

REVIEW ARTICLE

MECHANISMS OF DISEASE

Myelodysplastic Syndromes

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According to the 2008 World Health Organization (WHO) classification system for hematologic cancers, the primary myelodysplastic syndromes are one of five major categories of myeloid neoplasms (Table 1).¹ The main feature of myeloid neoplasms is stem-cell–derived clonal myelopoiesis with altered proliferation and differentiation. The phenotypic diversity of these neoplasms has been ascribed to different patterns of dysregulated signal transduction caused by transforming mutations that affect the hematopoietic stem cell. There is increasing evidence that haploinsufficiency, epigenetic changes, and abnormalities in cytokines, the immune system, and bone marrow stroma all contribute to the development of the myelodysplastic syndromes. In this review, we discuss these and other mechanisms in adult-onset primary myelodysplastic syndromes and summarize the classification of the disease and its prognosis and treatment.

POPULATION AT RISK

The onset of a myelodysplastic syndrome before the age of 50 years is rare, but the various forms of this disease are among the commonest hematologic cancers in patients over the age of 70 years, among whom the annual incidence exceeds 20 per 100,000 persons.² Incidence rates are higher in men by a factor of approximately 1.8.² Other risk factors include the receipt of chemotherapy or radiation treatment and, to a lesser extent, tobacco use and occupational exposure to solvents or agricultural chemicals.³

The risk of both the myelodysplastic syndromes and acute myeloid leukemia (AML) is increased in certain genetic syndromes: the Diamond–Blackfan syndrome (pure red-cell hypoplasia with craniofacial, skeletal, or cardiac defects), the Shwachman–Diamond syndrome (neutropenia, exocrine pancreatic insufficiency, and short stature), dyskeratosis congenita (anemia and thrombocytopenia with cutaneous pigmentation, nail dystrophy, and leukoplakia), Fanconi's anemia (aplastic anemia with short stature and other skeletal abnormalities), and severe congenital neutropenia.⁴ In contrast, there is little information on hereditary predispositions for nonsyndromic forms of the disease, with the exception of a familial platelet disorder associated with a monoallelic germ-line mutation in *RUNX1*, the gene encoding runt-related transcription factor 1 on chromosome 21q22. This genomic region is frequently involved in chromosomal translocations and somatic point mutations in the acute leukemias, sporadic myelodysplastic syndromes, myelodysplastic syndrome with myeloproliferative features, and therapy-related myeloid neoplasms.⁵

PATHOLOGICAL FEATURES

Patients with a myelodysplastic syndrome usually present with anemia and other cytopenias. A dimorphic red-cell population that includes oval macrocytes, nuclear

Table 1. Classification of Myeloid Neoplasms, According to World Health Organization Criteria.

Acute myeloid leukemia and related neoplasms*
Myelodysplastic syndromes
Refractory cytopenia with unilineage dysplasia†
Refractory anemia (ring sideroblasts <15% of erythroid precursors)
Refractory neutropenia
Refractory thrombocytopenia
Refractory anemia with ring sideroblasts (dysplasia limited to erythroid lineage and ring sideroblasts ≥15% of bone marrow erythroid precursors)
Refractory cytopenia with multilineage dysplasia (regardless of ring sideroblast count)
Refractory anemia with excess of blasts (RAEB)
RAEB-1 (2–4% circulating blasts or 5–9% marrow blasts)
RAEB-2 (5–19% circulating blasts or 10–19% marrow blasts or Auer rods present)
Myelodysplastic syndrome with isolated del(5q)
Myelodysplastic syndrome (unclassifiable)
Myeloproliferative neoplasms‡
Myelodysplastic–myeloproliferative neoplasms§
Molecularly characterized myeloid or lymphoid neoplasms associated with eosinophilia¶

* This category includes therapy-related myelodysplastic syndrome.

† Refractory cytopenia is defined as a hemoglobin level of less than 10 g per deciliter, an absolute neutrophil count of less than 1.8×10^9 per liter, or a platelet count of less than 100×10^9 per liter. However, higher blood counts do not exclude the diagnosis in the presence of unequivocal histologic or cytogenetic evidence of a myelodysplastic syndrome.

‡ Myeloproliferative neoplasms include chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, primary myelofibrosis, chronic neutrophilic leukemia, systemic mastocytosis, chronic eosinophilic leukemia (not otherwise specified), and myeloproliferative neoplasm (unclassifiable).

§ Myelodysplastic–myeloproliferative neoplasms include chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, atypical chronic myeloid leukemia (BCR-ABL1–negative), and myelodysplastic–myeloproliferative neoplasm (unclassifiable).

¶ This category includes genetic rearrangements involving platelet-derived growth factor receptor α or β or fibroblast growth factor receptor 1.

hyposegmentation of neutrophils (pseudo–Pelger–Huët cells), and hypogranulation of neutrophils and platelets are frequent in blood smears (Fig. 1A and 1B). Bone marrow dysplasia involving at least 10% of the cells of a specific myeloid lineage is the cardinal feature of the myelodysplastic syndromes (Fig. 1C and 1E). Ring sideroblasts, which reflect abnormal accumulation of iron in mitochondria, sometimes accompany signs of dyserythropoiesis (Fig. 1D).

Erythroid dysplasia can be a secondary change in a variety of disorders that must be excluded before the diagnosis of a myelodysplastic syndrome is made. These disorders include deficiencies of vitamin B₁₂, folate, and copper; viral infections, including infection with the human immunodeficiency virus; treatment with hydroxyurea or other chemotherapeutic agents; chronic alcohol abuse; lead or arsenic poisoning; and inherited disorders, such as congenital dyserythropoietic anemias.

