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# 1 **The gut microbiota in retinal diseases**

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13

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15 glaucoma; probiotics

16 **Abstract**

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

## 31 **1. Introduction**

32

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

53 The retina is the light-sensitive neural tissue that lines the back of the eyes. Both from  
54 an anatomical and a developmental aspect, the retina is considered an extension of the brain.  
55 Interestingly, many features of neurodegenerative processes in the CNS are similar to those  
56 observed in the retina, and some neurodegenerative disorders of the CNS can have  
57 repercussions in the retina and vice versa (Byun et al., 2021; London et al., 2013; Nucci et al.,  
58 2015). This review aims to present the current data from studies of humans and animal  
59 models that point to the role of the gut microbiota in maintaining retinal physiology. We also  
60 discuss the opportunities that may exist to use the gut microbiota as a target for preventive  
61 and therapeutic strategies as well as for the diagnosis of retinal diseases.

62

## 63 **2. Gut microbiota and its derived metabolites in patients with retinal** 64 **neurodegenerative diseases**

65

### 66 **2.1. Diabetic retinopathy**

67 Diabetic retinopathy (DR) is a complication that affects approximately 30% of individuals  
68 with diabetes (Wong et al., 2016). Prolonged duration of diabetes, hyperglycemia, and  
69 systemic hypertension are strongly associated with DR. The disease starts with a mild non-  
70 proliferative stage (retinal microaneurysms) that may evolve to a proliferative stage whose  
71 features include neovascularization and vitreous or preretinal hemorrhages. Patients with DR  
72 may also develop diabetic macular edema. Although DR has long been regarded a  
73 microvascular disease, recent studies suggest that retinal neurodegeneration precedes vascular  
74 changes (Lynch and Abramoff, 2017; Zafar et al., 2019). Alterations in the composition of the  
75 gut microbiota have been reported in patients with diabetes (Knip and Siljander, 2016; Yang  
76 et al., 2021) and evidence points to the contribution of these microbial changes to disease  
77 pathophysiology (de Groot et al., 2021; Vrieze et al., 2012; Wang et al., 2019; Yu et al.,  
78 2019). Although it had been suspected, the role of the gut microbiota in the development of  
79 DR has only recently been investigated. The fecal microbiota of a very small cohort in Saudi  
80 Arabia was analyzed using culture-based techniques and molecular identification targeting  
81 *Bacteroides* (**Table 1**) (Moubayed et al., 2019). No change was found between the fecal  
82 microbiota of diabetic patients with or without retinopathy. However, the small size of the  
83 cohort and the culture-based investigation methods used may have contributed to limitations  
84 in the study. More recently, two independent studies in China and in southern India reported  
85 alterations of the gut microbiota associated with DR (**Table 1**) (Das et al., 2021; Huang et al.,  
86 2021). In both studies, no difference in the alpha-diversity indices —which reflect the richness  
87 and diversity within the ecosystem — was observed between the fecal microbiota of diabetic  
88 patients without and those with DR. In addition to alterations associated with diabetes, several  
89 modifications were observed at phylum and genera levels between the fecal microbiota of DR  
90 patients and that of controls and/or diabetic patients without DR. However, these alterations  
91 were not similar in the two studies. Among the most represented phyla, a decrease in  
92 *Actinobacteria* was reported in DR patients compared to controls and to diabetic patients  
93 without DR in the Indian cohort, whereas the relative abundance of this phylum was  
94 unchanged in the Chinese cohort (Das et al., 2021; Huang et al., 2021). Moreover, in the  
95 Chinese cohort *Firmicutes* were less abundant in the DR group than in the two other groups

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

111 Choline, L-carnitine, betaine, and other choline-containing compounds that are present  
112 in the human diet are metabolized by the gut microbiota to generate trimethylamine (TMA),  
113 which is further converted to trimethylamine-*N*-oxide (TMAO) in the liver and transported to  
114 the tissues (Janeiro et al., 2018). Alterations in TMAO have been associated with pathological  
115 conditions in rodents and humans, including diabetes (Liu et al., 2021; Nowinski and Ufnal,  
116 2018; Shan et al., 2017). A cross-sectional study that included 40 patients without type 2  
117 diabetes, 50 diabetic patients without DR, and 74 diabetic patients with non-proliferative or  
118 proliferative DR revealed that elevated plasma levels of TMAO were associated with DR and  
119 its severity (Liu et al., 2021). Metabolomic studies also brought clues about the involvement  
120 of the gut microbiota in DR. Nuclear magnetic resonance (NMR)-based metabolomic  
121 exploration of eye fluids in controls and diabetic patients with and without DR led to the  
122 identification of DR-associated alterations in metabolic pathways of energy metabolism and  
123 amino acids (Barba et al., 2010; Jin et al., 2019). Among the changes observed was a  
124 decreased level of succinate in both the aqueous humor and the vitreous humor of DR patients  
125 compared to non-diabetic controls and/or diabetic patients without DR (Barba et al., 2010; Jin  
126 et al., 2019). Interestingly, succinate has been shown to be produced in large amounts during  
127 the fermentation of dietary fibers by the gut microbiota (De Vadder et al., 2016). However,  
128 whether the metabolic changes observed in eye fluid ensue from alterations in the gut  
129 microbiota remains to be determined.

