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Review

Diabetic gut microbiota dysbiosis as an inflammaging and immunosenescence condition that fosters progression of retinopathy and nephropathy☆

Rosa Fernandes[a], Sofia D. Viana[a,b], Sara Nunes[a], Flávio Reis[a,*]

[a] Institute of Pharmacology & Experimental Therapeutics, Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, CNC.IBILI Consortium & CIBB Consortium, University of Coimbra, Coimbra, Portugal
[b] Polytechnic Institute of Coimbra, ESTESC-Coimbra Health School, Pharmacy, Coimbra, Portugal

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ABSTRACT

The increased prevalence of type 2 diabetes mellitus (T2DM) and life expectancy of diabetic patients fosters the worldwide prevalence of retinopathy and nephropathy, two major microvascular complications that have been difficult to treat with contemporary glucose-lowering medications. The gut microbiota (GM) has become a lively field research in the last years; there is a growing recognition that altered intestinal microbiota composition and function can directly impact the phenomenon of ageing and age-related disorders. In fact, human GM, envisaged as a potential source of novel therapeutics, strongly modulates host immunity and metabolism. It is now clear that gut dysbiosis and their products (e.g. p-cresyl sulfate, trimethylamine-N-oxide) dictate a secretory associated senescence phenotype and chronic low-grade inflammation, features shared in the physiological process of ageing ("inflammaging") as well as in T2DM ("metaflammation") and in its microvascular complications. This review provides an in-depth look on the crosstalk between GM, host immunity and metabolism. Further, it characterizes human GM signatures of elderly and T2DM patients. Finally, a comprehensive scrutiny of recent molecular findings (e.g. epigenetic changes) underlying causal relationships between GM dysbiosis and diabetic retinopathy/nephropathy complications is pinpointed, with the ultimate goal to unravel potential pathophysiological mechanisms that may be explored, in a near future, as personalized disease-modifying therapeutic approaches.

1. Introduction

Diabetes is one of the world's fastest growing metabolic diseases. According to the International Diabetes Federation (IDF), it is estimated that diabetes affects > 425 million people, of which one-fourth are people older than 65 years [1], compared to 108 million in 1980 [2]. The total number of people with diabetes is expected to rise over 629 million in 2045 and, at the same time, a further 352 million people with impaired glucose tolerance are at high risk state for development of diabetes [1]. These epidemic numbers are mainly the result of substantial changes associated with the modern lifestyle that followed the industrialization era and the economic growth, including inactivity habits and unhealthy diets, with a rapid and massive transition to processed high-caloric foods. These two major factors cause an imbalance between energy intake and expenditure and the consequent body fat accumulation. Diabetes is associated with both micro and macrovascular complications. Diabetic retinopathy (DR) and diabetic nephropathy (DN) are microvascular complications that can develop within 5 years of the onset of diabetes and are responsible for the high rates of morbidity and mortality in diabetic people, contributing significantly to the burden of social and economic costs [1]. In the majority of developed and developing countries, DR is the leading cause of blindness in the population on working age, affecting around 60 and 90% of patients with type 2 diabetes mellitus (T2DM) and type 1 diabetes mellitus (T1DM), respectively [3,4]. Around 35% of all diabetic patients can develop DN, which is the primary cause of end-stage renal disease (ESRD) in the majority of World regions [5,6].

Important efforts were made during the last decades in order to better understand the key pathogenic features of DR and DN, so that new and more effective therapies and preventative strategies might be

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* Corresponding author at: Institute of Pharmacology & Experimental Therapeutics, Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal.
E-mail address: freis@fmed.uc.pt (F. Reis).

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developed [7–9]. Despite these, the multifactorial intervention strategies aimed to decrease the risk of microangiopathy in diabetic patients remain unsatisfactory, particularly because there are no treatment approaches able to specifically (and efficiently) target the molecular features of DR and DN. In addition, the great percentage (near 80%) of affected patients live in low-to-middle-income countries where some of the most important therapeutic options remain unavailable or strongly limited. Even though hyperglycaemia is undoubtedly a major contributor for the progression of both DR and DN, hypoglycaemic-based therapeutic strategies were unable to prove efficacy in reducing cardiovascular risk [10]. Very exciting findings coming during the last years strongly suggest the involvement of distinct mechanisms, adding complexity to what was already known [11]. Chronic low-grade inflammation, already recognized as a pivotal player in the development of diabetes and its complications, including DR and DN, has recently been associated with other mechanisms related with pathogen-host interactions, including gut microbiota (GM) and the innate immune system [12–14].

In a certain way, the human body may be viewed as supra(or meta)-organism because the human gastrointestinal tract (GIT), particularly the large intestine, is colonized by trillions of microbes (microbioma) which contains many hundredfold more genes (microbiome) than those present in the own genome [15]. GM composition and activity is co-developed with the host and modulated, from birth to ageing, by a dynamic and complex interplay between host genome, factors related with life-style, namely diet, which has been increasingly considered the key modulator of microbiota activity [16]. This microbial community exerts metabolic effects, referred to as co-metabolism, including vitamins synthesis and fermentation of macromolecules, namely carbohydrates, lipids, and proteins [17]. In addition, GM plays chief functions for the host homeostasis, including structural/protective effects against pathobionts, namely protecting intestinal barrier, as well as “education” of host immunity [17]. Normally, the intestinal barrier prevents the translocation of substances and microbes from the lumen to the bloodstream; however, deregulation or damage of the intestinal milieu and related disturbance of the gut flora composition – referred to as “intestinal dysbiosis” – may result in a “leaky gut syndrome”, with increased permeability that might activate the innate immune system and promote a state of low-grade inflammation. During the recent years, GM dysbiosis has been associated not only with intestinal disorders but also with extra-intestinal diseases, including chronic disorders that are highly prevalent in elderly individuals, such as diabetes and its major vascular complications [18–20].

Ageing is accompanied by a myriad of clinical issues; older adults (over age 65 years) have a high prevalence of co-morbid disease [21] and concomitant exposure to multiple medications, including antibiotics. The ageing alimentary tract is subject to a variety of changes: impaired dentition and salivary function, decreased motility with constipation, diverticular disease, and dietary modification [22]. Together, these factors may contribute to changes in the microbiota among older adults, and may ultimately enhance susceptibility to a plethora of chronic diseases [20,22,23]. Several studies have strongly suggested that the microbiota may shape the host immune system, contribute to “inflammaging”, lead to chronic health conditions, and modulate the ageing process [21,22]. The term inflammaging, originally described as an evolutionary perspective on immunosenescence [24], could be seen as the pro-inflammatory environment that exists in older adults, which have high concentrations of acute phase reactants and pro-inflammatory cytokines; this impaired inflammation is accompanied by deregulated immune responses to external factors, particularly to pathogens [25]. Inflammaging may relate to bacterial translocation from gut, which is supported by high blood levels of lipopolysaccharide (LPS) binding protein and high urinary excretion of microbial by-products among older adults [26,27]. It has becoming increasingly evident that GM dysbiosis is strongly associated with a state of chronic low-grade inflammation and to an immunosenescence phenotype, which are key signatures in the physiological process of ageing (inflammaging), as well as in the pathological mechanisms associated with chronic metabolic disorders, particularly to diabetes (“metaflammation”) and its vascular complications.

In the current review, we firstly overview GM composition and physiological functions in healthy conditions, GM remodeling that occurs from in utero until “healthy adult-like maturation”, as well as the role of GM for the inflammaging and immunosenescence phenotypes associated with ageing and to diabetes. In addition, we critically review recent updates on the molecular and epigenetic mechanisms underlying the diabetic GM dysbiosis and the progression of some of its microvascular complications (namely DR and DN). We will focus on the hypothetical involvement of diabetes-associated GM dysbiosis as an inflammaging and immunosenescence condition that boosts retinopathy and nephropathy aggravation.

2. GM composition and physiological functions in health

The term microbiota refers to the living microbial community inhabit within a specific environment and encompasses bacteria, archaea, viruses (mainly phages), eukaryotes (mainly yeasts), even though bacteria outnumber the other domains. There is a symbiotic relationship between the human host and microorganisms that reside there, contributing to the maintenance of host health [15]. GM is a complex ecosystem, not only by the diversity of species that inhabit the human GIT, but also by the way in which they interact with each other and the host [15]. The entire human GIT is inhabited by approximately 100 trillion of bacteria and harbors the most diversified and colonized natural environment with >1000 different bacteria species, overcoming in ten times the number of human body cells [28,29]. This ecosystem consists of many native species that permanently colonize the GIT (autochthonous) and several other transient microorganisms (allochthonous species) [30]. The mainly predominant bacterial phyla are Bacteroidetes (Gram-negative) and Firmicutes (Gram-positive), which together account over 90% of the total microbiota, while Actinobacteria (Gram-positive) and Proteobacteria (Gram-negative), Verrucomicrobia (Gram-negative), Fusobacteria (Gram-negative), and Cyanobacteria (Gram-negative) are present in lower abundance in the adult GIT [28,31].

In the last decade, the knowledge about GM diversity has been increased with the development of several culture-independent molecular techniques and approaches, in particular, with methods using regions of the 16S ribosomal RNA (16S rRNA) gene, a universally present microbial marker gene with highly conserved regions, which was used to establish prokaryotic phylogeny. Sequence analysis of the 16S rRNA gene was the first and one of the most used molecular tool applied to the identification of human microbiota [32]. Recent advances in sequencing technology driven the metagenomics, allowing an important step GM knowledge, which has made a huge contribution to the understanding of human physiology and health. The Human Microbiome Project, by the NIH and the European Project – MetaHIT (Metagenomics of the Human Intestinal Tract), developed with the purpose of characterize dominant microbial communities from different parts of body, has generated useful reference genomes for many of the representative species [29,33,34]. Metagenomic shot-gun sequencing approaches of whole microbial communities, such as those found in the gut, have yielded near-complete gene catalogs that describe the abundance and diversity of genes that contribute to the maintenance and metabolism of the microbiota [33]. In addition to metagenomics, functional approaches such as metatranscriptomics, metaproteomics and metabolomics also contribute for understanding the composition and abundance of gut microbiome and the subsequent impact on health and disease. These approaches have the potential to emphasize the complex crosstalk between humans and their microbial ecosystem as well as to emphasize the systemic influence of the latter beyond the intestine [35,36]. Despite all the technological advances, the high inter-

individual variability on the GM composition makes difficult to define a core microbiome (all members of a microbial ecosystem) patterns that is shared by all humans. Recently, there has been a great interest in identifying the "healthy microbiota" profiling/signature and its variability in microbial populations in order to assess the deviations that are associated with disease states. This might open avenues to develop strategies to prevent and/or treat a broad spectrum of conditions associated with impaired GM composition and/or function, also referred as GM dysbiosis.

2.1. GM composition along gastrointestinal tract

GM profile alters along the digestive tract and depends on the morphological and physiological characteristics of each part of the digestive system. In fact, its density substantially increases from the proximal to distal gut, with a shift of microbial composition from aerobes to anaerobes [37,38]. The microbiota composition of the first section of small intestine, particularly the duodenum, is similar to stomach. This likeness is due to the fact that the duodenum is the initial portion of the intestine where the chyme comes from the stomach and provide the acidic environment. In addition, biliary and pancreatic secretions also contribute for low pH, which explains why few species are housed in the stomach and proximal portion of the small intestine. The distal portion is characterized by a reduction in peristalsis, a low redox potential and a gradual increase in pH from duodenum to ileum, allowing a more diversified and increased number of bacteria (10^{7-8} cells per gram in the distal ileum). This portion is mainly composed by species of the Firmicutes phyla, such as *Lactobacillus* and *Clostridium*, by Bacteroidetes and also by gram-negative facultative anaerobes, of the Proteobacteria phyla (e.g. *Escherichia coli*) [38–40]. In contrast, the colonic conditions are favorable for bacterial growth due to its slow transit rate, nutritional environment and favorable pH (5,7–6,8). The greatest number of bacteria resides in large intestine, where colon houses a complex and dense microbial community, with about 10^{12} cells per gram, composed mainly by obligate anaerobes, due to low oxygen concentrations [38]. Typically, Firmicutes (such as *Ruminococcus*, *Lactobacillus* and *Clostridium* species) and Bacteroidetes (such as *Bacteroides* and *Prevotella*) are dominant in the colon. Other phyla that are also present in lower abundance in some adults include Actinobacteria (namely *Bifidobacterium*), Fusobacteria and Verrucomicrobia (such as *Akkermansia muciniphila*), and facultative anaerobic bacteria, such as *Escherichia coli* and other members of Proteobacteria phyla [38,40]. Although this bacterial composition is present in most individuals, there are always qualitative and quantitative variations in GM proportions, modulated by a number of intrinsic and extrinsic factors (see next Sections 2 and 3).

