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Scientists track metabolic pathways to find drug combination for pancreatic cancer

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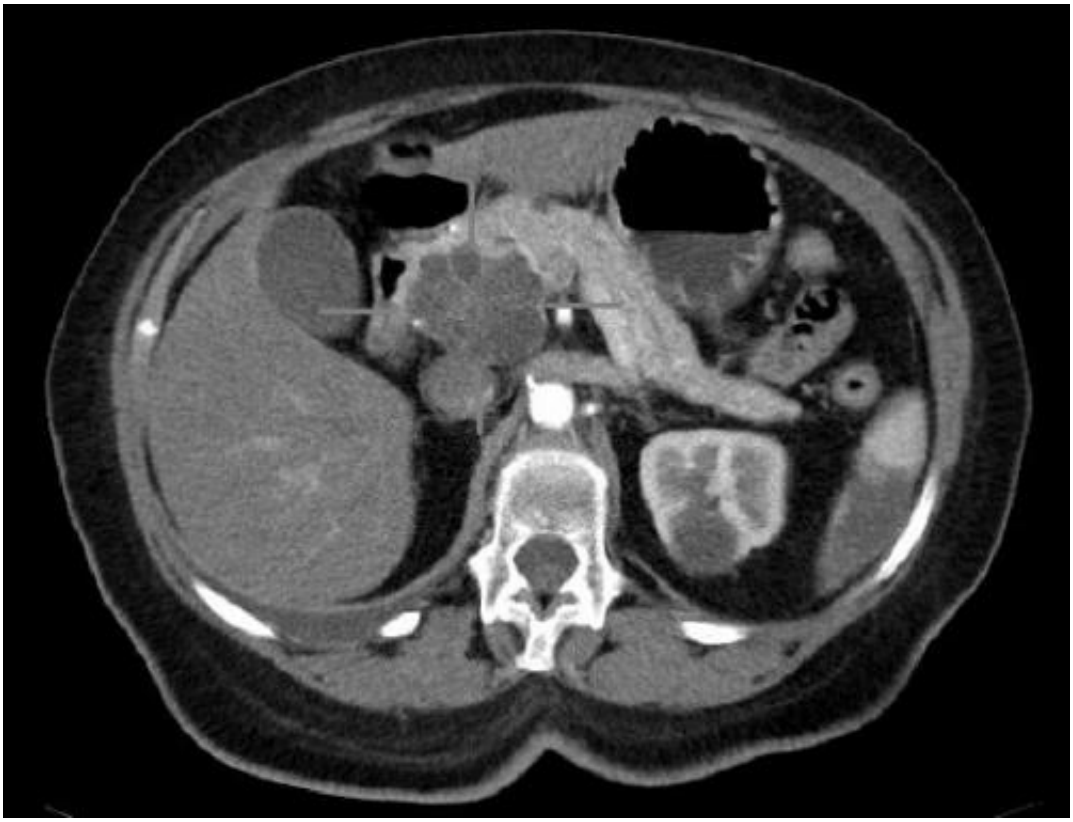

Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

Cancer researchers have long observed the value of treating patients with combinations of anti-cancer drugs that work better than single drug treatments. Now, in a new study using laboratory-grown cells and mice,

Johns Hopkins scientists report that a method they used to track metabolic pathways heavily favored by cancer cells provides scientific evidence for combining anti-cancer drugs, including one in a nanoparticle format developed at Johns Hopkins, that specifically target those pathways.

"We have to hit cancer cells from more than one angle, and that's made it important to learn how to combine drugs that hit the right combination of pathways," says Anne Le, M.D., H.D.R., assistant professor of pathology at the Johns Hopkins University School of Medicine and member of the Johns Hopkins Kimmel Cancer Center.

Le says that the study of so-called metabolomics to track biochemical reactions in cancer and other cells should help scientists decide how best to combine drugs. A report of the scientists' work will appear online the week of Aug. 22 in *Proceedings of the National Academy of Sciences*.

For the study, Le and her collaborators at Johns Hopkins, including Barbara Slusher, Ph.D., an expert in drug discovery, and Justin Hanes, Ph.D., a nanomedicine expert, started with an experimental drug called BPTES and injected it in mice with implanted human pancreatic tumors. BPTES has been used in animal models for a variety of cancers but has not substantially reduced tumor sizes, probably because the drug concentration in tumor tissue is not high enough when using conventional drug formulation methods, say the scientists.

With this in mind, scientists from the Center for Nanomedicine at Johns Hopkins, led by Hanes, encapsulated the BPTES in a nanoparticle capsule coated in polyethylene glycol, a molecule used widely in medicines and industrial products, using a method they developed to provide a more uniform coating. The nanoparticle, according to the scientists, helps the drug slip through capillaries near cancer cells and remain within the tumor longer than it would otherwise.

After 16 days, eight mice treated with encapsulated BPTES had tumors half the size of another eight mice treated with nanoparticles containing no drug. BPTES not encased in the nanoparticle delivery system had little effect on tumor size in 12 human tumor-bearing mice. "This shows that the nanoparticle-encapsulated drug is more effective in tumor reduction than the drug alone in these animal models," says Le.

But their overriding interest in BPTES, says Slusher, was in how it works: by blocking the production of glutamine, an amino acid that acts as a building block of cells and is used frequently by pancreatic cancers to create more cancer cells. When the Johns Hopkins scientists saw that their nanoparticle-encapsulated version of BPTES shrunk mice tumors by half, Le and her colleagues searched for what major metabolic pathway was driving the growth of the remaining half of the tumor.

To find it, the scientists injected the eight tumor-bearing mice with high levels of labeled glutamine and glucose, another metabolic compound commonly linked to the growth of pancreatic cancer cells. They then traced the compounds' biochemical breakdown through the mice and found that the remaining tumor cells had high amounts of lactate, an end product of the glucose pathway.

With this information, the scientists tested the glucose-blocking anti-diabetes drug metformin, combined with the nanoparticle-encapsulated BPTES, on another eight mice implanted with human pancreatic tumors. The drug combination shrunk tumors by at least 50 percent more than those treated with either drug alone.

Researchers elsewhere have been testing metformin in pancreatic cancer patients with little success, says Le, despite indications that it's a good candidate to treat glucose-dependent tumors. "But it appears the key may be to combine it with other drugs to shut off multiple key pathways in those tumors," she adds.

The scientists have filed a patent for the technology associated with nanoparticle-encapsulated BPTES. The drug's chemical name is bis-2-(5-phenylacetamido-1,2.4-thiadiazol-2yl)ethyl sulfide.

More information: Combination therapy with BPTES nanoparticles and metformin targets the metabolic heterogeneity of pancreatic cancer, *Proceedings of the National Academy of Sciences*, www.pnas.org/cgi/doi/10.1073/pnas.1611406113

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