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The role of the gut microbiome in eye diseases

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ABSTRACT

The gut microbiome is a complex ecosystem of microorganisms and their genetic entities colonizing the gastrointestinal tract. When in balanced composition, the gut microbiome is in symbiotic interaction with its host and maintains intestinal homeostasis. It is involved in essential functions such as nutrient metabolism, inhibition of pathogens and regulation of immune function. Through translocation of microbes and their metabolites along the epithelial barrier, microbial dysbiosis induces systemic inflammation that may lead to tissue destruction and promote the onset of various diseases. Using whole-metagenome shotgun sequencing, several studies have shown that the composition and associated functional capacities of the gut microbiome are associated with age-related macular degeneration, retinal artery occlusion, central serous chorioretinopathy and uveitis. In this review, we provide an overview of the current knowledge about the gut microbiome in eye diseases, with a focus on interactions between the microbiome, specific microbial-derived metabolites and the immune system. We explain how these interactions may be involved in the pathogenesis of age-related macular degeneration, retinal artery occlusion, central serous chorioretinopathy and uveitis and guide the development of new therapeutic approaches by microbiome-altering interventions for these diseases.

1. The human gut microbiome interaction with the immune system in age and disease

1.1. The importance to characterize the human gut microbiome

The human gut microbiome (GM) is a complex ecosystem of microorganisms including bacteria, viruses, archaea and eukaryotes and their genetic entities colonizing the gastrointestinal tract. It is involved in numerous host functions such as nutrient metabolism, stimulation and regulation of the immune system, protections against pathogens and maintenance of the intestinal barrier (Heintz-Buschart and Wilmes, 2018). Thus, a precise characterization of the GM is of crucial significance for hosts health and disease.

1.1.1. Taxonomic features of the gut microbiome

Although initial knowledge about the human GM was derived from labor-intensive culture-based methods, the introduction of culture-independent sequencing approaches allowed the exploration of the GM to a broader range. Today we know that the human GM consists of trillions of microorganisms distributed over more than 50 different phyla with *Bacteroidetes, Firmicutes, Proteobacteria* and *Actinobacteria* being the most abundant phyla. The phylum *Bacteroidetes* includes approximately 7000 different species of Gram-negative bacteria associated with lipopolysaccharide (LPS)- and flagellin-mediated immune reactions of the host. *Firmicutes* bacteria are Gram-positive bacteria that play a key role in host's metabolism through short-chain fatty acid synthesis (Stojanov et al., 2020). Even though the core microbial profile is relatively stable in healthy individuals, there are both temporal and spatial differences in distribution at genus level from the esophagus to the rectum and from the lumen to the mucosal surface of the intestine. While *Streptococcus* is the dominant genus in the distal esophagus, duodenum and jejunum, *Helicobacter* is dominant in the stomach. Over 70% of all microbes found in the human body are present in the large intestine with *Bacteroides, Bifidobacterium, Streptococcus, Enterobacteriacae, Enterococcus, Clostridium Lactobacillus* and *Ruminococcus* predominately present in the lumen and predominantly identified in stool samples (Toscano et al., 2017).

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Abbreviations

Gut microbiome (GM)
Short-chain fatty acids (SCFAs)
Ribosomal RNA (rRNA)
Age-related macular degeneration (AMD)
Retinal pigment epithelium (RPE)
Long-chain polyunsaturated fatty acids (LCPUFAs)
Reactive oxygen species (ROS)
Single nucleotide polymorphisms (SNPs)
Complement component 3 (C3)
Complement factor H (CFH)
NOD-like receptor (NOD)
Trimethylamine N-oxide (TMAO)
Trimethylamine (TMA)
Retinal artery occlusion (RAO)
Central retinal artery occlusion (CRAO)
Branch retinal artery occlusion (BRAO)
Central retinal artery (CRA)
Cardiovascular disease (CVD)
Central serous chorioretinopathy (CSCR)
Standardization of Uveitis Nomenclature (SUN)
Experimental autoimmune uveitis (EAU)
Lipopolysaccharide (LPS)

The knowledge about this bacterial composition of the GM is mainly based on a sequencing technique targeting variable regions of the bacterial 16S ribosomal RNA (rRNA) gene (Thursby and Juge, 2017). Compared to this 16s rRNA sequencing approach, whole-metagenome shotgun sequencing enables the identification of viruses, archaea and eukaryotes in addition to bacteria.

To get an overview of GM species variation independent of the cohort (demographic factors such as BMI, age, diet, drug intake and origin) and protocols (sampling, DNA isolation, sequencing and analysis), samples may be classified into groups, named enterotypes. Using multidimensional cluster analysis combined with principal component analysis of gut microbial communities, Arumugam et al. have defined three human gut enterotypes driven by the genera *Bacteroides, Prevotella* and *Ruminococcus* (Arumugam et al., 2011).

1.1.2. Functional features of the gut microbiome

Gut microbes experience selective pressure from the host as well as from microbial competitors, typically leading to homeostasis. In this symbiotic ecosystem some species are high and many are low in abundance. However, high-abundant species do not necessarily perform essential host functions and may be equally involved in the development of specific diseases as low-abundant species. Therefore, to explore the role of the GM in hosts health and disease, the identification of functional features in terms of microbial genes and pathways is as important as taxonomic profiling of the microbial metagenome.

In healthy individuals, the mature gut microbial core functions include genes encoding glycosaminoglycan degradation. Indigestible but fermentable polysaccharides are metabolized by the microbiota of the large intestine, resulting in the synthesis of short-chani fatty acids (SCFAs) such as butyrate, propionate and acetate. These SCFAs provide several essential functions such as protection against pathogen infiltration, reduction of local inflammation and maintenance of the intestinal barrier function (section 1.3).

Functional profiling is typically done by a two-step process involving first, the quantification of genes, proteins and protein families in the microbial community and second, individual gene families are merged into metabolic pathways (Turnbaugh et al., 2007). These functional features provide a set of potential targets for GM-altering therapeutic approaches.

1.2. Age-associated features of the human gut microbiome

The early life microbiome is highly unstable depending on the mode of delivery (cesarean versus natural birth) and nutrition (breast milk versus formula, transition to solid food) as well as family lifestyle, geographic location, host genetics and use of antibiotics (Zhuang et al., 2019a). Approximately up to 3–4 years of age it undergoes dynamic changes, finally converging towards a more stabilized adult microbiome (Kumbhare et al., 2019). With increasing age, senescence leads to changes in the microbiome composition and various degenerative diseases have been associated with the senescent microbiome. Mariat et al. have shown an altered *Bacteroidetes* to *Firmicutes* ratio in later life stages with an increased proportion of *Bacteroidetes* in the elderly (Mariat et al., 2009). This ratio has been shown to have an effect on several diseases also affecting eye diseases, such as age-related macular degeneration (AMD) (Zinkernagel et al., 2017). Therefore, to maintain a good quality of life, including the prevention of age-associated diseases, it seems quite important to understand the dynamics of the GM in the elderly. We showed that the two age groups above or equal to 65 years ($n = 145$) versus below 65 years of age ($n = 133$) could be separated based on taxonomic as well as associated functional features of the GM and were unevenly distributed among the three defined enterotypes (Fig. 1A). In the group of participants aged above or equal to 65 years, the class *Gammaproteobacteria* and its family *Enterobacteriaceae* were classified as potential biomarker for the corresponding age group (Fig. 1B) (Herzog et al., 2021). These alterations may have a significant effect on health since an increased prevalence of *Proteobacteria* was proposed as a diagnostic marker for an unstable GM and a higher risk of disease (Rizzatti et al., 2017). These findings may have implications for preventive strategies for age-associated degenerative processes and diseases, such as AMD and retinal artery occlusion (RAO) by applying microbiome-altering interventions such as antibiotics and probiotics. This review aims to underline the importance of the human GM in ocular health and disease thereby providing new treatment opportunities for eye diseases by targeting the microbiome.

1.3. Mutual regulation between the gut microbiome and the immune system

Dynamic interactions between the gut microbiome and the host's immune system are essential in maintaining intestinal homeostasis and inhibiting inflammation. The gut epithelium provides a physiological and biochemical barrier separating the host from exterior antigens including food antigens, commensals, pathogens, and toxins. On top of this epithelial lining is a mucin layer consisting of highly glycosylated gel-forming mucin and containing diverse molecules including immunoglobulin A as well as antimicrobial factors such as lactoferrin (Singh et al., 2002). In addition, there is an immunological barrier to microbes consisting of the organized lymphoid follicles called the Peyer's patches and isolated lymphoid follicles. These follicles contain a variety of cells including B cells, T cells, dendritic cells and neutrophils. Acquired luminal antigens are presented to CD103+ dendritic cells via goblet cells mainly in the small intestine by forming goblet cell-associated antigen passages (Howe et al., 2014).

Gut microbiota produces numerous metabolites (gut microbiota-derived metabolites), such as SCFAs or LPS that mediate cross-talk between the gut epithelium and immune cells, thereby playing a key role in inflammatory signaling. SCFAs bind directly to the epithelium and to G-protein coupled receptors such as GPR43 (known as free fatty acid receptor) and have several essential functions dependent on tissue and cell

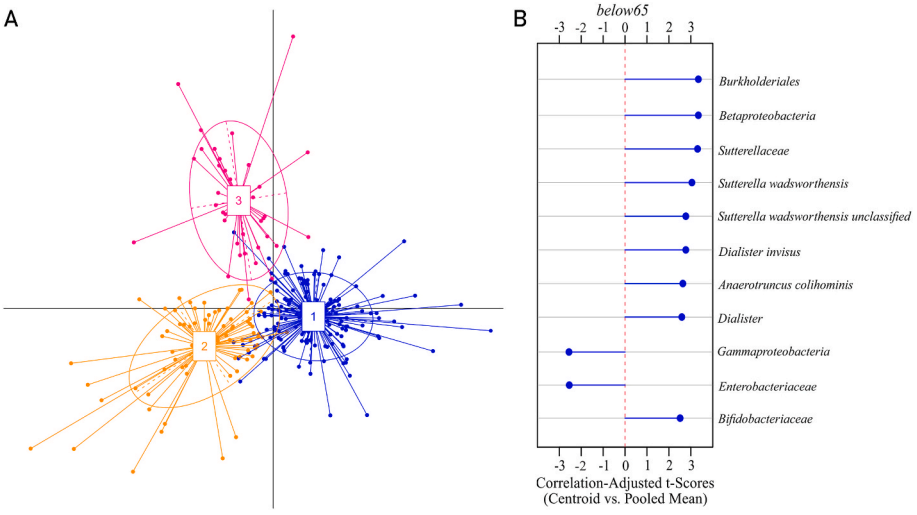

Fig. 1. Age-associated features of the gut microbiome. A threshold of 65 years was set to divide the cohort into the two sex-matched age groups 65 years and above (*above65;* n = 145) and below 65 years (*below65;* n = 133).
(A) Intestinal microbial enterotypes based on the abundance of microbial genera and driven by the genera *Bacteroides* (cluster 1), *Prevotella* (cluster 2) and *Subdoligranulum* (cluster 3). Subjects of the group *above65* were over-represented in cluster 2 (p = 0.0012) and under-represented in cluster 3 (p = 0.0036; Fisher's exact test), supposing an age-dependency of the proposed enterotypes. This figure was originally published in (Herzog et al., 2021). (B) Top ranked 11 bacteria as potential biomarkers for age. The length and direction of the blue bars indicate the involvement of a given biomarker on the discriminative power of the classification model; i.e. the order *Burkholderiales* within the class *Betaproteobacteria* have the highest potential for separation of the two age groups with a positive correlation-adjusted T-score indicating an over-representation in the *below65* group, while the family *Enterobacteriaceae* within the class *Gammaproteobacteria* have a negative score indicating an over-representation in the *above65* group. This figure was originally published in (Herzog et al., 2021).

type. In addition to the regulation of intestinal barrier function and protection against pathogen infiltration, SCFAs exhibit anti-inflammatory properties on immune cells by reducing the levels of pro-inflammatory mediators and promoting the production of anti-inflammatory cytokines (Yoo et al., 2020). Since LPS binds toll-like receptor 4, inflammatory cascades may be activated leading to local inflammation and access of immune cells to distant sites such as the retina (Hajjar et al., 2002). On the other hand, immune cells express metabolite-specific receptors (membrane-bound pattern recognition receptors such as toll-like receptors) recognizing these microbial molecules. This interaction is important for the immune system's ability to maintain the host's homeostasis by tolerating the microbial load (immune tolerance), while remaining reactive to microbial invasion. This relationship between the microbiome and the immune system is dependent on the ability to discriminate between non-pathogenic (mutual or commensal) and pathogenic symbionts. Symbionts are in either mutualistic, commensal or pathogenic relationship with their hosts. Commensals are symbionts that obtain food or other benefits from the host without either harming or benefiting the latter, while mutualistic symbionts live in beneficial association. Pathogenic symbionts are in harmful association with the host and cause disease (Tipton et al., 2019). Mutualistic microbes of the GM protect the host from pathogens through different strategies, including the competition for nutrients, affecting environmental conditions, modulation of immune cell maturation (immune-mediated resistance) and the generation of metabolites with growth-limiting or bactericidal effects (Mezouar et al., 2018). However, after translocation through the mucosa (see below) or under specific conditions (such as immunodeficiency) commensals can become pathogenic (commensal-to-pathogen transition) (Tlaskalova-Hogenova et al., 2011). If the balanced GM composition changes, leading to a reduction in the number of mutualistic symbionts and/or to an increase in the number of pathogens and their associated metabolites, this so-called dysbiosis may contribute to the development of several immune-mediated diseases (Lin, 2020).

1.4. The impact of dysbiosis on eye diseases

Dynamic interactions between the GM and the host's immune system are important to maintain intestinal homeostasis and inhibit inflammatory processes. Gut dysbiosis can dysregulate immune responses by inducing mucosal barrier dysfunction leading to the translocation of (pathogenic) microbes through the epithelial barrier, resulting in systemic inflammation primarily through the production of pro-inflammatory cytokines and alterations to B- and T-cell populations. This inflammation may proceed to tissue destruction favoring the onset of many diseases (including eye diseases). As a consequence of bacterial translocation, bacteria and their metabolites are transported via blood stream or mesenteric lymphatics to immune privileged extraintestinal organs and sites such as the eye.

