Review

MOLECULAR METABOLISM

Gut microbiota and immune crosstalk in metabolic disease

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ABSTRACT

Background: Gut microbiota is considered as a major regulator of metabolic disease. This reconciles the notion of metabolic inflammation and the epidemic development of the disease. In addition to evidence showing that a specific gut microbiota characterizes patients with obesity, type 2 diabetes, and hepatic steatosis, the mechanisms causal to the disease could be related to the translocation of microbiota from the gut to the tissues, inducing inflammation. The mechanisms regulating such a process are based on the crosstalk between the gut microbiota and the host immune system. The hologenome theory of evolution supports this concept and implies that therapeutic strategies aiming to control glycemia should take into account both the gut microbiota and the host immune system.

Scope of review: This review discusses the latest evidence regarding the bidirectional impact of the gut microbiota on host immune system crosstalk for the control of metabolic disease, hyperglycemia, and obesity. To avoid redundancies with the literature, we will focus our attention on the intestinal immune system, identifying evidence for the generation of novel therapeutic strategies, which could be based on the control of the translocation of gut bacteria to tissues. Such novel strategies should hamper the role played by gut microbiota dysbiosis on the development of metabolic inflammation.

Major conclusions: Recent evidence in rodents allows us to conclude that an impaired intestinal immune system characterizes and could be causal in the development of metabolic disease. The fine understanding of the molecular mechanisms should allow for the development of a first line of treatment for metabolic disease and its co-morbidities.

This article is part of a special issue on microbiota.

Keywords Type 2 diabetes; Obesity; Microbiota; Intestinal immune system; Bacterial translocation

1. INTRODUCTION

The hologenome theory of evolution proposes that natural selection acts not on the individual organism but on the "holobiont", which consists of the host organism together with its microbiome (its genes and metabolites). When a holobiont is challenged by dramatic changes, such as altered diet, reduced physical activity, aging, drugs, or a disease, it employs adaptive mechanisms in the form of reshuffling/balancing its microbiome, i.e. resident microbial communities (Figure 1). The host side of the holobiont should also evolve and adapt to the changes. The mechanisms of this binary evolution, i.e. molecular crosstalk, still remain to be precisely determined, although evidences are on the way.

Within the holobiont, the most intuitive counterpart to the microbiome, which can be considered as the best-fit candidate to the microbiome diversity and the hologenome theory of evolution, is the immune system. The swiftness of its adaptability and the plasticity of the genome of the immune cells are such that changes in microbiota can be detected within days or weeks, allowing an adapted response of the host. Consequently, a major dysregulation of one of the components is likely to dramatically impact the other and, therefore, the holobiont. However, Darwinian selection, inherent to the hologenome theory of evolution, allows a drastic elimination of all dysregulated relationships between the microbiome and the immune system, which are at risk to the health of the holobiont. Therefore, to explain the epidemic development of metabolic disease, it is necessary to understand the molecular mechanisms responsible for imbalances combining subtle or mild impairments to the microbiome and host adaptability to environmental or evolutionary conditions. To design treatments for chronic, metabolic impairments, one should consider the molecular underpinnings of both the impaired microbiome and the impaired immune system

The causal role of gut microbiota on metabolic diseases has been shown in rodents through microbiota transfer experiments [1] and in humans [2] demonstrating that the microbiota from a healthy donor could improve the body weight and glycemia of an obese and diabetic receiver, respectively. Specific mechanisms of the host adapting to the change in microbiota could be proposed but would not fit with the notion of holobiont adaptation. Conversely, the immune system is the first line of adaptation to changes in the microbiome, where the innate immune system is, in a broad and non-specific manner, the fastest to adapt. It is followed by the adaptive immune system, which provides

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Abbreviations: APC, antigen presenting cells; ILC, innate lymphoid cells; AMP, anti-microbial peptides

