Medical Xpress

Wistar researchers invigorate 'exhausted' immune cells

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In battles against chronic infections, the body's key immune cells often become exhausted and ineffective. Researchers at The Wistar Institute have found a way to restore vigor to these killer T cells by blocking a key receptor on their surface, findings that may advance the development of new therapies for diseases such as HIV, hepatitis B and C, and cancer.

In their study, published online September 15 in the *Proceedings of the National Academy of Sciences* (PNAS), Wistar Institute investigators and colleagues report that using an antibody to block the receptor, known as programmed death-1 (PD-1), dramatically restored immunity in chronically infected mice. Furthermore, they discovered a method to distinguish between T cells that can be revitalized in this way and those that can't.

The findings will help researchers develop PD-1 blocking agents, and also provide a way to select patients who may benefit most from such novel drugs, says the study's lead author E. John Wherry, Ph.D., an assistant professor in Wistar's Immunology Program.

"Blocking PD-1 may provide a novel tool to fight chronic infection as well as some cancers, like melanoma, that are susceptible to destruction by the immune system," Wherry said. Examples of infections that often result in T-cell exhaustion are HIV, hepatitis B, and hepatitis C, he says.

Wherry's continuing research on PD-1 has provided the groundwork for developing antibody therapies that inhibit the receptor. Wherry says he knows of a pharmaceutical company preparing to test one of these agents in patients with hepatitis C.

Researchers have known that T cells – white blood cells capable of inducing the death of infected or cancerous cells – become progressively less functional over time. In earlier studies, Wherry and his colleagues found that, during the course of a chronic infection, gene expression in killer T cells changed dramatically as the cells became exhausted and immune response to a pathogen slowed down. Wistar investigators then identified one gene that played a central role in this tamping down of immune response – PD-1, which produces PD-1 protein receptors that stud the surface of these T cells.

In follow-up experiments, they found that if they blocked PD-1 receptors in cell cultures using an antibody made up of one of the protein's natural binding ligands they could alleviate T-cell exhaustion. This demonstrated that PD-1 serves as a "brake" on T-cell function.

Wherry suspects that this reaction is designed to protect a body against the ravages that a chronically over-stimulated immune system can wreak. "The immune system can cause a lot of damage in an effort to control an infection. If you can't clear an infection and are making yourself sick trying to do so, it may be better off to live with the infection than die from the immune-mediated collateral damage," he said.

In the current study, Wherry and colleagues tested in mice infected with lymphocytic choriomeningitis virus the effect of plugging the PD-1 receptor with the antibody, thus releasing the "brake" on the immune system. And they studied two different subsets of killer T cells: those with the highest expression of PD-1 receptors and ones with an "intermediate" expression. Researchers theorized that those T cells with

the highest PD-1 expression, signifying the deepest exhaustion, would benefit most from an antibody to PD-1.

To their surprise, that is not what they found. They implanted these two different subsets of cells into infected mice, and then gave the mice a PD-1 antibody. Those mice implanted with T cells with intermediate expression of PD-1 recovered their vigor, while mice with the highest PD-1 expression did not. "It may be the killer T cells expressing a lot more PD-1 are already committed to cell death," Wherry said.

Knowing which subset of T cells will respond to an antibody drug will help physicians identify patients who could respond, if these novel agents reach extensive clinical testing, Wherry says. "We can optimize the promise of such a medical tool and minimize wasteful treatment," he said.

Source: The Wistar Institute

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