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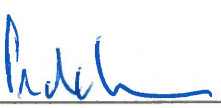
Assinatura conforme cartão de identificação: 

À Bea.
Aos que sempre acreditaram.

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Therapeutical uses of microbiote modulation

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Abstract

The human Microbiota consists of the 10-100 trillion symbiotic microbial cells harboured by each person that can therefore be considered as an ecosystem or a "super-organism". Microbiota is the microbial taxa associated with individuals while Microbiome is defined as the collective genomes of the microbes (bacteria, bacteriophage, fungi, protozoa and viruses) that live inside and on the human body.

The gut Microbiota is increasingly regarded as an 'invisible organ' of the human body and considered an important factor for host health, playing a major role in homeostasis. It is by far the most studied of all human ecosystems and arguably the one that most impacts global health status.

Recently a lot of investigation has been dedicated to the field of Microbiota/Microbiome namely in what concerns the association between quantitative and qualitative changes in Microbiota/Microbiome and several pathologies.

These pathologies include obesity and cardiovascular diseases, diabetes, central nervous system and degenerative diseases among many others.

Various strategies can be used in order to modulate Microbiota alterations including administration of antibiotics, prebiotics and probiotics, nutritional interventions and faecal transplants. Even though these strategies seem promising there is still a great need for more robust studies that can verify their effectiveness and evaluate the real relation between Microbiota changes and diseases reviewed.

Keywords: Microbiota, Gut Microbiota, Microbiome, Microbiota Interventions

1 – INTRODUCTION

Since Antoine van Leeuwenhoek first observed the microorganisms present in the human mouth in his microscope, in 1676, a lot has evolved in the field of Microbiology.

The late 19th century witnessed the development of bacteria culture techniques, instrumental in microbiological research. In the 1970s, strictly anaerobic culture techniques were developed. Yet, it was only after the advent of PCR and genome sequencing, in the 1980s that the field of Microbiota took off. In fact, the first step of the Human Microbiome Project was the sequencing of intestinal bacteria genome, performed by Steven R. Gill.

The initial phase of that project aimed to characterize the microbial communities from healthy individuals, across several different sites on the human body: nasal passages, oral cavity, skin, gastrointestinal tract, and urogenital tract using 16S rRNA sequencing [1]. This delivered the first characterization of the microbial variety and the understanding of the human body less as an entity and more as an ecosystem.

The continuous research on this field provided the first associations between microbial composition and some pathologies, the first being obesity, identifying organisms with either beneficial or harming properties.

The concept of bacteria that is beneficial for the health was first supported by Elie Metchnikoff, regarding the milk fermentation bacteria, and was later supported by the work of Louis Pasteur. The actual metagenomic era is seeing a great expansion of knowledge, evidenced by the ever increasing number of dedicated publications, and is considered by many as a new age for microbiology.

Microbiota is the microbial taxa associated with individuals. The human Microbiota consists of the 10-100 trillion symbiotic microbial cells harboured by each person [2].

Microbiome is defined as the collective genomes of the microbes (bacteria, bacteriophage, fungi, protozoa and viruses) that live inside and on the human body.

Dysbiosis is the condition of having imbalances in the microbial communities either in or on the body and its pathological relevance is increasing consistently.
Of all the human Microbiome ecosystems, the gut is by far the most diverse and probably the most influential on the global health status of an individual. Also, due to its importance and to study feasibility, it is the most thoroughly studied and that whose impact in pathophysiology is better understood.
This review aims to characterize the changes in Microbiota and Microbiome occurring in several pathologies as well as to describe therapeutic interventions that aim to increase health through gut Microbiota modulation.

2 - GUT MICROBIOME

The gut Microbiota is increasingly regarded as an 'invisible organ' of the human body and considered an important factor for host health [3], playing a major role in homeostasis. It is by far the most studied of all human ecosystems and arguably the one that most impacts global health status. Mainly composed of bacteria (but also of other eukaryotes, archae, virus and phages), it concentrates mostly in the colon.
The bacterial composition of the gut Microbiota changes along the GI length mainly due to host factors – pH, digestive enzymes, and immune system –, but also due to external factors – nutrients and environmental factors, and even microbial competition and synergies [4].
Over 30 bacterial phyla have been identified in the bacterial Microbiota with seven phyla accounting for its majority: *Firmicutes*, *Bacteroidetes*, *Actinobacteria, Cyanobacteria, Fusobacteria, Proteobacteria* and *Verrucomicrobia* [5]. The first two are by far the most representative of the gut Microbiota.
The gut Microbiota is established in early childhood and remains relatively stable throughout. Its composition is strongly influenced by factors like mode of birth, diet, diseases and medication [6]. Posterior imbalances or dysbiosis are associated with several pathologies and with the global quality of health of the individual.

2.1 - GUT MICROBIOME AND CARDIOVASCULAR DISEASE

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels that are currently the first cause of death worldwide. According to the World Health Organization (WHO), an estimated 17.7 million people died from CVDs in 2015, representing 31% of all global deaths [7]. Such numbers are expected to increase due to the marked incidence, prevalence and severity of the associated risk factors.

