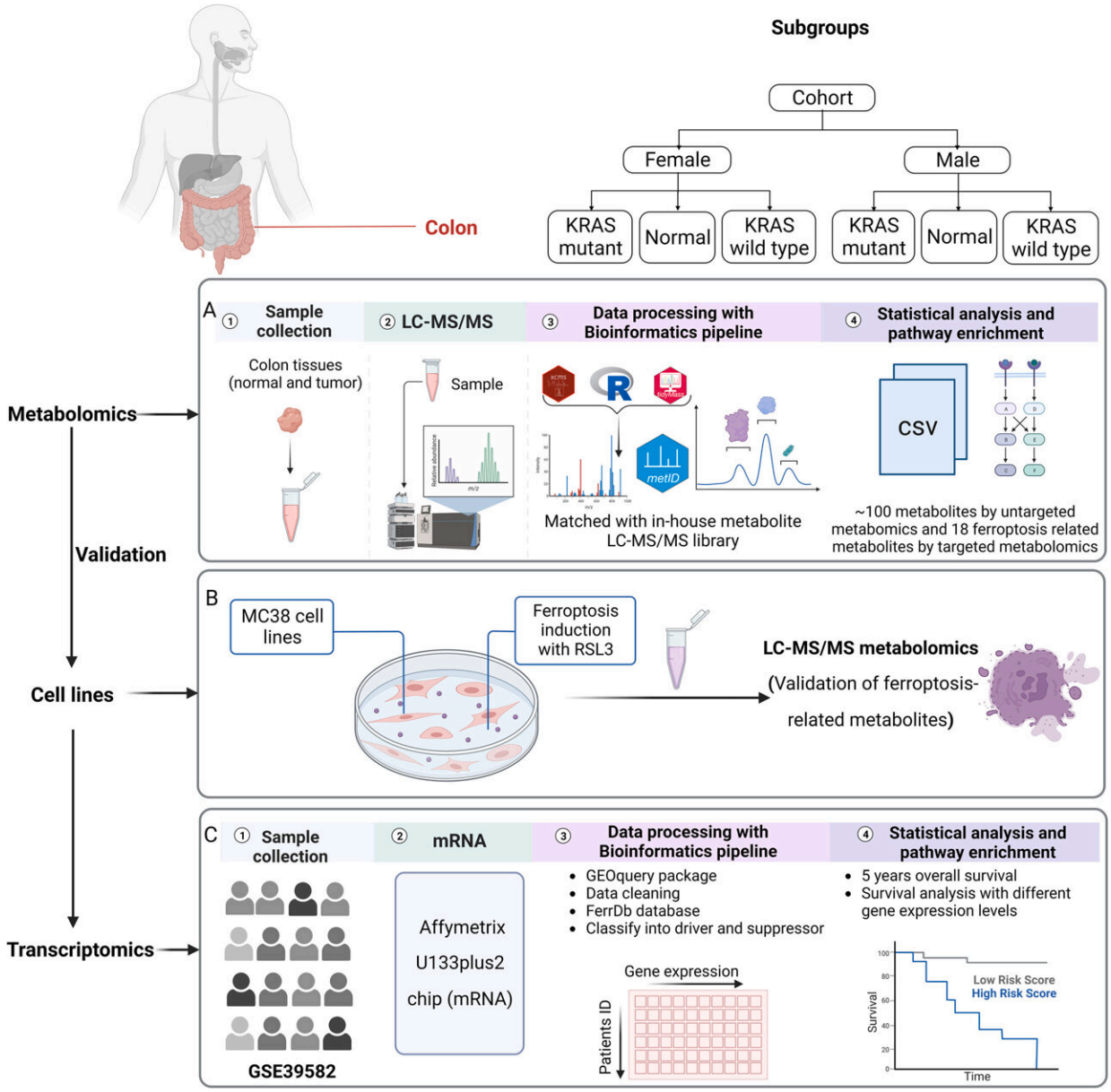
Study reveals potential target for precision colorectal cancer treatment

April 26 2023, by Mallory Locklear



Flowchart outlining the study. A: Metabolomics data collection and analysis; including targeted analysis of metabolites involved in ferroptosis pathways; B: Identification of ferroptosis metabolic phenotype in RSL3 treated MC38 cell lines; C: Validation with transcriptomics data from a publicly available dataset. Credit: *Redox Biology* (2023). DOI: 10.1016/j.redox.2023.102699

Around 40% of colorectal cancer patients have a particular gene mutation. A new study shows it's linked to reduced cell death and worse survival rates in men.

