A Novel Role for Adiponectin in the Regulation of Inflammation

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A ccumulating evidence indicates that chronic inflammation linked to obesity is closely associated with the development of diabetes and cardiovascular disorders. The inflammatory marker C-reactive protein (CRP) has been shown to be an independent predictor of future risk for cardiovascular events and a risk factor of developing diabetes. High levels of CRP are also associated with obesity and coronary heart disease, suggesting that CRP is a useful biomarker for obesity-linked chronic inflammatory states. Furthermore, although CRP is primarily made by liver, new studies have shown that CRP is also produced by diseased tissues (e.g., atherosclerotic lesions) and by various cell types including macrophages, smooth muscle cells, and endothelial cells. Increasing evidence indicates that CRP is not just a biomarker of inflammation but that it has a direct proinflammatory action through its ability to promote the induction of cytokines. Thus, agents that lower CRP levels have clinical utility for treatment of inflammatory diseases.

A number of experimental studies with genetic loss-of-function manipulations indicate that ablation of adiponectin contributes to diet-induced insulin resistance, increased vascular remodeling in response to injury, and severe cardiac damage under ischemic conditions. A series of in vitro experiments have demonstrated that adiponectin inhibits the production and action of TNFα, a key proinflammatory cytokine, in various types of cells including cardiac and vascular cells. Thus, adiponectin exerts beneficial actions on the obesity-related metabolic and cardiovascular complications, at least in part, through its ability to control inflammatory responses.

In this issue of ATVB, Devaraj et al demonstrate that physiological concentrations of adiponectin suppress CRP synthesis and secretion in human aortic endothelial cells under hyperglycemic conditions. In addition, adiponectin was shown to reduce CRP production in response to cytokine stimuli in primary rat hepatocytes. Devaraj et al demonstrated that adiponectin inhibits high glucose–induced CRP production through its ability to suppress nuclear factor-κ B (NF-κB) activation. These findings are consistent with previous studies showing that adiponectin attenuates TNF-α–induced NF-κB activation in endothelial cells, resulting in reduced expression of cell adhesion molecules and interleukin (IL)-8. Adiponectin has also been shown to inhibit agonist-stimulated NF-κB signaling and suppress TNF-α secretion from a number of cell types including macrophages.

Devaraj et al demonstrate that adiponectin inhibits CRP production in endothelial cells through its ability to modulate the AMP-kinase (AMPK) signaling pathways (Figure). Specifically they show that AMPK inhibition attenuates the ability of adiponectin to suppress NF-κB activity and CRP production. AMPK is a stress-activated protein kinase that promotes cell survival and activates catabolic cellular pathways under conditions of ischemia. Adiponectin activates AMPK signaling in hepatocytes, myocytes, and endothelial cells, and this increase in AMPK signaling is believed to contribute to the insulin-sensitizing and cardioprotective actions of adiponectin. Consistent with the findings of Devaraj et al, AMPK activation by AICAR has been shown to inhibit fatty acid–induced NF-κB activation in endothelial cells.

Besides the inhibition of NF-κB signaling in target cells, adiponectin may exert antiinflammatory actions through mechanisms that do not involve the activation of intracellular signaling. Adiponectin levels in serum are 1000-fold higher than many growth factors and cytokines. Thus, it is difficult to understand why adiponectin levels are so high if its only function is to serve as a ligand for a conventional receptor.
Adiponectin

AMPK → NF-κB

CRP
IL-8
Adhesion molecules
Endothelial cells

NF-κB → Clearance of apoptotic cells
TNF-α

Macrophages

Figure. Anti-inflammatory actions of adiponectin. Adiponectin inhibits NF-κB activation in endothelial cells, at least in part, by its ability to activate AMPK. Inhibition of NF-κB by adiponectin results in downregulation of CRP, IL-8, and adhesion molecule expression. In macrophages, adiponectin attenuates TNF-α production through its ability to suppress NF-κB activation, and it promotes the clearance of apoptotic cells by macrophages.

diseases. Although its beneficial actions of adiponectin in metabolic and cardiovascular homeostasis are reasonably well understood, the anti-inflammatory actions of this multifunctional protein involve a variety of mechanisms that are poorly defined. The study of Devaraj et al extends our knowledge of how adiponectin protects against the development of inflammation and provides an additional mechanistic link between obesity and vascular inflammation. Because immune system dysfunction is a component of many disease processes, further elucidation of the anti-inflammatory action of adiponectin may lead to the identification of new roles for this adipokine.

Disclosures

None.

References


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