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REVIEW

# Long-Chain Polyunsaturated Fatty Acids and Their Metabolites Regulate Inflammation in Age-Related Macular Degeneration

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**Abstract:** Age-related macular degeneration (AMD) is a blinding eye disease, whose incidence strongly increases with ages. The etiology of AMD is complex, including aging, abnormal lipid metabolism, chronic inflammation and oxidative stress. Long-chain polyunsaturated fatty acids (LCPUFA) are essential for ocular structures and functions. This review summarizes the regulatory effects of LCPUFA on inflammation in AMD. LCPUFA are related to aging, autophagy and chronic inflammation. They are metabolized to pro- and anti-inflammatory metabolites by various enzymes. These metabolites stimulate inflammation in response to oxidative stress, causing innate and acquired immune responses. This review also discusses the possible clinical applications, which provided novel targets for the prevention and treatment of AMD and other age-related diseases.

**Keywords:** inflammation, long-chain polyunsaturated fatty acids, age-related macular degeneration

## Introduction

Age-related macular degeneration (AMD) is a disease that damages the macular region of the retina and leads to progressive loss of central vision, which is the leading cause of blindness in the elderly population.[1] The overall prevalence in Europe was 16.2% for AMD, and the number of global population with AMD will increase to 288 million by 2040.[2,3] AMD is not simply a "macular" disease, but involves the entire retina.[4] With aging, retinal pigment epithelium (RPE) cells lose the phagocytic and digestive ability at the outer membrane of the optic disc. The residual bodies of the disc membrane remain and deposit on Bruch's membrane, forming drusen and leading to macular degeneration.[5] Upon Bruch's membrane rupture, choroidal capillaries migrate through the ruptured Bruch's membrane into the RPE and subcutaneous space of retinal nerve, forming choroidal neovascularization (CNV, Figure 1).[6] Dry AMD, also named non-neovascular, non-exudative or atrophic AMD, is characterized by the development of drusen,[7] while wet AMD, also known as neovascular or exudative AMD, is characterized by CNV.[8]

It is well recognized that AMD is a multifactorial disease,[9,10] including genetic predisposition,[11] oxidative stress,[12,13] neovascularization,[14,15] inflammatory responses[16] and remodeling processes of the retinal extracellular matrix.[17] Rozing et al proposed that the essence of AMD was a series of damages involved in aging and the consequently activated host immune responses to damages.[18] Low-grade inflammation is associated with many age-related complications including AMD and neurodegeneration.[19] Controlling low-grade inflammation can prevent or reduce age-related functional decline.[20] Pujol-Lereis et al stated that AMD resulted from three interrelated pathological processes, including inflammation, autophagy dysfunction and chronic oxidative stress, which led to RPE degeneration, ultimately photoreceptor cell death and vision loss.[21] Under oxidative stress, the drusen are formed in the retina, activating the complement system

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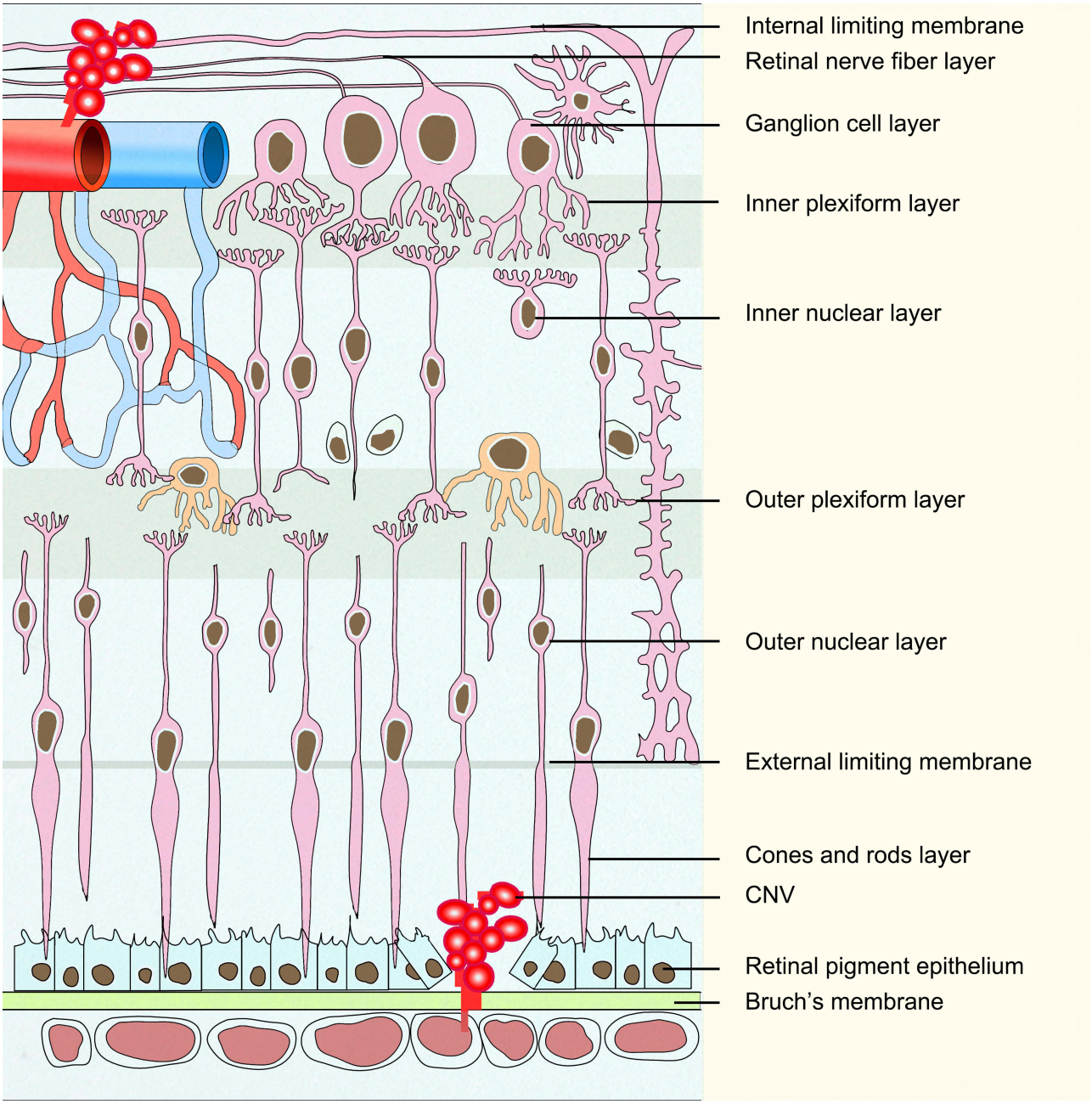


