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1 The gut microbiota in retinal diseases

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- 13
- 14 Keywords: gut microbiota; retina; age-related macular degeneration; diabetic retinopathy;
- 15 glaucoma; probiotics

16 Abstract

17 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 18 coevolves dynamically together with the host. The composition of the gut microbiota is under 19 the influence of a complex interplay between both host and environmental factors. Scientific 20 advances in the past few decades have shown that it is essential in maintaining homeostasis 21 22 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 23 24 mucosa and in distant organs such as the brain. Persistent imbalance between gut microbial communities, termed "dysbiosis," has been associated with several inflammatory and 25 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 several microbiota-targeting strategies that could constitute preventive and therapeutic tools 29 30 for retinopathies.

31 **1. Introduction**

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Although the relationship between the gut microbiota and the host remains to be fully 33 elucidated, our knowledge on the essential role that the gut microbiota plays in maintaining a 34 mens sana in corpore sana grows daily. The gut microbiota - an entity of the human body 35 that has been long neglected or underestimated- for the past few decades has taken center 36 stage in medical and scientific research while attracting the interest of the pharmaceutical 37 38 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-39 40 disciplinarity, enabling the identification of several pivotal pathways (e.g., neuronal, endocrine, and immune signaling pathways) and molecular factors (e.g., metabolic, 41 42 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 43 system (CNS) (Ahlawat et al., 2020; Morais et al., 2021; Schroeder and Backhed, 2016). It 44 45 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 46 be. As a result, the gut microbiota is now considered an essential contributor to CNS 47 development, functionality, and health. The importance of the gut microbiota in tipping the 48 balance between health and disease is supported by the association between gut microbiota 49 imbalance and numerous brain disorders, including neurodevelopmental (e.g., autism), 50 behavioral (e.g., depression and anxiety), and neurodegenerative (e.g., Parkinson's disease 51 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 an anatomical and a developmental aspect, the retina is considered an extension of the brain. 54 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., 2015). This review aims to present the current data from studies of humans and animal 58 59 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 60 and therapeutic strategies as well as for the diagnosis of retinal diseases. 61

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

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66 2.1. Diabetic retinopathy

Diabetic retinopathy (DR) is a complication that affects approximately 30% of individuals 67 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 nonproliferative stage (retinal microaneurysms) that may evolve to a proliferative stage whose 70 features include neovascularization and vitreous or preretinal hemorrhages. Patients with DR 71 may also develop diabetic macular edema. Although DR has long been regarded a 72 73 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 74 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 pathophysiology (de Groot et al., 2021; Vrieze et al., 2012; Wang et al., 2019; Yu et al., 77 78 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 79 Arabia was analyzed using culture-based techniques and molecular identification targeting 80 Bacteroides (Table 1) (Moubayed et al., 2019). No change was found between the fecal 81 microbiota of diabetic patients with or without retinopathy. However, the small size of the 82 83 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 84 85 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 86 87 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 88 modifications were observed at phylum and genera levels between the fecal microbiota of DR 89 patients and that of controls and/or diabetic patients without DR. However, these alterations 90 were not similar in the two studies. Among the most represented phyla, a decrease in 91 Actinobacteria was reported in DR patients compared to controls and to diabetic patients 92 without DR in the Indian cohort, whereas the relative abundance of this phylum was 93 unchanged in the Chinese cohort (Das et al., 2021; Huang et al., 2021). Moreover, in the 94 Chinese cohort *Firmicutes* were less abundant in the DR group than in the two other groups 95

(Huang et al., 2021). In the Indian cohort, a decrease in the abundance of 13 genera and an 96 97 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 98 changes for the host remain difficult to predict since the abundance of genera with 99 detrimental/pathogenic or with beneficial potential was found to be increased or decreased in 100 DR patients. The alterations observed in the Chinese cohort were different to those in the 101 Indian study, but so were the analysis methods (Huang et al., 2021). From this cohort, a 102 biomarker set of 25 bacterial families was identified that can distinguish diabetic patients with 103 104 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 105 106 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 107 108 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 109 considered a marker associated with DR development. 110

Choline, L-carnitine, betaine, and other choline-containing compounds that are present 111 112 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 113 the tissues (Janeiro et al., 2018). Alterations in TMAO have been associated with pathological 114 conditions in rodents and humans, including diabetes (Liu et al., 2021; Nowinski and Ufnal, 115 2018; Shan et al., 2017). A cross-sectional study that included 40 patients without type 2 116 diabetes, 50 diabetic patients without DR, and 74 diabetic patients with non-proliferative or 117 proliferative DR revealed that elevated plasma levels of TMAO were associated with DR and 118 119 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 120 exploration of eye fluids in controls and diabetic patients with and without DR led to the 121 identification of DR-associated alterations in metabolic pathways of energy metabolism and 122 123 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 124 125 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 126 the fermentation of dietary fibers by the gut microbiota (De Vadder et al., 2016). However, 127 whether the metabolic changes observed in eye fluid ensue from alterations in the gut 128 129 microbiota remains to be determined.

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

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141 2.2. Glaucoma

142 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 143 144 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 145 146 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 composition of the fecal microbiota from a Chinese cohort comprising 30 patients with 148 primary open-angle glaucoma (POAG), the main form of glaucoma, and 30 age- and sex-149 matched non-POAG controls (Table 2) (Gong et al., 2020). No difference in alpha-diversity 150 was observed between the POAG and non-POAG patients. An over-representation of 151 Prevotellaceae, Escherichia coli, and another unidentified Enterobacteriaceae was found in 152 the fecal microbiota of POAG patients, whereas Megamonas and Bacteroides plebeius were 153 more prevalent in controls. The authors speculated that the pro-inflammatory properties of 154 Prevotella spp. and E. coli could contribute to neuronal inflammation and immune damage in 155 glaucoma. In addition to the composition of the gut microbiota, Gong and colleagues also 156 157 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 158 showed that some of them correlated with changes in the abundance of some bacteria in gut 159 microbiota, particularly that of Megamonas (Gong et al., 2020). However, more studies are 160 needed to prove a causal relationship. Another study investigated the composition of the gut 161 microbiota in Caucasian female patients with normal-tension glaucoma (NTG), in those with 162 163 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 164 165 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 96 166 years of age). Besides, other studies suggest a role of the pathogenic Gram-negative bacteria 167 Helicobacter pylori in the pathogenesis of glaucoma. However, an association of H. pylori 168 infection with POAG is still debated (Doulberis et al., 2020). Another feature suggesting that 169 microbiota could influence glaucoma is modulation of the levels of some metabolites that are 170 related to the gut microbiota metabolism in host fluids of patients with glaucoma. Comparison 171 172 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 173 174 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 175 176 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 177 178 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 179 180 in glaucoma (Anne Katrine Toft-Kehler, 2020; Astafurov et al., 2014; Lim et al., 2021; Polla 181 et al., 2017).

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2.3. Age-related macular degeneration

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

inflammatory environment as well as to the development of metabolic disorders, both of 198 which are pathological conditions associated with AMD (Al Bander et al., 2020; Dabke et al., 199 2019; Rozing et al., 2020; Shanahan and Sheehan, 2016; Sonnenburg and Backhed, 2016; Tan 200 et al., 2020b). The fecal microbiota in patients with neovascular AMD has been determined 201 by shotgun metagenomic sequencing in two studies from the same Swiss research group 202 (Table 3) (Zinkernagel et al., 2017; Zysset-Burri et al., 2020). This technology enables the 203 identification and the profiling of the microbial genes of a sample (the metagenome). In the 204 first study, the number of participants enrolled was small (12 patients with neovascular AMD 205 206 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 phylum Bacteroidetes were observed in the patients with AMD. In addition, the fecal 209 210 microbiota of AMD patients was enriched in bacteria belonging to the genera Anaerotruncus and Oscillibacter and the species Ruminococcus torques and Eubacterium ventriosum, 211 212 whereas the fecal microbiota of controls was enriched in *Bacteroides eggerthii*. Apart from providing information about the taxonomic composition of the microbiota, comparison of the 213 214 metagenomes revealed differences in the functional profiles of the fecal microbiota between patients with neovascular AMD and healthy controls. Indeed, the fecal microbiota of AMD 215 patients lacked bacteria responsible for fatty acid elongation, whereas it was enriched in 216 bacteria with increased L-alanine fermentation, glutamate degradation, and arginine 217 biosynthesis capabilities. 218

A higher number of patients were enrolled in the second study (57 patients with 219 neovascular AMD and 58 age- and sex-matched healthy controls (Zysset-Burri et al., 2020). 220 Principal component analyses revealed differences in the relative abundance of microbial 221 species but not in the relative abundance of functional profiles between patients with 222 neovascular AMD and controls. Comparison of the relative abundances between the two 223 groups identified the class *Negativicutes* as being increased in the fecal microbiota of patients 224 225 with neovascular AMD, and the genera *Bacteroides*, and to a lesser extent *Oscillibacter*, as being increased in controls (Zysset-Burri et al., 2020). Interestingly, using multivariate 226 association with linear models, Zysset-Burri and colleagues identified a correlation between 227 polymorphisms in the gene encoding complement factor H that are associated with AMD 228 (Maller et al., 2006) and variations in the abundance of a cluster of bacteria, including 229 Bacteroides species, Ruminococcus torques, the order Clostridiales, and the class 230 Negativicutes, belonging to the phylum Firmicutes. In addition, the fecal microbiota of 231

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 239 240 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 241 242 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*, 243 244 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 245 246 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 247 248 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 potentially harmful bacteria (IgA-bound bacteria) (Lin et al., 2021). 250

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

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).

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

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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 with the highest lipid content in the body after adipose tissue and the brain. Lipids play 275 critical roles in the development of the retina and the maintenance of its structure and 276 277 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, which can represent up to 50% of total fatty acids in the photoreceptor outer segments, is 279 involved in visual processes and the maintenance of retinal homeostasis. Retinal lipids consist 280 mostly of phospholipids (87.3% and 58.3% of total lipids in the human neuroretina and retinal 281 pigment epithelium, respectively), with plasmalogens (Pls) representing approximately 10% 282 283 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 284 from diacylglycerophospholipids and their ester bond. Plasmenyl-ethanolamine (PlsEtn) is the 285 most widely represented class of Pl in both the neural retina and the RPE (Acar et al., 2007). 286 In the neural retina, the major species of PlsEtn are those containing PUFAs, arachidonic acid 287 (AA, C20:4n-6; in PlsEtn16:0/20:4 and PlsEtn18:0/20:4), or DHA (C22:6n-3; in 288 PlsEtn18:0/22:6) at their sn-2 position (Saab et al., 2014b). Such PUFAs are the precursors of 289 290 bioactive molecules such as prostaglandins, leukotrienes, resolvins, and protectins. Apart from 291 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 292 293 pathophysiology of retinopathies such as glaucoma and retinopathy of prematurity (Acar et 294 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 298 et al., 2018; Velagapudi et al., 2010; Villette et al., 2020). One of the first pieces of evidence 299 showing that the gut microbiota could influence the retinal lipid content was provided over 10 300 301 years ago by Orešič and colleagues when they compared the lipidome of retinas from germfree mice (i.e., mice raised without microbiota) and conventionally raised mice (Oresic et al., 302 2009). Their study showed that the presence of the gut microbiota was associated with an 303 elevation of the retinal content in PlsEtn, particularly in PlsEtn18:0/20:4. Recent data from 304 our laboratory complete this observation by showing that, beyond its presence, the 305 306 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 307 308 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. 309 310 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 311 312 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 313 314 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 PUFAs such as DHA from short-chain precursors. This finding makes sense considering the 316 pathophysiology of AMD, for which a high supply of long-chain PUFAs such as DHA has 317 318 been shown to be protective (Liu et al., 2010; Zinkernagel et al., 2017).

