Scientists find approach to enhance and prolong immune attack against tumor cells

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(Medical Xpress) -- Investigators have identified a new class of human immune cells that behave like stem cells. These cells, a subtype of T lymphocytes, which comprise a small fraction of white blood cells, may prove more effective than any previously reported type of T cell for treating tumors. The study, by scientists at the National Cancer Institute (NCI), part of the National Institute of Health, describes how these stem cell-like T cells can trigger a prolonged immune attack against tumor cells by continuously generating killer T cells and regenerating themselves. The findings were published online Sept. 18, 2011, in *Nature Medicine*.

"It was known that such a T cell subset should theoretically exist in humans, and many groups have been hunting for these cells. Fortunately we were able to identify them. They are rare and elusive, comprising only 1 to 2 percent of T cells in most donor blood," said lead investigator Nicholas P. Restifo, M.D., Center for Cancer Research, NCI.

Many therapies currently used to treat patients with metastatic cancers only persist for short periods of time after administration. The type of living cell therapy described in this study could be capable of continually refreshing itself and able to integrate with a patients' immune system for long periods of time and perhaps even permanently, continuing the fight against tumor cells, according to Restifo.

All cells within an organism experience aging, and lymphocytes are no exception, explain the scientists. As T cells age, their ability to replicate

themselves and respond to the challenge of a tumor or a pathogen becomes diminished. However, not all T cells age at the same rate. Chronic exposure to an antigen, a substance that triggers an immune response, can accelerate T cell aging. Yet even very old people, such as those age 100 years or older, have some T cells that are young. It was always believed that such a T cell subset must exist because humans who live for a very long time need to somehow replenish their defenses against cancer and infectious diseases. The problem is that the thymus — the organ responsible for generating new T-cells — essentially shuts down during adolescence.

The researcher's strategy was to study T cells that had many of the characteristics of very young immune cells (termed fully undifferentiated or naive). By looking at these very young T cells, the scientists were able to isolate ones that showed the first changes in gene expression that occur when lymphocytes make a memory response — that is, when they remember antigens they have seen previously and can quickly react to them. These stem cell-like memory cells had physical characteristics of very young immune cells. Stem cells have the potential to differentiate and become many different types of cells, which makes them extremely valuable.

"Because we identified the genetic characteristics of the stem cell-like T cells, we may be able to manipulate certain genes to regenerate younger T cells from older ones, and this has possible importance for regenerative medicine," said first author, Luca Gattinoni, M.D., also with the Center for Cancer Research.

This study built upon previous findings in mice, which showed that T cells acquire stem cell-like behavior when they are stimulated in the presence of drugs designed to mimic an important signaling pathway called Wnt, which the scientists used to generate and characterize candidate stem-cell-like T cells in humans. The scientists then studied

blood samples from over 100 healthy human donors and cancer patients to confirm that these T cells naturally occur in human beings. They further discovered, in a humanized mouse model (a mouse that carries functioning human genes) that the stem cell-like T cells had rapid growth capacity and triggered more effective anti-tumor responses than any previously described T lymphocytes.

More information: L Gattinoni et al. A human memory T-cell subset with stem cell-like properties. Nature Medicine. Online Sept. 18, 2011.

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