**Figure 1** Composition of the retina and ocular neovascularization. Retinal vessels grow through the retinal nerve epithelium to form retinal neovascularization. The choriocapillaris enter under the RPE through the ruptured Bruch's membrane to form CNV.

to trigger chronic inflammation, and subsequently activate immune cells, such as macrophages.[22] Invasive immune cells facilitate pathology in the retina, resulting in impairment of photoreceptor cells and Bruch's membrane integrity.[23]

Although the progressive course of AMD is increasingly known, current medical treatments are still limited.[24–28] Intravitreal injection of anti-vascular endothelial growth factor (VEGF) is currently the most widely used therapy,[29,30] which still have many disadvantages, such as the loss of visual acuity in long-term treatment,[31] the potential increase in macular atrophy after long-term usage,[32] increased risk of complications,[33] damage to ganglion cells and interfere with RPE function.[34,35]

Eye is one of the organs with high lipid content.[36] Defects in essential fatty acid metabolism arise in many age-related diseases, such as obesity, type 2 diabetes, hypertension, atherosclerosis, coronary heart disease, immune dysfunction, and cancer.[37–39] As an important component of retina, the metabolism of long-chain polyunsaturated fatty acids (LCUFCA) is

closely related to the function of retina.[40] In recent years, the roles of inflammation and lipid metabolism in retinal diseases have been highlighted.[41–43] This review mainly focused on the regulation of inflammation by LCPUFA metabolism to facilitate drug development and clinical research.

## LCPUFA and AMD

The retina is one of the tissues with the highest lipid content in the human body.[44] The rod outer segment of photoreceptor cells consists of a light-sensitive disc containing proteins and lipids including phospholipids (90–95% of total lipids) and cholesterol (4–6%).[45] Among retinal phospholipids, LCPUFA account for approximately 45% of total phospholipids, saturated fatty acids account for approximately 37%, and monounsaturated fatty acids account for approximately 10%.[45] The retinas of healthy older adults contain 16.7% ω-6 LCPUFA and 16.6% ω-3 LCPUFA.[46] High concentration of LCPUFA maintains proper fluidity of cell membrane, which is the premise of effective visual transduction and essential to the function of retina.[47] Genomic analysis shows that variations in lipid metabolism pathways are important contributors to early and late AMD,[48] ω-3 and ω-6 LCPUFA, as well as their metabolites, are associated with AMD pathogenesis and prognosis.[49] Omega-3 LCPUFA include docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA),[50] while ω-6 LCPUFA include arachidonic acid (AA) and linoleic acid (LA).[51] The major ω-3 LCPUFA, DHA, comprises ~20% of retinal weight,[52] and the major ω-6 LCPUFA, AA, comprises ~10% of retinal weight.[53]

Omega-3 and ω-6 LCPUFA cannot be synthesized by human body itself, which must be obtained from diet.[54] The ratio of AA to DHA and EPA can be changed by oral administration of DHA and EPA.[55] High LA intake is associated with 49% increases in the risks of AMD, while high DHA intake is associated with 30% decreases.[56] Most nutrition guidelines recommend increased intake of food-based EPA, DHA and their precursors (250–1000 mg/day) to reduce the prevalence of AMD.[49] Many clinical studies show that the high intake of food-based ω-3 LCPUFA (100–800 mg DHA + 30–60 mg EPA/day) is associated with lower AMD incidence rate and less development.[57–60]

