Myelodysplastic syndromes (MDS) are defined as stem cell disorders caused by various gene abnormalities. Recent analysis using next-generation sequencing has provided great advances in identifying relationships between gene mutations and clinical phenotypes of MDS. Gene mutations affecting RNA splicing machinery, DNA methylation, histone modifications, transcription factors, signal transduction proteins and components of the cohesion complex participate in the pathogenesis and progression of MDS. Mutations in RNA splicing and DNA methylation occur early and are considered “founding mutations”, whereas others that occur later are regarded as “subclonal mutations”. RUNX1 mutations are more likely to be subclonal; however, they apparently play a pivotal role in familial MDS. These genetic findings may lead to future therapies for MDS.

Myelodysplastic syndromes (MDS) are a heterogeneous group of refractory hematological malignancies characterized by peripheral blood cytopenias due to ineffective hematopoiesis and risk for progression to acute myeloid leukemia (AML). Myelodysplastic syndromes have been presumed to be stem cell disorders, and it has been suspected that the development of MDS results from accumulation of multiple gene abnormalities, similar to solid cancers. In MDS, gene mutations, rather than karyotype abnormalities, are the major genetic abnormalities. Recent large-scale analysis using next-generation sequencing has greatly improved our understanding of the molecular pathogenesis, biological implications, clinical effects, subclassifications and prognostication of gene mutations associated with MDS. Elucidation of associations between gene mutations and clinical phenotypes has advanced rapidly, whereas the molecular pathogenesis based on the function of each variant has not been fully clarified yet. Among the gene mutations identified to date, we have attempted to clarify that RUNX1 mutations are a pivotal player in the molecular pathogenesis of MDS. It is becoming increasingly clear that RUNX1 mutations, cooperating with other various gene abnormalities, may promote the development of MDS /AML.

In this review, we initially summarize the various gene mutations that play an important role in the development of MDS. Next, we focus on RUNX1 mutations, which are key players in familial MDS and are a subject of active research. Finally, we attempt to propose comprehensive molecular mechanisms to achieve a better understanding of MDS, including implications for novel targeted therapies.

Gene Mutations
It has been reported that gene mutations involved in RNA splicing machinery, DNA methylation, histone modifications, transcription factors, signal transduction proteins and components of the cohesion complex participate in the pathogenesis and progression of MDS. Recent large-scale analysis using next-generation sequencing has gradually clarified the roles of various gene mutations in MDS. The median number of gene mutations affecting amino acid sequences detected in MDS is approximately 10 per patient. However, most of these are randomly acquired non-pathogenic mutations (i.e. passenger mutations), while the recurrent mutations that are causally related to the pathogenesis of MDS (i.e. driver mutations) are limited. Myelodysplastic syndromes are...
characterized by such driver mutations in about 40 genes, and approximately 80% of patients have one or more driver mutations. The most common genes with driver mutations are listed in Table 1.

**Mutations of RNA splicing machinery.** To generate a mature mRNA, an RNA splicing process that removes introns from pre-mRNA, mediated by a protein complex called a spliceosome, is essential. Splicing factor mutations, mainly SF3B1, SRSF2, U2AF1 (U2AF35), and ZRSR2, are detected with high frequency in MDS (45–85%), and they occur in a mutually exclusive manner. Because they are rare (<10%) in AML or myeloproliferative neoplasms, we can regard them as MDS-specific mutations. The mutations of these genes seem to have different impacts on cellular functions, manifesting as unique MDS phenotypes and suggesting that MDS phenotypes may be driven by alterations in splicing machinery.

Mutations in SF3B1 are detected at an extremely high frequency (60–70%) in refractory anemia with ring sideroblasts, and the SF3B1 mutation status has a positive predictive value for the MDS phenotype with ring sideroblasts of 98%. Heterozygous mutations are clustered at amino acids 622–700, especially K700E. It is possible that mutations may affect splicing of transcripts coding for proteins associated with iron handling in erythroid precursors, leading to abnormal localization of ferritin in mitochondria, as one of the target genes is SLC25A37.

The SRSF2 gene is also frequently mutated in MDS and more commonly in chronic myelomonocytic leukemia (CMML). Heterozygous mutations occur almost exclusively at position P95, which is essential for forming extensive contact with the target RNA through stacking.

