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INVITED REVIEW ARTICLE

# Genetic abnormalities and pathophysiology of MDS

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**Abstract**
Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid malignancies characterized by peripheral blood cytopenia and dishematopoiesis and frequently progress to acute myeloid leukemia. Genetic defects play a major role in pathogenesis of MDS, including cytogenetic abnormalities, gene mutations, and abnormal gene expression. Chromosomal abnormalities have been detected in approximately 50–60% of MDS patients, including the deletions of chromosome 5q and 7q, trisomy 8, and complex karyotypes. Newer genomic technologies, such as single-nucleotide polymorphism array and next-generation sequencing, revealed the heterozygous deletions resulting in haploinsufficient gene expression (e.g., *CSNK1A1, DDX41* on chromosome 5, *CUX1, LUC7L2, EZH2* on chromosome 7) involved in the pathogenesis of MDS. In addition, recurrent somatic mutations in more than 50 genes have been identified in 80–90% of MDS. The most recurrent genetic mutations are involved in the RNA splicing (e.g., *SF3B1*, *SRSF2*, *U2AF1*, *ZRSR2, LUC7L2, DDX41*) and epigenetic modifications, such as histone modification (e.g., *ASXL1*, *EZH2*) and DNA methylation (e.g., *TET2*, *DNMT3A*, *IDH1/IDH2*). TP53 mutation is associated with aggressive disease and frequently coincides with deletion of chromosome 5q. This review summarizes the recent progress in molecular pathogenesis of MDS. A better understanding of the specific subgroups of MDS patients will also aid in the development of new therapeutic approach for MDS.

**Keywords** MDS · Genetic defects · del(5q) · del(7q) · Somatic mutation

## Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of disorders characterized by progressive cytopenia and morphologic features of dysplasia in bone marrow and frequently progress to acute myeloid leukemia (AML) [1]. Over the last decade, recurrent genetic alterations, genetic mutations, and epigenetic dysregulation have recently been implicated in the pathogenesis of MDS/AML; however, the molecular mechanisms leading to leukemic transformation have not been precisely elucidated. High-resolution analytical platforms, such as single-nucleotide polymorphism array (SNP-A), next-generation sequencing (NGS) and whole-exome sequencing (WES), have uncovered novel genetic alterations and made large advancements in the understanding of the molecular pathogenesis of hematological malignancies, especially MDS/AML [2]. Here, the author discusses the molecular pathogenesis of MDS, which frequently progresses to AML, focusing on various genetic abnormalities, including chromosomal aberrations, somatic mutations, copy-number alterations, and abnormal gene expression, in a set of recurrently involved genes (Fig. 1).

## Cytogenetic abnormalities in MDS

Cytogenetic abnormalities contribute to the International Prognostic Scoring System (IPSS) and revised IPSS (IPSS-R) score used in the prediction of prognosis of patients with MDS [3–5]. Clonal and recurrent cytogenetic abnormalities, including trisomy 8, monosomy 7, deletion of the long arm of chromosome 7 (del(7q)), deletion of the long arm of chromosome 5 (del(5q)), and complex karyotypes, are found in 40–50% of cases with MDS and are summarized in Table 1. They are often present at disease presentation and play a crucial role in disease progression. Evaluation of cytogenetic abnormalities at diagnosis is an important factor to decide therapeutic approach and monitoring response to efficacy. According to cytogenetics, patients are divided into

