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Abstract

The gut microbiota is a complex ecosystem that inhabits the gastrointestinal tract and consists of archaea, fungi, viruses, and bacteria, with bacteria being dominant. From birth onwards, it coevolves dynamically together with the host. The composition of the gut microbiota is under the influence of a complex interplay between both host and environmental factors. Scientific advances in the past few decades have shown that it is essential in maintaining homeostasis and tipping the balance between health and disease. In addition to its role in food digestion, the gut microbiota is implicated in regulating multiple physiological processes in the host gut mucosa and in distant organs such as the brain. Persistent imbalance between gut microbial communities, termed "dysbiosis," has been associated with several inflammatory and metabolic diseases as well as with central nervous system disorders. In this review, we present the state of the art of current knowledge on an emerging concept, the microbiota–retina axis, and the potential role of its disturbance in the development of retinopathies. We also describe several microbiota-targeting strategies that could constitute preventive and therapeutic tools for retinopathies.

1. Introduction

Although the relationship between the gut microbiota and the host remains to be fully elucidated, our knowledge on the essential role that the gut microbiota plays in maintaining a *mens sana in corpore sana* grows daily. The gut microbiota —an entity of the human body that has been long neglected or underestimated— for the past few decades has taken center stage in medical and scientific research while attracting the interest of the pharmaceutical industry. It is now well established that the roles of the gut microbiota are not restricted to the gastrointestinal compartment. Indeed, basic research in recent decades moved toward trans-disciplinarity, enabling the identification of several pivotal pathways (e.g., neuronal, endocrine, and immune signaling pathways) and molecular factors (e.g., metabolic, immunological, and neurochemical host factors, metabolites derived from the microbiota) that connect the gut microbiota to the rest of the body, and particularly to the central nervous system (CNS) (Ahlawat et al., 2020; Morais et al., 2021; Schroeder and Backhed, 2016). It also led us to assess how complex the dialogue is between the gut microbiota and the host and how powerful the influence of the microbiota on the physiological functions of the host may be. As a result, the gut microbiota is now considered an essential contributor to CNS development, functionality, and health. The importance of the gut microbiota in tipping the balance between health and disease is supported by the association between gut microbiota imbalance and numerous brain disorders, including neurodevelopmental (e.g., autism), behavioral (e.g., depression and anxiety), and neurodegenerative (e.g., Parkinson's disease and Alzheimer's disease) diseases (Morais et al., 2021).

The retina is the light-sensitive neural tissue that lines the back of the eyes. Both from an anatomical and a developmental aspect, the retina is considered an extension of the brain. Interestingly, many features of neurodegenerative processes in the CNS are similar to those observed in the retina, and some neurodegenerative disorders of the CNS can have repercussions in the retina and vice versa (Byun et al., 2021; London et al., 2013; Nucci et al., 2015). This review aims to present the current data from studies of humans and animal models that point to the role of the gut microbiota in maintaining retinal physiology. We also discuss the opportunities that may exist to use the gut microbiota as a target for preventive and therapeutic strategies as well as for the diagnosis of retinal diseases.

2. Gut microbiota and its derived metabolites in patients with retinal neurodegenerative diseases

2.1. Diabetic retinopathy

Diabetic retinopathy (DR) is a complication that affects approximately 30% of individuals with diabetes (Wong et al., 2016). Prolonged duration of diabetes, hyperglycemia, and systemic hypertension are strongly associated with DR. The disease starts with a mild non-proliferative stage (retinal microaneurysms) that may evolve to a proliferative stage whose features include neovascularization and vitreous or preretinal hemorrhages. Patients with DR may also develop diabetic macular edema. Although DR has long been regarded a microvascular disease, recent studies suggest that retinal neurodegeneration precedes vascular changes (Lynch and Abramoff, 2017; Zafar et al., 2019). Alterations in the composition of the gut microbiota have been reported in patients with diabetes (Knip and Siljander, 2016; Yang et al., 2021) and evidence points to the contribution of these microbial changes to disease pathophysiology (de Groot et al., 2021; Vrieze et al., 2012; Wang et al., 2019; Yu et al., 2019). Although it had been suspected, the role of the gut microbiota in the development of DR has only recently been investigated. The fecal microbiota of a very small cohort in Saudi Arabia was analyzed using culture-based techniques and molecular identification targeting *Bacteroides* (**Table 1**) (Moubayed et al., 2019). No change was found between the fecal microbiota of diabetic patients with or without retinopathy. However, the small size of the cohort and the culture-based investigation methods used may have contributed to limitations in the study. More recently, two independent studies in China and in southern India reported alterations of the gut microbiota associated with DR (**Table 1**) (Das et al., 2021; Huang et al., 2021). In both studies, no difference in the alpha-diversity indices —which reflect the richness and diversity within the ecosystem — was observed between the fecal microbiota of diabetic patients without and those with DR. In addition to alterations associated with diabetes, several modifications were observed at phylum and genera levels between the fecal microbiota of DR patients and that of controls and/or diabetic patients without DR. However, these alterations were not similar in the two studies. Among the most represented phyla, a decrease in *Actinobacteria* was reported in DR patients compared to controls and to diabetic patients without DR in the Indian cohort, whereas the relative abundance of this phylum was unchanged in the Chinese cohort (Das et al., 2021; Huang et al., 2021). Moreover, in the Chinese cohort *Firmicutes* were less abundant in the DR group than in the two other groups

(Huang et al., 2021). In the Indian cohort, a decrease in the abundance of 13 genera and an increase in the abundance of six genera were observed in DR patients compared to diabetic patients without DR (Das et al., 2021). However, the biological consequences of these changes for the host remain difficult to predict since the abundance of genera with detrimental/pathogenic or with beneficial potential was found to be increased or decreased in DR patients. The alterations observed in the Chinese cohort were different to those in the Indian study, but so were the analysis methods (Huang et al., 2021). From this cohort, a biomarker set of 25 bacterial families was identified that can distinguish diabetic patients with DR from patients without DR and from controls (Huang et al., 2021). However, these results have to be confirmed in independent cohorts. Very recently, the relative abundance of the predominant phyla was compared in the fecal microbiota of Indian diabetic patients with or without sight-threatening DR (Khan et al., 2021)**.** No difference was observed between the two groups (**Table 1**). However, data from this study suggest that the relative abundance ratio of *Bacteroidetes* to *Firmicutes*, which are the dominant gut microbial phyla, might be considered a marker associated with DR development.

Choline, L-carnitine, betaine, and other choline-containing compounds that are present in the human diet are metabolized by the gut microbiota to generate trimethylamine (TMA), which is further converted to trimethylamine-*N*-oxide (TMAO) in the liver and transported to the tissues (Janeiro et al., 2018). Alterations in TMAO have been associated with pathological conditions in rodents and humans, including diabetes (Liu et al., 2021; Nowinski and Ufnal, 2018; Shan et al., 2017). A cross-sectional study that included 40 patients without type 2 diabetes, 50 diabetic patients without DR, and 74 diabetic patients with non-proliferative or proliferative DR revealed that elevated plasma levels of TMAO were associated with DR and its severity (Liu et al., 2021). Metabolomic studies also brought clues about the involvement of the gut microbiota in DR. Nuclear magnetic resonance (NMR)-based metabolomic exploration of eye fluids in controls and diabetic patients with and without DR led to the identification of DR-associated alterations in metabolic pathways of energy metabolism and amino acids (Barba et al., 2010; Jin et al., 2019). Among the changes observed was a decreased level of succinate in both the aqueous humor and the vitreous humor of DR patients compared to non-diabetic controls and/or diabetic patients without DR (Barba et al., 2010; Jin et al., 2019). Interestingly, succinate has been shown to be produced in large amounts during the fermentation of dietary fibers by the gut microbiota (De Vadder et al., 2016). However, whether the metabolic changes observed in eye fluid ensue from alterations in the gut microbiota remains to be determined.

