News Release

Intestinal Faf2 Identified as a Novel Regulator of Dietary Fat Absorption: A Potential Therapeutic Target for Obesity and Steatotic Liver Disease

Key Points

- Researchers discovered that Faf2, a protein expressed in intestinal epithelial cells, plays a critical role in dietary fat absorption and systemic lipid metabolism.
- Mice lacking Faf2 specifically in the intestine were resistant to obesity and showed reduced fatty liver development and improved glucose tolerance, even under a high-fat diet.
- Targeting intestinal Faf2 may represent a new therapeutic strategy for obesity and metabolic dysfunction-associated steatotic liver disease (MASLD).

Summary

A research group led by Dr. Norihiro Imai from the Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, has identified a previously unrecognized role for the protein Faf2 in regulating intestinal lipid transport and whole-body energy metabolism.

Using a genetically engineered mouse model in which Faf2 was selectively deleted from intestinal epithelial cells, the researchers found that loss of intestinal Faf2 suppressed body weight gain and fat accumulation under both normal and high-fat dietary conditions. In addition, these mice exhibited reduced hepatic fat deposition and improved glucose tolerance when challenged with a high-fat diet.

Further analyses revealed abnormalities in chylomicron formation, including intracellular retention of apolipoprotein B48, a key structural component required for lipid transport from the intestine to peripheral tissues. These findings demonstrate that intestinal Faf2 is an important regulator of dietary fat absorption and systemic lipid homeostasis.

The study provides new insights into the mechanisms underlying obesity and metabolic dysfunction-associated steatotic liver disease (MASLD) and may facilitate the development of novel therapeutic approaches targeting intestinal lipid transport.

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Research Background

Obesity and metabolic dysfunction-associated steatotic liver disease (MASLD) have become major global health concerns. These conditions are closely associated with type 2 diabetes, cardiovascular disease, and other metabolic disorders. Excessive absorption and accumulation of dietary lipids are thought to play a central role in their development.

Dietary fats absorbed by intestinal epithelial cells are packaged into lipoprotein particles called chylomicrons and subsequently transported throughout the body via the lymphatic circulation. Although this process is essential for maintaining energy balance, the molecular mechanisms regulating intestinal lipid transport remain incompletely understood.

Faf2 (Fas-associated factor family member 2) is a protein localized primarily to the endoplasmic reticulum and lipid droplets. Previous studies have implicated Faf2 in lipid metabolism within the liver; however, its physiological function in the intestine has remained largely unknown.

To investigate the role of intestinal Faf2, the research team generated mice lacking Faf2 specifically in intestinal epithelial cells (Faf2-IKO mice) and comprehensively analyzed their metabolic phenotypes.

Research Results

The researchers first demonstrated that Faf2 is highly expressed in the villous epithelium of the small intestine. Intestine-specific Faf2 knockout mice developed normally and exhibited no differences in body weight at weaning compared with control mice. However, as they matured, Faf2-IKO mice displayed significantly lower body weight under both normal chow and high-fat diet conditions (Figure 1).

Further analyses revealed reduced white adipose tissue mass and smaller adipocyte size in Faf2-IKO mice. Expression of genes involved in lipolysis was also elevated, suggesting that intestinal Faf2 deficiency influences systemic fat metabolism.

