

The background features a central, glowing blue tunnel with concentric, swirling lines that create a sense of depth and movement. Scattered throughout this tunnel are numerous spherical particles of varying sizes, each covered in smaller, protruding dots, resembling a microscopic view of a microbiome or a collection of viruses. Two short, horizontal pink lines are positioned above and below the main title text.

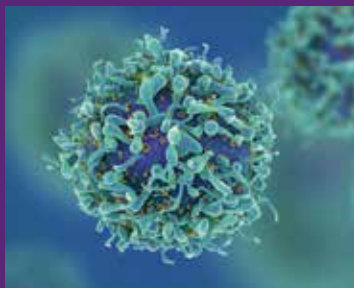
# GUT MICROBIOTA AND **IMMUNE DEFENSES**

BIOCODEX   
*Microbiota Institute*

**Often referred to as a “new organ” in the scientific literature, the gut microbiota could also play a role in immunity.** The involvement of this unsuspected function in the normal and pathological physiology of the human body could be significant: type 1 diabetes mellitus, chronic inflammatory bowel diseases, host-versus-graft disease, and even the prevention of some infections... Could the gut microbiota become a “new immune organ”?

# TABLE OF CONTENTS

---



**1**

## **ROLE OF THE GUT MICROBIOTA IN THE DEVELOPMENT OF THE IMMUNE SYSTEM**

The gut microbiota, first bastion against aggressions  
P. 5

Role of the gut microbiota in immune regulation  
P. 6



**2**

## **INTERACTIONS AND PATHOLOGIES**

Type I diabetes mellitus  
P. 8

Chronic inflammatory bowel diseases  
P. 9

Stem cell transplant and graft rejection  
P. 10

Respiratory infections  
P. 11



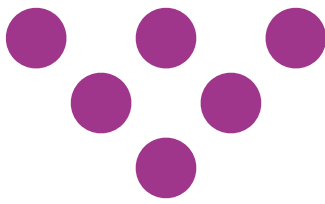
**3**

## **WHAT IS THE POTENTIAL ROLE OF MICROBIOTA MODULATION?**

Preventing the risk of graft rejection  
P. 12

Stimulation of innate and adaptive immune responses  
P. 13

**EXPERT INTERVIEW**  
Pr Patrice Debré P. 14

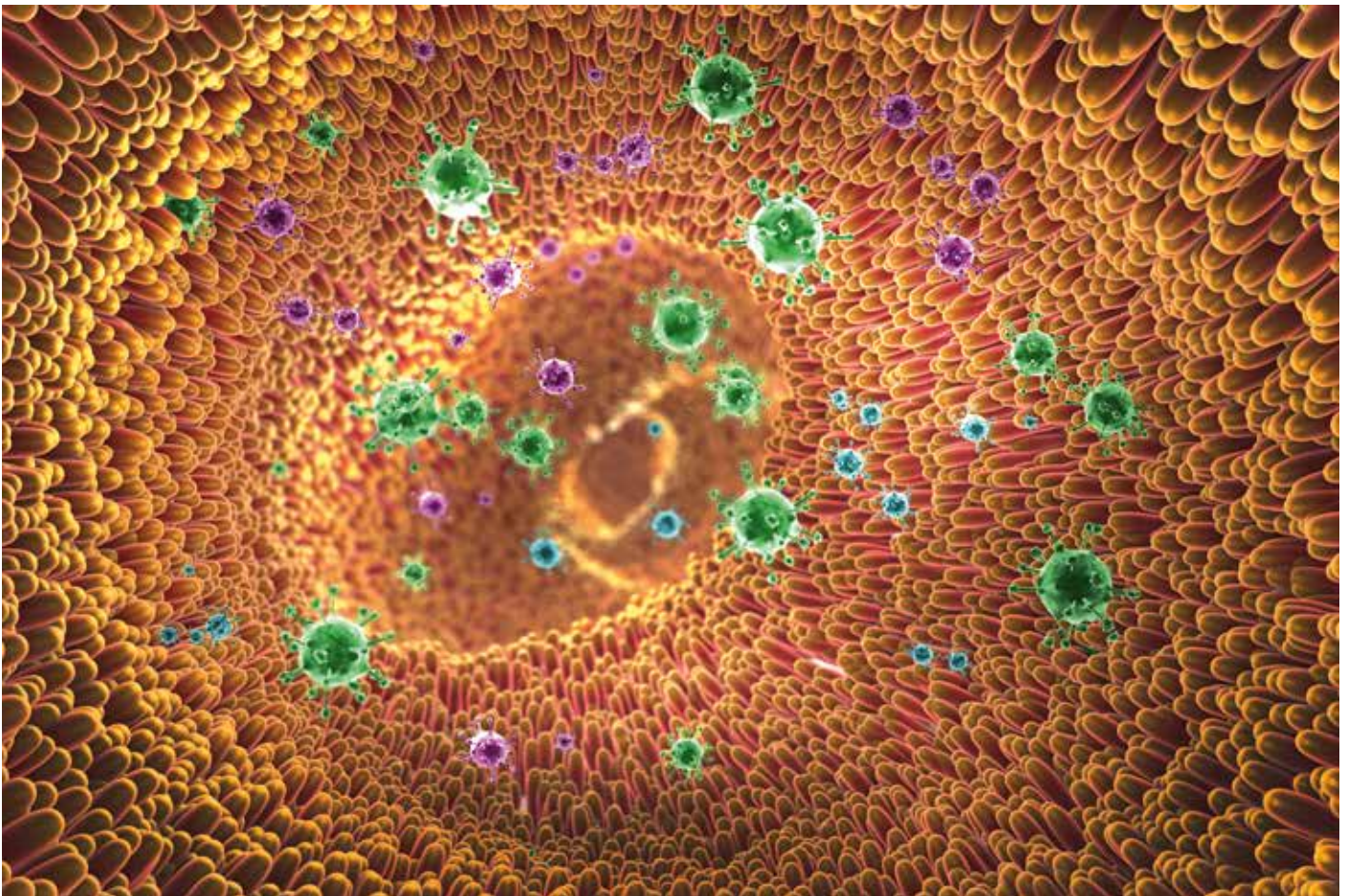


# 1



## ROLE OF THE GUT MICROBIOTA IN THE DEVELOPMENT OF THE IMMUNE SYSTEM

The immune system is known to be naive early in life and constantly evolving in response to subsequent antigenic contacts. We now discovered that there is an adjuvant to its structuration: the gut microbiota, which is present from the start of its development and never leaves. This balance is based on complex interactions; it develops at an early stage and allows all the participants to coexist.



Intestinal lumen.

# The gut microbiota, first bastion against aggressions

The epithelial barrier is where the interface between immune system and gut microbiota is located, and it is a key site where a true dialogue between host's immunity and bacteria is established.



With  $10^{14}$  microorganisms, the gut microbiota could quickly invade the host if a pacific coexistence had not been established throughout human evolution. The intestinal barrier is the main component ensuring this coexistence: epithelial cells from the intestines secrete a thick mucus from which bacteria in the gut lumen draw nutritional resources, without being able to cross the barrier in non-pathological conditions.

