

Scientists find key to strengthening immune response to chronic infection

August 6 2009

A team of researchers from The Wistar Institute has identified a protein that could serve as a target for reprogramming immune system cells exhausted by exposure to chronic viral infection into more effective "soldiers" against certain viruses like HIV, hepatitis C, and hepatitis B, as well as some cancers, such as melanoma.

Effective response by key [immune cells](#) in the body, called T cells, is crucial for control of many widespread chronic viral infections such as HIV and [hepatitis B](#) and C. Virus-specific [CD8 T cells](#), also known as "killer" T cells, often lose their ability to control viral replication and become less effective over time, a process known as T cell exhaustion. Understanding how optimal antiviral T cell responses are suppressed in these circumstances is crucial to developing strategies to prevent and treat such persisting infections.

In the August 6 on-line issue of *Immunity*, the research team led by Wistar assistant professor E. John Wherry, Ph.D., describes how the protein Blimp-1 (B-lymphocyte-induced maturation protein 1) represses the normal differentiation of CD8 T cells into memory T cells, which recognize disease-causing agents from previous infections and enable the body to mount faster, stronger immune responses. The team also reports that Blimp-1 causes exhausted CD8 T cells to express inhibitory receptors, which prevent recognition of specific antigens, further weakening immune response.

The researchers describe how complete deletion of Blimp-1, which is

overexpressed in CD8 T cells during chronic viral infection, reversed these aspects of T cell exhaustion. By identifying Blimp-1 as a transcription factor associated with T cell exhaustion the findings open the window for reprogramming exhausted killer T cells back into prime infection-fighting form.

"We are very excited by the identification of Blimp-1 as a key transcriptional regulator of T cell exhaustion," says senior author Wherry. "[Transcription factors](#) like Blimp-1 are key molecules involved in global control of cell fate and differentiation, and Blimp-1 in particular prevents cells from de-differentiating or re-differentiating.

"In other words," continues Wherry, "if we want to make an exhausted T cell a more effective soldier against an infection like HIV, we need to change its differentiation state. Much like scientists are now re-programming terminally differentiated tissues cells to become tissue stem cells, the identification of Blimp-1 in terminally differentiated exhausted T cells suggest that future therapeutics could target this molecule to help re-differentiate exhausted T cells into more functional antiviral effector and/or memory T cells."

To determine whether Blimp-1 expression is associated with T cell exhaustion in chronic infection, the team examined Blimp-1 expression in mouse models of acute and chronic lymphocytic choriomeningitis virus (LCMV). In the mice with acute infection, Blimp-1 decreased modestly after the first week of infection. Conversely, Blimp-1 was highly upregulated in CD8 T cells in chronically infected mice by 15 days post-infection, and remained highly expressed for at least one month. The pattern of Blimp-1 expression suggested a correlation between Blimp-1 expression and T cell dysfunction and/or terminal differentiation.

In further studies to explore how Blimp-1 expression affects T cell

differentiation, the team administered LCMV to mice in which a gene encoding Blimp-1 was conditionally deleted. Results showed increased numbers of antigen-specific CD8 T [cells](#), restoration of some key aspects of normal memory CD8 T cell differentiation, and partial restoration of antigen-specific CD8 T cell populations that were otherwise terminally differentiated and deleted during chronic viral infection.

Source: The Wistar Institute

Citation: Scientists find key to strengthening immune response to chronic infection (2009, August 6) retrieved 11 July 2023 from <https://medicalxpress.com/news/2009-08-scientists-key-immune-response-chronic.html>

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