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Synopsis

THE BARCELONA DEBATES ON THE HUMAN MICROBIOME

FROM MICROBES TO MEDICINES

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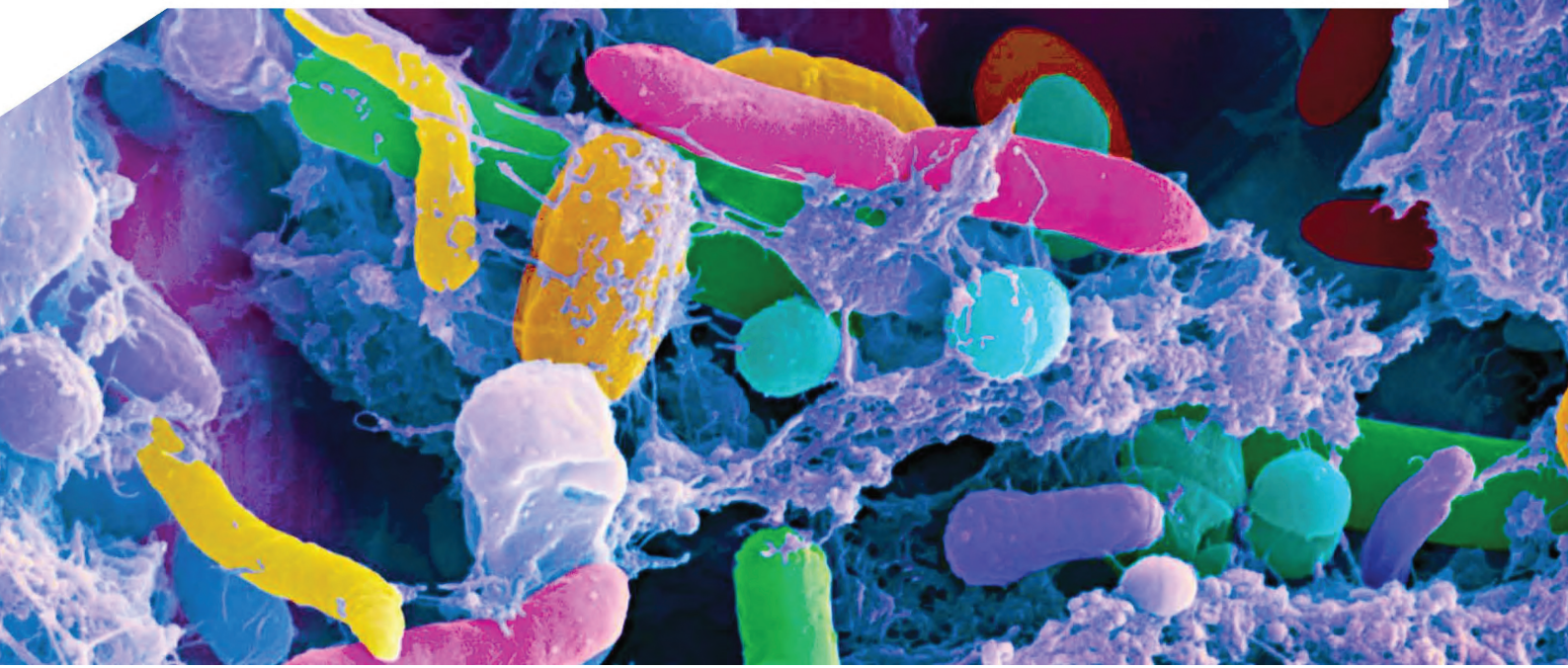

MICROBIOME: FROM MICROBES TO NEW MEDICINES

An old, and old-fashioned, dream of medicine was to live without bacteria. However today we now know how wrong that was. We play host to approximately 2 kg of them, coexisting and having an impact on a wide range of processes, many of which were unimaginable just a few years ago. It has been called the last organ: the microbiome.

Research into its importance in terms of health is one of the main areas of activity in the field of biomedicine. Some of the latest discoveries include, for example, that **pregnancy isn't a sterile process**, as previously thought, as the placenta has its own microbiome that can influence fetal development; that there seems to be a critical window, at around three months old, when changes in the bacterial ecosystem can predispose a child to developing asthma; that **it is possible to administer certain bacteria to boost cancer treatment**, which has given rise to what is called 'oncomicrobiotics'; and that scientists continue to work to perfect what is known as a feces transplant, a new form of treatment that could change the course of illnesses like diabetes.

To share and discuss these and other advances, some of the top experts in the world met for another session of B·Debate, an initiative of Biocat and the "la Caixa" Foundation to promote scientific debate, which is beginning to establish Barcelona as a scientific hub for studying the microbiome.