CLASSIFICATION

A century ago, the myelodysplastic syndromes were known as pseudoaplastic anemia because of the combination of cytopenia and hypercellular bone marrow.⁶ In 1941, pseudoaplastic anemia was lumped with other forms of anemia that were unresponsive to the therapy that was known at the time; collectively, these disorders were referred to as “refractory anemia.”⁷ Subsequently, many other terms were used before the disease acquired its official designation, the myelodysplastic syndromes.

In 1982, the French–American–British (FAB) Cooperative Group published a seminal classification system that distinguished five subcategories of the myelodysplastic syndromes: refractory anemia, refractory anemia with ring sideroblasts (RARS), refractory anemia with excess of blasts (RAEB), RAEB “in transformation” (RAEB-T), and chronic myelomonocytic leukemia (CMML).⁸ The

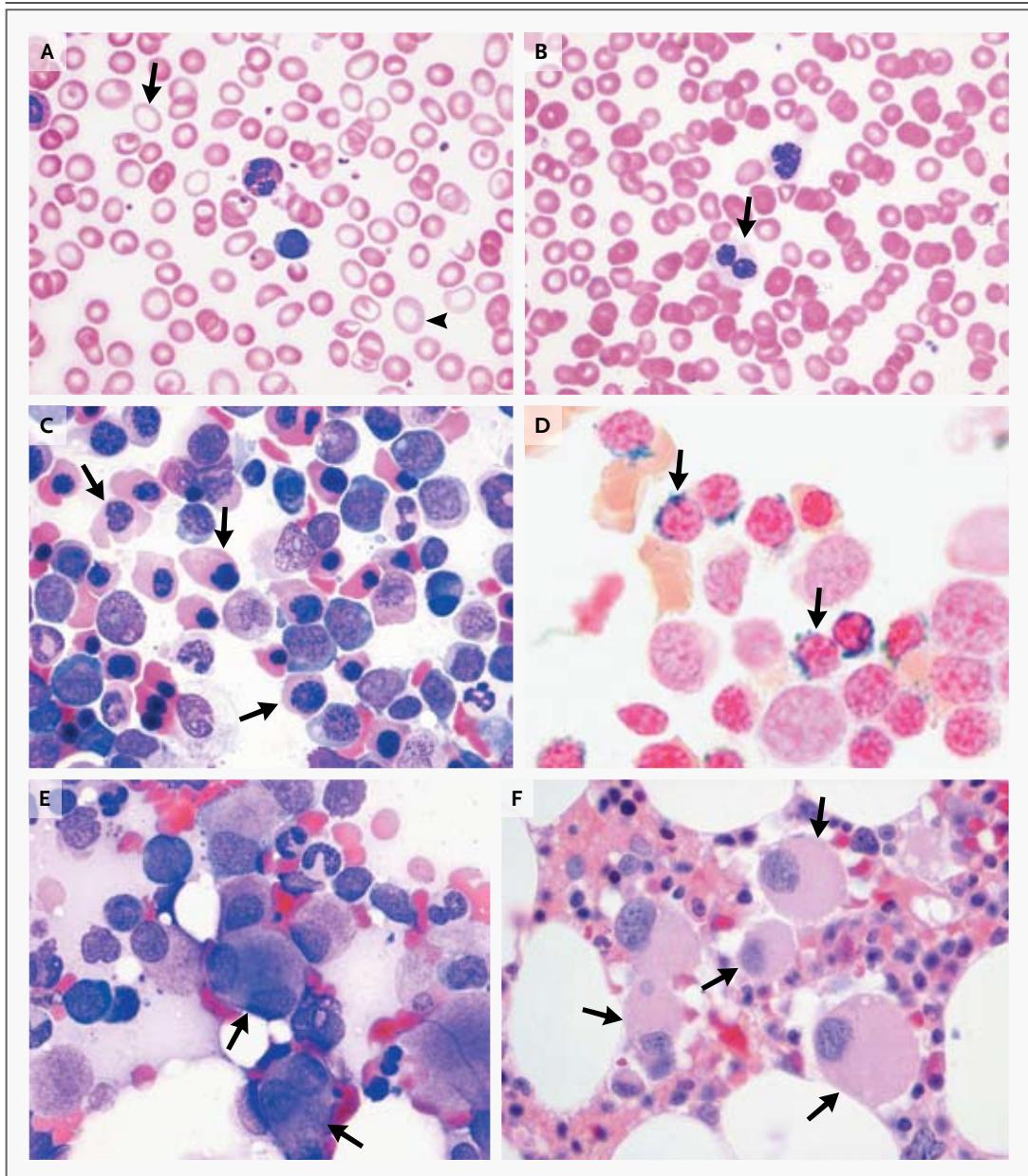


Figure 1. Morphologic Features of Peripheral Blood and Bone Marrow in the Myelodysplastic Syndromes.

