

Diabetes: when the microbiota causes insulin resistance

Do the bacteria in our gut influence insulin resistance and hence the onset of type 2 diabetes? Which bacteria are involved? How do they act? In the context of the MetaHIT¹ consortium, an international team involving INRA scientists has for the first time demonstrated the impact of the microbiota on insulin resistance and revealed the principal bacterial species involved. Their work, which has just been published in *Nature*, offers promising opportunities to reduce the incidence of metabolic and cardiovascular diseases.

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In France, type 2 diabetes affects 4.5% of the population and has an annual cost close to €12 billion. Characterised by chronic hyperglycaemia (or in other words, excessively high blood glucose levels), this disease is very often associated with insulin resistance. Indeed, affected patients produce insulin but cells lose their sensitivity to this hormone and can no longer store glucose. This results in a certain number of malfunctions, leading to the onset of cardiovascular and metabolic diseases that are now considered to have reached truly global epidemic proportions.

Numerous studies have suggested the existence of a link between the microbiota and metabolic health. In diabetic (or pre-diabetic) individuals, scientists have notably evidenced high levels of branched chain amino acids (BCAA) (valine, leucine and isoleucine). These are essential amino acids that come from the diet or from bacteria in our microbiota. In the context of the MetaHIT¹ project, an international team involving INRA scientists tried to establish whether this microbiota might contribute significantly to the increased levels of BCAA in the blood, and if so, how. To achieve this, they examined plasma and microbiota samples from 277 non-diabetic individuals and 75 diabetics. And they did indeed see that the higher the BCAA levels, the stronger the insulin resistance. They examined metabolites (stable organic compounds resulting from metabolism) and lipids in plasma from non-diabetic individuals. Out of the thousand metabolites analysed, they identified 19 groups of bacterial metabolites associated with insulin resistance (either positively - favouring insulin resistance - or negatively - hampering insulin resistance). In parallel, they studied the composition of the microbiota and evidenced 23 functional groups implicated in the synthesis or use of BCAA. Their results showed that the amount of BCAA in the plasma was indeed closely linked to the microbiota and not to the diet. In addition, four microbial species involved in these interactions between the microbiota and insulin resistance were evidenced: *Prevotella copri* and *Bacteroides vulgatus* were associated with BCAA biosynthesis and hence insulin resistance, while *Butyrivibrio crossotus* and *Eubacterium siraeum* were involved in the transport and utilisation of these amino acids and contributed to lowering their levels in the blood.

In order to directly evaluate the role of gut bacteria, the scientists studied the effects of *Prevotella copri* in the mouse. They demonstrated that this bacterium could indeed induce insulin resistance and increase the quantity of BCAA in the blood. These results offer promising perspectives for human health: if *Prevotella copri* is a risk factor for insulin resistance in humans, the next step will

consist in modulating and reducing the levels of this bacterium in order to achieve an optimum equilibrium between the bacterial species in our microbiota and optimisation of our diet.

1. Launched in 2008, the European MetaHIT programme (Metagenomics of the Human Intestinal Tract) coordinated by INRA, involved 13 academic and private sector partners from a total of eight countries until 2012. Thanks to an innovative approach called quantitative metagenomics, MetaHIT scientists opened the way towards new perspectives for human health and well-being. In particular, they showed that in the same way as each of us belongs to a particular blood group, we also belong to one of three types of gut bacterial composition, or enterotypes. Based on this, they started to determine relationships between the bacteria present in the gut and certain pathologies, such as Crohn's disease and obesity. <http://www.metahit.eu/>

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