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Hepatic CREBZF as a novel transcriptional regulator of the lipogenic pathway

Hepatic aberrant de novo lipogenesis and excessive triglyceride accumulation are linked to hepatic steatosis [1]. In a recent, interesting research article entitled "Hepatic CREBZF Couples Insulin to Lipogenesis by Inhibiting Insig activity and Contributes to Hepatic Steatosis in Mice", Zhang F. et al. sought to investigate the mechanism of hormonal regulation of lipogenesis [2].

Insulin is critical for the regulation of glucose homeostasis and de novo fatty acid synthesis. Insulin resistance may lead to excessive triglyceride accumulation in the liver, the hallmark of nonalcoholic fatty liver disease (NAFLD) pathology. It is known that insulin-Akt signaling inhibits Insig-2a through mTORC1-independent pathway, which leads to promotion of SREBP nuclear translocation and activation of lipogenic genes. Nevertheless, the underlying mechanisms are poorly understood. In particular, the mechanisms of insulin signal transduction into the cell and the regulation of lipogenesis need to be fully elucidated. Zhang F. et al. demonstrated that a novel ATF/CREB family transcription cofactor, called CREBZF, senses insulin signaling and stimulates the expression of lipogenic genes. They also demonstrated that CREBZF-dependent inhibition of Insig represents a molecular mechanism by which extracellular hormonal cues are transduced into the cell, and then regulate Insig-mediated feedback regulation of lipogenesis, which may contribute to hepatic steatosis, dyslipidemia and insulin resistance.

In vivo and in vitro studies illustrated that CREBZF activity is elevated in obesity and nutrient overload, which promotes lipogenesis and hepatic steatosis via Insig. Insig, which is an endoplasmic reticulum (ER) protein blocking the ER-to-Golgi transportation and activation of SREBPs, exhibits a negative feedback mechanism on hepatic lipogenesis [3]. During refeeding, insulin-induced activation of CREBZF inhibits Insig-2a expression in hepatocytes, allowing SREBP-1 to be processed in order to activate fatty acid synthesis. The CREBZF/ATF4 heterodimer serves as the direct regulator of the transcriptional regulation of Insig-2a via the putative C/EBP-ATF composite sequence. Therefore, CREBZF may be the missing link between insulin-Akt signaling and Insig-2a, and plays a pivotal role in hepatic fatty acid synthesis in physiologic and pathologic states via a transcriptional regulation.

Together with the recent findings that AMPK-mediated phosphorylation of SREBP-1c and regulation of lipogenesis at the post-translational level [4], these findings conceptually advance our understanding of the hormonal regulation of hepatic lipogenesis via the novel ATF/CREB family transcription factor. Hyperactivation of CREBZF may underscore the potential role of CREBZF in the development of sustained lipogenesis in the liver under insulin resistance conditions. As CREBZF may be associated with the pathogenesis of hepatic steatosis in mice and humans, these findings may present an important therapeutic potential in NAFLD, dyslipidemia, insulin resistance and metabolic syndrome-associated atherosclerosis. Inhibiting CREBZF function could be a promising strategy in the therapeutic armamentarium of NAFLD.

It is notable that CREBZF regulates de novo lipogenesis in the liver. It is of interesting to identify whether and how CREBZF plays roles in other metabolic tissues. Moreover, although these findings demonstrate that Insig, the key negative feedback regulator of SREBP-mediated lipogenic program, is regulated by CREBZF at the transcription levels, the upstream signaling that mediate the

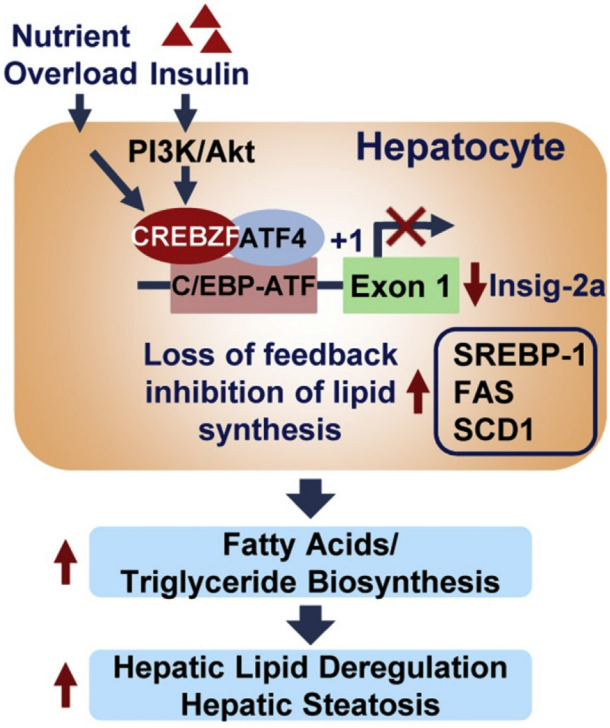

Fig. 1. The proposed model for the transcriptional regulation of Insig by CREBZF in the live. Obesity and nutrient excess induce CREBZF activity. Insulin-induced activation of CREBZF inhibits Insig-2a expression in hepatocytes during refeeding, allowing SREBP-1 to be processed and activation of fatty acid synthesis. The CREBZF/ATF4 heterodimer serves as the regulator transducing excessive nutrient and hormonal signaling to the transcriptional regulation of Insig-2a. CREBZF hyperactivation may play important roles in the development of sustained lipogenesis in the liver under selective insulin resistance conditions.

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post-translational regulation of Insig and its roles in the regulation of lipid metabolism in the liver remains to be investigated. (see Fig. 1).

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