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

140

## 141 **2.2. Glaucoma**

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

164 in the fecal microbiota composition was found between the groups (**Table 2**). However, this  
165 study had some limitations, including the number of participants, the medications taken by  
166 patients, and the wide age range of the participants enrolled in the study (between 50 and 96  
167 years of age). Besides, other studies suggest a role of the pathogenic Gram-negative bacteria  
168 *Helicobacter pylori* in the pathogenesis of glaucoma. However, an association of *H. pylori*  
169 infection with POAG is still debated (Doulberis et al., 2020). Another feature suggesting that  
170 microbiota could influence glaucoma is modulation of the levels of some metabolites that are  
171 related to the gut microbiota metabolism in host fluids of patients with glaucoma. Comparison  
172 of the metabolomic profiles of the plasma and of the aqueous humor in POAG and non-  
173 POAG patients revealed, among other changes, a reduced concentration of polyamines such  
174 as spermine and spermidine in POAG patients (Buisset et al., 2019; Leruez et al., 2018).  
175 Interestingly, polyamines can be synthesized by intestinal bacteria and gain the bloodstream  
176 via the colonic mucosa (Kibe et al., 2014; Tofalo et al., 2019). Another example is the  
177 elevated levels of TMA, a bacteria-derived metabolite that has been reported in the aqueous  
178 humor of patients with advanced POAG compared to patients with cataract (Skrzypecki et al.,  
179 2021). Finally, it should be noted that some other studies suggest a role of the oral microbiota  
180 in glaucoma (Anne Katrine Toft-Kehler, 2020; Astafurov et al., 2014; Lim et al., 2021; Polla  
181 et al., 2017).

182

### 183 **2.3. Age-related macular degeneration**

184 Age-related macular degeneration (AMD) is a progressive chronic disease of the retina that  
185 causes damage to the macula, a small central retinal area specialized in central vision  
186 (Chakravarthy et al., 2010). Two stages of the disease are distinguished. The early stage is  
187 characterized by the formation of large deposits called “drusen” and pigmentary abnormalities  
188 in the retina. The late stage of AMD can be subdivided into two forms: a non-exudative (or  
189 dry) form and an exudative (or wet) form. The non-exudative form is characterized by  
190 macular atrophy caused by an accumulation of drusen beneath the retinal pigment epithelium  
191 (RPE) and Bruch’s membrane that damages the RPE and may cause indirect photoreceptor  
192 cell death. The exudative form is characterized by choroidal neovascularization (CNV), which  
193 leads to RPE detachment and to RPE and photoreceptor cell death. The etiology of AMD is  
194 complex and not yet fully understood (Lambert et al., 2016). Interestingly, some  
195 environmental risk factors associated with AMD, such as diet, influence the composition and  
196 functions of the gut microbiota (Redondo-Useros et al., 2020; Singh et al., 2017). In addition,  
197 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

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

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

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

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

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

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

269

### 270 **3. The gut microbiota and its derived metabolites: what animal models tell** 271 **us about their influence on retinal physiology**

