Liver cancer 'signature' in gut holds clues to cancer risk

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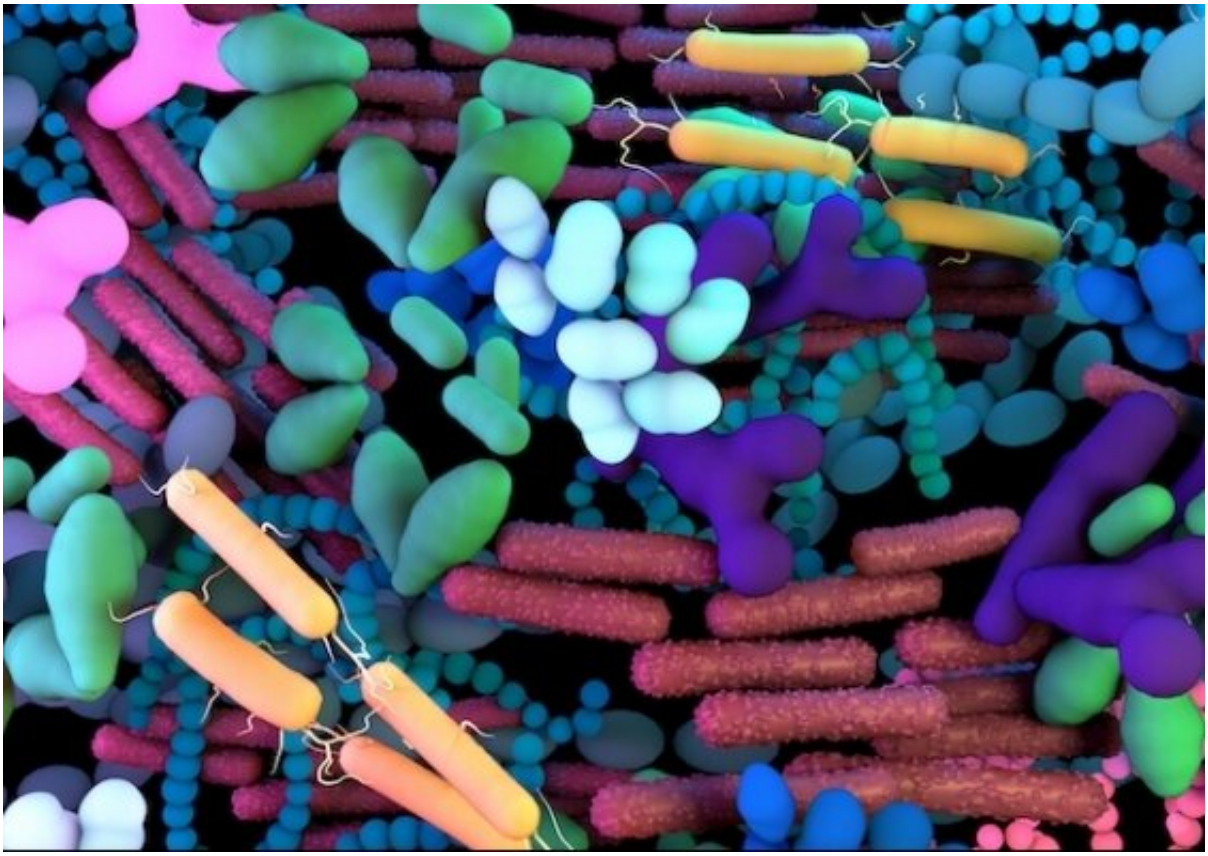

UNSW researchers have found the gut microbiome – the kingdom of microorganisms living in our digestive tracts as illustrated above – can modulate the immune response in liver cancer patients with non-alcoholic fatty liver disease, in a way that promotes the cancer's survival. Credit: Shutterstock

People with non-alcohol-related liver cancer have a unique gut

microbiome profile which could help predict disease risk, a UNSW Sydney study has found.

The distinctive gut microbiome profile of a person with liver cancer linked to non-alcoholic fatty liver disease (NAFLD) could be the key to predicting someone's risk of developing the cancer, say researchers from the UNSW Microbiome Research Centre (MRC).

Their new study, published in *Nature Communications* recently, found the gut microbiome—the kingdom of microorganisms living in our digestive tracts—can modulate the immune response in liver cancer patients with NAFLD, in a way that promotes the cancer's survival.

While the research is still in its early stages, this finding could lead to more effective preventative and therapeutic treatments for people at risk of developing NAFLD-related liver cancer.

People develop NAFLD in the context of obesity and metabolic risk factors such as diabetes, hypertension and high cholesterol.

Senior author Associate Professor Amany Zekry, of UNSW Medicine & Health, said the researchers looked at the most common type of primary liver cancer—hepatocellular carcinoma or HCC—which is the third leading cause of cancer-related deaths worldwide.

"Chronic liver inflammation and liver cirrhosis—or scarring—are key to a patient developing liver cancer, with NAFLD a common risk factor," A/Prof. Zekry said.

"So, because of the global pandemic of obesity and type 2 diabetes, NAFLD is emerging as the key reason for liver disease and liver cancer—particularly in Western countries.

