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TRANSCRIPTIONAL STIMULATION BY THE LIPID SENSING SREBPs

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TF Osborne

Department of Molecular Biology and Biochemistry, University of California, Irvine, Calif., USA

SREBPs are dimeric bHLHLZ proteins that activate genes in lipid metabolism. They are expressed as precursors and insert into ER and nuclear envelope membranes. To increase lipids, they are released from the membrane by regulated proteolysis and imported into the nucleus to activate gene expression. The normal physiological signal that triggers their proteolytic maturation is a change in membrane sterol content. Recently, some HIV protease inhibitors have been shown to alter adipocyte and hepatic lipid metabolism possibly by altering SREBP maturation. Thus, a key to designing more specific protease inhibitors may require a better understanding of SREBP activity. Three SREBP isoforms, 1a, 1c and 2, are expressed at varying levels in different tissues. Homo- and heterodimers probably form and contribute to overall SREBP activity, yet no studies have directly evaluated formation or activation properties of individual SREBP homo- and heterodimers. To assess activation by each particular SREBP dimer, we fused DNA encoding individual monomers together via a flexible polypeptide tether. The expressed tethered 1a and 2 homodimers, like their monomeric forms, activate more robustly than 1c homodimers. 1c as a heterodimer with either 1a or 2 attenuates activity relative to 1a or 2 homodimers. These experiments provide the first information showing that both activation domains in a dimeric transcription factor are required for maximal activity, and support a model where changes in SREBP-1c protein that occur in response to insulin and LXR would increase or decrease SREBP activity in cells where initial ratios of SREBP-1a to 1c are low or high, respectively. This model could explain why over-expression of SREBP-1a and SREBP-1c, specifically in liver, have similar phenotypes but their over-expression in adipose tissue has dramatically opposite effects. Here, 1c over-expression results in a phenotype resembling lipodystrophy including insulin resistance and diabetes. In contrast, similar over-expression of SREBP-1a resulted in massive adipocyte hypertrophy. Because the ratio of 1c to 1a varies from a high in liver (10:1) to a low in spleen (1:10), regulated expression of SREBP-1c by developmental, hormonal and

nutritional signals would have pronounced different tissue specific effects on SREBP dependent gene expression.

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