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Expert interview

Bacterial flora of the gut: how useful is its analysis?

Microorganisms in the human gut have been linked to obesity, inflammation, cardiovascular disease, liver disease, cancer and mental disorders. Stool analyses of intestinal flora can be ordered on the Internet from 130 euros upwards, and some also come with recommendations on what to eat for healthy gut bacteria growth. BIOPRO talked with Prof. Dr. Nisar Malek from the University of Tübingen about how useful such microbiome analyses really are.

Prof. Dr. Nisar P. Malek, medical director of the new M3 Institute for Microbiome and Cancer Research in Tübingen
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Professor Malek, one gramme of human faeces contains an estimated 100 billion bacteria. How can the different types of bacteria be identified in stool samples?

I believe most vendors use analyses based on the bacterial 16S rRNA gene, which differs slightly from one species to another. The analysis provides information about the bacterial ratio in the stool. Such analyses however do not produce a detailed genetic analysis that would also enable the analysis of the enzymatic composition of the intestinal bacteria.

The German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS) has published a statement in which it called microbiome analyses such as those offered on the Internet "expensive and pointless"[1]. As a member of the DGVS advisory board, what do you think about such analyses?

I fully share the DGVS' opinion. At present, it is not possible to derive information on specific diseases from such analyses, nor are there any reliable methods that would enable us to alter the composition of intestinal bacteria for the benefit of patients with a given disease. At the moment, microbiome analyses play no role in disease prevention or therapy.

Why can so little information be derived from microbiome analysis for an individual patient?

Sequencing of bacterial 16S rRNA for determining the range of microorganisms in a stool sample.
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The composition of the microbiome changes over and over again, for example due to nutrition or living conditions. An increase in the proportion of proteins, fats or fibre in a person's diet affects the microbiome. It is very difficult to say whether disease symptoms are actually related to the ratio of intestinal bacteria. In addition, at the moment we cannot say exactly which intestinal bacteria have a positive effect and which have a negative one.

Nevertheless, is it true to say that researchers suspect a correlation between the composition of the microbiome – i.e. the microorganisms that live in and on us - and certain diseases?

There are, of course, findings from mouse experiments and also from some studies in humans that suggest that certain bacteria might under certain conditions have a positive effect on human health. But we are far from being able to say, 'if you eat this or that, the number of a certain bacteria will increase and you will experience beneficial effects on your health!' Such claims are totally unfounded.

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Why is microbiome research still in its infancy?

Many intestinal bacteria cannot be grown in the laboratory. That's why for a long time we have not known which bacteria actually colonise the gut. We have made major progress in that we are now able to analyse the microbiome using high-throughput sequencing to identify homologous gene sequences in different bacteria. The problem is that the microbiome varies from person to person and is regulated by many external factors. This makes it difficult to create controlled conditions that would allow us to derive a cause-and-effect relationship. With the new Institute for Microbiome and Cancer Research in Tübingen we are trying to gain further insights into how the microbiome and metabolic changes affect tumorigenesis.

You are of course referring to the M3 research institute, which in 2017 received funds totalling 55 million euros from the German federal government, the Baden-Württemberg government and the medical faculty in Tübingen. It is currently being built near the university hospital[2], isn't it?

Exactly. M3 stands "malignome", i.e. malignant tumours, "metabolome", which is the sum of metabolic products, and "microbiome".

What is known about the connection between cancer, metabolites and the microbiome?

The microbiome determines many different processes in the human body. We are particularly interested in the uptake and utilisation of nutrients via the intestines. Depending on the composition of intestinal bacteria, for example, fats are metabolised differently. The resulting metabolites then enter the liver from the intestine through the portal vein. There they can lead to fatty liver or even liver carcinoma.

Can you give us any other examples?

Certain short-chain fatty acids produced by some dietary bacteria can directly damage the intestinal epithelial cells. It has already been shown that the metabolisation of fats can contribute to colon cancer. There is also evidence that gynaecological tumours may be influenced by the composition of the microbiome. In addition, there is now very good data to show that the effect of cancer immunotherapies heavily depends on gut microbiota.

How are the 18 future research groups of the M3 institute intending to investigate the connection between microbiome and cancer?

For example, we can colonise germ-free mice with certain gut bacteria strains and then measure the effects on the metabolisation of food constituents. These experiments can be combined with the physical activity of the mice, or with a diabetic metabolism, and so on. This means that we can study the influence of the microbiome, the genetic composition of the host and the environmental influences on the metabolism, and in particular on the development of liver, intestine and breast tumours. We can therefore demonstrate cause-and-effect relationships, and, more importantly, we can do so reproducibly.

Will other methods be used in addition to mouse microbiome analyses?

Yes. One issue that we are particularly concentrating on is the study of metabolic products. We are planning to set up a core facility that will specifically focus on this. Only around 20 percent of metabolites of the murine and human fat metabolisms are known. We know nothing about the remaining 80 percent, which we are sure greatly influence metabolic processes, signal transmission and the like. At the moment, this is terra incognita. We also intend to use imaging techniques to study very closely the development of tumour disease in mice. Bioinformaticians and mathematicians will use the laboratory results to construct mathematical models of the complex overall system. These models will help us find suitable ways to influence the system.

Are you planning any clinical trials?

They will hopefully emerge from these results. The major goal is for M3 to perform basic research as well as translational research. Based on this, we will try to identify approaches to develop targeted therapies that we can test in clinical trials. The big challenge is to reproducibly and stably modulate the microbiome in human clinical trials - as in the mouse model - and to show that we can achieve an effect by changing the composition of intestinal bacteria. But I don't believe that this kind of complex microbiome modulation is the future.

Which therapy would you chose?

I think that we are moving more towards prokaryotic pharmacology, in other words, bacterial pharmacology. By identifying metabolites and drugs that are created by the gut microbiome, we will come across a variety of chemicals. We will then be able to use these to influence diseases such as diabetes, cancer and degenerative diseases. This is where I see the future, rather than the analysis and manipulation of the gut microbiome.

Professor Malek, thank you for taking the time to talk to us.

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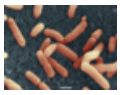
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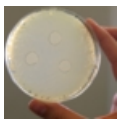
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