The retina is considered an immune privileged tissue that is protected from internal and environmental insults through both the blood-retina barrier and the blood-aqueous barrier as well as through tolerogenic immune response. The blood-retina barrier is the posterior barrier of the eye composed of an inner and an outer barrier. The outer barrier is formed at the retinal pigment epithelial cell layer with tight junctions regulating the transfer of nutrients from the choroid to the sub-retinal space. The inner barrier (similar to the blood-brain barrier) is located in the inner retinal microvasculature comprising the microvascular endothelium with tight junctions mediating selective diffusion of molecules from the blood to the retina. The blood-aqueous barrier is the anterior barrier of the eye composed of endothelial cells of blood vessels in the iris and tight junctions between adjacent epithelial cells of the inner nonpigmented ciliary epithelium, regulating the diffusion of large molecules from the blood to the aqueous humor (Campbell and Humphries; Cunha-Vaz, 1979). Variations in these blood retina barriers may lead to the development of retinal disease such as uveitis through the recruitment of inflammatory cells and subsequent intraocular inflammation (section 5.1). To maintain retinal homeostasis, the retina is also protected by its own innate immune system composed of the microglia and the complement system. In case of an insult, microglia cells migrate to sites of damage, release pro-inflammatory cytokines and reactive oxygen species (ROS) to neutralize the damage and phagocyte cellular debris to prevent accumulation of waste products. The complement system consists of over 30 proteins and can be activated by three pathways. These pathways are dependent on different molecules for their initiation, but converge to generate the same set of effector molecules for opsonization and killing of pathogens as well as recruitment of inflammatory cells. The classical pathway is triggered by antigen antibody complexes, the mannose-binding lectin pathway by the serum constituent mannan-binding lectin and the alternative pathway is triggered directly on pathogen surfaces. Its role in the pathogenesis of AMD has been studied and reviewed extensively (sections 2.2. and

2.3.4.) (Akhtar-Schafer et al., 2018; de Jong et al., 2021). Normally, immune privilege functions as a homeostatic mechanism preserving specific tissue functions and preventing harmful immune response by modulating both the induction and the expression of intraocular inflammation but with limited capacity for renewal and repair processes (Forrester and Xu, 2012). Thus, compared to immunocompetent tissue, privileged tissues such as the eye are more prone to develop inflammatory diseases caused by GM alterations. A possible mechanisms is bacterial translocation from the gut to the eye. However, although many studies have shown that the GM contributes to the pathogenesis of specific diseases, it is not known if mucosal inflammation is a cause for or a consequence of dysbiosis. However, to maintain gut barrier function and homeostasis, microbiome-modulating strategies may be beneficial to prevent systemic inflammation.

In this review, we will provide a comprehensive review on the role of the gut microbiome on retinal diseases including AMD, RAO, central serous chorioretinopathy (CSR) and inflammatory eye diseases such as uveitis. We will discuss bacterial translocation of gut microbes and their metabolites as common pathogenesis mechanisms and highlight the role of the immune system in the development of these diseases.

2. The gut microbiome and age-related macular degeneration

2.1. Definition, risk factors and pathogenesis of age-related macular degeneration

Age-related macular degeneration is one of the most common ophthalmic pathologies in the elderly in industrialized nations. It affects the macula, thereby leading to irreversible central vision loss and eventually to legal blindness.

The key features for AMD severity classification are drusen and retinal pigment epithelium (RPE) abnormalities (Ferris et al., 2005) which in late stages can develop into to geographic atrophy (dry AMD) or choroidal neovascularization (wet AMD). Drusen are subretinal deposits containing lipids, RPE cell fragments, lipofuscin (non-degradable product of oxidation of unsaturated fatty acids and proteins accumulating with age) immune cells as well as proteins (e.g. proteins of the complement system) that are involved in inflammatory and immune responses (Hageman et al., 2001). RPE abnormalities are changes in pigmentation, reduction in cell density and accumulation of lipofuscin granules. Geographic atrophy is characterized by irreversible degradation of the RPE and photoreceptor cells, gradually involving the macula. Choroidal neovascularization is characterized by abnormal growth of blood vessels contains infiltrating immune cells, myofibroblasts and an excessive amount of extracellular matrix proteins. It also shows serous sensory retinal detachment or sub-retinal fibrosis leading to irreversible blindness (Ferris et al., 2005; Fleckenstein et al., 2021; Tenbrock et al., 2022). In 10–20% of patients, dry AMD develops into wet AMD, and the triggering factors for its conversion are still unknown (Ma and Liutkevičienė, 2021).

AMD is a multifactorial disease with age as well as environmental, epigenetic and genetic risk factors contributing to its pathogenesis (Fig. 1B). A lifestyle increasing both, oxidative and metabolic stress, thus accelerating the physiological age, seems to be the major risk factor. Smoking, high BMI, alcohol consumption and/or hypertension may be linked to this lifestyle (Seddon et al., 2006; Yu et al., 2012; Zhang et al., 2016). Furthermore, diet has a profound impact on the onset and progression of AMD (see point 2.3.1). Although the exact mechanisms are still poorly understood, research indicates that AMD is likely to be the result of age-associated features such as alterations of the immune system (immunosenescence) and sterile low-grade chronic inflammation (inflammaging) in the retina. Immunosenescence is the age-associated decrease of immunological competence, resulting in progressive deterioration of innate and adaptive immune responses. Inflammaging is the long-term result of chronic low-level over-stimulation of the innate immune system that is sustained by an over-activation of the complement system and inflammasomes (cytosolic multimeric protein complexes of the innate immune system resulting in downstream inflammatory cascades upon activation (Guo et al., 2015)) and the recruitment of immune cells as well as a variety of inflammatory products including pro-inflammatory cytokines (Franceschi et al., 2018; Peters et al., 2009; Romano et al., 2010; Salvioli et al., 2006). Chronic low-grade inflammation leads to damage of the RPE and the endothel, causing photoreceptor cell death and choroidal neovascularization as observed in AMD (Chen and Xu, 2015). AMD may be triggered by the non-specific systemic inflammation and immune system dysregulation caused by GM dysbiosis through increase of pathogenic symbionts or decrease of mutualistic symbionts and/or their metabolites (such as SCFAs) (sections 1.3. and 1.4.). Furthermore, increase in intestinal permeability and resulting translocated microbes and metabolites from the gut to the RPE may promote the formation and deterioration of drusen and RPE abnormalities. They may locally induce inflammation and/or impairment of the immune response by causing an increase of pro-inflammatory cytokines and ROS. One might even speculate that these onsite GM-induced mechanisms even promote the conversion from dry to wet AMD by causing major RPE damage and endothelial damage triggering choroidal neovascularization. Resulting breach of the blood-retina barrier may further accelerate disease progression trough translocation of microbes and metabolites onto the retina. The role of the complement system in pathogenesis of AMD has been underlined by a genetic study conducted by the “Catalog of Human Genome-Wide Association Studies”. They identified 103 genetic risk loci for AMD (Deng et al., 2021b) of which thesingle nucleotide polymorphisms (SNPs) within the complement factor H (CFH) gene is the major heritable determinant of AMD followed by SNPs within the ARMS2/HTRA1 genes (Haines et al., 2005; Maller et al., 2006; May et al., 2021; Mohamad et al., 2019; Thee et al., 2022; Tzoumas et al., 2021). Interestingly, associations between GM, AMD and CFH have been found in our study (see point 2.3.4).

2.2. The gut microbiome in age-related macular degeneration

2.2.1. The influence of diet on age-related macular degeneration

The initial AREDS (Age-Related Eye Disease Study) study and the AREDS2 follow-up study evaluated the effect of vitamins on the progression of AMD and cataract. They demonstrated that dietary supplementation with carotenoids and zinc can prevent or delay the progression of these eye diseases, likely through their anti-oxidative and anti-inflammatory properties (Gorusupudi et al., 2017). The two major macular pigment carotenoids are the two xanthophylls lutein and zeaxanthin that are naturally concentrated in the macula lutea (yellow spot) of the human eye. They act as optical filter for blue light and as resident antioxidant and free radical scavenger to reduce oxidative stress-induced damage (Lima et al., 2016). Because humans cannot synthesize carotenoids, the supply depends on carotenoid-containing food such as leafy vegetables, broccoli, peas, corn and egg yolks (Mrowicka et al., 2022). The bioavailability of carotenoids depends on various factors including genetic factors, sex, age, health and nutritional status (Bohn et al., 2017; Ma and Liutkevičienė, 2021; Mrowicka et al., 2022). Since gut microbes may influence the bioavailability of several micronutrients including folic acid, vitamin B12 and iron (Maynard and Weinkove, 2020), this may be the case for carotenoids and zinc as well.

Furthermore, several studies have shown that a high intake of omega-3 long-chain polyunsaturated fatty acids (LCPUFAs) is associated with a decreased risk of AMD, whereas a high intake of omega-6 LCPUFA is associated with an increased risk. LCPUFAs are highly concentrated in the eye and are essential for the visual function of the retina. Moreover, they are important regulators of pro- and anti-inflammatory immune responses to oxidative stress. The ratio between omega-3 and omega-6 LCPUFs seems to be of importance in preventing chronic low-grade inflammation. However, whether dietary supplementation with omega-3 LCPUFAs is protective for AMD is still under investigation

(Jiang et al., 2021; Ren et al., 2022; Roh et al., 2020). Similar to carotenoids, humans obtain omega 3 and omega 6- LCPUFA only through diet, such as certain fatty fish, flax seeds and algae (Harauma et al., 2017).

Another study has shown that dietary polyphenols (found for example in cloves, cocoa powder, berries, red wine or green tea) reduce oxidative stress, have anti-inflammatory effects in RPE cells and are associated with the regulation of various interleukins and signaling pathways (Pawlowska et al., 2019).

These studies underline the influence of diet on AMD (Fig. 2B). Diet seems to influence the disease progression through anti-oxidative and anti-inflammatory mechanisms. Since its involvement in immune system modulation and inflammation (sections 1.3. and 1.4.) together with the strinking influence of diet on GM composition (Singh et al., 2017), gut microbes and their metabolites may be play a key role in linking diet with AMD. To investigate this hypothesis, we compared the GMs of patients with neovascular AMD and healthy age- and sex-matched controls with no difference in BMI between the two groups by whole-metagenome shotgun sequencing (see below).

2.2.2. *Associations between the gut microbiome and age-related macular degeneration*

We have recently identified associations between the GM and AMD in humans (Fig. 2) (Zinkernagel et al., 2017; Zysset-Burri et al., 2020). The class *Negativicutes* was more abundant in AMD patients, whereas the genus *Oscillibacter* and *Bacteroides* species were more abundant in healthy controls (Fig. 2B) (Zysset-Burri et al., 2020). Moreover, we observed at the phylum level a shift of relative abundance in *Firmicutes* at the expense of *Bacteroidetes* in AMD patients (Fig. 2A) (Zinkernagel et al., 2017). Since numerous studies have shown that a high *Firmicutes* to *Bacteroidetes* ratio is typically associated with obesity (Mathur and Barlow, 2015), the latter representing a risk factor for AMD, these results are in agreement with previous observations. Moreover, using a classification model, we identified the top seven ranked microbial taxa as potential biomarkers of which *Negativicutes,* that belong to the phylum *Firmicutes* had the highest potential for the separation of AMD patients and healthy controls (Fig. 2B) (Zysset-Burri et al., 2020). This represents the potential diagnostic value of the GM to predict AMD among a mixture of stool samples from patients and controls.

Two other research groups have provided evidence for diet inducing exacerbations of AMD-like features and concomitant GM alterations in mice, using 16S rRNA gene sequencing.

Andriessen et al. found that high-fat diets exacerbate laser-induced choroidal neovascularization in a mouse model of AMD and alter the GM. *Firmicutes* and *Proteobacteria* were of higher abundance in mice fed with high-fat-diet, whereas *Bacteroidetes* were of higher abundance in mice fed with a normal diet. This shift was also observed in our study with an increased *Firmicutes* to *Bacteroidetes* ratio in AMD patients as mentioned above. Interestingly, the neovascular response to laser injury in the study of Andriessen et al. was diminished in high-fat-diet fed mice after fecal transplantations from mice fed with a normal diet. Moreover, they concluded that gut dysbiosis may lead to increased intestinal permeability and chronic low-grade inflammation with elevated production of pro-inflammatory cytokines and vascular endothelial growth factor that ultimately aggravates pathological angiogenesis as observed in AMD (Andriessen et al., 2016).

Similar conclusions were revealed by Rowan et al.. While high-glycemic (HG) diet led to AMD features in the murine retina, mice fed with low-glycemic (LG) diet did not develop these features. Moreover, switching from HG to LG diet arrested or reversed the AMD features. As anticipated, these diets were associated with different GM compositions as well. Similar to high-fat-fed mice, the GMs of HG diet fed mice were rich in *Firmicutes* and *Proteobacteria*, especially of the *Clostridia* and *Bacilli* class. The GMs of LG diet-fed mice were rich in *Bacteroidetes* and *Erysipelotrichia* (Rowan et al., 2017; Rowan and Taylor, 2018).

In conclusion, normal or LG diet may favor the mutualistic symbionts that maintain intestinal homeostasis and inhibit inflammatory processes (section 1.3.) protective for AMD, whereas high-fat-diet and HG diet may favor the pathogenic symbionts inducing gut dysbiosis and dysregulation of immune responses through bacterial translocation (section

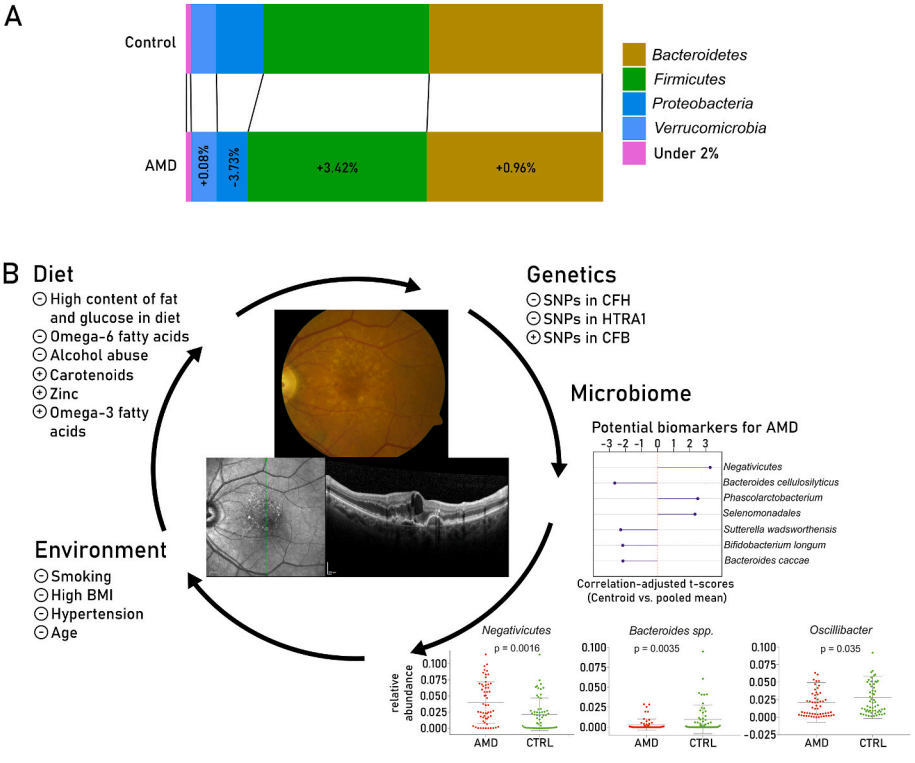

Fig. 2. Associations between the gut microbiome and AMD.
(A) Relative abundance of gut microbes at phylum level in neovascular AMD patients (n = 57) compared to healthy age- and sex-matched controls (n = 58) averaged for study groups. Phyla contributing less than two percent to the composition on average are grouped in the *under 2%* group. Data are adapted from (Zysset-Burri et al., 2020). (B) Representative color photograph (above) and optical coherence tomography (below) of a patient with neovascular AMD. AMD is a multifactorial disease with environmental factors, diet, genetic risk factors as well as alterations in the GM contributing to the pathogenesis. Top ranked 7 bacteria as potential biomarkers for neovascular AMD. The length and direction of the blue bars indicate the involvement of a given biomarker on the discriminative power of the classification model; i.e. *Negativicutes* has the highest potential for separation of AMD patients and controls, with positive correlation-adjusted T-scores indicating an over-representation in AMD and negative scores an over-representation in controls. Point graphs representing the mean abundance±s.d. of taxonomic features associated with AMD (Kruksal-Wallis test, $p < 0.05$). These figures were originally published in (Zysset-Burri et al., 2020). Risk factors are marked with a minus symbol. Protective factors are marked with a plus symbol. CFH, complement factor H; BMI, body mass index; SNPs, single nucleotide polymorphisms; HTRA1, high-temperature requirement-A.

