

'Pep talk' can revive immune cells exhausted by chronic viral infection

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Chronic infections by viruses such as HIV or hepatitis C eventually take hold because they wear the immune system out, a phenomenon immunologists describe as exhaustion.

Yet exhausted [immune cells](#) can be revived after the introduction of fresh cells that act like coaches giving a pep talk, researchers at Emory Vaccine Center have found. Their findings provide support for an emerging strategy for treating [chronic infections](#): infusing immune cells back into patients after a period of conditioning.

The results are published this week in [Proceedings of the National Academy of Sciences](#) Early Edition.

The first author of the paper is Rachael Aubert, a student in Emory's Immunology and Molecular Pathogenesis program who completed her doctorate in 2009. Senior author Rafi Ahmed, PhD, is director of the Emory Vaccine Center and a Georgia Research Alliance Eminent Scholar.

Ahmed's laboratory has extensive experience studying mice infected with lymphocytic choriomeningitis virus (LCMV). Immune responses against LCMV are driven by CD8 or "killer" [T cells](#), which destroy virus-infected cells in the body. But a few weeks after exposure to LCMV, the mice develop a chronic infection that their immune systems cannot shake off, similar to when humans are infected by viruses like HIV and hepatitis C.

Aubert and her co-workers examined what happened to mice chronically infected with LCMV when they infused CD4 or "helper" T cells from uninfected mice. After the infusion, the CD8 cells in the infected mice revived and the levels of virus in their bodies decreased by a factor of four after a month. Like coaches encouraging a tired athlete, the [helper cells](#) drove the killer cells that were already in the infected mice to emerge from exhaustion and re-engage.

The cell-based treatment was especially effective when combined with an antibody that blocks the molecule PD-1, which appears on exhausted T cells and inhibits their functioning. The antibody against PD-1 helps the exhausted T cells to revive, and enhances the function of the helper cells as well: the combination reduced viral levels by roughly ten-fold, and made the virus undetectable in some mice.

"We have not seen this sharp of a reduction in viral levels in this system before," says co-author Alice Kamphorst, a postdoctoral fellow.

The helper cells were all genetically engineered to recognize LCMV, a difference between mouse experiments and potential clinical application. However, it may be possible to remove helper T cells from a human patient and stimulate them so that all the cells that recognize a given virus grow, Kamphorst says.

"This is an active area of research and several laboratories are looking at how best to stimulate T cells and re-introduce them," she says.

In addition, she and her co-workers are examining what types of hormones or signaling molecules the helper cells provide the [killer cells](#). That way, that molecule could be provided directly, instead of cell therapy, she says.

The molecule PD-1 was previously identified by Ahmed and colleagues

as a target for therapy designed to re-activate exhausted immune cells. Antibodies against PD-1 have been undergoing tests in clinical studies against [hepatitis C](#) and several forms of cancer.

More information: R.D. Aubert et al. Antigen-specific CD4 T-cell help rescues exhausted CD8 T cells during chronic viral infection. *PNAS* Early Edition (2011).

Provided by Emory University

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