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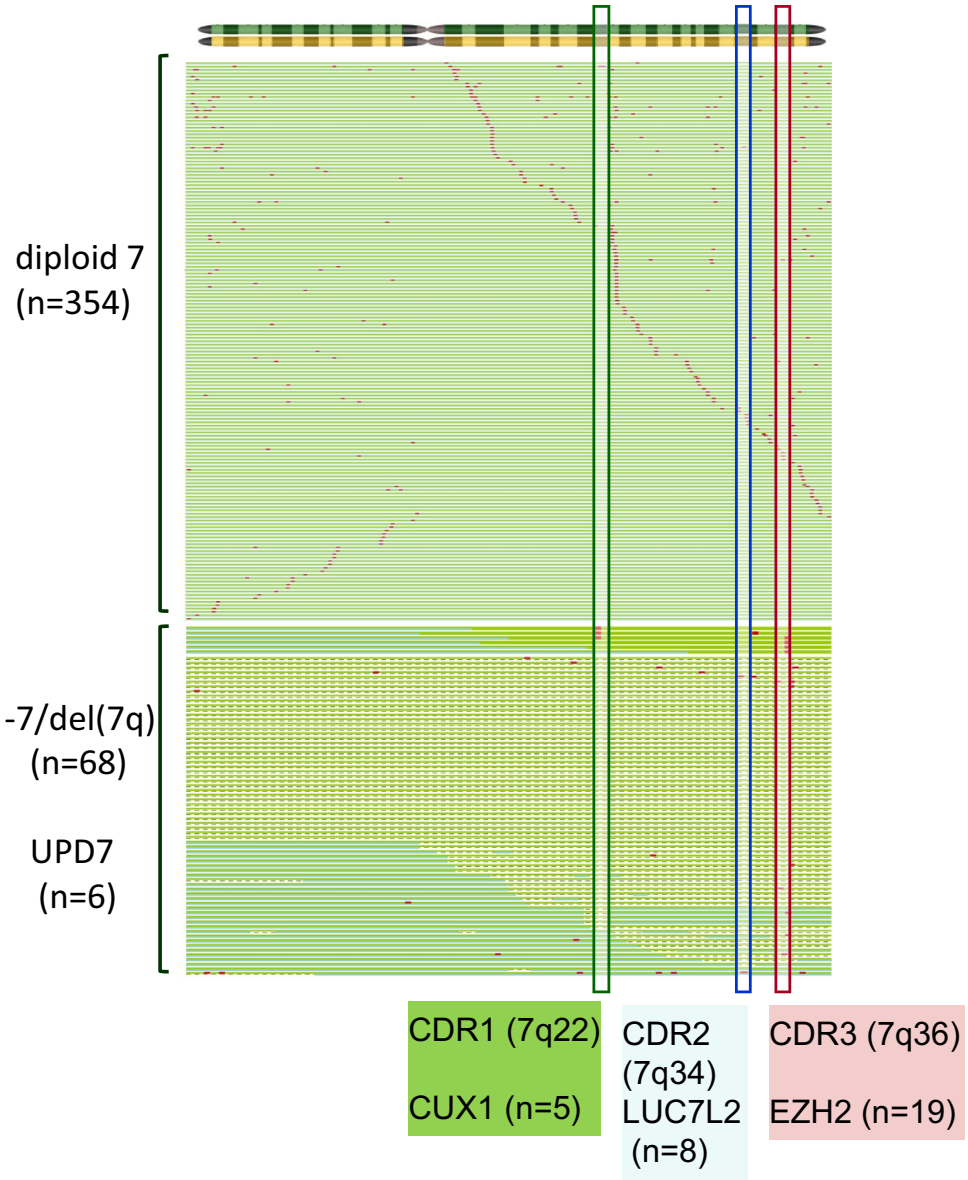


**Fig. 1** Mutations and loss of heterozygosity on chromosome 7. Mutations of chromosome 7 detected by whole-exome sequencing in the 428 cases of various myeloid are shown in red. Neoplasms. Deletion of chromosome 7 was demonstrated as a dashed line. Three distinct commonly deleted regions (CDRs), indicated by vertical rectangles, were identified on 7q by mapping of SNP-A karyotyping. A number of somatic mutations of CUX1, LUC7L2, and EZH2 were indicated in each CDR [30]

5 prognostic subgroups (Table 2). The precise mechanisms by which cytogenetic abnormalities contribute to the pathogenesis of MDS remain unclear, but haploinsufficiency of tumor suppressor genes results in the deletion of one allele involved in the clinical phenotype of MDS. Representative cytogenetic abnormalities are discussed here.

