The Mechanism for Adipose Endotrophin Production

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The extracellular matrix (ECM) not only provides a structural support network for the assembly of individual cells into tissues but also affects growth, recruitment, differentiation, and function of the composing cells. In obesity, adipose tissue ECM undergoes remodeling, with dramatic changes in the absolute amount and composition of the components, contributing to the development of adipose tissue dysfunction (1). Adipose tissue ECM contains multiple types of collagen but is most enriched with collagen VI (COL6) (2,3). COL6 is a collagenous glycoprotein composed of three chains (α1, α2, and α3, encoded by 6 genes, Col6a1 to Col6a6) forming heterotrimeric monomers, which can be further assembled into dimers or tetramers. The COL6 α3 subunit (COL6A3) is the longest subunit (with the chain length ranging from 2,500 to 3,100 amino acids), and the expression of COL6A3 is increased in obese mouse adipose tissue compared with that of lean mice. ob/ob mice lacking Col6a3 show reduced adipose tissue inflammation and improved glucose tolerance (4), suggesting that the accumulation of COL6A3 in obese adipose tissue contributes to the development of adipose tissue dysfunction, leading to systemic metabolic defects.

Once secreted into extracellular space, COL6A3 first associates into microfibrils to support organizing ECM components. COL6A3 can then be cleaved into smaller fragments by enzymes existing in the extracellular space. A cleavage product of the carboxyterminal C5 domain of COL6A3 (containing 77–80 amino acids), termed endotrophin, accumulates in obese adipose tissue and serves as a signaling molecule enhancing adipose tissue inflammation and fibrosis (5,6). Inducible overexpression of endotrophin in adipocytes exacerbates insulin resistance, whereas administration of endotrophin-neutralizing antibodies improves insulin sensitivity with reduced adipose tissue inflammation and fibrosis in obese mice (6). However, it was not known how COL6A3 is processed to produce endotrophin in the ECM or whether the cleavage process is regulated.

Obesity-induced adipose tissue ECM remodeling (or adipose tissue fibrosis) is largely associated with decreased tissue oxygen tension (or hypoxia) that occurs due to increased adipocyte oxygen consumption and decreased supply (vascular rarefaction and vascular dysfunction) (7–9). This stabilizes hypoxia-inducible factor 1α (HIF-1α), which reprograms adipocyte metabolism to increase nitric oxide (arginine metabolism) and lactate (glycolysis) production, causing insulin resistance and increased hepatic glucose output. HIF-1α also stimulates fibro-inflammatory gene expression (including Col6a3), the chronic activation of which leads to adipose tissue dysfunction and systemic insulin resistance (7–9). Adipocyte-specific depletion of HIF-1α improves, whereas adipocyte-specific overexpression of HIF-1α induces, adipose tissue inflammation, fibrosis, insulin resistance, and glucose intolerance in obese and lean mice, respectively (7–9). In humans, adipose tissue oxygen tension is lower in individuals with obesity than in lean individuals (10). Moreover, adipose tissue oxygen tension is positively correlated with metabolic health in individuals with obesity (10).

In this issue of Diabetes, Jo et al. (11) provide new insights that fill the gaps in our understanding of how adipose tissue endotrophin production is increased in obesity. They find that matrix metalloproteinase 2 (MMP2), MMP9, and MMP16 mediate stepwise cleavage of COL6A3 to efficiently produce endotrophin (Fig. 1). Interestingly, they also show that the expression of these MMPs is maintained at relatively low levels in normal/lean mouse adipose tissue by a microRNA, miR-29. However, in obesity, hypoxia-dependent suppression of miR-29 expression derepresses MMP2, MMP9, and MMP16 expression, contributing to increased COL6A3 cleavage and endotrophin production. Of interest, all three of these MMPs were produced mainly by stromal vascular cells instead of adipocytes, suggesting that adipose endotrophin production is coordinated by adipocyte COL6A3 and stromal MMP2, MMP9, and MMP16 expression. Indeed, they show that overexpression of miR-29...
locally in adipose tissue of obese mice using an adenovirus-associated viral vector system reduced adipose endotrophin production and improved glucose and insulin tolerance in adipocyte-specific enzyme system mediating adipose endotrophin production. The authors suggest that targeting HIF-1α and miR-29 in combination can provide additive metabolic benefit by reducing adipose endotrophin production in obese adipose tissue.

These results are consistent with a previous report that MMP9 expression is increased in the adipose tissue of subjects with obesity (12) and widen our understanding on the enzyme system mediating adipose endotrophin production and how this activity is regulated by hypoxia in obesity. Since pharmacological inhibition of MMPs (with relative specificity for gelatinases, e.g., MMP2 and MMP9) (13) or genetic deletion of MMP2 or MMP9 does not change glucose tolerance or blood glucose levels in mice fed high-fat diet (12,14,15), it is likely that the three MMPs (MMP2, MMP9, and MMP16) can work collectively to enhance endotrophin production, and the absence of one MMP can be compensated for by the others. Therefore, although the relative contribution of each MMP to endotrophin production and metabolic dysfunction in vivo remains a subject of future study, from a translational point of view, strategies to reduce endotrophin production should be focused on suppressing all three MMPs together. The use of miR-29 looks prominent as a tool to suppress all three MMPs to reduce endotrophin production. However, caution should be taken when considering miR-29 as a suitable potential target of a novel antidiabetes therapy, since overexpression of miR-29 can also reduce glucose-stimulated insulin secretion in β-cells (16) and insulin sensitivity in skeletal muscle, adipocytes, and liver (17–19). Therefore, it is possible that systemic increases in miR-29 expression offset the beneficial effect of adipose miR-29 overexpression (and subsequent reduced endotrophin production) on glycemic control. Along the same lines, it was shown that MMP9 can also protect against the development of muscle insulin resistance in diet-induced obese mice (20). Therefore, it is likely that strategies to suppress MMP9 or induce miR-29 to improve metabolic profile should be targeted specifically to adipose tissue instead of systemically.
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