New discoveries pave the way for early screening of liver cancer patients for targeted therapy

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Latest research findings by scientists at the Cancer Science Institute of Singapore (CSI Singapore) at the National University of Singapore (NUS) could enable early screening of patients with hepatocellular carcinoma (HCC), a major form of liver cancer, for more aggressive treatment to improve survival rate. The researchers have also proposed a way to inactivate SALL4 - a stem cell gene - to kill HCC cells and block tumour formation.

The NUS research group was led by Professor Daniel Tenen, Director of CSI Singapore, and the study was conducted in collaboration with the Brigham and Women's Hospital in Boston, the National University Health System (NUHS), Queen Mary Hospital Hong Kong, Queen's University Belfast and Harvard Stem Cell Institute. Two patent applications have been filed for this work and the group's findings were reported in the prestigious *New England Journal of Medicine* on 13 June 2013.

The findings may lead to the development of personalised treatments and targeted therapeutics for HCC. As SALL4 is also with associated other types of cancers such as leukaemia and other solid tumors including ovarian, endometrial, gastric, breast and lung cancers, the findings could contribute towards improving the treatment of such diseases.

High mortality rate of liver cancer

Liver cancer is the third leading cause of cancer-related deaths globally. In Singapore, it is the fourth most frequently diagnosed cancer. As most liver cancer cases are diagnosed at a late stage, treatment remains abysmal, with a five-year survival rate of less than 10 percent.

Current treatment of liver cancer is based solely on its clinical features. Recognising the need to understand the molecular pathogenesis of the fatal disease, Prof Tenen and his team investigated the molecular characteristics of tumours.

Commenting on the significance of their work, Prof Tenen said, "Surgical resection is the most viable treatment option for liver cancer. However, only early stage liver tumors are resectable, and most HCCs present at late stage and are not resectable. Combination chemotherapy has been used for the treatment of liver cancer for many years, yet the overall survival rate has not seen much improvement. What urgently needs to be addressed is the development of more effective targeted therapies, and this is where our research comes in."

Sall4 - Genetic marker for prognosis of HCC

SALL4 is a stem cell gene that is expressed abundantly in the livers of human fetuses, but is inactive in non-cancerous adult livers. In particular, the expression of SALL4 is associated with a more aggressive subgroup of HCC.

By studying the tissue samples from nearly 400 liver cancer patients from the National University Hospital in Singapore and the Queen Mary Hospital in Hong Kong, the international team of scientists found that 10 to 20 per cent of the liver cancer patients expressed high levels of SALL4, while 50 per cent of the patients expressed low levels of the gene.

The team hence established SALL4 as an independent marker for prognosis for HCC, and this is critical for the management of the disease. Patients who are found to express SALL4 should be given a more aggressive treatment regimen if

possible, as their condition will be more critical.

Targeted therapeutics

In this study, scientists also identified the role of SALL4 in liver tumor formation. By knocking down SALL4, the scientists found that HCC cells are more susceptible to cell death and they are also less likely to form tumours. Using a therapeutic peptide, the team succeeded in switching off SALL4 in an experimental environment, and by doing so, killing the liver cancer cells or blocking their tumour-forming capability.

The team is currently developing a screening assay to find small molecules that work in a similar way as the peptide, in the hope of developing a drug that has the potential to treat liver cancer

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