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

It is now well established that the gut microbiota contributes to the development of the 322 immune system and that dysbiosis is a central player in the promotion of inflammatory 323 conditions, ranging from localized acute colitis to low-grade systemic inflammation (Aldars-324 325 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 326 well characterized in several animal models (Chassaing and Gewirtz, 2014). In humans, 327 dysbiosis has been linked to inflammation in numerous pathological conditions such as 328 inflammatory bowel diseases, metabolic disorders, and some age-related neuroinflammatory 329 diseases, including Alzheimer's disease (Megur et al., 2020; Neurath, 2020; Tilg et al., 2020). 330 331 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 334 microbiota on retinal inflammation in various pathological contexts. In the eye, autoimmune 335 uveitis is characterized by inflammation of the uvea (iris, ciliary body, choroid) and 336 neuroretina (Amador-Patarroyo MJ, 2013). Studies on mouse models of experimental 337 autoimmune uveitis (EAU) have provided evidence for a role of the gut microbiota in the 338 modulation of the responses and behavior of uveitogenic T lymphocytes as well as in the 339 340 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 341 342 (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 343 344 been shown to attenuate immune-mediated uveitis in a mouse strain-dependent manner (Nakamura et al., 2017). 345

346 A role of the gut microbiota in inflammation associated with the development of retinopathy in diet-induced metabolic disorders has also been demonstrated. Increased 347 348 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 diet (HFD; (Andriessen et al., 2016). The phenotype was reversed following oral intake of a 350 broad-spectrum antibiotic, neomycin, and partially reversed following the transfer of fecal 351 microbiota from mice fed a regular-chow diet to recipient HFD-fed mice (Andriessen et al., 352 2016). Other data suggest that the gut microbiota influences the retinal inflammatory status in 353 354 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 a decrease in circulating peptidoglycans – leads to a reduction in the number of IBA-1⁺ cells 356 that are markers of microglial activation as well as to decreased infiltration by CD45⁺ 357 hematopoietic cells in the retina (Beli et al., 2018). In addition, it has been reported that 358 administration of ursodeoxycholic acid (UDCA), a secondary bile acid generated by gut 359 bacteria, improves the DR-like phenotype in a streptozotocin (STZ)-induced diabetic mouse 360 model through the attenuation of retinal inflammation (Chung et al., 2017; Ouyang et al., 361 2018). Oral administration of UDCA reduced the number of IBA-1⁺ cells in retinal ganglion 362 cells and retinal inner plexiform layers, and also decreased the activation of the NF-kappaB 363 pathway and the expression level of mRNAs encoding pro-inflammatory cytokines (TNF-364 alpha, IL-1beta, and IL-6) in retinas of STZ-induced diabetic mice (Ouyang et al., 2018). 365

Similarly, the increased retinal expression of MCP-14 and TNF-alpha observed in STZinduced 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).

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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, two diseases whose hallmarks include retinal neovascularization processes (Adams et al., 379 380 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 381 382 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 inflammation as well as an exacerbated CNV. A set of experiments, including the transfer of 384 cecal microbiota from HFD- or chow-diet-fed mice to recipient mice, revealed that the gut 385 microbiota drives the vascular phenotype. Although a causal relationship was not firmly 386 demonstrated, the influence of the gut microbiota composition on the development of retinal 387 vascular abnormalities was strengthened by another study. The authors showed that long-term 388 exposure of mice to intermittent fasting altered the gut microbiota composition and prevented 389 the development of acellular capillaries in the retina of *db/db* mice, a potential model for DR 390 (Beli et al., 2018). 391

Several studies support a protective role of bile acids in mechanisms related to 392 393 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 394 protection of the vascular integrity in an STZ-induced DR model (Chung et al., 2017; Ouyang 395 et al., 2018). Long-term exposure to intermittent fasting, a condition associated with the 396 prevention of diabetic microvascular complications, was associated with an increase in 397 plasma levels of TUDCA (Beli et al., 2018). TUDCA is an agonist of the bile acid receptor 398 TGR5. Interestingly, pharmacological activation of TGR5 by the bile acid agonist INT-767 399

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

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

The dry form of AMD is characterized by a progressive macular degeneration of the retinal 405 pigment epithelium that precedes photoreceptor cell loss and by lipofuscin accumulation and 406 drusen formation. Feeding mice a high-glycemic-index diet (HD) is associated with age-407 408 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 agerelated eye disorders. In this study, although the experimental setting did not identify a causal 411 412 relationship, it was shown that modifications in the microbiome and metabolome were associated with the retinal phenotype (Rowan et al., 2017). 413

414 Chen and colleagues recently provided evidence that the gut microbiota is a contributing factor to glaucoma pathophysiology (Chen et al., 2018). They showed that 415 416 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 T-cell responses targeted both human and bacterial heat shock proteins (HSP). Interestingly, 418 HSP-specific T-cell response and neurodegeneration were abolished in germ-free mice, thus 419 420 suggesting that exposure to the commensal microbial flora is required to induce HSP-specific T-cell response in neurodegeneration (Chen et al., 2018). 421

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

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 influence of the gut microbiota on the development and progression of retinal disorders. 436 Hence, manipulating the gut microbiota appears to be an attractive and promising strategy for 437 preventing or limiting symptoms of retinal diseases. Several strategies for modifying the gut 438 microbiota in this context are discussed hereafter. Their precision range from the transfer of 439 440 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 441 we present, some induce shift in bacterial communities (e.g., prebiotics and diet) while others 442 introduce selected bacterial species (e.g., probiotics) into the gut microbiota or are designed to 443 deplete the gut microbiota of some bacterial species (e.g., phage therapy). 444

445

446 *4.1. Probiotics*

The term "probiotic" refers to "live microorganisms that, when administered in adequate 447 amounts, confer a health benefit on the host" (Hill et al., 2014). The most common strains 448 used as probiotics are lactic acid bacteria and bifidobacteria. However, other species such as 449 450 Akkermansia muciniphila or Faecalibacterium prausnitzii are considered promising nextgeneration probiotic candidates (Cani and de Vos, 2017; Martin et al., 2018). The general 451 452 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 453 454 have extraintestinal effects. Indeed, the beneficial effects of specific probiotics on neurological disorders have been described in animal models and in humans (Sasmita, 2019; 455 Westfall et al., 2017). Interestingly, results from experimental studies suggest that 456 supplementation with probiotics could also protect the retina from deleterious conditions. 457 Some proof in this regard originated from the organism model Drosophila melanogaster, in 458 which the administration of Lactiplantibacillus plantarum DR7 was shown to alleviate eye 459 neurodegeneration (rough eye phenotype) induced by the expression of Alzheimer's Aβ42 460 peptide (Tan et al., 2020a). In addition, oral administration of the probiotic strains Escherichia 461 coli Nissle 1917 or IRT-5 (a mixture consisting of Lacticaseibacillus casei, Lactobacillus 462 acidophilus, Limosilactobacillus reuteri, Bifidobacterium bifidum, and Streptococcus 463 thermophilus) was able to reduce the severity of EAU in mice, at least partly by modulating 464

the immune system (Dusek et al., 2020; Kim et al., 2017). The positive effects of oral 465 supplementation with probiotics have also been described for ocular structures other than the 466 retina. Indeed, L. plantarum NK151 and B. bifidum NK175 as well as the ITR5 probiotics 467 have been shown to improve dry eye symptoms in mice (Choi et al., 2020; Kim et al., 2017; 468 Moon et al., 2020; Yun et al., 2021). In addition, dietary supplementation with the probiotic 469 strain Lacticaseibacillus rhamnosus GG has been shown to be effective in antagonizing the 470 disturbances in retinoid metabolism caused by the pollutant perfluorobutane sulfonate in the 471 472 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 well as engineering tools that have been developed, several lactic acid bacteria and 476 477 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 478 479 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 480 481 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 nontoxic subunit B of cholera toxin, a transepithelial carrier. A protective role has been reported 483 for ACE2/Ang-(1-7) in uveitis and DR (Dominguez et al., 2016; Qiu et al., 2014; Shil et al., 484 2014; Verma et al., 2012). Oral administration of ACE2- or Ang-(1-7)-L. paracasei showed 485 efficacy in limiting retinal inflammation and neurovascular degeneration in mouse models of 486 DR (Verma et al., 2020a; Verma et al., 2020b). Although they are considered as safe and well 487 tolerated by healthy subjects, long-term use of probiotics might entail risk under certain 488 contexts (e.g., probiotic translocation to extra intestinal sites in patients with damaged 489 490 intestinal barrier or compromised immunity, transfer of antibiotic-resistant traits to commensal or pathogenic intestinal bacteria) (Yelin et al., 2019). 491

492

493 *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 499 500 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 501 come from carbohydrates (e.g., non-digestible oligosaccharides fructans and galactans). 502 503 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 504 the composition of the gut microbiota by COS have been documented, involvement of these 505 microbial changes in the beneficial effects of COS on the retina remains to be evaluated since 506 507 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 508 509 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 with resveratrol has been shown to have beneficial effects on retinopathies (Abu-Amero et al., 512 513 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 514 515 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).

520

521 *4.3. Synbiotics*

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

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

Paraprobiotics are defined as "non-viable microbial cells (either intact or broken) or crude cell 534 extracts which when administered (either orally or topically) in adequate amounts confer a 535 benefit to the consumer" (Nataraj et al., 2020). Their beneficial health effects are mediated by 536 the metabolites/molecules contained in the inactivated microorganisms. Morita and colleagues 537 explored the efficacy of heat-killed L. paracasei KW3110 in protecting the retina against 538 several stress conditions. They showed that long-term intake of this paraprobiotic modulated 539 540 the gut microbiota composition in aged mice. Among other changes, the relative abundance of bifidobacteria (health-promoting bacteria) was increased and that of Streptococcaceae 541 542 (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 543 544 (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 545 546 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 547 548 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., 549 2018a; Yamazaki et al., 2020). 550

551

552 *4.5. Postbiotics*

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

563

564 4.6. Fecal microbiota transplant

FMT consists in transferring stool from a donor in a "healthy" state to the gastrointestinal 565 tract of a recipient individual. The aim is to recover the homeostatic status of the gut 566 microbiota at the compositional and functional levels (Ng et al., 2020). The potential of such a 567 568 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 569 FMT (Turnbaugh et al., 2006). In addition, the efficacy of FMT has also been demonstrated in 570 the treatment of *Clostridioides difficile* infections in patients (Mullish et al., 2018). These 571 findings turned attention to the use of FMT for the treatment of other diseases associated with 572 573 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 574 575 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). Two groups of bacteriophages are distinguished according to their replication cycle: the lytic 583 cycle and the lysogenic cycle. The lytic (or virulent) bacteriophages infect bacterial hosts and 584 subvert them to produce phage progeny. Then, they induce bacterial host death upon lysis, 585 thus releasing newly formed phages. The lysogenic (or temperate) bacteriophages integrate 586 their nucleic acid in the genome of the host bacterium or as an extrachromosomal plasmid. 587 They can be maintained as prophages in their bacterial host for several generations until 588 induction of the lytic cycle. Bacterial surface molecules and phage receptor-binding proteins 589 590 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). 591 592 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 593 antibiotic resistance due to the extensive use of antibiotics in human health and agriculture, 594 phage therapy is re-emerging as an attractive alternative. Among the advantages that phage 595 therapy offers over antibiotics is the targeting of specific bacterial strains. Knowledge has 596 accumulated over the past decade on phage-bacteria interactions (Sausset et al., 2020). Data 597 598 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.

