The Genetic Basis of Myelodysplastic Syndromes

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KEYWORDS

• Myelodysplastic syndromes • Genetic mutations
• Myeloid neoplasms • Karyotypic abnormalities

Myelodysplastic syndromes (MDS) represent a broad group of hematologic disorders characterized by ineffective hematopoiesis, cytopenias, and in many cases, progression to acute myeloid leukemia (AML). Recurrent somatic genomic abnormalities include gains or losses of chromosomal segments, balanced translocations, point mutations, and epigenetic modifications. These lesions alter the differentiation, self-renewal, or proliferation of an MDS stem cell and its progeny. A complete description of the molecular lesions in MDS will enable more accurate prognostic predictions, a molecular taxonomy of MDS, and the identification of novel therapeutic targets in MDS.

Approximately 50% of patients with MDS have diseased cells with an abnormal karyotype.[1] The most common of these cytogenetic alterations are loss of the long arm of chromosome 5 (-5q), loss of chromosome 7 or 7q (-7/7q-), deletion of chromosome arm 20q (20q-), and gain of chromosome 8 (+8) (**Fig. 1**). The International Prognostic Scoring System (IPSS) for MDS incorporates the most common karyotypic abnormalities into its risk score, attributing the worst risk to patients that carry three or more chromosomal irregularities. Less is known about how these large regions contribute to disease pathogenesis at a molecular level, but some insights have been made recently.

The analysis of mononuclear cell karyotypes is currently the only genetic test in routine clinical use for MDS diagnosis. However, many cases harbor submicroscopic deletions or amplifications, acquired uniparental disomy, and point mutations that can

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Hematol Oncol Clin N Am 24 (2010) 295–315
doi:10.1016/j.hoc.2010.02.001 **hemonc.theclinics.com**
0889-8588/10/$ – see front matter