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NUS researchers uncover a bidirectional regulator in cancer cells

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Singapore - An in-depth study on the regulation of adenosine-to-inosine (A-to-I) RNA editing by researchers from the Cancer Science Institute of Singapore (CSI Singapore) at the National University of Singapore found that a protein, known as DHX9, acts as a bidirectional regulator of the molecular process which is linked to various types of cancer such as esophageal cancer. The discovery suggests that DHX9 is a potential cancer drug target, and its role in A-to-I RNA editing can be interfered to mitigate the development of these cancers. The findings of the study were recently published in the scientific journal, Nucleic Acids Research.

RNAs are an essential class of biomolecules that is critical in regulating core genetic function. They are often altered in the cell by a molecular process known as RNA editing. A-to-I RNA editing is a type of RNA editing which alters RNAs in a manner that affects how genes are read and how proteins are produced in the cell through contributing to molecular diversity that is essential for spatiotemporal regulation of cellular functions. Dysregulated A-to-I editing has been associated with neurological disorders and cancer, however, the factors impacting the regulation of A-to-I editing remain largely unknown.

A research team from CSI Singapore therefore embarked on a research study to deepen the understanding on the regulation of A-to-I RNA editing in cancer. A-to-I RNA editing is carried out by two main ADAR proteins – ADAR1 and ADAR2, each performing different functions. In the team's analysis on cancer cells of 11 different cancer types, they identified that cancer cells express more DHX9 protein than normal cells, and that DHX9 may lead to the development of cancer by modulating A-to-I RNA editing through its interactions with the ADAR proteins.

Interestingly, further experiments showed that DHX9 is able to effect different outcomes in the cell. DHX9 enhances A-to-I RNA editing carried out by ADAR1. Conversely, A-to-I RNA editing carried out by ADAR2 is reduced when DHX9 interacts

with ADAR2. DHX9 therefore acts as a bidirectional regulator of A-to-I RNA editing in cancer cells. Earlier studies conducted by the team has suggested that increased ADAR1-regulated RNA editing and decreased ADAR2-regulated RNA editing are implicated in cancer. The observation can be attributed to the bidirectional regulation of DHX9 in cancer cells, as supported by the current study. DHX9, which is required for cancer cell survival, therefore offer as a promising target for novel therapeutic strategies against cancer to be developed.

Assistant Professor Polly Chen, Principal Investigator at CSI Singapore who led the study, said, “This is the first time a bidirectional regulator of A-to-I RNA editing in human has been uncovered. With this new knowledge, we can now look into how they can intervene the interactions between DHX9 and ADAR proteins in order to stop cancer-driven processes mediated by RNA editing in the cell.”