Endothelial Cell IL-8, a New Target for Adiponectin
Implications in Vascular Protection
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Adipose tissue is no longer considered an inert energy storage tissue, but an active participant contributing to physiological and pathological processes associated with inflammation, immunity, appetite, insulin sensitivity, endocrine and reproductive systems, bone metabolism, and endothelial function. Adipose tissue synthesizes and secretes proinflammatory and antiinflammatory metabolically- and hormonally-active substances, collectively called adipokines or adipocytokines and include leptin, adiponectin, resistin, and visfatin. Adipose tissue also produces cytokines and chemokines, such as tissue necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-8, IL-10, transforming growth factor (TGF)-β, nerve growth factor, and the acute-phase response plasminogen activator inhibitor-1, haptoglobin, and serum amyloid. Although adipose tissue produces various polypeptide and non-protein factors, only leptin, adiponectin, resistin, adipin, and visfatin are primarily synthesized by adipocytes. Whereas leptin plays a role mainly in appetite regulation, resistin insulates insulin resistance and is proinflammatory whereas visfatin acts as an insulin mimetic and is antiapoptotic.

Of all the adipokines, adiponectin is found in highest concentrations in the circulation. It is secreted specifically from adipocytes and it regulates insulin sensitivity. Low serum levels are causally linked to insulin resistance, obesity, and type 2 diabetes and are predictive for development of diabetes and cardiovascular disease. Obesity is associated with decreased adiponectin levels, and adiponectin is now being considered a putative therapeutic agent in the management of obesity. Administration of adiponectin causes glucose-lowering effects and ameliorates insulin resistance in mice. Conversely, adiponectin-deficient mice exhibit insulin resistance and diabetes. This insulin-sensitizing effect of adiponectin seems to be mediated by an increase in fatty-acid oxidation through activation of AMP kinase and peroxisome proliferator-activated receptor-γ (PPAR-γ).

Emerging evidence indicates that adiponectin has functions beyond insulin modulation. Recent studies demonstrated that adiponectin is synthesized and secreted not only by adipocytes, but also by human and murine cardiomyocytes and hepatocytes. It is a multifunctional protein with protective roles against the development of insulin resistance, dyslipidemia, nonalcoholic fatty liver disease, atherosclerosis, cardiac hypertrophy, and ischemic injury. These actions are mediated in large part through the antiinflammatory properties of adiponectin. However, the understanding of the molecular mechanisms whereby adiponectin achieves these effects is still poor, and there is still much debate as to whether adiponectin is indeed an antiinflammatory hormone or merely a modulator of innate immunity.

Kobashi et al show that adiponectin also downregulates IL-8. But why focus on IL-8? IL-8, or CXCL8, is a chemokine initially characterized for its leukocyte chemotactic activity but now known to possess tumorigenic, proangiogenic, proinflammatory, and proatherogenic properties as well. Interleukin-8 plays a causative role in acute inflammation by recruiting and activating neutrophils. It also promotes vascular smooth muscle cell proliferation and migration and is critical for chemotaxis and adhesion of monocytes to endothelial cells, a pivotal step in the initiation of atherogenesis. In addition, circulating levels of these proinflammatory cytokines increase in patients with acute myocardial infarction and unstable angina. IL-8 is upregulated in the infarcted area and induces neutrophil infiltration and inflammation. Hence inhibition of IL-8 by adiponectin may have important antiinflammatory, antiatherogenic, and cardiovascular protective effects.

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However, what still remains unclear is the signaling network underlying the inhibitory effects of adiponectin on TNF-\(\alpha\) and how it attenuates IL-8 synthesis. Kobashi et al elegantly demonstrate that adiponectin modulates the inflammatory response to TNF-\(\alpha\) by inhibiting NF-\(\kappa\)B, a proinflammatory transcription factor, through decreased phosphorylation of I\(\kappa\)B, which normally induces activation and nuclear translocation of N-FkB. This inhibitory effect is accomplished through protein kinase A (PKA)-dependent pathways, because PKA inhibition abrogated adiponectin-mediated inhibition of TNF-\(\alpha\) actions. Similar findings were reported by Ouchi et al who demonstrated that adiponectin inhibits TNF-\(\alpha\)-dependent phosphorylation and degradation of I\(\kappa\)B through a cAMP–PKA-sensitive pathway. In addition, Kobashi et al show that adiponectin reduces IL-8 generation through activation of PI3K-sensitive pathways by enhancing Akt phosphorylation. Pharmacological inhibition of PI3 kinase and siRNA silencing of Akt attenuated adiponectin-induced Akt activation and TNF-\(\alpha\)-elicited IL-8 synthesis, thus identifying a second mechanism for adiponectin–IL-8 effects. Taken together these findings suggest that IL-8–mediated anti-inflammatory actions of adiponectin involve two distinct processes. Firstly through PKA-regulated inhibition of NF-\(\kappa\)B, and secondly through activation of PI3 kinase/Akt, a well-established cell survival pathway (Figure).

The study of Kobashi and colleagues certainly expands our knowledge exploring some mechanisms by which adiponectin negatively modulates IL-8 and inflammatory responses. However, a few thought-provoking questions and limitations of the study arise that warrant further consideration. Firstly, what is the clinical significance of an adipokine that is produced by adipose tissue that may be physically unrelated to endothelial cells? Histological examination has shown that perivascular white adipose tissue is actually in very close proximity to vascular walls, particularly at sites that have a tendency to develop atherosclerosis. Henrichot et al demonstrated that at a functional level, supernatant from subcutaneous and perivascular white fat strongly induced chemotaxis of peripheral blood leukocytes. The migration of granulocytes and monocytes was mediated primarily by IL-8 and MCP-1, respectively, whereas both chemokines contributed to the migration of activated T cells. Moreover, human perivascular white adipose tissue produces IL-8 as shown by immunohistochemistry and by explant culture. Accumulation of macrophages and T cells at the interface between adipose tissue and the vascular wall may thus reflect a prochomotactic activity of adipocyte-derived adiponectin, supporting an important relationship between adipose tissue and vascular cells.

Secondly, how does adiponectin mediate signaling events in endothelial cells? Recently, cloning of adiponectin receptors I and II (adipoRI and adipoRII) was reported. Whereas in mice adipoRI is abundantly expressed in skeletal muscle, adipoRII is predominantly expressed in the liver. HL-1 cells (a cultured line derived from murine atrial cardiomyocytes and cultured human cardiomyocytes) have also been shown to express genes for AdipoRI and AdipoRII. These receptors are predicted to contain 7 transmembrane domains but are structurally, topologically, and functionally distinct from GPCRs. They do not seem to be coupled with G protein but activate unique sets of signaling molecules such as PPAR-\(\alpha\), AMPK, and p38 MAPK. Thus, adiponectin receptors may comprise a new receptor family. Whether vascular cells, and particularly endothelial cells, express adiponectin receptors I and II is unknown. It would have been interesting and important for Kobashi’s group to demonstrate that AdipoRI and AdipoRII are present and functionally active in their experimental paradigm of human aortic endo-
Adiponectin inhibits TNF-α-mediated IL-8 synthesis, and multiple signaling pathways are involved in adiponectin-induced actions. Whether these findings will have (patho)physiological significance in the regulation of endothelial function in intact vessels and whether these processes contribute to antiinflammatory and antiatherogenic actions of adiponectin in pathological conditions associated with atherosclerosis and vascular disease remain to be elucidated.

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References


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