Immunity: CNIC scientists discover how the gut modulates the development of inflammatory conditions

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Scientists at the CNIC have discovered how gut bacteria that cross a weakened intestinal barrier induce changes in bone marrow that strengthen the immune response

A study led by David Sancho at Centro Nacional de Investigaciones Cardiovasculares (CNIC) in Madrid reveals how an increase in intestinal permeability allows the natural gut bacteria to cross the intestinal barrier and reach the bone marrow, where they induce epigenetic changes—modifications that alter gene activity without affecting DNA sequence—in the stem cells that give rise to immune cells. The epigenetic changes induced by the translocated gut bacteria generate “trained” immune cells primed to respond more efficiently to future infections. However, this same ability to amplify the immune response can also aggravate the inflammatory conditions such as cardiovascular and neurodegenerative diseases. The new study highlights the key role in this process of a protein called Mincle, expressed in cells of the innate immune system.

The study is published in the journal *Immunity* and was conducted in collaboration with research teams led by José Luis Subiza (Inmunotek S.L., Alcalá de Henares), Carlos del Fresno (IdiPaz, Madrid), Salvador Iborra (Universidad Complutense de Madrid) and Juan Duarte (Universidad de Granada).

Trained immunity, explained David Sancho, who leads the Immunobiology lab at the CNIC, allows macrophages and other cells of the innate immune system to respond more efficiently to future encounters with bacteria, fungi, or viruses. “The protection this mechanism provides against viral and fungal infection has been demonstrated in animals with heightened intestinal permeability, which resulted in a stronger inflammatory response and greater resistance to infection.”

Until very recently, scientists believed that specific—or adaptive—immunity was the only type with memory, able to generate cells that ‘remember’ previous encounters with pathogens and unleash a specific immune response. In contrast, the innate immune response, which is not specific to a particular pathogen, was believed to lack memory. “We now know that innate immunity can be ‘trained’ to produce a stronger response to later, unrelated infections. What is more, the effects of this training are long-lasting,” explained Dr. Sancho.

First author **Iñaki Robles** added that, “the main intestinal bacteria we find in the bone marrow is *Enterococcus faecalis*. These bacteria interact with and activate Mincle in hematopoietic precursors, inducing epigenetic changes that generate immune cells with an augmented inflammatory capacity.” [*Enterococcus faecalis* is a Gram-positive bacterial species that lives in the gastrointestinal tracts of humans and other mammals and can cause difficult-to-treat infections in humans, especially in hospital settings].

A double-edged sword

Although trained immunity can help the fight against infection, it can also contribute to the development of inflammatory diseases. As David Sancho warned, “cardiovascular conditions such as atherosclerosis, and also neurodegenerative diseases, are linked to trained immunity, and these conditions can worsen when this process is exacerbated by elevated intestinal permeability.”

In animal models, increased intestinal permeability causes colonic inflammation (colitis). This inflammatory reaction does not occur in mice engineered to lack Mincle, suggesting that the detection of translocated bacteria by Mincle plays an important role in the inflammation associated with trained immunity. Strategies aimed at blocking Mincle could thus be protective in the context of these systemic inflammatory diseases.

A poor diet (especially a high intake of processed foods), excessive alcohol consumption, chronic stress, and some medicines can all weaken the intestinal barrier and promote bacterial translocation. Maintaining a balanced diet rich in fruit and vegetables helps to maintain a healthy intestine, reduce systemic inflammation, and prevent chronic diseases.

The findings of the study open new routes to understanding the relationship between gut health and systemic diseases, underlining the importance of a healthy diet and a balanced microbiota as key

elements in disease prevention.

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