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An immune defence guide

Which cellular processes ensure that immune responses are controlled precisely? A new study by the Institute of Cell Biology and Immunology Thurgau (BITG) and the University of Konstanz decodes a decisive signalling pathway.

Our body receives and processes a vast number of signals. Chemical signals serve as guidance cues and ensure, for example, that immune cells arrive exactly where they are needed. Many vital processes such as sensory perception, immune responses, cardiovascular function and communication between neurons are regulated by a large group of proteins on the cell surface: G protein-coupled receptors (GPCRs) pick up signals from the environment and transmit them to the cytoplasm of the cell. "Because such a large number of drugs act on GPCRs, it is key that we have a comprehensive understanding of how they work, such that we understand diseases better and develop more targeted therapies to treat them", explains Daniel Legler, head of the Kreuzlingen-based Institute of Cell Biology and Immunology Thurgau (BITG), an associated institute of the University of Konstanz and a legal entity of the Foundation for Science and Research of the Canton Thurgau (TSWF). Research on GPCRs can help to make drugs more effective and reduce their side effects.

Chemical signals show immune and cancer cells the way

For good health, it is essential that immune cells reach the parts of our body that need them. Once there, they fight infections, regulate inflammation or contribute to the healing process in damaged tissue. To find their way through the body, immune cells use chemical signals from their environment – or "chemokines" – for orientation. The chemokines thus act as guidance cues.

The surface of immune cells contains chemokine receptors from the family of GPCRs that detect the chemical signals and use them to steer cell movement. Once their work is done, the chemical signals must be removed from the tissue. This is a task for a new family of GPCRs: the atypical chemokine receptors. It is via these atypical receptors that tissue cells take superfluous chemokines inside the cell for degradation. Atypical chemokine receptors thus fulfil two essential functions: They shape chemokine gradients in tissues that help guide immune cells, and they dispose of corresponding chemical signals after a successful immune response to a pathogen.

This is particularly relevant, since cancer cells also use chemokines to migrate into lymphoid organs and to form metastases. "We want to understand these processes better since abnormal cell migration contributes to chronic inflammation, autoimmune diseases or the spread of cancer, for example", says Oliver Gerken, first author of the study.

Signal transmission within cells

Against this backdrop, research has begun to focus increasingly on understanding the signal transmission processes taking place inside cells, instead of focusing on the cell surface only. A study conducted at the BITG has now decoded the signalling pathway of the atypical chemokine receptor ACKR4 responsible for the internalization and degradation of chemokines that are no longer needed. "We found that ACKR4 continuously traffics back and forth between the cell surface and different organelles within the cell. Every time the receptor reaches the cell's surface, it binds a chemokine and takes it along into the cell where it is degraded", explains Professor Daniel Legler, who led the study funded by the Swiss National Science Foundation (SNF).

The research team including Gerken and Legler also identified signalling proteins that interact with ACKR4 and thus accelerate the uptake of the messengers. In addition, the study shows that the signal transduction pathways of ACKR4 do not correspond to prevailing dogmas but rather follow a mechanism that had remained unknown until now. This lays the groundwork for future research on the complex and diverse mechanisms of these receptors, the authors of the study published in Nature Communications say. Overall, this work contributes to better understanding atypical chemokine receptors in particular, and GPCRs in general, while generating new insights into key signal processing within cells.

Original publication:

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Further information

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