Worldwide, more than 1 billion adults are overweight, and obesity constitutes a key contributor to chronic disease. The conventional wisdom is that this rising epidemic reflects societal adaptation to a sedentary lifestyle and nutritional transition to overconsumption of inexpensive and calorie-dense diets. Implementing behavioral lifestyle modifications to promote weight loss and maintenance, including physical activity and a healthy diet, constitutes a major clinical challenge and remains difficult to achieve. Similarly, there is concern about the safety and potential long-term complications associated with enforcing caloric restriction through bariatric surgery. Finally, the currently available two pharmacological agents, orlistat and phentermine, have limited efficacy and side effects. Consequently, there is an unprecedented need for the development of effective and safe weight loss strategies, and understanding the physiology of obesity may provide novel therapeutic opportunities.

Adipose tissue displays a remarkable plasticity and constitutes one of the few tissues with the ability to considerably expand or regress in adulthood. An extensive vasculature supplies the adipose tissue, and a capillary network surrounds essentially every adipocyte. Like the growth of other tissues, adipose tissue expansion during increased caloric intake requires angiogenesis. The potential of adipose tissue to promote angiogenesis is well established and has been used therapeutically for at least half a century. Conversely, there is compelling evidence that treatment of obese mice with pharmacological angiogenesis inhibitors decrease adipose tissue mass and prevents obesity. Because Id3 deletion has been demonstrated to inhibit angiogenesis, Cutchins et al logically hypothesized that the prevention of diet-induced adipose tissue expansion noted in Id3-deficient mice might be due to altered angiogenesis. As suspected, the authors confirmed decreased microvascular blood volume in the adipose tissue of Id3-deficient mice, indicative of reduced vascular density and altered angiogenesis, lending further support for the concept that inhibition of angiogenesis in adipose tissue may prevent diet-induced obesity.

In their study, the authors provide a well-defined mechanism underlying Id3-dependent adipose tissue angiogenesis. During obesity the expanding adipose tissue becomes hypoxic, and both differentiation and hypoxia induce vascular endothelial growth factor (VEGF) expression by adipocytes. Being unequivocally a major determinant of angiogenesis, VEGF is abundantly secreted by adipose tissue, and inhibition of VEGF signaling prevents adipose tissue expansion during diet-induced obesity. Intriguingly, Cutchins et al noted that diet-induced VEGF secretion from adipose tissue was attenuated in Id3-deficient mice. As a molecular mechanism by which Id3 positively regulates VEGF expression, the author’s reporter studies support a paradigm in which Id3 releases the repression of VEGF transcriptional activity by the E-protein E12 (see Figure). Id3 functions to repress the activity of E-proteins through direct protein binding, preventing the association of E-proteins with target DNA. Considering the concept of Id3-dependent release of VEGF promoter repression, currently unresolved questions are the extent to which E-proteins repress VEGF in the adipose tissue and whether the increase in endogenous Id3 expression during obesity is sufficient to release this repression in vivo. Nevertheless, these seminal observations provide a novel mechanistic basis underlying the increase in VEGF expression during obesity and the regulation of angiogenesis during adipose tissue expansion.

Probably the most fascinating observation from the present study is that the prevention of adipose tissue mass expansion during high-fat diet feeding of Id3-deficient mice did not negatively affect glucose metabolism. Although further detailed analysis of glucose metabolism and insulin sensitivity will be required in future studies, the development of hyperinsulinemia associated with diet-induced obesity in wildtype mice was prevented by Id3-deletion. One might assume that the similar caloric intake observed in Id3-deficient mice in the absence of adipose tissue expansion would have resulted in ectopic lipid accumulation in muscle and liver leading to insulin resistance and potentially hyperglycemia, a phenotype reminiscent of partial lipodystrophy. However, paradoxically, Id3-deficient mice fed a high-fat diet exhibited decreased free fatty acid levels, normal glucose levels, and decreased insulin levels. Energy balance obeys the first law of thermodynamics

See accompanying article on page 317

From the Division of Endocrinology and Molecular Medicine (D.B.), Saha Cardiovascular Research Center, University of Kentucky College of Medicine, Lexington, KY.

Correspondence to Dennis Bruemmer, University of Kentucky, Wethington Building, Room 575, 900 South Limestone Street, Lexington, KY 40536-0200. E-mail Dennis.Bruemmer@uky.edu

Publisher’s Note: Arterioscler Thromb Vasc Biol is available at http://atvb.ahajournals.org

DOI: 10.1161/ATVBAHA.111.241992
and implies that the deceased weight gain in Id3-deficient mice is the result of increased energy expenditure, considering that food intake was similar between genotypes. Analysis of energy balance confirmed this notion and documented increased energy expenditure and resting metabolic rate in Id3-deficient mice fed a high-fat diet. The observation that the prevention of adipose tissue expansion in Id3-deficient mice increases energy expenditure is consistent with studies using pharmacological inhibition of angiogenesis. Therefore, the question arising is how does the inhibition of visceral adipose tissue expansion by limiting angiogenesis positively affect energy balance. Addressing this question becomes particularly important when considering that limiting angiogenesis of the brown adipose may decrease thermogenesis and subsequently energy expenditure. Because energy intake was not affected by Id3-deficiency, it is rather unlikely that the increased energy expenditure is the result of a regulation of energy balance through the hypothalamus. Therefore, it appears to be conceivable to hypothesize that the remodeled adipose tissue of Id3-deficient mice secretes factors that positively affect metabolically active tissues. These intriguing observations by Cutchins et al support future investigation to identify these factors and their target tissues to ultimately provide insight into how Id3-deficiency increases energy expenditure. Understanding the role of Id3 in adipose tissue biology and energy balance will expand our present knowledge of mechanisms that modulate obesity and may provide novel therapeutic approaches to treat obesity and its associated comorbidities. Until these become available, the prevailing approach to treat obesity follows precisely the laws of nature: exercise more and eat less.

Figure. Regulation of adipose tissue vascular endothelial growth factor (VEGF) expression and angiogenesis by inhibitor of differentiation-3 (Id3) during diet-induced obesity. In response to high-fat diet feeding, endothelial cells of capillaries within adipose tissue express Id3. Id3 associates with the E-box protein E12, which prevents E12 binding and transrepression of the VEGF promoter. The ensuing increase in VEGF promoter activity induces transcription and VEGF secretion, which subsequently facilitates angiogenesis and adipose tissue expansion during obesity.

References


Key Words: angiogenesis ■ obesity
Targeting Angiogenesis as Treatment for Obesity
Dennis Bruemmer

doi: 10.1161/ATVBAHA.111.241992

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/32/2/161

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/