The Role of Cytogenetics in the Diagnosis of Hematopoietic Neoplasms
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The diagnosis of hematopoietic neoplasms is one of the more challenging areas of pathology, requiring correlation of clinical, morphologic, immunophenotypic and cytogenetic data for meaningful classification. Historically, the “Philadelphia chromosome” (t[9;22](q34;q11)) was the first cytogenetic alteration defined in a characteristic hematopoietic neoplasm (chronic myelogenous leukemia). This translocation results in a novel fusion protein by juxtaposition of the BCR and ABL genes. Cytogenetic data are currently evaluated for diagnosis in most cases of myeloid neoplasms to include acute myelocytic leukemia (AML), myelodysplastic syndrome (MDS) and chronic myeloproliferative disorders. Characteristic cytogenetic abnormalities also characterize lymphoid disorders, such as Burkitt lymphoma, which arises from either a t(8;14)(q24;q32), t(2;8)(q11;q24) or t(8;22)(q24;q11).

The rational classification of hematopoietic neoplasms is based on the separation of diseases with distinct clinicopathologic features. Recurrent chromosomal abnormalities that correlate with morphologic, clinical and/or immunophenotypic subsets of leukemia or lymphoma provide further objective criteria for distinction. For example, acute promyelocytic leukemia (APL) is a subtype of acute myelocytic leukemia (AML) which is associated with t(15;17)(q22;q12). This disease is characterized by a well-recognized spectrum of morphologic findings, an increased frequency of disseminated intravascular coagulation (DIC) and response to specific therapy with all-trans-retinoic acid (ATRA). Methods to detect the occurrence of this translocation are widely applied to rapidly distinguish APL from other types of AML because it requires a unique therapeutic approach. Recognizing the association between certain cytogenetic abnormalities and specific morphologic and clinical features, the World Health Organization (WHO) has re-classified four unique subtypes of AML based on cytogenetics.

Some cytogenetic abnormalities are not specific to either morphologic subsets of disease or associated with specific clinical features; however, they remain valuable independent prognostic variables. Such findings have been used to stratify patients with MDS, chronic lymphocytic leukemia (CLL) and precursor B-cell acute lymphoblastic leukemia (ALL) into favorable and unfavorable prognostic categories, thus allowing for varied intensities of therapy.
Cytogenetic abnormalities also characterize a variety of low and intermediate grade lymphomas. Unlike myeloid malignancies that result in novel fusion proteins, translocation in lymphoid malignancies serves to alter the regulation of proto-oncogenes by juxtaposing them with the promoters of the immunoglobulin genes in B-cells or receptor genes in T-cells. This results in the overexpression of a normal protein that is generally more easily assessed by immunohistochemical means rather than by cytogenetic studies.

For example, overexpression of bcl-2 is observed in follicular lymphoma, cyclin-D1 is elevated in mantle cell lymphoma and ALK is upregulated in anaplastic large cell lymphoma. Still, a variety of cytogenetic and/or molecular strategies may be employed in difficult cases when routine morphologic and/or immunohistochemical findings are indeterminate.

As newer genetic techniques are developed to more rapidly and sensitively detect cytogenetic alteration, it is expected that further improvements in the classification and diagnosis of hematopoietic neoplasms will continue.

Bibliography
