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Discovery in liver cancer cells provides new target for drugs

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Researchers at Virginia Commonwealth University Massey Cancer Center and VCU Institute of Molecular Medicine (VIMM) have discovered a novel mechanism in gene regulation that contributes to the development of a form of liver cancer called hepatocellular carcinoma (HCC). Currently, there is virtually no effective treatment for HCC, and this breakthrough identifies a promising new target for therapeutic intervention.

In the journal *Hepatology*, Devanand Sarkar, M.B.B.S., Ph.D., Harrison Endowed Scholar in Cancer Research at VCU Massey Cancer Center, a Blick scholar and assistant professor in the Department of Human and Molecular Genetics and a member of the VIMM at VCU School of Medicine, describes for the first time how RNA-induced silencing complex (RISC) contributes to the development of liver cancer.

RISC is an important factor in post-transcriptional gene regulation, which occurs between transcription (where DNA is converted to RNA) and translation (where RNA is converted to protein). These processes regulate functions such as cellular growth, division and death. Sarkar and his team identified the proteins AEG-1 and SND1 as factors that increase RISC activity and lead to the development of liver cancer.

For years, Sarkar has been studying the role of AEG-1 in cancer with his collaborator on this research, Paul B. Fisher, M.Ph., Ph.D., Thelma Newmeyer Corman Endowed Chair in Cancer Research at VCU Massey, professor and chair of the Department of Human and Molecular

Genetics and director of the VIMM.

"AEG-1 works as a scaffold protein," says Sarkar. "If you think about scaffolding outside of a biological setting, its function is to help facilitate things like construction. In this case, AEG-1 was found to work with another protein, SND1, to provide the scaffold for the formation of RISC. Since both AEG-1 and SND1 are increased in HCC, the net effect is increased RISC activity."

The study clearly identifies SND1 as a novel regulator of liver cancer. As SND1 is a molecule that can be inhibited by drugs, Sarkar's findings open up a novel avenue for treating liver cancer by targeting SND1.

"RISC works by degrading tumor-suppressor mRNAs, which transmit genetic information in a cell that prevents the formation of tumors. This allows other cancer-causing factors to go unchecked and aid tumor growth," says Sarkar. "Since we've shown that RISC activity is higher in cancer cells than normal, healthy cells, we're hopeful that inhibiting SND1 to decrease RISC activity will do little, if any, damage to healthy liver cells while stopping cancer progression."

Sarkar's team is working hard to find the most clinically-relevant SND1 inhibitors. Once these are found, the researchers will need to prove their effectiveness in several more experiments. The ultimate goal is to move these findings to Phase I clinical trials for patients with liver cancer.

More information: onlinelibrary.wiley.com/doi/10 … 2/hep.24216/abstract

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