Genetic Alterations in Leukemia: Events on a Grand Scale

By Kevin Shannon

LABORATORY investigation of the molecular basis of hematopoietic cancer has increasingly focused on single genes. This approach has been extraordinarily productive particularly when applied to the molecular cloning of recurring chromosomal translocation breakpoints. Genes implicated in diverse aspects of proliferation and growth control have been identified by studying hematopoietic malignancies and are mutated in cancer cells. One important insight from this work is the realization that a single molecular event in a susceptible progenitor is only rarely both necessary and sufficient for the expression of a fully malignant phenotype. Moreover, recent evidence implicates gene dosage and epigenetic events such as genomic imprinting in oncogenesis. In this issue, Onodera et al examine phenomena which, from the cell's perspective, transpire on a grand scale. Their report reminds us that understanding how losses and gains of entire chromosomes occur, and how these alterations contribute to leukemic transformation, are both important and poorly understood.

The investigators used probes that detected restriction fragment length polymorphisms to investigate the mechanisms underlying the formation of hyperdiploid karyotypes in 15 cases of childhood acute lymphoblastic leukemia (ALL). They reported a number of interesting findings. Three leukemias showed loss of constitutional heterozygosity (LOH); in two this involved allelic loss from multiple chromosomes (near-haploid karyotype) and in one LOH affected a single chromosome. Among the 11 patients who did not show widespread LOH and had four copies of chromosome 21 (tetrasomy 21), 10 had duplications of both maternal and paternal alleles. These data argue that most cases of hyperdiploidy arise during a single round of mitosis (disomy-to-tetrasomy) rather than by serial acquisition of one parental chromosome (disomy-to-trisomy-to-tetrasomy).

The first question suggested by these results is whether the two general types of hyperdiploid ALL exhibit different biologic behavior. Children with this type of ALL generally fare well: hyperdiploidy is associated with many "good risk" clinical features and high cure rates. Nevertheless, 10% to 15% of children with hyperdiploid ALL relapse despite modern therapy. This is similar to the incidence of near-haploid karyotypes observed by Onodera et al. The number of patients studied by Onodera et al is far too small for meaningful analysis, and it will be interesting to extend these observations to a large group of children to ask if the mechanism responsible for hyperdiploidy confers prognostic significance. Near-haploid and duplicated-diploid leukemias are genetically quite different, particularly as homozygous loss of function mutations of one or more tumor-suppressor genes is easy to envision with the former, but not the latter, mechanism.

A second question involves the contribution of chromosomal duplication and by inference, of gene dosage, to the pathogenesis of leukemia. It is striking that the chromosomal gains seen in ALL are nonrandom and most often affect chromosome 21. Infants and children with Down's syndrome are at increased risk of developing leukemia (see Fong and Brodeur for a review). Neonates with trisomy 21 also exhibit a variety of hematologic abnormalities including leukocytosis, anemia, polycythemia, thrombocytopenia, and a syndrome clinically indistinguishable from acute myelogenous leukemia that usually resolves without treatment. Taken together, data demonstrating frequent gains of chromosome 21 in childhood ALL and clinical experience in infants and children with Down's syndrome suggest that trisomy and tetrasomy 21 predispose hematopoietic cells to clonal proliferation by gene dosage. This effect may be accentuated in utero and early in life while the hematopoietic system is expanding rapidly. By analogy with chromosome 21, it seems likely that duplications of the X chromosome and trisomy 8 stimulate unregulated growth by gene dosage.

A final issue involves how leukemic clones with hyperdiploid karyotypes emerge and proliferate. Gene amplification and chromosomal duplication are common features of cancer cells and reflect underlying genetic instability. By definition, these processes involve a loss of normal growth...
control. Tlsty et al. recently found that the ability to suppress gene amplification in human cell hybrids segregates as a recessive genetic trait. A similar regulatory gene (or genes) might normally act in mitosis to restrain proliferation unless cells have the correct number of chromosomes. Inactivation of such a gene could be an early, rate-limiting step in the development of hyperdiploid leukemias. Regardless of how leukemic cells gain or lose chromosomes, it seems certain that these "grand" events are of pathologic significance, particularly because hyperdiploid leukemias rarely show any of the chromosomal translocations characteristic of ALL. This, in turn, implies that the molecular basis of leukemic transformation in hyperdiploid patients differs from that seen in cases associated with translocations. Understanding how hyperdiploidy occurs, how the gain of specific chromosomes deregulates growth, and how the underlying genetic mechanism affects prognosis are important goals.

REFERENCES

Genetic alterations in leukemia: events on a grand scale [editorial; comment]

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