A large cohort study, which involved 38,022 Americans, showed that the incidence rate of AMD in population with higher plasma concentration of ω-3 LCPUFA was 42% lower than that in patients with lower levels.[60] The age-related eye disease study (AREDS) suggests that bilateral drusen of those with higher intake of ω-3 LCPUFA are 30% less likely to develop into geographic atrophy (GA) or CNV.[61] A prospective control study based on 75,889 females and 38,961 males in the United States indicated that higher intakes of EPA and DHA prevented or delayed the occurrence of visually significant intermediate AMD.[7] Similar results were obtained in both European and Asian countries.[62–65]

However, AREDS2 reported conflicting results. Omega-3 LCPUFA supplementation (350 mg DHA + 650 mg EPA/day) does not benefit patients with the lowest fish intake.[66] These results suggested that a minimum concentration of ω-3 LCPUFA may be required to maintain retinal stability, and above this threshold, supplement of ω-3 LCPUFA may not increase benefits.[67] Nutritional AMD Treatment-2 (NAT-2), a clinical trial on oral supplementation of ω-3 LCPUFA (840 mg DHA + 270 mg EPA/day) in 263 patients with early lesions of AMD, indicated no significant difference in visual acuity, drusen progression and CNV incidence after oral supplementation. However, the risk of CNV occurrence in individuals with high levels of erythrocyte membrane EPA+DHA within 3 years was reduced by 68%.[68] One reason for this discrepancy is the inability to measure retinal ω-3 LCPUFA content directly.[69] Acar et al developed a more robust prediction model of retinal ω-3 LCPUFA content in AMD based on seven plasma cholesteryl esters, rather than the use of red blood cells or total plasma.[69] The blood and retinal levels of ω-3 and ω-6 LCPUFA and their relationship with AMD may also depend on genetic polymorphism.[70] Interestingly, previous studies also suggested that the protective effects of ω-3 LCPUFA on retinal neovascularization may be based on its interaction with AA.[71,72] The protective and therapeutical effects of LCPUFA on AMD are still to be investigated.

## Inflammation and AMD

Inflammation involves a series of processes aimed at ultimately clearing pathogens and repairing damaged tissues, and is an important pathogenesis in AMD. Local inflammation causes edema of macular and retinal, degeneration of RPE and photoreceptor outer segments (POS), destruction of Bruch's membrane and the development of CNV.[73] RPE cells help to maintain the health of the retina, including the formation of outer blood–retinal barrier, the phagocytosis of POS,

screening of growth factor screening and scavenging of damaged reactive oxygen species (ROS).[74] When the barrier is disrupted, the inflammatory responses are activated in the retina, resulting in the release of pattern recognition receptors (PRRs) and inflammasomes, and the activation of complement system, immune cells and cytokines.[22] RPE and immune cells produce cytokines and chemokines leading to the inflammatory cascades.[75] These cytokines include interleukin (IL)-4/5/6/8/10/13/17, interferon-β/γ, transforming growth factor (TGF)-α, monocyte chemoattractant protein-1 (MCP-1), and VEGF.[76] Many studies demonstrated that the levels of pro-inflammatory factor such as IL-6, IL-8, MCP-1 and VEGF were elevated in intraocular fluid of patients with dry and wet AMD.[77,78] Inflammatory cytokines also enhance VEGF secretion, which initiates and causes pathological CNV and retinal neovascularization in AMD.[79,80] When the long-term struggle between pro- and anti-inflammatory responses ultimately loses balance, AMD occurs.[81] In addition, innate immune cells such as macrophages, microglias, dendritic cells, and neutrophils are closely associated with the development of AMD,[82–85] but whether adaptive immunity has a role in AMD is highly debated.[86]

Inflammatory responses contribute to both dry and wet AMD through different mechanisms.[82] CNV is closely linked to inflammatory cytokines, complement system activation, and promotion.[87] Animal and in vitro experiments showed that complement activation and membrane attack complex (MAC) formation induced CNV and that inhibiting C3a, C5a and MAC effectively inhibited CNV.[88,89] After anti-VEGF treatment, the elevated concentrations of interferon gamma-inducible protein-10 (IP-10), IL-6, IL-8, C-X-C motif chemokine-12 (CXCL12), CXCL13, IL-10 and MCP-1 in the aqueous humor of AMD patients were decreased,[90,91] while Sato et al found IL-6 and IP-10 were considerably increased.[92]

