Study uncovers genetic driver of inflammation, uses it to prevent and treat liver cancer

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This is Devanand Sarkar, M.B.B.S., Ph.D., Harrison Endowed Scholar in Cancer Research and member of the Cancer Molecular Genetics research program at VCU Massey Cancer Center, Blick Scholar and associate professor in the Department of Human and Molecular Genetics and member of the VCU Institute of Molecular Medicine (VIMM) at VCU School of Medicine. Credit: VCU Massey Cancer Center

Inflammation has been shown to be a driving force behind many chronic diseases, especially liver cancer, which often develops due to chronic inflammation caused by conditions such as viral hepatitis or alcoholism and has relatively few effective treatment options. Now, scientists at Virginia Commonwealth University Massey Cancer Center have demonstrated for the first time in preclinical studies that blocking the expression of a gene known as astrocyte elevated gene-1 (AEG-1) halts the development and progression of liver cancer by regulating inflammation. This research could impact not only the treatment of liver cancer, but many inflammation-associated diseases.

Led by Devanand Sarkar, M.B.B.S., Ph.D., a team of researchers developed a mouse model that no longer expresses AEG-1, a gene that has been previously shown to be expressed in the vast majority of cancers. Results from their experiments, recently published in the OnlineFirst edition of *Cancer Research*, a journal of the American Association for Cancer Research (AACR), demonstrated that, without AEG-1, the mice were resistant to liver cancer development and protected from aging-associated inflammation and tumor development. The scientists discovered that this resistance was because AEG-1 plays a key role in the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), which is a protein complex that regulates immune responses, such as inflammation.

"Our findings provide exciting new evidence that AEG-1 plays a fundamental role in regulating inflammation through NF-kB signaling," says Sarkar, Harrison Endowed Scholar in Cancer Research and member of the Cancer Molecular Genetics research program at VCU Massey Cancer Center, Blick Scholar and associate professor in the Department of Human and Molecular Genetics and member of the VCU Institute of Molecular Medicine (VIMM) at VCU School of Medicine. "Blocking AEG-1 using drugs or other methods may potentially lead to new treatments for a variety of inflammation-associated diseases."

Previous studies had led the researchers to hypothesize that AEG-1 is required for the progression and metastasis of liver cancer, but not initial tumor formation. However, the current results show AEG-1 initiates liver cancer through NF-kB interaction. In addition, they discovered for the first time that AEG-1 and NF-kb interact not only within cancer cells, but also in cells in surrounding tissue. This finding suggests that AEG-1 may play a role in regulating immune function as well as chronic inflammatory diseases.

Sarkar and his colleagues at VCU and other institutions are currently working to develop small molecules, or drugs, designed to block the expression of AEG-1.

"This new understanding of AEG-1 opens a vast realm of possibilities," says Sarkar. "Moving forward, we plan to use this mouse model to further explain the role of AEG-1 in the regulation of immunity and inflammation. The knowledge we gain could impact the treatment of countless diseases."

More information: cancerres.aacrjournals.org/con … 4-1357.full.pdf+html

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