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Molecular dissection of bile duct cancer reveals subtypes with different origins and varying potential treatments

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Researchers have discovered that cholangiocarcinoma (CCA), a form of liver cancer also known as bile duct cancer, consists of several molecular subtypes with distinct potential therapies and prognoses.

An international collaboration led by Patrick Tan of A*STAR's Biomedical Research Council, analyzed tumors collected from almost 500 bile duct cancer patients in 10 countries, in a study that is part of the International Cancer Genome Consortium. By examining a large, diverse group, the researchers were able to uncover patterns missed in earlier investigations, such as one that included only North American patients, all of whom were free of the liver-fluke infection that is a common catalyst for bile duct cancer in Southeast Asian patients.

Using modern high-throughput DNA sequencing, the team investigated the genomic sequences of the tumors and their epigenomic and gene expression profiles. They divided the cancers into four groups with different patterns of mutations and other genetic defects, two of which were associated with liver-fluke infection. "The current way of classifying CCAs is by their anatomical subtype. Our data shows that if you look at molecular data, you get more clinically relevant subtypes that have different potential therapies and prognoses," says Bin Tean Teh of the National Cancer Centre Singapore, one of the study's senior authors.

One of the clusters was characterized by changes in genes associated

with immune response, suggesting that it might be a candidate for immunotherapy treatment. Likewise, the characteristics of some of the tumors indicated that they might respond to therapeutic interventions currently in use or under development. "We've shown that about a third of the patients can be treated using existing therapies, if experimental drugs were included it would be even more", says lead author, Apinya Jusakul. Currently, surgery is the only treatment for bile duct cancer.

The molecular clusters can also guide researchers in understanding the development of CCA. Two of the clusters had an excess of methylation, a DNA modification. Differences in the methylation patterns offer clues about the processes acting in each cluster. "Based on molecular data, we can speculate about the different mechanisms leading to different DNA changes in the development of CCA. You really can't see that from just the anatomical information," says co-lead author Chern Han Yong.

These findings demonstrate that distinct molecular subtypes can result from different cancer triggers. Learning more about these subtypes and how they link with various carcinogenic processes may reveal the mechanisms behind these cancers and guide the development of therapeutic interventions.

More information: Apinya Jusakul et al. Whole-Genome and Epigenomic Landscapes of Etiologically Distinct Subtypes of Cholangiocarcinoma, *Cancer Discovery* (2017). DOI: 10.1158/2159-8290.CD-17-0368

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