Panel A shows a peripheral-blood sample from a patient with refractory anemia with ring sideroblasts, with dimorphic red cells; some of the cells are normochromic whereas others are hypochromic (arrow). There is also anisocytosis with occasional macroovalocytes (arrowhead). Panel B shows a peripheral-blood sample from a patient with refractory anemia with excess of blasts, demonstrating pseudo-Pelger-Huët cells with hypercondensed chromatin and hypobulbated nuclei and virtually colorless cytoplasm (arrow). Panel C shows dyserythropoiesis (arrows) in a bone marrow sample obtained from a patient with refractory cytopenia with multilineage dysplasia. Panel D shows ring sideroblasts (arrows) from a patient with refractory anemia. The ring sideroblasts are characterized by at least five granules of iron that encircle the nucleus of the erythroid precursor. Panel E shows numerous dysplastic small megakaryocytes (arrows) with monolobed or bilobed nuclei and mature granular cytoplasm in the aspirate smear of a patient with refractory anemia with excess of blasts. Panel F shows a tissue section from bone marrow of a patient with a myelodysplastic syndrome and isolated $\text{del}(5q)$. The megakaryocytes are of medium size, with hypobulbated nuclei (arrows).

main distinguishing feature of these subgroups is the proportion of myeloblasts in the bone marrow: less than 5% in refractory anemia and RARS, 5 to 20% in RAEB, 21 to 30% in RAEB-T, and 0 to 20% in CMML. In addition, RARS is notable for more than 15% ring sideroblasts in the erythroid precursor population, and CMML is notable for monocytosis ($>1.0 \times 10^9$ cells per liter). Ring sideroblasts, a defining feature of RARS, can also be seen in disease variants and probably represent defective iron transport between mitochondria and cytoplasm.⁹

In 2001, a WHO committee modified the FAB system by lowering the level of myeloblasts required for the diagnosis of AML (to 20%), by folding the RAEB-T category into the AML category, by placing CMML into a new category of myeloid neoplasms that have both myelodysplastic and myeloproliferative features (MDS-MPN), and by acknowledging multilineage dysplasia and isolated del(5q) as distinctive features in forms of the disease with a low blast count.¹⁰ The revised 2008 WHO document maintains these modifications and makes additional adjustments in classifying adult-onset primary myelodysplastic syndromes into six subcategories (Table 1).¹

DIAGNOSIS

The minimal morphologic criterion for the diagnosis of a myelodysplastic syndrome is dysplasia in at least 10% of cells of any one of the myeloid lineages. However, such changes can also be seen in other myeloid neoplasms, which must be excluded before a diagnosis is made. These include AML, which is defined by at least 20% myeloblasts in bone marrow or peripheral blood; MDS-MPN, in which dyserythropoiesis or dysgranulopoiesis is associated with leukocytosis or monocytosis ($>1.0 \times 10^9$ cells per liter), as in CMML; and MPN, in which both dyserythropoiesis and dysgranulopoiesis are absent.

Figure 2 shows an algorithm for WHO-based subcategorization of the myelodysplastic syndromes, in which the diagnosis of four of the six variants requires a blast count of less than 5% in the bone marrow and less than 1% in the blood. RARS features erythroid dysplasia and at least 15% ring sideroblasts in the erythroid precursor population and must be distinguished from the provisional WHO entity of RARS that is associ-

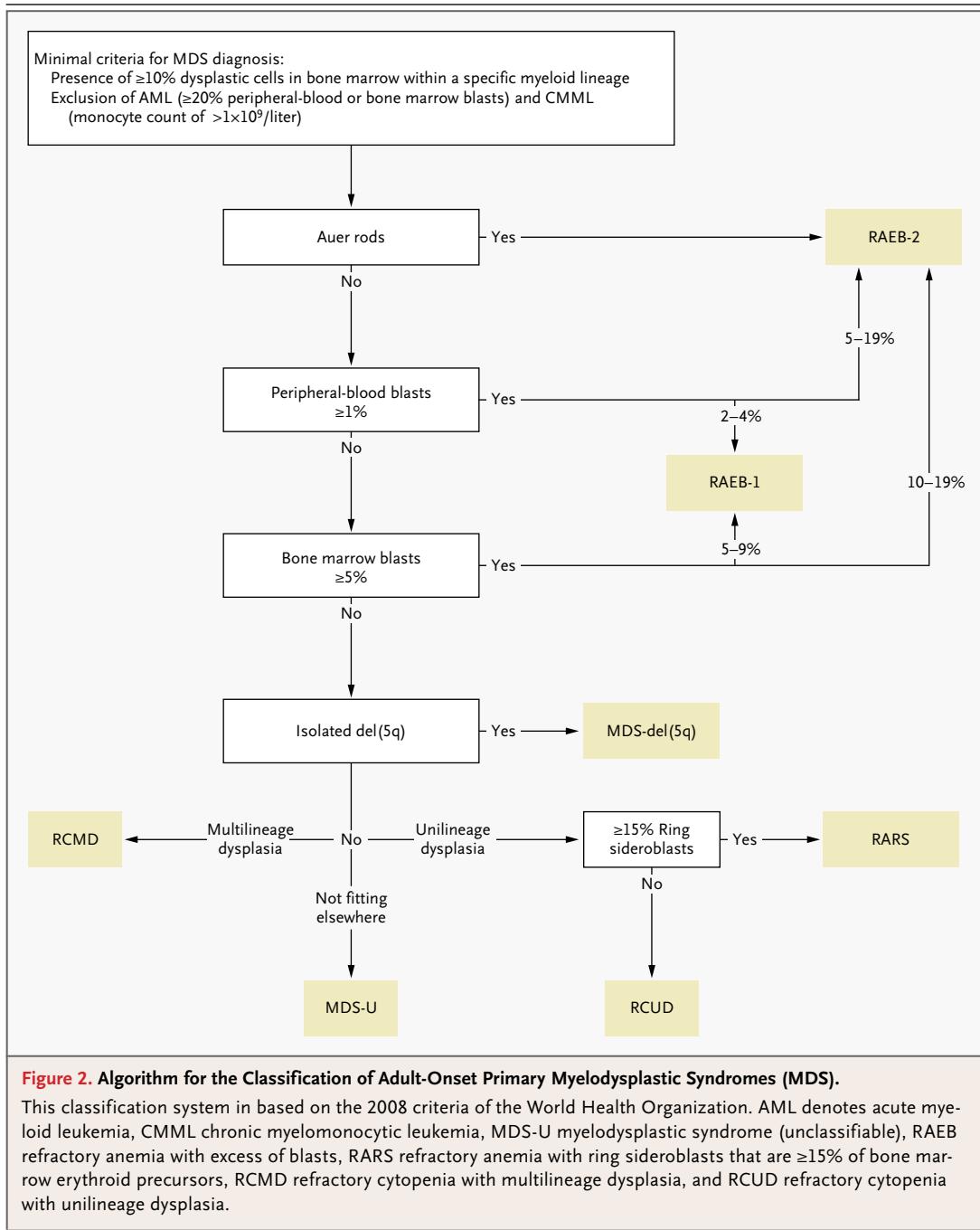
ated with marked thrombocytosis and dyserythropoiesis (RARS-T), a platelet count of at least 450×10^9 per liter, MPN-like megakaryocyte morphology, and a higher frequency of Janus kinase 2 (JAK2) V617F variant (20 to 50%) than in the myelodysplastic syndromes.¹ The JAK2 mutation is a typical feature of MPN but not of the myelodysplastic syndromes; the frequency of this mutation exceeds 90% in polycythemia vera and 50% in essential thrombocythemia or myelofibrosis but is less than 5% in the myelodysplastic syndromes.¹¹