606

607 *4.8. Diet*

The composition of diet and dietary habits are recognized as modulators of the gut microbiota 608 609 (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, studies suggest that long-term habits play a role in shaping an individual's stable gut 612 613 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; 614 615 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 microbiota. Indigestible carbohydrates (fermentable dietary fibers; see "Prebiotics" section) 617 and omega-3 PUFAs are among the best-documented macronutrients, which have been 618 619 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-3 620 PUFAs have been demonstrated in various pathological conditions, including metabolic and 621 neurodegenerative disorders and retinal diseases (Bousquet et al., 2008; Calon et al., 2004). 622 At least in part, the beneficial effect of omega-3 PUFAs in metabolic disorders seems to be 623 related to their impact on the gut microbiota (Bidu et al., 2019). 624

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

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 639 affect retinal physiology is that of Western diet (WD). Consumption of WD is associated with 640 641 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 well as the pathological vascularization of the retina in mice (Andriessen et al., 2016). 644 645 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., 646 647 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-648 649 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; Thierry et al., 2015). However, the role of the gut microbiota in such phenotype remains also 651 to be demonstrated. In addition, and as discussed in section 3.4, Rowan and colleagues 652 reported that consuming high-glycemia (HG) diet was associated with the development of 653 AMD features, which could be prevented/reversed by switching from HG to low-glycemia 654 diet (Rowan et al., 2017). These retinal phenotypes correlated with compositional and 655 656 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

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).

670

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 genometargeting 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).

678

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

689

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

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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.).

704

705 **6. Conclusion**

It has become evident that the physiology of the retina is under the influence of the gut 706 microbiota. Indeed, although more data are needed, studies in humans suggested that 707 708 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 microbiota-brain dialogue is already well advanced, little is known about the gut microbiota-711 712 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 713 714 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 715 716 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 arise from several factors such as the low number of independent studies available 718 (particularly for AMD) but also to the influence of genetic and/or environmental factors (e.g. 719 dietary habits, drug treatments or stool collection). In addition, more microbiota-health studies 720 will help to allow distinguishing correlation from causation. To date, most of the studies have 721 722 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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733 **References**

- Abu-Amero, K.K., Kondkar, A.A., Chalam, K.V., 2016. Resveratrol and Ophthalmic Diseases. Nutrients8, 200.
- 736 Acar, I.E., Lores-Motta, L., Colijn, J.M., Meester-Smoor, M.A., Verzijden, T., Cougnard-Gregoire, A.,
- Ajana, S., Merle, B.M.J., de Breuk, A., Heesterbeek, T.J., van den Akker, E., Daha, M.R., Claes, B.,
- Pauleikhoff, D., Hense, H.W., van Duijn, C.M., Fauser, S., Hoyng, C.B., Delcourt, C., Klaver, C.C.W.,
- 739 Galesloot, T.E., den Hollander, A.I., Consortium, E.-R., 2020. Integrating Metabolomics, Genomics,
- and Disease Pathways in Age-Related Macular Degeneration: The EYE-RISK Consortium.
- 741 Ophthalmology 127, 1693-1709.
- 742 Acar, N., Berdeaux, O., Juaneda, P., Gregoire, S., Cabaret, S., Joffre, C., Creuzot-Garcher, C.P.,
- 743 Bretillon, L., Bron, A.M., 2009. Red blood cell plasmalogens and docosahexaenoic acid are
- independently reduced in primary open-angle glaucoma. Exp Eye Res 89, 840-853.
- Acar, N., Gregoire, S., Andre, A., Juaneda, P., Joffre, C., Bron, A.M., Creuzot-Garcher, C.P., Bretillon, L.,
- 746 2007. Plasmalogens in the retina: in situ hybridization of dihydroxyacetone phosphate
- 747 acyltransferase (DHAP-AT)--the first enzyme involved in their biosynthesis--and comparative study of
- retinal and retinal pigment epithelial lipid composition. Exp Eye Res 84, 143-151.
- Adams, M.K., Simpson, J.A., Aung, K.Z., Makeyeva, G.A., Giles, G.G., English, D.R., Hopper, J., Guymer,
- R.H., Baird, P.N., Robman, L.D., 2011. Abdominal obesity and age-related macular degeneration. Am J
 Epidemiol 173, 1246-1255.
- Ahlawat, S., Asha, Sharma, K.K., 2020. Gut-organ axis: a microbial outreach and networking. Lett ApplMicrobiol.
- Al Bander, Z., Nitert, M.D., Mousa, A., Naderpoor, N., 2020. The Gut Microbiota and Inflammation:
- 755 An Overview. Int J Environ Res Public Health 17.
- Albouery, M., Buteau, B., Gregoire, S., Cherbuy, C., Pais de Barros, J.P., Martine, L., Chain, F., Cabaret,
- 57 S., Berdeaux, O., Bron, A.M., Acar, N., Langella, P., Bringer, M.A., 2019. Age-Related Changes in the
- 758 Gut Microbiota Modify Brain Lipid Composition. Front Cell Infect Microbiol 9, 444.
- Albouery, M., Buteau, B., Gregoire, S., Martine, L., Gambert, S., Bron, A.M., Acar, N., Chassaing, B.,
- Bringer, M.A., 2020. Impact of a high-fat diet on the fatty acid composition of the retina. Exp Eye Res196, 108059.
- 762 Aldars-Garcia, L., Marin, A.C., Chaparro, M., Gisbert, J.P., 2021. The Interplay between Immune
- 763 System and Microbiota in Inflammatory Bowel Disease: A Narrative Review. Int J Mol Sci 22.
- Amador-Patarroyo MJ, C.P.A., Teresa Bernal M, 2013. Autoimmunity: From Bench to Bedside. Bogota
 (Colombia): El Rosario University Press Chapter 37: Autoimmune uveitis.
- Andriessen, E.M., Wilson, A.M., Mawambo, G., Dejda, A., Miloudi, K., Sennlaub, F., Sapieha, P., 2016.
- 767 Gut microbiota influences pathological angiogenesis in obesity-driven choroidal neovascularization.
- 768 EMBO Mol Med 8, 1366-1379.
- 769 Anne Katrine Toft-Kehler, J.V., Miriam Kolko, Gus Gazzard, 2020. Investigation of the Association
- between the Oral and the Gut Microbiome in Glaucoma. Journal of Clinical & ExperimentalOphthalmology 11.
- Arora, K., Green, M., Prakash, S., 2020. The Microbiome and Alzheimer's Disease: Potential and
- Limitations of Prebiotic, Synbiotic, and Probiotic Formulations. Front Bioeng Biotechnol 8, 537847.
- Askari, G., Moravejolahkami, A.R., 2019. Synbiotic Supplementation May Relieve Anterior Uveitis, an
- 775 Ocular Manifestation in Behcet's Syndrome. Am J Case Rep 20, 548-550.
- Astafurov, K., Elhawy, E., Ren, L., Dong, C.Q., Igboin, C., Hyman, L., Griffen, A., Mittag, T., Danias, J.,
- 2014. Oral microbiome link to neurodegeneration in glaucoma. PLoS One 9, e104416.

- 778 Baba, Y., Konishi, H., Yokoi, Y., Wakabayashi, H., Sato, J., Yamamoto, K., Yamane, W., Kawaraya, H.,
- 1989. [Clinical pictures and echocardiograms of three cases of severe myocarditis]. J Cardiol Suppl 22,27-28.
- 781 Backhed, F., Ding, H., Wang, T., Hooper, L.V., Koh, G.Y., Nagy, A., Semenkovich, C.F., Gordon, J.I.,
- 2004. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U
 S A 101, 15718-15723.
- 784 Barba, I., Garcia-Ramirez, M., Hernandez, C., Alonso, M.A., Masmiquel, L., Garcia-Dorado, D., Simo,
- 785 R., 2010. Metabolic fingerprints of proliferative diabetic retinopathy: an 1H-NMR-based
- 786 metabonomic approach using vitreous humor. Invest Ophthalmol Vis Sci 51, 4416-4421.
- 787 Barber, T.M., Valsamakis, G., Mastorakos, G., Hanson, P., Kyrou, I., Randeva, H.S., Weickert, M.O.,
- 788 2021. Dietary Influences on the Microbiota-Gut-Brain Axis. Int J Mol Sci 22.
- 789 Beli, E., Yan, Y., Moldovan, L., Vieira, C.P., Gao, R., Duan, Y., Prasad, R., Bhatwadekar, A., White, F.A.,
- 790 Townsend, S.D., Chan, L., Ryan, C.N., Morton, D., Moldovan, E.G., Chu, F.I., Oudit, G.Y., Derendorf, H.,
- Adorini, L., Wang, X.X., Evans-Molina, C., Mirmira, R.G., Boulton, M.E., Yoder, M.C., Li, Q., Levi, M.,
- Busik, J.V., Grant, M.B., 2018. Restructuring of the Gut Microbiome by Intermittent Fasting Prevents
 Retinopathy and Prolongs Survival in db/db Mice. Diabetes 67, 1867-1879.
- 794 Belizario, J.E., Napolitano, M., 2015. Human microbiomes and their roles in dysbiosis, common
- diseases, and novel therapeutic approaches. Front Microbiol 6, 1050.
- Bermudez-Humaran, L.G., Langella, P., 2017. Use of Traditional and Genetically Modified Probiotics in
 Human Health: What Does the Future Hold? Microbiol Spectr 5.
- Bidu, C., Escoula, Q., Bellenger, S., Spor, A., Galan, M., Geissler, A., Bouchot, A., Dardevet, D., Morio-
- Liondor, B., Cani, P.D., Lagrost, L., Narce, M., Bellenger, J., 2019. Erratum. The Transplantation of
- 800 omega3 PUFA-Altered Gut Microbiota of fat-1 Mice to Wild-Type Littermates Prevents Obesity and
 801 Associated Metabolic Disorders. Diabetes 2018;67:1512-1523. Diabetes 68, 235.
- 802 Bousquet, M., Saint-Pierre, M., Julien, C., Salem, N., Jr., Cicchetti, F., Calon, F., 2008. Beneficial effects
- of dietary omega-3 polyunsaturated fatty acid on toxin-induced neuronal degeneration in an animal
 model of Parkinson's disease. FASEB J 22, 1213-1225.
- 805 Bretillon, L., Thuret, G., Gregoire, S., Acar, N., Joffre, C., Bron, A.M., Gain, P., Creuzot-Garcher, C.P.,
- 2008. Lipid and fatty acid profile of the retina, retinal pigment epithelium/choroid, and the lacrimal
- gland, and associations with adipose tissue fatty acids in human subjects. Exp Eye Res 87, 521-528.
- 808 Brites, P., Waterham, H.R., Wanders, R.J., 2004. Functions and biosynthesis of plasmalogens in health 809 and disease. Biochim Biophys Acta 1636, 219-231.
- 810 Buford, T.W., 2017. (Dis)Trust your gut: the gut microbiome in age-related inflammation, health, and 811 disease. Microbiome 5, 80.
- 812 Buisset, A., Gohier, P., Leruez, S., Muller, J., Amati-Bonneau, P., Lenaers, G., Bonneau, D., Simard, G.,
- 813 Procaccio, V., Annweiler, C., Milea, D., Reynier, P., Chao de la Barca, J.M., 2019. Metabolomic
- 814 Profiling of Aqueous Humor in Glaucoma Points to Taurine and Spermine Deficiency: Findings from
- 815 the Eye-D Study. J Proteome Res 18, 1307-1315.
- 816 Byun, M.S., Park, S.W., Lee, J.H., Yi, D., Jeon, S.Y., Choi, H.J., Joung, H., Ghim, U.H., Park, U.C., Kim,
- 817 Y.K., Shin, S.A., Yu, H.G., Lee, D.Y., Group, K.R., 2021. Association of Retinal Changes With Alzheimer
- Disease Neuroimaging Biomarkers in Cognitively Normal Individuals. JAMA Ophthalmol 139, 548-556.
- Calon, F., Lim, G.P., Yang, F., Morihara, T., Teter, B., Ubeda, O., Rostaing, P., Triller, A., Salem, N., Jr.,
- Ashe, K.H., Frautschy, S.A., Cole, G.M., 2004. Docosahexaenoic acid protects from dendritic pathology
 in an Alzheimer's disease mouse model. Neuron 43, 633-645.
- Cani, P.D., Amar, J., Iglesias, M.A., Poggi, M., Knauf, C., Bastelica, D., Neyrinck, A.M., Fava, F., Tuohy,
- 823 K.M., Chabo, C., Waget, A., Delmee, E., Cousin, B., Sulpice, T., Chamontin, B., Ferrieres, J., Tanti, J.F.,
- 824 Gibson, G.R., Casteilla, L., Delzenne, N.M., Alessi, M.C., Burcelin, R., 2007. Metabolic endotoxemia
- 825 initiates obesity and insulin resistance. Diabetes 56, 1761-1772.
- 826 Cani, P.D., de Vos, W.M., 2017. Next-Generation Beneficial Microbes: The Case of Akkermansia
- 827 muciniphila. Front Microbiol 8, 1765.
- 828 Chakravarthy, U., Evans, J., Rosenfeld, P.J., 2010. Age related macular degeneration. BMJ 340, c981.

