B·DEBATE International Center for Scientific Debate BARCELONA

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Synopsis

THE BARCELONA DEBATES ON THE HUMAN MICROBIOME 2017

FROM MICROBES TO MEDICINES

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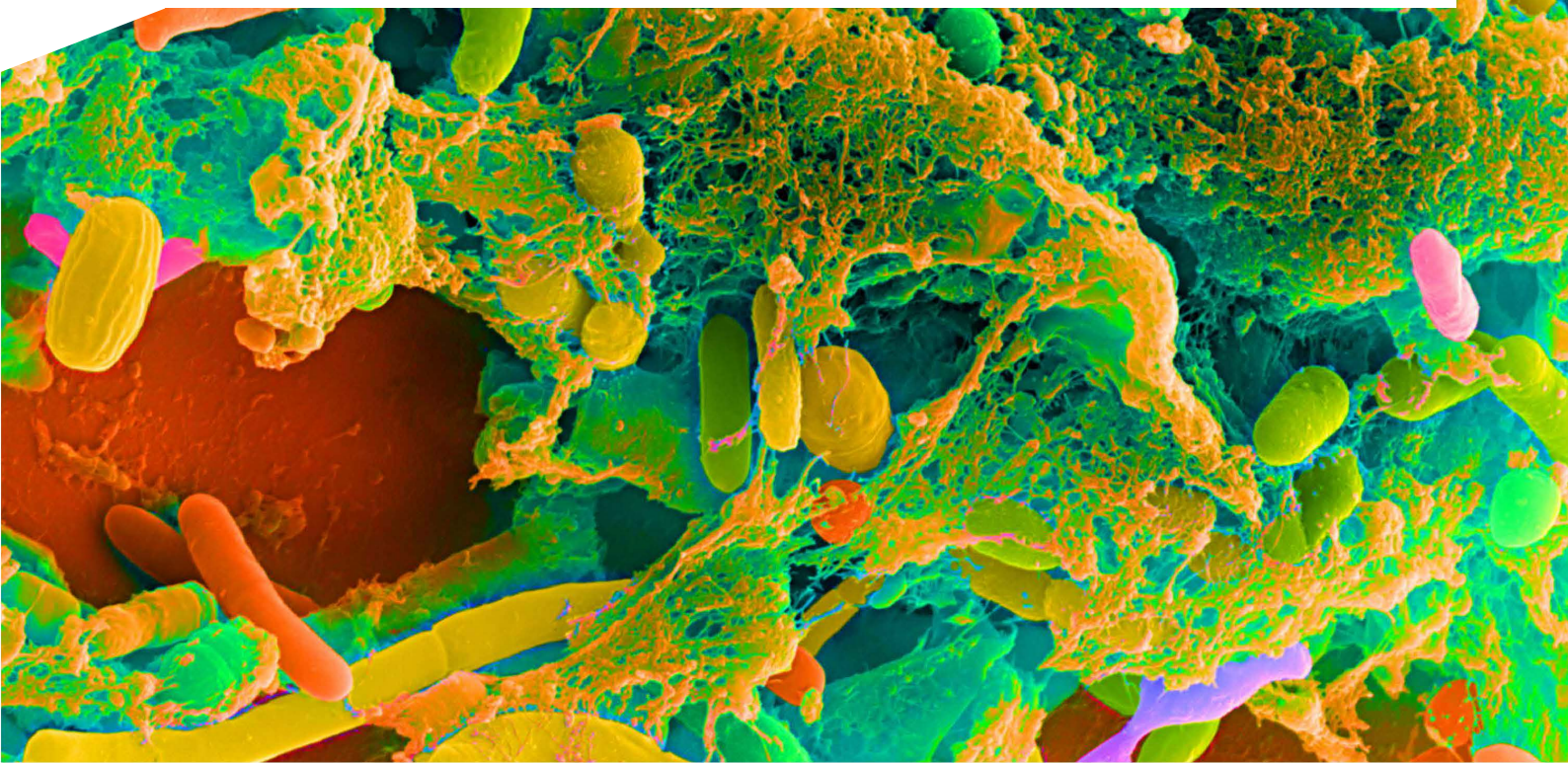

FROM MICROBES TO MEDICINES

On 29 and 30 June 2017, researchers from around the world met for a B·Debate session to **review the present and point to the future of the microbiome**, the collection of microbes that live in the human intestines. The microbiome is involved in a wide variety of vital functions and has been proven to have an impact on both human health and illness.

