A Novel Role for Adiponectin in the Regulation of Inflammation

Noriyuki Ouchi, Kenneth Walsh

Accumulating 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. 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 signaling pathway system. Because of its high abundance, it is conceivable that adiponectin possesses another function that involves low affinity macromolecular interactions. Recently, it has been shown that adiponectin binds apoptotic cells and promotes their phagocytosis by macrophages through its ability to form a bridge between dead cells and macrophages. This activity is mediated through the binding of adiponectin to a new receptor, calreticulin, on the macrophage cell surface and recognition motifs referred to as apoptotic cell-associated molecular patterns (ACAMPS) on the dead cell surface. It is well documented that impaired removal of apoptotic debris by phagocytic cells results in exacerbated symptoms of systemic inflammation and immune dysfunction. The accumulation of dead cells will promote inflammation because they release noxious substances and trigger a robust inflammatory response when they are encountered by immune cells. Accordingly, it has been shown that adiponectin deficiency leads to impaired clearance of early apoptotic cells, and this is associated with severe systemic inflammation under certain pathological conditions.

Like adiponectin, the structurally-related collectin family proteins including C1q, and the abundant lung surfactant proteins limit systemic inflammatory and immune responses through their ability to opsonize dying cells and accelerate their removal by macrophages. These collectin family proteins share homology with adiponectin. Like adiponectin, these proteins possess a collagenous tail and a globular head, and they form multimeric structures. In this regard, the multimeric form of adiponectin was recently shown to be structurally similar to C1q by dynamic light scattering and electron microscopic analyses. Furthermore, adiponectin has been shown to activate the classical pathway of complement through its ability to bind to C1q. Collectively, these data indicate that adiponectin functions, like other members of the collectin family of proteins, to suppress inflammation through its ability to promote the removal of early apoptotic cells by macrophages.

It is becoming increasingly clear, from a number of clinical and experimental studies, that adiponectin plays an important role in the development of obesity-linked inflammatory 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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