Preclinical study identifies 'master' proto-oncogene that regulates ovarian cancer metastasis

January 29 2013

Scientists at The University of Texas MD Anderson Cancer Center have discovered the signaling pathway whereby a master regulator of cancer cell proteins – known as Src – leads to ovarian cancer progression when exposed to stress hormones. The researchers report in the current issue of *Nature Communications* that beta blocker drugs mitigate this effect and reduce cancer deaths by an average of 17 percent.

Src (pronounced "sarc," short for sarcoma) is a proto-oncogene – a normal gene that can become an oncogene due to increased expression – involved in the regulation of cell growth and division. Known to be instrumental to changes that cause normal cells to go awry, this study sheds light on its functional role as a key molecular switch affecting a downstream signaling pathway that spurs disease progression.

Led by Anil K. Sood, M.D., professor in MD Anderson's Departments of Gynecologic Oncology and Cancer Biology, researchers found that noradrenaline (NA; a stress hormone) directly affects tumor growth and spread through beta-adrenergic (ADRB) receptors expressed on tumor cells. The study demonstrated that ADRB signaling leads to Src activation via a unique protein kinase A (PKA)-mediated mechanism, which is critical to the regulation of cellular activity and cancer metastasis. This is the first time that scientists have been able to show that ADRB receptors play a direct role in Src activation by this mechanism.

"When Src is triggered by stress, it works like a dam letting out water that causes a flood downstream. Src, like the dam, is a master regulator switch that causes a chain reaction in the cells," said Sood.

Based on existing findings of Sood's ongoing work exploring potential interventions against the effects of stress, the researchers examined data on outcomes of cancer patients treated with beta blocker drugs from the U.S. Food and Drug Administration Adverse Event Reporting System. They found that mortality in patients treated with a beta blocker was reduced by an average of 17 percent across all major cancer types. Moreover, they observed a nearly 15 percent decrease in mortality among patients with ovarian and cervical cancer.

Beta blockers, also called beta-adrenergic blocking agents, treat a variety of conditions, such as heart disease, high blood pressure, glaucoma and migraines. They act on the ADRB receptors, which are also found on the heart – causing the heart to beat harder and faster under stress – and are involved in maintaining blood flow.

When the ADRB receptors on cancer cells are activated, they set into motion a chain of events that leads to formation of new blood vessels that feed tumor growth – a process known as angiogenesis. New blood vessel formation allows tumors to grow and spread more rapidly. Beta blocking agents stop this process.

"Prior to our work, the concept of stress hormones driving cancer growth was very new and only very limited information about the effect of beta blockers on cancer outcomes in humans has been available," said Guillermo Armaiz-Pena, Ph.D., instructor of Gynecologic Oncology and Reproductive Medicine and first author of the study. "This study provides incentive to further explore beta blockers as a possible supplement to traditional cancer therapies."

A Mystery Pathway Revealed

While NA – the most abundant stress hormone in the ovary – has been proven to modulate multiple cellular functions important for cancer progression, how it does so had remained a puzzle. Sood's team used a multi-step process to determine how the tumor microenvironment is disrupted by stress hormones.

First, the researchers exposed ovarian cancer cells to NA and identified a number of proteins altered by stress hormones. Using bioinformatics analysis, they narrowed potential mediators to Src.

A series of subsequent experiments designed to verify the biological roles of Src in promoting ovarian cancer tumor growth in response to stress hormones revealed the signaling pathway involved in NA-mediated Src activation. Specifically, they showed:

- PKA (also known as cAMP-dependent protein kinase) is the switch that "turns on" NA-induced Src activation;
- The signaling pathway occurs at a particular site on the cell known as S17; and
- This specific mechanism is key to mediating ADRB/cAMP/PKA-induced Src activation.

Building on the Stress-Cancer Connection

For the past 13 years, Sood's research efforts have focused on the effects of chronic stress on cancer metastasis. The latest study helps form a more comprehensive picture on the impact of and biological mechanics of chronic stress on ovarian cancer, as well as the role of beta blockers in slowing disease progression. Previous studies have shown:

- Chronic stress triggers a chain of molecular events that protects breakaway ovarian cells from destruction, as heightened levels of the fight-or-flight hormones epinephrine and norepinephrine permit more malignant cells to safely leave the primary tumor – a necessary step in metastasis and cancer progression.
- When mice with ovarian cancer are stressed, their tumors grow and spread more quickly, but the effect can be blocked using propranolol, a beta blocker commonly prescribed for heart disease.

Future research will focus on other biological mechanisms that may be affected by stress. Eventually, Sood hopes his studies will help identify the cancer patients most likely to benefit from beta blockers and other stress interventions. He is also looking at the impact of stress on other diseases, such as gastrointestinal disorders.

"This is a major step forward in understanding the biology and impact of stress on cancer progression and it opens the door to study drugs that could inhibit this unique signaling pathway," Sood said.

Provided by University of Texas M. D. Anderson Cancer Center

Citation: Preclinical study identifies 'master' proto-oncogene that regulates ovarian cancer metastasis (2013, January 29) retrieved 20 March 2024 from https://medicalxpress.com/news/2013-01-preclinical-master-proto-oncogene-ovarian-cancer.html