Soy-based compound may reduce tumor cell proliferation in colorectal cancer

April 11 2013

Research on a soy-based treatment for colorectal cancer, a promising agent in ovarian cancer, and a new drug target for advanced prostate cancer was presented at the American Association for Cancer Research 2013 Annual Meeting. The meeting took place April 6-10, 2013 in Washington, DC.

Natural Product From Soy May Be Effective in Combination with Chemotherapy

The development of colorectal cancer (CRC) is largely driven by cellular signaling in the Wnt pathway, a network of proteins critical to cellular growth. Hyperactivity of the Wnt signaling pathway occurs in more than 85 percent of colon and rectal cancers. Previous research has shown that genistein, a natural supplement containing soy, modulates Wnt signaling through epigenetic mechanisms.

Led by Randall Holcombe, MD, and Sofya Pintova, MD, both from Mount Sinai, the research team treated colon cancer cell lines with genistein and found that it inhibited cell growth and blocked Wnt signaling hyperactivity. The findings are counter to some other tumor types, such as breast, for which soy, because it has estrogen-like properties, increases the risk of developing tumors. Drs. Holcombe and Pintova are launching a clinical trial later this year for patients with metastatic colorectal cancer, which utilizes genistein in combination with chemotherapy based on this research.

"Genistein is a natural product with low toxicity and few side effects and our research shows that it may be beneficial in treating colorectal cancer," said Randall Holcombe, MD, Professor of Medicine in the Division if Hematology and Oncology at the Icahn School of Medicine at Mount Sinai. "This is an exciting area of research and we look forward to studying the benefits of this compound as an adjunctive treatment in colorectal cancer in humans."

Mount Sinai Researchers Identify Promising Therapy for Treatment-Resistant Ovarian Cancer

Platinum-based therapies are the standard of care in treating ovarian cancer, however 60 percent of patients relapse requiring additional treatment. During cancer development, certain proteins that might otherwise block tumor growth are inappropriately shuttled out of the cell's nucleus, and rendered unable to attack a tumor's mutated genome. Researchers led by John A. Martignetti, MD, PhD, Associate Professor of Genetics and Genomic Sciences and Oncological Sciences at Mount Sinai, in collaboration with investigators at Karyopharm Therapeutics, inhibited a nuclear shuttle protein called exportin 1 (XPO1, also called CRM1) using a novel class of drugs called a selective inhibitor of nuclear export (SINE) that can be taken by mouth.

Ying Chen, PhD, a post-doctoral student in Dr. Martignetti's laboratory, injected tumor cells removed from ovarian cancer patients treated at Mount Sinai into mice, and then treated them with a SINE XPO1 inhibitor, KPT-330. All mice treated with KPT-330 had no visible evidence of tumor and survived six times longer than control mice.

Similarly, in another mouse model of chemotherapy-resistant ovarian cancer, KPT-330 significantly reduced the tumor burden and improved overall survival when compared against the current gold-standard

platinum treatment. Moreover, mice treated with a combination of KPT-330 and platinum survived even longer. Human trials of KPT-330 are currently ongoing, and will include patients with ovarian cancer later this year.

In part, these experiments arose from a unique scientific resource established by Dr. Martignetti and Dr. Peter Dottino, MD, Associate Clinical Professor, Obstetrics, Gynecology and Reproductive Science. The Ovarian Cancer Translational Research Program preserves cancerous and normal tissues removed in the operating room from all consenting patients for genetic, genomic and therapeutic discoveries. Studies presented at AACR used patient-derived tumor tissues to create mouse tumor avatars to directly test KPT-330 provided by Karyopharm Therapeutics.

"This is truly a translational research initiative where our own Mount Sinai patients are simultaneously contributing to a potential next generation therapy for incurable ovarian cancer and gaining insight into personalized treatment of their own cancers," said Dr. Martignetti. "These results show that new oral XPO1 inhibitors may be quite promising in treating patients who do not respond to, or relapse after, treatment with platinum-based therapy. We look forward to evaluating oral KPT-330 in our patients."

These studies were in part funded through a gift from Sally and Michael Gordon, a gift from Varadi Ovarian Cancer Research Program at Mount Sinai, and a research grant from Karyopharm Therapeutics.

Researchers Identify New Drug Target for Prostate Cancer

During cancer progression, cancer cells constantly interact with and

modify their surrounding tumor microenvironment through regulating the expression of a group of enzyme inhibitors called tissue inhibitors of metalloproteinases (TIMPs). Previously, William Oh, MD, Professor and Chief of the Division of Hematology/Oncology in the department of Medicine at Mount Sinai and his colleagues showed that elevated TIMP-1 levels in the blood predicted decreased survival in advanced prostate cancer patients. However, the regulation of TIMP-1 expression in prostate cancer was not fully understood and the source of TIMP-1 overproduction remains unknown.

In the current study led by Yixuan Gong, PhD, in Dr. Oh's lab, the researchers show for the first time that resistance to androgen therapy, the most common treatment for prostate cancer, was associated with TIMP-1 overproduction in both prostate cancer patients and in cell culture models. They found that two signaling pathways called MEK and NF-κB were critical for TIMP-1 production in certain prostate cells and the production could be completely blocked by drugs that inhibit the pathways.

"Disrupting TIMP-1 signaling prevented androgen resistance providing a promising drug target for this hard-to-treat tumor type," said Dr. Gong. "We look forward to further investigating drugs that block TIMP-1 in a clinical setting."

Provided by The Mount Sinai Hospital