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Blocking receptor in key hormone fires up enzyme to kill pancreatic cancer cells

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Pancreatic cancer researchers at Thomas Jefferson University have shown, for the first time, that blocking a receptor of a key hormone in the renin-angiotensin system (RAS) reduces cancer cell growth by activating the enzyme AMPK to inhibit fatty acid synthase, the ingredients to support cell division.

With that, a new chemopreventive agent that inhibits the angiotensin II type 2 receptor—never before thought to play a role in tumor growth—could be developed to help treat one of the fastest-moving cancers that has a 5-year survival rate of only 5 percent.

Hwyda Arafat, M.D., Ph.D., associate professor of Surgery at Jefferson Medical College of Thomas Jefferson University and the co-director of the Jefferson Pancreatic, Biliary and Related Cancers Center, and her fellow researchers, including the chair of the Department of Surgery at Jefferson, Charles J. Yeo, M.D., FACS, present their findings in the August issue of Surgery.

Angiotensin II (AngII) is the principal hormone in the RAS that regulates our blood pressure and water balance; it has two receptors: type 1 and type 2. AngII is also generated actively in the pancreas and has been shown to be involved in tumor angiogenesis.

Previous studies have pointed to the hormone's type 1 receptor as the culprit in cancer cell proliferation and tumor inflammation; however, the idea that type 2 had any effect was never entertained.

By looking at pancreatic ductal adenocarcinoma (PDA) cells in vitro, Jefferson researchers discovered that the type 2 receptor, not just type 1, mediates the production of fatty acid synthase (FAS), which has been shown to supply the cell wall ingredients necessary for cancer cells to multiply.

FAS was previously identified as a possible oncogene in the 1980s. It is up-regulated in breast cancers and is indicator of poor prognosis, and thus believed to be a worthwhile chemopreventive target.

"AngII is not just involved in cell inflammation and angiogenesis; it's involved in tumor metabolism as well," said Dr. Arafat, a member of the Kimmel Cancer Center at Jefferson. "It promotes FAS with both receptors, which makes the tumor grow."

"Blocking the type 2 receptor reduces PDA cell growth with the activation of AMPK, revealing a new mechanism by which chemoprevention can exploit," she added. "In fact, maybe combined blocking of the two receptors would be more efficient than just blocking one receptor."

AMPK, or adenosine monophosphate-activated protein kinase, is the focus of several agents today, including ones for diabetes and related metabolic diseases. It is a master metabolic regulator for cells that is activated in times of reduced energy availability, like starvation. Activation of AMPK has been shown to improve energy homeostasis, lipid profile and blood pressure. The enzyme also activates a well-known tumor suppressor, p53.

"The main thing is activation of AMPK in tumor cells," said Dr. Arafat. "AMPK is the perfect candidate as it regulates multiple targets that both halt tumor cell division and activate programmed cell death. Although it is yet to be determined how the type 2 receptor imposes deregulation of

AMPK activity, identification of the type 2 receptor as a novel target for therapy is very exciting"

Next, Dr. Arafat and fellow researchers are proposing to take this research into animal studies. They hope to target the receptors early on in the disease to better understand its prevention capabilities and also study its treatment potential. Considering pancreatic cancer is typically detected in later stages, finding better ways to treat cases that have progressed further along would be of great benefit to patients.

Provided by Thomas Jefferson University