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Scientists find key to keeping killer T cells in prime shape for fighting infection, cancer

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Like tuning a violin to produce strong, elegant notes, researchers at The Wistar Institute have found multiple receptors on the outside of the body's killer immune system cells which they believe can be selectively targeted to keep the cells in superb infection- and disease-fighting condition.

In a study published online November 30 in *Nature Immunology*, the researchers describe their discovery of seven different receptors on T cells that can tamp down immune responses during a prolonged battle with an infectious pathogen or against developing cancer.

Chronic over-stimulation of the immune system can lead to poor control of infections and cancer, so the results explain why it is that these key immune cells gradually become "exhausted" and ineffective over time, says the study's lead author, E. John Wherry, Ph.D., an assistant professor in Wistar's Immunology Program.

Wherry had recently been involved in discovering a single receptor involved in turning off T cells but this new study shows that at least six more receptors can also restrain or negatively regulate immune responses. According to Wherry, a key finding is that these new receptors likely control different aspects of T cell responses, such as division or expansion, controlling viral replication, and local killing of infected cells versus secretion of long-range active antiviral proteins.

"This amount of control over T cells' response is remarkable. It suggests

that layers of negative regulation exist on exhausted T cells from co-expression of multiple inhibitory receptors," he says. "My bet is that these receptors inhibit different aspects of the T cells' response, but that the net result of their activation is to turn specific T cell populations off.

"We are starting to see a picture emerging of a really tuneable array of inhibitory receptors expressed on T cells," Wherry says. "That suggests it may be possible to not only dramatically enhance antiviral or antitumor T cell responses, but also to fine tune which response you want to enhance in order to reverse T cell exhaustion and continue fighting an infection or disease.

"This presents us with a great clinical opportunity," Wherry says. "T cells have a lot of weapons at their disposal to control viral infection and most of them are disarmed when these cells become exhausted. It may be possible to selectively rearm T cells while generally reinvigorating them."

The researchers made their discoveries in a mouse model of chronic infection with lymphocytic choriomeningitis virus. They had earlier found that a receptor known as programmed death-1 (PD-1) was highly expressed by exhausted T cells from chronically infected mice but not from mice that had cleared the infection. In a study published September 15 in the Proceedings of the National Academy of Sciences (PNAS), the researchers extended previous studies on the role of the PD-1 pathway in regulating T cell exhaustion. In these studies, blocking PD-1 increased T cell response, but not completely, so the researchers suspected other negative regulatory pathways were activated as well.

In the newest report in *Nature Immunology*, Wherry and colleagues compared the global patterns of gene expression for exhausted killer T cells compared to other types of T cells (naïve, effector and memory). A "nearest neighbor" analysis to PD-1 revealed up-regulation of six other

inhibitory receptor genes. They are LAG3, 2B4, CD160, CTLA-4, PIR-B and GP49. While the function of many of these receptors has been characterized, they had not been known to play a role in chronic viral infection. LAG-3, for example, is associated with an antitumor response. These observations may explain why PD-1 blockade did not completely restore T cell responses in previous work.

The investigators discovered that the severity of chronic infection correlated with the number and intensity of inhibitory receptor expression, suggesting a cumulative impact of inhibitory receptor expression. They also found that blocking both PD-1 and LAG-3 together led to substantially greater improvement in T cell responses and viral control compared to either blockade alone.

"The goal now is to understand the pathways the receptors control, and then to learn how to fine tune reversal of exhaustion by targeting pathways that selectively control the desired type of T cell response," Wherry says.

Source: The Wistar Institute