Embryonic signal drives pancreatic cancer and offers a way to kill it

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Pancreatic cancer is a particularly challenging one to beat; it has a tendency to spread and harbors cancer stem cells that stubbornly resist conventional approaches to therapy. Now, researchers reporting in the November issue of *Cell Stem Cell*, a Cell Press publication, have evidence to suggest there is a way to kill off those cancer stem cells. The target is a self-renewal pathway known for its role not in cancer but in embryonic stem cells.

"I don't think the cancer stem cells have any direct link to embryonic development, rather they are using this developmental pathway for their uncontrolled self-renewal capacity," said Christopher Heeschen of the Spanish National Cancer Research Centre in Madrid. "This pathway is completely inactive in adult tissue. We've checked many tissues and there is zero – no detectable expression at all."

The so-called Nodal/Activin pathway's embryonic ties and absence from other tissues present a real opportunity. It suggests you could target the molecular pathway without harming other adult cells. Heeschen's team has now shown that approach to therapy does seem to work in mice.

They first demonstrated the important role of the Nodal/Activin pathway in cancer stem cells derived from human pancreatic cancer. When that signal was blocked, normally resistant pancreatic cancer stem cells became sensitive to chemotherapy.

The researchers then moved on to experiments in mice with established

tumors seeded from human cancer cells. Treatment of those animals with the pathway inhibitor plus standard chemotherapy eliminated those stem cells.

"The dual combination therapy worked strikingly well," Heeschen said. "The mice responded with 100 percent survival after 100 days." That's compared to mice not receiving the therapy, which bore large tumors and died within 40 days of implantation.

That two-part treatment wasn't enough to tackle pancreatic cancer when intact tumor tissue was implanted into mice as opposed to just cancer cells, the researchers found. Heeschen says that's because those cells were nestled within a supportive "stroma." That protective tissue delivered the Activin signal and prevented the drug combination from reaching the cells.

To get around that, Heeschen and his colleagues added a third ingredient to therapy, an inhibitor intended to target the stroma. The three-pronged approach translated into long-term, progression-free survival for the mice.

Interestingly, Heeschen says the animals' tumors didn't show signs of shrinking even as they were defeated. "They were more or less dead tissue. They were senescent with no cancer stem cells – just sitting there," he said.

Those tissues apparently had no ability to form new tumors. The findings suggest that tumor regression isn't always the key thing to look for. It also shows that drugs designed to target cancer stem cells alone are promising, but only in combination with other drugs.

"The concept that you can hit cancer stem cells and tumors will melt away must be abandoned," Heeschen said. "You have to treat the entire

cancer - the stroma, cancer stem cells and differentiated cells - as a complex. "

Heeschen says there are hints that this embryonic pathway might have important roles in other forms of cancer, including breast, lung and colorectal cancers. That's something they will now test in further studies.

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