## Del(5q)

Interstitial deletion of the long arm of chromosome 5 (del(5q)) is the most common chromosomal abnormalities in myeloid neoplasms, observed in 10–15% of patients with MDS [6–8] or up to 40% of patients with secondary AML [9]. The patients with the isolated del(5q) show a homogenous clinical phenotype and favorable prognosis [10, 11]. The majority of myeloid neoplasms with del(5q) are morphologically heterogeneous and associated with additional cytogenetic abnormalities [12, 13]. Using SNP-A-based karyotyping, Jerez et al. demonstrated that deletions involving the centromeric (centromere to 5q14.2) and extreme telomeric regions (5q34 to the telomere) of the 5q chromosome are more likely to have additional chromosomal lesions and leukemic transformation [8].

Patients with the isolated del(5q), also called "5q-syndrome", exhibit macrocytic anemia and thrombocytosis. Due to the deletion of a commonly deleted region (5q32–5q33.1) [7], haploinsufficiency of *RPS14*, which encodes a ribosomal structural protein, causes dyserythropoiesis via activation of the p53 pathway [14], and haploinsufficiency of miR-145 and miR-146a results in thrombocytosis [15]. *CSNK1A1*, a serine/threonine

**Table 1** Recurrent chromosomal abnormalities and their frequencies in MDS at diagnosis

| Chromosomal abnormality | Frequency | |
|---|---|---|
| | MDS (%) | Therapy-related MDS (%) |
| Loss of chromosome 7 or del(7q) | 10 | 50 |
| del(5q) | 10 | 40 |
| Gain of chromosome 8* | 10 | – |
| del(20q) | 5–8 | – |
| Loss of Y chromosome[a] | 5 | – |
| Isochromosome 17q or t(17p) | 3–5 | 25–30 |
| Loss of chromosome 13 or del(13q) | 3 | – |
| del(11q) | 3 | – |
| del(12p) or t(12p) | 3 | – |

[a]As a sole cytogenetic abnormality in the absence of morphological criteria, gain of chromosome 8, del(20q) and loss of Y chromosome are not considered definitive evidence of MDS [1]

kinase, is located in commonly deleted region (CDR) and plays a significant role in hematopoiesis. Haploinsufficiency of *CSNK1A1* results in β-catenin activation and induces hematopoietic stem cell expansion [16]. Furthermore, treatment with lenalidomide has been shown to be beneficial in the patients with isolated del(5q) by targeting *CSNK1A1* for ubiquitin-mediated degradation [17]. *G3BP1* is also located in the CDR region and regulates p53 activity through a dual pathway involving direct protein interaction of G3BP1-p53 and deubiquitination by regulating the ubiquitine-specific peptidase USP10 [18]. *G3BP1* also showed haploinsufficiency in deleted cases, and low expression of *G3BP1* predicts a poor prognosis [19].

Deletion of extreme telomeric regions (5q34 to the telomere) is related to an aggressive disease course [8]. Recently, autosomal dominant familial MDS/AML syndrome characterized by inherited *DDX41* mutations has been noted [20]. The patients with myeloid neoplasms with germ-line *DDX41* mutation have been found to be associated with the development of high-grade myeloid neoplasms with long latency [20]. *DDX41* is located on 5q35.3, the expression of *DDX41* is significantly decreased in deleted cases, and haploinsufficiency of *DDX41* predicts poor survival [19–21]. Thus, the loss of function of *DDX41* is considered to play a pathogenic role in disease progression of MDS in extreme-deleted del(5q) cases.

The presence of *TP53* mutations is the most common mutational event associated with del(5q) [19]. *TP53* mutation is present in almost 20% of cases and is associated with increased risk of leukemic transformation. Furthermore, *TP53* mutation with del(5q) cases tends to have an inferior response to lenalidomide and shorter survival [22–24]. The pathogenesis of *TP53* mutations selectively coinciding with del(5q) is still unclear . The clusters of negative regulators of p53 (e.g., *PPP2CA*, *RPS14*, *CSNK1A1* and *G3BP1*) [7, 14, 16, 25] are located on 5q. These inhibitory functions in deleted cases might be abolished by the acquisition of *TP53* mutations, a result that promotes leukemic evolution in *TP53*-mutated del(5q) cases.

