# Fast track to vascular disease

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In Western societies, atherosclerosis of the arteries is one of the leading causes of death. Chronic, localized inflammation of the blood vessel wall facilitates the growth of fibrous plaques, which leads to narrowing or occlusion of the vessel, and thereby promotes heart attacks and stroke. The persistence of the inflammatory reaction is due to a loss of control over the activity of the immune system.

So-called dendritic cells are known to play a central role in the adaptive immune response, functioning as activators of other classes of immune cells. Their precise contribution to the pathogenesis of atherosclerosis has, however, been unclear. An international team of researchers led by Professor Christian Weber of Ludwig-Maximilians-Universität (LMU) Munich and Privatdozentin Alma Zernecke of Würzburg University has now demonstrated that dendritic cells release the chemokine CCL17 as a signal molecule, which inhibits a feedback mechanism that normally limits the activity of the immune system. This explains why the normally transient inflammatory response is not turned off and becomes chronic. The new study has also identified a potential antidote to the signal molecule. As Professor Weber reports, "We were able to prevent the progression of atherosclerosis using an antibody raised against CCL17." In other words, CCL17 offers a promising starting point for the development of new therapeutic strategies.
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Atherosclerosis can become manifest in various ways. In particular, plaques may suddenly rupture, promoting the formation of a clot that occludes the vessel. If this afflicts the vessels of the heart or brain the

result is a heart attack or a stroke. The narrowing of vessels caused by plaque growth can also lead to reduction of the blood supply to the lower limbs and to so-called vascular dementia. Atherosclerosis is initiated by lipid accumulation that occurs directly beneath the inner lining of the blood vessel, and can induce and chronically perpetuate an inflammatory response. Cells of the immune system migrate to the site of the primary lesion and release signaling molecules that attract other types of immune cells which facilitate plaque formation. The atherosclerotic plaques in turn serve as sources of additional signals and mediators, the inflammation reaction gets out of control and continues unchecked, and plaque growth progressively obstructs the flow of blood.

So-called dendritic cells are responsible for determining the targets against which the immune response is directed. They do so by using fragments of target-specific proteins displayed in a molecular complex on their surfaces to activate immune cells called T cells. The T cells have highly variable receptors that enable them to recognize such complexes and to identify the intact target. "Dendritic cells are detectable in arteries and in atherosclerotic tissue, but their precise function in the pathogenesis of plaques has been unclear," explains Weber. "We were particularly interested in learning more about the role of the chemokine CCL17 - a signal protein that is specifically synthesized by mature dendritic cells - in the activation of T cells and in regulating T cell homeostasis."

For their experiments the researchers made use of a transgenic mouse strain in which the gene for CCL17 had been replaced by a DNA sequence encoding the genetic information for the Green Fluorescent Protein (GFP). Thus, in this strain, GFP acts as a proxy for CCL17-producing cells. Since GFP can be visualized by virtue of its fluorescence, the team was able to determine where CCL17-producing cells would normally congregate. This approach also allowed them not only to work out the effects of the lack of CCL17, but also to use

advanced methods of microscopy, in particular multiphoton microscopy, to follow how the dendritic cells intrude and accumulate in atherosclerotic plaques and interact with T cells.

In further experiments, the researchers destroyed the T cells of normal mice and replaced them with T cells from the CCL17-deficient mice. Conversely, regulatory T cells were specifically removed from CCL17-deficient mice. "The results of these investigations led us to conclude that CCL17 drives atherosclerosis by inhibiting an important regulatory circuit that acts to restrain the immune response," says Weber. Under normal circumstances, immune reactions are attenuated by regulatory T cells (Tregs) that inhibit other types of immune cells and so ensure that the whole system returns to a balanced state. The new study shows that, in the presence of CCL17, fewer Tregs in the inflamed tissue are activated. In effect, CCL17 disables the Treg-dependent braking mechanism.

"This finding makes CCL17 a promising target for new therapeutic approaches," says Weber, who is anxious to ensure that the results of basic research are transferred as quickly as possible into the clinical setting and find practical medical application. In this case, the first step has already been taken. Using an antibody against CCL17, the authors of the new study were able to block the action of the signal and prevent the progression of atherosclerosis. CCL17 therefore offers a possible handle for new approaches to treatment of the condition. In the next step, Weber and his colleagues hope to clarify the function of the CCL17 receptors on the plasma membrane of the regulatory T cells.

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