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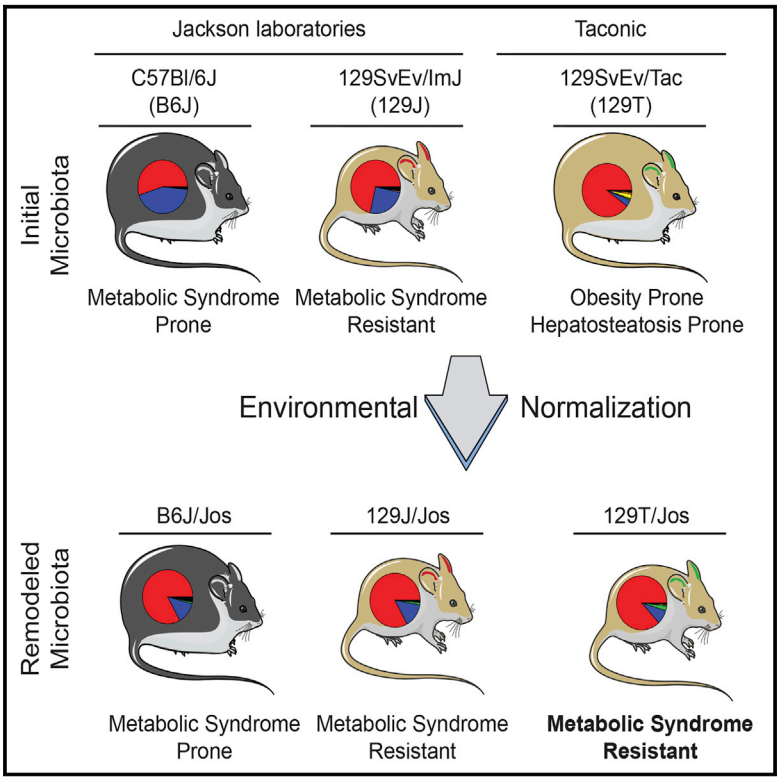
Interactions between Gut Microbiota, Host Genetics and Diet Modulate the Predisposition to Obesity and Metabolic Syndrome

Graphical Abstract



Highlights

- Host genetics determine changes in gut microbiota in response to high-fat diet
- Environmental history impacts on gut microbiota and response to dietary challenges
- Specific bacterial taxa correlate with metabolic phenotypes within and across strains
- Diet, host genetics, and gut microbiota interact in development of metabolic syndrome

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In Brief

In a longitudinal analysis of host genetics, diet, and gut microbiota interations, Ussar et al. demonstrate how interactions between the gut microbiota, host genetics, and diet influence the development of metabolic syndrome. The authors find that specific bacterial taxa appear to be linked to specific phenotypes. Changing the environment in early life not only changes the microbiota but also changes development of metabolic syndrome.

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SUMMARY

Obesity, diabetes, and metabolic syndrome result from complex interactions between genetic and environmental factors, including the gut microbiota. To dissect these interactions, we utilized three commonly used inbred strains of mice—obesity/diabetes-prone C57Bl/6J mice, obesity/diabetes-resistant 129S1/SvImJ from Jackson Laboratory, and obesity-prone but diabetes-resistant 129S6/SvEvTac from Taconic—plus three derivative lines generated by breeding these strains in a new, common environment. Analysis of metabolic parameters and gut microbiota in all strains and their environmentally normalized derivatives revealed strong interactions between microbiota, diet, breeding site, and metabolic phenotype. Strain-dependent and strain-independent correlations were found between specific microbiota and phenotypes, some of which could be transferred to germ-free recipient animals by fecal transplantation. Environmental reprogramming of microbiota resulted in 129S6/SvEvTac becoming obesity resistant. Thus, development of obesity/metabolic syndrome is the result of interactions between gut microbiota, host genetics, and diet. In permissive genetic backgrounds, environmental reprograming of microbiota can ameliorate development of metabolic syndrome.

INTRODUCTION

We are in the midst of worldwide epidemics of obesity, type 2 diabetes (T2D), and metabolic syndrome. These disorders present as a spectrum of overlapping phenotypes from metabolically healthy obese individuals to those with full-blown T2D and metabolic syndrome, arising from a complex set of interactions between genetic risk factors and environmental influences. Genome-wide association studies both in humans (Ng et al., 2014; Saxena et al., 2007; Speliotes et al., 2010; Xia and Grant, 2013) and rodents (Almind et al., 2003; Davis et al., 2012; Yazbek et al., 2011) have identified multiple loci that contribute to obesity and its associated metabolic abnormalities, each with a small effect. A number of environmental modifiers of disease expression have been defined, including caloric intake, dietary composition, levels of activity, and non-exercise-related energy expenditure (Franks et al., 2013; Kahn et al., 2006; Tuomi et al., 2014).

Recent studies in both rodents and humans indicate that the gut microbiota is also a contributor to metabolic disorders (reviewed in Khan et al., 2014). In general, obese humans and rodents have less diverse gut communities than their lean counterparts (Le Chatelier et al., 2013; Serino et al., 2012; Turnbaugh et al., 2009). Likewise, metagenomic studies have documented differences in the microbial gene repertoires represented in the gut communities of individuals with obesity (Greenblum et al., 2012), T2D (Karlsson et al., 2013; Larsen et al., 2010), or nonalcoholic fatty liver disease (Zhu et al., 2013). Evidence for a causal relationship between the gut microbiota and metabolic dysfunctions has come from studies showing that cohousing (Henao-Mejia et al., 2012; Upadhyay et al., 2012) or antibiotic treatment (Cox et al., 2014; Keeney et al., 2014) can modify obesity and metabolic phenotype in rodent models. Transplantation of fecal microbiota from obese versus lean mice, obese versus lean humans, and human twin pairs stably discordant for obesity into germ-free mouse recipients transmits donor adiposity and metabolic phenotypes (Le Roy et al., 2013; Million et al., 2013; Ridaura et al., 2013). Some of the effects of gastric bypass surgery on obesity and metabolic dysfunction have also been related to changes in gut microbiota (Liou et al., 2013). While cross-sectional studies and short-term experiments assessing effects of microbiota transfer have provided important insights into the role of gut microbiota in metabolic syndrome, additional approaches are needed to assess the long-term nature of normal environmental changes and the complex interaction between