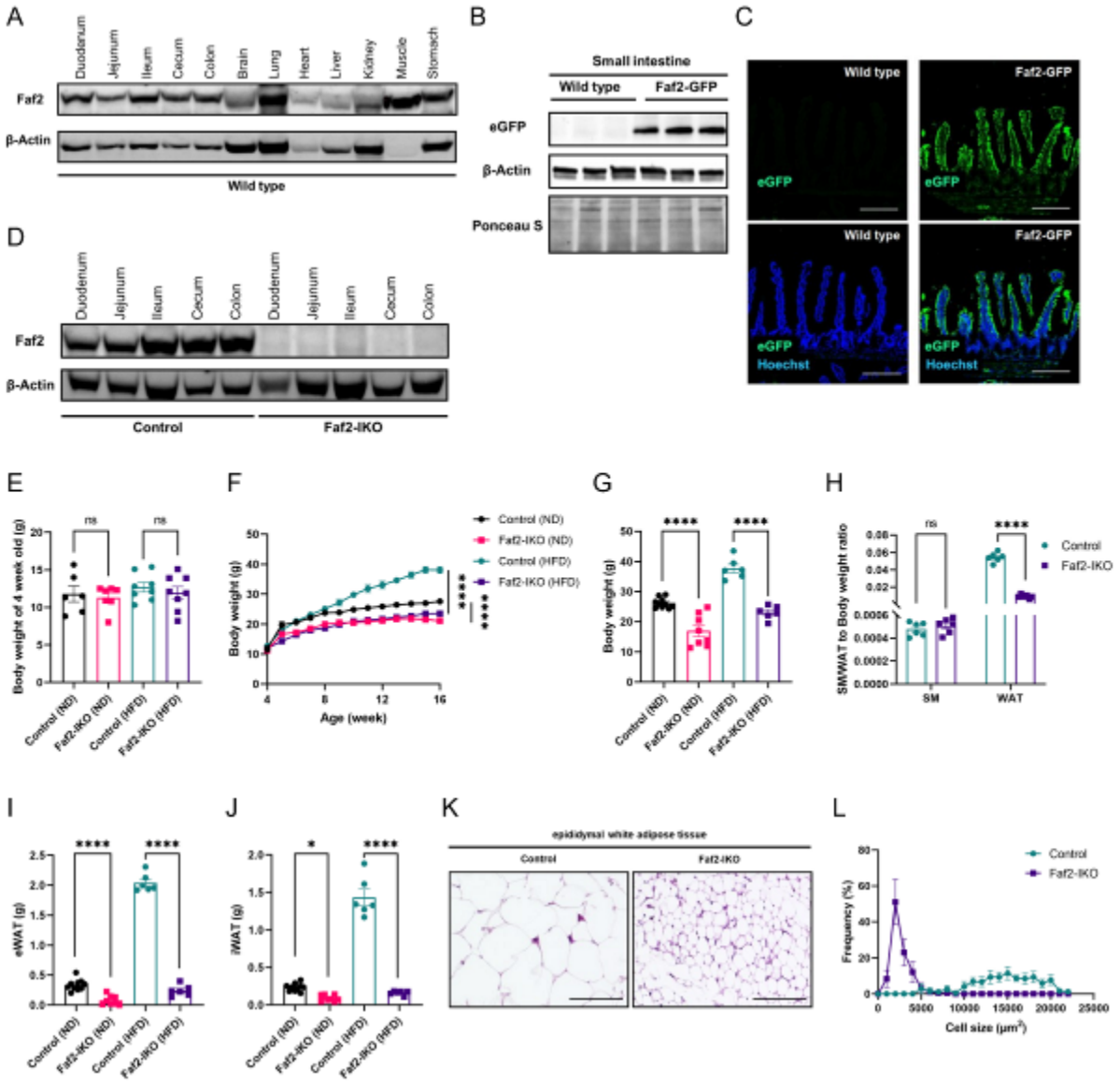


Figure 1.

The team next examined hepatic phenotypes. Under high-fat dietary conditions, control mice developed marked hepatic steatosis characterized by extensive lipid droplet accumulation within hepatocytes. In contrast, Faf2-IKO mice exhibited significantly reduced hepatic lipid deposition and lower serum alanine aminotransferase (ALT) levels, indicating attenuation of fatty liver disease (Figure 2).

To evaluate glucose metabolism, glucose tolerance tests were performed. Faf2-IKO mice showed improved glucose tolerance following glucose administration, whereas insulin sensitivity remained largely unchanged. These findings suggest that intestinal Faf2 deficiency ameliorates glucose dysregulation associated with obesity.

