

Healthcare industry BW

Innate immune defence: using peptides against fungi and bacteria

Part of the human immune defence relies on antimicrobial peptides. These peptides, so-called defensins, are present in the gastrointestinal tract where they play a role in the pathogenesis of Crohn's disease. Prof. Jan Wehkamp and his team of researchers at the University Hospital in Tübingen study how this knowledge can be put to good use for the treatment of Crohn's and other diseases.



Professor Jan Wehkamp has held a W3 Heisenberg Professorship for Innate Immunity in Inflammation and Infection since 2014.
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Considering our daily exposure to numerous microbial pathogens, it is surprising that we do not get sick whenever we encounter them. This is because humans are protected against such invaders by their immune system. The human immune system consists of many structures and defence mechanisms that protect against disease, including immune cells and proteins that destroy viruses and bacteria. Moreover, the skin and mucosae (e.g. intestinal mucosa) act as external defence mechanisms against invading pathogens.

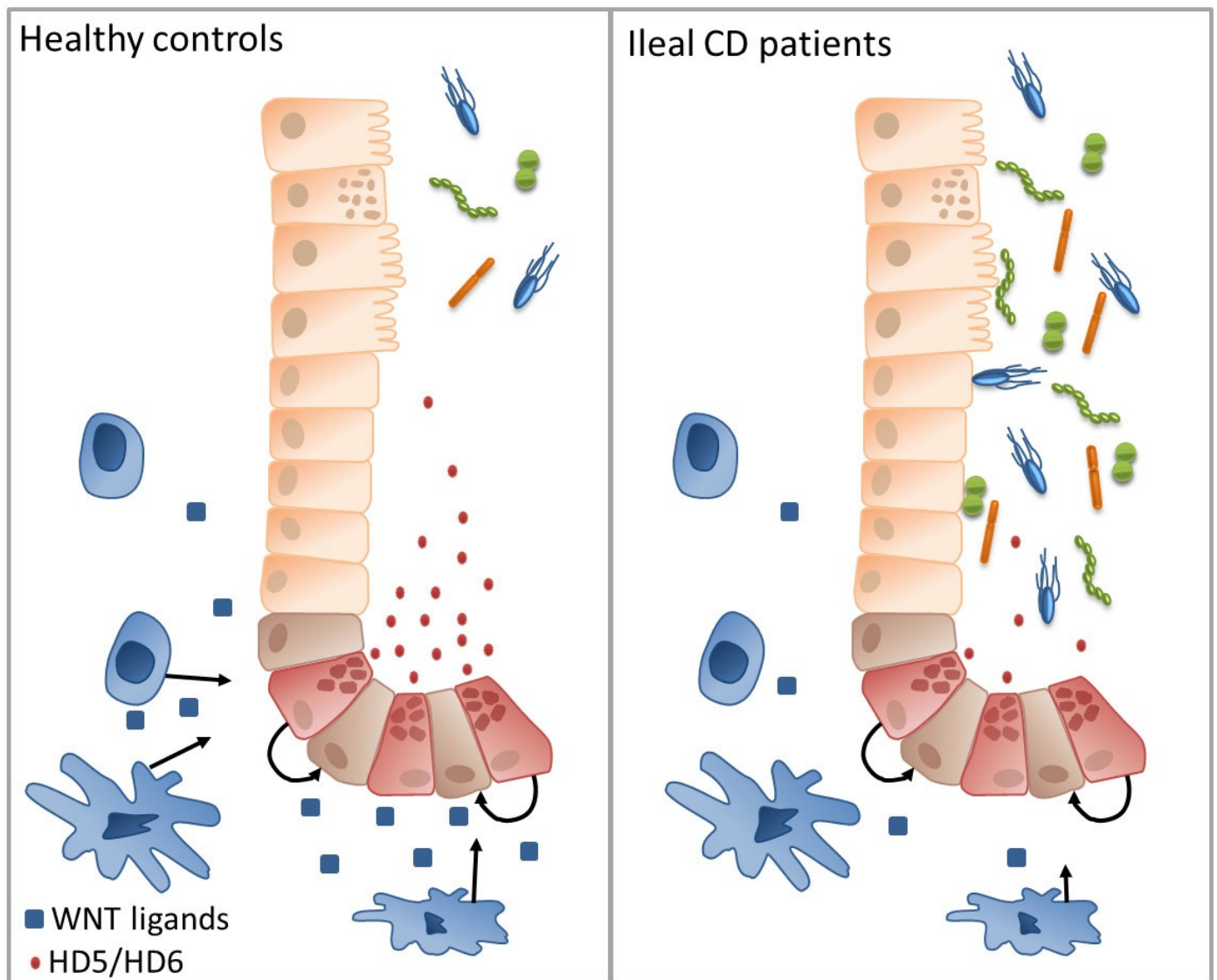
But how is it that the skin is not constantly afflicted by fungal infection nor the intestines constantly inflamed? Prof. Dr. Jan Wehkamp, who has held a W3 Heisenberg Professorship for Innate Immunity in Inflammation and Infection (sponsored by the DFG – German Research Foundation) since 2014, and his team at the University Hospital in Tübingen are dealing with just this issue. Back in 1998, Wehkamp already caused big waves in the scientific community when he and Prof. Dr. Eduard Stange postulated that Crohn's disease is not an autoimmune disorder, but is caused by intestinal mucosal cells not producing any defence molecules (antibodies). Crohn's disease and ulcerative colitis are two types of chronic inflammatory bowel diseases that may affect any part of the gastrointestinal tract. Crohn's disease mainly affects the small intestine, whereas ulcerative colitis usually affects the large intestine (colon). Despite initial scepticism from the medical profession, Wehkamp and Stange's theory has since been widely accepted and further evidence has also been provided by other research groups.

