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New mechanism that attacks viral infections discovered

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An innovative mechanism that the innate immune system uses to control viral infections has been uncovered by researchers at the University Medical Centers in Mainz and Freiburg. Central to this is the discovery that two different but related elements of the immune system can act together in concert to fight, for example, rotavirus infections. Infection with rotavirus is the most common cause of diarrhea in children around the world. The results of the research have recently been published in the eminent scientific journal *Nature Immunology*.

The innate immune system is able to combat infective pathogens such as viruses, bacteria, and parasites on several levels. Among other things, so-called 'interferons' play an important role in antiviral defense. These are special proteins which are quickly released in response to a viral infection and which can trigger a relevant immune response against the cells under attack. At the same time, so-called 'innate lymphoid cells' (ILCs) are a significant factor in the functioning of the innate immune system. ILCs are mainly active in inner and outer body surfaces where they produce special proteins, in this case interleukins, and thus participate in an early stage of the immune response to infection by viruses, bacteria, and parasites.

The researchers were able to use the example of the rotavirus to demonstrate how such an infection could be very effectively battled. The mechanism involves the interaction of special interferons (interferon-lambda, IFN-λ) with special interleukins (IL-22), the latter of which are expressed by a subgroup of ILCs called ILC3 cells. Rotaviruses are

highly contagious pathogens which cause vomiting and diarrhea. Rotavirus infection is the most frequent cause of diarrhea in children and is responsible for more than 500,000 deaths around the world each year. It attacks the epithelial cells that coat the intestine and damages them.

"We were able to show that interferon-lambda (IFN-λ), although a required factor, is not capable by itself to control rotavirus infection but that the presence of interleukin-22 (IL-22) is also necessary to effectively combat rotavirus," explained Professor Andreas Diefenbach of the Department of Medical Microbiology and Hygiene of the Mainz University Medical Center. The researchers were able to identify the mechanism underlying this synergistic effect. They discovered that both messenger substances act jointly to optimally fight rotavirus by triggering the formation of antiviral proteins particularly in the epithelial cells of the intestine; these effectively prevent the synthesis of new virus particles.

It is already known that the messenger substance interleukin-22 has a variety of functions in immune response reactions, such as, for example, defending the intestines and lungs against bacterial infections. In addition, interleukin-22 makes an important contribution to tissue repair processes in the intestines following damage to the intestinal epithelium following exposure to radiation. "Our new discovery that interleukin-22 acts as a sort of reinforcement for interferon is so exciting because it could have implications for the design of future immunotherapy concepts", said Diefenbach. Interferons are used, for example, in the immunotherapy of often refractory chronic viral infections such as hepatitis.

The researchers postulate that the innovative mechanism in which two components of the innate immune system collaborate effectively in the epithelial cells may have developed in the course of evolution as a

secondary line of immune defense in an environment in which viruses have continually changed and adapted. Because rotavirus is a particular threat to children, the researchers also hope to acquire insight into the functioning of the immune system at the beginning of life before the acquired immune system has had time to fully develop.

More information: P. Hernández et al., Interferon-λ and interleukin 22 act synergistically for the induction of interferon-stimulated genes and control of rotavirus infection, *Nature Immunology*, 25 May 2015, DOI: 10.1038/ni.3180

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