272

#### 273 **3.1. Gut microbiota and lipid composition of the retina**

274 Lipids represent approximately 20% of the dry weight of the retina, making this the tissue  
275 with the highest lipid content in the body after adipose tissue and the brain. Lipids play  
276 critical roles in the development of the retina and the maintenance of its structure and  
277 functionality. A specific feature of the retina is its high content of polyunsaturated fatty acids  
278 (PUFAs) and in particular docosahexaenoic acid (DHA), a PUFA of the n-3 series. DHA,  
279 which can represent up to 50% of total fatty acids in the photoreceptor outer segments, is  
280 involved in visual processes and the maintenance of retinal homeostasis. Retinal lipids consist  
281 mostly of phospholipids (87.3% and 58.3% of total lipids in the human neuroretina and retinal  
282 pigment epithelium, respectively), with plasmalogens (PIs) representing approximately 10%  
283 of these glycerophospholipids (Acar et al., 2007; Bretillon et al., 2008). PIs are characterized  
284 by a vinyl-ether bond at the *sn*-1 position of the glycerol backbone, which differentiates them  
285 from diacylglycerophospholipids and their ester bond. Plasmenyl-ethanolamine (PIsEtn) is the  
286 most widely represented class of PI in both the neural retina and the RPE (Acar et al., 2007).  
287 In the neural retina, the major species of PIsEtn are those containing PUFAs, arachidonic acid  
288 (AA, C20:4n-6; in PIsEtn16:0/20:4 and PIsEtn18:0/20:4), or DHA (C22:6n-3; in  
289 PIsEtn18:0/22:6) at their *sn*-2 position (Saab et al., 2014b). Such PUFAs are the precursors of  
290 bioactive molecules such as prostaglandins, leukotrienes, resolvins, and protectins. Apart from  
291 being a reservoir for these PUFAs, PIs play a role in the protection against oxidative stress  
292 (Brites et al., 2004; Stables and Gilroy, 2011). Defects in PIs are suspected to contribute to the  
293 pathophysiology of retinopathies such as glaucoma and retinopathy of prematurity (Acar et  
294 al., 2009; Saab et al., 2014a; Saab et al., 2014b).

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

298 host tissue (Backhed et al., 2004; Ghazalpour et al., 2016; Kindt et al., 2018; Martinez-Guryn  
299 et al., 2018; Velagapudi et al., 2010; Villette et al., 2020). One of the first pieces of evidence  
300 showing that the gut microbiota could influence the retinal lipid content was provided over 10  
301 years ago by Orešič and colleagues when they compared the lipidome of retinas from germ-  
302 free mice (i.e., mice raised without microbiota) and conventionally raised mice (Oresic et al.,  
303 2009). Their study showed that the presence of the gut microbiota was associated with an  
304 elevation of the retinal content in PlsEtn, particularly in PlsEtn18:0/20:4. Recent data from  
305 our laboratory complete this observation by showing that, beyond its presence, the  
306 composition of the gut microbiota may also influence the lipid content of nervous tissues  
307 (Albouery et al., 2019). Indeed, we showed that colonization of germ-free mice by the fecal  
308 microbiota from old donor mice results in significant changes in the cortex lipidome  
309 compared with germ-free mice colonized by the fecal microbiota from young donor mice.  
310 Another study that analyzed the functional activity of the gut microbiota in patients with  
311 AMD by metagenomics supported the hypothesis of an influence of the gut microbiota on the  
312 retinal lipids. In this work, although no causal relationship was established with the retinal  
313 lipid content, a reduction in the expression of genes involved in fatty acid elongation was  
314 observed in the gut microbiota of AMD patients compared with age-matched controls  
315 (Zinkernagel et al., 2017). Fatty acid elongation serves in the biosynthesis of long-chain  
316 PUFAs such as DHA from short-chain precursors. This finding makes sense considering the  
317 pathophysiology of AMD, for which a high supply of long-chain PUFAs such as DHA has  
318 been shown to be protective (Liu et al., 2010; Zinkernagel et al., 2017).

319

### 320 ***3.2. Influence of gut microbiota and gut microbiota-derived metabolites on retinal*** 321 ***inflammation***

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

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

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

346 A role of the gut microbiota in inflammation associated with the development of  
347 retinopathy in diet-induced metabolic disorders has also been demonstrated. Increased  
348 amounts of pro-inflammatory cytokines (interleukin [IL]-1beta, IL-6, and tumor necrosis  
349 factor [TNF]-alpha) were observed at both systemic and choroid levels in mice fed a high-fat  
350 diet (HFD; (Andriessen et al., 2016). The phenotype was reversed following oral intake of a  
351 broad-spectrum antibiotic, neomycin, and partially reversed following the transfer of fecal  
352 microbiota from mice fed a regular-chow diet to recipient HFD-fed mice (Andriessen et al.,  
353 2016). Other data suggest that the gut microbiota influences the retinal inflammatory status in  
354 DR conditions. Indeed, long-term exposure of *db/db* mice to intermittent fasting — a condition  
355 associated with restructuring of the gut microbiota, reinforcement of gut barrier integrity, and  
356 a decrease in circulating peptidoglycans— leads to a reduction in the number of IBA-1<sup>+</sup> cells  
357 that are markers of microglial activation as well as to decreased infiltration by CD45<sup>+</sup>  
358 hematopoietic cells in the retina (Beli et al., 2018). In addition, it has been reported that  
359 administration of ursodeoxycholic acid (UDCA), a secondary bile acid generated by gut  
360 bacteria, improves the DR-like phenotype in a streptozotocin (STZ)-induced diabetic mouse  
361 model through the attenuation of retinal inflammation (Chung et al., 2017; Ouyang et al.,  
362 2018). Oral administration of UDCA reduced the number of IBA-1<sup>+</sup> cells in retinal ganglion  
363 cells and retinal inner plexiform layers, and also decreased the activation of the NF-kappaB  
364 pathway and the expression level of mRNAs encoding pro-inflammatory cytokines (TNF-  
365 alpha, IL-1beta, and IL-6) in retinas of STZ-induced diabetic mice (Ouyang et al., 2018).

