■ METABOLISM

Calcium-mediated control

Glucose production by the liver is key to the maintenance of glucose homeostasis and is regulated by the actions of hormones such as insulin and glucagon. Two new studies uncover details of how glucagon regulates glucogenic transcription factors, highlighting a role for calcium signaling in hepatic glucose homeostasis.

Previous studies had linked intracellular calcium to regulation of gluconeogenesis, so Lale Ozcan *et al.* (*Cell Metab.* doi:10.1016/j.cmet.2012.03.002) focused on the calcium-sensing enzyme calcium calmodulin-dependent kinase II (CaMKII). They showed that this enzyme is activated by cyclic AMP (cAMP) and glucagon in a calcium-dependent and inositol 1,4,5-triphopshate receptor (IP_3R)-dependent manner in hepatocytes. IP_3R channels in the endoplasmic reticulum release calcium in response to ligand binding and are important in calcium homeostasis. CaMKII was also activated in the livers of mice in response to glucagon and fasting. A mouse knockout of CaMKIIγ had defective hepatic glucose production and failed to show the phosphorylation and nuclear translocation of the glucogenic transcription factor FoxO1 observed when wild-type mice were subjected to fasting. By contrast, a constitutively active CaMKII mutant had the opposite effects.

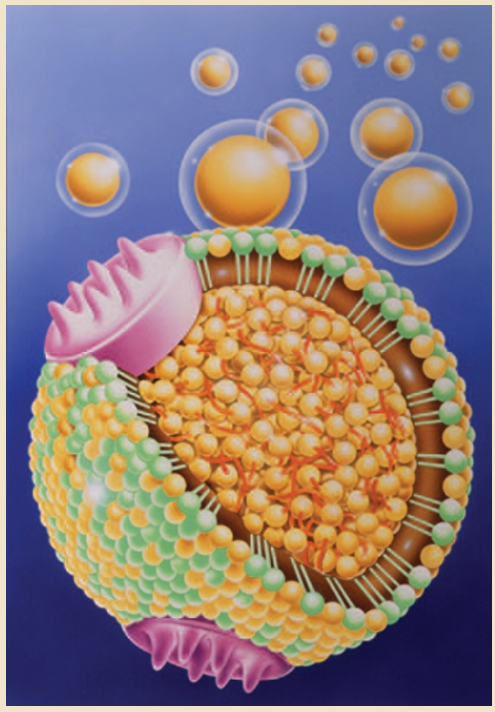
Ozcan *et al.* then examined the CaMKII pathway in two mouse models of obesity and found that the amounts of phospho-CaMKIIγ were higher in the livers of the obese mice than in those of wild-type mice. Genetic knockdown of CaMKII improved the metabolic deficits of the obese mice, lowering fasting glucose concentrations and the expression of FoxO1 target genes.

A second study by Yiguo Wang *et al.* (*Nature* doi:10.1038/nature10988) identifies how glucagon can affect the nuclear localization of another important glucogenic transcription factor, CRTC2, through a different calcium-sensing enzyme, calcineurin. This mechanism was also IP_3R dependent, and the authors showed that hepatic calcineurin activity was increased in two mouse models of diabetes and that knockdown of calcineurin or IP_3R could improve circulating glucose concentrations in these mice.

Together, these studies provide new mechanistic insights into the regulation of hepatic glucose production, and their findings may also be relevant in the settings of obesity and diabetes, although first it will be important to see whether these regulatory mechanisms also operate in humans. —*MS*

CARDIOVASCULAR DISEASE

Lipoprotein traffic control



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Insulin signaling in the liver affects lipid synthesis and uptake in many ways. Two new papers by Ai *et al.* in the *Journal of Clinical Investigation* show how an insulin-regulated signaling protein complex, mTORC1, acts to promote both lipoprotein secretion and uptake (doi:10.1172/JCI61248; 122, 1262–1270).

In the first paper, the authors showed in genetic or dietary mouse models of obesity that mTORC1 promotes secretion of apoB, the major apolipoprotein of the atherogenic lipoproteins very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL). Activation of hepatic mTORC1 triggers an endoplasmic reticulum stress response, and the researchers found that an effector of this pathway, the transcription factor Atf3, directly represses expression of the protein sortilin-1. This protein is involved in the intracellular trafficking of secreted proteins from the Golgi to lysosomes. It has previously been linked by genome-wide association studies in humans to LDL cholesterol levels and the risk of myocardial infarction and has also been reported to negatively regulate hepatic VLDL secretion in mice.

In the second paper, the authors showed that the effect of mTORC1 on lipoprotein uptake goes through a separate pathway involving the protein PCSK9, whose expression mTORC1 controls by signaling through the transcription factor HNF-1α. PCSK9, which like sortilin-1 is involved in intracellular protein trafficking, is thought to divert LDL receptor recycling into an endosomal-lysosomal pathway that leads to LDL receptor degradation. PCSK9 is known to affect LDL receptor function in humans: individuals with *PCSK9* mutations have high LDL receptor levels and low LDL cholesterol levels. —*MB*

■ BRAIN

Bouncing back after brain injury

Changes in neural circuitry after brain injury can help the nervous system to heal. In a recent study, researchers have demonstrated that molecules known for their functions in the immune system can constrain brain plasticity after stroke (*Neuron* **73**, 1100–1107).

Major histocompatibility class I (MHCI) molecules present antigens on the surface of cells to stimulate the immune system, and paired immunoglobulin-like receptor B (PirB) is a receptor for MHCI molecules. MHCI and PirB are both expressed on neurons and are known to have a role in neural plasticity during development, so Jaimie D. Adelson *et al.* asked whether they could also be targeted to induce functional recovery after stroke.

The researchers found that stroke increased the expression of two MHCI subtypes as well as PirB in the mouse brain; mice lacking these proteins had better functional outcomes and less brain damage after stroke. This improvement seemed to be linked to an increase in axon projections from the uninjured cortex of these mice to the affected side of the body, although exactly how the MHCI molecules and PirB receptor affect this process remains to be determined. —*EC*

■ BONE

Repairing joints

Osteoarthritis afflicts most adults over 55 and is caused by the progressive degeneration