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Press Release

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LIH scientists discover an unknown immune mechanism

Master detox molecule boosts immune defences

Scientists of the Luxembourg Institute of Health (LIH) have discovered a so far unknown molecular mechanism by which the human immune system activates its immune cells: T cells, a particular type of white blood cells, effectively ward off pathogens if a gene known as Gclc is expressed within them. The Gclc gene encodes a protein instrumental for the production of a substance called glutathione – a molecule that was previously known only to eliminate harmful waste products of metabolism such as reactive oxygen species and free radicals. A team led by LIH researcher Prof Dirk Brenner, FNR ATTRACT fellow and Head of the Experimental & Molecular Immunology research group at the Department of Infection and Immunity, has discovered that glutathione also stimulates T cells' energy metabolism. This way, when in contact with pathogens, T-cells can grow, divide and fight off intruders such as viruses. Glutathione is thus an important molecular switch for the immune system. This discovery offers starting points and perspectives to develop new therapeutic strategies for targeting cancer and autoimmune diseases.

The scientists publish their findings today in the world's most prestigious immunology journal, "Immunity" (DOI: 10.1016/j.immuni.2017.03.019.).

"*Our body has to keep our immune system in a carefully balanced equilibrium*", says Prof Dirk Brenner. "*If the body's innate defences are overactive, then they turn against the body. This is what happens in autoimmune diseases like multiple sclerosis or arthritis, for example. However if the defences are too weak, then infections cannot be handled or body cells can proliferate uncontrolled and grow to form tumours, which can become life threatening*." Immune cells such as T cells therefore normally reside in a state of alert hibernation, with their energy consumption reduced to a minimum. If pathogens or parts thereof dock onto their outer envelope, then the T cells wake up and boost their metabolism. This necessarily creates greater amounts of metabolic waste products, such as reactive oxygen species (ROS) and free radicals, which can be toxic for the cells.

When the concentration of these oxidants increases, the T cells have to produce more antioxidants so as not to be poisoned. No previous research group had studied the mechanism of action of antioxidants in T cells to great detail before. In exploring this phenomenon, Prof Brenner's team discovered that the antioxidant glutathione produced by T cells serves not only as a garbage collector to dispose of ROS and free radicals, it is

also a key switch for energy metabolism that controls the immune response, and is thus of high relevance to various diseases. "*These fascinating results form a basis for a targeted intervening in the metabolism of immune cells and for developing a new generation of immunotherapies*," explains Prof Markus Ollert, Director of LIH's Department of Infection and Immunity.

For their investigations, the scientists employed genetically modified mice in whose T cells the Gclc gene was removed and therefore these cells could not produce glutathione. "In these mice, we discovered that the control of viruses is impaired – mice that lack the Gclc gene have an immunodeficiency. But by the same token, this also meant the mice could not develop any autoimmune disease such as multiple sclerosis." Further tests performed by Prof. Brenner's team demonstrated the reason for this: "*The mice cannot produce any glutathione in their T-cells,*" Prof Brenner continues, "*and so a number of other signalling events that directly boost metabolism and increase energy consumption are lacking*." As a result, without glutathione, T-cells do not become fully functional; they remain in their state of hibernation and no self-destructive autoimmune response occurs. Prof Karsten Hiller from the Braunschweig University of Technology who collaborated with the Luxembourgish scientists adds: "*It is intriguing to see that cellular metabolism and immune activation are so tightly entangled and that a fine-grained interplay is essential to achieve a correct function.*"

Prof Brenner sees his T cell experiments as a prelude to more in-depth investigation of the energy balance of immune cells in general. A number of different autoimmune diseases, for example, are related to malfunctions in various subgroups of T cells. "*If we understand the differences in the molecular mechanisms by which they stimulate their metabolism during defensive or autoimmune responses, then we can discover clues as to possible attack points for therapeutic agents regulating the immune response.*" The distinguished researcher sees a similar situation in cancer: "*In this context too, it is important to know why the immune cells that are actually supposed to fight cancer cells drop to a low metabolic state and in some cases even actively suppress an immune response against the tumour. Counteractive metabolism-stimulating measures could make the immune cells work more efficiently and fight off cancer more effectively.*"

In follow-up projects, the researchers are planning to gain new indications for potential sites of therapeutic interventions. The groups from Luxembourg and Braunschweig are currently applying for new research funding for a joint project supported by the German Research Foundation (DFG) and the Luxembourg National Research Fund (FNR).

Involved research teams

Prof Dirk Brenner is the Deputy Head of Research & Strategy at LIH's Department of Infection and Immunity. He received a prestigious ATTRACT Consolidator grant from the Luxembourg National Research Fund (FNR), in 2015 to set up the Experimental & Molecular Immunology research group. The FNR-ATTRACT programme supports the national research institutions by expanding their competences in strategic research areas – by attracting outstanding young researchers with high potential to Luxembourg.

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The present study was performed in close collaboration with the former FNR ATTRACT fellow Prof Karsten Hiller from the Metabolomics Group at the Luxembourg Centre for Systems Biomedicine of the University of Luxembourg (now full Professor at the Integrated Centre of Systems Biology (BRICS) of the Braunschweig University of Technology, Germany) and with Prof Tak W. Mak the Director of the Campbell Family Institute for Breast Cancer Research at the University of Toronto, Canada.

About the Luxembourg Institute of Health: Research dedicated to life

The Luxembourg Institute of Health is a public research organisation at the forefront of biomedical sciences. With its strong expertise in population health, oncology, infection and immunity as well as storage and handling of biological samples, its research activities are dedicated to people's health. At the Luxembourg Institute of Health, more than 300 individuals are working together, aiming at investigating disease mechanisms and developing new diagnostics, innovative therapies and effective tools to implement personalised medicine. The institution is the first supplier of public health information in Luxembourg, a strong cooperation partner in local and international projects and an attractive training place for ambitious early-stage researchers.

About the Department of Infection and Immunity

LIH's Department of Infection and Immunity is a basic clinical-translational research entity aiming at understanding the complex mechanisms of infectious and inflammatory disease processes to enable new ways to diagnose, prevent and cure human diseases. Building on a highly interdisciplinary research environment, the research strategy of the Department of Infection and Immunity focuses on experimental discovery and validation, bridging to clinical application and technology development to address major unsolved medical needs in the areas of immune-mediated inflammation (such as in allergy, asthma, autoimmunity), cancer and infectious diseases (AIDS, measles and rubella virus infection, amongst others).

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