Bhagyashree Deka

# Studies on the regulation of RNA binding protein with serine-rich domain 1 and its implication in cervical cancer cells


## ABSTRACT

Since the discovery of split genes in eukaryotes, it has been known that a single gene can generate many mRNA and protein isoforms via the process of alternative splicing. Alternative splicing is a critical mechanism during cellular signalling and regulation of cell-type-specific functions. Several studies have indicated that perturbations in alternative splicing contribute to tumor progression. Cancer cells exploit the process of alternative splicing to generate advantageous protein isoforms that drive oncogenesis. In recent years, we have begun to understand that most tumor-related splicing modifications are due to changes in components of the splicing machinery.

RNA-binding protein with serine-rich domain 1, RNPS1, is an essential regulator of the splicing process. However, the defined role of RNPS1 in tumorigenesis still remains elusive. In silico analysis of publicly available TCGA dataset unveiled interesting finding. The expression of RNPS1 was higher in cervical carcinoma samples compared to normal tissue. This alteration in the expression of RNPS1 in cervical cancer provided a rationale to investigate the possible role of RNPS1 in cancer. In this study, we identified for the first time that RNPS1 is involved in the survival, migration, and invasion of cervical cancer cells. Knockdown of RNPS1 in HeLa and SiHa reduced the migration and invasion of cervical cancer cells. Using RNA-Sequencing analysis, we identified that RNPS1 facilitates the generation of cancer-specific splice isoforms of genes involved in cell migration and invasion events. Our results showed that RNPS1 is involved in the alternative splicing of components of Rho GTPases, including Rac1 and RhoA. We found that RNPS1 switches alternative splicing of the *RhoA* transcript from a non-coding isoform to the major, translatable isoform, thus resulting in an increase in RhoA protein levels in cervical cancer cells. In addition, we elucidated the mechanism of how RNPS1 is dysregulated in cervical cancer cells and discovered that RNPS1 is subjected to post-transcriptional gene regulation via miR-6893-3p. We found decreased expression of miR-6893-3p in cervical cancer cells and a concomitant higher expression of RNPS1 in cancer cells, suggesting a negative correlation of expression between miR-6893-3p and RNPS1 levels. In summary, the study revealed a novel mechanism of how RNPS1 is aberrantly expressed in cervical cancer cells and provides a detailed molecular insight into the role of RNPS1 in cancer.