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Splicing factor gene mutations in the myelodysplastic syndromes: impact on disease phenotype and therapeutic applications

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ABSTRACT

Splicing factor gene mutations are the most frequent mutations found in patients with the myeloid malignancy myelodysplastic syndrome (MDS), suggesting that spliceosomal dysfunction plays a major role in disease pathogenesis. The aberrantly spliced target genes and deregulated cellular pathways associated with the commonly mutated splicing factor genes in MDS (*SF3B1, SRSF2* and *U2AF1*) are being identified, illuminating the molecular mechanisms underlying MDS. Emerging data from mouse modeling studies indicate that the presence of splicing factor gene mutations can lead to bone marrow hematopoietic stem/myeloid progenitor cell expansion, impaired hematopoiesis and dysplastic differentiation that are hallmarks of MDS. Importantly, recent evidence suggests that spliceosome inhibitors and splicing modulators may have therapeutic value in the treatment of splicing factor mutant myeloid malignancies.

Contents

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1. Introduction

The myelodysplastic syndromes (MDS) represent a heterogeneous group of myeloid malignancies that originate from a neoplastic hematopoietic stem cell (HSC) in the bone marrow (Heaney and Golde, 1999; Jhanwar, 2015; Pellagatti and Boultwood, 2015; Tefferi and Vardiman, 2009). Patients with MDS suffer from ineffective hematopoiesis resulting in peripheral blood cytopenias, and many cases show an increasing number of malignant blasts in the bone marrow over time (Heaney and Golde, 1999; Jhanwar, 2015; Pellagatti and Boultwood, 2015; Tefferi and Vardiman, 2009). Approximately 30–40% of MDS patients progress to acute myeloid leukemia (AML) (Heaney and Golde, 1999; Tefferi and Vardiman, 2009). MDS is as frequent as *de novo* AML, and the incidence is 4–5 per 100,000 people per year (Poledak, 2013). Patient survival in MDS is variable, but cases with excess blasts (RAEB1 and RAEB2) have a median overall survival of less than 24 months, demonstrating the poor prognosis of patients with advanced MDS.

Current treatments for low-risk MDS are erythropoietin (EPO) and lenalidomide (MDS with the 5q-), and for high-risk MDS azacitidine, decitabine and chemotherapy (Garcia-Manero, 2014). Allogenic bone marrow transplantation is the only curative treatment for MDS and is generally considered only appropriate for a small proportion of patients. There is clearly a need for more effective treatments for MDS (Jonas and Greenberg, 2015; Steensma, 2015).

The molecular landscape of MDS has been illuminated in recent years and splicing factor gene mutations, which occur in over half of all patients, have been shown to be the most common molecular abnormality found in this disorder (Graubert et al., 2012; Haferlach et al., 2014; Makishima et al., 2012; Papaemmanuil et al., 2011, 2013; Walter et al., 2013; Yoshida et al., 2011). Splicing factor gene mutations are found in other myeloid malignancies including AML, but are strongly associated with the phenotype of MDS and closely related conditions.

The splicing of pre-mRNA by the excision of intronic sequences results in the production of mature mRNAs and is an essential process for the expression of >95% of human genes (Boultwood et al., 2014; Hoskins and Moore, 2012; Pan et al., 2008). Splicing of mRNA plays a major role in protein diversity since it enables the generation of multiple protein isoforms from a single pre-mRNA transcript. For the vast majority of human genes, splicing is performed by the major spliceosome, a complex of five small nuclear ribonucleoproteins (snRNPs), U1, U2, U4, U5 and U6, and a myriad of associated proteins. During the splicing process the formation of the active spliceosome occurs in a number of discrete stages involving the ordered assembly of distinct factors on the pre-mRNA substrate (Hoskins and Moore, 2012). *SF3B1*, *U2AF1*, *SRSF2* and *ZRSR2* are the most frequently mutated splicing factor genes in MDS (Haferlach et al., 2014; Papaemmanuil et al., 2013) and are part of the E/A splicing complex that orchestrates 3′ splice site recognition during the early phase of pre-mRNA processing (Yoshida et al., 2011). In this process, SF1 binds to the branch point upstream of the 3′ splice site, and SRSF2 and ZRSR2 bind to the exon splicing enhancer (ESE) site of the next exon to aid the binding and stability of U2AF1 (U2AF35) and U2AF2 (U2AF65) (complex E) (Hoskins and Moore, 2012). The SF3B1 protein is a core component of the U2 snRNP and is involved in the recognition of the branch point, targeting the U2 snRNP to the 3′ splice site (complex A) (Schellenberg et al., 2011). It is recognized that the common splicing factor mutations in MDS result in aberrant 3′ splice site recognition and spliceosome dysfunction is a major feature of MDS (Yoshida et al., 2011).

SF3B1 gene mutations are the most frequent mutations found in MDS and are more common in low-risk MDS (Malcovati et al., 2011). In many studies it has been shown that approximately 80% of MDS patients with refractory anemia with ring sideroblasts (RARS) and refractory cytopenia with multilineage dysplasia and ring sideroblasts (RCMD-RS) carry mutations of *SF3B1* (Malcovati and Cazzola, 2016; Malcovati et al., 2011; Papaemmanuil et al., 2011). *U2AF1* and *SRSF2* mutations are more common in high-risk MDS, and are associated with an increased risk of transformation to AML (Graubert et al., 2012; Thol et al., 2012).

The splicing factor mutations found in MDS are typically heterozygous and occur in a mutually exclusive manner (Haferlach et al., 2014; Papaemmanuil et al., 2013). Mutations in *SF3B1*, *U2AF1* and *SRSF2* are considered to be change of function/neomorphic or gain of function mutations due to the presence of hotspots and the absence of nonsense or frameshift changes, while mutations in *ZRSR2* are loss-of-function (Papaemmanuil et al., 2011; Yip et al., 2016; Yoshida et al., 2011). While splicing factor mutations can be found in isolation (Mian et al., 2013), several studies have shown that splicing factor mutations show specific associations with epigenetic regulators and also oncogenes mutated in MDS (Haferlach et al., 2014; Mian et al., 2013; Papaemmanuil et al., 2013), indicative of epistatic interactions involving these genes. These findings are of great interest as they link pathways involved in MDS pathophysiology. Co-mutation of *ASXL1* and *U2AF1*, and *SF3B1* and *DNMT3A*, for example are frequently reported in MDS, whilst co-mutation of *TET2* with *SRSF2* or *ZRSR2* is highly predictive of a CMML disease phenotype (specificity of 98%) (Haferlach et al., 2014; Malcovati et al., 2014; Papaemmanuil et al., 2013). Thus, co-operation between splicing factor mutations and mutations in other genes is likely required for the development of the MDS phenotype. The relationship between the proteins encoded by these genes and how they interact and contribute to the MDS phenotype remains poorly understood, however.

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