Today, **the challenge is to understand the relationship between the microbiome and the human body, and how it can be regulated**, opening up new opportunities in preventative medicine and for managing chronic illnesses. Other fields, like the food and pharmaceutical industries, can also benefit. New sequencing technology has revolutionized the scene and allowed for profiling and better understanding of the human microbiome.

However, many questions remain unanswered and participants tried to find answers to them at this year's 'The Barcelona Debates on the Human Microbiome 2017. From Microbes to Medicines', organized by B·Debate –an initiative of Biocat and the "la Caixa" Foundation to promote scientific debate– with the IrsiCaixa AIDS Research Institute.

CONCLUSIONS

- The microbiome is the collection of microbiomes in the human intestines and **is involved in numerous vital functions**.
- Research in this field currently focuses on understanding the relationship between the microbiome and the human body. And on **how to regulate the microbiome**, which could open up new opportunities in fields like **preventive medicine, chronic illnesses** and the **pharmaceutical industry**.
- **New sequencing tools** are particularly useful for studying changes to the microbiome, although standardizing processes and processing of the huge amount of data obtained are two major challenges to tackle.
- New treatment strategies for brain disorders **will probably include targets and mechanisms associated with the microbiome**, as well as changes in diet and lifestyle.

1. EAT HEALTHY TO LIVE LONGER

One of the things that have become clear is that a **healthy diet promotes healthy ageing**. As explained Ian Jeffery, researcher at University College Cork APC Microbiome Institute (Ireland), the connection between unhealthy diets and any cause of death has been clear for years now, but **only recently has it become clear what role microbiota and changes in microbial flora play in age-related diet changes**.

For Joël Doré, scientific director of the Industrial Demonstrator MetaGenoPolis, **regulating the microbiota should be considered a target for personalized nutrition** and a support strategy/adjuvant to current treatments.

One of the most promising studies is the **fecal microbiota transplant**, from a healthy donor to a patient. Positive results have been proven for both gastrointestinal and non-gastrointestinal illnesses, with success rates of 90% for *Clostridium difficile* infections. But, according to Peer Bork, head of bioinformatics for the European Molecular Biology Laboratory (EMBL) in Heidelberg (Germany), the mechanism behind it remains unknown.

2. KEY ROLE IN MEDICINE

The microbiome plays a key role in medicine, as explained Dusko Ehrlich, head researcher on the Metagenopolis project in Jouy-en-Josas (France) and director of the Center for Host Microbiome Interaction at King's College London (United Kingdom).

In his opinion, gut microbiota is a forgotten organ, made up of 100 trillion microorganisms, which is **more than the number of cells in the human body**.

"The microbiota is altered in patients with chronic illnesses. This alteration is often due to the loss of microbial richness and can even happen in healthy people. So, **an intestinal microbiome poor in microbes is less healthy**," he warned.

New sequencing tools have proven particularly useful in studying alterations in the microbiome, as shown by studies like MetaHIT, although standardization of processes is key.

"**Microbiome-based biomarkers can predict an illness precisely. And even the risk of developing a disease**. This is why treating the microbial parts of our body to stay healthy and cure diseases is highly useful. And, as alterations in the microbiome can make diseases worse, restoring it should be beneficial," he said.

3. THE MICROBIOME IN INFECTIOUS DISEASES

Vaginal microbiota also contributes to the risk of transmitting HIV, regardless of pre-exposure prophylaxis, as explained Nichole Klatt, professor at University of Washington (USA): Tenofovir in gel format was three times more effective in women with predominant vaginal *Lactobacillus*. This drug was not effective in women with non-*Lactobacillus* communities with large amounts of *G. vaginalis*.

Roger Paredes, head of Microbial Genomics at IrsiCaixa AIDS Research Institute and one of the scientific leaders of this B·Debate, is also doing research in this field. In his opinion, findings prove that **after HIV infection the microbiome adapts to oxidative stress**.

"This adaptation process can be self-perpetuating and contribute to chronic inflammation in the HIV infection. Acute HIV inflammation is characterized, among other factors, by a quick loss of gene richness, which doesn't seem to recover," he described.

4. DIGESTIVE DISEASES

Advances have also been made in Crohn disease. As explained Mahmoud Ghannoum, director of the Center for Medical Mycology at Case Western Reserve University in Cleveland (USA), Iliev's work proved that fungi –and not bacteria- are responsible for increasing inflammation and the severity of intestinal disease, more than being a cause of these symptoms. In 2016, Hoarau confirmed the key role one fungus plays in the development of Crohn disease.

