Editorial

Chromosomal aberrations in hematological malignancies: A guide to the identification of novel oncogenes

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Over the past several years, cytogenetics, including fluorescence *in situ* hybridization (FISH), has become a powerful technique used in the detection of chromosomal abnormalities. FISH using repetitive DNA, chromosome-specific libraries or site-specific cosmids is an indispensable method for identifying chromosomes both in metaphase and interphase cells. The high sensitivity and specificity of FISH and the speed with which the assays can be performed have made FISH a pivotal cytogenetic technique that has provided significant advances in both the research and the diagnosis of hematological malignancies and solid tumors.[1] From a medical perspective, FISH can be applied to detect genetic abnormalities such as gene fusions, loss of a chromosomal region or a whole chromosome or to monitor the progression of an aberration, serving as a technique that can help in both the diagnosis of genetic or suggesting prognostic outcomes. In this issue, Amare *et al*.[2] studied a large group of patients with acute promyelocytic leukemia (APL), which results from a reciprocal translocation t(15; 17)(q 22; q21), molecularly PML-RARA fusion gene. The authors highlighted variant translocations, insertions and deletions of RARA gene in APL patients using D-FISH. Although D-FISH is a difficult task to evaluate the patients with variant chromosome aberrations, it has an excellent advantage to detect various additional anomalies, with expertise in cancer genetics. However, prognosis of the disease needs to be established in such patient groups. The commercially available dual-color dual-fusion FISH probes have revolutionized cancer cytogenetics. Using these probes, it has become easy to analyze the genetic abnormalities on metaphases even in interphase cells. The advantage of D-FISH is that, it is helpful in identification of variant translocations, deletions and gene fusions. In chronic myeloid leukemia (CML), 9q and 22q deletions have been reported in a good number of patients in the literature, and such patients behave as classical CML. In some CML patient groups, there may be a chance of deletions of ABL1 gene flanking regions, and these regions need to be mapped using locus-specific probes and the microRNA expression studies, which is an emerging tool in cancer genetics and can be used to assess the patients.

The reciprocal translocation represents the most chromosome aberrations in hematological malignancies. These translocations usually affect oncogenes that have been identified in almost all of the cancer conditions that lead to the genesis of abnormal fusion genes, resulting in the mutation or overexpression of components of the fused genes.[3] The CML, which is associated with Philadelphia chromosome resulting from t(9;22)(q34.1; q11.2), has been well characterized. The identification of the BCR and ABL genes involved in the translocation has led the discovery of BCR-ABL1 fusion protein, a constitutively active protein tyrosine kinase (PTK). This in turn has been the major achievement in the

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development of PTK inhibitors that are effective not only against the BCR-ABL1 chimeric protein but also against other neoplasms producing PTKs.[4] Identification of abnormalities in leukemia is useful not only for diagnostic and treatment purposes, such as the t(15;17)(q24; q21) in APL, but also for prognostic risk assessment, such as the t(8;21)(q22; q22) in acute myeloid leukemia. It is still not completely understood what causes identical translocations to yield different effects, a mechanism observed in leukemia. It is now well understood that mutations of genes such as KIT and WTI can change the prognostic outcome associated with favorable cytogenetic markers such as t(8;21)(q22; q22) and inv(16)(p13.1;q22.1). Other common abnormalities that may modify prognosis, even in patients with a normal karyotype or intermediate cytogenetic risk, include mutations in the FLT3, CEBPA and NPM1 genes. However, there is a need of more work at the molecular level to understand the disease development and progression.[5] The chromosomal aberrations in lymphomas provide diagnostic and prognostic information similar to leukemias. The CCND1–IGH fusion is the molecular hallmark of mantle cell lymphoma, resulting from t(11;14) (q13; q32.3), and is detectable by Southern blotting, polymerase chain reaction and FISH. Rarely, t(11;14) is found in B-cell chronic lymphocytic leukemia, prolymphocytic leukemia and plasma cell myeloma. These patients have better prognostic outcome than the 14 chromosome translocations to other chromosomes. Likewise, translocations involving BCL6 located on 3q27 are present in 50% B-cell lymphomas and 10% of follicular lymphomas. Hence, cytogenetic studies are necessary for prognostic and follow-up of cancer patients. Also, chromosome changes play an important role in identification of the genes affected by the rearrangements.

As modern tools of cytogenetics and molecular biology are increasingly applied to various hematological malignancies, inherent heterogeneity leading to biological differences in the ultimate outcome of these patients on various therapies are coming to the fore. Moreover, depending on this molecular pathology, various molecular targeted therapies are being increasingly applied in these conditions with salutary results. It is hoped that many more such studies will complete our understanding of the heterogeneity of various hematological malignancies.

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