Scientists Pinpoint a New Molecular Mechanism Tied to Pancreatic Cancer

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New research led by scientists at The University of Texas Health Science Center at Houston (UTHealth) and Baylor College of Medicine could aid efforts to diagnose and treat one of the most lethal and hard-to-treat types of cancer.

In the EMBO Molecular Medicine [1] journal, the investigators report that they have identified a new molecular mechanism that contributes to the spread of malignant tumors in the pancreas. The hope is that drugs could one day be developed to block this pathway.

Most people with pancreatic cancer die within one to two years of diagnosis and it is expected to claim 38,460 lives in the United States in 2013 [2]. There are currently no effective tests for early detection and no effective therapies for the fast-spreading form.

The study focused on the previously established link between zinc and pancreatic cancer and sought to identify a molecular mechanism responsible for the elevated levels found in human and animal cells. Zinc is an essential trace element and small amounts are important for human health.

“We were the first to show that zinc transporter ZIP4 was a marker for pancreatic cancer,” said Min Li, Ph.D [3]., the study’s senior author and associate professor and director of the Cancer Research Program in the Vivian L. Smith Department of Neurosurgery at the UTHealth Medical School. “We knew there was a link but we didn’t know what it was.”

Li is on the faculty of The University of Texas Graduate School of Biomedical Sciences at Houston, which is a joint venture of UTHealth and The University of Texas MD Anderson Cancer Center.

Zinc levels are regulated by ZIP4, which acts as a master switch, and the researchers designed experiments to determine what happens when the switch is flipped on, Li said.

In an animal model of pancreatic cancer, the scientists observed how the initiation of ZIP4 triggered the activation of two downstream genes, which in turn accounts for the increased tumor growth. Scientists describe this as a signaling cascade.

“Pancreatic cancer is among the worst of all cancers. It is imperative to define the mechanism of this deadly disease. We have recently demonstrated a novel biological role for the zinc transporter ZIP4 in pancreatic cancer; however, the molecular pathway controlling this phenomenon remains elusive. This study

provides a comprehensive mechanism for ZIP4-mediated pancreatic cancer growth involving the activation of a transcription factor CREB and an oncogenic miR-373, and reduction in key tumor suppressor genes," said Yuqing Zhang, Ph.D., co-first author of the study.

Jingxuan Yang, Ph.D., [4] co-first author and research scientist at the UTHealth Medical School, said, "Our findings in this study define a novel signaling axis promoting pancreatic cancer growth, providing potential mechanistic insights on how a zinc transporter functions in cancer cells and may have broader implications as abnormal zinc concentration in the cells plays an important role in many other diseases."

"The results we reported in this study may help the design of future therapeutic strategies targeting the zinc transporter and microRNA pathways to treat pancreatic cancer," said Xiaobo Cui, M.D., Ph.D. [4], study co-first author and postdoctoral research fellow at the UTHealth Medical School.

Co-authors include: Yong Chen, Ph.D., Vivian F. Zhu, and John P. Hagan, Ph.D., [5] of UTHealth; Huamin Wang, M.D., Ph.D., Paul Chiao, Ph.D., and Craig D. Logsdon, Ph.D., of The University of Texas MD Anderson Cancer Center; Sally E. Hodges, William E. Fisher, M.D., F. Charles Brunicardi, M.D., Changyi Chen, M.D., Ph.D., and Qizhi Yao, M.D., Ph.D., of Baylor College of Medicine; Martin E. Fernandez-Zapico, M.D., of the Mayo Clinic; Xianjun Yu, M.D., Ph.D., of Fudan University in Shanghai, China; and Jing Fang, Ph.D., of the Chinese Academy of Sciences in Shanghai.

The study titled "A novel epigenetic CREB-miR-373 axis mediates ZIP4-induced pancreatic cancer growth" [6] received support from National Institutes of Health Grants (R01CA138701, R21CA133604), and the William and Ella Owens Medical Research Foundation.

Links:
[1] http://onlinelibrary.wiley.com/journal/10.1002/%28ISSN%291757-4684
[2] http://www.cancer.org/cancer/pancreaticcancer/overviewguide/pancreatic-cancer-overview-key-statistics
[3] http://www.uth.tmc.edu/schools/med/neurosurg/faculty-staff/bio-li-min.html
[4] http://www.uth.tmc.edu/schools/med/neurosurg/research/lab-li/team-members.html
[5] http://www.uth.tmc.edu/schools/med/neurosurg/faculty-staff/bio-hagan-john.html
[6] http://onlinelibrary.wiley.com/doi/10.1002/emmm.201302507/full