating ceramide pathway may protect against DR progression (Fox et al., 2006; Opreanu et al., 2011).

Autophagy is induced in under stress (nutrient starvation, infection, or excess reactive oxygen species and recycles cytosolic components to remove damaged and dysfunctional cellular material to maintain cellular homeostasis, provide fuel, and recycle building blocks. In the retina, autophagy-related proteins are mostly located in cellular layers that are rich in mitochondria and have high energy needs (Mitter et al., 2012). In addition, autophagy also plays an important role in phototransduction and rod integrity (Rodriguez-Muela et al., 2012; Zhou et al., 2015). Aged mice with mutated autophagy genes have AMD-like RPE defects (Zhang et al., 2017). Autophagy defects are also reported in human cells from AMD patients (Golestanineh et al., 2017). Some of the defects associated with autophagy deficiency are lipofuscin accumulation, reduced mitochondrial activity, and higher levels of reactive oxygen species—all of which affect angiogenesis. FGF21 influences autophagy. In mice, FGF21 is induced in neurons with mitochondrial dysfunction (Restelli et al., 2018). FGF21, induced with fasting, dephosphorylates transcription factor EB to induce genes involved in autophagy and lipid metabolism (Chen et al., 2017). In monosodium L-glutamate-induced obese mice, modeling nonalcoholic fatty liver disease, FGF21 induces autophagy to correct metabolic parameters (decreases triglycerides, improves insulin sensitivity) (Zhu et al., 2016). Further exploration of FGF21 in retinal lipid metabolism and autophagy is of great interest to evaluate its impact on retinal neurovascular stability.

**Fenofibrate (PPARα agonist and CYP2C antagonist)**

Fenofibrate, a PPARα agonist, increases fatty acid β-oxidation and improves mitochondrial function. Deficiency of PPARα leads to shortage of retinal energy production and neurodegeneration (Pearsall et al., 2017). In two large-scale clinical trials, fenofibrate prevents the progression of DR. In the FIELD study, fenofibrate was found to reduce the need for laser-treatment of DR in type 2 diabetes patients by ~30% (Keech et al., 2007). In the ACCORD Eye study, fenofibrate was found to reduce DR progression by ~40% (ACCORD Study Group et al., 2010). Fenofibrate prevents pathological neovascularization in the rat OIR model by suppressing hypoxia-inducible factor and VEGF (Chen et al., 2013). Fenofibrate also reduces retinal vascular leakage in a murine diabetic model (Chen et al., 2013). Fenofibrate administration reduces retinal vascular leakage and downregulates VEGF production in the mouse model of type 1 diabetes (Chen et al., 2013). Fenofibrate is also a CYP2C antagonist (Schoonjans et al., 1996; Walsky et al., 2005). CYP2C metabolites from ω-3 and ω-6 LCPUFA show pro-angiogenic effects in mouse models of ROP and AMD (Shao et al., 2014; Gong et al., 2016a). Inhibition of CYP2C with fenofibrate decreases retinal neovascularization (Gong et al., 2016b). Therefore, fenofibrate is a potential candidate to treat neurovascular defects in retinal metabolic disorders.

**Dietary ω-3 LCPUFA intervention**

The essential ω-3 LCPUFA, DHA, influences neovascularization in retinopathy both in human patients and animal models. In AMD, increasing fish intake or ω-3 LCPUFA supplementation (DHA, EPA) is associated with a decreased risk of AMD progression (Tan et al., 2009; Christen et al., 2011; Pinazo-Duran et al., 2014). In premature infants and diabetic patients, plasma ω-3 LCPUFA levels correlate with circulating APN and dietary intake of ω-3 LCPUFA modulates circulating APN levels (Ito et al., 2014; Fu et al., 2015). In type 2 diabetic patients on a “healthy” Mediterranean diet, additional dietary intake of fish is associated with a 48% decreased incidence of proliferative DR (Sala-Vila et al., 2016). In mouse models of proliferative ROP, DR, and AMD, dietary ω-3 LCPUFA,
mediated by APN, inhibits ocular neovascularization (Fu et al., 2015, 2017b).

**Free fatty acid receptor 1 (FFAR1)**

FFAR1, which is activated by medium- and long-chain fatty acids (Briscoe et al., 2003), governs glucose transport by regulating the expression of retinal GLUT1 (Joyal et al., 2016). In mice lacking VLDLR, a genetic deficiency in FFAR1 decreases retinal neovascularization, while FFAR agonist increases retinal neovascularization (Joyal et al., 2016). FFAR1 also mediates actions of nonenzymatically generated nitro-oxidative products, transarachidonic acids, and induces cerebral microvascular degeneration in rats (Honore et al., 2013). Targeting FFAR1 may prevent pathologic endothelial cell proliferation and degeneration.

**Conclusions and perspectives**

Generally, photoreceptor metabolism controls retinal neuronal and vascular development. Therefore, maintaining normal photoreceptor function will likely improve retinal vascular abnormalities in disease. As dyslipidemia contributes to disease progression in many retinal metabolic disorders, we may improve photoreceptor energy production by regulating lipid use and increasing lipid fuel sources, including those generated from autophagy. Targeting lipid metabolic modulation may improve neurovascular retinal function and decrease neovascularization.

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**Conflict of interest**

The authors declare that they have no conflict of interest.

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