- Chassaing, B., Gewirtz, A.T., 2014. Gut microbiota, low-grade inflammation, and metabolic syndrome.
 Toxicol Pathol 42, 49-53.
- Chen, H., Cho, K.S., Vu, T.H.K., Shen, C.H., Kaur, M., Chen, G., Mathew, R., McHam, M.L., Fazelat, A.,
- Lashkari, K., Au, N.P.B., Tse, J.K.Y., Li, Y., Yu, H., Yang, L., Stein-Streilein, J., Ma, C.H.E., Woolf, C.J.,
- 833 Whary, M.T., Jager, M.J., Fox, J.G., Chen, J., Chen, D.F., 2018. Commensal microflora-induced T cell
- responses mediate progressive neurodegeneration in glaucoma. Nat Commun 9, 3209.
- 835 Chisari, G., Chisari, E.M., Francaviglia, A., Chisari, C.G., 2017. The mixture of bifidobacterium
- associated with fructo-oligosaccharides reduces the damage of the ocular surface. Clin Ter 168, e181-e185.
- 838 Chiu, C.J., Chang, M.L., Zhang, F.F., Li, T., Gensler, G., Schleicher, M., Taylor, A., 2014. The relationship
- of major American dietary patterns to age-related macular degeneration. Am J Ophthalmol 158, 118-127 e111.
- Choi, S.H., Oh, J.W., Ryu, J.S., Kim, H.M., Im, S.H., Kim, K.P., Kim, M.K., 2020. IRT5 Probiotics Changes
- 842 Immune Modulatory Protein Expression in the Extraorbital Lacrimal Glands of an Autoimmune Dry
 843 Eye Mouse Model. Invest Ophthalmol Vis Sci 61, 42.
- 844 Chung, Y.R., Choi, J.A., Koh, J.Y., Yoon, Y.H., 2017. Ursodeoxycholic Acid Attenuates Endoplasmic
- Reticulum Stress-Related Retinal Pericyte Loss in Streptozotocin-Induced Diabetic Mice. J DiabetesRes 2017, 1763292.
- 847 Collins, S., Reid, G., 2016. Distant Site Effects of Ingested Prebiotics. Nutrients 8.
- 848 Cotillard, A., Kennedy, S.P., Kong, L.C., Prifti, E., Pons, N., Le Chatelier, E., Almeida, M., Quinquis, B.,
- 849 Levenez, F., Galleron, N., Gougis, S., Rizkalla, S., Batto, J.M., Renault, P., consortium, A.N.R.M., Dore,
- J., Zucker, J.D., Clement, K., Ehrlich, S.D., 2013. Dietary intervention impact on gut microbial gene
 richness. Nature 500, 585-588.
- 852 Crackower, M.A., Sarao, R., Oudit, G.Y., Yagil, C., Kozieradzki, I., Scanga, S.E., Oliveira-dos-Santos, A.J.,
- da Costa, J., Zhang, L., Pei, Y., Scholey, J., Ferrario, C.M., Manoukian, A.S., Chappell, M.C., Backx, P.H.,
- Yagil, Y., Penninger, J.M., 2002. Angiotensin-converting enzyme 2 is an essential regulator of heart
- 855 function. Nature 417, 822-828.
- Babke, K., Hendrick, G., Devkota, S., 2019. The gut microbiome and metabolic syndrome. J Clin Invest
 129, 4050-4057.
- Daruich, A., Picard, E., Boatright, J.H., Behar-Cohen, F., 2019. Review: The bile acids urso- and
- tauroursodeoxycholic acid as neuroprotective therapies in retinal disease. Mol Vis 25, 610-624.
- B60 Das, T., Jayasudha, R., Chakravarthy, S., Prashanthi, G.S., Bhargava, A., Tyagi, M., Rani, P.K., Pappuru,
- R.R., Sharma, S., Shivaji, S., 2021. Alterations in the gut bacterial microbiome in people with type 2
 diabetes mellitus and diabetic retinopathy. Sci Rep 11, 2738.
- 863 Datilo, M.N., Sant'Ana, M.R., Formigari, G.P., Rodrigues, P.B., de Moura, L.P., da Silva, A.S.R., Ropelle,
- 864 E.R., Pauli, J.R., Cintra, D.E., 2018. Omega-3 from Flaxseed Oil Protects Obese Mice Against Diabetic
 865 Retinopathy Through GPR120 Receptor. Sci Rep 8, 14318.
- de Groot, P., Nikolic, T., Pellegrini, S., Sordi, V., Imangaliyev, S., Rampanelli, E., Hanssen, N., Attaye, I.,
- 867 Bakker, G., Duinkerken, G., Joosten, A., Prodan, A., Levin, E., Levels, H., Potter van Loon, B., van Bon,
- A., Brouwer, C., van Dam, S., Simsek, S., van Raalte, D., Stam, F., Gerdes, V., Hoogma, R., Diekman,
- 869 M., Gerding, M., Rustemeijer, C., de Bakker, B., Hoekstra, J., Zwinderman, A., Bergman, J., Holleman,
- 870 F., Piemonti, L., De Vos, W., Roep, B., Nieuwdorp, M., 2021. Faecal microbiota transplantation halts
- progression of human new-onset type 1 diabetes in a randomised controlled trial. Gut 70, 92-105.
- 872 De Vadder, F., Kovatcheva-Datchary, P., Zitoun, C., Duchampt, A., Backhed, F., Mithieux, G., 2016.
- Microbiota-Produced Succinate Improves Glucose Homeostasis via Intestinal Gluconeogenesis. Cell
 Metab 24, 151-157.
- 875 DeFronzo, R.A., Ferrannini, E., Groop, L., Henry, R.R., Herman, W.H., Holst, J.J., Hu, F.B., Kahn, C.R.,
- 876 Raz, I., Shulman, G.I., Simonson, D.C., Testa, M.A., Weiss, R., 2015. Type 2 diabetes mellitus. Nat Rev
- 877 Dis Primers 1, 15019.
- Do, M.H., Lee, E., Oh, M.J., Kim, Y., Park, H.Y., 2018. High-Glucose or -Fructose Diet Cause Changes of
- the Gut Microbiota and Metabolic Disorders in Mice without Body Weight Change. Nutrients 10.

- Dominguez, J.M., 2nd, Hu, P., Caballero, S., Moldovan, L., Verma, A., Oudit, G.Y., Li, Q., Grant, M.B.,
- 2016. Adeno-Associated Virus Overexpression of Angiotensin-Converting Enzyme-2 Reverses Diabetic
 Retinopathy in Type 1 Diabetes in Mice. Am J Pathol 186, 1688-1700.
- 883 Doulberis, M., Papaefthymiou, A., Polyzos, S.A., Bargiotas, P., Liatsos, C., Srivastava, D.S., Zavos, C.,
- 884 Katsinelos, P., Kountouras, J., 2020. Association between Active Helicobacter pylori Infection and
- 885 Glaucoma: A Systematic Review and Meta-Analysis. Microorganisms 8.
- B86 Dusek, O., Fajstova, A., Klimova, A., Svozilkova, P., Hrncir, T., Kverka, M., Coufal, S., Slemin, J.,
- 887 Tlaskalova-Hogenova, H., Forrester, J.V., Heissigerova, J., 2020. Severity of Experimental Autoimmune
- 888 Uveitis Is Reduced by Pretreatment with Live Probiotic Escherichia coli Nissle 1917. Cells 10.
- 889 Fang, I.M., Yang, C.H., Yang, C.M., Chen, M.S., 2013. Chitosan oligosaccharides attenuates oxidative-
- 890 stress related retinal degeneration in rats. PLoS One 8, e77323.
- 891 Ferrari, S., Di Iorio, E., Barbaro, V., Ponzin, D., Sorrentino, F.S., Parmeggiani, F., 2011. Retinitis
- pigmentosa: genes and disease mechanisms. Curr Genomics 12, 238-249.
- Galtier, M., De Sordi, L., Sivignon, A., de Vallee, A., Maura, D., Neut, C., Rahmouni, O., Wannerberger,
- 894 K., Darfeuille-Michaud, A., Desreumaux, P., Barnich, N., Debarbieux, L., 2017. Bacteriophages
- 895 Targeting Adherent Invasive Escherichia coli Strains as a Promising New Treatment for Crohn's
- 896 Disease. J Crohns Colitis 11, 840-847.
- Ghazalpour, A., Cespedes, I., Bennett, B.J., Allayee, H., 2016. Expanding role of gut microbiota in lipid
 metabolism. Curr Opin Lipidol 27, 141-147.
- Gibson, G.R., Hutkins, R., Sanders, M.E., Prescott, S.L., Reimer, R.A., Salminen, S.J., Scott, K., Stanton,
- 900 C., Swanson, K.S., Cani, P.D., Verbeke, K., Reid, G., 2017. Expert consensus document: The
- 901 International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the 902 definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol 14, 491-502.
- 903 Gomaa, A.A., Klumpe, H.E., Luo, M.L., Selle, K., Barrangou, R., Beisel, C.L., 2014. Programmable
- 904 removal of bacterial strains by use of genome-targeting CRISPR-Cas systems. mBio 5, e00928-00913.
- 905 Gong, H., Zhang, S., Li, Q., Zuo, C., Gao, X., Zheng, B., Lin, M., 2020. Gut microbiota compositional
- profile and serum metabolic phenotype in patients with primary open-angle glaucoma. Exp Eye Res191, 107921.
- Gong, Y., Fu, Z., Liegl, R., Chen, J., Hellstrom, A., Smith, L.E., 2017. omega-3 and omega-6 long-chain
- 909 PUFAs and their enzymatic metabolites in neovascular eye diseases. Am J Clin Nutr 106, 16-26.
- 910 Gupta, N., Brown, K.E., Milam, A.H., 2003. Activated microglia in human retinitis pigmentosa, late-
- 911 onset retinal degeneration, and age-related macular degeneration. Exp Eye Res 76, 463-471.
- Gurung, M., Li, Z., You, H., Rodrigues, R., Jump, D.B., Morgun, A., Shulzhenko, N., 2020. Role of gut
 microbiota in type 2 diabetes pathophysiology. EBioMedicine 51, 102590.
- Hammond, B.R., Jr., Johnson, M.A., 2002. The age-related eye disease study (AREDS). Nutr Rev 60,283-288.
- Hassan, A.Y., Lin, J.T., Ricker, N., Anany, H., 2021. The Age of Phage: Friend or Foe in the New Dawn
- 917 of Therapeutic and Biocontrol Applications? Pharmaceuticals (Basel) 14.
- 918 Hazel, K., O'Connor, A., 2020. Emerging treatments for inflammatory bowel disease. Ther Adv
- 919 Chronic Dis 11, 2040622319899297.
- 920 Hill, C., Guarner, F., Reid, G., Gibson, G.R., Merenstein, D.J., Pot, B., Morelli, L., Canani, R.B., Flint, H.J.,
- 921 Salminen, S., Calder, P.C., Sanders, M.E., 2014. Expert consensus document. The International
- 922 Scientific Association for Probiotics and Prebiotics consensus statement on the scope and
- 923 appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol 11, 506-514.
- 924 Horai, R., Silver, P.B., Chen, J., Agarwal, R.K., Chong, W.P., Jittayasothorn, Y., Mattapallil, M.J.,
- 925 Nguyen, S., Natarajan, K., Villasmil, R., Wang, P., Karabekian, Z., Lytton, S.D., Chan, C.C., Caspi, R.R.,
- 926 2013. Breakdown of immune privilege and spontaneous autoimmunity in mice expressing a
- 927 transgenic T cell receptor specific for a retinal autoantigen. J Autoimmun 44, 21-33.
- 928 Horai, R., Zarate-Blades, C.R., Dillenburg-Pilla, P., Chen, J., Kielczewski, J.L., Silver, P.B., Jittayasothorn,
- 929 Y., Chan, C.C., Yamane, H., Honda, K., Caspi, R.R., 2015. Microbiota-Dependent Activation of an
- 930 Autoreactive T Cell Receptor Provokes Autoimmunity in an Immunologically Privileged Site. Immunity
- 931 43, 343-353.