"Liver cancer generally has a bad outcome because it's usually detected at the late stages of the disease due to the liver's resilience—liver cirrhosis can go undiagnosed for many years until cancer develops."

In Australia, people have a 20 percent chance of surviving for at least five years after being diagnosed with liver cancer.

The UNSW-led study included medical researchers from UNSW's St George and Sutherland Clinical School and major hospitals in NSW.

A/Prof. Zekry, who is also the Head of Gastroenterology and Hepatology at St George Hospital, said their research was the first paper to comprehensively investigate the microbiome in the context of NAFLD-related liver cancer.

"Another unique feature of our research is how we used a human cell culture model to examine the effect of the gut microbiome on the immune response in liver cancer patients," she said.

"This study is part of a larger research project we are doing involving about 200 patients—with the ultimate aim of identifying gut microbiome biomarkers or indicators, to predict someone's risk of developing liver cancer.

"The gut microbiome plays an important role in diseases generally and a person's overall health—so, our lifestyle and the food and drink we consume can influence this kingdom of microorganisms living in all of us."

Early stage cancer patients studied

The researchers recruited 90 adult patients from several Sydney hospitals, two-thirds of whom had just been diagnosed with either

NAFLD-related liver cancer or cirrhosis.

The remaining third of patients was a control group without liver disease.

The patients with liver cancer, aged in their 50s to 70s, were selected because their cancer had been detected early.

A/Prof. Zekry said this was the best cohort to examine because researchers wanted to understand what occurred in the early stage of the disease.

All patients provided blood and stool samples, which the researchers used to create cell culture models for analysis.

A/Prof. Zekry said: "If we know what happens in the early stage, then we can intervene to stop the cancer progressing to the late stage.

"So, if people can be diagnosed early with liver cancer, there is the potential to cure them with definitive therapy.

"Our study findings also open the door to harness gut-based interventions, by manipulating the microbiome, as a preventative strategy against the development of liver cancer."

Discovery of a liver cancer 'signature'

The researchers found patients with NAFLD-related liver cancer had a distinctive and characteristic gut microbiome profile, which was different to those with liver disease generally.

The study's first author Dr. Jason Behary, Conjoint Associate Lecturer at UNSW Medicine & Health, said it was an exciting discovery because no

past studies had reported a NAFLD-related liver cancer "signature."

"This means in the future, we will be able to harness the gut microbiome to predict disease occurrence, which is highly relevant for liver cancer because it's almost always detected in the late stages," he said.

"We also found the genes and function of the gut microbiome in NAFLD-related liver cancer patients promoted increased production of short-chain fatty acids—namely butyrate—which stem from intestinal microbial fermentation of indigestible foods, like beans and grains.

"Excess butyrate in the context of liver cancer is hazardous, because we found it obstructs the immune system from functioning.

"In addition, we found certain bacteria species correlated with this unfavorable immune response."

Dr. Behary, a gastroenterologist and hepatologist and Ph.D. candidate, said the cell culture studies confirmed the gut microbiome of patients with NAFLD-related liver cancer modulated the immune response in a way that favored the cancer's survival—rather than its elimination.

"So, because we have shown the gut microbiome can influence the immune response at an early stage to tolerate the liver cancer, this opens the door for intervention," he said.

"And, given the growing interest in new liver cancer treatments like immunotherapy—drugs which change the immune response to make it fight the cancer, rather than welcome it—our findings will pave the way for future studies to look at how we can change the microbiome to increase the chances of immunotherapy being successful."

A vision for predicting cancer risk

A/Prof. Zekry acknowledged the researchers were several years away from their work having a direct impact for people at risk of developing NAFLD-related liver cancer.

"What we have is a proof of concept—so, now we need to define a pilot study to prove that concept and provide more definitive answers," she said.

"For example, we need to find a control group with diabetes but not liver disease, in order to examine the effect of diabetes on the gut microbiome without the presence of NAFLD.

"But it is difficult to recruit such a group in clinical practice because liver disease is present in almost 80 percent of patients with diabetes."

Despite these challenges, A/Prof. Zekry said the team had new research in train at the MRC under the leadership of study co-author Professor Emad El-Omar, the Professor of Medicine at St George and Sutherland Clinical School.

Their new work includes animal studies to understand the mechanisms of how the gut microbiome influences immune response.

A/Prof. Zekry said: "We have exciting projects ongoing—we are trying to understand how the microbiome influences the immune response to cause liver cancer, as well as finding out how to switch off a 'bad' microbiome and switch on the 'good' ones to prevent liver cancer.

"We are also investigating microbiome-based biomarkers to predict liver cancer risk.

"It is our vision for people to be able to get a test, via a mouth swab, blood or stool sample, to determine if they carry a 'signature' which

shows they are at risk of developing liver cancer."

More information: Jason Behary et al. Gut microbiota impact on the peripheral immune response in non-alcoholic fatty liver disease related hepatocellular carcinoma, *Nature Communications* (2021). DOI: 10.1038/s41467-020-20422-7

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