### Table 1. Summary of driver mutations in myelodysplastic syndromes (MDS)

| Mutated genes | Associated phenotypes | MDS types | Other disease | Frequency in MDS (%) | Effect on outcome | Application to treatment |
|---------------|-----------------------|-----------|---------------|----------------------|------------------|--------------------------|
| **RNA splicing** (mutually exclusive) | | | | | | |
| SF3B1 | Ring sideroblasts | RARS, RCMD-RS | RARS-T | 15–30 | Good | None |
| SRSF2 | | RCMD, RAEB | CMML | 10–20 | Poor | None |
| U2AF1 | | RCMD, RAEB | CMML | 5–10 | Poor | None |
| ZRSF2 | | RCMD, RAEB | CMML | 5–10 | None | None |
| **DNA methylation** (TET2 and IDH1/2 are exclusive) | | | | | | |
| TET2 | Myeloid dominance | All MDS, normal karyotype | CMML | 20–30 | None | IDH1/2 inhibitors |
| IDH1/2 | | RCMD, RAEB | CMML | 5 | Poor (IDH2) | None |
| DNMT3A | | All MDS | AML | 10 | None | None |
| **Chromatin modification** (TET2 and IDH1/2 are exclusive) | | | | | | |
| ASXL1 | -7/7q | RCMD, RAEB | CMML | 15–20 | Poor | None |
| EZH2 | | RCMD, RAEB | CMML | 5 | Poor | None |
| BCOR | | RCMD, RAEB | CMML | 5 | Poor | None |
| **Transcriptional factor** (mutually exclusive) | | | | | | |
| RUNX1 | Thrombocytopenia | RCMD, RAEB | CMML, AML | 10 | Very poor | Kinase inhibitors |
| CEBPA | | RCMD, RAEB | AML | <5 | None–poor | Kinase inhibitors |
| ETV6 | | RCMD, RAEB | AML | <5 | Poor | Kinase inhibitors |
| **Signal transduction** (mutually exclusive) | | | | | | |
| NRAS/KRAS | | All MDS | JMM, CMML | 10 | Poor | None |
| CBL | | All MDS | JMM, CMML | 5 | Poor | None |
| JAK2 | Megakaryocytosis | All MDS | RARS-T, MPN | 5 | None | JAK inhibitors |
| NF1 | | All MDS | JMM | <5 | Poor | None |
| FLT3 | | All MDS | AML | <5 | Poor | FLT3 inhibitors |
| **Cohesion complex** (mutually exclusive) | | | | | | |
| STAG2 | Complex karyotype | RCMD, RAEB | AML, CMML | 5–10 | None–poor | None |
| TP53 | | RAEB, isolated del(5q) | | 10 | Very poor | None |

AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; JMM, juvenile monomyelocytic leukemia; MPN, myeloproliferative neoplasms; RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ring sideroblasts; RARS-T, refractory anemia with ring sideroblasts with thrombocytosis; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, refractory cytopenia with multilineage dysplasia with ring sideroblasts.
mutations are associated with mutations of RUNX1, IDH2, ASXL1, TET2, and STAG2. (3,7,16) Co-mutation of TET2 and SRSF2 was highly predictive of a myeloid neoplasm characterized by myelodysplasia and monocytosis, including but not limited to CMMML. (3)

Mutations of U2AF1 (U2AF35) are detected in 5–12% of MDS. (7,8,19) U2AF1 mutations are associated with ASXL1 mutations. (4) Mutations in U2AF1 recurrently alter two amino acid residues, S34 in the zinc finger 1 domain or Q157 in the zinc finger 2 domain. (8) U2AF1 mutants induce global abnormalities of RNA splicing, resulting in increased transcripts with unspliced intronic sequences and suppressed cellular proliferation (7) or they promote enhanced splicing and exon skipping (19).

Mutations in ZRSF2 are also detected in 3–11% of MDS. The mutations are widely distributed along the entire protein without a dominant location. (7)

**DNA methylation.** In MDS, gene mutations involved in DNA replication are frequently detected, resulting in aberrantly hypermethylated promoter-associated CpG islands. TET2 and IDH1/2 mutations occur in a mutually exclusive manner. TET2 is a critical regulator of hematopoietic stem cell (HSC) homeostasis, (20) and TET2 mutants induce self-renewal and clonal expansion in hematopoietic stem/progenitor cells in both normal and malignant hematopoiesis. Loss-of-function mutations or deletion of the gene leads to impaired DNA demethylation. Somatic TET2 mutations are found in elderly individuals with clonal hematopoiesis without hematological malignancies, (21) suggesting that the mutation is an aging-associated factor of hematopoietic cells or an initiating mutation. IDH1/2 mutants inhibit TET2 function, resulting in a similar effect of TET2 mutants. (22)

