Missing molecules hold promise of therapy for pancreatic cancer

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By determining what goes missing in human cells when the gene that is most commonly mutated in pancreatic cancer gets turned on, Johns Hopkins scientists have discovered a potential strategy for therapy.

The production of a particular cluster of genetic snippets known as microRNAs is dramatically reduced in human pancreatic tumor cells compared to healthy tissue, the researchers report in a study published Dec. 15 in Genes and Development. When the team restored this tiny regulator, called miR-143/145, back to normal levels in human pancreatic cancer cells, those cells lost their ability to form tumors.

"Our finding that these specific microRNAs are downstream of the most important oncogene in pancreatic cancer sets the stage for developing methods to deliver them to tumors," says Josh Mendell, M.D., Ph.D., an associate professor in the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, and an early career scientist of the Howard Hughes Medical Institute. "When we restore microRNAs to cancer cells in which their levels are repressed, the cells no longer are tumorigenic. We have every reason to believe that the efficient delivery of miR-143/145, if achievable, would be therapeutically beneficial."

The team focused its investigation on KRAS, a member of the important RAS family of oncogenes that is mutated in almost all cases of the most common form of pancreatic cancer.

The researchers conducted their studies in a multitude of model systems - human cells growing in culture as well as those harvested directly from tumors, and also in mice and zebrafish. First, using cell lines derived from pancreatic tumors and growing in culture, they added gene products such as mutant KRAS and an inhibitor of mutant KRAS, and then measured the microRNA responses.

Next, they conducted the same experiments using cells from patients' pancreatic tumors. Finally, they looked at pancreatic tissue from mice and zebrafish to see what happened when KRAS was activated.

Every time, the team noted the same robust findings. When KRAS was activated, the microRNA cluster miR-143/145 was powerfully repressed, to a fraction of the levels in normal, non-cancerous cells. Restoring the expression of miR-143/145 back to the level of normal cells was sufficient to confer "a very striking change in behavior of those cells," Mendell says. When human pancreatic cancer cells with low microRNA levels were injected into mice, they formed tumors within 30 days. However, when the team restored the levels of microRNAs to the levels of normal cells and injected them into mice, tumors failed to form.

"Our findings showed that repression of the miR-143/145 microRNA cluster is a very important component of the tumor-promoting cellular program that is activated when KRAS is mutated in cancer cells," says Oliver Kent, a postdoctoral fellow in the Mendell laboratory and first author on the paper.

At some point in the process of a normal cell evolving into a tumor cell, it loses microRNAs. When the KRAS gene is mutated - a common event in pancreatic cancer - it somehow purges cells of miR-143/145, the cluster of microRNAs that normally put the brakes on tumorigenesis.

"It is likely that some microRNAs will have very broad antitumorigenic effects in many different types of cancers," says Mendell, whose lab is building animal models to investigate how different microRNAs participate in different tumor types. "In fact, there is already evidence that miR-143/145 can suppress other types of tumors such as colon and prostate cancer. On the other hand, the effects of some microRNAs will likely be very tumor-specific."

Merely 22 nucleotides in length, microRNAs are enigmatic bits of genetic material that, despite being pint-sized, apparently are mighty. This field of study is less than a decade old; scientists still don't have a good grasp on the fundamental role of microRNAs in normal biology.

"We need a better understanding of their basic functions to more fully understand how microRNAs participate in diseases," Mendell says.

Having studied microRNAs in the context of several types of cancer, Mendell says delivery remains a major issue for nucleic acid-based therapies.

"There is a lot of work going on to develop ways to deliver microRNAs to different tissue sites," Mendell says. "I'm optimistic that the liver and even the pancreas will become accessible to these types of therapies and benefit from them."

More information: Genes and Development: genesdev.cshlp.org/

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