Gut dysbiosis is associated with several pathologies that are a cause of or a consequence of cardiovascular disease, namely atherosclerosis, hypertension, heart failure, obesity, type 2 diabetes mellitus, chronic kidney disease and myocardial infarction. The ratio *Firmicutes*-to-*Bacteroides* is the most studied parameter and the one that shows the greater association with different cardiovascular diseases. Additionally, the metabolic potential of gut Microbiota has been identified as a contributing factor in the development of diseases [8]. Gut Microbiota-host interactions occur through many pathways, including trimethylamine-N-oxide and the short-chain fatty acids acetate, propionate and butyrate [9].

It is known that bacterial composition is affected by many parameters like lifestyle factors, including diet and concomitant diseases. However, the real impact of dysbiosis and its role as a biomarker or as a therapeutic target is yet to be fully disclosed.

2.1.1. GUT MICROBIOME AND HIGH BLOOD PRESSURE

Elevated blood pressure is defined as 120 to 129 mm Hg systolic with a diastolic pressure below 80 mm Hg; Stage 1 hypertension as 130 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic; and Stage 2 hypertension as 140/90 mm Hg or higher [10].

High blood pressure is a complex and multifactorial condition influenced by a combination of genetic and environmental factors, including physical inactivity, obesity, high intake of fat, sugar and salt, smoking, and alcoholism [11]. On the opposite hand, high dietary intake of fruit, vegetables and fibre is associated with lower blood level pressures.

Since all these factors are also known to affect gut Microbiota composition, with a special emphasis on dietary choices [12], it is reasonable to postulate that gut dysbiosis is linked to regulating blood pressure and to preventing or treating hypertension.

In fact, one of the most important roles of the gut Microbiota is to yield energy and nutrients (metabolites and vitamins) by digesting dietary fibre, working symbiotically with the human body.

The consumption of a diet richer in fibre causes an increase in gut Microbiota that generates short-chain fatty acids, mainly by fibre fermentation [13], and is associated with a decrease in the incidence of cardiovascular disease and high blood pressure levels [14], even if the magnitude and type of effect is dependent on the type of ingested dietary fibre.

The main short-chain fatty acids that are produced are Acetate, Propionate and Butyrate and their relative percentage changes according to the qualitative and quantitative composition of the Microbiota present in the gut.

Butyrate is mainly used locally by colonocytes to maintain the integrity of the intestinal barrier and to lower inflammatory levels. Acetate and small quantities of both Butyrate and Propionate (metabolised in the liver) enter systemic circulation and reach organs that regulate blood pressure. [15]

The vast majority of the published studies that link gut dysbiosis with high blood pressure levels was performed in animal studies and therefore must be observed with caution when translating results and inferences to humans.

The first studies, published more than 40 years ago, described that germ free rats presented a decreased microvasculature response to catecholamine and a lower cardiac output than control rats [16].

Other studies, performed in hypertension genetic models, reported changes in the composition of gut Microbiota composition (namely in the *Firmicutes*-to-*Bacteroidetes* ratio, arguably the most described marker of dysbiosis), presenting a reduced number of species that produce Acetate and Butyrate, and an increased percentage of lactate producers [17].

The same research group performed Microbiota diversity analysis in a cohort of controls, a cohort of pre-hypertensive and a cohort of patients with primary hypertension. Interestingly they found no significant differences between

Microbiota diversity for the pre-hypertension and the primary hypertension cohorts, and did find that these groups presented a decreased microbial richness and diversity, a *Prevotella*-dominated gut enterotype, a distinct metagenomic composition of reduced bacteria associated with healthy status and overgrowth of bacteria such as *Prevotella* and *Klebsiella*, and a disease-linked microbial function [18]. The fact that pre-hypertension and primary hypertension groups presented similar gut Microbiota patterns alerts us to the potential use of gut dysbiosis as an early marker for cardiovascular disease.

In the same paper [19], the authors conducted a faecal transplantation from hypertensive human donors to germ-free mice, elevated blood pressure was observed to be transferrable through Microbiota, and the direct influence of gut Microbiota on blood pressure of the host was demonstrated. Facts like this not only strengthen the association between gut dysbiosis and hypertension, but also should be taken into account when conducting faecal transplantation in humans.

The increase in blood pressure in spontaneously hypertensive rat was associated with gut pathology that included increased intestinal permeability and decreased tight junction proteins, but in this study pre-hypertensive rats presented similar profiles to that of control ones, with *Firmicutes*-to-*Bacteroidetes* dysbiosis being evident only for the hypertensive group [20].

Reduced Microbiota richness had also been demonstrated in animal models of hypertension, like the angiontensin II induced hypertensive mice with a decrease in *Bacteroidetes* when compared to sham-salt mice, but a higher prevalence of *Proteobacteria* and *Cyanobacteria* [17].

The importance of salt in hypertension is well established. The proximal colon is a primary site for gut Microbiota and an important site for dietary absorption. The role played by gut Microbiota was investigated using rats genetically modified either to be sensitive to or resistant to high salt intake diets. These authors observed a gut Microbiota composition difference between the sensitive and the resistant strains, with a higher prevalence of *Bacteroidetes* for the

sensitive group, a lower level of faecal bacteria of the family *Veillonellaceae* and increased plasma acetate and heptanoate were features associated with the increased blood pressure observed in the sensitive rats given resistant rat Microbiota compared with the S rats given S rat Microbiota, indicating a plausible link between microbial content and blood pressure regulation [18,19,20].