Complement components, the important component of drusen, and inflammasomes are involved in the inflammatory responses in AMD.[93–95] The activated complement component C3a was higher in both the blood and drusen of patients with dry AMD, and the inhibitors of complement such as complement factor H (CFH), CD59 and CD46 were reduced, implicating a hyperactive complement system in AMD.[96–98] Upon oxidative stress, lysosomal destabilization and P2X7 receptor activation, inflammasomes can be activated by the nucleotide-binding and oligomerization domain-like receptor (NLR) family containing 1 (NLRP1), NLRP3, NLR-family CARD-containing protein 4, absent-in-melanoma 2 or pyrin, ultimately cause pyroptosis.[99] Immunohistochemistry revealed the presence of the NLRP3 inflammasomes in the lesion area of the eye in both GA and CNV.[100] In an acute model of AMD, inflammasome activation and increased IL-18 prevent CNV, but lead to RPE cell loss during a chronic model of GA,[101] which may be related to the degree and duration of inflammation.

Taken together, pathological processes of AMD are delicately regulated by various immune-mediated inflammatory events, including oxidative stress, mitochondrial dysfunction, autophagy, endoplasmic reticulum stress and cellular senescence, which are associated and interacted with each other.[102,103]

## Regulation of Inflammation by LCPUFA in AMD

The metabolites of LCPUFA, metabolized by enzymatic or non-enzymatic pathways, regulate inflammatory processes and have complex effects on AMD. For instance, ω-3 LCPUFA downregulate insulin-like growth factor-1, attenuate the activation of nuclear factor-κB (NF-κB), IL-β, VEGF and tumor necrosis factor-α (TNF-α), and suppress inflammation,[104–106] in part through the sphingomyelinase pathway.[107] Currently, there are many drugs, such as saffron and fenofibrate, targeting lipid metabolism and inflammatory process at different periods of development (Table 1). Several lipid metabolites are being investigated as therapeutical products as well (Table 2).

### Effects of LCPUFA Oxidative Metabolites on Inflammation in AMD

LCPUFA participate in processes that cause or resolve inflammation through oxidized lipids.[107] Phospholipase A2 catalyzes the hydrolysis of cell membrane lipids, releasing them for further metabolism and signaling.[129] Membrane-bound ω-3 and ω-6 LCPUFA are oxidized by three pathways, the cyclooxygenases (COXs), lipoxygenases (LOXs) and cytochrome P450 oxidases (CYPs).[130] The metabolites of ω-6 LCPUFA through COX are prostaglandin (PG) E2 and thromboxane, while the metabolites of ω-3 LCPUFA through COX are PGE3 and resolvins (Figure 2). PGE2 stimulates pathological retinal neovascularization.[131] PGE3 antagonizes PGE2, inhibiting endothelial tubule formation via reducing angiopoietin 2 and matrix metalloproteinase (MMP) 9 production.[125] Resolvins have anti-inflammatory properties,[128]

**Table 1** Drugs Targeting Lipid Metabolism and Inflammatory Processes

| Medicine | Period | Target | Mechanism |
|---|---|---|---|
| NAC,[108] saffron,[109] vitamin C, E, zinc,[110] resveratrol[111] | Clinical experiment | SOD, GPx, GSH activator | Reduce ROS levels, stimulate autophagy[112] |
| Troglitazone, rosiglitazone[113] | Clinical experiment | PPARγ activator | Anti-inflammatory, inhibit CNV[114] |
| Celecoxib[115] | Clinical experiment | COX-2 inhibitor | Anti-inflammatory, inhibit CNV |
| NS-398[116] | Cell experiment | | |
| Fenofibrate[117] | Animal experiment | PPARα, CYP2C activator | Anti-inflammatory, inhibit CNV |
| SH-11037[118,119] | Clinical experiment | sEH inhibitor | Anti-inflammatory, inhibit CNV |
| SR1001[120,121] | Cell experiment | RORα inhibitor[122] | Control transcription of lipid metabolism, reduce inflammation |
| MRZ-99030[115] | Clinical experiment | Amyloid-β inhibitor | Reduce drusen formation |
| Avacincaptad pegol[123] | Clinical experiment | C5 inhibitor | Inhibit complement activation |

**Abbreviations**: NAC, acetyl-L-cysteine; SOD, superoxide dismutase; GPx, glutathione peroxidase; GSH, glutathione reductase; ROR, retinoic acid receptor-related orphan receptor.

