Hemorrhagic fevers: Countering inflammation to prevent circulatory failure

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Hemorrhagic fevers are severe viral diseases that are often fatal. Researchers from the University of Basel have now identified messenger substances of the immune system, which in infected mice lead to the development of shock. These results, published in the scientific journal *Cell Host & Microbe*, open up new possibilities for the development of life-saving therapies.

Lassa virus, a member of the arenavirus family, is transmitted from rodents to humans. In West Africa, it causes several tens of thousands of deaths from hemorrhagic fevers every year, in a similar way to Ebola virus. The terminal stage is often characterized by shock. However, little was known about the mechanisms underlying fatal circulatory failure.

Researchers around Professor Daniel Pinschewer from the Department of Biomedicine at the University of Basel now report that a main cause of circulatory failure upon arenavirus infection consists in the excessive inflammatory response triggered by the virus.

Key messenger substances identified

T-cells represent an essential element of our immune system's defense against viral infections. In earlier studies, however, Professor Pinschewer's group found that when infected with Lassa virus, these immune cells paradoxically contribute to the development of disease. The current study used a related arenavirus to decipher the underlying

mechanisms.

Overeager T-cells apparently stimulate scavenger cells to produce large amounts of nitric oxide (NO). Although this is an important defense mechanism in bacterial infections, it does not help to combat viruses. In arenavirus-infected animals, however, NO dilated the blood vessels, leading to an exudation of fluids into tissues and thus to a reduction of the effective blood volume, ultimately leading to circularity failure.

The researchers also discovered that the scavenger cells' production of NO required the messenger substance interferon gamma, which is produced by T-cells. When this messenger substance was blocked, the mice remained susceptible to the viral infection, but did not suffer any circulatory collapse and survived largely unscathed.

Hope for new treatment methods

The treatment options in Lassa virus infection and other viral hemorrhagic fevers are still unsatisfactory. Medications to block interferon gamma and its effects are already being used in humans, and Professor Pinschewer is hopeful that the results of the present study will contribute to the repurposing and successful use of these drugs in the treatment of hemorrhagic fevers.

More information: Interferon-γ-Driven iNOS: A Molecular Pathway to Terminal Shock in Arenavirus Hemorrhagic Fever , *Cell Host & Microbe* (2017). DOI: 10.1016/j.chom.2017.07.008

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