A case-control study of the association between Metabolome, the global collection of all low molecular weight metabolites that are produced by cells during metabolism,and Hypertension Risk identified multiple metabolites associated with hypertension risk. For example, higher levels of lyxose, a fermentation product of gut microbes, were associated with higher risk of hypertension, strengthening the thesis that gut Microbiome plays an important role in the pathogenesis of hypertension [21].
Besides those metabolites, short chain fatty acids produced by bacteria are also known to mediate arterial resistance [22], which is consistent with findings indicating that Acetate and Propionate reduce blood pressure levels in animal models, mainly due to a combination of actions in renal mechanisms [23].

The association between gut dysbiosis seems to be ever more clear, even if causality or consequence is yet to be established and understood. More and more studies are being conducted in this field and there is also evidence being gained of prebiotics and probiotics impact in regulating blood pressure. Preliminary data also seems to suggest interaction between gut Microbiota composition and blood pressure drug's effectiveness.

2.1.2 GUT MICROBIOME AND DYSLIPIDAEMIA AND ATHEROSCLEROSIS

Dyslipidaemia is an elevation of plasma low-density lipoprotein (LDL) cholesterol, triglycerides (TGs), or both, or a low high-density lipoprotein (HDL) level.
Due to the fact that gut Microbiota is directly involved in the lipid metabolism, it is understandable that it plays a role in dyslipidaemia.

The colonic fermentation of carbohydrates and fibre produces short-chain fatty acids (SCFA), which may impact a number of physiological processes related to human energy metabolism, including satiety, hepatic lipogenesis, adipocyte fat deposition and thermogenesis [24]. Also, a variety of signalling molecules produced by gut bacteria potently affect hepatic lipid and bile metabolism, reverse cholesterol transport, energy expenditure, and insulin sensitivity in peripheral tissues, thus playing a major role in many metabolic pathways [25].

Associations have been established between gut Microbiota and the levels of serum triglycerides and HDL cholesterol, as well as between a total of 34 intestinal bacteria taxonomies and body mass index (BMI) and blood lipids. The gut Microbiome appears to make a significant contribution to the variance seen in individual BMI and to the blood levels of triglycerides and HDL, beyond that of clinical risk factors and genetics, whilst manifesting little effect on LDL or TC levels [26].

Other studies confirmed not only previously known associations between obesity and certain bacterial taxa (such as *Akkermansia*, *Christensenellaceae*, and *Tenericutes*), but also that some of the associations with microbial composition were shared between BMI and levels of triglycerides and HDL and novel associations with *Eggerthella, Pasteurellaceae*, and *Butyricimonas* [27].

Interestingly, only weak correlations were found between Microbiota variation and total cholesterol or LDL cholesterol levels, suggesting that gut Microbiota intervenes more specifically in other lipoproteins [25].

Another consequence described, effects on reverse cholesterol transport – a crucial atheroprotective function of HDL –, could subsequently influence the development of atherosclerosis [28].

Modulation of gut Microbiota using different strategies has proved efficient in either repairing gut dysbiosis, but also in treating dyslipidaemias. Soluble fibres, like Polydextrose (PDX), present lipid lowering effects. PDX reduces triglycerides and cholesterol by influencing the gut Microbiota, which in turn modulates intestinal gene expression. In mice fed with western diet PDX promoted systemic changes via regulation of the gut Microbiota and gene expression in intestinal

tract [29]. Faecal transplants and the use of other prebiotics and probiotics have also proved to be effective. This suggests that the gut Microbiota can be a concomitant target for treating dyslipidaemias and other vascular related disease.

Atherosclerosis is a condition where the arteries become narrowed and hardened due to a build-up of plaque lining their walls and is directly related to lipid levels and inflammation.

Gut Microbiota changes have also been found between patients suffering from atherosclerotic cardiovascular disease (ACVD) and healthy controls. An abundance of differences was found between the two groups in major genera of the gut Microbiome, such as a relative reduction in *Bacteroides* and *Prevotella*, enrichment in *Streptococcus* and a higher proportion of *Enterobacteriaceae* (including *Escherichia coli, Klebsiella spp*., and *Enterobacter aerogenes*) in ACVD patients [30]. The same authors described a reduced potential for the synthesis of tetrahydrofolate and altered potential for homocysteine metabolism in the gut microbiome of ACVD patients compared with controls.

Factors like trimethylamine N-oxide (TMAO), trimethylamine (TMA)-Lyases (choline, betaine, carnitine) and other bacterial virulence factors play an important role also on the severity and intensity of atherosclerotic cardiovascular disease. Dietary supplementation of mice with choline, TMAO or betaine promoted upregulation of multiple macrophage scavenger receptors linked to atherosclerosis, and supplementation with choline or TMAO promoted atherosclerosis [31].

