Jan Wehkamp to investigate the causes of chronic inflammatory bowel diseases

It takes a great deal of courage to question a common scientific doctrine, especially for scientists at the very beginning of their careers. But, around ten years ago, Dr. Jan Wehkamp did not shy away from doing just that and as a result he and his scientific partner Professor Dr. Eduard Stange came up with a new explanation for the pathogenesis of chronic inflammatory bowel diseases. Many Crohn's disease and ulcerative colitis patients may soon benefit from Wehkamp's tenacity, as his research at the Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology at the Stuttgart-based Robert Bosch Hospital gives good reason to hope that innovative therapies will soon become available.

Back in 1993 when Jan Wehkamp started his medical studies in Lübeck (Germany), the chronic inflammatory bowel disorders Crohn's disease and ulcerative colitis were still regarded as classic autoimmune diseases. Both disorders are associated with recurrent, painful diarrhoea, which severely reduces patients' quality of life. There is no pharmaceutical or surgical cure for either disease; treatment is limited to controlling complications, which can involve the removal of large sections of the intestines. The prevailing view at the time was that the diseases resulted from an impaired innate immunity, which led to repeated bouts of inflammation of the intestinal mucosa. "Numerous research groups around the world were focusing exclusively on the role of T-cells in the pathogenesis of the disease," Wehkamp recalled. This view was supported by the treatment outcome obtained with drugs which, although associated with severe adverse effects for patients, provided help by suppressing the patients' immune system.

However, the young medical student, whose doctoral thesis dealt with the role of heat-shock proteins in chronic inflammatory bowel diseases, found the prevailing view difficult to accept. "Many scientific papers reported on rather complicated and frequently quite contradictory models of the immunological processes in the intestinal wall," said Wehkamp going on to add, "I was constantly wondering whether I was the only one who found all this difficult to believe". Wehkamp talked with his supervisor, gastroenterologist Professor Dr. med. Eduard Stange, about his doubts and he found an ally. They discussed and reflected on the issue for several months before they eventually came to the conclusion that chronic inflammatory bowel diseases were the result of an impaired defence of the body against bacteria rather than being generated by autoimmune reactions.

No inflammation without bacteria

PD Dr. med. Jan Wehkamp is focused on chronic inflammatory bowel diseases.
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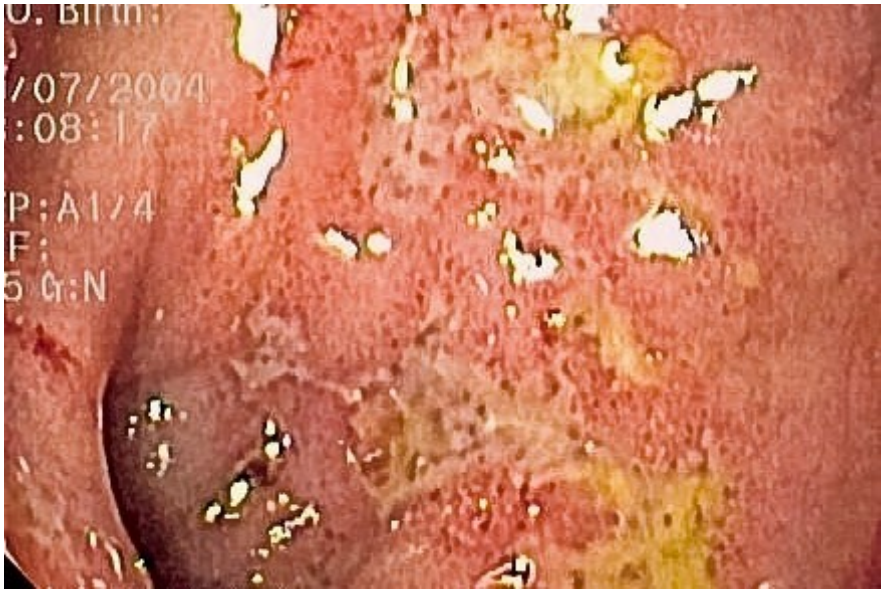
Initial evidence that bacteria are involved in the pathogenesis of Crohn's disease was provided in the