"**There is clear proof of the microbiome's contribution to colitis**," highlighted the expert. Harry Sokol, professor of Gastroenterology at Hospital Saint Antoine in Paris (France), reiterated the **central role the microbiota plays in the pathogenesis of inflammatory intestinal diseases** and that this is influenced by both genetic and environmental factors.

Another area of interest is the interaction of iron, vitamin D and uric acid in insulin resistance, fatty liver and the microbiota, as indicated José Manuel Fernández Real, chief of section at the Biomedical Research Institute of Girona (IdIBGi). "There is more and more proof that **the microbiota regulates development of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis**. And these findings could have **therapeutic implications**," he believes.

5. FROM CITIZEN SCIENCE TO SYSTEMS BIOLOGY

Advances in sequencing technology have allowed for new approaches to the study of the microbiome. One example is the Stick Out Your Tongue initiative, which studies the microbes living in our mouths and was explained by Toni Gabaldón, researcher at the Center for Genomic Regulation in Barcelona.

"We've taken high-resolution photos of the oral microbiome of healthy Spanish teenagers and seen how it changes as a result of some dietary habits," he explained. The work established **two main stoma types, which include specific bacterial communities that can be described and show some geographical variation**," he explained.

The thousands of samples were obtained through public collaboration, which in his opinion is an example showing that **citizen science "offers both opportunities and challenges for microbiome research**. The correlations we've discovered allow us to pose hypotheses that will later be tested in specific, more controlled studies."

One key challenge is processing the huge amount of data obtained. Elhanan Borenstein, associate professor of Genome Sciences at the University of Washington, stressed that the massive amount of multi-omic information obtained normally focuses on statistical associations, often ignoring prior knowledge of mechanisms, dependence and regularities that link these different facets of the microbiome. For this reason, **systems integration and multi-omic data modeling are key, developing new computing tools that include taxonomic, genomic, metagenomic and metabolomic information on the microbiome**.

According to his criteria, this integration will lead to greater understanding –and on different levels- of the microbiome, both in healthy individuals and those with an illness, giving rise to **microbiome-based personalized treatments**.

6. GUT-BRAIN AXIS

Preclinical studies published in the past decade clearly established the important role intestinal microbiota plays in the behavior and regulation of key components of the gut-brain axis, including brain function and structure.

Emeran A. Mayer, professor at the University of California, Los Angeles (USA), published with his group the first evidence that **an alteration in the gut microbiome of healthy individuals may lead to altered brain response to emotional stimuli**.

"The gut-brain axis is a fully integrated system, programed when life begins, in the pre- and post-natal stages. Communication along this axis is regulated throughout a person's life by diet, medication and stress. Alterations to this communication seem to **play a role in regulating various brain disorders, including depression, obesity and irritable bowel syndrome**. Imbalances can begin either in the brain or the gut," he warned.

In his opinion, **new treatment strategies for brain disorders will probably include microbiome-related targets and mechanisms**, including changes in diet and lifestyle.

Parkinson is another field of interest. As explained Filip Scheperjans, neurologist at Helsinki University Hospital (Finland), so far nine studies have analyzed the composition of the microbiota in patients with this disease, "but the methods and results have varied."

These studies have shown that, compared to healthy control subjects, **Parkinson patients have an abundance of *Akkermansia* and *Lactobacillus* and a lack of *Prevotella***. Bacterial alterations may be tied to the integrity of the mucosa layer of the intestines, production of short-chain fatty acids and immune regulation.

Metagenomic studies that have been conducted point to alterations in numerous pathways, including metabolism of amino acids and production of lipopolysaccharides, among others. Also, lower levels of short-chain fatty acids that supposedly promote good health have been described in patients with Parkinson disease.

The evidence from experiments with mouse models suggests a possible interaction of the intestinal microbiota, alfa-synucleins, short-chain fatty acids, neuroinflammation and motor dysfunction. However, findings associated with short-chain fatty acids were contrary to what was expected in human studies.

7. MICROBIOTA AND CANCER

Finally, Laurence Zitvogel, researcher at the Gustave Roussy center in Paris (France) shared her belief that **anti-cancer probiotics like *Enterococcus hirae* and *Barnesiella intestinihominis* will usher in a new age of immuno-oncology**, with promising results already published for advanced lung tumors, ovarian cancer and kidney cancer.