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EDITORIAL

GUT MICROBIOTA AND THE IMMUNE SYSTEM: AN INTIMATE PARTNERSHIP IN HEALTH AND DISEASE

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In recent years there have been increased rates of autoimmune diseases, possibly associated to altered intestinal microflora. In this brief review article, after a description of the structure and function of the gut microbiota organ and its cross-talk with the human host, we give a report on findings indicating how the host immune system responds to bacterial colonization of the gastrointestinal tract. The disturbances in the bacterial microbiota will result in the deregulation of adaptive immune cells, which may underlie autoimmune disorders. The mammalian immune system, which seems to be designed to control microorganisms, could be instead influenced by microorganisms, as suggested in recent literature. Alterations in both the structure and function of intestinal microbiota could be one of the 'common causative triggers' of autoimmune and/or autoinflammatory disorders.

Immunological deregulation is the cause of many non-infectious human diseases such as autoimmunity, allergy and cancer. The gastrointestinal tract is the primary site of interaction between the host immune system and microorganisms, both symbiotic and pathogenic. Partly responsible for an increased prevalence of allergic and autoimmune disorders in later life (1), could be the so-called 'hygiene hypothesis': a diminished exposure of humans to parasites and pathogens. The lack of such exposure may cause the immune system to shift its immunological response away from a balance between type 1 and type 2 T-helper cells (2). This raises the possibility that the mammalian immune system, which seems to be designed to control microorganisms is, in fact, itself controlled by microorganisms (3). In agreement with this hypothesis, it was recently found that uncultivable members of the Clostridiale family could exert a protective role against pathogenic bacteria challenge (4). Many autoimmune and autoinflammatory pathologies have recently been associated to an altered intestinal microflora. Inflammatory bowel diseases (IBD), a multi-factorial pathology where genetic susceptibility, environmental factors and intestinal bacteria are the main proposed etiological triggers could be classified as an autoinflammatory disorders. These autoinflammatory disorders are caused by primary dysfunction of the innate immune system, without evidence of adaptive immune deregulation (5), and the intestinal tissue injury is principally caused by loss of immune tolerance against the intestinal microbiota. Studies on intestinal bacteria composition in IBD patients have reported an altered balance of beneficial versus aggressive microbial species (dysbiosis). In conclusion, it

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seems conceivable that alterations in both structure and function of intestinal microbiota could be one of the 'common causative triggers' of autoimmune and/or autoinflammatory disorders, or, on the other hand, could be a consequence of an imbalanced immune response in the human host.

HUMAN GUT 'MICROBIOTA'

The human body is colonized by a vast number of microbes. Humans have been proposed to be "meta-organisms" consisting of 10-fold greater numbers of bacterial than animal cells that are metabolically and immunologically integrated. The gastrointestinal (GI) tract harbors the largest and most complex bacterial ecosystem in the human body (6). The mucosal surface of the human gastrointestinal tract is colonized by roughly 10^{14} bacteria of greater than 1000 different species and subspecies, as detectable by ordinary culture methods and molecular techniques. The number of bacterial cells within the gastrointestinal tract outnumbers the host cell populations by 10:1 (low estimate), highlighting the relative importance of microbiota composition and metabolic activity on host homeostasis. The majority of the gut microbiota is composed of strict anaerobes (7). An increasing gradient in bacterial concentration characterizes the human gastrointestinal tract, from stomach, to jejunum, ileum and colon, where the concentration peaks to 10^{11}-10^{12} bacterial cells per gram of stool (7). Molecular profiling methods, such as Temporal Temperature Gel Electrophoresis (TTGE), Denaturant Gradient Gel Electrophoresis (DGGE), PhyloChip, Microarray, and High-throughput sequencing (Pyrosequencing), revealed a high level of variability between individuals at the bacterial species level. Even though over 50 bacterial phyla have been described to date, human gut microbiota is dominated only by Bacteroidetes and Firmicutes, whereas Proteobacteria, Verrucomicrobia, Actinobacteria, Fusobacteria, and Cyanobacteria are present in minor proportions (7). The microbiota composition may change in unpredictable ways as a function of many features such as: sex, diet, lifestyle, geographic origins, and genetic background (8). Shaped by millennia of co-evolution, host and bacteria have developed beneficial relationships, creating a suitable environment for mutualism.