**Table 2** The comprehensive cytogenetic scoring system for MDS

| Prognostic subgroup | Cytogenetic abnormalities |
|---|---|
| Very good | Loss of Y chromosome |
| | del(11q) |
| Good | Normal |
| | del(5q) |
| | del(12p) |
| | del(20q) |
| | Double: including del(5q) |
| Intermediate | del(7q) |
| | Gain of chromosome 8 |
| | Gain of chromosome 19 |
| | Isochromosome 17q |
| | Single or double abnormalities not specified in other subgroups |
| | Two or more independent non-complex clones |
| Poor | Loss of chromosome 7 |
| | Inv(3), t(3q) or del(3q) |
| | Double: including loss of chromosome 7 or del(7q) |
| | Complex:3 abnormalities |
| Very poor | Complex: > 3 abnormalities |

Based on information for Schanz et al. [28]

### -7/Del(7q)

Monosomy 7 and del(7q) (-7/del(7q)) occur in 10% of de novo MDS and in 50% of therapy-related MDS [26, 27]. This also occurs in MDS/myeloproliferative neoplasms (MDS/MPN) and primary and secondary AML. The presence of -7/del(7q) carries a uniformly poor prognosis [28]. Using metaphase cytogenetics and SNP-array-based karyotyping, minimal CDRs were identified as 7q22, 7q34, and 7q35-q36 [29, 30].

*CUX1* is located on 7q22 and encodes a homeodomain protein, which acts as a transcription factor in DNA repair mechanisms [31]. *CUX1* is thought to act as a tumor suppressor in myeloid progenitor cells by regulating genes involved in cell cycle and DNA repair [32, 33]. Due to the deletion of 7q22, haploinsufficiency of *CUX1* impairs base excision repair [34, 35] and contributes to the clonal expansion of del(7q) hematopoietic stem cells [32]. Inactivated mutations of the *CUX1* genes have also been reported in patients with MDS/AML [30, 33]. Therefore, loss of function of *CUX1* is thought to play a central role in tumorigenesis and disease progression in myeloid malignancies.

LUC7L2 is located in the most commonly deleted region of -7/del(7q); 7q34, which is deleted in 85% of -7/del(7q) patients [29]. The function of LUC7L2 is largely unknown; however, it is considered as a mammalian splicing factor which comprises a U1 snRNP [36]. The deficiency of *LUC7L2,* which is caused by haploinsufficiency or loss of function mutation, results in aberrant splicing of transcripts, including the genes involved in differentiation, which may contribute to the pathogenesis of MDS [30, 37].

The histone H3 methyltransferase *EZH2*, a member of the polycomb repressive complex 2 (PRC2), which binds to the trimethylation of H3K27, is also located on 7q36. Due to the deletion of 7q36, *EZH2* showed haploinsufficiency in deleted cases [30]. Trimethylation of H3K27 is generally associated with gene repression [38]. Inactivating mutations of *EZH2* occurred in patients with MDS, MDS/MPN, and MPN [39–41]. These somatic mutations exhibited frameshift, nonsense, and missense mutations which commonly affect the SET domain that is responsible for catalytic functions. Deficiency of *EZH2* would be associated with loss of H3K27 trimethylation at specific gene targets, although this remains to be determined. Loss of function of *EZH2* mutation in myeloid neoplasms is completely different from activating mutations of *EZH2* in lymphomas.

The expression of *SAMD9L*, which is located on 7q21.2, is also decreased in -7/del(7q) cases [42]. *SAMD9L* negatively regulates cell proliferation and is considered to be a tumor suppressor gene in hematopoietic cells. Heterozygous and homozygous *Samd9l* knockout mice exhibited leukocytopenia and anemia with dysplasia in multiple hematopoietic lineages and developed MDS with long latency [42, 43].

