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New insights into how immune system fights atherosclerosis

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A study led by Columbia University Medical Center (CUMC) researchers has found that an important branch of the immune system, in reaction to the development of atherosclerotic lesions, mounts a surprisingly robust anti-inflammatory T cell response that helps prevent the disease from progressing. The findings may help inform the design of anti-atherosclerosis vaccines and other therapies that can take advantage of this aspect of the immune system. The study was published today in the online edition of the *Journal of Clinical Investigation*.

When the body encounters viruses, bacteria, or other potential threats, dendritic cells—the sentinels of the immune system—are dispatched to take a sample of the pathogen and present it to T cells. This activates the production of pro-inflammatory effector T cells (which attack the pathogen) and anti-inflammatory regulatory T cells (which keep the pro-inflammatory response in check).

"Normally, the pro-inflammatory response dominates, and that is what people assumed to be the case in atherosclerosis," said study leader Ira Tabas, MD, PhD, the Richard J. Stock Professor, Department of Medicine, and professor of pathology & cell biology (in physiology and cellular biophysics) at CUMC. "However, we found that the T cell response to atherosclerosis is mostly anti-inflammatory."

The researchers, led by postdoctoral scientist Manikandan Subramanian, PhD, used mice whose dendritic cells lacked MYD88, a signaling protein that initiates the cells' maturation. Since immature dendritic cells

cannot activate T cells, the elimination of MYD88 effectively disabled the production of both effector and regulatory T cells. The mice were also bred to lack the LDL receptor, leaving them prone to the development of atherosclerosis.

The net effect of these changes in the mice was to increase the size of atherosclerotic lesions. "What this means is that the dominant effect of dendritic cells in the setting of atherosclerosis is to promote the development of protective regulatory T cells," said Dr. Tabas.

Earlier studies had suggested just the opposite: that effector T cells dominate in response to atherosclerosis. "In those studies, researchers disabled dendritic cells at an earlier stage, creating all sorts of compensatory processes," said Dr. Tabas. "That's probably why they came to a different conclusion. In our model, we were able to knock out only the step involved in activating T cells, leaving everything else alone."

The researchers found that T regulatory cells act by suppressing pro-inflammatory effector T cells and macrophages, which was expected. They also identified a new mechanism that directly links regulatory-T-cell activation with protection from atherosclerosis. According to Dr. Tabas, regulatory T cells secrete TGF-beta (a cytokine, or signaling molecule), which suppresses MCP-1 (monocyte chemoattractant protein-1), a protein that recruits monocytes, a type of white blood cell.

"Now we have a specific mechanism that could explain the preclinical success of dendritic vaccines and that provides a new understanding of how these vaccines might be improved," said Dr. Tabas.

More information: "Treg-mediated suppression of atherosclerosis requires MYD88 signaling in DCs." *Journal of Clinical Investigation*.