In addition, some bacteria are predominant in the intestinal lumen and others can be attached to the mucus layer covering the intestinal mucosa. Interestingly, it has been reported that these two distinct domains differ in terms of microbiota composition and function [28,31,41]. Some studies evidenced that the ratio between anaerobic and aerobic bacteria is lower in the intestinal epithelium surface compared to the gut lumen [42,43]. This differential distribution may justify one of the major limitations of research methods (fecal microbiota analysis), since there is a limited sampling to microorganisms that remain adherent to the epithelium and are not excreted in the feces.

2.2. GM physiological functions

In brief, gut mucosa is a complex ecosystem with three main interacting components: 1) a monolayer of intestinal epithelial cells (IECs) comprising enterocytes, microfold (M) cells, Globlet cells and Paneth cells with its neuronal connections; 2) gut-associated immune tissue (namely intestinal lymphoid structures, including the Peyer's plaques) and 3) commensal microbiota [44]. This sophisticated cellular niche was well detailed by others [45–47] and is here summarized in Table 1. IECs form an organized network with the microbiota and underlying immune cells, providing the first line of defense against noxious luminal stimuli [46]. Such trialogue occurs mainly through pattern recognition receptors (PRRs), like the toll-like receptors (TLRs), the nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) and receptors for advanced glycation end-products (RAGE) expressed in mucosal cells, enabling them to recognize and interact with microbial signals [cell wall components, such as lipopolysaccharide (LPS) and DNA segments metabolites], collectively referred as microbial associated molecular patterns (MAMPs) [45,48–50]. These immune sensors continuously check microbial population and restrain overt inflammatory to commensal community while promptly "sound the alarm" through the activation of adaptive immune cascades towards noxious microbial antigens [50,51].

The healthy GM plays a central role in the maintenance of intestinal homeostasis and is responsible for distinct homeostatic functions, namely: i) the maintenance of intestinal epithelium integrity and barrier protection; ii) metabolic and nutritional balance and iii) mucosal and systemic immunity maintenance [52].

2.2.1. GM exerts barrier protection functions

The integrity of the mucosa and the gut permeability control are critical to the successful maintenance of intestinal homeostasis [53]. Structurally, the gut barrier can be established as a functional entity formed by mechanical elements such as mucus and the epithelial cell layer. The intestinal mucosa constitutes a dynamic physical and biochemical barrier that separates intestinal bacteria from the underlying lamina propria, restricting the entry of antigenic and pathogenic molecules while preventing commensal bacteria infiltration to underlying tissues [54]. This physiological defense mechanism is supported by the microbial recognition, secretion of antimicrobial peptides (AMPs) and mucus production. Indeed, the protection afforded by GIT can be attributed, in part, to the presence of the intestinal epithelium and related structures (see Table 1) that separate the internal and external environment, allowing a dialogue between GM and mucosa cells that is also crucial for the "bacterial resistance" [46,55,56]. Indeed, bacteria might regulate the production of immune mediators, including mucus, immunoglobin A (IgA), and AMPs in order to avoid opportunistic disruption of the intestinal barrier, as well as invasion of the IEC layer [56–58].

Barrier function is reinforced by the mucus layer, which is comprised by mucins (a highly glycosylated secretory proteins), that helps to prevent luminal bacteria invasion to epithelium, by one hand, acting as a lubricant for intestinal motility, on the other hand [59,60]. Mucins are synthesized and secreted by Goblet cells through baseline secretion and active exocytosis [61,62]. Mucin 2, also known as Muc2, is an oligomeric mucus-gel forming and the major component of the mucus layer. Mutations involving this glycoprotein result in uncontrolled invasion of commensal bacteria to the IECs and consequent chronic intestinal inflammation [63,64]. Mucins act as a protective physical barrier against bacterial translocation. Nevertheless, some anaerobic bacteria, such as *Akkermansia muciniphila*, *Prevotella strain RS2*, *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Helicobacter pylori*, among others, have developed several ways (e.g. enzymatic) to degrade mucus allowing microbes to cross the intestinal protective barrier [65–69]. Moreover, specialized Paneth cells, located in the base of the crypts, produce AMPs, such as defensins, with a broad spectrum of antimicrobial effects in bacterial presence at the crypt space. AMPs, through their enzymatic abilities, are essential for the intestinal microbial control, promoting bacterial death and maintaining normal microbial density. Secreted IgA, released mainly by IECs following antigen presentation, serve as host defense mechanisms that limits the bacterial association with epithelial surface, thus preventing the bacteria entry into the epithelium. In fact, IgA can form immunocomplexes with bacteria, retaining them in the lumen, as well as to neutralize MAMPs.

Table 1
Cellular components of gut mucosal immunity.

Mucosal immunity components	Cell subsets	Main functions	
Intestinal epithelial cells (IECs)	Enterocytes (Small intestine) Colonocytes (Colon) Globlet cells Paneth cells Tuft cells Enteroendocrine cells Microfold (M) cells	Physical barrier Nutrient/water absorption Secrete antimicrobial factors Mucin secretion Stem cell niche support Helminth detection Secrete hormones Antigen uptake	[46,395–398]
Innate lymphoid cells (ILCs)	Group I: "T-helper cell 1" (Express T-bet transcription factor; Secrete IFN-γ) Group II: "T-helper cell 2" (Regulated by Gata-3, Secrete IL-5 and IL-13) Group III (Rorγt^{+}), (Secrete IL-7R, c-kit, LTα1β2, and IL-22)	T cell expansion control Antibacterial activity Immunoglobulin (Ig)A induction Tissue metabolic homeostasis	[399–402]
Intraepithelial T lymphocytes (IELs)	γδ (+) T cells (most abundant)	Limit the entrance of commensal bacteria after epithelial injury via antimicrobial factors release	[403]
Mucosal-associated invariant T cells (MAIT)	Vα7.2-Jα33 (T cell receptor α chain)	Microbial infections control	[404]
Granulocytes	NOD1+ neutrophils	Protection against pathobionts	[102]
Natural Killer T-lymphocytes	Cd1d-NKT cells	Regulation of Paneth cells	[102]
Dendritic cells and macrophages	CD103+ DCs CXCR1+ macrophages CD11c+ macrophages	Important roles both for tolerance and for immunity induction Th17 cells induction	[405]
B lymphocytes	Regulatory B cells (B regs)	Immunoglobulin (Ig)A induction	[45]
T lymphocytes	Foxp3+ Tregs	Tissue inflammation restrain Immune tolerance maintenance	[45]

Despite the presence of an intestinal physical and chemical barrier, some pathogens are capable to pass this barrier and to interact with IECs. As previously mentioned, IECs express several sensing PRRs, crucial for homeostasis of the intestinal mucosal immune response [70]. Depending on bacteria signals, PRRs may trigger a physiological inflammatory response which determine the elimination of pathogens, favors progenitor cell proliferation and epithelial cells survival, thus enhancing intestinal integrity [71]. Importantly, IECs are joined by intercellular junctional complexes composed of tight junctions (TJ), adherent junctions (AJ), desmosomes and gap junctions (GJ) that, altogether establish the intercellular communication, regulate paracellular permeability and the passive entry of nutrients, ions and water. Maintaining intracellular adhesion constitutes a semipermeable defensive barrier that helps to prevent commensal/pathogenic microorganisms and antigens to reach lamina propria [72,73]. In fact, the role of GM in the enhancement of intestinal barrier function, and protection against pathogens has been demonstrated in several studies through the use of probiotics in gastrointestinal disorders, which were shown to reduce both the intestinal permeability and epithelial barrier dysfunction [74,75]. Additionally, GM is also able to stimulate the production of AMPs, enhancing the barrier function. The introduction of gut-resident bacteria to germfree mice strongly triggers the coordinated expression of antimicrobial lectin REGIIIγ in Paneth cells, which binds to the peptidoglycan of luminal bacteria thus restricting bacterial invasion [76]. Compromised epithelial barrier integrity and function can result in enhanced bacterial molecules translocation that have been implicated with the development of several disease.

2.2.2. GM displays chief metabolic functions

A major metabolic function of GM is the fermentation that occurs in the colon. The main substrates involved in this process are mucus, dietary carbohydrates and fibers that are not digested in the upper GIT, including resistant starch and polysaccharides, namely oligosaccharides [76]. In this fermentation process, colonic bacteria use a variety of enzymes that hydrolyse complex carbohydrates to produce gases (hydrogen, methane and carbon dioxide), lactate and short chain fatty acids (SCFAs), mainly acetate, propionate and butyrate. These SCFAs play key roles in colon physiology since they: i) are the main source of energy for enterocytes and colonocytes; ii) stimulate cellular proliferation of the epithelium; iii) inhibit intestinal inflammation and oxidative stress and iv) contribute to glucose homeostasis [43]. SCFAs also are involved in immune and metabolic regulation through the G protein-coupled receptors, such as GPR43 and GPR41, respectively. Indeed, the activation of GPR41 by SCFAs in L cells of the small intestine and colon stimulates the secretion of glucagon-like peptide 1 (GLP-1), improving insulin and peptide YY (PYY) secretion, the last one responsible for intestinal motility inhibition, prolongation of intestinal transit and subsequent improvement of nutrient absorption and reduction of appetite [73,77].

Other relevant functions of the GM include the endogenous synthesis of several vitamins and shorter peptides and participation in the metabolism of many amino acids and bile acids, as recently described [77]. In addition, it has been increasingly recognized the relevant uremic toxins are derived by intestinal microbial metabolism [78]. Approximately 10 g of proteins reach the colon daily, where they are then degraded by intestinal bacteria to metabolites, such as ammonium, amines, thiols, phenols and indoles. These fermentation products in the colon are mainly eliminated by the feces, although part is absorbed and further eliminated by the kidney [79]. These toxins include phenols and indols that are bound to proteins [80], as well as products of phenylalanine and tyrosine metabolism by anaerobic bacteria, such as p-cresol (PC) and p-cresyl sulfate (PCS) [78]. Regarding indoles, the more relevant are indoxyl sulfate (IS) and indoleacetic acid originated from tryptophan degradation by GM. Moreover, amines and polyamines are also generated by the intestinal microbial metabolism; choline, for instance, an important nutrient required for lipid metabolism and hepatic production of very-low-density lipoproteins (VLDLs), is metabolized by the GM into toxic trimethylamine (TMA), which is further metabolized in the liver to form trimethylamine-N-oxide (TMAO). This metabolite exhibits pro-atherogenic properties and has been shown to aggravate cardiovascular diseases that are particularly prevalent among diabetic patients [81,82]. For instance, elevated plasma TMAO levels were significantly associated with higher long-term mortality risk among patients with stable coronary artery (CAD) disease managed with optimal

medical treatment [83]. Notably, these patients display a GM dysbiosis signature that is strongly correlated with increased serum TMAO levels in CAD-T2DM subjects [84,85]. Likewise, TMAO deleterious roles are currently well established on kidney dysfunction [86,87], as will be further exploited in the context of diabetic nephropathy progression (Section 5). Although a direct correlation between GM dysbiosis and coronary microvascular injury is not yet established n diabetic patients, some evidences suggest that could be relevant for myocardial ischemia/infarction and risk of atherothrombosis [88–90], which might be due to changes on arterial stiffness and endothelial dysfunction [91].

