New hope for HIV treatment: Cells exhausted from fighting HIV infection can be revitalized

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Researchers at the University of Toronto and the University of California, San Francisco, have revealed new hope for HIV treatment with the discovery of a way to 'rescue' immune cells that are exhausted from fighting off HIV infection.

The team lead by Drs. Mario Ostrowski, of the University of Toronto's Faculty of Medicine, and Douglas Nixon, of the Division of Experimental Medicine at the University of California, San Francisco, has discovered that a molecule called Tim-3 is present at high levels on poorly functional immune system cells which are 'exhausted' from fighting HIV infection. The researchers found that blocking the activity of Tim-3 on these cells improved their function and allowed them to rejoin the battle against HIV.

"In the typical course of HIV infection, an initial burst of very high levels of the HIV virus is brought partially under control by the infected person's immune system, specifically by an immune system cell called a CD8+ killer T cell. In the majority of cases without antiretroviral drug treatment, the immune system is eventually overwhelmed and progression to AIDS occurs," said co-principal author Brad Jones, a PhD candidate in Immunology at the University of Toronto.

Progression to AIDS is associated with a breakdown in those CD8+ T immune system cells. In a typical viral infection, those cells rapidly

multiply, kill off virus-infected cells and stimulate other cells in the immune system. But over time, in the battle to fight off HIV infection these CD8+T cells become less functional and enter into a state known as 'exhaustion.' "The mechanisms that lead to this exhausted state are not well known," said Jones. "We felt that if we could understand these mechanisms then we may be able to intervene and re-energize the immune system." The research team theorized that this exhausted state may result from the Tim-3 molecule sending a signal to shut down CD8+ T cells in HIV-infected individuals.

The researchers observed that Tim-3 expression on T cells, in particular the CD8+ T cells, associated remarkably strongly with clinical parameters of HIV disease progression in a diverse group of HIV-infected individuals. "From these results we predicted that the Tim-3 pathway might be manipulated to potentially confer clinical benefit and serve as a promising new target for clinical intervention to decrease the severity of HIV infection," said co-principal author Lishomwa Ndhlovu, MD, PhD in the Division of Experimental Medicine, University of California, San Francisco.

"To test this, we produced a molecule capable of blocking the Tim-3 signal and studied the effect that this had on CD8+ T cell function in vitro," said Mario Ostrowski, MD, Associate Professor in the Department of Immunology, University of Toronto. "We observed that blocking the Tim-3 pathway rescued those cells and restored their ability to fight off infection."

This discovery, published in the November 24th issue of the *Journal of Experimental Medicine* opens up the possibility of new therapies aimed at blocking the Tim-3 signal and reinvigorating the immune system's natural ability to battle infection.

"We still do not know how the virus triggers Tim-3 or if this restricted to

HIV infection," said Dr. Ndhlovu, "but our findings may provide a new direction to vaccines and therapies that will potentially reverse these dysfunctional cells and allow them to control HIV-1 replication."

"Our hope is this will enable those infected with HIV to turn the tide in the long battle between the immune system and HIV. Future studies which block Tim-3 signaling in animal models of chronic viral infection will help to evaluate the therapeutic potential of this approach," said Jones.

Source: University of California - San Francisco