'Collateral' lethality may offer new therapeutic approach for cancers of the pancreas, stomach and colon

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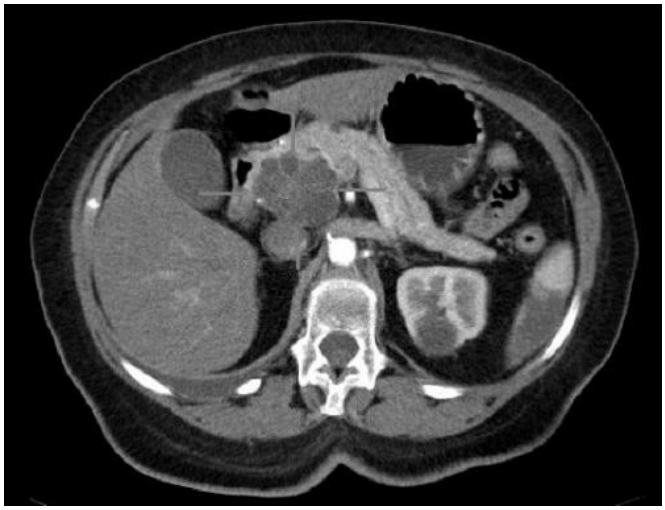

Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

Cancer cells often delete genes that normally suppress tumor formation. These deletions also may extend to neighboring genes, an event known as "collateral lethality," which may create new options for development of therapies for several cancers.

Scientists at The University of Texas MD Anderson Cancer Center have discovered that during early cancer development when a common tumor suppressor known as SMAD4 is deleted, a nearby metabolic enzyme gene called malic enzyme 2 (ME2) also is eradicated, suggesting the possibility of malic enzyme inhibitors as a novel therapy approach. Study findings were published in the Jan. 18 online issue of *Nature*.

"In an effort to expand therapeutic strategies beyond oncogenic targets to those not directly linked to cancer development, we have identified collateral lethal vulnerability in pancreatic cancers that can be targeted pharmacologically in certain patient populations," said Prasenjit Dey, Ph.D., postdoctoral fellow in Cancer Biology and co-author of the *Nature* article. "Genomic data across several cancers further suggest this therapeutic strategy may aid many cancer patients, including those with stomach and colon cancers."

Collateral lethality occurs when tumor suppressor genes are deleted, a nearly universal occurrence in cancer. Correspondingly, a large number of genes with no direct role in tumor progression also are deleted as a result of their proximity to tumor suppressor genes.

SMAD4 is deleted in one-third of pancreatic cancers. The research team found that when the SMAD4 gene is eradicated in mice, it also results in depletion of ME2 levels. The genetic depletion of ME3, a sister gene to ME2, sets off a complex chain of events that ultimately regulates an amino acid group called branched chain amino acid (BCAA), which are crucial to cancer's ability to thrive. Thus, if a therapy could be developed that inhibits ME3, it might prevent ME2-deleted tumor growth.

"Our work suggests a mechanism for cell lethality involving the regulation of BCAAs as crucial elements in pancreatic cancer by regulating ME3," said Ronald DePinho, M.D., professor of Cancer Biology, senior author of the *Nature* paper and president of MD Anderson. "We propose that highly specific ME3 inhibitors could provide an effective therapy for many cancer patients, but more research must be done."

More information: Genomic deletion of malic enzyme 2 confers collateral lethality in pancreatic

cancer, *Nature*,
nature.com/articles/doi:10.1038/nature21052

Provided by University of Texas M. D. Anderson Cancer Center