- Hu, C., Tang, L., Liu, M., Lam, P.K.S., Lam, J.C.W., Chen, L., 2020. Probiotic modulation of
- 933 perfluorobutanesulfonate toxicity in zebrafish: Disturbances in retinoid metabolism and visual934 physiology. Chemosphere 258, 127409.
- Huang, Y., Wang, Z., Ma, H., Ji, S., Chen, Z., Cui, Z., Chen, J., Tang, S., 2021. Dysbiosis and Implication
- 936 of the Gut Microbiota in Diabetic Retinopathy. Front Cell Infect Microbiol 11, 646348.
- Janeiro, M.H., Ramirez, M.J., Milagro, F.I., Martinez, J.A., Solas, M., 2018. Implication of
- 938 Trimethylamine N-Oxide (TMAO) in Disease: Potential Biomarker or New Therapeutic Target.939 Nutrients 10.
- Janowitz, C., Nakamura, Y.K., Metea, C., Gligor, A., Yu, W., Karstens, L., Rosenbaum, J.T., Asquith, M.,
- Lin, P., 2019. Disruption of Intestinal Homeostasis and Intestinal Microbiota During Experimental
 Autoimmune Uveitis. Invest Ophthalmol Vis Sci 60, 420-429.
- Jin, H., Zhu, B., Liu, X., Jin, J., Zou, H., 2019. Metabolic characterization of diabetic retinopathy: An
- 944 (1)H-NMR-based metabolomic approach using human aqueous humor. J Pharm Biomed Anal 174,945 414-421.
- 946 Kang, D.W., Adams, J.B., Coleman, D.M., Pollard, E.L., Maldonado, J., McDonough-Means, S.,
- 947 Caporaso, J.G., Krajmalnik-Brown, R., 2019. Long-term benefit of Microbiota Transfer Therapy on
 948 autism symptoms and gut microbiota. Sci Rep 9, 5821.
- 949 Khan, R., Sharma, A., Ravikumar, R., Parekh, A., Srinivasan, R., George, R.J., Raman, R., 2021.
- 950 Association Between Gut Microbial Abundance and Sight-Threatening Diabetic Retinopathy. Invest
- 951 Ophthalmol Vis Sci 62, 19.
- 952 Kho, Z.Y., Lal, S.K., 2018. The Human Gut Microbiome A Potential Controller of Wellness and
- 953 Disease. Front Microbiol 9, 1835.
- 954 Kibe, R., Kurihara, S., Sakai, Y., Suzuki, H., Ooga, T., Sawaki, E., Muramatsu, K., Nakamura, A.,
- 955 Yamashita, A., Kitada, Y., Kakeyama, M., Benno, Y., Matsumoto, M., 2014. Upregulation of colonic
- 956 luminal polyamines produced by intestinal microbiota delays senescence in mice. Sci Rep 4, 4548.
- 957 Kim, J., Choi, S.H., Kim, Y.J., Jeong, H.J., Ryu, J.S., Lee, H.J., Kim, T.W., Im, S.H., Oh, J.Y., Kim, M.K.,
- 2017. Clinical Effect of IRT-5 Probiotics on Immune Modulation of Autoimmunity or Alloimmunity in
- 959 the Eye. Nutrients 9.
- 960 Kindt, A., Liebisch, G., Clavel, T., Haller, D., Hormannsperger, G., Yoon, H., Kolmeder, D., Sigruener, A.,
- 961 Krautbauer, S., Seeliger, C., Ganzha, A., Schweizer, S., Morisset, R., Strowig, T., Daniel, H., Helm, D.,
- Kuster, B., Krumsiek, J., Ecker, J., 2018. The gut microbiota promotes hepatic fatty acid desaturationand elongation in mice. Nat Commun 9, 3760.
- Knip, M., Siljander, H., 2016. The role of the intestinal microbiota in type 1 diabetes mellitus. Nat RevEndocrinol 12, 154-167.
- 966 Kootte, R.S., Levin, E., Salojarvi, J., Smits, L.P., Hartstra, A.V., Udayappan, S.D., Hermes, G., Bouter,
- 967 K.E., Koopen, A.M., Holst, J.J., Knop, F.K., Blaak, E.E., Zhao, J., Smidt, H., Harms, A.C., Hankemeijer, T.,
- 968 Bergman, J., Romijn, H.A., Schaap, F.G., Olde Damink, S.W.M., Ackermans, M.T., Dallinga-Thie, G.M.,
- 2017. 2017. Zoetendal, E., de Vos, W.M., Serlie, M.J., Stroes, E.S.G., Groen, A.K., Nieuwdorp, M., 2017.
- 970 Improvement of Insulin Sensitivity after Lean Donor Feces in Metabolic Syndrome Is Driven by
- 971 Baseline Intestinal Microbiota Composition. Cell Metab 26, 611-619 e616.
- 272 Lambert, N.G., ElShelmani, H., Singh, M.K., Mansergh, F.C., Wride, M.A., Padilla, M., Keegan, D.,
- 973 Hogg, R.E., Ambati, B.K., 2016. Risk factors and biomarkers of age-related macular degeneration.
- 974 Prog Retin Eye Res 54, 64-102.
- Leeming, E.R., Johnson, A.J., Spector, T.D., Le Roy, C.I., 2019. Effect of Diet on the Gut Microbiota:
 Rethinking Intervention Duration. Nutrients 11.
- 977 Leruez, S., Marill, A., Bresson, T., de Saint Martin, G., Buisset, A., Muller, J., Tessier, L., Gadras, C.,
- 978 Verny, C., Gohier, P., Amati-Bonneau, P., Lenaers, G., Bonneau, D., Simard, G., Milea, D., Procaccio,
- 979 V., Reynier, P., Chao de la Barca, J.M., 2018. A Metabolomics Profiling of Glaucoma Points to
- 980 Mitochondrial Dysfunction, Senescence, and Polyamines Deficiency. Invest Ophthalmol Vis Sci 59,
- 981 4355-4361.

- 982 Lim, S.H., Shin, J.H., Lee, J.W., Lee, Y., Seo, J.H., 2021. Differences in the eyelid and buccal
- 983 microbiome of glaucoma patients receiving long-term administration of prostaglandin analog drops.984 Graefes Arch Clin Exp Ophthalmol.
- Lin, P., McClintic, S.M., Nadeem, U., Skondra, D., 2021. A Review of the Role of the Intestinal
 Microbiota in Age-Related Macular Degeneration. J Clin Med 10.
- 987 Liu, A., Chang, J., Lin, Y., Shen, Z., Bernstein, P.S., 2010. Long-chain and very long-chain
- 988 polyunsaturated fatty acids in ocular aging and age-related macular degeneration. J Lipid Res 51,
 989 3217-3229.
- Liu, W., Wang, C., Xia, Y., Xia, W., Liu, G., Ren, C., Gu, Y., Li, X., Lu, P., 2021. Elevated plasma
- trimethylamine-N-oxide levels are associated with diabetic retinopathy. Acta Diabetol 58, 221-229.
- London, A., Benhar, I., Schwartz, M., 2013. The retina as a window to the brain-from eye research toCNS disorders. Nat Rev Neurol 9, 44-53.
- Lynch, S.K., Abramoff, M.D., 2017. Diabetic retinopathy is a neurodegenerative disorder. Vision Res139, 101-107.
- Maller, J., George, S., Purcell, S., Fagerness, J., Altshuler, D., Daly, M.J., Seddon, J.M., 2006. Common
- 997 variation in three genes, including a noncoding variant in CFH, strongly influences risk of age-related998 macular degeneration. Nat Genet 38, 1055-1059.
- 999 Marin, J.J., Macias, R.I., Briz, O., Banales, J.M., Monte, M.J., 2015. Bile Acids in Physiology, Pathology 1000 and Pharmacology. Curr Drug Metab 17, 4-29.
- 1001 Martin, R., Bermudez-Humaran, L.G., Langella, P., 2018. Searching for the Bacterial Effector: The
- 1002 Example of the Multi-Skilled Commensal Bacterium Faecalibacterium prausnitzii. Front Microbiol 9,1003 346.
- 1004 Martinez-Guryn, K., Hubert, N., Frazier, K., Urlass, S., Musch, M.W., Ojeda, P., Pierre, J.F., Miyoshi, J.,
- 1005 Sontag, T.J., Cham, C.M., Reardon, C.A., Leone, V., Chang, E.B., 2018. Small Intestine Microbiota
- 1006 Regulate Host Digestive and Absorptive Adaptive Responses to Dietary Lipids. Cell Host Microbe 23,1007 458-469 e455.
- Megur, A., Baltriukiene, D., Bukelskiene, V., Burokas, A., 2020. The Microbiota-Gut-Brain Axis and
 Alzheimer's Disease: Neuroinflammation Is to Blame? Nutrients 13.
- 1010 Menni, C., Zierer, J., Pallister, T., Jackson, M.A., Long, T., Mohney, R.P., Steves, C.J., Spector, T.D.,
- 1011 Valdes, A.M., 2017. Omega-3 fatty acids correlate with gut microbiome diversity and production of
 1012 N-carbamylglutamate in middle aged and elderly women. Sci Rep 7, 11079.
- 1013 Miles, J.P., Zou, J., Kumar, M.V., Pellizzon, M., Ulman, E., Ricci, M., Gewirtz, A.T., Chassaing, B., 2017.
- Supplementation of Low- and High-fat Diets with Fermentable Fiber Exacerbates Severity of DSS-induced Acute Colitis. Inflamm Bowel Dis 23, 1133-1143.
- 1016 Mithul Aravind, S., Wichienchot, S., Tsao, R., Ramakrishnan, S., Chakkaravarthi, S., 2021. Role of 1017 dietary polyphenols on gut microbiota, their metabolites and health benefits. Food Res Int 142,
- 1018 110189.
- 1019 Moon, J., Ryu, J.S., Kim, J.Y., Im, S.H., Kim, M.K., 2020. Effect of IRT5 probiotics on dry eye in the 1020 experimental dry eye mouse model. PLoS One 15, e0243176.
- 1021 Morais, L.H., Schreiber, H.L.t., Mazmanian, S.K., 2021. The gut microbiota-brain axis in behaviour and 1022 brain disorders. Nat Rev Microbiol 19, 241-255.
- 1023 Morita, Y., Jounai, K., Miyake, M., Inaba, M., Kanauchi, O., 2018a. Effect of Heat-Killed Lactobacillus
- 1024 paracasei KW3110 Ingestion on Ocular Disorders Caused by Visual Display Terminal (VDT) Loads: A
- 1025 Randomized, Double-Blind, Placebo-Controlled Parallel-Group Study. Nutrients 10.
- 1026 Morita, Y., Jounai, K., Sakamoto, A., Tomita, Y., Sugihara, Y., Suzuki, H., Ohshio, K., Otake, M.,
- 1027 Fujiwara, D., Kanauchi, O., Maruyama, M., 2018b. Long-term intake of Lactobacillus paracasei
- 1028 KW3110 prevents age-related chronic inflammation and retinal cell loss in physiologically aged mice.
- 1029 Aging (Albany NY) 10, 2723-2740.
- 1030 Morita, Y., Miwa, Y., Jounai, K., Fujiwara, D., Kurihara, T., Kanauchi, O., 2018c. Lactobacillus paracasei
- 1031 KW3110 Prevents Blue Light-Induced Inflammation and Degeneration in the Retina. Nutrients 10.

