When Interleukin-18 Conducts, the Preludio Sounds the Same no Matter Who Plays

Giuseppina Caligiuri, Sрини Kaveri, Antonino Nicoletti

The 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.

See page 791

In recent years, the role of the adaptive immune response, evoked by activated T cells present within the plaque, has attracted growing attention. Experimental studies have confirmed that B and T cells play a modulatory role in atherogenesis. On one hand, B cell response is atheroprotective. On the other, fully immunodeficient proatherosclerotic mice develop substantially smaller lesions than do immunocompetent siblings. Reconstitution with CD4+ T cells alone reestablishes full-blown atherosclerotic plaques in immunodeficient mice. As a consequence, a number of studies have focused on the mechanisms by which T cells are activated and become pathogenic in atherosclerosis. It has been proposed that pathogenicity of T cells is conferred by a proinflammatory Th1 polarization of atherosclerosis-related T cells. In this perspective, IL-12 and IL-18 are regarded as the cytokines synergistically responsible for differentiation of naïve Th cells into interferon (IFN)-γ-producing Th1 cells. A number of strategies have corroborated this concept, including the use of recombinant IL-12 and IL-18 in the atherosclerotic apoE knockout mouse model.

IL-18 has received particular attention because it has a strong predictive value of cardiovascular death in patients with coronary artery disease. Since its discovery in 1995, 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, macrophages, endothelial cells, and smooth muscle cells, 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 bacterial and viral 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. 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.

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, macrophages, natural killer (NK) cells, and perhaps B cells. Similar to ligands of Toll-like receptors, IL-18 signals via MyD88, which activates tumor necrosis factor (TNF) receptor–associated factor and NF-κB. This has two implications: (1) the protective effect observed in atherosclerosis-prone MyD88 knockout mice 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, which is antiatherogenic. IL-18 directly enhances cytotoxic NK cell activity, which likely contributes to atherogenesis. Finally, IL-18–driven IFN-γ production can be induced not only in T cells but also in macrophages and NK cells.

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. The authors show that IL-18–induced IFN-γ production in macrophages and NK cells is accompanied by 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
phages; DC, dendritic cells; NOS, NO synthase; COX2, cyclooxygenase 2; MMP3, stromelysin; TIR, Toll/IL-1R domain; IL-18BP, IL-18 binding protein; IRAK, IL-1 receptor–associated kinase; TRAF6, TNF receptor–associated factor 6; IL-18R, α, β, α and β chains of IL-18 receptor.

macrophages and smooth muscle cells act as targets in the absence of lymphocytes and (2) the source of IFN-γ, whether produced by innate or adaptive immune cells, is not critical for scavenger receptor upregulation and foam cell formation. However, 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 perceiveably modulate the orchestra during the acts that follow.

The inflammatory orchestra conducted by IL-18. IL-18 is produced by several cells from the innate (MØ and DC) and adaptive (T, B cells) immune systems, on stimulation by lipopolysaccharide (LPS), FasL, or interferons. The target cells of IL-18 include innate as well as adaptive immune cells. In most of the cells, IL-18 exerts a synergistic effect with IL-12 (or IL-10 for certain cells). The synergistic effect is most probably caused by the mutual upregulation of the corresponding cytokine receptors. IL-18 signals through a heterodimeric receptor which recruits MyD88 and leads to the activation of the NF-κB and AP-1 transcription factors (right inset). IL-18 signaling drives (top inset) the transcription of a set of cytokines (IFN-γ, TNF, IL-4, IL-6), chemokines (IL-8), growth factors (GM-colony-stimulating factor [CSF]), and enzymes (NOS, COX-2, MMP3). However, IFN-γ is considered to be the key molecule induced by IL-18. The study by Tenger et al shows that IL-18 can induce the production of IFN-γ in the absence of the players of the adaptive immune response. In this setting, IFN-γ exerts its effects on the innate immune cells as well as on vascular cells; the proatherogenic effect of IL-18 and IFN-γ could be caused by the upregulation of the CXCL16 scavenger receptor on macrophages and smooth muscle cells leading to enhanced foam cell formation and fatty streak growth. MØ indicates macrophages and smooth muscle cells leading to enhanced foam cell formation and fatty streak growth.

**References**


27. Zhang T, Kawakami K, Qureshi MH, Okamura H, Kurimoto M, Saito A. Interleukin-12 (IL-12) and IL-18 synergistically induce the fungicidal activity of murine peritoneal exudate cells against *Cryptococcus neoformans* through production of gamma interferon by natural killer cells. *Infect Immun*. 1997;65:3594–3599.
When Interleukin-18 Conducts, the Preludio Sounds the Same no Matter Who Plays
Giuseppina Caligiuri, Srini Kaveri and Antonino Nicoletti

doi: 10.1161/01.ATV.0000154921.49792.ef
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/25/4/655

An erratum has been published regarding this article. Please see the attached page for:
/content/25/10/e140.full.pdf

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/
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.\(^{14a}\)