Editorial

Sterol regulatory element binding proteins (SREBPs) are transcription factors that help activate a variety of sterol responsive genes. These include genes encoding enzymes in the cholesterol biosynthetic pathway and the saturated and unsaturated fatty acid biosynthetic pathway, as well as the low-density lipoprotein receptor (LDLR) gene (for review see reference 1).

SREBPs were first discovered as specific transcription factors that bind to the 10-bp sterol regulatory element (SRE) within the promoters of LDLR and 3-hydroxy-3-methylglutaryl Co-A synthase (an enzyme in the sterol synthesis pathway). It is now known that there are at least two different genes that produce at least three different SREBP proteins: SREBP-1_a and SREBP-1_c (two isoform proteins) and SREBP-2. Although the functions of these three proteins are similar, they are not identical (1). The SREBP-1 gene was discovered independently by its ability to stimulate fatty acid synthesis and adipocyte differentiation, in a rat preadipose cell line (2). Subsequently, it was shown that the promoters of genes that encode enzymes in the fatty acid synthesis pathway contain the SRE element and are regulated by the SREBP proteins (3).

The functions of the SREBPs have been assigned almost entirely through in vitro and tissue culture studies. Thus, it is important that their physiological functions be tested in the intact animals. Earlier work from the laboratory of Brown and Goldstein (4) demonstrated that mice overexpressing the active SREBP-1_a protein caused marked elevations of messenger RNA levels for LDLR and for enzymes in cholesterol and fatty acid biosynthesis, and caused overaccumulation of cholesterol and triacylglycerols in the liver. In this issue of *The Journal*, through a series of extensive and carefully executed experiments, the same group reports the consequence of knocking out the SREBP-1 gene in mice (5). In brief, without a functional SREBP-1 gene, most (but not all) of the mice (−/− mice) died in utero around embryonic day 11. This elevated but incomplete embryonic lethality in the −/− mice suggests that the SREBP-1 gene plays an important but nonessential function in embryonic development.

Surviving −/− mice appeared physically normal at birth and throughout adulthood. They also had a moderate elevation in the SREBP-2 mRNA and a moderate increase (two- to threefold) in the mature SREBP-2 protein in the liver nuclei. Sterol synthesis rate and mRNAs for enzymes in the cholesterol synthesis pathway in livers of these mice were significantly elevated. In contrast, the fatty acid synthesis rate and the amount of mRNA for enzymes in the saturated and unsaturated fatty acid synthesis in the SREBP-1 knockout mice were not significantly elevated. In addition, the amount of white adipose tissue in these mice was not decreased, plasma cholesterol and triacylglycerol levels were slightly reduced, and the mRNAs for apo AI, apo B, apo E, and for microsomal triglyceride transfer protein (necessary for hepatic lipoprotein assembly) were essentially unchanged. These results, taken together with the earlier work (4), suggest that there is no direct relationship between sterol synthesis driven by SREBPs and the rate of lipoprotein secretion in the liver. Although a definite answer regarding the roles of SREBP-1 and SREBP-2 in intact animals awaits the production of animals in which the SREBP-1 and SREBP-2 genes are both inactivated, the available data are consistent with the idea (1) that the SREBPs play a dominant role in regulating cholesterol synthesis and an auxiliary role in saturated and unsaturated fatty acid synthesis.

It is well-known that lipogenic enzymes in the liver are mainly regulated by dietary carbohydrates, not by dietary cholesterol. Why should SREBPs be involved in regulating fatty acid biosynthesis? Inside cells, fatty acids form the building blocks of phospholipids and triacylglycerols. Phospholipids interact with cholesterol and constitute the bulk of the lipid components in animal cell membranes. Most of the fatty acids present in membrane phospholipids are unsaturated (such as oleic acid) rather than saturated (such as stearic acid). The function of triacylglycerol is to serve as energy depots; its content in cell membranes is negligible. Thus, within a single cell type, the role of SREBPs in fatty acid synthesis may be related to its role in controlling membrane phospholipid synthesis. This could explain why animal cell mutants that are unable to produce the active form of SREBP proteins (6) require both cholesterol and unsaturated fatty acid for optimal growth in lipid-free medium (for review see reference 7). In these cells, the need for unsaturated fatty acid cannot be met by saturated fatty acid; this need may be for maintaining the structural and functional integrity of the cell membranes, not for maintaining proper triacylglycerol synthesis, storage, and secretion. Future experiments should determine the exact physiological roles of the SREBP proteins in controlling membrane lipid synthesis, in LDLR expression, and perhaps in triacylglycerol synthesis in cultured mammalian cells and in intact animals.

What about the role of fatty aids in regulating SREBP expression? In various animal species and in humans, diets rich in cholesterol and saturated fat (instead of unsaturated fat) cause a large increase in plasma LDL concentration (for review see reference 8). One plausible explanation is that saturated fatty acid (instead of unsaturated fatty acid) is a less efficient substrate for the enzyme acyl Co-A (cholesterol acyltransferase), which converts cholesterol to cholesteryl esters for storage, thus sparing a larger cholesterol pool to exert its regulatory action within the liver (8). Fatty acids may exert other regulatory effects. Can fatty acids also regulate the actions of SREBPs, which are known to be regulated by sterols (1)? Is it possible that, with cholesterol, saturated fatty acid inhibits the expression of SREBPs more efficiently than unsaturated fatty acid? This would lead to a more efficient downregulation of the LDLR and cause a larger increase in the plasma LDL concentration. Again, future experimentation should determine any specific role for fatty acids in regulating the expressions of SREBPs.

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J. Clin. Invest.

0021-9738/97/10/1905/02 $2.00
Volume 100, Number 8, October 1997, 1905–1906
http://www.jci.org

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