When splicing turns bad

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RNA splicing, the process that removes introns from pre-mRNA and links exons together to generate the fully mature messenger RNA (mRNA), is a complicated and highly regulated process. Splicing is catalyzed by the spliceosome, a large RNA-protein complex composed of several small nuclear ribonucleoprotein complexes (snRNPs) that each have a specific task during splicing. Correct splicing is important, since RNAs that retain introns or parts of introns will not be translated correctly into proteins and may even be degraded.

In two studies using whole exome sequencing of myelodysplasia cases, recurrent mutations involving components of the RNA splicing machinery, including *SF3B1*, *SRSF2*, *U2AF35*, *ZRSR2*, *PRPF40B*, *U2AF65* and SF1, have been identified.[1,2] Myelodysplastic syndromes (MDS) and related disorders (myelodysplasia) are a group of myeloid neoplasms characterized by deregulated, dysplastic blood cell production and a predisposition to develop acute myeloid leukemia (AML).[3] Analysis of the various mutations indicated that the mutations were not random loss-of-function mutations, but they appeared to be selected to retain structural integrity.[2] Thus, rather than loss of splicing activity, which would probably lead to cell death, it is expected that the mutated splicing factors will have an altered function.

How can splicing defects lead to myelodysplasia? The answer to this question is still unknown, but experiments in cell lines have provided some first indications. When expressed in HeLa cells, the mutant U2AF35 induced global abnormalities of RNA splicing, leading to increased production of transcripts having unspliced intronic sequences, and thereby activating the nonsense mediated RNA decay pathway (a surveillance pathway that degrades mRNAs that have premature stop codons).[1] The biological consequences were studied in HeLa cells and mouse hematopoietic stem/progenitor cells, where a negative effect on cell proliferation and a compromised reconstitution capacity of the hematopoietic stem/progenitor cells was observed for cells expressing the U2AF35 mutants.[1]

What are the clinical consequences of these mutations? In a follow-up study, somatic mutations of SF3B1 were identified in 150 of 533 (28 %) patients with MDS, 16 of 83 (19 %) with MDS/MPN, and only in 2 of 38 (5 %) with AML.[4] The association of SF3B1 mutations with the presence of ring sideroblasts was highly significant, and the mutant gene had a positive predictive value for ring sideroblasts of almost 98 percent.[4,5] In multivariate analysis including established risk factors, SF3B1 mutations were found to be independently associated with better overall survival and lower risk of transformation to AML.[4] These findings suggest that the incorporation of SF3B1 mutation analysis into the risk stratification systems might further improve risk assessment in MDS. Interestingly, SF3B1 mutations have recently also been identified in chronic lymphocytic leukemia (CLL), where the highest frequency of SF3B1 mutations was found in fludarabine-refractory cases.[6] These studies suggest that mutations in splicing factors may be common in various hematologic malignancies.

These data provide the first evidence that genetic alterations of splicing components can be implicated in the pathogenesis of human disease, and may lead to the development of novel therapeutic possibilities to treat myelodysplasia.

References

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