Microbiota is involved in atherosclerosis via different pathways. Gut permeability and translocation of bacteria and their metabolites (LPS) into the circulation occur as a result of gut dysbiosis. The elevated levels of the circulating LPS promote inflammation and foam cell formation [32].

This increased knowledge of gut Microbiota changes and atherosclerotic cardiovascular disease opens space to identification of early disease biomarkers and to new therapeutic targets.

2.1.3. GUT MICROBIOME AND MYOCARDIAL INFARCTION AND STROKE

Atherosclerosis, dyslipidaemias and a combination of environmental and genetic factors are on the genesis of events like myocardial infarction and stroke that are worldwide amongst the leading causes of morbidity and mortality.

Since cardiovascular diseases are strongly influenced by dietary styles which also strongly affect the gut Microbiota and since gut Microbiota is, in turn, known to influence lipid metabolism, insulin resistance, and inflammation, it is of little surprise that there is an association between gut Microbiota and both myocardial infarction and stroke.

In fact, Zunini Vahed et al [32] elegantly described disturbed Microbiota as an enemy for the cardiovascular system, responsible for an increased incidence and severity of cardiovascular disease.

Trimethylamine N-oxide induces platelets hyper-reactivity and consequently creates a pro-thrombotic status. It may also induce gut Microbiota dysbiosis. On the other hand, gut Microbiota plays a major role in the generation of TMAO via conversion of dietary nutrients that possess a TMA moiety (such as choline, phosphatidylcholine, and L-carnitine) into TMA by specific microbial choline trimethylamine lyases [8].

A mechanistic link between the gut Microbiota and the severity of myocardial infarction has been reported in animal models where antibiotic-induced changes in the abundance of individual groups of intestinal Microbiota dramatically altered the host's metabolism. The most affected pathway was the catabolism of the aromatic amino acids phenylalanine, tryptophan and tyrosine and resulted in the decreased severity of an induced myocardial infarction [33].

Gut Microbiota also seems to attenuate post myocardial infarction events by means of modulating inflammatory and immune response, attenuating post infarction vulnerability to apoptosis and depression, and delaying post-infarction heart failure [32].

Again, gut Microbiota modulation strategies can prove effective in successfully treating these pathologies.

2.2 GUT MICROBIOME AND OBESITY

World Health Organization defines overweight and obesity as abnormal or excessive fat accumulation that may impair health. Obesity is considered an epidemic disease in developed and developing countries and is escalating in all population groups. Some possible explanations include increases in energy intake, changes in the composition of diet, reduced physical activity, and changes in the gut Microbiome [34].

The relation between gut Microbiota and obesity has been the focus of several investigations. It has been shown that the gut Microbiota influences energy balance by producing SCFA from complex polysaccharides either by digestion or fermentation (together with residual proteins that cannot be digested by human enzymes; this also creates branched-chain fatty acids, gases, and other metabolites). Acetate (C2), Propionate (C3) and Butyrate (C4) are the main products with impact on health [35].

Obese patients often present with intestinal dysbiosis, creating changes in the quali-quantitative composition of intestinal commensal bacteria, reversible through weight loss.

In obesity, gut Microbiota usually shows decreased diversity, a decreased *Bacteroidetes*-to-*Firmicutes* ration (with increased capacity to harvest energy from diet), and altered fermentation products (mainly SCFA).

It is also known that long-term diet habits influence the composition of gut Microbiota [36]. Intestinal bacteria react to daily dietary fat and carbohydrates, changing their metabolic pattern. Still, the extent, mechanisms and consequences of a dietary shift remain unknown [37].

Such studies imply the participation of SCFA production in obesity (by sourcing extra energy). However, SCFA are also responsible for opposite mechanisms of energy expenditure, such as the production of anorectic hormones and appetite regulation, that may prevail in a non-obese person.

Furthermore, the chronic inflammation linked to obesity is associated with changes in Microbiota composition and intestinal permeability [38], in mechanisms yet to be understood, but that can eventually be used to prevent and to treat these disorders.

For research purposes germ-free mice were inoculated with normal gut microbial cells from conventionally raised mice, which resulted in a 60% increase in body fat and insulin resistance, even with a 27% reduction in food intake. They also found that bacterial colonization increased the storage of triglycerides in the adipocytes of the inoculated mice [39].

Other authors also performed a study in which germ-free mice were colonized by faecal Microbiota of twins discordant for obesity or by cultured collection of lean or obese animals. Faecal cultured or uncultured faeces of obese animals originate significantly higher increase in body mass and adiposity than those of lean animals, whereas transplanted Microbiota of lean animals was correlated to higher quantity of SCFA in lean animals. When the animals were cohoused (obese and lean) the obese animals stopped their body weight gain modifying also their Microbiota profile like lean animals (increasing *Bacteroides*). The study was also conducted under 2 types of diet (low saturated fat and high saturated fat). The bacterial invasion colonization and phenotype change only occur in low saturated fat diet revealing a diet-dependent mechanism between diet and Microbiota [40].
Interestingly, not only does the Microbiota, but also the Mycobiota – related to the fungal composition –, seem to be altered in obese individuals [41].

