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SHORT COMMUNICATION

CIS-REGULATORY ELEMENTS AND TRANS-ACTING FACTORS MODULATING POST-TRANSCRIPTIONAL SPLICING IN CANCER: A SHORT COMMUNICATION

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Abstract

The key post-transcriptional process of alternative splicing (AS) generates transcriptomic and proteomic diversity through its mechanism. The precise regulation of AS depends on cis-regulatory RNA elements together with trans-acting protein factors whose alterations frequently occur in cancer cases. Cancer progression occurs through the generation of abnormal isoforms which emerge from mutations together with altered splicing factors and epigenetic transformations. The combination of modern sequencing approaches with computational tools allows scientists to study cancer-specific splicing patterns which enables both biomarker development and targeted therapeutic applications. This paper discusses the basic molecular mechanisms behind AS control as well as cancer-related abnormalities and new precision oncology therapeutic approaches through splice-switching oligonucleotides and small-molecule modulators and CRISPR-based strategies.

Keywords: *alternative splicing, cis-regulatory elements, trans-acting factors, cancer, spliceosome*

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Introduction:

The process of alternative splicing (AS) extends protein diversity because it produces multiple isoforms from a single gene[1, 2]. Splicing processes depend on cis-elements including exonic and intronic enhancers/silencers and trans-acting splicing factors that consist of SR proteins and heterogeneous nuclear ribonucleoproteins (hnRNPs) for their regulation[3]. Cancer progression and therapy resistance and immune evasion occur due to disruptions in these networks when they alter isoform proportions[4]. Precision oncology depends on cancer-specific splicing codes to develop biomarkers and targeted treatments.The spliceosome functions as an assembly of U1, U2, U4/U6 and U5 snRNPs to perform two transesterification reactions that remove introns. ESEs, ISEs, ESSs, and ISSs located in the cis-elements determine whether exons will be included or excluded from the final transcript while SR proteins (e.g., SRSF1, SRSF2) and hnRNPs (e.g., hnRNPA1) function as either activators or repressors[5, 6, 7]. The cancer-specific isoforms emerge from somatic mutations that affect splice sites along with mutations in splicing factors including SF3B1, U2AF1 and SRSF2 which disrupt the spliceosome's ability to be faithful[8]. DNA methylation along with histone modifications function as epigenetic regulators to control co-transcriptional splicing processes (Figure 1).

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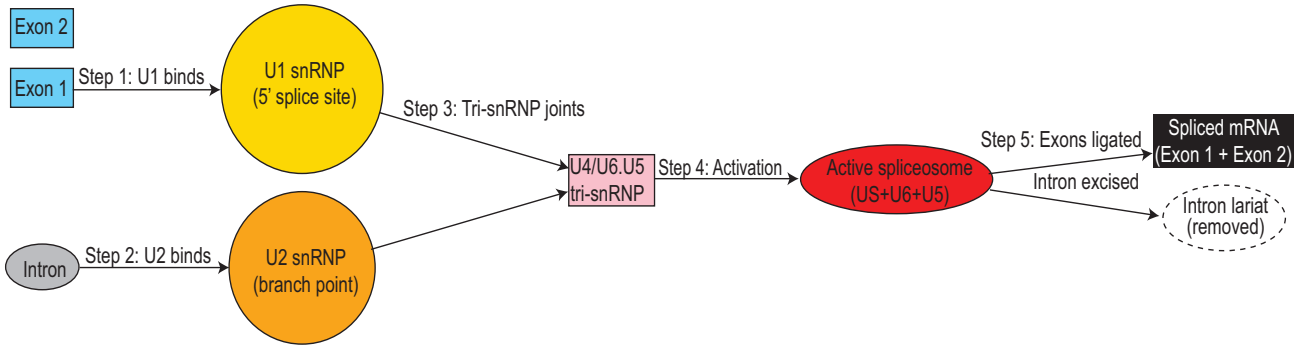

Figure 1. The spliceosome's gradual construction and activation during pre-mRNA splicing is depicted in this image. The recruitment of the U4/U6.U5 tri-snRNP complex follows the binding of U1 and U2 snRNPs to the 52 splice site and branch point, respectively. The ensuing active spliceosome removes the intron as a lariat, ligates the exons, and creates mature spliced mRNA.

