Review

MOLECULAR METABOLISM

Interactions between host genetics and gut microbiome in diabetes and metabolic syndrome

Siegfried Ussar [1,2,**], Shiho Fujisaka [3], C. Ronald Kahn [4,*]

ABSTRACT

Background: Diabetes, obesity, and the metabolic syndrome are multifactorial diseases dependent on a complex interaction of host genetics, diet, and other environmental factors. Increasing evidence places gut microbiota as important modulators of the crosstalk between diet and development of obesity and metabolic dysfunction. In addition, host genetics can have important impact on the composition and function of gut microbiota. Indeed, depending on the genetic background of the host, diet and other environmental factors may produce different changes in gut microbiota, have different impacts on host metabolism, and create different interactions between the microbiome and the host.

Scope of review: In this review, we highlight how appropriate animal models can help dissect the complex interaction of host genetics with the gut microbiome and how diet can lead to different degrees of weight gain, levels of insulin resistance, and metabolic outcomes, such as diabetes, in different individuals. We also discuss the challenges of identifying specific disease-associated microbiota and the limitations of simple metrics, such as phylogenetic diversity or the ratio of Firmicutes to Bacteroidetes.

Major conclusions: Understanding these complex interactions will help in the development of novel treatments for microbiome-related metabolic diseases. This article is part of a special issue on microbiota.

Keywords Obesity; Metabolic syndrome; Microbiome; Microbiota; Microbial diversity; Host genetics; Environment

The potential importance of gut microbiota in human disease was recognized more than 1000 years ago in China where fecal transplants, referred to as "yellow soup", were used to treat gastrointestinal disorders. Over the past two decades, the scientific community has begun to rediscover the fact that not all gut bacteria are harmful and that transplantation of intestinal or fecal bacteria can be clinically useful in treatment of recurrent *Clostridium difficile* infection and possibly other diseases [1]. A key question is how important are gut microbiota in the control of metabolism and in the pathogenesis of obesity and diabetes.

The human body is a complex ecosystem hosting trillions of microbiota amounting to about 1.5 kg in mass. These colonize all surfaces of the body but especially the gastrointestinal tract. Using genetic techniques such as 16S sequencing, more than 1000 bacteria have been identified in the intestine, with ~200 defining the core gut microbiome, i.e., constituting at least 0.5% of the microbial sequences detected [2,3]. These bacteria exhibit important functions in the defense against foreign pathogens and the breakdown of otherwise indigestible dietary polysaccharides to produce short chain fatty acids, such as acetate, butyrate, and propionate, which can serve as important metabolites, a direct energy source for intestinal epithelial cells, modifiers of insulin resistance and modulators of insulin secretion [4–6]. Moreover, bacteria produce a wide range of other metabolites, as well as modifying human produced metabolites, such as bile acids, that can be taken up into the bloodstream where they have the potential to modulate host metabolism and other functions, including even behavioral and neural functions [7–11]. The microbiome can also influence the immune system [12,13] and the integrity of the intestinal epithelium allowing bacterial products, including endotoxins, to enter the blood stream, leading to insulin resistance and other immune mediated disorders [4,14].

The core gut microbiome in humans is established within the first three years of life and is subject to multiple influences (Figure 1) [15,16]. The initial colonization occurs during birth with vaginal microbiota from the mother, or, in the case of children born via cesarean section, with skin microbiota [17]. Not surprisingly, breast versus formula feeding also results in differences in the gut microbiota [18,19]. The gut microbiota acquired during early life are further modified by environmental factors, such as diet, antibiotic treatment, and the microbiome of close family members. This early transfer of the microbiome allows it to potentially contribute to what is viewed as the inheritability of a disease [20]. These can be distinguished by twin studies, since, in contrast to

[1]JRG Adipocytes and Metabolism, Institute for Diabetes and Obesity, Helmholtz Diabetes Center at Helmholtz Zentrum München, 85748 Munich/Garching, Germany [2]German Center for Diabetes Research (DZD), 85764 Neuherberg, Germany [3]First Department of Internal Medicine, University of Toyama, 930-0194 Toyama, Japan [4]Section on Integrative Physiology and Metabolism, Joslin Diabetes Center, Harvard Medical School, Boston, MA, USA

*Corresponding author. Section on Integrative Physiology and Metabolism, Joslin Diabetes Center, One Joslin Place, Boston, MA 02215, USA. Fax: +1 (617) 309 2593. E-mail: C.Ronald.Kahn@joslin.harvard.edu (C.R. Kahn).

**Corresponding author. JRG Adipocytes and Metabolism, Helmholtz Center Munich, Parkring 13, 85748 Munich/Garching, Germany. E-mail: Siegfried.ussar@helmholtz-muenchen.de (S. Ussar).

