Insig: a significant integrator of nutrient and hormonal signals

Alan D. Attie
Department of Biochemistry, University of Wisconsin-Madison, Madison, Wisconsin, USA.

Lipogenesis is regulated by sterols and by insulin through the regulated expression and activation of the sterol regulatory element–binding proteins (SREBPs). A new study shows one way in which sterol and insulin regulation can be decoupled (see the related article beginning on page 1168). In transgenic mice overexpressing a protein that regulates SREBP activation, lipogenesis is more sensitive to cholesterol and less sensitive to insulin.

Nonstandard abbreviations used: insulin receptor substrate-2 (IRS-2); SREBP cleavage–activating protein (SCAP); sterol regulatory element–binding protein/adipocyte differentiation factor-1 (SREBP/ADD1).

Conflict of interest: The author has declared that no conflict of interest exists.

Citation for this article: J. Clin. Invest. 113:1112–1114 (2004). doi:10.1172/JCI200421450.

of MEF2C for maintenance of endothelial integrity is also intriguing in light of the recent association of premature coronary artery disease and myocardial infarction with a mutation in the human MEF2A gene (20). Since MEF2A is highly expressed in the endothelium and is a substrate for BMK1, it is likely to act within the same EC survival pathway as MEF2C.

A remarkable number of processes within the cardiovascular system are dependent on signaling from MAPKs to MEF2 (7). In addition to its requirement for EC survival, this signaling pathway is important for differentiation and morphogenesis of cardiac and smooth muscle cells, and has been implicated in numerous cardiovascular disorders, including cardiac hypertrophy, dilated cardiomyopathy, coronary artery disease, and myocardial infarction. Further insights into the functions and mechanisms of action of this signaling module promise to provide new opportunities for its therapeutic manipulation in the settings of human disease.

Address correspondence to: Eric N. Olson, Department of Molecular Biology, The University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd., NA8.602, Dallas, Texas 75390-9148, USA. Phone: (214) 648-1187; Fax: (214) 648-1196; E-mail: eric.olson@UTSouthwestern.edu.

Insig-1 overexpression reduces the sensitivity of lipogenesis to insulin

The first link between SREBP and insulin came from the discoveries that insulin increases the expression of SREBP-1c (10, 11), that transgenic mice overexpressing SREBP-1c do not suppress lipogenesis in response to fasting (12), and that lipogenesis is not induced in mice lacking SREBP-1c when they are fed a high-carbohydrate diet (13). Given that lipogenesis is regulated by insulin, inevitable questions arise: How do cells integrate regulation of lipogenesis by insulin with regulation by lipids? What molecules “sense” lipid and hormonal status? When they act together, which signals are dominant?

Normally, fasting causes a downregulation of SREBP-1c and thus a reduction in mature SREBP-1c. Refeeding leads to an induction of SREBP-1c and Insig-1 and greatly increased levels of mature SREBP-1c (Figure 1). Surprisingly, transgenic overexpression of Insig-1 blunted the insulin response; refeeding produced only a modest increase in SREBP-1c (8). In contrast, the sensitivity of SREBP-1c to cholesterol was enhanced.

Insulin cycling during the transition from feeding to fasting causes the liver to switch from glycolysis/lipogenesis to gluconeogenesis/ketogenesis. After refeeding, insulin suppresses the expression of insulin receptor substrate-2 (IRS-2) and phosphoenolpyruvate carboxykinase, resulting in decreased gluconeogenesis (14, 15). This pathway was intact in the Insig-1 transgenic mice (8).

Left undefined is the role of Insig-2a, a liver-specific isoform of Insig-2. Like Insig-1, Insig-2a causes retention of SREBP in the ER; however, it does so only in the presence of a concentration of sterols (7). Unlike Insig-1, Insig-2a is suppressed by insulin and induced by fasting. Early in the transition from fasting to feeding, Insig-1 levels are low and Insig-2a expression is repressed, allowing the insulin-induced SREBP-1c protein to be processed. Increased SREBP-1c induces Insig-1 gene expression.

