Cell Metabolism
Previews

Intestinal Ecology in the Metabolic Syndrome

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Nutritional and genetic factors alter the intestinal microflora, predisposing individuals toward metabolic syndrome. Gewirtz and coworkers (Vijay-Kumar et al., 2010), employing Toll-like receptor 5 null mice, present evidence for a direct relationship between malfunction of the innate immune system, changes in gut microbiota composition, and development of metabolic syndrome.

The intestinal microbiota represents a community of trillions of bacteria dwelling in our intestine, with an aggregate bacterial genome (microbiome) outweighing by far our own human genome (Xu and Gordon, 2003). Past evidence on the role of the microbiota in human disease focused largely on inflammatory bowel disease and liver cirrhosis. Recent discoveries of a heretofore unrecognized role of the intestinal microflora offer new hints for a deeper understanding on the hidden origins of the metabolic syndrome. The metabolic syndrome represents more than a simple cluster of clinical conditions associated with increased cardiovascular risk. Glucose intolerance, dyslipidemia, hypertension, and visceral obesity are entwined by common and mutually dependent pathophysiological events, namely insulin resistance and low-grade chronic systemic inflammation, which uphold metabolic impairment and lead to the development of diabetes and atherosclerosis (Eckel et al., 2005). Exciting discoveries in the last few years support a role for gut microbiota as responsible for, and involved in, the perpetuation of both insulin resistance and low-grade chronic inflammation (Figure 1). Very recently, Gewirtz and coworkers (Vijay-Kumar et al., 2010), using transgenic mice, provided evidence of the direct relationship between development of the metabolic syndrome, malfunction of the innate immune system, and changes in the composition of the gut microbiota.

A few years ago, the horizon of the gut microbiota was extended to the direct embracement of obesity and metabolic impairment. In a seminal article unveiling the essential role of microbiota in promoting nutrient absorption and weight gain in rodents, Bäckhed et al. showed that germ-free mice are leaner than those harboring microbiota (Bäckhed et al., 2004). Of note, restoring the bacterial content in adult germ-free mice rapidly rescued the lean phenotype, resulting in weight gain and insulin resistance. Many of the bacterial genes are crucial for proper degradation and absorption of nutrients, as those responsible for carbohydrate hydrolysis; increased processing of ingested carbohydrates fostered monosaccharide uptake from the gut and was responsible for increased lipogenesis in the liver (Bäckhed et al., 2004). Having established the effects of the microbiota on nutrient absorption and metabolic regulation, the next step was to assess whether the opposite held true. Both animal and human studies confirmed that obesity alters the intestinal microbial ecology (Ley et al., 2005; Ley et al., 2006; Turnbaugh et al., 2009). In particular, the characterization of the intestinal flora in obese and lean twins led to the discovery that, whereas covariation is similar in monozygotic and dizygotic twin pairs, obesity results in a significant change in microbiota composition, both in terms of bacterial phylum-level diversity and bacterial genes composition (Turnbaugh et al., 2009). We also know that the gut microbial community is shaped by environmental, nutritional, and genetic factors (Hehemann et al., 2010; Slack et al., 2009). Only a few months ago, the employ of different genetically modified mouse models led to the identification of the role of innate and adaptive immune functions in determining the composition of intestinal gut microflora (Slack et al., 2009). To close the circle, it remained to show that genetic manipulations of the immune system leading to modifications in the gut microbiota would entrain metabolic outcomes.

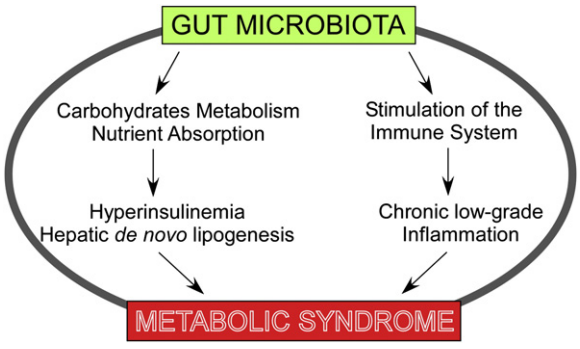

Figure 1. Proposed Pathophysiological Events Linking Gut Microbiota and the Development of Metabolic Syndrome
Recent evidence suggests that the microbiota may lead to the instauration of metabolic impairment by a dual mechanism involving the pathophysiological hallmarks of metabolic syndrome, namely insulin resistance and low-grade chronic inflammation. On one hand, the microbiota provides unique enzymes for the degradation of ingested food, thereby promoting the absorption of nutrients, mainly carbohydrates; the increased influx of carbohydrates from the gut to the liver results in increased lipogenesis that leads to insulin resistance, and it is turbo-boosted by hyperinsulinemia. On the other hand, the antigenic stimulus of the gut microbiota directly sustains a condition of systemic low-grade chronic inflammation. Although less well elucidated, metabolic impairment shapes the gut microbiota, probably on the basis of selection of bacteria species as dictated by the quantity and quality of ingested nutrients.

The issue was elegantly addressed last month in *Science*, wherein Gewirtz and coworkers unveiled the metabolic derangement in Toll-like receptor 5 (TLR5) null mice (Vijay-Kumar et al., 2010). Due to the absence

of TLR5, which is a main component of the innate immune system in the gut mucosa, *TLR5*$^{-/-}$ mice differ from *TLR5*$^{+/+}$ mice in the composition of bacterial communities harboring the intestine. Intriguingly, *TLR5*$^{-/-}$ mice presented increased adiposity, which was associated with clinical sequelae of metabolic syndrome, i.e., elevated serum triglycerides and cholesterol levels, increased blood pressure, and insulin resistance. Furthermore, feeding *TLR5*$^{-/-}$ mice a high-fat diet rapidly caused these mice to become diabetic. Treating *TLR5*$^{-/-}$ mice with broad spectrum antibiotics decimated the gut microbiota and rescued the metabolic phenotype, thus causally linking these two events. Conversely, transplantation of the gut microbiota from *TLR5*$^{-/-}$ mice to *TLR5*$^{+/+}$ germ-free mice recapitulated the metabolic phenotype. On a molecular level, the phenotype observed in *TLR5*$^{-/-}$ mice was linked to increased food intake and absorption and induction of low-grade inflammatory signaling, which acted both in association and independently. Therefore, the study of Gerwitz and coworkers should be considered a landmark for the direct genetic connection between microbiota, innate immune system, and metabolic syndrome. Additional studies will show to what extent it is possible to finely manipulate the composition of our intestinal flora in order to ameliorate the metabolic profile. Also, it will be crucial to determine whether potential modification of the gut microbiota, leading to decreased food absorption and energy storage, is achievable without compromising the assimilation of vitamins and other fundamental nutrients. Finally, the intriguing connection between microbiota ecology and hyperphagia deserves a complete mechanistic scenario. When these issues are solved, the employ of anti-, pre-, or pro-biotics in the arsenal of medications to treat metabolic syndrome will definitively be of enormous help.

The study of Gewirtz and coworkers once more drives our attention to the intestinal microflora as a causative agent in the metabolic syndrome. While these exciting discoveries reveal new hints on the individual predisposition toward disease, the search for molecules that can help us manage metabolic impairment goes along with the need to admit that fighting obesity and metabolic syndrome will not be as easy as swallowing a pill. We know that the genetic background influences body weight as well as response to dietary regimens and physical exercise. Nevertheless, modification of lifestyle habits remains the most important strategy to fighting metabolic diseases, both at individual and community levels (Knowler et al., 2002). We now know that, together with physical activity, it is imperative to check the food that we eat and the bacteria that it brings into our intestine.

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