A human gut bacterium triggers obesity and Non-alcoholic Fatty Liver Disease in germ-free Mice through Lps-dependent mechanism

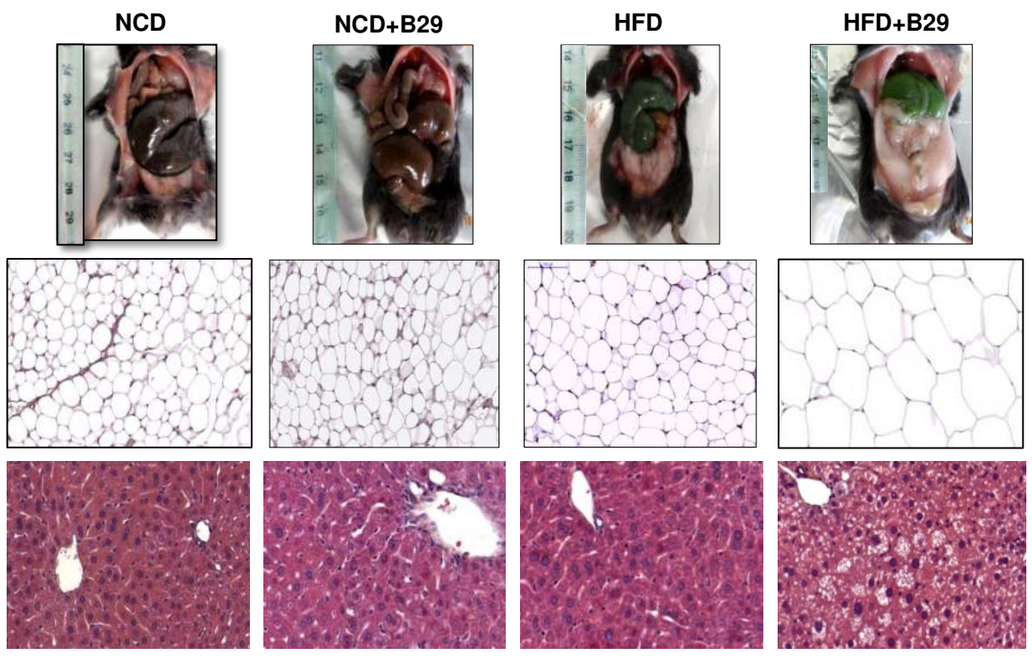
Na Fei[1], Aurélia Bruneau[1], Liping Zhao[2], Philippe Gérard[1]

[1]Micalis Institute, INRA, AgroParisTech, Université Paris-Saclay, 78350 Jouy-en-Josas, France

[2]School of Life Sciences and Biotechnology and Shanghai Center for Systems Biomedicine, Shanghai Jiao Tong University, 200240, Shanghai, China

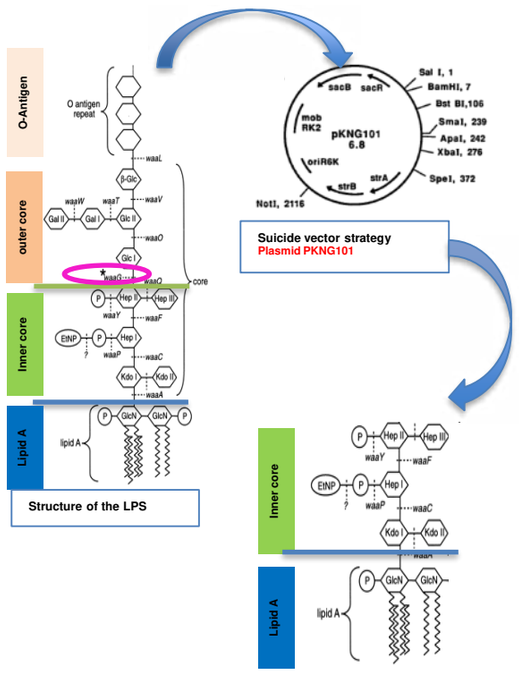
Introduction: Non-alcoholic fatty liver disease (NAFLD) is an important cause of chronic liver injury in the world. Several lines of evidence suggest a link between the gut microbiota and the etiology of NAFLD. Among the potential mediators of this association, lipopolysaccharides (Lps) from the gut may play a key role in the pathogenesis of NAFLD. We have already demonstrated that the *Enterobacter* spp. B29, isolated from a morbidly obese volunteer's gut could cause obesity in germ-free (GF) mice. Here, we assessed the capacity of B29 to trigger NAFLD in GF mice and deciphered the role played by the Lps.

Enterobacter spp. B29 induced obesity and NAFLD in GF mice



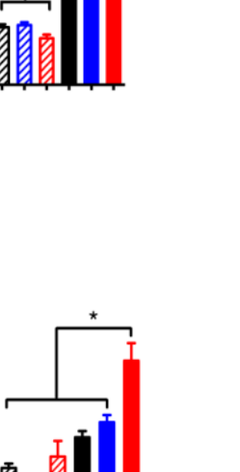
While GF mice did not develop obesity or steatosis whatever the diet, C57BL/6J mice mono-associated with B29 display adipocyte hypertrophy and hepatic steatosis on high-fat diet (HFD) but not on normal chow diet (NCD). Moreover, B29 triggers liver inflammation both on HFD or NCD.