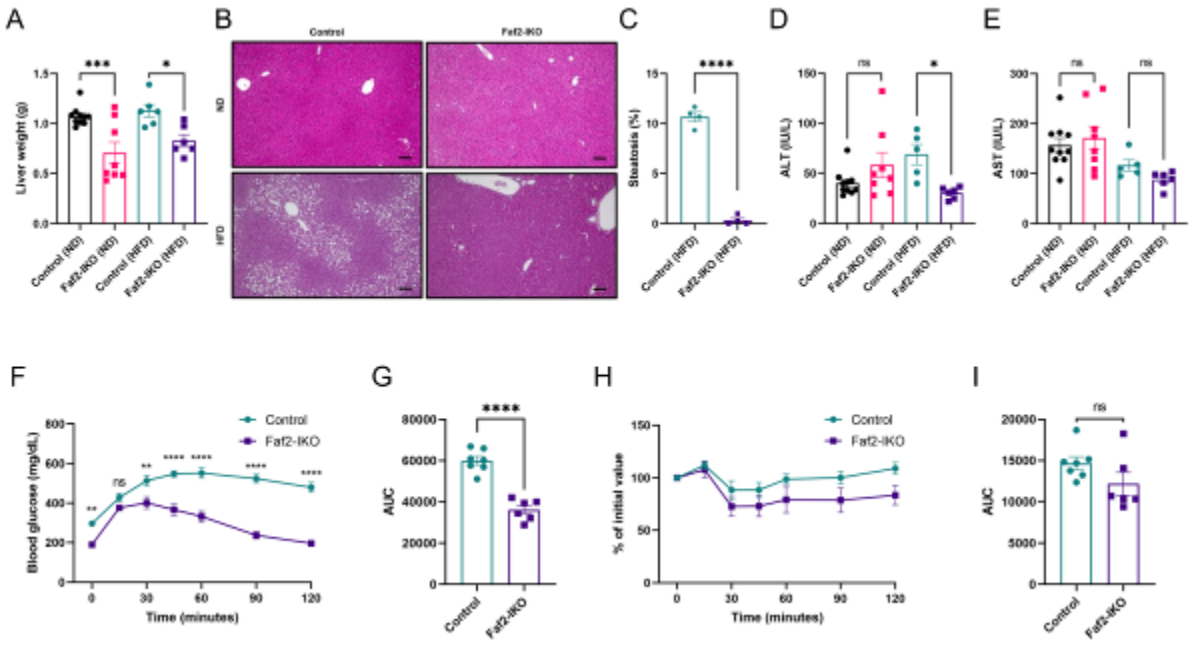
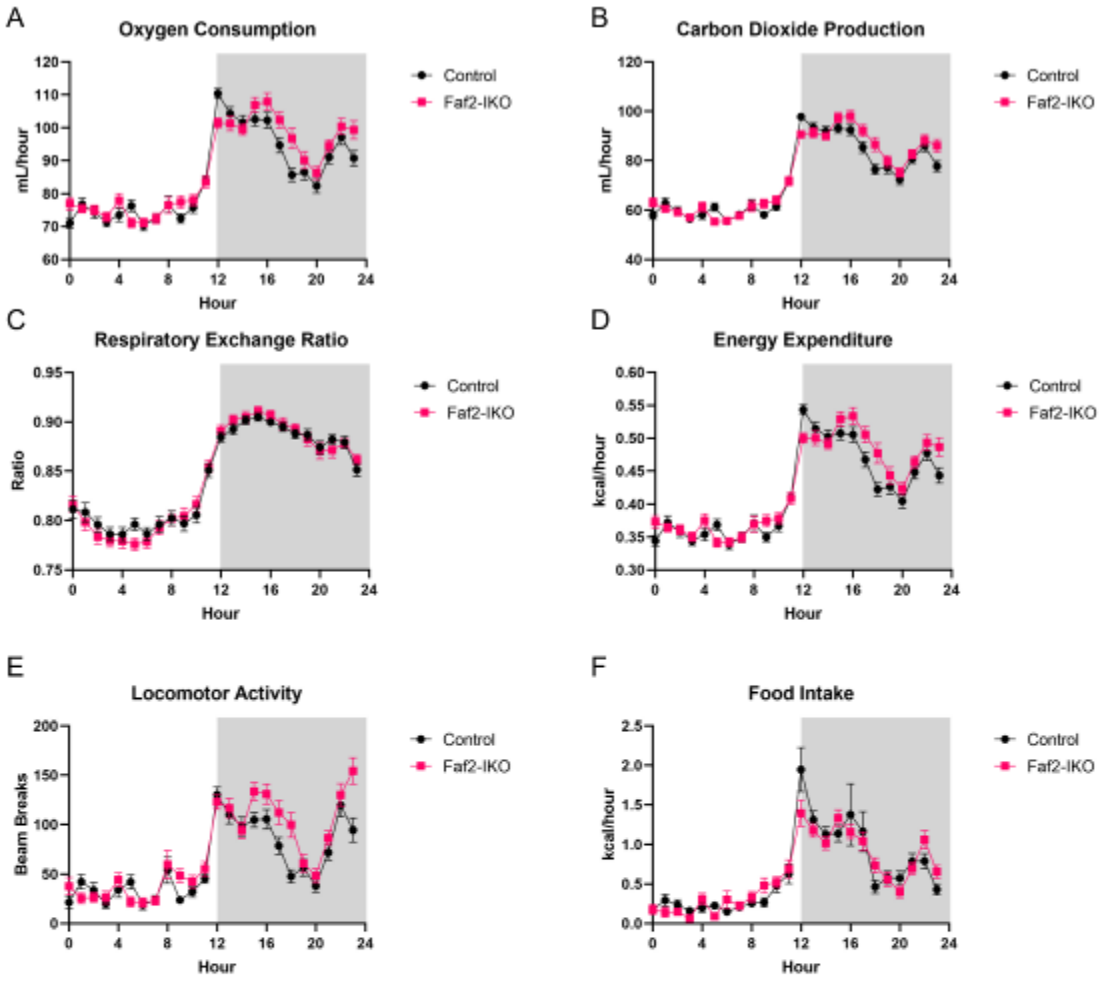


