Keeping viruses at bay: How our organism definitively detects RNA viruses

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This image depicts Marion Goldeck, Dr. Martin Schlee (sitting), Dr. Winfried Barchet, Thomas Zillinger and Prof. Dr. med. Gunther Hartmann, Director of the Institute of Clinical Chemistry and Clinical Pharmacology of the University of Bonn Hospital. Credit: (c) Claudia Siebenhener/UKB

Our immunosensory system detects virus such as influenza via specific characteristics of viral ribonucleic acid. Previously, it was unclear how the immune system prevents viruses from simply donning molecular

camouflage in order to escape detection. An international team of researchers from the University of Bonn Hospital and the London Research Institute have now discovered that our immunosensory system attacks viruses on a molecular level. In this way, a healthy organism can keep rotaviruses, a common cause of diarrheal epidemics, at bay. The results have been published in the renowned journal *Nature*.

Every day our bodies are confronted with a variety of viruses and other pathogens. Our immune systems must constantly decide what is "foreign" and what is part of the body itself so that the body's own cells are not inadvertently attacked by its own defense troops. Viruses imitate the body's own structures and thus represent a special challenge for the immune system. In this way, the immune system works like a sensory organ which continuously detects dangers and initiates the appropriate defense mechanisms. This immunosensory system searches for viruses by surveilling the body's own ribonucleic acid (RNA) for RNA with characteristics typical of viruses. In RNA viruses, RNA is the carrier of the virus's genetic information. To reproduce, viruses must multiply their RNA, and this multiplication leads to the development of molecular patterns which are in turn used to detect the viruses themselves.

It has been known for some time that RIG-I-like receptors (RLRs) play a crucial role in the detection of RNA viruses. These receptors act as "fire alarms" within the immune system: When RNA molecules from viruses bind to these receptors, a signal chain is initiated that leads to the production of substances that can ultimately combat the viruses. "During amplification of viral RNA, a so-called triphosphate group, consisting of three phosphates, inevitably develops at one end of the newly formed RNA. A few years ago, we were the first to show that it is this triphosphate group which allows RIG-I to detect newly formed viral RNA. Previously, it was believed that viruses can elude this detection via simple deceptive molecular maneuvers," said Prof. Gunther Hartmann, Director of the Institute of Clinical Chemistry and Clinical

Pharmacology of the University of Bonn Hospital.

RIG-I: A Molecular Attack Against Viruses

Together with scientists from the Immunobiology Laboratory of the London Research Institute in England, the scientists working with Dr. Martin Schlee and Prof. Dr. Gunther Hartmann at the University of Bonn Hospital investigated the immunorecognition of reoviruses. This family includes rotaviruses, which cause serious diarrheal illness and are responsible for the deaths of more than a million children worldwide every year. The immunorecognition of reoviruses was previously unclear since their RNA does not contain a triphosphate group. Now the researchers discovered that, surprisingly, an RNA structure with two phosphates at the end of the RNA double-strand in reoviruses can likewise trigger RIG-I and alarm the immune system.

"This finding has significance for the detection of RNA viruses that extends far beyond reoviruses: It is comparatively simple for a virus to molecularly change the triphosphate in the course of its development," said Dr. Schlee. The first step in this process is generally to split off the outermost phosphate of the triphosphate group, which leads to a diphosphate. This step is necessary for the virus to perform further modifications to its RNA and thus don a molecular cloak of invisibility. However, any form of further molecular camouflage is made extremely difficult for the virus due to the additional highly specialized RIG-I-mediated immunorecognition of the diphosphate. Thus, RIG-I attacks the virus on both fronts, significantly restricting its further development. "Without the investigation into reoviruses, we would not have discovered this universal mechanism of virus detection," said Prof. Hartmann. Since members of the reovirus family also contain a diphosphate group in their viral RNA, a healthy organism can also detect these viruses and curb these illnesses within a few days. However, malnourished children cannot summon these reserves, and the illness can become life-

threatening.

The Immune System: A Sensory System for Health

The researchers see a major application potential in the decoding of virus detection: "We are already currently developing artificially produced copies of viral RNA in order to alert our immune system to viruses in a targeted fashion," said Prof. Hartmann who is also director of the project "Novel Anti-infective Agents" at the German Centre for Infection Research (DZIF).

Prof Hartmann is also currently speaker of the Cluster of Excellence ImmunoSensation, which is supported by a 28-million Euro grant from the German Research Foundation (DFG). The Cluster brings together experts from a variety of disciplines at the site and connects them to international research structures.

More information: Antiviral immunity via RIG-I-mediated recognition of RNA bearing 5'diphosphates, *Nature*, DOI: 10.1038/nature13590

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