The myeloproliferative disorders (MPD) and myelodysplastic syndromes (MDS) encompass a pathologically and clinically heterogeneous group of hematologic entities that are united by their putative origin from pluripotent hematopoietic stem cells. The World Health Organization classifies these entities into three broad categories: (1) the chronic myeloproliferative diseases, (2) the myelodysplastic syndromes, and (3) the myelodysplastic/myeloproliferative diseases1 (see Table 35-1). Though all are true hematopoietic stem cell disorders characteristically associated with bone marrow hyperplasia, they are divergent in that MPD typically are associated with effective hematopoiesis, while MDS are associated with ineffective hematopoiesis, reflected by high or low peripheral blood counts, respectively.

Of the 17 discrete diseases currently recognized, the molecular pathogenesis of chronic myelogenous leukemia (CML) is best understood and ultimately has resulted in the development and application of targeted molecular therapy. As a result, molecular techniques play an integral and well-established role in the diagnosis of CML, in the determination of therapeutic response and efficacy, and in the detection of minimal residual disease. Consequently, most of this chapter focuses on the role of molecular pathology in the laboratory assessment of CML. However, the molecular pathogenesis of some of the other MPDs has recently been elucidated, with the potential for the development of clinically useful molecular tests. By contrast, the molecular underpinnings of MDS have not yet been as well delineated; nonetheless, molecular pathology testing has emerging utility in the diagnosis and assessment of these disorders and also is discussed briefly.

### CHRONIC MYELOGENOUS LEUKEMIA

#### Molecular Basis of Disease

CML comprises ~20% of all leukemias and is diagnosed at a median age of approximately 50 years. The disease originates from the transformation of a hematopoietic stem cell with resultant expanding myelopoiesis that characteristically evolves through three phases when untreated: (1) a chronic phase of 4 to 5 years’ duration manifest by myeloid hyperplasia with circulating granulocytes that are present in all stages of maturation; (2) an accelerated phase of shorter duration during which myeloid elements begin to lose the ability to differentiate; and (3) inevitably, a blast phase of acute leukemia of myeloid (70%) or lymphoid (30%) phenotype.

The reciprocal t(9;22)(q34;q11) translocation is identified as the initial transforming event in the development of CML, although some data suggest that it may be preceded by clonal hematopoiesis. The translocation yields a shortened chromosome 22 called the Philadelphia chromosome (Ph)2 (Figure 35-1). With the translocation, two distinct genes are fused: (1) BCR that encodes a cytoplasmic protein of uncertain function but with oligomerization, serine-threonine kinase, and GTPase-activating domains, and (2) ABL1 that encodes a nonreceptor tyrosine kinase normally localized to the nucleus.3 The resultant chimeric gene and fusion transcript yield a fusion protein with constitutively increased tyrosine kinase activity that is relocated from the nucleus to the cytoplasm and phosphorylates a variety of cellular substrates. The result is growth factor–independent proliferation, decreased apoptosis, and defective adhesion in the transformed cells.

The t(9;22) translocation can involve several different breakpoints in the BCR and ABL1 genes, resulting in different chimeric fusion proteins that confer somewhat specific clinicopathologic features and highlight the fact that this translocation is not pathognomonic for CML4 (Figure 35-2). These breakpoints are indistinguishable by traditional karyotyping and can be differentiated only using molecular techniques. For all fusions, most of ABL1 is juxtaposed to variable 5′ portions of BCR. Whereas the breakpoint involving ABL1 is relatively conserved, usually arising in the intron before exon 2 (a2), the breakpoints involving BCR are more variable.

BCR breakpoints arising in the major breakpoint cluster region (M-bcr) occur after either exon 13 (e13 or b2) or exon
The World Health Organization Classification of MPD and MDS

Chronic Myeloproliferative Diseases
- Chronic myelogenous leukemia
- Chronic neutrophilic leukemia
- Chronic eosinophilic leukemia/hyper eosinophilic syndrome
- Polycythemia vera
- Chronic idiopathic myelofibrosis
- Essential thrombocythemia
- Chronic myeloproliferative disease, unclassifiable

Myelodysplastic Syndromes
- Refractory anemia
- Refractory anemia with ringed sideroblasts
- Refractory cytopenia with multilineage dysplasia
- Refractory anemia with excess blasts
- Myelodysplastic syndrome, unclassifiable
- Myelodysplastic syndrome associated with isolated del (5q) chromosome abnormality

Myelodysplastic/Myeloproliferative Diseases
- Chronic myelomonocytic leukemia
- Atypical chronic myelogenous leukemia
- Juvenile myelomonocytic leukemia
- Myelodysplastic/myeloproliferative diseases, unclassifiable

Table 35-1. The World Health Organization Classification of MPD and MDS

Chronic Myeloproliferative Diseases
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- Chronic eosinophilic leukemia/hyper eosinophilic syndrome
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The occurrence of additional specific cytogenetic and molecular genetic events subsequent to the initial t(9;22) translocation heralds disease progression prior to hematologic or clinical manifestations or both. The acquisition of such cytogenetic abnormalities as a second Philadelphia chromosome (Ph’), isochromosome 17q, trisomy 8, trisomy 19, and others commonly indicates an impending blast crisis.8,9 Other molecular abnormalities associated with disease progression include overexpression of BCR-ABL1, upregulation of EVII gene expression, mutations in tumor suppressor genes such as P16, TP53, CDKN2A, and RB1, and aberrant DNA methylation of the translocated ABL1 allele and of the calcitonin gene.10 The presence of a derivative chromosome 9 deletion in addition to the t(9;22) translocation may serve as an independent prognostic factor predicting a rapid progression to blast crisis with a worse response to therapy and, hence, a shortened survival.11