Researchers find link between cancer gene and obesity

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This is an image of a weight scale. Credit: CDC/Debora Cartagena

Virginia Commonwealth University Massey Cancer Center researchers have discovered that a gene known to cause cancer also may play a role in determining if someone becomes obese.

Recent discoveries suggest that the gene Astrocyte elevated gene-1 (AEG-1) could even be controlled with certain therapies to prevent or reverse obesity and obesity-related cancers.

"This is a completely new function of AEG-1, and we did not expect this," said Devanand Sarkar, Ph.D., Harrison Endowed Scholar in Cancer Research and member of the Cancer Molecular Genetics research program at VCU Massey Cancer Center, associate professor in the Department of Human and Molecular Genetics at the VCU School of Medicine and member of the VCU Institute of Molecular Medicine.

AEG-1 interacts with a variety of proteins to regulate genetic functions related to vitamins, hormones and lipids. Sarkar and his colleagues have been studying the gene for years, investigating its role in disease formation and metabolism.

Last year, they showed that AEG-1 blocks the ability of Vitamin A to kill liver cancer cells. The team is delving deeper with its research as documented in a series of papers recently published online in the *Journal of Biological Chemistry* and *Bioconjugate Chemistry*.

In one paper, the team describes the creation of a novel therapy that inhibits AEG-1 and stops the growth of liver cancer cells.

In another, they show that AEG-1 blocks thyroid hormone function and contributes to nonthyroidal illness syndrome, a condition common in patients with liver cancer and others who are starving or gravely ill.

And in the third, the team details its finding that AEG-1 may play a key role in regulating fat metabolism.

That paper demonstrates that the absence of AEG-1 leads to increased activity of several factors in the intestines that prevents absorption of fat. Mice without AEG-1 stay lean and live longer, leading researchers to conclude that overexpression of the gene causes the accumulation of fat.

"Fatty liver is a main cause of liver cancer, so we have that direct correlation between liver cancer and obesity," Sarkar said. "This also is important because we now know that all cancers can be caused by obesity."

As such, the recent papers and research combine to create a promising new outlook for cancer prevention and treatment, Sarkar said.

In preclinical experiments in the lab, researchers created a new drug therapy to target liver cancer

cells. They took molecules that block the expression of AEG-1 and combined them with retinoic acid (Vitamin A), which is already approved by the Food and Drug Administration to fight cancer. Using nanoparticles, they developed a system to deliver the combination intravenously to mice with transplanted human liver cancer cells.

"What we found is that the tumor disappears," Sarkar said. "Anything delivered intravenously goes to the liver first, so the success of our experiments suggests that this might also be an effective way to treat liver cancer in human patients."

Researchers are continuing to look more closely at the role of AEG-1 in metabolism and obesity-associated cancers by studying effects in mice being fed high-fat diets.

More information: "Combination of Nanoparticle-Delivered siRNA for Astrocyte Elevated Gene-1 (AEG-1) and All-trans Retinoic Acid (ATRA): An Effective Therapeutic Strategy for Hepatocellular Carcinoma (HCC)." *Bioconjugate Chem*., Article ASAP DOI: 10.1021/acs.bioconjchem.5b00254

"Astrocyte Elevated Gene-1 (AEG-1) Contributes to Nonthyroidal Illness Syndrome (NTIS) Associated with Hepatocellular Carcinoma (HCC)." *J. Biol. Chem*. jbc.M115.649707. First Published on May 5, 2015, DOI: 10.1074/jbc.M115.649707

"Astrocyte elevated gene-1 (AEG-1) regulates lipid homeostasis." *J. Biol. Chem*. jbc.M115.661801. First Published on June 11, 2015, DOI: 10.1074/jbc.M115.661801

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