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The immunomodulatory effect of the diet. Implications for health and disease.

Efecto inmunomodulador de la dieta. Implicaciones para la salud y la enfermedad.

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ABBREVIATIONS

AhR: aryl hydrocarbon receptor.
ALA: alpha-linolenic acid.
ALD: alpha-linolenic acid.
ARA: arachidonic acid.
ASD: autism spectrum disorder.
ATRA: all-trans-retinoic acid
BA: bile acid.
BAT: brown adipose tissue.
BBB: brain blood barrier.
BDNF: brain-derived neurotrophic factor.
BMI: body mass index.
CAZymes: carbohydrate-active enzymes.
CD: Crohn's disease.
CR: caloric restriction.
CTLs: $CD8^+$ T lymphocytes
DALYs: disability-adjusted life-years.
DAMPs: damage-associated molecular patterns.
DCs: dendritic cells.
DHA: docosahexaenoic acid.
DMB: 3,3-dimethyl-1-butanol.
ds-DNA: double stranded-deoxyribonucleic acid.
EPA: eicosapentaenoic acid.
4-EPS: 4-ehtylphenylsulfate.
FAs: fatty acids.
FFARs: free fatty acid receptors.
FMD: fasting-mimicking diet.
GH: growth hormone.
GI: gastrointestinal.
GLP-1: glucagon-like peptide-1.
GM: genetically modified.
GPCRGs: G Protein-Coupled Receptors.
HDAC: histone-deacetylase.
HDL: high-density lipoproteins.
HFD: high-fat diet.
HMOs: human milk oligosaccharides.
HMP: Human Microbiome Project.
IBD: inflammatory bowel disease.
IELs: intestinal intraepithelial lymphocytes.
IF: intermittent fasting.
IGF1: insulin-like growth factor 1.

IL: interleukin.
LA: linoleic acid.
LCFAs: long-chain fatty acids.
LDL: low-density lipoprotein.
LPS: lipopolysaccharide.
LXR: liver X receptors.
MACs: microbiota-accessible carbohydrates.
MAITs: Mucosal-associated invariant T cells.
MAMPs: microbe-associated molecular patterns.
MS: multiple sclerosis.
MUFAs: mono-unsaturated fatty acids.
NAFLD: non-alcoholic fatty liver disease.
NAS: non-alcoholic artificial sweetener.
NASH: non-alcoholic steatosis hepatitis.
NCDs: non-communicable diseases.
NGS: Next Generation Sequencing.
NSAIDs: nonsteroidal anti-inflammatory drugs.
OA: osteoarthritis.
PGE2: prostaglandin E2.
PRRs: pattern-recognition receptors.
Ps: psoriasis.
PUFAs: poly-unsaturated fatty acids.
PYY: peptide tyrosine tyrosine.
RA: rheumatoid arthritis.
RAR: RA receptor.
rRNA: ribosomal RNA.
RXR: retinoid X receptor.
SCFAs: short-chain fatty acids.
SFAs: saturated fatty acids.
SLE: systemic lupus erythematosus.
TFG-β: transforming growth factor-β.
TGR5: Takeda G-protein coupled receptor 5.
TLR: Toll-like receptors.
TMA: trimethylamine.
TMAO: trimethylamine N-oxide.
Treg: regulatory T cells.
TRF: time-restricted feeding.
T1D: diabetes type 1.
T2D: diabetes type 2.
TβMCA: tauro-β-Muricholic acid.
UC: ulcerative colitis.

VDR: vitamin D receptor.
VitK1: vitamin K 1.
VitK2: vitamin K 2.
WAT: white adipose tissue.

ABSTRACT

Modern dietary patterns, collectively termed Western diet, are characterized by an inadequate composition that leads to an excessive intake of sugar, unsaturated fatty acids, salt, etc. and a lack of essential nutrients. Undoubtedly, this type of nutrition has important consequences on health and affects an individual's risk for developing diseases such as hypertension, heart disease, stroke, cancer, and many immune-mediated diseases. A great gathering of evidence has demonstrated that following an incorrect diet may result in altered microbiota (dysbiosis), which is currently considered to be the central element that links diet and physiological homeostasis. This essential interaction is mediated through many different pathways that frequently involve the immune system. However, the exact mechanisms are yet to be established. This review tries to profoundly explain the most recent investigations that shed light on these mechanisms and their consequences, focusing on the role of the microbiota. Consequently, it will allow understanding of the pathophysiology behind the development of many diseases conditioned by diet. Finally, possible dietary interventions that could be very useful in the treatment and prevention of many increasingly prevalent medical conditions are discussed.

Keywords: Western diet; gut microbiota; microbial metabolism; dysbiosis; immune-mediated disease.

Los patrones dietéticos modernos, denominados colectivamente Dieta occidental, se caracterizan por una composición inadecuada que conduce a una ingesta excesiva de azúcar, ácidos grasos insaturados, sal, etc. y a la falta de nutrientes esenciales. Sin lugar a dudas, este tipo de nutrición tiene consecuencias importantes para la salud y aumenta el riesgo individual de desarrollar enfermedades como hipertensión, cardiopatías, ictus, cáncer y muchas enfermedades inmumediadas. Una gran recopilación de evidencia ha demostrado que seguir una dieta incorrecta puede producir una alteración de la microbiota (disbiosis), considerada actualmente el elemento central que vincula la dieta y la homeostasis fisiológica. Esta interacción esencial está mediada a través de muchas vías diferentes que frecuentemente involucran al sistema inmunológico. Sin embargo, los mecanismos exactos aún no se han establecido. Esta revisión trata de explicar en profundidad las investigaciones más recientes que arrojan luz sobre estos mecanismos y sus consecuencias, centrándose en el papel de la microbiota. En consecuencia, permitirá comprender la fisiopatología detrás del desarrollo de muchas enfermedades condicionadas por la dieta. Finalmente, se discuten posibles intervenciones dietéticas que podrían ser muy útiles en el tratamiento y la prevención de muchas afecciones médicas cada vez más prevalentes.

Palabras clave: dieta occidental; microbiota intestinal; metabolismo microbiano; disbiosis; enfermedad inmunomediada.

INTRODUCTION

Society in developed countries is changing rapidly and constantly, adapting to the modern lifestyle. These social changes (including higher hygienic standards, more exposure to air pollution and to newly generated synthetic compounds, etc.) occur continuously, have important consequences and affect all areas of life. Undoubtedly, many of them have an important impact on health. Owing to high standards of hygiene, individuals are generally less exposed to microorganisms, which might impair the correct development and function of the immune system. However, they are more exposed to potentially dangerous or harmful contaminants due to frequent high levels of contamination. Furthermore, a sedentary lifestyle is disturbingly frequent and it is combined with insufficient rest, a consequence of stressful atmospheres. Television, cell phones, video games, etc. are indoor sedentary activities that occupy a lot of time in modern society, while outdoor sports, reading or more intellectual activities are less widespread. There are also unhealthy habits that remain strong in society, like the consumption of cigarettes and alcohol. Besides all of these issues, one fundamental aspect that has greatly influenced general health is the changes in the dietary habits that have occurred in the last years.

Frequently called the *Western diet*, this modern way of understanding nutrition is characterized by excess saturated fatty acids, red meat, salts, sugar, additives, etc *in lieu of* fruits, vegetables, legumes, fish and whole grains. Fast food, precooked meals, and ultra-processed food are consumed almost everyday by the general population, as an essential part of the routine of modern families. Furthermore, there is a continuous and abundant supply of food, in which it is too easy and cheap to obtain it, resulting in excess calorie intake. The typical Western diet is about 2,200 calories per day, in which 50% of them are from carbohydrates, 15% from protein, and 35% from fat, approximately. These numbers fall within the recommendation of health organizations, but another problem might be the type and quality of the products. As previously exposed, meals are overloaded with low nutritious but high-calorie constituents that have strong consequences on an individual's health. Through many different mechanisms, this type of nutrition is clearly linked to increased inflammation, reduced control of infections, increased rates of cancer and increased risk of allergic and auto-inflammatory disease (1).

The relationship between diet and chronic non-communicable diseases (NCDs) has been extensively investigated. Although difficult, long-term prospective observational studies and short-term trials of intermediate outcome have been able to demonstrate a causal relationship between specific dietary factors (eggs, fruits, vegetables, legumes, meat, etc) and NCDs (ischemic heart disease, diabetes and colorectal cancer). Importantly, a recent study has been able to gather information from 195 countries from a period of time between 1990-2017 and study diet and health globally. They studied the effect of 15 food groups that act as dietary risk factors on health by analyzing data on dietary intake at population level of these 15 food groups, dietary optimal intake and their relative risk of mortality and morbidity, among other important statistics (2). The findings demonstrated that no country showed optimal intake of these different dietary risk factors, with a few specific exceptions. Therefore, they were able to conclude that the consumption of almost all

beneficial foods and nutrient was suboptimal in 2017 worldwide, while daily intake of all harmful foods and nutrients surpassed the ideal level globally. Furthermore, in 2017, dietary risk factors caused 11 million deaths (22% of all deaths among adults) and 255 million disability-adjusted life-years (DALYs) (15% of all DALYs among adults). Notably, there were three dietary risk factors that showed a tremendous impact on health outcomes and are considered the most relevant ones: high intake of salt, low intake of whole grain and low intake of fruit.

Dietary habits have, therefore, a tremendous impact on human health, affecting an individual's risk for developing multiple diseases like hypertension, cardiovascular disease, metabolic disorders or cancer. Moreover, they can greatly influence the progression and manifestation of immune-mediated diseases, a type of diseases that result from dysfunction of the immune system. The etiology of these illnesses is yet to be defined, but they share common inflammatory pathways that lead to inflammation. As a result, they cause end-organ damage and are related to increased morbidity and mortality. There are many examples of this type of diseases (i.e. inflammatory intestinal disease, allergy, type 1 diabetes or systemic erythematosus lupus), and we will talk about some of the most important ones and their relationship with diet.

This reviewing work attempts to show, in a comprehensive way, the recent evidence relating diet and immunity through gut microbiota-host interactions, which has been established from investigations carried out in animal models and thanks to clinical evidence in humans. It will be exposed how the Western diet affects the immune system by multiple complex mechanisms, giving great importance to the gut microbiota, as it seems to be the most important connection between diet and health. The *microbiota* is the complex community of microorganisms inhabiting the intestine of animals, being the *microbiome* their genetic material. Human beings and their microbiota can be seen as a clear example of symbiosis (3), a long-term and reciprocal interdependence of two different biological organisms. This symbiosis guarantees health. However, this concept is recently suffering important changes and there is a new way of understanding the organization of the living world, in with horizontal or lateral gene transfer is very important. This new conceptual idea implies that genes are not only transmitted from parents to offspring but also horizontally, creating nets that connect the different individuals. These networks are called *holobionts* and refer to new categories of biological organization (3). Undoubtedly, this new concept also affects the way of understanding the relationship between the microbiota, the host and their environment. In either case, if the microbiota suffers dysbiosis, multiple consequences will arise affecting the whole organism. Dysbiosis takes place when there is an imbalance between the microorganisms that form the microbiota. This means that normally dominant species, which have beneficial effects and ensure homeostasis, are underrepresented, while there is an overpopulation of other bacteria that might have pathogenic activity. Dysbiosis might result from very different etiologies, but antibiotic treatment, alcohol intake and inappropriate diet seem to be of extremely determinant.

The exact mechanisms by which the interaction microbiota-host occurs are not clear yet but seem to take place on account of cell-to-cell communication and through

mediators or metabolites. The set of metabolites present in an organism is called *metabolome* and includes exogenous metabolites, coming either from the diet or from the environment, and also endogenous, which are produced or modified through different metabolic processes both from the host as well as from the microbiota. Some of these mediators are bioactive and are determinant on the physiological responses of the host, depending on their nature and concentration, when coupled with the different host receptors (4). They will be capable of affecting not only the gastrointestinal immune system but will also have critical effects on distant organs, through the bloodstream and also by enteroendocrine and enteric nervous routes.

Importantly, the influence that nutrition has over the microbiome can either be positive or negative and the shaping of the gut microbiota by diet occurs already during early life, where events such as type of infant nutrition (breast vs. formula-feeding) or mother´s diet seem to impact infant´s health (5). Establishing well-founded conclusion is crucial and more research needs to be done since the investigations already carried out in animals often fail to obtain valuable results applicable to humans. A central process being studied is the acquisition of the microbiota and specially, the mechanisms that take place during gestation and that condition the heritage of the microbiota. Furthermore, important investigations are also being carried out on the factors that modify the microbiota throughout life, and the exact consequences these modifications have on the different host's organs and on its health as a global. However, this work might be very challenging as the investigations are very complex and difficult to design. For example, there are intra-individual changes in the gut microbiota associated with intestine anatomical regions, infant transitions, age, and environmental factors (antibiotics use, smoking, pollution, etc.). Moreover, it is very important to consider the inter-individual variations as well. These are principally due to enterotypes, body mass index (BMI) level, and external factors such as lifestyle, exercise frequency, ethnicity, and dietary and cultural habits, and will have a great impact on the outcome (6). Over the next years, more advanced methodologies will need to be designed if wanted to acquire profound knowledge on the effect of nutrition.

This work is focused on describing the already demonstrated effects of the diet, the main factor modulating the microbiota-host cross talk through metabolism, on general health and the immune system specifically. We will expose the most recent investigations carried out and we will discuss their conclusions, trying to understand the mechanism behind the relationship between nutrition and health. Especially, we will focus on the constituents of the Western diet that have an important effect on the diet-microbiota cross-talk. These constituents can act in a direct way (by creating a metabolic competition between the different types of microorganisms) or in an indirect manner (by affecting the functioning of the immune system).

In conclusion, the aim of this review is to offer a descriptive and integrated approach of the impact diet has on health and its ultimate goal is to illustrate future possible medical interventions. It is now well known that dietary habits have a tremendous impact on an individual's status health, and we are making progress in the knowledge of the biological reasons and mechanisms underlying. Therefore, we must be aware of the importance of a proper nutrition, which should be addressed with the

relevance it really has and should be understood as a valuable tool through which health can be obtained.

1. DIET-MICROBIOTA INTERACTIONS.

During the last four decades, it was commonly assumed that human beings are a cell population composed of at least 90% bacteria, based on the 10:1 ratio (cell bacteria number: human cell number) (7). However, this estimation was recently revisited and Sender et. all established that a "reference man" (one who is 70 kilograms, 20-30 years old and 1.7 meters tall) contains on average about 10^{13} bacteria and 3.0×10^{13} human cells (including non nucleated cells), so representing a bacterial cells: human cells ratio nearby to 1:1 (8). As previously exposed, the human being is now studied as a "holobiont" organism, considering it the result from a mutualistic symbiotic relationship between human cells and microbiota cells. Consequently, it is only natural to expect a major role for the microbiota in human physiology, giving rise to the concepts of "metagenome", to define all genes present in the holobiont, and "metabolome" to refer to the whole metabolism taking place into the holobiont (9).

This microbiota is distributed between major body habitat groups (airway, skin, oral, gut and urogenital tract). Nevertheless, these regional microbiomes are connected with each other through diffusions and migrations. The human gastrointestinal (GI) tract comprises the majority of the abundance and diversity of microorganisms, gathering more than 100 trillion microorganisms (10). This gut microbiome encodes over 3 million genes producing thousands of metabolites, whereas the human genome consists of approximately 23,000 genes. Therefore, while the gut supplies the space and the nutrients required for the development of the microorganisms, its symbiotic microbiota carries out many crucial functions for the host, such as defense (inhibiting pathogens growing by competing for nutrients or by secreting inhibitory metabolites and creating a mucus layer acting as a barrier over the epithelial surface), contribution to gut immune structures development and immune cell activation, and metabolic activity (extraction, synthesis, and absorption of many nutrients and metabolites, including bile acids, lipids, amino acids, vitamins, and short-chain fatty acids or SCFAs) (11).