CONCLUSIONS

- Contrary to previous beliefs, pregnancy isn't a sterile process. The placenta has its own microbiome that seems to have an impact on fetal development. Furthermore, scientists are starting to question the association between cesarean birth and changes to the microbiome.
- Children with a tendency to develop asthma have a different microbiome when they're three months old, but not when they're one. This window of time could be a therapeutic opportunity.
- A new concept has developed, oncomicrobiotics: bacteria administered to boost the effectiveness of cancer therapies by improving immune response.
- Research continues on feces transplants, but looking to the future, selecting more effective bacteria for each situation and administering them in a more controlled manner.

A NEW ERA OF MEDICINE, EVEN BEFORE BIRTH

“In developed countries no one dies of tuberculosis, leprosy or syphilis anymore, but 20% of Europeans suffer from asthma, 5% will develop colon cancer and the number of cases of multiple sclerosis doubles every 10 years. **Many of these non-transmittable chronic illnesses are increasing, we don't know what is going on,**” explained Francisco Guarner, department head at the Vall d´Hebron University Hospital and one of the scientific leaders of this B·Debate.

He doesn't know, but he suspects it has something to do with the changes to the microbiome. It is, in part, what is been called the hygiene hypothesis: as we live in "cleaner" societies, have less contact with microorganisms and take more antibiotics, our defenses don't have as much practice, don't get the right stimuli and tend to behave incorrectly over time.

“**The bacteria that live with us** are a window to discover the causes of this thing that's going on, and **could be a new era in the history of medicine, as they were in Pasteur’s time (for other reasons)**." They seem to be important even before birth.

A placental microbiome

Until very recently, pregnancy was considered a sterile process, free of microorganisms. The first contact the baby was thought to have with the bacterial world was at birth, in the mother's birth canal, for example. However, this theory seems to have fallen by the wayside. Dr. Kjersti Aagaard, vice-president of the Division of Maternal-Fetal Medicine at Houston’s Baylor College of Medicine, presented data from a study that has found that, **long before birth, there is a placental microbiome that could have a significant impact on fetal development**.

It could, for example, have an impact on the birth process. "We found differences in the placental microbiome of spontaneous and programmed pre-term births," said Aagaard. The interesting thing is that, when compared to other areas of the body, the **microbiome of the placenta is most similar to that of the mouth**. The hypothesis is that some of these bacteria may reach the placenta through the blood, and this would explain the links that have been seen for years between periodontal disease (infections of the mouth) and a greater risk of premature birth.

Aagaard called into question other theories that have been close to taking hold, like the importance of vaginal birth versus cesarean in establishing the newborn's microbiome. On one hand, because it could already be developing long before birth. On the other, because when you look at them just weeks after birth, data shows that "**there's no lasting variation in the microbiome that correlates with type of birth**." She even showed data, although preliminary, that suggests that an unhealthy, high-fat diet during pregnancy may alter the child's microbiome. In this case, the

changes seem to persist, and may even be tied to increased anxiety. Whether this behavior is caused by bacteria is yet to be seen (it is important to remember that in this type of studies correlation does not imply causality).

A WINDOW OF TIME FOR ASTHMA

"Asthma is the most common chronic childhood illness, we still don't know what causes it," explained Stuart Turvey, professor of Pediatric Immunology at the University of British Columbia in Vancouver, Canada. What is clear is that more and more children have asthma, and data points to the hygiene hypothesis: occurrence seems to increase in developed countries and with the use of antibiotics, but is lower in families with more siblings and children who spend time near farms with animals.

The CHILD study is a large-scale project that is following 5,000 children from birth for six years. Researchers, including Turvey, have analyzed their intestinal microbiome at several points and observed a curious, possibly revealing fact**. Children with early symptoms of asthma have a different microbiome at three months**, but not when they are one year old. This means that there seems to be a window of time that somehow predisposes them to developing the illness when we could intervene. In fact, in the laboratory, Turvey's team has prevented the onset of asthma in mice by administering a cocktail of four bacteria. Nevertheless, the scientist is cautious: "We don't know if it will work in humans yet. Or even if it's safe."

ONCOMICROBIOTICS TO FIGHT CANCER, BACTERIA'S ROLE IN AIDS AND A WHOLE ECOSYSTEM TO DISCOVER

New knowledge of the microbiome has given rise to a new term. In addition to what is known as probiotics, **we may soon be talking about oncomicrobiotics:** cocktails of microorganisms that could boost the effectiveness of cancer therapies.

