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Researchers Identify Gene Linked to Aggressive Progression of Liver Cancer

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(PhysOrg.com) -- Virginia Commonwealth University researchers have identified a gene that plays a key role in regulating liver cancer progression, a discovery that could one day lead to new targeted therapeutic strategies to fight the highly aggressive disease.

Hepatocellular carcinoma, HCC, or liver cancer, is the fifth most common cancer and the third leading cause of cancer deaths in the world. Treatment options for HCC include chemotherapy, chemoembolization, ablation and proton-beam therapy. Liver transplantation offers the best chance for a cure in patients with small tumors and significant associated liver disease.

In the study, published online in the February issue of the Journal of Clinical Investigation, researchers reported that the astrocyte elevated gene-1, AEG-1, plays a key role in regulating HCC in series of cellular models. By examining human liver tumor cells of patients with HCC, the team found that the expression of AEG-1 gradually increases as the tumor becomes more and more aggressive. Using microarray technology, they analyzed cDNA from the tumor cells and determined that AEG-1 modulates expression of genes relevant to the progression of HCC, including invasion, metastasis, resistance to chemotherapy, the formation of new blood vessels, and senescence. cDNAs are complementary DNAs that are generated from mRNAs to analyze gene expression profiles.

“AEG-1 also activates multiple intracellular signaling pathways that are known to be involved in HCC progression. So, strategies to inhibit

AEG-1 that could lead to the shutdown of these pathways, either by small molecules or by siRNAs, might be an important therapeutic modality for HCC patients," said principal investigator Devanand Sarkar, Ph.D., MBBS, assistant professor in the Department of Human and Molecular Genetics in the VCU School of Medicine, and Harrison Endowed Scholar in Cancer Research at the VCU Massey Cancer Center.

siRNAs are small inhibitory RNAs that can specifically inhibit targeted mRNA and protein production. siRNAs may be used in the future for targeted inhibition of AEG-1 in patients, Sarkar said.

According to Sarkar, the team found a significantly higher expression of AEG-1 protein in more than 90 percent of tumor samples from HCC patients compared to normal human liver cells.

"The expression of AEG-1 protein gradually increases as the disease becomes more aggressive. No other genes have been shown to be upregulated in such a high percentage of HCC patients," said Sarkar.

Further, he said that findings from a separate pool of 132 HCC patients revealed significant overexpression of AEG-1 mRNA compared to normal liver. In a subset of these patients, the team detected an increased number of copies of the AEG-1 gene.

"We observed an increase in AEG-1 DNA, mRNA and protein in HCC patients, which indicates a significant involvement of AEG-1 in HCC progression. Stable overexpression of AEG-1 converts non-tumorigenic human HCC cells into highly aggressive vascular tumors and inhibition of AEG-1 abrogates tumorigenesis by aggressive HCC cells," he said.

Previous studies suggest that the expression of AEG-1 is very low in normal cells or tissues such as breast, prostate and brain. However, in

cancers of the same organs, expression of AEG-1 is significantly increased.

The team will conduct studies to further understand the molecular mechanisms by which AEG-1 works and identify other proteins with which it interacts.

More information: A copy of the study is available for reporters at www.jci.org/articles/view/36460 .

Provided by Virginia Commonwealth University