KARYOTYPIC ABNORMALITIES

Cytogenetic abnormalities have been found at diagnosis in 20 to 70% of patients with variants of the myelodysplastic syndromes. The highest frequencies were found in patients with RAEB-1 (characterized by 5 to 9% blasts in bone marrow) or RAEB-2 (characterized by 10 to 19% blasts in bone marrow) and the lowest in those with RARS.¹² Approximately 5% of cases are classified as the myelodysplastic syndrome with isolated del(5q). The most frequent single cytogenetic abnormalities in this and other studies were del(5q), monosomy 7 or del(7q), trisomy 8, and del(20q) (see Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).¹³⁻¹⁵ The loss of the Y chromosome is also prevalent in patients with a myelodysplastic syndrome but is usually considered an age-related phenomenon and not always indicative of a clonal disorder.¹⁶

Certain cytogenetic abnormalities in patients with a myelodysplastic syndrome are associated with a characteristic morphology and clinical phenotype. One of these abnormalities is the isolated del(5q), which is associated with the presence of small, hypolobulated megakaryocytes, a relatively indolent clinical course, and a favorable response to treatment with lenalidomide¹⁷ (Fig. 1F). The other abnormality is del(17p), which is associated with the presence of pseudo-Pelger-Huët cells containing small vacuoles, a deletion of TP53, and a relatively high risk of leukemic transformation.¹⁸

In general, cytogenetic abnormalities that are associated with a myelodysplastic syndrome also occur in other myeloid neoplasms and vice versa. Patients with a myelodysplastic syndrome never



have certain AML-associated karyotypic abnormalities and rarely have the MPN-associated trisomy 9 and del(13q).¹⁹ As compared with primary myelodysplastic syndromes, the therapy-related form of the disease is associated with an increased frequency of abnormal karyotypes, complex cytogenetic abnormalities, and deletions involving either chromosome 5 or chromosome 7 or both.

PATHOGENESIS

The myelodysplastic syndromes probably originate from a primitive hematopoietic stem cell.¹⁶ The initiating mutation or molecular pathway is unknown. Given the histologic and cytogenetic heterogeneity, the disease in its various forms probably constitutes a group of molecularly distinct entities with variable degrees of ineffective hema-