- 1032 Moubayed, N.M., Bhat, R.S., Al Farraj, D., Dihani, N.A., El Ansary, A., Fahmy, R.M., 2019. Screening
- 1033 and identification of gut anaerobes (Bacteroidetes) from human diabetic stool samples with and
- 1034 without retinopathy in comparison to control subjects. Microb Pathog 129, 88-92.
- 1035 Muanprasat, C., Chatsudthipong, V., 2017. Chitosan oligosaccharide: Biological activities and 1036 potential therapeutic applications. Pharmacol Ther 170, 80-97.
- 1037 Mullish, B.H., Quraishi, M.N., Segal, J.P., McCune, V.L., Baxter, M., Marsden, G.L., Moore, D.J.,
- 1038 Colville, A., Bhala, N., Iqbal, T.H., Settle, C., Kontkowski, G., Hart, A.L., Hawkey, P.M., Goldenberg,
- 1039 S.D., Williams, H.R.T., 2018. The use of faecal microbiota transplant as treatment for recurrent or
- 1040 refractory Clostridium difficile infection and other potential indications: joint British Society of
- 1041 Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. Gut 67, 1920-1941.
- 1042 Murase, H., Tsuruma, K., Shimazawa, M., Hara, H., 2015. TUDCA Promotes Phagocytosis by Retinal 1043 Pigment Epithelium via MerTK Activation. Invest Ophthalmol Vis Sci 56, 2511-2518.
- 1044 Mushegian, A.R., 2020. Are There 10(31) Virus Particles on Earth, or More, or Fewer? J Bacteriol 202.
- 1045 Nakamura, Y.K., Janowitz, C., Metea, C., Asquith, M., Karstens, L., Rosenbaum, J.T., Lin, P., 2017.
- 1046 Short chain fatty acids ameliorate immune-mediated uveitis partially by altering migration of 1047 lymphocytes from the intestine. Sci Rep 7, 11745.
- 1048 Nakamura, Y.K., Metea, C., Karstens, L., Asquith, M., Gruner, H., Moscibrocki, C., Lee, I., Brislawn, C.J.,
- 1049 Jansson, J.K., Rosenbaum, J.T., Lin, P., 2016. Gut Microbial Alterations Associated With Protection 1050 From Autoimmune Uveitis. Invest Ophthalmol Vis Sci 57, 3747-3758.
- 1051 Nataraj, B.H., Ali, S.A., Behare, P.V., Yadav, H., 2020. Postbiotics-parabiotics: the new horizons in
- 1052 microbial biotherapy and functional foods. Microb Cell Fact 19, 168.
- 1053 Neurath, M.F., 2020. Host-microbiota interactions in inflammatory bowel disease. Nat Rev
- 1054 Gastroenterol Hepatol 17, 76-77.
- 1055 Ng, S.C., Kamm, M.A., Yeoh, Y.K., Chan, P.K.S., Zuo, T., Tang, W., Sood, A., Andoh, A., Ohmiya, N.,
- 1056 Zhou, Y., Ooi, C.J., Mahachai, V., Wu, C.Y., Zhang, F., Sugano, K., Chan, F.K.L., 2020. Scientific frontiers
- 1057 in faecal microbiota transplantation: joint document of Asia-Pacific Association of Gastroenterology
- 1058 (APAGE) and Asia-Pacific Society for Digestive Endoscopy (APSDE). Gut 69, 83-91.
- 1059 Noailles, A., Fernandez-Sanchez, L., Lax, P., Cuenca, N., 2014. Microglia activation in a model of 1060 retinal degeneration and TUDCA neuroprotective effects. J Neuroinflammation 11, 186.
- 1061 Noriega, B.S., Sanchez-Gonzalez, M.A., Salyakina, D., Coffman, J., 2016. Understanding the Impact of 1062 Omega-3 Rich Diet on the Gut Microbiota. Case Rep Med 2016, 3089303.
- 1063 Norman, J.M., Handley, S.A., Baldridge, M.T., Droit, L., Liu, C.Y., Keller, B.C., Kambal, A., Monaco, C.L.,
- 1064 Zhao, G., Fleshner, P., Stappenbeck, T.S., McGovern, D.P., Keshavarzian, A., Mutlu, E.A., Sauk, J.,
- 1065 Gevers, D., Xavier, R.J., Wang, D., Parkes, M., Virgin, H.W., 2015. Disease-specific alterations in the 1066 enteric virome in inflammatory bowel disease. Cell 160, 447-460.
- 1067 Nowinski, A., Ufnal, M., 2018. Trimethylamine N-oxide: A harmful, protective or diagnostic marker in 1068 lifestyle diseases? Nutrition 46, 7-12.
- 1069 Nucci, C., Martucci, A., Cesareo, M., Garaci, F., Morrone, L.A., Russo, R., Corasaniti, M.T., Bagetta, G.,
- 1070 Mancino, R., 2015. Links among glaucoma, neurodegenerative, and vascular diseases of the central
- 1071 nervous system. Prog Brain Res 221, 49-65.
- 1072 O'Toole, P.W., Jeffery, I.B., 2015. Gut microbiota and aging. Science 350, 1214-1215.
- 1073 Oresic, M., Seppanen-Laakso, T., Yetukuri, L., Backhed, F., Hanninen, V., 2009. Gut microbiota affects 1074 lens and retinal lipid composition. Exp Eye Res 89, 604-607.
- 1075 Osborn, M.P., Park, Y., Parks, M.B., Burgess, L.G., Uppal, K., Lee, K., Jones, D.P., Brantley, M.A., Jr.,
- 1076 2013. Metabolome-wide association study of neovascular age-related macular degeneration. PLoS 1077 One 8, e72737.
- 1078 Ott, S.J., Waetzig, G.H., Rehman, A., Moltzau-Anderson, J., Bharti, R., Grasis, J.A., Cassidy, L., Tholey,
- 1079 A., Fickenscher, H., Seegert, D., Rosenstiel, P., Schreiber, S., 2017. Efficacy of Sterile Fecal Filtrate
- 1080 Transfer for Treating Patients With Clostridium difficile Infection. Gastroenterology 152, 799-811 e797.
- 1081

- 1082 Ouyang, H., Mei, X., Zhang, T., Lu, B., Ji, L., 2018. Ursodeoxycholic acid ameliorates diabetic
- retinopathy via reducing retinal inflammation and reversing the breakdown of blood-retinal barrier.Eur J Pharmacol 840, 20-27.
- Patel, V.B., Zhong, J.C., Grant, M.B., Oudit, G.Y., 2016. Role of the ACE2/Angiotensin 1-7 Axis of the
 Renin-Angiotensin System in Heart Failure. Circ Res 118, 1313-1326.
- 1087 Peterson, C.T., 2020. Dysfunction of the Microbiota-Gut-Brain Axis in Neurodegenerative Disease:
- The Promise of Therapeutic Modulation With Prebiotics, Medicinal Herbs, Probiotics, and Synbiotics.
 J Evid Based Integr Med 25, 2515690X20957225.
- Plavec, T.V., Berlec, A., 2019. Engineering of lactic acid bacteria for delivery of therapeutic proteinsand peptides. Appl Microbiol Biotechnol 103, 2053-2066.
- Polkade, A.V., Mantri, S.S., Patwekar, U.J., Jangid, K., 2016. Quorum Sensing: An Under-Explored
 Phenomenon in the Phylum Actinobacteria. Front Microbiol 7, 131.
- 1094 Polla, D., Astafurov, K., Hawy, E., Hyman, L., Hou, W., Danias, J., 2017. A Pilot Study to Evaluate the
- 1095 Oral Microbiome and Dental Health in Primary Open-Angle Glaucoma. J Glaucoma 26, 320-327.
- Principi, N., Silvestri, E., Esposito, S., 2019. Advantages and Limitations of Bacteriophages for the
 Treatment of Bacterial Infections. Front Pharmacol 10, 513.
- 1098 Prokopiou, E., Kolovos, P., Georgiou, C., Kalogerou, M., Potamiti, L., Sokratous, K., Kyriacou, K.,
- Georgiou, T., 2019. Omega-3 fatty acids supplementation protects the retina from age-associated
 degeneration in aged C57BL/6J mice. BMJ Open Ophthalmol 4, e000326.
- 1101 Qin, J., Li, Y., Cai, Z., Li, S., Zhu, J., Zhang, F., Liang, S., Zhang, W., Guan, Y., Shen, D., Peng, Y., Zhang,
- 1102 D., Jie, Z., Wu, W., Qin, Y., Xue, W., Li, J., Han, L., Lu, D., Wu, P., Dai, Y., Sun, X., Li, Z., Tang, A., Zhong,
- 1103 S., Li, X., Chen, W., Xu, R., Wang, M., Feng, Q., Gong, M., Yu, J., Zhang, Y., Zhang, M., Hansen, T.,
- 1104 Sanchez, G., Raes, J., Falony, G., Okuda, S., Almeida, M., LeChatelier, E., Renault, P., Pons, N., Batto,
- 1105 J.M., Zhang, Z., Chen, H., Yang, R., Zheng, W., Li, S., Yang, H., Wang, J., Ehrlich, S.D., Nielsen, R.,
- Pedersen, O., Kristiansen, K., Wang, J., 2012. A metagenome-wide association study of gutmicrobiota in type 2 diabetes. Nature 490, 55-60.
- 1108 Qiu, Y., Shil, P.K., Zhu, P., Yang, H., Verma, A., Lei, B., Li, Q., 2014. Angiotensin-converting enzyme 2
- 1109 (ACE2) activator diminazene aceturate ameliorates endotoxin-induced uveitis in mice. Invest1110 Ophthalmol Vis Sci 55, 3809-3818.
- 1111 Redondo-Useros, N., Nova, E., Gonzalez-Zancada, N., Diaz, L.E., Gomez-Martinez, S., Marcos, A.,
- 1112 2020. Microbiota and Lifestyle: A Special Focus on Diet. Nutrients 12.
- 1113 Ren, Z., Li, A., Jiang, J., Zhou, L., Yu, Z., Lu, H., Xie, H., Chen, X., Shao, L., Zhang, R., Xu, S., Zhang, H.,
- 1114 Cui, G., Chen, X., Sun, R., Wen, H., Lerut, J.P., Kan, Q., Li, L., Zheng, S., 2019. Gut microbiome analysis
- as a tool towards targeted non-invasive biomarkers for early hepatocellular carcinoma. Gut 68, 1014-1023.
- Ridlon, J.M., Kang, D.J., Hylemon, P.B., Bajaj, J.S., 2014. Bile acids and the gut microbiome. Curr OpinGastroenterol 30, 332-338.
- 1119 Rinninella, E., Cintoni, M., Raoul, P., Ianiro, G., Laterza, L., Lopetuso, L.R., Ponziani, F.R., Gasbarrini,
- A., Mele, M.C., 2020. Gut Microbiota during Dietary Restrictions: New Insights in Non-CommunicableDiseases. Microorganisms 8.
- 1122 Rinninella, E., Cintoni, M., Raoul, P., Lopetuso, L.R., Scaldaferri, F., Pulcini, G., Miggiano, G.A.D.,
- 1123 Gasbarrini, A., Mele, M.C., 2019. Food Components and Dietary Habits: Keys for a Healthy Gut
- 1124 Microbiota Composition. Nutrients 11.
- 1125 Rinninella, E., Mele, M.C., Merendino, N., Cintoni, M., Anselmi, G., Caporossi, A., Gasbarrini, A.,
- 1126 Minnella, A.M., 2018. The Role of Diet, Micronutrients and the Gut Microbiota in Age-Related
- 1127 Macular Degeneration: New Perspectives from the Gut(-)Retina Axis. Nutrients 10.
- 1128 Rowan, S., Jiang, S., Korem, T., Szymanski, J., Chang, M.L., Szelog, J., Cassalman, C., Dasuri, K.,
- 1129 McGuire, C., Nagai, R., Du, X.L., Brownlee, M., Rabbani, N., Thornalley, P.J., Baleja, J.D., Deik, A.A.,
- 1130 Pierce, K.A., Scott, J.M., Clish, C.B., Smith, D.E., Weinberger, A., Avnit-Sagi, T., Lotan-Pompan, M.,
- 1131 Segal, E., Taylor, A., 2017. Involvement of a gut-retina axis in protection against dietary glycemia-
- 1132 induced age-related macular degeneration. Proc Natl Acad Sci U S A 114, E4472-E4481.