Oncogenic Splicing Events and Isoforms:

The process of alternative splicing produces cancer-causing isoforms which promote tumor growth and make tumors resistant to treatment and lead to metastasis[1]. BCL-XL functions to protect cells from chemotherapy while BCL-XS triggers programmed cell death and PTBP1 drives the transition from FGFR2-IIIb to FGFR2-IIIc which leads to increased metastasis potential and MDM2-S accelerates p53 degradation and CD44v isoforms enable stemness and invasion. The Wnt/β-catenin signaling pathway becomes active through RAC1b while TP53 and BRCA1 and RB1 undergo aberrant splicing which disrupts tumor suppression and DNA repair and cell-cycle regulation[9,10,11]. The therapeutic approach includes antisense oligonucleotides to restore isoform balance and SF3B1-targeting H3B-8800 for leukemia treatment and CRISPR-based exon editing to fix mutations[12]. The research demonstrates that splicing functions as both a cancer biological mechanism and a therapeutic opportunity (Figure 2).

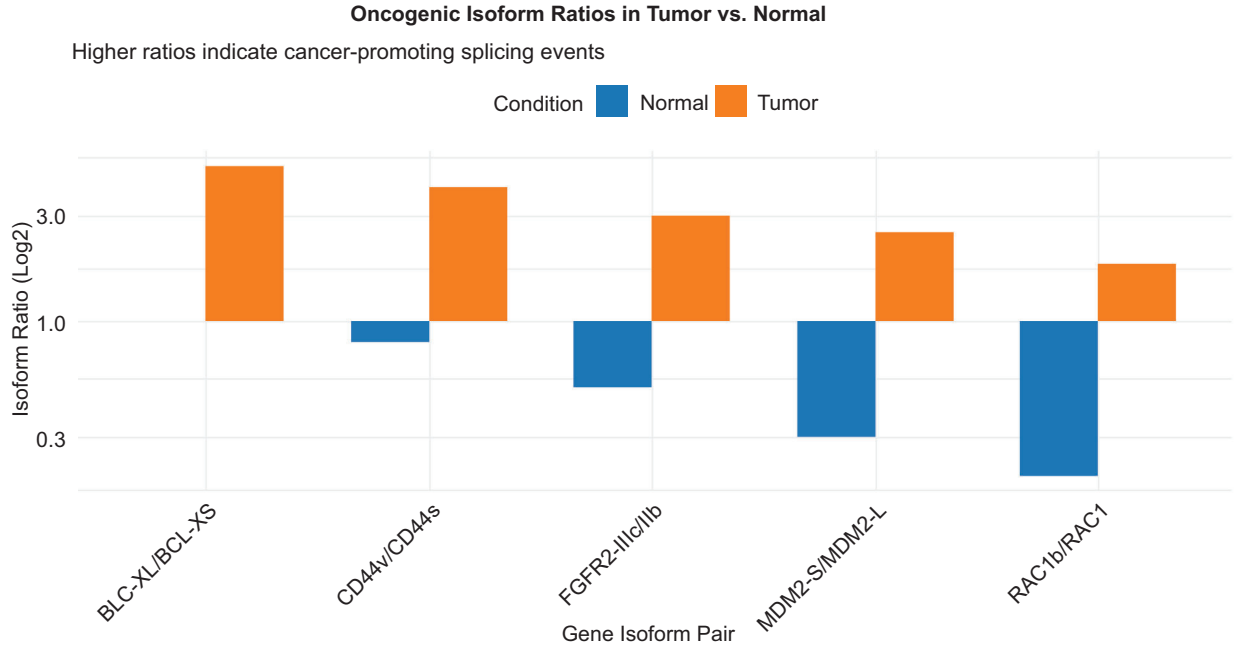

Figure 2: The expression ratios of splice isoforms linked to cancer (such as FGFR2 variations and BCL-XL/BCL-XS) in tumor and normal tissues are contrasted in this bar plot. Tumor-specific overexpression of carcinogenic isoforms is indicated by higher log2-transformed ratios (orange bars), whereas normal splicing patterns are reflected by lower ratios (blue bars). Important isoform transitions that promote tumor growth and could be targets for treatment are highlighted in the figure.

Table I

Therapies Targeting Splicing in Cancer

Therapy Type	Mechanism of Action	Examples	Clinical Applications
Splice-Switching Oligonucleotides (SSOs)	Bind to pre-mRNA to redirect splicing decisions	Eteplirsen, SSOs for BCL2L1	Alter oncogenic isoform balance
Splicing-Modulating Small Molecules	Inhibit components like SF3B1 to alter splicing in cancer cells	H3B-8800, E7107, Spliceostatin A	Myelodysplastic syndromes, leukemias
Antisense Therapy / CRISPR Correction	Target abnormal transcripts or correct splice sites using genome or RNA editing tools	Antisense drugs, CRISPR/Cas9/13	Rare cancers with defined splice mutations
Isoform-Based Biomarkers	Use tumor-specific splicing isoforms for detection or immune targeting	AR-V7, CD44v6, FGFR2 IIIc	Diagnosis, prognosis, immunotherapy targeting