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

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

375

### 376 ***3.3. Influence of gut microbiota and gut microbiota-derived metabolites on pathological*** 377 ***vascularization in the retina***

378 Obesity and type 2 diabetes are conditions that influence the development of AMD and DR,  
379 two diseases whose hallmarks include retinal neovascularization processes (Adams et al.,  
380 2011; DeFronzo et al., 2015; Zhang et al., 2016). Andriessen and colleagues have elegantly  
381 demonstrated that the gut microbial dysbiosis associated with diet-induced metabolic  
382 disorders contributes to retinal neovascularization (Andriessen et al., 2016). Indeed, they  
383 showed that an HFD-fed mouse model of exudative AMD displayed systemic and choroidal  
384 inflammation as well as an exacerbated CNV. A set of experiments, including the transfer of  
385 cecal microbiota from HFD- or chow-diet-fed mice to recipient mice, revealed that the gut  
386 microbiota drives the vascular phenotype. Although a causal relationship was not firmly  
387 demonstrated, the influence of the gut microbiota composition on the development of retinal  
388 vascular abnormalities was strengthened by another study. The authors showed that long-term  
389 exposure of mice to intermittent fasting altered the gut microbiota composition and prevented  
390 the development of acellular capillaries in the retina of *db/db* mice, a potential model for DR  
391 (Beli et al., 2018).

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

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

402

### 403 ***3.4. Influence of gut microbiota and gut microbiota-derived metabolites on retinal*** 404 ***neurodegeneration***

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

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

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

431

## 432 **4. Targeting the gut microbiota as a strategy for the prevention and the** 433 **treatment of retinal diseases**

434

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

445

### 446 **4.1. Probiotics**

447 The term “probiotic” refers to “live microorganisms that, when administered in adequate  
448 amounts, confer a health benefit on the host” (Hill et al., 2014). The most common strains  
449 used as probiotics are lactic acid bacteria and bifidobacteria. However, other species such as  
450 *Akkermansia muciniphila* or *Faecalibacterium prausnitzii* are considered promising next-  
451 generation probiotic candidates (Cani and de Vos, 2017; Martin et al., 2018). The general  
452 features of probiotics are to support homeostasis of the digestive tract, to modulate the  
453 immune system, and to balance the gut microbiota. Supplementation with probiotics can also  
454 have extraintestinal effects. Indeed, the beneficial effects of specific probiotics on  
455 neurological disorders have been described in animal models and in humans (Sasmita, 2019;  
456 Westfall et al., 2017). Interestingly, results from experimental studies suggest that  
457 supplementation with probiotics could also protect the retina from deleterious conditions.  
458 Some proof in this regard originated from the organism model *Drosophila melanogaster*, in  
459 which the administration of *Lactiplantibacillus plantarum* DR7 was shown to alleviate eye  
460 neurodegeneration (rough eye phenotype) induced by the expression of Alzheimer’s A $\beta$ 42  
461 peptide (Tan et al., 2020a). In addition, oral administration of the probiotic strains *Escherichia*  
462 *coli* Nissle 1917 or IRT-5 (a mixture consisting of *Lacticaseibacillus casei*, *Lactobacillus*  
463 *acidophilus*, *Limosilactobacillus reuteri*, *Bifidobacterium bifidum*, and *Streptococcus*  
464 *thermophilus*) was able to reduce the severity of EAU in mice, at least partly by modulating



