T cells making brain chemicals may lead to better treatments for inflammation, autoimmune diseases

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Scientists have identified a surprising new role for a new type of T cell in the immune system: some of them can be activated by nerves to make a neurotransmitter (acetylcholine) that blocks inflammation. The discovery of these T cells is novel and suggests that it may be possible to treat inflammation and autoimmune diseases by targeting the nerves and the T cells. The study was published this week in *Science*.

"The discovery that 2 percent of T cells can make acetylcholine under the control of nerves gives a new insight into how the nervous system regulates immunity," said Kevin J. Tracey, MD, president and chief executive officer of The Feinstein Institute for Medical Research, and principal investigator of the study. "The arrival of electrical signals from nerves activates these specialized T cells to produce the acetylcholine necessary to block inflammation, and protect against damage. It is possible to transfer these cells to cross-protect mice from inflammation, and to control these T cells by electrically stimulating the nerves directly."

The present study followed years of work from Dr. Tracey's lab that identified the role of the vagus nerve, named for its wandering course from the base of the brain to the liver, spleen and other organs, in blocking inflammation. Applying electrodes to stimulate the vagus nerve blocked the release of tumor necrosis factor (TNF) and other cytokines that underlie the tissue damage in arthritis, inflammatory bowel disease and other syndromes. Stimulating this nerve pathway led to increased production of acetylcholine, a neurotransmitter that binds to the alpha 7 nicotinic acetylcholine receptor. Activating this receptor on macrophages blocked the release of immune molecules (the cytokines,) suggesting a novel strategy for developing anti-inflammatory agents.

But these results raised an important question because the nerve fibers in spleen release norepinephrine, another neurotransmitter, but not acetylcholine. The search for the cells that produce acetylcholine led these investigators to use "nude" mice, devoid of T cells. Then they examined the spleen cells that make acetylcholine and that led them to a subset of T cells. Transferring these acetylcholine producing T-cells into nude mice restored the vagus nerve circuit that blocked inflammation.

"Our results point to a population of acetylcholine-synthesizing memory T cells in spleen that is integral to the function of the inflammatory reflex, the nerve circuit that regulates inflammation and immunity," said Dr. Tracey. "It is as if these T cells occupy a nerve-like function in this important circuit."

It should be possible to target these T cells and to modulate this neural circuitry to develop therapeutic modalities for inflammatory and autoimmune diseases. In the future, it may be possible to isolate these T cells and exploit their anti-inflammatory activity. In the meantime, there is a more direct route to use this discovery for therapy. Rheumatoid arthritis patients in Europe are being studied in clinical trials where vagus nerve stimulators are implanted and turned on to stimulate this circuit and suppress inflammation.

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