

# **Systemic Inflammation And The Gut–Retina Axis In Age-Related Macular Degeneration: Emerging Mechanisms And Therapeutic Implications**

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## **Abstract**

### **Purpose**

*To review emerging evidence linking systemic inflammation and gut microbiome dysbiosis with AMD pathogenesis and to explore how these mechanisms may inform novel therapeutic strategies.*

### **Methods**

*A narrative review of the literature was conducted using PubMed, Scopus, and Web of Science databases to identify studies published between 2000 and 2025 examining interactions between systemic inflammation, gut microbiota, and retinal disease. Both human clinical studies and experimental models investigating microbiome–immune interactions relevant to AMD were included.*

### **Results**

*Accumulating evidence suggests that gut microbiome dysbiosis may influence AMD through multiple interconnected mechanisms, including increased intestinal permeability, metabolic endotoxemia, complement activation, inflammasome signaling, oxidative stress, and immune dysregulation. Microbiota-derived metabolites—such as short-chain fatty acids, bile acids, and tryptophan-derived compounds—can modulate systemic inflammatory responses and may influence retinal immune homeostasis. Experimental studies demonstrate that alterations in gut microbial composition can modify retinal inflammatory signaling and choroidal neovascularization, supporting the existence of functional immune communication between the gut microbiome and retinal tissues.*

### **Conclusion**

*Recognition of AMD as a systemic immunometabolic disorder influenced by host–microbiome interactions provides new insights into disease pathogenesis and potential therapeutic targets. Interventions aimed at modulating the gut–retina axis—including dietary modification, microbiome-directed therapies, and pharmacologic targeting of inflammatory pathways such as complement and inflammasome signaling—may represent promising adjunctive approaches for AMD prevention and treatment. Further translational research is required to determine whether manipulation of the gut microbiome or its metabolic products can modify disease progression in patients with AMD.*

### **Keywords**

*Age-related macular degeneration, Gut microbiome, gut-retina axis, Systemic inflammation, Complement activation, Inflammasome*

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## I. Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible central visual loss in older adults in many areas of the world and will affect nearly 300 million people worldwide by 2040 [4]. AMD places important social and healthcare burdens due to its potential for causing severe and permanent visual loss when advanced to its "wet" form known as choroidal neovascularization or to advanced geographic atrophy. Classically AMD has been understood as a local degenerative process involving retinal pigment epithelium (RPE), photoreceptors and Bruchs membrane. Recently however, immune system genetics, immunology and metabolism have emerged as key components in understanding AMD and are shifting a more narrow retinal focus to one that includes broader systemic mechanisms. Many systemic factors including cardiovascular disease, metabolic syndrome, smoking and diet have been linked to AMD [5-8] showing that chronic systemic inflammation, oxidative stress and metabolic dysfunction may play roles in retinal disease.

Recent research has explored how and if the gut microbiota plays a role in modulation of these systemic inflammatory responses. The human gastrointestinal tract harbors a diverse and metabolically active community of microbes that play roles in immune system regulation, nutrient processing and epithelial barrier homeostasis [28]. Changes to microbiota composition (dysbiosis) have been implicated in numerous diseases characterized by chronic inflammation including metabolic syndrome, cardiovascular disease and neurodegeneration. Recent research suggests that intestinal microbiota may also play roles in modulating retinal health via systems-level immunological and metabolic mechanisms - a process that has been termed the gut-retina axis [9-12]. Microbiota may modulate immune function via effects on epithelial barrier function and mucosal immunity and could influence systemic levels of pro-inflammatory molecules including those that activate complement, Toll-like receptors and NLRP3 (NACHT, LRR and PYD domains-containing protein 3) inflammasome. This concept can be seen as an extension of the more widely studied gut-brain axis [13], in which intestinal microbiota modulate CNS immune responses. Since the retina is derived embryonically from neural tissue and maintains tightly controlled immune responses, it may be uniquely sensitive to immunometabolic cues originating from the gut microbiota. Therefore, a detailed understanding of how host genetic and microbiota derived immune and inflammatory signals interact to modulate AMD pathogenesis is important.

