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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[1], 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[2]. Adipose tissue as an endocrine organ secretes proteins (adipokines), which modulate appetite, nutrient metabolism, insulin sensitivity, stress responses and inflammation[3]. 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 $P<0.01$). Treatment with H_2O_2 induced a dose-dependent increase in MIC-1 mRNA ($P<0.01$) while 15-deoxy-12,14-PGJ_2 (15d-PGJ_2) caused a marked up-regulation of MIC-1 transcripts (19-fold; $P<0.001$).

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 H_2O_2 and 15d-PGJ_2 (all $P<0.01$). 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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