Obesity, characterized by an excess of adipose tissue mass, is closely associated with an increase in cardiovascular morbidity and mortality attributable to atherosclerosis. Obesity is a major underlying risk factor for atherosclerosis through other well-known risk factors, including the major risk factors (hypercholesterolemia, hypertension, hyperglycemia) and emerging risk factors (atherogenic dyslipidemia, insulin resistance, proinflammatory and prothrombotic state). The clinical value of novel risk factors such as high-sensitivity C-reactive protein are currently subject of ongoing discussions. The clustering of major and emerging risk factors that is found in most obese patients is defined as the metabolic syndrome.

Among various cytokine-like hormones secreted by adipose tissue, the most abundant and adipose-specific is adiponectin (Figure). Reduced plasma levels of adiponectin, which are found in obese patients, are closely associated with obesity-related diseases, including atherosclerotic cardiovascular diseases, type 2 diabetes, hypertension, and dyslipidemia. Emerging experimental evidence indicates that adiponectin mediates antiatherogenic and antithrombotic effects through direct protective actions on endothelial cells, smooth muscle cells, macrophages, and platelets.

Growing evidence suggests a close association between inflammatory processes in obesity/the metabolic syndrome and atherosclerosis. Besides, it is now well accepted that immune responses participate in all phases of atherosclerosis, from its initiation through its complications, with prominent roles for both adaptive and innate immunity. Local and systemic soluble inflammatory mediators are pivotal players during the development of atherosclerotic plaques. Cytokines, chemokines, hormones, and growth factors orchestrate the recruitment and activation of immunoinflammatory cells within the plaque, with the subsequent induction of a systemic proinflammatory state, involving adipose tissue and liver.

Now it appears that obesity is associated with a low-grade inflammation of white adipose tissue resulting from chronic activation of the innate immune system, which can subsequently lead to insulin resistance, impaired glucose tolerance, and even diabetes. This may explain the close association between obesity and atherosclerosis; however, the precise underlying mechanisms of this low-grade inflammation in obesity remain to be clarified.

In the current issue of Circulation Research, Okamoto et al report new findings that clarify the underlying antiinflammatory mechanisms of adiponectin in human macrophages. The authors provide in vitro and in vivo evidence for a novel antiinflammatory property of adiponectin on macrophages that consequently inhibits T-lymphocyte recruitment and accumulation. In lipopolysaccharide (LPS)-stimulated human monocyte-derived macrophages, adiponectin suppressed the expression of T-lymphocyte chemokine attractants interferon (IFN-α)-inducible protein (IP)-10 (CXCL10), IFN-inducible T-cell α chemoattractant (I-TAC) (CXCL11), and Mig (CXCL9). These 3 chemokines, together with their corresponding receptor CXCR3, are expressed by macrophages, endothelial cells, and smooth muscle cells within human atheroma.

All 3 chemokines are potent inducers of T-lymphocyte chemotaxis and are considered to play crucial roles in the recruitment and retention of activated T lymphocytes during atherogenesis. Okamoto et al established that adiponectin suppressed the LPS-induced chemokine expression by macrophages in a concentration-dependent manner. The functional relevance of the adiponectin-mediated suppression of chemokine secretion was further demonstrated by in vitro chemotaxis assays with CXCR3-transfected lymphocytes (Figure). The CXCR3 surface expression was not altered by adiponectin, suggesting that the reduced chemotactic activity was a consequence of the strong inhibition of the CXCR3 chemokine ligands (IP-10/I-TAC/Mig) released by LPS-stimulated macrophages. On the molecular level, the authors demonstrate that the adiponectin-mediated downregulation of IP-10 expression was attributable to a reduced transcriptional activity at the promoter level, without an effect on mRNA stability.

An important finding is that adiponectin did not affect the ability of IFN-γ to induce the three CXCR3-binding chemokines in macrophages. The observation that adiponectin is able to inhibit only the LPS-induced chemokine expression suggests that adiponectin selectively acts on the Toll-like receptor (TLR)4 signaling pathway, which has been implicated recently in the development of atherosclerosis and insulin resistance. TLRs, typically known to activate innate immunity by recognizing specific patterns of microbial components, may also interact with proinflammatory pathways through activation induced by endogenously generated inflammatory ligands. To clarify the underlying pathways of TLR4 signaling, the authors investigated the potential...
induction of IFN-β, characteristic of an early response in the MyD88-independent TLR4 signaling pathway. The reduced expression of IP-10 by adiponectin was indeed preceded by a transcriptional inhibition of IFN-β expression, involving attenuation of transcription factor IFN regulatory factor (IRF) activation. On the other hand, adiponectin was shown to reduce the activation of transcription factor nuclear factor κB and, at least in part, c-Jun and activating transcription factor 2, which are involved in the MyD88-dependent pathway. The attenuation of nuclear factor κB activation by adiponectin corresponds with previously published results obtained in tumor necrosis factor-α-stimulated human aortic endothelial cells and LPS-stimulated macrophages. Based on their findings, Okamoto et al conclude that adiponectin may interact with both MyD88-dependent and -independent TLR4 signaling pathways.

It is important to note that the effective concentrations of adiponectin used in these in vitro experiments correspond well with the physiological range of adiponectin plasma levels (1 to 10 μg/mL) that can be measured in healthy (non-obese) individuals. It is of note that the lower concentration of adiponectin (0.1 μg/mL) partially suppressed the chemokine expression in LPS-stimulated macrophages on the mRNA level; however, only the physiological concentration of adiponectin (≥1 μg/mL) dose-dependently suppressed IP-10 protein secretion and CXCR3 chemotactic activity in LPS-stimulated macrophage. This may have biological importance, suggesting that higher concentrations of adiponectin found in nonobese individuals may effectively reduce proinflammatory functions of these chemokines. The physiological relevance of these new antiinflammatory properties of adiponectin was confirmed in vivo. In agreement with their in vitro findings, the authors demonstrate that adiponectin deficiency in apolipoprotein E–null mice raises plasma levels of IP-10, increases accumulation of T lymphocytes within lesions, and accelerates the development of atherosclerosis.

Figure. Antiatherogenic effects of adiponectin. The cytokine-like hormone adiponectin, which is selectively expressed by adipose cells, exhibits antiatherogenic properties through direct and indirect effects on endothelial cells (EC), smooth muscle cells (SMC), platelets, macrophages, and T lymphocytes. IL indicates interleukin; IL-1RA, IL-1 receptor antagonist; NF-κB, nuclear factor κB.

The work by Okamoto et al unveils a new unexpected bridge across obesity-related metabolic disorders and adaptive immunity. Evidence suggests that low levels of adiponectin associated with obesity favors the recruitment of T lymphocytes, which are key contributors to adaptive immune response during atherogenesis. This knowledge may be of crucial importance to better understand the complex interactions between pro- and antiatherogenic factors implicated in cardiovascular diseases.

Sources of Funding
Work performed by the authors is supported by grants from the Swiss National Science Foundation (to S.S. and F.M.). The authors belong to the European Vascular Genomics Network, a Network of Excellence supported by the European Community.

Disclosures
None.

References


**KEY WORDS:** adiponectin ■ atherogenesis ■ adaptive immunity ■ T lymphocyte ■ chemokine