Here we review the available evidence linking gut microbiota dysbiosis to the initiation of systemic inflammatory responses involved in AMD and summarize new mechanistic data implicating complement activation and NLRP3 activation. We also discuss emerging therapeutic strategies focused on manipulating the gut-retina axis.

### **AMD as a Systemic Inflammatory Disease**

From what we've learned so far from all the research evidence it seems clear that AMD isn't just a problem in the eyes but connected with wider issues involving inflammation and metabolism. Studies that look across lots of people and look very into the biology of diseases have shown that people with AMD have more inflammation in the form of higher levels of things called C-reactive protein, interleukin-6, tumor necrosis factor-alpha and interleukin-1 beta in the blood [13 - 15]. This type of inflammation seems to hurt the eye by making blood vessels not work well, making too much damage of cells from unstable molecules and turning on immune cells in the eye, in the retinal pigment epithelium and Bruch's membrane. One of the most important ways that problems everywhere in the body affect AMD is through the complement system, part of the immune system. Study after study that looks at the genes of people across the whole world have shown that variations in genes that make complement proteins are associated with AMD [1 - 3].

We know that one of these genes, the gene for complement factor H, has a particular variation that results in the body not being able to turn off this part of the complement system, called the alternative pathway,

enough. That results in too much complement being made that stimulates inflammation in the eyes. When complement is turned on it gets broken down into smaller parts and higher amounts of these activated bits of complement, such as C3a, C5a and Ba, have been found in people with AMD. This tells us that complement is being made more than usual not only in the eye but possibly elsewhere in the body as well, something we will come back to later [16].

Activation of complement is a strong stimulus for inflammation, helping attract immune cells to an area, turning up the activation of brain and eye immune cells called microglia and hurting the layer that lines blood vessels, the endothelium. Within the eye, chronic activation of the complement system would cause chronic inflammatory stress and damage to the cells that take care of the retina, resulting in accumulation of material between these supporting cells, drusen. The biggest risk factor for AMD is getting older and there are some changes that happen when the body's immune system ages. This state has been called "inflammaging" and consists of low-grade inflammation happening across the full body, caused by the aging immune system, the endoplasmic reticulum and mitochondria. Changes in the immune system with age result in lower levels of immune-controlling cells, more of inflammation-causing chemicals in the blood and stronger reactions to immune stimuli from the immune system's first line of defense, the NLRP3 inflammasome [17, 41].

All these factors make the body's tissues easier to trigger to make inflammation and the retina more susceptible to damage from unstable molecules and complement. In addition to problems with complement, damage from unstable molecules also plays a big role in AMD. The retina experiences a lot of damage from unstable molecules because it uses a lot of energy, deals with light directly and has many fats in it that can be easily damaged. More of markers of this type of cellular damage, such as a type of fat in the blood, oxidized low-density lipoprotein and products of fat break down, have been found in people with AMD [18, 19]. These damaged molecules can damage the mitochondria of the retinal support cells, disrupt cellular recycling processes and make signaling molecules such as the NLRP3 inflammasome, causing damage to light-sensing cells in the retina and loss of vision. AMD also shares several underlying causes with other pervasive problems affecting metabolism and the heart and blood vessels. AMD is linked to being overweight, high blood pressure, unhealthy cholesterol levels and cardiovascular disease, across large studies of the population [5 - 8, 49]. All these issues involve chronic low grade inflammation, poor blood vessel functioning and problems with handling fats in the body, which could also damage the eye. The material that builds up between cells in AMD, drusen, contains fats, complement proteins and inflammation causing substances similar to what is found in the blockage of arteries [7], suggesting AMD shares many causes with these widespread problems. The research supports the idea that AMD involves problems beyond the eye, including inflammation and metabolic issues.