- 1133 Rozing, M.P., Durhuus, J.A., Krogh Nielsen, M., Subhi, Y., Kirkwood, T.B., Westendorp, R.G., Sorensen,
- T.L., 2020. Age-related macular degeneration: A two-level model hypothesis. Prog Retin Eye Res 76,100825.
- 1136 Saab, S., Buteau, B., Leclere, L., Bron, A.M., Creuzot-Garcher, C.P., Bretillon, L., Acar, N., 2014a.
- 1137 Involvement of plasmalogens in post-natal retinal vascular development. PLoS One 9, e101076.
- 1138 Saab, S., Mazzocco, J., Creuzot-Garcher, C.P., Bron, A.M., Bretillon, L., Acar, N., 2014b. Plasmalogens
- 1139 in the retina: from occurrence in retinal cell membranes to potential involvement in pathophysiology
- 1140 of retinal diseases. Biochimie 107 Pt A, 58-65.
- 1141 Sala-Vila, A., Diaz-Lopez, A., Valls-Pedret, C., Cofan, M., Garcia-Layana, A., Lamuela-Raventos, R.M.,
- 1142 Castaner, O., Zanon-Moreno, V., Martinez-Gonzalez, M.A., Toledo, E., Basora, J., Salas-Salvado, J.,
- 1143 Corella, D., Gomez-Gracia, E., Fiol, M., Estruch, R., Lapetra, J., Fito, M., Aros, F., Serra-Majem, L.,
- 1144 Pinto, X., Ros, E., Prevencion con Dieta Mediterranea, I., 2016. Dietary Marine omega-3 Fatty Acids
- and Incident Sight-Threatening Retinopathy in Middle-Aged and Older Individuals With Type 2
- 1146 Diabetes: Prospective Investigation From the PREDIMED Trial. JAMA Ophthalmol 134, 1142-1149.
- Salvador, R., Zhang, A., Horai, R., Caspi, R.R., 2020. Microbiota as Drivers and as Therapeutic Targets
 in Ocular and Tissue Specific Autoimmunity. Front Cell Dev Biol 8, 606751.
- SanGiovanni, J.P., Chew, E.Y., 2005. The role of omega-3 long-chain polyunsaturated fatty acids in
 health and disease of the retina. Prog Retin Eye Res 24, 87-138.
- Sasmita, A.O., 2019. Modification of the gut microbiome to combat neurodegeneration. Rev Neurosci 30, 795-805.
- 1153 Sausset, R., Petit, M.A., Gaboriau-Routhiau, V., De Paepe, M., 2020. New insights into intestinal
- 1154 phages. Mucosal Immunol 13, 205-215.
- Schroeder, B.O., Backhed, F., 2016. Signals from the gut microbiota to distant organs in physiologyand disease. Nat Med 22, 1079-1089.
- 1157 Shan, Z., Sun, T., Huang, H., Chen, S., Chen, L., Luo, C., Yang, W., Yang, X., Yao, P., Cheng, J., Hu, F.B.,
- Liu, L., 2017. Association between microbiota-dependent metabolite trimethylamine-N-oxide and
- 1159 type 2 diabetes. Am J Clin Nutr 106, 888-894.
- Shanahan, F., Sheehan, D., 2016. Microbial contributions to chronic inflammation and metabolicdisease. Curr Opin Clin Nutr Metab Care 19, 257-262.
- 1162 Shil, P.K., Kwon, K.C., Zhu, P., Verma, A., Daniell, H., Li, Q., 2014. Oral delivery of ACE2/Ang-(1-7)
- bioencapsulated in plant cells protects against experimental uveitis and autoimmune uveoretinitis.Mol Ther 22, 2069-2082.
- 1165 Singh, R.K., Chang, H.W., Yan, D., Lee, K.M., Ucmak, D., Wong, K., Abrouk, M., Farahnik, B.,
- Nakamura, M., Zhu, T.H., Bhutani, T., Liao, W., 2017. Influence of diet on the gut microbiome and
 implications for human health. J Transl Med 15, 73.
- Singh, V., Yeoh, B.S., Chassaing, B., Xiao, X., Saha, P., Aguilera Olvera, R., Lapek, J.D., Jr., Zhang, L.,
- 1169 Wang, W.B., Hao, S., Flythe, M.D., Gonzalez, D.J., Cani, P.D., Conejo-Garcia, J.R., Xiong, N., Kennett,
- 1170 M.J., Joe, B., Patterson, A.D., Gewirtz, A.T., Vijay-Kumar, M., 2018. Dysregulated Microbial
- 1171 Fermentation of Soluble Fiber Induces Cholestatic Liver Cancer. Cell 175, 679-694 e622.
- 1172 Skrzypecki, J., Izdebska, J., Kaminska, A., Badowska, J., Przybek-Skrzypecka, J., Bombuy, J.,
- 1173 Samborowska, E., Szaflik, J.P., 2021. Glaucoma patients have an increased level of trimethylamine, a
- toxic product of gut bacteria, in the aqueous humor: a pilot study. Int Ophthalmol 41, 341-347.
- 1175 Skrzypecki, J., Zera, T., Ufnal, M., 2018. Butyrate, a Gut Bacterial Metabolite, Lowers Intraocular
- 1176 Pressure in Normotensive But Not in Hypertensive Rats. J Glaucoma 27, 823-827.
- 1177 Sonnenburg, J.L., Backhed, F., 2016. Diet-microbiota interactions as moderators of human
- 1178 metabolism. Nature 535, 56-64.
- 1179 Stables, M.J., Gilroy, D.W., 2011. Old and new generation lipid mediators in acute inflammation and
- 1180 resolution. Prog Lipid Res 50, 35-51.
- 1181 Suzumura, A., Kaneko, H., Funahashi, Y., Takayama, K., Nagaya, M., Ito, S., Okuno, T., Hirakata, T.,
- 1182 Nonobe, N., Kataoka, K., Shimizu, H., Namba, R., Yamada, K., Ye, F., Ozawa, Y., Yokomizo, T., Terasaki,
- 1183 H., 2020. n-3 Fatty Acid and Its Metabolite 18-HEPE Ameliorate Retinal Neuronal Cell Dysfunction by
- 1184 Enhancing Muller BDNF in Diabetic Retinopathy. Diabetes 69, 724-735.

- 1185 Swanson, K.S., Gibson, G.R., Hutkins, R., Reimer, R.A., Reid, G., Verbeke, K., Scott, K.P., Holscher, H.D.,
- 1186 Azad, M.B., Delzenne, N.M., Sanders, M.E., 2020. The International Scientific Association for
- Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. NatRev Gastroenterol Hepatol 17, 687-701.
- 1189 Tan, F.H.P., Liu, G., Lau, S.A., Jaafar, M.H., Park, Y.H., Azzam, G., Li, Y., Liong, M.T., 2020a.
- 1190 Lactobacillus probiotics improved the gut microbiota profile of a Drosophila melanogaster
- 1191 Alzheimer's disease model and alleviated neurodegeneration in the eye. Benef Microbes 11, 79-89.
- 1192 Tan, W., Zou, J., Yoshida, S., Jiang, B., Zhou, Y., 2020b. The Role of Inflammation in Age-Related
- 1193 Macular Degeneration. Int J Biol Sci 16, 2989-3001.
- 1194 Thierry, M., Pasquis, B., Acar, N., Gregoire, S., Febvret, V., Buteau, B., Gambert-Nicot, S., Bron, A.M.,
- 1195 Creuzot-Garcher, C.P., Bretillon, L., 2014. Metabolic syndrome triggered by high-fructose diet favors
- 1196 choroidal neovascularization and impairs retinal light sensitivity in the rat. PLoS One 9, e112450.
- 1197 Thierry, M., Pasquis, B., Buteau, B., Fourgeux, C., Dembele, D., Leclere, L., Gambert-Nicot, S., Acar, N.,
- Bron, A.M., Creuzot-Garcher, C.P., Bretillon, L., 2015. Early adaptive response of the retina to a pro-
- diabetogenic diet: Impairment of cone response and gene expression changes in high-fructose fedrats. Exp Eye Res 135, 37-46.
- 1201 Tilg, H., Zmora, N., Adolph, T.E., Elinav, E., 2020. The intestinal microbiota fuelling metabolic
- 1202 inflammation. Nat Rev Immunol 20, 40-54.
- 1203 Tofalo, R., Cocchi, S., Suzzi, G., 2019. Polyamines and Gut Microbiota. Front Nutr 6, 16.
- 1204 Turnbaugh, P.J., Ley, R.E., Mahowald, M.A., Magrini, V., Mardis, E.R., Gordon, J.I., 2006. An obesity-
- associated gut microbiome with increased capacity for energy harvest. Nature 444, 1027-1031.
- 1206 Uchiki, T., Weikel, K.A., Jiao, W., Shang, F., Caceres, A., Pawlak, D., Handa, J.T., Brownlee, M., Nagaraj,
- 1207 R., Taylor, A., 2012. Glycation-altered proteolysis as a pathobiologic mechanism that links dietary
- 1208 glycemic index, aging, and age-related disease (in nondiabetics). Aging Cell 11, 1-13.
- 1209 van Leeuwen, E.M., Emri, E., Merle, B.M.J., Colijn, J.M., Kersten, E., Cougnard-Gregoire, A.,
- 1210 Dammeier, S., Meester-Smoor, M., Pool, F.M., de Jong, E.K., Delcourt, C., Rodrigez-Bocanegra, E.,
- 1211 Biarnes, M., Luthert, P.J., Ueffing, M., Klaver, C.C.W., Nogoceke, E., den Hollander, A.I., Lengyel, I.,
- 2018. A new perspective on lipid research in age-related macular degeneration. Prog Retin Eye Res67, 56-86.
- 1214 Velagapudi, V.R., Hezaveh, R., Reigstad, C.S., Gopalacharyulu, P., Yetukuri, L., Islam, S., Felin, J.,
- Perkins, R., Boren, J., Oresic, M., Backhed, F., 2010. The gut microbiota modulates host energy and
 lipid metabolism in mice. J Lipid Res 51, 1101-1112.
- 1217 Verma, A., Shan, Z., Lei, B., Yuan, L., Liu, X., Nakagawa, T., Grant, M.B., Lewin, A.S., Hauswirth, W.W.,
- 1218 Raizada, M.K., Li, Q., 2012. ACE2 and Ang-(1-7) confer protection against development of diabetic 1219 retinopathy. Mol Ther 20, 28-36.
- 1220 Verma, A., Xu, K., Du, T., Zhu, P., Liang, Z., Liao, S., Zhang, J., Raizada, M.K., Grant, M.B., Li, Q., 2020a.
- 1221 Erratum: Expression of Human ACE2 in Lactobacillus and Beneficial Effects in Diabetic Retinopathy in
- 1222 Mice. Mol Ther Methods Clin Dev 17, 400.
- 1223 Verma, A., Zhu, P., Xu, K., Du, T., Liao, S., Liang, Z., Raizada, M.K., Li, Q., 2020b. Angiotensin-(1-7)
- 1224 Expressed From Lactobacillus Bacteria Protect Diabetic Retina in Mice. Transl Vis Sci Technol 9, 20.
- 1225 Villette, R., Kc, P., Beliard, S., Salas Tapia, M.F., Rainteau, D., Guerin, M., Lesnik, P., 2020. Unraveling
- Host-Gut Microbiota Dialogue and Its Impact on Cholesterol Levels. Front Pharmacol 11, 278.
- 1227 Vrieze, A., Van Nood, E., Holleman, F., Salojarvi, J., Kootte, R.S., Bartelsman, J.F., Dallinga-Thie, G.M.,
- 1228 Ackermans, M.T., Serlie, M.J., Oozeer, R., Derrien, M., Druesne, A., Van Hylckama Vlieg, J.E., Bloks,
- 1229 V.W., Groen, A.K., Heilig, H.G., Zoetendal, E.G., Stroes, E.S., de Vos, W.M., Hoekstra, J.B., Nieuwdorp,
- M., 2012. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals
 with metabolic syndrome. Gastroenterology 143, 913-916 e917.
- 1232 Walker, A.W., Ince, J., Duncan, S.H., Webster, L.M., Holtrop, G., Ze, X., Brown, D., Stares, M.D., Scott,
- 1233 P., Bergerat, A., Louis, P., McIntosh, F., Johnstone, A.M., Lobley, G.E., Parkhill, J., Flint, H.J., 2011.
- 1234 Dominant and diet-responsive groups of bacteria within the human colonic microbiota. ISME J 5, 220-
- 1235 230.

