OCTOBER 8-10, 2014

HERRENHAUSEN PALACE, HANOVER

CONFERENCE SUMMARY

"BEYOND THE INTESTINAL MICROBIOME – FROM SIGNATURES TO THERAPY"

HERRENHAUSEN CONFERENCE

There is more to the human body than just human cells. The human intestine is covered with a plethora of bacteria, fungi, and viruses collectively termed the microbiome, that have co-evolved with us for millennia to form a complex "super-organism". In fact, microorganisms in the human body outnumber human cells 10 in 1, accounting for more than 3 million genes – that is 150 times more than human genes. By numbers alone we are more microorganism than human. However, not until recently have scientists begun to understand the relevance of this microbial ecosystem for health and diseases. Microbiota impact on our metabolism, help protect the body against pathogens, and play a key role in shaping our immune system. Disturbances of the intricate balance between immune tolerance and pathogen defense in our intestines may promote a variety of diseases, ranging from inflammatory bowel diseases to diabetes, obesity, multiple sclerosis, and brain disorders.

Who is there?

Cultivating intestinal microbiota in the laboratory was, for a long time, the standard approach to their investigation. However, microbiota are well adapted to the extreme conditions of the intestine and depend on complex food chains and interactions with other bacteria. Only a small fraction can be grown in the lab and culture-dependent methodology has never been able to provide the full picture. Recently, progress in high-throughput sequencing technology has allowed exploring the full diversity of the microbiome and has been instrumental in advancing the field to a central theme in biology.

KARSTEN KRISTIANSEN uses meta-genome sequencing to characterize the microbiome of pigs, mice, and humans. In his opening lecture he showed how diet, gender, age, genetics, and environment influence the microbiome. The human catalogue revealed reduced microbiome diversity in the Chinese as compared to the Danish population, which coincides with an increased occurrence of inflammatory diseases.

But the exact causal relationships between these different factors remain to be resolved. Does diet cause changes in the microbiome, and how exactly do alterations in microbiota composition impact on disease development? Indeed, a major challenge in the field, as identified by Kristiansen, is the need to establish causality. (For more information, please find attached the audio)

Getting at causality

The gut forms a barrier against the external environment, protecting the host from pathogens. This is a delicate task: On the one hand, the intestinal immune system needs to keep pathogens in check while, on the other hand, tolerating commensal bacteria. How the immune system accomplishes this task and how it is shaped by the microbiome to do so are central questions in microbiome research. To investigate the causal relationship between the different players – who triggers what and why – many researchers turn to animal models, where it is possible to directly manipulate specific factors and observe the consequences. Rather than looking at the whole microbial composition of the gut, they resort to a lower level of complexity, focusing on specific molecules or cells.

OLIVER PABST and **SIDONIA FAGARASAN** investigated the role of Immunoglobulin A (IgA) as an important aspect of the host's immune response. IgA is a highly abundant class of antibodies, secreted into the intestinal lumen to protect the host from toxins and pathogens. Pabst analyzed the dynamics of the IgA repertoire, demonstrating that it is relatively stable once it is established through microbial interactions. Memory-B cells are probably involved in maintaining this constancy. Fagarasan showed that IgA plays a role not only in pathogen defense, but also in developing and maintaining a diverse set of microbiota.

JAN WEHKAMP and **ARTHUR KASER** maintained that defects in the development of so-called "Paneth cells" in the epithelium of the small intestine are a common cause for Crohn's disease. Kaser showed how two cellular pathways – a response to unfolded proteins and autophagy – interact in Paneth cells. This interaction could be a therapeutic target – at least for some patients. Wehkamp illustrated how Paneth cells exert their effect by expressing antimicrobial α-defensins that form nets that enlace and trap pathogens.

ERIC PAMER and **GABRIEL NUÑEZ** took a closer look at the role of microbiota in fending off bacterial infections. Clostridium difficile infections often occur after antibiotic treatment, suggesting a role of microbiota in resistance to this pathogen. Pamer identified specific commensal taxa that convey this effect and showed that their metabolites may halt pathogen growth. Nuñez presented a mouse model for human EPEC/EHEC infections. Microbiota use different protection strategies – directly competing for nutrients or inducing an immune response – in different phases of the infection.

Finally, **ANDREAS DIEFENBACH** discussed how the microbiome impacts on the immune system beyond the gut. He unraveled a novel mechanism by which gut bacteria influence the chromatin structure of immune cells, permitting the expression of inflammatory cytokines. This mechanism also trains the immune system at non-mucosal sites, such as in the spleen or thymus.

A wide range of approaches

As microbiome research is a new and growing science, researchers are entering the field from various different angles. They may come from gastroenterology, immunology, molecular biology, genomics, epigenetics, or developmental and evolutionary biology. They bring a versatile set of questions, ideas, and methodological approaches. The research of Margaret McFall-Ngai and **ARNE TRAULSEN** are two extraordinary examples of how unconventional approaches can enrich the field. (For more information, please find attached the audio)

MCFALL-NGAI, who was deputized by **JULIA SCHWARTZMAN** at the conference, uses the squid light organ as a model for host-symbiont interactions, addressing how they initiate and establish their relationship. Traulsen uses evolutionary game theory to investigate bacterial colonization in hydra. With the help of mathematical modeling of bacterial dynamics, he determines whether bacterial fitness depends on bacterial abundance, host interactions, or both.