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

473 The use of probiotics as live vectors to deliver therapeutic molecules is a strategy  
474 drawing the attention of scientists and pharmaceutical companies. Thanks to accumulating  
475 knowledge on their safety (GRAS and QPS certifications) and beneficial health effects, as  
476 well as engineering tools that have been developed, several lactic acid bacteria and  
477 bifidobacteria are considered good candidates for such a strategy (Bermudez-Humaran and  
478 Langella, 2017; Plavec and Berlec, 2019). The potential of two engineered lactobacilli in  
479 protecting the mouse retina from DR has been investigated by Li and colleagues (Crackower  
480 et al., 2002; Verma et al., 2020b). They designed two recombinant *Lacticaseibacillus*  
481 *paracasei* ATCC 27092 to express and secrete ACE2 or angiotensin-(1-7) (Ang-(1-7)), two  
482 proteins belonging to the renin–angiotensin system (Patel et al., 2016), in fusion with the non-  
483 toxic subunit B of cholera toxin, a transepithelial carrier. A protective role has been reported  
484 for ACE2/Ang-(1-7) in uveitis and DR (Dominguez et al., 2016; Qiu et al., 2014; Shil et al.,  
485 2014; Verma et al., 2012). Oral administration of ACE2- or Ang-(1-7)-*L. paracasei* showed  
486 efficacy in limiting retinal inflammation and neurovascular degeneration in mouse models of  
487 DR (Verma et al., 2020a; Verma et al., 2020b). Although they are considered as safe and well  
488 tolerated by healthy subjects, long-term use of probiotics might entail risk under certain  
489 contexts (e.g., probiotic translocation to extra intestinal sites in patients with damaged  
490 intestinal barrier or compromised immunity, transfer of antibiotic-resistant traits to  
491 commensal or pathogenic intestinal bacteria) (Yelin et al., 2019).

492

#### 493 **4.2. Prebiotics**

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

499 prebiotics are not restricted to the gastrointestinal compartment; evidence showing that they  
500 can also influence the health status of extraintestinal organs was reported for the brain  
501 (Collins and Reid, 2016). The most extensively studied and documented dietary prebiotics  
502 come from carbohydrates (e.g., non-digestible oligosaccharides fructans and galactans).  
503 Intra-gastric administration of chitosan oligosaccharide (COS) have been shown to attenuate  
504 oxidative stress-induced retinal damages in rats (Fang et al., 2013). Although alterations of  
505 the composition of the gut microbiota by COS have been documented, involvement of these  
506 microbial changes in the beneficial effects of COS on the retina remains to be evaluated since  
507 COS can be absorbed through the intestinal epithelia (Muanprasat and Chatsudthipong, 2017;  
508 Zhang et al., 2018). Other substances such as polyphenols are also regarded as prebiotics  
509 since their beneficial effects on health involve their biotransformation by the gut microbiota,  
510 modulation of the gut microbiota composition, and production of microbial metabolites  
511 (Collins and Reid, 2016; Mithul Aravind et al., 2021). Interestingly, oral supplementation  
512 with resveratrol has been shown to have beneficial effects on retinopathies (Abu-Amero et al.,  
513 2016). However, it remains challenging to determine which part of the observed effects is  
514 related to resveratrol per se, its derived metabolites, or modifications of the gut microbiota  
515 consecutive to its administration.

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

520

### 521 **4.3. Synbiotics**

522 The term “synbiotic” refers to “a mixture comprising live microorganisms and substrate(s)  
523 selectively utilized by host microorganisms that confers a health benefit on the host”  
524 (Swanson et al., 2020). The substrate(s) is called a “synergistic synbiotic” when it is  
525 selectively utilized by the allochthonous microorganisms. If the synbiotic includes a prebiotic  
526 that has been designed to be utilized by the autochthonous microorganisms, it is then called a  
527 “complementary synbiotic.” The effects of oral supplementation with synbiotic formulations  
528 on neurodegenerative or ocular diseases have been little explored to date, either in model  
529 organisms or in humans (Arora et al., 2020; Askari and Moravejolahkami, 2019; Chisari et al.,  
530 2017; Peterson, 2020).

531

532 **4.4. Paraprobiotics (also called “ghosts,” “non-viable probiotics,” or “inactivated**  
533 **probiotics”)**

534 Paraprobiotics are defined as “non-viable microbial cells (either intact or broken) or crude cell  
535 extracts which when administered (either orally or topically) in adequate amounts confer a  
536 benefit to the consumer” (Nataraj et al., 2020). Their beneficial health effects are mediated by  
537 the metabolites/molecules contained in the inactivated microorganisms. Morita and colleagues  
538 explored the efficacy of heat-killed *L. paracasei* KW3110 in protecting the retina against  
539 several stress conditions. They showed that long-term intake of this paraprobiotic modulated  
540 the gut microbiota composition in aged mice. Among other changes, the relative abundance of  
541 bifidobacteria (health-promoting bacteria) was increased and that of *Streptococcaceae*  
542 (bacteria with pro-inflammatory potential) was decreased in the gut microbiota of aged mice  
543 supplemented with heat-killed *L. paracasei* KW3110 compared to age-matched controls  
544 (Morita et al., 2018b). Supplementation with this paraprobiotic was effective in alleviating  
545 inflammation associated with aging (at the gut, systemic, and retinal levels) or induced in the  
546 retina by blue light exposure (Morita et al., 2018b; Morita et al., 2018c). It also protected  
547 against age-related retinal ganglion cell loss and blue light-induced photoreceptor  
548 degeneration (Morita et al., 2018b; Morita et al., 2018c). Some data suggest that heat-killed *L.*  
549 *paracasei* KW3110 could prevent chronic eye disorders, including eye fatigue (Morita et al.,  
550 2018a; Yamazaki et al., 2020).

