Researchers identify UHRF1 as oncogene driving liver cancer

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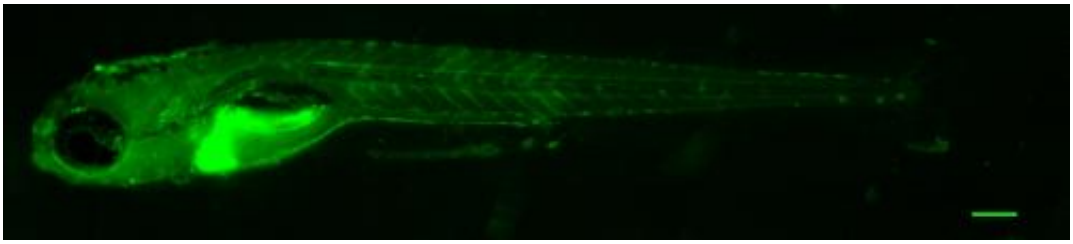

This shows a 5-day old zebrafish expressing green fluorescent protein in hepatocytes (liver cells) to highlight the liver. Credit: Kirsten C. Sadler, PhD.

Patients with advanced hepatocellular (or liver) cancer have high mortality rates, with existing drugs demonstrating only a small, but significant survival advantage. By combining a zebrafish model of liver cancer with data from human tumors, researchers from the Icahn School of Medicine at Mount Sinai hope to identify potential genes of interest that can be targeted for new treatments for hepatocellular carcinoma, the most common form of liver cancer to develop from liver cells.

Using transgenic zebrafish as an emerging, powerful whole animal model for cancer gene discovery, in combination with cultured cells and data from human tumors, they found that a gene called UHRF1, which is highly expressed in many types of cancers, can cause liver cancer at an unprecedented rate and incidence – with tumors forming in 75% of fish within 20 days. Results from the study are published online in the

journal *Cancer Cell*.

"This is the first time that UHRF1 has been shown to be sufficient on its own to cause any kind of cancer when it is highly expressed," said the study's senior investigator, Kirsten C. Sadler, PhD, Associate Professor Medicine in the Division of Liver Diseases and of Developmental and Regenerative Biology, and Director of the Zebrafish Research Facility at the Icahn School of Medicine at Mount Sinai. UHRF1 has generated a lot of interest because it is a central regulator of epigenome – which is a collection of reversible modifications to DNA and the DNA packaging proteins – that are important for deciding which genes are expressed and how the DNA is transmitted during cell division. The cancer cell epigenome is dramatically different from normal cells, and the field of cancer epigenetics is exploding because of the hope that these changes could be reversed, and thereby reverse the aggressive nature of cancer cells. "Down the road, we hope to develop drugs to target UHRF1 and thereby reset the cancer epigenome to activate anti-tumor mechanisms and halt liver cancer.," added Dr. Sadler.

UHRF Levels Important in Human Liver Cancers, Too

When the team analyzed patient-derived liver tumors, they found that high levels of the UHRF1 were also found there, too. Most strikingly, the changes in gene expression caused by high UHRF1 levels in zebrafish were reflected in the human tumors expressing high UHRF1 levels. This points to similar mechanisms underlying UHRF1-driven liver tumor formation in both species. One of these is the ability of the cancer-prone cells to bypass the tumor suppressive mechanisms that are activated in most cells when they receive a cancer-causing stimulus.

Cellular senescence is one such mechanism, and this study found that

tumors associated with UHRF1 levels in both fish and humans only those cells that could escape senescence were the ones that could go on to form the tumors. This lays the groundwork to use this model to test new therapies that would target UHRF1 to re-activate the senescence program and halt cancer formation.

Dr. Sadler pointed to several advantages of using zebrafish in preclinical liver disease research. Zebrafish reproduce rapidly and abundantly, they are translucent until about three weeks of age, enabling researchers to directly visualize tumor growth, and the cells in the liver function similarly to those in humans. Zebrafish are also inexpensive to raise, making this study uniquely powerful, as they analyzed nearly 300 fish for tumors in this study– a scope that would be extremely costly using traditional mammalian cancer models.

UHRF1 is overexpressed in around 40%-50% hepatocellular cancers in humans and predict poor outcome. This overexpression is associated with poorer prognosis in terms of high recurrence rate and low term overall survival. "We have little to offer people in the setting of advanced disease – and this points to an entirely new direction," Dr. Sadler said. "It raises the hope that epigenetic drugs could be applied to liver cancer in the future."

Commenting on the research, Scott Friedman, MD, Dean for Therapeutic Discovery, and Fishberg Professor of Medicine, and Chief of the Division of Liver Diseases, at the Icahn School of Medicine at Mount Sinai, said: "Dr. Sadler's team has conducted a remarkable study that combines the power of the zebrafish model with state of the art genomic analysis of a devastating and poorly treated human cancer. This kind of comprehensive study not only uncovers a new approach to treating hepatocellular carcinoma, but also provides a vital roadmap to unlocking cancer's secrets more quickly and effectively."

The need for better treatments for hepatocellular cancer was underscored by Josep M. Llovet, MD, a study coauthor, and Professor of Medicine, and Director, Mount Sinai Liver Cancer Program. "The incidence of hepatocellular cancer is increasing worldwide and the median outcome at advanced stages with the sole effective molecule available, Sorafenib, is one year. Thus, identification of novel targets for HCC therapies are an unmet medical need. The current study points to the fact that UHRF1 is an oncogene driver and a potential target for therapies"

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