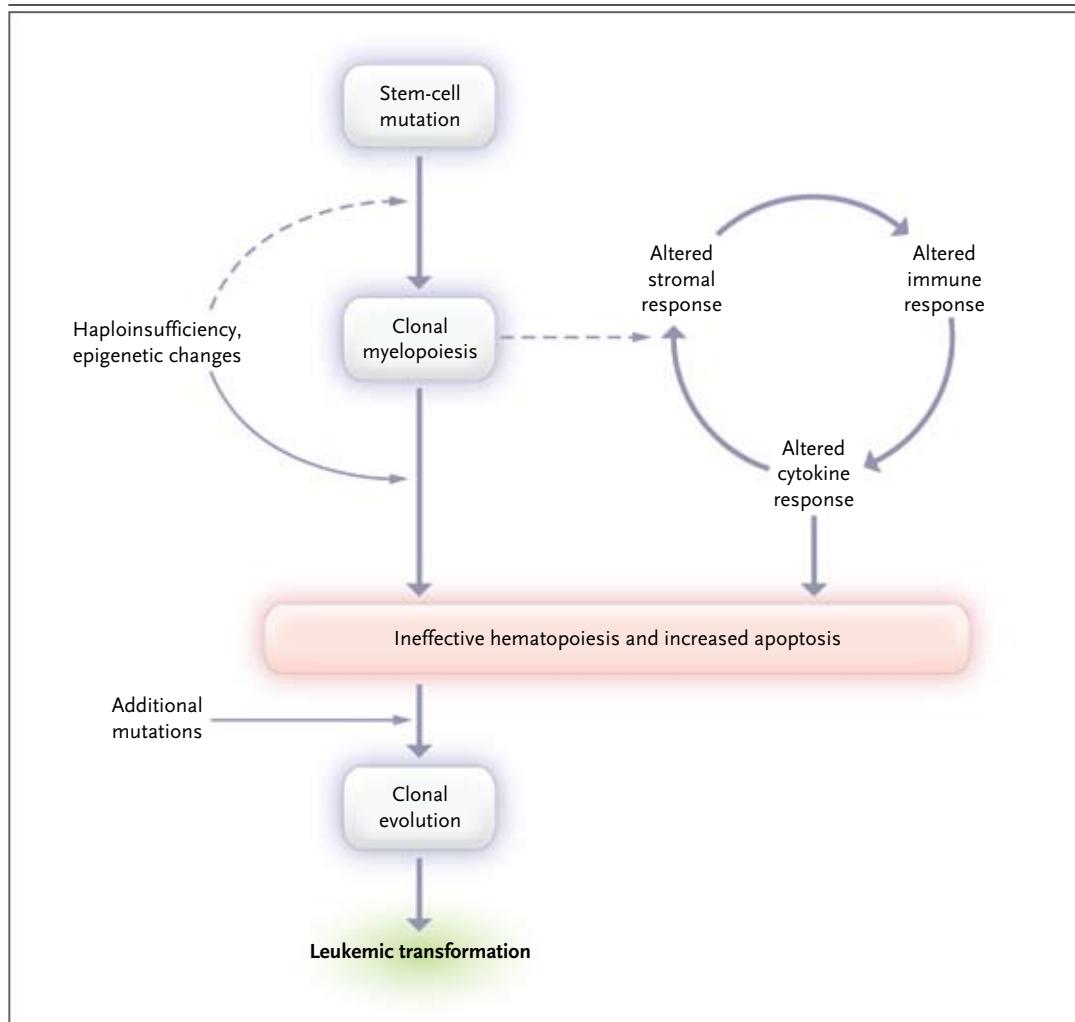


Figure 3. Putative Pathogenic Mechanisms and Their Interaction in the Myelodysplastic Syndromes.

The myelodysplastic syndromes probably arise from a genetically transformed, primitive hematopoietic stem cell. However, subsequent genetic and epigenetic changes contribute to phenotypic diversity, hematopoietic efficiency, and susceptibility to leukemic transformation. Immune, cytokine, and stromal responses in the host also contribute to the disease phenotype.

topoiesis and susceptibility to leukemic transformation. Furthermore, secondary mutations, haploinsufficiency, epigenetic changes, and altered responses in cytokines, the immune system, and bone marrow stroma also contribute to the disease phenotype (Fig. 3).

CLONALITY AND THE STEM CELL

Studies that have been based on the phenomenon of X-chromosome inactivation in female patients²⁰ and on abnormal karyotypes in patients with a myelodysplastic syndrome have uncovered clonal populations of cells of the myeloid lineage in the disease. Cells of the lymphoid lineage have been

found to contain clonal populations but only inconsistently.²¹ There is also evidence of clonal populations of mesenchymal stem cells,²² circulating endothelial cells,²³ and primitive hematopoietic stem cells.²⁴ These stem cells give rise to a myelodysplastic syndrome–like phenotype when transplanted into severely immunodeficient mice, thus meeting a principal criterion for a cancer stem cell.^{25,26}

Stem cells that are associated with the myelodysplastic syndromes are relevant to treatment. Dormant stem cells and their residence in a protective niche in the marrow²⁷ could explain in part the inadequate and transient response of

the myelodysplastic syndromes to conventional chemotherapy. Pharmacologic interference with self-renewal or interruption of pathways that sustain clonal stem cells or that disturb the interaction between stem cells and the protective marrow niches could overcome resistance to treatment.^{28,29}

Chemosensitivity of stem cells in the myelodysplastic syndromes might be enhanced by drugs such as plerixafor (also called AMD3100) that interfere with the binding of stromal cell-derived factor 1 to its receptor, CXCR4.³⁰ Plerixafor induces a rapid exit of hematopoietic cells from the marrow into the blood. It is also possible that pharmacologic inhibition of the tumor-suppressor promyelocytic leukemia protein with arsenic trioxide could arouse clonal stem cells from their quiescent state.³¹ Since clonal and polyclonal stem cells probably coexist in the myelodysplastic syndromes,^{32,33} the biologic and immunophenotypic differences between these two types of cells could be exploited for the development of therapies directed specifically against clonal stem cells.^{29,34}

MUTATIONS

A number of nonspecific mutations have been described in patients with a myelodysplastic syndrome (Table 2 in the Supplementary Appendix). The most recent additions include mutations in *TET2* (encoding TET oncogene family, member 2 on chromosome 4q24)³⁵ and *ASXL1* (encoding additional sex combs-like 1 on chromosome 20q11).³⁶ *TET2* is probably a tumor-suppressor gene, and the *ASXL1* proteins regulate chromatin remodeling. Most nonspecific mutations occur infrequently in patients with a myelodysplastic syndrome and are also found in other myeloid neoplasms.³⁷⁻⁴⁰ The role of these mutations in the pathogenesis or progression of the disease is unclear.