551

552 **4.5. Postbiotics**

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

563

564 **4.6. Fecal microbiota transplant**

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

579

#### 580 **4.7. Phage therapy**

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

599 valuable approach to target gut pathogens and bacteria resistant to antibiotics (Galtier et al.,  
600 2017; Ott et al., 2017; Principi et al., 2019). The use of phage therapy to re-establish eubiosis  
601 in a pathological condition associated with dysbiosis or to help maintain its stability is also  
602 being extensively explored. Interestingly, a shift in the virome composition has been observed  
603 in the gut microbiota of patients with inflammatory bowel diseases (Norman et al., 2015).  
604 Whether this change in phage composition is a cause or a consequence of bacterial dysbiosis  
605 remains to be elucidated.

606

#### 607 **4.8. Diet**

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

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

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

639 Another example illustrating how diet-induced changes in the gut microbiota can  
640 affect retinal physiology is that of Western diet (WD). Consumption of WD is associated with  
641 the development of diabetes and progression of AMD (Chiu et al., 2014). As discussed in the  
642 sections 3.2 and 3.3, Andriessen and colleagues have shown that the alterations of the gut  
643 microbiota associated with the consumption of a HFD influence the inflammatory status as  
644 well as the pathological vascularization of the retina in mice (Andriessen et al., 2016).  
645 Although more studies are needed to prove a causal relationship with changes in the gut  
646 microbiota, HFD-fed mice also exhibited an altered retinal lipid composition (Albouery et al.,  
647 2020). In addition to the high fat and low fiber content, the high content of WD in sugar is  
648 also a factor that affects the gut microbiota (Do et al., 2018). Exposition of rodents to high-  
649 fructose diet has been reported to impair the functionality of cone photoreceptors as well as to  
650 exacerbate the development of choroidal neovascularization in rats (Thierry et al., 2014;  
651 Thierry et al., 2015). However, the role of the gut microbiota in such phenotype remains also  
652 to be demonstrated. In addition, and as discussed in section 3.4, Rowan and colleagues  
653 reported that consuming high-glycemia (HG) diet was associated with the development of  
654 AMD features, which could be prevented/reversed by switching from HG to low-glycemia  
655 diet (Rowan et al., 2017). These retinal phenotypes correlated with compositional and  
656 functional changes of the gut microbiota (Rowan et al., 2017).

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

661  
662 Finally, besides the nature of the diet, dietary practices could also support healthy gut  
663 microbiota. Notably, an emerging body of evidence suggests that nutritional restriction could  
664 have beneficial effects on the gut microbiota, particularly by enriching it in  
665 protective/beneficial bacteria (Rinninella et al., 2020). Data from FMT experiments indicate  
666 that these nutritional restriction-induced microbial changes contribute to improving metabolic

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

670

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

678

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

689

## 690 **5. The profile of the gut microbiota and/or its derived metabolites as a** 691 **valuable tool for the diagnosis of retinal diseases**

692

693 Using the gut microbiota composition and/or its related metabolite profile as a diagnostic tool  
694 for diseases associated with dysbiosis is a concept whose strength and reliability have been  
695 tested in compelling studies for diseases such as cancers (e.g., colorectal cancer,  
696 hepatocellular carcinoma) or type 2 diabetes (Baba et al., 1989; Qin et al., 2012; Ren et al.,  
697 2019). In combination with other biomarkers it could constitute a valuable tool for the early  
698 diagnosis of retinal diseases. Microbiota-based biomarkers to discriminate between patients  
699 with and without retinopathies have already been proposed (Huang et al., 2021; Khan et al.,

700 2021; Zysset-Burri et al., 2020). However, more cross-sectional studies with diverse  
701 populations are needed to strengthen this tool, particularly to make emerging robust microbial  
702 signatures specific to the disease and take into account host-related heterogeneity (lifestyle,  
703 dietary habits, ethnicity, etc.).

