Breathing Room: The (Un)Natural History of Adipose Microhypoxia and Insulin Resistance

Kyle D. Copps and Morris F. White

The basis for the clustering of obesity with insulin resistance, type 2 diabetes, and related pathologies of the metabolic syndrome is complex but involves altered metabolic function and substrate flow both within and between insulin-responsive fat, muscle, and liver tissues (1,2). Since the discovery of leptin in the 1990s, the focus on the normal endocrine and (more recently) the pathological inflammatory roles of adipose tissue has been rewarded with ever-accelerating advancements in our understanding of metabolic disease. However, it is worth noting that endocrine/inflammatory dysfunction of adipose tissue does not naturally occur independently of insulin resistance within adipocytes themselves. Rather, both naturally emerge from the history of the expanding adipose compartment in obesity (2,3). While a complete description of adipose tissue expansion is lacking, an increase in size of existing adipocytes (hypertrophy) appears to predominate in early stages, followed only later by the appearance of smaller, apparently newer adipocytes (hyperplasia) (4).

A key element in diagnosis of the metabolic syndrome, as well as an important diabetes risk factor, is expanded central, or visceral, adiposity. For example, stepwise and multiple regression models involving MRI-determined masses of all adipose depots— controlled for age, obesity, and serum triglyceride and nonesterified fatty acid levels—identify visceral fat as a significant risk factor for insulin resistance (5). Moreover, human visceral adipocytes examined ex vivo have been known for some time to be insulin resistant relative to subcutaneous adipocytes. (For one example, see ref. 6). The basis for this resistance is complex but likely involves increased exposure to cortisol, adrenergic stimulation, and, perhaps, developing hyperinsulinemia.

In the absence of postprandial insulin, adrenergic stimulation causes cyclic AMP (cAMP)-dependent phosphorylation of both perilipin, which coats the adipocyte lipid droplet, and hormone-sensitive lipase, allowing hydrolytic release of fatty acids from triglyceride for their use as fuel elsewhere (7). Insulin exerts antilipolytic activity by activating PDE3B, a cAMP phosphodiesterase, as well as promoting reesterification of fatty acids to newly generated glycerol 3-phosphate. Thus, the visceral focus of adipose insulin resistance contributes strongly to another feature of the metabolic syndrome, nonalcoholic fatty liver disease, via increased return of hydrolyzed fatty acid to the portal circulation (8). Increased lypolysis owing to adipocyte insulin resistance may also contribute to muscle insulin resistance and impairment of β-cell secretory function via lipotoxicity (2,3).

A somewhat recently appreciated feature of the expanding adipose compartment of obesity is the occurrence of localized hypoxia (reviewed in ref. 9). The presence of hypoxic regions within adipose tissues of obese rodents has been demonstrated by anaerobic adductive chemistry in vivo, increased local lactate concentrations, and specific hypoperfusion of adipose tissue (10). The presence of hypoxia in human adipose tissue is at least strongly implied, given the similar hypoperfusion that is characteristic of human obesity (9).

The principle sensor and mediator of the adipocyte response to hypoxia is hypoxia-inducible factor (HIF)-1, a heterodimeric (α/β) transcription factor, of which the α-subunit (HIF-1α or HIF-2α) is directly regulated by oxygen tension. HIF-1α protein is expressed at higher levels in adipose tissue of obese rodents, and its mRNA has been reported to be upregulated in fat and infiltrating macrophages of obese humans (9). Under normoxic conditions, HIF-1α undergoes prolyl hydroxylation and is degraded by the ubuiquitin/proteasomal route; by contrast, in hypoxia, its hydroxylation is disfavored, allowing newly synthesized HIF-1α to accumulate, complex with its β-subunit, and activate gene transcription. At some promoters, at least, this takes place in cooperation with cAMP-responsive element–binding protein (CREB) and its coactivator p300.

In general, the transcription of HIF-1 target genes serves to alter the local microenvironment by promoting angiogenesis (vascular endothelial growth factor), tissue remodeling (matrix metalloproteinases), and inflammation (interleukin-6, plasminogen activator inhibitor-1, and, perhaps, tumor necrosis factor-α). As with HIF-1α itself, genes in the last category may also be upregulated in nearby macrophages, which cluster about dying adipocytes; this suggests a potentiation of localized inflammation by the hypoxic microenvironment (2,10). Another class of HIF-1 target genes likely promotes adipocyte survival via adaptation to anaerobic metabolism. Among these are pyruvate dehydrogenase kinase—which shunts acetyl-CoA away from mitochondrial oxidation via conversion into lactate—and GLUT1, which promotes insulin-independent uptake of glucose. Importantly, production of the insulin-sensitizing adipokine adiponectin/Acrp30 is also decreased during hypoxia, paralleling the decrease in serum adiponectin levels in human obesity. Thus, activation of the HIF-1 program seems likely to worsen inflammation, impair healthy adipose endocrine function, and contribute to whole-body insulin resistance.

