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Scientists identify molecular switch that suppresses development of liver cancer

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A team of scientists from the National University of Singapore (NUS) has found that activating a family of small protein, known as Rho, could suppress liver malignancies. This is the first time that a research group has provided evidence to show that the signaling crosstalk between different protein switches has an influence on the development of cancer tissues. The findings pave the way for the development and application of therapeutics targeted at liver cancer.

The team, led by Associate Professor Low Boon Chuan from the Department of Biological Sciences at the NUS Faculty of Science and the Mechanobiology Institute at NUS, first published the research in the journal *Oncogene*.

Importance of signalling crosstalk between proteins

The proteins Ras and Rho are among the key molecular switches that control cell dynamics, cell growth and tissue development through their distinct signalling pathways. Although much has been studied about their individual functions, the underlying molecular mechanism of signalling crosstalk between these two proteins in an in vivo context remains largely unknown, especially in the area of liver development and formation of liver tumours.

In order to identify the consequences of their signalling crosstalk, the research team generated different scenarios with different liver-specific

proteins and genes that have the potential to cause cancer, using the zebrafish as an in vivo model.

Due to its ability to reverse and forward genetics and low incidence of spontaneous tumours, the zebrafish is fast becoming a popular model for studying human cancers.

Through the use of quantitative bioimaging and molecular markers, the team found that when the zebrafish is induced to produce an active state of Kras (a form of Ras), which is an oncogene, liver enlargement is observed, and liver cancer that resembles the human liver cancer was formed. Subsequently, in adult zebrafish, the hepatocellular carcinoma, a major form of liver cancer, was developed. However, when the same cells were made to turn on Rho, these abnormalities were abated.

The team also found that when an inactive form of Rho was introduced when Kras is kept active, the Kras-mediated liver overgrowth and tumour formation were elevated.

These findings provided evidence about the significance of the previously understudied signalling crosstalk between the proteins Kras and Rho in regulating liver overgrowth, transformation of liver tissue and cancer mortality. As Rho is a known inducer of mechanical force, the team's findings also implicate the possible role of mechanical and physical forces in regulating cancer development and other functions in the liver.

Provided by National University of Singapore