1.1. Gut microbiota.

For years, scientists have been interested in gut microbiota, but one of the major difficulties found when designing the investigations has been the ability to culture the gut microorganisms. The human microbiota is now better characterized thanks to modern Next Generation Sequencing (NGS) techniques, including 16s ribosomal RNA (rRNA) gene pyrosequencing (12). Taxonomically, bacteria are classified according to phyla, classes, orders, families, genera, and species. The human microbiota is constituted by a biomass of about 1.5 kg to 2.0 kg., accounting for more than 160 species albeit only a few phyla are represented. It includes microorganisms belonging to all three domains Archaea, Bacteria and Eukarya (including Archaea, mainly bacteria and Eukarya like yeast, fungi, protozoa, phages, and viruses). The most represented gut bacterial phyla are *Actinobacteria*, *Verrucomicrobia*, *Proteobacteria*, *Fusobacteria*, *Firmicutes* and *Bacteroidetes*, with the last two representing 90% of gut

microbiota (13). As previously mentioned, individual variations are frequent and the composition of the microbiota shows a strong variation from one person to another, depending on genetic and environmental factors. The collective microbial genome, known as “the microbiome”, encodes 500 times more genes than the human genome (14).

Gut microbiota changes according to the intestine anatomical regions, which vary in terms of physiology, pH and O_2 tension, digestion flow rates (rapid from the mouth to the caecum, slower afterwards), substrate availability, and host secretions (10). Therefore, the microbiota increases in bacterial density distally, with the small intestine providing a more challenging environment for microbial colonizers given the fairly short transit times (3–5 h) and the high bile concentrations. The large intestine, which is characterized by slow flow rates and neutral to mildly acidic pH, harbors by far the largest microbial community (dominated by obligate anaerobic bacteria), although it also contains fungal and viral genomes. The density of bacterial cells in the colon has been estimated at 10^{11} to 10^{12} per milliliter which makes the colon one of the most densely populated microbial habitats known on earth (15). So there is a microbiota quantitative increasing gradient and a microbiota qualitative decreasing gradient with a progressive aerobic bacteria decrease for the benefit of strictly anaerobic bacteria.

In the gut, there is an optimal balance of bacterial species with different functions that, altogether, ensure the correct functioning of this organ. Health is reached when an equilibrium that allows the accomplishment of the above commented basic functions of the microbiota is found (3). Therefore microbiota inhabiting the intestine is very important for the maintenance of gut health. The intestine is the main absorption interface for nutrients, vitamins and water but the nutritional value of food is affected by the state of health of the consumer’s microbiome. Likewise, as already mentioned, the constituents of the diet affect the populations of the microbiota (16). A vicious circle is created, in which the microbiota seems to play the central role. This is the reason why it is starting to be conceived as a true organ by some researchers (3).

Indeed, nowadays there are accumulating evidence for the involvement of gut microbiota dysbiosis in the development of various intestinal and extra-intestinal disorders. In order to better evaluate the role of the microbiome in health and disease, the NIH launched the Human Microbiome Project (HMP) in 2007, which focused on surveying microbiomes present in different organ systems. The project was divided into 2 phases: Phase 1 surveyed the microbiomes of major body regions in healthy individuals and in those diseased, and Phase 2 focused on the biological properties of these microbiomes. The initial studies focused on the digestive tract and demonstrated tremendous complexity as well as the functional potential of the human microbiome (17).

1.2. Gut microbiota-host cross talk.

Nutritional habits have an important impact on health, as they induce changes on the composition of the host’s microbiota, alterations on its gene expression and modifications in the microbiota-produced metabolites, which act locally and

systemically. Of special importance are the changes that affect the constitution of the microbiota, which are believed to explain most of the consequences, favorable and unfavorable, that nutrition exerts on health. The constituents of the Western diet act as agents that determine the composition and functioning of the microbiome, but temporal and geographical contexts are also of great importance, as discussed all through this section.

The microbiome responds to food both through direct and indirect mechanisms (18). Nutrients can directly interact with the microorganisms inhabiting the intestine to promote or inhibit their growth, affecting their growth kinetics (19). In the microbiota, there are selected microorganisms with the ability to extract more energy from food, which have a competitive advantage compared to the rest. The most important nutrients in this mechanism are indigestible carbohydrates called glycans, mostly derived from plants, and digested by carbohydrate-active enzymes (CAZymes). The human genome does not encode a great number of these enzymes, allowing glycans to reach the large intestine undigested. In contrast, the bacteria located in the intestine synthesize thousands of CAZymes. In particular, the primary degraders are bacteria that own these enzymes and are therefore able to digest glycans, obtaining energy from them. Some examples are *Bacteroides*, *Bifidobacterium* and *Ruminococcus* genera. They are able to predict bacterial abundance according to glycan degradation patterns and, according to this information, are able to adapt their source of energy depending on the abundance of food. As a consequence, they have a great survival advantage. Primary degraders are followed by secondary degraders, bacteria that carry out the fermentation of the glucose produced by the first. This results in the formation of acetate, propionate, formate, butyrate, lactate, and succinate, important molecules collectively known as SCFAs that will be examined later, and it starts a complex cross-feeding metabolic network. Importantly, by studying these interactions, bacterial community structure can be predicted. Additionally, some nutrients can also inhibit bacterial growth; quinones, flavonoids, terpenoids, and alkaloids, derived from plants, have antimicrobial activity.

Metabolites from nutrient digestion can act as extracellular signaling molecules by interaction with their sensors, the family of free fatty acid receptors (e.g. FFARs) and cognate Protein-Coupled Receptors (GPCRGs) expressed on the same cells that produce or transport these metabolites into the body, or receptors on neighboring cells, such as immune cells (20,21). Therefore, they can function in an autocrine and/or paracrine manner. In this way, diet constituents affect host metabolism and immune system (as described in section 2) and as a result, gut microbiota is altered in an indirect way. For example, the aryl hydrocarbon receptor (AhR) is necessary for the maintenance of intestinal intraepithelial lymphocytes (IELs). Activation of the AhR by fruit or vegetable derived fiber allows maintenance and expansion of IELs, which are crucial in the defense against infected or damaged epithelial cells and in the regeneration of the intestinal epithelium (22). When the activity of AhR is aberrant, there are consequences in the microbiota, like the growth of Bacteroidetes phylum. Another example is the deficiency of vitamin D, which produces a great deal of changes on the gut microbiota since vitamin D is essential for gut mucosal immune defense (23). Importantly, there is a specific type of immune cells that are crucial in maintaining homeostasis in the gut, the regulatory T cells (Treg). Treg cells are

extremely important as they ensure commensal tolerance by the immune system by suppressing aberrant T cell responses (24). Consequently, a decrease in Treg will lead to inflammation, disease, and dysbiosis. Diet affects the population of Treg through many mechanisms including fiber fermentation, white adipose accumulation, etc. More specifically, bacterial fermentation of fiber produces SCFAs, which have many other functions and are very important for gut health, but importantly regulate Treg development and functioning (Figure 1). Some examples of SCFAs are: formate, acetate, butyrate, and propionate. It is important to understand the effect that the microbiome has over the Treg/Th17 balance. Depending on the composition of the microbiota, it could be an enhancement of the anti-inflammatory Treg population or an increased differentiation of pro-inflammatory Th17 cells, which will have great influence in the immune state of the host. Finally, many other diet constituents have determinant indirect effects on the gut barrier, allowing inflammation and disease. For example, bile acids (BA) are able to indirectly inhibit bacterial growth, and emulsifiers promote metabolic syndrome through erosion of the intestinal wall.

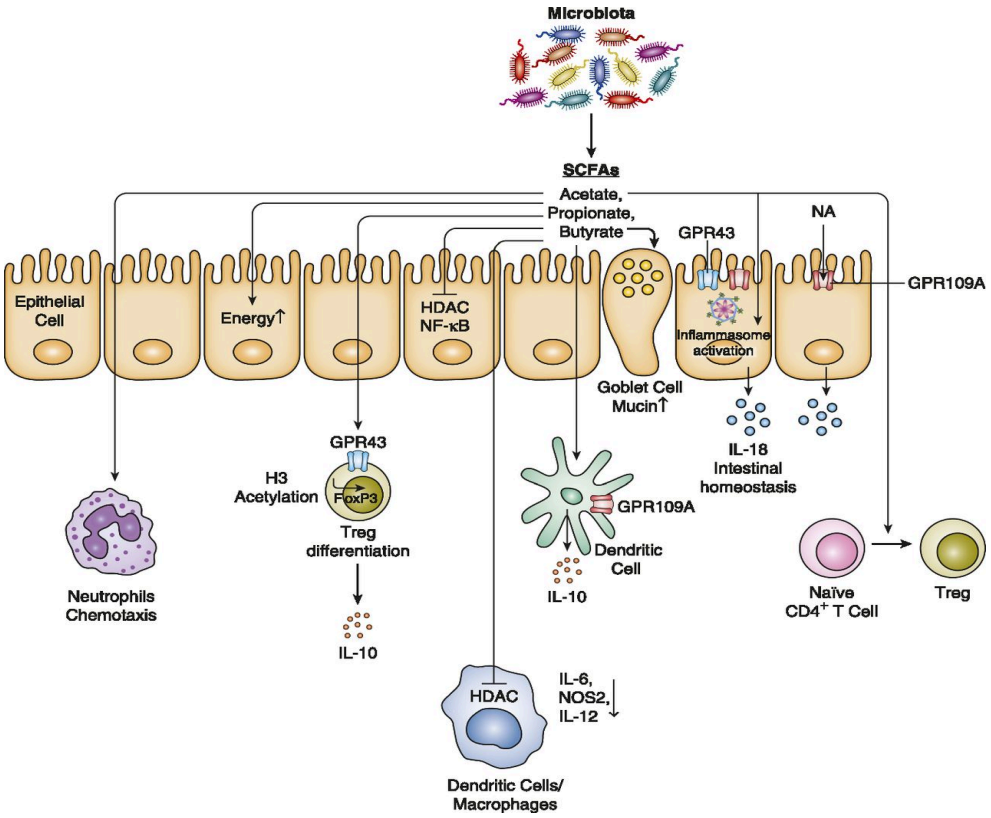

Figure 1. Microbiota-associated metabolites shape mucosal immunity. SCFAs are important molecules produced by the microbiota through the fermentation of fiber. They have important actions modulating the immune system. Reproduced from (4).

Interestingly, individual microbiota is stable unless changes in diet take place, as occurs while growing up (Figure 2). Since the beginning of life, the contribution that the dietary components have over its consumer's gut is obvious. In early infancy, maturation of the microbiota is influenced by human milk oligosaccharides (HMOs), so the uptake and utilization of lactose, galactose, and sucrose is very important. Consequently, the microbiota during lactation period consists mainly of Bifidobacteria.

Afterwards, as solid and varied foods start gaining importance as part of the nutritional patterns, the microbiota increases in richness and variety, depending on the type of diet followed and personal variations. Then, fermentation and vitamin biosynthesis pathways gain importance (25). During adulthood, diet acquisition, quantity and quality, as well as perturbations (for example, antibiotic treatment, infections, traveling, etc.) control the gut microbiota stability (14). Finally, as a result of ageing, the diet becomes less varied and the microbiota also decreases in richness, reason why the composition of the microbiota has been proposed as a marker of frailty (18). Therefore, maturation and ageing are associated with long-term alterations in gut microbiota, which can evolve over time (26).

Changes in food intake affecting microbiota can occur of different timescales. A calorie-restrictive diet maintained during 4 weeks produces changes in bacterial populations and, interestingly, a reduction in butyrate production in the short-term. Although the effect of this reduction is not clear, it could potentially be detrimental, and it points out the importance of designing a diet that allows goal achievement but does not alter negatively the microbiota (27). If the calorie restriction is maintained as long as 10 weeks, it creates evident changes in microbiota: reduction in *Blautia coccoides* and increase in *Bacteroides*. Longer interventions of approximately one year increase faecal *Bacteroidetes* and decrease Actinobacteria relative abundance. This will take place over different time periods in a person-specific manner. All these changes might be responsible for the beneficial effects of low-calorie intake and might explain the potential benefits of fasting, that will be discussed later (28) (described in section 4). It is interesting to take this knowledge into account when studying loss weight strategies. A diet low in calories is effective for this purpose, but might also have an important effect on the microbiota composition. By balancing both effects, maximal advantages could be obtained.

Apart from the caloric intake, timing is also relevant. Circadian rhythms of sleep-wakefulness and feeding-fasting are extremely short-term behavioral changes that have strong effects on the microbiota, affecting the three most important phyla, *Bacteroidetes*, *Firmicutes,* and *Proteobacteria*. Theses alternations consequently affect the levels of metabolites in the stool and the circulation. Moreover, some dietary modifications can alter the microbiota within days in a person-specific manner, depending on the host. One clear example is the introduction of fiber in the diet that might result in microbiome modifications since day one in some individuals. However, in some other cases, changes might not be observable after 12 weeks of supplementation with fiber. Interestingly, some studies have been able to demonstrate a rapid change in human microbiota composition when switching to an animal-based diet, which did not occur when changing to a plant-based diet. This could be explained by the characteristics of the first diet: low fiber, high fat and high animal protein, and was reversible when cessation of the change of diet (18). However, studies in mice have demonstrated that other changes caused by diet might not always be reversible after the dietary switch, showing a more persistent pattern (18). Finally, dramatic diet perturbations (antibiotic treatment, infections, traveling, etc) might induce important changes in the microbiota within days. On the contrary, an antibiotic-disturbed microbiota may respond much more slowly, and restoration might take even months, or not happen at all (14). Timing is, therefore, very important.

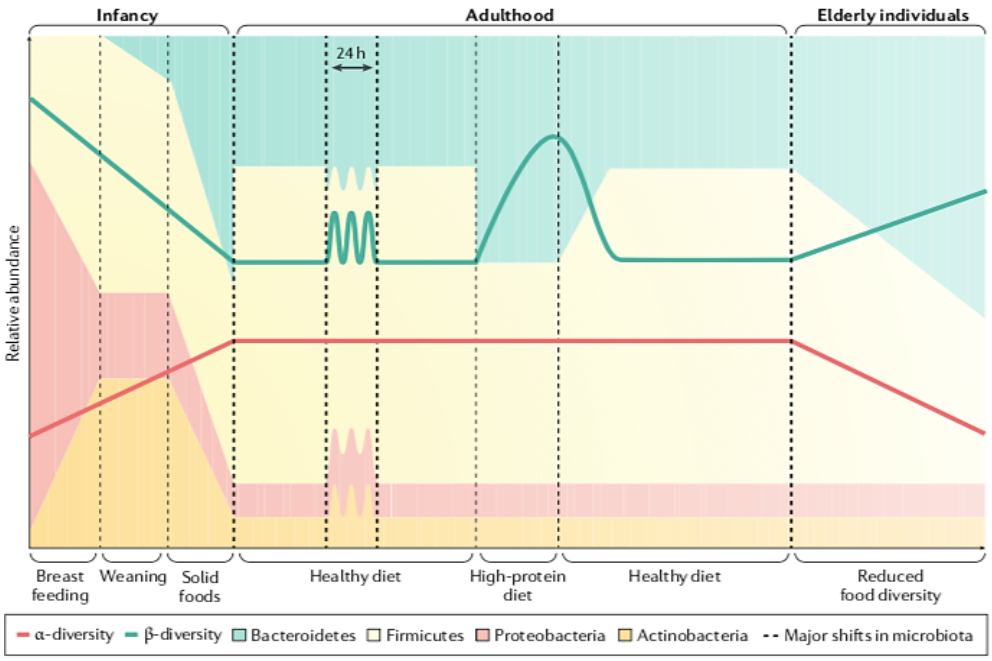

Figure 2. Temporal dietary modulation of the gut microbiota. Variations in the microbiota composition occur because of aging, but also when dietary modifications take place. Taken from (18).