1.4.). However, it is unclear what role the identified microbes play in the pathogenesis of AMD and what functions are characteristic for pathogenic and mutualistic symbionts, respectively. Therefore, we investigated functional features of these microbes in terms of microbial genes and pathways.

2.2.3. *Metabolic pathways of the gut microbiome*

In addition to compositional shifts in the GM (see above), we observed variations in metabolic functions of the GM of AMD patients compared to healthy controls. We revealed that the patient's GMs were enriched in genes of the L-alanine fermentation, glutamate degradation and arginine biosynthesis and decreased in genes of the fatty acid elongation pathway (Fig. 3) (Zinkernagel et al., 2017). Decreased availability of the excitatory neurotransmitter glutamate has been shown to result in deficient neurotransmission in the retina (Bui et al., 2009), probably providing the link between enhanced glutamate degradation in the patient's microbiomes and AMD pathogenesis. Since an increase in arginine levels in patients with reduced ornithine aminotransferase activity is associated with progressive chorioretinal atrophy (Simell and Takki, 1973), arginine may play an important role in the development of retinal degeneration. The protective role of omega3 LCPUFs in AMD has been discussed previously (see point 2.3.1.) and supports the decreased levels of the fatty acid elongation pathway in patients.

2.2.4. *The role of the complement system*

As briefly mentioned before, genetic risk factors have been identified to play a role in the etiology of AMD. It is widely agreed that SNPs within the CFH gene are the major heritable determinant of AMD (Haines et al., 2005; Tzoumas et al., 2021). Among 116,204 SNPs genotyped in a genome-wide screen of 96 AMD patients and 50 controls that participated in the AREDS study, a variant within the CFH gene increases the likelihood of AMD by a factor of 7.4 in participants homozygous for this variant (Klein et al., 2005). This genetic link was further extended by several studies showing associations between AMD and SNPs within genes of other complement factors such as complement component 3 (C3), complement component 2 and complement factor B (Gold et al., 2006; Maller et al., 2007).

In our cohort of 57 AMD patients and 58 healthy controls, we showed associations between SNPs within the CFH gene and AMD (Fig. 2B) as well as with alterations in the GM. Most interesting, the class *Negativicutes* that we proposed as potential biomarker for neovascular AMD in our cohort positively correlated with a specific SNP in the CFH gene (Fig. 3). This result confirms the suggestion that increased *Negativicutes* levels (or more broadly an increased *Firmicutes* to *Bacteroidetes* ratio) may influence the development and/or progression of AMD via uncontrolled regulation of the complement system. SNPs within the HTRA1 gene, the second most AMD-associated genetic dysregulation, were also associated with AMD in our cohort but no associations with the GM were detected. SNPs within the complement factor B gene on the other hand seemed to have a protective effect (Fig. 1B) (Zysset-Burri et al., 2020).

The CFH plays an important role in the regulation of the innate immune system. CFH is the main inhibitor of the alternative pathway of the complement cascade. It is a key component of the regulation of both inflammatory and oxidative stress responses. It ensures that the complement system is directed towards pathogens rather than damaging host tissue. People with SNPs within the CFH gene might present an over-activated or de-regulated complement system, damaging host tissue and inciting inflammatory and degenerative diseases (Romero-Vazquez et al., 2021). In the eye, an over-activated complement system and its resulting low-grade inflammation may lead to damage and dysfunction of the RPE (Cashman et al., 2011).

Given the potential implication of SNPs within the CFH gene in the etiology of AMD on one side, and the evidence for interactions of the immune system and the GM on the other side, we also screened for associations between the GM and the complement system. For this

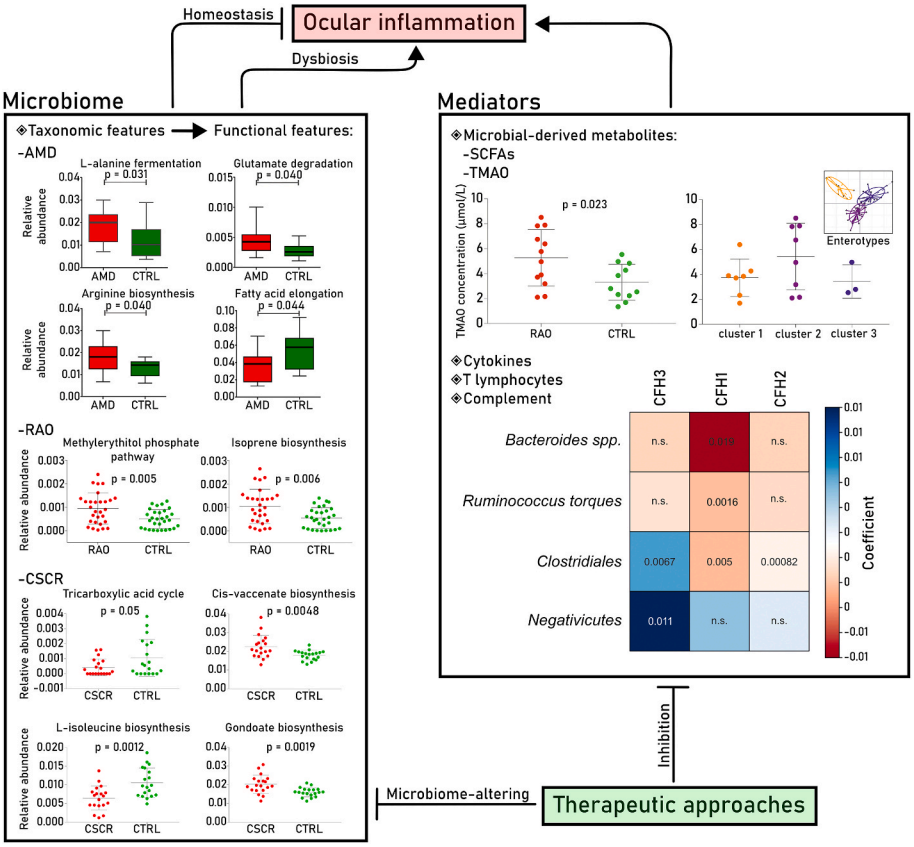

Fig. 3. Gut microbiome-altering therapeutic approaches to prevent ocular inflammation.
New therapeutic approaches target taxonomic and functional features of the GM and associated microbial-derived metabolites and components of the immune system. Plots of functional features representing the mean abundance±s.d. of metabolic pathways associated with AMD (originally published in (Zinkernagel et al., 2017)), RAO (originally published in (Zysset--Burri et al., 2019)) and CSCR, respectively (own unpublished data; Kruksal-Wallis test, $p < 0.05$). Levels of the gut-derived pro-atherogenic metabolite TMAO are increased in RAO patients compared to controls (Fisher's exact test), while there is no significant difference of the TMAO concentration among the three enterotypes (Kruksal Wallis test, $p > 0.05$). These figures were originally published in (Zysset-Burri et al., 2019). Correlation between SNPs in the CFH gene and microbial taxa (color gradient for R-coefficients and corresponding q-values from multivariate association by linear models are shown; red indicates negative correlation, blue positive correlation), indicating that the GM may influence the AMD pathogenesis via uncontrolled regulation of the complement system. This figure was originally published in (Zysset-Burri et al., 2020). CFH, complement factor H; SCFAs, short-chain fatty acids; SNPs, single nucleotide polymorphisms; TMAO, trimethylamine-N-oxide.

purpose, we compared the GMs of 16 C3-deficient mice to 16 wildtype mice. Since all three activation pathways of the complement system converge in the activation of C3, mice lacking C3 do not have an effective complement system. Furthermore, studies have shown that C3 deficiency as well as C3 overexpression in mice harmed retinal health with functional and morphological features similar to AMD features in humans (Cashman et al., 2011; Hoh Kam et al., 2013). We demonstrated that the GM of C3-deficient mice showed similar taxonomic features as the GM of neovascular AMD patients. For instance, the *Firmicutes* to *Bacteroidetes* ratio was higher in C3-deficient mice compared to wildtypes. Hence, we speculated that *Firmicutes* may contribute to AMD development in C3-deficient mice, whereas *Bacteroidetes* may have a protective role. Even though it remains unclear how C3-deficiency and the GM are linked, this study suggests a connection between the GM and the complement system in the development of neovascular AMD (Zysset-Burri et al., 2020). Since there is a crosstalk between the complement system and toll-like receptors expressed on different cells along the gastrointestinal tract where they recognize microbe-specific molecules (Abreu et al., 2005; Hajishengallis and Lambris, 2016), toll-like receptors may be crucial in signaling between the complement system and the GM. However, whether alteration of the microbiome is merely a consequence of AMD and/or is involved in its pathogenesis via uncontrolled activation of the complement system needs more investigation. With this in mind, we performed a functional analysis of the murine GMs, detecting an enrichment of genes of the 5-aminoimidazole ribonucleotide biosynthesis pathway in C3-deficient mice compared to wildtypes. 5-aminoimidazole ribonucleotide is an intermediate of purine nucleotide biosynthesis (Zysset-Burri et al., 2020) which in return, might be a key point in the interactions between the GM and the complement system. This correlates with the discovery of aberrant purine signaling being implicated in immune dysregulation as observed in the pathogenesis of autoimmune diseases (Longhi et al., 2017). Although autoimmunity in terms of autoantibody production is associated with a variety of ocular diseases including AMD (Morohoshi et al., 2009), the detailed triggers for ocular autoimmunity are still unknown.

3. The gut microbiome and retinal artery occlusion

3.1. Definition of retinal artery occlusion

Central retinal artery occlusion (CRAO) was first described in 1859 in a patient with endocarditis (v. Graefe, 1859). It is caused by partial or complete obstruction of the central retinal artery (CRA) leading to permanent retinal ischemia and irreversible cell death within a few hours. The CRA originates from the ophthalmic artery, which is the first branch of the internal carotid artery and supplies together with its branches blood to the inner retina including the macula and fovea. Branch retinal artery occlusion (BRAO) is caused by the occlusion of a branch of the CRA. Similar to cerebral infarctions, CRAO and BRAO mainly result from emboli from the internal carotid artery, aortic arch or heart and are referred to as nonarteritic RAO. Rarely, CRAO and BRAO occur in the context of a systemic inflammatory condition, i.e. vasculitis, mainly in patients with giant cell arteritis, referred to as arteritic RAO.

The incidence of CRAO is approximately 1–2 in 100,000 with an exponential increase with age. In patients aged over 80 years, the incidence may be as high as 10 in 100,000, most likely due to the higher prevalence of cardiovascular diseases in this age group (Park et al., 2014). Acute RAO results in a sudden, painless mononuclear loss of vision and/or visual field in the involved eye with severity related to the size of the occluded vessel (BRAO versus CRAO) and the duration of occlusion (transient versus permanent).

In 2013, the American Heart Association and American Stroke Association defined a stroke as “brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury” (Sacco et al., 2013). Hence, a CRAO is a stroke equivalent, classified as an ophthalmologic and medical emergency that needs immediate care to prevent additional ischemic complications, such as a myocardial or cerebral infarction. Since occlusion of the CRA by an embolus is the most common cause of CRAO, examination of patients with CRAO must focus on detection of an underlying source of emboli. Treatment of CRAO can be divided into acute treatment, aiming at the resolution of CRAO and improvement of the visual outcome, and secondary prevention of further ischemic events.

However, since no current acute therapeutic intervention has been shown to improve visual outcomes, particular emphasis should be aimed at the secondary prevention of systemic ischemic events. Furthermore, since therapeutic options for CRAO are very limited, preventive strategies are all the more important. Targeting the GM to prevent the development of atherosclerotic disease and thus the most common cause of CRAO may therefore be an attractive concept.

3.2. The gut microbiome in retinal artery occlusion

3.2.1. Pathogenesis and the influence of diet on cardiovascular diseases and retinal artery occlusion

Since the pathogenesis of RAO is primarily thromboembolic, often from carotid plaques, there is a close association between atherosclerosis and RAO (Hayreh et al., 2009). Factors contributing to atherosclerosis and cardiovascular disease (CVD) arise generally from a combination of genetic and environmental causes. In addition to obesity, hypertension, diabetes, stress, alcohol, smoking, unhealthy dietary patterns (such as high intake of sodium and processed foods, added sugars, unhealthy fats and low intake of fruit, vegetables, whole grains, fiber and legumes) are the major risk factors for CVD (Fig. 3B). The increasing incidence of CVD over the last 3 decades has become a public health priority, especially the prevention of CVD by lifestyle interventions such as nutrition (Casas et al., 2018).

Early stages of atherosclerosis are characterized by the internalization of lipids mainly low-density lipoproteins in the intima, the innermost layer of the blood vessel wall. This leads to the disruption of the endothelial function, promoting inflammatory responses and thrombus formation (Kwon et al., 2008). Circulating monocytes are attached to the endothelium and transformed into infiltrating macrophages, which are further converted into foam cells after ingestion of oxidized low-density lipoproteins particles (Chistiakov et al., 2017). Furthermore, endothelial dysfunction favors the adhesion of platelets that secrete chemotactic substances and growth factors, promoting plaque progression. It has been shown that these atherosclerotic plaques contain bacterial DNA with phylotypes common to the gut microbiota such as *Actinobacteria* (Koren et al., 2011), suggesting an involvement of gut microbes in plaque formation in atherosclerosis. Thus, in sections 3.4.2 and 3.4.3, we elucidate the role of the GM in the development and/or progression of CVD, atherosclerosis and RAO.

