Investigations show that telomerase inhibitor PinX1 is a key tumor suppressor

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It's been nearly 10 years since Beth Israel Deaconess Medical Center (BIDMC) scientists Kun Ping Lu, MD, PhD and Xiao Zhen Zhou, MD, discovered PinX1, the first potent endogenous protein shown to inhibit telomerase in mammals.

Now the scientific team has discovered a vitally important new function for this telomerase inhibitor.

The investigators report in today's on-line edition of the Journal of Clinical Investigation (JCI) that low levels of PinX1 contribute to cancer development, providing the first genetic evidence linking telomerase activation to chromosome instability and cancer initiation, and suggesting a new avenue of treatment for cancers.

"Although telomerase is activated in 85 to 90 percent of human cancers, little has been known about the significance of telomerase activation in chromosome instability and cancer initiation," explains Lu, the paper's senior author and a Professor of Medicine at Harvard Medical School. "We have discovered, for the first time, a novel role for abnormal telomerase activation in cancer initiation. This suggests that telomerase inhibition using PinX1 or other small molecules may be used to treat certain cancers with activated telomerase."

Of particular note, the group's discovery that most PinX1-mutant mouse tumors share tissues of origin with human cancer types linked to genetic alterations in chromosome 8p23 suggests a possible role for deregulation

of the PinX1-telomerase complex for the treatment of several common carcinomas, including breast, lung, liver and gastrointestinal cancers.

Telomeres cap the ends of linear chromosomes and are essential for maintaining chromosome stability. In the majority of human cells, telomeres are slightly shortened each time a cell divides, a process that, over time, leads to cell death. However, cancer cells have the unique ability to turn on telomerase, an enzyme that elongates telomeres, preventing them from growing shorter and enabling cancer cells to divide – and survive -- indefinitely.

It has been well-recognized that telomerase activation is critical for most cancer cell growth. But, as Lu explains, to this point, there has been no genetic evidence that actually links telomerase activation to chromosomal instability, a defining characteristic of most malignant human tumors.

"A normal cell has 46 chromosomes," Lu explains. "The consequence of chromosomal instability is an imbalance in this number, which allows a cell to evade its normal regulatory mechanism and become a cancer cell. The gene encoding the telomerase inhibitor PinX1 is located at human chromosome 8p23, one of the most frequent regions showing genetic changes in common human malignancies. We, therefore, wanted to find out if PinX1 might have a hand in this."

To address this question, the scientists first looked at PinX1 expression in human breast cancer tissue and cells.

"We found that PinX1 expression was much lower than normal in these cells," explains Zhou, an Assistant Professor of Medicine at HMS and the paper's first author. "Only 10 percent of the tissue expressed PinX1 levels even close to normal, with the remaining 90 percent expressed much lower than PinX1."

To determine the consequence of this significant PinX1 reduction, the researchers next created cells and mouse models in which the PinX1 gene was partially or completely removed. They observed that while mice or cells completely lacking PinX1 could not survive, the deletion of just one copy of the PinX1 gene actually reduced PinX1 expression -- and activated telomerase activity in both mice and cells.

"Surprisingly, we found that the reduced PinX1 in cells not only caused telomerase activation, but also triggered chromosome instability, a phenotype that was fully prevented by inhibiting telomerase," explains Zhou. "More important, most of the PinX1 mutant mice spontaneously developed carcinomas." These mouse tumors, she adds, exhibited features commonly seen in advanced human carcinomas, including distant metastasis and shared tissues of origin with human cancer types linked to 8p23 alterations.

"This paper confirms the role of PinX1 as a potent telomerase inhibitor and demonstrates that low levels of PinX1 can contribute to cancer development by activating telomerase and inducing chromosomal instability," says Lewis Cantley, PhD, Director of the BIDMC Cancer Center. "These findings suggest that PinX1 might be a strong therapeutic candidate for one of the most sought-after tumor suppressors at chromosome 8p23."

The Lu and Zhou laboratories are currently testing the effectiveness of using PinX1 and other telomerase inhibitors to treat cancers that overexpress telomerase. "Going forward, we are also interested in determining the genetic changes that underlie PinX1 reduction in cancers," says Lu. "This might lead to new diagnostic tools to better identify individuals who are susceptible to certain cancers, and therefore, might be suitable for treatment with telomerase inhibitors."

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