Altogether, these data suggest a role of the gut microbiota in the development of DR. However, discrepancies in the studies regarding the microbial signature that could be associated with the disease show that other studies are needed to better characterize the microbial alterations that are specifically associated with DR, particularly the changes that drive the switch from diabetic status without DR to a diabetic status with DR. Indeed, diabetes - the pathological condition that constitute the pre-requisite to develop DR - is already associated with deep restructuration of the gut microbiota (Gurung et al., 2020). Prospective cohort studies would be valuable and would represent powerful tools for better characterizing the temporal remodeling of the gut microbiota in relation to the evolution of the diabetes and the development of DR.

2.2. Glaucoma

Glaucoma comprises a group of optic neuropathies characterized by progressive and irreversible damage to the optic nerve (Wang et al., 2020). It leads to visual impairment if untreated. The causes of glaucoma are complex, but elevation of intraocular pressure has been identified as a major risk factor. However, the mechanisms that lead to glaucomatous degeneration are still not fully understood. Only a few studies have analyzed the composition of the gut microbiota in glaucomatous patients. Gong and colleagues determined the composition of the fecal microbiota from a Chinese cohort comprising 30 patients with primary open-angle glaucoma (POAG), the main form of glaucoma, and 30 age- and sex-matched non-POAG controls (**Table 2**) (Gong et al., 2020). No difference in alpha-diversity was observed between the POAG and non-POAG patients. An over-representation of *Prevotellaceae, Escherichia coli,* and another unidentified *Enterobacteriaceae* was found in the fecal microbiota of POAG patients, whereas *Megamonas* and *Bacteroides plebeius* were more prevalent in controls. The authors speculated that the pro-inflammatory properties of *Prevotella* spp. and *E. coli* could contribute to neuronal inflammation and immune damage in glaucoma. In addition to the composition of the gut microbiota, Gong and colleagues also analyzed and compared the serum metabolic phenotype of POAG and non-POAG patients. Interestingly, they identified alterations in the metabolomic profile in POAG patients and showed that some of them correlated with changes in the abundance of some bacteria in gut microbiota, particularly that of *Megamonas* (Gong et al., 2020). However, more studies are needed to prove a causal relationship. Another study investigated the composition of the gut microbiota in Caucasian female patients with normal-tension glaucoma (NTG), in those with ocular hypertension (OHT), and in controls (Anne Katrine Toft-Kehler, 2020). No difference

in the fecal microbiota composition was found between the groups (**Table 2**). However, this study had some limitations, including the number of participants, the medications taken by patients, and the wide age range of the participants enrolled in the study (between 50 and 96 years of age). Besides, other studies suggest a role of the pathogenic Gram-negative bacteria *Helicobacter pylori* in the pathogenesis of glaucoma. However, an association of *H. pylori* infection with POAG is still debated (Doulberis et al., 2020). Another feature suggesting that microbiota could influence glaucoma is modulation of the levels of some metabolites that are related to the gut microbiota metabolism in host fluids of patients with glaucoma. Comparison of the metabolomic profiles of the plasma and of the aqueous humor in POAG and non-POAG patients revealed, among other changes, a reduced concentration of polyamines such as spermine and spermidine in POAG patients (Buisset et al., 2019; Leruez et al., 2018). Interestingly, polyamines can be synthesized by intestinal bacteria and gain the bloodstream via the colonic mucosa (Kibe et al., 2014; Tofalo et al., 2019). Another example is the elevated levels of TMA, a bacteria-derived metabolite that has been reported in the aqueous humor of patients with advanced POAG compared to patients with cataract (Skrzypecki et al., 2021). Finally, it should be noted that some other studies suggest a role of the oral microbiota in glaucoma (Anne Katrine Toft-Kehler, 2020; Astafurov et al., 2014; Lim et al., 2021; Polla et al., 2017).

2.3. Age-related macular degeneration

Age-related macular degeneration (AMD) is a progressive chronic disease of the retina that causes damage to the macula, a small central retinal area specialized in central vision (Chakravarthy et al., 2010). Two stages of the disease are distinguished. The early stage is characterized by the formation of large deposits called “drusen” and pigmentary abnormalities in the retina. The late stage of AMD can be subdivided into two forms: a non-exudative (or dry) form and an exudative (or wet) form. The non-exudative form is characterized by macular atrophy caused by an accumulation of drusen beneath the retinal pigment epithelium (RPE) and Bruch’s membrane that damages the RPE and may cause indirect photoreceptor cell death. The exudative form is characterized by choroidal neovascularization (CNV), which leads to RPE detachment and to RPE and photoreceptor cell death. The etiology of AMD is complex and not yet fully understood (Lambert et al., 2016). Interestingly, some environmental risk factors associated with AMD, such as diet, influence the composition and functions of the gut microbiota (Redondo-Useros et al., 2020; Singh et al., 2017). In addition, dysbiosis of the gut microbiota contributes to the establishment and strengthening of an

198 inflammatory environment as well as to the development of metabolic disorders, both of
199 which are pathological conditions associated with AMD (Al Bander et al., 2020; Dabke et al.,
200 2019; Rozing et al., 2020; Shanahan and Sheehan, 2016; Sonnenburg and Backhed, 2016; Tan
201 et al., 2020b). The fecal microbiota in patients with neovascular AMD has been determined
202 by shotgun metagenomic sequencing in two studies from the same Swiss research group
203 (**Table 3**) (Zinkernagel et al., 2017; Zysset-Burri et al., 2020). This technology enables the
204 identification and the profiling of the microbial genes of a sample (the metagenome). In the
205 first study, the number of participants enrolled was small (12 patients with neovascular AMD
206 and 11 age- and sex-matched healthy controls) (Zinkernagel et al., 2017). Differences in the
207 bacterial communities were observed between AMD patients and controls. Notably, an
208 increase in the relative abundance of the phylum *Firmicutes* and a decrease in that of the
209 phylum *Bacteroidetes* were observed in the patients with AMD. In addition, the fecal
210 microbiota of AMD patients was enriched in bacteria belonging to the genera *Anaerotruncus*
211 and *Oscillibacter* and the species *Ruminococcus torques* and *Eubacterium ventriosum*,
212 whereas the fecal microbiota of controls was enriched in *Bacteroides eggerthii*. Apart from
213 providing information about the taxonomic composition of the microbiota, comparison of the
214 metagenomes revealed differences in the functional profiles of the fecal microbiota between
215 patients with neovascular AMD and healthy controls. Indeed, the fecal microbiota of AMD
216 patients lacked bacteria responsible for fatty acid elongation, whereas it was enriched in
217 bacteria with increased L-alanine fermentation, glutamate degradation, and arginine
218 biosynthesis capabilities.
219 A higher number of patients were enrolled in the second study (57 patients with
220 neovascular AMD and 58 age- and sex-matched healthy controls (Zysset-Burri et al., 2020).
221 Principal component analyses revealed differences in the relative abundance of microbial
222 species but not in the relative abundance of functional profiles between patients with
223 neovascular AMD and controls. Comparison of the relative abundances between the two
224 groups identified the class *Negativicutes* as being increased in the fecal microbiota of patients
225 with neovascular AMD, and the genera *Bacteroides,* and to a lesser extent *Oscillibacter*, as
226 being increased in controls (Zysset-Burri et al., 2020). Interestingly, using multivariate
227 association with linear models, Zysset-Burri and colleagues identified a correlation between
228 polymorphisms in the gene encoding complement factor H that are associated with AMD
229 (Maller et al., 2006) and variations in the abundance of a cluster of bacteria, including
230 *Bacteroides* species, *Ruminococcus torques*, the order *Clostridiales,* and the class
231 *Negativicutes,* belonging to the phylum *Firmicutes*. In addition, the fecal microbiota of

patients with neovascular AMD was enriched in genes of the ribonucleoside degradation pathway, and the species *Bacteroides uniformis*, *Odoribacter* unclassified, and *Eubacterium eligens* were negatively correlated with the pyrimidine ribonucleoside degradation pathway.

