GUT MICROBIOTA

Ganoderma lucidum, a new prebiotic agent to treat obesity?

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Refers to Chang, C. J. *et al. Ganoderma lucidum* reduces obesity in mice by modulating the composition of the gut microbiota. *Nat. Commun.* **6**, 7489 (2015)

Modulation of the gut microbiota is one of the promising tools to tackle obesity. Chang and colleagues have recently shown that an extract of the mushroom *Ganoderma lucidum*, a traditional remedy in Asia, can reduce obesity in mice by modulating the gut microbiota, thereby exerting a prebiotic effect.

The prebiotic concept typically refers to nondigestible compounds that are not absorbed in the upper part of the gastrointestinal tract and can be used as substrates for the microbes that inhabit your gastrointestinal tract, with the vast majority of them residing in the lower part of the gut. By being substrates for microorganisms, prebiotics favour the growth of bacteria that can confer physiological benefits to the host. The collection of data published to date enabled us to propose that the prebiotic concept relies on the causal relationship between gut microbiota modulation and the beneficial effects of a compound.[1] This causal relationship between modulation of the gut microbiota and beneficial physiological effects has been evaluated by Chang and colleagues[2] in mice given a water extract of *Ganoderma lucidum* (WEGL).

Ganoderma lucidum (also known as lingzhi or reishi) is a mushroom that has been consumed for its broad medicinal properties in Asia for over 2,000 years. This mushroom is becoming increasingly popular in Western countries as a complementary medicine for cardiovascular health.[3] In an article published in *Nature Communications*, Chang *et al.*[2] investigated the anti-obesity properties of *Ganoderma lucidum* in a mouse model of diet-induced obesity. They showed in a very convincing manner that daily administration of a WEGL at concentrations from 2–8% to mice fed a high-fat diet improved obesity and obesity-related features such as fat mass, glucose homeostasis and liver and adipose tissue inflammation. Furthermore, they reported that administration of WEGL reduced serum lipopolysaccharide levels and prevented the hepatic activation of the Toll-like receptor 4 pathway. On the basis of the work that our laboratory and others published,[4,5] the authors of this new study formulated the hypothesis that modulation of the gut microbiota by WEGL might contribute to its beneficial effects (Figure 1).

Interestingly, WEGL changed the abundance of several bacterial species. Furthermore, horizontal transfer of the gut microbiota, a process also known as cross-faunation, recapitulates the anti-obesity effect of the WEGL. The researchers thus suggested a key role for the gut microbiota in the metabolic improvements of the WEGL.[2] Finally, to discover the bioactive compound(s) in this context, WEGL polysaccharides were isolated and separated into four fractions based on their molecular weight. Interestingly, two fractions (containing high-molecular-weight and intermediate-molecular-weight polysaccharides) had anti-obesity properties,[2] suggesting that the beneficial effect of WEGL does not rely on a single molecule, but rather on several polysaccharides of various sizes.

A key question raised by this work is: what are the other potential mechanisms beside a reduction of serum lipopolysaccharide level that are involved in the anti-obesity effect of the WEGL? Indeed, reduction of endotoxaemia by WEGL could explain some of the metabolic improvements, but not all of them. For instance, reduction of endotoxaemia cannot explain the increased number of regulatory T (T_{REG}) cells in the liver and adipose tissue observed upon WEGL supplementation. Several microbial, immune and metabolic pathways could conjointly contribute to this beneficial effect. As a first example, WEGL increased the abundance of a *Roseburia* species by 10-fold. This genus is known to produce butyrate, a short-chain fatty acid able to improve insulin sensitivity and energy expenditure in mice.[6] Secondly, the WEGL also favoured the growth of species from the *Clostridium* clusters XIVa and XVIII, which might have immunomodulatory properties, such as induction of colonic T_{REG} cells.[7] Whether those bacteria are responsible for the induction of T_{REG} cells observed in the liver and in the adipose tissue of the

