LUXEMBOURG INSTITUTE OF HEALTH

PRESS RELEASE

For immediate release

Luxembourg, 7th August 2024

Getting to the "guts" of intestinal immune defence

LIH study unveils the key role of antioxidants and metabolism in gut immunity

In a revolutionary new study, Professor Dirk Brenner's research group from the Department of Infection and Immunity (DII) at the Luxembourg Institute of Health (LIH) revealed the essential role of antioxidants produced by immune cells in protecting against bacterial infections that affect the gastrointestinal tract. These unprecedented results, which open up new therapeutic strategies for gastrointestinal disorders based on the modulation of immune cell metabolism, were published in the prestigious journal Cell Metabolism and selected to be featured as the cover story of its August issue due to their significance.

The human body exhibits special immune cells called T helper (Th) cells that are essential for mediating effective immune responses. One type of Th cells, known as Th17, play a vital role in protecting the lining of the gastrointestinal (GI) tract, helping balance the "friendly" bacteria in the gut while also defending against harmful germs. These immune cells produce a substance called interleukin 22 (IL-22), which triggers the release of proteins that kill harmful microbes and protect the gut lining from damage caused by certain bacteria. This helps keep the intestinal barrier strong and healthy, ensuring our overall well-being. Accumulation of reactive oxygen radicals (ROS), commonly known as oxidative stress, is known to significantly contribute to inflammation-related diseases in the gut. The researchers at the LIH especially focussed on how T cells protect themselves against these detrimental molecules and how this influences the outcome of gastrointestinal infections.

"*A damaged and excessively permeable mucosal gut layer is the hallmark of inflammatory bowel disease (IBD). T cells are important to protect our mucosal surfaces, but are however sensitive to accumulating oxidative stress, which makes antioxidant-mediated defence mechanisms an area of extreme interest in the fight against this debilitating syndrome. Our aim was therefore to shed light into these currently poorly understood processes*", says Prof Dirk Brenner, head of Experimental & Molecular Immunology at the DII, and leader of the study.

To neutralise excess oxidative stress, T cells produce antioxidant molecules to maintain their oxidative balance and their function in the GI tract. Using a sophisticated genetic approach, the scientists unravelled a complex mechanism that links the control of these reactive molecules to the regulation of intracellular metabolism, which is crucial for the protective function of Th17 cells in the gut. "*Our study significantly contributes to understanding how environmental changes, often associated with the accumulation of oxidative stress, can alter the metabolism of immune cells and affect their protective functions,*" explains Prof Brenner. "*In simpler terms, we have uncovered how these gut-protective cells operate under stress. Understanding these complex mechanisms is crucial as we face a significant rise in inflammatory and autoimmune diseases in all modern societies".*

The study found that, in the absence of antioxidants in T cells, a bacterial infection in the gut induced oxidative stress, which disrupted the functioning of mitochondria – the cell's energy factories – leading

to a decreased energy production. "*In principle, without antioxidants our protective T cells run out of fuel – in situations when they need fuel to execute their protective function*" explains Dr Lynn Bonetti, former doctoral candidate in Prof Brenner's group at the LIH and first author of the study. This in turn impaired a series of further cellular reactions, ultimately leading to the reduced production of certain immune modulators by Th17 cells in response to a bacterial infection. The result was a poor ability to kill the pathogen, with ensuing enhanced damage to the gut lining, inflammation and consequent high mortality in pre-clinical models. *"Controlling oxidative stress and mitochondrial metabolism, which are linked to the intracellular processes that lead to the secretion of protective molecules such as IL-22 by Th17 cells, is essential for maintaining gut integrity*. *When these processes are compromised by environmental factors like oxidative stress, this protective function is lost, leading to gut leakage. This increased gut permeability allows bacteria to spread throughout the body, potentially resulting in sepsis"*, explains Prof Brenner. *"Indeed, in line with our findings, we were able to treat the infection by giving IL-22 either directly or by genetically reconstituting IL-22 in T cells, which helped clear the infection and prevented intestinal damage"*, added Dr Bonetti.

These findings bear important implications for human health. Indeed, an impaired intestinal barrier function, increased oxidative stress and decreased antioxidant capacity are known to be linked to chronic inflammation in patients suffering from inflammatory bowel disease like Crohn's disease or ulcerative colitis. In line with this, the research team further showed that gut lining integrity is positively influenced by antioxidants by analysing data from ulcerative colitis patients, thereby providing evidence for exploring antioxidant treatment as a strategy to regulate Th17-derived IL-22 production in GI disorders.

"*Our research highlights a critical but previously overlooked connection between antioxidants produced by Th17 cells, mitochondrial function and the production of protective immune modulators like IL-22 for optimal gut health and protection against gut infections. It also shows how slight impairments at the mitochondria can lead to detrimental physiological outcomes"* says Prof Brenner. *"Understanding the relationships between metabolism and immune cell function opens up exciting new avenues for the treatment of inflammatory gastrointestinal and autoimmune diseases*", concludes Prof Brenner, whose research group belongs to the leading laboratories in the innovative field of immunometabolism in Europe.

The study was published in the August 2024 issue of *Cell Metabolism* with the full title "A Th17 cell-intrinsic glutathione/mitochondrial-IL-22 axis protects against intestinal inflammation".

Funding and collaborations

The research was carried out in collaboration with the Luxembourg Centre for Systems Biomedicine (LCSB); the University of Luxembourg; the Laboratoire National de Santé (LNS); the University of Zurich (Switzerland); the Center for Fundamental Immunology, Benaroya Research Institute (US); the Yale School of Public Health (US); the Wilmot Cancer Institute, University of Rochester Medical Center (US); the University Düsseldorf (Germany); and the Johannes Gutenberg-University Mainz (Germany). It was funded by the Luxembourg National Research Fund (FNR) through several FNR-ATTRACT, FNR-CORE, FNR-PRIDE, FNR-PEARL and FNR-RIKEN grants; by the Fondation Cancer Luxembourg; by FNRS-Televie grants; and by numerous other prestigious international funding bodies.

About the Luxembourg Institute of Health (LIH)

The Luxembourg Institute of Health (LIH) is a public biomedical research organisation focused on precision health and invested in becoming a leading reference in Europe for the translation of scientific excellence into meaningful benefits for patients.

The LIH places the patient at the heart of all its activities, driven by a collective obligation towards society to use knowledge and technology arising from research on patient derived data to have a direct impact on people's health. Its dedicated teams of multidisciplinary researchers strive for excellence, generating relevant knowledge linked to immune related diseases and cancer.

The institute embraces collaborations, disruptive technology and process innovation as unique opportunities to improve the application of diagnostics and therapeutics with the long-term goal of preventing disease.

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