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Microbiology

Studies of the bugs within: telling sickness from cure

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Each of us carries intestinal gardens, where microbes process food for our own consumption. We evolved to benefit from this, but as our guests are selfish single-cell creatures, tense diplomacy was always needed. Since these bacterial communities in our gut play surprisingly large roles in how our bodies grow and function, when their "social equilibrium" is unbalanced, their carefully-adapted human hosts suffer consequences.

It was long suspected that unbalanced bacterial communities might increase the risk of type 2 diabetes, where the body cannot adjust properly to blood sugar spikes. That, in turn, increases the risks of many other diseases, like heart failure and stroke - therefore, understanding how gut microbiota influence these risk factors represents an important asset. Nowadays, using modern machinery, it is possible to sequence and discriminate the DNA of bacterial communities made up of billions of cells. Our team, in the MetaHIT consortium, set out to do so, and likewise did two other teams, in Sweden and in China. Each reported how the intestinal bacterial communities of diabetics differed from those of healthy volunteers. But these two studies disagreed on which exactly those differences were, and in our own cohort of participants (from Denmark), we saw yet another incompatible but strong signature. What to do?

The breakthrough came through testing systematically if there was any other factor (aside from simply considering whether the donor was healthy or diabetic) that could predict what their gut microbiome looked like. Numerous factors were recorded, most showing no effect. However, one stood out – diabetics receiving metformin, a drug commonly used against diabetes, had very different gut communities from either differently-treated diabetics or healthy volunteers. This led us to suspect that much of the previously reported patterns in the bacterial landscape reflected anti-diabetic treatment, rather than a property of diabetes itself.

It was very interesting to note that, between the Chinese and Swedish studies, there were large differences in how likely the diabetics were to have been treated with metformin, and with a similar pattern, the differences, concerned those bacteria affected by such treatment. Considering this factor directly, and also analyzing other relevant aspects (differences in patient recruitment, analysis methods and approach), we merged the three databases of information coming from the three studies and analyzed them computationally. We were able to see a core signature supported by all the available data. There were two main aspects of the results that we collected.

First, unrelated to any kind of treatment, diabetics seem to have fewer bacteria in their gut that can produce short-chain fatty acids (SCFAs) like butyrate from dietary fibre. It is increasingly recognized that such compounds improve health in several ways, including: (i) reducing insulin resistance, (ii) dampening inflammation, and (iii) protecting the intestinal lining. This finding, therefore, seems robust, and many teams now go forward to try to use it to develop better treatments for both diabetes and

other diseases.

Second, when someone is given metformin, the changes in their gut microbiota (overgrowth of some specific strains of the bacterial community) are associated with some of the metformin's more common side effects as abdominal pain and bloating. Based on the shifts of the bacterial community, these side effects might then possibly be prevented through a combined treatment with probiotics. More interestingly, the bacterial community shifts seem to increase the potential for short-chain fatty acid production. This suggests that some of the beneficial effects of the drug might take place exactly through changing the composition of the gut microbiota!

After we reported this, the Swedish team carried out a follow-up study where they were able to prove that such mediation actually takes place. They tracked volunteers taking metformin over time, and showed that if their gut microbiota from before and/or after such treatment was transferred into germ-free mice, that is, having no microbiota of their own, the mice seeded with post-metformin gut microbiota showed improved glucose tolerance, demonstrating the ability to counter the glucose tolerance impairment which is central to diabetes.

Thus the results of our study confirmed that the shifts in the gut microbiota of diabetic patients were mainly driven by metformin rather than by the disease. More than that, we also provided clues about the fact that some of the beneficial effects of the drug take place indirectly through its impact on the gut microbiota.

Going forward, these discoveries prove that, in clinical studies, we cannot ignore anymore the effects of treatments on the gut microbiota. Moreover, given that gut microbiota are complex communities, slightly different for each of us, such findings represent opportunities for innovative and more efficient applications in the field of personalized medicine.