DEVELOPMENT OF INTESTINAL MICROBIOTA

In the first few days/weeks of life, the microbiota of newborns is highly variable and subject to waves of temporal fluctuations to coordinately assemble a stable microbiota (9) (Fig. 1). The adult-like structure of the gut microbiota is established between the second and the seventh year of life (9). The first years of life are also a time of great post-natal development of the immune system. As the microbiota has marked influence on the immune system, deviations from the normal development of the microbiota (through caesarean section, formula-based diet, hygiene, vaccination and use of antimicrobials in infants) may alter the outcome of immune development and potentially predispose individuals to various inflammatory diseases later in life. On the basis of clinical, epidemiological and immunological evidence, it seems possible that changes in the intestinal microbiota may be an essential factor in the incidence of numerous inflammatory disorders (9).

HUMAN GUT 'MICROBIOME'

The gut microbiota seems to be characterized by a marked 'functional redundancy' to ensure that the key functions of the microbial community remain unaffected by the individual variability in terms of species composition (10). The existence of a 'human core gut microbiome', defined as those genes which are common to the gut microbiomes of all or the majority of humans, has been hypothesized to be responsible for the functional stability of gut microbiota (10). On the contrary, a 'human core gut microbiota', defined as a number of species which are common to all humans, could hardly be defined, since different combinations of species could fulfill the same functional role (11). The gut microbiota has a 10-fold higher coding capability than total human cells. Apart from the core, the set of genes present in smaller subsets of human, represents the 'human variable microbiome'. This wide variation from the core is the result of a combination of host-specific factors, such as genotype, physiological status, host pathologies, lifestyle, diet, environment, and the presence of transient bacterial species. In return, core

and variable components of the human microbiome influence different aspects of the human health, including nutrient responsiveness and immunity (11).

FUNCTION OF THE GUT MICROBIOTA ORGAN

Not much is known yet about the possible roles of microbes in human-associated communities outside the intestinal tract, but it becomes increasingly clear that the gut microbiota exerts many beneficial effects on the human body system. Our intestinal symbionts play many important roles in: nutrient digestion and synthesis; energy metabolism; vitamin synthesis; epithelial development, immune responses (12). In addition, host-microbe interactions are essential for the host's defense against pathogenic infections.

I) Trophic functions and metabolic activity

Collectively, the flora has a metabolic activity equal to a virtual organ within an organ (11). The presence of an intestinal microbiota is not essential for survival of the host, but germ-free (GF) mice require 30% more energy in their diet, showing the rule of the indigenous microbiota in energy scavenging from food. This energy utilization by the gut microbiota works on different levels. The intestinal microbial community is well equipped to degrade biomolecules such plant polysaccharides (13). Microbial fermentation generates butyrate and other short-chain fatty acids that the host can use as energy sources and which help maintain the integrity of the intestinal epithelium (12). In addition, the presence of a gut microbiota regulates fat storage in the host, promoting the absorption of monosaccharides from the gut lumen. The metabolic activity of this 'forgotten organ' has profound implications also for medical treatments. An interesting study showed how the gut microbiota has the ability of inactivating around 37% of drugs delivered into the intestine, with a potential of generating toxic compounds or by-products (14).

II) Barrier effect

The intestinal symbionts provide an important barrier, called 'colonization resistance', to the colonization of potential pathogens by competing for the same nutrients and attachment sites (15). When an intestinal niche is occupied by a predominant bacterial species, that species binds to specific cell epitopes (cellular receptors) extruding from the brush border, or directly inserted into the mucin layer (sugar residues). At the same time, this species could induce, in the underlying eukaryotic cell, the production of specific 'binding receptors' or 'feeding receptors'. A particular adhesive and invasive *E. coli* pathovar (AIEC) can induce the expression of a mannosylated-rich eukaryotic receptor, called CEACAM (16), enhancing its own adhesion. Otherwise, *B. thetaiotaomicron* establish their own competitive niche through a cross-talk with the underlying epithelium, inducing the *FUT2* gene expression (17), thus enhancing its own source of energy. From these observations, it could be arguable that the barrier effect can be set up by both beneficial (*B. thetaiotaomicron*) and harmful (AIEC) bacterial species, leading to the intriguing hypothesis of a differential competition for the 'barrier effect' within the gut microbiota.