Therapeutic Targeting of Splicing in Cancer:

The therapeutic approach of targeting aberrant splicing presents new possibilities for cancer treatment. BCL2L1-targeting SSOs function as splice-switching oligonucleotides to change BCL-XL into its pro-apoptotic form BCL-XS. The small-molecule modulators H3B-8800, E7107 and spliceostatin A target SF3B1 to produce selective cell death in SF3B1-mutant cancer cells. CRISPR-based editing provides exact modifications to splice sites and intronic mutations and regulatory elements and CRISPR/Cas13 enables RNA-guided modulation for treating rare cancers. The clinical relevance of isoforms such as CD44v6, FGFR2 IIIc and AR-V7 enables their use as biomarkers for both prognosis and therapy monitoring[13-20]. The abnormal splicing products create neoantigens which serve as targets for vaccines and immunotherapy while uniting diagnostic and therapeutic approaches to enhance precision oncology (Table I).

Computational tools for alternative splicing analysis:

Computational and Multi-Omics Approaches for Alternative Splicing Analysis The precise identification and measurement of cancer-related alternative splicing (AS) requires sophisticated computational methods together with integrated omics approaches[21, 22]. The tools rMATS and SUPPA2 and MAJIQ and LeafCutter enable sensitive detection of differential and novel splicing events through their ability to model exon inclusion across replicates and detect major splicing types and quantify transcript levels for large-scale multi-condition studies and model local splicing variations directly from splice junction reads and perform annotation-free clustering of junction usage[22-26]. Bulk RNA sequencing (RNA-seq) delivers wide-ranging information yet fails to show cellular diversity which single-cell RNA-seq (scRNA-seq) addresses through its ability to detect infrequent isoforms and cell-type-specific patterns despite its limited coverage and technical noise[27]. The advancement of computational pipelines enhances scRNA-seq resolution while combining bulk and single-cell data provides a more detailed understanding of tumor splicing dynamics. The combination of genomics with transcriptomics and epigenomics through multi-omics analysis shows how DNA methylation and histone modifications and chromatin remodeling and somatic mutations work together to control splice site recognition and cancer development. These approaches work together to improve biomarker discovery and therapeutic development which drives progress in precision oncology (Table II).

Table III

Key Tools and Approaches for Splicing Analysis

Category	Tool/Approach	Description	Applications
Alternative Splicing Tools	rMATS	Statistical detection of differential splicing with replicate support	Cancer vs normal splicing comparisons
	SUPPA2	Fast transcript-based quantification and differential splicing analysis	Large-scale multi-condition studies
	MAJIQ	Annotation-free detection of local splice variations	Discovery of novel splice junctions
	LeafCutter	Clustering of splice junctions to identify differential splice site usage	Rare or complex splicing event detection
Transcriptomics Approaches	RNA-Seq	Bulk sequencing to measure gene and isoform expression	Tumor-wide splicing profiling
	Single-Cell RNA-Seq	High-resolution transcriptomics capturing cell-specific splicing events	Tumor heterogeneity and microenvironment
Multi-Omics Integration	Genomics +Transcriptomics+ Epigenomics	Integrates splice site mutations, splicing profiles, and chromatin modifications to elucidate mechanisms	Comprehensive mechanism and biomarker studies

Summary of the study:

The process of aberrant alternative splicing functions as a key driver of cancer development and its progression and metastasis and therapy resistance while providing valuable diagnostic and prognostic and predictive biomarkers such as SF3B1 mutations in myelodysplastic syndromes and CD44 variant isoforms in metastasis and BRCA1/TP53 exon skipping. The precise detection of these alterations becomes possible through high-resolution RNA sequencing and nanopore sequencing and PCR assays and single-cell transcriptomics which receive computational support from tools such as rMATS, SUPPA2, MAJIQ. The multi-omics approaches reveal regulatory mechanisms that include somatic mutations together with epigenetic changes and splicing factor dysregulation. The advancement of therapeutic strategies includes splice-switching oligonucleotides and small-molecule modulators (H3B-8800) and CRISPR-based exon editing yet tumor heterogeneity and off-target effects and delivery limitations continue to be challenges. The integration of splicing modulation into personalized oncology advances through emerging solutions which include AI-driven models (SpliceAI, Pangolin) and base/prime editing and cancer-specific splicing codes that enhance biomarker discovery and therapeutic precision.

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Author Contributions:

Shafee Ur Rehman collected the data and wrote the manuscript.

Conflicts of interest:

The author has no conflict of interest

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Data Availability:

All the data is available in the manuscript.

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