Even though these studies are quite promising it should be stressed that they were conducted in vitro or in animals and that translation to humans is hard and should be taken carefully. Nevertheless, strategies that modulate the gut microbial composition will be of increasing utility for the treatment of obesity and are expected to enter the clinical practice during the next years.

2.3 GUT MICROBIOME AND DIABETES

Diabetes is a worldwide disease whose incidence has been increasing steadily over the last decades. Diabetes is highly influenced by diet and intimately related

to other pathologies described in this review and, therefore, expectedly associated with gut dysbiosis.

Gut Microbiota interferes with diabetes pathogenesis in several ways, including energy metabolism, gut permeability, metabolic endotoxemia and by interacting with the immune system [42].

The gut Microbiota of patients with type 2 diabetes (T2DM) shows decreased levels of butyrate-producing bacteria (e.g. *F. prausnitzii*) and increased levels of *Firmicutes* and *Proteobacteria* [43]. These changes are accompanied by an increased expression of the Microbiota genes that enhance oxidative stress and inflammation [44]. Likewise, the altered levels of SCFA have implications concerning the inflammatory status.

The decreased levels of *Bifidobacteri*a stimulate the secretion of GLP1 and peptide YY that decrease resistance to insulin and enhance the functionality of β cells. These bacteria are also known to reduce intestinal permeability [45]. The marked increase in gut permeability, together with differences in Microbiota composition, has also been associated with the pre-pathological condition of Type 1 Diabetes T1DM [46]. An increase in gut permeability was similarly observed in T2DM patients, a situation that promotes endotoxemia and an increase of the systemic levels of LPS, inducing a deleterious continuous inflammatory state [47].

Firmicutes and *Actinobacteria* metabolize choline, producing metabolites demonstrated to induce Diabetes. The same *Firmicutes* are associated with a decrease in the levels of secondary biliary acids that play an insulin sensitizer role [48].

T1DM is also associated with gut Microbiota changes. Faecal analysis from these patients showed decreased butyrate-producing bacteria and less butyryl-CoA transferase genes (with a marked decrease in plasma levels of acetate and propionate). The levels of strains *Christensenella* and *Subdoligranulum* correlated with glycemic control, inflammatory parameters and SCFA [49]. Children with beta-cell autoimmunity have also shown low abundance of butyrate-producing bacteria and increased abundance of members of the Bacteroidetes phylum in faecal Microbiota [50].

Interestingly, metformin, a drug used in the treatment of diabetes, also modulates gut Microbiota [51].
Compared to participants without diabetes, participants with diabetes taking metformin had higher relative abundance of *Akkermansia muciniphila*, a Microbiota known for mucin degradation, and several gut Microbiota known for the production of SCFAs, including *Butyrivibrio, Bifidobacterium bifidum, Megasphaera*, and an operational taxonomic unit of *Prevotella* [52].

The association between gut Microbiota changes and Diabetes opens space not only to early disease biomarkers, but also to new therapeutic strategies, including the use of prebiotics, probiotics and faecal transplantation. Again, further and more robust clinical studies are necessary.

2.5 GUT MICROBIOME AND CHRONIC KIDNEY DISEASE

Kidney disease is closely linked to cardiovascular disease and is generally associated to a poorer prognosis of the latter.
Chronic kidney patients' gut Microbiota is significantly different from that of healthy controls, with an increase in pathogenic flora compared to symbiotic flora [53].
The most frequently described changes in the gut Microbiome of these patients include a reduction of the *Bifidobacteriaceae* and *Lactobacillaceae* levels and an increase of the *Enterobacteriaceae* levels [54].
Gut dysbiosis, responsible for a disruption of the intestinal epithelial barrier complex can then play an important part in the development of systemic inflammation by enabling the influx of endotoxins and other noxious luminal contents into systemic circulation [55]. Such contents include metabolites like ammonia, indoxyl sulphate and p-cresyl sulphate – associated with poor cardiovascular outcomes [56] –, and some products of the fermentation of undigested foods like sulphates, mainly associated with the family of tryptophanases of the phylum *Bacteroides*.

TMAO, a gut-microbial-dependent metabolite of dietary choline, phosphatidylcholine (lecithin), and L-carnitine, is elevated in chronic kidney disease and is also a good biomarker for cardiovascular disease, as it is an important regulator of fibrosis [57].

Modulation of the gut Microbiome composition in chronic kidney disease, either by prebiotics, probiotics or even selective antibiotics, may contribute to a decreased accumulation of gut-derived uremic toxins, high circulating level of lipopolysaccharides and immune deregulation, all of which play a critical role in the pathogenesis of chronic kidney disease and its complications [58].

2.6 GUT MICROBIOME AND LIVER DISEASE

Due to its anatomical location and physiological activity, the liver is in a key position to interact with gut Microbiota and the metabolites it generates. The liver receives 70% of its blood supply from the intestine, via the portal vein, and bile acids have been shown to facilitate the communication between the intestine and the liver [59].

Of all liver pathologies, non-alcoholic fatty liver disease appears to be one of the most directly associated with gut dysbiosis.

