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The role of splicing factor mutations in the pathogenesis of the myelodysplastic syndromes

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A B S T R A C T

Accurate pre-mRNA splicing by the spliceosome is a fundamental cellular mechanism required to remove introns that are present in most protein-coding transcripts. The recent discovery of a variety of somatic spliceosomal mutations in the myelodysplastic syndromes (MDS), a heterogeneous group of myeloid malignancies, has revealed a new leukemogenic pathway involving spliceosomal dysfunction. Spliceosome mutations are found in over half of all MDS patients and are likely founder mutations. The spliceosome mutations are highly specific to MDS and closely related conditions and, to some extent, appear to define distinct clinical phenotypes in MDS. The high frequency of mutations in different components of the RNA splicing machinery in MDS suggests that abnormal RNA splicing is the common consequence of these mutations. The identification of the downstream targets of the spliceosome mutations is an active area of research. Emerging data from the study of the MDS transcriptome suggests that spliceosomal mutations have effects on specific genes, including some previously shown to play a role in MDS pathogenesis. The effects of the spliceosomal mutations on RNA splicing and cell growth have been evaluated only in a limited context to date, however, and the determination of the impact of these mutations in primary human hematopoietic cells is essential in order to elucidate fully the molecular mechanism by which they contribute to MDS pathogenesis.

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Introduction

The myelodysplastic syndromes (MDS) represent a heterogeneous group of clonal hematopoietic stem cell (HSC) malignancies that are characterized by ineffective hematopoiesis resulting in peripheral cytopenias, and typically a hypercellular bone marrow (Corey et al., 2007; Greenberg, 2013). The MDS are pre-leukemic conditions showing frequent progression (approximately 40% of patients) to acute myeloid leukemia (AML). Until recent years the genetic aberrations that play an important role in the molecular pathogenesis of MDS were largely unknown. The application of various new high throughput technologies over the past decade, including SNP-array analysis and next-generation sequencing, to the study of MDS has resulted in the identification of a host of genes that are recurrently mutated in this disorder (Graubert and Walter, 2011; Raza and Galili, 2012; Lindsley and Ebert, 2013).

We now recognize that the most common mutations found in MDS occur in genes that are epigenetic modifiers (*TET2*, *ASXL1*, *DNMT3A*, *EZH2*, *IDH1* and *IDH2*) or regulators of RNA splicing (*SF3B1*, *SRSF2*, *U2AF1* and *ZRSR2*), providing an important link between genetic and epigenetic alterations in this disease. Several regulators of signal transduction (*NRAS*, *JAK2*) and a number of transcription factors (*RUNX1*, *TP53*) are also frequently mutated in MDS (Bejar et al., 2011; Shih and Levine, 2011; Kulasekararaj et al., 2013; Lindsley and Ebert, 2013). Emerging evidence suggests that specific combinations of these genes may cooperate to give the MDS phenotype (Abdel-Wahab et al., 2012; Mian et al., 2013). The identification of mutations in members of the RNA splicing machinery in MDS represents one of the most important new findings, and implicate abnormalities of mRNA splicing, a pathway not previously known as a target for mutation, in the pathogenesis of this disorder. Splicing factor mutations occur in approximately half of all MDS patients and, unlike most other recurrent gene mutations in MDS, are highly specific for this disorder (Papaemmanuil et al., 2011; Yoshida et al., 2011; Makishima et al., 2012; Ogawa, 2012; Visconte et al., 2012a). The remarkable discovery of frequent mutation of the splicing factor machinery in MDS has the potential to illuminate our understanding of the molecular pathogenesis and biology of MDS and for the development of new treatment options for this disorder.

Identification of frequent mutation of splicing factor genes in MDS

The recent discovery of a variety of somatic spliceosomal mutations in MDS has revealed a new leukemogenic pathway involving spliceosomal dysfunction. Papaemmanuil et al., used whole-exome sequencing analysis in low-risk MDS and identified frequent mutation of the splicing factor *SF3B1* in this patient group (Papaemmanuil et al., 2011). *SF3B1* mutations were found in over 70% of patients whose disease is characterized by ring sideroblasts (Malcovati et al., 2011; Papaemmanuil et al., 2011). The close association between *SF3B1* mutation and ring sideroblasts is consistent with a causal relationship, and makes this the first gene to be strongly associated with a specific feature of MDS. *SF3B1* is the most commonly mutated gene found in MDS to date, with approximately 15–28% of all MDS patients harboring *SF3B1* mutations (Table 1) (Malcovati et al., 2011; Papaemmanuil et al., 2011; Yoshida et al., 2011; Bejar et al., 2012; Damm et al., 2012; Thol et al., 2012). At around the same time Yoshida et al., in a landmark study, identified frequent recurrent mutations in *SF3B1* and several other genes encoding other members of the RNA splicing machinery, including *U2AF35* (*U2AF1*), *ZRSR2* and *SRSF2* in MDS using whole-exome sequencing analysis (Yoshida et al., 2011). These splicing pathway mutations were shown to be frequent in MDS (occurring in 130 of 228 patients; 57%), and highly specific to this disorder. Thus spliceosome mutations represent the most common molecular abnormality found in MDS. Most of the mutations occurred in a mutually exclusive manner and affected genes involved in the 3′ splice site recognition during pre-mRNA processing (Yoshida et al., 2011). Mutations in *SRSF2*, *U2AF1* and *ZRSR2* have been reported in approximately 10–15%, 5–16% and 3–11% of MDS patients, respectively (Table 1) (Yoshida et al., 2011; Bejar et al., 2012; Damm et al., 2012; Thol et al., 2012). Mutations in the splicing factors *PRPF40B*, *SF1*, *SF3A1* and *U2AF65* (*U2AF2*) are more rarely found in MDS, each occurring in approximately 1–2% of patients (Yoshida et al., 2011; Makishima et al., 2012).

Most mutations identified to date are missense and affect rather invariant positions in *SF3B1*, *SRSF2*, *U2AF1* and other spliceosomal proteins (Papaemmanuil et al., 2011; Yoshida et al., 2011). In *U2AF1*, the