JCI The Journal of Clinical Investigation

Fatty livers and reduced adipose tissue, who wants it?

P A Edwards

J Clin Invest. 1996;98(7):1506-1507. https://doi.org/10.1172/JCI118940.

Editorial

Editorial

The paper by Shimano et al. (1) in this issue of *The Journal* reports a series of remarkable findings that were obtained with transgenic mice that expressed a truncated form of sterol regulatory element binding protein-1a (SREBP-1a) under the control of a liver-specific promoter. The livers of these mice were loaded with both cholesterol and triglycerides. Surprisingly, plasma lipid levels were unchanged and white adipose tissue mass decreased significantly. These results may have broad implications regarding the control of lipid metabolism by SREBP.

It was over 40 yr ago that Gould et al. first demonstrated in dogs that high levels of dietary cholesterol resulted in negative feedback on the hepatic cholesterol biosynthetic pathway (2). We now know that the transcription of a number of genes involved in both cholesterol biosynthesis and cellular uptake of cholesterol-rich low density lipoproteins is negatively regulated by dietary sterols, by a process involving a unique transcription factor termed SREBP (3). The purification and subsequent cloning of SREBP in 1993 represented a major breakthrough in our understanding of the mechanisms controlling cholesterol homeostasis (3). Subsequent studies demonstrated that there were two genes, SREBP-1 and SREBP-2, that produce at least three proteins (SREBP-1a, SREBP-1c, also called ADD1, and SREBP-2) of $\sim$ 125 kD. ADD1 was cloned independently, based on its role in adipocyte differentiation (4). The observation that the SREBPs contained two transmembrane domains that anchored the proteins to the endoplasmic reticulum posed a conundrum. How could a membrane-bound protein function as a transcription factor and how could sterols regulate this process? It is now clear that the proteolytic release of the mature, 68-kD transcriptionally active, NH_2-terminal domain of SREBP from the endoplasmic reticulum is regulated by sterols; the proteolysis is prevented in sterol-loaded cells but is enhanced in sterol-deprived cells (5). Once released, the mature SREBP is targeted to the nucleus where it activates the transcription of SREBP-responsive genes. The demonstration that sterols inhibit the release of mature SREBP from the endoplasmic reticulum and that this in turn results in a decrease in the transcription of key genes in the cholesterol biosynthetic pathway provided the molecular mechanism to explain the original observations of Gould et al. (2).

Recent studies with cultured cells suggest that SREBPs have a more general role in the control of lipid biosynthesis. SREBP/ADD1 was shown to stimulate the transcription of genes involved in fatty acid biosynthesis (4, 6). In addition, cells that overexpressed SREBP-2 were shown to accumulate triglycerides in addition to cholesterol (7). Finally, ADD-1, the mouse homologue of human SREBP-1c, was shown to have an important role in the regulation of a number of genes during the differentiation of preadipocytes to triglyceride-rich adipocytes (8).

It is not known whether the different SREBPs function in a similar manner in animals or whether the results on the regulation of this transcription factor in cultured cells are directly applicable to intact animals. The studies by Shimano et al. (1) represent an initial approach to answer these important questions. The results illustrate the power of using transgenic mice; overexpression of truncated SREBP-1a caused both a massive accumulation of cholesterol and triglyceride in the abnormally enlarged liver and unexpected effects on white adipose tissue. The overexpression of SREBP-1a was hypothesized to result in a "triglyceride steal" syndrome in which triglycerides accumulated in the liver and were decreased in adipose tissue (1). Future studies will surely determine whether transgenic mice that overexpress different mature SREBPs, either in the liver or in other organs, have this same phenotype. It will also be important to determine the effects of expression of different SREBPs in vivo at levels that more closely resemble the normal physiological levels of the mature protein. Finally, the results with the transgenic mice raise the question as to whether humans might be identified who inappropriately express elevated levels of mature, transcriptionally active, SREBPs. Such a phenotype could result from mutations in the genes encoding either one of the SREBPs or the sterol-regulated protease that releases the mature protein from the membrane. These individuals might have normal plasma lipids but tissues that contain cells that are overloaded with lipid, as a result of inappropriate expression of SREBP.