2.2.3. Healthy immune fingerprints arising from GM-enteric mucosa crosstalk

As previously mentioned, host and microbial interactions are reciprocally interdependent within gut mucosal milieu: while host digestive processes deeply require microbiome catalytic activities, GM capitalizes endogenous intestinal compounds, mainly from dietary anaerobic fermentation, for their own purposes [92,93]. Noteworthy, a plethora of evidences highlight beneficial outcomes on host immunity arising from this bidirectional partnership. For instance, under a controlled load of GM, tryptophan metabolic products from *Lactobacillus* (e.g. L. *reuterii*) modulate innate lymphoid cells (Group III: ILCs Rorγt +/NCR+ subtype) to increase interleukin (IL)-22 production, a cytokine involved in epithelial cell repair [94]. This protective cytokine is also induced by lamina propria CD103-DC after bacterial flagellin-TLR5 binding [95]. Butyrate and niacin, other GM metabolic products, display a chief modulatory activity on intestinal immune cells through their interaction with GPR109A receptor (expressed in both CD11c+ and CD11b+ phagocytes) and downstream IL-10 production/Treg cells differentiation [96]. Different *Lactobacillus* species concurrently activate dendritic cells (DCs), leading to a positive balance between the T helper (Th) cells (Th1, Th2 and Th3) and proper mucosal tolerance, as well as natural killer (NK) cells activation, paramount for gastrointestinal immunity [97].

B cells maturation is another prime example of a positive GM-mucosal immune interaction. There is a strong dependence of gut bacterial species (namely *E. coli* and *Bifidobacteria* in the infant human gut) for differentiation of gut B cells into IgA-producing cells (the majority of intestinal B cells) [98]. IgA is normally found in mucosal surfaces where it restricts pathobionts expansion (e.g. segmented filamentous bacteria) while simultaneously promote autochthonous gut bacteria colonization [99]. GM alterations due to large spectrum antibiotics or germ-free mice have profound consequences in immunoglobulins isotype secretion, enhancing IgE production (rather than IgA) that ensues allergic responses [100–102]. Moreover, in a scenario of IgA/B cells absence, intestinal epithelium was found to up-regulate gamma interferon (IFN-γ)-inducible immune responses and reduce Gata4-related metabolic functions, pointing towards a fundamental role of intestinal B cells/IgA in both gut metabolism and immunity [44].

A bilateral dialogue is also established between GM and intraepithelial lymphocytes (IELs). $\gamma\delta$(+)-IELs thwart invading pathobionts by releasing AMPs, a phenomenon mediated by epithelial TLR/MyD88 signaling [103]. Yet, GM seems to display a key role in this response as germ-free mice present a drastically reduced inflammatory and antimicrobial response after intestinal epithelial disruption [104]. Moreover, of the $\gamma\delta$(+) IELs in the intestinal lamina propria, a significant subset of IL-17 producing T cells (Th17) and regulatory T (Treg) cells are expanded by intestinal microbiota [105,106]. Remarkably, a positive impact on IL-17 producing T-helper cells from peripheric lymphoid tissues and splenic T-helper cell expansion was also correlated with higher levels of Bacteroidetes colonization in the gut [107,108]. These data reveal that continuous exposure to microbial ligands may be also able to shape systemic immune effector cells that express a memory phenotype [109]. Even though the mechanisms underlying this phenomenon are largely unknown, one possible explanation relies on epigenetic modification of innate genes, due to commensals bacteria-derived signals, influencing overall gene expression profile of immune cells towards a host-defense scenario [110].

Altogether, a healthful bidirectional communication between indigenous intestinal microbiota and enteric mucosa reinforces gut barrier functions, maintains a state of immune tolerance to commensals microbes, their metabolites and dietary antigens and, presumably, fits systemic immunity at both steady state and within injury.

3. GM remodeling in healthy, in ageing and in diabetes

3.1. From in utero to “adult-like” maturation

In a temporal perspective, the human microbial colonization begins in intrauterine life from the maternal microbiota and develops throughout the life. For many years, it was suggested that the healthy fetus was in a physiologically sterile environment and that gut colonization began during birth [111]. This widely accepted concept is mainly due to observation and to the strong correlation between the occurrence of preterm deliveries accompanied by intrauterine infections. However, within a healthy uterine environment, there are studies showing the presence of microbial communities in the amniotic fluid [112], maternal placenta [113], umbilical cord blood [114] and in meconium (the earliest “feces-like excretion”) [115], thus suggesting maternal commensal bacterial transmission to the infant as a way to adapt to life outside the uterus. The process continues throughout childbirth and with a breastfeeding; in fact, in early life there are several factors, such as prenatal stress, antibiotics usage and prolonged gestational period [116–118], that may greatly affect the GM population with potential long-lasting implications in immune and metabolic functions of adult human health [119,120]. Bacteria communities involved in the initial colonization of the gut of vaginally delivered infants are similar to their mother's vaginal microbiota, being dominated by *Lactobacillus* and *Prevotella* species [121].

Molecular techniques showed that GM of breast-fed infants is predominantly dominated by *Bifidobacterium* genus, which is considered to have a beneficial effect on host health; in contrast, formula milk-fed infants have a different microbial composition associated with much lower amounts of *Bifidobacterium* and large amounts of *Bacteroides*, *Clostridium*, *Staphylococcus*, *E. coli* and *Streptococcus* [122,123]. Moreover, human breast milk differs from formula feeding in terms of nutrients, hormones, growth factors, immunoglobulins and enzymes; and formula-fed newborns have a broader spectrum of microorganisms than those who are breast-fed [124,125]. The microbiota diversity increases and changes the composition with the introduction of solid food, reaching the maturation during the first two years of life. By adulthood, a relatively stable bacterial is achieved and in a healthy status it is mainly composed of Firmicutes and Bacteroidetes phyla [31,126,127], the majority of genera being composed by anaerobic bacteria [128].

It has been suggested that GM composition remains highly stable between 30 and 70 years-old [129]. However, after GM maturation, lifestyle-related factors like diet, antibiotics intake, physical exercise and environmental factors (e.g. psychological and physical stress, geographical and cultural factors) can modify the GM composition. Moreover, the genetic background and the inflammatory state of the host seem to be important, although their specific role remains almost unknown [130]. There are hypotheses that the distribution patterns of adhering bacterial sites are influenced by the individual's genetics and some studies have already shown a greater similarity between the microbiota pattern of identical twins compared to non-twin siblings [131,132]. Other intrinsic factors include anatomical structure of gut and host's physiology features, including pH, microbial's interactions, ageing and age-related diseases, discussed in detail in future sections of the article.

Overall, “microbial programming” along lifespan is strategic to fit the organism to a set of new environmental features [111]. Early gut microbial establishment can later influence symbiotic host-bacterial

interactions, modulating host immune system and increasing the susceptibility to diseases in adulthood, such as allergy and autoimmune diseases (e.g. T1DM), intestinal disorders (e.g. irritable bowel syndrome and chronic intestinal inflammation) and metabolic disorders (e.g. obesity and T2DM) [133,134]. In fact, this conserved process paired the course of the evolutionary history, from Paleolithic to modern Westernized cultures, driven the passage from hunter-gathering societies into a high-abundant food supply [135].

3.2. GM and ageing: Inflammaging and immunosenescence phenotypes of elderly and centenarians

Ageing, a nearly universal biological process in multicellular organisms, is a major determinant of human lifespan [136,137]. Old age is a condition characterized by a time-dependent decline of physiological integrity and tissues renewal, culminating in functional adaptation disabilities and multiple organ deficits [137]. This dynamic process oscillates between a “successful” (healthy ageing) or a pathological condition, in which there is an increase in individual's vulnerability to develop negative health-related events, defined as frailty [138,139]. Epidemiological studies show a dramatic increase in world's population over 60 years of age [140]. Since ageing remains a strong risk factor for the most prevalent chronic diseases, the pool of people experiencing age-related disorders is continuously growing, strongly challenging the public health care expense and negatively impacting social welfare [140]. Therefore, major efforts have been made to disclose genetic and epigenetic processes underlying the biology of ageing and implement appropriate interventions to promote a good health for the last part of human's life [137,139]. In this regard, centenarians, who subsisted to the major age-related diseases, are currently the focus of extensive research worldwide [137,141].

Among distinct and well-recognized age-related molecular hallmarks, a status of systemic, sterile, low-grade chronic inflammation - “inflammaging” - is almost universally present in old age [24,142]. Acute inflammation is envisaged as a beneficial process to harmful conditions; however, this conserved program for development and survival can turn disadvantageous when persists for a period time longer than that predicted by evolution [143]. In fact, the progressive increase of chronic and asymptomatic inflammatory tone [e.g. elevated IL-1, IL-6, IL-15, IL-18, tumor necrosis factor (TNF), C-reactive protein (CRP), Von Willebrand factor, resistin and complement C1q plasmatic levels] within ageing is accompanied by a reduced endurance to distinct antigenic, physical and/or nutritional stressors [136,144–147]. Therefore, inflammaging is nowadays considered a biological pillar of age-related decline [146]. Low-grade inflammation is largely due to “self” (cell debris, glycated proteins, etc.), “non-self” (persistent infections) and “quasi-self” (gut microbiome) components – damage-associated molecular patterns (DAMPs)/pathogen-associated molecular pattern (PAMPs)/MAMPs - that chronically activate PRRs signaling [148–150]. Continuous adaptation of the body to lifelong antigenic load and unresolved “sterile” inflammation can result in both innate and adaptive immune remodeling, a process globally referred as “immunosenescence” where several functions of the immune system are reduced, while others remain unchanged or even increased [146,151–153]. Accumulated senescent cells dynamically propagate their phenotype to neighboring tissues through senescence-associated secretory phenotype (SASP), stimulating pro-inflammatory pathways [e.g. IL-6, IL-1β, IL-8, chemokine (C-X-C motif) ligand 1 (CXCL1), matrix metalloproteinases and plasminogen activator inhibitors 1 and 2 (PAI-1 and PAI-2)] without an appropriate anti-inflammatory response [150,154,155]. Overall, immune system deregulation seems to be a major player in the “silent killer” inflammaging process [156]. Immunosenescence is a dynamic process encompassing multiple reorganizational variations in distinct organs and cellular populations, rather than a unidirectional failure of immune function [136]. The first and well-known process occurring by the age of 45 years comprises thymic involution [157,158]. This early collapse of thymic microenvironment characterized by a loss of developing T cells is compensated through homeostatic expansion of preexisting effector memory (E/M) T cells in a thymus-independent manner [159]. However, long lasting restriction of T cell diversity observed in ageing is correlated with the deterioration of immune competence that appears later in life and may be responsible, at least in part, for certain cancers, emerging infections and vaccination failures in the elderly [160,161].