These are the conclusions of the work presented by Laurence Zitvogel, director of Research at the Institut Gustave Roussy in Villejuif, France, who believes, "**The microbiome could have an impact on cancer treatment, both for chemotherapy and immunotherapy**."

Her studies are surprising and are based on the fact that tumors are always being watched by our immune system. Although tumor development implies that it has insufficient control, this can be improved. This is the aim of new treatments based on immunotherapy, but it is also what traditional chemotherapy does indirectly. The latter, in destroying the tumor cells, sends many of

its foreign substances into the body, which in theory makes them easier for our defenses to identify if they are working properly. This is where oncomicrobiotics could help.

When patients are given chemotherapy like that based on cyclophosphamide, “There is a translocation of bacteria from the intestine into the bloodstream," explains Zitvogel. Some of them "train" our defenses’ CD8 lymphocytes, making them more effective in fighting the tumor. In fact, the effectiveness of the treatment decreases significantly in the presence of antibiotics in lab mice, but increases enormously when combined with to specific types of bacteria. These are the ones that, if their role is confirmed, could be considered as oncomicrobiotics.

The microbiome and AIDS: what do they have to do with each other?

This apparent paradox was mentioned in the press conference by Bonaventura Clotet, director of the HIV Unit of the irsiCaixa Foundation: “You're probably wondering what an AIDS researcher is doing on a panel about the microbiome." The answer lies in part in the fact that the virus, in attacking the immune system, makes it easier for intestinal bacteria to move into the bloodstream. Once there, their presence causes chronic inflammation and accelerated aging. This is why Clotet doesn't hesitate in saying that “**an AIDS vaccine will require a healthy microbiome**”.

Moreover, the intestinal ecosystem seems to change in the presence of the disease. This was proven by Roger Paredes, irsiCaixa Microbial Genomics group leader. Patients, especially those not as strictly monitored, lose bacterial diversity, similar to what happens under other circumstances like metabolic syndrome. And, as explained by Dusko Ehrlich, emeritus director of the Institut National de la Recherche Agronomique of France, “In terms of the microbiome, it's also better to be rich than poor." This is why scientists are working to identify the bacteria affected and those that should be repopulated to improve the health of AIDS patients.

AN ECOSYSTEM OF MICROORGANISMS

The microbiome doesn't refer only to bacteria, but also to other microorganisms like viruses. These are omnipresent in all of us. There are very old viruses inside our DNA; there are viruses from illnesses we have already had or that lie in wait in some of our cells, like the rear-guard; there are active infections, and there is the huge amount of bacteriophage viruses that we host in our intestines and that only infect bacteria (and that, according to Frederic Bushman, president of the Department of Microbiology at the University of Pennsylvania in Philadelphia, "**kill between 0.1% and 10% of all of our bacteria each day**). Despite their importance, they are more difficult to study than bacteria, and aren't as well profiled.

And the microbiome **also includes fungi**, which don't tend to be mentioned as much because they also don't demand this importance. For example, as highlighted by Gary Wu, professor of Medicine at the University of Pennsylvania, "Frequent use of antibiotics is associated with increased risk of inflammatory intestinal disease an increased amounts of fungi in the intestine." In fact, some hypotheses believe they could play a role in developing the disease, whose origin is still unknown.

FECES TRANSPLANTS AND NEW TREATMENTS

There are different ways to modify the microbiome in an attempt to improve health. There are probiotics and prebiotics, but the most radical method is a feces transplant from a healthy donor. This procedure has been proven effective in treating stubborn and potentially serious diarrhea caused by *Clostridium Difficile*.

Nevertheless, the procedure has many drawbacks: it is difficult to analyze the sample with certainty, it's nearly impossible to standardize it, and there are many differences in how patients tolerate it. In fact, one of the top experts in the field, Dr. Max Niewdorp of the Academic Medical Center in Amsterdam, doesn't hesitate to say, "**Ten years from now we won't be doing feces transplants, we'll be using targeted drugs**." This means identifying the bacteria that are potentially beneficial and administering them in a controlled manner, surely as part of a cocktail.

This is the focus of work being done by Bernat Ollé, CEO of Compañía Vedanta Biosciences, to design drugs based on bacteria selected not empirically but rationally, based on their potential pharmacological properties.

What are their prospects? Which will be the first diseases treated in this way? According to Ollé

and Niewdorp, the next step could be preventing certain infections and the damage caused to the microbiome by antibiotics. Perhaps after that we could improve pathologies like inflammatory intestinal disease. It will be more difficult and improbable to attack type-2 diabetes and particularly unrealistic to reverse neurological diseases like autism, with which the microbiome has also been associated. These are the levels in a theoretical pyramid in which each step now seems more hopeful and less sure than the previous one.