New approaches to treating diverse bile duct cancers prevalent in southeast Asia

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An international study has effectively targeted three distinct groups in cholangiocarcinoma (CCA)—or cancer of the bile duct—with drug inhibitors. These findings, published in the journal *Gut*, deepen our understanding of the mechanisms that cause CCA to develop and propose new therapeutic targets for this lethal disease. This research is of particular relevance to the Southeast Asian region, where bile duct

cancer is endemic.

CCA is widespread in the Northeast of Thailand, and neighboring Laos and Cambodia. In that region, it is typically caused by exposure to a liver fluke parasite, which is transmitted by eating raw or undercooked fish. Alarmingly, CCA incidence is also on the rise in Taiwan, Korea and China, where bile duct inflammation, hepatitis, liver stones or exposure to the herbal carcinogen aristolochic acid are among the potential causes of the disease.

As incidence rises worldwide, so too does the need to detect the disease early and improve treatments. Currently, chemotherapy is the first-line treatment for CCA, and targeted therapy and immunotherapy are second line treatments. Unfortunately, all are largely ineffective, and most patients have a poor prognosis with five-year survival rates of only 5%.

Noting the urgent clinical need for new and effective therapies for CCA, a team of scientists from the National Cancer Center Singapore (NCCS), Duke-NUS Medical School, A*STAR's Genome Institute of Singapore (GIS), Sun Yat-sen University (Guangzhou, China) and Khon Kaen University (Thailand) sought to understand how they could target the dysregulation and genomic abnormalities that causes CCA formation.

In 2017, the same team identified different subtypes of CCA, with different causes, mutations and DNA activity, as part of a major international effort to improve understanding of CCA led by the International Cancer Genome Consortium (ICGC).

In their latest study, the team built on their previous study and looked at enhancer activities, which control regulatory DNA sequences responsible for switching genes on or off, in the different CCA subtypes. They found that the enhancer activities rely on different pathways that could potentially be targeted with drugs.

The first group, linked to the liver fluke parasite, had increased activity in estrogen signaling. The second group of CCAs, not caused by the liver fluke parasite, showed higher activity in a pathway related to metabolism. The third group is related to immune activities and may be linked to the consumption of herbal plants containing aristolochic acid.

The researchers discovered that specific treatments targeting these different pathways slowed the growth of these cancers in experimental models. Drugs that block MTOR were effective against the first group, while inhibitors of oxidative phosphorylation worked better against the second group.

"There are currently no effective targeted treatments for CCA patients, resulting in dismal prognoses. Our latest research presents novel therapeutic approaches in the personalized treatment of CCA, showing that it's possible to use multiomic profiling to segment patients into groups and tailor treatment accordingly using targeted therapies that are effective for the type of CCA identified," said Professor Teh Bin Tean, Deputy Chief Executive Officer (Research) at NCCS and a co-senior author of the study.

"By bringing together the best experts in the field, integrating cutting-edge multiomics technologies and interrogating CCA through fresh approaches, our research has yielded insights that may pave the way for more targeted, personalized treatments that can prolong and improve patients' lives," said Professor Patrick Tan, Senior Vice-Dean for Research at Duke-NUS and a co-author of the study.

"As clinicians and scientists, it is incredibly rewarding to see our research translate from lab to bedside. We hope our findings will open new therapeutic avenues and spur progress against this difficult-to-treat cancer that impacts many in Singapore and beyond."

The scientists hope the results will accelerate the clinical development of personalized therapies for CCA patients. The use of multiple latest and cutting-edge technologies, including VISIUM, VECTRA and tissue ChiP-Sequencing in this study, enabled better understanding of this challenging disease to accelerate the discovery of new therapeutic strategies.

The team plans to advance personalized drug development for CCA patients and bring novel drugs targeting different groups of CCA patients to clinical trials in the near future.

More information: Jing Han Hong et al, Integrative multiomics enhancer activity profiling identifies therapeutic vulnerabilities in cholangiocarcinoma of different etiologies, *Gut* (2023). DOI: 10.1136/gutjnl-2023-330483

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