## MULTIFACTORIAL BALANCE

Constant exchanges between the host and the microbiota appear to be key for the physiological balance of the intestinal immunity. In the villous crypts of the small intestine, the binding of bacteria to some receptors (NOD2<sup>1</sup>) of Paneth cells<sup>2</sup> leads to the production of antimicrobial peptides such as lysozyme. The activation of Toll-like receptors (TLR) by bacteria at the membrane level of

epithelial and lymphoid cells triggers the recruitment of phagocytes, lymphocytes and dendritic cells (innate immunity players) located in the sub-epithelial layer. This activation occurs through the NF- $\kappa$ B signaling pathway, which is regulated by short-chain fatty acids (SCFA) produced by some bacterial strains and by the production of chemokines and cytokines<sup>3</sup>. A balance is thus achieved between integrity of the intestinal mucosa, bacterial activation of immune defenses and regulation of the responses from the microbiota itself. The disruption of only one of these chain links leads to chronic inflammatory processes.

## DELIVERY MODE AND INFANT FEEDING: TWO KEY FACTORS

Infants born by caesarean section have a larger proportion of B lymphocytes than those born vaginally, which is a sign of a more active immunity as early as the neonatal period<sup>4</sup>. Maternal milk also promotes the development of natural defenses and intestinal maturation through its composition and supplies such as: lysozyme; IgA (antibodies located on the surface area of the intestinal mucosa); kappa casein (whose degradation products can compete with pathogens for the intestinal epithelial cell receptor in breastfed babies); lactoferrin, whose degradation product –lactoferricin– is an antimicrobial peptide with bacteriostatic and bactericidal action. It also contains about  $10^9$  bacteria/L as well as fructans, prebiotics that promote the growth of bifidobacteria and lactobacilli. As for infant formula, it promotes a greater multiplication of enterococci and enterobacteria<sup>5</sup>.

<sup>1</sup> Nucleotide-binding Oligomerization Domain 2

<sup>2</sup> Epithelial cells residing at the bottom of the small intestine crypts and involved in the immune defense of the gastrointestinal system.

<sup>3</sup> Gaboriau-Routhiau V et al. *Microbiote intestinale et développement du système immunitaire*. Médecine/Science. 2016

<sup>4</sup> Clemente JC, Ursell LK, Parfrey LW, Knight R. *The impact of the gut microbiota on human health: an integrative view*. Cell (2012) 148(6):1258–70. doi:10.1016/j.cell.2012.01.035

Cited in Lazar V et al. *Aspects of gut microbiota and immune system interactions in infectious diseases, immunopathology, and cancer*. Frontiers in Immunology. 15 August 2018

<sup>5</sup> Lazar V et al. *Aspects of gut microbiota and immune system interactions in infectious diseases, immunopathology, and cancer*. Frontiers in Immunology. 15 August 2018

By participating in the regulation of innate and adaptive immune responses, the gut microbiota becomes one of the pillars of defense mechanisms, especially thanks to the presence of specific bacteria called “segmented filamentous bacteria” (SFB)<sup>3</sup>. The microbiota is able to act on immunity, and its composition and diversity can in turn be controlled by that same immune system.