**Table 2** Products of Lipase Metabolism with Anti-Inflammatory Effects

| Metabolism | Enzyme | Mechanism |
|---|---|---|
| 4-HDHA[124] | COX, CYP | Activate PPARγ |
| PEG3[125] | COX | Antagonize PEG2 |
| Neuroprotectin D1[126] | LOX | Attenuate CNV formation and inflammation |
| Maresins[127] | COX, LOX | Anti-inflammatory and pro-resolving |
| Resolvins[128] | COX | Activate chemokine receptor 23 and antagonize LTB4R |

**Abbreviations**: 4-HDHA, 4-hydroxydocosahexaenoic acid; PEG, polyethylene glycol; LTB4R, leukotriene B4 receptor.

activating chemokine receptor 23 and antagonizing leukotriene B4 (LTB4) receptor, which mediates the pro-inflammatory effects of LTB4.[132]

Aspirin and other nonsteroidal anti-inflammatory drugs are the most commonly used COX inhibitors in the clinic, and COX inhibition does not affect proliferative retinopathy, possibly due to the concomitant reduction in the intraocular anti-inflammatory ω-3 and pro-inflammatory ω-6 LCPUFA mediators.[133] However, the COX-2-selective antagonist NS-398 reduced VEGF and TGF-β secretion, and attenuated experimental CNV lesions and retinal fibrosis in vivo.[116]

LOX is a lipid peroxidase devoid of heme containing iron that catalyzes the dioxygenesis of LCPUFA to form various bioactive lipids.[134] 5-LOX and 12/15-LOX were reported to regulate chronic inflammation and oxidative stress.[135] Previous studies showed that 5-LOX and its metabolite 4-hydroxydocosahexaenoic acid mediated the protective effects of ω-3 LCPUFA against AMD.[124] The metabolites of ω-3 LCPUFA through LOX pathways contained anti-inflammatory factors, but also pro-inflammatory catabolism such as D-series resolvins, neuroprotectins, and maresins.[107] Resolvins were powerful regulators of innate immune cells during inflammation and reduced ROS.[127] Neuroprotectin D1 attenuated CNV and significantly inhibited ROS-mediated damage, apoptosis, and inflammation, resulting in photoreceptor cell integrity.[126] Maresins are synthesized by macrophages and potent anti-inflammatory mediators.[127]

The roles of LCPUFA metabolites from CYPs are currently attracting increasing attentions. AA is metabolized to hydroxyeicosatetraenoic acids and epoxyeicosatrienoic acids (EETs) by CYPs, while EPA and DHA are metabolized to epoxyeicosatetraenoic acids (EEQs) and epoxyeicosapentaenoic acids (EDPs).[136] These products are all further metabolized into substances with low activity by soluble epoxide hydrolase (sEH).[137] Both the ω-6 LCPUFA metabolite 14,15-EET and the ω-3 LCPUFA metabolite 19,20-EDP of CYP2C promote ocular neovascularization.[138] Inhibition of CYP2C activity increased the protective effects of dietary ω-3 LCPUFA on pathological retinal and choroidal angiogenesis.[139] However, Hasegawa et al found the inhibitory effects of ω-3 LCPUFA on CNV were impaired by the metabolic degradation of EDP and EEQ.[140] Other studies showed that 11,12-EET and 19,20-EDP reduced TNFα-induced NF-κB activity and the expression of IL-1β, IL-6 and leukocyte adhesion protein VCAM1 in human retinal