Defensins are antimicrobial peptides

The intestinal mucosa protects the intestines against invaders. In Crohn's disease patients, this barrier does not seem to function properly, resulting in the intracellular survival of the bacteria and induction of inflammation. The aforementioned defensins function as host defence peptides. They are produced by the so-called Paneth cells, which are granular cells in the epithelium of the small intestine. They are active against microbial pathogens that enter the body and are found in animals (e.g. mammals and insects) as well as in plants. Defensins are therefore highly conserved immune structures. In 2011, Wehkamp, who was then working at the Dr. Margarete Fischer Bosch Institute for Clinical Pharmacology in Stuttgart, and his team made another important discovery that contributes to our understanding of the body's immune defence systems.

Defence molecules must be activated

The scientists were able to show with human beta defensin 1 that defensins need to be activated before they can become effective against invaders. "In our 2011 Nature paper, we showed that there was an interesting antimicrobial peptide. This peptide did not exert any function in the test tube. However, when we altered the peptide's environment by removing oxygen, the peptide became highly active against fungi and bacteria," explains Wehkamp. The researchers found that the defensins undergo post-translational modification. "This was a spectacular discovery, as it was the first time researchers had shown that environmental changes in the intestinal ecosystem controlled the body's defence against bacteria and fungi," says Wehkamp.



Defensins regulate the composition of the gut flora (left: healthy individual). Bone marrow monocytes (blue) release signalling substances (blue spots) that control the maintenance of the antimicrobial barrier function. Paneth cells (red) then secrete defensins into the intestine (red granules). Crohn's disease patients (photo on the right) produce fewer Paneth cell defensins than healthy people. The patients' monocytes (blue) can only inadequately stimulate antimicrobial function because they produce too few stem cell differentiation factors (blue spots). Figure from PNAS article "Crohn's disease-derived monocytes fail to induce Paneth cell defensins". © University Hospital of Tübingen

Wehkamp's team carried out additional experiments to find out how the production of Paneth cell defensins can be regulated. The scientists showed that the bone marrow monocytes were able to regulate the production of antimicrobial peptides. Monocytes form so-called stem cell differentiation markers (Wnt factors) that stimulate the production of defensins. "The Wnt factors enable a crosstalk between the monocytes and the Paneth cells," explains Wehkamp. "As a result, the mucosal barrier is kept intact." The scientists showed that the monocytes of healthy donors were able to induce the production of defensins in tissue sections of Crohn's disease patients, while the monocytes of Crohn's patients were unable to activate defensin production in healthy gut biopsies. "Our experiments showed that monocytes play a crucial role in the pathogenesis of Crohn's disease. They produce too few Wnt factors, which is why Crohn's disease patients have a defective antimicrobial defence system," says Wehkamp. "This finding is another important clue in understanding the pathogenesis of Crohn's disease," concludes Wehkamp. It goes without saying that such findings make it possible to develop innovative approaches for treating Crohn's disease. "We believe that healthy monocytes are able to cure, or at least improve, the disease," says Wehkamp.

Of course, bone marrow transplantations will never be broadly applied to treat the disease; this is usually only used in cases where people are seriously ill. "Patients who come to Tübingen's specialised outpatient clinic with chronic inflammatory bowel diseases are currently treated using standard methods. However, Wehkamp believes that in the medium term defensin therapy will also be used for treating this disease.

Immune defence principle

With these findings, the researchers have made an important contribution to the treatment of inflammatory bowel diseases. However, the scientists are not just interested in this particular situation. Wehkamp also wants to understand the innate immune defence principle. "When we published the 2011 Nature paper on the activation of beta defensin 1, we thought it was a general biological principle, but we were far from knowing that for sure," says Wehkamp. A new paper by researchers from Kiel (Germany) and Japan, to which the researchers from Tübingen have also contributed, has now shown that other molecules also only reach their full defence potential when their environment changes.

In cooperation with Japanese researchers and Wehkamp's team, scientists led by Professor Jens-Michael Schröder from the University of Kiel have shown that psoriasin, a peptide that occurs predominantly in the skin, but also in some body fluids, only becomes active against fungi when structural modifications have occurred. The researchers from Tübingen showed that thioredoxin reduces psoriasin in vitro, resulting in the activation of the molecule. "We were delighted to find that what we had described in 2011 is really a general principle, and we are particularly pleased that there are always new and exciting aspects that did not initially even occur to us," says Wehkamp highlighting that post-translational reduction provides our body with complex ways of controlling defence against

fungi, bacteria and viruses. "The fact that different forms of the same peptide have different functions expands antimicrobial defences enormously," says Wehkamp. "Nature is just phenomenal."

References

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