The DNA methyltransferase DNMT3A is expressed at high levels in HSCs. (23) DNMT3A mutations are frequently detected in AML, and less frequently in MDS. (24) In a mouse model, Dnmt3a-null HSCs showed DNA methylation changes and up-regulated HSC multipotency genes, including Runx1 and Gata3, resulting in stem cell expansion and reduced differentiation. (23)

**Chromatin modification.** Gene mutations associated with post-translational modifications of histones are also detected in MDS. ASXL1 plays critical roles both in activation and suppression of Hox genes in axial patterning through regulating the polycomb group and trithorax group proteins. ASXL1 is mutated in patients with the entire spectrum of myeloid malignancies. Asxl1–mutated mice displayed multilineage myelodysplasia, pancytopenia, and occasional progression to overt leukemia, which is similar to human MDS. (25) This phenotype is associated with derepression of Hoxa9 and microRNA-125a.

EZH2 is a component of the polycomb repressive complex-2 and encodes a histone methyltransferase that initiates trimethylation of lysine 27 in histone 3 (H3K27me3). Somatic loss-of-function mutations of EZH2 were identified in MDS (26,27). EZH2 loss also occurs in MDS by -7/-q chromosome anomalies and reduced expression of EZH2 in CD34+ cells. (28) EZH2 mutations in lower-risk MDS are correlated with a significantly worse prognosis. (29)

BCOR/BCORL1 is also a polycomb complex component and BCOR/BCORL1 mutations are detected in MDS associated with an unfavorable outcome. (3,4,30)

**Transcriptional factors.** Gene mutations of transcriptional factors associated with differentiation of HSCs are also detected in MDS, and they contribute to the differentiation impairment of hematopoietic cells. Furthermore, germ-line mutations of these genes have been described in familial MDS/AML. (31)

The RUNX1/AML1 gene has been investigated in the pathogenesis of hematopoietic diseases, and RUNX1 mutations have been frequently detected in patients with various types of hematological malignancies. A heterozygous germline mutation of the RUNX1 gene is known to cause a familial platelet disorder with a predisposition to AML (FPD/AML), which is regarded as familial MDS. (31) RUNX1 mutations are detected in 10–20% of MDS, (1) and they are especially frequent in higher-risk MDS and therapy-related myeloid neoplasms, (32,33) where they are associated with severe thrombocytopenia and very poor outcomes. (1,3,4) RUNX1 mutations have been shown to play a pivotal role in the pathogenesis of MDS/AML in both mouse models and human CD34+ cells. (34,35)

The transcription factor ETV6 is required for HSC maintenance. ETV6 mutations and deletions are detected in <5% of MDS patients. (1,4) ETV6 mutations are one of the predictors of poor overall survival in MDS. (1) Other mutations of transcriptional factors, including CEBPA, NPM1, and GATA2, have been described not only in AML but also in <5% of MDS. Most AML patients with CEBPA mutations have two different types of mutations simultaneously and show a favorable outcome, whereas MDS patients have only single CEBPA mutations and do not show a variety of associated gene alterations and show a poor prognosis. (36)

**Signal transduction.** Gene mutations involved in the signal transduction pathways occur in a mutually exclusive manner in individual patients with MDS. (1) One of the mutations in this category induces hypersensitive proliferation of MDS stem cells, contributing to the development of MDS. Genes involved in this category are more frequently involved in the pathogenesis of MDS/myeloproliferative neoplasms, especially juvenile nonerythroid myelocytic leukemia.

Genes involved in the RAS signaling pathway are mutated in hematopoietic malignancies. In MDS, NRAS or KRAS mutations are present in approximately 10% of patients, and these typically occur during transformation to AML. Mutations of receptor tyrosine kinases (FLT3 and KIT), commonly seen in de novo AML, are infrequent in MDS. Other members of the RAS pathway (NF1, BRAF, and PTPN11) are rarely mutated. CBL is involved in negative modulation of tyrosine kinase signaling. CBL mutations are also found in 5% of MDS, resulting in aberrant tyrosine kinase signaling. Activation of the JAK/STAT signaling pathway also associates with MDS pathogenesis. JAK2 mutations found in 5% of MDS contribute to megakaryocyte proliferation. (13)