The SREBP-regulated genes are of considerable clinical relevance since one class of hypocholesterolemic drugs, generally known as Statins, function by regulating (indirectly) the levels of the transcriptionally active, mature SREBPs. Statins, such as Lovastatin, partially inhibit hepatic HMG-CoA reductase activity and consequently decrease both cholesterol synthesis and cholesterol levels in the liver. The decrease in intracellular hepatic cholesterol levels in rodents results in the proteolytic release of mature SREBP-2 from the endoplasmic reticulum and increased transcription of the LDL receptor and other SREBP-responsive genes. The elevated hepatic LDL receptor levels promote the increased clearance of plasma LDL and IDL and the normalization of plasma cholesterol levels. Studies with transgenic mice that overexpress only one of the SREBPs will allow investigators to determine whether transcription of the hepatic LDL receptor is equally sensitive to each SREBP in vivo. Such information should prove to be of great clinical value if it resulted in the development of drugs that target specific SREBPs that are involved in the regulation of different lipid pathways.

Peter A. Edwards
Departments of Biological Chemistry and Medicine
and The Molecular Biology Institute
University of California, Los Angeles

References

1. Shimano, H., J.D. Horton, R.E. Hammer, I. Shimomura, M.S. Brown, and J.L. Goldstein. 1996. Overproduction of cholesterol and fatty acids causes massive liver enlargement in transgenic mice expressing truncated SREBP-1a.

J. Clin. Invest.

0021-9738/96/10/1506/02 $2.00
Volume 98, Number 7, October 1996, 1506–1507

J. Clin. Invest. 98:1575–1584.

2. Gould, R.G., B. Taylor, J.S. Hagerman, I. Warner, and D.J. Cambell. 1953. Cholesterol metabolism. I. Effect of dietary cholesterol on the synthesis of cholesterol in dog tissue *in vitro. J. Biol. Chem.* 201:519–523.

3. Yokoyama, C., X. Wang, M.R. Briggs, A. Admon, J. Wu, X. Hua, J.L. Goldstein, and M.S. Brown. 1993. SREBP-1, a basic-helix-loop-helix-leucine zipper protein that controls transcription of the low density lipoprotein receptor gene. *Cell.* 75:187–197.

4. Tontonoz, P., J.B. Kim, R.A. Graves, and B.M. Spiegelman. 1993. ADD1: a novel helix-loop-helix transcription factor associated with adipocyte determination and differentiation. *Mol. Cell. Biol.* 13:4753–4759.

5. Sakai, J., E.A. Duncan, R.B. Rawson, X. Hua, M.S. Brown, and J.L. Goldstein. 1996. Sterol-regulated release of SREBP-2 from cell membranes requires two sequential cleavages, one within a transmembrane segment. *Cell.* 85: 1037–1046.

6. Bennett, M.K., J.M. Lopez, H.B. Sanchez, and T.F. Osborne. 1995. Sterol regulation of fatty acid synthase promoter: coordinate feedback regulation of two major lipid pathways. *J. Biol. Chem.* 270:25578–25583.

7. Jackson, S.M., J. Ericsson, J.E. Metherall, and P.A. Edwards. 1996. A role for sterol regulatory element binding protein in the regulation of farnesyl diphosphate synthase and in the control of cellular levels of cholesterol and triglyceride: evidence from sterol regulation-defective cells. *J. Lipid Res.* 37: 1712–1721.

8. Kim, J.B., and B.M. Spiegelman. 1996. ADD1/SREBP1 promotes adipocyte differentiation and gene expression linked to fatty acid metabolism. *Genes Dev.* 10:1096–1107.