Two genes linked to postpartum immunity revival in women with persistent hepatitis C

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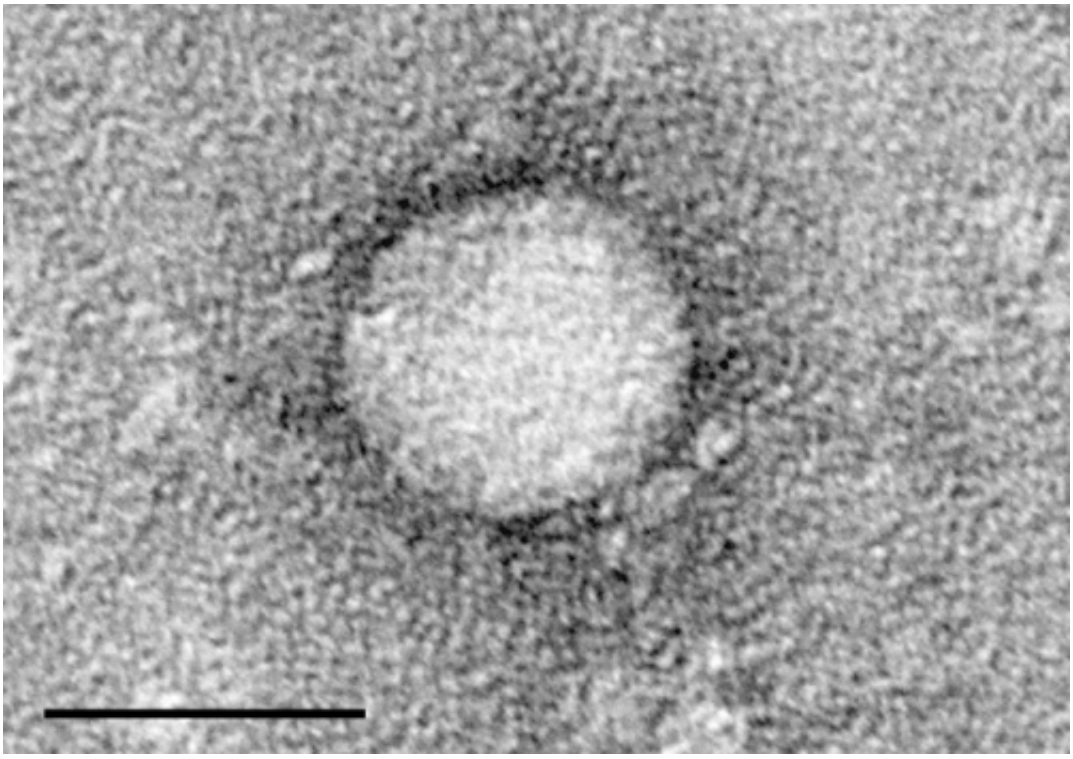

Electron micrographs of hepatitis C virus purified from cell culture. Scale bar is 50 nanometers. Credit: Center for the Study of Hepatitis C, The Rockefeller University.

Alternative forms of two genes are associated with a boost in immunity to hepatitis C after childbirth, a study led by a Nationwide Children's Hospital physician-researcher shows.

At three months postpartum, the number of viruses circulating in the blood declined sharply in most women who carried particular versions of IFNL3 and HLA-DPB1 genes. Mothers lacking these gene variants experienced little change in viral levels after delivery.

The research is published in the *Proceedings of the National Academy of Sciences*. The study focused on hepatitis C, but it may serve as a model for identifying factors that restore immunity to other chronic infections, the researchers suggest.

"Immunity is normally exhausted in people who have chronic hepatitis C. The liver produces about a trillion viruses per day, and the T-cells that should attack the virus don't work," says Jonathan R. Honegger, MD, principal investigator at the Center for Vaccines and Immunity in The Research Institute at Nationwide Children's, and lead study author.

While studying hepatitis C transmission from mother to baby, he noticed that some mothers experienced unusual sharp declines (10-1000 fold) in blood viral levels after childbirth. Women with these viral load declines also had improved T-cell activity against hepatitis C after delivery.

"These initial observations really piqued our interest. There's a lot of effort underway to find ways to turn on exhausted T-cells, and the months following pregnancy appeared to provide a unique opportunity to study this," says Dr. Honegger, who is also assistant professor of clinical pediatrics at The Ohio State University College of Medicine.

Among 34 women in this study, five had consecutive pregnancies. "The postpartum viral load decline was very similar with each consecutive pregnancy, which made you think it wasn't just a random event—that some stable factor was controlling how viremia fell after delivery," Dr. Honegger says.

The team focused on genes.

Interferon lambda 3, a signaling protein that induces antiviral activity, is known to affect control hepatitis C in non-pregnant people. The researchers found that a common variant in the IFNL3 gene also increases the likelihood of controlling hepatitis C after pregnancy.

Human leukocyte antigen (HLA) molecules present small pieces of proteins to T-cells, enabling T-cells to recognize the presence of foreign pathogens such as viruses. The team found that women who possessed particular variants of HLA-DBP1 genes demonstrated greater T-cell recovery and virus control than women lacking these variants. HLA-DPB1 molecules present peptides to a type of T-cell called CD4+ "helper" T-cells. "This finding was important because helper T-cells are thought to be particularly dysfunctional in chronic hepatitis C. These findings suggest that HCV-specific helper T-cells may regain function after delivery. This is now an active line of investigation for us."

Reversal of T-cell exhaustion may also be relevant for controlling other persistent infections such as hepatitis B or HIV, the researchers say.

In another study to be published, the researchers examined effects of the IFNL3 genotype on immune gene signaling after childbirth in un-infected women.

Provided by Nationwide Children's Hospital