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Mouse model shows that Notch activation can drive metastatic prostate cancer

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Notch signaling is involved in prostate cancer and, in a paper published today in *The Journal of Clinical Investigation*, researchers from Baylor College of Medicine and other institutions have shown that, in a mouse model of the disease, Notch promotes metastasis, or the ability of the tumors to spread to other organs.

Notch is an evolutionarily conserved signaling pathway that is crucial for tissue development and homeostasis. A consensus has been reached that Notch signaling is deregulated during prostate carcinogenesis, but its role in prostate cancer remains inadequately defined.

"Most previous studies on the role that Notch plays in prostate cancer were performed in cultured cells in the laboratory. These studies produced contradictory results. Some studies concluded that Notch was an oncogene, that it promoted cancer development, and others that it was a tumor suppressor gene," said Dr. Li Xin, associate professor of molecular and cellular biology at Baylor. "To gain a better understanding of Notch in prostate cancer we decided to study its role in an animal model in a defined genetic context."

Pten is a tumor suppressor gene whose loss of function has been shown to correlate with prostate cancer progression. "In a human prostate cancer specimen dataset, we found that there is an inverse correlation between the expression level of Pten and the level of Notch activity," said Xin. Therefore, the researchers used a prostate specific loss-of-function of Pten mouse model of prostate cancer to determine the role

of Notch in prostate cancer progression.

In this mouse model, the scientists discovered that Notch activation can drive tumor metastasis to major internal organs such as lung and liver. To determine how Notch drives metastasis, the scientists carried out further molecular studies. "Our major conclusion is that Notch is able to upregulate another molecule called FoxC2, which is very important for the metastatic potential of the cells. If we suppress FoxC2, we can attenuate Notch-mediated metastatic activity," said Xin.

"This mouse study demonstrated directly in vivo that increased Notch activity can drive prostate cancer metastasis," said Xin. "Future studies will aim to address whether Notch inhibition can suppress tumor metastasis. These studies will serve as solid rationale for treating human prostate cancer with Notch inhibitors."

Provided by Baylor College of Medicine