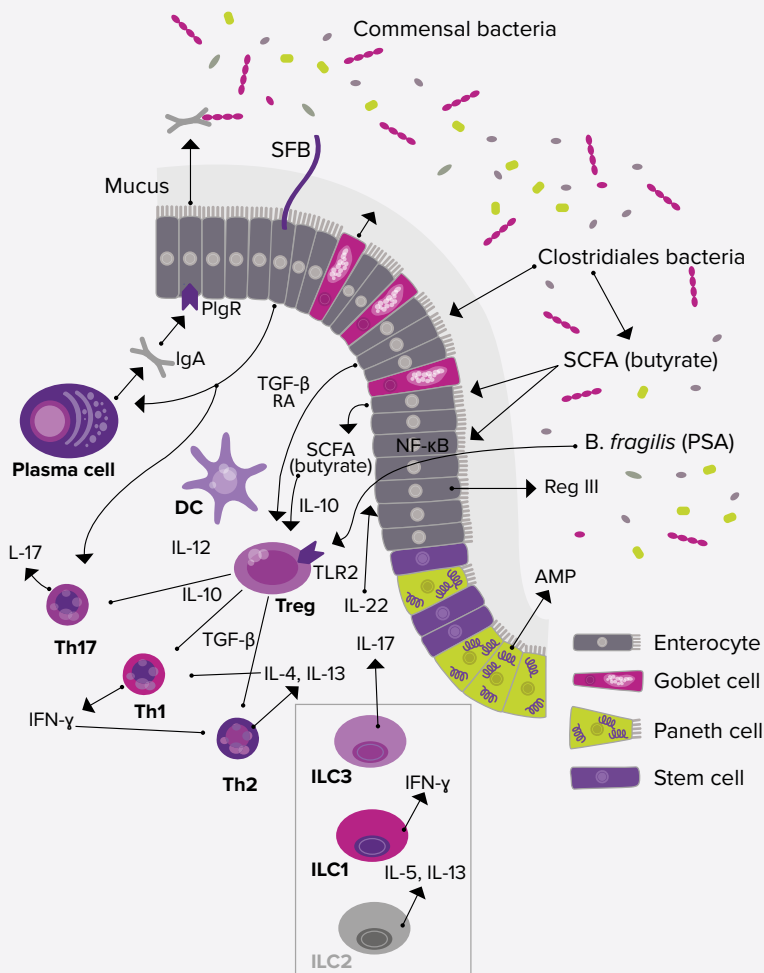
## Role of the gut microbiota in immune regulation<sup>3,5</sup>

Innate lymphoid cells (ILC) are a type of specialized innate immune cells. They are a group of lymphocytes that do not have antigen-specific receptors<sup>6</sup> and have been recently identified and divided into three groups based on the type of secreted cytokines: ILC1 that produces interferon gamma (IFN-γ) and similar to T-helper cells Th1, ILC2 similar

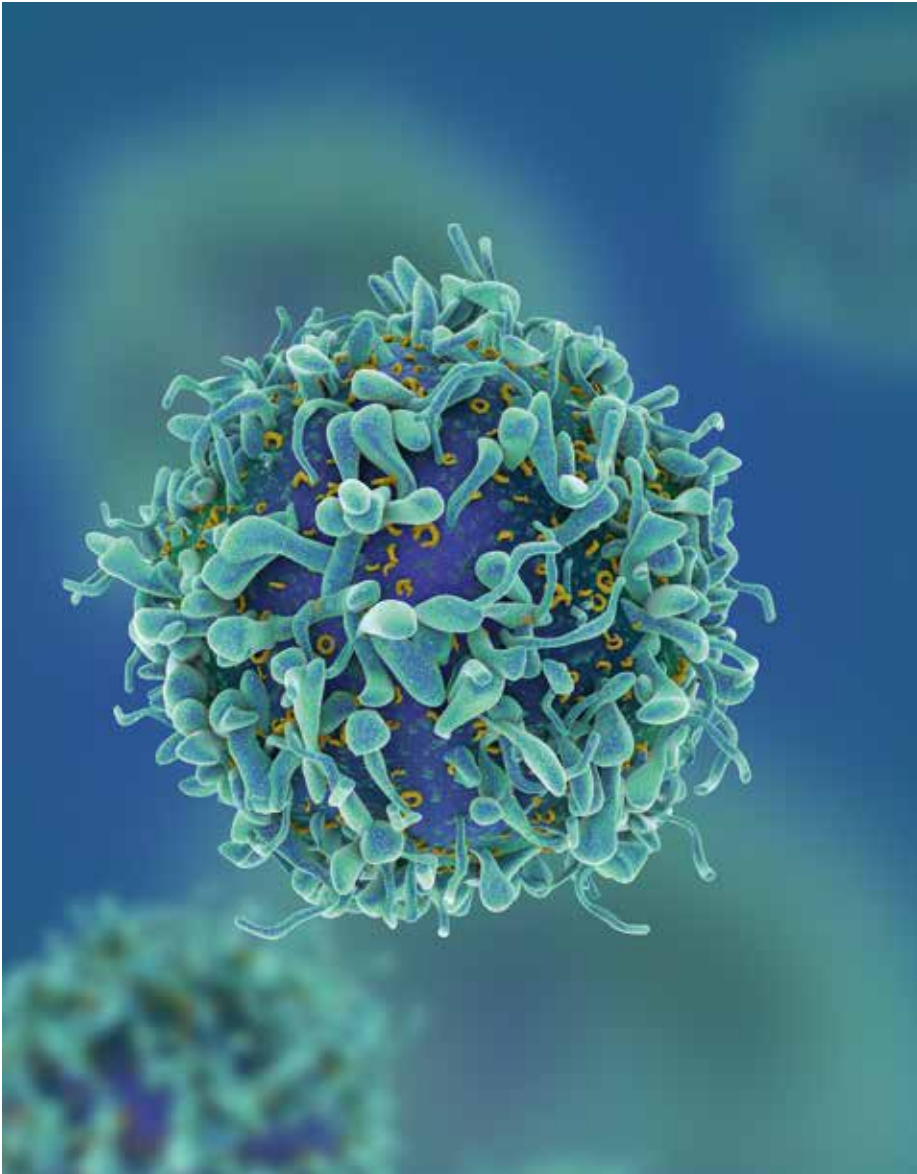
to Th2 (IL-5, IL-6, IL-13) and ILC3 similar to Th17 (IL-17, IL-22). The studies on the microbiota and ILCs, currently booming, also show that the microbiota seems to be necessary to the development and functions of ILCs, especially Group 3 ILCs. ILC3 are the main intestinal source of IL-22, a cytokine that is key to the production of antimicrobial proteins<sup>6</sup>.