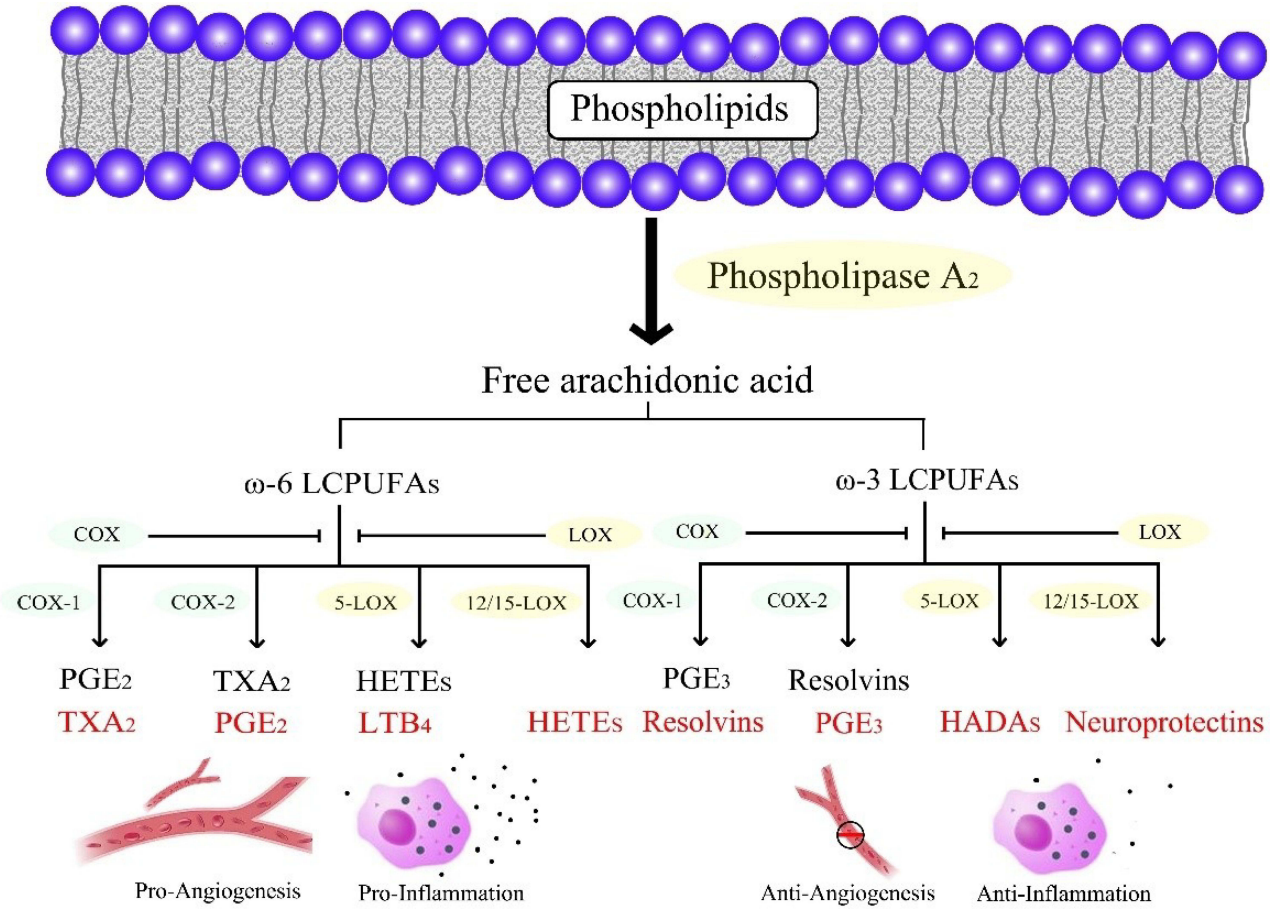


**Figure 2** Schematic of the COX and LOX pathways metabolizing ω-6 and ω-3 LCPUFA. The metabolites derived from ω-6 LCPUFA are pro-inflammatory and pro-angiogenic, whereas those derived from ω-3 LCPUFA are anti-inflammatory and anti-angiogenic.

microvascular endothelial and Müller cells.[141,142] Fenofibrate, a peroxisome proliferator activated receptor α agonist and CYP2C antagonist,[117] was reported to suppress CYP2C activity and add to the protective effects of ω-3 LCPUFA on the retina in both in vivo AMD mouse model and ex vivo angiogenesis, via downregulating the levels of 19,20-EDP.[143]

Peroxidation products of non-enzymatic pathways can also modulate cytokines. Acid-N-retinoic ethanolamine (A2E) can increase the secretion of inflammatory cytokines and chemokine such as IL-6, MCP-1, CXCL8, TNF and VEGF both in vitro and in vivo.[22,23,144]

## LCPUFA Peroxidation and Its Effects on Inflammation in AMD

Lipid peroxidation is an important component of oxidative stress, which causes ROS-induced cell damage and has been linked to many degenerative diseases.[145,146] The unsaturated structure of LCPUFA is particularly susceptible to oxidative degradation by lipid peroxidation, generating harmful end products that lead to irreversible alterations in cellular components.[147] ROS and oxidized lipoproteins cause cellular stress, resulting in innate immune responses through the activation of cell-associated and soluble PRRs.[148] Kim et al applied a rat model with subretinal injection of human lipid hydroperoxide to mimic the pathogenesis of AMD.[149] Pro-inflammatory factors, including TNF-α, IL-1β and IL-6, were upregulated both in the retinal and choroidal tissues, followed by the increase of LCPUFA peroxidation products such as 4-hydroxynonenal (4-HNE), lipofuscin and carboxy ethyl pyrrole (CEP),[149] which bind to cellular proteins to form advanced lipoxidation end products (ALEs).[150]

Oxidized lipoproteins were taken up through the CD36 receptor, together with the lipid peroxidation end product 4-HNE (Figure 3), activate the NLRP3 inflammasomes in RPE cells through the activation of toll-like receptors (TLRs), receptor for advanced glycation end products (RAGEs), and NF-κB.[151–153] When inflammasomes were initiated, RPE

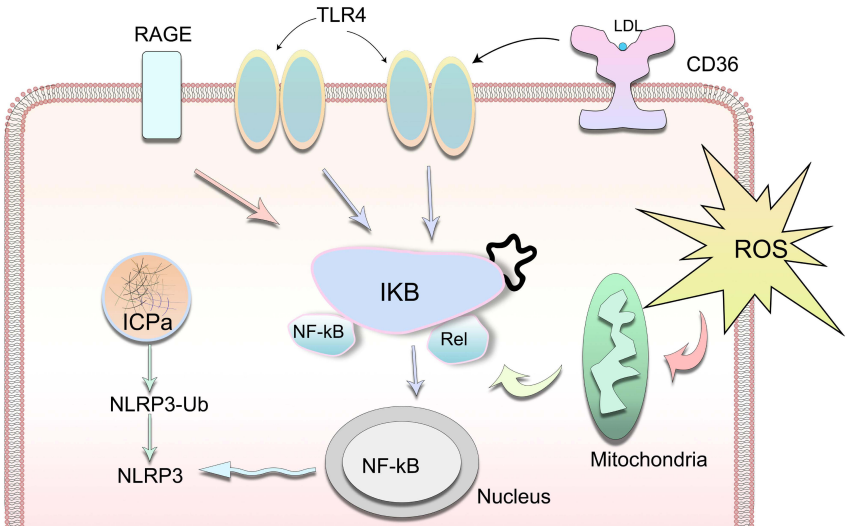


**Figure 3** Oxidative stress results in innate immunity responses through the activation of TLRs, CD36, RAGEs, NF-κB and NLRP3 in stressed RPE cells.