Colorectal tumors found in men with a certain genetic mutation display different metabolism than those found in other patients, according to a new Yale study. One key difference in these tumors, the researchers discovered, is a reduced tendency to undergo cell death, a finding that may reveal a potential new avenue for precision colorectal cancer treatment.

The study was published April 20 in the journal *Redox Biology*.

Cancer cells undergo metabolic changes in order to generate the fuel they need to grow and replicate.

"The tumor adapts to survive, so it will actually rewire metabolism to ensure that it can stay alive and grow," said Caroline Johnson, associate professor of epidemiology at Yale School of Public Health and co-senior author of the study.

Because these metabolic changes are so critical for the survival of cancer cells, they can also be targets for treatment, researchers say.

Around 40% of patients with colorectal cancer have a mutation in a gene

known as KRAS. When not mutated, the KRAS gene encodes for a protein that promotes normal cell growth and division. But mutated versions of the gene are linked to several types of cancer, including lung cancer, pancreatic cancer, and colorectal cancer.

Colorectal tumors with this mutation are more drug resistant than others, making them more difficult to treat.

The Yale researchers wondered whether metabolic differences might play a role.

"Our aim was to see if there were specific altered metabolic pathways in tumors with KRAS mutations," said Hong Yan, a postdoctoral associate in Johnson's lab and lead author of the study.

For the study, the researchers used tissue samples from 200 patients, including colon tissue samples from 39 healthy patients, tumor samples from 60 patients with KRAS mutations, and tumor samples from 101 patients without KRAS mutations. They then analyzed the metabolites—small molecules produced through various biological processes—found in those tissues.

They found that not only were there metabolite differences between tumors and healthy tissue, there were also differences between the tumors found in men and those found in women and between the tumors of men with KRAS mutations and men without.

Further analysis revealed that compared to other patients, men with KRAS mutations had tumor cells with suppressed ferroptosis, which is a type of cell death.

"You want cell death to be occurring in cancer. You want the drugs to be killing the cells. So it's important to have ferroptosis occurring," said

Johnson.

In a separate dataset, the researchers looked at genes that regulate ferroptosis in cells. Bolstering their initial finding, they observed that expression of those genes differed between KRAS-mutated tumors in men and tumors found in other patients.

Greater expression of some of these genes were also linked to poorer five-year survival rates for male colorectal cancer patients with KRAS mutations, the researchers said.

"Our findings were quite unexpected," said Yan. "Particularly the gene expression differences, which were strong."

The results also may yield new opportunities for colorectal cancer treatment, said the researchers.

"It reveals a new target for precision-based treatment," said Johnson. "We may be able to tailor treatment based on sex and mutation status."

In the future, for instance, a drug that targets ferroptosis could be used to treat men with KRAS mutations. Among the first steps toward that goal, said Johnson, would be to validate these findings in additional patient samples and use mouse models to answer more targeted questions, both of which her lab is exploring.

"We're also using machine learning to identify additional biomarkers related to colorectal cancer," said Yan.

Other Yale authors include Ronan Talty, Abhishek Jain, Yuping Cai, Jie Zheng, Xinyi Shen, Marcus Bosenberg, and Sajid Khan.

More information: Hong Yan et al, Discovery of decreased

ferroptosis in male colorectal cancer patients with KRAS mutations, *Redox Biology* (2023). DOI: 10.1016/j.redox.2023.102699