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Researchers expose molecular secrets of bile duct cancers from different countries

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Singapore-led scientific team discovers critical genes in bile duct cancers from different parts of the world. New molecular insights point to potentially different treatment regimens for the same cancer type depending on underlying genetic alterations.

A team of scientists from the National Cancer Centre Singapore, Duke-NUS Graduate Medical School Singapore, Fundeni Clinical Institute (Romania) and Koen Kaen University (Thailand), have made a seminal breakthrough in understanding the molecular basis of bile duct cancer or cholangiocarcinoma, a rare but highly lethal form of liver cancer. The team, led by Professors Teh Bin Tean, Patrick Tan, Steve Rozen, Irinel Popescu and Vajaraphongsa Bhudhisawasdi, used advanced DNA sequencing technologies to map the complete repertoire of human genes disrupted in cholangiocarcinoma.

The team's findings may lead to new cholangiocarcinoma treatments, and have shed light on some of the oldest questions in cancer research. The group is also affiliated with the Genome Institute of Singapore and the Cancer Science Institute in Singapore. This work was published online today in the scientific journal *Nature Genetics*.

Cholangiocarcinoma (CCA), is a cancer involving uncontrolled growth of the bile ducts, the part of the liver that drains bile into the intestine. In most countries, CCA is considered a rare cancer, but the incidence of CCA is rising worldwide and in certain countries such as the North East of Thailand and neighbouring Laos, CCA is already widespread due to

patients in this region being exposed to liver flukes. Other potential causes of CCA include bile duct inflammation, congenital cysts, hepatitis, and the presence of liver stones. Patients diagnosed with CCA have a dismal prognosis as the disease is considered incurable, with a 5-year survival rate of 5%.

New Potential Avenues for Treatment

By studying CCAs from Singapore, Thailand and Romania, the team identified several genes that were repeatedly disrupted in order for CCA to develop. Importantly, the cellular pathways controlled by these genes have suggested new potential avenues to treat CCA. One such gene identified, BAP1, participates in the unpacking of DNA, and drugs targeting this process (called "chromatin modifier drugs") are being developed. Prof Teh said "While further research needs to be done, this may pave the way for identifying which bile-duct cancer patients may benefit from chromatin-modifier drugs."

Findings from the study have also deepened our basic understanding of how cancer develops. Prof Rozen said "A poorly-understood question in cancer research is whether different carcinogens, applied to the same cancer type, will cause disruptions in the same sets of genes, or if different carcinogens will cause different type of genes to be disrupted".

The team reasoned that CCAs could be used to answer these questions, as these cancers are caused by different carcinogenic exposure in different parts of the world. They found that while CCAs from Thailand, Singapore and Romania appeared very similar under the conventional microscope, at the molecular level they were in fact very different. This provides one of the first key pieces of evidence that different types of carcinogen exposures, although acting on the same type of tissue, are associated with disruptions in different sets of genes. Such findings have practical applications as well. Prof Tan said "Based on these results, it

may be possible to investigate a patient's cancer and by looking at the types of disrupted genes, infer what caused the cancer." Such information would have major implications for cancer prevention efforts.

This most recent work is the latest in a series of high-profile papers from the Singapore team applying genomic analysis to cancers prevalent in Asia. In August, the same team reported their findings on a specific type of urinary tract cancer prevalent in Taiwan, which was caused by a carcinogen found in certain herbal remedies.

Invitation to join leading International Cancer Genome Consortium

The success of the team has not gone unnoticed by the international community. In October, the team of Professors Teh, Tan and Rozen was invited to join the International Cancer Genome Consortium (ICGC), a multi-national consortium composed of the world's leading scientists in cancer genomics, which aims to analyze over 50 different types of cancer. The Singapore team will take the lead in organizing the ICGC CCA sequencing program. "The ICGC Executive committee welcomes the participation of Singapore with great enthusiasm. The cholangiocarcinoma project will fit an important gap in the ICGC list of cancer types and the Singapore team has a track record of proven expertise and experience in this field", said Dr Tom Hudson, Chair of ICGC Executive Committee.

To-date, the Singapore team has raised funds from charities including a million dollar donation from a patient, and research institutions in Singapore to support the ICGC effort. Prof Teh concluded "This will be first time that Singapore has participated in such a large international cancer consortium. We will do our utmost to make this international

effort a success but our greatest hope is that our findings will ultimately benefit cancer patients worldwide"

More information: Exome sequencing identifies frequent inactivating mutations in BAP1, ARID1A and PBRM1 in intrahepatic cholangiocarcinomas, DOI: 10.1038/ng.2813

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