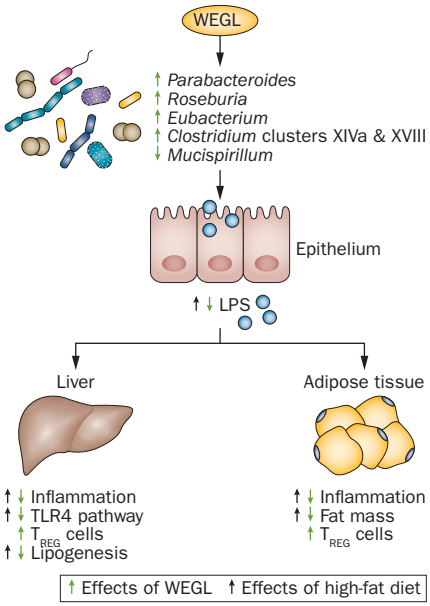

Figure 1 | Metabolic improvements conferred by WEGL administration to obese mice. High-fat diet consumption is associated with increased serum levels of LPS, also called metabolic endotoxaemia.[4,5] Metabolic endotoxaemia induces hepatic and adipose tissue inflammation and can activate the TLR4 pathway in the liver. High-fat diet consumption is also accompanied by increased hepatic lipogenesis due to insulin resistance. WEGL reduced metabolic alterations and changed the relative abundance of several bacterial taxa (a few of which are indicated in the figure). Abbreviations: LPS, lipopolysaccharide; TLR, Toll-like receptor; T_{REG} cell, regulatory T cell; WEGL, water extract of *Ganoderma lucidum*.

mice receiving WEGL remains to be investigated. Moreover, we cannot rule out that the effect of the WEGL is driven by one or a few bacteria through still uncharacterized pathways. For instance, WEGL administration to high-fat-fed mice increased the abundance of *Parabacteroides goldsteinii* from 3% to 25%, a bacterial species with unknown effects on metabolism. Finally, other microbe–host interaction pathways could be involved in the physiological benefits of the WEGL and would deserve further investigation, such as the bile-acid-related pathways, known to influence glucose homeostasis and energy expenditure.[8]

The effects of *Ganoderma lucidum* have already been investigated in clinical trials[3] and a clinical trial to test WEGL as an anti-obesity agent would be quite straightforward to set up. However, determining which microbes are key players in the anti-obesity effect of WEGL might become crucial for the success of such a future clinical trial, mainly in view of the interindividual variations in human gut microbiota. Indeed, interindividual variations in the composition and activity of the gut microbiota are much more important in humans than in laboratory mice. The dietary responsiveness of an individual's microbiota has been proposed to vary substantially and individuals might be stratified into responders and nonresponders based on the features of their intestinal microbiota, such as the microbial diversity or the abundance of certain species.[9,10] As an example of this concept of responders and nonresponders, Dao *et al.*[10] have shown that a higher abundance of *Akkermansia muciniphila* at baseline is associated with increased improvement in glucose homeostasis and body composition after calorie restriction compared with a lower abundance of the bacteria. The authors suggested that *Akkermansia muciniphila* could be used as a tool to predict the success of a calorie restriction diet.[10]

Achieving such a responder or nonresponder classification based on features of the initial gut microbiota might contribute to a successful clinical trial for WEGL in obese patients. Indeed, as WEGL reduces obesity by modulating the composition of the gut microbiota, one could anticipate interindividual variation regarding the microbial response to WEGL, and thus the anti-obesity effect of WEGL. Determining specifically which changes in the gut microbiota, in terms of composition and/or activity, are responsible for the metabolic benefits of the WEGL would help in the classification of participants prone to be responders or nonresponders.

In conclusion, this work by Chang and colleagues[2] supports the concept of prebiotics and the interest in modulating gut microbiota to treat obesity and associated metabolic disorders. We believe that further understanding of the microbial and physiological mechanisms underlying the beneficial effects of WEGL and similar compounds would contribute to the success of future clinical trials aimed at investigating the anti-obesity potential of gut-microbiota-targeted interventions, taking into account the knowledge issued from plant-based traditional medicine.

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Competing interests
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