Zinkernagel and Zysset-Burri studies indicate a shift toward *Firmicutes* being increased in patients with AMD and *Bacteroidetes* being more abundant in controls. Interestingly, changes in the *Firmicutes* and *Bacteroidetes* abundances have been associated with obesity and various other diseases (Kho and Lal, 2018).

Lin and colleagues recently revealed in a review article results raising from the analysis of the gut microbiota composition in an independent clinical case-control study enrolling 85 advanced AMD and 49 healthy control subjects (Lin et al., 2021). Although details of the study have not yet been published, they reported alterations in the gut microbiota of AMD patients that were characterized by an enrichment in *Prevotella*, *Holdemanella*, *Desulfovibrio*, and a reduced abundance in *Oscillospira*, *Blautia*, and *Dorea* (Lin et al., 2021) (**Table 3**). They also showed that intake of AREDS supplement (vitamins C and E, beta-carotene, copper and zinc; (Hammond and Johnson, 2002)) was associated with an enhancement of the alpha diversity (Lin et al., 2021). Interestingly, they also observed that AMD-associated risk alleles, particularly *ARMS2* and *CFH* risk alleles, were associated with alterations of the gut microbiota including a decrease in the alpha-diversity and an increase in potentially harmful bacteria (IgA-bound bacteria) (Lin et al., 2021).

Some discrepancies between the studies (e.g., for *Oscillibacter*) and a lack of consensus in the observation highlight the need to examine other independent cohorts in order to better characterize the gut microbiota associated with AMD as well as factors that may influence the modulation of its composition in such a disease context. Age is a major risk factor of AMD and this demographic factor as well as other environmental factors related with ageing (e.g., medication, place of residence) are associated with gut microbiota changes (O'Toole and Jeffery, 2015). Thus, it appears important to take into consideration such confounding factors. Based on the available data, it appears that, as for other chronic diseases, host genetic factors as well as dietary supplements might contribute in shaping the gut microbiota of AMD patients.

Beyond data on fecal microbiota obtained *via* metagenomics, it is interesting to note that data from metabolomic analyses on the plasma of patients with AMD also suggest changes in the composition and functionality of the gut microbiota are associated with the disease (Acar et al., 2020; Osborn et al., 2013). Indeed, the gut microbiota is involved in producing secondary bile acids by modifying primary bile acids. A metabolome-wide

association study identified among other metabolite changes that bile acids were decreased in patients suffering from neovascular AMD (Marin et al., 2015; Osborn et al., 2013; Ridlon et al., 2014).

3. The gut microbiota and its derived metabolites: what animal models tell us about their influence on retinal physiology

3.1. Gut microbiota and lipid composition of the retina

Lipids represent approximately 20% of the dry weight of the retina, making this the tissue with the highest lipid content in the body after adipose tissue and the brain. Lipids play critical roles in the development of the retina and the maintenance of its structure and functionality. A specific feature of the retina is its high content of polyunsaturated fatty acids (PUFAs) and in particular docosahexaenoic acid (DHA), a PUFA of the n-3 series. DHA, which can represent up to 50% of total fatty acids in the photoreceptor outer segments, is involved in visual processes and the maintenance of retinal homeostasis. Retinal lipids consist mostly of phospholipids (87.3% and 58.3% of total lipids in the human neuroretina and retinal pigment epithelium, respectively), with plasmalogens (Pls) representing approximately 10% of these glycerophospholipids (Acar et al., 2007; Bretillon et al., 2008). Pls are characterized by a vinyl-ether bond at the *sn*-1 position of the glycerol backbone, which differentiates them from diacylglycerophospholipids and their ester bond. Plasmenyl-ethanolamine (PlsEtn) is the most widely represented class of Pl in both the neural retina and the RPE (Acar et al., 2007). In the neural retina, the major species of PlsEtn are those containing PUFAs, arachidonic acid (AA, C20:4n-6; in PlsEtn16:0/20:4 and PlsEtn18:0/20:4), or DHA (C22:6n-3; in PlsEtn18:0/22:6) at their *sn*-2 position (Saab et al., 2014b). Such PUFAs are the precursors of bioactive molecules such as prostaglandins, leukotrienes, resolvins, and protectins. Apart from being a reservoir for these PUFAs, Pls play a role in the protection against oxidative stress (Brites et al., 2004; Stables and Gilroy, 2011). Defects in Pls are suspected to contribute to the pathophysiology of retinopathies such as glaucoma and retinopathy of prematurity (Acar et al., 2009; Saab et al., 2014a; Saab et al., 2014b).

Accumulating evidence from human and animal studies points to the key role of the gut microbiota in the modulation of host lipids through regulation of several aspects of lipid metabolism, such as de novo biosynthesis or intestinal absorption, transport, and storage in

host tissue (Backhed et al., 2004; Ghazalpour et al., 2016; Kindt et al., 2018; Martinez-Guryn et al., 2018; Velagapudi et al., 2010; Villette et al., 2020). One of the first pieces of evidence showing that the gut microbiota could influence the retinal lipid content was provided over 10 years ago by Orešič and colleagues when they compared the lipidome of retinas from germ-free mice (i.e., mice raised without microbiota) and conventionally raised mice (Oresic et al., 2009). Their study showed that the presence of the gut microbiota was associated with an elevation of the retinal content in PlsEtn, particularly in PlsEtn18:0/20:4. Recent data from our laboratory complete this observation by showing that, beyond its presence, the composition of the gut microbiota may also influence the lipid content of nervous tissues (Albouery et al., 2019). Indeed, we showed that colonization of germ-free mice by the fecal microbiota from old donor mice results in significant changes in the cortex lipidome compared with germ-free mice colonized by the fecal microbiota from young donor mice. Another study that analyzed the functional activity of the gut microbiota in patients with AMD by metagenomics supported the hypothesis of an influence of the gut microbiota on the retinal lipids. In this work, although no causal relationship was established with the retinal lipid content, a reduction in the expression of genes involved in fatty acid elongation was observed in the gut microbiota of AMD patients compared with age-matched controls (Zinkernagel et al., 2017). Fatty acid elongation serves in the biosynthesis of long-chain PUFAs such as DHA from short-chain precursors. This finding makes sense considering the pathophysiology of AMD, for which a high supply of long-chain PUFAs such as DHA has been shown to be protective (Liu et al., 2010; Zinkernagel et al., 2017).

3.2. Influence of gut microbiota and gut microbiota-derived metabolites on retinal inflammation

It is now well established that the gut microbiota contributes to the development of the immune system and that dysbiosis is a central player in the promotion of inflammatory conditions, ranging from localized acute colitis to low-grade systemic inflammation (Aldars-Garcia et al., 2021; Buford, 2017; Tilg et al., 2020). The contribution of the gut microbiota through its presence and its composition in driving inflammatory-related pathologies has been well characterized in several animal models (Chassaing and Gewirtz, 2014). In humans, dysbiosis has been linked to inflammation in numerous pathological conditions such as inflammatory bowel diseases, metabolic disorders, and some age-related neuroinflammatory diseases, including Alzheimer's disease (Megur et al., 2020; Neurath, 2020; Tilg et al., 2020). Among other mechanisms, studies have highlighted the role of bacterial cell wall compounds

(e.g., lipopolysaccharide and peptidoglycan) or bacterial-derived metabolites (e.g., short-chain fatty acids [SCFAs]) in driving low-grade inflammation (Cani et al., 2007).

