Unknown actor in adipose tissue metabolism hiding in plain sight

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In PNAS Eom et al. (1) report that viperin (virus-inhibitory protein, endoplasmic reticulum-associated, interferon-inducible), which is best known as a nuclear factor κB-induced protein in macrophages involved in the innate immune response, has a heretofore unknown role in the adipocyte. In this paper, the authors investigate the possibility that viperin, a protein that is classically known to modulate metabolism in the service of viral reproduction, plays a role in adipocyte thermogenesis. They find that expression of genes characteristic of "thermogenic" adipocytes is increased in adipose tissue and cultured adipocytes from viperin knockout mice. The knockout mice have reduced fat mass and are more glucose-tolerant, and the authors observe a significant effect on fatty acid β-oxidation in the adipocyte, as specific inhibitors of enzymes in this pathway ablate this effect. Since fatty acid β-oxidation is necessary for adaptive thermogenesis in adipocytes, the absence of viperin in the adipocytes seems to release a brake on β-oxidation.

Evolving Concepts About Inflammation and Adipose Tissue

More than 2 decades ago, a connection between inflammation and insulin resistance began to emerge with evidence connecting tumor necrosis factor α to insulin resistance (2). In 2003 Ferrante and coworkers (3) made note of the phenomenon of so-called crown-like structures containing macrophages surrounding adipocytes in obese adipose tissue. These early observations were followed up by others [a few here cited, not to exclude the many others (4–6)], and since then there has been an enormous effort to understand this connection between obesity, insulin resistance, and inflammation (see refs. 7 and 8). In the simplest view, usually we think about adipose inflammation in terms of proinflammatory M1-polarized macrophage infiltration and inflammatory cytokine production that elicits further inflammation. However, even here it is debated: Is the macrophage there to "clean up a mess and then depart" as a normal function of a macrophage by definition?—but then again with unmitigated adipocyte hypertrophy it becomes an "enemy" that consequently wreaks havoc in the tissue as an interminable aggravating factor. There is now, however, also evidence of "good-guy" antiinflammatory M2-polarized macrophages in adipose tissue, and questions in the field now ask what the signals are that modulate the recruitment and localization of these 2 different macrophage populations, and what functions they are performing there (9, 10).

Viperin is best known as a protein that is made in response to viral infection (see ref. 1 and references therein). However, Eom et al. (1) show that viperin is expressed in adipose tissue of pathogen-free and germ-free mice, and that it is expressed in the adipocyte itself, not in preadipocytes or immune cells within the stromal vascular fraction of isolated adipose tissue. These are important findings because they show that the protein is not just expressed in response to an infection/inflammatory challenge but is regulated by other signals and pathways that still need to be understood.

Questions Raised by the Study

While this work opens another avenue for understanding the plasticity of adipocytes and their ability to "store" vs. "burn" caloric energy, it raises many questions that need to be addressed. Is there nevertheless a role for viperin in macrophages to modulate this phenotype? Bone marrow transplant studies would help to address this question. Obviously, tissue-specific deletion of viperin in adipocytes (and perhaps other cell types) is needed to more specifically and unequivocally ascribe a role of viperin in the adipocyte to regulate thermogenesis and energy balance.

One curious observation made by Eom et al. (1) is that cold exposure causes an increase in viperin expression in adipose tissue. The authors propose that viperin may function as a brake on uncontrolled increases in the process of fatty acid oxidation and thermogenesis. Is this some ancient mechanism for allowing heat generation as necessary but acting as a counterbalance to the cold-induced sympathetic drive, so that only the minimum thermogenesis necessary is

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allowed to consume "expensive" and "valuable" fatty acids? In addition to the complex manner in which viperin seems to control cellular fatty acid metabolism for virus reproduction, is there also a role for viperin to suppress fatty acid oxidation in the face of an infection as a means to try to protect the organism from a rampant catabolic state? This strategy, also relevant to the adipose tissue situation, would not be unlike how β-adrenergic receptors become desensitized with persistent catecholamine stimulation.

Clearly more needs to be understood here and targeted models such as inducible transgenic and knockout mice should provide significant insight. Given this rather surprising finding that a protein known for its role in the response to viral infection seems to have a separate role in adipose tissue and energy balance, are there additional unappreciated roles for this protein that are yet to be discovered?

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1 J. Eom *et al*., Intrinsic expression of viperin regulates thermogenesis in adipose tissues. *Proc. Natl. Acad. Sci. U.S.A.* **116**, 17419–17428 (2019).
2 G. S. Hotamisligil, B. M. Spiegelman, Tumor necrosis factor alpha: A key component of the obesity-diabetes link. *Diabetes* **43**, 1271–1278 (1994).
3 S. P. Weisberg *et al*., Obesity is associated with macrophage accumulation in adipose tissue. *J. Clin. Invest.* **112**, 1796–1808 (2003).
4 R. Cancello *et al*., Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. *Diabetes* **54**, 2277–2286 (2005).
5 I. Murano *et al*., Dead adipocytes, detected as crown-like structures, are prevalent in visceral fat depots of genetically obese mice. *J. Lipid Res.* **49**, 1562–1568 (2008).
6 C. M. Apovian *et al*., Adipose macrophage infiltration is associated with insulin resistance and vascular endothelial dysfunction in obese subjects. *Arterioscler. Thromb. Vasc. Biol.* **28**, 1654–1659 (2008).
7 C. Crewe, Y. A. An, P. E. Scherer, The ominous triad of adipose tissue dysfunction: Inflammation, fibrosis, and impaired angiogenesis. *J. Clin. Invest.* **127**, 74–82 (2017).
8 P. E. Scherer, The many secret lives of adipocytes: Implications for diabetes. *Diabetologia* **62**, 223–232 (2019).
9 L. Russo, C. N. Lumeng, Properties and functions of adipose tissue macrophages in obesity. *Immunology* **155**, 407–417 (2018).
10 G. S. Hotamisligil, Inflammation, metaflammation and immunometabolic disorders. *Nature* **542**, 177–185 (2017).