T
he first event in atherogenesis is the extravasation of lipoproteins into the subintimal layers of arteries, where they are trapped by extracellular matrix molecules such as proteoglycans and undergo oxidative modifications that in turn lead to endothelial cell activation and local recruitment of inflammatory cells. The monocyte-derived macrophages transform into foam cells by an unlimited upload of oxidized lipoproteins. Foam cells accumulated in the subintimal space constitute the fatty streaks. During this process, macrophages become activated and release a number of cytokines and proteases, which perpetuate the local inflammatory environment. It is now recognized that such a chronic inflammatory process is the fundamental pathogenic mechanism of atherogenesis. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Tenger et al address the role of a key molecule, interleukin (IL)-18, in the regulation of this inflammatory condition.1

IL-18 has received particular attention because it has a strong predictive value of cardiovascular death in patients with coronary artery disease.10 Since its discovery in 1995,10 IL-18, or IFN-γ–inducing factor, has been demonstrated to play multiple roles in immune responses. It can be produced by several cell types, including dendritic cells,11 macrophages, endothelial cells, and smooth muscle cells,12 all of which are intimately related to atherogenesis. Little is known concerning inducers of IL-18. IL-18, however, might provide a link between infection and atherosclerosis because it is produced after bacterial13 and viral14 infections.

Previous studies have shown that blocking IL-18 signaling by overexpression of the IL-18 binding protein (the endogenous inhibitor of IL-18) prevents fatty streak formation and slows progression to mature plaque. Similarly, IL-18 deficiency leads to significantly fewer lesions in apoE knockout mice.15 The proatherogenic effect of IL-18 has been elegantly confirmed by a recent work by Whitman et al. The authors, in addition, demonstrated that IFN-γ is required for this effect.16 In all of these studies, IL-18 has been considered to be proatherogenic, mostly through the induction of the Th1 pathway of adaptive T-cell responses. However, IL-18 also influences the innate arm of the immune response (Figure). In fact, IL-18 is at the crossroad between innate and adaptive immune responses in atherogenesis because its major targets include T cells,17 macrophages, natural killer (NK) cells,18 and perhaps B cells.19 Similar to ligands of Toll-like receptors, IL-18 signals via MyD88, which activates tumor necrosis factor (TNF) receptor–associated factor and NF-κB.20 This has two implications: (1) the protective effect observed in atherosclerosis-prone MyD88 knockout mice21,22 might be partially attributable to disruption of the IL-18 signaling; (2) IL-18 can function beyond its pro-Th1 action as IFN-γ inducer. Indeed, IL-18 inhibits the production of IL-10,23 which is antiatherogenic.24 IL-18 directly enhances cytotoxic NK cell activity,25 which likely contributes to atherogenesis.16 Finally, IL-18–driven IFN-γ production can be induced not only in T cells but also in macrophages26 and NK cells.27

In this issue, an elegant study by Tenger et al demonstrates that the proatherogenic role of IL-18 goes beyond its effect on the Th1 polarization, because IL-18–mediated acceleration of atherosclerosis is detected in apoE−/−/SCID mice in the absence of T cells.1 The authors show that IL-18–induced IFN-γ production in macrophages and NK cells is accompanied by an upregulation of the CXCL16 scavenger receptor in lesions. This cascade of events is likely to be responsible for increased foam cell formation and fatty streak development under IL-18 treatment. This work highlights the fact that the effect of IFN-γ on foam cell formation does not require T cells and suggests that at this stage of atherogenesis (1)
macrophages and smooth muscle cells act as targets in the absence of lymphocytes and (2) the source of IFN-\(\gamma\).

In the absence of T cells, the increase in lesion size reflects an enhanced accumulation of foam cells and therefore plaques stagnate at the stage of fatty streaks.

Thus, cells from both innate and adaptive immunity play their part in the inflammatory orchestration of atherogenesis. If the course of atherosclerotic disease were an opera, fatty streak formation would be the Preludio.

Thanks to the study by Tenger et al we now know that, if IL-18 conducts, the Preludio sounds the same even in the absence of some of the instruments. Yet, when present, these instruments certainly play notes that might perceivably modify the opera during the acts that follow.

### References


When Interleukin-18 Conducts, the Preludio Sounds the Same no Matter Who Plays
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An erratum has been published regarding this article. Please see the attached page for:/content/25/10/e140.full.pdf
In the April 2005 issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, in the editorial by Caligiuri et al (*Arterioscler Thromb Vasc Biol*. 2005;25:655–657.), a reference was mistakenly omitted from the first line of the fourth paragraph. The complete statement, with the appropriate citation and reference, is listed below. The authors regret this error.

Previous studies have shown that blocking IL-18 signaling by overexpression of the IL-18 binding protein (the endogenous inhibitor of IL-18) prevents fatty streak formation and slows progression to mature plaque.\textsuperscript{14a}