Another important factor to take into account when speaking of the association between diet and human gut microbiota is the geographical context, due to the differences in gut microbiota diversity according to dietary habits related to geographical provenance. These geographical variations have such a strong impact that is able to explain why healthy vegans and omnivores living in the USA do not show significant differences in their microbiota composition (18). Importantly, when implementing dietary modifications, these variations need to be considered. For example, even though iron and folic acid supplementation are frequent and beneficial in developed countries, they have been related to enrichment in enteric pathogens leading to an increase in malaria and other infection-related deaths among children in Zanzibar. Therefore, some dietary recommendations that might be beneficial in some parts of the world could be detrimental in other areas (18). In addition, according to the holobionts concept already explained, the microbiome is modulated through processes like interspecies genetic rearrangements, gene duplications, and lateral gene transfers. Consequently, the microbiome is modulated by the meta-community in which the host lives (29). Influences of the host virome, mycome, protozoa and other eukaryotes have also been suggested, according to preliminary data (18). To end with, the host genetic material also influences microbiota composition, through conditioning of digestion, although to a very limited extent. Diet seems to be dominant over genotype in mice and humans (30,31).

There is no doubt that the microbiota is essential in maintaining gut health and a general homeostatic state of the whole organism, but it also has important effects on specific distant organs. The production of metabolites by the microbiota is of great importance in order to understand these long-distance effects, in which the immune system is also involved. Owing to metabolite production and secretion, the gut microbiota is able to connect, for example, with the immune and hormone system, the

brain and the host metabolism (Figure 3). This communication is essential for the correct functioning of these systems or organs, and might also explain some of the physiopathology behind numerous diseases.

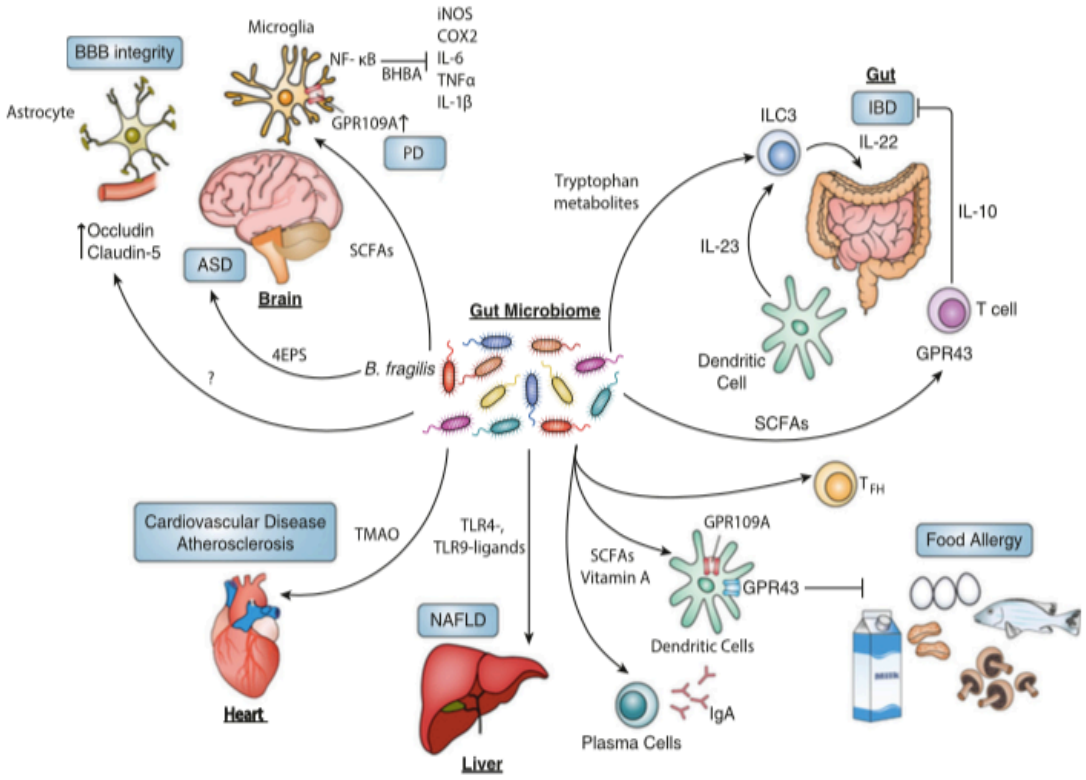

Figure 3. The systemic effect of altered gut microbiome. As represented in this image, the microbiota produces a great variety of mediators, which will have very important effects in many distant organs and will be responsible for the development of many diseases. Reproduced from (4).

There are different types of metabolites through which the microbiota exerts some of its effects. Firstly, immune signals act as metabolites. Microbe-associated molecular patterns (MAMPs), like lipopolysaccharides (LPS), bind to pattern-recognition receptors (PRRs) located on epithelial and immune cells, which prevent the translocation of the bacteria across the epithelial barrier. However, small amounts of bacterial products might cross the intestinal barrier and reach the blood and lymphatic circulation, leading to disease development. Importantly, depending on the specific structure of those MAMPs, the effect might vary. Furthermore, there are probably more specific bacterial signals, yet unknown.

Other important metabolites are SCFAs. As already exposed, they are important sources of energy for the organism and have an extremely important action ensuring the correct functioning of the immune system in the gut. However, their effect as signaling molecules is also crucial. They can act stimulating the secretion of molecules, like Peptide Tyrosine Tyrosine (PYY) and glucagon-like peptide- 1 (GLP-1), which will act as regulators of energy metabolism and appetite, respectively. Additionally, SCFAs are able to bind to receptors on afferent nerves close to the gut, having a direct effect on

the brain and nervous system. They seem to improve metabolism and suppress appetite, though their effects are not all clear and some investigations have concluded the opposite effect. Whether they are able to act as hormones or not is also yet to study but it seems that they are unable to reach sufficiently high concentrations in blood.

Finally, bile acids (BAs) have been recently identified as important signaling molecules and exert their effect when they bind to nuclear receptors or G-coupled receptors. Their metabolism is a very important mechanism by which the microbiota has important effects on the rest of the body. Primary BAs are produced in the liver and secreted to the small intestine, where they can be modified by the microbiota to enable them to reach the colon without being re-absorbed. Specifically, tauro-β-Muricholic acid TβMCA is an abundant primary BA that has important effects as an antagonist of the nuclear receptor FXR. Microbial metabolism of TβMCA liberates FXR, which initiates a cascade resulting in decreased BA production. This constitutes a gut-microbiota-liver feedback loop and demonstrates how important BA can be. Secondary BAs bind more preferably to Takeda G-protein coupled receptor 5 (TGR5), a G-coupled receptor, and are believed to have beneficial metabolic consequences. These include GLP-1 secretion and thermogenesis potentiation in brown adipose tissue (BAT). These processes might be, therefore, important therapeutic tools. However, conflicting data have been found.

In summary, the gut microbiota is extremely important in maintaining metabolic balance and self-tolerance. Following, the reported effects of different nutrients on immune components are described.

2. IMPACT OF DIETARY CONSTITUENTS ON THE IMMUNE SYSTEM.

Understanding the effect of macro and micronutrients on health is an issue more and more important, as it would help to understand the global effect of diet and to apply this knowledge in medicine. Many studies have been carried out reaching important conclusions. However, it is necessary to take into account the fact that the studies are usually carried out using isolated synthetic molecules. These might show different effects from the ones they exert when included in the food product that contains them (1). Similarly, when analyzing human microbiota, it is frequent to use fecal material, as it is accessible. Then again, it might not reflect exactly the microbes inhabiting the GI tract and cannot accurately link their presence with the development of any disease (14).

Nowadays there are known several links between nutrient- and pathogen-sensing pathways, and the mechanisms interfacing of metabolic and inflammatory responses are being unraveled. As mentioned at the beginning, microbial dysbiosis seems to be just in the core and can lead to common metabolic and inflammatory diseases. Below are described some immune effects of these discovered links.

2.1. Dietary microbiota-accessible carbohydrates (MACs).

Based on their chemical complexity, carbohydrates are divided into four groups: monosaccharides, disaccharides, oligosaccharides, and polysaccharides. The first two are generally referred to as sugars and are highly consumed as part of the Western diet (e.g. sucrose, fructose syrup, etc.). Undoubtedly, the consumption of carbohydrates has different effects on the microbiota, reason why the term "microbiota-accessible carbohydrates" (MACS) was proposed, referring to the ability of some carbohydrates to alter the composition of the microbial community, and, therefore, change de functionality and metabolic output (22). As next described, MACS are important substrates for gut microbial metabolism and are mainly fermentable fibers that lead to SCFA production.

Although more recent studies need to be done, it seems that processed, simple sugars lead to dysbiosis. Intake of carbohydrates, especially refined sugars, is worryingly high as they are risk factors for the development of obesity, type 2 diabetes, cardiovascular disease, and many more. They appear to have a direct effect by changing local nutrient concentrations and bacterial functions in the gut. Furthermore, they exert a pro-inflammatory effect, as they inhibit phagocytosis and increase inflammatory cytokine markers. Moreover, high consumption of sugar and soft drinks, together with low intake of vegetable, increases the risk of developing immune diseases like inflammatory bowel disease (IBD) or asthma (22). In contrast, complex carbohydrate fiber from vegetables and fruits reduce inflammation (1).

2.1.1. Microbiota-fermentable fiber.

Dietary fiber (commonly plant-derived) comprises complex carbohydrates resistant to the small intestinal and pancreatic enzymatic digestion in the human gastrointestinal tract. Many of them (e.g. non-starch polysaccharides, resistant starch, and oligosaccharides) are digested and fermented in the distal colon by gut commensal bacteria, such as those belonging to the genera *Butyrivibrio*, *Clostridium*, and *Eubacterium* (32). The resulting end products from this fermentation are SFCAs lactate and gas (33). Thus, bacterial fermentation of dietary fiber results in the production of SCFAs in the colon, which are important sources of energy representing up to 10% of the body's energy (22). However, they also act as signaling molecules and have positive effects over the microbiota and host physiology.

SCFAs signal via the central nervous system and several GPCRs affecting diverse processes such as energy homeostasis, carbohydrate and lipid metabolism, gut barrier integrity, suppression of inflammatory responses, and gene expression (by inhibition of histone-deacetylation) (34,35). While some SFCAs are partially metabolized by the colonocytes and remain in to be used by the epithelial cells (mostly butyrate), the remaining SCFAs (mostly propionate and acetate) are readily cleared in the liver and then enter systemic circulation (36–38). Thus, they affect not only the gastrointestinal tract but also distant organs and tissues. Indeed, these metabolites seem to be transported across the placenta to the developing fetus and are also present in the breast milk. Therefore, the mother's diet could affect the offspring's physiology (39,40).

SCFAs promote gut homeostasis through several mechanisms (Figure 4): 1) by "competitive exclusion", whereby high fiber diets result in an expansion of commensal bacterial (such as *Bifidobacterium,* and *Lactobacillus* genera), thus limiting the access of pathogenic bacteria to the gut epithelium (41); 2) by promoting mucus production by the gut epithelial cells (42); 3) by enhancing the epithelial barrier integrity and wound healing (43); 4) by stimulating the production of IgA in B cells (44); 5) by promoting $CD4^+$ T cell differentiation into Treg (45,46); 6) by inhibition of inflammatory molecular pathways (such as NFκB) (47).

Besides the first described effects of SCFAs on Treg development, recent experimental studies in vitro and in vivo have shown modulation of several innate adaptative immune cell populations by SCFAs, through either GPRs or FFARs signaling, mTOR-stimulation and histone-deacetylase (HDAC)-inhibitory activity (48). Butyrate, depending on its concentration and immunological milieu, may exert either beneficial or detrimental effects on the mucosal immune system. Low butyrate concentrations promote differentiation of Tregs in vitro and in vivo under steady-state conditions. In contrast, higher concentrations of butyrate in regulatory or conventional $CD4^+$ T cells induce the expression of factors associated with Th1 profile (49). Moreover, the effects of SCFAs may relay on cytokine milieu, that in turns is dependent on the immune state (50). Butyrate and, to a lesser degree, propionate, have been shown to directly enhance the cytotoxic activity of $CD8^+$ T lymphocytes (CTLs) by increasing IFN-γ and granzyme B expression (51). SCFAs could also influence effector T responses by inducing tolerogenic DCs (52) and by rendering lamina propia macrophages hyporesponsive to commensal bacteria through the down-regulation of pro-inflammatory effectors (53). Therefore, SCFAs are capable of crossing the intestinal epithelium and of reaching the lamina propia, where they can directly shape mucosal immune responses. Consequently, deficiency of dietary fiber might result in the disruption of gut homeostasis and could contribute to the development of certain diseases, such as IBD, asthma, allergy, metabolic syndrome and certain autoimmune diseases (22).

SCFAs have been shown to mediate protective effects in experimental models of colitis, multiple sclerosis, type 1 diabetes, allergic airway inflammation, and food allergy (54). Although it is challenging to translate these experimental animal findings to humans, a recent study on the causal relationships among the human gut microbiome, fecal SFCAs, and metabolic diseases, has reached important conclusions. It has found that there is an association between fecal microbiota-produced butyrate and improved insulin response, whereas abnormalities in microbial production or absorption of propionate increase the risk of Type 2 diabetes (T2D) (55).

Furthermore, high MAC diets can alter human microbiota composition quickly (56), whereas mice under low dietary MACs conditions show reduced gut microbiota diversity and intestinal mucus layer degradation by certain bacterial species, either mucin-degrading specialists or those that are able to use its glycoproteins as an alternative energy source, and thus it might compromise the epithelial barrier integrity (57).

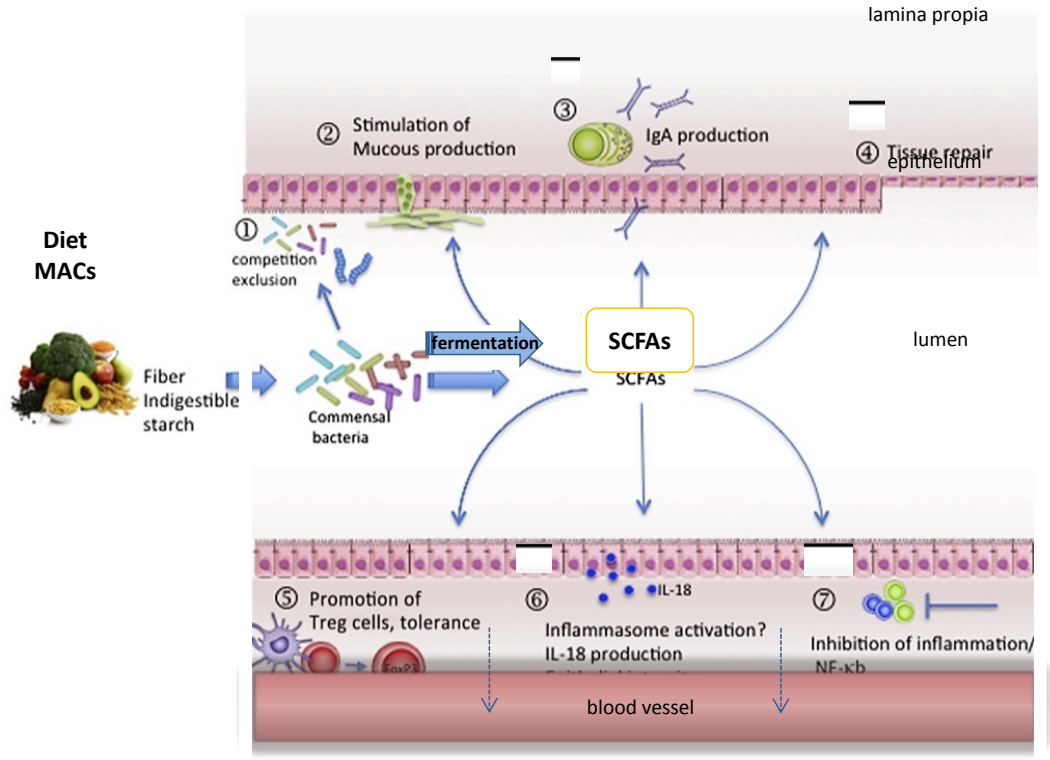

Figure 4. Multiple mechanisms whereby SCFAs might promote gut homeostasis. Adapted from (58).