### **The Gut–Retina Axis**

The intestine produces systemic factors that affect other organs through inflammatory and metabolic pathways, which we have termed the gut-retina axis [9-12]. Gut microbiota modulate immune cell function including T-cells, macrophages and dendritic cells through metabolite production and pattern recognition signals [28, 29]. Intestinal dysbiosis promotes production of pro-inflammatory cytokines such as IL-6, IL-1 $\beta$  and TNF- $\alpha$ , which may impact the retina through microglia activation, complement deposition and RPE stress [12]. Systemic inflammation as a bridge between gut microbiota and AMD development Mechanisms exist linking gut microbiota changes to systemic inflammation relevant for AMD pathogenesis. Impaired barrier function from intestinal dysbiosis promotes luminal LPS translocation, triggering systemic TLR4/NF- $\kappa$ B activity and chronic inflammation [27, 29, 42]. Metabolite production represents another pathway by which the gut microbiota influence AMD. For example, SCFA production, including acetate, propionate and butyrate, maintains barrier function and reduces inflammation by inhibiting NF- $\kappa$ B activity and regulating regulatory T-cells [29, 35].

Loss of SCFA production in the setting of dysbiosis might contribute to systemic inflammation. Other metabolites, such as bile acids, tryptophan-derived products, aryl hydrocarbon receptor and farnesoid X-receptor ligands may promote immune modulation with consequences for retinal diseases. Clinical Evidence supporting gut-retina axis in AMD Several studies have reported clinical associations between gut microbiota and AMD. Differing gut microbiota compositions between control and neovascular AMD subjects were described, with important associations between microbiota and complement factor H genotype (CFH) in these groups [9, 10]. Greater abundance of the genera Ruminococcus, Prevotella and Streptococcus and lesser amounts of Bacteroides and Akkermansia were associated with systemic inflammation and complement deposition [15, 36, 43]. Experimental Evidence linking Gut Microbiota and AMD in animal models A causal link between gut microbiota and neovascular AMD has been explored using germ-free mouse models. Germ-free mice showed decreased neovascularization and inflammatory cytokines compared to conventionally raised controls, whereas microbiota depletion resulted in decreased neovascularization [12, 31]. Also, diet-induced dysbiosis (using high fat diet) promoted intestinal permeability, endotoxemia and increased choroidal neovascularization [34, 12].

### **Molecular Mechanisms Linking Gut Dysbiosis to AMD**

Several interacting molecular pathways have been proposed to link gut microbiome disturbances to retinal degeneration in AMD, including complement activation, inflammasome activation, endotoxemia, oxidative stress and lipid metabolism. Complement activation One mechanism that has been proposed is excessive complement activation. Gut dysbiosis may increase complement activation through systemically elevated levels of endotoxin/lipopolysaccharide (LPS), promoting the alternative complement pathway and producing inflammatory fragments (C3a, C5a) to recruit immune cells and amplify local retinal inflammation [27, 41]. Complement activation enhances microglial activation, endothelial dysfunction and RPE damage [18]. Inflammasome activation Another mechanism that has been proposed is activation of the NLRP3 inflammasome. Endotoxemia caused by dysbiosis may promote inflammasome activation through Toll-like receptor and NF- $\kappa$ B signaling pathways, increasing IL-1 $\beta$  and IL-18 production and triggering inflammatory damage to retinal pigment epithelial cells [41, 42]. Excessive inflammasome activation leads to retinal degeneration and geographic atrophy, while activating complement component C3 to complete the self-reinforcing inflammatory cycle [18].

Oxidative stress Another mechanism is excessive oxidative stress. Dysbiosis is associated with increased systemic oxidative stress and reactive oxygen species (ROS), damaging mitochondria in retinal pigment epithelial cells and promoting inflammation [19, 37]. Lipid dysregulation Another mechanism is disrupted lipid homeostasis. Dysbiosis is associated with altered systemic lipid metabolism, increasing levels of oxidized lipoprotein that accumulates in the Bruch's membrane to induce drusen that contain complement and inflammatory factors [7, 37]. Toll-like receptors LPS also activates Toll-like receptors such as TLR4, which improve inflammation by activating the NF- $\kappa$ B pathway, stimulating production of inflammatory cytokines such as IL-6, IL12 and TNF $\alpha$  and inducing expression of VEGF to help pathological angiogenesis. Indeed, inhibition of TLR4 signalling significantly reduces choroidal neovascularization in animal models [27, 42].