A number of genes showed haploinsufficiency for genes located in the CDRs and were found to be responsible for the development of myeloid neoplasms carrying -7/del(7q). The exact mechanisms by which genes contribute to pathogenesis remain unclear. However, the haploinsufficiency of multiple genes may provide insights into the complex nature of MDS.

### Other cytogenetic abnormalities

Isolated trisomy 8 is a characteristic cytogenetic abnormality in 5–7% of MDS cases [44] and is classified as an intermediate cytogenetic risk group according to clinical outcomes [5]. Trisomy 8 is thought to be a secondary or late event in the MDS transformation process [45, 46]. The precise mechanisms of the contribution to tumorigenesis remain unclear, but trisomy 8 cells showed resistance to apoptosis by the downstream upregulation of the anti-apoptotic elements survivin, c-myc, and CD1 [47].

Other common chromosomal abnormalities, such as 3q abnormalities, isochromosome 17q (i(17q)), trisomy 21, or del(20q) are relatively rare in MDS [6]. The pathogenesis of rare cytogenetic abnormalities is largely unknown, but the advancements of genetic technology may provide deeper insights into MDS pathophysiology in the near future.

## Recurrently mutated genes in MDS

### Somatic mutation in MDS

Somatic mutations in many of the genes play an important role in the pathogenesis and prognosis of MDS. Mutations in the spliceosome machinery (e.g., *SF3B1*, *SRSF2*, *U2AF1*), histone modification (e.g., *EZH2*, *ASXL1*), DNA methylation (e.g., *DNMT3A*, *IDH1*, *IDH2*, *TET2*), and cell cycle control (*TP53*) are particularly involved (Table 3).

### Spliceosome machinery

Somatic mutations in genes that are involved in the spliceosome complex have been identified in up to 50–89% of patients with MDS and are associated with disease development [4, 48]. The spliceosome is a large complex which is involved in the excision of introns from pre-mRNA with concurrent ligation of the flanking exon. Precise pre-mRNA splicing is essential for translation of appropriate protein; therefore, the splicing machinery plays a crucial role in the recognition of splice sites. Commonly mutated spliceosome genes are *SF3B1* (20–25%), *SRSF2* (10%), and *U2AF1* (8%), which are involved in the U2 snRNP complex [49]. Mutations in these genes induce RNA splicing defects, resulting in the production of intron-containing unspliced RNAs. The

**Table 3** Recurrent genetic mutations in MDS

| Gene | Frequency (%) | Location | Function |
|---|---|---|---|
| SF3B1 | 20–30 | 2q33 | RNA splicing |
| TET2 | 20–30 | 4q24 | DNA methylation |
| ASXL1 | 15–20 | 20q11 | Histone modification |
| SRSF2 | ~15 | 17q25 | RNA splicing |
| DNMT3A | ~10 | 2p23 | DNA methylation |
| RUNX1 | ~10 | 21q22 | Transcription factor |
| TP53 | 5–10 | 17p13 | Tumor suppressor |
| U2AF1 | 5–10 | 21q22 | RNA splicing |
| EZH2 | 5–10 | 7q36 | Histone modification |
| ZRSR2 | 5–10 | X chromosome | RNA splicing |
| STAG2 | 5–7 | X chromosome | Cohesin complex |
| NRAS | ~5 | 1p13 | Transcription factor |
| CBL | ~5 | 11q23 | Signal transduction |
| IDH1/IDH2 | ~5 | 2q33/15q26 | Cell metabolism DNA methylation |
| BCOR | ~5 | X chromosome | Transcription factor |

Mutations were found in at least 5% of MDS cases [33, 51, 66]

mutations in U2AF1 have been reported to possess distinct hot spots (e.g., Ser34 and Gln157) without any frameshift or nonsense alterations, suggesting a different mechanism of the pathogenesis of MDS [4, 50]. DDX41 and LUC7L2 are also involved in the splicing pathway, and somatic mutations of these genes have been reported in MDS cases [20, 30].

