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LETTER TO THE EDITOR

Gut microbiota and metabolic diseases: myth or reality?

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Microorganisms inhabiting human gastro-intestinal tract exceed the overall number of eukaryotic cells of about one order of magnitude [1–4]. Among the estimated 500–1,000 species [3], the majority has an unknown function, is neither beneficial nor harmful to host and represents the so-called "normal flora" or "microbiota" [5].

Noteworthy, the development of "next-generation" sequencing techniques, as part of the so-called "Omics", provided an holistic investigation allowing the study of the totality of gut microbiota, avoiding the need for lab-cultivation. These new molecular approaches opened the route toward a deeper investigation of the relationship between gut microbiota and host metabolism, focusing on multiple sides. Nowadays, Metagenomics [6, 7], Metatranscriptomics, Metabolomics [8] and Proteomics [9, 10] allow the study of gut microbiota genome, transcriptome and its impact on host metabolic profiles, respectively.

In the last decade, an increasing attention has been paid on gut microbiota, given its involvement in functions other than digestion, as the etiology of inflammatory bowel diseases [11–13], autoimmunity [14–16], allergy [17] and even cancer [2]. However, the inner relationship between gut microbiota and host metabolism has been extensively investigated especially focusing on metabolic diseases [5, 18], even if the molecular actors underlying this inner link are yet to be fully understood. Gordon's team performed pioneering studies using axenic (germfree) mice as a powerful model to study the impact of gut microbiota. Albeit these mice represent a non-physiologic model since the lack of gut microbiota impairs gut physiology [19], it has been shown that the establishment of a gut flora by colonization of axenic recipient mice with gut microbiota from donor mice is able to reverse this phenotype [20]. In addition, axenicity makes these mice resistant to diet-induced obesity, through a mechanism involving the enzyme lipoprotein lipase (LPL) and its inhibitor, the intestinal Fasting-induced adipocyte factor (Fiaf), which is over-activated in germfree conditions. This results in a diminished capacity to harvest energy from nutrients [21].

Gut microbiota ecology has been shown as deeply unbalanced in relation to metabolic diseases and on the top of it, obesity. The division of Firmicutes, a major phylum of gut microbiota in adulthood [22], has been positively correlated to body weight gain and obesity [23, 24]. Conversely, the division of Bacteroidetes, the second most represented phylum of gut bacterial ecology, characterizes a lean phenotype, both in humans and mice [23, 24]. Gordon's team was even the first to show the transmissibility of obesity by transferring its microbial component (gut microbiota issued from obese mice) into axenic recipient and showing an increased adipose tissue development when compared to recipient mice colonized with gut microbiota issued from lean mice [25].

However, metabolic diseases are always associated with a low-grade chronic inflammation in metabolically active tissues [26, 27]. Therefore, in the quest of a missing link between gut microbiota and inflammation, Burcelin's team was the first to link inflammation to intestinal microbiota and metabolic diseases by showing that an increase in lipopolysaccharides (LPS) plasma levels (referred to as "metabolic endotoxemia") was the initiator of metabolic

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diseases both in human [28] and mice [29]. Burcelin's research further demonstrated that a high-fat diet was responsible for gut microbiota ecology unbalance by decreasing the Gram positive bacteria count and, hence, by increasing the Gram negative to Gram positive ratio, leading to augmented endotoxemia [29]. Furthermore, using mice knock-out for the LPS receptor CD14 (part of the TLR-4 machinery of the innate immune system [30]), or continuously infusing subcutaneously low rates of LPS, we also provided a molecular evidence of the causal role of LPS in inducing metabolic diseases since CD14KO mice were protected from the metabolic effects of endotoxemia [29].

The demonstration of the causal role of gut microbiota within the etiology of metabolic diseases has led to the development of different strategies, i.e. the use of antibiotics, prebiotics and probiotics, aiming at impacting gut microbiota to ameliorate host metabolism. In detail, a chronic treatment of diabetic obese mice with antibiotics improved the glycemic control, by dramatically changing gut microbiota ecology [31, 32].

In the effort to modify gut microbiota ecology by enriching only bacteria that are beneficial for host metabolism, prebiotics [33] treatment has been shown to induce strong metabolic amelioration by reducing the inflammatory tone in diabetic mice, acting via an improved secretion of GLP-1 [34], a gut hormone which increases glucose-stimulated insulin secretion [35, 36].

Furthermore, gut microbiota modification can even lead to improved drug metabolism as the case of some probiotics (live microorganisms) which have been shown capable to reduce glicazide bioavailability in healthy rats, whereas it increased in diabetic rats, leading to ameliorated glycemic control by insulin-independent mechanisms [37].

The studies reported above state the new role that gut microbiota is acquiring day-by-day as a profound modifier of host metabolism, meaning that gut microbiota is no longer considered as a passive actor of host physiology nor involved in digestive function only. For instance, short-chain fatty-acids, which represent the major product of polysaccharide fermentation by gut bacteria, have been shown to modulate host-adiposity by acting as ligands of the G protein-coupled receptor Gpr41, expressed by a special type of epithelial enteroendocrine cells of the gut [38]. Moreover, gut microbiota balance modification represents a metabolic switch that can address host status toward physiology or pathology as shown in human by analyzing gut bacterial ecology in lean and obese twins [39]. This study yielded to the identification of a core gut microbiome (a specific set of bacterial genes) that is shared among individuals with divergent gut microbiota, meaning that an organismal divergence in bacterial ecology can, however, yield to common functions. Nonetheless, deviations from this core have been associated with different metabolic state, i.e. lean compared to obesity [39].

Therefore, novel therapy can be developed to treat metabolic diseases and other pathologies such as allergy or cancer, for which gut microbiota modification represents an important and causative risk factor.

Conflict of interest None.

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