Researchers identify a novel therapeutic approach for liver cancer

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Scientists from Dana-Farber Cancer Institute use a micro-RNA tool to block a cancer-causing molecular circuit in liver cells. Credit: Dana-Farber Cancer Institute

Cancer of the liver – rare in the United States but the third-leading cause of cancer death worldwide – can result from environmental exposures or infections like chronic hepatitis, but the link is poorly understood.

Now, researchers at Dana-Farber Cancer Institute have identified a mechanism in mice that triggers inflammation in the liver and transforms normal cells into cancerous ones. In addition, they demonstrated in a mouse model that a particular micro-RNA (miR-124) - a member of a recently discovered class of molecular regulators – could be harnessed to treat or even prevent liver cancer.

"In this study we are describing for the first time a micro-RNA that is able to prevent and treat liver cancer," said Dimitrios Iliopoulos, of Dana-Farber's Department of Cancer Immunology and AIDS. The findings are being published today in the journal *Cell*.

The authors said they plan to start a phase I clinical trial using miR-124 in liver cancer patients in 2012.

Iliopoulos and his colleagues found that in mice given a carcinogenic chemical, DEN, liver cancer is initiated by the activation of a molecular circuit that sets up an inflammatory state in the cells, leading to cancer. Once this inflammatory circuit is turned on even for a few days, it becomes permanent, sustaining its activity through a never-ending feedback loop – a "snowball effect," as Iliopoulos termed it.

Iliopoulos previously identified a similar feedback circuit implicated in the development of breast cancer.

One element of the circuit is a micro-RNA called miR-124, the Dana-Farber team reported.

Micro-RNAs are extremely short lengths of RNA – a messenger molecule that helps the cell build proteins according to DNA instructions - which are not translated into proteins. MiRNAs have been recently implicated in the pathogenesis of human diseases including different types of cancer. The Dana-Farber team found that miR-124 and another key controller of the feedback circuit, HNF4α, showed reduced activity in the cancer cells.

HFN4α is an essential factor in formation of liver cells and their proper function. When HNF4α is suppressed, said Iliopoulos, it creates a temporary state of inflammation in the cell – a forerunner of cancer. "After only a few days, this transient inflammatory response is converted

into a chronic inflammatory response by this feedback circuit that is continuously amplified," he said.

Because HNF4α and miR-124 interact with each other, the scientists hypothesized that boosting activity of miR-124 might restore normal activity in HNF4α, halting the runaway inflammatory cycle and causing tumors to stop growing.

To test this notion they administered systemically miR-124 once a week for four weeks to mice that had developed liver cancer by exposure to DEN. "We found that miR-124 suppressed more than 80 per cent of tumor growth and size" by causing the cancer cells to self-destruct, the scientists wrote. They observed no toxic effects in other essential organs, such as the kidneys, spleen, heart and lungs.

Further, they showed that giving miR-124 to mice exposed to DEN actually prevented the development of liver tumors.

"Our hope is that miR-124 potentially could be used as a preventive in patients at high risk of liver cancer because they have chronic hepatitis C or as a therapeutic agent in patients with liver cancer" said Iliopoulos.

Provided by Dana-Farber Cancer Institute

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