Two-sided immune cell could be harnessed to shrink tumors, study shows

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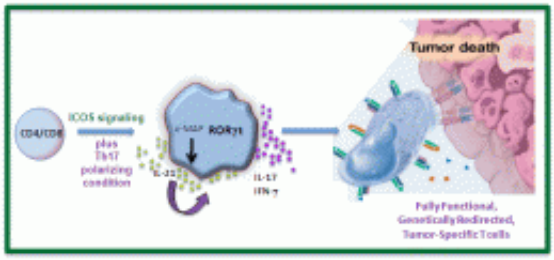

Sending the right signals to human Th17 cells to break self-tolerance to tumors. Chrystal Paulos PhD, University of Pennsylvania School of Medicine

(PhysOrg.com) -- A recently identified immune cell that directs other cells to fight infection plays a critical role in regulating the immune system in both health and disease. Researchers from the University of Pennsylvania School of Medicine have discovered how a stimulatory molecule and a protein found on the membrane of another immune cell make T helper 17 cells multi-taskers of sorts. Th17 cells protect the body against infection and cancer, but are also culprits in some autoimmune diseases and out-of-control, cancerous cell growth.

This new understanding that Th17 cells manage to play both sides of the fence suggests that targeting or inhibiting the involved protein pathways might be a new way to treat cancer, chronic infection, and some autoimmune diseases. Previous studies have linked excessive amounts of Th17 cells in the body to such autoimmune diseases as multiple sclerosis,

psoriasis, rheumatoid arthritis, and Crohn's disease.

First author and postdoctoral fellow Chrystal Paulos PhD; senior author Carl June, MD, professor of Pathology and Laboratory Medicine, and colleagues have found that a protein called inducible costimulator (ICOS) is necessary for the growth and function of human Th17 cells, while CD28, a transmembrane protein on CD4 cells, stops the ICOS signal. What's more, human Th17 stimulated with ICOS shrank human tumors implanted in a mouse model faster than those stimulated with CD28. The findings appear in this week's *Science Translational Medicine*. June is also the Program Director of Translational Research for the Abramson Family Cancer Research Institute at Penn.

These findings were surprising to the researchers given that CD28 has historically been used by investigators to study and expand human Th17 cells. The new data on Th17 cells raises the possibility that the full inflammatory potential of human Th17 cells had not been fully reflected by previous lab studies.

To move this knowledge closer to the clinic, the team also demonstrated that Th17 cells cannot only be expanded to large numbers, but could also be maintained by stimulating them with ICOS proteins. Th17 polarizing cytokines have previously been shown to support Th17 cells from naïve CD4 cells but this is the first demonstration that the ICOS costimulatory molecule used to expand the Th17 cells is important.

Tilting the balance between spurring and suppressing the growth of Th17 cells may be a key to tailoring immunotherapy, a form of cancer treatment. Adoptive transfer of tumor-specific cells expanded with ICOS and polarized to a Th17 cell type might further improve treatment.

These basic findings on Th17 cells in both peripheral and cord blood cells has broad implications, providing the basis of a new human cancer

treatment protocol. T-cell-based therapies that incorporate the ICOS signal are being planned at Penn to treat patients with leukemia.

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