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Making immunotherapy against bile duct cancer more effective

MHH gastroenterologist Dr Bernd Heinrich is investigating how bacteria and immune cells exchange information in the tumour environment. The Else Kröner Fresenius Foundation has honoured him with a Memorial Fellowship worth 250,000 euros for his work.

Bile duct cancer is a rare but serious disease that is usually fatal. Known technically as cholangiocarcinoma (CCA), it can affect the bile ducts inside and outside the liver. The frequency of cases is increasing worldwide and the chances of recovery are considered poor. If the tumour is completely removed by surgery, there is a chance of recovery, but the cancer is usually only discovered late. In advanced tumour stages, cancer medicine relies on chemotherapy and, more recently, also on immunotherapies. However, the response rates are still low. The immediate area around the cancer site, the so-called tumour microenvironment, apparently plays an important role. This is where cells of the innate immune system and bacteria interact with each other. How this influences the course of the disease is still largely unknown.

This is where Dr Bernd Heinrich, assistant physician at the Clinic for Gastroenterology, Hepatology, Infectiology and Endocrinology at Hannover Medical School (MHH), wants to start. Using modern sequencing methods, he and his team want to investigate the network of innate lymphoid cells (ILCs) and bacteria in bile duct cancer and its microenvironment. The new findings should help to improve the effect of immunotherapies. The Else Kröner Fresenius Foundation has awarded the scientist the Memorial Scholarship for particularly talented young doctors and is funding the project with 250,000 euros over two years.

Three different CCA subgroups

Depending on its location in relation to the liver, bile duct cancer is divided into three subgroups, which also differ genetically from one another. ‘In various studies, we have already identified certain bacterial compositions in the bile or stool of patients with CCA,’ says Dr Heinrich. ‘We were able to see that the bacterial composition differs between the three subgroups, which obviously influences the course and prognosis of the disease. ’This is because the bacteria not only play a role in the repair of the bile ducts, but can also trigger infections, which in turn favour uncontrolled growth of the bile ducts. At the same time, the tumour microenvironment also contains cells of the innate immune system, the first line of defence of our body's own defences. These ILCs influence the immune response against tumours and interact with the bacteria.

Determining bacterial flora

In preliminary studies on patients with liver cancer, Dr Heinrich has already established that a change in the intestinal microbiome following the use of broad-spectrum antibiotics influences the growth of liver cancer and liver metastases. ‘We assume that ILCs play a decisive role in tumour immunity and are important regulators in the tumour microenvironment in CCA,’ says the physician. ‘We want to understand how the ILCs interact with the bacteria inside and outside the tumour and what influence this has on the development of the disease. ’ILCs react very quickly when

their environment changes. This may also happen if, in addition to the local bile duct bacteria, other bacteria from the neighbouring intestine migrate into the liver.

Dr Heinrich wants to isolate the ILCs from surgically removed CCA tissue from the three tumour subgroups. 'We use these to prepare sections, which we also analyse for bacteria and compare with healthy controls.' In addition, oral and rectal swabs taken before the operation will provide information about the bacterial flora of the patients and the relationship between the microbiota in the intestine, liver and bile ducts. The bacterial composition of the tissue samples and swabs is analysed in cooperation with the Comprehensive Cancer Centre Lower Saxony (CCC-N).

Investigating the influence of antibiotics

'Our aim is to identify specific subgroups of ILCs, bacteria or their metabolic products, which can then be used to improve the immune response against the tumour,' explains Dr Heinrich. 'So far, we have been treating the three subtypes in the same way, which is probably not correct These new therapeutic approaches will then be tested in tissue models and compared with the immunotherapy currently used. The aim is to develop new treatment combinations for optimised immunotherapy of bile duct cancer.

The researchers also want to investigate the effects of antibiotics prescribed for chronic inflammation of the bile ducts, which increase the risk of developing bile duct cancer. 'We want to find out whether strong broad-spectrum antibiotics tend to prevent tumour development by combating inflammation or whether they actually promote cancer by adversely altering the mirobiome,' says the gastroenterologist. 'Ultimately, our investigations will take us a step closer to personalised medicine and precision oncology.'

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Looking for ways to make immunotherapies against bile duct cancer more effective: Gastroenterologist Dr Bernd Heinrich.
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