2.2. Dietary fats.

Fat is an important macronutrient as it exerts structural and metabolic functions and is also an important source of energy, being the most energetic macronutrient. However, fat consumption also has a profound impact on the host´s health, not only by direct activation of immune cells but also indirectly through microbiota-mediated immune stimulation.

It is generally well known that high-fat diets (HFD) are strongly linked to obesity and its complications. Obesity leads to an excessive accumulation of white adipose tissue (WAT), which is a potent endocrine tissue that liberates strong pro-inflammatory mediators such as TNF-α, IL-6, leptin, resistin, and C-reactive protein (59). Therefore, WAT stimulates a pro-inflammatory state, which has undoubtedly many implications on the immune system. Furthermore, WAT has a profound impact on $CD4^+$ T cell populations and, specifically, on regulatory T cells (Treg), which have already been explained as important cells for immune homeostasis. Leptin, an adipose-derived hormone, might be an important connection between calorie intake and autoimmune inflammation, and seems to control body weight as well as T cell population, favoring the differentiation and activation of Th1 cells and, therefore, favoring inflammation. Furthermore, HFD intake in rats leads to decreased levels of SCFAs (60).

Importantly, recent studies have been able to determine that total fat intake is not as important as the specific type of fat consumed (18). Fatty acids can rise from the digestion of dietary lipids (oils and fats converted into triglycerides by pancreatic lipases) but can also be biosynthesized from metabolites of dietary carbohydrates.

Polyunsaturated fatty acids (PUFAs) are generally considered to have a positive effect while saturated or trans fats should be avoided due to their negative effect. Recently, some immune diseases like rheumatoid arthritis (RA), ankylosing spondylitis and Crohn's disease have been associated with specific fatty acid profiles (as it will be later commented in section 5). This information can be used to design effective diets for patients suffering from these conditions (as it will be discussed in section 6) (23).

Therefore, the quality of ingested fats seems to be more important than quantity. Next, are described the effects of different types of fatty acids (FAs) on the crosstalk between gut microbiota (commensal, pathobionts and pathogens) and the immune system and the subsequent consequences for the host.

2.2.1. Saturated fatty acids (SFAs).

This group includes fatty acids that have no double carbon bonds. They can contain 12 or fewer carbon atoms (here excluding the SCFAs raising from fermentation of MACs and previously commented), like the ones found in vegetable oils, cocoa butter o palm oil, and more than 12 carbon atoms, like those present in lard, butter, meat from beef, pork or chicken, eggs and vegetable oils (like myristic, palmitic or stearic acids) (61).

There are many reasons why SFAs are reported to cause detrimental effects on health. Firstly, they enhance the prostaglandin system, therefore creating an increased level of arachidonic acid and prostaglandin E2 (PGE2), which are pro-inflammatory mediators (62) and enhance the production of IL-17 and the activation of macrophages. Furthermore, these fatty acids alter lipids on the immune cell membranes, disrupting the normal cellular interactions and affecting the immune functions globally Finally, they are able to activate the immune response directly (16).

This direct activation of the immune system is mediated through the Toll-like receptors (TLR), which are in charge of recognition of any pathogen entering the organism. TLR4 is a specific TLR that recognizes gram-bacteria by binding to its membrane LPS, which contains mainly saturated palmitic and stearic fatty acids. When increased levels of these saturated fatty acids, they can activate TLR4, generating an inappropriate TLR signaling in which the immune cells attacks the white adipose tissue. It results in a mutual stimulation between the recruited immune cells and the WAT, leading to continuous local inflammation (22). This situation, called metabolic endotoxemia, causes gut inflammation and can be triggered by other additional mechanisms (18).

SFAs could promote Gram-negative bacteria derived LPS translocation from the enteric lumen to the portal circulation by paracellular movement (between epithelial cells which have internalized tight junction membrane proteins in response to lipids) and by transcellular transport across the epithelial cells (which adsorb lipids into micelles). To this respect, several trials in humans have reported a transient increase of circulating LPS following consumption of energy-rich meals, named “postprandial endotoxaemia”. Under certain circumstances, like damage or inflammation at the gastrointestinal tract, it is possible that this LPS could stimulate systemic inflammation

by TLR4 signaling in different tissues and organs (63). Moreover, a high intake of SFAs leads to the modification of the gut microbiota in favors of Gram-negative bacteria (and thereby LPS) to increase intestinal permeability, allowing the microbiota and potential pathogens translocation into the lamina propia and the subsequent stimulation of innate immune cells (such as macrophages, ILCs, neutrophils, etc.) located there by TLR signaling (64). This situation seems reversible by antibiotic treatment (18). SFAs can also increase plasma levels of oxidized low-density lipoprotein (LDL) that is damage-associated-molecular-pattern (DAMP) stimulating TLR mediated inflammatory response (65).

Therefore, altogether these multiple mechanisms could contribute to a mucosal and systemic low-grade chronic inflammatory state, which in turn may contribute to the development of a great variety of immune-based and metabolic diseases (IBD, allergy, asthma, rheumatoid arthritis, multiple sclerosis, diabetes, fatty liver, cardiovascular disease, etc.). Although the specific mechanisms are just beginning to be unraveled, it is clear that there is an association between high-fat Western diets, obesity and increased risk of these diseases (4,16).

2.2.2. Monounsaturated fatty acids (MUFAs) and derived oils.

Monounsaturated fatty acids (MUFAs), for example, palmitoleic acid and oleic acid, have only one double carbon bond. They are normally obtained from olive oil, canola oil, avocado, blue-green algae, macadamia nuts, and beef.

MUFAs appear to have beneficial effects on health. Frequent intake of MUFAs seems to reduce LDL while increasing high-density Lipoprotein (HDL), having a positive metabolic effect. Additionally, they have anti-inflammatory properties on macrophages (66,67). Dietary oleic acid has been shown inversely associated with UC development (68) and olive oil ameliorated colitis in experimental murine models by reducing oxidative stress, pro-inflammatory proteins and promoting intestinal LPS detoxification (69).

However, MUFAs have also been related to detrimental effects in mucosal homeostasis. For example, MUFA intake led to an increase in wheeze in pre-schoolers, while oleic acid has been linked to non-atopic asthma also in pre-schoolers (70). Moreover, in-vitro treatment of intestinal epithelial cells with palmitoleic and oleic acids impaired the barrier function (71). Therefore, the effect of MUFAs in the development of immune-mediated diseases like IBD or asthma is still not characterized, as they seem to have both pro and anti-inflammatory properties.

2.2.3. Polyunsaturated fatty acids (PUFAs).

PUFAs are long chain fatty acids (LCFAs) that have more than one double carbon bond. Among LCFAs, ω3 and ω6 are essential FAs, meaning that the human body is unable to synthesize them, thus they must be ingested in order to reach optimal levels as they carry out very important functions (72). They are metabolized into bioactive lipid mediators by several series of oxidative enzymes, such as cyclooxygenases, lipoxygenases, and cytochrome P450 monooxygenases (73).

Long-chain Omega-3 or ω-3 (n-3) PUFAs include alpha-linolenic acid (ALA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) and are generally considered to be anti-inflammatory. Foods like fish, seafood, nuts and flaxseeds are rich in ω-3. ALA is an essential FA as it must be intaken in the diet and is the precursor of EPA and DHA. These two last compete for enzymes involved in the arachidonic acid metabolism, preventing the formation of binding to the inflammatory eicosanoids (74). Furthermore, ω-3 fatty acids can also exert anti-inflammatory actions through GPCRs inhibiting TLR4 signaling, by inhibition of NF-κB and activation of the transcription factor PPARγ (75,76). DHA can also increase de expression of tight junction proteins, thus improving the integrity of the epithelial barrier in pigs (77). In asthma patients, fish oils can ameliorate symptoms (78).

Very importantly, PUFAs have been associated with reduced risk of autoimmune diseases and, particularly, RA and systemic lupus erythematosus (SLE). Many of these diseases have a common genetic factor (certain HLA-DR allele) and, even in individuals carrying this factor, consumption of this type of fatty acids produced a reduction in the rheumatoid factor. In the case of arthritis, following their consumption, it was possible to observe a reduced number of swollen joints, less joint pain and morning stiffness duration, and decreased use of nonsteroidal anti-inflammatory drugs (NSAIDs). In the case of SLE, studies in mouse demonstrated that consumption of PUFAs was associated with decreased titers of antibodies against double-stranded DNA (DNA-ds), cardiolipin, proteinuria and transforming growth factor-β (TFG-β). Some clinical trials carried out in patients of SLE have reached similar conclusions (23).

PUFAs have also been reported to ameliorate other diseases, such as atherosclerosis and cardiovascular disease, IBD and allergic diseases, which have a strong inflammatory component. There are many mechanisms by which PUFAs might exert this effect. Down-regulation of pro-inflammatory gene expression, inhibition of TLR4 signaling and production of anti-inflammatory mediators are some of them and reduction of T cell proliferation and autoantibody production (1,23). Remarkably, maternal intake of ω-3 n-3 during gestation is also beneficial, as it is protective against the development of allergies and other inflammatory diseases in the child and DHA may reduce the incidence or severity of neonatal morbidities in preterm infants due to inflammatory responses, such as brain injury, sepsis or necrotizing enterocolitis (79).

Linoleic (LA) and arachidonic (ARA) acids are Omega-6 (n-6) or ω-6 fatty acids. ARA is an essential FA found ubiquitously in plasma membranes, where it is bound to phospholipid and its metabolism produces inflammatory eicosanoids (prostaglandins, leukotrienes, prostacyclins, and thromboxanes). The ratio n-6/n-3 PUFAs present in food has increased very importantly in the USA and Europe, due to food processing, the way farm animals are fed and reduced fish and fiber intake (80). Increased consumption of omega-6 (n-6) instead of omega-3 fatty acids might be an important explanation for the modern diet-induced immune dysfunction. Indeed, higher ARA/EPA ratio has been found in the mucosa of UC patients (81). Similarly to saturated fatty acids, although less strongly, n-6 seem to be related to the immune response through common mechanisms. These include effects on TLR4 and production of pro-inflammatory mediators, being PGE2 the only pro-inflammatory mediator that has

been demonstrated to increase following high intake of n-6. Nevertheless, the effect of n-6 fatty acids has been studied in cell cultures and animal models, but it has not been well established in human physiology. Thus, further investigations are needed (1).

2.2.4. Cholesterol.

Cholesterol is derived from animal foods and it is an important molecule, as it owns multiple functions in the body. It is a component of the cell membrane, necessary for cell growth and proliferation. Moreover, cholesterol is metabolized to produce oxysterols and BAs, which are secreted into the upper gastrointestinal tract and emulsify fats, thus contributing to the breakdown of triglycerides. To exert their biological activities, oxysterols and BAs act through the nuclear receptors LXR (liver X receptors) and FXR (farnesoid X receptor), respectively. They associate with other nuclear receptors, such as retinoid X receptors (RXRs), to form heterodimers that function as active transcription factors. LXRs and FXRs are expressed in liver, intestinal epithelium and immune cells, being therefore very important for correct immune functions. FXR in innate immune cells negatively regulates pro-inflammatory mediators (82). LXR participates in the activity of macrophages (antibacterial response, apoptotic cell clearance, maintenance of immune tolerance, etc.) and can also inhibit T cell proliferation and Th17 differentiation (83–85).

As previously mentioned, BAs are produced from the catabolism of cholesterol in the liver and then transported into the intestinal lumen through the gallbladder. In the distal small intestine and colon, the primary BAs can be modified by the gut microbiota (by dihydroxylation, dehydrogenation and deconjugation), so producing activating metabolites of FXR and TGR5. These signals inhibit pro-inflammatory innate immune response attenuating several diseases, such as non-alcoholic fatty liver disease (NAFLD), IBD or atherosclerosis (86–88).

However, oxysterols and other cholesterol derivates can promote Th17 differentiation of $CD4^+$ T cells by activating RORγt (89). Therefore, the pro- or anti-inflammatory role of cholesterol and its metabolites can relay on the cellular metabolism to affect the Th17/Treg cell balance (90). A link between IL-17A production and cholesterol metabolism has been shown in keratinocytes from patients of Psoriasis. During IL-17A signaling total cholesterol levels were elevated, which in turn resulted in the suppression of genes of cholesterol and fatty acid biosynthesis. As the accumulation of cholesterol was essential for IL-17A signaling, this metabolic event may explain the strong association between psoriasis and dyslipidemia (91).

Finally, gut commensal microbiota acts as a sensor of cholesterol. It negatively regulates BAs production from cholesterol in the liver by suppressing the expression of cholesterol 7α-hydroxylase through FXR signaling, showing once again the important link between microbiota and BAs (92).

2.3. Animal protein.

Proteins are essential nutrients that contain the essential primary bioelements (C, H, O, N) and participate in virtually all the physiological functions. Host-gut microbiota plays an important role in the metabolism of amino acids from the dietary

proteins, and the source of these proteins seems to determine the output of the microbial metabolism.

The association between red and processed meat with many diseases is well known by the general population and it is a frequent topic of discussion. Its consumption is related to atherosclerosis and thrombosis, as well as gastric, colon and colorectal cancer, through different mechanisms. In general, it increases the risk of CVD, probably due to its association with atherosclerosis and hyperlipidaemia (93). Carnitine is an amino acid derived from lysine and methionine, synthesized primarily in the liver and kidneys. Red meat has a high concentration on L-carnitine, which is metabolized by the microbiota to trimethylamine (TMA), which is then converted into trimethylamine N-oxide (TMAO) in the liver. TMAO plasma levels are strongly associated with cardiovascular events, such as atherosclerosis and thrombosis, and have also been implicated in the development of fatty liver disease in mice (94). This metabolic conversion was stronger in individuals with high consumption of L-carnitine, compared to vegans or vegetarians, and was reversible with antibiotic treatment. *Prevotella*, a specific member of the microbiota, were identified as important in this process, both in mice and humans (95). However, TMAO seems to also have protective functions, for example, by protecting cells from hydrostatic and osmotic damage. IBD patients (where gut microbiota is enriched in anaerobe and facultative anaerobe microorganisms) show decreased TMAO levels (96). Furthermore, TMAO can also arise from TMA oxidation in seafood, fish, etc., and oily fish consumption can protect against asthma in children (97).

