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Bile duct cancer study sheds light on triggers that cause disease

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Scientists have identified a molecule that drives the development of bile duct cancer.

The research in mice sheds new light on what triggers the disease and how the illness progresses.

Experts say that further research will be needed but the findings could eventually reveal opportunities to improve diagnosis and develop new therapies.

Researchers at the University of Edinburgh focused on a family of molecules called Notch, which are critical for the formation of bile ducts as the liver develops in an embryo.

The team looked at whether these molecules are involved in bile duct cancer and found that one of them - Notch 3 - is a key driver of tumour development.

Mice that do not have the Notch 3 gene develop fewer tumours and those that do form are much smaller in size, the study found.

The researchers showed that Notch 3 triggers a pathway of signalling molecules called AKT, which drives cells in the tumour to reproduce uncontrollably.

Tissue samples from patients with bile duct cancer had higher levels of

Notch 3 than samples from normal liver, suggesting that blocking the molecule could offer a new way of treating the disease in people.

The researchers caution that much more research is needed before a therapy could be developed but the findings could help to improve diagnosis.

Bile ducts are found in the liver and are important for helping to drain toxins. Cancer of the bile ducts - known as cholangiocarcinoma - is the second most common primary liver cancer and has a very poor prognosis.

The disease is difficult detect and often isn't accurately diagnosed until the tumour is too advanced for surgery, which is the only curative treatment. Other treatment options are limited as the cancer typically does not respond well to chemotherapy.

Cases of bile duct cancer have risen steeply and steadily across the world over the past decades. In 2013, more than 2000 people died from the disease in England alone and fewer than one in 20 patients will survive for five years after diagnosis.

The study, published in the *Proceedings of the National Academy of Sciences*, was funded by Wellcome, the Medical Research Council, AMMF - the Cholangiocarcinoma Charity, Cancer Research UK and the European Research Council.

Professor Stuart Forbes, of the MRC Centre for Regenerative Medicine at the University of Edinburgh, said: "Identifying the signals that drive bile duct cancer growth gives us hope of finding new ways of tackling the disease. We next need to assess how Notch 3 could be targeted with drugs so that we can investigate whether this approach offers the potential for a new therapy."

Miss Rachel Guest, a Clinical Lecturer in General Surgery at the University of Edinburgh, said: "It is crucial that we find methods to diagnose bile duct cancer earlier and this molecule may be one opportunity to do this. Although more studies are needed before this becomes a reality, cholangiocarcinoma has previously been under-researched and this work is a welcome insight into a very deadly cancer."

Helen Morement, Chief Executive Officer of AMMF - The Cholangiocarcinoma Charity, commented: "The Notch 3 findings by the Edinburgh team are potentially very important. Cholangiocarcinoma is a truly devastating disease, with very little in the treatment armoury - to have discovered an area that may lead to a novel therapy is certainly welcomed by AMMF."

Provided by University of Edinburgh