MOUSE MODELS

Models in mice can display typical features of the myelodysplastic syndromes, including cytopenias, bone marrow dysplasia, intramedullary apoptosis, and transformation to acute leukemia (Table 2 in the Supplementary Appendix).⁴¹⁻⁴⁵ Some of these models support the concept of multistep clonal progression in patients with a myelodysplastic syndrome.^{46,47} One example is *NUP98-HOXD13*, a translocation that inhibits the differentiation of hematopoietic stem cells. Leukemic transformation in *NUP98-HOXD13* transgenic mice is associ-

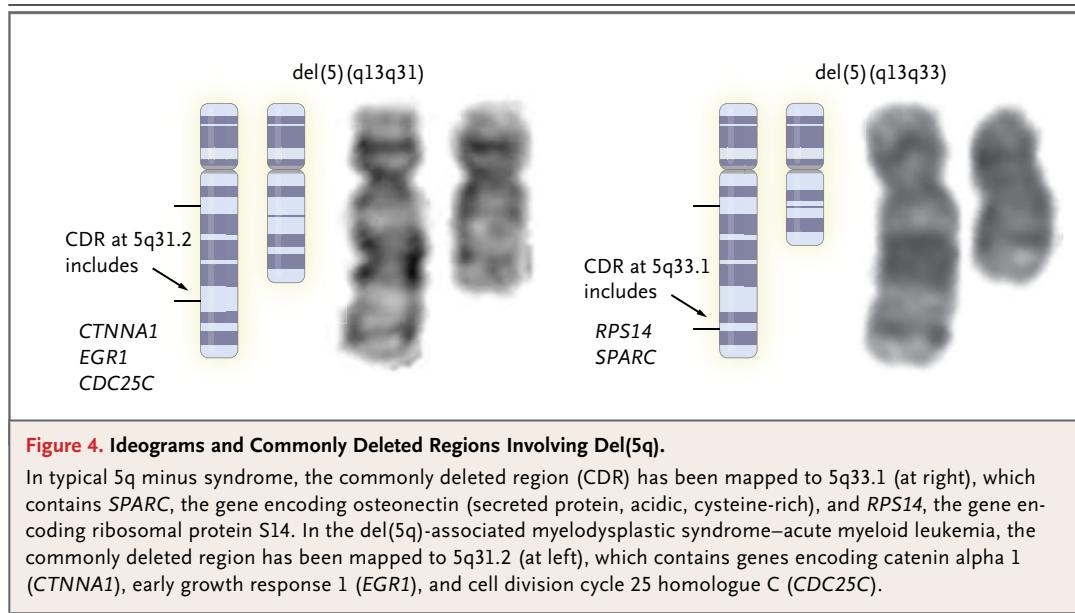
ated with the emergence of mutations of *NRAS* and *KRAS*, two related genes involved in the regulation of cell growth.⁴⁶ Progenitor cells of primary human myelodysplastic syndromes can repopulate mice that have nonobese diabetes and severe combined immunodeficiency and are deficient in β_2 -microglobulin, thus providing a xenograft model for a high-risk myelodysplastic syndrome.^{25,26}

THE 5q MINUS SYNDROME, DEL(5q), AND HAPLOINSUFFICIENCY

The 5q minus syndrome, which is associated with the deletion of the long arm of chromosome 5, is characterized by macrocytic anemia, erythroid hypoplasia, a normal or elevated platelet count, hypolobulated megakaryocytes, and isolated del(5q).⁴⁸ was initially considered to be a subcategory of the myelodysplastic syndromes. However, most patients who have a myelodysplastic syndrome with isolated del(5q) do not fit neatly into this morphologic category. In patients with typical 5q minus syndrome, the commonly deleted region, 5q33.1, contains *SPARC*, the gene encoding osteonectin (secreted protein, acidic, cysteine-rich), and *RPS14*, the gene encoding ribosomal protein S14.^{49,50} The more centromeric 5q31.2 deleted region in del(5q)-associated MDS-AML (which is morphologically different from the classic 5q minus syndrome) contains genes for catenin alpha 1 (*CTNNA1*), early growth response 1 (*EGR1*), cell division cycle 25 homologue C (*CDC25C*), and others (Fig. 4).⁵¹

In global gene-expression studies of the 5q minus syndrome, the expression of these and other deleted genes has been found to be decreased, whereas high-throughput resequencing did not reveal somatic mutations of the intact alleles.^{51,52} These observations suggest that haploinsufficiency (the loss of one functional allele), rather than homozygous inactivation, underlies the pathogenic contribution of del(5q) in patients with a myelodysplastic syndrome.

Decreased expression of *RPS14* in cultured normal myeloid progenitor cells causes a phenotype that mimics the 5q minus syndrome, whereas the forced expression of this gene in vitro reverses the defect in erythropoiesis in del(5q) cells.⁴⁹ *RPS14* is part of the 40S subunit of ribosomes. Haploinsufficiency of *RPS14* in the 5q minus syndrome (5q33.1) is associated with deregulation of ribosomal- and translation-related genes. Moreover, loss-of-function mutations in-



volving other ribosomal components (e.g., RPS19 and RPS24) occur in certain congenital syndromes (e.g., Diamond–Blackfan anemia) that share histologic and clinical features with the myelodysplastic syndromes.⁵³ Presumably, haploinsufficiency of ribosomal genes causes inadequate formation of ribosomal subunits, which in turn alters the translation of genes and activation of proteins involved in differentiation and apoptosis (e.g., p53).⁵⁴

SPARC is a tumor-suppressor gene that is affected by haploinsufficiency in 5q33.1.⁵² In vitro, this gene is specifically up-regulated by lenalidomide in erythroblasts in the 5q minus syndrome.⁵⁰ This drug is clinically active in patients with the 5q minus syndrome,^{50,55} which suggests that the *SPARC* protein contributes to the pathogenesis of the disease.

