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## **Immune system keeps the intestinal flora in balance**

**Trillions of benign bacteria live in the intestine. They are kept in a continuous balance by the immune system, which thereby makes them harmless to humans. Researchers in the Department for BioMedical Research (DBMR) at the University of Bern and Inselspital, Bern University Hospital, and German Cancer Research Center have been able to show how certain natural antibodies keep these bacteria in check. The findings could make an important contribution to the development of superior vaccines.**

The bacteria living in the intestine consist of some 500 to 1000 different species. They make up what is known as the intestinal flora, which plays a key role in digestion and prevents infections. Unlike pathogens that invade from the outside, they are harmless and tolerated by the immune system. The way in which the human immune system manages to maintain this delicate balance in the intestine largely remains unknown. It is known that type A immunoglobulins, referred to as IgA antibodies, play an important role. These natural defense substances are part of the immune system, and recognize an exogenous pathogen very specifically according to the lock-and-key principle.

A group of researchers led by Dr. Tim Rollenske and Prof. Andrew Macpherson from the Department of BioMedical Research (DBMR) at the University of Bern and the University Hospital for Visceral Surgery and Medicine at the Inselspital have recently been able to show in a mouse model that IgA antibodies specifically limit the fitness of benign bacteria at several levels. This enables the immune system to fine-tune the microbial balance in the intestine. “We have succeeded in demonstrating that the immune system recognizes and restricts these bacteria very specifically,” explains Tim Rollenske, PhD, lead author of the study. The results have been published in the journal *Nature*.

### **IgA antibodies created in natural form for the first time**

IgA antibodies are the most common antibodies in the human immune system, and are secreted by specialist cells in the mucous membranes. They account for two-thirds of human immunoglobulins. Surprisingly, most IgA antibodies produced by the body are directed against benign bacteria in the intestinal flora. Without this immune protection, these microorganisms could also have a detrimental effect on health and cause intestinal diseases. However, the mystery of the way in which IgA antibodies regulate the consensual coexistence in the intestine has remained unsolved.

The reason for this: Until now, studying IgA antibodies in their natural form in animal models was not possible. In their experiment, the researchers led by Tim Rollenske and Andrew Macpherson were able to overcome this hurdle, however. They succeeded in producing a sufficient amount of IgA antibodies specifically directed against a type of Escherichia coli bacteria, a typical intestinal bacterium. The antibodies recognized and bound a building block on the membrane of the microorganisms.

### **Antibodies impair the fitness of the bacteria**

In their experiment, which the researchers worked on for three years, they succeeded in tracking the in-vitro and in-vivo effect in the intestines of germ-free mice with pinpoint accuracy. The antibodies were found to affect the fitness of the bacteria in several ways. The mobility of bacteria was restricted, for example, or they hindered the uptake of sugar building blocks for the metabolism of the bacteria. The effect depended on the surface component that was specifically recognized. "This means that the immune system is apparently able to influence the benign intestinal bacteria through different approaches on a simultaneous basis", explains Hedda Wardemann of the German Cancer Research Center, co-author. The researchers therefore speak of IgA parallelism.

The question of why the immune system achieves an equilibrium with the benign bacteria in the intestine while effectively destroying pathogenic invaders remains to have been conclusively clarified. "However, our experiment shows that IgA antibodies can fine-tune the balance between the human organism and the intestinal flora," explains Andrew Macpherson of the DBMR and Inselspital, co-author. The findings not only build on the basic understanding of the immune system in the intestine, they can also contribute to the development of vaccines. "Understanding exactly how and where antibodies recognize microorganisms in the intestine will also allow us to develop vaccines against pathogenic organisms on a more targeted basis", Tim Rollenske adds.

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### **Publication details:**

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**Department for BioMedical Research (DBMR)**

The Department for BioMedical Research (DBMR) of the Faculty of Medicine of the University of Bern, led by Prof. Mark A. Rubin, MD, was established in 1994 by the University of Bern and the Inselspital (Bern University Hospital). The DBMR is divided in 13 Research Programs with about 100 participating individual labs and several Independent Research Labs whose research spans across all biomedical fields. To realize its mission to bridge the gap between bench and bedside, the DBMR promotes an integrative perspective to clinical research with a strong emphasis in the development of translational approaches, the use of omics and other cutting-edge technologies, and extensive interaction and collaboration between laboratory-based and patient-oriented clinical research. The DBMR is also committed to fostering the careers of young academics.

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