Research Focus of Maria Rescigno

The microbiota is made up of billions of microorganisms (weighing about 1.5 kg), including bacteria, fungi, viruses, and protozoa that coexist with each other and with our body. Each of us has a microbiota that is unique — a true biological fingerprint. However, unlike a fingerprint, which does not change over time, our microbiota is dynamic. This means that my microbial "imprint" today is not only different from everyone else's, but it could also differ from my own tomorrow, or the day after, and so on.

We should think of the microbiota as a condominium or an orchestra, where each tenant or musician plays their part and coexists with the others. This creates harmony and pleasant coexistence. However, if one tenant becomes overbearing, they might try to impose their will on the others, participating to disorder establishment. Similarly, if a musician in an orchestra plays the wrong note, the whole ensemble loses harmony, and the resulting sound is distorted.

The same happens within the microbiota: when balance is maintained, everything functions smoothly, but if an aggressive species takes over, it can lead to *dysbiosis* — a loss of balance, a discordant note. Almost all diseases studied so far have been associated with some form of dysbiosis, and only now are we beginning to understand whether this is a cause or an effect of the disease.

For example, we know from preclinical models that certain bacteria are associated with the development of tumors: *Fusobacterium nucleatum* with colon cancer, *Helicobacter pylori* with stomach cancer, and so on. Likewise, preclinical studies have shown that transferring the microbiota from obese patients can induce obesity, suggesting that the microbiota plays an active role in the development of disease, rather than merely being a consequence of it.

The intestine is considered as a second brain because it contains a true neural network — the **enteric nervous system** — which directly responds to external stimuli and sends signals to the brain. The intestine therefore mediates a remarkably high number of signals that reach the brain.

Moreover, many bacteria in the microbiota produce neurotransmitters — the mediators of neuronal responses — or their precursors, releasing genuine signals that can reach the brain either directly through the bloodstream or indirectly by stimulating the enteric nervous system.

It is no coincidence, then, that we speak of the **gut–brain axis**, or that we use expressions such as "gut feeling" or "thinking with your gut."

The microbiota is beneficial to us because it performs a range of essential functions for our well-being, such as digestion and the production of nutrients and key molecules. At the same tim, however, it can also pose a risk. For this reason, our body has developed several defense mechanisms that prevent the microbiota from entering our internal systems.

It's as if we had a gate — a front door — in the intestine that controls who is allowed to enter the building. If this gate is damaged, intruders (bacteria or potentially harmful bacterial substances) can get inside and, through the circulation — like using the building's staircase — reach the apartments and the headquarters: the brain.

Normally, the door to the “apartment” (the brain) remains fairly permissive as long as the main gate is intact. However, when that gate is breached, the brain’s door closes tightly to block the entry of unwanted substances and inflammatory mediators. This protective isolation of the brain can lead to states of anxiety and depression.

Specific tests can be performed, such as **microbiota analysis**, which allows us to assess — with varying levels of detail depending on the test — the composition of the microbial community. At present, these tests mainly tell us how different is one’s microbiota from that of a healthy population and which microorganisms have expanded or decreased, but we are still not fully able to determine precisely how to restore balance.

Maintaining a **healthy diet** - rich in vegetables and fibers - is the first and most important step toward rebalancing the microbiota. Besides that, one can use food supplements to reshape an unhealthy microbiota. There are three alternatives: **Prebiotics** which are dietary fibers — the food that helps good bacteria grow. These good bacteria are the **probiotics**, live microorganisms that can improve our health. A new frontier is represented by **postbiotics**, the metabolic products released by bacteria during the digestion of food — the true mediators of our well-being.

When we think about dietary supplementation, we can imagine **prebiotics** as the seed that helps **probiotics** (the tree) grow, which in turn produces the **postbiotics** — the fruit. Each of these supplements can be useful, but their timing and effectiveness depend on the individual’s starting condition. In any case, maintaining a **varied and balanced diet** remains essential.

Fecal microbiota transplantation is a fast way to replace a dysbiotic microbiota. It is already an established treatment for infections caused by *Clostridioides difficile*, a hospital-acquired infection. These bacteria circulate in healthcare settings and are often multi-resistant to antibiotics, making them extremely difficult for patients to eradicate. Through microbiota transplantation, however, it is possible to restore balance, inhibit bacterial overgrowth, and help patients return to normal health. At present, it is performed only in a few major hospitals, as it is considered equivalent to an organ transplant due to the potential toxicity of the material, which depends on the donor, and the possible risk of pathogen transmission. For this reason, donor material must undergo very rigorous screening.

Fecal microbiota transplantation is now being tested for many other conditions, including neurological disorders, but results are still not conclusive, and to enhance the efficacy of cancer immunotherapy.

It has been observed indeed that some cancer patients who respond to immunotherapy have a microbiota composition different from those who do not respond. Moreover, when microbiota from responding patients is transplanted into non-responding patients, around 40% of the latter begin to respond to treatment. This provides clear evidence that the microbiota plays a fundamental role in the response to immunotherapy.

In our own work, we have shown that certain **postbiotics** can make tumor cells visible again to the immune system, thereby enhancing the effectiveness of immunotherapy. We are now conducting several clinical studies across different types of cancer to demonstrate their efficacy in patients as well.

Hence, the microbiota is emerging as a true ally to our well-being, and its modulation is poised to revolutionize medicine within the framework of precision medicine.