3.2.2. The role of the gut microbiome in cardiovascular diseases

Jie et al. performed a metagenome-wide association study of stool samples from 218 individuals with atherosclerotic cardiovascular disease compared to 187 healthy controls. They found an increased abundance of *Enterobacteriaceae* and *Streptococcus* spp. in the gut of patients. Moreover, functional alterations in patient’s GMs were detected compared to the microbiome of controls. Consistent with the enrichment of Gram-positive *Enterobacteriaceae* in the patient’s microbiomes, genes required for the synthesis of the O-antigen of LPS were enriched, whereas the lipid A synthesis was reduced in agreement with the reduction of Gram-negative *Bacteroides* (Jie et al., 2017). In another study analyzing the GMs of 12 patients with symptomatic atherosclerosis compared to 13 age- and sex-matched healthy controls using whole-metagenome shotgun sequencing, Karlsson et al. demonstrated an enrichment of the genus *Collinsella* and a decline of the genera *Roseburia* and *Eubacterium* in patients. Functional analysis of the metagenomes revealed an enrichment of genes encoding peptidoglycan

synthesis that may contribute to atherosclerosis by priming the innate immune system and enhancing neutrophil function. Due to these findings and together with the decrease of genes involved in the synthesis of anti-inflammatory molecules in patient's microbiome and associated decreased serum levels of the anti-oxidant β-carotene, the authors suggested that the GM may act as a regulator of host inflammatory pathways in atherosclerosis (Karlsson et al., 2012).

Given the association between RAO and atherosclerosis, we suppose that the development and/or progression of RAO may also be associated with alterations in the GM. To this issue, we compared the GMs of 29 patients with non-arteritic RAO and 30 healthy age- and sex-matched controls using whole-metagenome shotgun sequencing (Fig. 4) (Zysset-Burri et al., 2019). At the phylum level, we found a decrease in the relative abundance of *Bacteroidetes* with respect to *Proteobacteria* in RAO patients (Fig. 4A). Since an elevated prevalence of *Proteobacteria* has been suggested as a biomarker for dysbiosis and risk of disease (Shin et al., 2015), this result lets us suggest a correlation between atherosclerotic diseases and dysbiosis. Furthermore, on a deeper taxonomic rank, the class *Actinobacteria* and the species *Bifidobacterium adolescentis*, *Bifidobacterium bifidum*, *Bacteroides stercoris* and *Faecalibacterium prausnitzii* were enriched in RAO patients, whereas the family *Lachnospiraceae*, the genera *Odoribacter* and *Parasutterella* were enriched in controls (Fig. 4B). Several studies have identified bacterial DNA in atherosclerotic plaques of which a high proportion could be assigned to

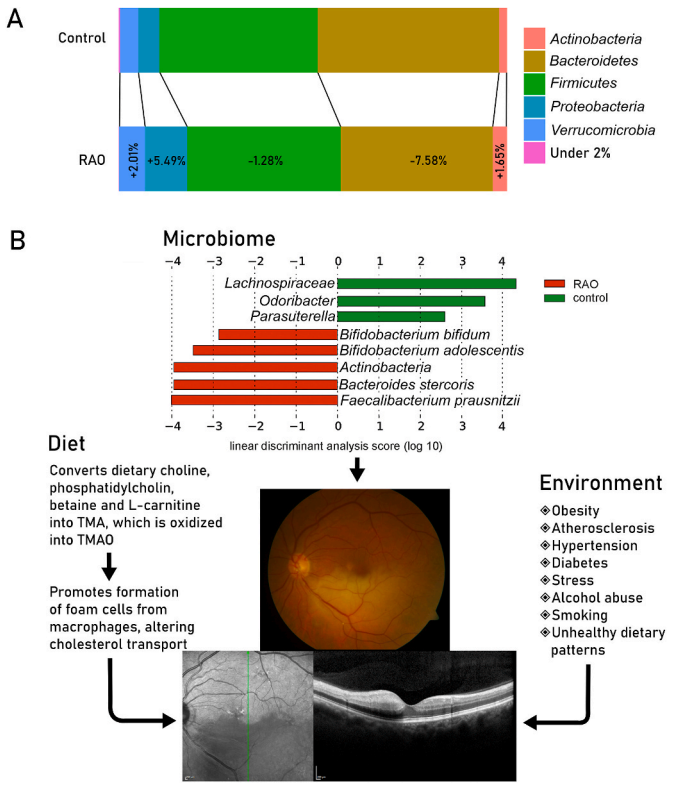

Fig. 4. Associations between the gut microbiome and RAO.
(A) Relative abundance of gut microbes at phylum level in RAO patients (n = 29) compared to healthy age- and sex-matched controls (n = 30) averaged for study groups. Phyla contributing less than two percent to the composition on average are grouped in the *under 2%* group. Data are adapted from (Zysset-Burri et al., 2019). (B) Representative color photograph (top) and optical coherence tomography (bottom) of a patient with RAO with ischemia and edema of the retina and a cherry-red spot. Environmental factors and alterations in the GM associated with diet contribute to RAO pathogenesis. Linear discriminant analysis score plot of differentially abundant taxonomic features between RAO patients and controls (score for discriminative features >2.0). This figure was originally published in (Zysset-Burri et al., 2019). TMA, trimethylamine; TMAO, trimethylamine-N-oxide.

Actinobacteria (Koren et al., 2011). The upregulation of this class in patients supports the hypothesis that the gut microbiota can be a source for plaque-associated bacteria and, as a consequence, that bacterial translocation may represent a common pathogenetic mechanism of atherosclerotic diseases as well as eye diseases in general. However, the upregulation of *Bifidobacterium species* in RAO patients seems surprising because they are known as probiotics with beneficial effects on blood lipid concentration (Cho and Kim, 2015). A possible explanation for this upregulation is a commensal-to-pathogen transition. On the other hand, higher proportions of *Bifidobacterium species* have been identified in inflammatory bowel disease, which in turn is associated with early atherosclerosis (Papa et al., 2006). In addition to taxonomic features, we revealed a separation of RAO patients from healthy controls by functional features of the GM, especially in genes of the methylerythritol phosphate pathway and isoprene biosynthesis (Fig. 3), both involved in cholesterol metabolism (Zysset-Burri et al., 2019). This is especially interesting given recent findings, showing enteric microbiome metabolites that correlate with response to simvastatin treatment (Kaddurah-Daouk et al., 2011). Statins are HMG-CoA reductase inhibitors used to reduce plasma levels of low-density lipoproteins cholesterol to prevent both, the early stages of atherosclerosis (point 3.4.1) and further systemic ischemic events following CRAO (section 3.3). Moreover, several studies have reported associations between microbial-derived metabolites such as trimethylamine-N-oxide (TMAO, section 3.4.3) and SCFAs and hypercholesterolemia, which play a causal role in the development of atherosclerosis and is a risk factor for CVD (Vourakis et al., 2021). Although the exact mechanisms behind these associations are unclear, therapeutic approaches modulating gut microbes and their metabolites, that in turn regulate cholesterol homeostasis, may represent novel therapeutics for hypercholesterolemia and therefore for atherosclerosis and associated diseases such as RAO.

3.2.3. *The link between trimethylamine-N-oxide and the gut microbiome*

The gut microbiota-derived metabolite trimethylamine-N-oxide (TMAO) has gained much attention as a biomarker for CVD in clinical studies and a mediator of atherosclerosis in animal models (Koeth et al., 2013; Wang et al., 2011). It is proposed that increased dietary consumption of red meat, eggs, fish and dairy products enhances levels of choline, phosphatidylcholine, betaine and L-carnitine that are converted by gut microbes to trimethylamine, which is oxidized by hepatic flavin monooxygenase into TMAO (Fig. 2B) (Vourakis et al., 2021). Elevated blood TMAO levels have been associated with major adverse CVD events (Tang and Hazen, 2014) as well as diabetes (Zhuang et al., 2019b) and have been proposed as a biomarker of metabolic syndrome (Barrea et al., 2018). There is strong evidence that TMAO is not only a risk factor but also a therapeutic target for CVD in terms of inhibiting gut microbiota-dependent TMAO production (Wang et al., 2015). Although the exact mechanisms are not yet fully understood, it is believed that TMAO promotes atherosclerosis through the formation of foam cells from macrophages and interfering with cholesterol transport (Fig. 3B) (Koeth et al., 2013). Since we found an upregulation of genes of the cholesterol metabolic pathway in the microbiome of RAO patients (Zysset-Burri et al., 2019), this may provide a potential target for therapeutic interventions for CVD. Toward this aim, it is of interest to identify the gut microbes that may be involved in TMAO production. It has been shown that the main producers of TMAO derive from the two phyla *Firmicutes* and *Proteobacteria* and include *Escherichia fergusonii, Proteus penneri, Providencia rettgeri, Anaercoccus hydrognealis, Clostridium asparagiforme* and *Edwardsiella tarda* (Koeth et al., 2014; Romano et al., 2015). In our study, an increased TMAO concentration was observed in blood samples from RAO patients compared to healthy controls. The TMAO concentration among the three enterotypes identified in our cohort was not significantly different (Fig. 3). However, significant differences were given with the genera *Parasutterella* and *Lachnospiraeae* negatively correlating and the genus *Akkermansia* positively correlating with TMAO levels (Zysset-Burri et al., 2019). These results are in

agreement with the upregulation of *Parasutterella* and *Lachnospiraeae* in the metagenomes of controls (section 3.4.2). However, whether increased TMAO levels are essentially causative for CVD including atherosclerosis and RAO or whether they merely represent a biomarker for alterations in the GM needs more investigation.

4. The gut microbiome and central serous chorioretinopathy

4.1. Definition, pathogenesis and risk factors of central serous chorioretinopathy

Central serous chorioretinopathy is characterized by a localized serous detachment of the neurosensory retina involving the macula. Most cases are unilateral.

Traditional classification differentiates between acute (duration shorter than 4–6 months) and chronic (duration longer than 4–6 months) disease. The pathogenesis remains poorly understood.

It is assumed to be multifactorial, latest theories assume the presence of localized choroidal hyperpermeability with subsequent secondary changes in the retinal pigment epithelium. The symptoms of acute CSCR include central blurred vision, often with deterioration in visual acuity typically perceived as a grey disc in the central visual field. The natural course of the disease is often self-limiting, and the visual prognosis is good in most cases with visual acuity returning to normal within a few months after the fluid has been resolved.

CSCR often affects men between 30 and 50 years of age having demanding careers and are burdened by job responsibilities. Recent psychological stress is considered one of the most important risk factors to develop CSCR (Fig. 5B). Moreover, several personality traits such as competitiveness, overachievement, sense of urgency or hostile temperament are associated with CSCR (Semeraro et al., 2019). Although the precise mechanisms are poorly understood, associations between CSCR, stress and specific personality traits are proposed to be mediated by circulating stress hormones. Many clinical studies have suggested that high blood levels of steroids may contribute to the pathogenesis of CSCR (Fig. 5B) and that nasal, oral and intravenous steroids may be important risk factors for CSCR (Haimovici et al., 2004). Furthermore, associations between CSCR and shift work as well as sleep disturbances have been proposed. Genetic risk factors, including genetic variants in CFH and ARMS2 that are also associated with AMD, may play a role in CSCR (Kaye et al., 2020; Schellevis et al., 2018; Semeraro et al., 2019) (Fig. 5B).

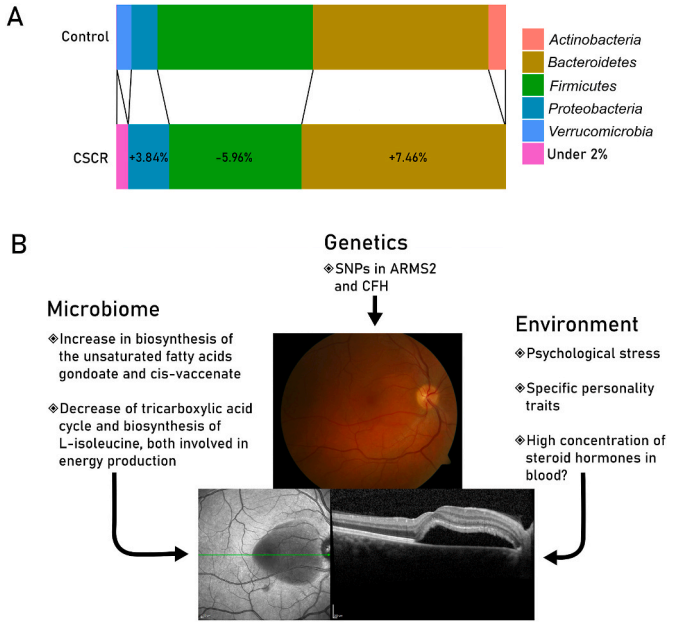

Fig. 5. Associations between the gut microbiome and CSCR
(A) Relative abundance of gut microbes at phylum level in CSCR patients (n = 19) compared to healthy age- and sex-matched controls (n = 19) averaged for study groups. Phyla contributing less than two percent to the composition on average are grouped in the *under 2%* group (unpublished data).
(B) Representative color photograph (above) and optical coherence tomography (below) of a patient with CSCR. Although more investigation is needed, environmental factors, genetic risk factors and functional alterations of the GM are proposed risk factors for CSCR. ARMS2, age-related maculopathy susceptibility protein 2; CFH = complement factor H.

