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An increase in insulin sensitivity of 3T3-L1 adipocytes induced by transmembrane Tumor Necrosis Factor-α

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Tumor necrosis factor (TNF)-α is a proinflammatory cytokine that links obesity and insulin resistance. However, the effect of transmembrane TNF-α (tmTNF-α) on insulin resistance remains unknown. Here, we demonstrated that high concentration of glucose(25mM) significantly reduced insulin-induced glucose uptake by 3T3-L1 adipocytes that was concomitant with a decrease in tmTNF-α expression but an increase in soluble TNF-α(sTNF-α) secretion. This insulin resistance, however, could be reversed in part by neutralization of TACE using a specific antibody to prevent the cleavage of tmTNF-α into sTNF-α, as manifested by enhancement of insulin-induced glucose uptake, pointing out a possible different role of tmTNF-α in insulin resistance. Then, we stimulated 3T3-L1 adipocytes with exogenous tmTNF-α and sTNF-α respectively, and found that sTNF-α inhibited insulin-induced tyrosine phosphorylation of IRS-1 and AKT phosphorylation, leading to suppression of the glucose uptake induced by insulin. In contrast, tmTNF-α has been shown to elevate insulin-induced glucose uptake by twofold as a result of promoting the insulin signaling. Furthermore, we found that tmTNF-α downregulated the expression of IL-6 and MCP-1 through inactivation of NF-κB and upregulated the expression of adiponectin through PPAR-γ in 3T3-L1 adipocytes. Inhibition of PPAR-γ expression by GW9662, an inhibitor of PPAR-γ, could decrease tmTNF-α-induced adiponectin transcription, blocking tmTNF-α-enhanced AKT phosphorylation and glucose uptake. These data suggest that tmTNF-α may contribute to the improvement of insulin resistance, which is opposite to sTNF-α, thereby specific blockage of tmTNF-α conversion into sTNF-α may be useful to increase insulin sensitivity for the clinical treatment of type 2 diabetes.

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