### **Therapeutic Implications**

Understanding how the gut and eyes connect can lead to new ways to treat age-related macular degeneration. Right now, the main treatments for wet AMD involve injecting medicines into the eye to block a substance called VEGF. While these treatments have greatly improved care for wet AMD, they mainly deal with problems happening later on, not the early inflammation and body chemistry issues that start and worsen the disease. New ideas about the gut-retina connection show that learning how the gut's tiny organisms control the

immune system might offer new treatment paths for macular degeneration. People have suggested a few different plans.

First, changing the gut's tiny organisms with things like probiotics, prebiotics or synbiotics could bring back a healthy balance, fix the gut's lining and lower the body's inflammation that hurts the retina<sup>[27,36,43]</sup>. Second, eating plans, especially those that fight inflammation like the Mediterranean diet, might change the gut's organisms for the better and cause more helpful substances, like short-chain fatty acids which is an anti-inflammatory microbial metabolite, to be made<sup>[6,16,35]</sup>. Third, focusing on the inflammation signals involved in AMD, like how the complement system works or the NLRP3 inflammasome, is a key drug strategy. We saw this recently with drugs that block the complement system for geographic atrophy<sup>[22-24,38]</sup>. Finally, more and more people are looking at what substances made by gut organisms, such as short-chain fatty acids, bile acids and tryptophan breakdown products, can do. These are known to affect how the body's immune system works and how it uses energy<sup>[14,44]</sup>. These ideas are still mostly being tested but they suggest that treatments aimed at the gut-retina connection could work alongside current eye treatments and offer new ways to stop or slow down AMD.

Changing the gut's tiny organisms could be a way to affect the body's inflammation that plays a role in AMD. Changing what you eat is one of the easiest ways to alter the types of organisms in your gut and how they affect your body's chemistry. Eating lots of fruits, vegetables, whole grains and omega-3 fats - like in the Mediterranean diet - has been linked to a lower chance of AMD getting worse<sup>[6,16]</sup>. These eating habits encourage good gut organisms that create anti-inflammatory substances like short-chain fatty acids. Plant-based foods also have compounds that might protect the eye by changing what the gut organisms do and reducing damage from stress. On the other hand, Western diets high in unhealthy fats and processed carbs are linked to an imbalance in gut organisms, toxins in the bloodstream and more body-wide inflammation. These diet-caused changes in gut organisms could contribute to eye damage through body-wide inflammation and metabolism problems<sup>[39]</sup>.

Probiotics and prebiotics are looking like good ways to fix the balance of tiny gut organisms and improve the gut's barrier. Certain probiotics, like *Lactobacillus* and *Bifidobacterium*, have been shown to make the gut lining stronger, reduce bad stuff leaking out and change how the body's immune system responds. Prebiotics, which are fibers that help good bacteria grow, can increase the production of short-chain fatty acids and lower inflammatory signals in the body<sup>[36]</sup>. Even though there are not many studies yet on using probiotics for AMD specifically, these approaches might be promising for future research.

Blocking the complement system is a recent idea for treating inflammation in geographic atrophy. Studies looking at drugs that block the complement system, like pegcetacoplan (which blocks C3) and avacincaptad pegol (which blocks C5), have shown a slight slowing of geographic atrophy in people with advanced AMD<sup>[22-24]</sup>. These results confirm that inflammation involving the complement system is important in the disease's progression. While these drugs do not directly affect the gut's tiny organisms, they target inflammation happening later on, which might be influenced by signals from the gut. Body-wide metabolism treatments could also affect eye disease. Drugs like metformin and GLP-1 receptor agonists have been shown to improve how the body handles energy and change the makeup of gut organisms. Statins, often used for high cholesterol, might also affect inflammation linked to fat buildup and drusen but their effect on AMD progression is not clear yet<sup>[21]</sup>.

