Diet-Induced Intestinal Mucosal Disequilibrium Contributes to Insulin-Resistant Metabolic Disease

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**Background**

Mice can develop obesity and type 2 diabetes (T2D) through high-fat diets (HFDs). These mice are often used as models for human obesity and T2D. However, these models may not fully recapitulate human dysmetabolic states due to differences in the gut microbiota between humans and mice. It is well-established that gut microbiota play a crucial role in regulating host metabolism.

**Objective**

Nutrients influence the intestinal microbiota, which in turn affect host metabolism and health. Previous studies have shown that diet-induced changes in the gut microbiota can contribute to T2D. However, the role of the gut microbiota in the development of T2D and the mechanisms underlying these changes are not well understood.

**Methods**

**High-Fat-Diet-Induced Obesity Mouse Model**

- C57BL/6J mice were fed a 45% fat HFD or a 25% fat diet (2% LM) for 52 weeks. The mice were monitored daily for body weight and food intake.
- The mice were sacrificed after 52 weeks, and the intestines were removed and weighed.

**GIP Receptor Antagonist Combined with GLP-1 Receptor Agonism in DIO Mice**

- Mice received a single intraperitoneal (i.p.) injection of a GIP receptor antagonist or GLP-1 receptor agonist before or after HFD intervention.
- The mice were monitored for changes in body weight, food intake, and plasma glucose levels.

**Human and Mouse Intestinal Organoids**

- Mouse duodenal and terminal ileum were isolated and grown as organoids in vitro.
- Human duodenal and terminal ileum were isolated from healthy individuals and grown as organoids in vitro.

**Results**

**RESULTS**

1. High-Fat Diet Induces Intestinal Mucosal Disequilibrium

- HFD mice show increased mucosal thickness and decreased gut permeability compared to control mice.
- The mucosal disequilibrium is associated with changes in gut microbiota.

2. GIP Receptor Antagonist Combined with GLP-1 Receptor Agonism Restores Intestinal Mucosal Homeostasis

- The combination of GIP receptor antagonist and GLP-1 receptor agonist restores mucosal thickness and gut permeability in HFD mice.
- The combination of the two drugs also reduces gut inflammation.

3. Human and Mouse Intestinal Organoids

- Human and mouse intestinal organoids show similar responses to high-fat diet intervention.
- The organoids can be used as a model to study the effects of high-fat diet on the gut microbiota.

**Conclusions**

- The results suggest that diet-induced changes in the gut microbiota contribute to the development of T2D.
- The combination of GIP receptor antagonist and GLP-1 receptor agonist can be used to restore intestinal mucosal homeostasis in HFD mice.
- Human and mouse intestinal organoids can be used as a model to study the effects of diet on the gut microbiota.