III) Host's defense development

Recently, it was proposed that the mammalian genome information could be insufficient to achieve all functions required to maintain health, and that by-products of our microbiome are essential in protecting us from different diseases (18). It is possible that alterations in the development or composition of the microbiota could affect the cross-talk between microbiota and human immune system, eventually leading to an altered immune response that may trigger various human inflammatory disorders. Germ-free animals show a defective development of gut-associated lymphoid tissues, lesser antibody production, and have fewer and smaller quantities of both Peyer's patches (PPs) and mesenteric lymph nodes (MLNs) (19). These structures could be collectively called 'inducible structures', due to their *ex-novo* formation following the introduction of gut bacteria. An evolutionary coalition has been forged between mammals and beneficial bacteria that is crucial for maintaining the long-term survival of both. In other words, our well-being seems to be dependent to the microorganisms we harbor.

GUT MICROBIOTA AND THE IMMUNE SYSTEM

A key factor of innate immunity is the ability

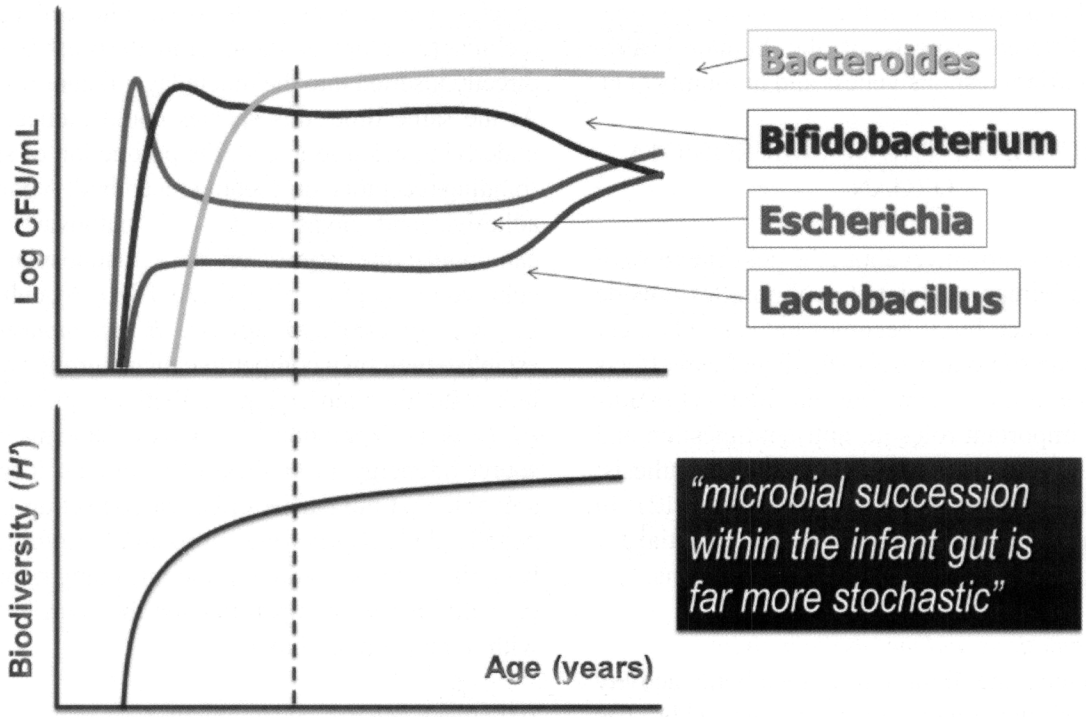

Fig. 1. *Microbial community succession during life course. Relative bacterial abundance in fecal samples of newborn, pediatric, adult and elderly healthy patients. The vertical line (at 7 years of age) shows the partition between pediatric and adult ages, in relation to microbiota development. Bacterial species are depicted as follows: solid line, Escherichia spp., Streptococcus spp.; dotted line, Bifidobacteria spp.; dashed line, Lactobacillus spp.; long-dashed line, Bacteroides spp., Peptococcus spp. H', Shannon-Weaver index of biodiversity, taking into account the number of species and their relative abundance (solid-bold line)*