Besides shifts from the naïve to the memory T-cell phenotype, age-related changes in T-cell compartment also affect the effector Th cells triade (Th1, Th2 and Th 17 phenotypes). Briefly, upon distinct antigen type/load, costimulatory molecules and cytokine signaling, committed progenitor naïve CD4+ T cells may differentiate into Th1, Th2 and/or Th17 phenotypes (with distinct cytokine products) or evolve into the inducible Treg lineage (with immunomodulatory functions) [162]. Through the secretion of an array of cytokines that induce the activation of other immune and non-immune cells, Th cell subsets orchestrate context- and pathogen-specific responses of the immune system [163]. Effector cytokines of Th17 cells (e.g. IL-17, IL-21, IL-22), for instance, are crucial for tissue immunity and display chief-roles in chronic tissue inflammation once deregulated [164]. Importantly, a misshape of Tregs cells towards decreased secretion of immunosuppressive cytokines [e.g. IL-10 and transforming growth factor beta (TGF-β)] may fuel Th1-, Th2-, and Th17-mediated inflammation, a common feature of age-related diseases [165]. Actually, Th17 cells are increased in aged mice and humans [166]. Moreover, an age-dependent impaired balance between Th17/Treg ratio was observed in human peripheral blood mononuclear cells (PBMC) [165]. Overall, a Th17/Treg disproportion in aged individuals may reflect an imbalanced pro- and/or anti-inflammatory immune response, with increased susceptibility to the chronic inflammatory phenotype observed in aged individuals [165,167]. On the other hand, Treg-mediated immune suppression may also explain the induction of age-associated tolerance and increased risk for developing autoimmune diseases [168].

Another major hallmark of ageing is the deficient maintenance of proteostasis and autophagy decline. Subsequent accumulation of extracellular waste products (DAMPs) and derived activation of NLRs may lead to the inflammassome assembly and consecutive secretion of proinflammatory mediators [136]. Notably, a disturbed interplay between autophagy and inflammasomes has been postulated to link inflammaging with multiple organs failure [158,169]. For instance, it has been shown that age-accumulation of intrathymic “lipotoxic danger signals” cause NLRP3 inflammasome recruitment, caspase-1 activation, thymic involution and T cell senescence. Hence, strategies aimed to restrain thymic NLRP3 inflammasome-dependent caspase-1 activation have been hypothesized to re-establish T cell repertoire diversity within ageing [158]. Another example of NLRP3 inflammasome recruitment relies on vascular pathology [170,171]. Interestingly, Wu and colleagues (2015) demonstrated that gene expression of inflammasome components in PBMC of vascular patients increases with age. Given this systemic priming of inflammasomes, the threshold for full inflammasome activation by a “second hit” in different tissues might be reached easier with ageing, probably predisposing these individuals to vascular and other chronic diseases (e.g. renal ageing and age-related macular degeneration) through a pre-activated first line of defense of innate immunity [172–174].

Systemic inflammaging also ends up in a localized inflammatory environment at intestinal mucosa [22]. As previously mentioned (please see 2.2), a three-dimensional mutualism between IECs, gut-associated lymphoid tissue and GM allows the distinction between harmful and symbiotic microorganisms, a vital network for intestinal epithelium integrity and mucosal immunity homeostasis. However, alterations in intestinal microbiota composition seems to correlate with aged-related changes in GIT (e.g. salivary function impairment and intestinal motility reduction), frailty scores, nutritional deficiency and mucosal immunosenescence [136,175,176]. This is aligned with the

Table 2
Gut microbiota composition in elderly and T2DM patients.

Phylum	Genera/Species	Main function	Type 2 diabetes mellitus	Elderly (> 65 years of age)/frailty
Firmicutes (Gram-positive)	*Clostridium cluster XIVa*	SCFAs - producers Maintenance of gut immune homeostasis ↑ energy harvesting	↓ [406]	↓ [407]
	Roseburia intestinalis	SCFAs - producers Anti-inflammatory properties	↓ [266,267]	= [129]
	Eubacterium limosum	SCFAs - producers Anti-inflammatory activity	– 	↑ [408]
	Lactobacillus	Immunomodulating properties Some species are probiotic	↑ [267,409]	↓ [410]
	Faecalibacterium prausnitzii.	SCFAs - producer Anti-inflammatory activity Metabolic modulator	↓ [249,266,411]	↓ [408,410]
Bacteroidetes (Gram-negative)	*Bacteroides vulgatus*	Proinflammatory properties	↑ [412]	↑ [413]
	Prevotella	SCFAs and H2 producer ↑ energy harvesting	↑ [414]	↓ [410]
Actinobacteria (Gram-positive)	*Bifidobacterium*	Probiotic Metabolic health	↓ [415]	↓ [129,416]
	Eggerthella lenta	Bile acid oxidizing bacteria SCFAs producer Opportunistic bacteria	↑ [266]	↑ [408]
Proteobacteria (Gram-negative)	*Escherichia coli*	Pro-inflammatory bacteria Opportunistic bacteria/Pathobionts	↑ [266]	↑ [127]
Verrucomicrobia (Gram-negative)	*Akkermansia muciniphila*	Mucin degrading bacteria Immunomodulator and metabolic control Protection of gut barrier integrity	↓ [411]	↓ [417]

Changes relative to healthy subjects. Increase: ↑; Decrease: ↓; Information unavailable: —.

fact that elderly population is more susceptible to develop various gut-related diseases [109]. In fact, a breakdown in the homeostatic equilibrium between GM and the ageing host favors an inflammatory shift from protective symbionts, favoring opportunistic pathogens and gut dysbiosis [177]. Moreover, pathobionts may also take advantage of age-associated mucosal immunity weakness and organ decline (constipation and subsequent "bacterial load challenge") to overgrow [22,178]. Importantly, the composition of GM has a major influence on the properties of the inner colon mucus barrier and may be linked with the leaky gut [177,179]. Accordingly, claudin-2 and IL-6 elevated concentrations, as well as increased intestinal permeability, were demonstrated in ileal tissues from older adults [179]. Hence, gut dysbiosis during advanced age (see Table 2) may be responsible not only for mucosal inflammation but also for intestinal barrier leakage, allowing harmful substances (e.g. endotoxins and DAMPs) to reach bloodstream, nurturing systemic inflammaging [180].

On the other hand, alterations in the intestinal microflora attends gut mucosa immunosenescense in the elderly, a population more prone to infectious diseases acquired via mucosal exposures [181,182]. This knowledge is of the utmost interest as the feedback impact of intestinal microflora composition on distinct immunosenescence phenotypes observed in elderly/centenarian's populations are apparently correlated [129,183,184]. Indeed, the accumulation of senescent cells characterized by a pro-inflammatory secretory profile is present in both elderly populations with poor health outcomes and extreme longevity centenarians. Yet, this apparent paradox may be partially explained by compensatory mechanisms arising from the dynamic phenomenon of anti-inflammation [e.g. elevated levels of adiponectin and IL-1 receptor antagonist (IL-1RA), anti-inflammatory arachidonic acid compounds] that seems to remain well-preserved in centenarians [146,185–187]. Such heterogeneity of immune responses in the elderly can be explain, at least partially, in light of the very elegant theory preconized by Franceschi and co-authors (2017) termed "immunobiography". Briefly, it is suggested that an accurate anamnesis of type, intensity and temporal sequence of antigens that everyone is exposed during the whole life is determinant to shape not only adaptive immunological memory, but also a sort of memory of innate immune cells dubbed "trained immunity". Innate immune cells [e.g. NK cells, DCs, macrophages, lymphoid lineages (such as γ/δ T cells) and innate lymphoid cells (ILCs)] are indeed provided with the capacity to respond more promptly to a second challenge (resembling adaptive memory), with the crucial difference that these responses are not limited to the specific antigen that triggered the first response [188–191]. Even though the underlying mechanisms remain largely elusive, the molecular response of this "trained immunity" appears to be of epigenetic nature. For instance, macrophages and DCs trained immunity seems to correlate with epigenetic modifications following PAMPs or DAMPs exposure [192]. Moreover, bone marrow epigenetic remodeling of DC progenitors in mice can be stimulated by gut microbiota [193].

Overall, it is currently hypothesized whether the maintenance of a "healthy" gut microbiota signature could help in delaying or preventing the immunosenescence and inflammaging process [22]. Elderly GM declines SCFAs production [133] with probable noxious outcomes on host immunity (see 2.2.3). In this regard, distinct profiles of gut dysbiosis are observed in elderly and centenarians populations. Thus, age-related trajectory of GM composition is very likely to display a chief role on individual immunobiography. Such differences may help to explain the immune heterogeneity that becomes particularly evident at settings of inflammaging and immunosenescence in elderly and extreme centenarians, dictating poor/beneficial outcomes later in life. This also holds truth for age-related disorders, namely metabolic disorders, where crucial changes in GM composition are observed as well, namely for diabetes and vascular complications of diabetes, such as DR and DN.

3.3. GM and T2DM: Inflammaging and immunosenescence phenotypes

In strict accordance with previous section, the prevalence of age-related diseases, namely T2DM, is rising [194]. Gradually, T2DM leads to secondary complications (e.g. retinopathy, nephropathy and neuropathy) and has become an important public health issue worldwide [189,190,195,196]. Noteworthy, the incidence of T2DM is essentially linked to overweight and obesity, the major epidemic of the 21st century, and is clinically hallmarked by hyperglycemia, insulin resistance

(IR) and pancreatic β-cell decompensation [197]. The decrease glucose uptake from the blood can result in chronic hyperglycemia, leading to IR in which the hormone insulin's effectiveness is decreased at lowering blood glucose. Over time, IR can lead to insufficient production of insulin by the pancreatic β-cells and eventually contribute to the development of T2DM. Both IR and T2DM are associated with obesity, sedentary lifestyle and ageing [198]. Besides the deregulation of metabolic pathways and impairment of metabolic flexibility, the thesis that a status of low-grade inflammation plays a causal role in the progression of diabetes has been suggested for many years [199–202]. It is now well recognized that a variety of tissues and organs (e.g. adipose tissue, muscle and liver) can set up inflammation. Hence, T2DM and a series of apparently different age-related pathologies (atherosclerosis, osteoporosis, metabolic syndrome, cognitive decline, cardiovascular diseases) are currently being considered in a global inflammatory pathogenesis perspective, a kind of diseasome of inflammaging [146,203].

Sterile low-grade inflammation observed in T2DM, recently referred as “metaflammation”, is a process where metabolic hallmarks, such as high levels of lipids, free fatty acids (FFAs), glucose and reactive oxygen species (ROS), incite immune cells (namely macrophages, neutrophils and T, B, NK cells) to infiltrate insulin responsive tissues (e.g. colon, liver, muscle and adipose tissue). This mechanism causes chronic activation of senescence-associated secretory phenotype and pro-inflammatory molecules secretion [e.g. TNF, IL-1β, IL-6, IFN-γ, inflammatory adipokines, chemokines], in part through the activation of NLRP3 inflammasome [204–207]. Metaflammation resembles ageing-induced low-grade inflammation (or inflammaging) in terms of clinical presentation and molecular profile, pointing to overlapping and multifactorial mechanisms for both conditions. In fact, the life expectancy of T2DM patients is about 6 years shorter than age-matched nondiabetic individuals and, in some respects, diabetes is suggested to be an interesting model of “accelerated ageing” [208]. Noteworthy, immunological factors and cellular senescence, namely the secretory phenotype acquired by endothelial cells - “*endo*-SASP” - are currently held to be large contributors for the pathophysiology of ageing and of diabetic complications [209,210].