Figure 2.

To explore the mechanisms underlying resistance to obesity, metabolic cage analyses were conducted (Figure 3). No major differences were observed in food intake, respiratory exchange ratio, or locomotor activity. Although energy expenditure showed modest sex-dependent variations, fecal caloric content was increased in Faf2-IKO mice, suggesting reduced efficiency of nutrient absorption.



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Mass-dependent

	Full Day	Light	Dark
Food Consumed (kcal/period)	0.9519	0.5653	0.0422 *
Water Consumed (ml/period)	0.7952	0.8719	0.7982
Energy Expenditure (kcal/period)	0.0450 *	0.0076 **	0.2510
Oxygen Consumption (ml/hr)	0.0443 *	0.0064 **	0.2473
Carbon Dioxide Production (ml/hr)	0.0514	0.0160	0.2776

Mass-independent

	Full Day	Light	Dark
Pedestrian Locomotion (m)	0.1135	0.1150	0.1128
Total Distance in Cage (m)	0.0965	0.0983	0.0954
Respiratory Exchange Ratio	0.9356	0.6194	0.0751
Locomotor Activity (beam breaks)	0.1084	0.3000	0.1053
Energy Balance (kcal/period)	0.9605	0.5298	0.7342

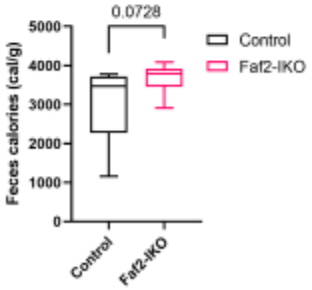

Figure 3.

The investigators then assessed circulating lipid profiles (Figure 4). Intestinal Faf2 deficiency resulted in lower serum concentrations of triglycerides, phospholipids, and cholesterol. Lipoprotein fraction analyses further demonstrated alterations in chylomicron and other lipoprotein subclasses, indicating that intestinal Faf2 influences

systemic lipid transport.

