Integrative Analysis of Gut Microbiota and Host Gene Expression Reveals Distinct Obesity Mechanisms

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Abstract:

Background: Obesity develops through multiple etiologies, yet interactions between host metabolism, gut microbiota, and microbial metabolites remain incompletely understood. This study investigated whether diet-induced and genetic obesity exhibit distinct host–microbiome–metabolite networks.

Methods: Male C57BL/6J control, diet-induced obese (DIO) and genetically obese ob/ob (leptin-deficient) mice were evaluated longitudinally. Gut microbial composition was assessed by 16S rRNA gene sequencing, including alpha- and beta-diversity, taxonomic profiling, and microbial network analysis. Metabolic and inflammatory markers (PPARγ, HSL, TNF and IL-10) were quantified in liver tissue. Plasma short-chain fatty acids (SCFAs) were measured, and correlation analyses integrated microbial, metabolic, and host gene expression data.

Results: DIO and ob/ob mice exhibited greater weight gain than controls, with ob/ob mice showing the most severe phenotype. Gut microbial communities significantly differed among distinct groups, with beta-diversity clustering and taxonomic profiles. Alpha-diversity was highest in ob/ob mice and lowest in DIO mice. Key taxa, including Mailhella massiliensis, Bacteroidales, and Helicobacter ganmani, differed between obesity models. Ob/ob mice showed increased HSL and IL-10 expression, while SCFA–gene correlations varied substantially between DIO and ob/ob mice.

Conclusions: Diet-induced and genetic obesity exhibit distinct microbiome–metabolic architectures, supporting obesity as multiple biological endotypes and highlighting opportunities for precision microbiome-targeted interventions.