Over the past few decades, evidence has accumulated on the influence of the gut microbiota on retinal inflammation in various pathological contexts. In the eye, autoimmune uveitis is characterized by inflammation of the uvea (iris, ciliary body, choroid) and neuroretina (Amador-Patarroyo MJ, 2013). Studies on mouse models of experimental autoimmune uveitis (EAU) have provided evidence for a role of the gut microbiota in the modulation of the responses and behavior of uveitogenic T lymphocytes as well as in the development of intraocular inflammation (Horai et al., 2013; Horai et al., 2015; Janowitz et al., 2019; Nakamura et al., 2016). This topic has been extensively discussed in a recent review (Salvador et al., 2020). Interestingly, oral administration of propionate, one of the SCFAs produced in the colon through the fermentation of dietary fibers by intestinal bacteria, has been shown to attenuate immune-mediated uveitis in a mouse strain-dependent manner (Nakamura et al., 2017).

A role of the gut microbiota in inflammation associated with the development of retinopathy in diet-induced metabolic disorders has also been demonstrated. Increased amounts of pro-inflammatory cytokines (interleukin [IL]-1beta, IL-6, and tumor necrosis factor [TNF]-alpha) were observed at both systemic and choroid levels in mice fed a high-fat diet (HFD; (Andriessen et al., 2016). The phenotype was reversed following oral intake of a broad-spectrum antibiotic, neomycin, and partially reversed following the transfer of fecal microbiota from mice fed a regular-chow diet to recipient HFD-fed mice (Andriessen et al., 2016). Other data suggest that the gut microbiota influences the retinal inflammatory status in DR conditions. Indeed, long-term exposure of *db*/*db* mice to intermittent fasting —a condition associated with restructuring of the gut microbiota, reinforcement of gut barrier integrity, and a decrease in circulating peptidoglycans— leads to a reduction in the number of IBA-1$^+$ cells that are markers of microglial activation as well as to decreased infiltration by CD45$^+$ hematopoietic cells in the retina (Beli et al., 2018). In addition, it has been reported that administration of ursodeoxycholic acid (UDCA), a secondary bile acid generated by gut bacteria, improves the DR-like phenotype in a streptozotocin (STZ)-induced diabetic mouse model through the attenuation of retinal inflammation (Chung et al., 2017; Ouyang et al., 2018). Oral administration of UDCA reduced the number of IBA-1$^+$ cells in retinal ganglion cells and retinal inner plexiform layers, and also decreased the activation of the NF-kappaB pathway and the expression level of mRNAs encoding pro-inflammatory cytokines (TNF-alpha, IL-1beta, and IL-6) in retinas of STZ-induced diabetic mice (Ouyang et al., 2018).

Similarly, the increased retinal expression of MCP-14 and TNF-alpha observed in STZ-induced diabetic mice was limited by intraperitoneal injection of UDCA (Chung et al., 2017).

Retinitis pigmentosa (RP) is a heterogeneous group of inherited neurodegenerative retinal disorders characterized by a progressive bilateral degeneration of the photoreceptors, leading to night blindness and progressive visual field defects (Ferrari et al., 2011). RP is associated with chronic activation of microglial cells, which are resident immune cells within the retina (Gupta et al., 2003). Systemic treatment with tauroursodeoxycholic acid (TUDCA), a secondary biliary acid, was shown to reduce the number and the activation of microglial cells in P23H rats, a model of RP (Noailles et al., 2014).

3.3. Influence of gut microbiota and gut microbiota-derived metabolites on pathological vascularization in the retina

Obesity and type 2 diabetes are conditions that influence the development of AMD and DR, two diseases whose hallmarks include retinal neovascularization processes (Adams et al., 2011; DeFronzo et al., 2015; Zhang et al., 2016). Andriessen and colleagues have elegantly demonstrated that the gut microbiotal dysbiosis associated with diet-induced metabolic disorders contributes to retinal neovascularization (Andriessen et al., 2016). Indeed, they showed that an HFD-fed mouse model of exudative AMD displayed systemic and choroidal inflammation as well as an exacerbated CNV. A set of experiments, including the transfer of cecal microbiota from HFD- or chow-diet-fed mice to recipient mice, revealed that the gut microbiota drives the vascular phenotype. Although a causal relationship was not firmly demonstrated, the influence of the gut microbiota composition on the development of retinal vascular abnormalities was strengthened by another study. The authors showed that long-term exposure of mice to intermittent fasting altered the gut microbiota composition and prevented the development of acellular capillaries in the retina of *db*/*db* mice, a potential model for DR (Beli et al., 2018).

Several studies support a protective role of bile acids in mechanisms related to abnormal vascularization. It has been shown in rats that systemic administration of UDCA and TUDCA reduced laser-induced CNV lesions (Woo et al., 2010). UDCA also provides protection of the vascular integrity in an STZ-induced DR model (Chung et al., 2017; Ouyang et al., 2018). Long-term exposure to intermittent fasting, a condition associated with the prevention of diabetic microvascular complications, was associated with an increase in plasma levels of TUDCA (Beli et al., 2018). TUDCA is an agonist of the bile acid receptor TGR5. Interestingly, pharmacological activation of TGR5 by the bile acid agonist INT-767

led to a reduction in the development of acellular capillaries in DBA/2J mice treated with STZ and fed an HFD, an accelerated model of DR (Beli et al., 2018).

3.4. Influence of gut microbiota and gut microbiota-derived metabolites on retinal neurodegeneration

The dry form of AMD is characterized by a progressive macular degeneration of the retinal pigment epithelium that precedes photoreceptor cell loss and by lipofuscin accumulation and drusen formation. Feeding mice a high-glycemic-index diet (HD) is associated with age-related retinal lesions (Rowan et al., 2017; Uchiki et al., 2012; Weikel et al., 2012). Interestingly, Rowan and colleagues showed that switching mice from an HD to an isocaloric low-glycemic-index diet during the last 6 months of life prevented the development of age-related eye disorders. In this study, although the experimental setting did not identify a causal relationship, it was shown that modifications in the microbiome and metabolome were associated with the retinal phenotype (Rowan et al., 2017).

Chen and colleagues recently provided evidence that the gut microbiota is a contributing factor to glaucoma pathophysiology (Chen et al., 2018). They showed that transient elevation of intraocular pressure induced T-cell infiltration into the retina, an event mediating prolonged retinal neurodegeneration. In addition, they observed that glaucomatous T-cell responses targeted both human and bacterial heat shock proteins (HSP). Interestingly, HSP-specific T-cell response and neurodegeneration were abolished in germ-free mice, thus suggesting that exposure to the commensal microbial flora is required to induce HSP-specific T-cell response in neurodegeneration (Chen et al., 2018).

Another element linking the gut microbiota to the physiology of the neural retina is the neuroprotective effects of certain secondary biliary acids. This topic has been extensively reviewed recently (Daruich et al., 2019). Briefly, TUDCA was shown to protect retinal ganglion cells and photoreceptors from cell death and stress and to preserve the retinal function in several models of retinal disorders (Daruich et al., 2019). In addition, it was reported that TUDCA promotes the phagocytosis of photoreceptor outer segments by retinal pigment epithelial cells, a crucial process for retinal homeostasis (Murase et al., 2015). Finally, other data suggest that SCFAs such as butyrate could modulate intraocular pressure (Skrzypecki et al., 2018).

