Identification of macrophage inhibitory cytokine-1 (MIC-1) in adipose tissue and its secretion as an adipokine by human adipocytes

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MIC-1, a divergent member of the transforming growth factor-β superfamily, is involved in the control of multiple cellular functions. Recently, MIC-1 has been implicated as a cachexia mediator inducing weight loss through the inhibition of appetite. Adipose tissue as an endocrine organ secretes proteins (adipokines), which modulate appetite, nutrient metabolism, insulin sensitivity, stress responses and inflammation. Given the diverse roles of MIC-1, adipose tissue could be important in the physiological function of this factor. The aim of the present study was therefore to examine whether MIC-1 is expressed in adipose tissue and whether it is a secretory product of adipocytes. The study also investigated factors that modulate MIC-1 production and the potential role of MIC-1 in adipocytes.

Mouse adipose tissues were collected from different depots of C57Bl/6 mice. Adipose tissue (visceral and subcutaneous) was also collected from human subjects with a wide range of BMI, undergoing general or bariatric surgery. For in vitro studies 3T3-L1 pre-adipocytes and human preadipocytes (Zen-Bio) were used and induced to differentiate into adipocytes in cell culture.

MIC-1 mRNA was detected in the major mouse adipose tissue depots (epididymal, perirenal, subcutaneous). In these depots MIC-1 gene expression was evident in both isolated mature adipocytes and stromal vascular cells. In 3T3-L1 adipocytes MIC-1 mRNA was detected before and after differentiation. Administration of leptin and IL-1β led to a reduction in MIC-1 mRNA levels (both Pf0.01). Treatment with H2O2 induced a dose-dependent increase in MIC-1 mRNA (P<0.01) while 15-deoxy-12,14-PGJ2 (15d-PGJ2) caused a marked up-regulation of MIC-1 transcripts (19-fold; Pf0.001).

MIC-1 mRNA and protein secretion were evident in human preadipocytes as well as differentiated adipocytes. MIC-1 gene expression and protein secretion by human adipocytes were stimulated by H2O2 and 15d-PGJ2 (all Pf0.01). In addition, recombinant MIC-1 increased adiponectin secretion by differentiated human adipocytes. MIC-1 mRNA and protein were also observed in human subcutaneous and visceral fat. MIC-1 mRNA levels were positively correlated with adiponectin mRNA in both visceral (r 0.43, P<0.05, n 23) and subcutaneous (r 0.65, P<0.01, n 16) depots. Moreover, MIC-1 mRNA was negatively associated with BMI (r −0.53, P<0.01, visceral; r −0.56, P<0.05, subcutaneous) and body fat mass (r −0.47, P<0.05, visceral; r −0.49, P<0.05, subcutaneous) in human subjects.

It is concluded that MIC-1 is expressed in adipose tissue and secreted from adipocytes and is therefore a new adipokine. Recombinant MIC-1 enhances adiponectin release, suggesting that it is a positive regulator of adiponectin. Taken together, MIC-1 as a novel adipokine may well have a paracrine role in the modulation of adipose tissue function and body fat mass.

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