The catabolism of proteins yields also multiple other metabolites, which are able to affect human health. These include SCFAs (already commented above), branched chain fatty acids, ammonia, indoles, phenols and amines. The last three one can combine with nitric oxide to form genotoxic N-nitroso compounds, such as heterocyclic amines, by enzymatic reduction involving microbiota. Processed meat, therefore, results in the production of carcinogenic heterocyclic amines, which induce DNA damage and result in an increased risk of colon and gastric cancer (98). According to experimental evidence, lactic-acid-producing bacteria, like *Lactobacillus,* seem to have a protective effect, as they bind to these amines, preventing the induction of neoplasia in the host (99). Red meat has been reported to increase levels of carcinogenic N-nitroso compounds as well, which have been related to colon and gastric cancers. Finally, high animal-derived protein intake increased the risk of CD, and cured meat is related to worsening of the symptoms of asthma (22).

On the contrary, there are beneficial effects derived from proteins. Gut microbial metabolism of tryptophan, an essential amino acid found in red meat, fish, eggs, yogurt and many vegetables, results in metabolites with beneficial effects on the host. Indolepropionic acid maintains intestinal homeostasis protecting from experimental colitis (100), while indole-3-acetate reduces hepatocyte and macrophage inflammation (101). Furthermore, indole-3-aldehyde produced by lactobacilli and kineurin produced by immune cells act as agonists of AhR, contributing to the gut homeostasis and immune tolerance by promoting the production of IL-22, antimicrobicidal factors, Treg cells activity, suppression of T cell responses, etc. (22).

Moreover, lower serum tryptophan is associated with active Crohn´s disease (102), whereas supplementing tryptophan showed beneficial effects in a porcine IBD model (103). Finally, studies have revealed that supplementation with dietary peptides (such as alanine-glutamine) promotes mucosal recovery in a colitis mouse model; by increasing mucin2 expression while decreasing inflammatory factors expression (104).

As shown, specific members of the microbiota might have an important role in regulating the effect of proteins on health and the proteins from foodstuffs could affect the microbiota composition. However, yet again, further investigation should be carried out.

2.4. Dietary salts.

Salt has been an important product all through human history, used for cooking, food preservation and even as a currency. Its consumption varies greatly between different cultures, but it is generally higher than it should, as fast and processed foods have a very high content in salt. While the effect of sodium chloride (salt) intake on our cardiovascular system has been well studied, its exact impact on the immune system is yet to be elucidated.

The effect of sodium intake in autoimmune diseases in vivo is now starting to be understood. Through many and complex investigations, the classic concept of sodium homeostasis is changing, showing many different mechanisms by which sodium modulates the immune system. The previous idea maintained that sodium concentration was controlled by urinary excretion, ensuring isotonicity between plasma and tissues. However, physiological accumulation of sodium has been found in different tissues, demonstrating that higher concentrations of this solute are required in order to maintain their function. This is the case, for example, of secondary lymphatic organs in mice, where sodium allows adequate T cell functioning. Furthermore, daily sodium excretion has been studied in humans who consumed different quantities of salt under controlled conditions and revealed periodic sodium storage. Therefore, sodium content in the different tissues is flexible, maintaining a physiological status that could be disrupted and lead to pathophysiological conditions. Importantly, it has important consequences in the immune system (16).

It seems that the intake of excessive amounts of salt could increase the release of pro-inflammatory cytokines and worsen autoimmune diseases. Osmotic stress is, therefore, considered to produce a rise in pro-inflammatory substances, being this the reason why infusion with hypertonic saline for plasma expansion activates the immune system. sodium concentration also affects Treg cells and macrophage function. In the first case, it generates a reduction in the suppressive capacity of Treg by increasing their production of IFNγ. This effect is reversible upon anti- IFNγ antibodies exposure. In the second case, salt stimulates a shift towards the differentiation of more pathogenic strains of macrophages, through increased production of pro-inflammatory markers and a reduction in anti-inflammatory markers. Salt also stimulates the differentiation of Th17 cells and production of IL-17, which are related to autoimmune diseases such as RA, SLE, multiple sclerosis and psoriasis. If well understood, once more, therapeutic strategies targeting this mechanism could be developed (16,23).

2.5. Micronutrients: vitamins.

Micronutrients are essential elements required by the organism in small quantities in order to maintain its correct functioning. Therefore, they are acquired through diet and they include metals like iron, cobalt, copper, Zinc, and vitamins. However, the microbiota is also important in their bioavailability. Micronutrient deficiency is associated with immune system impairment and worsens the progress of many diseases.

Vitamins are necessary components and many of them cannot be generated by humans, so they must be absorbed from the diet (Figure 5). The gut commensal bacteria also produces and simultaneously consumes dietary vitamins. Therefore both, diet and gut microbiota are important to determine vitamin contents and bioavailability. Vitamins display multiple biological activities, by acting as antioxidants, transcription factors, and cofactors for metabolic enzymes in the generation, conversion, and digestion of fatty acids, nucleotides, carbohydrates, and amino acids. Thus, vitamins are required for the development, differentiation, and activation of immune cells and therefore vitamin deficiency is frequently associated with increased risk of infectious, allergic, and inflammatory diseases (105).

Vitamin A.

It is an essential fat-soluble compound obtained from plants, like carotenoids (e.g. β-carotene), and from animal material. Vitamin A can be converted in the intestine epithelial, stromal and $CD103^+$ dendritic cells into several bioactive metabolites, such as retinal and retinoic acid. The last one is present as two isomers, all-trans-retinoic acid (ATRA) and 9-cis RA. These can bind to heterodimers of RXR and retinoic acid receptor (RAR), which act as transcription factors to regulate several functions in immune cells, mainly in the gut. Retinoic acid can modulate T cell sensitivity to the environment by regulating cytokine receptors and the expression of signaling components, thus promoting Treg differentiation in response to TGF-β and Th17 inhibition (106). Retinoic acid can also control the formation of lymphoid tissue in the small intestine, the presence of $ROR\gamma^+$ ILCs and the gut-homing of ILCs (107), T and B lymphocytes (by the up-regulation of the integrin α4β7 and the chemokine receptor CCR9) (108). Gut IgA production is also promoted by retinoic acid in B cells (109).

Owing to all these diverse immune modulatory roles of vitamin A that contribute to the maintenance of gut tolerance and immune homeostasis, deficiency in vitamin A can lead to intestinal inflammation (80). Conversely, supplementation of vitamin A or retinoic acid seems to attenuate intestinal inflammation (110,111).

Vitamin D.

Vitamin D can be obtained from the diet while vitamin D3 can be photochemically synthesized in the skin exposed to ultraviolet B radiation from pro-vitamin D3 (7-dehydrocholesterol). Its physiologically active metabolite is calcitriol, which is produced in the liver and kidneys. Calcitriol exerts its biological activity through the binding to heterodimers of vitamin D receptor (VDR) and RXR, that is a complex regulating gene transcription. Calcitriol is well known from its implication in

bone mineralization and optimal intestinal absorption of Ca, Fe, Mg, phosphate and Zn. However, vitamin D also regulates epithelial integrity/barrier function (by up-regulation of tight junction proteins) (112) and modulates immune response acting on several immune cell types In T cells calcitriol promotes Treg directly inducing differentiation by binding of VDR-RXR to an enhancer in the FOXP3 gene in activated CD4 T cells (113). The anti-inflammatory effect of vitamin D seems to be mediated by TLR signaling and NFκB activity inhibition (114). In addition, vitamin D suppresses Th17 differentiation by gene regulation and also Th17 cytokine production by post-transcriptional mechanism (115,116).

Moreover, there is a strong negative correlation between the frequency of CD and exposure to sunlight (117) and the potential benefits of vitamin D supplementation for inflammatory diseases are currently under investigation (118).

Vitamin B.

The vitamin B complex contributes to energy metabolism. Vitamin B1, also known as thiamine, is mainly obtained from whole grains, trout, pork, beans and peas and. It has been recently revealed that quiescent or regulatory-type cells such as naïve T and B cells, Treg cells, and M2 macrophages use anabolic pathways for energy generation from the fatty acid oxidation and tricarboxylic acid cycle, whereas activated or inflammatory cells (e.g., Th1, Th2, Th17, IgA-producing plasma cells, and M1 macrophages) use catabolic pathways and shift to glycolysis for energy generation (24). Importantly, vitamin B1 (also known as thiamine) and its derivatives (e.g., thiamine pyrophosphate), as well as vitamin B2 and its active forms (e.g., flavin adenine dinucleotide) function as cofactors in the TCA cycle and in fatty acid oxidation (119). Diets lacking the vitamin B complex lead to impaired immunity in mice (120). Vitamins B have also direct effects on immune cells. Vitamin B3 exerts anti-inflammatory properties through attenuation of the release of TNF-α, IL-6, and monocyte chemotactic protein-1 on monocytes and also IL-1β in macrophages (121).

Moreover, microbial metabolites derived from the metabolism of vitamins exert immunomodulatory actions. Mucosal-associated invariant T cells (MAITs), are innate-like T cells which help exclude infectious bacteria and also seems to contribute to inflammatory disease. They are activated by a microbial metabolite of B2 and are able to recognize a microbial vitamin B9 metabolite but do not activate them (122).

Vitamin B6 (pyridoxine), a water-soluble vitamin is contained in fruits, vegetable, fish, meat and grains. It can be metabolized by some commensal bacteria, such as *Eubacterium rectale*, to yield the bioactive form pyridoxal 5´-phosphate, which is involved in the metabolism of carbohydrates, lipids, and proteins and it also modulate immune inflammatory response in colitis experimental models (123).

Vitamin B9, also known as folic acid or folate, is another water-soluble vitamin obtained from vegetables and fruits and through bacterial biosynthesis by Bifidobacteria and Lactobacilli (124). Vitamin B12 or cobalamin is found in animal foods and it participates in the absorption of vitamin B9. Deficiency in vitamins B9 and B12 has been described in patients of Crohn's disease (125) and associated with a reduction in colonic $Foxp3^+$ Tregs (126). B12 deficiency, sometimes caused by

vegetarian or vegan diets, leads to a reduction in $CD8^+$ T cells and NK cells numbers and activity (127).

Furthermore, B vitamins could be exchanged cooperatively by gut bacteria to ensure their survival (128).

Other vitamins.

Vitamin K is a fat-soluble vitamin obtained from meats, cheeses, and eggs (VitK1) or synthesized (VitK2) by the colonic microbiota. It is involved in blood coagulation and calcification. Vitamin K deficiency has been associated with both adult and pediatric Crohn's disease patients and it is also protective in an experimental model of colitis (129,130).

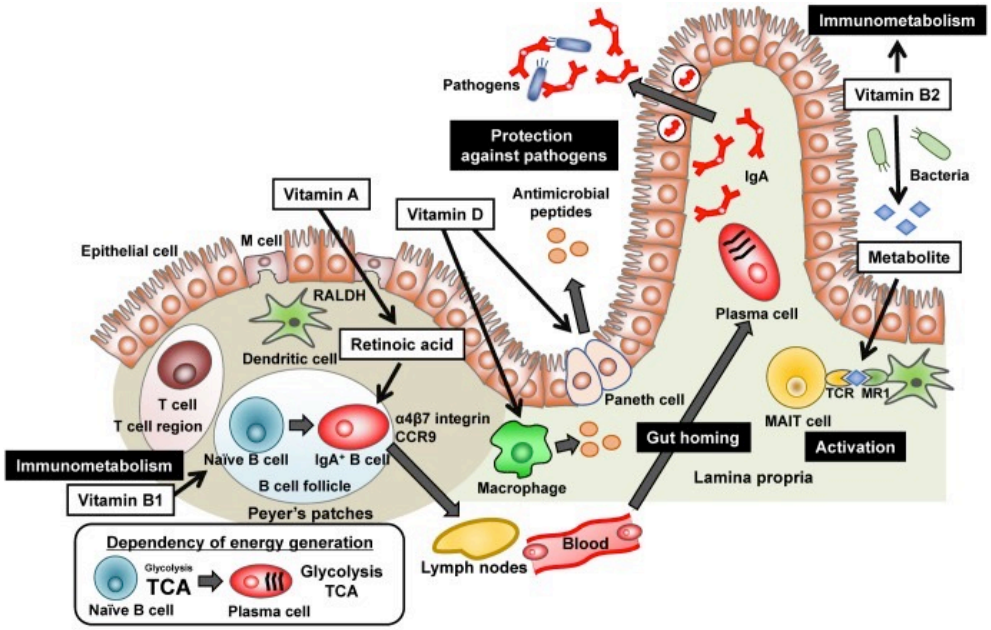

Figure 5. Role of vitamins in the immune function and gut homeostasis. Taken from (131).

2.6. Other non-nutritive natural components: capsaicin, curcumin, coffee, cocoa, and resveratrol.

Plants from the human diet contain, in addition to fiber, many bioactive compounds with effects in health, including autoimmune diseases (23) (Figure 6).

Capsaicin is the main active ingredient of the chili peppers, responsible for the spiciness of this fruit. It also has multiple pharmacological and physiological effects. Firstly, it is well known for its topical analgesic effect against peripheral neuropathic pain. It has shown a positive effect on osteoarthritis (OA), RA and severe fibromyalgia, being a better analgesic than placebo on clinical trials. Furthermore, capsaicin has also been associated with positive effects on the cardiovascular and gastrointestinal system, as well as antihypertensive, anticancer effects and immunomodulatory properties. When capsaicin binds to its receptor, TRPV1, pro-inflammatory and anti-inflammatory substances are released thus modifying the outcome of the disease.

Specifically, it is believed to participate in the activation of anti-inflammatory macrophages and down-regulation of tumorigenic T-cells (132). Finally, capsaicin is gaining importance due to its bactericidal effect towards different bacteria: *Helicobacter Pylori, Staphylococcus aureus and Porphyromonas gingivalis* (133).

Curcumin has demonstrated beneficial effects in mouse models of lupus nephritis, multiple sclerosis and myasthenia gravis on mouse models since it acts as an anti-inflammatory, antioxidative and antiarthritic substance. Moreover, studies on humans found some improvement in the course of RA and lupus nephritis, although the conclusions were not statistically significant (134). Curcumin has been associated with increased Treg proliferation and anti-inflammatory gene expression, plus suppression of Th1 cell proliferation (23). Therefore, according to more recent studies, it seems to have a positive but small impact, due to its low bioavailability and its unstable reactive nature.

Coffee has been considered to have a negative effect on general health and, specifically, on the cardiovascular system for a long time. Recent studies have reversed this thought, establishing a protective correlation between coffee and mortality. The main active ingredient of coffee is caffeine, which has shown anti-inflammatory properties through the activation of the cAMP-PKA pathway: induces suppression of TNF production by murine splenocytes, lymphocyte proliferation, and antibody production. However, in the case of autoimmune diseases, the relationship seems to be more complicated, as the effect of caffeine might vary greatly depending on the specific disease. On the one hand, coffee was associated with reduced risk of multiple sclerosis and ulcerative colitis (135). On the other hand, it has been correlated to the production of rheumatoid factor, thus inducing RA, and SLE (136,137). It is therefore difficult to establish conclusions until further research is carried out.

Cocoa is highly rich in polyphenols and low-molecular-weight flavanols, which have direct and indirect anti-oxidative effects. As a consequence, consumption of cocoa has been linked with improved blood pressure, insulin resistance, vascular function and platelet function, as well as many other cardio-protective properties. Additionally, flavanols also have anti-inflammatory properties, affecting both innate and acquired immunity (23). They down regulate pro-inflammatory (IL-1β and IL-2) cytokines and up-regulate anti-inflammatory ones (IL-4). Furthermore, one study demonstrated a reduction in pro-inflammatory substances like TNF, monocyte chemoattractant protein 1 and nitric oxide. Finally, another important action of cocoa is the reduction of antibody secretion. All these actions together seem to explain the reason why cocoa might be an adjuvant therapy for diseases with inflammatory autoimmune pathogenesis.

