

Fighting Fire with Fire, Immunologically

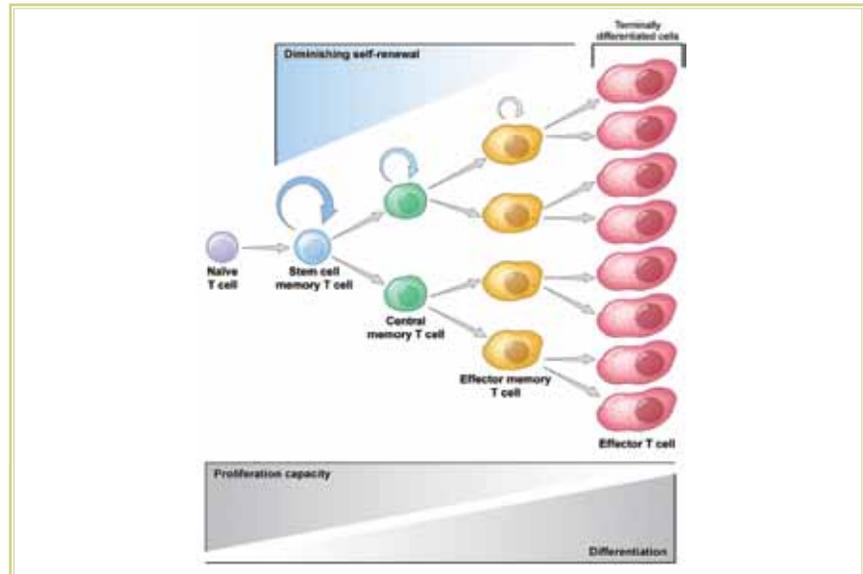
CCR scientists describe a new stem-cell-like memory T cell with potential to enhance and prolong immune responses against tumor cells.

Immunological memory refers to the ability of certain immune cells to “remember” an encounter with an antigen and to then react more swiftly and effectively to that antigen should it return. The complex mechanisms by which this occurs are not fully understood, but it has long been speculated that a subpopulation of memory lymphocytes with stem-cell-like attributes must be involved.

For the first time, Luca Gattinoni, M.D., and Nicholas Restifo, M.D., of CCR’s Surgery Branch, and colleagues have documented this putative memory T subpopulation. These human stem-cell-like memory T cells displayed enhanced self-renewal and the ability to differentiate into diverse, mature immunological cell types, including memory T cells. The findings were published in the September 18, 2011, online issue of *Nature Medicine*.

Stem-cell-like lymphocytes were previously described in mice, but the key marker used to identify these cells had no counterpart in humans. To overcome this roadblock, Gattinoni and Restifo artificially created a population of human T cells by activating a key developmental pathway named “Wnt” that had previously enabled the scientists to generate stem-cell-like T cells in mice.

The next challenge was to determine if their artificially constructed stem-cell-like human memory cells had a counterpart among *naturally occurring* human lymphocytes. The researchers analyzed samples from both healthy human donors and cancer patients, and found that around two to three percent of all circulating T lymphocytes expressed the same markers as the artificially



Stem-cell-like memory cells have physical characteristics of very young immune cells. They still have the potential to differentiate and become many different types of immune cells, making them extremely valuable.

created stem-cell-like T cells. Upon stimulation, these cells demonstrated the ability to retain “memory” and to rapidly proliferate and acquire effector functions, but importantly, they also exhibited the classical stem-cell-like properties of self-renewal and multipotency. Tests of adoptive transfer into immunodeficient mice showed that the newly characterized memory stem-cell-like T cells had enhanced replication and survival capabilities compared to fully differentiated memory T cells, and they exhibited potent antitumor activity. In fact, the stem-cell-like memory T cells triggered enduring tumor regressions in mice that would otherwise have died within two to three weeks.

The identification of a human stem-cell-like memory T cell population is an exciting step in the rapidly growing fields of regenerative medicine and immunotherapies for cancer.

“Many current therapies are short-lived in nature, but using modified immune cells that are capable of continually refreshing themselves and fully integrating with the patients’ own immune system provides potential for far more sustained assaults on tumor cells in the future,” said Gattinoni.

The team is currently working towards the goal of creating stem-cell-like memory T cells to enhance immune responses against tumors. “Tumors are in many ways similar to stem cells—both self-renew and can adapt quickly to environmental changes—so fighting tumors with immune cells that function similarly is like fighting fire with fire,” concluded Restifo.

To learn more about Dr. Restifo’s research, please visit his CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?Name=restifo>.

(Image: NIH Medical Arts)