Surprisingly, a relationship between hypoxia and insulin resistance within adipocytes per se has not, until now,

From the Howard Hughes Medical Institute and Children's Hospital, Boston, Massachusetts.
Corresponding author: Morris F. White, morris.white@childrens.harvard.edu.
DOI: 10.2337/db08-1517

See accompanying original article, p. 95.

been described. In the accompanying article, Regazetti et al. (11) close this loop by demonstrating that in murine preadipocyte cell lines and human subcutaneous abdominal adipocytes, examined in vitro, hypoxia leads to insulin resistance. This appears to occur solely through inhibition of insulin receptor phosphorylation. While the universality of this finding—say in muscle under exercise—remains to be determined, it is somewhat satisfying, intellectually, given the important oppositional roles of cAMP/CREB- and insulin-mediated signaling in adipocyte metabolism. Though the exact mechanism by which insulin receptor autophosphorylation is inhibited remains unclear, it does depend upon the activity of HIF-1. A curious aspect of this dependence is its rapid reversibility; insulin receptor phosphorylation was restored after a quite brief return of adipocytes (45 min) to normoxic conditions. Thus, it is at least formally possible that the inhibition of insulin receptor phosphorylation might depend on HIF-1 itself. More probably, some activity of unknown downstream targets of HIF-1 causes the inhibition of insulin receptor phosphorylation, and this activity is rapidly downregulated by the return to normoxic conditions.

But what is the net contribution of this insulin resistance to disease progression? As expected, the hypoxia-induced insulin resistance reported by Regazetti et al. was accompanied by increased lipolysis (monitored through glycerol production). The released fatty acids might be expected to further perturb the local tissue environment, or—if they actually enter the circulation—promote systemic insulin resistance. However, it is unclear whether hypoxia is likely to be more (or less) prevalent in visceral adipose tissue important to disease than it is elsewhere. Further, a known feature of insulin resistance in human visceral adipose tissue is the presence of postreceptor signaling defects, including—but perhaps not limited to—the downregulation of IRS-1 (6). This was not observed by Regazzetti et al. At this point, an examination of rodents with, for example, decreased HIF-1 function might be informative concerning whether the HIF-1 program in hypoxic adipose tissue, including the associated insulin resistance, is purely pathological or is instead an adaptive process.

This could depend on whether the hypoxia is intermittent or chronic. Because of its rapid reversibility, it is certainly tempting to view HIF-1–mediated insulin resistance as part of a dynamic solution to the problem of how to best "pack" hydrophobic triglyceride into hypertophic adipocytes while maintaining perfusion. To put it most simply, increased lipolysis would slow hypertrophy while the HIF-1 program would modify the local environment to promote perfusion and genesis of the new, smaller adipocytes typical of later obesity (4,9). Indeed, well-defined ($CD34^+CD31^-$) adipocyte progenitor cells—isolated from the stromal vascular fraction of adipose tissue of obese adults—display elevated HIF-1α expression that is positively correlated with BMI (4). Moreover, exposure of these progenitors to hypoxia and its related cytokine profile (e.g., interleukin-6) promotes differentiation into adipocytes. Given the therapeutic value of even moderate weight loss in the early stages of diabetes, it thus appears that hypoxia-induced insulin resistance may be just one feature of a normally adaptive remodeling process that becomes pathological only in the continued presence of hypernutrition or other external stimulus.

ACKNOWLEDGMENTS

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Saltiel AR: New perspectives into the molecular pathogenesis and treatment of type 2 diabetes. *Cell* 104:517–529, 2001
2. Schenk S, Saberi M, Olefsky JM: Insulin sensitivity: modulation by nutrients and inflammation. *J Clin Invest* 118:2992–3002, 2008
3. Spiegelman BM, Flier JS: Obesity and the regulation of energy balance. *Cell* 104:531–543, 2001
4. Maumus M, Sengenes C, Decaunes P, Zakaroff-Girard A, Bourlier V, Lafontan M, Galitzky J, Bouloumie A: Evidence of in situ proliferation of adult adipose tissue-derived progenitor cells: influence of fat mass microenvironment and growth. *J Clin Endocrinal Metab* 93:4098–4106, 2008
5. Chana D, Watts G, Sussekov A, Barrett P, Yang Z, Hua J, Song S: Adipose tissue compartments and insulin resistance in overweight-obese Caucasian men. *Diabetes Res Clin Pract* 63:77–85, 2004
6. Zierath JR, Livingston JN, Thorne A, Bolinder J, Reynisdottir S, Lonnqvist F, Arner P: Regional difference in insulin inhibition of non-esterified fatty acid release from human adipocytes: relation to insulin receptor phosphorylation and intracellular signalling through the insulin receptor substrate-1 pathway. *Diabetologia* 41:1343–1354, 1998
7. Jaworski K, Sarkadi-Nagy E, Duncan RE, Ahmadian M, Sul HS: Regulation of triglyceride metabolism. IV. Hormonal regulation of lipolysis in adipose tissue. *Am J Physiol Gastrointest Liver Physiol* 293:G1–G4, 2007
8. Tamura S, Shimomura I: Contribution of adipose tissue and de novo lipogenesis to nonalcoholic fatty liver disease. *J Clin Invest* 115:1139–1142, 2005
9. Trayhurn P, Wang B, Wood IS: Hypoxia in adipose tissue: a basis for the dysregulation of tissue function in obesity? *Br J Nutr* 100:227–235, 2008
10. Hosogai N, Fukuhara A, Oshima K, Miyata Y, Tanaka S, Segawa K, Furukawa S, Tochino Y, Komuro R, Matsuda M, Shimomura I: Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation. *Diabetes* 56:901–911, 2007
11. Regazzetti C, Peraldi P, Gremeaux T, Najem-Lendom R, Ben-Sahra I, Cormont M, Bost F, le Marchand-Brustel Y, Tanti J-F, Giorgetti-Peraldi S: Hypoxia decreases insulin signaling pathways in adipocytes. *Diabetes* 58:95–103, 2009