of distinguishing between potentially pathogenic microbial components and harmless antigens by using pattern recognition receptors (PRRs). Toll-like receptors (TLRs) enable mammalian cells to recognize conserved characteristic molecules present on microorganisms and described as pathogen-associated molecular patterns (PAMPs) (20). All PAMPs are present also on commensal bacteria (e.g. lipopolysaccharides, peptidoglycans, flagellin, formylated peptides and others), thus they could be collectively named microbe-associated molecular patterns (MAMPs). In mammals, TLRs are present on macrophages, neutrophils, dendritic cells (DCs), intestinal epithelial cells (IECs) and other cells belonging to the innate immune system. Cells of innate immunity are able to produce cytokines essential for inflammatory reactions, as well as factors critical for the subsequent initiation of specific immunity.

Literature data show how the microbiota may regulate the intestinal innate immune system by modulating TLR expression on immunosensory cells surface through MAMPs. Recognition of microbes leads to activation of nuclear factor-kappa B (NF-κB) signalling pathway, leading to enhanced cytokine production, up-regulation of co-stimulatory molecules on antigen presenting cells that ultimately activate the T cells. In this scenario, the innate immunity is tightly linked to the adaptive immunity (20). The differential regulation of TLR expression on the surface of DCs, which represents the link between innate and adaptive immunity, and of IECs, exerts a precise role in regulating the mucosal immune responses, both in healthy and disease status, such as IBD (21). TLR receptors are differentially expressed by many distinct cell types throughout the

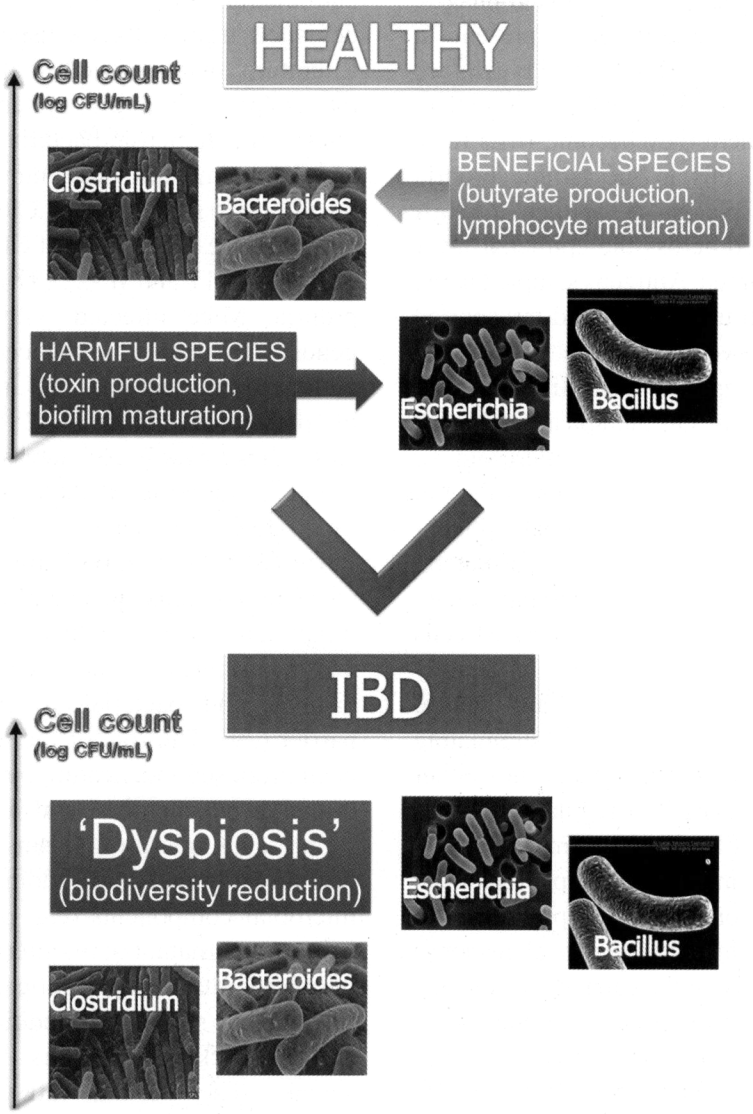

Fig. 2. *Dysbiosis of the microbial community in IBD. Independent groups of investigators using culture and molecular techniques have reported a decrease in beneficial bacterial groups, such as members of Firmicutes and Bacteroidetes phyla, and an increase in potentially pathogenic bacteria such as Proteobacteriaceae and Bacillus spp.*