Colon of a Crohn's disease patient showing serpiginous ulcer, a classic finding in Crohn's disease.
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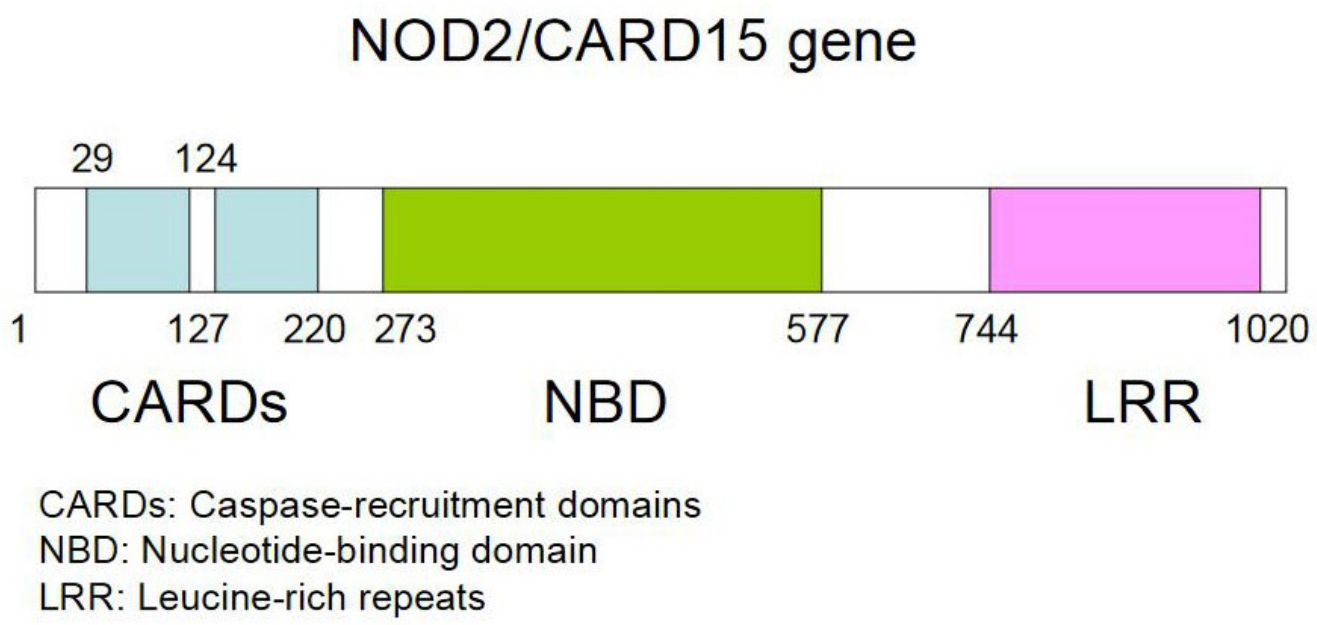
mid-90s when a Belgian group of researchers showed that the inflammation of the intestinal mucosa went away relatively quickly in Crohn's disease patients with an artificial stoma in whom the posterior "idle" colon section was no longer in contact with faeces. Inflammatory reactions recurred when the colon was sown together and came in contact with faeces again.

Colon biopsies also provided evidence for Wehkamp and Stange's assumption: while a thick film of intact bacteria is found directly on the epithelium of Crohn's disease patients, the intestinal mucosa of healthy people is more or less sterile. "Although millions of bacteria inhabit the human gastrointestinal tract, they do not normally directly attach to the surface of intestinal epithelial cells," Wehkamp said. The only explanation Wehkamp and Stange could think of was that the colon of healthy people had an effective mechanism to keep the bacteria under control locally. They further reasoned that if this defence was impaired, the bacteria were able to enter the intestinal mucosa and lead to severe inflammatory reactions. "In this case, it is not a misdirected immune reaction, but a barrier defect of the intestinal mucosa," explained Wehkamp.

Defensins open up a new field of research



NOD2 gene mutations are associated with Crohn's disease. NOD2 is an intracellular receptor and plays a key role in the recognition of bacteria and the subsequent activation of an inflammatory cascade.
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During a skiing holiday, Stange came up with the idea that the barrier defect observed might be due to the lack of antibiotics that occur naturally in the body. Wehkamp was immediately excited about the idea, and this led him to look beyond his own discipline. The existence of endogenous antimicrobial peptides is well known from the animal and plant kingdoms. "Whether in bees, lice or apples – all eukaryotes investigated so far have been found to produce defensins," said Wehkamp. Defensins function as host defence peptides and consist of around 35 amino acids. Cells of the immune system contain such peptides, which protect plants against rot and animals against inflammation. When the defensins were identified in the human colon and kidneys in the mid-90s, Wehkamp and Stange immediately realized that these peptides opened up an exciting new field of research. "99.9% of all living organisms on earth do not possess any immunologically active T-cells and do quite well without them," Wehkamp said. "On the other hand, the defensin system is a highly conserved system that has remained largely unchanged throughout evolution." The two scientists did not doubt for a second that these antibiotics also had an important function for humans.

From being an outsider to a hopeful tool

Wehkamp and his colleagues were able to show that certain defensins were only produced in low quantities in Crohn's disease patients and concluded that Crohn's disease is not an autoimmune disease. Instead, they believed that the most plausible concept of pathogenesis of Crohn's disease is a defensin deficiency syndrome. "We were aware that this was a rather daring assumption," said Wehkamp with a smile. Wehkamp and Stange postulated their thesis in 1998, but nobody believed them. It took four years before they were able to publish their findings in a relatively unknown scientific journal. "At first, nobody took us seriously," said Wehkamp, also recalling that they had difficulties getting research proposals funded, as reviewers tended to regard their assumption as a bit strange. A renowned researcher colleague even joked that Wehkamp would have to change his name if his theory turned out to be wrong.

