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New target for the therapy of hepatocellular carcinoma discovered

Hepatocellular carcinoma is the second most common cause of cancer deaths worldwide. If the tumour is at an advanced stage, doctors have few treatment options. Researchers led by Prof. Dr. Lars Zender from the University of Tübingen have now identified one of the cancer's Achilles' heels, namely, the interaction between C-MYC and AURKA proteins, which can be destabilised with a drug, thus killing cancer cells.

"Hepatocellular carcinomas are among the cancers with very poor prognosis because the tumour usually develops from liver cirrhosis and grows aggressively," said Lars Zender, head of the Section for Translational Gastrointestinal Oncology at the University Hospital of Tübingen. The tumour is often only discovered when it is already at an advanced stage. By then, targeted drug therapies are the last chance for destroying the tumour and prolonging survival. A drug called Sorafenib, which is currently standard cancer treatment, increases the life expectancy of advanced stage hepatocellular carcinoma patients by around three months. "The problem is that the tumour quickly finds ways to adapt and become resistant to the drug," says Zender.

The researchers have known about one of the tumour's particular weak spots for quite some time: the protein C-MYC. C-MYC is produced in larger than normal amounts in more than 50% of human tumours. C-MYC is a transcription factor that ensures that growth-promoting and tumour-maintaining genes are transcribed. "We have observed in mice with cancer that when we switch off the C-MYC protein, the tumour is no longer able to adapt quickly and shrinks," said Zender. This approach could mean a breakthrough in the treatment of many cancers. However, all attempts to block the transcription have so far failed because its surface has no depressions where small inhibitory molecules could dock.

Detours to success

Prof. Dr. med. Lars Zender from the University Hospital of Tübingen is looking for the Achilles' heel of hepatocellular carcinoma.
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Zender's team has now found an indirect way to reduce the quantity of C-MYC protein. This involves using small molecules to alter the conformation of one of C-MYC's binding partners called AURKA, which stabilises C-MYC. As a result, C-MYC can no longer dock to AURKA and degrades, resulting in the death of the tumour cells. The effect of the inhibitor has already been demonstrated in preclinical mouse models.

"The approach could be very promising for a specific group of hepatocellular carcinoma patients," says Zender. The researchers from Tübingen have so far only found this protein complex in patients in whom the tumour suppressor protein p53 has lost its important watchdog position due to a mutation, or is completely missing. This is the case in around 50% of hepatocellular carcinoma patients. "It appears that the formation of the C-MYC-AURKA complex is a particularity of liver cells with altered p53," said Zender, adding that the researchers have so far only examined a few types of cancer and further research is needed to confirm the astounding finding.

The discovery is a happy coincidence. Although most of Zender's projects have an applied aspect, the researchers' initial objective was simply to gain a thorough understanding of the p53 signalling pathway in hepatocellular liver carcinoma patients. They were surprised to see that liver cells with defective p53 temporarily stop dividing before starting to grow incessantly, and were looking for a reason for this.

A protein with two faces

Zender and his team have published their discovery in the renowned journal Nature Medicine.
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The researchers used RNA interference, a Nobel Prize-winning method which uses RNA molecules to inhibit gene expression, to silence specific genes in a realistic tumour mouse model which they specifically developed for this purpose. They discovered that AURKA halted the cell cycle, but also found that when further damage triggers liver renewal, the liver cells produce more C-MYC. C-MYC then binds to AURKA, a decisive connection that causes tumour cells to proliferate. By targeting the AURKA protein, it might be possible to stop the growth of p53-altered liver cancers.

The researchers are now planning to test a pharmacological inhibitor produced by the pharmaceutical company Takeda which changed the conformation of the AURKA protein in a clinical trial carried out with hepatocellular carcinoma patients in Tübingen. Takeda is already testing the drug in Phase I studies on other types of cancer, including leukaemias. “At present, the inhibitor is used as a shotgun approach for all hepatocellular carcinoma patients without knowing whether they will respond to treatment or not. Based on our findings, we now have a biomarker that we can use to predict in which hepatocellular carcinoma patients the application of the inhibitor will be successful, namely those with defective p53,” says Zender.

Drug development in Tübingen

The oncologist is convinced that the therapeutic effect observed in preclinical studies could be improved with better inhibitors. “The drug was not originally developed for this purpose,” says

Zender. With the AURKA inhibitors currently in clinical development, the pharmaceutical companies focused on the enzymatic activity of the potential cancer proteins, which is, however, irrelevant for C-MYC-AURKA binding. Another happy coincidence was that Takeda's inhibitor also altered the conformation of AURKA, thus preventing binding to C-MYC.

Together with Prof. Dr. Stefan Lauter, a pharmacist from the Centre for Academic Drug Development in Tübingen, Zender is currently working on improving the AURKA inhibitors that change the protein's conformation. "Over the past twenty years we have realised that, with no contact with academic research, the pharmaceutical industry produces fewer drugs," said Zender. Although this is not the case with this project, it will still take at least five years before the drug can be used in patients.

Article

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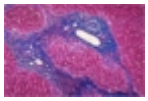

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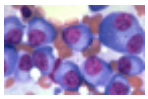

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