## Histone modification

Histone modification plays an important role in chromatin remodeling and gene expression. *EZH2* encodes the catalytic subunit of PRC2, which contributes to chromatin compaction, and catalyzes the methylation of histone H3K27. The somatic mutation of *EZH2* was found to be 6% of MDS and is an independent unfavorable prognostic factor [40, 51]. As mentioned previously, *EZH2* is located on chromosome 7q36, a commonly deleted region on del(7q), and thus loss of function of *EZH2* via deletion or mutation promotes tumorigenesis of myeloid neoplasms. In addition to *EZH2*, the mutations of *EED*, *JARID2,* and *SUZ12*, which encode other PRC2 subunits, have also been found in MDS [52–54]. Loss of function mutations of PRC2 components are involved in the pathogenesis of myeloid neoplasms through the derepression of key genes, including the posterior HOXA clusters, in hematopoietic progenitor cells [55].

*ASXL1* also recruits PRC2 to exert its transcriptional repression through increasing H3K27 methylation [56]. Mutations in *ASXL1* are detected in 11–14% of MDS [51, 56, 57]. Importantly, the majority of mutations in *ASXL1* occur as heterozygous exon 12 frameshift or nonsense mutations, which affect the c-terminal region containing a PHD domain. There has been controversy regarding whether the pathophysiology of *ASXL1* mutations causes loss-of-function, dominant-negative, or gain-of-function mutations. The mutations of *ASXL1* are almost always heterozygous and, thus, *ASXL1* mutations reveal the gain-of-function. In contrast to wild-type *ASXL1,* truncated mutant *ASXL1* recruits BRD4, resulting in enhanced expression of genes [58]. The presence of an *ASXL1* mutation also predicts inferior prognosis in MDS [57].

## DNA methylation

Aberrant DNA methylation is associated with gene silencing, including tumor suppressors, and plays a central role in the pathogenesis of MDS. Mutations in the epigenetic modifiers, such as DNA methyltransferases 3A (*DNMT3A*) and tet methylcytosine dioxygenase 2 (*TET2*), have been identified in 8% and 19% of MDS patients, respectively [58–60], and are associated with changes in global and gene-specific methylation. *DNMT3A* encodes an enzyme involved in de novo DNA methylation of cytosine to methylated cytosine at CpG residues, and most common mutations in *DNMT3A* are detected with the missense R822 methyltransferase domain [59]. Mutation with *DNMT3A* is associated with inferior prognosis and an increased incidence of progression to AML.

TET2 catalyzes the conversion of 5-methyl-cytosine (5-mC) to 5-hydroxymethyl-cytosine (5-hmC) and promotes DNA demethylation [61]. Therefore, loss of function of *TET2* mutations impairs the ability of this catalytic function and is associated with altered DNA methylation patterns and decreased 5-hmC levels in MDS [62, 63].

*IDH1* and *IDH2* are also commonly mutated in approximately 5–10% of MDS and AML cases [64–67], occurring in a mutually exclusive manner in most cases. *IDH1* and *IDH2* encode isocitrate dehydrogenase that catalyzes the conversion of isocitrate to α-ketoglutarate (α-KG), a crucial mediator of downstream pathways of DNA methylation [68]. *IDH* mutations cause loss of the normal catalytic activities and produce an oncometabolite, R-2-hydroxyglutalate (2-HG) (Fig. 2). 2-HG acts as an antagonist of α-KG to competitively inhibit the activity of multiple αKG-dependent dioxygenases, such as histones and DNA demethylases, which contribute to the MDS phenotype. Selective targeting inhibitors of the mutant *IDH1/IDH2* enzyme, enasidenib (AG-221) and ivosidenib (AG-120), are currently available for patients with IDH-mutated AML.