**FIGURE 1:**  
**DIALOGUE BETWEEN THE GUT MICROBIOTA AND THE IMMUNE SYSTEM<sup>6</sup>**

- SFB: segmented filamentous bacteria
- SCFA: short-chain fatty acids
- PSA: capsular polysaccharide A
- AMP: antimicrobial peptide
- PlgR: polymeric immunoglobulin receptor
- Ig: immunoglobulin
- TGF: Transforming growth factor
- RA: retinoic acid
- IL: interleukin
- DC: dendritic cell
- Th: T helper cell
- IFN: interferon
- ILC: innate lymphoid cell
- NF-κB: nuclear factor-kappa B
- Reg III: regenerating islet-derived genes III
- Treg: regulatory T cell



<sup>6</sup> Marteau P, Dore J. *Le microbiote intestinal, un organe à part entière*, chapitre “microbiote intestinal et système immunitaire”. John Libbey Eurotext. 2017



T-cell.

## ADAPTATIVE IMMUNITY

The gut microbiota is also core to the activation of the adaptative response. At the T-cell level, it induces the maturation of naïve T-cells into IL-17-producing cells (Th17) which stimulate the production of antimicrobial peptides by the intestinal epithelium. It also promotes the synthesis of some CD4<sup>+</sup> regulatory T-cells (Treg) that have an anti-inflammatory action. Finally, it contributes to the development of secondary lymphoid tissues in the intestines where

T-cells are stored. Regarding B-cells, the gut microbiota ensures, through IL-17, that secretory IgA produced by B-cells crosses through the intestinal mucosa to join the lumen and neutralize harmful toxins and bacteria. The combination of strong IgA responses and pro-inflammatory (Th17) and anti-inflammatory (Treg) responses from T-cells create a state of physiological inflammation controlled by the gut microbiota<sup>3,5</sup>.

---

## KEY FACTS

### SEGMENTED FILAMENTOUS BACTERIA (SFB)

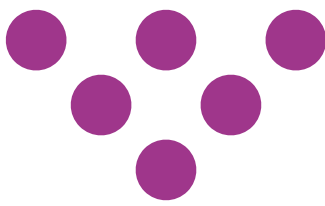
Commensal bacteria (*Clostridiales* order) previously identified in vertebrate animals and detected in humans thanks to molecular sciences

They are necessary to the maturation of the intestinal and pulmonary immune barrier and induce the production of IgA and the activation of proinflammatory and regulatory T-cells.

They have a protective effect against type 1 diabetes mellitus (non-obese diabetic [NOD] mouse model), pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA), and some bacterial (*Citrobacter rodentium*) and parasitic (*Entamoeba histolytica*) infections.

They can have adverse effects by promoting the development of autoimmune diseases in autoimmune encephalitis or arthritis models.

---



## 2



# INTERACTIONS AND PATHOLOGIES

The gut microbiota is placed at the center of the immune machinery and is becoming a major parameter in the development of diseases with strong immune and inflammatory components. It is true for type I diabetes mellitus for instance, chronic inflammatory bowel diseases (CIBD) and graft-versus-host disease (GVHD) in patients who received a hematopoietic stem cell transplant. These pathologies seem to share various mechanisms: increased gut permeability and disrupted homeostasis between healthy stimulation by commensal bacteria and moderated response from immune cells. Once this balance has been compromised, the inflammatory process is triggered. These are all potential lines of research to improve –or change–some dietary and therapeutic habits.