Non-alcoholic fatty liver disease (NAFLD), the most common liver disease in developed countries, has two main clinical phenotypes: non-alcoholic fatty liver (hepatic steatosis with minimal lobular inflammation) and non-alcoholic steatohepatitis (NASH, ballooning hepatocellular injury and an initial distinctive fibrosis pattern of perisinusoidal fibrosis surrounding the central veins [60]). It has been described as directly related to other pathologies like the metabolic syndrome, diabetes, and a combination of genetic and environmental factors like diet and lifestyle [61].

The gut Microbiota has been linked to non-alcoholic fatty liver disease in several ways. Altered gut Microbiota can activate the innate immune system, as it is an inducer of proinflammatory T helper 17 cells and regulatory T cells in the

intestine [61]; it can also make the intestinal barrier more permeable, allowing the passage of bacterial products into the blood stream [62].

Changes in gut Microbiome may also be the direct cause of hepatic inflammation. On the one hand, increased populations of gut *Enterobacteriales* and *Escherichia coli* generate LPS [63] which in turn interact with Toll-like receptors (TLRs), ultimately inducing cellular death; on the other hand, the previously referred increase in intestinal permeability raises the endotoxins load in portal circulation, promoting hepatic inflammation [64]. This constant inflammation is responsible for activating the inflamassome in a two-step process that generates a heavy hepatic inflammatory response [65].

Another crucial factor in liver steatosis is obesity, also well connected to gut dysbiosis and to changes in microbial induced metabolism (as described elsewhere in this review). The heavy lipid load associated with obesity acts as a cell stress inducer that activates the immune system. Also contributing to gut dysbiosis are the increased dietary levels of carbohydrates and fat, leading to lesser microbial diversity and to decreased *Bacteroidetes* levels relative to *Firmicutes* [66.] Furthermore, the chronic inflammation linked to obesity is associated with changes in Microbiota composition and intestinal permeability [38], in mechanisms yet to be understood, but that can eventually be used to prevent and treat this type of diseases. Additionally, in processes directly linked to the obesity pathways, exercise has demonstrated to be an effective non-pharmacological treatment for NAFLD.

Hepatic fibrosis is the main component of tissue remodelling eventually leading to cirrhosis, condition in which the liver does not function properly due to long-term damage. The process of fibrosis is linked to the Microbiota again via the TLR that not only signal for an increased expression of chemokines and adhesion molecules, but also, when activated, down-regulate the activin membrane bound receptor (BAMBI) and remove the fibrogenic brake thus facilitating disease progression [67].

Many studies revealed differences in Microbiota composition between controls and patients with fatty liver disease. While *Bacteroidetes* and *Firmicutes* remain the dominant phyla among NAFLD patients, their proportional abundance and genera detection vary among different studies [68]. *Proteobacteria* seem to play a protective role regarding steatosis while bacteria from the *Firmicutes* phylum are correlated to higher fatty liver disease risk [69]. Different studies associated *Bacteroides* to NASH and *Ruminococcus* to significant fibrosis. NAFLD severity associates with gut dysbiosis and a shift in metabolic function of the gut Microbiota [70].

Several other studies demonstrated an association between changes in the gut Microbiome and liver disease. It should however be emphasized that association is very different from causality and from a complete understanding of the underlying mechanisms and pathological pathways. Also many of the studies were performed either in animal models or in small human cohorts and using different methods; therefore, translation to clinic should be cautiously performed.

That said, it is unequivocal that gut Microbiota analysis adds information to classical predictors of NAFLD severity and suggests novel metabolic targets for pre-/probiotics therapies. Strategies like the increase in the consumption of fibre like pectin or probiotic treatment have been successfully studied [62], but are yet far from being used standardly in the clinics. Absorbable, enteral-active antibiotics like polymixin B and neomycin have also been studied for the treatment of dysbiosis and influence the outcome of chronic liver disease or cirrhosis [71].

Probiotics like *lactobacillus* are the components of many commercially available multispecies formulations such as VSL#3. In the rat gut, VSL#3 fortifies the intestinal barrier by increasing the amount of secreted mucus and upregulating Muc2 in the colon and occludin levels in the ileum [72]. Faecal transplants, however controversial, have also demonstrated to be effective and helpful when dealing with fatty liver disease.

By now, it is clear that gut Microbiome plays an important role in liver disease even if the pathophysiological mechanisms are not yet fully understood.

Precision medicine and the targets and prevention methods that will arise from the continuous study of this area will certainly bring new therapeutic tools in the next years.

2.7 GUT MICROBIOME AND INTESTINAL DISEASE

The effect of gut Microbiota dysbiosis in intestinal disease is probably the most logical, due to the local effect of the Microbiota. The best example that comes to mind is diarrhoea, a pathology in which gut Microbiota plays a major role in several ways, not only as cause, but also with protective effects [73].

Another frequent intestinal problem is constipation. Growing evidence indicates that alterations of intestinal Microbiota may contribute to constipation and constipation-related symptoms, namely by modulating gut mobility [74]. Differences in the composition of the intestinal Microbiota have been demonstrated when constipated patients and healthy controls were compared. Probiotics are frequently and successfully used for constipation treatment or prevention.

