Knowledge about spliceosome mutations in people suffering from myelodysplastic syndromes.

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Introduction

The majority of recurrent somatic mutations in acute myeloid leukemias (AML), myeloproliferative neoplasms (MPN), and myelodysplastic syndromes (MDS) impact genes involved in the regulation of gene expression (RUNX1, TEL/ETV6, TP53, TET2, ASXL1, EZH2, and DNMT3A). The aetiology of myeloid diseases may be influenced by changes in the control of translation, according to high throughput sequencing in MDS that compared DNA from bone marrow mononuclear cells to germ-line DNA and found about 10 acquired mutations per patient sample. The erythroid lineage of individuals with a 5q- syndrome, a specific MDS subtype characterised by the haplo-insufficiency of the RPS14 gene encoding a ribosomal protein of the small ribosome subunit, had previously been linked to impaired protein translation [1].

Exome sequencing of MDS samples revealed that abnormal translation might possibly be linked to recurrent mutations in spliceosomal protein genes (SF3B1, SRSF2, ZRSR2, U2AF35), whose products regulate pre-messenger RNA (pre-mRNA) splicing. Similar studies in chronic lymphocytic leukaemia (CLL), which analysed the DNA of tumour CD19+CD5+ lymphocytes and non-tumor cells, also discovered alterations altering the systems that regulate splicing.

Spliceosome functioning

Pre-mRNA is converted into mature forms of mRNA in eukaryotic cells by the splicing of introns and exons in the nucleus. This process is known as gene expression. By using an alternative splicing mechanism, which involves the alternate inclusion or exclusion of coding exons, or portion of coding exons, in a cell type-specific way, the majority of human genes are processed to produce two or more transcripts. This mechanism produces a wide variety of mRNA species and submits them to a "nuclear surveillance" for quality control. The nuclear exosome is called upon to destroy incorrectly spliced and read-through pre-mRNA when 3' processing/polyadenylation is ineffective or weakened by gene mutations.

The many, massive tiny nuclear ribonucleoprotein (RNP) complexes that make up the spliceosomes are responsible for catalysing the splicing reaction. A so-called "U2-dependent spliceosome" is responsible for splicing approximately 99% of introns. More than 150 proteins and 5 small nuclear (sn) RNAs (U1, U2, U4/U6, and U5) make up the primary U2-dependent spliceosome. The identification of 5' and 3' exon/intron junctions requires the early recruitment of snRNP complexes to newly transcribed pre-mRNA, and later steps involve the interaction of the 5' and 3' complexes to catalyse the excision of introns.

An U1 snRNP complex recognising the 5' splice site triggers the start of RNA splicing. By binding to the branchpoint sequence upstream of the 3' end of the intron, the splicing factor 1 (SF1) complex, through its subunit SF3B1, shields the area before the splicing process. The polypyrimidine tract between the branchpoint and the 3' splice site is recruited by SRSF1 or SRSF2, one of the serine-arginine (SR)-rich splicing factors, and a complex containing a U2 auxiliary factor (AF) 35/65 heterodimer, ZRSR2. Exon skipping is prevented by SRSF1 and SRSF2, which controls alternative splicing [2].

Most co-transcriptional pre-RNA splicing events take place. The binding of U1 snRNP to a newly created 5' splice site is followed by U2 and U5 snRNP when the intron is fully synthesised in the recruitment of spliceosome complexes to actively transcribed genes. The relationship between transcription and mRNA splicing is suggested by the direct interaction of U1 snRNP and/or splicing regulatory proteins with DNA polymerase II. The SR family of proteins mediate the connection between splicing, mRNA export from the nucleus, and translation. These proteins are recruited to pre-mRNA for splicing in a hyperphosphorylated state, and as the splicing reaction develops, they begin to become partially dephosphorylated. When hypophosphorylated, they also serve as adaptors for the export of spliced mRNA.

Consequences of spliceosome alterations

The majority of splice factors, some of which are involved in splicing or alternative splicing as well as some extra-splicing functions, can be altered in solid tumours or haematological malignancies. Modifies in their expression level have also been connected to the aetiology of cancer. Knockdown of these factors changes the splicing pattern of a group of genes. For instance, the Warburg effect, which promotes aerobic glycolysis in tumour cells, is caused when the embryonic M2 isoform of the pyruvate kinase is re-expressed by alternative splicing in lung tumours. Three heterogeneous nuclear RNPs, the polypyrimidine tract binding protein PTB, hnRNPA1 and hnRNPA2, which bind to flanking regions of exon 9 and suppress the exclusion of exon 10, are involved in the mechanism of this re-expression.

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***Received:** 28-Sept-2022, Manuscript No. AAHBD-22-78533; **Editor assigned:** 30-Sept-2022, PreQC No. AAHBD-22-78533 (PQ); **Reviewed:** 14-Oct-2022, QC No. AAHBD-22-78533; **Revised:** 19-Oct-2022, Manuscript No. AAHBD-22-78533 (R); **Published:** 26-Oct-2022, DOI:10.35841/aahbd-5.5.123*

***Citation:** Raphael F. Knowledge about spliceosome mutations in people suffering from myelodysplastic syndromes. Hematol Blood Disord. 2022;5(5):123*

Alternative splicing may be impacted by chromatin shape and histone modification since splicing is frequently closely correlated with transcription. For instance, the splice factor MRG15/MORF4L1 may be directly recruited to the H3K36me3 chromatin. In contrast, SF3B1 interacts with the Polycomb repressive complex (PRC), and its absence compromises PRC performance, which may have an impact on the chromatin structure and HOX gene transcription. In addition, it's likely that mutations that impact the nuclear exosomal degradation of non-coding RNA have a role in cell metamorphosis. Inactivating mutations in the exoribonuclease gene SEP1/KEM1 or the exonuclease gene DIS3, which encodes the catalytic subunit of the exosome, may cause an accumulation of non-coding RNA species and impair transcription. AML has already been linked to DIS3 mutations [3].

Impact of Splice Gene Mutations

In MDS, SF3B1 mutations cluster with the existence of ringed sideroblasts and DNMT3A mutations and are linked to lower haemoglobin levels than other splicing gene variants. Regardless of the WHO classification, SF3B1 mutations are highly predictive of the occurrence of ringed sideroblasts. In addition, Sf3b1+/ mice have an overabundance of ring sideroblasts in the bone marrow without any signs of anaemia, whereas homozygous Sf3b1 knockdown causes embryonic lethality. Different clinical symptoms are correlated with splice gene mutations. For instance, patients with advanced stages of MDS usually have mutations in the genes SRSF2 and U2AF35. Patients with SRSF2 mutations show significant thrombocytopenias, whereas ZRSR2 mutations frequently show isolated neutropenias. Compared to just by chance, the two mutations are more frequently linked to TET2 mutations.

Targeting the splice

Spliceosome inhibitors are a class of anticancer medications. The primary effect of heterozygous splice gene mutations is an increase in function for the protein that has to be suppressed. Given that homozygous splice gene inactivation causes death in mice, heterozygous mutant cells must be more toxic to spliceosome inhibitors than normal cells. The biflavonoid isogenkgetin, another anti-tumor agent, hinders the steady recruitment of the U4-U6/U5 tri-snRNP to the pre-mRNA, leading to the buildup of pre-complex A. Based on the inclusion or removal of particular exons, several genes can create both oncogenic and tumour suppressor proteins. Numerous genes' alternative splicing is unregulated in the majority of malignancies [4].

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Citation: *Raphael F. Knowledge about spliceosome mutations in people suffering from myelodysplastic syndromes. Hematol Blood Disord. 2022;5(5):123*