The notion that atherosclerosis has an inflammatory component was already proposed in the 19th century by Virchow, on the basis of light microscopic analysis of human plaques. The hypothesis was later supported by electron microscopic studies and was confirmed when immunohistochemical analysis revealed that the CD14+ macrophage indeed was the major cell type in the plaque. More surprising was the finding that T lymphocytes were also present in substantial numbers in human plaques. The presence of cellular representatives of the specific, adaptive immune system in this disease has since then inspired a whole area of research, and our knowledge has certainly grown. T lymphocytes are designed to perform effector functions after activation by a specific antigen via the T-cell receptor. A first obvious question was, therefore, what these antigen-specific cells might be reactive to. Are there atherosclerosis-related antigens taking part in atherogenesis? This inquiry constitutes something of a “needle-in-a-haystack” problem, and the question of clonal composition is easier to address. The presence of clonal T-cell expansions would suggest reactivity to a limited number of antigens in early experimental atherosclerosis. More advanced human plaques, however, demonstrate a polyclonal T-cell composition. This characteristic does not constitute evidence that T cells are “nonspecific” (ie, carrying reactivities not related to atherosclerosis), but it does suggest that no single antigen reactivity dominates the T-cell population. This result in itself is not surprising, because it is known from other inflammatory conditions, with known eliciting antigens, that antigen-specific cells in general constitute a minority of all infiltrating T cells. Furthermore, very few data support the concept of antigen-specific T-cell recruitment, suggesting instead that T-cell infiltrates arise by predominantly non–antigen-specific recruitment, which may be followed by local, clonal, antigen-driven proliferation. Indeed, several studies have demonstrated the presence of T cells in atherosclerotic plaques with specificity to atherosclerosis-related antigens, such as oxidized LDL, heat shock proteins, and Chlamydia pneumoniae. Many studies in recent years have demonstrated pronounced effects on experimental atherosclerosis by immune system modulation, such as immunization or different approaches to immunosuppression. This line in current working hypothesis stating that antigen-specific T-cell activation is an important component of the atherosclerotic process.

In the present issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Houtkamp et al present data that suggest that antigen-specific activation may not be the only way to induce T-cell activity in atherosclerosis. The authors demonstrated the presence of interleukin-15 (IL-15), a cytokine with the potential to trigger T-cell activation and proliferation in the absence of specific T-cell receptor engagement, in human atherosclerotic plaques. Analyzing human carotid and coronary arteries by in situ hybridization, these authors detected IL-15 mRNA in lipid-rich plaques, predominantly colocalizing with CD68-reactive macrophages. Immunohistochemical staining showed IL-15 protein reactivity in the same areas while surrounding T cells were negative. Independently, by a gene expression array technique, we recently detected this cytokine ourselves in mouse atherosclerotic plaques (Wuttge et al). Aortas of apo E−/− mice showed elevated levels of IL-15 mRNA, by gene array hybridization, after 10 and 20 weeks of consuming a cholesterol-enriched diet compared with aortas from normal C57BL6 mice. The result was confirmed by quantitative polymerase chain reaction and at the protein level by immunohistochemistry. Similar to Houtkamp et al, we could also demonstrate IL-15 protein in human lesions. Because IL-15 stands out among cytokines by the strong posttranscriptional regulation of its expression, demonstration of the protein product is crucial.

What then, are the properties and actions of IL-15? IL-15 was discovered as a factor stimulating T-cell proliferation in vivo. Importantly, IL-15 is a strong chemoattractant for T cells.
IL-15 is constitutively expressed in a wide variety of cells, such as monocytes, skeletal muscle cells, endothelial cells, epithelial cells, and fibroblasts but not by T cells. IL-15 has been detected in inflammatory conditions such as rheumatoid arthritis. Inflammatory stimuli such as bacterial lipopolysaccharide and IFN-α upregulate IL-15 mRNA in freshly isolated monocytes, and nuclear factor-κB (NF-κB) and interferon regulatory factor motifs are conserved in the 5′-flanking region of the IL-15 gene in both humans and mice. How may the activities of IL-15 be involved in atherogenesis?

“Naive” T cells, ie, T cells that since their release from the thymus have never been exposed to their antigens, are basically inert cells. At their first encounter with their specific antigen, they are activated, proliferate, and perform effector functions such as cytotoxicity and cytokine secretion. When antigen challenge recedes, the cells turn into memory T cells. These cells are characterized by their cell surface protein expression and are poised for vigorous response to a renewed antigen challenge. In fact, a majority of plaque T cells are such memory cells. Non–antigen-specific activation of memory T cells would represent a waste of specificity and is potentially dangerous. Yet in recent years, several examples of non–antigen-dependent T-cell activation have been presented. The demonstration of cytokines with this potential in atherosclerosis is an important finding and suggests that cytokine secretion by the large number of memory “bystander” T cells may significantly contribute to local inflammatory activity.

Furthermore, Houtkamp et al in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology demonstrate colocalization of IL-15–positive macrophages and immunoreactive oxidized LDL. Because oxidized LDL may activate NF-κB, it seems likely that oxidized LDL and other proinflammatory components of the forming lesion could induce IL-15 secretion. CD40 ligation may also promote IL-15 secretion, and this event could be particularly important in atherosclerotic lesions, in which CD40 as well as its ligand CD40L are abundantly expressed on vascular as well as immune cells. IL-15 induced through either of these mechanisms could in turn exacerbate local inflammation by activating proinflammatory CD4+CD45RO+ memory T cells.

It has recently been shown that IL-15 is involved in the recruitment of activated memory T cells to sites of inflammation by a novel, recently described mechanism. IL-15 induces the expression of hyaluronan by endothelial cells, thereby promoting binding to the hyaluronan receptor CD44 on activated T cells. This event is followed by secondary CD44/VLA-4–mediated adhesion that leads to extravasation of the activated T cells. The potential importance of this mechanism in immune-mediated inflammatory disorders is illustrated by the fact that antibodies to CD44 and integrin-α4 prevented experimental autoimmune encephalomyelitis induced by the transfer of myelin basic protein–specific T cells in rats. CD44 is expressed by memory T cells, the predominating phenotype among plaque T cells, suggesting that this recruitment pathway may be important in atherogenesis.

In conclusion, IL-15 is a potent proinflammatory cytokine with several proinflammatory activities, including the capacity to recruit T cells and to antigen-independently induce T-cell cytokine secretion. Hopefully, further investigation will reveal whether either of these mechanisms, or both, indeed constitute the driving force in atherogenesis.

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Plaque T-Cell Activity: Not So Specific?
Sten Stemme

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