“Really good ideas in the field of medicine are always outsiders at first,” said Wehkamp. There are numerous examples to substantiate this theory. One good example is the fact that for a long time the scientific world refused to believe that the bacterium Helicobacter pylori causes stomach ulcer. In the end, Barry Marshall and Robin Warren were awarded the Nobel Prize in Physiology or Medicine in 2005 for their discovery of the bacterium Helicobacter pylori and its role in gastritis and peptic ulcer disease.

Wehkamp’s tenacity has since been rewarded: his research results were confirmed by numerous other research groups and Wehkamp was awarded the career prize of the Ernst-Jung-Stiftung für Wissenschaft und Forschung in 2006. The German Research Foundation (DFG) also provided him with funds under its Emmy Noether programme, which enabled him to follow his supervisor Stange to the Stuttgart-based Robert Bosch Hospital following a research stay in the USA and establish his own research group.

The last of a rather impressive collection of scientific awards is the Paul Martini Prize which Wehkamp received in 2012. Wehkamp does not feel any satisfaction: “It was always the pure pleasure of carrying out research that has driven me forward, and not the search for recognition.”

On the right track

Stange and Wehkamp have known since 2001 that they were on the right track. In 2001 a French group of researchers showed that mutations of the NOD2 gene were associated with the pathogenesis of Crohn’s disease. NOD2 encodes an intracellular receptor that plays a key role in the recognition of bacteria. Wehkamp recalls: “An entire field of research suddenly found itself boxed in, as the discovery could not be explained with the common school of thought that an immunological dysregulation was the cause of Crohn’s disease.”

In contrast, Wehkamp finally found himself confirmed in his belief, especially as he and Stange were shortly after able to show that NOD2 mutations led to the formation of lower than normal levels of defensins. However, to his surprise, Wehkamp found that only the defensins produced by paneth cells in the small intestine were affected. The production of defensins in the colon was not affected. Wehkamp and Stange were thus able to come up with an explanation as to why many patients only developed inflammatory reactions in specific parts of the intestines. “The finding that Crohn’s disease is not an homogeneous disorder, but that there are clear differences between Crohn’s disease of the small intestines and the colon is most likely one of the key findings in the field of gastroenterology in the last ten years,” Wehkamp said.

New therapeutic concepts

This knowledge also formed the basis for a completely new therapeutic concept. Commonly used immunosuppressive drugs are only effective against secondary inflammatory reactions. “Such drugs do not often lead to long-term success,” said Wehkamp, referring to his own experience of their use. Instead, the side effects of immunosuppressive drug therapies tend to make the situation worse. Antibiotics are also largely ineffective as they do not act specifically enough on a local level. “We do not want the gastrointestinal tract to be completely bacteria-free; we only want the intestinal epithelium to be bacteria-free,” Wehkamp explained. If it were possible to administer defensins directly or to specifically stimulate the paneth cells, we would at least be able to causally treat Crohn’s disease of the small intestine. Wehkamp is currently working on strategies to treat the disorder involving genetically engineered defensins amongst other things.

New approaches are also being developed for the treatment of ulcerative colitis, which in contrast to Crohn's disease is not the result of impaired defensin production. Ulcerative colitis is characterized by a much narrower than normal mucosal layer, which represents a buffer zone between the cell surface and the intestinal lumen and which is formed by the goblet cells of the intestinal mucosa. This layer ensures that the defensins that are formed in the intestines remain close to the mucosa and exert their antimicrobial activity there. "Damage to this buffer zone leads to a loss of defensins, which impairs the barrier function of the intestinal epithelium and enables bacteria to invade," Wehkamp said. Interesting approaches for treating inflammatory intestinal disorders would be to restore the integrity of the mucosa and to increase the production of defensins in the colon.

Several clinical trials have shown that new bouts of ulcerative colitis can be prevented effectively using the probiotic bacterium E. coli Nissel. "At first, many people thought this was nonsense," Wehkamp recalled. However, Wehkamp and his team of researchers have since been able to come up with a molecular genetic explanation for this unexpected effect: "We have shown that flagellin, which is a structural protein of E. coli Nissel, enhances the production of certain defensins in the colon. And this also has a protective effect." Wehkamp is now aiming to identify other substances with a protective effect. If he succeeds, it can be safely assumed that immunosuppressive therapies currently used to treat chronic inflammatory intestinal disorders will eventually become a thing of the past.

2012 ERC Starting Grant

Dr. Jan Wehkamp was awarded one of the prestigious 2012 ERC (European Research Council) Starting Grants with a purse of 1.5 million euros for his project "Defensin activity". Dr. Jan Wehkamp from the Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology (IKP) of the Robert Bosch Hospital in Stuttgart focuses on the elucidation of the causes of chronic inflammatory bowel diseases. ERC Starting Grants are aimed at up-and-coming research leaders with 2-7 years of experience after completion of their PhD and a highly promising scientific track record.

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Article

10-Sept-2012
sb (29.08.2012)
BioRegio STERN