## Type I diabetes mellitus<sup>5</sup>

**While it was long known that the destruction of pancreatic beta-cells is related to an autoimmunity process, the involvement of the gut microbiota in this process has only been recently discovered. This could become a turning point to supplement insulin therapy which is currently the standard treatment for type I diabetes mellitus.**

Studies in humans have not yet helped us understand the causal relation between microbiota and immune system. However, several studies have shown that diversity and composition of the gut microbiota are different between healthy individuals and patients with type I diabetes mellitus (T1DM) or at risk of contracting it. One of the hypotheses put forward is the increase of gut permeability, which leads to increased levels of macromolecules in the blood derived from food and LPS (lipopolysaccharides, fragments from the wall of gram-negative bacteria). Because of a breach in the mucus barrier, these bacterial fragments seem to lead to the release of proinflammatory cytokines and the destruction of pancreatic beta-cells<sup>5</sup>.





## HORMONAL INFLUENCE

Hormones and gut microbiota could be associated with autoimmune diseases and impact the immune response. The gut microbiota could also be at the origin of the protective effect of testosterone which has been observed in male NOD<sup>7</sup> mice (female NOD mice develop this disease more often than males). As a result, young female NOD mice have a decreased risk of developing T1DM following a microbiota transplant from an adult male. Sexual hormones and some bacterial strains could act together through cytokines (IFN- $\gamma$  and

IL-1 $\beta$ ) that have a regulating effect on immunity, thus limiting the disappearance of pancreatic beta-cells<sup>8</sup>.

## IMPACT OF DIET

Some links between diet and T1DM could also be related to the microbiota<sup>8</sup>: for instance, depriving mice of gluten leads, among others, to an increase in Treg and *Akkermansia*, a bacterium that is generally beneficial to the metabolism. Gluten-free diet could play a role in the mediation of the functions of pancreatic beta-cells by modifying the gut microbiota: this

could impact the incidence of T1DM. Moreover, the intake of micronutrients could also play a role in the process: retinoic acid, derived from vitamin A, seems to have a protective effect against the disease. By inhibiting the differentiation of proinflammatory Th17 under the influence of IL-6 and by promoting the differentiation of anti-inflammatory Treg, it could help limit the incidence of the disease. In the same way as for type 2 diabetes mellitus, a proinflammatory state is observed in mice fed with a high-fat diet<sup>9</sup>.

# Chronic inflammatory bowel diseases

**Recent studies on the interactions between immunity and microbiota shed a new light on the complex etiology of chronic inflammatory bowel diseases. Several mechanisms have been described and genetic predispositions have been identified thanks to animal models. But many factors remain unknown, especially those that trigger these diseases.**

It has now been proven that dysbiosis and CIBD go hand in hand. Thinner or disrupted gut mucosa promotes the invasion of pathogenic bacteria into the epithelium, the mobilization of innate immune cells (macrophages and monocytes) and the production of TNF- $\alpha$ , inducing a chronic inflammatory state. Tolerance to commensal bacteria would be compromised, thus maintaining—or even worsening—the dysbiosis, and as a result the persistence of the inflammatory processes. The proof of this is that germ-free animal models for

CIBD do not spontaneously develop the disease.

## SEVERAL POSSIBLE ALTERATIONS

Underlying interactions between immunity and gut microbiota have been described in mouse models: the presence of bacteria from the *Lachnospiraceae* family seems to promote epithelial infiltration of proinflammatory monocytes and macrophages, which is alleviated by the administration of vancomycin. Moreover, hydrogen peroxide-produc-



<sup>7</sup> *Non-Obese Diabetic* (unrelated to Nucleotide-binding Oligomerization Domain 2). Frequently used model in T1DM, born from a line created in Japan in 1980 whose young mice spontaneously develop symptoms mimicking human T1DM (glycosuria, weight loss...).

<http://www.animalresearch.info/fr/avances-medicales/maladies-et-recherche/le-diabete/>

<sup>8</sup> Han H et al. *Gut Microbiota and Type 1 Diabetes*. Int J Mol Sci. 2018 Mar 27

<sup>9</sup> 72% of corn oil, polyunsaturated and monounsaturated fat, bacon, saturated fat, 28% of proteins, and no carbohydrates

ing bacteria in the colon could induce oxidative stress harmful to the intestinal mucosa. In a mouse model of ulcerative colitis, colonization of the intestines by a human microbiota with low content of Firmicutes led to the induction of proinflammatory Th17. Similar results were found in Crohn's disease: in mice colonized by a patient's microbiota, the activation of proinflammatory responses was observed, contrary to what occurs in mice colonized by other healthy mice/donors. Finally, in subjects with CIBD, the abundance of *Faecalibacterium prausnitzii* is reduced<sup>5</sup>. This prominent species of the fecal microbiota in healthy individuals (5 to 20%) produces

butyrate, has anti-inflammatory properties thanks to part of its microbial anti-inflammatory molecule (MAM) and is necessary to the good functioning of intestinal cells<sup>10</sup>.

