Letters to the Editor

Response to Comment on: Goldstein et al. (2007) Globular Adiponectin Activates Nuclear Factor-κB and Activating Protein-1 and Enhances Angiotensin II–Induced Proliferation in Cardiac Fibroblasts: *Diabetes* 56:804–808

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Goldstein et al. (1) expressed concern that our findings of nuclear factor-κB (NF-κB) activation by the globular domain adiponectin appear to contradict a substantial body of published and ongoing work. We showed that globular adiponectin activates redox-sensitive transcription factors in two different cell types: vascular endothelial cells and cardiac fibroblasts (2,3). These findings do not always contrast with a substantial body of published work. Indeed, a very recent report suggests that adiponectin exerts proinflammatory activities in colon by inducing production of proinflammatory cytokines and inhibiting bioactivity of protective growth factors (4). As initially reported by Ouchi et al. (5), adiponectin suppresses inflammatory endothelial responses, including reversing the activation of NF-κB and reducing adhesion molecule expression. In their study, however, endothelial cells were preincubated for 18 h with adiponectin and then exposed to tumor necrosis factor (TNF)-α (5). This long preincubation may cause hyporesposiveness or desensitization to TNF-α through preactivation of NF-κB. Indeed, our data show that TNF-α–induced NF-κB–mediated gene transcription was suppressed by globular adiponectin pretreatment in a dose-dependent manner when cells were pretreated with various concentrations of globular adiponectin for 16 h and followed by stimulation with TNFα, while coactivation of adiponectin with TNFα further increased the TNF-α–induced NF-κB–mediated gene transcription (2,3). Thus, timing of addition of adiponectin appears to be an important factor, at least in experiments with cultured cells.

We are now investigating the effects of high–molecular weight (HMW) adiponectin on endothelial cells compared with globular adiponectin, as experimental and clinical data suggest that the oligomeric complex distribution of adiponectin is critical for the antidiabetic and antiatherogenic activity of this hormone (6). We purified HMW adiponectin, which mainly consists of 18 molecules, from human plasma (7). Microarray analysis of cDNA from the RNA prepared from vascular endothelial cells untreated or treated with HMW adiponectin for 8 h revealed that HMW adiponectin modestly increased the expression of intracellular adhesion molecule-1, E-selectin, and vascular cell adhesion molecule-1. HMW adiponectin was found to modestly activate NF-κB and needs a shorter preincubation time to be inhibitory against TNF-α–induced NF-κB activation when compared with globular adiponectin. On the other hand, HMW adiponectin activated AMPK, which causes increased phosphorylation of endothelial nitric oxide synathase at Ser1177, and increased nitric oxide production in a manner similar to that of globular adiponectin (8). HMW and globular adiponectin may activate similar cell-signaling pathways, but to different degrees, through the same receptors (9). However, the manner of interaction with receptors and postbinding events probably differ. We are currently investigating this issue.

Waki et al. (10) demonstrated that adiponectin can be cleaved by leukocyte elastase secreted from activated monocytes and/or neutrophils, and this cleavage could be a possible mechanism for the generation of the globular fragment of adiponectin in plasma. However, it is unknown whether adiponectin cleavage in inflammatory sites results in sufficient globular adiponectin concentration to activate NF-κB. Under normal conditions, higher concentrations of HWM adiponectin flow in the vessels. This indicates that the basic function of adiponectin is to protect against inflammatory stimuli, whereas adiponectin cleavage at inflammatory sites might facilitate the atherogenic process and cardiac hypertrophy.

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