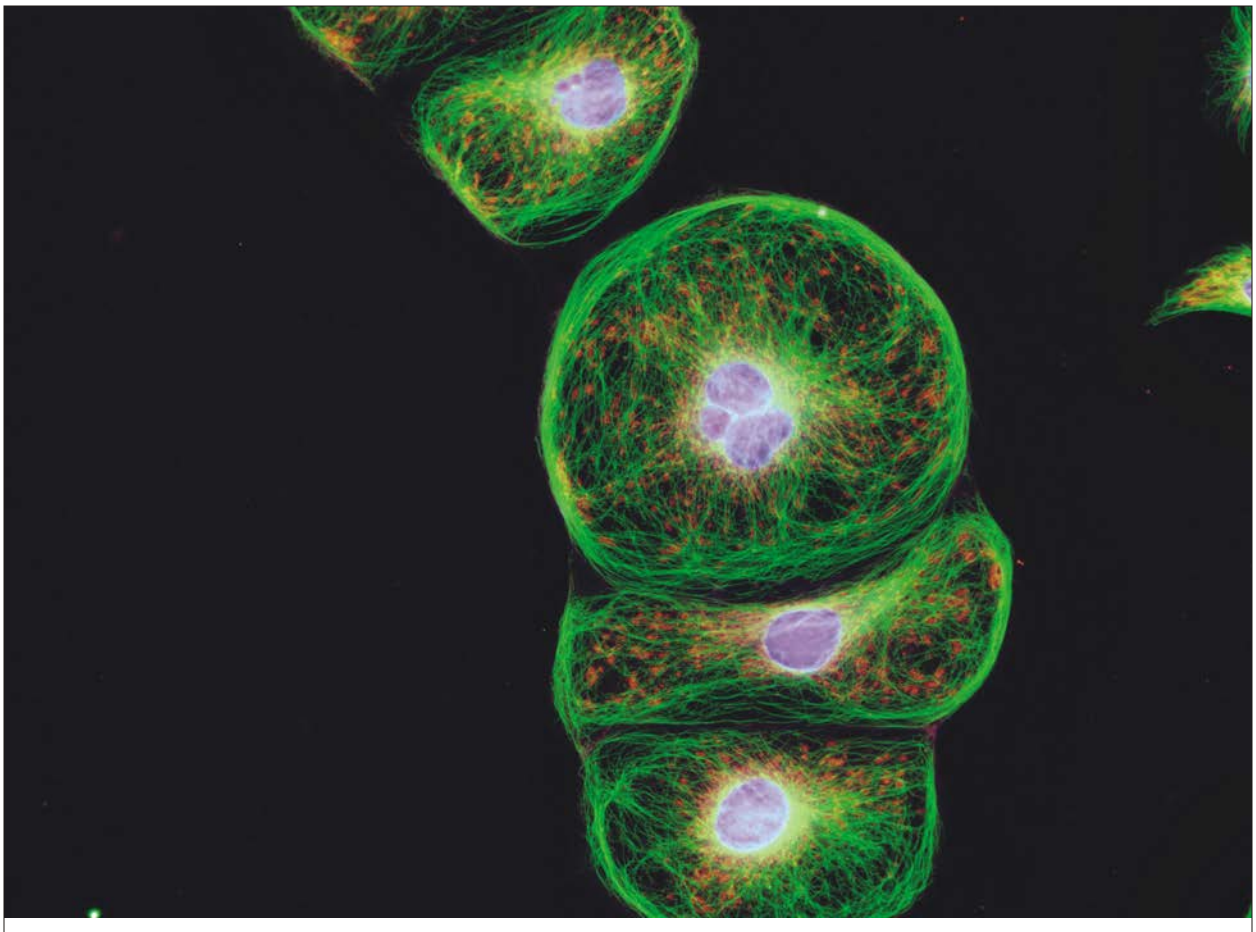

Asian Journal of Cell Biology

ISSN 1814-0068

Academic Journals Inc.

www.academicjournals.com

SRC-1 Controls Liver's 'Sweet Spot' for Glucose Production

SRC-1 (steroid receptor coactivator) orchestrates glucose production in the liver, regulating the activity of a cascade of enzymes that turns sugar production on and off in the liver, said Baylor College of Medicine and Duke University Medical Center researchers in a report that appears in the current issue of Cell Metabolism.

As we achieve a better understanding of gluconeogenesis (production of glucose) in the liver, we can look for new ways to treat metabolic diseases such as type 2 diabetes," said Dr. Jean-Francois Louet, instructor in molecular and cellular biology at BCM and a first author of the report. Dr. Atul R. Chopra, a resident physician at BCM, is the other first author.

SRC-1 is a member of a family of steroid receptor coactivators that control important processes in the body. Dr. Bert O'Malley, chair of molecular and cellular biology at BCM and a senior author of the report, discovered SRC-1 and has been a pioneer in uncovering the role of these molecules as cellular master regulators.

"For some years, cell and animal studies have indicated a 'missing control protein' in gluconeogenesis," said O'Malley. "In this study, we identify SRC-1 as this missing factor. Our identification of the coactivator SRC-1 as a 'master actor' in this tight control provides a possible therapeutic target for regulating liver glucose production."

The liver plays an important role in gluconeogenesis -- the production of glucose (from non-sugar source) in response to need, as when you fast. It keeps glucose levels in balance -- increasing the levels when needed and turning off that "spigot" when you eat and the levels of glucose increase.

"Ninety percent of endogenous (within the body) glucose production is in the liver," said Louet. He and his colleagues showed that mice that lack SRC-1 have hypoglycemia (too little sugar in their blood) when they have just eaten and when they are fasting.

"Without SRC-1, glucose production is impaired in the animals," he said. When he and his colleagues restored the SRC-1 to the liver tissues in the animal, glucose levels in the blood became normal.

In collaboration with members of the laboratory of Dr. Christopher B. Newgard (another senior author of the report) at Duke, the team used metabolomics to see what was happening in the tissue and blood from the mice that lacked SRC-1. Metabolomics is the study of a complete collection of metabolites present in a cell or tissue under a particular set of conditions. The collection is called the "metabolome".

"We found something we had never seen before. There was strong disorganization of the production of some metabolites that are important for regulating gluconeogenesis," said Louet.

As the group collaborated, it found that SRC-1 controls a gene for a transcription factor called C/EBP alpha that in turn targets a gene for an enzyme called pyruvate carboxylase, which is crucial to beginning the process of gluconeogenesis. (A transcription factor regulates the copying of specific genes [DNA] into a form of RNA the cell's machinery uses to build a protein.) Mice born lacking C/EBP alpha die soon after birth, an indication of the importance of this gene.

SRC-1 keeps these genes in tight control, insuring that the production of glucose in the liver goes up and down as the body needs.

Others who took part in this research include Jorn V. Sagen, Brian York, Mounia Tannour-Louet, Pradip K. Saha, Suoling Zhou, Franco DeMayo and Jianming Xu of BCM, and Jie An, Robert D. Stevens, Brett R. Wenne, Olga R. Ilkayeva and James R. Bain of Duke. O'Malley is the Thomas C. Thompson Professor of Molecular and Cellular Biology at BCM.

Funding for this work came from the National Institutes of the Health, the Norwegian Cancer Society, the University of Bergen and the Norwegian Society of Endocrinology.