Several studies have reported differences between the Microbiota of inflammatory bowel disease (IBD; like Crohn disease and ulcerative colitis) patients and healthy subjects. A lower microbial diversity was found in IBD patients with an emphasis in a decrease of the *Firmicutes* quantity and an increase in the taxa belonging to the *Proteobacteria* phylum, generally associated with an increase in facultative anaerobes [75]. The reduction in this species lowers the production of SCFA increase regulatory T cells, which support immune tolerance and also have anti-inflammatory effects. This outgrowth of facultative anaerobic organisms may be driven by a change in the gut redox potential associated to the chronic inflammatory status [76]. A special role seems to be played by *F. Prausnitzii*, known to induce the production of IL-10 and inhibit the production of inflammatory cytokines, such as IL-12 and IFN-γ [77,] whose significantly lower levels in IBD lead to an increased probability of disease recurrence.

Colorectal cancer, another high prevalence intestinal pathology, is also strongly influenced by gut Microbiota [78]. This paper addresses the influence of dietary

patterns, fibre consumption, dietary supplements and concomitant disease on the Microbiota composition, and studied bacterial metabolites and how they can disrupt the gut barrier integrity and challenge immune homeostasis, increasing the probability of cancer.

The ever growing knowledge on gut Microbiota and its association with several intestinal pathologies opens new space for the identification of early biomarkers and for new therapeutic targets and strategies that will likely increase the life quality of these patients.

Arguably the most successful case of treating intestinal disease using gut Microbiota is the treatment of multi-resistant *Clostridium difficile* infection (CDI) using faecal Microbiota transplantation. CDI is a worldwide leading cause of mortality and morbidity and is becoming more and more resistant to antibiotics. This procedure, not yet fully regulated by the medicines agencies, has proven to be extremely effective in cases where administration of antibiotics failed. Strategies for performing effective treatments using faecal transplants were described in detail in papers like the ones referred by Dowle [79] and range from colonoscopy administration of enemas to oral administration of lyophilized contents inserted in capsules.

Faecal Microbiota transplantation (FMT) is emerging as a treatment option in the United States of America and in Europe, and a conference consensus paper [80] was recently published on this thematic. In the supplement of that paper other applications for FMT are evaluated even if they are not as strongly adequate as for refractory CDI treatment. These include Crohn disease and Irritable Bowel Syndrome.

2.8 GUT MICROBIOME AND CNS RELATED DISEASES

The connection between the gut and the central nervous system may not appear to be a direct one, but since the definition of the so-called gut-brain axis it is becoming more and more discussed and studied.

The first time an association between gut Microbiota and brain disease was reported was in the early 20th century, when the administration of lactic acid was tested in the treatment of depressive symptoms [81].

Perhaps the most evident established connection was between gut Microbiota and stroke/ischemic brain damage. As previously described, these patients may present some Microbiota alterations (namely decreased diversity, decreased levels of *Bacteroides*, increased *Atopobium* levels and changes in the microbial metabolism [82]), all of which are responsible for an increase in gut permeability, with consequent systemic inflammation and increased risk of infection, as well as an increased risk for thrombosis, due to an increase in the levels of TMAO[83]. Also, the composition of gut Microbiota is likely to affect the level of neuroinflammation by modulating T Cells and IL-17 levels [84].

Gut Microbiota is known not only to intervene in the synthesis of GABA, noradrenaline and dopamine, but also in the production of SCFA, that also present neuroactive actions. The fact that gut Microbiota plays such a key role in modulating neurotransmitters helps explain the fact that gut dysbiosis interfere in disorders like anxiety and depression. Neurotransmitters play a major role in several central nervous related diseases.

Gut Microbiota dysbiosis has been reported in preclinical data [85] and also in patients diagnosed with depression [86], namely by a noticeable decrease in microbial diversity. Prebiotics like galactooligosaccharide (GOS) have been found to be effective in reducing activation of the preclinical models of anxiety and depression and also in lowering cortisol levels in human volunteers [87]. Probiotics like *B. longum* effectively increased scores of depression even if it did not affect anxiety levels [88]. Evidence of the association between gut Microbiota and other psychiatric disorders was also found during faecal transplant procedures [89]; yet, there is still need for more robust clinical data.

Attention-deficit/hyperactivity disorder (ADHD) is associated with abnormalities in dopamine neurotransmission. The role of gut Microbiota is not clear, but a nominal increase in the *Bifidobacterium* genus was observed in ADHD cases with metagenomic revealing an increase in the bacterial gene

functionality encoding cyclohexadienyl dehydratase, an enzyme involved in the synthesis of phenylalanine, a dopamine precursor [90].

Gut Microbiota dysbiosis is also associated with a variety of neurodegenerative diseases like Alzheimer, Parkinson and Multiple Sclerosis.
In Parkinson, a degenerative disorder primarily affecting dopaminergic neurons of the substancia nigra, gastrointestinal dysfunction is frequently noticed before motor symptoms. Also, α-synuclein protein aggregates, characteristic of Parkinson disease, are also found in the enteric nervous system. Some parkinsonian patients present a decrease in the *Prevotella* species, combined with an increase in the *Akkermansia muciniphillia* [91]. The *Prevotella* species produces mucin that limits intestinal permeability and therefore helps prevent bacteria translocation to systemic circulation. A different study [92] demonstrated higher levels of proinflammatory bacteria and lower levels of anti-inflammatory bacteria in Parkinson patients compared to healthy controls. The accumulating preclinical and clinical data suggest than the Microbiota-gut-brain axis may be an interesting additional target for Parkinson therapeutics.