**Other pathways.** The cohesin complex is involved in cohesion of sister chromatids, post-replicative DNA repair, and transcriptional regulation. Gene mutations and deletions of the cohesin complex, including STAG2, RAD21, SMC1A, and SMC3, are mutually exclusive and occur in different myeloid neoplasms. (37) STAG2 mutations are detected in 10% of MDS and result in loss of function. The mutations are significantly associated with RUNX1 mutations and are most prevalent in higher-risk MDS. (3,38)

TP53 is a tumor suppressor that responds to cellular stress by activating various protective pathways such as cell cycle regulation, apoptosis, and DNA repair. (60) TP53 mutations occur in approximately 10% of MDS, and they are more frequent in higher-risk or therapy-related cases. The mutations are strongly associated with a complex karyotype, resulting in loss of TP53 function. (1) A subpopulation of isolated del(5q) MDS patients has TP53 mutations at the early stage of the disease, which is...
associated with an increased risk of leukemic evolution.\(^{(39)}\)
Furthermore, \(TP53\) mutations are associated with the worst prognosis among the gene mutations in MDS, even after adjustment for other prognostic variables.\(^{(1)}\)

**Clonal Evolution and Genetic Abnormalities in MDS**

Although MDS have been presumed to be a stem cell disorder, chromosomal aberrations were found to be restricted to committed myeloid progenitor cells in MDS.\(^{(5)}\) Recently, the clonality and stemness of MDS have been clarified. Nearly all of the bone marrow cells are clonally derived in patients with both MDS and AML developing from MDS, regardless of the myeloblast count.\(^{(2)}\)

Furthermore, the existence of rare multipotent MDS stem cells was established and all cells identified somatically acquired genetic lesions that were backtracked to distinct MDS stem cells.\(^{(40)}\) Similarly, in isolated del(5q)-MDS the acquisition of del(5q) preceded diverse recurrent driver mutations.\(^{(40)}\)

Therefore, driver mutations occurring in MDS definitely occur in cells with a stem cell phenotype, proving that MDS are a stem cell disease.\(^{(41)}\)

By targeted deep sequencing techniques, it has become possible to find driver mutations involved in clonal evolution of MDS\(^{(3,4,42)}\). The mean number of gene mutations in a patient with MDS tends to be higher in the higher-risk subtypes, supporting the idea that some MDS stem cells gain the ability to proliferate by accumulation of gene mutations, leading to clonal expansion and disease progression.\(^{(4)}\)

Using pairwise precedences comparing the frequencies of mutated alleles, MDS genes were ranked in an attempt to elucidate how early in disease evolution they were mutated. The results suggested that mutations in genes involved in RNA splicing and DNA methylation occur early, that is, they are “founding mutations”, whereas driver mutations in genes involved in chromatin modification and signaling often occur later, that is, they are “subclonal mutations”\(^{(3,5)}\). Figure 1 shows the relations among founding mutations and subclonal mutations in a clonal evolution from MDS to subsequent AML.\(^{(42)}\)

Furthermore, combinations that do or do not significantly coexist have been found for each gene mutation, suggesting that the type of founding mutations tends to prescribe the type of subclone mutations.\(^{(3,4)}\) In particular, gene mutations involved in RNA splicing are supposed to decide disease types and clinical phenotypes of MDS.\(^{(3)}\)

\(TET2\) mutations are also detected in the blood of normal elderly individuals without hematological malignancies,\(^{(21)}\) and \(DNMT3A\) mutations are found in pre-leukemic HSCs in AML patients.\(^{(43)}\)

Furthermore, MDS-associated gene mutations including \(DNMT3A\), \(TET2\), \(JAK2\), \(ASXL1\), \(TP53\), \(BCORL1\), and \(SF3B1\) have been recurrently detected in the peripheral blood of patients with cancer without apparent hematological malignancies, the majority being associated with advanced age.\(^{(24)}\) The frequency of the gene mutations, which result in clonal expansion, reaches 5–6% of people older than 70 years. These findings support the idea that MDS is an aging disease, and it raises a possibility that anticancer therapies for elderly patients may easily induce therapy-related MDS.