### THE WEIGHT OF GENETICS

Genetic predispositions involving dysfunctions of the innate response were also described. For instance, mutations of genes related to autophagy or to the identification of fungi by dendritic cells seem to predispose to Crohn's disease. In this pathology, the mutation of the gene encoding NOD2 protein opens another avenue of research: this intracellular receptor of intestinal innate im-

mune cells is able to bind many bacterial components (peptidoglycan, flagellin...) and activate the inflammatory immune cascade. However, the deactivation of the NOD2 gene alone is not enough to trigger the spontaneous onset of the disease in rodents. This suggests that commensal bacteria play a joint role. The effects of this mutation differ between animal models: in a chemically-induced colitis model, the mutation of the NOD2 protein has a protective role. Thus, the recurring question remains: is the inflammation the cause or the consequence of dysbiosis? Researchers have yet to reach a conclusion.

## Stem cell transplant and graft rejection

**A reevaluation of antibiotic prophylaxis in hematopoietic stem cell transplants would be welcome as this treatment causes gut dysbiosis increasing the harmful effects of the immune response in graft-versus-host disease.**



Antibiotic prophylaxis prior to an allogeneic hematopoietic stem cell (HSC) transplant is common practice in hematology-oncology. Its purpose is to prevent bacterial infections associated with chemotherapy and radiation therapy, which both cause serious damage to the intestinal epithelium. However, this practice is believed to increase morbidity and mortality related to graft-versus-host disease (GVHD) in which T-cells from the donor turn against the recipient's epithelial cells—mainly skin, liver and gastrointestinal tract cells. By killing commensal bacteria, antibiotics lower the resistance of the recipient's gut to colonization. In addition, they are believed to promote the emergence of antibiotic-resistant bacteria<sup>12,13</sup>.

<sup>10</sup> Marteau P, Doré J, Seksik P. Microbiote et MICI. POST'U (2018)

<sup>11</sup> Goethel A et al. *The interplay between microbes and the immune response in inflammatory bowel disease*. J Physiol. 2018 Sep

<sup>12</sup> Noor F et al. *The Gut Microbiota and Hematopoietic Stem Cell Transplantation: Challenges and Potentials*. J Innate Immun. 2018 Oct

<sup>13</sup> Laterza L et al. *The Gut Microbiota and Immune System Relationship in Human Graft-versus-Host Disease*. Mediterr J Hematol Infect Dis. 2016 May 1

## A HARMFUL DECREASE IN BACTERIAL DIVERSITY

The use of antibiotics also results in gut dysbiosis with decreased bacterial diversity, sometimes characterized by the proliferation of a single taxon such as *Enterococcus*, which may become predominant to the detriment of other bacteria including *Faecalibacterium spp.* and *Ruminococcus spp.* (both belonging to the *Clostridiales* order)<sup>13</sup>. This has a negative impact as these species produce butyrate, a compound that has the potential to induce growth and differentiation of Treg cells, which may reduce inflammation caused by the donor's T-cells. As a result, the decline in these species could cause inflamma-

tion. Likewise, the presence of *Blautia (Clostridiales)* seems to be associated with lower mortality from GVHD. When combined with immunosuppressant and cytotoxic drugs, antibiotics could increase the risk of bacterial translocation, and therefore the propagation of pathogens to the various organs affected by GVHD<sup>13</sup>.

## TOWARDS PERSONALIZED MICROBIOTIC MEDICINE?

Real-time microbial profiling could help reduce potential harmful effects from antibiotic prophylaxis. Being able to detect a decrease in *Clostridiales* levels or lower diversity in the recipient's gut microbiota would help identify high-

risk patients and adapt the treatment (narrower-spectrum antibiotics, pro- or prebiotics or even direct SCFA supplementation, fecal transplant, etc.). Bacterial profiling could also prove useful in the follow-up phase to prevent the risk of relapse, especially by testing for the presence of *Enterobacteriaceae* in stools (*Escherichia coli*, *Klebsiella spp.*, *Enterobacter spp.*) in order to prevent *Enterobacter* bacteremia. Donor gut microbiota should also be considered as low *Bacteroides* and *Parabacteroides* levels are typically associated with low SCFA concentrations. These are all promising avenues that could help improve the prognosis of allogeneic HSCT patients<sup>12</sup>.

## Respiratory infections

**The microbiota plays a part in the resistance against respiratory infections, but the mechanism is still poorly defined. A recent study revealed that, in gnotobiotic mice<sup>14</sup>, the gut microbiota and the respiratory microbiota are involved in the immune response to fight viral or bacterial infections of the upper respiratory tract (in that case caused by *Streptococcus pneumoniae* or *Klebsiella pneumoniae*).**

NOD-like receptors of innate immune cells are activated by commensal bacteria of the microbiota: among others, *Staphylococcus aureus* and *S. epidermidis* in the upper respiratory tract and *Lactobacillus reuteri*, *L. crispatus*, *Enterococcus faecalis* as well as *Clostridium orbiscindens* in the gastrointestinal tract. This leads to the production of IL-17A, probably through the activa-

tion of TH17 cells in the intestines and through lymphocytes, NK cells and alveolar macrophages in the upper respiratory tract causing a resistance to pulmonary infections through a specific mechanism<sup>15</sup>.