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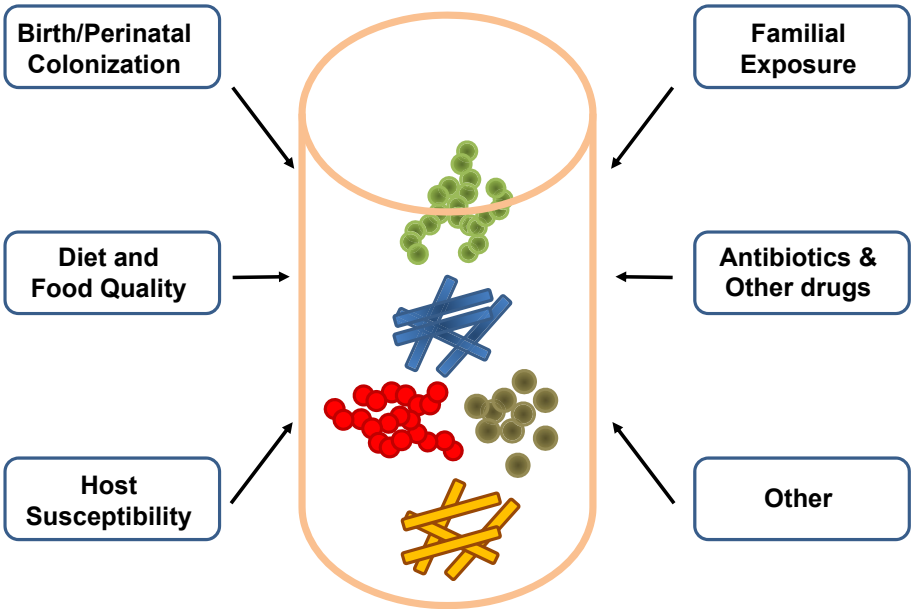

Figure 1: Factors contributing to the development of the microbiome. The development and composition of the gut microbiome is highly dependent on a multitude of environmental and host factors, especially those present in early life. Although core components of the gut microbiome tend to remain stable in adults, they continue to rapidly respond to alterations in the envrionment such as diet, medication and other factors.

classical genetic traits, transmission of gut microbiota is similar between mono- and dizygotic twins [21]. However, in most genetic studies, such as those used for genome wide association (GWAS) analysis, how transfer of microbiota between family members affects interpretation of data on the genetics of diabetes and obesity remains to be determined. Likewise, to what extent these initial differences in colonization result in altered risk for developing obesity or other diseases later in life remains controversial since the microbiome continues to remodel. However, as discussed below, this programming of the microbiome can lead to persistent effects even generations later. As the number of studies measuring microbiota composition in states of health and disease steadily rises, we are beginning to understand both the complexity of this system and its potential to interact with many physiological and pathological processes. Despite the ability of fecal transfer to mimic some disease characteristics, establishing causality, remains a challenge when evaluating the impact of individual gut microbiota on the regulation of host metabolism and metabolic disease. In an ideal case, a potential causative gut microbe involved in diabetes/obesity should be able to fulfill Koch's postulates, i.e., one can demonstrate that the specific microorganism is present in diabetic and/or obese individuals and that after isolation from an affected individual, it produces the same disease when reintroduced into a normal recipient (Figure 2, left panel). For metabolic diseases, such as diabetes, obesity, and metabolic syndrome, however, it appears that the effect of the microbiome is mediated through an interaction with larger microbial communities that together create a functional network. Moreover, many gene functions contributed by the gut microbiome are likely not present in just one microbe but are found in several bacterial strains. Conversely, the machinery involved in metabolic pathways may be split among different species of microbes, requiring the co-occurrence of multiple species to metabolize dietary components into specific metabolites (Figure 2 right panel). Furthermore, this community may interact with critical host factors and other environmental factors ultimately modifying disease development and progression. Determining the relative impact of these components, their hierarchy and interactions is a challenging task.

1. GENETICS AND ENVIRONMENT IN THE PATHOGENESIS OF OBESITY AND DIABETES

Obesity and its associated morbidities, such as type 2 diabetes, cardiovascular disease, and metabolic syndrome, are increasing in numbers worldwide. Despite the fact that knockout or overexpression of many single genes can lead to obesity and/or diabetes in mice [22–24], in humans less than 5–7% of individuals appear to have disease due to single gene alteration [25,26]. Indeed, genome-wide association studies in humans have identified a large number of genetic polymorphisms associated with increased risk for obesity and diabetes, with each gene having very small effects [27]. In fact, even if one considers all common gene variants combined, they explain only a small part of the development of obesity and type 2 diabetes. These findings point to the strong role of environmental factors driving the growth in disease prevalence. Much epidemiological evidence suggests that two important environmental drivers are a more sedentary lifestyle and a changing diet. Together, increased consumption of refined sugars, saturated fats, and, most importantly, total calories strongly correlate with the increased prevalence of obesity, diabetes, and other components of the metabolic syndrome.

Within the population, however, it is clear that there is significant individual variation in response to these environmental challenges. Perhaps the best example is the study by Bouchard et al. in which identical twins were kept relatively sedentary and challenged by overfeeding 1000 kilocalories (4.2 MJ) per day, six out of seven days for 100 days [28]. While weight gain between individuals in a given twin pair correlated very closely, there was more than a two-fold difference in weight gain between the twins that gained the most weight and those that gained the least weight, indicating that some factor(s) accounts for major differences in caloric efficiency. Likewise,

