Leukemia Research 39 (2015) 6–17

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Review Article

The molecular basis and clinical significance of genetic mutations identified in myelodysplastic syndromes

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ARTICLE INFO

Article history:
Received 14 August 2014
Accepted 25 October 2014
Available online 6 November 2014

Keywords:
Myelodysplastic syndromes
Next generation sequencing
Mutation
RNA slicing
Transcription regulation
DNA methylation/histone modification
DNA repair/tumor suppressor
Signal transduction
Cohesion complex

ABSTRACT

Myelodysplastic syndromes (MDS) are a heterogeneous cluster of clonal hematopoietic neoplasms manifested by peripheral cytopenias, lineage dysplasia, and a predisposition to acute myeloid leukemia. The pathophysiology of MDS has not been well illustrated. Nevertheless, studies have implicated the MDS phenotype in a broad spectrum of genetic abnormalities. In addition to the known numerical and structural chromosomal abnormalities, with novel genomic sequencing technologies, approximately 80% of MDS patients have been shown to harbor somatic or acquired gene mutations. The mutations have been found to be related to RNA slicing, transcription regulation, DNA methylation, histone modification, DNA repair/tumor suppressor, signal transduction, and the cohesion complex. The clinical significance of the majority of genetic events has been validated based on a large cohort study that identified mutations as predictors for risk stratification in MDS patients and biomarkers for potential targeted therapies. In this review, we describe all novel key mutations in MDS and their significance in pathophysiology and clinical practice.

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http://dx.doi.org/10.1016/j.leukres.2014.10.006
0145-2126/

1. Introduction

Myelodysplastic syndrome (MDS) is a clonal hematopoietic neoplasm characterized by peripheral cytopenia, bone marrow dyspoiesis with or without excess blasts, and >30% transformation rate to acute myeloid leukemia (AML) [1]. The disease poses a unique diagnostic challenge for both hematologists and pathologists because of its clinicopathologic diversity and its benign or malignant mimickers. Although the current evaluation of a suspected MDS includes clinical history, peripheral blood value, bone marrow morphology and architecture, flow cytometry, and cytogenetics study, many cases of true MDS remain diagnostically challenging. Preclinical studies have clearly shown that the development of MDS is derived from acquired genetic mutations independent of their phenotypic or morphologic presentation [2,3]. Further evidence also supports that a wide spectrum of genetic aberrations has been implicated in the prognosis and behavior of individual MDS cases [3]. Several informative clinical prognostic tools exist for the risk stratification of MDS, but it has become apparent that incorporation of genetic mutations may further enhance the efficacy of current clinical tools [4,5].

Most patients with MDS have a detectable gene mutation, making its clinical implementation broadly applicable. According to recent large cohort studies of MDS patients, 72–90% of cases carried at least one mutation (average of 3/per case) [6–8]. Currently, various driver mutations identified in MDS represent genes involved in pathways important in epigenetic regulation, including chromatin modification and DNA methylation, transcriptional regulation, DNA repair/tumor suppressor, signal transduction, RNA splicing machinery, and the cohesion complex (Table 1). Although over 60 genes have been recently identified, there are 6 genes (*TET2, SF3B1, ASXL1, SRSF2, DNMT3A, and RUNX1*) that are consistently mutated in 10% or more of MDS patients [6,7,9]. Herein, we review the clinical and pathological significance of these mutations as grouped by corresponding pathways that they dysregulate.

2. DNA methylation

Epigenetic pathways are involved in manipulation of the level of DNA methylation and the modification of DNA or its protein interactions, including methylation, acetylation, and phosphorylation of histone residues of nucleosomes around which the DNA double helix winds [10,11]. Of note, DNA methylation and direct DNA and DNA-associated histone modification represent critical mechanisms of altered epigenetic regulation in MDS (Fig. 1). Abnormalities in cytosine methylation may result from mutations in *TET2*, *DNMT3A*, and *IDH1/2*. Below is a summary of frequently mutated genes in MDS relevant to this pathway and their consequences.

2.1. TET2 (ten-eleven translocation (TET) oncogene family member 2)

Tet methylcytosine dioxygease 2 (*TET2*) belongs to the TET oncogenic family and is mapped to 4q24. The proteins of this family are critical for the hydroxylation of methylated cytosine residues. TET2 enzymatically converts 5-methylcytosine (5mC) to 5-hydroxymethyl-cytosine (5hmC) [12]. Dynamic DNA methylation and demethylation balance occur via 5-hydroxymethylcytosine (5hmC)-dependent active demethylation, which controls DNA replication and cancer development in mammalian cells. 5hmC, an oxidation product of 5mC by the TET family of iron(II)/alpha-ketoglutarate-dependent dioxygenases, is considered a novel and important epigenetic marker that constitutes the initial process of DNA demethylation pathway (Fig. 1). When cells/DNA are exposed to carcinogens, acquisition of 5hmC and loss of 5mC occur in the promoter regions of these genes, ultimately resulting in an aberrant methylation pattern found in tumor cells [12–15].

Somatic *TET2* mutations were initially reported in myeloid neoplasms, including MDS in 2009 [16]. The use of next-generation sequencing and mass spectrometry has subsequently revealed genetic abnormalities, which have been verified in 20–25% of patients with MDS [2,17] and in 30–60% of patients with chronic myelomonocytic leukemia (CMML) [18,19].

TET2 mutations are primarily located in conserved functional domains and the N terminus that predict a loss-of-function [20–22]. These mutations have been reported to result in a decreased global 5hmC level with a concomitant increase in 5mC genomic DNA [24]. *TET2* mutations lead to increased self renewal of hematopoietic stem cells and myeloid hyperplasia [22–25]. Other genetic aberrations (e.g., loss of heterozygosity or deletion) may also result in inactivation or decreased gene function [17,26,27].

Despite a relatively high frequency of *TET2* mutations in MDS, its clinical significance and pathogenesis have not been well defined. Murine models have demonstrated that mutations in *TET2* are sufficient to induce a myeloid neoplasm by increased hematopoietic stem cell self-renewal and myeloid transformation [22,28,29]. The mechanism by which this occurs and the presumed targets of epigenetic modification remain elusive.

Conflicting data exist regarding the prognostic impact of *TET2* mutations in MDS. Two large cohort studies have indicated that *TET2* mutations do not impact overall survival [3,30] while another study showed that patients with mutant *TET2* experienced a superior overall survival when compared with well-matched wild-type controls [19]. Regarding treatment, *TET2* mutations appear to be a genetic predictor of response to azanucleosides [(5-azacitidine (AZA) and decitabine (DAC))], primarily in higher-risk MDS [31–33], although these observations require prospective validation.

The relationships between *TET2* mutations and other somatic events have also been explored. Several studies have confirmed that, unlike mutations in splicing and cytokine signaling, mutual