704

## 705 **6. Conclusion**

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

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

726

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

Country	Effective <i>n</i> (control group)	Method	Microbiota alterations <sup>7</sup>
Saudi Arabia <sup>1</sup>	<i>n</i> =9 T2DM <sup>5</sup> without DR; <i>n</i> =8 T2DM with DR; ( <i>n</i> =18)	Inoculation on different selective culture media; enumeration on agar plates; PCR amplification on presumptive <i>Bacteroides</i> 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 <sup>2</sup>	<i>n</i> =25 T2DM without DR; <i>n</i> =28 T2DM with DR; ( <i>n</i> =30)	Amplification of the V3–V4 region of 16S rRNA gene and sequencing on Illumina HiSeq platform	<p><u>At the phylum level</u><sup>8</sup>:</p> <p>↓ in DR: <i>Actinobacteria</i></p> <p><u>At the genera level</u>:</p> <p>↓ in DR: <i>Bifidobacterium</i>, <i>Mitsuokella</i>, <i>Streptococcus</i>, <i>Klebsiella</i>, <i>Desulfovibrio</i>, <i>Lachnobacterium</i>, <i>Erwinia</i>, <i>Treponema</i>, <i>Methanobrevibacter</i>, <i>Haemophilus</i>, <i>Asteroleplasma</i>, <i>Anaerovibrio</i>, <i>Weissella</i>,</p> <p>↑ in DR: <i>Akkermansia</i>, <i>Phascolarctobacterium</i>, <i>Alistipes</i>, <i>Shigella</i>, <i>Cloacibacillus</i>, <i>Enterococcus</i></p>
China <sup>3</sup>	<i>n</i> =25 DM <sup>6</sup> without DR; <i>n</i> =25 DM with DR; ( <i>n</i> =25)	Amplification of the V3–V4 region of 16S rRNA gene and sequencing on Illumina MiSeq platform	<p><u>At the phylum level</u><sup>8</sup>:</p> <p>↓ in DR: <i>Firmicutes</i></p> <p><u>At the genera level</u>:</p> <p><b>8 genera detected only in the DM</b> including <i>Dielma</i>, <i>Pygmaio bacter</i>, <i>Anaerostignum</i>, <i>Murdochiella</i>, <i>Azospira</i> and with 90% belonging to <i>Erysipelotrichaceae</i>, unclassified_c_Bacilli, and <i>Ruminococcaceae</i> families</p> <p><b>22 genera detected only in the DR</b></p>

India <sup>4</sup>	<i>n</i> =21 T2DM without DR; <i>n</i> =37 T2DM with DR	Amplification of the V4 region of 16S rRNA gene and sequencing on Illumina MiSeq platform	<p>including <i>Acidaminococcus</i>, <i>Coriobacteriaceae</i>, <i>Dolosigranulum</i>, <i>Comamonas</i>, <i>Paraeggerthella</i>, <i>Leptolyngbya</i>, <i>Uruburuella</i>, <i>Oscillospira</i>, <i>Sulfuritalea</i>, <i>Rikenellaceae</i>, <i>Chryseobacterium</i> and with 89% belonging to <i>Acidaminococcaceae</i>, <i>Muribaculacea</i>, <i>Atopobiaceae</i>, and norank_o_Coriobacteriales families.</p> <p><u>Gut microbial biomarkers:</u> identification of 25 bacterial families that could distinguish DR from DM and controls and with <i>Pasteurellaceae</i> being the best discriminating value.</p> <p><u>At the phylum level:</u> No statistically significant difference in the relative abundance among the 17 identified phyla</p>
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1288 <sup>1</sup>(Moubayed et al., 2019); <sup>2</sup>(Das et al., 2021); <sup>3</sup>(Huang et al., 2021); <sup>4</sup>(Khan et al., 2021)  
1289 ;<sup>5</sup>T2DM (type 2 diabetes mellitus); <sup>6</sup>DM (diabetes mellitus); <sup>7</sup>Only results of the comparison  
1290 between diabetic patients with or without DR are presented; <sup>8</sup>Among the 4th most abundant  
1291 phyla (*Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*)

1292 **Table 2. Bacterial alterations observed in the fecal microbiota of patients with glaucoma**