Among other factors, autophagy slowing is a major driver for age-related senescent cells [211]. Interestingly, cogent data have recently showed an association between reduced autophagy and increased PBMCs' inflammatory profile of T2DM patients [212]. Between distinct noxious outcomes, elevated inflammatory cytokines can directly impair the bioavailability of endothelium-derived relaxing/contracting factors and promote vascular insulin resistance, a probable common mechanism of both atherogenesis and diabetes [213–216]. Notably, clinical data demonstrate that inflammatory markers conferring atherothrombotic risk (e.g. CRP and IL-6) may predict the development of new-onset diabetes [217,218]. Furthermore, an inflammatory process fueled by the non-enzymatic glycation and over-activation of AGE-RAGE pathways seems to be also involved in obesity, T2DM and related complications at the levels of arteries, eyes and kidneys [219,220]. Hence, some efforts have been made to understand the clinical progress of anti-inflammatory drugs [e.g. IL-1/TNF/monocyte chemoattractant protein 1 (MCP-1) receptor blockers, and the factor nuclear kappa B (NF-kB) inhibitor salsalate] aimed to decrease glycaemia and/or combat multiple T2DM manifestations [221]. For instance, the Cantos trial (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) addressed the potential of IL-1β antagonist canakinumab on reducing the incidence of new-onset diabetes. However, on despite of profound reductions in high-sensitivity CRP (hsCRP) and IL-6 levels, the incidence of new diabetes remained unchanged after treatment [216]. Therefore, whereas inflammation is closely linked with glucotoxicity, lipotoxicity, and other pathophysiological mechanisms within T2DM, it should be noted that multiple inflammatory pathways with overlapping functions probably complicate any anti-inflammatory pharmacological strategy. It is also worth to mention that a range of cytokines and proteins with anti-inflammatory properties (e.g. adiponectin, omentin, IL-1RA and TGF-β) are concurrently elevated in T2DM patients [222–224]. However, such counter-regulatory anti-inflammatory circuits that pair good health outcomes in extreme centenarians (see Section 3.2) seems to turn out futile and redundant within the permanent subclinical inflammatory scenario associated with T2DM complications [225]. Therefore, the causal mechanisms fostering metaflammation deserve further research to identify new druggable targets [210].

Among a myriad of factors that collectively contribute to obesity and T2DM, contemporary experimental evidence withstands the physician Hippocrates' quote “all disease begins in the gut” nearly 2500 years ago [33]. As a matter of fact, a wealth of studies substantiates GM dysbiosis as one of the crucial mediators of obesity/T2DM pathogenesis and major efforts on microbiome assessment/characterization have been made in the recent years [195,226]. High throughput amplicon sequencing of 16S rRNA gene reveals substantial changes in bacterial composition (including in Bacteroidetes and Firmicutes) and T2DM persons (see Table 2) and a causal relationship between gut dysbiosis and obesity/IR outcomes has been demonstrated [227]. One of the mechanisms proposed to explain the crosstalk between abnormal intestinal microflora and obesity-related diseases is metabolic endotoxemia [228]. Briefly, dysbiotic alterations in GM leads to gut mucosa barrier integrity breakdown (e.g. altered expression of TJ proteins) [229] and increased intestinal permeability that favors bacteria fragments translocation [lipopolysaccharide (LPS) and peptidoglycan (PG)] through PRRs (e.g. TLR4, TLR5 and NOD2), from the intestinal lumen to the bloodstream [230]. Consequently, MAMPs become elevated in peripheral tissues, thereby continuously triggering pro-inflammatory responses [205]. For instance, LPS binding to TLR4 and co-receptors triggers a cascade of responses that ultimately result in the release of pro-inflammatory molecules that interfere with the modulation of glucose and insulin metabolism and/or signaling [226].

In addition, many pieces of evidence highlight that signals from the GM modify immunometabolism via gut-associated epithelial and immune cells. For instance, IL-22 derived from ILCs and CD4+ T cells was found indispensable for epithelial integrity, endocrine functions and insulin sensitivity. Notably, decreased IL-22 levels under various immune challenges were found in obese mice [231,232]. Similarly, $ROR\gamma^{+}$-ILCs subtype has been also implicated in the regulation of glucose metabolism and insulin sensitivity [233]. Moreover, exacerbated IL-17 responses were observed upon feeding mice an obesity-causing high fat diet (HFD) as well as in obese patients [234,235]. Interestingly, activated mucosal-associated invariant T cells (innate-like T cells able to recognize bacterial ligands) towards elevated Th1/Th17 cytokine production were found in circulation of both obese and T2DM patients [235]. Finally, and even though T1DM is long considered an autoimmune disease, it was recently suggested that GM may influence host immunometabolism responses as well, highlighting a common molecular basis of both T1DM and T2DM [236]. Worthwhile, almost a direct proportion between glycaemia and the inflammatory state of immune cells has been established in circulating immune cells of diabetic patients [237]. Data from epidemiological and prospective studies [e.g. Diabetes Complications and Control Trial (DCCT), Epidemiology of Diabetes Interventions and Complications (EDIC) Trial, United Kingdom Prospective Diabetes Study (UKPDS)] have consistently established that early metabolic control has enduring beneficial effects on diabetes clinical outcomes. Similar results were observed in retina and kidneys of diabetic animal models [238,239]. Such evidences support the concept that early glycaemic environment is remembered, a phenomenon coined as “metabolic memory” [220,240]. A variety of cells (e.g. immune cells, fibroblasts, endothelial cells) and mechanisms are potentially involved in the propagation of this “memory”, mostly depending on the previous production of plasmatic AGEs and RAGE persistent activation as well as of mitochondrial proteins glycation [220,241]. Glycated mitochondrial proteins lead to unavoidable decline of mitochondrial function and free radicals overproduction,

raising a catastrophic cycle of mitochondrial DNA (mtDNA) damage and cellular injury which may persist even when glycemia is normalized [220,241]. More recently, epigenetic mechanisms such as DNA methylation, post-translational histone modifications and microRNAs (miRNA) deregulation have been also associated with the enduring gene expression changes that withstands metabolic memory. For instance, a tissue-specific increased in miR-21 has been reported in diabetic patients with proliferative DR and was correlated with renal fibrosis in DN [242–244].

Epigenetic mechanisms are believed to be a crucial interface between genetic and environmental factors. Depending on the nature of the stimuli and the type of epigenetic modifications, cells maintain a deregulated status for weeks, months or may become irreversibly modified over time [244–248]. Notably, changes in GM are involved in the epigenetic regulation of innate immune sensors (e.g. TLR2 DNA methylation) in T2DM [249]. Hence, GM-induced epigenetic changes may also help to explain the long-term harmful effects of metabolic memory [244,250–252].

4. GM dysbiosis and progression of diabetic retinopathy

4.1. DR as a complex and multifactorial disease

DR, a very common long-term microvascular complication in patients with diabetes, remains a leading cause of vision loss worldwide in working age-adults [253,254]. Although the development of the disease appears to be similar in both diabetes types, within 20 years of diagnosis, the incidence of any degree of DR was found to be higher in patients with T1DM compared with patients with T2DM [255]. With the increasing number of people with undiagnosed and diagnosed diabetes, mainly as a result of the population ageing and increased life expectancy of those with diabetes, the number of people with DR is expected to rise significantly over the coming decades [254]. Ophthalmoscopic examination and fundus photography are the mainstay techniques for detecting and grading this condition and are based mainly on the severity of microvascular lesions. DR is characterized by the presence of microaneurysms, increased vascular permeability, intraretinal hemorrhages, exudates, abnormalities in the venous caliber, intraretinal microvascular abnormalities and neovascularization [256]. These structural and functional changes can be easily seen since erythrocytes in retinal capillaries are visualized in the eye fundus. Besides diabetes-induced alterations in the vascular component of the retina, the neurosensory retina is also affected by diabetes. However, it is difficult to assess the transparent retina by clinical evaluation [256]. This disease progresses from an earlier mild non-proliferative to a moderate or severe non-proliferative DR, and can finally lead to proliferative DR, a severe stage in which new blood vessels proliferate on the surface of the retina and posterior surface of the vitreous [257]. Diabetic macular edema is an additional category of DR, representing both the most common form of advanced disease and cause of impaired vision in patients with diabetes [257,258].

Clinical studies have demonstrated that implementation of a “tight control” early in the course of T1DM or T2DM, and its maintenance over time, significantly decreases the development and progression of DR and other microvascular complications associated with diabetes [257,259]. However, if an early stage of poor glycemic control is able to establish a “glycaemic or a metabolic memory”, an imprint for diabetes-related damage in the retina is generated and retinopathy will develop, even in diabetic patients with a good glycemic control. These deleterious effects may be permanent due to epigenetic changes [240]. In fact, one of the first pre-clinical studies evaluating whether improved glycemic control could inhibit the development or progression of retinopathy with alloxan-induced diabetes, in a 5-year experiment, was carried out by Engerman and Kern [260]. After 2.5 years of poor metabolic control, as yet without any evidence of retinopathy, diabetic dogs were switched to an intensive regimen of good glucose control for an additional period of 2.5 years. After five years, these dogs experienced severe retinopathy as the dogs that had been in poor control throughout [260], suggesting a continued injury mediated by “glycemic memory”. These findings are similar to several studies in T2DM patients, in whom the onset of disease in asymptomatic and progressive over many years, making disease duration and cumulative exposure to prior hyperglycemia difficult to determine.

Chronic hyperglycemia-elicited metabolic and structural derangements lead to impaired responses in a range of retinal cell types including neurons, glial cells, and microvasculature [261]. Although the precise mechanisms underlying pathogenesis of DR remain incompletely understood, persistent low-grade inflammation and related processes, such as the influx of leukocytes, are now thought to contribute to neuronal, glial, microvascular damage, and cell death [262–264]. Despite hyperglycemia is crucial for making a diagnosis of DR, is still far from being the exclusive or the primary cause of retinal lesions. Other factors, such as dyslipidemia, chronic inflammation and high blood pressure, may contribute as risk factors for developing DR [265]. In fact, DR is considered a multifactorial disease and the exact mechanism underlying its pathogenesis remains unclear. A complex interplay between biochemical and cellular signaling mechanisms that regulates interaction between immunological, microvascular, neurodegenerative, genetic/epigenetic and inflammation-related factors is implicated in development and progression of the disease. Furthermore, in the last few years, it has become increasingly evident the activation of immune responses and intraocular inflammation, at least in the context of uveitis, an inflammatory process of the uvea (the middle layer of the eye between the retina and the sclera), might be associated to changes in gut microbiota. However, in the case of DR, if there is any direct, cause-effect association between retinal processes (inflammatory/neurodegenerative/increased vascular permeability) and the change in the GM, remains to be elucidated.

4.2. GM dysbiosis and inflammation in DR

As previously mentioned, the microbiome has become a lively field research in the last years, with both rodent and human studies suggesting that changes in GM and some degree of gut dysbiosis have a critical role in the susceptibility to various diseases, including obesity and T2DM [132,266–268]. However, the link between gut dysbiosis and diabetic microvascular complications, such as DR, remains elusive. A recent study in an animal model of diabetes (db/db mice) has revealed its fecal bacterial composition. The most represented phyla were Bacteroidetes (45.8%), Firmicutes (23.8%), Verrucomicrobia (25.2%), Tenericutes (3.8%), Actinobacteria (1.2%) and Proteobacteria (0.2%) in diabetic mice presenting impaired intestinal barrier function and replicating some features of DR, such as acellular capillaries, activation of retinal microglia and infiltration of peripheral immune cells into the retina. Interestingly, although the ratio of Bacteroidetes to Firmicutes (B/F) has been previously found to correlate with plasma glucose concentration on T2DM [269], no changes were observed at the phyla level between diabetic (db/db) and control (db/m) mice. This report documented, at the genus level, an abundance of *Lactobacillus*, *Bifidobacterium*, *Bacteroides* and *Akkermansia* and decreased proportions in species of *Oscillospira* and *Ruminococcus* in diabetic mice [269]. T2DM is associated with the high abundance of *Bacteroides* genus [228,270] and bacterial species, such as *Akkermansia muciniphila*, and *Bacteroidetes thetaiotaomicron* have been shown to enhance gut permeability and increased levels of endotoxins, such as LPS in the circulation, leading therefore to endotoxemia [195,270]. A cross sectional observational study performed in patients with T1DM (both without and with diabetic retinopathy) demonstrated that they had higher levels of LPS and serum inflammatory cytokines levels [TNF, IL-6, IL-1β and granulocyte-macrophage colony-stimulating factor (GM-CSF)] compared to normal glucose tolerants, which indicates that chronic inflammation is present in the early stages of diabetes and persists till the onset of DR (Fig. 1);

