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A new signaling pathway of the immune system is elucidated

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A new signaling pathway, which is important for the regulation of the immune response and inflammation, was discovered by an international team of scientists led by prof Ivan Dikic from the Goethe University, Frankfurt, Germany. The scientists studied the involvement of ubiquitin, a universally present signaling protein in the cell. In today's issue of the scientific journal "*Nature*" the scientists report a novel type of modified ubiquitin chains involved in regulation of various processes within the cell.

The researchers have shown that linear ubiquitin, where ubiquitin proteins are attached to each other in a head to tail fashion, regulates signaling cascades initiated by cytokine receptors at the cell membrane. Cytokines are essential for the proper immune response – e. g. tumor necrosis factor (TNF-alpha) alpha is released mainly by the macrophages and plays an important role in local and body-wide inflammation.

When a cytokine docks on the receptor of a cell, it induces a signaling cascade in many cell types, which transmits a signal to the nucleus – the DNA centre of the cell. After cytokine activation of its receptor, the linear ubiquitin ligase complex (LUBAC), which links ubiquitin into head-to-tail chains, is activated at the start of this cascade. This enzyme stimulates nuclear factor kappaB (NF-kappaB), which coordinates the expression of important genes for the immune response, including the production of antibodies. However, how the molecules of this cascade function in detail and which structures interact is still under investigation.

The Dikic group solved an integral part of this puzzle. Sharpin, a protein containing a Ubiquitin-like and Ubiquitin-binding domain (UBD), constitutes a key component of the linear Ubiquitin ligase complex. Using animal models, they show that a lack of Sharpin causes heavy inflammation of numerous organs and in particular the skin. This is characterized as chronic proliferative dermatitis with death of keratinocytes, the predominant cells of the epidermis in charge of protecting the skin against environmental damage. This effect is dependent on the TNF signaling pathways.

The research reported allows us to reshape our thinking about how chronic proliferative dermatitis arises in humans, as well as opening new avenues of therapeutic intervention in the TNF-alpha signalling pathway. Moreover, a potential source of this disease may arise from mutations in a critical region of the linear ubiquitin ligase complex (LUBAC) allowing identification of patients that may respond well to targeted therapy. "In patients suffering from chronic proliferative dermatitis with unclear origin, it is now possible to specifically look for a mutation in LUBAC components", suggests Ivan Dikic.

Provided by Goethe University Frankfurt

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