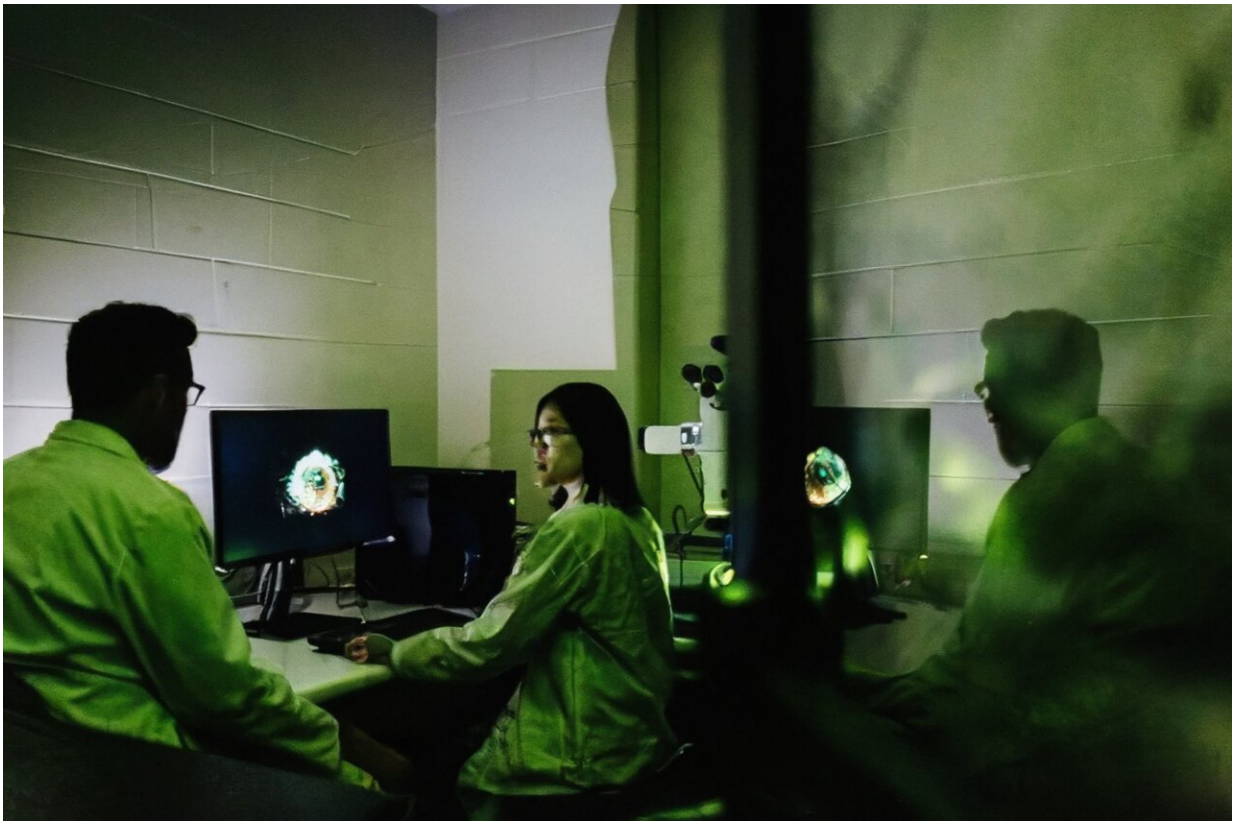
Study uncovers how the gut's microbiome boosts immune development

October 11 2023, by Betty Zou



Arthur Mortha, left, and Pailin Chiaranunt led new research that unveils new insights into how our resident gut microbes influence immune development. Credit: Mark Bennett

A study is shedding new light on how the gut's microbial communities contribute to a well-functioning immune system and defend against

harmful pathogens.

The findings, published in the journal *Science Immunology*, include important insights on how monocytes, a type of white blood cell, transform into macrophages, which play a key role in eliminating foreign microbes and initiating an immune response.

Lead author Pailin Chiaranunt, a Ph.D. student in the department of immunology at University of Toronto's Temerty Faculty of Medicine, says she first learned about the microbiome as an undergraduate student and then fell in love with immunology as a research technician.

"The fact that there are these vast ecosystems of bacteria, fungi, viruses and other microbes living inside us really reshaped the way I see the human body," Chiaranunt says.

In the study, the researchers turned their attention to macrophages, key immune cells whose job is to gobble up cellular debris and foreign microbes and kick start the immune response.

They found that the transformation of monocytes, a type of white blood cell, into macrophages in the gut requires both a diverse microbiome and a host factor called CSF2. Then, in a series of experiments, Chiaranunt and her colleagues identified the microbial factor driving macrophage development as ATP, a molecule that is used as energy currency across all forms of life.

Their work also uncovered how microbial and host factors work together to support a robust immune environment in the gut: ATP produced by resident bacteria in the gut activates immune cells within a network of small, lymph node-like structures across the intestinal tract. These cells then produce the host factor CSF2 which spurs monocytes in the structures to become response-ready macrophages.

The researchers further showed that the macrophages born from this pathway have high metabolisms and as a result, produce a lot of antimicrobial chemicals called reactive oxygen species. The abundance of these chemicals, in turn, contribute to the immune system's ability to ward off microbial intruders in the gut.

"That was a really cool finding because it suggests a new way in which microbial metabolism can directly impact immune cell metabolism," says Chiaranunt, who recently defended her Ph.D. thesis and is preparing to start a postdoctoral fellowship at the University of California, San Francisco.

The collection of microorganisms that live in and on our bodies plays a critical role in health and disease. Certain microbiome features—for example, whether there is more of one species or less of another—have been linked to a variety of health outcomes, from autoimmune and mood disorders to cancer risk and treatment response.

Chiaranunt says her interest in how the microbiome and immune system interact with each other, particularly in the gut, led her to U of T to pursue a Ph.D. with Arthur Mortha, an associate professor of immunology in the Temerty Faculty of Medicine who studies the crosstalk between the immune system and gut microbiome.

"The gut is probably one of the most dynamic ecosystems in the body because you essentially have the outside environment inside of you," Chiaranunt says. "There's a lot of work the immune system must do to maintain a balance between tolerating helpful microbes, food and other outside factors, and being able to mount an effective defense against pathogens like salmonella that might show up."

In addition to other members of Mortha's lab, the study also included collaborators Slava Epelman, a scientist at the Toronto General Research

Institute, University Health Network and clinician scientist in U of T's department of medicine in the Temerty Faculty of Medicine, and Thierry Mallevaey, an associate professor of immunology in the Temerty Faculty of Medicine. Mortha, Epelman and Mallevaey are all members of the Emerging and Pandemic Infections Consortium, a U of T Institutional Strategic Initiative focused on developing innovative responses to infectious threats.

While other studies have also found a link between the microbiome and macrophage development, the researchers' recent paper is one of the first to uncover how gut bacteria trigger white blood cells to become macrophages. The identification of CSF2 as a key contributor to that process also highlights the potential of CSF2-targeting treatments to modulate the immune response in people with autoimmune disorders and inflammatory bowel disease.

"Our results bring us a big step closer to understanding the biochemical language spoken by the microbiota," says Mortha. "Assembling a comprehensive dictionary for this language will help us to interpret when and why friendly and offensive messages are used by gut microbes to communicate with our immune system."

More information: Pailin Chiaranunt et al, Microbial energy metabolism fuels an intestinal macrophage niche in solitary isolated lymphoid tissues through purinergic signaling, *Science Immunology* (2023). DOI: 10.1126/sciimmunol.abq4573

Provided by University of Toronto

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