## ROLE OF GM-CSF

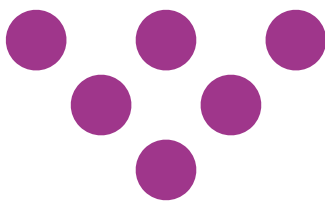
The IL-17A then acts on the lungs by activating the granulocyte-macrophage

colony-stimulating factor (GM-CSF), which in turn activates alveolar macrophages through ERK (extracellular signal-regulated kinase) signaling pathway, that allows the neutralization of the pathogen by producing reactive oxygen species (ROS). The reason why this specific GM-CSF-ERK transduction pathway is used remains unclear<sup>15</sup>.



<sup>14</sup> Models with simplified microbiota, or even carriers of a single bacterium (mono-associated animals) or carriers of partially-inactivated bacteria

<sup>15</sup> Brown RL et al. *The microbiota protects against respiratory infection via GM-CSF signaling*. Nat Commun. 2017 Nov 15



# 3



## WHAT IS THE POTENTIAL ROLE OF MICROBIOTA MODULATION?

The newly-acquired knowledge on the microbiota-immunity interaction opened up possibilities for new therapeutic solutions based on diet and modulation of commensal gut bacterial populations. Initial tests have produced encouraging results.

### Preventing the risk of graft rejection

**Although limited in immunosuppressed patients because of an increased infectious risk, the use of prebiotics or probiotics and fecal microbiota transplant (FMT) can have significant benefits for patients who underwent HSCT. Combined to new techniques to analyze, characterize and monitor the gut microbiota, this use could transform the prevention of infections and graft rejection.**



In a study with 30 children and adolescents, the use of probiotics, especially a *Lactobacillus* species, during the antibiotic prophylaxis phase or the follow-up phase of HSCT, prevented the onset of GVHD in 70% of cases, with no subsequent *Lactobacillus* bacteremia<sup>13</sup>. Regarding FMT, its safety and beneficial effects against *C. difficile* infection were recently proven on small cohorts of patients who underwent HSCT<sup>13</sup>: in one trial, fecal transplants led to remission in 3 out of 4 cases, and in another study, it led to a decrease of symptoms in GVHD after several grafts. The microbiota of antibiotic-treated patients who received an

autologous fecal microbiota transplant was restored on D+100 following the HSCT<sup>16</sup>. Some scientists thus suggest performing FMT before HSCT in patients carrying *C. difficile*-resistant strains.

#### DIET AND PROBIOTICS

Short-chain fatty acids (such as butyrate) have shown positive effects against GVHD. They serve as energy source as well as anti-apoptotic agents for enterocytes, and they have an anti-inflammatory action by promoting the synthesis of Treg. Beneficial effects on the intestinal mucosa were observed on other components metabolized by the gastrointestinal microbiota: indole derivatives produced by the fermentation of Brassicaceae (cabbage, broccolis...), tryptophan (dairy products, banana<sup>17</sup>...), bile acids. The association of fiber, glutamine and oligosaccharides reduced morbimortality in 44 transplant patients. A trial is currently ongoing regarding the benefits of resistant starch, a prebiotic that promotes the production of butyrate<sup>12</sup>.

## OTHER INNOVATIONS UNDER DEVELOPMENT

The therapeutic arsenal could also be broadened by innovations such as targeted antibiotic therapy that aims at limiting the destruction of the digestive barrier and the emergence of

multidrug resistant bacteria (antibiotics guided by pathogen-specific antibodies or synthetic bacteria that compete with pathogens are currently under trial). Thanks to new technologies, we are able to recreate *in vitro* interactions that occur *in vivo* within the gastroin-

testinal microbiota. As for bacterial profiling tools, they open the way to personalized medicine adapted to the microbiota of each patient in order to choose the most adequate therapeutic protocol<sup>12</sup>.

## Stimulation of innate and adaptative immune responses

**Some studies brought to light the potential use of targeted modulation of the gut microbiota in the prevention of respiratory infections. Some strains might be able to modulate the immune function and improve quality of life. The intake of some probiotics and prebiotics could thus contribute to improving resistance against this type of infections and decrease morbidity.**

In 2011, 198 students from the Massachusetts campus participated in a randomized, double-blind, placebo-controlled study that assessed the effects of probiotics during 3 weeks in the prevention of morbidity associated with upper respiratory tract infections<sup>18</sup>. These infections are common among young people that are possibly stressed, lacking sleep and living in crowded dorms. On average, volunteers who received a daily dose of a strain of *Lactobacillus* and *Bifidobacterium* were ill 2 days less (over a total duration of 6 days on average for infections that occurred in the cohort), and the severity of their symptoms was down by 34%. Probiotics thus improved

their quality of life and increased their resistance to environmental respiratory pathogens.