gastrointestinal tract, including intestinal epithelial cells (IECs) and professional immune cells, such as dendritic cells (21). Human intestinal IECs express CD14, an important lipopolysaccharide-binding molecule that, together with TLRs, can maintain the intricate balance between the self and the environment in the gut (21). Gut microbiota may modulate the expression of the mucin proteins produced by intestinal goblet cells. These proteins are encoded by around 15 genes. It was shown how butyrate, that is mainly produced by the genera *Clostridium*, *Roseburia*, and by the bacterium *Fecalibacterium prausnitzii,* could enhance the expression of *MUC2* gene in goblet cells when it is the only energy source available (22). The mucus also provides a medium in which bacterial-derived metabolites, with signaling functions, are secreted and concentrated. Another important immune compartment in the bowel is the

lamina propria, where a large number of macrophages, DCs, T cells, and IgA-secreting B cells is present. In the lamina propria, resident CD4, CD8 and B cells are also present while some CD8 lymphocytes migrate to the tip of the villous where they become IELs (23). Once activated, the B cells in the lamina propria become IgA-producing plasma cells, then the IgA molecules are transported across the epithelial layer and secreted in the gut lumen. Antigens sampled in the lamina propria are taken up by DCs and transported via draining lymphatic vessels to the MLNs and secondary to the gut lymphoid tissue (mainly PPs) to response to gut antigens. On the apical surface of PPs there are specialized IECs, called microfold, or M cells. The M-cells sample the antigens in the gut lumen and transport bacteria to professional antigen-presenting-cells, such as DCs on their basolateral surface (24). The larger part of the bacteria are killed by macrophages while those transferred by M-cells to DCs can survive for several days. In healthy individuals, DCs sample the antigens and induce T-cell unresponsiveness, probably by stimulating balanced differentiation of naïve T cells into either effectors cells (Th1, Th2, Th17) or regulatory T cells (Tr1, Th3) to maintain tolerance to commensal and food antigens. This tolerance is called 'physiological inflammation'. The concept of 'physiological inflammation' was introduced as a normal response to the colonizing flora. When the capacity to develop or maintain physiological intestinal inflammation is lost, pathological inflammation takes over, resulting in disease (25). It was found how the NALP3 (NACHT domain-, leucine-rich repeat-, and PYD-containing protein 3) large cytoplasmic complex, called inflammasome, links the sensing of microbial products and metabolic stress to the activation of the proinflammatory cytokines, IL-1β (Interleukyne-1β) and IL-18 (Interleukyne-18) (26). Inflammasome has been associated with several autoinflammatory conditions. An altered microbiota could exert its function on underlying mucosal immune system both directly, through bacterial PAMPs or MAMPs, and indirectly, through bacterial by-products.