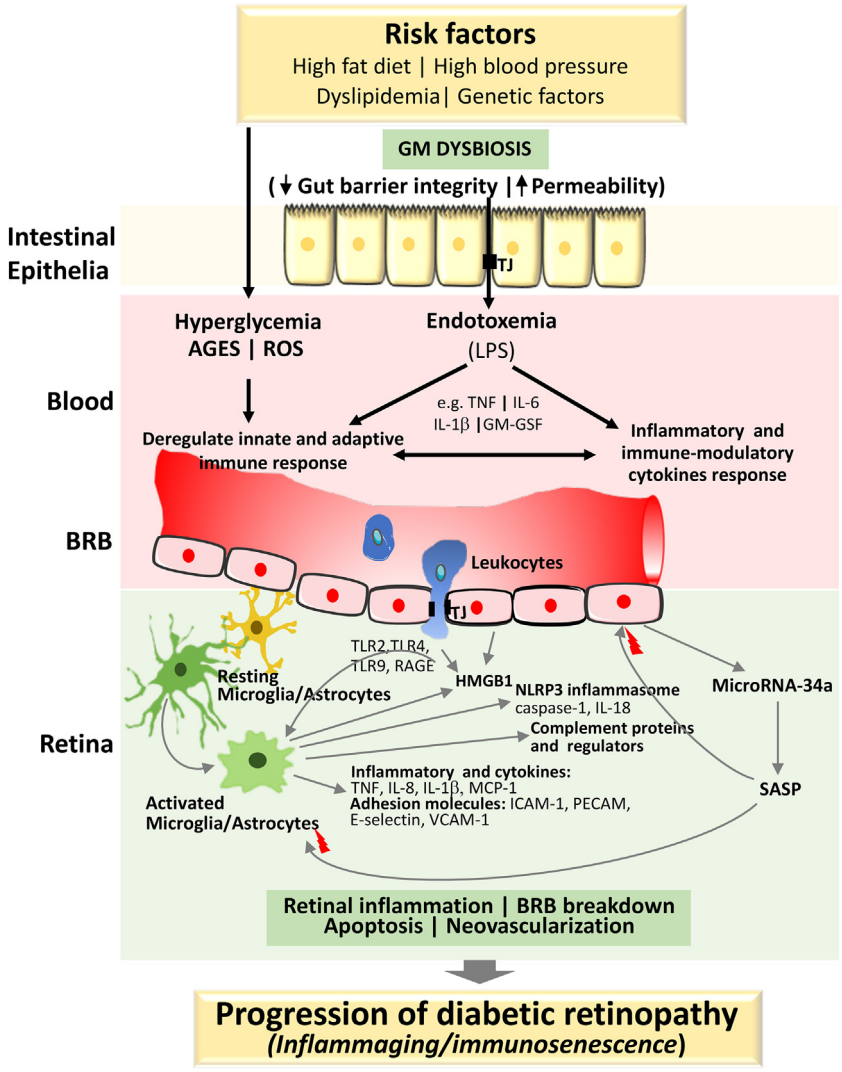

Fig. 1. The putative relationship between gut dysbiosis and diabetic retinopathy onset and progression. Hyperglycemia induced gut barrier alterations lead to the loss of immune homeostasis via a low grade chronic inflammatory systemic state, which altogether contribute to retinal inflammation, blood-retinal barrier breakdown, apoptosis and neovascularization.

but, due to the nature of the study, no direct cause-consequence association between endotoxemia and inflammation could be made. A further relationship between GM and DR, even indirect, may exist. In fact, metabolic factors-associated with chronic low-grade inflammation and oxidative stress, that link altered intestinal microbiota composition and T2DM, are the same influencing the onset and progression of DR [271–273].

4.3. Activation of innate-immunity and inflammation in DR

The retina is considered an immune privileged tissue, armed of a highly effective protection system. It is physically separated from the systemic immune system by the blood retinal barrier, formed by tight junctions between retinal endothelial cells (inner blood-retina barrier: BRB) and retinal pigment epithelial cells (outer BRB), that prevents the free access of circulating inflammatory cells or molecules to the retinal parenchyma. In addition, the retina has also an immune defense system, comprised by perivascular macrophages, microglia and complement system. Perivascular macrophages are myeloid cells that overlap phenotypically with microglia since they both express F4/80 and CD11b. The former express high levels of CD45 and LPS receptor, CD14, and microglia express low levels of CD45, but not CD14 [14]. Under normal conditions, resident macrophage-like microglial cells monitor the surrounding milieu and have the ability to eliminate invading microbes and clear cellular debris. They are localized to the ganglion cell layer, inner and outer plexiform layers of the retina [263]. Besides that, retinal cells can produce complement proteins (such as, C1q, C3, factor B) and regulators (such as factor H, CD46 and CD56). This defense system can recognize PAMPs or DAMPs and elicit a controlled immune response to restore retinal homeostasis [14].

In DR, the BRB is disrupted and the immune privilege is compromised. Although multiple mechanisms may be involved, increased production of inflammatory cytokines and related processes, such as leukostasis, are thought to induce cell death, leading to increased permeability of serum constituents (immunoglobulins and complement proteins) that may gain access to neural retina [274]. One of the most convincing demonstrations for the inflammation as an important factor in the onset and development of DR comes from studies of diabetic patients with rheumatoid arthritis. It was demonstrated that diabetic patients who took salicylates to treat rheumatoid arthritis had a lower incidence of DR [275]. Since then, there is verified evidence of the relationship between chronic low-grade inflammation of retina and DR [276–280], as it contributes to the development of edema and neovascularization [279,281–284]. In humans, the levels of inflammatory cytokines IL-1β, IL-6, IL-8, IL-17 and TNF in aqueous humor were associated with the pathogenesis, severity and prognosis of DR [280].

Upregulation of various proinflammatory cytokines, including TNF, IL-1b, IL-8 and MCP-1 and adhesion molecules [intercellular adhesion molecule 1 (ICAM-1), E-selectin, platelet endothelial cell adhesion molecule 1 (PECAM-1) and vascular cell adhesion molecule 1 (VCAM-1)] has been also reported in the vitreous samples of diabetic patients with retinopathy [285–289]. It has been also shown that LPS-binding protein and monocyte derived CD14 (soluble form, sCD14) are elevated in the vitreous fluid of T2DM patients with proliferative DR [290], suggesting sCD14 as a player in the innate immune response triggered by the inflammatory damage characteristic of this disease (Fig. 1).

High mobility protein 1 (HMGB1) is a highly conserved, ubiquitous protein that is secreted by monocytes/macrophages and endothelial cells [291]. It has been found in increased levels in diabetic retinas and vitreous samples from patients with proliferative DR [292,293]. It serves as a DAMP and participates in several biological processes, including proinflammatory cytokine release, mainly through TLRs and RAGE [294], leading to activation of the transcription factors extracellular signal-regulated kinase 1 and 2 (ERK1/2) and nuclear factor-kappa B (NF-kB), which may lead to inflammation and exacerbates oxidative stress, two processes that may play a role in retinal cell dysfunction and neurodegeneration in diabetic retinopathy [295–297]. TLRs are essential mediators of retinal innate immune response. At least three TLR paralogues - namely TLR2, TLR4 and TLR9 - are expressed in multiple cells in the retina, such as photoreceptor cells, endothelial cells, glial cells and retinal pigment epithelial cells [292,298]. As mentioned before, TLR recognize PAMPs and can be stimulated by microbial stimuli, facilitating the inflammatory process through stimulation of cytokines or chemokines production. In DR, TLR can promote the production of TNF and IL-6 that are implicated in insulin resistance [299]. In addition, TLR can induce the production of growth factors, contributing therefore to neovascularization [292]. In vitro, a human microvascular endothelial cell line exposed to high glucose and stimulated with the recombinant protein HMGB1, exhibited an induction of NF-kB activation and synthesis of proinflammatory cytokines and chemokines, which were prevented by TLR2 and TLR4 signaling inhibition [291]. Collectively, these studies suggest that activation of HMGB1-TLR plays a key role in induction of a pro-inflammatory phenotype of retinal cells (Fig. 1).

Evidence supports that aberrant activation of the NLRP3 [comprising NLRP3 (NLR family pyrin domain containing 3), apoptosis associated speck-like protein (ASC) and caspase-1] [300] is associated with pathogenesis of chronic inflammatory and metabolic diseases, including obesity and type 2 diabetes [301]. Inflammasome has a crucial role in inflammation and innate immunity. NLRP3 can recognize danger signals and interact with ACS to activate caspase-1, leading to the secretion of IL-1β and IL-18. Cytokines can then regulate other intracellular signaling pathways driving proinflammatory processes [302–304]. Several studies also found NLRP3 inflammasome activation involved in age-related macular degeneration [305], a disease of the outer retina that causes damage to the macula, mostly in the elderly. However, limited information is available on the association of NLRP3 with DR. A recent study has found the presence of NLRP3 inflammasome activation in the vitreous samples of diabetic patients with retinopathy. Moreover, levels of caspase-1 and the inflammasome-related cytokine IL-18 were found to be increased, namely in the vitreous samples of diabetic patients with proliferative DR [306]. In an animal model (a double transgenic mouse model, Akimba ($Ins2^{Akita}xVEGF^{+/-}$) that displays characteristic features of advanced stages of diabetic retinopathy, such as vascular hyperpermeability and neovascularization, high levels of IL1β along with increased mRNA and protein levels of NLRP3, ASC and caspase-1 were observed in the retina of Akimba mice. Also, the genetic ablation of NLRP3 delayed and reduced the development of diabetes [307]. Due to the unavailability of suitable animal models able to reproduce characteristics features seen in diabetic patients with proliferative DR, most of the studies performed with rodent models to date represent early stages of DR. Further research should focus on the regulatory mechanism of NLRP3 inflammasome in the various stages of DR, in order to better clarify the key players involved in the onset and progression of the disease.

4.4. Inflammaging in DR

Mechanisms underlying retinal vascular dysfunction and cell death due to diabetes include oxidative and nitrative stress [308,309]. They are associated with an impaired endogenous antioxidant defense system [310] and can lead to inflammatory responses [308]. Evidence during physiological ageing indicate that oxidative stress-induced vascular inflammation is also present [311–314]. It is now appreciated that vascular senescence and consequent pro-inflammatory processes may be accelerated by oxidative stress and nitrative stress in diabetes [315–318], suggesting that diabetes causes ageing-like changes to retinal microvasculature. Cells approaching senescence develop SASP consisting in the secretion of factors that contribute to the maintenance of a low-grade inflammation characteristic of aged vasculature. One study found an upregulation of senescence-associated markers SA-β-Gal, $p16^{INK4a}$ and miR34a, which correlated with a decrease in expression levels of SIRT1, a target of miR34a in retinal microvasculature of adult rats (4.5 months old) with 12 weeks of diabetes. Interestingly, the levels of these senescence-associated markers exceeded levels in diabetic rats as compared to normoglycemic ageing rats (12 and 14 months old) [318]. Of particular interest, miR34a was shown to be produced in both retinal vascular and non-vascular cells, suggesting that different retinal cells can contribute to hyperglycemia-induced senescence of vascular endothelial cells via expression and release of miR34a [318]. In accordance with those findings, another study, using an animal model of ischemic retinopathy, has shown that ischemic retinal cells adopt a SASP, in which retinal ganglion neurons stimulate production of pro-inflammatory mediators that spread senescence to both retinal microglia and endothelial cells, and inflaming pathological angiogenesis. Accelerated senescence in some of the retinal microvessels may make the retina more susceptible to future age-related complications. Moreover, SASP-associated cytokines, such as plasminogen activator 1, IL-6, IL-8 and vascular endothelial growth factor (VEGF), were found in the vitreous of diabetic patients with proliferative DR. These data suggest that SASP can contribute to a premature senescence in retinal ischemic cells, which release pro-inflammatory cytokines and angiogenic factors that lead to pathological vessel growth and disrupt vascular repair [319] (Fig. 1).