4. Targeting the gut microbiota as a strategy for the prevention and the treatment of retinal diseases

Evidence is accumulating on the existence of a gut microbiota–retina axis and on the influence of the gut microbiota on the development and progression of retinal disorders. Hence, manipulating the gut microbiota appears to be an attractive and promising strategy for preventing or limiting symptoms of retinal diseases. Several strategies for modifying the gut microbiota in this context are discussed hereafter. Their precision range from the transfer of complex microbial communities (e.g., fecal microbiota transplant, FMT) to the delivery of specific microbiota-derived metabolites (e.g., postbiotics). Among the other approaches that we present, some induce shift in bacterial communities (e.g., prebiotics and diet) while others introduce selected bacterial species (e.g., probiotics) into the gut microbiota or are designed to deplete the gut microbiota of some bacterial species (e.g., phage therapy).

4.1. Probiotics

The term "probiotic" refers to "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (Hill et al., 2014). The most common strains used as probiotics are lactic acid bacteria and bifidobacteria. However, other species such as *Akkermansia muciniphila* or *Faecalibacterium prausnitzii* are considered promising next-generation probiotic candidates (Cani and de Vos, 2017; Martin et al., 2018). The general features of probiotics are to support homeostasis of the digestive tract, to modulate the immune system, and to balance the gut microbiota. Supplementation with probiotics can also have extraintestinal effects. Indeed, the beneficial effects of specific probiotics on neurological disorders have been described in animal models and in humans (Sasmita, 2019; Westfall et al., 2017). Interestingly, results from experimental studies suggest that supplementation with probiotics could also protect the retina from deleterious conditions. Some proof in this regard originated from the organism model *Drosophila melanogaster*, in which the administration of *Lactiplantibacillus plantarum* DR7 was shown to alleviate eye neurodegeneration (rough eye phenotype) induced by the expression of Alzheimer's Aβ42 peptide (Tan et al., 2020a). In addition, oral administration of the probiotic strains *Escherichia coli* Nissle 1917 or IRT-5 (a mixture consisting of *Lacticaseibacillus casei*, *Lactobacillus acidophilus*, *Limosilactobacillus reuteri*, *Bifidobacterium bifidum*, and *Streptococcus thermophilus*) was able to reduce the severity of EAU in mice, at least partly by modulating

the immune system (Dusek et al., 2020; Kim et al., 2017). The positive effects of oral supplementation with probiotics have also been described for ocular structures other than the retina. Indeed, *L. plantarum* NK151 and *B. bifidum* NK175 as well as the ITR5 probiotics have been shown to improve dry eye symptoms in mice (Choi et al., 2020; Kim et al., 2017; Moon et al., 2020; Yun et al., 2021). In addition, dietary supplementation with the probiotic strain *Lacticaseibacillus rhamnosus* GG has been shown to be effective in antagonizing the disturbances in retinoid metabolism caused by the pollutant perfluorobutane sulfonate in the gut and the eye of zebrafish (Hu et al., 2020).

The use of probiotics as live vectors to deliver therapeutic molecules is a strategy drawing the attention of scientists and pharmaceutical companies. Thanks to accumulating knowledge on their safety (GRAS and QPS certifications) and beneficial health effects, as well as engineering tools that have been developed, several lactic acid bacteria and bifidobacteria are considered good candidates for such a strategy (Bermudez-Humaran and Langella, 2017; Plavec and Berlec, 2019). The potential of two engineered lactobacilli in protecting the mouse retina from DR has been investigated by Li and colleagues (Crackower et al., 2002; Verma et al., 2020b). They designed two recombinant *Lacticaseibacillus paracasei* ATCC 27092 to express and secrete ACE2 or angiotensin-(1-7) (Ang-(1-7)), two proteins belonging to the renin–angiotensin system (Patel et al., 2016), in fusion with the non-toxic subunit B of cholera toxin, a transepithelial carrier. A protective role has been reported for ACE2/Ang-(1-7) in uveitis and DR (Dominguez et al., 2016; Qiu et al., 2014; Shil et al., 2014; Verma et al., 2012). Oral administration of ACE2- or Ang-(1-7)-*L. paracasei* showed efficacy in limiting retinal inflammation and neurovascular degeneration in mouse models of DR (Verma et al., 2020a; Verma et al., 2020b). Although they are considered as safe and well tolerated by healthy subjects, long-term use of probiotics might entail risk under certain contexts (e.g., probiotic translocation to extra intestinal sites in patients with damaged intestinal barrier or compromised immunity, transfer of antibiotic-resistant traits to commensal or pathogenic intestinal bacteria) (Yelin et al., 2019).

4.2. Prebiotics

The term “prebiotic” refers to “a substrate that is selectively utilized by host microorganisms conferring a health benefit” (Gibson et al., 2017). This later relies on changes in the microbiota composition (e.g., stimulation of bifidobacteria and lactobacilli but also other taxa such as *Faecalibacterium* spp. or *A. muciniphila*) and metabolism (e.g., fermentation of the substrate and production of metabolic products such as SCFAs). Beneficial effects of

prebiotics are not restricted to the gastrointestinal compartment; evidence showing that they can also influence the health status of extraintestinal organs was reported for the brain (Collins and Reid, 2016). The most extensively studied and documented dietary prebiotics come from carbohydrates (e.g., non-digestible oligosaccharides fructans and galactans). Intragastric administration of chitosan oligosaccharide (COS) have been shown to attenuate oxidative stress-induced retinal damages in rats (Fang et al., 2013). Although alterations of the composition of the gut microbiota by COS have been documented, involvement of these microbial changes in the beneficial effects of COS on the retina remains to be evaluated since COS can be absorbed through the intestinal epithelia (Muanprasat and Chatsudthipong, 2017; Zhang et al., 2018). Other substances such as polyphenols are also regarded as prebiotics since their beneficial effects on health involve their biotransformation by the gut microbiota, modulation of the gut microbiota composition, and production of microbial metabolites (Collins and Reid, 2016; Mithul Aravind et al., 2021). Interestingly, oral supplementation with resveratrol has been shown to have beneficial effects on retinopathies (Abu-Amero et al., 2016). However, it remains challenging to determine which part of the observed effects is related to resveratrol per se, its derived metabolites, or modifications of the gut microbiota consecutive to its administration.

To note that besides the abundant literature describing their beneficial effect on health, some studies reported that the use of certain prebiotics such as inulin could have possible harmful effects under specific contexts such as genetical susceptibility or pre-existing microbial dysbiosis (Miles et al., 2017; Singh et al., 2018).

4.3. Synbiotics

The term "synbiotic" refers to "a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host" (Swanson et al., 2020). The substrate(s) is called a "synergistic synbiotic" when it is selectively utilized by the allochthonous microorganisms. If the synbiotic includes a prebiotic that has been designed to be utilized by the autochthonous microorganisms, it is then called a "complementary synbiotic." The effects of oral supplementation with synbiotic formulations on neurodegenerative or ocular diseases have been little explored to date, either in model organisms or in humans (Arora et al., 2020; Askari and Moravejolahkami, 2019; Chisari et al., 2017; Peterson, 2020).

