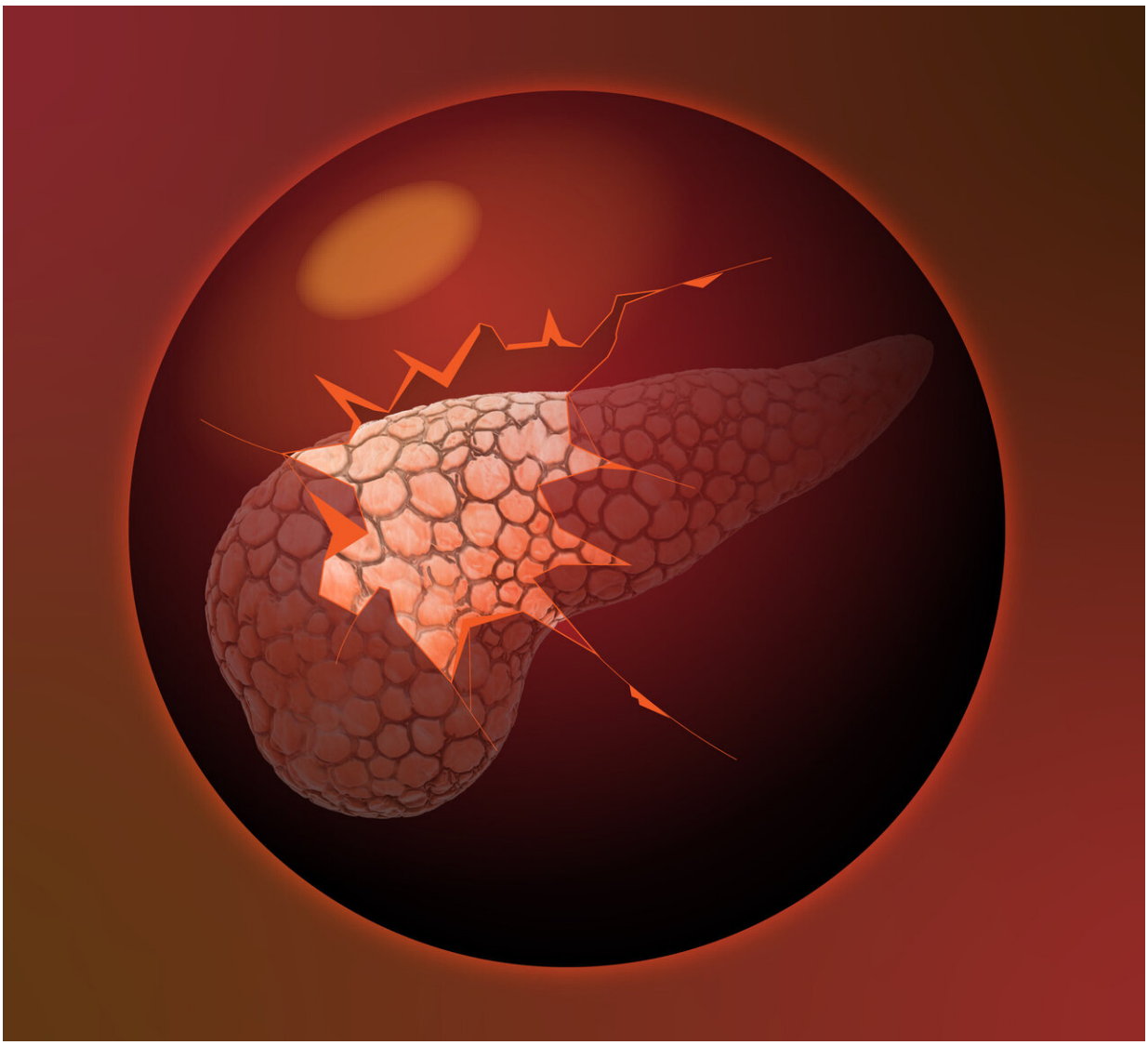
Chemoresistance in pancreatic cancer: Disrupting cellular metabolism offers potential treatment

January 24 2020, by Suman Mukhopadhyay



Artist’s conceptual depiction of a pancreatic cancer cell which is hard to treat. Credit: Suman Mukhopadhyay

Pancreatic cancer is one of the most formidable human malignancies.

Current therapeutic options are limited, and the National Cancer Institute estimates that only one in 10 patients survives for five years after starting treatment. Many pancreatic tumors resist chemotherapies, which poses a significant clinical challenge for doctors and patients and contributes to a high rate of recurrence.

Mutated KRAS proteins are a critical driver of pancreatic cancer, and studies have linked them to altered metabolism in pancreatic tumor cells. Tumors harboring these cancer-causing mutations remain among the most difficult to treat, so there is an urgent need for effective therapies.

I and my colleagues at the Frederick National Laboratory for Cancer Research, working as part of the National Cancer Institute's RAS Initiative, have identified a novel way to boost the effectiveness of chemotherapy on pancreatic cancer cell lines and in a laboratory model of pancreatic cancer.

Our strategy targets and inhibits glutamine metabolism, specifically a pathway marker called GLS1, to disrupt the pathway that makes the cancer cells resistant to chemotherapeutic drugs. Future studies may show that this strategy, when used in combination with chemotherapy, creates a distinct opportunity for treatment and opens a new route for combating resistance to chemotherapy.

Our team, led by Frank McCormick, Ph.D., FRS, D.Sc. (Hon), RAS national program advisor at the Frederick National Laboratory and

professor emeritus, UCSF Helen Diller Family Comprehensive Cancer Center, assessed the relationship between metabolic signaling and the KRAS-driven cancer cells' survival. We found that the cells are uniquely dependent on metabolic activities to resist current chemotherapies. In particular, we pinpointed an association between glutamine metabolism and NRF2, a master regulator of the antioxidant system, which is critical for the cancer cells' protection. Our investigation revealed that high levels of NRF2 on pancreatic cancer cells are associated with poor prognosis, and furthermore, that altering those levels by inhibiting glutamine metabolism helps regulate the cells' sensitivity to chemotherapy.

Importantly, we also observed that manipulating glutamine metabolism restrains the assembly of stress granules, which are an indicator of resistance to chemotherapy.

Our team tested the combination therapy in mice by using glutaminase inhibitors alongside gemcitabine, a first-line chemotherapy. The results were encouraging: The treated mice lived longer, and tumor size decreased compared to untreated mice, supporting the idea that glutamine inhibition improves the effectiveness of chemotherapy.

The work demonstrates the feasibility of making pancreatic tumors susceptible by exploiting the reprogrammed metabolic processes in KRAS-mutant cancer cells. The findings are published in *Cancer Research*, a journal of the American Association for Cancer Research.

As first author of the study, I believe further research is warranted to determine if this represents a therapeutic intervention for the significant percentage of pancreatic cancer patients harboring KRAS mutations that, to date, have been resistant to current therapies.

Additionally, it will be worthwhile in future studies to evaluate whether

the findings from this work have implications for cancers with similar KRAS mutations.

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More information: Suman Mukhopadhyay et al. Undermining glutaminolysis bolsters chemotherapy while NRF2 promotes chemoresistance in KRAS-driven pancreatic cancers, *Cancer Research* (2020). DOI: 10.1158/0008-5472.CAN-19-1363