Construction of a B29 mutant modified in Lps structure



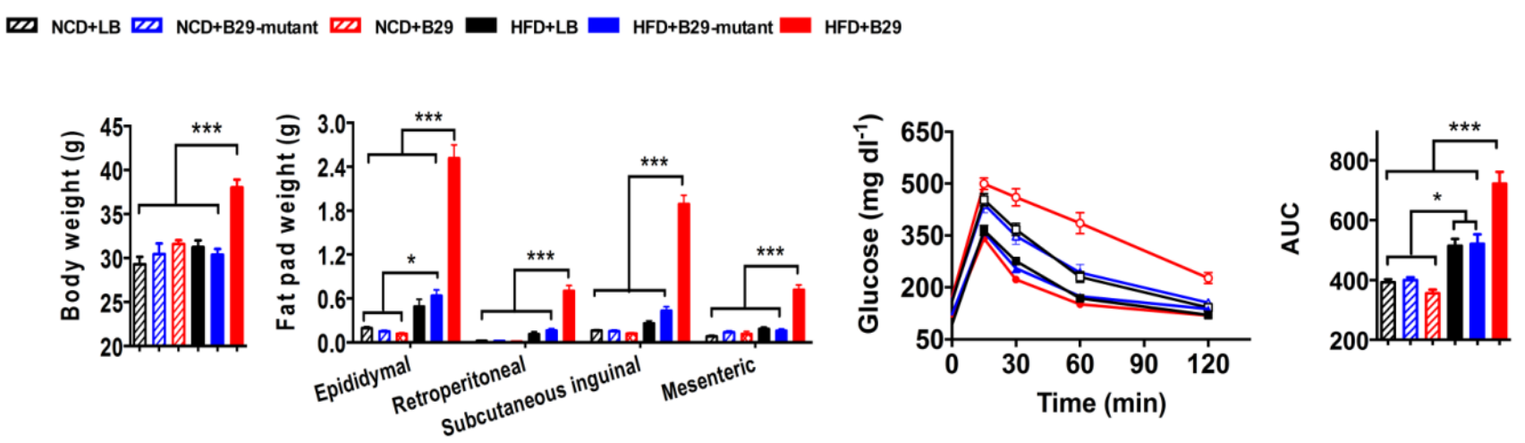
In order to determine if Lps is the molecular factor responsible for the effect of B29 on the host, we knock out the *waaG* gene, involved in Lps biosynthesis, in the B29 wild-type strain.

The resulting B29 mutant (B29Δ*waaG*) possesses a Lps lacking the outer core and the O-Antigen,

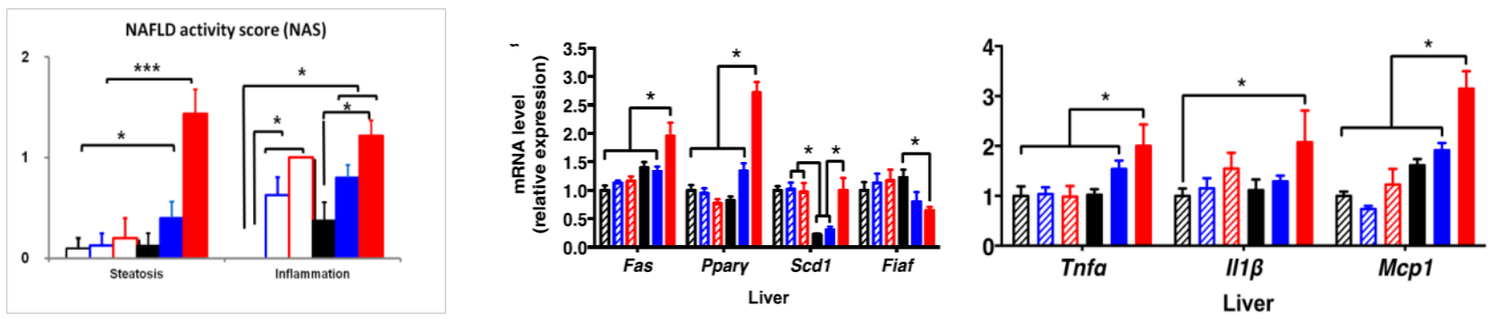


A limulus amebocyte lysate (LAL) test showed that the LPS endotoxin activity of B29Δ*waaG* was nearly 600-fold lower than the one of B29 wild-type strain,

The B29 lps-mutant lost the capacity to induce obesity, glucose intolerance and NAFLD in GF mice under HFD feeding



Wild-type B29 strain induced obesity and glucose intolerance in GF mice under HFD feeding but not NCD. These effects are abolished with B29 lps-mutant,



Wild-type B29 strain induced NAFLD in GF mice : B29 lead to steatosis under HFD only, while B29 triggers liver inflammation on both diet. It is associated with increased hepatic expression of genes involved in lipogenesis and inflammation.

These effects are abolished with B29 lps-mutant,

Conclusion : *Enterobacter* spp. B29, isolated from a morbidly obese volunteer's gut triggers obesity, glucose intolerance and NAFLD in germ-free mice under a high-fat feeding. A modification of its Lps structure abolished all these effects indicating that endotoxin is the main molecular mechanism linking this gut bacterial species to metabolic disorders. Our results suggest that pro-inflammatory molecular crosstalk between human hosts and their gut pathobionts is essential for the development of obesity and related liver diseases, and may provide promising targets for managing these chronic diseases.