## TP53

The tumor suppressor *TP53* mutations are detected in 8–13% of de novo MDS and 30% therapy-related MDS cases. *TP53* mutations are significantly more frequent in del(5q) cases

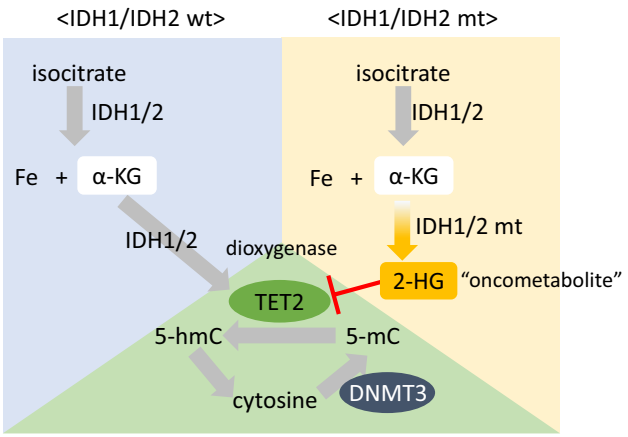


**Fig. 2** Molecular pathway of IDH-associated metabolism. Wild-type IDH1/2 (IDH1/2 wt) catalyzes isocitrate to α-KG. Mutated IDH1/2 (IDH1/2 mt) converts α-KG to the oncometabolite 2-HG, which inhibits members of the protein family of α-KG-dependent dioxygenases, including TET2. *α-KG* α-ketoglutarate, *2-HG* R-2-hydroxyglutalate, *5-mC* 5-methyl-cytosine, *5-hmc* 5-hydroxymethyl-cytosine

[19]. The presence of *TP53* mutations is strongly correlated with inferior survival, risk factors for leukemic transformation, and early relapse after various treatments [69–72]. Furthermore, *TP53* mutations are more prevalent in therapy-related MDS and easy to expand after chemotherapy [73, 74], which may reflect intrinsic resistance to chemotherapeutic agents. The patients with *TP53* mutation with del(5q) cases also show resistance to lenalidomide [22]. Recently, Welch et al. reported that *TP53* mutations predict decitabine-induced complete responses in patients with MDS and AML [75, 76]. Decitabine (5-aza-2′-deoxycytidine), a hypomethylating agent which inhibits DNA methyltransferase, is commonly used as a single agent to treat patients with MDS and elderly patients with AML. The mechanisms of response in patients with *TP53* mutation are unclear, but methylation signatures driven by *TP53* mutations may epigenetically prime. However, the efficacy of azacytidine in *TP53*-mutated cases remains unknown. A novel small molecule agent, APR-246, has been shown to restore wild-type conformation of missense mutant *TP53* and induce apoptosis [77]. APR-246 is currently in clinical investigation.

## Future directions

High-resolution array platforms for genome-wide copy number variation analysis and massive parallel sequencing have provided insight into the molecular pathogenesis of MDS and AML. Cytogenetics analysis alone seems to be insufficient for the evaluation of the risk of leukemic transformation and treatment failure. At present, the presence of *TP53* mutation predicts significantly adverse clinical outcomes in MDS; therefore, testing for *TP53* mutations should be considered in the specific population for allogeneic hematopoietic stem cell transplantation eligibility, which to date remains the only curative option. Although the functional roles of several driver mutations in pathogenesis remain unclear, much effort has been devoted to elucidating the pathogenesis, treatment responsiveness, and prognosis. Furthermore, it has been reported that over 30% of patients with unexplained cytopenia which does not meet diagnostic criteria for MDS, namely idiopathic cytopenia of undetermined significance (ICUS), carries MDS-associated somatic mutations [78]. The presence of the somatic mutation in the context of ICUS is now regarded as clonal cytopenia of undetermined significance (CCUS). The clinical implications of these findings are less clearly understood [79]. Based on the genome-wide profiling and clinical observations, diagnostic criteria of MDS may be revised to reflect disease prognosis. Moreover, genetic characterization may provide a therapeutic advantage to the patients with MDS/AML, while receiving the targetable drugs and participation in a prospective clinical trial depend on individual genetic abnormalities. Increase in understanding of pathogenetic mechanisms and technological improvements of detecting genetic alterations will provide a precise indicator for prognosis and a strategy to develop novel therapeutic opportunities.

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## Compliance with ethical standards

**Conflict of interest** No author has any conflict of interest.

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