4.2. The role of the gut microbiome in central serous chorioretinopathy

Since the effects of CSCR on the retina are usually self-limited and acute CSCR often resolves spontaneously, it is not clear whether there is a clinically relevant benefit to treating acute CSCR (Semeraro et al., 2019). Since in the case of the chronic form subretinal fluid persists causing persisting visual abnormalities, new therapeutic approaches to reduce the severity of the disease and especially preventing the chronic form of CSCR are of great interest. Since dysbiosis in the GM is associated with several eye diseases and the microbiome can be modulated by microbiome-altering interventions such as probiotics and antibiotics, the exploration of interactions between the GM and the development of CSCR may provide the basis for such therapies. To this issue, we taxonomically and functionally characterized the GMs of CSCR patients (n = 19) versus age- and sex-matched healthy controls (n = 19) using whole-metagenome shotgun sequencing (Fig. 5; own unpublished data). Whereas no differences in the microbial composition have been detected between the two groups (Fig. 5A), functional alterations in pathways associated with fatty acid metabolism and energy production have been found. The biosynthesis of the two unsaturated fatty acids gondoate and cis-vaccenate are both elevated in the GMs of patients, whereas the tricarboxylic acid cycle and the biosynthesis of L-isoleucine, both are involved in energy production are decreased (Fig. 3; own unpublished data). Although these findings need more investigation, the functional capacities of the GM may represent a potential target for new therapeutic approaches for CSCR especially targeting the fatty acid metabolism and energy production. Since tissues with high metabolic rates such as the retina often use both lipid and glucose for energy production (Joyal, 2018), further studies may explore the interactions between the GM and retinal homeostasis. Using high-throughput RNA sequencing of whole retinas, Dao et al. have compared the retinal transcriptome from germ-free mice fed with a regular diet to germ-free mice fed with a high-fat-diet (Dao et al., 2021). Among the 53 differentially expressed genes, key genes involved in retinal inflammation, angiogenesis and RPE function were identified. To identify biological processes and pathways affected by high-fat-diet, functional enrichment and pathway analysis have been performed, respectively. In particular, they showed an involvement of processes implicated in the regulation of blood vessel diameter, inflammatory response and negative regulation of endopeptidase, and of the complement and coagulation cascades pathways. Although using germ-free mice, Dao et al. were able to investigate transcriptomic changes without the influence of the GM, it remains unclear how the GM itself affects the retinal transcriptome. However, the study provides an idea for further approaches.

Several studies have shown associations between the GM and steroid hormones, especially in terms of sex differences in the gut microbiome (in mice and humans) and alterations in the gut microbiome of pregnant and postmenopausal women. Moreover, there is evidence that perturbations in the gut microbiota can alter stress via regulation of the endocrine system (Tetel et al., 2018). In this context, alterations in the GM may influence the level of stress hormones that are proposed to be involved in the development of CSCR.

5. The gut microbiome and inflammatory eye diseases

5.1. Definition and pathogenesis of uveitis

Uveitis is an umbrella term describing a range of intraocular inflammatory diseases of the uvea, which consists of the iris, the ciliary body and the choroid. Uveitis is one of the leading causes of blindness in the developed world and has been reported to be causative of up to 10–15% of severe visual handicaps (Miserocchi et al., 2013). Depending on its etiology uveitis can be classified into two major groups: Infectious and non-infectious uveitis. Noninfectious uveitis is the most common form and may be associated with systemic inflammatory diseases such as systemic sarcoidosis, Behçet's disease and Vogt-Koyanagi-Harada disease.

Depending on the primary anatomical location within the segments of the eye, uveitis can be classified as anterior, intermediate and posterior. A panuveitis describes a generalized intraocular inflammation with all segments affected (de Smet et al., 2011). The Standardization of Uveitis Nomenclature (SUN) working group is generally used to classify specific uveitic conditions (Jabs et al., 2005).

Our general understanding of the disease etiology of many forms of autoimmune uveitis has evolved in the last decades. One of the main drivers of the disease is an aberrant immune response leading to autoinflammation and/or autoimmunity. Whereas autoinflammation is caused by innate immune cell activation, autoimmunity results when adaptive immune cells break self-tolerance. Both autoimmune and autoinflammatory pathways are thought to be required for the full expression of autoimmune uveitis (Forrester et al., 2018). The intraocular space is considered an immune-privileged site (Streilein, 2003) and the intraocular cavity is considered sterile unless there is an infection.

Most of our understanding of the pathogenesis of autoimmune uveitis derives from experimental models of uveitis induced by blood-retina barrier breakdown and induction of autoreactive T cells directed against retinal antigens. This has been studied extensively in the model of experimental autoimmune uveitis (EAU) (Caspi, 2011). To activate an autoimmune response, the autoantigen has to be recognized by the T cell receptor on T cells in conjunction with MHC class II (Zinkernagel and Doherty, 1974). MHC restriction is particularly important for self-tolerance which makes sure that our immune system does not target ourselves.

However, previous studies have shown that retinal specific T cell responses are also present in patients without a history of uveitis and that the presence of autoreactive T cells is not sufficient to trigger uveitis (De Smet et al., 2001). In addition, a breach of the blood-retina or blood-aqueous barrier is required. Whereas the blood-retina barrier is compromised in intermediate and posterior uveitis, anterior uveitis involves a breakdown of the blood-aqueous barrier, involving structures such as the ciliary body and the iris. The blood-aqueous barrier consists of tight junction complexes between the non-pigmented epithelial cells of the ciliary epithelium (Coca-Prados, 2014).

At least in experimental autoimmune uveitis, an adjuvant is needed to initiate the disease. These adjuvants act by activating pattern-recognition receptors such as toll-like receptors and/or NOD-like receptors in the innate immune system that sense microorganisms through conserved molecular structures (Thaiss et al., 2016). However, the triggers for the onset and relapses of intraocular inflammation in non-infectious uveitis in humans remain unknown.

The cascades leading to autoinflammation, autoimmunity and ultimately uveitic disease are complex (Willermain et al., 2012). It is thought that only an orchestrated occurrence of autoinflammation at the target tissue or systemically, breach of the blood-retina barrier, autoimmune retinal specific T cells and possibly a suitable human leukocyte antigen predisposition ultimately lead to a fully mounted immune response within the eye. Different uveitic conditions have been associated with distinct human leukocyte antigen haplotypes (e.g., B27, B51, A29, DR4, DQ4) substantiating the autoimmune nature of this condition. However, the link between these haplotypes and the generation of an autoimmune response against retinal proteins remains ambiguous.

Despite the many insights that experimental models, first and foremost EAU, have revealed into pathomechanisms, no model fits all human uveitis entities.

Given this wide range of uveitic conditions in humans, there is probably a large variability in terms of whether there is predominantly autoinflammation or true autoimmunity. Furthermore, there may be large variability in terms of triggering factors.

In the last decade infectious agents and the ensuing chronic inflammation have been associated with autoimmune or autoinflammatory diseases. Infectious agents may serve as a trigger by activating pattern-recognition receptors or as shown in the EAU model, by activation of autoreactive T cells by antigen mimicry. Molecular mimicry is caused by sequence homology between foreign and self-peptides leading to cross-activation of autoreactive T cells (Rojas et al., 2018). Molecular antigen mimicry from environmental antigens such as viruses or dietary components entering through the gastrointestinal tract, can cross-react with retinal S antigen, a major component of rod outer segments, due to amino acid sequence homologies (Hirsch et al., 1999) and cause experimental uveitis in Lewis rats (Wildner and Diedrichs-Mohring, 2003).

5.2. The gut microbiome in uveitis

A number of publications have suggested that systemic microbial infection such as sequela of GM dysbiosis in particular, may be an important driving mechanism in uveitis (Horai et al., 2015a; Huang et al., 2018; Jayasudha et al., 2019; Ye et al., 2020).

Microbes might be implicated directly or indirectly in many forms of noninfectious uveitis. However, the associations between the commensal microbiome and host autoimmunity are rather complex and multifactorial. In addition to the growing recognition that foreign antigens derived from the GM may serve as an adjuvant, the possibility that the microbiome might result in differentiation of autoreactive Th17 cells and other T helper cells that cause immune-mediated ocular inflammation has now been demonstrated experimentally (Horai et al., 2015a; Rojas et al., 2018).

5.2.1. The role of microbial metabolites

In pathologic conditions such as inflammatory bowel disease, the permeability of the epithelial lining may be compromised allowing the passage of pathogenic symbionts and metabolites from the gastrointestinal lumen into the blood stream. Even in homeostatic conditions, gut microbes produce thousands of metabolites. On the other hand, the permeability of the intestines can be impacted by the composition of the GM itself. Certain species may increase this permeability leading to increased influx of bacterial components including LPS, cell capsule carbohydrates and other endotoxins into the host (Mu et al., 2017). This in turn may trigger an inflammatory host response via pattern-recognition receptors due to the production of cytokines including type I interferons and other inflammatory mediators and serve as a trigger to induce uveitis. Indeed, a perturbed microbiome composition has been associated with various autoimmune diseases such as type 1 diabetes, multiple sclerosis or rheumatoid arthritis. In addition, uveitis accounts for approximately 4%–6% of complications in inflammatory bowel disease (Vavricka et al., 2011) suggesting a link between GM dysbiosis and uveitis (Fig. 6).

Another intriguing syndrome with association to enteric infection is reactive arthritis. It has been known for many centuries as a triad of arthritis, nongonococcal urethritis, conjunctivitis and/or non-granulomatous anterior uveitis (Aceves-Avila et al., 1998) and is known to be triggered by a bacterial infection, possibly shedding of microbes from dysbiosis in the gut, particularly of the genitourinary (*Chlamydia trachomatis*) or gastrointestinal tract (*Shigella*, *Salmonella*, and *Campylobacter*) (Wu and Schwartz, 2008). Human leukocyte antigen B27

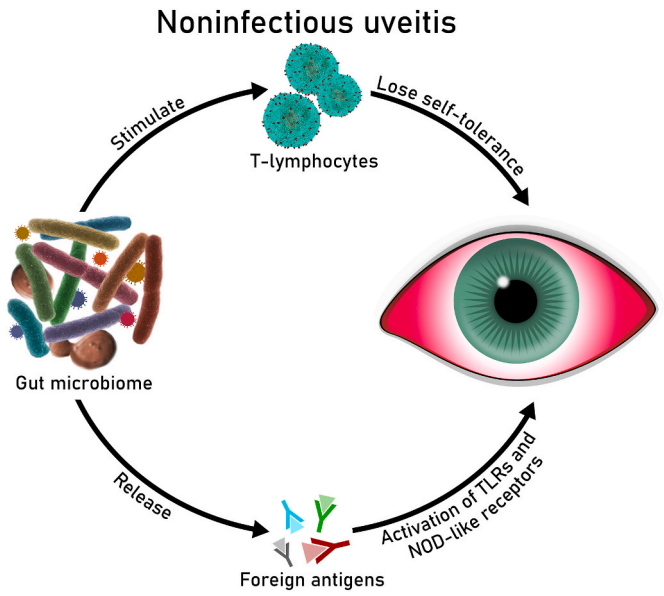

Fig. 6. Associations between the GM and non-infectious uveitis
Compositional alterations of the gut microbiome may trigger or influence intraocular inflammation via autoreactive T cells or via microbial components or metabolites. TLRs, toll-like receptors; NOD-like receptors, nucleotide-binding oligomerization domain-like receptors.

is strongly associated with Reiter's syndrome with about 60%–80% of patients being positive, compared with 10% in the general population (Al-Khonizy and Reveille, 1998; Callen and Mahl, 1992). The exact pathophysiology of this disease is unknown. Studies have found *Chlamydia* DNA and RNA in joints of patients with reactive arthritis, suggesting a direct connection of this organism with joint symptoms (Gerard et al., 2000). A recent study has identified a low-biomass intraocular microbiome in aqueous humor samples taken from multiple human donors, with or without associated ocular pathology (Deng et al., 2021a). The authors found a disease-specific microbial signature in patients with AMD and glaucoma suggesting that host–microbe interactions within the eye may lead to disease. These findings may lead to a paradigm shift in our understanding of various eye diseases and need to be corroborated by additional studies.

Previous studies have shown that microbial metabolites such as SCFAs or LPS that are abundant in the gut regulate intestinal adaptive immune responses and promote disease or health (section 1.3). Microbial SCFAs are thought to modulate autoimmune uveitis through regulatory T cell induction in EAU. Other studies have described the impact of microbial SCFAs on blood–brain barrier integrity (Braniste et al., 2014) and the same could apply to the blood-retina barrier.

Another impact component deriving from gut microbes is bacterial LPS. LPS plays a role in several diseases in which autoantibodies or self-antigen-specific T cells are involved. LPS, also known as endotoxins, form the key cell wall component of Gram-negative bacteria. Increased levels of LPS are observed in obesity and other metabolic disorders as well as adipose tissue inflammation and pancreatic beta-cell dysfunction. For example, LPS has been shown to aggravate experimental autoimmune myocarditis (Kato et al., 1993), EAU (Yokochi et al., 1993) and experimental autoimmune enterocolitis (Paeng et al., 1999). In addition, LPS appears to play an important role as an adjuvant in the induction of autoimmune arthritis in a mouse model (Yoshino et al., 2000).

Thus, microbial metabolites such as LPS or other endotoxins may trigger uveitis as it is well known in animal models and has been suspected in uveitis associated with reactive arthritis.

5.2.2. The role of the gut microbiome in molecular mimicry leading to autoreactive T cells

The discovery of perturbed gut microbiota in autoimmune disease suggests association but not necessarily causation of uveitis. The first clue implicating the pathogenetic role of the gut microbiota came from germ-free animal models that failed to develop autoimmune disease. Germ-free mice are protected from experimental autoimmune encephalomyelitis development which could be linked to reduced Th1 and Th17 responses (Berer et al., 2011). The importance of the GM has recently also been shown in a spontaneous uveitis model where T cell receptor transgenic mice specific for a retinal protein (Horai et al., 2013) develop EAU. In this model, EAU fails to develop in germ-free mice (Horai et al., 2015b). An activation step of autoreactive T cells in the periphery is required because the antigens that are targeted in uveitis are sequestered behind the blood-retina or blood-aqueous barrier and retina-specific lymphocytes must be activated to reach the eye. The activation of uveitis-relevant T lymphocytes can be achieved in this model through commensal antigen in the lamina propria of the gastrointestinal tract. In this model, neither LPS, heat-killed *Mycobacterium tuberculosis* extracts nor microbial super-antigens were able to activate retina-specific T cells. This supports the notion that retina-specific T cells in these mice are primed via non-cognate, probably microbial antigens in the gut. These findings are further substantiated by other studies showing that antibiotics can reduce the mean uveitis score in EAU (Nakamura et al., 2016; Wen et al., 2018).

5.2.3. Associations between the gut microbiome and human uveitis

So far, only a few studies have investigated a link between the GM and uveitis in humans. This is probably partly due to the heterogeneity of the disease and the only recent availability of high-throughput DNA sequencing technologies to characterize the entire GM. A small study using 16S rRNA amplification showed dysbiosis in the gut bacterial communities of a uveitis cohort with an enrichment of *Prevotella* and *Streptococcus* operational taxonomic units (Kalyana Chakravarthy et al., 2018). However, another study did not reveal a difference in gut microbiota composition between patients with acute anterior uveitis compared to the non-uveitic cohort but did show that the fecal metabolic phenotype in these patients was significantly different (Huang et al., 2018). Furthermore, altered GM signatures have been found in patients with ankylosing spondylitis and Behçet's syndrome, both of which are associated with anterior uveitis (Consolandi et al., 2015; Costello et al., 2015; Shimizu et al., 2016).

