Master detox molecule boosts immune defenses

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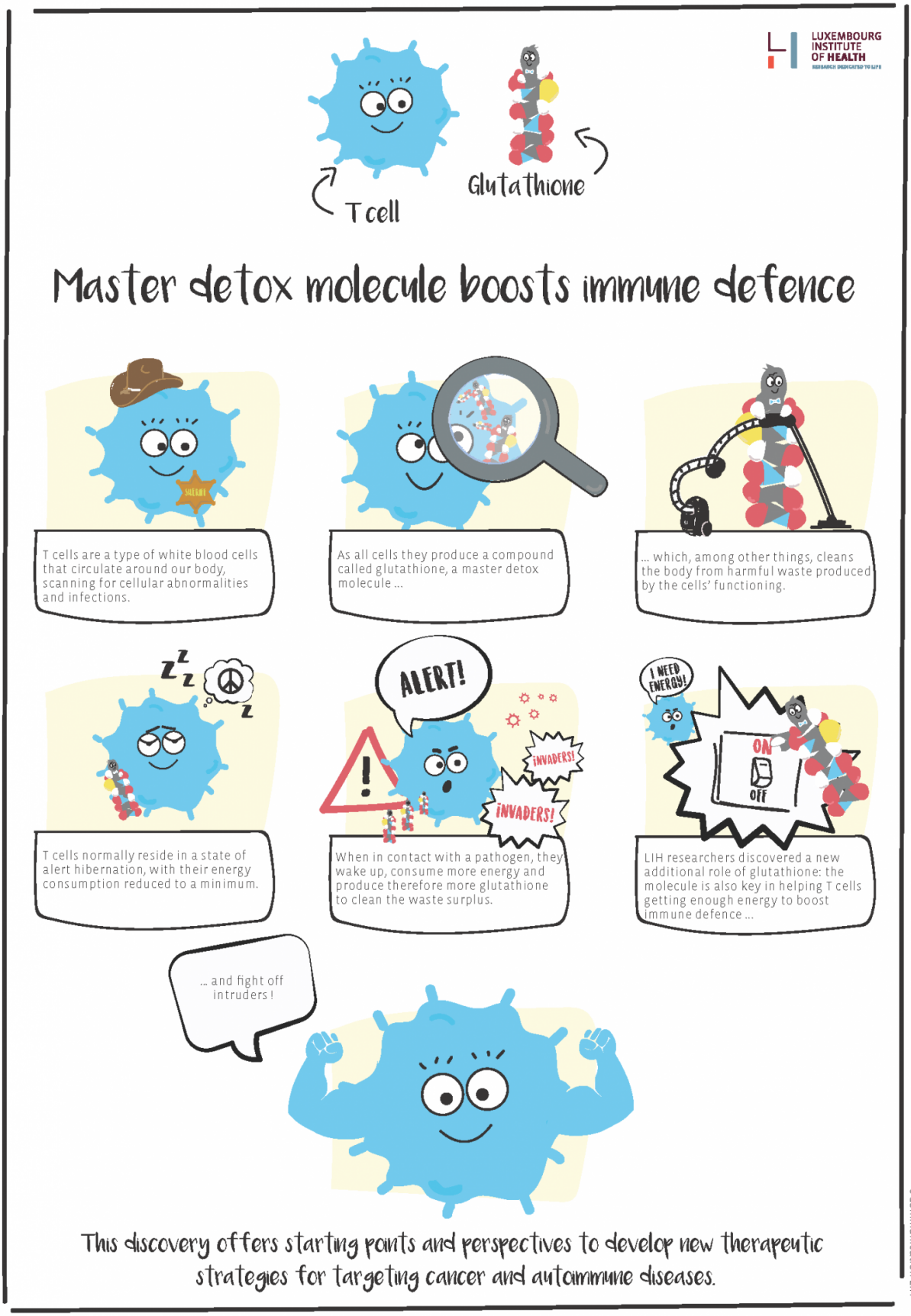
LUXEMBOURG INSTITUTE OF HEALTH
RESEARCH DEDICATED TO LIFE
T cell
Glutathione
Master detox molecule boosts immune defence
T cells are a type of white blood cells that circulate around our body, scanning for cellular abnormalities and infections.
As all cells they produce a compound called glutathione, a master detox molecule ...
... which, among other things, cleans the body from harmful waste produced by the cells' functioning.
T cells normally reside in a state of alert hibernation, with their energy consumption reduced to a minimum.
ALERT!
INVADERS!
INVADERS!
When in contact with a pathogen, they wake up, consume more energy and produce therefore more glutathione to clean the waste surplus.
I NEED ENERGY!
ON
OFF
LIH researchers discovered a new additional role of glutathione: the molecule is also key in helping T cells getting enough energy to boost immune defence ...
... and fight off intruders !
This discovery offers starting points and perspectives to develop new therapeutic strategies for targeting cancer and autoimmune diseases.
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Scientists of the Luxembourg Institute of Health (LIH) have discovered an unknown molecular mechanism promoting the activation of the human immune system. The team has been studying the glutathione molecule known for its role in cleaning the body from harmful metabolic wastes and revealed that glutathione also stimulates T cells energy metabolism. This discovery offers perspectives to develop new therapeutic strategies for targeting cancer and autoimmune diseases. Credit: Communication LIH

Scientists at the Luxembourg Institute of Health (LIH) have discovered hitherto unknown molecular mechanism by which the human immune system activates its immune cells. T cells that express a gene known as Gclc effectively ward off pathogens. 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 has discovered that glutathione also stimulates T cell energy metabolism. 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 published their findings in the journal *Immunity*.

"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 they cannot handle infections, or body cells can proliferate uncontrolled and to form

tumours, which can become life threatening."

Immune cells such as T cells therefore normally reside in a state of alert hibernation, with minimal energy consumption. If pathogens or parts thereof dock onto their outer envelope, then the T cells activate 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 in great detail. 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 multiple 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 Professor Markus Ollert, Director of LIH's Department of Infection and Immunity.

For their investigations, the scientists employed mice that were genetically modified such that their T cells did not express Gclc and thus 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 signaling 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 a state of hibernation and no self-destructive autoimmune response occurs. Prof Karsten Hiller from the Braunschweig University of Technology 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 autoimmune diseases 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.

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