Pathophysiology of spliceosome mutations in MDS

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The myelodysplastic syndromes (MDS) are common myeloid malignancies. Mutations in genes encoding different components of the spliceosome (including SF3B1, SRSF2, U2AF1 and ZRSR2) occur in over half of MDS patients and result in aberrant pre-mRNA splicing of many target genes, indicating that aberrant spliceosome function plays a major role in MDS disease pathogenesis. Recent functional studies have illuminated the impact on hematopoiesis of some aberrantly spliced target genes associated with splicing factor mutations. Emerging data show that some of the downstream effects of different mutated splicing factors converge on common cellular pathways/processes, such as hyperactivation of NF-κB signaling and increased R-loops, providing novel insights into MDS disease pathophysiology. The combination of induced pluripotent stem cell (iPSC) and CRISPR/Cas9 technologies has been harnessed for the modeling and study of clonal evolution of myeloid malignancies, including the investigation of the impact of splicing factor gene mutations on the cellular phenotype. The aberrantly spliced target genes and the dysregulated pathways and cellular processes associated with splicing factor mutations provided the rationale for new potential therapeutic approaches to target splicing factor mutant MDS cells.