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What is the current state of Germany's research landscape with respect to microbiome science?

There is an active microbiome research community in Germany and several large-scale projects. The DFG is currently funding a Priority Program (SPP 1656) that focuses on the intestinal microbiota. Here in Kiel, we are studying host-microbiome interactions in various model organisms within the Collaborative Research Center 1182 and, of course, inflammatory diseases within the DFG Excellence Cluster "Inflammation at Interfaces". While most microbiologists have focused on classical pathogens in the past, there are more and more microbiology labs that are now investigating the microbiome as well. This makes perfect sense, since the microbiota is also relevant in pathogen defense. For example, our commensals occupy ecological niches that can be exploited by pathogens if the ecosystem is disturbed. Unfortunately, we lack large-scale efforts in Germany and the EU that can compete with the US-driven Human Microbiome Project (HMP). The European MetaHIT program was discontinued. A program such as HMP would be important to bring together expertise in Germany and to work jointly on examining the human microbiome in our general population. It would also improve our understanding of what is shaping the microbiome and what exact regional differences exist within Germany. This resource would serve as a basis for all disease-related projects.

How did you become interested in microbiome analysis and the impact on the immune system?

Since I am not a microbiologist by training, this is a fair question to ask. My previous work focused on the identification of susceptibility genes in inflammatory diseases such as Crohn's disease and ulcerative colitis, both inflammatory bowel diseases. For the latter, we were able to identify almost 250 variants in the human genome that are partially explaining the exact disease cause. We did observe that many of these disease genes have something to do with our immune system and the actual host-microbiome interaction. We also knew from our previous studies that the gut microbiome is clearly different, especially less diverse, in patients with inflammatory bowel diseases. Through modern sequencing technologies you can now analyze the entire microbiome of a person in great detail without culturing any

bacteria. In Kiel, we are operating one of Germany's largest next generation sequencing centers, and therefore much of our research is focused on the human microbiome.

Please elaborate on some of your current research projects concerning genome-wide association studies.

Our current genome-wide studies focus on identifying the relevant genes in the human genome that may be involved in host-microbiome interactions. Simply put, which genes shape our intestinal microbiome? To this end, we have collected almost 10,000 stool samples from the general German population from three different areas, Northern, Northeastern, and Southern Germany. In addition, we have deep genetic and phenotypic data available for these 10,000 people. Eventually, we hope to find more lifestyle indicators and other factors that influence our microbiome. From previous studies, we know that people's age, BMI, gender, and the stool composition correlate with a different microbiome composition. It is also important to note that different therapies, e.g. antibiotics and metformin (used by diabetics), have an impact on our microbiome.

What are the advantages of next generation sequencing technology for genomic projects?

Next generation sequencing is a very revolutionary method, which is almost equally important as the polymerase chain reaction (PCR) method for which the Nobel Prize was awarded in 1993. While array and other targeted technologies only provide a "snapshot" of a sample, sequencing provides an almost "ultimate" resolution. Nearly every DNA or RNA molecule in a single sample can be analyzed at a single-base resolution. This implies that subtle changes in the DNA sequence will also be detected. Importantly, mixed samples can also be analyzed, such as in the case of a stool sample, in which hundreds of different bacteria and viruses, fungi, and archaea can be found. Therefore, a typical computer scientist can gain deep insights into the microbiome. Of course, our *in silico* hypotheses and associations need to be followed up by hypothesis-driven experiments using germ-free mice or other models. When you study the microbiome, you always deal with the hen-egg problem. For example, the following question often arises: is this person's microbiome different, because he has the disease or did he get the disease, because his microbiome was already different before?

Are there any ethical or safety issues associated with this technology?

I am obviously biased in answering this question, because I would always make my own genome publicly available for research. I honestly think that a personal genome is nothing else than another diagnostic test, such as an MRT in the clinic. But to answer more precisely, yes, there are issues that we have to deal with.

Every study that we conduct is properly reviewed by our local ethics board, which also consists of consulting experts in data privacy and protection. Essentially, the issues most often boil down to data privacy/protection issues that can be solved technically. In our institute, we only work with de-identified data and the current standard in Germany is a double pseudonymization, i.e. biological specimen and data are stored under a different identifier. The person's real name and address are removed from the data using a so-called trustee server. After this process, it is nearly impossible and also illegal, to find out the real identity of a person again. If everyone follows this process, we ensure that patients and participants trust us. This also means that such research should be carried out by academic university hospitals that are behind a properly configured firewall. So far, I cannot think of any major scandal where genetic data was leaked. Looking at social networks and the Internet of Things (IoT), there are much more severe data privacy/protection issues that need to be resolved. So why are (especially the Germans) so concerned about genetic research?

What genetic and non-genetic factors shape the microbiome? And what can individuals do to keep their microbiome intact?

Several larger microbiome studies have yielded interesting associations, which remain to be validated by more functional experiments. In our Northern German study cohort, for example, we identified 40 variants in the human genome, which explain almost 10% of the gut microbiome variability. This is in the same range of what dietary, lifestyle and demographic factors explain according to our and other research lab's data. We do know that people who drink a lot of alcohol or smoke have an altered microbiota. The microbiome in vegetarians also differs from people who eat meat. Based on the data that has come out in the last years, I think it is safe to say that a healthy microbiome normally results from very diverse factors. Eating lots of fiber is important to feed our microbes, which would, in the absence of sugar molecules (from breakdown of fiber), start to digest the sugars of our mucus on our gut surface. If this natural barrier gets thinner, our intestine is more susceptible to infections and this can result in inflammatory responses, which can further destroy our intestinal barrier. The intake of antibiotics is clearly not good for our microbiota and we observed that microbes become extinct due to excessive antibiotics usage. In particular in the early childhood, when our immune system is trained and shaped, the intake of antibiotics can clearly leave "scars" in the immune system and the microbiome itself. Unfortunately, such changes in the microbiome can then be transferred to the next generation, since we tend to share many microbes with our parents and household members.

Compared to other ecosystems in the world - think of the rainforest vs. a forest monoculture - we are actively reducing the diversity of our own microbiome, which can eventually set the stage for many diseases once this ecosystem breaks down.

In a rich ecosystem, redundancy exists so that species can compensate disturbances if a specific microbe and function is lost. In a less diverse ecosystem, this compensation is not working and we eventually see a dysbiosis. Going back to the forest example, a monoculture will always be more susceptible to a storm compared to a natural and more diverse forest.