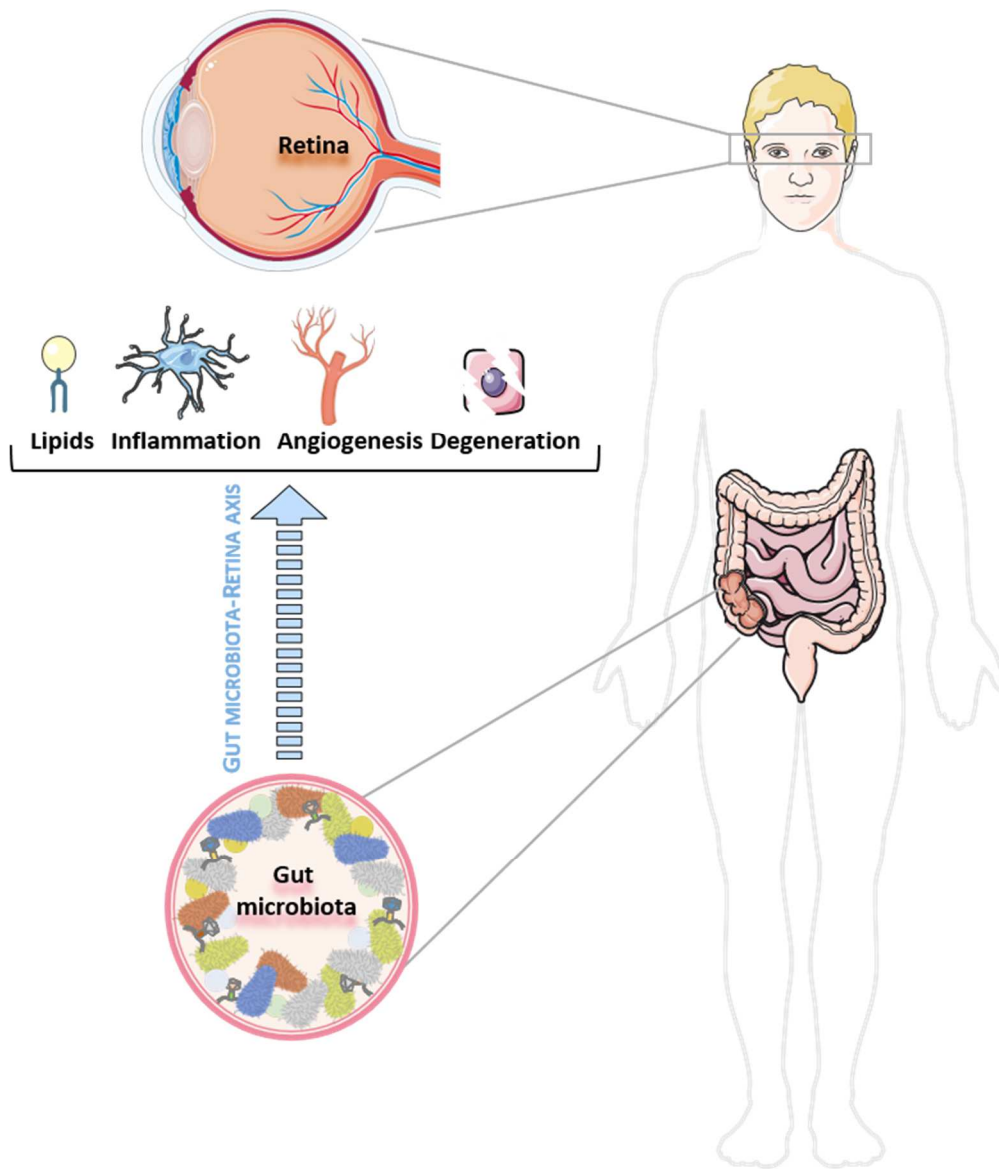
Country	Effective <i>n</i> (control group)	Method	Microbiota alterations
China <sup>1</sup>	<i>n</i> =30 POAG <sup>3</sup> ( <i>n</i> =30)	Amplification of the V4 region of 16S rRNA gene and sequencing on Illumina MiSeq platform	<u>At the family level<sup>4</sup>:</u> ↑ <i>Prevotellaceae</i> <u>At the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

1293 <sup>1</sup>(Gong et al., 2020); <sup>2</sup>(Anne Katrine Toft-Kehler, 2020); <sup>3</sup>POAG (primary open-angle  
 1294 glaucoma); <sup>4</sup> in POAG patients compared with non-POAG patients ; <sup>5</sup>NTG (normal tension  
 1295 glaucoma); <sup>6</sup>OHT ocular hypertension; <sup>7</sup>in OHT patients compared with NTG patients.

1296 **Table 3. Bacterial alterations observed in the fecal microbiota of patients with age-**  
 1297 **related macular degeneration (AMD)**

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

1298 <sup>1</sup> (Zinkernagel et al., 2017); <sup>2</sup> (Zysset-Burri et al., 2020); <sup>3</sup> (Lin et al., 2021); <sup>4</sup> in AMD patients  
 1299 compared with controls.



**Figure 1**

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1303 **Figure Legend**

1304 **Figure 1. Gut microbiota–retina axis: what we have already learned from animal**  
 1305 **models.** Evidence has been provided on the influence of the gut microbiota on retinal  
 1306 physiology (lipid composition) as well as on the regulation of different processes in the retina,  
 1307 particularly inflammation, angiogenesis, and neurodegeneration.

1308