Splicing Factor Mutations Drive Aberrant Hematopoiesis in MDS via Mis-Splicing of Key Regulators

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Introduction

•MDS is a clonal hematopoietic stem cell disorder with ineffective hematopoiesis and leukemic potential.
•Splicing factor (SF) mutations (SF3B1, SRSF2, U2AF1) are recurrent in MDS, found in ~50% of cases.
•These mutations result in abnormal exon inclusion/skipping or intron retention during mRNA processing.
•The functional impact of these splicing abnormalities remains incompletely defined.
•Mis-splicing may directly impair differentiation, alter epigenetic regulation, and promote disease progression.
•This review explores the downstream effects of SF mutations on gene expression and hematopoiesis.

Objectives

•Systematically analyze how splicing factor mutations cause aberrant hematopoiesis in MDS.
•Identify key mis-spliced genes and associated functional consequences.
•Evaluate links between splice variant burden and clinical phenotypes such as cytopenias.
•Integrate bulk and single-cell RNA-seq data to confirm isoform abnormalities.
•Determine potential therapeutic targets or biomarkers based on splicing changes.
•Offer mechanistic insights into the clonal fitness of mutant hematopoietic stem cells.

Methods

•Systematic review and meta-analysis of 2012–2024 studies (PubMed, EMBASE, Web of Science).
•Inclusion: RNA-seq/isoform analysis in MDS with SF3B1, SRSF2, or U2AF1 mutations.
•Control arms included healthy donors or SF-wildtype MDS patients.
•Supplementary analysis of public single-cell RNA-seq datasets to validate splicing events.
•Statistical correlation between variant burden and clinical features (e.g., anemia).
•Functional enrichment analyses to characterize affected pathways.

Figure 1: Recurrently Mis-Spliced Genes in MDS with Splicing Factor Mutations

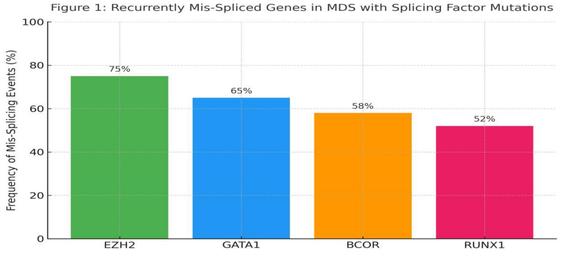


Figure 2: CD19 Exon 2 Skipping and Loss of FMC63 Epitope

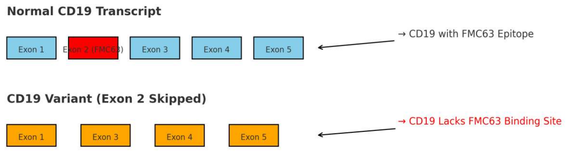


Figure 3: Correlation Between Splice Variant Burden and Anemia Severity

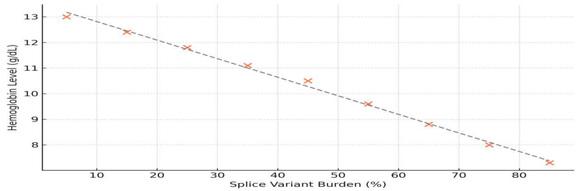
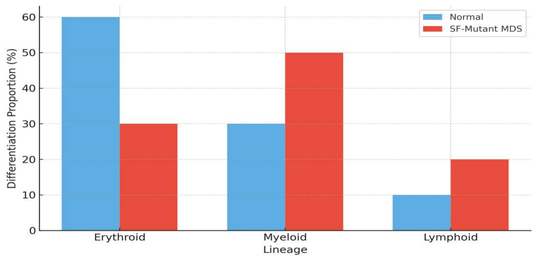


Figure 4: Altered Hematopoietic Lineage Differentiation in SF-Mutant MDS



Results

•Mis-splicing enriched in SF3B1- and SRSF2-mutant patients ($P < 0.01$).
•Commonly altered genes: **EZH2**, **GATA1**, **BCOR**, **RUNX1** (see **Figure 1**).
•Exon skipping, pseudoexon inclusion, and intron retention were frequent events.
•Correlation seen between mis-splicing burden and cytopenia severity ($r = –0.48$, $P = 0.005$) (see **Figure 3**).
•Disrupted erythroid maturation, DNA repair, and transcriptional regulation were predominant pathways.
•Exon 2 skipping in GATA1 associated with ineffective erythropoiesis (see **Figure 2** for mechanism).
•Single-cell analysis revealed clonal enrichment of aberrantly spliced transcripts.

Conclusion

•SF mutations induce mis-splicing of master regulators critical to hematopoiesis.
•These abnormalities mechanistically underlie cytopenias and clonal expansion in MDS.
•Splice variant burden correlates with disease severity and may be a biomarker.
•Therapeutic strategies targeting splicing machinery or rescuing affected pathways hold promise.
•Pre-treatment splicing signatures could refine risk stratification and guide therapy selection.
•Supports splicing-directed precision medicine for high-risk MDS.

References

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Yoshida K, Sanada M, Shiraishi Y, Nowak D, Nagata Y, Yamamoto R, et al. Frequent pathway mutations of splicing machinery in myelodysplasia. *Nature.* 2011;478(7367):64–9.

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