More experimental ways to change gut organisms include fecal microbiota transplantation. In studies before humans, giving gut organisms from healthy people helped reduce inflammation signals and blood vessel growth in the eye, while gut organisms from people with AMD made the retina more likely to be injured<sup>[35]</sup>. Even though these findings are early, they show the possibility of using gut organism-based strategies to target

the body's inflammation that drives eye disease. Lifestyle changes that affect body-wide inflammation could also help prevent AMD. Regular exercise has been linked to more types of gut organisms and better metabolism<sup>[14]</sup>. Stopping smoking is especially important because tobacco causes damage from stress, problems with blood vessels and inflammation that are part of AMD<sup>[8]</sup>.

Altogether, these new treatment ideas suggest that changing body-wide inflammation and metabolism, including things affected by gut organisms, could work well with current eye treatments for AMD.

## **II. Limitations And Future Directions**

While there has been an increasing interest in the gut retina axis, several important caveats should be considered. Many of the gut microbiome studies in AMD have been cross-sectional and do not allow the establishment of cause and effect between observed microbial alterations and AMD progression <sup>[36, 43]</sup>. Longitudinal cohort studies should clarify if alterations in the gut microbiome precede the onset of AMD or if they are instead a consequence of secondary factors such as aging, diet and system-wide comorbidities. There is large heterogeneity between microbiome studies based on differences in sequencing technology, geographic regions, dietary patterns and distinct patient populations. Common standards will be required to compare microbiome results across studies, particularly to identify strong microbial signatures predictive of AMD. Much of the evidence implicating gut dysbiosis as a cause of retinal degeneration comes from studies in animal models. While these studies have been very informative regarding putative mechanisms, they cannot accurately recapitulate the complex environment of the human retina with regard to age-related changes and disease progression <sup>[31-34]</sup>. Therefore, translational research studies involving human subjects will be critical to confirm findings in experimental animal models. A important gap in this area is the lack of large scale randomized clinical trials testing the efficacy of microbiome-targeted treatments. While diet modification, probiotic use and microbiome-based treatment theoretically hold some promise, firm clinical data are still lacking. Extra future directions could involve multi-omics approaches combining microbiome sequencing with metabolomics, proteomics and cutting edge retinal imaging techniques, which may uncover microbial derived metabolites, and/or immune based pathways driving retinal degeneration <sup>[44]</sup>. Longitudinal studies assessing the temporal relationship between microbiome composition and AMD progression might further aid in identification of AMD-specific microbial signatures. Future personal medicine approaches incorporating individual factors of genetic susceptibility, metabolism and microbiome composition might better allow for AMD risk stratification and the development of targeted therapeutic strategies.

## **III. Conclusion**

A gut-retina axis represents a new model for considering systemically-driven factors in age-related macular degeneration (AMD). Emerging evidence supports a role for gut microbiome dysbiosis in contributing to retinal disease via a network of inflammatory and oxidative stress mechanisms, including increased intestinal permeability, endotoxemia, complement activation, inflammasome signalling, oxidant stress and metabolic dysregulation <sup>[27, 41-44]</sup>. Observational and experimental evidence support a model where modifications in gut microbiota could influence retinal immune responses and pathological neovascularisation, intersecting with other environmental factors, such as diet, smoking, metabolic health and ageing. Recognising AMD as a systemic immunometabolic disorder implies that alternative treatments targeting upstream contributors to retinal inflammation in the gut and systemically, including modification of diet, microbiome-based interventions and systemic metabolic control might complement existing ocular treatments including anti-VEGF and complement inhibitors. However further investigation will be needed to demonstrate causality and potential for clinical application.

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