Resveratrol, a flavonoid (polyphenolic phytoalexin), is a natural component of wine, where it is found in high concentrations. It is attributed to many actions including anti-inflammatory, antioxidant, anti-carcinogenic and immunomodulatory properties. After moderate consumption of wine, polyphenols are found in plasma at a concentration that acts as an important cofactor in innate immune reactions. This molecule acts through different mechanisms: down-regulation of NF-kB activation, cyclooxygenase 2 activity, and ROS production. Consequently, it seems to have an

important role in tumorigenesis and inflammation. Rewarding autoimmune diseases, resveratrol has shown positive effects in type 1 diabetes mellitus induced cerebrovascular dysfunction, inflammatory arthritis in animal models and as a preventive tool for attacks of gout. Furthermore, resveratrol was associated with positive alterations in HFD inducted microbiota dysbiosis.

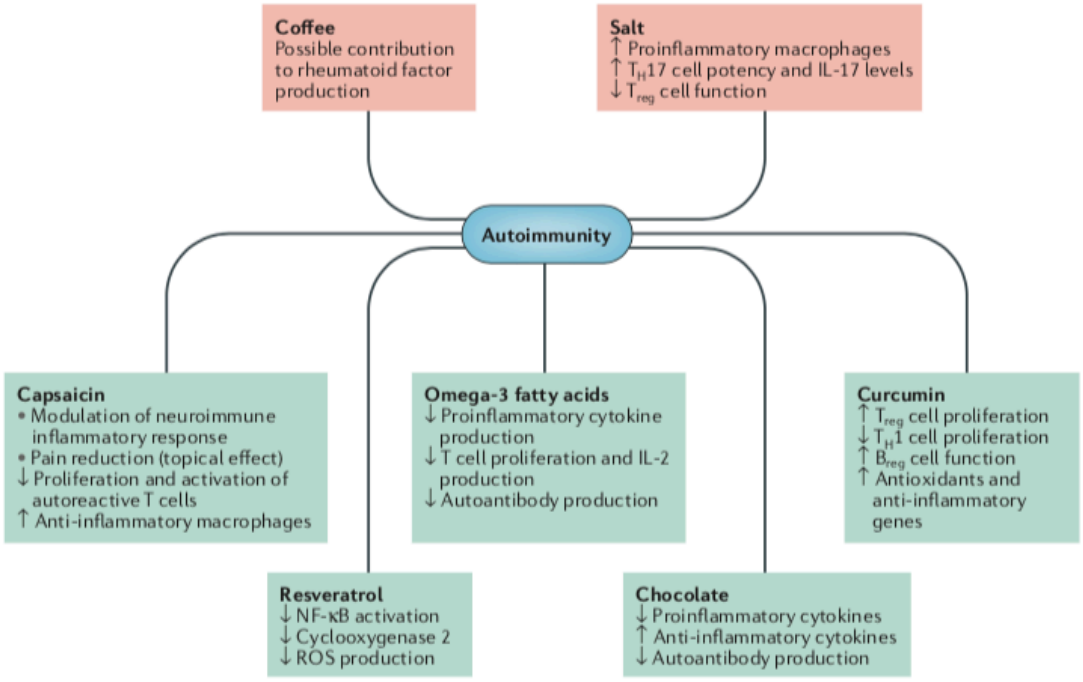

Figure 6. Dietary factors associated with autoimmunity. Coffee, salt, capsaicin, resveratrol, omega-3 fatty acids, chocolate, and curcumin have important effects on the immune system. Taken from (23).

2.7. Food additives.

Food additives are being more and more consumed, as the consumption of processed foods, which are rich on them, has increased greatly during the past decades. They can be natural or synthetic and some examples are preservatives, sweeteners, emulsifiers, fortifying agents, etc. Although they undergo investigations before being approved for use, modern techniques that could allow a better understanding of the relationship between additives and the microbiota have been developed recently.

Dietary emulsifiers, and specially carboxymethylcellulose and polysorbate-80, have been reported to promote dysbiosis in the microbiota both in mice and human, followed by low-grade inflammation, metabolic syndrome, and colitis (18,22).

Another emulsifier, phosphatidylcholine (a type of lecithin) has been associated with increased levels of TMAO and risk of CVD.

However, the case of non-caloric artificial sweeteners (NAS), like saccharin, sucralose, aspartame, etc, is much less clear. While some studies attribute them a positive effect on rewarding weight loss, others associate them with metabolic

derangements, including weight gain. Studies carried out in both humans and mice resulted in mixed and contradictory conclusions, possibly due to interpersonal variations of the participants as well as microbiome susceptibility. The consumption of NAS could, therefore, be beneficial for some individuals, while others should avoid them. However, further investigations need to be carried out (1,18).

2.8. Genetically modified (GM) foods.

GM food can be a tool by which we can obtain important benefits. One significant possible use is the design of GM food enriched with nutrients, as a way of treating important nutritional deficiencies. For example, in geographical areas where vitamin A deficiency is frequent, implantation of food modified to produce high levels of β-carotene has the same benefits as medication, is an easier and more affordable approach to treat the deficiency. Furthermore, food could be design to resist environmental conditions characteristic of the place where it is produced. Such modifications could make food resistant to pests or drought. This could be a tremendous advantage, though further investigation on the consequences on our health needs to be done, as this type of food could also imply some detrimental effects.

However, this type of food could also imply some detrimental effects. For example, allergic reactions have been reported. As a consequence, GM foods are tested for homology against all known allergens. Moreover, some GM plants produce pesticide or pesticide inhibitors, being this issue a strong source of concern as it increases the need for pesticides used in the crops, which are reported to be dangerous. Some animal models fed with pesticide-producing GM maize and pesticide-resistant GM soy suffered stomach inflammation, which did not occur when feeding with pesticide-producing GM maize alone. This shows the important impact of pesticide-resistant GM food. Finally, another concern is the fact that these functional modified genes could be transferred to the bacteria inhabiting the intestine. This would lead to the production of functional proteins, whose impact on health is unknown, and could even be inherited via microbiome transfer, having negative effects on the offspring (1).

3. INFLUENCE OF DIET IN DIFFERENT IMMUNE-MEDIATED DISEASES.

As previously discussed, the microbiota fuels on the macronutrients and micronutrients that constitute its host's diet and helps maintain a homeostatic state in the whole organism. Although not completely well understood, it is clear that the diet has an important effect on the gut microbiota, which then can mediate immune imbalance through the previously described interactions. This will have strong consequences all over the organism and will be a determinant factor influencing the development of many diseases (Figure 7).

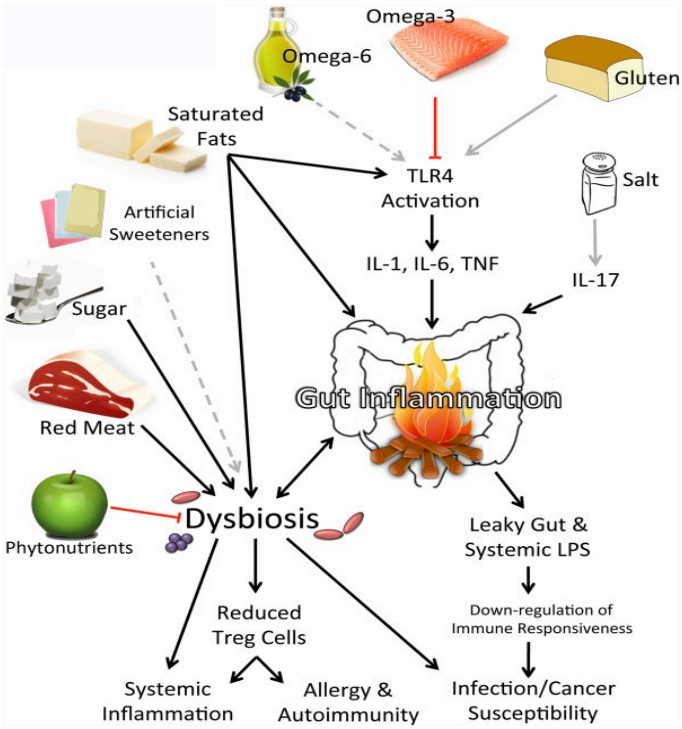

Figure 7. Immune-mediated disease susceptibility associated with dysbiosis driven by typical foods from the Western diet. Reproduced from (1).

3.1. Inflammatory/Autoimmune disease.

Autoimmune diseases such as multiple sclerosis (MS), RA, IBD, type 1 diabetes (T1D) and psoriasis (Ps) are heterogeneous diseases that share some common factors. They all have multifactorial etiologies that include deregulation of the immune response and are characterized by a chronic clinical course. Genetic factors are crucial for the development of these diseases but, undoubtedly, environmental factors, like diet, play an important role as triggers of the diseases (16). Importantly, many immune diseases show a higher prevalence in Western societies, compared to the Eastern world and developing countries. In addition to having higher prevalence, Western societies show an increased incidence rate of these diseases and countries that are now adapting to a westernized lifestyle are also starting to experience augmented levels of affected individuals (22). There is, therefore, a positive relationship between economic improvement and westernization and immune disease, being diet an important determinant.

The exact role of diet as a risk factor for the development of immune diseases is not clear yet, and it is thought to involve many different mechanisms. Numerous studies have been carried out trying to clarify how nutrients determine the development of IBD, T1D, MS, etc., but they have reached controversial results (16). However, there are some mechanisms that have been well established. For example, exogenous and endogenous macronutrients regulate the inflammatory response through the liberation of diverse metabolites. The NLRP3 inflammasome complex can be activated by a wide range of stimuli and is important for the correct functioning of the innate immune response, thus it is the most clinically implicated inflammasome. It acts as a sensor of structurally diverse metabolic DAMPs and has been associated with

many inflammatory disorders that are linked to caloric excess, adiposity and aging (138). Therefore, the inflammasome is activated when it recognizes danger molecules and then liberates IL-1β and IL-18. They will form a complex with their primary receptor and an accessory receptor and will determine the progression of inflammation and the development of disease. It is very important to note that many nutritional components like glucose, fatty acids and cholesterol are able to act as DAMPs. An inadequate diet in which these compound are excessive, as occurs with diets associated with obesity, will determine chronic inflammation partially through this mechanism. This will be, therefore, an important link between diet and inflammation and will have detrimental consequences.

3.1.1. Intestinal Bowel Disease (IBD).

IBD is a multifactorial chronic immune-mediated gastrointestinal disease. It includes two different forms: Crohn's disease (CD) and ulcerative colitis (UC), both characterized by abdominal pain, fever, and diarrhea with blood and/or mucus excretion (22). Although similar, these two diseases have important differences. CU has a higher prevalence in our society, and it is characterized by a continuous inflammation that affects only the most superficial layer, the intestinal mucosa. The lesion starts on the rectum and extends proximally to the colon, being the extension the main determinant of the symptoms. CD is less prevalent but its incidence is rising worryingly. It involves segmentary inflammation of any part of the GI tract, although it is more common in the terminal ileum, and resulting symptoms depend mainly in the location where it develops. Its inflammation affects the whole intestinal wall.

The microbiota seems to be of particular interest in the development of this disease in genetically susceptible individuals. In patients suffering from IBD, a strong intestinal dysbiosis is established, characterized by aberrant functioning of immunomodulatory metabolites. This situation may determine an impaired cross-talk between immune cells and the microbiome (4). Additionally, the microbial flora of these patients suffers modifications on its composition, including decreased *Firmicutes* and *Bacteroidetes* and increased *Enterobacteriaceae*. Importantly, within the *Firmicutes* phylum, there are bacteria that produce a high amount of butyrate. A reduction of these bacteria was revealed in patients with CD and UC, resulting in loss of the immune regulatory function of butyrate. Furthermore, a decrease in anti-inflammatory commensals has been observed in CD. The expansion of several pathogenic bacteria is thought to explain, at least partly, the etiology of IBD, but these bacteria have not been characterized yet. However, commensal bacteria with potential pathological power, known as pathobionts, have been isolated, including adherent and invasive *E. coli* (22).

Diet is important in the progression of IBD. A recent investigation carried out in Europe has not been able to establish an association between BMI and IBD, but epidemiological studies correlate high intake of red and/or processed meat, dietary fat, sugars and low levels of vitamin D with an increased risk of IBD (22). Additionally, the intake of total fat and high n-6/n-3 PUFAs ratio was associated with disease activity in patients suffering CD (139). Some studies also correlate milk protein with CD and

cheese with the development of both CD and UC. On the contrary, diets rich in n-3 PUFAs, fermentable fibers, vegetables, and fruits lower the risk for IBD (22).

Understanding of the importance of diet and microbiota in the development of IBD could allow new and more optimal ways of treatment. New treatments include inhibitors of cytokines, inflammasome, etc. Another example could be the colonic irrigation with butyrate that showed beneficial effects in UC patients, by limiting inflammation and modifying the microbial composition (22).

3.1.2. Rheumatoid Arthritis (RA).

RA is an autoimmune disease in which the body attacks the joints, producing typically warm, swollen and painful joints, although it can also affect other parts of the body. The causes of this long-term disease are not clear, but genetic and environmental factors have been claimed to be causative. Emerging data suggest that the microbiota is involved in its aetiology and it is believed that mucose tissue exposed to high concentrations of bacterial antigens (i.e. gut) may be the initial site of tolerance break in RA, Ps arthritis and related diseases.

The metabolome is implicated in the development of RA through both direct mechanisms, by interactions with DC, T cells and macrophages, and indirect mechanism, by modulating energy metabolism and allowing obesity, a strong risk factor for RA, Ps, and OA. The effect that diet has on the composition of the microbiota and on its metabolite production is, once again, important in the course of this disease. Recent studies have been able to correlate the beneficial effects of SCFAs already explained with an arthroprotective effect (140). However, future research needs to be done as many of the investigations already carried out trying to elucidate the involvement of diet on RA arrive at contradictory conclusions.

It seems that the Mediterranean diet ameliorates the symptoms of patients with already diagnosed RA, compared to the Western diet, possibly due to an increase in SCFAs levels. A study carried out in Sweden showed a reduced risk of developing RA when oily fish was part of the diet. Moreover, it has been proposed that oily fish also improve the symptoms of RA patients. This is probably due to the high ω-3 concentration found in oily fish. Similarly, oil-derived omega fatty acids could also help prevent RA. Increased consumption of fruits and vegetables (especially cruciferous vegetables), probably due to their antioxidant effect, appears to be protective against the development of RA. On the contrary, the involvement of red meat is still very controversial, though it seems to increase the risk of RA probably due to its high levels of iron, which accumulates in the joints of patients with RA. All these correlations between different components of diet and RA are very controversial (140).

In the future, a better understanding of the implication of diet in RA could allow designing specific diets to treat patients. Furthermore, SCFAs could be used as important therapeutic tools to ameliorate this disease. The potential benefit of probiotics and prebiotics is also starting to be investigated.

3.2. Metabolic disease (obesity, diabetes, cardiovascular disease).

The consumption of a Westernized diet is related to the augmented incidence of metabolic diseases, such as diabetes or obesity. Obesity is understood as abnormal or excessive fat accumulation that is linked to increased risk of illness, disability or death. This condition has doubled worldwide since 1980 (16), which will undoubtedly have a tremendous impact on epidemiology and health systems in the future. It is often accompanied by metabolic syndrome, defined as insulin resistance, high triglyceride, and low high-density lipoprotein levels. Hypertension and many chronic diseases, including immune-mediated diseases like IBD, are also strongly associated with obesity.