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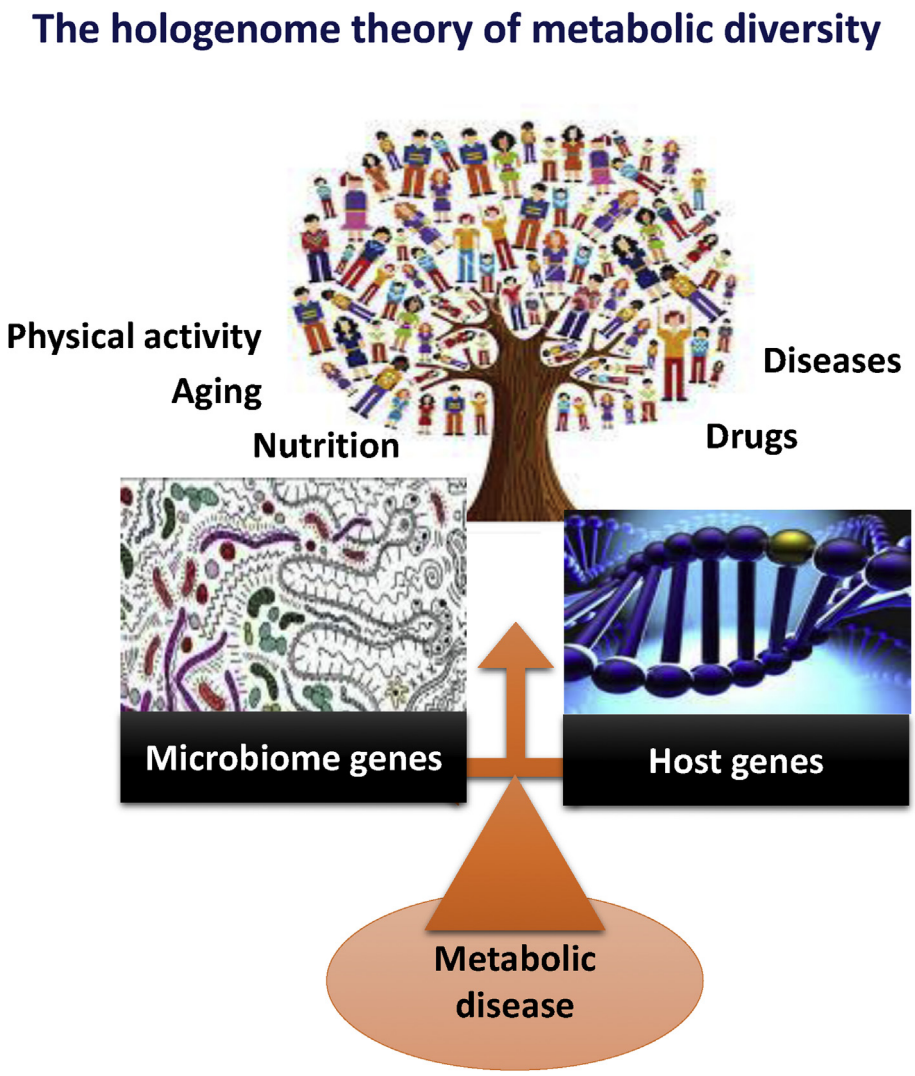

Figure 1: The hologenome theory of metabolic diversity. Gut microbiota metagenomics diversity and the host genetic diversity regulate human metabolic diversity. This balance is under the control of aging, food, drugs, physical exercise, and diseases to cite a few.

specificity, swiftness, and a memory to the dysbiotic microbiome. This crosstalk could be the first concept integrating the impact of the environment (social, nutritional, chemical, and behavioral) with the genetic of the host to explain the diversity and the development of metabolic disease in light of the definition of the holobiont.

This review will highlight the recent discoveries in the microbiota to host immune crosstalk with respect to metabolic disease. It will also aim to promote the concept that the development and treatment of metabolic disease should take into consideration that the holobiont, including the microbiome and immune system as the master regulatory mechanism, is a complex organism adapted to the environment. A change of the environment could impact both the host and the microbiome, leading to the development of metabolic disease. The role of the immune system as a key adaptor to the impact of the environment on the microbiome will be developed within the framework of metabolic disease.

It could be thought that at the cutting edge of the buffering capacity of the host and of the microbiota to adapt to the environment would be a thin line separating homeostasis and pathology. One should consider, however, that homeostasis and pathology are on a continuum, resulting from the adaptive capacity of the microbiome ecology and of the host, i.e. the immune system, to adapt to the environment. The threshold of a given molecular mechanism of the microbiome to host crosstalk, classifying individuals in a state of health or of metabolic disease, should always be considered for a specific homogeneous group of individuals in a specific environment. Classifying biomarkers and tailoring medicine/nutrition strategies should be based on an understanding of the adaptation of the holobiont — the host, its immune system, and its microbiome.

2. METABOLIC DISEASE: THE "INFECTIOUS" ORIGIN AND THE ROLE OF BACTERIAL TRANSLOCATION

Metabolic diseases, obesity, and type 2 diabetes are multifactorial, chronic, non-communicable diseases for which the past decades of research have aimed at identifying a genetic origin. After extensive analyses, no more than 2—3% of the incidence of metabolic diseases can be explained by more than 30 gene loci when combined together [3]. This resides in the fact that a novel paradigm engulfing numerous causal mechanisms is needed to uncover the epidemic development of

