

Targeting Aberrant mRNA Splicing Driven by Mutant p53 as a Novel Cancer Therapeutic Approach

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Background*: Aberrant regulation of alternative splicing is often linked to tumor initiation and progression. RNA-sequencing confirmed that mutant p53 affects splicing in lung, colon, pancreatic, and head and neck cancers. These results also enabled us to identify genes affected by splicing in the presence of mutant p53. We demonstrated experimentally the interaction between SR proteins, SRPK1 and mutant p53. The effect of alternative protein isoforms on the phenotype of cancer cells was assessed. A new therapeutic protocol targeting mutant p53, splicing and proteins that undergo alternative splicing was developed based on obtained results. The effectiveness of targeted drug combinations was tested using cancer patient-derived organoids and cell lines.

Methods*:

RNA Immunoprecipitation (RIP) assay

Proximity Ligation Assay (PLA)

Cancer organoids and cell lines drug assay

Phenotypic tests

Results*:

1. SR proteins and SRPK1 interacts with mutant p53. Mutant p53 affects phosphorylation of SR proteins.
2. SR proteins binds to mRNA of genes that undergo alternative splicing.
3. The presence of selected protein isoforms affects cancer phenotype.
4. Selected drugs effectively lower the viability of cancer organoids/cells and influence the assembly of splicing isoforms.

Conclusion*: Mutant p53 influences alternative splicing of protein isoforms in cancer by affecting the activity of SR proteins through phosphorylation. The phenotype of cancer may be influenced by modulation of alternative splicing. Cancer cells and organoid models confirm efficacy of the new therapeutic protocol that targets investigated mechanism.