Induced obesity studies carried out in Germ-free mice have revealed the crucial role of environmental factors besides genetics in the susceptibility to obesity, as these animals are protected from diet-induced obesity (141). Then the microbiota emerged as an important player. Even though several mechanisms have been suggested to explain the role of the gut microbiota in the aetiology of obesity (such as SFCAs production, hormone secretion stimulation, lipoprotein and bile acid metabolism, induction of chronic low-grade inflammation, etc.), as of now there is controversial evidence from animal and human studies in establishing whether changes in the gut microbiota are the cause or the effect in obesity. More recent metagenomics studies indicate that the functionality rather than the composition of gut microbiota may be important.

The microbiota has an important effect on lipid metabolism, fat storage, and energy regulating both BAT and white adipose tissues (WAT). The development of obesity depends on the balance between food intake and energy expenditure and also on the balance between WAT and BAT. WAT is the main energy reservoir and secretes a huge number of hormones and cytokines that regulate metabolism and insulin sensitivity. BAT is specialized in increasing energy expenditure and heat production. In addition, BAT could affect body metabolism and alter insulin sensitivity and, consequently, its expansion or activation can protect against diet-induced obesity, at least in experimental models (142,143). BAT is produced during embryogenesis, β-adrenergic stimulation, and cold exposure. Browning of WAT, in which WAT cells take up characteristics of BAT cells (144), also occurs under these circumstances and has beneficial metabolic effects. Furthermore, exercise also increases WAT browning and recent experimental studies have demonstrated that the microbiota is affected under low temperatures in mice, which helps in the activation of BAT and the browning of WAT (145). Also, in these conditions, a plasma bile acid profile similar to that previously found in Germ-free mice was observed (146).

Furthermore, decreased microbial community has been related to obesity in humans, but results from human studies are controversial mainly due to marked interindividual variations in the gut microbiota. Albeit the first studies indicated that an increase in Bacteroidetes and decrease in Firmicutes phyla could be responsible for obesity, the type of gut microbiota and their exact phylogenetic level at which they exhibit differences are still under investigation (147). Moreover, whether this finding is casual or causal has yet to be clarified, as both obesity and altered microbiota could be

the result of an inappropriate diet. Additionally, both diabetes and obesity are associated with systemic low-grade inflammation attributed to metabolic endotoxemia (21). When the microbiota interacts with saturated dietary lipids, it secretes pro-inflammatory molecules to the plasma. These activate TLR in adipocytes and, consequently, recruit macrophages into the adipose tissue. Endotoxin has been demonstrated to induce proliferation of adipocyte precursors (148), adipose inflammation and impaired glucose metabolism in mice. In human, levels of peripheral endotoxin are increased by dietary lipids (149). Importantly, animal studies have found that Gram-negative bacteria are able to translocate from the gut to the blood and adipose tissue, causing impaired glucose metabolism. Treatment with probiotic *Bifidobacterium animalis ssp. lactis* was able to ameliorate this situation (150). The exact mechanism of bacterial translocation if not well defined. However, the resulting diabetic state might cause impaired immune defense, which seems to enable the movement of bacteria across the intestinal wall. Another important mechanism is mediated through the NLRP3 inflammasome: as already explained, metabolites like glucose, fatty acids and cholesterol act as DAMPS and activate inflammation, resulting in numerous metabolic diseases. Furthermore, lean mouse individuals present an adipose tissue characterized by an anti-inflammatory cytokine and adipokine profile. In contrast, obese mice present a pro-inflammatory profile, in which an initial CD8+ T cells infiltration is followed by macrophages, resulting in inflammation. This sustained low-grade inflammatory state will have several consequences and it is certainly linked to the development of many diseases that involve the whole organism and might affect very different organs. For example, its association with IBD is not confirmed but seems to be positive (22). In the case of asthma, the correlation between obesity and its development and severity has been specifically identified.

The microbiota is, therefore, crucial for the development of metabolic diseases such as obesity and diabetes. However, it is also essential for the correct development and growth of the organism since early moments. At the beginning of life, HMOs serve as important fuels for the microbiota. It has been observed that, under circumstances of lack of HMOs, growth is severely impaired as a result of the subsequent microbiota alterations. Similarly, undernourished children were found to have an immature gut microbiota, increasing the risk of growth impairment. In one study, this immature microbiota was transplanted to mice and, afterwards, they were treated with bacterial species (*Ruminococcus gnavus, Clostridium symbiosum* and *Lactobacillus plantarum*), which was sufficient to rescue growth impairment. Another study found that mice with germ-free microbiota were not able to grow at a normal rate when nourished with a diet sufficient to produce adequate grow in colonized mice. Although the exact mechanism by which de microbiota determines growth is not clear, the growth hormone (GH)-insulin-like growth factor-1 (IGF1) axis has been involved.

Recently, alterations of the microbiota have been linked to the physiopathology of cardiovascular diseases through different mechanisms. Cardiovascular disease is extremely important, as it is a leading cause of death worldwide. As previously mentioned, meat is rich in L-carnitine, that is converted into TMAO by the microbiota. A diet characterized by excessive intake of meat induces increased levels of TMAO in mice, which is atherogenic. A similar result has been reported in humans, where increased levels of TMAO during fasting periods were associated with major adverse

cardiovascular events like myocardial infarction or stroke, increasing overall mortality (4). An analogous process happens with choline, which is present in seafood, cheese and eggs, and has been linked to increased cardiovascular risk as well. Specifically, L-carnitine is transformed into TMA by TMA lyases, and then into TMAO. Therefore, inhibition of TMA lyases was suggested as protective against atherosclerosis development. Indeed, 3,3-dimethyl-1-butanol (DMB) was able to inhibit TMA lyases in mice showing a very promising therapeutic tool that needs to be studied in humans. Interestingly, DMB was naturally found in balsamic vinegar, extra virgin olive oil and red wine (14). Atherosclerosis is originated when cholesterol crystals and oxidized LDL deposit on the vascular wall, which induce activation of the NLRP3 inflammasome and uncontrolled inflammation (140).

3.3. Infectious disease.

The control of infections by the immune system is greatly influenced by diet. One example is the production of SCFAs by the microbiota, which promotes B cells metabolic activity, plasma cell differentiation and production of antibodies, both in mice and humans (24).

On the other hand, during chronic infections, the functioning of the immune system is altered. One important mechanism is due to the release pro-inflammatory cytokines, which consequently induce appetite suppression, leading to an increased risk for nutrient deficiencies and, consequently, a worsening in the immune function, deregulation in the metabolic system and a general state of cachexia (1,24).

3.4. Tumors.

The Western diet was associated with one-third of cancers in developed countries in 2014, although this number has probably increased following better studies on the immune-nutrition impact in cancer development. Such studies are difficult to carry out, since nutritional compounds may act enhancing or inhibiting each other, and their effects might be confounded by exposure to other environmental factors like smoking or infections. In general, chronic inflammation is characterized by an increased risk of cancer through mechanisms not well established (1).

Some foods that have been linked with the development of neoplasms are hot food or drinks, red meat, fat (specifically palmitic acid) and salt-preserved meat, plus alcohol and tobacco. Others like vitamin E, vitamin D, and selenium seem to have anti-tumoral activity. Importantly, tumors are able to generate a microenvironment that affects enormously the immune system, being this crucial for their development and capability or malignancy (24).

3.5. Allergic disease and Asthma.

The relationship between diet and allergic disease is not well studied, but two aspects should be considered. Firstly, based on current evidence and contrary to previous knowledge, early introduction of solid foods may be protective against allergy development. Secondly, the development of allergic disease in a child might be followed by implementation of diet in which frequent allergens like nuts, dairy, egg or

fish are avoided. Special caution needs to be taken, as these allergy-driven elimination diets have an increased risk for deficiencies, including calcium and omega-3 (1). Food allergies constitute a specific and frequent type of allergy of great importance in this review. Mucosal dendritic cells (DCs) seem to be very important as they regulate Treg. According to a study performed with mouse models, fiber and vitamin A were able to influence the composition of the microbiota so that it showed increase tolerance toward food antigens (22). Therefore, a diet high in fiber and vitamin A seems to be protected against food allergies. This effect was dependent on epithelial GPR43 and immune GPR109A receptors (4).

Asthma is a heterogeneous chronic inflammatory disease characterized by airway immune hyperresponsiveness, which leads to wheezing, breathlessness, chest tightness and coughing which altogether impair lung function. The pathophysiology of the disease responds to the induction of a complex immune response in the lungs, characterized by pro-inflammatory cytokine production, T cell activation, eosinophil, and neutrophil activation and, ultimately, the production of immune infiltrates that are responsible for the symptoms of asthma. The lungs suffer a remodeling process in which airway wall thickens and lung microbiota is altered. Genetic studies have identified asthma susceptibility genes, which increase the risk of asthma, but delivery by caesarian section, formula feeding, antibiotic treatment early in life and urban living are also important risk factors for allergic asthma (14). Importantly, all of these events alter the gut microbiota, and recent studies carried out in mice and humans have concluded that gut microbiota is clearly linked to the allergic immune response characteristic of asthma. For example, murine models showed improved symptoms after treatment with probiotics but worsened symptoms after treatment with antibiotics. Furthermore, children at risk of developing asthma showed altered gut composition, with reduced levels of some genera like *Faecalibacterium* (22).

This link allows an understanding of interactions between diet and asthma. High intake of fats increases the risk of asthma and obesity raises eosinophil numbers in the airway, inducing the production of pro-inflammatory cytokines and consequently worsening asthma (22). On the contrary, consumption of milk, specifically raw milk, seems to be protective against asthma development (151). The effects of the intake of n-3 PUFAs, fermentable fibers, vegetables and fruits on asthma are much less clear. High intake of fiber during pregnancy seems to protect the child from cough or wheeze (152).

Fruits and n-4 PUFAs, but not vegetables, could protect against the development of asthma in children, whereas no effect was observed in adults (22).

3.6. Non-alcoholic steatosis hepatitis (NASH).

The most frequent chronic liver disease in the developed countries is non-alcoholic fatty liver disease (NAFLD), being more common among individuals who suffer other conditions associated with metabolic syndrome. It is really considered to be a spectrum, ranging from fatty infiltration alone, known as steatosis, to fatty infiltration along with inflammation, termed non-alcoholic steatohepatitis (NASH). NAFLD leads to NASH in 20% of the cases, which can finally end in liver dysfunction,

cirrhosis, and life-risking complications (4). Even though experimental research has shown that saturated fat, trans-fatty acid, carbohydrate, and simple sugars (fructose and sucrose) may notably contribute to the intrahepatic fat accumulation and dietary interventions in patients achieved histological improvement, the specific nutrients associated with the development of this disease remain unclear (153). Accordingly, several experimental studies support a potential link between diet and gut microbiota alterations.

Recent investigations carried out in mice suggest that this progression from NAFLD to NASH is enhanced by translocation of bacteria from the intestine to the liver (14). In the portal vein blood of susceptible mice, there were higher bacterial TLR4 and TLR9 agonists, which activate the corresponding TLRs in the liver and originate the hepatotoxicity process that allows the development of NASH. Although the bacterial family *Porphyromonadaceae* was increased in these mice, it would be important to identify the exact bacteria producing TLR4 and TLR9 agonists. Furthermore, NAFLD patients showed altered microbiota composition, higher levels of pro-inflammatory metabolites and increased gut permeability. Therefore, there is no doubt that the microbiome is involved in the development of NAFLD and NASH, through different mechanisms involving the immune system. A wide-spectrum antibiotic was able to abolish the transition from NAFLD to NASH (4). Again, further investigation is needed.

3.7. Neurological and Behavioral disorders (anxiety, depression; autism).

Studies relating diet and brain morphology have been carried out, of course, in mice. Germ-free mice show alterations in the structural integrity of the amygdala and hippocampus, increased hippocampal neurogenesis and hypermyelination of the prefrontal cortex. Thanks to these findings, the conclusion is that the structure of the (mouse) brain is conditioned by gut microbiota. Further studies will be able to determine the specific bacteria capable of having this effect, and the affected regions of the brain where they act.

The brain is protected by the blood-brain barrier (BBB), constituted by tight-junctions formed by proteins including occludin and claudin-5. Germ-free mice have also been demonstrated to have weaker and more permeable BBB. This was reversible after colonization with SCFA-producing *Clostridium tyrobutyricum* or *Bacteroides thetaiotaomicron*, as it leads to an increase in occludin and claudin-5. Additionally, some immunomodulatory effects on the brain were dependent on resident immune cells. Particularly, the microglia is responsible for the immune defense in the brain and is affected by nutrition-induced metabolites. Germ-free and antibiotic-treated mice show immature microglia, which is unable to protect them correctly from bacterial and viral products. Gut microbiota has, therefore, an important role in the morphology and physiology of microglia, mediated in part by SCFAs. Consequently, supplementation with SCFAs could restore most of these alterations, as observed in the case of Parkinson disease (4). However, the lack of SCFAs receptor was also associated with these alterations in the microglia. Recent data have established a link between gut microbiota and ischemic brain injury, by showing that altered microbiota was linked to reduced infarct volume in a mouse model of stroke.

Moreover, alterations in the microbiota also showed an effect on behavior. Once again, germ-free mice have elevated stress response and reduced levels of brain-derived neurotrophic factor (BDNF). While colonization with *Bifidobacterium infantis* decreased this stress response, colonization with enteropathogenic *E. coli* aggravated it, showing how different bacteria have different effects on the brain (14). Although most pathways of communication between the gut and the brain are not known, a few have been demonstrated. *Lactobacillus rhamnosus* was able to regulate the expression of GABA receptors in mice brain (154). Furthermore, some strains showed the ability to activate the vagus nerve. As part of the parasympathetic nervous system, when activated, it induces a reduction in anxiety and depression. In mice, colonization with *Bifidobacterium longum* modulated anxiety owing to activation of the vagal system (155). However, it is not well established which bacterial strains are able to activate this pathway. Very importantly, the behavioral phenotypes were transmissible via cecal transplantation independently of other factors like cytokines, vagus nerve activation of intestinal levels of serotonin and dopamine. Related to this finding, it was demonstrated that the gut microbiota is able to regulate serotonin production not only in the gut but also in the brain.

Gut microbiota might also be important in the development of diseases like autism spectrum disorder (ASD), and it has been observed that children who developed ASD frequently had a history of recurrent ear infection and antibiotic treatment. As already mentioned, the gut microbiota can affect behavior in mice through different metabolites. In this case, 4-ehtylphenylsulfate (4-EPS) production in the gut is increased in ASD mouse models, showing that this metabolite may be important. Treatment with *Bacteroides fragilis* restored gut permeability pathology and ASD neurologic symptoms, probably by regulation of 4-EPS (156). Direct microbial alterations have also been related to autism and three species of Proteobacterium *Desulfovibrio* were increased in a small cohort of children suffering from this disease. Interestingly, higher concentrations of SCFAs have also been reported in the feces of children with ASD, and investigations carried out in mouse models demonstrated that SCFAs injected directly to the brain were able to induce ASD-like behavior (157). SCFAs have, therefore, some negative effects. Social deficits might also have a background of intestinal alterations. Mice whose mothers followed a high-fat diet showed altered gut microbiota composition, which was possibly inherited from their unhealthy mothers (as explained below), and could justify these behavioral alterations. Importantly, these alterations were reversible following close contact with healthy mice or supplementation with live *Lactobacillus reuteri* (158).