Alzheimer, also a neurodegenerative disease, is characterized by the accumulation of amyloid plaques and tau fibrils in the brain. It has been associated with gut Microbiota dysbiosis either in preclinical or clinical studies. Again, an increase in the levels of bacteria associated with inflammation was found, combined with an increase in intestinal permeability, suggesting that gut Microbiota plays an important role in the earlier stages of the neuroinflammation associated with Alzheimer [93]. Evidence is growing that intervening in the Microbiota-gut-brain axis, either with prebiotics, probiotics or dietary changes can ameliorate this neurodegenerative disease.

Another high prevalence neurodegenerative disease is Multiple Sclerosis (MS), characterized by the progressive loss of myelin in axons. Similarly to other neurodegenerative diseases, an increase in intestinal permeability was found in MS patients, allowing an increase in the translocation of bacteria and LPS to the systemic circulation and thus increasing systemic inflammation [94]. Additionally,

when compared to healthy controls, MS patients presented lower levels of *Faecalibacterium, Prevotella* and *Anaerostiples* and a striking depletion of species belonging to the *Clostridi*a XIVa and IV Clusters [95].

Gut Microbiota dysbiosis was also associated with psychiatric pathologies like schizophrenia whose patients showed significant correlations between increases in *Lactobacillus* group bacteria and the severity of different symptom domains [96].

The ever-growing information regarding the Microbiota-gut-axis, both in characterization and in mechanistic pathways, opens doors to the identification of early biomarkers and new therapeutic targets that can be used to treat or ameliorate central nervous systems diseases. Gut Microbiota modulation, though in need of more robust clinical data, presents itself as a promising strategy.

2.9 GUT MICROBIOME AND OTHER PATHOLOGIES

Several other pathologies have been associated to significant changes in gut Microbiota even though it is not clear if the dysbiosis is their cause or their consequence, or even the extension to which it affects the pathology.
Ankylosing spondylitis (AS) is a type of arthritis that is referred to a group of chronic immune-mediated inflammatory diseases termed as seronegative spondyloarthropathies or spondyloarthritis. Even if the mechanisms remain unclear, there is some evidence that gut Microbiota and the IL-23/IL-17 pathway are pivotal in the pathogenesis of spondyloarthritides [97]. A similar association was found between gut dysbiosis and rheumatoid arthritis (RA). There is also growing evidence that different drugs, such as antibiotics and immunosuppressants, can influence and be influenced by the Microbiota in RA and AS patients [98].

Recently, suggestions arose of the involvement of a gut-retina axis in the protection against dietary glycemia-induced age-related macular degeneration (AMD). Metabolomics revealed microbial co-metabolites, particularly serotonin,

as protective against AMD and *Bacteroidales* as protective towards de the development of the disease [99].

Choroidal neovascularization can also be aggravated by gut Microbiota dysbiosis. Gut dysbiosis known effects of heightened intestinal permeability and chronic low-grade inflammation, characteristic of inflammaging, associated with elevated production of IL-6, IL-1β, TNF-α, and VEGF-A, ultimately aggravate pathological angiogenesis [100].

Gut Microbiota dysbiosis has also been associated with dermatological diseases like atopic dermatitis [101] and eczema [102], as well as with other several allergies related pathologies, mainly due to mechanisms of mucosal immune tolerance [103].

Finally, another very interesting effect of gut Microbiota is the influence it plays in the effectiveness of drugs. The first studies of alterations in drug effectiveness are now published and demonstrate that gut Microbiota is an additional factor that should be taken into consideration when prescribing a drug. This interaction has been demonstrated in chemotherapeutics [104], antihypertensive drugs [105], antibiotics [106] and immunotherapeutics [107], and is naturally expected to interfere with many other drugs and therapeutic processes.

3 - CONCLUSION

The impact of Microbiome and Microbiota on numerous diseases has been increasingly documented in the last decade.

It remains doubtful if dysbiosis is a cause or a consequence of those diseases, and to which extension it may affect clinical result. Nevertheless, the Microbiota is now being considered a “virtual organ”, with its metabolic and immune relevance becoming ever more clear and increasingly taken into consideration in the clinical approach.

As such, several Microbiota modulation strategies have been suggested, including the use of prebiotics, probiotics, antibiotics, dietary changes and faecal transplant, all with moderate success. For some of these strategies the regulatory framework is developing together with the knowledge increase.

Also, the interaction between Microbiota and administered medication is now being considered, as clinical data demonstrate that drug effectiveness is also dependent on the Microbiota composition.

More robust and powerful clinical studies are being performed or planned in order to better understand the impact of Microbiota and its modulation. Preclinical data is of extreme relevance but translation to humans needs to be done carefully. New analytical techniques, more sensitive and more precise, will similarly improve our insight into its role in the health status of an individual, not only regarding bacterial composition, but also the importance of fungi, virus and phages.

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