Yet another innovative approach, in this case concerning medical application, was presented by **LOTHAR STEIDLER**. He pioneered the use of recombinant Lactococcus lactis, a food bacterium, to deliver therapeutic proteins directly to the intestine. Current trials investigate the use of this technology in the treatment of oral mucositis and inflammatory bowel disease.

Beyond the intestine – multiple sclerosis, diabetes, and more

Five to ten years ago, investigating the impact of the microbiome on diseases such as multiple sclerosis (MS), asthma, or diabetes was a research field virtually unheard of. However, this has changed. A number of researchers at the conference represented this extraordinary growing field. They develop models to investigate disease cause and provide insights that point to potential therapies.

Using a mouse model of MS, **GURUMOORTHY KRISHNAMOORTHY** revealed the impact of microbiota on disease development and scrutinized the underlying mechanisms. His model is relevant for human diseases, as microbiota from MS patients also triggered disease in these mice.

Females are at higher risk for type 1 diabetes. **ALEXANDER CHERVONSKY** showed that males are protected by concerted action of the microbiota and testosterone.

FREDRIK BÄCKHED emphasized the role of microbiota in regulating insulin sensitivity. Vertical sleeve gastrectomy, a weight loss surgery to reduce stomach size, might exert its effect through changes in microbiota and bile acids as their metabolic products. **MAX NIEUWDORP** analyzed which aspects of the microbiome regulate insulin sensitivity. He discussed the possibility of using E. hallii, a butyrate producing commensal, to treat metabolic syndrome.

These examples show how a better understanding of the link between disease and microbiome could eventually lead to improved therapeutics. In addition, several researchers pointed to the importance of understanding the microbiome for diagnosis. According to **KRISTIANSEN**, for example, microbiome signatures can be used to identify subjects with an increased risk of type 2 diabetes or colon cancer. Moreover, conference participants repeatedly stressed the potential of gut microbiome analysis for disease stratification – i.e., defining subgroups of patients that will more likely respond to a treatment. For example, **KASER** and **WEHKAMP** emphasized that causes for Crohn's disease may vary between individuals or populations and that treatment strategies should take these differences into account.

Lifestyle and disease

Autoimmune diseases have increased considerably in industrialized countries in the past 50 years, and this has been attributed to the effect of changes in lifestyle and diet on the microbiome. A number of researchers at the conference carefully scrutinized the intricate link between these factors, ultimately leading to the question: Can we interfere?

For example, are probiotics beneficial? According to **MICHIEL KLEEREBEZEM**, there is no simple answer. Although probiotics consumption reproducibly alters the microbiome and mucosal gene expression, its potential benefit depends on each individual's microbial profile. Care must be taken as to who takes them and to which avail.

Dietary fiber is metabolized by commensals into short-chain fatty acids (SCFAs). **CHARLES MACKAY** revealed how dietary fiber and SCFAs affect inflammatory conditions via two different molecular pathways- metabolite sensing GPCRs, and HDACs. He discussed the possibility that maternal diet might affect epigenetics through inhibition of histone de-acetylation, to protect children from asthma and autoimmune diseases. (For more information, please find attached the audio)

Also **HARALD RENZ** pointed to the possibility of a developmental origin of autoimmune disease – not only via diet, but also via pathogen exposure. He explained how prenatal development and early childhood are windows of opportunity for acquiring immune tolerance. Pathogen exposure of the mother during pregnancy is linked to increased microbiota diversity and decreased autoimmune disease risk of the child. (For more information, please find attached the audio)

What does this imply? Should children play outdoors or have pets, should pregnant women eat fiber? Apart from the simple answer that probably neither of these is harmful, it is still too early to tell. Nonetheless, these examples indicate that there is great potential in the field, not only in disease treatment but also in developing preventive strategies.

Meta-genomic sequencing of the microbiome has marked the beginning of the field's exponential growth phase, providing a first view on "who is there". Meanwhile, the field has been taken to the next level, gaining a better understanding of the functional interactions between the members. Although the field is

still in its infancy, the conference showed that it has great potential for the development of therapeutics, diagnostics, and preventive measures.

Speakers

FREDRIK BÄCKHED, University of Gothenburg

ALEXANDER CHERVONSKY, University of Chicago

ANDREAS DIEFENBACH, University of Mainz Medical Centre

SIDONIA FAGARASAN, Riken Center for Integrative Medical Sciences

ARTHUR KASER, University of Cambridge

MICHIEL KLEEREBEZEM, NIZO food research and Wageningen University

GURUMOORTHY KRISHNAMOORTHY, Max Planck Institute of Neurobiology

KARSTEN KRISTIANSEN, University of Copenhagen and BGI-Shenzhen

CHARLES R. MACKAY, Monash University

MARGARET MCFALL-NGAI (deputized by **JULIA SCHWARTZMAN**), University of Wisconsin-Madison

MAX NIEUWDORP, AMC Amsterdam and University of Gothenburg

GABRIEL NUÑEZ, University of Michigan

OLIVER PABST, RWTH Aachen University Medical Clinic

ERIC G. PAMER, Memorial Sloan-Kettering Cancer Center

HARALD RENZ, University of Marburg

LOTHAR STEIDLER, ActoGeniX NV

ARNE TRAULSEN, Max Planck Institute for Evolutionary Biology

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