Colon and liver cancer: Gut microbiota offers future diagnosis and treatment options

The gut microbiota can be involved in the development of colorectal and liver cancer. The unveiling of the underlying processes provides promising starting points for creating novel diagnostic and therapeutic measures. This was demonstrated by the findings Prof. Robert F. Schwabe (Columbia University, New York, USA) and Dr. Peer Bork (University of Heidelberg, Germany) presented at the Gut Microbiota for Health World Summit in Barcelona (March 14-15, 2015).

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Gut microbiota: a promising avenue for liver cancer management

Every year over 700.000 patients die of liver cancer worldwide, which makes this disease the second leading cause among cancer-induced deaths. "Only a small percentage of patients are eligible for curative approaches such as liver transplantation.The development of new drugs has remained an important goal, with an average survival of less than one year. Also, attempts to develop efficient prevention strategies have not been successful so far," said Prof. Robert F. Schwabe (Columbia University, New York, USA).

In 80 per cent of the cases liver cancer develops in cirrhotic livers following decades of chronic injury, inflammation and wound healing. However, the precise causal links have remained obscure until recently. Now, Prof Schwabe and his colleagues pinpointed the interaction between intestinal bacteria and liver cell receptors as a major contributing factor that promotes development of the disease. In contrast to the gut the liver does not contain a microbiota of its own. Instead, bacteria and their metabolites reach the liver via the portal vein. In the blood of patients with chronic liver disease the amount of these intestinal components is increased. A crucial role is played by lipopolysaccharides (LPS) which are inflammatory components of bacterial cell walls. Their counterparts is toll-like receptor 4

(TLR4) belonging to the innate immune system. When this receptor encounters LPS, it triggers an immune response leading to chronic inflammation. Although this does not necessarily cause the onset of the liver cancer it is largely responsible for the promotion of the disease through an increased proliferation of liver cells. Prof Schwabe and his colleagues demonstrated the causal role of this interplay between receptor and bacteria by experiments with mice in which one of the two components was missing: Mice whose TLR4 gene had been rendered inactive showed a significantly reduced tumour development and the same applied to mice who had intact TLR4s but were raised germ-free or had their intestinal microbiota diminished by antibiotics[1,2]. These effects showed up even at late disease stages. The results were inversely confirmed by the fact that, on the other hand, infusion of LPS increased the growth of liver cancer. "Our findings indicate that targeting the gut microbiota in order to prevent liver cancer or at least stop the increase of cancerous cells is a promising avenue. The key role of the intestinal microbiota in hepatocarcinogenesis was further

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confirmed by the group of Prof. Eiji Hara, who also presented his results at the Gut Microbiota for Health World Summit. Prof. Hara's group demonstrated a key role of the gut microbiota in liver cancer promotion in the setting of obesity[3]. Of particular importance for the development of future treatments is the success we have achieved through the administration of antibiotics in mice," explained Prof Schwabe. According to him, non-absorbable antibiotics such as rifamixin, which exert their effects only on the gut microbiota and are already in use in patients with liver disease for other indications, might be suitable for the prevention of liver cancer in patients with advanced liver disease. "However, in order to translate our findings into clinical practice we need further studies," said Prof. Schwabe.

> **Colorectal cancer (CRC) is among the three most common kinds of cancer with an annual 600.000 deaths and more than 1.2 million new cases worldwide.**

Fecal Microbiota analysis for early detection of colorectal cancer

If CRC is detected at an early stage the patient's prospects are fairly good with a 5-year survival rate of over 80 per cent, but this decreases to less than 10 per cent if the cancer has already metastasized when being diagnosed. Therefore screening and prevention programs play a key role in fighting this disease, as Dr. Peer Bork pointed out. A wide-spread screening procedure is fecal occult blood testing (FOBT) which aims at detecting blood in the stool that results from gastrointestinal bleeding and is otherwise not visible. One of several potential sources of this kind of blood loss is CRC or its precursors. However, FOBT is not sensitive and specific enough to identify CRC for sure so that in case of positive test results a colonoscopy is required for confirmation. In order to find an alternative screening technique that combines the non-invasive approach of FOBT with the diagnostic precision of colonoscopy Dr. Peer Bork and his team set out to explore the potential of fecal microbiota for detection of CRC. The reason to follow this path of investigation were indications that certain gut bacteria might be crucially involved in the onset of CRC. To examine associations between the intestinal microbiota and CRC the researchers started by analyzing the genes contained in the feces of 156 patients who underwent colonoscopy in order to establish whether polyps – as potential precursors of CRC – were present in their guts[4]. The results of the analysis of the fecal microbiota showed significant microbial changes in the samples of patients who were diagnosed with CRC as compared to cancer-free patients. The applied methodology proved to be reliable with regard to both, metastasized as well as early stage tumours, which makes it a suitable tool for prevention of CRC. By comparing the fecal CRC data to those of IBD patients the researchers could confirm that the microbial characteristics found in the feces were really specific to CRC and not just indicative of inflammatory intestinal conditions in general. "At present the highest precision and specificity can be achieved by combining our

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> **Dr. Peer Bork**

fecal microbial analysis with FOBT," said Dr. Bork. "The future use of fecal microbial CRC detection for mass screening will depend on the development of procedures that are more cost-effective than the ones we used for research purposes. We have already made some first steps in this direction by testing the accuracy of less expensive gene sequencing techniques and the results are rather promising", said Dr. Bork.

The results achieved by CRC-related fecal microbiota analysis do not only offer a promising approach to new non-invasive screening procedures. They also point to mechanisms underlying the genesis of CRC. "Several of the bacterial species prominent in the CRC patients' fecal samples also belong to the microbial composition which we found in the environment of the tumour. We now start to investigate whether those enhance the development of the disease or might even play a causal role", said Dr. Bork.

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