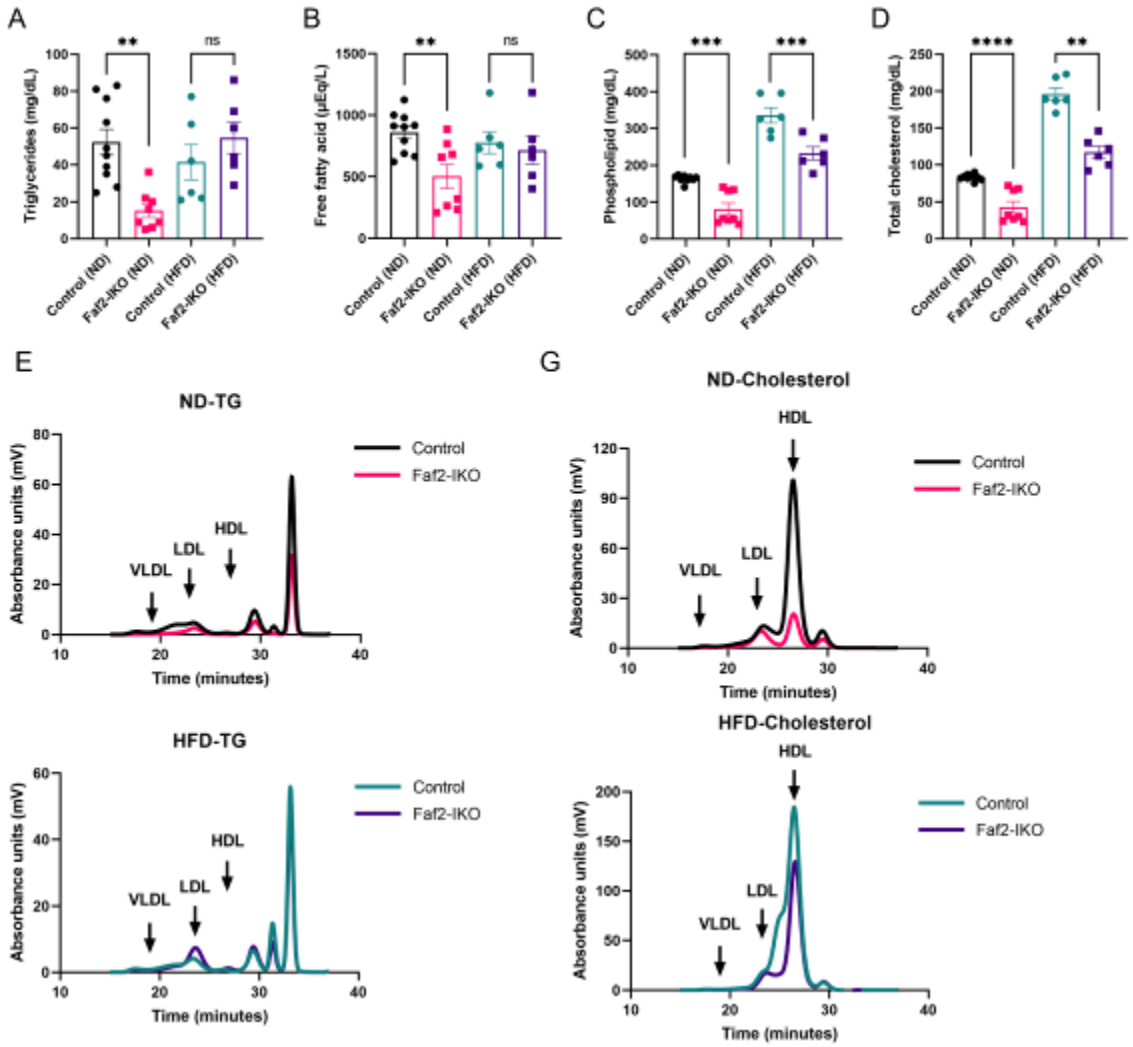

Figure 4.

To clarify the underlying molecular mechanisms, the researchers examined intestinal tissues in greater detail (Figure 5). Electron microscopy revealed lipid droplet accumulation and ultrastructural alterations within intestinal epithelial cells lacking Faf2. Moreover, apolipoprotein B48 accumulated intracellularly, while chylomicron secretion appeared impaired.

