

Linking adipocyte stress to insulin resistance in obesity

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A developing paradigm suggests that obesity induces adipose tissue alterations that activate stress-sensitive signaling pathways. These in turn alter adipose tissue metabolic/endocrine function. A typical example is the putative link between visceral fat inflammation, JNK1 activation, adipose tissue IL-6 secretion, hepatic steatosis and insulin resistance.

We have addressed several outstanding questions related to this paradigm and its (patho)physiological implications: *(i) How is stress signaling transmitted in human adipose tissue in obesity?* Comparing omental to subcutaneous-abdominal adipose tissue from lean and obese women, we propose that obesity is associated with activation of a signaling cascade involving the MAP3K Ask1 (but not Tak1 or MLK3), the MAP2Ks MKK4,3,6 (but not MKK7), and the MAPKs JNK and p38MAPK. *(ii) What is the stress type that develops in intra-abdominal fat in human obesity?* Ask1 is a MAP3K typically activated by inflammatory, oxidative, and endoplasmic reticulum stress. To this end we show increased carbonylation and S-nitrosylation of omental adipose tissue proteins in obesity, consistent with elevated oxidative stress. In addition, omental Ask1 highly correlates with the degree of adipose tissue macrophage infiltration, and can be activated in cultured adipocytes by TNF α and IL-1 β , suggesting a role for inflammatory processes. *(iii) What is the functional significance of activation of this stress signaling pathway?* Ask1 in omental (but not in subcutaneous) fat is an independent predictor of whole-body insulin resistance by a multivariate model. To assess whether this may be due to altered secreted products from adipocytes, we utilized cellular models. Conditioned medium from adipocytes pre-treated with TNF α (an Ask1 activator) induces insulin resistance in hepatoma cells, with IL-1 β playing a mediatory role, acting in a combined autocrine (inducing IL-6) and endocrine manner. Furthermore, we unraveled a novel cellular mechanism for TNF-induced lipolysis (contributing to elevated FFA release), whereby protein degradation rate of perilipin increases via lysosome-related processes, possibly autophagy.

In conclusion, we propose that (central) obesity activates a particular stress-sensing MAP kinase pathway, potentially reflecting adipocyte inflammatory and oxidative stress. Its functional significance may be the alteration of secreted products from adipocytes, characterized by elevated proinflammatory cytokines and FFA, which mediate disturbed autocrine-paracrine-endocrine crosstalk that results in hepatic and whole-body insulin resistance.