EGR1 is a candidate tumor suppressor that is located in the commonly deleted segment of 5q31.2. Haploinsufficiency of *EGR1* renders mice that are treated with a DNA-alkylating agent more susceptible to myeloid cancers than their wild-type counterparts.⁵⁶ Another 5q31.2 gene, *CTNNA1*, is down-regulated in leukemia-initiating stem cells with the 5q deletion.⁵⁷ Furthermore, in HL-60 cells, which have the 5q deletion, *CTNNA1* expression in the retained allele is epigenetically suppressed, and its reexpression reduces the proliferation rate of the cells and increases apoptosis.⁵⁷ The mechanism of action of lenalidomide has also been linked to a 5q31.2 gene,

CDC25C, whose product, a cell-cycle-regulating phosphatase, is inhibited by the drug.⁵⁸

GLOBAL GENE-EXPRESSION STUDIES

Gene-expression studies of progenitor cells (identified by cell-surface markers AC133 or CD34)^{59–62} or neutrophils⁶³ from patients with a myelodysplastic syndrome have underlined the heterogeneity of the disease at a molecular level, differences in gene expression between low-risk and high-risk disease,^{60,61} and differences among specific cytogenetic subcategories of the myelodysplastic syndromes.^{62,63} Additional studies are needed to determine the value of gene-expression signatures to classify the disease or predict leukemic transformation.^{64,65}

Gene-expression studies in the myelodysplastic syndromes have also revealed up-regulated or down-regulated genes whose individual contributions to the disease have not been fully sorted out. Examples of up-regulated genes include interferon-induced genes, *DLK1* on chromosome 14q32 (encoding delta-like 1 homologue, a protein of uncertain hematopoietic function), and *BMI1* (encoding BMI1, a protein in the polycomb ring finger family that is important in self-renewal of cells).^{59–63}

SINGLE-NUCLEOTIDE POLYMORPHISMS

Genomewide scanning on the basis of single-nucleotide-polymorphism (SNP) arrays can detect a loss or gain of gene copy numbers and copy-

neutral loss of heterozygosity in cytogenetically normal chromosomal regions.⁶⁶⁻⁶⁸ For example, one study showed that homozygous deletions or amplifications were infrequent in the myelodysplastic syndromes, whereas heterozygous deletions and regions of uniparental disomy (both alleles of a gene derived from the same parent) were detected on several chromosomes, including a common region on chromosome 3 that contains the heme synthesis enzyme 5-aminolevulinate synthase.⁶⁷ Another SNP study suggested that the complement of genomic aberrations in any given patient with a myelodysplastic syndrome is not necessarily shared by all myeloid lineages, underscoring the need to consider cell-type-specific biologic effects of molecular abnormalities.⁶⁹

INEFFECTIVE HEMATOPOIESIS, ACCELERATED APOPTOSIS, AND BONE MARROW STROMA

Ineffective hematopoiesis in patients with a myelodysplastic syndrome has been attributed to an abnormal susceptibility to apoptosis in progenitor cells and limited responsiveness of these cells to growth factors.^{70,71} Proapoptotic signals in patients with a myelodysplastic syndrome are believed to stem from abnormal signaling, an excess of proinflammatory cytokines, and altered immune responses in T cells.⁷²⁻⁷⁶ Specific cytokines and cell-surface receptors have been implicated as mediators of increased apoptosis, but a unifying evaluation is lacking. Whether bone marrow stromal changes, including increased microvessel density,⁷⁷ are an epiphenomenon or a pathogenetically important element of the disease is unknown.

EPIGENETIC CHANGES

The epigenetic mechanisms of altered DNA methylation and histone acetylation can alter gene transcription. Abnormal methylation of transcription promoter sites is universal in patients with a myelodysplastic syndrome, and the number of involved loci is increased in high-risk disease and during disease progression.⁶⁸ Such epigenetic changes could worsen the already decreased production of tumor-suppressor proteins if they affect haploinsufficient genes, such as *FZD9* on chromosome 7q11.23 (encoding the Wnt protein receptor)⁶⁸ and *RBM22* on chromosome 5q33.1 (encoding an RNA-binding protein).⁵²

ALTERED IMMUNE RESPONSES

There is evidence of immune dysregulation in patients with a myelodysplastic syndrome, which may cause autoimmune myelosuppression and contribute to ineffective hematopoiesis.⁷⁸ Several studies have shown polyclonal expansion of helper T cells (CD4+) and oligoclonal or clonal expansion of cytotoxic T cells (CD8+) in the blood and bone marrow of patients with a myelodysplastic syndrome.^{79,80} These changes are more pronounced in low-risk disease, which is characterized by a decrease in the number of regulatory T cells (CD4+, CD25^{high}, and FOXP3+).^{73,81} There is also evidence of autologous cytotoxicity against precursor cells.⁷⁸ Consistent with these observations, immunosuppressive therapy is sometimes effective in patients with a low-risk myelodysplastic syndrome by attenuating clonal T-cell expansion.⁸² Late-stage disease is characterized by an increase in the number of regulatory T cells. By suppressing the autoimmune response against precursor cells, such regulatory cells could favor unregulated clonal proliferation and disease progression.^{81,83}

LEUKEMIC TRANSFORMATION

The incidence of AML in certain histologic or cytogenetic variants of the myelodysplastic syndromes is high enough that these disorders could be considered to be preleukemic states. Such variants include RAEB-2 and a myelodysplastic syndrome with cytogenetic abnormalities associated with a poor outcome (e.g., monosomy 7, deletion of the long arm of chromosome 7, trisomy 8, and deletion of the short arm of chromosome 17). The estimated risk of leukemic transformation in such patients is more than 50%.¹⁴ In patients with non-RAEB-2 myelodysplastic syndromes, the presence of excess blasts in bone marrow, multilineage dysplasia, unfavorable cytogenetic abnormalities, or lineage infidelity markers significantly increases the risk of leukemic transformation (Table 1 in the Supplementary Appendix).⁸⁴⁻⁸⁶ In contrast, the incidence of AML in strictly WHO-defined RARS is less than 5%.¹⁴

