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Singapore: A team of researchers from the Cancer Science Institute of Singapore (CSI Singapore) at the National University of Singapore (NUS) has found that changes in ribonucleic acid (RNA) sequences play a major role in the development of gastric cancer. Further research into this novel driving force for gastric cancer may potentially contribute towards early detection of gastric cancer and better treatment of the deadly disease.

Specifically, the research team discovered that proteins ADAR1 and ADAR2, which are involved in the editing of RNA, could potentially be used as a biomarkers to detect disorder leading to gastric cancer. The study also suggested that measuring the editing levels in patient gastric samples, which can be obtained through a simple biopsy, particularly at the pre-malignant stage, may help in identifying individuals at risk for subsequent gastric cancer development.

Findings of the study, which was led by Assistant Professor Polly Chen and Professor Patrick Tan from CSI Singapore, were first published in scientific journal Gastroenterology in June 2016.

Uncovering the role of RNA editing in gastric cancer

RNA is an intermediate product between deoxyribonucleic acid (DNA) and the protein coded by DNA. During RNA's involvement as a messenger, it is subjected to a multitude of changes - also known as RNA editing - resulting in haywire transmission of information from DNA, and leading to an altered gene product with cancer-causing qualities.

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"Currently, most molecular studies on gastric cancer have focused on the alterations in DNA sequences. Despite recent discoveries that shed light on the cancer-causing role of RNA in cancer progression, the alterations in these RNA sequences and its contribution to the development of gastric cancer have not been well studied. Our team is the first to conduct a

comprehensive analysis demonstrating that changes in RNA sequences, which are caused by the differentially expressed RNA editing enzymes ADAR1 and ADAR2 in gastric tumours, may serve as a novel driving force for gastric cancer," said Asst Prof Chen.

ADAR1 and ADAR2 are two upstream regulators fine-tuning the editing of RNAs and have opposing effects on gastric cancer development. ADAR1 functions as a cancer-promoting gene while ADAR2 functions as a cancer suppressor.

The team had compared editing levels at different stages of gastric lesions along the normal to cancer continuum and observed increasing levels of RNA editing disorder. The researchers also found that patients with developed gastric cancer demonstrated the highest levels of ADAR imbalance, predicting the poorest clinical prognosis.

Unlike DNA alterations, which usually occur at the advanced stages of cancer, RNA editing occurs more frequently and can be steadily detected in precancerous or premalignant samples at early stages of the disease. Hence, the team's finding suggests that measuring the ratio of the amount of ADAR1 and ADAR2 present in patients, especially at the early stages, could be significant in ascribing prognosis for gastric cancer patients.

"The utmost value of this discovery stems from its potential to translate into molecular therapy, given that gastric cancer is prevalent in Asia and is one of the most common and deadliest cancers worldwide. Moving forward, we will further investigate the key RNA editing events driving gastric cancer development and explore safe and efficient methods to correct this process. We are currently looking into designing small molecules such as specific peptide nucleic acids, which are stable and can be easily delivered to block the cancer-driven RNA editing process," said Prof Tan, who is also from the Duke-NUS Medical School and Genome Institute of Singapore (GIS).

This project was an international collaboration involving scientists and clinicians from the Singapore Gastric Cancer Consortium, GIS, NUS, and clinicians from the National University Health System, as well as the Samsung Medical Center and Yonsei Cancer Center in South Korea.

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