6. Conclusions and further directions

The human GM is a complex ecosystem composed of microorganisms and their genetic material, performing a mutual relationship with the host's immune system to maintain the intestinal homeostasis and to inhibit inflammatory processes. However, if the balanced GM composition changes due to age, dietary change, alcohol consumption or drug intake, the resulting dysbiosis may be involved in the development and/or progression of several diseases. Although it is unknown how microbes and their metabolites exactly trigger the pathogenesis, associations between compositional and functional features of the GM and eye disease have been shown in our studies. Such studies are pointing out correlations between dysbiosis and specific diseases rather than exploring potential causality. However, these associations open various opportunities for further studies to develop therapeutic approaches through targeted manipulation of the microbiome (Fig. 3). For instance, the class *Negativicutes* was proposed as a potential biomarker for neovascular AMD correlating with genetic risk factors in the complement system (Zinkernagel et al., 2017; Zysset-Burri et al., 2020). Thus, signaling between the complement system and the GM through toll-like receptors expressed on gut epithelial cells and recognizing microbial-derived molecules such as SCFAs may represent potential therapeutic targets for AMD. For secondary prevention of systemic

cardiovascular events following RAO, the GM and its metabolites have also emerged as potential candidates for targeted manipulation of the microbiome. In particular, the pro-atherogenic metabolite TMAO and its GM-derived producers, especially bacteria of the genus *Akkermansia* may be targets due to their involvement in the cholesterol metabolism pathway important for the development of atherosclerosis (Zysset-Burri et al., 2019). Furthermore, unpublished data from our lab showed that the functional capacities of the GM are potential target for new therapeutic approaches of eye diseases such as in the case of CSCR. In particular, alterations in pathways associated with fatty acid metabolism and energy production have been found in the GM of CSCR patients. Due to the self-limited nature and good visual prognosis in most cases following CSCR, therapeutic approaches to prevent the chronic form have to be the focus of future research for this retinal disease.

In conclusion, the existence of the GM is now well-established knowledge and associations between gut dysbiosis and eye diseases have been shown. It has been assumed that microbial derived-metabolites such as TMAO and SCFAs are involved in pathogenesis by acting as mediators between the GM and the intestinal immune system (Fig. 3). Gut dysbiosis can dysregulate immune responses by inducing mucosal barrier dysfunction leading to the passage of pathogenic symbionts and their metabolites from the gastrointestinal lumen into the blood-stream. This bacterial translocation may represent a common pathogenetic mechanism involving the GM for the discussed retinal diseases by inducing systemic as well as local inflammation. In the case of uveitis, gut microbes and their metabolites may lead to activation of autoreactive T cells antigen presentation on intestinal host cells triggering pathological inflammation. However, the exact mechanisms behind the proposed associations between taxonomic as wells as functional features of the GM and the discussed diseases need further investigation.

The gut is not the only body site where microbiomes have been defined. In addition to the gastrointestinal tract, the Human Microbiome Project (Turnbaugh et al., 2007) characterized microbiomes of the skin, oral cavity, nasal passages and urogenital tract in healthy humans. Regarding the eyes, the ocular surface microbiome and its role in eye diseases have recently become a field of research. We performed a taxonomic and functional characterization of the ocular surface microbiome in healthy humans and showed associations with the tear proteome with a role in human immune defense (Zysset-Burri et al., 2021).

Author statement

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Data availability

Data will be made available on request.

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References

Abreu, M.T., Fukata, M., Arditi, M., 2005. TLR signaling in the gut in health and disease. J. Immunol. 174, 4453–4460.
Aceves-Avila, F., Medina, F., Moreno, J., Fraga, A., 1998. Descriptions of Reiter's disease in Mexican medical texts since 1578. J. Rheumatol. 25, 2033–2034.
Akhtar-Schafer, I., Wang, L., Krohne, T.U., Xu, H., Langmann, T., 2018. Modulation of three key innate immune pathways for the most common retinal degenerative diseases. EMBO Mol. Med. 10.
Al-Khonizy, W., Reveille, J.D., 1998. 2 the immunogenetics of the seronegative spondyloarthropathies. Bailliere's Clin. Rheumatol. 12, 567–588.
Andriessen, E.M., Wilson, A.M., Mawambo, G., Dejda, A., Miloudi, K., Sennlaub, F., Sapieha, P., 2016. Gut microbiota influences pathological angiogenesis in obesity-driven choroidal neovascularization. EMBO Mol. Med. 8, 1366–1379.
Arumugam, M., Raes, J., Pelletier, E., Le Paslier, D., Yamada, T., Mende, D.R., Fernandes, G.R., Tap, J., Bruls, T., Batto, J.M., Bertalan, M., Borruel, N., Casellas, F., Fernandez, L., Gautier, L., Hansen, T., Hattori, M., Hayashi, T., Kleerebezem, M., Kurokawa, K., Leclerc, M., Levenez, F., Manichanh, C., Nielsen, H.B., Nielsen, T., Pons, N., Poulain, J., Qin, J., Sicheritz-Ponten, T., Tims, S., Torrents, D., Ugarte, E., Zoetendal, E.G., Wang, J., Guarner, F., Pedersen, O., de Vos, W.M., Brunak, S., Dore, J., Meta, H.I.T.C., Antolin, M., Artiguenave, F., Blottiere, H.M., Almeida, M., Brechot, C., Cara, C., Chervaux, C., Cultrone, A., Delorme, C., Denariaz, G., Dervyn, R., Foerstner, K.U., Friss, C., van de Guchte, M., Guedon, E., Haimet, F., Huber, W., van Hylckama-Vlieg, J., Jamet, A., Juste, C., Kaci, G., Knol, J., Lakhdari, O., Layec, S., Le Roux, K., Maguin, E., Merieux, A., Melo Minardi, R., M'Rini, C., Muller, J., Oozeer, R., Parkhill, J., Renault, P., Rescigno, M., Sanchez, N., Sunagawa, S., Torrejon, A., Turner, K., Vandemeulebrouck, G., Varela, E., Winogradsky, Y., Zeller, G., Weissenbach, J., Ehrlich, S.D., Bork, P., 2011. Enterotypes of the human gut microbiome. Nature 473, 174–180.
Barrea, L., Annunziata, G., Muscogiuri, G., Di Somma, C., Laudisio, D., Maisto, M., de Alteriis, G., Tenore, G.C., Colao, A., Savastano, S., 2018. Trimethylamine-N-oxide (TMAO) as novel potential biomarker of early predictors of metabolic syndrome. Nutrients 10.
Berer, K., Mues, M., Koutrolos, M., Rasbi, Z.A., Boziki, M., Johner, C., Wekerle, H., Krishnamoorthy, G., 2011. Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination. Nature 479, 538–541.
Bohn, T., Desmarchelier, C., Dragsted, L.O., Nielsen, C.S., Stahl, W., Ruhl, R., Keijer, J., Borel, P., 2017. Host-related factors explaining interindividual variability of carotenoid bioavailability and tissue concentrations in humans. Mol. Nutr. Food Res. 61.
Braniste, V., Al-Asmakh, M., Kowal, C., Anuar, F., Abbaspour, A., Toth, M., Korecka, A., Bakocevic, N., Ng, L.G., Kundu, P., Gulyas, B., Halldin, C., Hultenby, K., Nilsson, H., Hebert, H., Volpe, B.T., Diamond, B., Pettersson, S., 2014. The gut microbiota influences blood-brain barrier permeability in mice. Sci. Transl. Med. 6, 263ra158.
Bui, B.V., Hu, R.G., Acosta, M.L., Donaldson, P., Vingrys, A.J., Kalloniatis, M., 2009. Glutamate metabolic pathways and retinal function. J. Neurochem. 111, 589–599.
Callen, J.P., Mahl, C.F., 1992. Oculocutaneous manifestations observed in multisystem disorders. Dermatol. Clin. 10, 709–716.
Campbell, M., Humphries, P., The Blood-Retina Barrier: Tight Junctions and Barrier Modulation.
Casas, R., Castro-Barquero, S., Estruch, R., Sacanella, E., 2018. Nutrition and cardiovascular health. Int. J. Mol. Sci. 19.
Cashman, S.M., Desai, A., Ramo, K., Kumar-Singh, R., 2011. Expression of complement component 3 (C3) from an adenovirus leads to pathology in the murine retina. Investig. Ophthalmol. Vis. Sci. 52, 3436–3445.
Caspi, R.R., 2011. Understanding autoimmune uveitis through animal models. The Friedenwald Lecture. Investig. Ophthalmol. Vis. Sci. 52, 1872–1879.
Chen, M., Xu, H., 2015. Parainflammation, chronic inflammation, and age-related macular degeneration. J. Leukoc. Biol. 98, 713–725.
Chistiakov, D.A., Melnichenko, A.A., Myasoedova, V.A., Grechko, A.V., Orekhov, A.N., 2017. Mechanisms of foam cell formation in atherosclerosis. J. Mol. Med. (Berl.) 95, 1153–1165.
Cho, Y.A., Kim, J., 2015. Effect of probiotics on blood lipid concentrations: a meta-analysis of randomized controlled trials. Medicine 94, e1714.
Coca-Prados, M., 2014. The blood-aqueous barrier in health and disease. J. Glaucoma 23, S36–S38.
Consolandi, C., Turroni, S., Emmi, G., Severgnini, M., Fiori, J., Peano, C., Biagi, E., Grassi, A., Rampelli, S., Silvestri, E., Centanni, M., Cianchi, F., Gotti, R., Emmi, L., Brigidi, P., Bizzaro, N., De Bellis, G., Prisco, D., Candela, M., D'Elios, M.M., 2015. Behcet's syndrome patients exhibit specific microbiome signature. Autoimmun. Rev. 14, 269–276.
Costello, M.E., Ciccia, F., Willner, D., Warrington, N., Robinson, P.C., Gardiner, B., Marshall, M., Kenna, T.J., Triolo, G., Brown, M.A., 2015. Brief report: intestinal dysbiosis in ankylosing spondylitis. Arthritis Rheumatol. 67, 686–691.
Cunha-Vaz, J., 1979. The blood-ocular barriers. Surv. Ophthalmol. 23, 279–296.
Dao, D., Xie, B., Nadeem, U., Xiao, J., Movahedan, A., D'Souza, M., Leone, V., Hariprasad, S.M., Chang, E.B., Sulakhe, D., Skondra, D., 2021. High-fat diet alters the retinal transcriptome in the absence of gut microbiota. Cells 10, 2119.
de Jong, S., Gagliardi, G., Garanto, A., de Breuk, A., Lechanteur, Y.T.E., Katti, S., van den Heuvel, L.P., Volokhina, E.B., den Hollander, A.I., 2021. Implications of genetic variation in the complement system in age-related macular degeneration. Prog. Retin. Eye Res. 84, 100952.