4.4. Paraprobiotics (also called "ghosts," "non-viable probiotics," or "inactivated probiotics")

Paraprobiotics are defined as "non-viable microbial cells (either intact or broken) or crude cell extracts which when administered (either orally or topically) in adequate amounts confer a benefit to the consumer" (Nataraj et al., 2020). Their beneficial health effects are mediated by the metabolites/molecules contained in the inactivated microorganisms. Morita and colleagues explored the efficacy of heat-killed *L. paracasei* KW3110 in protecting the retina against several stress conditions. They showed that long-term intake of this paraprobiotic modulated the gut microbiota composition in aged mice. Among other changes, the relative abundance of bifidobacteria (health-promoting bacteria) was increased and that of *Streptococcaceae* (bacteria with pro-inflammatory potential) was decreased in the gut microbiota of aged mice supplemented with heat-killed *L. paracasei* KW3110 compared to age-matched controls (Morita et al., 2018b). Supplementation with this parabiotic was effective in alleviating inflammation associated with aging (at the gut, systemic, and retinal levels) or induced in the retina by blue light exposure (Morita et al., 2018b; Morita et al., 2018c). It also protected against age-related retinal ganglion cell loss and blue light-induced photoreceptor degeneration (Morita et al., 2018b; Morita et al., 2018c). Some data suggest that heat-killed *L. paracasei* KW3110 could prevent chronic eye disorders, including eye fatigue (Morita et al., 2018a; Yamazaki et al., 2020).

4.5. Postbiotics

Postbiotics refers to "non-viable bacterial products, cell constituents or metabolic products from microorganisms that have biologic activity in the host" (Nataraj et al., 2020). Like prebiotics and paraprobiotics, since postbiotics do not contain live microorganisms the risks associated with their intake are minimized, while their beneficial effects are promoted, at least partly. Examples of postbiotics are (a) cell-free supernatants obtained from microorganism cultures and containing secreted bioactive molecules having beneficial health effects (e.g., anti-inflammatory and/or anti-oxidant properties and/or ability to reinforce the intestinal barrier), (b) exopolysaccharides that are produced and released by microorganisms, and (c) metabolites produced by the gut microbiota such as SCFAs, which are generated from dietary fibers or urolithin A, which is generated from dietary polyphenols (Zolkiewicz et al., 2020).

4.6. Fecal microbiota transplant

FMT consists in transferring stool from a donor in a "healthy" state to the gastrointestinal tract of a recipient individual. The aim is to recover the homeostatic status of the gut microbiota at the compositional and functional levels (Ng et al., 2020). The potential of such a strategy to influence host physiology was highlighted by Gordon's research group in 2006, who reported that the phenotype of obese mice could be transferred to germ-free mice via FMT (Turnbaugh et al., 2006). In addition, the efficacy of FMT has also been demonstrated in the treatment of *Clostridioides difficile* infections in patients (Mullish et al., 2018). These findings turned attention to the use of FMT for the treatment of other diseases associated with dysbiosis such as inflammatory bowel diseases, metabolic syndrome, or autism (Hazel and O'Connor, 2020; Kang et al., 2019; Kootte et al., 2017; Vrieze et al., 2012). However, several issues are still under debate and research is ongoing before this technique can be further used in humans (e.g., the safety of donor feces regarding the risks of transmitting other pathogenic microorganisms, criteria for donor selection, better formulations and better methodology for delivery, etc.).

4.7. Phage therapy

Phages are viruses that infect and kill bacteria. They are present in all microbial environments, including the gastrointestinal tract (Mushegian, 2020; Sausset et al., 2020). Two groups of bacteriophages are distinguished according to their replication cycle: the lytic cycle and the lysogenic cycle. The lytic (or virulent) bacteriophages infect bacterial hosts and subvert them to produce phage progeny. Then, they induce bacterial host death upon lysis, thus releasing newly formed phages. The lysogenic (or temperate) bacteriophages integrate their nucleic acid in the genome of the host bacterium or as an extrachromosomal plasmid. They can be maintained as prophages in their bacterial host for several generations until induction of the lytic cycle. Bacterial surface molecules and phage receptor-binding proteins define the tropism of the phage to the bacteria. Phage therapy in bacterial infection relies on the use of phages to attack the targeted bacteria (Hassan et al., 2021; Principi et al., 2019). Used a century ago to cure patients with dysentery, cholera, or plague, their utilization was eclipsed in Western countries by the advent of antibiotics. However, faced with the rise of antibiotic resistance due to the extensive use of antibiotics in human health and agriculture, phage therapy is re-emerging as an attractive alternative. Among the advantages that phage therapy offers over antibiotics is the targeting of specific bacterial strains. Knowledge has accumulated over the past decade on phage–bacteria interactions (Sausset et al., 2020). Data obtained from experimental models and humans suggest that phage therapy could be a

valuable approach to target gut pathogens and bacteria resistant to antibiotics (Galtier et al., 2017; Ott et al., 2017; Principi et al., 2019). The use of phage therapy to re-establish eubiosis in a pathological condition associated with dysbiosis or to help maintain its stability is also being extensively explored. Interestingly, a shift in the virome composition has been observed in the gut microbiota of patients with inflammatory bowel diseases (Norman et al., 2015). Whether this change in phage composition is a cause or a consequence of bacterial dysbiosis remains to be elucidated.

4.8. Diet

The composition of diet and dietary habits are recognized as modulators of the gut microbiota (Barber et al., 2021; Leeming et al., 2019). Intrinsic and extrinsic factors influence the efficacy and responsiveness of dietary interventions. The composition and function of the gut microbiota can be rapidly modulated upon short-term, substantial dietary changes. However, studies suggest that long-term habits play a role in shaping an individual's stable gut microbiota. In addition, responsiveness to dietary interventions might depend on the starting composition of the individual's gut microbiota and the disease status (Cotillard et al., 2013; Sonnenburg and Backhed, 2016; Walker et al., 2011). Both the balance (low versus high intake) and the nature of macronutrients (carbohydrates, proteins, and fats) influence the gut microbiota. Indigestible carbohydrates (fermentable dietary fibers; see "Prebiotics" section) and omega-3 PUFAs are among the best-documented macronutrients, which have been reported to support a healthy gut microbiota (Menni et al., 2017; Noriega et al., 2016; Rinninella et al., 2019; Watson et al., 2018). Interestingly, protective effects of omega-3 PUFAs have been demonstrated in various pathological conditions, including metabolic and neurodegenerative disorders and retinal diseases (Bousquet et al., 2008; Calon et al., 2004). At least in part, the beneficial effect of omega-3 PUFAs in metabolic disorders seems to be related to their impact on the gut microbiota (Bidu et al., 2019).

Several observational studies suggest that dietary omega-3 PUFAs protect the retina against AMD initiation and progression (van Leeuwen et al., 2018). In this context, it has been recently reported that a 2-month supplementation with omega-3 PUFAs (eicosapentaenoic acid [EPA] and DHA) to aged mice delays features of normal age-related retinal degeneration (Prokopiou et al., 2019). Moreover, the results of studies in humans and experimental models support the beneficial effects of dietary omega-3 PUFAs against DR (Datilo et al., 2018; Sala-Vila et al., 2016; Suzumura et al., 2020; Yee et al., 2010). The beneficial effects of omega-3 PUFAs in retinal diseases have been attributed to their structural

role in membranes, their functional roles as signaling molecules, and their precursor role for bioactive molecules that regulate numerous biological processes such as inflammation, cell survival and differentiation, metabolism, and oxidative stress (Gong et al., 2017; SanGiovanni and Chew, 2005). However, in light of their impact on the composition and function of the microbiota, one can assume that part of the beneficial effects of dietary omega-3 PUFAs on the retina could be driven indirectly by the gut microbiota.