The relationship between diet, microbiota, immune system and autoimmune pathology is not completely established, but there is no doubt that diet affects the microbiota, with corresponding negative or positive consequences on health. Diet should be considered very important in medicine as a preventive and therapeutic tool, together with probiotics and even new techniques, like fecal transplants. Further investigation needs to be done.

4. DIET-BASED THERAPEUTIC PRINCIPLES.

Most of the diseases mentioned in this review are conditioned by lifestyle and, importantly, by diet. Recent studies have demonstrated the relationship between nutrition, intestinal microbiota, gut mucosal immune system, and autoimmune pathology. The human microbiota seems to be crucial as a mediator between diet and the immune system, affecting both the innate and adaptive responses, and controlling the general health state of the organism. Moreover, the accumulated knowledge demonstrates the hereditary facet of microbiota and its sustained epigenetic effects on the host cells. Thus, this "microbiological memory" could be causative of non-genetic heritability to produce disease inheritance (159). Many dietary choices in today's modern society negatively affect gut microbiota and controlling or reversing these harmful effects might be an important goal not only for the current generation but also for the future ones. Probiotics have demonstrated a positive effect but are unable to correct the damaging effects of an unhealthy diet. Therefore, direct dietary interventions represent a promising therapeutic tool, through modulation of gut microbiota composition (3).

It is true that several dietary approaches might have universal positive or negative effects on health. However, the diet-microbiota-host crosstalk is so complicated that the effect of multiple components of diet might be different depending on the clinical context and individual variations. One clear example is SCFAs that, in general, have a very positive effect regulating gut homeostasis. Yet, in some cases, they seem to be related to ASD development. Given these potential variations, some considerations should be taken into account when designing a dietary intervention: the desired health benefit, microbiota variations, and dietary preferences. Consequently, it is no longer possible to talk about a "healthy" product as if it was an inherent property on its own. Instead, it should be considered specifically within the patient's context.

Following, potential ways to modulate gut microbiota and control disease development are commented.

4.1. Inheritance.

As mentioned, an extremely important concept, that has been described recently, is that all the damaging consequences that nutrition has upon the microbiota might be inherited in future generations, meaning that the dietary habits of the parents will have an impact on their child through different pathways (1). Dietary habits might have cross-generational consequences, which can be inverted over a single generation or stay permanent during many generations if maintained longer. This long-term dysbiosis was observed in mice and primates (18). Importantly, this knowledge makes it possible to design interventions on the parents, and especially on the mother, that could have important consequences on their offspring. For example, as previously exposed, maternal intake of n-3 PUFAs and fiber protects the child against developing food allergy or cough and wheeze, respectively. Even more, in the case of allergic asthma, the data suggests that high concentration of acetate in the

maternal GI tract reduced the risk of the infant of developing asthma. Consequently, maternal adjustment of SCFAs production before birth could protect the offspring (14).

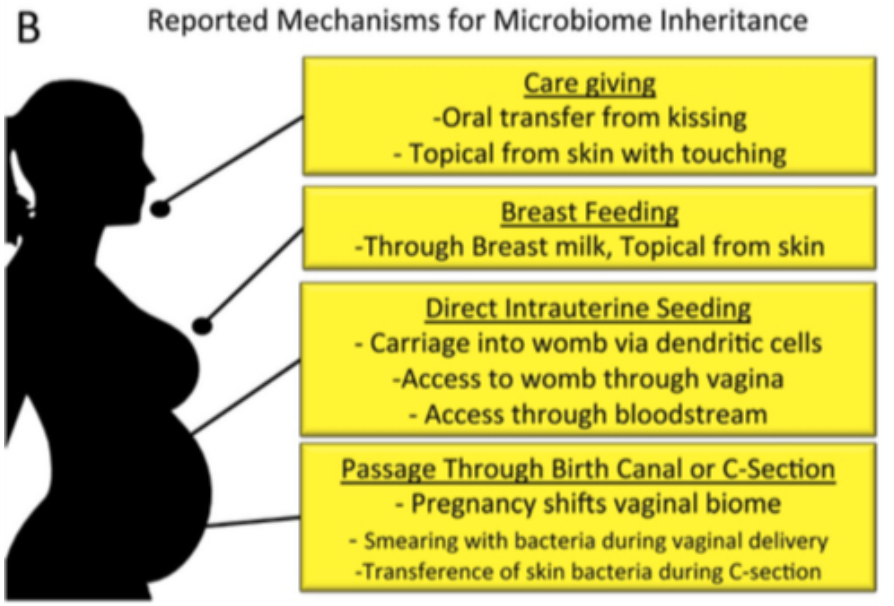

Figure 8. Currently reported mechanisms for the inheritance of the microbiome from mother to child. Taken from (1).

There are three main mechanisms that explain how this inheritance takes place (Figure 8). Firstly, the microbiota of a pregnant woman can be transferred to her child. This occurs mainly during labour, but breast-feeding is also important and the influence of the mother will be crucial until the maturation of the child's microbiota around two to four years of age. Furthermore, according to recent evidence, the transfer of bacterial populations might take place even during pregnancy. Consequently, the microbiota state of the mother is very important, as alterations on it will affect her child since birth and for the rest of his o her life. If born with abnormal microbiota, the offspring will be less prepared to fight infections and proper to suffer from autoimmune and allergic diseases. Specifically, studies carried out in mice and primates have demonstrated that the harmful effect of HFD over the microbiota is inherited on their descents. Consequently, they are prone to suffer many illnesses, mediated through an LPS-dependent mechanism. Interestingly, this effect is not reversible by the establishment of a low-fat diet on the newborn (18). Secondly, it is possible that the nutritional patterns of the mother will determine the dietary preferences of her child. Even before birth, a child can have a certain predisposition and prefer eating sugars, or fats, or vegetables, for example. This will be important, therefore, in the way he or she will understand nutrition in the future. Finally, it is believed that immune system development is also imprinted by microbiota driven epigenetics (related to methylation of DNA and histones). Thus, maternal dietary choices might be translated into epigenetic signals even before birth, conditioning the further state of health or disease of the offspring both in early and adult life (4).

The father's epigenetics is, of course, also important in this process. Alterations in microbiota together with high-risk epigenetics could worsen a child's immunologic development.

4.2. Prebiotics and Probiotics.

Prebiotics are substances that stimulate and promote the growth and activity of beneficial bacterial inhabiting the intestine, and are considered important therapeutic tools. One example is fermentable fibers, like inulin, oligofructose, FOS or galacto-oligosaccharide, which have demonstrated a positive effect increasing the abundance of *Bifidobacterium* and *Lactobacillus spp.* in human stool. Some more examples are whole grain barley and brown rice, diets based on vegetable and fruit juice, nopal, berberine, conjugated linoleic acid, etc. Even some medications very frequently used have a prebiotic action (18). Nevertheless, intake of prebiotics may have very different properties and consequences, due to individual variations and initial microbiota composition.

Probiotics are specific bacteria strains that show advantageous metabolic properties. It is nowadays quite frequent to use them as some strains have demonstrated benefits in different settings. However, their use remains controversial, as it has not been possible to establish well-founded conclusions (18).

4.3. Faecal microbiota transplantation (FMT).

Faecal transplantation consists of the transplantation of a healthy microbial flora from a healthy individual, to a recipient host that will benefit from it. Its use is more and more frequent, especially as it has proven efficacy for the treatment of *Clostridium difficile* infection (160) and glucose metabolism improvement in individuals with metabolic syndrome (161). Following this success, a new concept is starting to gain importance: *bacteriotherapy*, in which the microbiota is understood as a real therapy. This idea goes even further as new approaches are looking into the possibility of genetically manipulate the microbiota. These approaches could be much more effective and coordinated and less invasive and expensive. However, before being able to implement these therapies, much research needs to be done.

4.4. Personalized nutrition and fasting.

Nutrient composition and total calorie intake have been long used as important aspects taken into account when designing an optimized diet. Recently, meal size and frequency, together with periods of fasting, have emerged as strategies that could have deep health benefits both in the short-term and in the long-term (162).

Direct diet interventions are starting to be conceived as an important tool in medicine. Controlling the composition of the diet, the quality of the products, total calorie intake and other dietetic factors (like for example, timing or energy expenditure) could be an important way of improving health. However, designing a perfect diet is not easy due to important individual variations. When using diet as a therapy, menus should be designed taking into account all possible factors related to the patient. These include age, gender, geographical location, food preferences (in

order to maximize dietary compliance), metabolic status, initial microbiota status, and general health state (Figure 9). Furthermore, the goal of the intervention should be always very present. Diet could be used as a way of treatment but, even more importantly, diet education should be more and more used as a way to prevent disease.

Another approach that could be used synergistically with the previous one is fasting. Positive outcomes have been associated both with a prolonged reduction in daily caloric intake and periodic fasting cycles. There are four main modalities that have further studied and seem to have beneficial effects on human health: caloric restriction (CR), time-restricted feeding (TRF), intermittent fasting (IF), and fasting-mimicking diets (FMD).

CR is characterized by a daily reduction in calorie intake of 15 to 40%. This intervention opposes several age-associated pathophysiological processes and induces profound metabolic and molecular alterations that affect important components of the nutrient-sensing and stress-responsive pathways, like growth hormone, insulin, etc. (3). There is an initial weight loss followed by metabolic adaptation, which results in important changes that lead to fat mobilization and glycolytic inhibition. Furthermore, CR also improves autophagy and reduces oxidative stress, reducing inflammation (138). CR without malnutrition has been able to increase life span by up to 50% in rodents. In primates, studies have reached controversial conclusions. In both cases, variations like sex, age, genetic background, the onset of the intervention, feeding practices, and diet composition, were determinant. In humans, short-term trials and observational studies have shown many benefits of long-term CR at physiological, metabolic and molecular levels. CR is able to improve several markers of health like body weight, metabolic rate, and oxidative damage, decreasing CV and cancer risk (163). Thus, CR seems to be able to maintain youthful functionality. However, studying the effects of this intervention is very challenging, owing to a lack of clinical data, safety concerns, the difficulty of compliance and interindividual variability.

TRF involves restriction of daily consumption of food to a window of 4 to 12 hours. It is based on the belief that timing might be very important in the metabolic hemostasis, independently of total calorie intake. Studies in mice have shown many positive effects like for example reduction in body weight, increased energy expenditure, improved glycemic control, etc., and consequently protection from the negative consequences associated with the Western diet. Importantly, studies carried out in monkeys and mice concluded that the way meals were distributed during the day was determinant. The same conclusion was reached from TRF trials in humans, demonstrating a positive effect specially when feeding was limited to the first half of the day. Furthermore, the beneficial consequences of TRF were observed regarding diabetes control and cancer risk reduction.

IF implies an eating pattern in which there is no food intake from one to several days, followed by no restrictions the rest of the time. Nowadays this pattern is clearly very difficult to maintain due to the overexposure to food that is so frequent. However, from an evolutionary perspective, periods of fasting were a natural and

common phenomenon and are believed to have positive pleiotropic consequences. In mice, IF has proven to extend life span, protect against obesity, cardiovascular disease, hypertension, etc. Periods of fasting of 48 or longer reduced leptin levels and, therefore, inflammation (16). It also has a positive effect on cancer prevention and treatment, and brain function. Benefits have also been demonstrated in short-term human clinical trials when an alternate-day fasting pattern was adopted (164).

Finally, there are two important challenges associated with CR, TRF, and IF: compliance and possible important side effects. That is the reason why another intervention was designed, the fasting-mimicking diet (FMD). It is characterized by low-carbohydrate and high-fat consumption during 5 days each month for 3 months. The results of this intervention in rodents showed similar benefits relating to metabolic control and cancer prevention than the previous ones. However, it is important to note that it also showed positive effects for the control of autoimmune diseases like multiple sclerosis. Nevertheless, it did not improve life span. Studies in humans are yet to carry out.

To conclude, dietary interventions together with a reduction in long-term calorie intake and cycles of fasting have emerged as important medical tools. However, much research needs to be done, as the specific mechanisms are not fully understood. Moreover, these interventions are associated with some detrimental consequences and have also been liked with eating disorders (162). Therefore, maximal caution needs to be used when implementing these strategies.

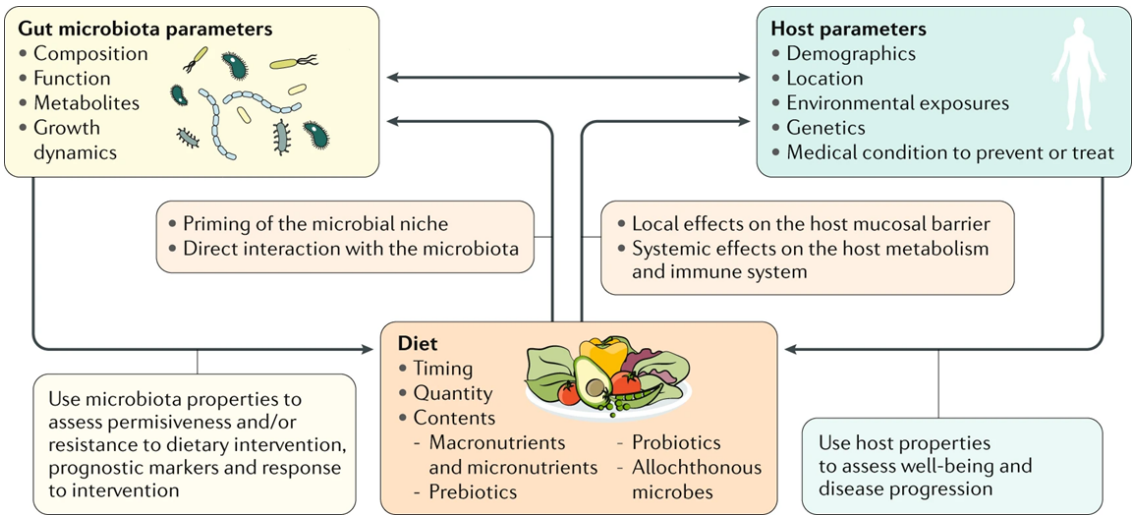

Figure 9. Microbiota-oriented interventions to achieve health and well-being. Different aspects to be considered related to the individual host, his or her gut microbiota status, and diet adaptation. Reproduced from (18).

5. CONCLUSIONS.

An appropriate diet is crucial in order to maintain a healthy organism. The frequently consumed Western diet differs greatly from this optimal nutrition and, unfortunately, it is well established in modern societies in developed countries. Furthermore, it is more and more common in emerging economies. Financial limitation

is frequently exposed as an impairment to follow a healthy diet. However, saving money on food means saving it on health. Diet should start to be considered as an important tool to achieve and maintain health and awareness should be promoted (1).

Life expectancy has increased worldwide but it has not been followed by an increase in healthy aging. Proper nutrition seems to have an important effect on general homeostasis, influencing health and survival, and delaying the onset and progression of many diseases. On the contrary, both hypo and hypernutrition are associated with increased risk of many chronic diseases and even, premature death. The composition of the diet seems to be of special importance for health owing to its effect on the microbiota, but other factors like total calorie intake and timing are also crucial (162). It has been demonstrated that an inappropriate diet is linked to more deaths annually than any other risk worldwide, which highlights how urgent it is to improve the human diet globally. High sodium intake and low whole grains, low intake of fruit, low intake of nuts, seeds, vegetable, and omega-3-fatty acids account each on them individually for more than 2% of global deaths annually. It is necessary that the general population understands the importance of diet, and health-promoting systems urgently need to focus on diet education. Dietary policies should promote an optimal intake of components of the diet, which will surely allow better general health (2).

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