De Smet, M.D., Bitar, G., Mainigi, S., Nussenblatt, R.B., 2001. Human S-antigen determinant recognition in uveitis. Investig. Ophthalmol. Vis. Sci. 42, 3233–3238.
de Smet, M.D., Taylor, S.R., Bodaghi, B., Miserocchi, E., Murray, P.I., Pleyer, U., Zierhut, M., Barisani-Asenbauer, T., LeHoang, P., Lightman, S., 2011. Understanding uveitis: the impact of research on visual outcomes. Prog. Retin. Eye Res. 30, 452–470.
Deng, Y., Ge, X., Li, Y., Zou, B., Wen, X., Chen, W., Lu, L., Zhang, M., Zhang, X., Li, C., Zhao, C., Lin, X., Zhang, X., Huang, X., Li, X., Jin, M., Peng, G.H., Wang, D., Wang, X., Lai, W., Liang, J., Li, J.J., Liang, Q., Yang, L., Zhang, Q., Li, Y., Lu, P., Hu, X., Li, X., Deng, X., Liu, Y., Zou, Y., Guo, S., Chen, T., Qin, Y., Yang, F., Miao, L., Chen, W., Chan, C.C., Lin, H., Liu, Y., Lee, R.W.J., Wei, L., 2021a. Identification of an intraocular microbiota. Cell Discov 7, 13.
Deng, Y., Qiao, L., Du, M., Qu, C., Wan, L., Li, J., Huang, L., 2021b. Age-related macular degeneration: epidemiology, genetics, pathophysiology, diagnosis, and targeted therapy. Genes Dis 9, 62–79.
Ferris, F.L., Davis, M.D., Clemons, T.E., Lee, L.-Y., Chew, E.Y., Lindblad, A.S., Milton, R. C., Bressler, S.B., Klein, R., Age-Related Eye Disease Study Research, G, 2005. A simplified severity scale for age-related macular degeneration: AREDS Report No. 18. Arch. Ophthalmol. 123, 1570–1574.
Fleckenstein, M., Keenan, T.D.L., Guymer, R.H., Chakravarthy, U., Schmitz-Valckenberg, S., Klaver, C.C., Wong, W.T., Chew, E.Y., 2021. Age-related macular degeneration. Nat. Rev. Dis. Prim. 7, 31.
Forrester, J.V., Kuffova, L., Dick, A.D., 2018. Autoimmunity, autoinflammation, and infection in uveitis. Am. J. Ophthalmol. 189, 77–85.
Forrester, J.V., Xu, H., 2012. Good news-bad news: the Yin and Yang of immune privilege in the eye. Front. Immunol. 3, 338.
Franceschi, C., Garagnani, P., Parini, P., Giuliani, C., Santoro, A., 2018. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat. Rev. Endocrinol. 14, 576–590.
Gerard, H.C., Schumacher, H.R., El-Gabalawy, H., Goldbach-Mansky, R., Hudson, A.P., 2000. Chlamydia pneumoniae present in the human synovium are viable and metabolically active. Microb. Pathog. 29, 17–24.
Gold, B., Merriam, J.E., Zernant, J., Hancox, L.S., Taiber, A.J., Gehrs, K., Cramer, K., Neel, J., Bergeron, J., Barile, G.R., Smith, R.T., , Group, A.M.D.G.C.S, Hageman, G.S., Dean, M., Allikmets, R., 2006. Variation in factor B (BF) and complement component 2 (C2) genes is associated with age-related macular degeneration. Nat. Genet. 38, 458–462.
Gorusupudi, A., Nelson, K., Bernstein, P.S., 2017. The age-related eye disease 2 study: micronutrients in the treatment of macular degeneration. Adv. Nutr. 8, 40–53.
Guo, H., Callaway, J.B., Ting, J.P., 2015. Inflammasomes: mechanism of action, role in disease, and therapeutics. Nature med. 21, 677–687.
Hageman, G.S., Luthert, P.J., Victor Chong, N.H., Johnson, L.V., Anderson, D.H., Mullins, R.F., 2001. An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. Prog. Retin. Eye Res. 20, 705–732.
Haimovici, R., Koh, S., Gagnon, D.R., Lehrfeld, T., Wellik, S., Central Serous Chorioretinopathy Case-Control Study, G., 2004. Risk factors for central serous chorioretinopathy: a case-control study. Ophthalmology 111, 244–249.
Haines, J.L., Hauser, M.A., Schmidt, S., Scott, W.K., Olson, L.M., Gallins, P., Spencer, K. L., Kwan, S.Y., Noureddine, M., Gilbert, J.R., Schnetz-Boutaud, N., Agarwal, A., Postel, E.A., Pericak-Vance, M.A., 2005. Complement factor H variant increases the risk of age-related macular degeneration. Science 308, 419–421.
Hajishengallis, G., Lambris, J.D., 2016. More than complementing Tolls: complement-Toll-like receptor synergy and crosstalk in innate immunity and inflammation. Immunol. Rev. 274, 233–244.
Hajjar, A.M., Ernst, R.K., Tsai, J.H., Wilson, C.B., Miller, S.I., 2002. Human Toll-like receptor 4 recognizes host-specific LPS modifications. Nat. Immunol. 3, 354–359.
Harauma, A., Yasuda, H., Hatanaka, E., Nakamura, M.T., Salem Jr., N., Moriguchi, T., 2017. The essentiality of arachidonic acid in addition to docosahexaenoic acid for brain growth and function. Prostaglandins Leukot. Essent. Fatty Acids 116, 9–18.
Hayreh, S.S., Podhajsky, P.A., Zimmerman, M.B., 2009. Retinal artery occlusion: associated systemic and ophthalmic abnormalities. Ophthalmology 116, 1928–1936.
Heintz-Buschart, A., Wilmes, P., 2018. Human gut microbiome: function matters. Trends Microbiol. 26, 563–574.
Herzog, E.L., Wafler, M., Keller, I., Wolf, S., Zinkernagel, M.S., Zysset-Burri, D.C., 2021. The importance of age in compositional and functional profiling of the human intestinal microbiome. PLoS One 16, e0258505.
Hirsch, J.A., Schubert, C., Gurevich, V.V., Sigler, P.B., 1999. A model for arrestin's regulation: the 2.8 Å crystal structure of visual arrestin. Cell 97, 257–269.
Hoh Kam, J., Lenassi, E., Malik, T.H., Pickering, M.C., Jeffery, G., 2013. Complement component C3 plays a critical role in protecting the aging retina in a murine model of age-related macular degeneration. Am. J. Pathol. 183, 480–492.
Horai, R., Silver, P.B., Chen, J., Agarwal, R.K., Chong, W.P., Jittayasothorn, Y., Mattapallil, M.J., Nguyen, S., Natarajan, K., Villasmil, R., Wang, P., Karabekian, Z., Lytton, S.D., Chan, C.C., Caspi, R.R., 2013. Breakdown of immune privilege and spontaneous autoimmunity in mice expressing a transgenic T cell receptor specific for a retinal autoantigen. J. Autoimmun. 44, 21–33.
Horai, R., Zárate-Bladés, C.R., Dillenburg-Pilla, P., Chen, J., Kielczewski, J.L., Silver, P. B., Jittayasothorn, Y., Chan, C.-C., Yamane, H., Honda, K., 2015a. Microbiota-dependent activation of an autoreactive T cell receptor provokes autoimmunity in an immunologically privileged site. Immunity 43, 343–353.
Horai, R., Zarate-Blades, C.R., Dillenburg-Pilla, P., Chen, J., Kielczewski, J.L., Silver, P. B., Jittayasothorn, Y., Chan, C.C., Yamane, H., Honda, K., Caspi, R.R., 2015b. Microbiota-dependent activation of an autoreactive T cell receptor provokes autoimmunity in an immunologically privileged site. Immunity 43, 343–353.
Howe, S.E., Lickteig, D.J., Plunkett, K.N., Ryerse, J.S., Konjufca, V., 2014. The uptake of soluble and particulate antigens by epithelial cells in the mouse small intestine. PLoS One 9, e86656.
Huang, X., Ye, Z., Cao, Q., Su, G., Wang, Q., Deng, J., Zhou, C., Kijlstra, A., Yang, P., 2018. Gut microbiota composition and fecal metabolic phenotype in patients with acute anterior uveitis. Investig. Ophthalmol. Vis. Sci. 59, 1523–1531.
Jabs, D.A., Nussenblatt, R.B., Rosenbaum, J.T., Standardization of Uveitis Nomenclature Working, G, 2005. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am. J. Ophthalmol. 140, 509–516.
Jayasudha, R., Kalyana Chakravarthy, S., Sai Prashanthi, G., Sharma, S., Tyagi, M., Shivaji, S., 2019. Implicating dysbiosis of the gut fungal microbiome in uveitis, an inflammatory disease of the eye. Investig. Ophthalmol. Vis. Sci. 60, 1384–1393.
Jiang, H., Shi, X., Fan, Y., Wang, D., Li, B., Zhou, J., Pei, C., Ma, L., 2021. Dietary omega-3 polyunsaturated fatty acids and fish intake and risk of age-related macular degeneration. Clin. Nutr. 40, 5662–5673.
Jie, Z., Xia, H., Zhong, S.L., Feng, Q., Li, S., Liang, S., Zhong, H., Liu, Z., Gao, Y., Zhao, H., Zhang, D., Su, Z., Fang, Z., Lan, Z., Li, J., Xiao, L., Li, J., Li, R., Li, X., Li, F., Ren, H., Huang, Y., Peng, Y., Li, G., Wen, B., Dong, B., Chen, J.Y., Geng, Q.S., Zhang, Z.W., Yang, H., Wang, J., Wang, J., Zhang, X., Madsen, L., Brix, S., Ning, G., Xu, X., Liu, X., Hou, Y., Jia, H., He, K., Kristiansen, K., 2017. The gut microbiome in atherosclerotic cardiovascular disease. Nat. Commun. 8, 845.
Joyal, J.-S., 2018. Retinal lipid and glucose metabolism dictates angiogenesis. Investig. Ophthalmol. Vis. Sci. 59, 5995-5995.
Kaddurah-Daouk, R., Baillie, R.A., Zhu, H., Zeng, Z.B., Wiest, M.M., Nguyen, U.T., Wojnoonski, K., Watkins, S.M., Trupp, M., Krauss, R.M., 2011. Enteric microbiome metabolites correlate with response to simvastatin treatment. PLoS One 6, e25482.
Kalyana Chakravarthy, S., Jayasudha, R., Sai Prashanthi, G., Ali, M.H., Sharma, S., Tyagi, M., Shivaji, S., 2018. Dysbiosis in the gut bacterial microbiome of patients with uveitis, an inflammatory disease of the eye. Indian J. Microbiol. 58, 457–469.
Karlsson, F.H., Fak, F., Nookaew, I., Tremaroli, V., Fagerberg, B., Petranovic, D., Backhed, F., Nielsen, J., 2012. Symptomatic atherosclerosis is associated with an altered gut metagenome. Nat. Commun. 3, 1245.
Kato, N., Fujii, Y., Agata, N., Kido, N., Ohta, M., Naito, S., Yokochi, T., 1993. Experimental murine model for autoimmune myocarditis using Klebsiella pneumoniae O3 lipopolysaccharide as a potent immunological adjuvant. Autoimmunity 14, 231–236.
Kaye, R., Chandra, S., Sheth, J., Boon, C.J.F., Sivaprasad, S., Lotery, A., 2020. Central serous chorioretinopathy: an update on risk factors, pathophysiology and imaging modalities. Prog. Retin. Eye Res. 79, 100865.
Klein, R.J., Zeiss, C., Chew, E.Y., Tsai, J.Y., Sackler, R.S., Haynes, C., Henning, A.K., SanGiovanni, J.P., Mane, S.M., Mayne, S.T., Bracken, M.B., Ferris, F.L., Ott, J., Barnstable, C., Hoh, J., 2005. Complement factor H polymorphism in age-related macular degeneration. Science 308, 385–389.
Koeth, R.A., Levison, B.S., Culley, M.K., Buffa, J.A., Wang, Z., Gregory, J.C., Org, E., Wu, Y., Li, L., Smith, J.D., Tang, W.H.W., DiDonato, J.A., Lusis, A.J., Hazen, S.L., 2014. gamma-Butyrobetaine is a proatherogenic intermediate in gut microbial metabolism of L-carnitine to TMAO. Cell Metabol. 20, 799–812.
Koeth, R.A., Wang, Z., Levison, B.S., Buffa, J.A., Org, E., Sheehy, B.T., Britt, E.B., Fu, X., Wu, Y., Li, L., Smith, J.D., DiDonato, J.A., Chen, J., Li, H., Wu, G.D., Lewis, J.D., Warrier, M., Brown, J.M., Krauss, R.M., Tang, W.H., Bushman, F.D., Lusis, A.J., Hazen, S.L., 2013. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nature med. 19, 576–585.
Koren, O., Spor, A., Felin, J., Fak, F., Stombaugh, J., Tremaroli, V., Behre, C.J., Knight, R., Fagerberg, B., Ley, R.E., Backhed, F., 2011. Human oral, gut, and plaque microbiota in patients with atherosclerosis. Proc. Natl. Acad. Sci. U. S. A 108 (Suppl. 1), 4592–4598.
Kumbhare, S.V., Patangia, D.V., Patil, R.H., Shouche, Y.S., Patil, N.P., 2019. Factors influencing the gut microbiome in children: from infancy to childhood. J. Biosci. 44.
Kwon, G.P., Schroeder, J.L., Amar, M.J., Remaley, A.T., Balaban, R.S., 2008. Contribution of macromolecular structure to the retention of low-density lipoprotein at arterial branch points. Circulation 117, 2919–2927.
Lima, V.C., Rosen, R.B., Farah, M., 2016. Macular pigment in retinal health and disease. Int J Retina Vitreous 2, 19.
Lin, P., 2020. Altering the intestinal microbiota for therapeutic benefit in uveitis. Annals of Eye Science 5, 26-26.
Longhi, M.S., Moss, A., Jiang, Z.G., Robson, S.C., 2017. Purinergic signaling during intestinal inflammation. J. Mol. Med. (Berl.) 95, 915–925.
Ma, H.H., Liutkevičienė, R., 2021. Age-related macular degeneration: what do we know so far? Acta Med. Litu. 28, 36–47.
Maller, J., George, S., Purcell, S., Fagerness, J., Altshuler, D., Daly, M.J., Seddon, J.M., 2006. Common variation in three genes, including a noncoding variant in CFH, strongly influences risk of age-related macular degeneration. Nat. Genet. 38, 1055–1059.
Maller, J.B., Fagerness, J.A., Reynolds, R.C., Neale, B.M., Daly, M.J., Seddon, J.M., 2007. Variation in complement factor 3 is associated with risk of age-related macular degeneration. Nat. Genet. 39, 1200–1201.
Mariat, D., Firmesse, O., Levenez, F., Guimaraes, V., Sokol, H., Dore, J., Corthier, G., Furet, J.P., 2009. The Firmicutes/Bacteroidetes ratio of the human microbiota changes with age. BMC Microbiol. 9, 123.
Mathur, R., Barlow, G.M., 2015. Obesity and the microbiome. Expet Rev. Gastroenterol. Hepatol. 9, 1087–1099.
May, A., Su, F., Dinh, B., Ehlen, R., Tran, C., Adivikolanu, H., Shaw, P.X., 2021. Ongoing controversies and recent insights of the ARMS2-HTRA1 locus in age-related macular degeneration. Exp. Eye Res. 210, 108605.
Maynard, C., Weinkove, D., 2020. Bacteria increase host micronutrient availability: mechanisms revealed by studies in C. elegans. Genes & nutrition 15, 4.

Mezouar, S., Chantran, Y., Michel, J., Fabre, A., Dubus, J.-C., Leone, M., Sereme, Y., Mège, J.-L., Ranque, S., Desnues, B., Chanez, P., Vitte, J., 2018. Microbiome and the immune system: from a healthy steady-state to allergy associated disruption. Human Microbiome Journal 10, 11–20.

Miserocchi, E., Fogliato, G., Modorati, G., Bandello, F., 2013. Review on the worldwide epidemiology of uveitis. Eur. J. Ophthalmol. 23, 705–717.

Mohamad, N.A., Ramachandran, V., Mohd Isa, H., Chan, Y.M., Ngah, N.F., Ching, S.M., Hoo, F.K., Wan Sulaiman, W.A., Inche Mat, L.N., Mohamed, M.H., 2019. Association of HTRA1 and ARMS2 gene polymorphisms with response to intravitreal ranibizumab among neovascular age-related macular degenerative subjects. Hum. Genom. 13, 13.

Morohoshi, K., Goodwin, A.M., Ohbayashi, M., Ono, S.J., 2009. Autoimmunity in retinal degeneration: autoimmune retinopathy and age-related macular degeneration. J. Autoimmun. 33, 247–254.

Mrowicka, M., Mrowicki, J., Kucharska, E., Majsterek, I., 2022. Lutein and zeaxanthin and their roles in age-related macular degeneration-neurodegenerative disease. Nutrients 14.

Mu, Q., Kirby, J., Reilly, C.M., Luo, X.M., 2017. Leaky gut as a danger signal for autoimmune diseases. Front. Immunol. 8, 598.

Nakamura, Y.K., Metea, C., Karstens, L., Asquith, M., Gruner, H., Moscibrocki, C., Lee, I., Brislawn, C.J., Jansson, J.K., Rosenbaum, J.T., Lin, P., 2016. Gut microbial alterations associated with protection from autoimmune uveitis. Investig. Ophthalmol. Vis. Sci. 57, 3747–3758.

Paeng, N., Morikawa, A., Kato, Y., Sugiyama, T., Koide, N., Yoshida, T., Yokochi, T., 1999. Experimental murine model for autoimmune enterocolitis using Klebsiella pneumoniae O3 lipopolysaccharide as a potent immunological adjuvant. Microbiol. Immunol. 43, 45–52.

Papa, A., Danese, S., Urgesi, R., Grillo, A., Guglielmo, S., Roberto, I., Bonizzi, M., Guidi, L., De Vitis, I., Santoliquido, A., 2006. Early atherosclerosis in patients with inflammatory bowel disease. Eur. Rev. Med. Pharmacol. Sci. 10, 7.

Park, S.J., Choi, N.K., Seo, K.H., Park, K.H., Woo, S.J., 2014. Nationwide incidence of clinically diagnosed central retinal artery occlusion in Korea, 2008 to 2011. Ophthalmology 121, 1933–1938.

Pawlowska, E., Szczepanska, J., Koskela, A., Kaarniranta, K., Blasiak, J., 2019. Dietary polyphenols in age-related macular degeneration: protection against oxidative stress and beyond. Oxid. Med. Cell. Longev. 2019, 9682318.