Another example illustrating how diet-induced changes in the gut microbiota can affect retinal physiology is that of Western diet (WD). Consumption of WD is associated with the development of diabetes and progression of AMD (Chiu et al., 2014). As discussed in the sections 3.2 and 3.3, Andriessen and colleagues have shown that the alterations of the gut microbiota associated with the consumption of a HFD influence the inflammatory status as well as the pathological vascularization of the retina in mice (Andriessen et al., 2016). Although more studies are needed to prove a causal relationship with changes in the gut microbiota, HFD-fed mice also exhibited an altered retinal lipid composition (Albouery et al., 2020). In addition to the high fat and low fiber content, the high content of WD in sugar is also a factor that affects the gut microbiota (Do et al., 2018). Exposition of rodents to high-fructose diet has been reported to impair the functionality of cone photoreceptors as well as to exacerbate the development of choroidal neovascularization in rats (Thierry et al., 2014; Thierry et al., 2015). However, the role of the gut microbiota in such phenotype remains also to be demonstrated. In addition, and as discussed in section 3.4, Rowan and colleagues reported that consuming high-glycemia (HG) diet was associated with the development of AMD features, which could be prevented/reversed by switching from HG to low-glycemia diet (Rowan et al., 2017). These retinal phenotypes correlated with compositional and functional changes of the gut microbiota (Rowan et al., 2017).

Several studies also support the role of micronutrients such as zinc, carotenoids, and vitamins C, E and D, in protecting against AMD. The putative role of the gut microbiota in the retinal effects of these micronutrients has been widely discussed by Rinninella and colleagues (Rinninella et al., 2018).

Finally, besides the nature of the diet, dietary practices could also support healthy gut microbiota. Notably, an emerging body of evidence suggests that nutritional restriction could have beneficial effects on the gut microbiota, particularly by enriching it in protective/beneficial bacteria (Rinninella et al., 2020). Data from FMT experiments indicate that these nutritional restriction-induced microbial changes contribute to improving metabolic

and inflammatory phenotypes associated with the pathogenesis of various diseases (Rinninella et al., 2020). Interestingly, restructuring of the gut microbiota by intermittent fasting prevents features related to DR in mice (Beli et al., 2018).

Other promising approaches to control the composition and/or the functionality of microbial populations are the subject of intensive research. They include the use of genome-targeting CRISPR-Cas systems — an approach that would enable the selective removal of bacterial strains — or the use of compounds interfering with quorum-sensing systems. The latter systems are used by bacteria to communicate with each other and allow for the control of specific processes such as expression of virulence factors or production of secondary metabolites (Belizario and Napolitano, 2015; Gomaa et al., 2014; Polkade et al., 2016).

Several strategies to restore eubiosis or prevent dysbiosis have been developed and others are still under investigation, some of them being promising. However, to date little is known about the effectiveness of these therapies on retinal diseases, particularly in humans. To be effective, the choice of the strategy to restore / re-balance the gut microbiota should be adjusted to the type of dysbiosis targeted, which leads to consider personalized therapies rather than systematic therapies. In addition, in light of the potential harmful side effects that are associated with certain therapies based on the modulation of the gut microbiota or that seems to be driven by host factors, it appears that more researchers are needed in the field and that a specialized medical supervision should accompany implementation of such therapies in patients.

5. The profile of the gut microbiota and/or its derived metabolites as a valuable tool for the diagnosis of retinal diseases

Using the gut microbiota composition and/or its related metabolite profile as a diagnostic tool for diseases associated with dysbiosis is a concept whose strength and reliability have been tested in compelling studies for diseases such as cancers (e.g., colorectal cancer, hepatocellular carcinoma) or type 2 diabetes (Baba et al., 1989; Qin et al., 2012; Ren et al., 2019). In combination with other biomarkers it could constitute a valuable tool for the early diagnosis of retinal diseases. Microbiota-based biomarkers to discriminate between patients with and without retinopathies have already been proposed (Huang et al., 2021; Khan et al.,

2021; Zysset-Burri et al., 2020). However, more cross-sectional studies with diverse populations are needed to strengthen this tool, particularly to make emerging robust microbial signatures specific to the disease and take into account host-related heterogeneity (lifestyle, dietary habits, ethnicity, etc.).

6. Conclusion

It has become evident that the physiology of the retina is under the influence of the gut microbiota. Indeed, although more data are needed, studies in humans suggested that dysbiosis is associated with retinopathies. In addition, accumulating evidence from animal models indicates that the gut microbiota influences retinal physiology and health status (**Figure 1**). However, while the identification of the molecular actors and pathways in the gut microbiota–brain dialogue is already well advanced, little is known about the gut microbiota–retina axis. It now appears urgent to fill this gap. Especially if the involvement of the gut microbiota in the development of retinopathies is proven, it could constitute a target for the design of tools both for diagnosis and for preventive and/or therapeutic strategies.

Unlike other pathologies such as inflammatory bowel diseases or some cancers, for which a body of evidence points to specific alterations of the gut microbiota, there is not clear microbial signatures associated with retinal pathologies in humans to date. Discrepancies may arise from several factors such as the low number of independent studies available (particularly for AMD) but also to the influence of genetic and/or environmental factors (e.g. dietary habits, drug treatments or stool collection). In addition, more microbiota-health studies will help to allow distinguishing correlation from causation. To date, most of the studies have been descriptive, making it impossible to evaluate the contribution of the gut microbiota as the causative factor of retinopathies. More research is needed to better characterize how the compositional and functional restructuring of the gut microbiota in humans (not only when the disease is diagnosed but also in the early stages of disease) affects host physiology.

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1286 **Table 1. Bacterial alterations observed in the fecal microbiota of patients with diabetic**
1287 **retinopathy (DR)**

Country	**Effective *n*** (control group)	**Method**	**Microbiota alterations**[7]
Saudi Arabia[1]	*n*=9 T2DM[5] without DR; *n*=8 T2DM with DR; (n=18)	Inoculation on different selective culture media; enumeration on agar plates; PCR amplification on presumptive *Bacteroides* colonies and sequencing (Applied biosystem sequence analyzer) using 16S rRNA AllBac 296F and 412R primers	Slight and negligible variation among T2DM patients with or without retinopathy
India[2]	*n*=25 T2DM without DR; *n*=28 T2DM with DR; (n=30)	Amplification of the V3–V4 region of 16S rRNA gene and sequencing on Illumina HiSeq platform	At the phylum level[8]: ↓ **in DR**: *Actinobacteria* At the genera level: ↓ **in DR**: *Bifidobacterium, Mitsuokella, Streptococcus, Klebsiella, Desulfovibrio, Lachnobacterium, Erwinia, Treponema, Methanobrevibacter, Haemophilus, Asteroleplasma, Anaerovibrio, Weissella,* ↑ **in DR**: *Akkermansia, Phascolarctobacterium, Alistipes, Shigella*, *Cloacibacillus*, *Enterococcus*
China[3]	*n*=25 DM[6] without DR; *n*=25 DM with DR; (n=25)	Amplification of the V3–V4 region of 16S rRNA gene and sequencing on Illumina MiSeq platform	At the phylum level[8]: ↓ **in DR**: *Firmicutes* At the genera level: **8 genera detected only in the DM** including *Dielma*, *Pygmaiobacter, Anaerostignum, Murdochiella, Azospira* and with 90% belonging to *Erysipelotrichaceae*, unclassified_c_*Bacilli*, and *Ruminococcaceae* families **22 genera detected only in the DR**

			including *Acidaminococcus, Coriobacteriaceae, Dolosigranulum, Comamonas, Paraeggerthella, Leptolyngbya, Uruburuella, Oscillospira, Sulfuritalea, Rikenellaceae, Chryseobacterium* and with 89% belonging to *Acidaminococcaceae*, *Muribaculacea*, *Atopobiaceae*, and norank_o_*Coriobacteriales* families. Gut microbial biomarkers: identification of 25 bacterial families that could distinguish DR from DM and controls and with *Pasteurellaceae* being the best discriminating value. At the phylum level: No statistically significant difference in the relative abundance among the 17 identified phyla
India[4]	*n*=21 T2DM without DR; *n*=37 T2DM with DR	Amplification of the V4 region of 16S rRNA gene and sequencing on Illumina MiSeq platform	