EQUILIBRIUM IMBALANCE IN GUT MICROBIOTA

One could think that both autoimmune and autoinflammatory diseases may be influenced by deviances from well-established microbial equilibria. Literature data showed that specific aspects of the adaptive immune system are influenced by intestinal commensal bacteria (27). A clear example are the segmented filamentous bacteria (SFB), an uncultivable sub-group of Clostridiales family able to induce the appearance of CD4+ T helper cells that produce IL-17 and IL-22 (Th17 cells) in the lamina propria. Mice infected with SFB, by candidate genus *Arthromitus*, enhanced the production of antimicrobial peptides, and hindered the challenge of pathogenic bacteria (28). Elevated systemic antibodies towards commensal gut microbiota were found in autoinflammatory conditions, as reported by a study conducted on Familial Mediterranean Fever (FMF), an autoinflammatory disease. This is probably the consequence of hypersensitivity of the inflammasome in FMF that triggers the inflammation and contributes to the excessive translocation of bacteria and bacterial antigens through the gut barrier (29). The role of the microbiota in IBD has been proposed in literature by the following studies, that showed microbial and host specificity (30): i) suppressing micro-organisms (using antibiotics or germ-free animals); ii) adding micro-organisms or microbial components (e.g. probiotics, CpG-DNA, culture supernatants); iii) altering the composition of the microbiota using prebiotic substrates; iv) assessing microbiota structure modifications in knockout animals lacking receptors to specific microbial signals. The normal intestine secretes various peptides with anti-microbial properties including defensins, lysozyme, cathelicidins and secretory immunoglobulins. Defensins are synthesized in Paneth cells and released both in the intestinal crypts and at the epithelial surface, where they are embedded in the mucus layer. In literature studies are reported that showed a reduced expression of α-defensins in ileal CD and an attenuated induction of β-defensins in the colon of patients with colonic IBD, probably linked to a genetic defective background (autophagy gene ATG16L1 variant T300A) (31). Two genes with important polymorphisms, the intracellular bacterial sensor NOD2/CARD15 and the autophagy regulator ATG16L1, exert important functions in innate immune defense through intracellular bacterial recognition and destruction

of bacteria. Approximately 40% of CD patients carry the specified disease variant ATG16L1^{T300A}, whilst about 4% harbor a NOD2/CARD15 single nucleotide polymorphism (SNP). These variants drive a two-fold increase in susceptibility to Crohn's disease, and have been associated to a diminished innate and adaptive immune response (31). Mice that lack autophagy in immune cells show an increased susceptibility to dextran sulfate sodium (DSS) colitis. The inflammatory status may provide a selection pressure for microbiota enriched in inflammation-resistant microbes that may also be pro-inflammatory, resulting in a positive feedback loop that can be stopped only by the use of broad-spectrum antibiotics to block this altered microbial community. Compositional changes of the microbiota (dysbiosis) in IBD subsets may contribute to disease severity. Independent groups of investigators using cultural and molecular techniques have reported a decrease in beneficial bacterial groups, such as members of Firmicutes and Bacteroidetes phyla, and an increase in potentially pathogenic bacteria such as Proteobacteriaceae and *Bacillus spp.* (32) (Fig. 2). The 'gastroenteritis hypothesis' was proposed to explain the increased risk in developing IBD after an infectious gastroenteritis exposure (33). *Campylobacter-* or *Salmonella*-driven gastroenteritis were found to confer a 2.9 fold risk in developing IBD in a 15-year survey. The higher risk was found to range within a year from infection, opening the quest for additional time-dependent mechanisms involved in IBD development after short-term bacterial challenge. Furthermore, colitis could be vertically transmittable, pointing out a role for these organisms in maternal transmission of disease (34). Understanding the molecular mechanisms mediating host-microbiota symbiosis could redefine our vision of the evolution of adaptive immunity and, consequently, our approach in the treatment of numerous immunologic disorders.

IMPACTS OF A DISTURBANCE ON MICROBIAL GUT COMPOSITION AND/OR ECOSYSTEM PROCESSES

Perturbations on microbial composition might have different results, depending on the resistance or resilience characteristics of the gut microbiota. Generally, the gut microbiota of adults is more resistant, whilst the microbiota of children is more resilient, due to their developing microbiota up to the age of 7 years, when a 'climax' is reached (Fig. 1). It has been proposed that improved hygiene could be the origin of increased incidence of allergic and autoimmune diseases (35), as well as improvement in human health and longevity. In 1998, about one in five children in industrialized countries suffered from allergic diseases such as asthma, allergic rhinitis or atopic dermatitis. This proportion has tended to increase over the last 10 years, asthma becoming an 'epidemic' phenomenon (36). Moreover, dramatic changes in human ecology, including cleaner water, smaller families, an increase in the number of Caesarian sections, increased use of pre-term antibiotics, lower rates of breastfeeding and more than 60 years of widespread antibiotic use, particularly in young children, represent a deep microbiota perturbation (37). Our decreased sampling of the microorganisms could reflect the loss of our ancestral microorganisms. As the representation of particular species diminishes in one generation, the vertical transmission to the next generation (38) will decrease. For example, as *H. pylori* is disappearing from human populations, reflecting both diminishing transmission and increasing antibiotic treatment, both 'idiopathic' peptic ulcer disease and gastric cancer rates are diminishing, which is clearly salutary. However, esophageal reflux, Barrett's esophagus and adenocarcinoma are increasing, which is clearly deleterious. It is reasonable that the 'hygiene' and the 'disappearing' hypotheses, sometimes reported as alternatives, could instead coexist. The "clean life style" entails decreased sampling of microorganisms, and could progressively affect the composition of our indigenous microbiota, which in turn influence human physiology and, ultimately, disease risk.

