Innovative therapy strategy for pancreatic cancer uses engineered exosomes targeting mutated KRAS gene

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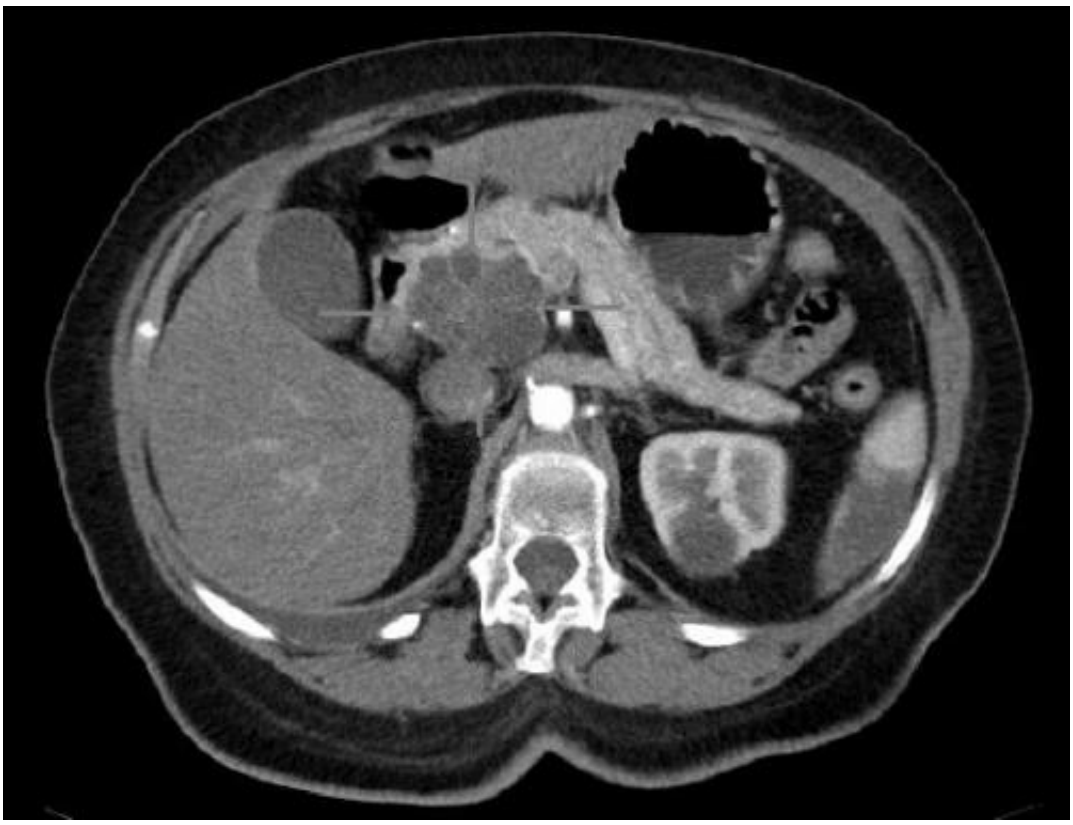

Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

Genetic manipulation of exosomes, virus-sized particles released by all cells, may offer a new therapeutic approach to treating pancreatic

cancer, according to a study at The University of Texas MD Anderson Cancer Center.

Findings from the study, led by Valerie LeBleu, Ph.D., assistant professor of Cancer Biology, and Sushrut Kamerkar, Ph.D., assistant student in the MD Anderson UT Health Graduate School of Biomedical Sciences and the Cancer Biology Program, were published in the June 7 online issue of *Nature*.

Earlier MD Anderson investigations demonstrated exosomes as a factor in detecting pancreatic cancer, but these latest findings reveal genetically altered exosomes as a potentially novel approach for direct and specific targeting of mutated KRAS, the cancer gene commonly linked to pancreatic cancer.

In the study, exosomes, which are generated by all cells and are naturally present in blood, were modified as "iExosomes," capable of delivering small RNA to specifically target mutant KRAS, resulting in disease suppression and increased overall survival in mouse models. The investigators utilized a targeting method called RNA interference (RNAi) which, when delivered via these natural nanoparticles or exosomes, zero in on mutant KRAS in pancreas cancer cells, impacting tumor burden and survival in multiple pancreas cancer models. The team showed that exosomes could serve as an efficient carrier of RNAi, given that these nano-sized vesicles easily travel across the body and enter cells, including cancer cells.

When mutated, KRAS acts as a molecular on-off switch that gets stuck in an "on" position. It is mutated in 80 to 95 percent of pancreatic ductal adenocarcinomas (PDAC), the most frequent mutation in this cancer. The study demonstrated that iExosomes were able to deliver KRAS-specific targeting genetic material called siRNA and shRNA, and were more efficient than their synthetic counterpart, iLiposomes, which do

not present with the natural complexities and advantages that exosomes display.

"Our studies suggest that exosomes exhibit a superior ability to deliver siRNA molecules and suppress aggressive pancreatic tumor growth when compared to liposomes," said LeBleu. "We also demonstrated that the presence of CD47 on exosomes' allows for evasion from phagocytosis by the circulating monocytes."

CD47 is a protein involved in many cellular processes, including cell death, growth and migration. Phagocytosis is a process by which white blood cells called macrophages digest cellular debris and foreign bodies and particles. Monocytes are the largest kind of white blood cell important to the immune system.

"CD47 basically initiates a 'don't eat me' signal that inhibits phagocytosis," said Kamerkar. "We identified how CD47 contributes to suppressing exosomes clearance from circulation, and enhancing their delivery to pancreatic cancer cells."

Despite current standard of care, the prognosis for patients with PDAC is poor and effective new therapies are needed. PDAC genetic analyses show that KRAS mutations are encountered in a majority of patients and play a significant role in cancer initiation, progression and metastasis. Dampening oncogenic KRAS using genetic manipulation in mice inhibited tumor progression despite the presence of other genetic defects. Until this study, a direct and specific targeting of KRAS has been elusive.

The team also showed that the cellular process macropinocytosis, which participates in cell scavenging nutrients and vesicles, contributes to exosomes uptake in cancer cells with mutant KRAS.

"The increased number of exosomes reaching the pancreas may gain further advantage to enter KRAS-associated cancer cells as a result of enhanced macropinocytosis, which concurs with previous findings," said Kamerkar. "Our results also support an efficient uptake of iExosomes despite the dense stroma in pancreatic tumors. Further study is needed to gain a better understanding about whether exosomes entering cells via macropinocytosis have other features that could enhance their anti-tumor capabilities."

More information: Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer, *Nature* (2017). nature.com/articles/doi:10.1038/nature22341

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