A new therapeutic vulnerability in pancreatic cancer

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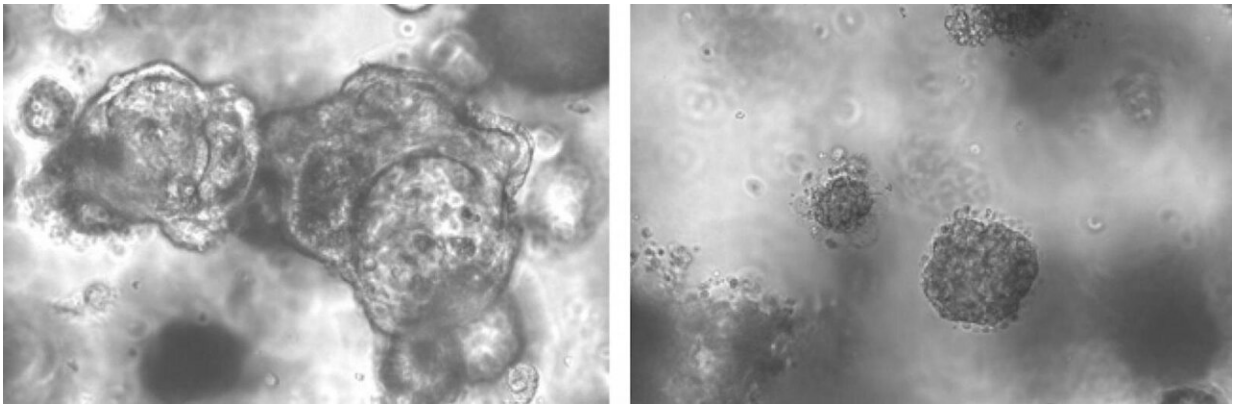

Organoids of human pancreatic cancer treated with anti-PTHrP antibodies (right) vs untreated (left). Credit: Jason Pitarresi, PhD.

Lowering levels of a hormone called PTHrP can prevent metastases and improve survival in mice with pancreatic cancer and could lead to a new way to treat patients, according to a study from cancer researchers at Columbia University Vagelos College of Physicians and Surgeons and Herbert Irving Comprehensive Cancer Center and with collaborators at the University of Pennsylvania.

When patients are first diagnosed with pancreatic cancer, the cancer usually has spread to other organs. Because of these metastases, nearly all patients will succumb to their cancer within one year of diagnosis, but

no drugs exist to prevent metastasis.

In an effort to find treatments, cancer researchers at Columbia—led by Anil K. Rustgi, MD, and Jason R. Pitarresi, Ph.D.—investigated a hormone called PTHrP. Although PTHrP (parathyroid hormone-related protein) is often highly active in patients with pancreatic cancer, its role in metastasis was unclear.

Loss of PTHrP dramatically improves survival in mice

The researchers first manipulated the levels of PTHrP in mice with pancreatic cancer. Elimination of PTHrP from mice—with genetic engineering or with an antibody that targets the hormone—not only eliminated metastasis and enhanced overall survival, but also dramatically reduced the size of the initial tumors in the pancreas.

Even in mice with a highly aggressive form of pancreatic cancer, the increase in survival was dramatic, increasing from a median of 111 days to 192 days, with near complete elimination of metastases. The 73% increase in survival, the researchers say, is one of the largest observed in mice with this type of pancreatic cancer, which closely resembles human cancers.

The striking results with mice led the researchers to test the anti-PTHrP antibodies in human pancreatic cancer cells. The results from these experiments were also encouraging: Among 3-D organoids derived from pancreatic cancer patients under an IRB-approved protocol, anti-PTHrP antibodies greatly reduced growth and viability of the cells.

Two-pronged attack on cell growth and metastasis

Targeting PTHrP attacks pancreatic cancer in two ways, the researchers

say. It reduces the ability of the tumor cells to transition from an epithelial state to a mesenchymal state, which is necessary for the creation of new metastases. And targeting PTHrP also prevents the growth of primary and secondary tumors.

"We think these findings provide a strong rationale for further developing anti-PTHrP therapy towards clinical trials," says Rustgi, who adds that the antibody used in the study has the potential to be used in people and credits Richard Kremer, MD, Ph.D., of McGill University for developing the antibodies.

"We are hopeful that a drug targeting PTHrP could be used to treat most patients with pancreatic cancer," he says, "because the vast majority have tumors with high levels of PTHrP. There is the potential application to other cancers as well."

Potential with other cancers

The researchers originally began investigating PTHrP because its gene is often amplified when another nearby gene, KRAS, is amplified. KRAS has long been recognized as a cancer-promoting gene in pancreatic and other cancers.

For patients, that may mean anti-PTHrP therapies may have potential in other cancers that are known to harbor KRAS amplifications.

For researchers, the finding also suggests a wider search for cancer-causing genes is needed.

"We feel that PTHrP may have been previously overlooked as a mere passenger gene co-amplified with KRAS, but our study shows that PTHrP has its own tumor-promoting functions," Pitarresi says. "It suggests other so-called 'passenger' genes may have bigger roles in

cancer than we initially thought and should be examined more closely." Rustgi notes "it might open up for combinatorial therapies of targeting the KRAS pathway with an antibody to PTHrP."

More information: Jason R. Pitarresi et al, PTHrP Drives Pancreatic Cancer Growth and Metastasis and Reveals a New Therapeutic Vulnerability, *Cancer Discovery* (2021). DOI: 10.1158/2159-8290.CD-20-1098

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