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# Genetic and epigenetic pathways in myelodysplastic syndromes: A brief overview

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ABSTRACT

Myelodysplastic syndromes (MDS) are a highly heterogenous group of hematopoietic tumors, mainly due to variable clinical features and diverse set of cytogenetic, molecular genetic and epigenetic lesions. The major clinical features of MDS are ineffective hematopoiesis, peripheral cytopenias, and an increased risk of transformation to acute myeloid leukemias, which in turn is most likely determined by specific genetic abnormalities and other presenting hematologic features. The risk of developing MDS is relatively higher in some genetic syndromes such as Fanconi anemia and receipt of chemotherapy and radiation treatment. In recent years a significant progress has occurred and a vast literatures has become available including the spectrum of cytogenetic abnormalities, gene mutations relating to RNA splicing machinery, epigenetic regulation of gene expression and signaling pathways associated with MDS pathogenesis, which have provided opportunities to understand the molecular mechanisms as well as employ targeted therapeutic approaches to treat MDS. The cytogenetic abnormalities detected in MDS varies from a single abnormality to complex karyotype not easily amenable to conventional cytogenetic analysis. In such cases, array based high resolution genomic analysis detected abnormalities, which are diagnostic as well as prognostic. The most common driver gene mutations detected in patients with MDS include RNA splicing (SF3B1,SRSF2,U2F1,ZRSR2), DNA methylation (TET2,DNMT3A,IDH1/IDH2), chromatin modification (ASXL1,EZH2), transcription regulation (RUNX1,BCOR) and DNA repair control p53. A small subset of MDS arise due to deregulation of RAS pathway, mainly due to NRAS/KRAS/NF1 mutations. Identification of these mutations and pathways have provided opportunities for

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oncologists to target these patients with specific therapies. Several drugs which either target the spliceosome, oncogenic RAS signaling, or hypomethylating agents have been employed to successfully treat MDS patients.



## Introduction

Myelodysplastic syndromes (MDS) are a highly heterogenous group of hematopoietic tumors, arising from hematopoietic stem cells, as evidenced from dysplasia in myeloid, erythroid and megakaryocytic dysplasia. MDS display variable clinical features and diverse set of cytogenetic, molecular genetic and epigenetic lesions. The major clinical features of MDS are ineffective hematopoiesis, peripheral cytopenias, and an increased risk of transformation to acute myeloid leukemias, which in turn is most likely determined by specific genetic abnormalities and other presenting hematologic features (Nimer, 2006, 2008). The risk of developing MDS is relatively higher in some genetic syndromes such as Fanconi anemia and receipt of chemotherapy and radiation treatment for an independent malignancy. In recent years a significant progress has occurred and a vast literatures has accumulated, according to which it has become increasingly evident that the spectrum of cytogenetic abnormalities, gene mutations relating to RNA splicing machinery, epigenetic regulation of gene expression and signaling pathways associated with MDS pathogenesis, which not only provide opportunities to understand the molecular mechanisms underlying pathophysiology of the disease, but also help direct targeted therapeutic approaches to treat MDS (Abdel-Wahab and Figueroa, 2012; Cazzola et al., 2013; Lindsley and Ebert, 2013). The cytogenetic abnormalities detected in MDS varies from a single chromosome abnormality such as monosomy of chromosomes 5, 7 to complex karyotype not easily amenable to conventional cytogenetic analysis. In such cases, SNP array based high resolution genomic analysis detected abnormalities, which are diagnostic as well as prognostic. In addition, SNP array has enhanced the ability to detect cryptic abnormalities including del(4q24), the chromosomal site of TET2 and uniparental disomy of several chromosomal regions of interest in MDS (Heinrichs et al., 2009; Jankowska et al., 2009; Langemeijer et al., 2009). The most common driver gene mutations detected in patients with MDS include RNA splicing (SF3B1,SRSF2,U2F1,ZRSR2), DNA methylation (TET2,DNMT3A,IDH1/IDH2), chromatin modification (ASXL1,EZH2), transcription regulation (RUNX1,BCOR) and DNA repair control pathway gene p53. A small subset of MDS arise due to deregulation of RAS pathway, mainly due to NRAS/KRAS/NF1 mutations (Abdel-Wahab and Figueroa, 2012; Cazzola et al., 2013; Lindsley and Ebert, 2013). Identification of these mutations and pathways have provided opportunities for oncologists to target these patients with specific therapies. Several drugs which either target the spliceosome, oncogenic RAS signaling, or hypomethylating agents have been employed to successfully treat MDS patients (Nimer, 2006, 2008). It is, however, important to mention that additional studies relating to genomic as well as epigenomic studies are needed to further understand the fundamental molecular basis of poor and transient response of some high risk patients to available therapeutic approaches, as well as a reliable marker predictive of transformation to AML (Jiang et al., 2009; Tothova et al., 2013). Recently, some studies have identified stem cell marker in MDS, which may be important step forward in our understanding of the cell of origin in MDS and the molecular basis of clinical as well as biologic heterogeneity detected in MDS, thereby enhancing our ability to achieve durable treatment response to therapies in some patient resistance to other treatments currently available (Keerthivasan et al., 2014). Similarly, it is expected that several mouse models developed by investigators may provide opportunities for preclinical models of MDS (Beachy and Aplan, 2010; Stoddart et al., 2014; Wang et al., 2014).

### *Cytogenetic abnormalities*

The recurrent cytogenetic abnormalities are detected in approximately 50% of the *de novo* MDS across all four subtypes. The abnormalities are both specific as well as predictive of prognosis combined