**Correlation between Phenotype and Genotype**

Myelodysplastic syndromes are distinguished from AML by the blast threshold, defined as 20% blasts in the blood or bone marrow, according to the WHO classification. Unlike the classification for AML, which is based on cytogenetic and genetic abnormalities, the classification for MDS, which is derived from unsatisfactory insights into the molecular pathogenesis, still relies on morphological findings except in the case of isolated del(5q). It will be necessary to clarify the molecular mechanisms of MDS in order to establish a new classification scheme with a characteristic constellation of clinical, genetic, and pathologic findings, similar to AML. Recent large-scale analyses of gene mutations in MDS and related diseases have identified molecular abnormalities (genotypes) that are specific for each MDS subtype (phenotype). \(SF3B1\) mutations have a strong positive predictive value for the ring sideroblasts phenotype.\(^{(3,12,13)}\) According to recent analyses, a classification based on morphologic and genetic criteria for MDS with no excess blasts (<5%) has been proposed.\(^{(13)}\)

Besides “isolated
del(5q)”, which has already been established as a disease category, MDS with “SF3B1 mutations” may be authorized as a subtype of MDS, corresponding to disease categories in the WHO classification of “refractory anemia with ring sideroblasts (RARS)” and “refractory cytopenia with multilineage dysplasia with ring sideroblasts (RCMD-RS)”. Moreover, mutations of genes involved in DNA methylation, the RAS pathway, and cohesion complex and splicing factors except SF3B1 are independently associated with multilineage dysplasia, and they are regarded as “multilineage dysplasia-associated mutations”. Myelodysplastic syndromes with “multilineage dysplasia-associated mutations” form a distinct subset of MDS corresponding to disease categories in the WHO classification of “refractory anemia with ring sideroblasts (RARS)” and “refractory cytopenia with multilineage dysplasia with ring sideroblasts (RCMD-RS)” (13). Hypocellular MDS without excess blasts is difficult to differentiate from a diagnosis of aplastic anemia. Acquired mutations of myeloid-related genes (ASXL1, DNMT3, BCOR, and TET2) are present in a proportion of aplastic anemia and these somatic mutations predict a higher risk of transformation to MDS.(45)

On the other hand, the refractory anemia with excess blasts (RAEB) subtype has not yet been clearly defined by gene mutations. Most patients with MDS-RAEB show clonal evolution into AML or CMML. The WHO classification that defines MDS-RAEB and AML is based solely on the percentage of blasts; however, gene abnormalities are similar between MDS-RAEB and AML with a low blast cell count. In particular, splice factor-mutant RAEB and splice factor mutant AML are clinically, cytologically, and molecularly highly similar, suggesting that these two disorders should be considered as related disease entities. Furthermore, co-mutation of TET2 and SRSF2 is highly predictive of myelodysplasia and monocytosis, including CMML. Therefore, these disease categories could be distinguished by gene abnormalities. Figure 2 shows a new classification scheme based on the molecular pathogenesis of MDS and related diseases.

**Familial/Congenital MDS**

Most MDS cases are sporadic, and familial or congenital MDS cases are very rare, but they are valuable for investigations of the molecular pathogenesis of MDS. Germline mutations of hematopoiesis-specific transcriptional factors are implicated in familial/congenital MDS. Familial platelet disorder with predisposition to AML (FPD/AML) is a rare autosomal dominant disorder characterized by congenital quantitative and qualitative platelet defects and a propensity to develop MDS or AML at a high incidence (20-50%). A heterozygous germline mutation of the RUNX1 gene is known to cause FPD/AML. Induced pluripotent stem cells from FPD/AML pedigrees are clearly defective in the emergence of hematopoietic progenitors and differentiation of megakaryocytes. Affected individuals in FPD/AML pedigrees may develop leukemia at various times throughout their lifespan, suggesting that the acquisition of additional mutations is needed to cause leukemia during this long latency period. CDC25C mutations are frequently found in FPD/AML and mutated CDC25C disrupts the G2/M checkpoint and promotes cell cycle progression. CDC25C mutations are suspected to define a founding pre-leukemic clone, followed by stepwise acquisition of subclonal mutations that contribute to leukemia progression. In some FPD/AML pedigrees, all of the affected members develop hematological malignancies, suggesting a possibility that some RUNX1 mutants may upregulate other genes through a gain-of-function mechanism leading to leukemogenesis.

Mutations in GATA2 have been reported in families that show a predisposition to MDS/AML with primary lymphedema (Emberger syndrome), a syndrome of monocytopenia, B-cell and natural killer cell lymphopenia, and mycobacterial, fungal, and viral infections (MonoMAC syndrome) or without preceding symptoms. Molecular mechanisms of processes leading to MDS/AML are being investigated in affected individuals with GATA2 mutations.

