

# Study examines ways to restore immunity to chronic hepatitis C infection

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The hepatitis C virus hijacks the body's immune system, leaving T cells unable to function. A new study in animal models suggests that blocking a protein that helps the virus thrive could restore immune function, allowing the body to fight infection. The work, led by teams at The Research Institute at Nationwide Children's Hospital and Emory University, was published online Aug. 26 in the *Proceedings of the National Academy of Sciences*.

Previous studies show that antibody treatments that inhibit the protein, called programmed cell death 1 (PD-1), can shrink tumors in humans. This new work suggests that anti-PD-1 antibodies might be equally effective in treating hepatitis C and other persistent human viral infections, says Christopher Walker, PhD, a senior author on the study and director of the Center for Vaccines and Immunity at Nationwide Children's.

PD-1 is a [regulatory protein](#) that helps keep the immune system in check. Normally, PD-1 acts as a switch to turn off immune responses when an infection is under control. Some viruses such as HCV manipulate the PD-1 off switch so that T [cells](#) lose their ability to fight the infection, a condition scientists call "T-cell exhaustion." The result is life-long persistence of HCV in the liver, which increases the risk of cirrhosis, [liver cancer](#) and other serious diseases.

The researchers treated animal models with persistent HCV infection with repeated doses of an anti-PD-1 antibody. Although the responses

were mixed, one animal did show a dramatic increase in HCV-specific T cell activity in the liver and a sharp decrease in [viral load](#). A closer examination of the data found that the animal had more HCV-specific T cells in the liver before therapy, which could mean that therapeutic success hinges on the amount of HCV-specific T cells in the liver before treatment.

"Our supposition is that these T cells remained in the liver for years at levels too low to detect before treatment, and had the capacity to expand after treatment," Dr. Walker says. "The animal that responded to therapy had a broad, strong response during the early acute phase of infection. This suggests that one predictor of response to an anti-PD-1 antibody is the quality of the T-cell response when the initial infection occurs."

Another interesting finding was the impact of the antibody on CD4+ T cells, helper cells that promote the development of killer T cells called CD8+, which target and destroy virus-infected liver cells. One hallmark of chronic HCV is the collapse of CD4+ cells.

"We have no information on whether PD-1 signaling is a primary mechanism for silencing helper cells, so recovery of the CD4+ helper cell response in this instance provides some indirect evidence that PD-1 signaling also impairs the helper cells," Dr. Walker says.

Because much of the research focus on HCV is now directed at developing antiviral therapies, it's likely that these new findings may have a greater impact on treatments for chronic hepatitis B (HBV), rather than the virus studied in this experiment, Dr. Walker says.

"Chronic hepatitis B is an even larger public health problem than HCV and direct-acting drugs control but do not eliminate the virus," he says. "Immune reconstitution is the holy grail for HBV."

Toward that end, Dr. Walker's team plans to explore the insight this new study provides into why anti- PD-1 antibody therapy sometimes succeeds and sometimes fails. Specifically, they want to know what role the quality of T-cell immunity before treatment plays in therapeutic response.

"There is wide variation in the strength of T-cell immunity when people are first infected with the virus, ranging from very strong and sustained to none," notes Dr. Walker, who also is a professor of pediatrics and molecular virology, immunology, and medical genetics at The Ohio State University.

"Those with very strong sustained responses tend to clear the virus. Anything less, and the virus persists," Dr. Walker says. "This study suggests that if your T-cell response to the initial infection is good, but not enough to clear the virus, then you may respond to PD-1 blockade years later. If your initial acute phase T cell response is limited and weak, there is less opportunity for PD-1 blockade to work."

**More information:** Fuller MJ, Callendret B, Zhu B, Freeman GJ, Hasselschwert DL, Satterfield W, Sharpe AH, Dustin LB, Rice CM, Grakoui A, Ahmed R, Walker CM. Immunotherapy of chronic hepatitis C virus infection with Q:1 antibodies against programmed cell death-1 (PD-1). *Proceedings of the National Academy of Sciences*. Epub Aug. 26, 2013.

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