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A new role for fat: Protective action of adiponectin

Two novel findings, observed using proteomics methodologies, are reported in the January 2007 *Journal of Clinical Investigation*. Kenneth Walsh, Ph.D., Professor of Medicine, and his group, who study "Circulating Endothelial Progenitor Cells" in Boston University School of Medicine's Cardiovascular Proteomics Center, describe a previously undocumented activity of adiponectin, binding to a previously undocumented adiponectin receptor, calreticulin, expressed on the surface of macrophages. Adiponectin, a protein produced by fat tissue, acts as a bridge molecule between macrophages that remove cellular debris, says Dr. Walsh. Thus this work demonstrates a new role for fat.

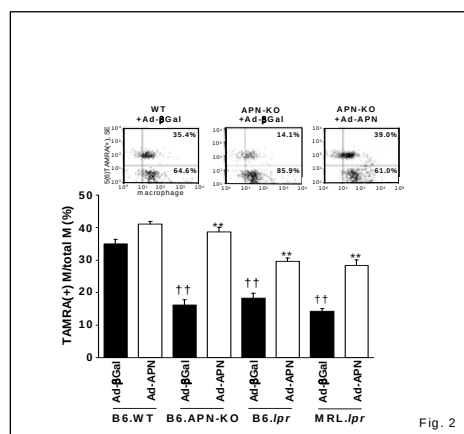
In a series of experiments using four different mouse models, adiponectin administration clearly increased the uptake of apoptotic debris versus control and did so with statistical significance. Because decreased immune function leads to an inability to clear apoptotic cells, the study suggests that adiponectin can downregulate the inflammatory process. To identify the novel adiponectin receptor, a proteomic analysis was used on membrane fractions that were precipitated with a tagged adiponectin protein.

The mechanism of action of adiponectin's anti-inflammatory properties is not clearly defined. Obesity contributes to chronic tissue inflammation and this dysfunctional state leads to a suppression of adiponectin expression. In their investigation of the molecular basis of inflammatory reactions, the researchers hypothesize that low levels of adiponectin contribute to obesity-linked inflammation and present evidence of the protective action of adiponectin by the calreticulin receptor pathway, prompting the question, are lean bodies, which have 2-3 times higher circulating adiponectin levels than obese, protected while obese are not?

Understanding inflammatory response systems is of importance in understanding the disease processes of atherosclerosis, diabetes, and heart disease.

Takemura Y, Ouchi N, Shibata R, Aprahamian T, Kirber MT, Summer RS, Kihara S, and Walsh K. Adiponectin modulates inflammatory reactions via calreticulin receptor-dependent clearance of early apoptotic bodies. *J Clin Invest* 2007; 117(2): 375-386. doi: 10.1172/JCI29709.

ABSTRACT: Obesity and type 2 diabetes are associated with chronic inflammation. Adiponectin is an adipocyte-derived hormone with anti-diabetic and anti-inflammatory actions. Here, we demonstrate



In figure 2, phagocytosis was scored as the percentage of F4/80-positive macrophages that also stained positive

for TAMRA, SE. Scatter plots show representative flow cytometry data for 3 experimental conditions. Dual-labeled cells are represented in the upper right quadrant. **P<0.01 versus Ad-β-gal; ++P<0.01 versus WT (n=6).

what we believe to be a previously undocumented activity of adiponectin, facilitating the uptake of early apoptotic cells by macrophages, an essential feature of immune system function. Adiponectin-deficient (APN-KO) mice were impaired in their ability to clear apoptotic thymocytes in response to dexamethasone treatment, and these animals displayed a reduced ability to clear early apoptotic cells that were injected into their intraperitoneal cavities. Conversely, adiponectin administration promoted the clearance of apoptotic cells by macrophages in both APN-KO and wild-type mice. Adiponectin overexpression also promoted apoptotic cell clearance and reduced features of autoimmunity in *lpr* mice whereas adiponectin deficiency in *lpr* mice led to a further reduction in apoptotic cell clearance, which was accompanied by exacerbated systemic inflammation. Adiponectin was capable of opsonizing apoptotic cells, and phagocytosis of cell corpses was mediated by the binding of adiponectin to calreticulin on the macrophage cell surface. We propose that adiponectin protects the organism from systemic inflammation by promoting the clearance of early apoptotic cells by macrophages through a receptor-dependent pathway involving calreticulin.

Journal of Clinical Investigation is the monthly peer-reviewed journal of the American Society for Clinical Investigation, an honor society of physician-scientists. JCI has published top-tier, biologically relevant findings with clinical significance since 1924. It's ISI Impact Factor® is 15.053 (2005).