Peters, T., Weiss, J.M., Sindrilaru, A., Wang, H., Oreshkova, T., Wlaschek, M., Maity, P., Reimann, J., Scharffetter-Kochanek, K., 2009. Reactive oxygen intermediate-induced pathomechanisms contribute to immunosenescence, chronic inflammation and autoimmunity. Mech. Ageing Dev. 130, 564–587.

Ren, J., Ren, A., Deng, X., Huang, Z., Jiang, Z., Li, Z., Gong, Y., 2022. Long-chain polyunsaturated fatty acids and their metabolites regulate inflammation in age-related macular degeneration. J. Inflamm. Res. 15, 865–880.

Rizzatti, G., Lopetuso, L.R., Gibiino, G., Binda, C., Gasbarrini, A., 2017. Proteobacteria: a common factor in human diseases. BioMed Res. Int. 2017, 9351507.

Roh, M., Shin, H.J., Laíns, I., Providência, J., Caseiro-Alves, M., Barreto, P., Vavvas, D.G., Miller, J.B., Kim, I.K., Gaziano, J.M., Liang, L., Silva, R., Miller, J.W., Husain, D., 2020. Higher intake of polyunsaturated fatty acid and monounsaturated fatty acid is inversely associated with AMD. Investig. Ophthalmol. Vis. Sci. 61, 20.

Rojas, M., Restrepo-Jimenez, P., Monsalve, D.M., Pacheco, Y., Acosta-Ampudia, Y., Ramirez-Santana, C., Leung, P.S.C., Ansari, A.A., Gershwin, M.E., Anaya, J.M., 2018. Molecular mimicry and autoimmunity. J. Autoimmun. 95, 100–123.

Romano, A.D., Serviddio, G., De Matthaeis, A., Bellanti, F., Vendemiale, G., 2010. Oxidative stress and aging. J. Nephrol. 23, S29–S36.

Romano, K.A., Vivas, E.I., Amador-Noguez, D., Rey, F.E., 2015. Intestinal microbiota composition modulates choline bioavailability from diet and accumulation of the proatherogenic metabolite trimethylamine-N-oxide. mBio 6, e02481.

Romero-Vazquez, S., Llorens, V., Soler-Boronat, A., Figueras-Roca, M., Adan, A., Molins, B., 2021. Interlink between inflammation and oxidative stress in age-related macular degeneration: role of complement factor H. Biomedicines 9.

Rowan, S., Jiang, S., Korem, T., Szymanski, J., Chang, M.-L., Szelog, J., Cassalman, C., Dasuri, K., McGuire, C., Nagai, R., 2017. Involvement of a gut–retina axis in protection against dietary glycemia-induced age-related macular degeneration. Proc. Natl. Acad. Sci. USA 114, E4472–E4481.

Rowan, S., Taylor, A., 2018. Gut microbiota modify risk for dietary glycemia-induced age-related macular degeneration. Gut Microb. 9, 452–457.

Sacco, R.L., Kasner, S.E., Broderick, J.P., Caplan, L.R., Connors, J.J., Culebras, A., Elkind, M.S., George, M.G., Hamdan, A.D., Higashida, R.T., Hoh, B.L., Janis, L.S., Kase, C.S., Kleindorfer, D.O., Lee, J.M., Moseley, M.E., Peterson, E.D., Turan, T.N., Valderrama, A.L., Vinters, H.V., American Heart Association Stroke Council, 2013. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. C. o.C.S., Anesthesia, Council on Cardiovascular, R., Intervention, Council on, C., Stroke, N., Council on, E., Prevention, Council on Peripheral Vascular, D., Council on Nutrition, P.A., Metabolism Stroke 44, 2064–2089.

Salvioli, S., Capri, M., Valensin, S., Tieri, P., Monti, D., Ottaviani, E., Franceschi, C., 2006. Inflamm-aging, cytokines and aging: state of the art, new hypotheses on the role of mitochondria and new perspectives from systems biology. Curr. Pharmaceut. Des. 12, 3161–3171.

Schellevis, R.L., van Dijk, E.H.C., Breukink, M.B., Altay, L., Bakker, B., Koeleman, B.P.C., Kiemeney, L.A., Swinkels, D.W., Keunen, J.E.E., Fauser, S., Hoyng, C.B., den Hollander, A.I., Boon, C.J.F., de Jong, E.K., 2018. Role of the complement system in chronic central serous chorioretinopathy: a genome-wide association study. JAMA Ophthalmol 136, 1128–1136.

Seddon, J.M., George, S., Rosner, B., 2006. Cigarette smoking, fish consumption, omega-3 fatty acid intake, and associations with age-related macular degeneration: the US Twin Study of Age-Related Macular Degeneration. Arch. Ophthalmol. 124, 995–1001.

Semeraro, F., Morescalchi, F., Russo, A., Gambicorti, E., Pilotto, A., Parmeggiani, F., Bartollino, S., Costagliola, C., 2019. Central serous chorioretinopathy: pathogenesis and management. Clin. Ophthalmol. 13, 2341–2352.

Shimizu, J., Kubota, T., Takada, E., Takai, K., Fujiwara, N., Arimitsu, N., Ueda, Y., Wakisaka, S., Suzuki, T., Suzuki, N., 2016. Bifidobacteria abundance-featured gut microbiota compositional change in patients with behcet's disease. PLoS One 11, e0153746.

Shin, N.R., Whon, T.W., Bae, J.W., 2015. Proteobacteria: microbial signature of dysbiosis in gut microbiota. Trends Biotechnol. 33, 496–503.

Simell, O., Takki, K., 1973. Raised plasma-ornithine and gyrate atrophy of the choroid and retina. Lancet 1, 1031–1033.

Singh, P.K., Parsek, M.R., Greenberg, E.P., Welsh, M.J., 2002. A component of innate immunity prevents bacterial biofilm development. Nature 417, 552–555.

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.

Stojanov, S., Berlec, A., Strukelj, B., 2020. The influence of probiotics on the firmicutes/bacteroidetes ratio in the treatment of obesity and inflammatory bowel disease. Microorganisms 8.

Streilein, J.W., 2003. Ocular immune privilege: therapeutic opportunities from an experiment of nature. Nat. Rev. Immunol. 3, 879–889.

Tang, W.H., Hazen, S.L., 2014. The contributory role of gut microbiota in cardiovascular disease. J. Clin. Invest. 124, 4204–4211.

Tenbrock, L., Wolf, J., Boneva, S., Schlecht, A., Agostini, H., Wieghofer, P., Schlunck, G., Lange, C., 2022. Subretinal fibrosis in neovascular age-related macular degeneration: current concepts, therapeutic avenues, and future perspectives. Cell Tissue Res. 387, 361–375.

Tetel, M.J., de Vries, G.J., Melcangi, R.C., Panzica, G., O'Mahony, S.M., 2018. Steroids, stress and the gut microbiome-brain axis. J. Neuroendocrinol. 30.

Thaiss, C.A., Levy, M., Itav, S., Elinav, E., 2016. Integration of innate immune signaling. Trends Immunol. 37, 84–101.

Thee, E.F., Colijn, J.M., Cougnard-Grégoire, A., Meester-Smoor, M.A., Verzijden, T., Hoyng, C.B., Fauser, S., Hense, H.W., Silva, R., Creuzot-Garcher, C., Ueffing, M., Delcourt, C., den Hollander, A.I., Klaver, C.C.W., 2022. The phenotypic course of age-related macular degeneration for ARMS2/HTRA1: the EYE-RISK Consortium. Ophthalmology 129, 752–764.

Thursby, E., Juge, N., 2017. Introduction to the human gut microbiota. Biochem. J. 474, 1823–1836.

Tipton, L., Darcy, J.L., Hynson, N.A., 2019. A developing symbiosis: enabling cross-talk between ecologists and microbiome scientists. Front. Microbiol. 10, 292.

Tlaskalova-Hogenova, H., Stepankova, R., Kozakova, H., Hudcovic, T., Vannucci, L., Tuckova, L., Rossmann, P., Hrncir, T., Kverka, M., Zakostelska, Z., Klimesova, K., Pribylova, J., Bartova, J., Sanchez, D., Fundova, P., Borovska, D., Srutkova, D., Zidek, Z., Schwarzer, M., Drastich, P., Funda, D.P., 2011. The role of gut microbiota (commensal bacteria) and the mucosal barrier in the pathogenesis of inflammatory and autoimmune diseases and cancer: contribution of germ-free and gnotobiotic animal models of human diseases. Cell. Mol. Immunol. 8, 110–120.

Toscano, M., De Grandi, R., Grossi, E., Drago, L., 2017. Role of the human breast milk-associated microbiota on the newborns' immune system: a mini review. Front. Microbiol. 8, 2100.

Turnbaugh, P.J., Ley, R.E., Hamady, M., Fraser-Liggett, C.M., Knight, R., Gordon, J.I., 2007. The human microbiome project. Nature 449, 804–810.

Tzoumas, N., Hallam, D., Harris, C.L., Lako, M., Kavanagh, D., Steel, D.H.W., 2021. Revisiting the role of factor H in age-related macular degeneration: insights from complement-mediated renal disease and rare genetic variants. Surv. Ophthalmol. 66, 378–401.

Graefe, A.v., 1859. Ueber Embolie der Arteria centralis retinae als Ursache plötzlicher Erblindung. Arch. Ophthalmol. 5, 136–157.

Vavricka, S.R., Brun, L., Ballabeni, P., Pittet, V., Prinz Vavricka, B.M., Zeitz, J., Rogler, G., Schoepfer, A.M., 2011. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am. J. Gastroenterol. 106, 110–119.

Vourakis, M., Mayer, G., Rousseau, G., 2021. The role of gut microbiota on cholesterol metabolism in atherosclerosis. Int. J. Mol. Sci. 22.

Wang, Z., Klipfell, E., Bennett, B.J., Koeth, R., Levison, B.S., Dugar, B., Feldstein, A.E., Britt, E.B., Fu, X., Chung, Y.M., Wu, Y., Schauer, P., Smith, J.D., Allayee, H., Tang, W.H., DiDonato, J.A., Lusis, A.J., Hazen, S.L., 2011. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature 472, 57–63.

Wang, Z., Roberts, A.B., Buffa, J.A., Levison, B.S., Zhu, W., Org, E., Gu, X., Huang, Y., Zamanian-Daryoush, M., Culley, M.K., DiDonato, A.J., Fu, X., Hazen, J.E., Krajcik, D., DiDonato, J.A., Lusis, A.J., Hazen, S.L., 2015. Non-lethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis. Cell 163, 1585–1595.

Wen, X., Hu, X., Miao, L., Ge, X., Deng, Y., Bible, P.W., Wei, L., 2018. Epigenetics, microbiota, and intraocular inflammation: new paradigms of immune regulation in the eye. Prog. Retin. Eye Res. 64, 84–95.

Wildner, G., Diedrichs-Mohring, M., 2003. Autoimmune uveitis induced by molecular mimicry of peptides from rotavirus, bovine casein and retinal S-antigen. Eur. J. Immunol. 33, 2577–2587.

Willermain, F., Rosenbaum, J.T., Bodaghi, B., Rosenzweig, H.L., Childers, S., Behrend, T., Wildner, G., Dick, A.D., 2012. Interplay between innate and adaptive immunity in the development of non-infectious uveitis. Prog. Retin. Eye Res. 31, 182–194.

Wu, I.B., Schwartz, R.A., 2008. Reiter's syndrome: the classic triad and more. J. Am. Acad. Dermatol. 59, 113–121.

Ye, Z., Wu, C., Zhang, N., Du, L., Cao, Q., Huang, X., Tang, J., Wang, Q., Li, F., Zhou, C., Xu, Q., Xiong, X., Kijlstra, A., Qin, N., Yang, P., 2020. Altered gut microbiome composition in patients with Vogt-Koyanagi-Harada disease. Gut Microb. 11, 539–555.

Yokochi, T., Fujii, Y., Nakashima, I., Asai, J., Kiuchi, M., Kojima, K., Kato, N., 1993. A murine model of experimental autoimmune lens-induced uveitis using Klebsiella O3 lipopolysaccharide as a potent immunological adjuvant. Int. J. Exp. Pathol. 74, 573.

Yoo, J.Y., Groer, M., Dutra, S.V.O., Sarkar, A., McSkimming, D.I., 2020. Gut microbiota and immune system interactions. Microorganisms 8.

Yoshino, S., Sasatomi, E., Ohsawa, M., 2000. Bacterial lipopolysaccharide acts as an adjuvant to induce autoimmune arthritisin mice. Immunology 99, 607–614.

Yu, A.L., Birke, K., Burger, J., Welge-Lussen, U., 2012. Biological effects of cigarette smoke in cultured human retinal pigment epithelial cells. PLoS One 7, e48501.

Zhang, Q.Y., Tie, L.J., Wu, S.S., Lv, P.L., Huang, H.W., Wang, W.Q., Wang, H., Ma, L., 2016. Overweight, obesity, and risk of age-related macular degeneration. Investig. Ophthalmol. Vis. Sci. 57, 1276–1283.

Zhuang, L., Chen, H., Zhang, S., Zhuang, J., Li, Q., Feng, Z., 2019a. Intestinal microbiota in early life and its implications on childhood health. Dev. Reprod. Biol. 17, 13–25.

Zhuang, R., Ge, X., Han, L., Yu, P., Gong, X., Meng, Q., Zhang, Y., Fan, H., Zheng, L., Liu, Z., Zhou, X., 2019b. Gut microbe-generated metabolite trimethylamine N-oxide and the risk of diabetes: a systematic review and dose-response meta-analysis. Obes. Rev. 20, 883–894.

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 neovascular age-related macular degeneration. Sci. Rep. 7, 40826.

Zinkernagel, R.M., Doherty, P.C., 1974. Restriction of in vitro T cell-mediated cytotoxicity in lymphocytic choriomeningitis within a syngeneic or semiallogeneic system. Nature 248, 701–702.

Zysset-Burri, D.C., Keller, I., Berger, L.E., Largiadèr, C.R., Wittwer, M., Wolf, S., Zinkernagel, M.S., 2020. Associations of the intestinal microbiome with the complement system in neovascular age-related macular degeneration. NPJ genomic medicine 5, 1–11.

Zysset-Burri, D.C., Keller, I., Berger, L.E., Neyer, P.J., Steuer, C., Wolf, S., Zinkernagel, M. S., 2019. Retinal artery occlusion is associated with compositional and functional shifts in the gut microbiome and altered trimethylamine-N-oxide levels. Sci. Rep. 9, 1–11.

Zysset-Burri, D.C., Schlegel, I., Lincke, J.B., Jaggi, D., Keller, I., Heller, M., Lagache, S.B., Wolf, S., Zinkernagel, M.S., 2021. Understanding the interactions between the ocular surface microbiome and the tear proteome. Investig. Ophthalmol. Vis. Sci. 62, 8.