CORNELL CHRONICLE

Key to rare aggressive liver cancer found in RNA molecule

By Krishna Ramanujan | February 27, 2019

A boy complaining of a stomach ache is brought to a doctor's office, only to learn he has an aggressive, untreatable tumor growing in his liver.

This is often the case for people who develop fibrolamellar carcinoma, a very rare metastasis-prone liver cancer that primarily affects adolescents and young adults. This cancer accounts for 1-5 percent of all liver cancers, but was not recognized by the World Health Organization as a distinct disease until 2010.

Now, a Cornell-led team has discovered that, at the onset of the rare disease, a small, non-coding RNA molecule – microRNA-375 – becomes silenced, a finding that may hold the key to treatment.

The paper, "**MicroRNA-375 Suppresses the Growth and Invasion of Fibrolamellar Carcinoma** (https://www.cmghjournal.org/article/S2352-345X(19)30010-4/fulltext)," was published Feb. 11 in the journal Cellular and Molecular Gastroenterology and Hepatology.

Comparisons from patient samples between fibrolamellar carcinoma cells and adjacent normal liver tissue revealed that "microRNA-375 is almost completely lost in patients who have this disease," said Praveen Sethupathy, associate professor of biomedical sciences at Cornell's College of Veterinary Medicine and a senior author of the study. Timothy Dinh, a doctoral student in Sethupathy's lab, is a co-first author of the paper, along with Matt Kanke, a senior bioinformatics analyst in the Sethupathy lab, and Mark Jewell, a postdoctoral associate in the lab of co-author Dr. Anna Mae Diehl at the School of Medicine at Duke University.

The researchers showed that the loss of microRNA-375 facilitates the growth of the tumor. "When it's present it serves as a kind of brake on the ability of cells to grow, and when you lose it, that brake is gone and you get unchecked growth," Sethupathy said. "It's the first mechanism that has been recognized for this [type of] tumor."

They found that adding microRNA-375 back into the tumor model greatly slowed the growth of cancer cells, and diminished the capacity of malignant cells to migrate and metastasize. Genetic sequencing studies revealed that an important signaling pathway implicated in other cancers, called the Hippo pathway, was compromised in the tumor but returned to normal activity when the microRNA was added.

In order to make this discovery, Sethupathy lab members worked closely with collaborators at Duke University to develop a cell model in a petri dish that allowed them to experiment with fibrolamellar tumor cells. Testing on animal models is the next step, which could lead to new therapies.

Using a National Institutes of Health-funded database called The Cancer Genome Atlas, the team analyzed microRNA data from approximately 10,000 tumor samples across many different tumor types. Out of 22 types of cancer, melanoma (skin cancer) had the highest level of microRNA-375 suppression, with the second highest level of suppression in fibrolamellar carcinoma. In addition, they found marked suppression of microRNA-375 in a few other more common cancers, including colon cancer, another major area of study in Sethupathy's lab.

Key to the study were tumor samples provided by the Fibrolamellar Cancer Foundation, which has created a network linking patients with clinicians and connecting researchers with clinics and hospitals for acquiring samples.

“That’s important because this isn’t a very common cancer for which samples might be much easier to obtain.” Sethupathy said. “Fibrolamellar is so rare that access to tissue is a huge limiting factor.”

Previous research has shown that virtually all fibrolamellar carcinoma patients carry the same complex mutation, an extremely rare occurrence in cancer. “Every patient we have analyzed has this mutation,” Sethupathy said. The mutation is not heritable, and its cause and cell type of origin are unknown. Importantly, in this work the team has shown that this mutation can inhibit microRNA-375.

Next steps will be to test microRNA-375’s efficacy to arrest fibrolamellar carcinoma in a mouse model that the Sethupathy lab has established together with the Progressive Assessment of Therapeutics (PATh) core at Cornell, and also to investigate its role in colon cancer.

Co-authors include researchers from the University of North Carolina at Chapel Hill, University of Washington and the Memorial Sloan Kettering Cancer Center.

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MEDIA CONTACT

Lindsey Hadlock

lmh267@cornell.edu (mailto:lmh267@cornell.edu)

607-269-6911 (tel:607-269-6911)

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