PRESS RELEASE

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At the wrong time in the wrong place

How the intestinal fungus *Candida albicans* shapes our immune system

Jena. Members of the Clusters of Excellence "Balance of the Microverse" and "Precision Medicine in Chronic Inflammation" have decoded a mechanism, how specific intestinal microbiomes exacerbate inflammatory diseases at other body sites, such as the lungs.

The composition of the microorganisms living in and on our body - the so-called microbiome - has an enormous influence on human health. So far, it has not been possible to use this influence therapeutically, as the underlying mechanisms are largely unknown. In the Clusters of Excellence "Balance of the Microverse" in Jena and "Precision Medicine in Chronic Inflammation" in Kiel various research groups are working together on deciphering these interactions between humans and the microbiome. A team from the Leibniz-Institute for Natural Product Research and Infection Biology, the Friedrich Schiller University Jena and other research institutions from all over Germany has now made a ground-breaking discovery. "We have discovered a mechanism how certain microbiota exacerbate inflammatory reactions in the lungs," said study leader Professor Petra Bacher. "The results now published in the scientific journal *Cell* offer new opportunities to better identify such disease processes and to provide targeted treatment," adds the spokesperson of the Cluster of Excellence in Jena, Axel Brakhage.

Humans live in close symbiosis with their microbiome, the countless bacteria, fungi and viruses that colonise the body surfaces, the skin, the intestines and the lungs. This coexistence is finely balanced and offers many benefits, such as protection against infections or help with the utilisation of nutrients. A disturbed microbiome is associated with a wide variety of diseases. These include chronic inflammatory bowel diseases, allergies, metabolic diseases, autoimmune diseases, cancer or even depression. Thus the microbiome recently attracted much attention, considering that influencing the microbiome could treat almost all major diseases in industrialized countries. But specific approaches are still lacking. The enormous diversity of the microbiome masks the essential components and the definition of cause and effect, preventing specific therapies.

The interaction with the microbiome is mainly controlled by the immune system. Cells of the immune system recognise specific microbes, and ensure a healthy balance. The key question is: how and by which microbes are the various effects on body functions triggered? A team of scientists from the Leibniz Institute for Natural Product Research and Infection Biology and the Friedrich Schiller University Jena as well as the Charité – Universitätsmedizin Berlin, the University Hospital Cologne, the RUB University Clinic in Bochum under the leadership of Petra Bacher and Alexander Scheffold from the Kiel University and the University Medical Center Schleswig-Holstein, has achieved a breakthrough. "We have identified the typically harmless fungus, *Candida albicans*, which colonises the intestine, skin and mucous membranes, as a central modulator of our immune system," explains Alexander Scheffold. "*Candida albicans* stimulates the immune system to produce certain immune cells, so-called Th17 cells. These enable a peaceful co-existence with the fungus." For the study, the researchers developed a sensitive method to isolate the Th17 cells that target *Candida albicans* from the blood. Further analysis revealed that some of these Th17 cells also recognise

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other fungi, such as the mould fungus *Aspergillus fumigatus*. This phenomenon is known as cross-reactivity.

Mould spores are inhaled daily with the breathing air, but are harmless for healthy people. On the other hand, moulds can colonize the lungs of people suffering from chronic lung diseases such as cystic fibrosis, chronic obstructive pulmonary disease or asthma. This is suspected of worsening the disease. “Surprisingly, we found that this group of patients has an increased population of cross-reactive Th17 cells in the lungs, which correlated with disease exacerbation. The protective Th17 response in the intestine seems to increase the disease-causing immune processes in the lungs,” adds lead author Petra Bacher.

The researchers were thus able to show how a single member of the microbiome, *Candida albicans*, influences the specific immune reaction against a larger group of microbes at other body sites. “However, cross-reactivity is probably a common immune mechanism by which the microbiome manipulates the immune system, with protective or harmful effects. The ability to measure such specific effects of individual microbes now enables to develop targeted treatments,” concludes Scheffold.

Original publication

Bacher P, Hohnstein T, Beerbaum E, Röcker M, Kaufmann S, Brandt C, Röhmel J, Stervbo U, Nienen M, Babel N, Milleck J, Assenmacher M, Cornely OA, Heine G, Worm M, Creutz P, Tabeling C, Ruwwe-Glösenkamp C, Sander LE, Brunke S, Hube B, Blango M, Kniemeyer O, Brakhage AA, Schwarz C, Scheffold A (2019) Instruction of human anti-fungal Th17 immunity and immune pathology by cross-reactivity against a single member of the microbiota. *Cell* DOI: 10.1016/j.cell.2019.01.041