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Studies on the inhibitory mechanism of soy isoflavone daidzein on obesity-induced inflammation

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Obesity-induced inflammation caused by adipocyte-macrophage interactions plays a critical role in developing insulin resistance, and peroxisome proliferator-activated receptors (PPARs) regulate inflammatory gene expression in these cells. Recently, the soy isoflavones were reported to act like an activator of PPARs. Although PPARs play a role in regulation of pro-inflammatory genes expression, it has not been well researched whether soy isoflavones affect expression of these genes. This study aimed to clarify the effects of daidzein, a soy isoflavone, on pro-inflammatory cytokines and adipose inflammation causing insulin resistance in obesity.

1. Favorable effects of isoflavone daidzein on inflammatory mediator through the PPARγ in cultured adipocytes.

We examined whether daidzein affected adipocyte via the regulation of PPARγ. 3T3-L1 adipocytes were treated with daidzein. The results showed that daidzein stimulated adipogenic differentiation in 3T3-L1 adipocytes with the activation of PPARγ. Daidzein also increased adiponectin mRNA levels and decreased monocyte chemo-attractant protein 1 (MCP-1) mRNA levels with the consistent regulation of their secretion. Furthermore, GW9662 (a PPARγ antagonist) cancelled induction of adiponectin mRNA levels by daidzein. In contrast, this inhibitor failed to cancel the daidzein-induced reduction of MCP-1 mRNA levels. These results suggest that daidzein might regulate adipokine expression through the PPARγ, in part, thereby improving the adverse effects of adipose inflammation, such as insulin resistance.

2. Suppressive effects of daidzein on chronic inflammation through the PPARα/γ and NF-κB/MAPK signal pathways.

We examined whether daidzein affected adipocyte-macrophage crosstalk via the regulation of PPARs. Direct activation of PPARα and PPARγ by daidzein was confirmed by a luciferase reporter assay. Then, co-cultures of 3T3-L1 adipocytes and RAW264 macrophages, or palmitate stimulated RAW264 macrophages were treated with daidzein in the presence or absence of specific inhibitors for PPARs: GW6471 (a PPARα antagonist), and GW9662 (a PPARγ antagonist). Inflammatory gene

expression and their secretion were then determined. Daidzein also significantly decreased MCP-1 and interleukin 6 (IL-6) mRNA levels with the consistent regulation of their secretion induced by co-culture. In 3T3-L1 adipocytes, daidzein inversed the attenuation of adiponectin gene expression by co-culture, and these effects were inhibited by the PPARγ specific inhibitor. Daidzein also decreased MCP-1 and IL-6 mRNA levels in RAW264 macrophages stimulated with palmitate or conditioned medium (CM) from hypertrophied 3T3-L1 adipocytes. This inhibitory effect on IL-6 expression was abrogated by a PPARα inhibitor. Additionally, we found that daidzein significantly inhibited palmitate-induced phosphorylation of c-Jun N-terminal kinase (JNK).

In conclusion, these studies provides in vitro evidence that daidzein regulates the pro-inflammatory gene expression in adipocyte-macrophage co-cultures via multiple pathways in which PPARα, PPARγ and JNK are involved. These effects might be favorable in improving adipose inflammation, thus, treatment of daidzein may be a therapeutic strategy for chronic inflammation in obese adipose tissue.