Effects of TWEAK (TNF superfamily member 12) on differentiation, metabolism, and secretory function of human primary preadipocytes and adipocytes.

Expansion of adipose tissue mass by hypertrophy and hyperplasia is the hallmark of obesity. An automated cDNA screen was established to identify secreted human proteins with an inhibitory effect on adipocyte differentiation and, thereby, a potential inhibitory effect on adipose tissue growth. A member of the TNF superfamily, TNF-like weak inducer of apoptosis (TWEAK; TNF superfamily 12) was identified by means of high-throughput screening with the lipophilic dye Nile Red as an inhibitor of murine adipocyte differentiation and, subsequently, also of human adipocyte differentiation. TWEAK inhibited lipid deposition in a dose-dependent manner without causing cytotoxic effects. This inhibitory action was mimicked by an agonistic antibody of the TWEAK receptor. The TWEAK receptor (fibroblast growth factor inducible 14; CD266) was expressed on human primary preadipocytes and mature adipocytes. Knockdown of TWEAK receptor by short-hairpin RNA abolished the inhibitory effect of TWEAK on cell differentiation, demonstrating that the effects of TWEAK are mediated by its specific receptor. Inhibition of differentiation was the result of interference at an early step of transcriptional activation as assessed by decreased peroxisome proliferator-activated.
receptor-gamma, CCAAT enhancer-binding protein alpha (C/EBPalpha), and CCAAT enhancer-binding protein beta (C/EBPbeta) mRNA expression. In contrast to TNFalpha, basal and insulin-stimulated glucose uptake and lipolysis of terminally differentiated mature adipocytes and secretion of proinflammatory cytokines were not altered in the presence of TWEAK, and nuclear factor kappa B activity was only weakly induced. We conclude from our findings that TWEAK and the corresponding agonistic antibody have the potential to prevent adipose tissue growth without adversely influencing central metabolic pathways or proinflammatory cytokine secretion in adipose tissue.