cells died of photo oxidative damage and pyroptosis.[154] DHA was reported to alter the composition of lipid rafts via entering the cell membrane, leading to the efflux of inflammatory receptors such as TLR2 and TLR4 from lipid rafts, and inhibiting their activation.[100] 4-HNE can also inhibit the production of IL-8 and MCP-1,[155] induce epidermal growth factor receptor activation to prevent oxidative stress damage at lower concentrations, but induces p53-mediated apoptosis in RPE cells at a higher concentration.[156,157]

Lipofuscin is the main source of ROS, and its main component is A2E, which is a by-product of vitamin A metabolism and lipid peroxidation.[158] The process of lipid peroxidation cleaves A2E, activating complement C2 and C3, releasing cytotoxic carbonyl species and aggravating RPE damage.[144,159] On one hand, these peroxidation products can activate the alternative lectin pathways of complement and enhance and amplify the inflammatory responses through many pathways, including enhancing the phagocytosis of macrophages, forming MAC to cause cell death, inducing many inflammatory mediators and recruiting inflammatory cells.[160] On the other hand, lipoproteins also compete with CFH for binding sites in Bruch's membrane.[161]

CEP can activate specific T cells to cause inflammatory M1 polarization of retinal macrophages to induce dry AMD, and are also involved in the TLR2-induced neovascularization, considered as an early marker of high-risk AMD development.[162–164] M2-like macrophages produced MMPs, which enhanced the penetration of CNV through Bruch's membrane, while M1 macrophages ameliorated CNV.[165–169] Previous studies also showed that CNV could be inhibited by downregulating M1 macrophage/microglia polarization.[170] Allingham et al suggested that the early recruitment of inflammatory M1 macrophages promoted the induction and initial development of CNV, followed by the sustained recruitment of reparative M2 macrophages that mediated the sustained CNV formation and growth.[160] ALEs are found in drusen and Bruch's membrane of AMD patients, and act as haptens to induce autoantibody formation against lipid peroxide-modified retinal proteins, causing inflammatory responses and complement activation, and damaging the RPE cells.[171]

A positive feedback loop of oxidative stress and related inflammation may be involved in the pathogenesis of AMD.[172,173] In animal models, dietary supplementation with antioxidants and ω-3 LCPUFA have been seen to rapidly modify the fatty acid content and to increase the retinal content of EPA by over 70% and protect the retina against light-induced oxidative stress.[174] Previous studies found that inhibition of inflammatory mediators, such as angiotensin II type 1 receptor blockers,[175] reduced ROS as antioxidants such as N-acetyl-L-cysteine,[154] saffron,[108] vitamin C, E and zinc.[110] In conclusion, oxidized lipoproteins increase oxidative stress, inflammation, and paracellular permeability of RPE cells, inducing outer blood retinal barrier dysfunction and causing VEGF production and wet AMD.[176,177]

An important target for lipid metabolism regulation is the peroxisome proliferator activated receptor (PPAR).[178] Three different subtypes of PPAR have been isolated so far: α, β, and γ.[179] Both DHA and EPA are the ligands of all the three PPAR isoforms.[180] PPARs advance the entry of LCPUFA into mitochondria and peroxisomes, and regulate their metabolism[181] via upregulating the expression of carnitine palmitoyl translocase, fatty acyl CoA dehydrogenase, and fatty acyl CoA dehydrogenase.[113,182] PPARs were reported to enhance the phagocytosis of apoptotic cells by macrophages,[183] promote M2 macrophage polarization,[184] reduce MMP2 and MMP9, and inhibit CNV.[114] They are also necessary for ω-3 LCPUFA to attenuate retinal neovascularization in mice.[181] Fontaine et al found that A2E promoted inflammation and angiogenesis partially via inducing the transactivation of PPARs and retinoid X receptors (RXR) in RPE cells.[185,186] PPARγ coactivator (PGC)-1α is a protein that increases RPE metabolism, maintains mitochondrial homeostasis, and protects against ROS damage.[187] Zhang et al found that PGC-1α$^{-/-}$ mice on a high-fat diet were more prone to developing AMD.[188] Loss of nuclear factor-erythroid 2-related factor-2 and PGC-1α leads to RPE damage and dry AMD.[189] Strong light stimulation not only enhances POS phagocytosis in RPE cells but also induces activation of the PGC-1α/EERα pathway, upregulating VEGF.[181] Therefore, targeting PGC-1α may be considered in anti-VEGF strategies to increase its efficacy for wet AMD.[190] PPARs and PGC-1α can regulate retinal lipid metabolism, and are avenues to manipulate in the treatment of diseases.