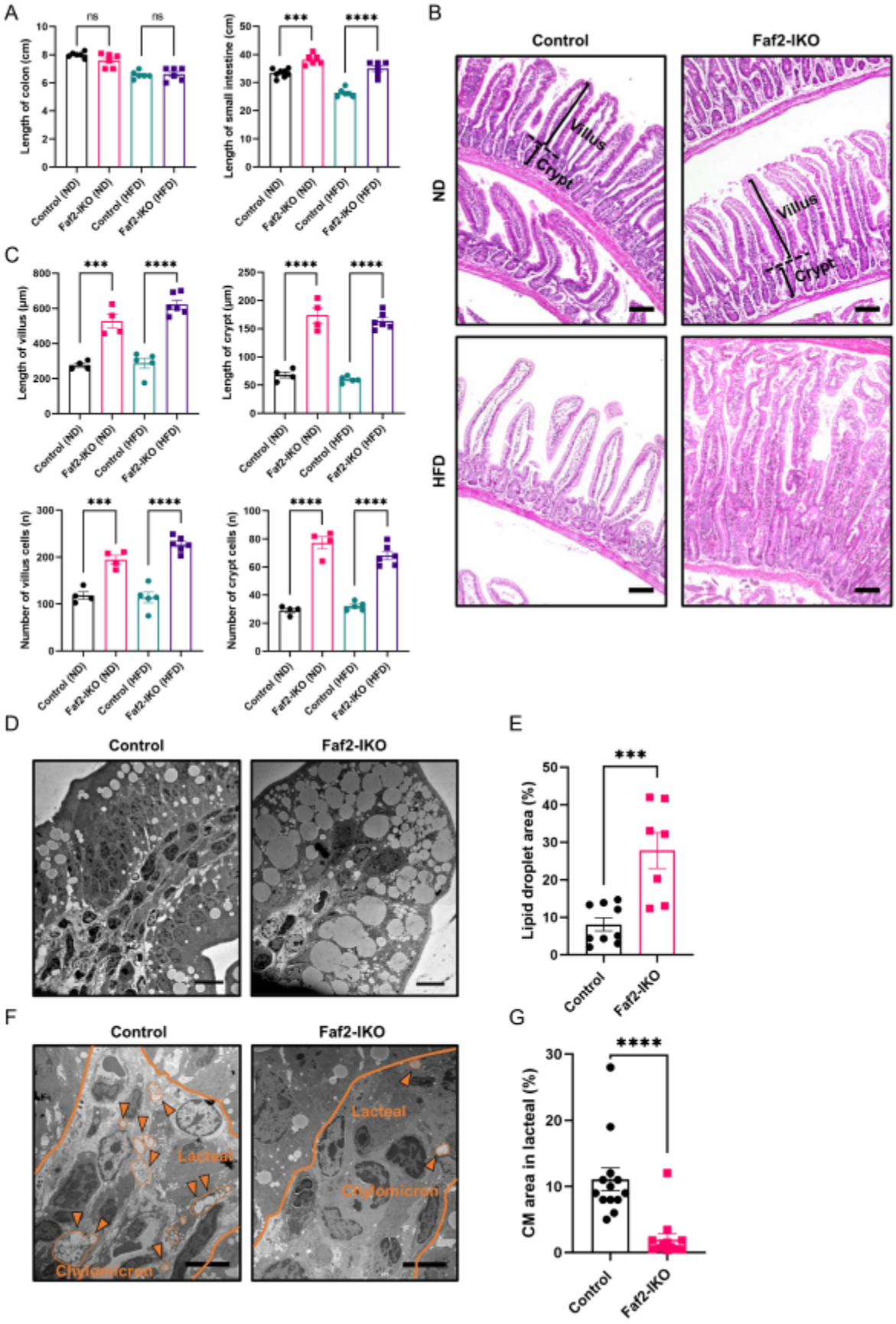

Figure 5.

Collectively, these findings indicate that Faf2 plays a crucial role in

chylomicron assembly and lipid export from intestinal epithelial cells. Loss of intestinal Faf2 disrupts dietary lipid transport, thereby reducing fat accumulation and protecting against obesity-associated metabolic abnormalities.

Research Summary and Future Perspective

This study identifies intestinal Faf2 as a previously unrecognized regulator of dietary fat absorption and whole-body energy metabolism.

Current therapeutic strategies for obesity and MASLD primarily focus on reducing appetite, improving insulin sensitivity, or enhancing energy expenditure. In contrast, the present findings suggest that modulation of intestinal lipid transport pathways may offer an alternative approach for preventing excessive fat accumulation.

By targeting Faf2, it may be possible to reduce the absorption and systemic distribution of dietary lipids, thereby attenuating obesity and its associated complications. Future studies will investigate the role of Faf2 in human obesity and MASLD and explore the feasibility of developing Faf2-based therapeutic interventions.

The discovery of intestinal Faf2 as a key regulator of lipid handling provides a new framework for understanding the pathogenesis of metabolic diseases and may pave the way for innovative treatment strategies targeting the intestine.

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Author: Jingjing Zhang[1], Norihiro Imai[1] (Corresponding), Jinglei Cheng[2], Akiko Sugiyama[3], Hanna Kawecka[1,4], Dongming Liu[1,5], Michitaka Suzuki[6], Yuki Ohsaki[7], Shinya Yokoyama[1], Kenta Yamamoto[1], Takanori Ito[1], Keiko Maeda[1], Yoji Ishizu[1], Takashi Honda[1], Tetsuya Ishikawa[1], Michał Woźniak[1], Hiroaki Wake[2], David E. Cohen[3], Hiroki Kawashima[1]

Affiliation:
1. Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, Aichi, Japan.

2. Department of Anatomy and Molecular Cell Biology, Nagoya University Graduate School of Medicine, Aichi, Japan.
3. Karsh Division of Gastroenterology & Hepatology, Cedars-Sinai Medical Center, CA, USA.
4. Department of Medical Chemistry, Medical University of Gdańsk, Gdańsk, Poland.
5. Department of Hepatobiliary Cancer, Liver Cancer Research Center, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China.
6. Department of Anatomy and Histology, Fukushima Medical University School of Medicine, Fukushima, Japan.
7. Division of Cell and Tissue Morphology, Department of Anatomy, Sapporo Medical University School of Medicine, Hokkaido, Japan.

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