### SYNBIOTICS UNDER INVESTIGATION

In 2008, an Italian team explored the impact of synbiotics (combination of prebiotics and probiotics) on the intestinal health (bloating and transit especially) and resistance to respiratory infections<sup>19</sup>. For 90 days, more than 230 participants were divided into groups who received different combinations of probiotics (3 to 5 strains of *Lactobacillus* and *Bifidobacterium*), prebiotics (fructooligosaccharides, FOS) and/or lactoferrin and/or galactooligosaccharides

(GOS). Beneficial effects were demonstrated on the intestinal functions and the resistance to respiratory infections (decrease of the incidence, duration and severity) in patients who received synbiotics. Lactoferrin did not provide any visible benefit compared to FOS or GOS. However, the combination of the 5 strains of probiotics with FOS or GOS seem to improve symptoms. FOS seem to act in synergy with bacteria by helping them colonize the gut mucosa and roll out their immunomodulating effects. According to researchers, this alternative could be very useful in the long-term prevention of this type of pathology, for which current treatments are associated with adverse effects.



<sup>16</sup> Taur Y et al. Reconstitution of the gut microbiota of antibiotic-treated patients by autologous fecal microbiota transplant. *Sci. Transl. Med.* 10, eaap9489 (2018)

<sup>17</sup> [https://www.passeportsante.net/fr/Nutrition/PalmaresNutriments/Fiche.aspx?doc=tryptophane\\_nu](https://www.passeportsante.net/fr/Nutrition/PalmaresNutriments/Fiche.aspx?doc=tryptophane_nu)

<sup>18</sup> Smith TJ et al. Effect of *Lactobacillus rhamnosus* LGG® and *Bifidobacterium animalis* ssp. *lactis* BB-12® on health-related quality of life in college students affected by upper respiratory infections. *Br J Nutr.* 2013 Jun

<sup>19</sup> Pregliasco F et al. A new chance of preventing winter diseases by the administration of synbiotic formulations. *J Clin Gastroenterol.* 2008 Sep

PR PATRICE DEBRÉ



Patrice Debré is Professor Emeritus of Immunology at the Sorbonne University and member of the French National Academy of Medicine. He was Head of Immunology at the Hospital Pitié-Salpêtrière (AP-HP, Paris) and led research units at CNRS and Inserm. According to him, the study of the gut microbiota is key to better understand many non-transmissible human diseases, and especially those that involve the immune system.

## IMMUNE SYSTEM: TAKING INTO ACCOUNT THE GUT MICROBIOTA IS VITAL

**W**hat is the current state of research on the relations between immunity and gut microbiota?

Although the microbiota has been known since the days of Louis Pasteur, it was forgotten for a long time. However, it has been better understood in the past twenty years. Thanks to technical innovations (bacterial culture, metagenomics), bacteria from the gastrointestinal tract, which used to be poorly accessible, have been better characterized. We now have to refine our knowledge regarding their interactions with the body's defense mechanisms, the way gut and other microbiotas are involved in the development of the immune system, which in turn has an impact on pathogen heterogeneity. The concept of "shaping" (or modulation of gut bacteria by the production of IgA in the gastrointestinal tract) is of foremost importance. This research approach is still poorly understood, but it should be critical in the years to come. Interactions between gut microbiota and immunity is a true shift in paradigm, and their results and study are not yet given their rightful place.

---

**“Interactions between gut microbiota and immunity is a true shift in paradigm”**

---

**Do we know all the diseases associated with these relations?**

There are many. Among those related to the immune system, in no hierarchical order, it is logical to mention autoimmune diseases and allergies, which are characterized by a breakdown of immune tolerance. Cancers are characterized by inflammatory processes and disruptions of the physiological balances between bacterial pop-

ulations (dysbiosis). Less directly, regarding the role of the immune system, we should also mention obesity and metabolic disorders: bacteria-related inflammatory processes in the fatty tissue have been identified. Neuropsychiatric diseases could also be concerned: the intestinal production of serotonin that is transported to the brain through the vagus nerve should be further explored, but the link with immunity disorders is not obvious. Autism has also been mentioned: although the association with the gut microbiota is not crystal clear, it has already been suggested in several studies. Convincing mechanisms must be identified for the hypothesis to be confirmed.

#### **Modulation of the gut microbiota: could it soon become a standard clinical practice?**

One possibility could be to correct dysbioses or improve the gut flora with second-generation probiotics that are more targeted depending on the dysbiosis, compared to those from the first generation. Fecal microbiota transplants remain difficult because of the lack of standardization regarding protocol, sample collection or storage conditions. Modulation of the gut microbiota should rather be seen as an adjuvant: for instance, although the links between some bacterial populations and some types of cancer have been demonstrated, it would be unthinkable to manage without anticancer treatments. Standardized tests should be conducted to determine which populations should be grown and which should be destroyed. In a second phase, the efficacy of induced modifications should be confirmed and a durable colonization should be ensured. Before concluding anything, we should let research the time to progress.



Find us also on  
our website  
[bmi-pro.com](http://bmi-pro.com)





**BIOCODEX**   
*Microbiota Institute*

[biocodexmicrobiotainstitute.com/pro](http://biocodexmicrobiotainstitute.com/pro)