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Researchers identify promising cancer drug target in prostate tumors

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Scientists at Dana-Farber Cancer Institute report they have blocked the development of prostate tumors in cancer-prone mice by knocking out a molecular unit they describe as a "powerhouse" that drives runaway cell growth.

In an article that is being published today as an advanced online publication by the journal *Nature*, the researchers say the growth-stimulating molecule called p110beta -- part of a cellular signaling network disrupted in several common cancers -- is a promising target for novel cancer therapies designed to shut it down. The report's lead authors are Shidong Jia, MD, PhD, Zhenning Liu, PhD, Sen Zhang PhD, and Pixu Liu, MD, PhD.

The p110beta molecule and a counterpart, p110alpha, are "isoforms" -- slightly different forms – of an enzyme called PI(3)K that is an intense focus of cancer research and drug development. PI(3)K is the linchpin of a cell-signal pathway that responds to growth factor signals from outside the cell.

When activated by growth factor receptors, PI(3)K turns on a cascade of genes and proteins that drives cells to divide and grow. The molecular accelerator is normally kept under control by a tumor-suppressor protein, PTEN, which acts like a brake to curb excess cell growth that could lead to cancer.

Mutations that inactivate PTEN -- in effect releasing the brake on

growth signals -- are found in a significant proportion of prostate, breast and brain tumors. The senior authors of the new report, Jean Zhao, PhD, and Thomas Roberts, PhD, previously showed that blocking p110alpha protein inhibits cancerous growth induced by various cancer-causing proteins, such as Her2 and EGFR. With that knowledge in hand, the researchers, in collaboration with pharmaceutical companies, are developing p110alpha blockers.

P110beta, by contrast, was thought to be a relatively insignificant player in tumors. However, "the surprise in this paper is that p110beta has been found to be a bigger player than p110alpha in tumors that result from PTEN loss," noted Zhao. "Now the drug companies, which have been focusing on p110alpha, will have to think about making p110beta inhibitors as well."

Both forms of the p110 molecule have dual tasks: they are involved in responding to insulin signals -- a metabolic function -- as well as relaying growth signals from outside the cell. But the importance of 110beta had been vastly underestimated, the researchers said, for reasons they don't entirely understand.

"We knew that when cells are stimulated with growth factor signals, the activity of p110alpha, but not p110beta, rises rapidly and sharply in triggering excess cell growth," Zhao said. "We speculate that 110beta may be providing a low-level but steady growth stimulus and when PTEN is lost, it becomes an important source of cell proliferation signals."

The new findings stem from experiments in which the scientists disabled the p110beta protein in mice as a way of exploring its normal functions. In one of the experiments, the researchers "knocked out" p110beta in mice that also lacked the PTEN tumor suppressor protein and were therefore highly prone to prostate cancer. Mice that lacked PTEN but

had functioning p110beta proteins all developed early prostate cancers by 12 weeks of age. In contrast, the "knockout" mice with no p110beta function remained free of prostate cancer even though the PTEN "brake" had been disabled.

The scientists concluded, as a result, that p110beta becomes a "powerhouse" to drive cancerous cell growth when PTEN function is missing.

In light of the new findings, there is likely to be great interest in finding drugs or other tools to block the p110beta protein in cancers where mutations in PTEN have unleashed the overactive growth signals, said Zhao, who is also an assistant professor of surgery at Harvard Medical School.

The task is made somewhat easier, said Roberts, by the fact that "we know what the inhibitor should look like because of our work on p110alpha inhibitors."

Roberts, who is also a professor of pathology at Harvard Medical School, said that drugs designed to block the p110alpha form are on their way to clinical testing, but he could not predict when p110beta inhibitors might become available for clinical testing.

Source: Dana-Farber Cancer Institute