New liver cancer research targets non-cancer cells to blunt tumor growth

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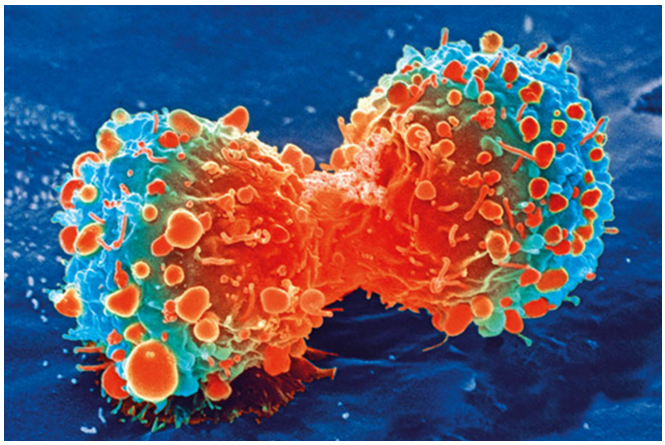

Cancer cell during cell division. Credit: National Institutes of Health

"Senotherapy," a treatment that uses small molecule drugs to target "senescent" cells, or those cells that no longer undergo cell division, blunts liver tumor progression in animal models according to new research from a team led by Celeste Simon, Ph.D., a professor of Cell and Developmental Biology in the Perelman School of Medicine at the University of Pennsylvania and scientific director of the Abramson Family Cancer Research Institute. The study was published in *Nature Cell Biology*.

"This kind of therapy is not something that has been tried before with liver cancer," Simon said. "And in our models, so-called 'senolytic' therapy greatly reduced disease burden, even in cases with advanced disease."

Loss of the enzyme FBP1 in human liver cells significantly increases tumor growth. Previous research has shown FBP1 levels are decreased in stage 1 tumors, and further reduced as the disease progresses. In this study, Simon and her team used RNA-sequencing data to identify FBP1 as universally under-expressed in the most common form of liver cancer, hepatocelluar carcinoma, regardless of underlying causes like obesity, alcoholism, and hepatitis.

The loss of FBP1 in liver cells activates the neighboring hepatic "stellate cells"—which make up ten percent of liver mass—causing fibrosis (tissue scarring) and subsequent stellate cell senescence, both of which promote tumor growth. Researchers found that these senescent stellate cells can be selectively targeted by senolytics, including Navitoclax (already in clinical trials for other diseases, like hematological malignancies), in order to blunt tumor progression driven by liver cell-specific FBP1 loss.

The team provides the first genetic evidence for FBP1 as a bona fide metabolic tumor suppressor in the liver and that its loss in liver cells promotes the growth of tumors because of effects on other cells within the tumor microenvironment.

Using genetically engineered mouse models, the team eliminated FBP1and found the disease progressed more rapidly and tumor burden greatly increased in carcinogen-mediated, dietary, and other forms of hepatocellular carcinoma.

"The case with liver cancer is very dire, once you get beyond a certain stage there are limited, if any, treatments available," Simon said. "As obesity rates continue to increase and viral infections continue to be a problem, there is going to be an increasing surge of liver cancer which currently has few treatment options. And since FBP1 activity is also lost in renal cancer, FBP1 depletion may be generally applicable to a number of human cancers. What's unique about our senotherapy approach is that we are specifically targeting other cells in the liver tumor environment rather than the cancer cells themselves."

Next steps, according to researchers will be to

begin to test these treatments in a clinical setting.

More information: Fuming Li et al. FBP1 loss disrupts liver metabolism and promotes tumorigenesis through a hepatic stellate cell senescence secretome, *Nature Cell Biology* (2020). DOI: 10.1038/s41556-020-0511-2

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