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Hemorrhagic fevers can be caused by body's antiviral interferon response

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Hemorrhagic fevers caused by Lassa, dengue and other viruses affect more than one million people annually and are often fatal, yet scientists have never understood why only some virus-infected people come down with the disease and others do not.

But now, virologists and immunologists at The Scripps Research Institute (TSRI) have found a major clue to the mystery of "hemorrhagic fever" syndromes. In findings reported this week in an Early Edition of the *Proceedings of the National Academy of Sciences*, the team showed that Interferon Type I (IFN-I) immune proteins are key drivers of a viral syndrome in mice that closely mimics these human hemorrhagic fevers.

"Blocking IFN-I signaling in certain genetic mouse strains completely prevented disease signs such as vascular leakage leading to death," said TSRI Associate Professor of Immunology Roberto Baccala, who, with TSRI Professor Michael Oldstone, led this study.

While IFN-I proteins traditionally have been considered essential for an effective antiviral response and are still used to treat some chronic viral infections, the new study suggests that these proteins sometimes do much more harm than good—and that blocking them, or specific biological pathways they activate, might be a good therapeutic strategy against hemorrhagic fevers.

Striking Impact

The discovery arose from the team's recent research with the New Zealand Black (NZB) mouse, an inbred laboratory strain whose overactive immune system leads, in midlife, to an autoimmune condition resembling lupus. Curious to see how a viral infection in early life would affect the mice, the team injected a group of the animals with a much-studied mouse virus called lymphocytic choriomeningitis virus (LCMV).

The parental LCMV Armstrong (Clone 53b) caused no symptoms and was quickly cleared by the NZB mice. But a variant (clone 13) that is efficient at infecting cells and causing a persistent infection—yet still causes only mild disease in most other mouse strains—had a strikingly different impact, showing serious signs of illness. Seven to eight days after infection, all the NZB mice that been injected with clone 13 had died.

Further examination revealed leaky blood vessels, fluid and immune virus-specific T cell infiltration into the lungs, decreased platelet counts and other pathological signs reminiscent of human hemorrhagic fevers.

As the scientists knew, LCMV is a member of the family of viruses that includes Lassa virus, which causes one of world's most common hemorrhagic fevers—with a high fatality rate—in a subset of infected patients. "Lassa virus and LCMV infect the same cell type via the same cell-surface receptor," Baccala said. Lassa virus infects hundreds of thousands of individuals annually, culminating in more than 20,000 deaths per year.

Most people infected with Lassa virus experience only mild illness, yet about 20 percent develop the hemorrhagic syndrome. Dengue virus manifests similarly, causing a hemorrhagic syndrome in only a subset of patients. The pathology seen in the LCMV clone 13-infected NZB mice suggested that they could serve as useful models of these human hemorrhagic syndromes, providing clues to how they develop and

therapeutic stop-points for their treatment.

A New Target

Baccala and his colleagues soon found evidence that the hyperactivity of the NZB mouse antiviral CD8 cytotoxic T cell response is chiefly to blame for its fatal hemorrhagic disease. The researchers observed powerful CD8+ T cells in higher than normal numbers in affected NZB mouse tissues and a greater number of immune-stimulating molecules on the CD8+ cells' surfaces. This CD8+ T cell overreaction damaged the endothelial cells that line pulmonary blood vessels, causing them to become leaky, which in turn led to the fatal buildup of fluid in the lungs.

IFN-I proteins historically have been known as the chief mobilizers of the protective antiviral response. When Baccala and his colleagues blocked IFN-I signaling, up to a day after infection, the CD8+ T cell response was virtually absent, and levels of clone 13 LCMV rose sharply in the NZB mice. Under these conditions, the mice showed no sign of disease and seemed able to tolerate the high viral load indefinitely—implying that the virus itself is virtually harmless when it doesn't prompt an immune reaction.

"We are now working to determine whether we can target IFN-I itself to treat such conditions or whether we need to target the more specific signals, downstream of IFN-I, that cause pathology," said Baccala.

More information: "Type I interferon is a therapeutic target for virus-induced lethal vascular damage," www.pnas.org/content/early/201 … /1408148111.abstract

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