Scientists find one-two punch for preclinical cancer models

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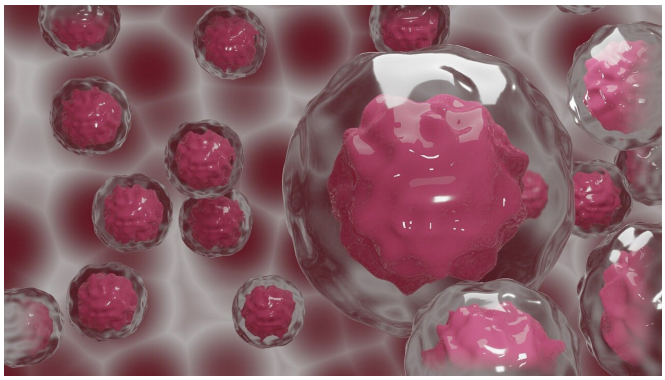

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A one-two punch of changing gene expression, then deploying immune checkpoint inhibitors, shows promise in battling one of the most treatment-resistant types of cancer in preclinical models, according to a new publication including authors from the Hackensack Meridian Center for Discovery and Innovation (CDI).

Their research findings published Aug. 14 in the journal *Cancer Research* suggest that since some cancer treatments can be undermined by epigenetic changes (altered DNA methylation affecting gene expression) in cancer cells before the treatments are even administered, a worthwhile strategy is to administer an epigenetically-acting drug—which can pave the way for more effective subsequent use of immune-acting cancer treatments, the authors found.

"Overall, these findings in a model of aggressive pancreatic cancer have clear and promising implications for the design of future studies, both in mice and in human patients, to improve the effectiveness of epigenetic modulation, in combination with immune checkpoint inhibition," said Benjamin Tycko, M.D., Ph.D., the CDI lab director who oversaw the study, along with his longtime colleague Tamas Gonda, M.D. "They also suggest a clear path forward for making further improvements."

The tumor type—pancreatic ductal adenocarcinoma—is among the most deadly cancer types, since it has proven to be stubbornly resistant both to standard chemotherapy and more recent immunotherapies.

The researchers tested four protocols, which included the sequential use of decitabine, a DNA-hypomethylating drug, followed by immune checkpoint inhibitors. Among the effects documented in the data: the increase in crucial, and tumor-infiltrating, effector T cells, with this one-two punch.

Compared against the control group, there were no adverse side effects of adding decitabine, and the one-two punch of decitabine and the immune-acting agents doubled the average survival time in the model.

However, treatment was still not a cure, and the cancers ultimately progressed—perhaps partly because of a decitabine-induced increase in M2 macrophages, immune system cells which can inhibit therapeutic responses.

The researchers' work continues, with further strategies including adding other epigenetic drugs, and also discovering ways to reduce the number of M2 macrophages—to potentially improve the response.

More information: Tamas A. Gonda et al, A DNA hypomethylating drug alters the tumor microenvironment and improves the effectiveness of immune checkpoint inhibitors in a mouse model of pancreatic cancer, *Cancer Research* (2020). DOI: 10.1158/0008-5472.CAN-20-0285

Provided by Hackensack Meridian Health

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