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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Stress-induced Regulators of Intestinal Fat Absorption

The global prevalence of metabolic syndrome has led to intensive research efforts on the regulation of fat homeostasis. Intestinal lipid absorption and transport are crucial for maintaining lipid homeostasis. More than 90% of dietary lipids are hydrolyzed in the small intestine and the products are taken up by enterocytes. Lipid absorption by enterocytes begins with emulsification and solubilization of cholesterol in the intestinal lumen by biliary lipids and salts. Enterocytes resynthesize lipids and package them into chylomicrons for transport. Although significant research progress in dissecting the processes of intestinal absorption and delivery of dietary and biliary lipids has been made, the understanding of the regulatory network that controls these processes is incomplete.

CREBH (cAMP-responsive element-binding protein, hepatic-specific), an endoplasmic reticulum resident, basic leucine zipper (bZIP)-containing protein, is known as a stress-inducible transcription factor that is primarily expressed in the liver and small intestine.[1–4] It has been established that CREBH functions as an important regulator of lipid and glucose homeostasis, and the defect of CREBH is associated with hyperlipidemia, nonalcoholic steatohepatitis, and atherosclerosis.[5–8] In response to energy fluctuations triggered by nutrient starvation, circadian cues, or inflammatory challenges, CREBH transits from the endoplasmic reticulum to the Golgi where it goes through "regulated intramembrane proteolysis" to release a cleaved, functional CREB transcription factor.[3,7] Activated CREBH drives expression of the genes encoding the key hepatic metabolic regulators or enzymes involved in lipolysis,[5,6] fatty acid oxidation,[5,9] gluconeogenesis,[10] glycogenolysis,[11] and hepatic autophagy.[12] Although the functions and mechanisms of hepatic CREBH have been well studied, the intestinal CREBH functions are incompletely understood.

In the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, Cheng et al[13] contribute to the understanding of intestinal lipid homeostasis by identifying FACI, a novel fasting- and CREBH-regulated protein factor that inhibits intestinal lipid absorption and reverses high-fat diet-induced obesity. Like CREBH, FACI is primarily expressed by the liver and small intestine. Expression of FACI is regulated by nutrient-sensing transcription factors, including CREBH, HNF4α, CREB, PGC1α, and SREBP1, in mouse livers. FACI localizes to plasma membrane and recycling endosomes but lacks any known enzymatic domain. Genetic deletion of Faci in mice leads to an increase in intestinal fat absorption, and promotes complex metabolic phenotypes, including obesity, insulin resistance, hepatic steatosis, and dyslipidemia, under a high-fat diet. Together, this work implicates that CREBH and FACI form a stress-induced regulatory axis that modulates intestinal lipid homeostasis in response to nutritional signals. However, because FACI is expressed in both the liver and small intestine, it is important to determine whether the phenotypes observed in FACI-knockout (KO) mice, such as body weight difference, hepatic steatosis, and insulin resistance, are partially attributed to the functional defect of hepatic FACI.

The metabolic phenotypes of FACI-KO mice are partially overlapped with those of CREBH-KO mice. In the small intestine, is FACI a major target of CREBH in regulating lipid absorption? In an early work, Kikuchi et al[14] reported that intestinal CREBH prevents hypercholesterolemia by reducing expression of Niemann-Pick C1-like 1 (Npc1l1), a rate-limiting transporter mediating intestinal cholesterol absorption, in CREBH-transgenic mice under a high-cholesterol diet. Intestinal CREBH overexpression leads to decreased plasma cholesterols, reduced hepatic supply, and increased excretion, caused by suppression of intestinal cholesterol absorption. CREBH suppresses expression of Npc1l1, by directly binding to the Npc1l1 gene promoter, and several other intestinal transporters, including Abca1, Abcg5/8, and Srb1. Conversely, CREBH-KO mice display increased intestinal Npc1l1 expression, elevated plasma and hepatic cholesterols, and reduced excretion. Both Cheng's and Kikuchi's works suggest that CREBH is a suppressor of intestinal lipid absorption under high-fat diets. Whether CREBH simultaneously or differentially regulates 2 targets, namely FACI and Npc1l1, to prevent intestinal lipid absorption is an interesting question to be investigated.

Collectively, the study by Cheng et al[13] sheds a new light on the multifaceted mode of action of CREBH in regulating energy metabolism. Particularly, identification of FACI as a functional target of CREBH in intestinal fat absorption adds an important insight into the regulatory network of intestinal lipid homeostasis under metabolic stress conditions. For future studies, it is important to delineate the specific targets and mechanistic basis by which the CREBH-FACI axis regulates intestinal lipid absorption and transport under overnutrition. The work of Cheng et al[13] has raised many intriguing questions. Although much work remains, the regulatory mechanisms of intestinal lipid homeostasis and their relevance to the development of metabolic syndrome are rapidly unfolding.

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Conflicts of interest
The author discloses no conflicts.

Funding
Portions of Kezhong Zhang's work were supported by National Institutes of Health grants DK090313 and DK126908.

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2352-345X
https://doi.org/10.1016/j.jcmgh.2022.01.024