## LCPUFA Metabolism Regulates Autophagy and Senescence

Autophagy is a protective, homeostatic mechanism, which is designed to remove faulty cellular components.[191] Compromised autophagy can result in dysfunctional RPE and induce an AMD-like phenotype in mice.[192] Toxic LCPUFA peroxidation products are mainly metabolized and cleared by lysosomal enzymes.[154] RPE lysosomal enzymes are important regulators in this process and targets of lipid peroxide-mediated damages.[193] Previous studies indicated that phagocytosis of lipid peroxide increased lipofuscin production and disrupted cell self-renewal through autophagy, resulting in release of undegraded POS proteins to the drusen.[194,195] Drusen contain lipids, carbohydrates, proteins, and cellular debris that are processed by autophagy.[196] It is well known that disturbed autophagy is one of the characteristics of AMD.[197]

In early AMD, RPE cells increase autophagy in response to acute oxidative stress. However, at the late stage of AMD, the autophagic process is unable to cope with the increased number of damaged organelles.[198] Autophagy inhibition leads to inflammasome activation and increased angiogenesis in RPE, and NLRP3 inflammasome activation induces pyroptosis.[199] In addition, lipid peroxide-related lysosomal dysfunction induces VEGF secretion from RPE cells, causing CNV generation and leading to wet AMD.[200]

A2E induces autophagy by activating the Akt/mTOR pathway in RPE cells.[199] The combination of A2E and autophagy inhibitor 3-methyladenine upregulates inflammation-related proteins IL-1β, IL-2, IL-6 and IL-8, promoting the production of ROS and leading to RPE cell death.[201] Rapamycin augments A2E-mediated autophagy and down-regulates inflammatory factors and VEGF.[202] Impaired autophagy or mitophagy in RPE cells leads to macrophage recruitment and inflammasome activation, thereby promoting RPE and photoreceptor degeneration.[203] Several researches implicated impaired mitochondria in AMD.[204,205] When the mitochondrial membrane is damaged, mitochondrial DNA, apoptosis-inducing factors and cytochrome c can be released, causing mitophagy, leading to necroptosis or pyroptosis and triggering chronic sterile inflammation.[206]

Elovanoids (ELVs) are a class of endogenous pro-homeostatic mediators synthesized from DHA.[207] When retinal cells need to counteract neuroinflammatory responses to protect their integrity and to sustain survival and functions, ELVs are made rapidly.[208] In AMD, amyloid-β peptide accumulates in the subretinal drusen. ELV was reported to abolish the destructive effects of RPE, preventing inflammation, autophagy, extracellular matrix remodeling and AMD.[209]

Senescence is a state of permanent inhibition of cell growth and an important pathological mechanism of AMD.[177] A large number of immune cells are present in the choroidal circulation.[210] Senescent immune cells reduce phagocytosis and clearance, and induce angiogenesis and pro-inflammatory mediators such as IL-6, IL-8 and TNF-α,[211] which are collectively known as aging-related secretory phenotype.[192] These cytokines promote a series of inflammatory cascades, and induce age-related inflammatory reactions, metabolic disorders, and chronic diseases.[212] Chronic sterile inflammation may be the core of AMD.[213]

Senescence decreases the biosynthetic capacity of LCPUFA.[214] Omega-3 LCPUFA supplementation can improve brain neurocognitive functions, limit neuroinflammation and stress response defects in aged animal models and clinical trials.[215–218] Meanwhile, peroxide products of LCPUFA, such as A2E, can cause telomere dysfunction and accelerate RPE cell senescence.[219]

## Conclusion

Dyslipidemia and chronic inflammation are both the manifestations of aging, and the common pathogenic factors of many age-related diseases. Oxidative stress, lipid disorder and inflammation are closely related. First, the metabolites of LCPUFA include anti-inflammatory and pro-inflammatory regulatory factors. Second, the peroxidation products of lipids promote the inflammatory process via activating complement and inflammasomes, and recruiting immune cells. Third, LCPUFA metabolism regulates inflammatory responses via modulating senescence and autophagy. The deposited lipids cause chronic sterile inflammation and innate immune responses. The combination of direct damage of oxidized lipid and maladjusted chronic inflammation leads to RPE degeneration, photoreceptor cell death, visual loss and macular degeneration.[43] Many drug targets have been identified to alleviate AMD. Epidemiological, clinical, and experimental studies have shown that ω-3 LCPUFA are associated with a decreased risk of AMD and that ω-6 LCPUFA are associated with an increased risk.[63,220]

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## Disclosure

The authors report no conflicts of interest in this work.

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