INTESTINAL MICROBIOTA AND AUTOIMMUNE DISORDERS

One of the major actions of the mammalian microbiota is its effect on the development and function of the immune system. The recent identification of symbiotic bacteria with potent anti-inflammatory properties, and their correlative absence during disease, suggests that certain aspects

of human health may depend on the status of the microbiota. If improvements in hygiene and health care have altered the process by which a healthy microbiota is assembled and maintained, then patients with autoimmune and/or autoinflammatory disorders should display signs of dysbiosis. This indeed seems to be the case, at least according to a growing number of studies that are now linking these diseases to alterations in the microbiota. The bacterial composition of the intestines of pediatric and adult patients with IBD is known to differ from that of healthy controls (32). Independent groups of investigators, using cultural and molecular techniques, reported dysbiosis in IBD patients with a decrease in members of Firmicutes and Bacteroidetes phyla, and an increase in potentially pathogenic bacteria such as Proteobacteriaceae and *Bacillus spp.* (32). The intestinal mucosa of adult and pediatric IBD patients abnormally colonized by *E.coli* has been reported (39). A specific adherent and invasive *E. coli* pathovar, called AIEC, was found in adult patients suffering from CD (40). This pathovar has enhanced adhesive and invasive properties. Otherwise, *E. coli* AIEC strains are normally found in intestinal mucosa of healthy and CD subjects. Many other microorganisms have been proposed as causative trigger of IBD, for example, *Mycobacterium avium subsp. paratuberculosis* (MAP), *M. kansaii*, *Diplostreptococcus sp*, *Lysteria monocytogenes*, *Fusobacterium necrophorum*, *Chlamydia sp.*, *Pseudomonas maltophila* and *Helicobacter hepaticus* (41), however no infectious organisms have been conclusively shown to be the causative agents of CD or UC. This raises the possibility that the targets of inflammation in IBD are not the classical exogenous pathogens, but are the endogenous flora mainly involved in the pathogenesis of the IBD, where a breakdown in immune tolerance to gut bacteria exists (42). In active Systemic Lupus Erythematous (SLE) patients, the quality of the colonization resistance (CR) of the intestinal micro flora is lower than in healthy individuals. A lower CR results in translocation of more species of foreign bacteria. Some of these bacteria may serve as antigen for the production of anti-bacterial antibodies. Among patients with Ankylosing Spondylitis (AS) an over-expression has been shown of Toll-Like Receptor 4 (TLR4) and TLR5 genes in peripheral blood cells (PBC), providing further support for the importance of TLR subtypes responsive to Gram-negative bacteria in the pathogenesis of AS (43). Epidemiological studies showed an altered intestinal microbiota associated to other allergic disorders, such as atopic eczema and rheumatoid arthritis (44). Although it is not clear whether dysbiosis is a cause or an effect of disease, it seems that deviations in the composition of the gut microbiota may be one factor underlying the development of disease in genetically predisposed individuals. The effects of the microbiota on the immune system are thus becoming increasingly evident.

BACTERIAL ROLE IN MAINTAINING BOWEL HEALTH - PROBIOTICS

The established definition, currently adopted by FAO/WHO, define the probiotic as a 'live microorganism which, when administered in adequate amounts, confer a health benefit on the host' (http://www.who.int/entity/foodsafety/publications/fs_management/en/probiotics.pdf).