[1](Moubayed et al., 2019); [2](Das et al., 2021); [3](Huang et al., 2021); [4](Khan et al., 2021) ;[5]T2DM (type 2 diabetes mellitus); [6]DM (diabetes mellitus); [7]Only results of the comparison between diabetic patients with or without DR are presented; [8]Among the 4th most abundant phyla (*Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*)

Table 2. Bacterial alterations observed in the fecal microbiota of patients with glaucoma

Country	Effective *n* (control group)	Method	Microbiota alterations
China[1]	*n*=30 POAG[3] (*n*=30)	Amplification of the V4 region of 16S rRNA gene and sequencing on Illumina MiSeq platform	At the family level[4]: ↑ *Prevotellaceae* At the genera level[2]: ↑ unidentified_*Enterobacteriaceae* ↓ *Megamonas* At the species level[2]: ↑ *Escherichia coli* ↓ *Bacteroides plebeius*
Europe[2]	*n*=10 patients with NTG[5]; n=11 patients with OHT[6] (*n*=11)	Amplification of the V4 region of 16S rRNA gene and sequencing on Illumina MiSeq platform	At the family level[7]: ↓ (trend) *Rikenellaceae*

[1](Gong et al., 2020); [2](Anne Katrine Toft-Kehler, 2020); [3]POAG (primary open-angle glaucoma); [4] in POAG patients compared with non-POAG patients ; [5]NTG (normal tension glaucoma); [6]OHT ocular hypertension; [7]in OHT patients compared with NTG patients.

Table 3. Bacterial alterations observed in the fecal microbiota of patients with age-related macular degeneration (AMD)

Country	Effective *n* (control group)	Method	Microbiota alterations [4]
Switzerland[1]	*n*=12 neovascular AMD (*n*=11)	Shotgun metagenomic sequencing on Illumina HiSeq platform	At the family level: ↑ *Oscillospiraceae* At the genera level: ↑ *Anaerotruncus, Oscillibacter* At the species level: ↑ *Ruminococcus torques, Eubacterium ventriosum* ↓ *Bacteroides eggerthii*
Switzerland[2]	*n*=57 neovascular AMD (*n*=58)	Shotgun metagenomic sequencing on Illumina HiSeq platform	At the class level: ↑ *Negativicutes* At the genera level: ↓ *Oscillibacter* At the species level: ↓ *Bacteroides* spp. Gut microbial biomarkers: identification of 7 bacterial taxa as potential biomarkers to discriminate between AMD patients and controls (the class *Negativicutes*, the order *Selenomonadales* and the species *Phascolarctobacterium, Bacteroides cellulosilyticus, Sutterella wadsworthensis, Bifidobacterium longum*, and *Bacteroides caccae*).
USA[3]	n=85 advanced AMD n=49	-	At the genera level: ↑ *Prevotella, Holdemanella, Desulfovibrio,* and other bacteria ↓ *Oscillospira, Blautia* and *Dorea*

[1] (Zinkernagel et al., 2017); [2] (Zysset-Burri et al., 2020); [3] (Lin et al., 2021); [4] in AMD patients compared with controls.

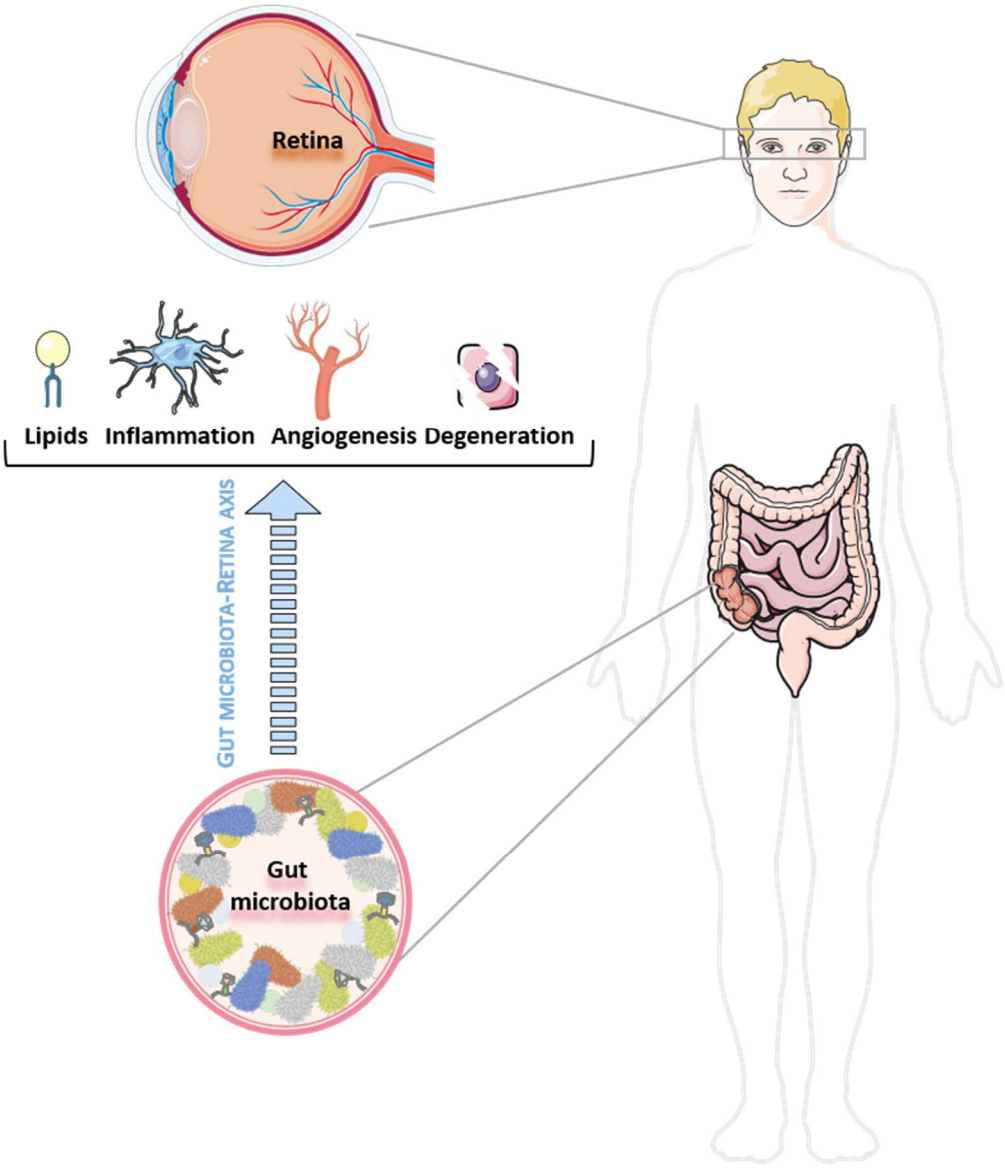

Figure 1

Figure Legend

Figure 1. Gut microbiota–retina axis: what we have already learned from animal models. Evidence has been provided on the influence of the gut microbiota on retinal physiology (lipid composition) as well as on the regulation of different processes in the retina, particularly inflammation, angiogenesis, and neurodegeneration.