- Wang, H., Deng, Y., Wan, L., Huang, L., 2020. A comprehensive map of disease networks andmolecular drug discoveries for glaucoma. Sci Rep 10, 9719.
- 1238 Wang, H., Lu, Y., Yan, Y., Tian, S., Zheng, D., Leng, D., Wang, C., Jiao, J., Wang, Z., Bai, Y., 2019.
- 1239 Promising Treatment for Type 2 Diabetes: Fecal Microbiota Transplantation Reverses Insulin
- 1240 Resistance and Impaired Islets. Front Cell Infect Microbiol 9, 455.
- 1241 Watson, H., Mitra, S., Croden, F.C., Taylor, M., Wood, H.M., Perry, S.L., Spencer, J.A., Quirke, P.,
- 1242 Toogood, G.J., Lawton, C.L., Dye, L., Loadman, P.M., Hull, M.A., 2018. A randomised trial of the effect
- 1243 of omega-3 polyunsaturated fatty acid supplements on the human intestinal microbiota. Gut 67, 1244 1974-1983.
- 1245 Weikel, K.A., Fitzgerald, P., Shang, F., Caceres, M.A., Bian, Q., Handa, J.T., Stitt, A.W., Taylor, A., 2012.
- Natural history of age-related retinal lesions that precede AMD in mice fed high or low glycemic
 index diets. Invest Ophthalmol Vis Sci 53, 622-632.
- 1248 Westfall, S., Lomis, N., Kahouli, I., Dia, S.Y., Singh, S.P., Prakash, S., 2017. Microbiome, probiotics and 1249 neurodegenerative diseases: deciphering the gut brain axis. Cell Mol Life Sci 74, 3769-3787.
- Wong, T.Y., Cheung, C.M., Larsen, M., Sharma, S., Simo, R., 2016. Diabetic retinopathy. Nat Rev Dis
 Primers 2, 16012.
- 1252 Woo, S.J., Kim, J.H., Yu, H.G., 2010. Ursodeoxycholic acid and tauroursodeoxycholic acid suppress
- 1253 choroidal neovascularization in a laser-treated rat model. J Ocul Pharmacol Ther 26, 223-229.
- 1254 Yamazaki, T., Suzuki, H., Yamada, S., Ohshio, K., Sugamata, M., Yamada, T., Morita, Y., 2020.
- 1255 Lactobacillus paracasei KW3110 Suppresses Inflammatory Stress-Induced Premature Cellular
- Senescence of Human Retinal Pigment Epithelium Cells and Reduces Ocular Disorders in HealthyHumans. Int J Mol Sci 21.
- Yang, G., Wei, J., Liu, P., Zhang, Q., Tian, Y., Hou, G., Meng, L., Xin, Y., Jiang, X., 2021. Role of the gut
 microbiota in type 2 diabetes and related diseases. Metabolism 117, 154712.
- Yee, P., Weymouth, A.E., Fletcher, E.L., Vingrys, A.J., 2010. A role for omega-3 polyunsaturated fatty acid supplements in diabetic neuropathy. Invest Ophthalmol Vis Sci 51, 1755-1764.
- Yelin, I., Flett, K.B., Merakou, C., Mehrotra, P., Stam, J., Snesrud, E., Hinkle, M., Lesho, E., McGann, P., McAdam, A.J., Sandora, T.J., Kishony, R., Priebe, G.P., 2019. Genomic and epidemiological evidence of
- bacterial transmission from probiotic capsule to blood in ICU patients. Nat Med 25, 1728-1732.
- 1265 Yu, F., Han, W., Zhan, G., Li, S., Jiang, X., Wang, L., Xiang, S., Zhu, B., Yang, L., Luo, A., Hua, F., Yang, C.,
- 2019. Abnormal gut microbiota composition contributes to the development of type 2 diabetesmellitus in db/db mice. Aging (Albany NY) 11, 10454-10467.
- 1268 Yun, S.W., Son, Y.H., Lee, D.Y., Shin, Y.J., Han, M.J., Kim, D.H., 2021. Lactobacillus plantarum and
- 1269 Bifidobacterium bifidum alleviate dry eye in mice with exorbital lacrimal gland excision by 1270 modulating gut inflammation and microbiota. Food Funct 12, 2489-2497.
- 1271 Zafar, S., Sachdeva, M., Frankfort, B.J., Channa, R., 2019. Retinal Neurodegeneration as an Early
- 1272 Manifestation of Diabetic Eye Disease and Potential Neuroprotective Therapies. Curr Diab Rep 19, 17.
- 1273 Zhang, C., Jiao, S., Wang, Z.A., Du, Y., 2018. Exploring Effects of Chitosan Oligosaccharides on Mice
- 1274 Gut Microbiota in in vitro Fermentation and Animal Model. Front Microbiol 9, 2388.
- 1275 Zhang, Q.Y., Tie, L.J., Wu, S.S., Lv, P.L., Huang, H.W., Wang, W.Q., Wang, H., Ma, L., 2016. Overweight,
- 1276 Obesity, and Risk of Age-Related Macular Degeneration. Invest Ophthalmol Vis Sci 57, 1276-1283.
- 1277 Zinkernagel, M.S., Zysset-Burri, D.C., Keller, I., Berger, L.E., Leichtle, A.B., Largiader, C.R., Fiedler,
- G.M., Wolf, S., 2017. Association of the Intestinal Microbiome with the Development of NeovascularAge-Related Macular Degeneration. Sci Rep 7, 40826.
- Zolkiewicz, J., Marzec, A., Ruszczynski, M., Feleszko, W., 2020. Postbiotics-A Step Beyond Pre- and
 Probiotics. Nutrients 12.
- 1282 Zysset-Burri, D.C., Keller, I., Berger, L.E., Largiader, C.R., Wittwer, M., Wolf, S., Zinkernagel, M.S.,
- 1283 2020. Associations of the intestinal microbiome with the complement system in neovascular age-
- 1284 related macular degeneration. NPJ Genom Med 5, 34.
- 1285

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

(control group)		
<i>n</i> =9 T2DM ⁵ without DR; <i>n</i> =8 T2DM with DR; (n=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
<i>n</i> =25 T2DM without DR; <i>n</i> =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
<i>n</i> =25 DM ⁶ without DR; <i>n</i> =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
	n=9 T2DM ⁵ without DR; $n=8$ T2DM with DR; $(n=18)$ n=25 T2DM without DR; $n=28$ T2DM with DR; $(n=30)$ n=25 DM ⁶ without DR; $n=25$ DM with DR; $(n=25)$	n=9 T2DM* 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 primersn=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 platformn=25 DM* without DR; n=25 DM without DR; n=25 DM without DR; n=25 DM without DR; n=25 DM without DR; (n=25)Amplification of the V3-V4 region of 16S rRNA gene and sequencing on Illumina MiSeq platform

			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:
India ⁴	<i>n</i> =21 T2DM without	Amplification of the V4 region of	No statistically significant
	DR; <i>n</i> =37 T2DM	16S rRNA gene and sequencing on	difference in the relative abundance
	with DR	Illumina MiSeq platform	among the 17 identified phyla

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

Microbiota alterations Country Effective *n* Method (control group) n=30 POAG³ (n=30) China¹ Amplification of the V4 At the family level⁴: region of 16S rRNA gene **↑** *Prevotellaceae* and sequencing on Illumina At the genera level²: MiSeq platform ↑ unidentified_*Enterobacteriaceae* **↓** Megamonas At the species level²: ↑ Escherichia coli **↓** *Bacteroides plebeius* Europe² <u>At the family level⁷:</u> n=10 patients with Amplification of the V4 NTG⁵; n=11 patients region of 16S rRNA gene $\mathbf{\Psi}$ (trend) *Rikenellaceae*

and sequencing on Illumina

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

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

MiSeq platform

with OHT^6 (*n*=11)

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

Country	Effective <i>n</i>	Method	Microbiota alterations ⁴
	(control group)		
	u-12 maayaaaylan	Chotaun mataganamia	At the family level
Switzerland	n=12 neovasculai		
	AMD $(n=11)$		At the series level
		Hiseq platform	At the genera level:
			Anderotruncus, Oscillibacter
			At the species level:
			$\mathbf{\uparrow}$ Ruminococcus torques, Eubacterium
			ventriosum
S. it	n=57 neovascular	Shotgun metagenomic	At the class level:
Switzerland ²	AMD (<i>n</i> =58)	sequencing on Illumina	↑ Negativicutes
		HiSeq platform	At the genera level:
		11	\checkmark Oscillibacter
			At the species level:
			Ψ Bacteroides spp.
			Gut microbial biomarkers: identification of 7
			bacterial taxa as potential biomarkers to
			discriminate between AMD patients and
			controls (the class <i>Negativicutes</i> , the order
			Selenomonadales and the species
			Phascolarctobacterium, Bacteroides
			cellulosilyticus, Sutterella wadsworthensis,
			Bifidobacterium longum, and Bacteroides
			caccae).
	n=85 advanced AMD	-	At the genera level:
USA	n=49		↑ Prevotella, Holdemanella, Desulfovibrio,
			and other bacteria
			Ψ Oscillospira, Blautia and Dorea

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





1303 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.