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Press Release



Human against virus – a molecular race **Immunologists discover a novel target to suppress a common virus**

Most people become infected with the human cytomegalovirus (CMV) at some point in life. Over millions of years, our immune system has evolved a trick or two to defend us against this virus, but unfortunately, CMV evolved its own tricks, too. New drugs to target viral genes that counter the immune response might support the immune system in the fight against this widespread virus. The idea was born at the Helmholtz Centre for Infection Research (HZI), where scientists recently defined how CMV keeps infected cells alive, although they should undergo programmed suicide and simultaneously kill off the viruses that grow in them.

While the majority of us are life-long carriers of the herpes virus CMV, the infection is in balance with the immune system and remains asymptomatic in most of us. If the immune system becomes deficient, as is the case in organ transplanted people, or in those with AIDS, CMV can quickly become a serious problem. HZI researchers, along with their colleagues at the Max von Pettenkofer Institute in Munich, have now characterized a novel way in which even the body of severely immunodeficient people may defend itself against the virus. The researchers published their findings in the scientific journal PLOS Pathogens.

It is known that the immune system prompts infected cells to undergo self-destruction. In a process called apoptosis, these cells practically commit suicide. By sacrificing infected cells at an early stage, the body prevents pathogen spreading. The trigger may come from within the cell itself or from neighboring immune cells. HZI immunologists focused on the latter scenario, in which cells receive the suicide signal via "death receptors" on their surfaces. "We have managed to identify the immune cells that send out the signaling molecules, which dock on death receptors," says HZI scientist Dr. Linda Ebermann. This "death signal" originates from macrophages, the immune system's scavenger cells that engulf invading pathogens. Activated macrophages migrate to places of inflammation where virus-infected cells abound. There, they release bioactive molecules, which induce suicide in surrounding cells. Up to now, it was unknown that macrophages contribute to virus control in this way.

Not only did the HZI immunologists identify the source of the signals. They also demonstrated what the viruses' evolutionary response in the molecular arms race with the host looks like. "Viruses are not alive. To replicate, they need a living host cell," Ebermann explains. "Cytomegalovirus forces infected cells to manufacture proteins from viral genes. One of those can suppress the cellular suicide program. That way, the virus can proliferate and spread undisturbed."

In their study, the researchers took advantage of a CMV variant that specifically infects mice. This strain closely resembles the one that infects humans: just as people with a weakened immune system would fall ill if infected with CMV, the murine CMV causes disease in immunocompromised mice, which lack certain components of their immune system. In these mice, the virus successfully shuts down the cellular suicide program with the help of a protein called M36 and thus ensures survival of its host cell. Remarkably, CMV mutants lacking this gene cannot replicate even in extremely susceptible mouse strains,

where a single infectious unit of the wild-type virus would be lethal. Chances are that the human virus may work in the same way. "The proteins that inhibit apoptosis in human and in the mouse model are highly similar. Therefore we can pretty much assume that our findings can readily be applied to humans," explains Prof. Luka Cicin-Sain, head of HZI's Immune Aging and Chronic Infections research group, and assistant professor at the MHH's Institute of Virology.

For the time being, the virus has the upper hand in an immunocompromised person, but the HZI researchers' work has helped to uncover a viral protein which is critical for viral replication and therefore may be a valid target for antiviral drugs. According to Cicin-Sain, "it is conceivable that, with the help of drugs, we may be able to prevent CMV from shutting down the cellular suicide program. In that case, we would deprive the virus of the chance to spread, which would benefit CMV infected patients with an already compromised immune system."

Original publication:

Linda Ebermann, Zsolt Ruzsics, Carlos A. Guzmán, Nico van Rooijen, Rosaely Casalegno-Garduño, Ulrich Koszinowski, Luka Čičin-Šain

Block of Death-Receptor Apoptosis Protects Mouse Cytomegalovirus from Macrophages and is a Determinant of Virulence in Immunodeficient Hosts

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These findings are the first results of the Helmholtz Virtual Institute for Viral Strategies of Immune Evasion (VISTRIE), an international consortium of scientists working at Helmholtz institutes and leading German and international universities that was initiated by HZI scientists led by Prof. Luka Cicin-Sain.

The group "Immune Aging and Chronic Infections" investigates the influence of pathogens on the aging of the immune system. To do so, the researchers are studying infection with cytomegalovirus (CMV).

The Helmholtz Centre for Infection Research (HZI):

The Helmholtz Centre for Infection Research contributes to the achievement of the goals of the Helmholtz Association of German Research Centres and to the successful implementation of the research strategy of the German Federal Government. The goal is to meet the challenges in infection research and make a contribution to public health with new strategies for the prevention and therapy of infectious diseases.

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