5. GM dysbiosis and progression of diabetic nephropathy

5.1. The GM dysbiosis - kidney disease vicious cycle

DN, a major microvascular complication in both T1DM and T2DM patients, is the leading cause of ESRD in many World regions, including in the United States and Western Europe; where approximately one-third of all diabetic individuals are affected by DN [6]. The increased worldwide prevalence of DN and of CKD [320], seems to be strongly related with the changes associated with the modern lifestyle that favors the development of diabetes and hypertension, the major causes of CKD in developed countries and in some of the developing ones [23,321]. Diabetes mellitus, in particular, is the primary cause of DN, CKD and ESRD [322]. The pathogenesis of DN is complex, multifactorial and involves direct effects of hyperglycaemia in many kidney cells, namely in glomerular, tubular, vascular and interstitial renal cells. Besides hyperglycaemia, genetic predisposition, age, obesity, hypertension and dyslipidaemia can also contribute to the induction and/or progression of DN. Kidney fibrosis, clinically starting by an increased glomerular filtration rate (GFR) and microalbuminuria, is a pivotal pathological process of advanced disease, but oxidative stress and inflammation are also key mechanisms of DN [323–325]. Cardiovascular disease is the main cause of death in patients with DN and CKD, due to a

myriad of risk factors, including hypertension, dyslipidaemia and diabetes; however, they do not fully account for the increased prevalence of CKD, and non-conventional risk factors has been received increasing attention during the last years, in particular chronic low-grade inflammation [326]. This condition is strongly associated with T2DM, CKD and ESRD [326–328]; however, while in T2DM patients, inflammation is typically viewed as a consequence of obesity and factors released from the inflamed adipose tissue [329], in CKD and ESRD patients other factors might contribute to the persistent inflammatory state [327,328]. Recent evidences suggest that kidney disease might be linked to changes in GM, although the cause-consequence relationship remains to be elucidated [330–333]. In any case, current knowledge suggests that both factors may influence each other. Indeed, intestinal dysbiosis could be a risk factor for renal disease development or progression, which, on the opposite direction, contributes to aggravate dysbiosis usually present in CKD individuals [23,334].

GM has been identified as a promoter or mediator of systemic inflammation [228,333]. Interestingly, patients with inflammatory bowel diseases (IBD) frequently suffer from renal disorders, such as nephrolithiasis or nephritis (tubulointerstitial and glomerular) [335]; in addition, in both CKD and IBD, *Prevotella* and *Lactobacillus* are reduced and Bacteroidetes and Enterobacteriaceae genres are increased [336,337]. The intestinal microbiome composition similarities suggest that gut dysbiosis could be involved in the development of systemic inflammation in both CKD and IBD. Regarding the kidney disease, the state of low-grade inflammation seems to be influenced by the aforementioned translocation of endotoxins (namely LPS) from the gut lumen to the blood, due to the augmented intestinal wall permeability [330,338]. Furthermore, gut microbiota seems to have a role on IgA nephropathy, a disease with a major involvement of the immune system, which is importantly influenced by the microbiota [339]. In addition, changes on GM composition, diversity and function could also affect host physiology, namely due to impact on metabolites synthesis and nutrient utilization [228].

As previously mentioned, diet has a pivotal impact on GM composition and metabolism [340,341], which is particularly relevant in the case of kidney disease patients due to dietary restrictions they are submitted, namely to control potassium levels. The principal diet sources of potassium and fiber (the main substrate for colonic bacterial fermentation) are vegetables and fruits, which are usually low in kidney disease patients' diet. These patients typically experience prolonged GI transit time due to low intake of fibers, together with other factors associated with their treatment measures (such as dialysis, phosphate binders, low fluid intake), with comorbidities (including malnutrition and diabetes) and with lifestyle (namely sedentarism). This condition causes increased fermentation of protein and carbohydrate in the gut proximal segments [342], which reduces its availability to the colonic bacteria. Furthermore, there is an impaired digestion and absorption of proteins in kidney disease patients [343] as a result of deregulated GI tract motility, hypochlorhydria, and bacterial overgrowth in the small bowel, which leads to an increment of intact protein in the colon for proteolytic bacteria [342,344,345].

Overall, strong evidences have been suggesting a causal relationship between kidney disease and GM dysbiosis in such a way that dysbiosis promotes chronic inflammation and contributes to kidney disease which, on the other hand, changes the gut milieu, thus modifying gut microbiome towards a dysbiosis, in a vicious cycle (Fig. 2) [346].

5.2. GM dysbiosis and inflammation in kidney disease

While the normal GM protect the kidney, dysbiosis can promote kidney disease development [334]. Changes in the GM composition have been documented in CKD patients, even at earlier stages of the disease [347]. Increased amounts of species from the families Enterobacteriaceae and Pseudomonadaceae of the Proteobacteria phylum, Bacteroidaceae, and Clostridiaceae have been documented. As recently reviewed by Kanbay et col. [330], these species are usually associated with directly and/or indirectly promotion of local and systemic inflammation. In fact, Enterobacteriaceae and Proteobacteriaceae, of the gram-negative phylum Proteobacteria, are promoters of several deleterious action, such as production of pro-inflammatory substances, namely IS, PCS, TMAO, bile acids lithocholic acid (LCA) and deoxycholic acid (DCA), augmented mucus permeability and translocation of bacterial products and LPS to the circulation, as well as increased ratio of intestinal Th17/Treg cell [348–351]. At the same time, kidney disease patients present decreased composition in species from Lactobacillaceae, Prevotellaceae and Bifidobacteriaceae families [337]. These kinds of microbial species are usually associated with protection of gut barrier function; production of anti-inflammatory mediators and beneficial components, such as SCFAs, γ-aminobutyric acid (GABA), ACh, nitric oxide (NO), chenodeoxycholic acid (CDCA), and ursodeoxycholic acid (UDCA), vitamin B complex, PYY, GLP-1 and GLP-2, as recently reviewed [330].

Inflammation and immune deregulation are key features of microbial dysbiosis in kidney disease (Fig. 2) [352]. As a result of gut inflammation and of the leaky gut syndrome, the NF-kB pathway is activated, there is a deregulated immune response, and a chronic production of pro-inflammatory cytokines which, collectively, causes systemic inflammation; LPS translocation stimulates immune system cells, in particular and endothelial cells, that in turn secrete larger amounts of different pro-inflammatory cytokines [353,354].

5.3. GM dysbiosis derived-uremic toxins contribute to progression of renal injury

GM dysbiosis is a source of uremic toxins. Due to dietary restrictions and impaired GI functions, the metabolism of bacteria shifts towards a primarily proteolytic fermentation pattern in kidney disease. There are several conditions, including changes in dietary pattern, able to affect GM towards dysbiosis, causing excessive production of uremic toxins, such as NH3, amines, indoles, thiols and phenols. Urea, a metabolite produced by the urea cycle in the liver from dietary/endogenous amino acids and their catabolism in peripheral tissues, is mainly (80%) excreted into urine and a minor part (20%) by the GIT. Mammals cannot break down urea, which is converted into ammonia (NH3) and carbon dioxide by urease, a role played by gut bacteria. Part of this ammonia is converted back to urea, while other part is transformed in ammonium hydroxide (NH_4OH) and eliminated in feces [355]. NH3/NH4OH formation and a rise in gut lumen pH alter commensals-pathogens balance and causes proliferation of pathogenic bacteria [356], which favors disruption of gut barrier integrity and translocation of bacteria and their metabolites (such as LPS), as well as uremic toxins, into the systemic circulation, resulting in kidney disease progression [354]. IS and PCS, which are end-products of protein fermentation, and TMAO, a metabolite of dietary choline, phosphatidylcholine (lecithin), and L-carnitine, are prototypes of uremic toxins derived from GM.

Tryptophan from the diet is metabolized by tryptophanase into indole by intestinal bacteria (e.g. *E. coli*), and then absorbed into the blood where it is metabolized to IS in the liver, which is mainly eliminated by the urine. Clinical and experimental data suggest a deep association between IS and kidney disease progression. In fact, a study performed in patients suggested that baseline IS levels might be used as a predictor of loss of kidney function [357]. In animal models, IS treatment was associated with kidney damage and increased expression of genes related to tubulointerstitial fibrosis [358,359]. PCS is a colonic fermentation product of the amino acids tyrosine and phenylalanine. Serum levels of IS and PCS are negatively correlated with renal function and gradually increases with kidney disease severity [360,361]. The reduced clearance of IS and PCS, due to albumin bound, causes progression of kidney and cardiovascular disease, and contributes to mortality in CKD patients [362]. The accumulation of uremic metabolites induces production of ROS and release of mediators of

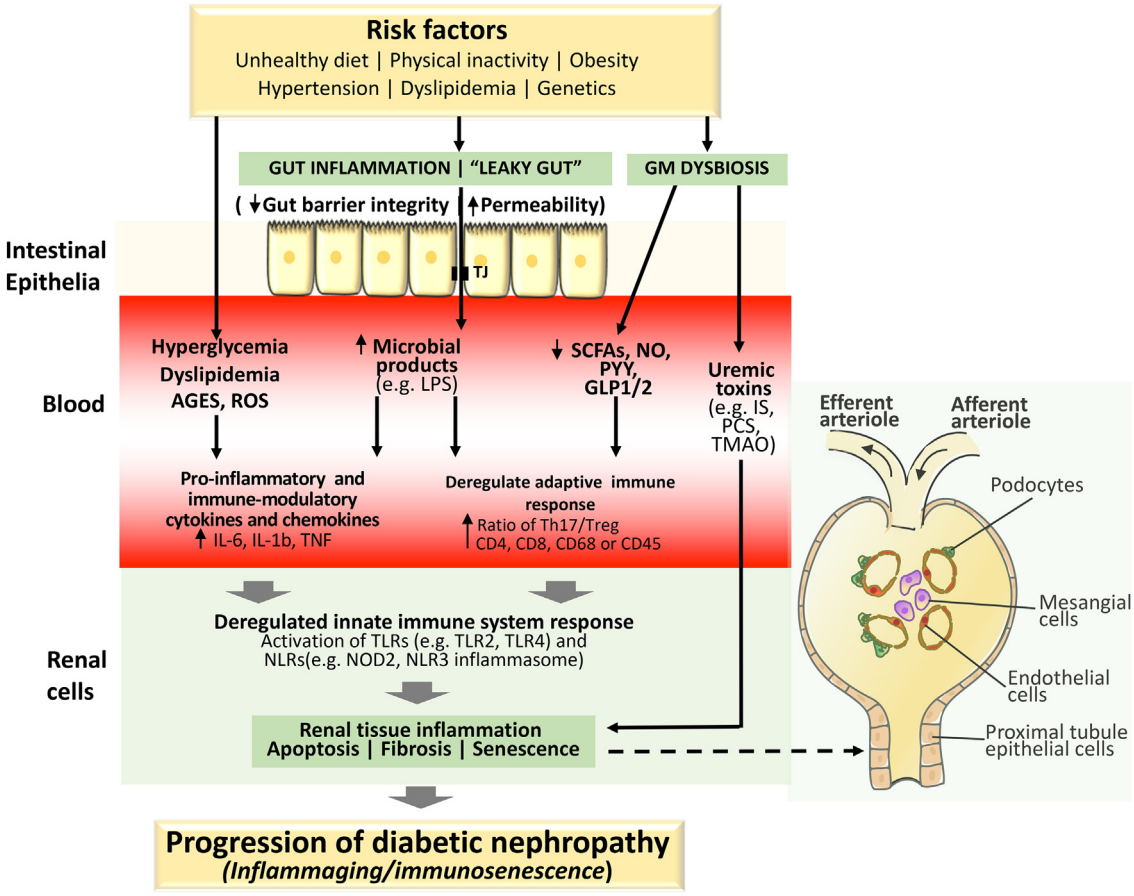

Fig. 2. Mechanisms linking diabetic risk factors and its major features, as well as gut microbiota dysbiosis, with the progression of diabetic nephropathy, via promotion of a state of systemic low-grade inflammation, activation of adaptive and innate immune responses, as well as production of uremic toxins, which collectively contribute to renal tissue inflammation, apoptosis, fibrosis and senescence, resembling the renal inflammaging process.

inflammatory (namely IL-6 and MCP-1 levels), which damages renal cells, including tubular cells and podocytes (Fig. 2) [363,364]. Podocytes, in particular, are pivotal for the glomerular filtration barrier and have a major role in the regulation of proteins passage from the lumen of capillaries to the Bowman's space; due to limited ability to regenerate, podocyte damage causes proteinuria and nephrotic syndrome development. Under conditions of gut dysbiosis, the IS receptor (arylhydrocarbon receptor: AhR) is persistently activated, thus causing evolution of renal disease by damaging the podocyte and the glomerulus, by means of changes on cell morphology, augmented expression of pro-inflammatory cytokines and chemokines, together with reduced expression of podocyte-specific genes and cell viability (cytoskeletal) proteins [364]. Other studies show evidences that proximal tubular cells exposed to IS and PCS develop an epithelial mesenchymal phenotypic transition with overexpression of transcription factors associated with interstitial fibrosis and glomerulosclerosis, such as Snail, fibronectin and alpha-smooth muscle actin [365]. Finally, TMAO has been associated with renal and cardiovascular disease, both in preclinical and in human studies. In animal models, increased TMAO levels were connected with augmented tubulointerstitial fibrosis, promotion of renal oxidative stress and inflammation [366]. In humans, TMAO levels were associated with atherosclerotic disease and long-term mortality in kidney disease patients [367,368].

