T cell immunity enhanced by timing of interleukin-7 therapy

February 2 2008

That the cell nurturing growth factor interleukin-7 can help ramp up the ability of the immune system to remember the pathogenic villains it encounters is well known.

But precisely how this natural protein works its magic on the cells of the immune system is not well understood. Now, however, in research that may have implications for developing vaccines against HIV and cancer, a team of scientists from the University of Wisconsin-Madison has found that the timing of interleuin-7 therapy is critical for increasing the number of killer cells that zero in on and destroy virus-infected cells.

Writing in the current online issue (Feb. 1, 2008) of the *Journal of Clinical Investigation*, a team led by UW-Madison School of Veterinary Medicine Professor of pathobiological sciences Marulasiddappa Suresh reports that therapeutic administration of interleukin-7 can be linked to a stage of early infection to effectively increase the number of a type of killer cell that recognizes and selectively assassinates virus-infected cells.

"These cells need to get interleukin-7 for their survival," explains Suresh, of the killer immune cell known as CD8 T cells, a type of white blood cell that attacks virus-infected cells, foreign cells and cancer cells. Interleukin-7 is produced in very small amounts in bone marrow, spleen, and the thymus, but scientists have been able to isolate and synthesize the agent, which is now in pre-clinical testing for a variety of conditions.

"This is one of the most exciting cytokines in pre-clinical human trials,"

says Suresh. "The idea is that it might be used as an immune restorative agent. It is absolutely essential for normal development and functioning of the immune system."

Effectively stimulating the immune system -- the complex of organs and cells that defends the body against infection and disease -- is a grail of biomedical science in the fight against infectious diseases.

Suresh explains that upon infection, the body unleashes an army of T cells to fight infected or rogue cells. But when the body perceives an infection may be contained, the number of T cells it deploys is dramatically reduced. However, a certain number of T cells, known as memory cells and that are capable of recognizing a recently vanquished foe, remain. Stimulating memory T and B cells is the basis of vaccination, but vaccines often do not induce a sufficient number of memory CD8 T cells.

Interleukin-7 is a well-studied growth factor that is known to help generate and maintain the immune system's “memory” CD8 T cells, which have the ability to remember the identity of its targets, such as cancer cells or cells that have been taken over by a virus. A paucity of interleukin-7 is believed to limit the survival and persistence of memoryCD8 T cells.

Despite the promise of interleukin-7 as a means to bolster immunity, an optimal treatment regimen has yet to be determined.

In studies in mice, Suresh and his colleagues found that T cell memory is best enhanced when interleukin-7 is administered during a phase of infection when the number of T cells is ramping down.

In the new Wisconsin study, Suresh's group gave interleukin-7 to mice during different stages of a viral infection. They found that by

administering interleukin-7 when the number of T cells is in decline, it is possible to increase the number of memory CD8 T cells that remain to stand guard and protect against re-infection.

"The purpose of the immune response is to expand these cells," says Suresh, explaining that T cells act like serial killers, snuffing one infected cell after another until the viral infection is controlled.

During the expansion phase of infection, when the body is generating the most T cells, administration of interleukin-7 seems to have no effect, according to Suresh. But during the contraction phase, memory is increased.

"We tried this in a DNA vaccine and it works," says Suresh. "Even with the weakest vaccine, we could increase the memory cells and improve protection against infection. What this shows is that the number of memory cells are not predetermined. You can increase them and interleukin-7 drives their proliferation."

Source: University of Wisconsin-Madison