Scientists enhance immune system attacks on cancer

October 21 2008

In an Early Edition issue of the *Proceedings of the National Academy of Sciences* (PNAS) published online on October 20, 2008, the scientists describe how they used multiple tactics to rev up both innate and adaptive immunity to enhance the body's ability to fight cancer.

"The problem with cancer is that it becomes part of what the immune system identifies as 'self' and there are ways the body learns to tolerate 'self' to prevent immune attack," says the study's senior investigator, Linda Sherman, Ph.D., a professor in the Scripps Research Department of Immunology. "Hitting it with these new tools basically gets the immune system to pay attention to the cancer, and go after it.

She continues, "What is needed is effective and non-toxic immunotherapy for cancer patients, and we believe this work provides a foundation for that. The concepts we have shown are directly translatable to human therapy."

Stimulating Killer T Cells

In the new study, the researchers basically used two different strategies. First, they worked out a way to force T cells—the immune system's killer cells—to become active and grow in the presence of tumor "antigens," the proteins on the outside of cancer cells that can stimulate an immune response. While these T cells recognize the tumor antigens, their response to them tends to be chronically weak because they are

'self'.

"We have been working for years to find ways to coax these so-called low affinity T cells to work better," Sherman says.

In this study, the investigators tested a novel complex developed by Professor Jonathan Sprent, M.D., Ph.D., a previous member of the Scripps Research faculty who is now at the Garvan Institute in Sydney, Australia, and Scripps Research co-author, Professor Charles Surh, Ph.D. The agent combines Interleukin-2 (IL-2) with an IL-2 antibody. IL-2 is a well-known stimulator of the growth of activated T cells, and is often used to boost immune system response in human therapy; T cells have IL-2 receptors on their surface. In previous studies, Sprent and Surh found that coupling IL-2 with a specific type of IL-2 antibody allows the complex to bind better to activated T cells and produces a more robust T cell response.

"The beauty of this complex is that, as we demonstrate in this paper, it has a much greater ability to bind to low affinity T cells, which IL-2 itself cannot do very well," says Sherman.

So, in order to jump start such an immune reaction, the researchers prime T cells by delivering this complex. When this complex binds to T cells, they grow and mature and deliver a signal to release cytotoxic granules that enter tumor cells and promote apoptosis, or cell death.

"A number of nice things begin to happen," says Sherman. "T cell growth is promoted as well as their killing function. There is a lot of good activity."

However, as soon as investigators withdraw the IL-2 complex, the T cells die quickly, as their growth stimulant has been removed.

The "Double Whammy"

The researchers' second strategy, then, was to also deliver an agent known as poly(I:C) that keeps T cells surviving longer. The agent also enhances the killing power of the T cells by stimulating the innate immune system, which provides an immediate defense against invaders.

"It is this trick of really stimulating T cell proliferation and killing functions, and then keeping the T cells alive, that provides the double whammy," Sherman says. "The T cells are hitting all their bases, and that is when we see the killing of tumors."

The researchers tested the system in mice that spontaneously develop tumors. The researchers delivered tumor antigen, the IL2 complex, and poly(I:C) all at the same time, and demonstrated the safety and effectiveness of the strategy.

Today, there are human cancer treatments that work in the same way, but they are highly toxic, Sherman says. For example, some patients with melanoma receive melanoma antigens, infusions of T cells, and high doses of IL2, which causes a lot of harmful side effects. Since the IL-2 complex can be used at ~50-fold lower doses than IL-2 with the same efficacy, the use of complex is likely to circumvent the toxicity problem. To further rev up the immune response, patients sometimes also receive whole body irradiation, which produces widespread inflammation.

"We think we can provide two very safe ways to hit these same bases," Sherman says.

However, more research needs to be done before human studies can begin, including finding an antibody to human IL-2 that works in the same way.

In addition to Sherman and Surh, study co-authors were Gregory Verdeil, Ph.D., and Kristi Marquardt of The Scripps Research Institute. For more information, see www.pnas.org/content/early/200 … /0805054105.abstract

Source: Scripps Research Institute