A recent study of bone marrow mononuclear cells from patients with a myelodysplastic syndrome showed that the gene-expression profile was AML-like in approximately 23% of the patients, myelodysplastic syndrome-like in 50%, and nonleukemic in 24% — findings that sup-

port the concept of intrinsically preleukemic variants.⁶⁵ The AML-like gene signature was found in 68% of patients with RAEB-2, which carries a high risk of leukemic transformation, whereas 86% of patients with RARS were classified as having myelodysplastic syndrome–like disease. As expected, patients with a myelodysplastic syndrome who had an AML-like gene signature had a short leukemia-free survival, whereas AML did not develop in any patient with a nonleukemic signature during a 5-year period.⁶⁵

PROGNOSTIC SCORING

The most commonly used prognostic tool in the evaluation of patients with a myelodysplastic syndrome is the International Prognostic Scoring System (IPSS), in which disease is categorized as low risk, intermediate-1 risk, intermediate-2 risk, and high risk on the basis of the percentage of myeloblasts in bone marrow, cytogenetic findings, and the number of hematopoietic lines affected by cytopenia (Table 1 in the Supplementary Appendix).⁶⁴ The IPSS was based on the FAB classification of the myelodysplastic syndromes and is applicable to the WHO classification system.⁸⁷ The median survival in these four risk categories is 97 months for low risk, 63 months for intermediate-1 risk, 26 months for intermediate-2 risk, and 11 months for high risk.⁸⁷

The WHO classification–based prognostic scoring system modifies the IPSS by considering multilineage dysplasia and dependency on red-cell transfusions as additional adverse prognostic variables.⁸⁸ Other proposed variables include age, performance status, new cytogenetic risk categories, thrombocytopenia, bone marrow fibrosis, serum levels of lactate dehydrogenase and β_2 -microglobulin, and immunophenotypes of myeloid progenitor cells.^{14,84,87,89-91} Revisions of the original IPSS are under way.

TREATMENT

At present, allogeneic hematopoietic stem-cell transplantation is the only treatment that can induce long-term remission in patients with a myelodysplastic syndrome.^{92,93} Such therapy, however, is not applicable for most patients, since the median age at diagnosis exceeds 70 years.² Stem-cell transplantation is associated with a high rate

of treatment-related death (approximately 39% at 1 year), suboptimal disease-free survival (approximately 29% at 5 years), and chronic graft-versus-host disease (approximately 15% at 1 year).⁹³ An HLA-identical sibling donor is preferred for transplantation, but transplantation from an HLA-matched unrelated donor can be effective.⁹² The use of reduced-intensity conditioning regimens has been found to decrease the toxic effects of stem-cell transplantation but at the cost of an increased relapse rate.^{93,94} All considered, allogeneic transplantation is recommended only for patients with advanced-stage disease.⁹⁵

Treatment with a demethylating agent (e.g., azacytidine and decitabine) or low-dose cytarabine results in superior remission rates, as compared with supportive care, and in some cases delays blastic transformation.⁹⁶⁻¹⁰⁰ In a recent randomized study that compared azacytidine treatment with conventional care in patients with high-risk disease, the median survival was 24.5 months in the azacytidine group, as compared with 15.0 months in the conventional-care group.⁹⁷ Complete remission rates of 9 to 17% with the use of newer demethylating agents^{97,99} are similar to rates obtained with low-dose cytarabine (11 to 18%)^{100,101} but lower than rates achieved with the induction chemotherapy used in patients with AML (>50%).¹⁰²

Lenalidomide can reduce the need for transfusion in about two thirds of patients and can induce complete cytogenetic responses in almost half the patients with low-risk or intermediate-1-risk disease associated with del(5q), but its effect on survival is unknown.⁵⁵ The drug's activity in other variants of the disease is less impressive, but a characteristic gene-expression signature, indicative of impaired erythroid differentiation, might predict responsiveness to lenalidomide.^{103,104} Treatment with erythropoiesis-stimulating agents helps patients with anemia who have low-risk disease and a serum erythropoietin level of less than 200 mIU per milliliter.¹⁰⁵ Granulocyte-stimulating growth factors are cost-effective only in the presence of neutropenia with fever or overt infection.¹⁰⁶

Other drugs, such as antithymocyte globulin, have had limited success in patients with a myelodysplastic syndrome. Many patients can be treated effectively with red-cell transfusion alone. The risk of clinically detrimental iron overload

and the need for iron chelation have been overstated and were not substantiated in a controlled study.¹⁰⁷ The need for transfusion is a marker of a biologically aggressive disease and not necessarily a predictor of death or morbidity from transfusion-induced hemosiderosis.¹⁰⁸

CONCLUSIONS

We are learning much about the molecular and biologic mechanisms of the myelodysplastic syndromes but have not yet learned to organize the facts into a unifying framework. One reason for this failure is that the myelodysplastic syndromes probably constitute several molecularly distinct en-

tities that share common changes in blood and bone marrow. From the standpoint of treatment, understanding the mechanisms of ineffective hematopoiesis and leukemic transformation could be as important as deciphering the primary oncogenic events. Increasing information on the identity and nature of transformed hematopoietic stem cells and advances in biotechnology are helping to create the “perfect storm” for breaking the current stalemate in our understanding of this disease.

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