**Insig-1 overexpression suppresses lipogenesis in vivo**

In this issue of the *JCI*, Engeling and co-workers show that hepatic overexpression of Insig-1 in transgenic mice caused a marked reduction in nuclear SREBPs, which further decreased when mice were fed a high-cholesterol diet (8). Thus, the in vitro titration experiments correctly predicted the effect of Insig-1 on the lipogenesis rate in vivo. The in vivo effects of cholesterol on expression of SREBP are complicated by the fact that sterols activate SREBP-1c (not SREBP-2) gene expression through the liver X receptor transcription factors (9). Thus, at low levels, dietary cholesterol decreases the level of mature SREBP-1c protein, but at higher levels, it induces SREBP-1c gene expression (8).
Potential implications for insulin resistance

With chronic hyperinsulinemia, the normally converse relationship between lipogenesis and gluconeogenesis can be disrupted (16). This occurs in models of leptin deficiency (e.g., the leptin<sup>ab</sup> mutation or congenital lipodystrophy) or leptin resistance. Deletion of IRS-2 leads to leptin resistance (17), suggesting a convergence between the leptin and insulin signaling pathways. Leptin resistance boosts lipogenesis in the liver through increased SREBP-1c. Deletion of SREBP-1c reduces the rate of lipogenesis of leptin-deficient animals but does not reverse insulin resistance, hence other aspects of leptin signaling influence insulin signaling (18).

The focus of the Insig story will likely turn to Insig-2a. Is Insig-2a affected by leptin deficiency or leptin resistance? What happens to Insig-2a under conditions of chronic hyperinsulinemia? We hope to learn why these two closely related proteins are oppositely regulated by insulin.

Address correspondence to: Alan D. Attie, Department of Biochemistry, University of Wisconsin-Madison, 433 Babcock Drive, Madison, Wisconsin 53706, USA. Phone: (608) 262-1372; Fax: (608) 263-9609; E-mail: attie@biochem.wisc.edu.


Experimental autoimmune hearing loss

Peter Billings
Division of Otolaryngology—Head and Neck Surgery, University of California, San Diego, and Research Service of the Department of Veterans Affairs, San Diego, California, USA.

Understanding of autoimmune sensorineural hearing loss (ASNHL) has been hindered by the inaccessibility of the inner ear to biopsy and the lack of workable animal models. A report in this issue of the JCI describes a mouse model of CD4<sup>+</sup> T cell–mediated ASNHL induced by immunization with peptides from the inner ear–specific proteins cochlin and β-tectorin (see the related article beginning on page 1210).

Nonstandard abbreviations used: antigen (Ag); autoimmune inner ear disease (AIED); autoimmune sensorineural hearing loss (ASNHL); inner ear (IE); sensorineural hearing loss (SNHL).

Conflict of interest: The author has declared that no conflict of interest exists.

Citation for this article: J Clin. Invest. 113:1114–1117 (2004). doi:10.1172/JCI200421632.

The inner ear (IE), like most other specialized tissues and organs, can become the target of an autoimmune attack. Sensorineural hearing loss (SNHL) is often an early, although presumably secondary, complication of various non–organ-specific autoimmune diseases; however, the IE can also represent the primary focus of a unique disease entity, autoimmune IE disease (AIED) (1). Fortunately the disease is rare, but the small population size of affected individuals and the inaccessibility of the IE during an acute attack have hindered progress in our understanding of the etiology, diagnosis, and treatment of this disease. AIED is diagnosed by exclusion of other disorders that mimic it. The hearing loss is typically bilateral, asymmetric, and fluctuating and deteriorates rapidly over weeks or months; balance and equilibrium may or may not be affected. Diagnosis of AIED is tentatively confirmed if there is a positive response to trial corticosteroid