Letter to the Editor

Comment on: Hosagai et al. (2007) Adipose Tissue Hypoxia in Obesity and Its Impact on Adipocytokine Dysregulation: *Diabetes* 56:901–911

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We noted with interest the article (1) where evidence for hypoxia in white adipose tissue (WAT) of two mouse models of obesity was presented. This study indicated that the expression of some adipokine genes, including leptin and plasminogen activator inhibitor-1, are increased in WAT of obese animals, that adiponectin is decreased, and that the effects mirrored those in studies on mouse 3T3-L1 cells (1).

These findings are consistent with our original proposition that hypoxia underlies the inflammatory response in WAT as tissue mass expands (2). We proposed that the dysregulation of the production of inflammation-related adipokines in obesity (underpinning the development of obesity-associated diseases) is a response to hypoxia in clusters of adipocytes distant from the vasculature (2). This is built on suggestions that hypoxia may stimulate angiogenic factor expression and neovascularization in WAT (3).

There are further important antecedents to acknowledge. In 2003, it was shown that the production of angiogenic factors, including vascular endothelial growth factor and leptin, increased in 3T3-F442A adipocytes in response to hypoxic conditions (3). In early 2006, a study with 3T3-L1 cells found that plasminogen activator inhibitor-1 expression and release is augmented by hypoxia (4). Importantly, this also showed that adiponectin production is inhibited under hypoxic conditions. Thus, hypoxia induces a proinflammatory/proangiogenic response in mouse WAT.

The reports linking hypoxia to adipokines have focused on mouse WAT and murine cells. However, in recent studies, we have demonstrated that hypoxia also induces the expression and secretion of inflammation-related adipokines in human adipocytes, including interleukin-6, leptin, vascular endothelial growth factor, angiopoietin-like protein 4, and migration inhibitory factor (5). In contrast, adiponectin production is inhibited by hypoxia in human adipocytes (5).

The concept that hypoxia may underlie the inflammatory state in WAT in obesity through changes in the production of inflammation-related adipokines (2) clearly has growing support. The effects of hypoxia on adipocytes extend, however, beyond adipokines because hypoxic conditions lead to increased GLUT1 gene expression in murine (1) and human (5) adipocytes. We also note that, in addition to adipocytes, hypoxia is likely to affect macrophages and other cells within WAT.

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