5.4. Innate immunity-evoked inflammation in DN as an inflammaging process

Although inflammation is a hallmark of most of the metabolic diseases, as DN has been considered, latest findings raised the hypothesis that innate immunity may play a major role in DN development and/or progression; in fact, the two mechanisms seem closely linked in several disorders, including in DN [13,369]. As previously mentioned, the innate immune system comprises a variety of classes of PRRs, including TLRs and NLRs, which recognize extracellular space PAMPs and DAMPs and mediate intracellular pathways by activating transcription factors able to regulate the expression of proinflammatory cytokines and chemokines that will eradicate pathogens. In addition to endogenous signals related with renal tissue damage, LPS and other microbial products can activate TLRs which are present not only in expressed in leukocyte subsets but also in non-immune cells, namely in kidney cells. This intricate link between the activation of innate immunity and inflammation seems to be pivotal for progression of DN by inducing mechanisms of renal tissue apoptosis, senescence and fibrosis (Fig. 2) [369–371].

An increasing amount of evidences suggest that TLRs (namely TLR2 and TLR4) activation is deeply involved in kidney injury under diabetic conditions, particularly due to the impact on innate immunity and associated cytokine response [369,372] (Fig. 2). This effect could result from infiltrating circulating cells, namely macrophages, or by direct activation of resident cells as a result of hyperglycaemia, LPS or DAMPS [369]. In the diabetic kidney, TLR4 overexpression was found in both in glomeruli and tubules, in both microalbuminuria and overt diabetic [373]. Macrophage infiltration in the renal tissue of DN db/db mice was associated with prolonged hyperglycaemia, glomerular and tubular damage, renal fibrosis, and kidney expression of macrophage chemokines [374]. When compared with mice with TLR4 ablation, the will-type animals treated with STZ showed overexpression of markers of fibrosis (type IV collagen and TNF), increased macrophage infiltration and NF-κB activity, augmented renal expression of TLR4, MyD88, IRF3,

TNF, IL-6, and MCP-1, as well as reduced number of podocytes and expression of podocin [375]. In macrophages from STZ-mice, predominantly from the pro-inflammatory M1 phenotype, TLR2 and MyD88-mediated signaling were increased; an effect that was blunted with TLR2 ablation, as well as other typical features of DN, including albuminuria, kidney hypertrophy and podocyte loss, accompanied by macrophages change to the M2 anti-inflammatory phenotype [376]. In human proximal tubular cells, TLR2 silencing prevented the HMGB1-induced NF-κB activation [377].

Similar participation of TLRs in cytokine response was demonstrated in the kidney of DN patients [378]. Although the inflammatory response might vary between microalbuminuria and macroalbuminuria, and among different renal compartments or cells, constitutive expression of TLRs (namely TLR2 and TLR4) was already found in tubular epithelial, glomerular endothelial cells and podocytes [379]. However, mRNA expression of inflammatory and immune system markers (such as IL-6, CCL2, CD4, CD8, CD68 or CD45 positive cells) was mainly detected in the kidney of diabetic patients under macroalbuminuria conditions [373]. In opposition, TLR4 expression was found in early stages (microalbuminuria) in the glomeruli while TNF overexpression was observed in the renal tubulointerstitium in overt DN; these observations led authors to suggest that initial activation in the glomerular compartment, under microalbuminuria circumstances, produce chemokines that recruit activated macrophages to induced a major inflammatory response in the tubulointerstitium, under conditions of overt DN [373]. In this sense, TLR4 overexpression in the glomerular cells could be viewed as a promising predictor of renal function decline in microalbuminuric patients.

A diversity of circulating factors could be recognized by kidney TLRs, thus inducing an inflammatory reaction, including hyperglycaemia, LPS and other microbial products, as well as PAMPs and DAMPs. Several in vitro and in vivo studies have been suggesting that hyperglycaemia induces an overexpression of TLRs (TLR2 and TLR4) that stimulates and inflammatory response, via cytokines, chemokines and adhesion molecules (such as IL-6, IL-8, NF-κB, CCL-2, MCP-1, ICAM-1 and VCAM-1); some of these responses are abolished in mice with TLR2 or TLR4 deficiency [291]. The upregulation of TLR4 by hyperglycaemia has been documented in almost all kidney cell types, such as podocytes, mesangial and proximal tubule cells [380]. Interestingly, hyperglycaemia-induced activation of the signaling pathways of TLR4/NFκB p65/NGAL (neutrophil gelatinase-associated lipocalin) in rat mesangial cells was accompanied by reduced expression of Klotho mRNA and promotion of fibrosis and inflammation, thus suggesting that the anti-ageing effect of Klotho may occur via TLR4 suppression [381]. Besides hyperglycaemia, hyperlipidaemia is an independent risk factor for the progression of DN; this effect seems to be also mediated by TLR4 in mice [382].

Various studies support a role for NLRs, including NOD2 and NLRP3 inflammasome, in the pathogenesis of DN. In particular, NOD2 overexpression was demonstrated in animal models of diabetes (such as HFD-induced and STZ-induced diabetic mice) and in T2DM patients [383]. Podocytes treated with high glucose levels or with other stimuli, such as AGEs or TNF, presented NOD2 overexpression; some of these effects, as well as hyperglycaemia-induced downregulation of the expression of nephrin, were absent in mice with NOD2 ablation. These, and other findings from other studies, collectively suggest that NOD2 play an important role in the association between kidney injury in DN and podocyte inflammation and insulin resistance [383]. The same influence seems to be exerted by NLRP3 inflammasome in DN. In fact, several danger signals are able to induce renal NLRP3 inflammasome activation, which then perpetuates inflammation in DN. Some of these signals include urate and lipids (hyperuricaemia and dyslipidaemia), extracellular ATP and mitochondria-derived ROS, which induced overexpression of NLRP3 inflammasome components (including ASC and caspase-1) and increased production of caspase-1 and IL-1β [384–387].

In addition, as previously mentioned, endotoxins in circulation are also involved in innate immunity activation in the kidney. Increased serum LPS activity has been associated with evolution from metabolic changes of diabetes to kidney disease in DN due to kidney TLR4 activation and evolution of albuminuria, as suggested by studies in T1DM that further progress to DN [388,389]. Besides glucose and LPS, other endogenous ligands (e.g. AGEs) are able to interact with TLRs, whose expression interestingly changed on more advanced forms of DN, being expressed throughout the brush border of proximal tubule cells; this location favors the interaction of these ligands in circulation with the receptors, as was recently suggested by Garibotto et al. [371]. These authors previously purposed that the increased glucose reabsorption that occurs in the proximal tubule in type 2 DN patients could be a pivotal driver for the activation of TLR4 that further triggers the mechanisms for interstitial fibrosis development and evolution of nephropathy, including through induction of inflammation, apoptosis and cell senescence [390,391]. Concomitantly, human proximal tubule cells under hyperglycemic conditions present features of an exacerbated oxidative stress response, as well as markers of apoptosis and cell senescent, including reduction of telomere lengths [391,392]. The accelerated senescent phenotype in tubule cells, also seen in podocytes, found in type 2 DN strongly suggests that diabetes induce pathways associated with kidney cell senescence similar to those that occur in “physiological ageing” in both animals and humans's kidneys [393,394]. The immune-inflammation seen in DN seems to share several features of “normal” uremic inflammation of ageing process, the so-called “inflammaging”, such as altered nutrient sensing, mitochondrial dysfunction, autophagy, telomere shortening and accelerated senescent phenotype of different types of renal cells, which is a major cause of reduced regenerative potential and aggravated functional loss of the kidney tissue (Fig. 2).

6. Conclusions

A paradigm is emerging, based on the outstanding advances of modern molecular techniques, whereby the relationship between GM composition and immunity influences host metabolism. It is now clear that gut dysbiosis and their products can dictate a secretory associated senescence phenotype and chronic low-grade inflammation, features shared in the physiological process of ageing (“inflammaging”) and of age-related disorders such as T2DM (“metaflammation) and its microvascular complications. Evidence from centenarian studies has shown an enhanced pro-inflammatory background accompanied by fine-tune immune training and enhanced anti-inflammatory phenotype, a sort of hormetic system argued as the main contributor to longevity. Paradoxically, the regular exposure to T2DM pro-inflammatory status appears useless to evoke an effective anti-inflammatory phenotype and an overwhelmed immune response chronically subsists. Lifestyles, genes and temporal sequence of antigens that everyone is exposed during the whole life imprint an immunobiography that probably predicts how each will respond to stressors, culminating in an “healthy” ageing or in the development of age-related pathologies.

Diabetic complications, especially DR and DN, have been difficult to treat with glucose-lowering medications, probably because much senescent cell burden occurs before diagnosis. This review focused on the link between GM dysbiosis and the most common mechanisms of ageing and diabetic microvascular outcomes, such as cellular immunosenescence and silent inflammation. In fact, low-grade inflammation is a critical factor contributing to the development of the T2DM related microvascular complications, DR and DN. It is highly likely that increased levels of bacterial endotoxins, such as LPS, in circulation can play a central role in the genesis of obesity- and diabetes- related inflammation. Leakage and translocation of microbial metabolites and structural bacterial components through the intestinal barrier to the circulation are able to trigger oxidative stress and pro-inflammatory pathways, that ultimately results in vascular dysfunction.

A possible mechanism linking the GM dysbiosis to microangiopathies can involve the activation of key mediators of the innate immunity, namely the TLRs, eliciting abnormal vascular and systemic inflammatory responses. In addition to alterations in other metabolic and signaling pathways caused by aberrant glucose and lipid metabolism, LPS-mediated signaling pathway may promote and exacerbate endothelial dysfunction. This review provides clues to the putative function of mediators that links GM dysbiosis and diabetic retinopathy/nephropathy complications. Much also remains to be learned about host immunity-GM homeostasis, one of the foremost challenge over the next decade. Since intestinal microflora represents an important source of host's metabolic variability, future research needs to consider not only the host genome and/or lifestyles, but also the GM within human susceptibility to T2DM management and progression of vascular complications. Such knowledge may open new avenues to the current arsenal of GM modulators (such as antibiotics, prebiotics, probiotics and/or symbiotics), paramount for the design of more successful personalized therapeutic approaches targeting patient's requests.

Transparency document

The Transparency document associated with this article can be found, in online version.

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