The use of probiotics is increasing in popularity for both the prevention and treatment of a variety of diseases. Several bacterial species have the ability to control the inflammatory response. Probiotic organisms can provide a beneficial effect on intestinal epithelial cells in numerous ways: i) some strains can block pathogen entry into the epithelial cell by providing a physical barrier, referred to as colonization resistance; ii) they can create a mucus barrier by causing the release of mucus from goblet cells; iii) other probiotics maintain intestinal permeability by increasing the intercellular integrity of apical tight junctions, for example, by up-regulating the expression of zonula-occludens 1 (a tight junction protein), or by preventing tight junction protein redistribution, thereby stopping the passage of molecules into the lamina propria; iv) some probiotic strains have been shown to produce antimicrobial factors; v) other strains stimulate the innate immune system by signaling dendritic cells, which then travel to mesenteric lymph nodes and lead to the induction of Treg cells and the production of anti-inflammatory cytokines, including IL-10 and TGF-β; vi) some probiotics (or their by-products) may also prevent or trigger an innate immune response

by initiating TNF production by epithelial cells and inhibiting (or activating) NFκB in macrophages. The human body can respond differently to the different species and strains of probiotics. This fact is often neglected in discussions on the outcome of clinical trials with probiotics. Also, many studies centred attention on the time of persistence and kind of delivery of selected probiotics both in healthy and disease status (45).

Bacterial species can act on several cell types (epithelial cells, DCs and T cells), but recent evidence suggests that the induction of regulatory T cells (Treg) by these microorganisms is crucial to their ability to limit inflammation and/or autoinflammatory diseases. Moreover, due to its lower abundance in CD patients, the potential role has been recently evaluated of *Faecalibacterium prausnitzii* on intestinal inflammation amelioration using cellular (peripheral blood mononuclear cell, PBMCs) and animal models (46). The authors found that stimulation by *F. prausnitzii* led to significantly lower Interleukin-12 (IL-12) and Interferon-γ (IFN-γ) production levels, and to higher secretion of Interleukin-10 (IL-10). Another gram negative bacterium linked to human innate immunity is *Bacteroides thetaiotaomicron*, able to elicit the overproduction of the small proline-rich protein-2 (sprr2a), an epithelial barrier fortifier, and the decay-accelerating factor (DAF), an apical epithelial inhibitor of complement-mediated cytolysis (47). Moreover, current evidence supports the idea that certain beneficial bacteria have evolved molecules (known as symbiosis factors) that induce protective intestinal immune responses. One of these is the polysaccharide A (PSA) produced by *Bacteroides fragilis,* which induces an immunoregulatory response that provides protection from inflammation induced by *Helicobacter hepaticus*. In particular, PSA suppresses pro-inflammatory interleukin-17 production by intestinal immune cells and protects from inflammatory disease through a functional requirement for interleukin-10-producing CD41 T cells (48). Gut bacteria could also interact with the underlying immune system in an indirect fashion, through their metabolic products. A better knowledge of the complex microbial networks existing in the intestinal human ecosystem will be an important step to assess their interplay with sub-mucosal immune system, especially from a probiotic point of view.

CONCLUSION

Accumulating evidence from various sources suggests that the increase in autoimmune and/or autoinflammatory diseases observed could be partly caused by a decline in infectious diseases and progress in hygiene. In many autoimmune and/or autoinflammatory diseases an unnatural shift in the composition of the microbiota, called dysbiosis, has been found. In this scenario, some microbial taxa may benefit from the inflammatory conditions and increase in number. The whole gut microbial community could be considered 'pathogenic' when its emergent properties contribute to disease status. In a 'pathogenic community' no single microbe is pathogenic alone. Genetic and habitual factors shape the composition of the microbiota, which, in turn, shapes the immune system of individuals that are predisposed to inflammatory disease. Symbiotic bacteria with potent anti-inflammatory properties were found in the healthy gut, along with their correlative absence during disease. On the other hand, we should consider the possibility of pathogen development from commensal bacteria under particular selective pressure. Our recent study (49) showed how selective pressure in IBD gut habitat could select a sub-population of *E. coli* strains possessing phenotypic properties of the new AIEC pathovar, along with peculiar *fimH* gene mutations (50). All these results could suggest overall that certain aspects of human health may depend on the status of the gut microbiota: understanding the intricate network existing in this complex ecosystem will be a necessary step to have insights on autoimmune and/or autoinflammatory diseases. In conclusion, the intimate interplay between bacteria and immune system needs to be deeply investigated, in order to design new therapy strategies aimed to restore human/microbiota interactions, and to enhance our knowledge on autoinflammatory and autoimmune disorders.

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