Blocking immune inhibitor improves response to HIV-like virus, prolongs survival in monkeys

December 10 2008

By blocking PD-1 (programmed death-1), an immune receptor molecule known to inhibit the immune response to chronic viral infections, scientists have safely and significantly reduced the plasma viral load and also prolonged survival of rhesus macaque monkeys severely infected with simian immunodeficiency virus (SIV), the nonhuman primate version of human immunodeficiency virus (HIV). The therapeutic strategy worked by boosting the function of anti-viral killer cells (CD8 T cells) and improving antibody response to the virus.

Scientists at the Yerkes National Primate Research Center of Emory University, the Emory Vaccine Center, Dana-Farber Cancer Institute, Harvard Medical School and the University of Pennsylvania Medical School conducted the research, which will be published in the current online issue of *Nature*, Dec. 10.

"Our findings raise the possibility that PD-1 blocking antibody treatment not only could improve the anti-viral T cell response to chronic HIV infections, but it also could generate an effective antibody response against the mutated virus of the infected host," says Rama Amara, PhD, principal investigator of the study.

"It also is important to note that this therapy was effective without anti-retroviral drugs and in monkeys with severe AIDS. It is critical to induce protective immune responses targeting the mutated virus for developing

a successful immune therapy to control HIV infection," Amara continues.

In the current study, which builds on findings from previous studies with mice, the researchers tested the potential of blocking PD-1 to control HIV infection using a macaque monkey model of SIV. They injected nine SIV-infected monkeys with an antibody to human PD-1 four times over 10 days. Gordon Freeman, PhD, of the Dana-Farber Cancer Institute and Harvard Medical School, provided the antibody.

Of the nine animals, five were infected for three months and four were infected for about 21 months at the time of antibody treatment. Another five SIV-infected monkeys received a control antibody at the same dose and schedule. The researchers then tested the function of the anti-SIV killer cells, antibody responses to the virus and plasma viral load.

Results showed that the improved anti-viral immune responses were associated with a reduction in plasma viral load and prolonged the survival of the infected animals. All nine animals receiving the PD-1 antibody survived more than seven months following initiation of treatment (the current time of the study), while four of the five animals receiving the control antibody died within four months following initiation of treatment.

The antibody treatment appeared to be safe and well tolerated. Within seven days of treatment, the number of anti-SIV killer T cells increased significantly and had improved function. This improvement was noted both in the blood and the gut, which is a major repository of SIV and HIV. The PD-1 antibody treatment also increased the proliferation of memory B cells and the level of antibody against SIV, a finding that had not been reported in earlier mouse studies.

"These findings are important not only because they highlight a potential

therapy for HIV, but also because of the insights they offer for other challenging chronic infectious diseases such as hepatitis C virus and tuberculosis," says Emory Vaccine Center Director Rafi Ahmed, PhD, who is a Georgia Research Alliance Eminent Scholar. "Through the Grand Challenges in Global Health initiative, which also funded the current study, we soon will begin testing the effectiveness of the PD-1 blockade against HCV in nonhuman primates."

Several years ago, Ahmed and his colleagues discovered that the immune receptor PD-1 essentially functions as a molecular switch to turn off an effective immune response by overwhelming T cells in their fight against chronic viral infections. By injecting an antibody that binds to PD-1 into mice infected with chronic lymphocytic choriomeningitis virus (LCMV), they were able to switch the immune response back on and control the virus. Dr. Ahmed is a co-principal investigator of the current study.

Other studies have since shown that anti-viral CD8 T cells express high levels of PD-1 during many human chronic infections, including HIV, hepatitis C virus and tuberculosis. However, until now the safety and effectiveness of blocking PD-1 in an appropriate animal model for these human viral infections had not been shown.

The current research team plans to continue testing the antibody therapy in combination with anti-retroviral drugs to try and improve its effectiveness. They also will explore the benefits of prolonged treatment (up to three months as opposed to 10 days in the current study). In addition, they are studying the effectiveness of antibodies against PD-1 ligands (target molecules), a strategy that was part of the earlier mouse research.

Reference: Enhancing SIV-specific immunity in vivo by PD-1 blockade. Velu, V., Titanji, K., Zhu, B., Husain, S., Pladevega, A., Lai, L., Vanderford, T.H., Chennareddi, L., Silvestri, G., Freeman, G.J., Ahmed,

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Source: Emory University