![Fig. 2. Myelodysplastic syndromes (MDS) and related hematological diseases caused by driver mutations. AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia.](image-url)
Molecular Mechanisms of MDS via RUNX1 Abnormalities

Mutations in RUNX1 are generally subclonal rather than founding mutations in MDS. However, in FPD/AML, RUNX1 mutations apparently play a pivotal role as founding mutations. The RUNX1 gene has been investigated in the pathogenesis of hematopoietic diseases, and RUNX1 mutations have been frequently detected in patients with various types of myeloid neoplasms, especially in higher-risk MDS. It is intriguing how RUNX1 mutations contribute to the development of divergent hematological neoplasms. Functionally, most of the RUNX1 mutants show an equal loss of normal RUNX1 trans-activation potential. Although a stem/progenitor cell with a RUNX1 mutation is suspected to have an MDS-genic potential to develop cell dysplasia and self-renewal capacity, it does not have enough proliferation ability for the development of MDS. Therefore, additional gene alterations that induce proliferation activity seem to be necessary. STAG2, EZH2, and ASXL1 mutations have significant relationships with RUNX1 mutations, suggesting that these mutations may functionally collaborate with RUNX1 mutations. The biological functions of RUNX1 mutants in human CD34+ cells and in a mouse bone marrow transplantation model show increased leukemogenic potential with high expression of Evi1 overexpression of BMI1, or loss of Ezh2. Furthermore, alterations of RUNX1 expression levels and splicing abnormalities, which can be changed by epigenetic modifications, microRNA alterations, and other known/unknown mechanisms, may be associated with the development of hematological malignancies.

Therapeutic Approaches from Molecular Pathogenesis

The current therapeutic algorithm for MDS, dividing cases into lower-risk and higher-risk according to some prognostic scoring systems, is based on the guidelines of the National Comprehensive Cancer Network. Because curative therapies have not been established, patients with MDS without symptoms are carefully monitored without therapy. Lower-risk patients are typically treated with supportive care including transfusion and antimicrobial agents for suspected infections. Iron chelation in erythrocyte transfusion-requiring patients may be considered. Patients with del(5q) are treated with lenalidomide. To stimulate hematopoiesis, erythropoiesis-stimulating agents, granulocyte colony stimulating factor, and thrombopoietin agonists are considered for carefully selected patients. A subset of the patients respond to immunosuppressive therapy. Patients with higher-risk MDS are typically treated with hypomethylating agents, and they can proceed to allogeneic hematopoietic stem cell transplantation, the only potentially curative therapy for MDS, if a donor is available and the patient is a suitable candidate. However, most MDS patients exceed the recommended age for safe transplantation. Overall, MDS treatment is disappointing because only some of the patients respond to drug therapy and their responses are often not durable. Genetic studies may provide both insights to better inform treatment choices and new therapeutic options.

Clinical predictors of responses to therapeutic agents have been developed. Isolated del(5q) is the best clinical predictor of responses to lenalidomide to alter treatment decisions. TET2 mutations and DNMT3A mutations can predict responses to hypomethylating agents in MDS patients, however their predictive value is insufficient and the mutations do not predict overall survival. The therapeutic agents for MDS still have unknown mechanisms, therefore, it is difficult to predict clinical responses by analyzing gene abnormalities at present. Furthermore, most of the currently available therapies fail within a few years even if initial responses are good. Therefore, new therapeutic agents based on the specific molecular pathogenesis are in great demand. A number of DNA methyltransferase inhibitors, deacetylase inhibitors, and kinase inhibitors are in clinical trials; however, molecular target therapies to normalize RNA splicing, transcriptional regulation, or TP53 function have not yet been established. It is expected that the development of these therapeutic agents will change MDS treatment dramatically in the future.
Conclusion

Figure 3 shows molecular pathways and gene mutations affected in MDS. Most of the gene abnormalities in MDS consist of minimum DNA changes with great individual differences. Therefore, diagnosis and classification based on molecular mechanisms cannot yet be readily established. The definition of molecular subclassifications of MDS has advanced gradually: “driver mutations” that lead to pathogenesis have been identified by exhaustive gene mutation analysis, molecular architecture has become clear by deep sequencing, and genotype-phenotype correlations have been clarified by large-scale analyses. However, gene mutation analysis is not yet performed routinely, and its use for diagnosis at the bedside is still far in the future. Establishment of molecular classifications based on pathogenesis, further progress in developing simple methods to detect gene mutations, and discovery of therapeutic agents targeting specific gene abnormalities will lead to the establishment of personalized medicines to treat MDS in the near future.

Disclosure Statement

The authors have no conflict of interest.
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