INTRODUCTION

Genetic Mechanisms in Neoplasia

By Arthur W. Nienhuis

HEMATOLOGY and oncology stand on the threshold of a molecular revolution. Many clues suggest that mutations in DNA cause neoplasia but the precise nature of these genetic events have remained tantalizingly elusive until recently. The next issues of Blood will contain several reviews that chronicle the rapid progress achieved in the last few years in understanding genetic mechanisms in neoplasia.

Application of modern recombinant DNA techniques to cancer biology required molecular probes for specific DNA sequences involved in neoplastic transformation. Many such probes have been provided by RNA tumor viruses. These retroviruses often owe their transforming potential to modified genes initially acquired from an animal cell genome by recombination during viral evolution. Because of this association with the transforming potential of tumor viruses, the pirated genes are called oncogenes. Of course, such genes are not normally oncogenic in animal cells. Rather, several for which a function has been identified encode for gene products that are essential for cellular function and differentiation. By mutation, translocation, recombination, or other genetic mechanisms, these normal genes—called proto-oncogenes or cellular oncogenes—may acquire the ability to contribute to, or cause, the neoplastic phenotype. These interrelationships, as exhibited by a proto-oncogene that encodes for one of the polypeptides of platelet-derived growth factor, the related oncogene of a monkey sarcoma virus, and some forms of human cancer, form the basis for the first article in this series.

Another powerful and deliberate effort to uncover the genetic mutations that result in neoplasia involves transfection of DNA from neoplastic cells into tissue culture cells. Cells that are recipients of the transfected DNA assimilate this foreign DNA, integrate it into their genome, and thereby their phenotype is transformed. By selection, namely the identification of a heritable alteration in the growth properties of transformed cells, one can—in a series of transfection experiments—identify the DNA sequences causing this phenotypic alteration. That this route has led to some of the same related oncogenes found in RNA tumor viruses represents a remarkable convergence of two diverse experimental approaches. The second article in this series, to appear next month, will provide an account of the molecular mechanisms of carcinogenesis as it has come to be understood by application of the DNA transfection assay.

Chromosomal rearrangements are common in neoplastic cells and often these rearrangements occur near proto-oncogenes. Molecular analysis of chromosomal translocations found in Burkitt’s lymphoma cells has shown that relocation of the myc proto-oncogene into an immunoglobulin gene locus alters myc gene function and regulation, thereby almost certainly contributing to development of neoplasia. These studies form the basis for the third review in this series. The Philadelphia chromosome translocation involves movement of two proto-oncogenes, c-sis from chromosome 22 to chromosome 9 and c-abl from chromosome 9 to chromosome 22. The translocation break points for many Philadelphia chromosomes apparently occur very close to the c-abl gene and recently an abnormal c-abl mRNA has been demonstrated in chronic myelogenous leukemia cells.

RNA tumor viruses may rarely cause human cancer directly by infection and cell transformation. The human T cell leukemia viruses (HTLVs) have been
unequivocally implicated as agents for this form of neoplasia; the genetic mechanism(s) by which these viruses transform T cells remains to be determined. Of more immediate impact is the recent identification of a member of this class of viruses as the probable causative agent for acquired immunodeficiency syndrome (AIDS). The exciting and evolving story of this class of viruses and their role as agents in causing neoplasia and immunodeficiency form the basis for the fourth review in this series.

One can anticipate many ways in which this explosive growth in knowledge about the genetic mechanisms of neoplasia will move rapidly from the arcane world of the experimentalist into the clinical area. The curious designations of the proto-oncogenes (eg, myc, abl, ras, sis, fms), "archeologic" evidence of their discovery via the transforming genes of the corresponding RNA tumor viruses, seem destined to become "household" words for those interested in hematology and oncology. Translocation, point mutations, and amplification involving proto-oncogenes may be very common in neoplastic cells. Our knowledge of these is surely rudimentary but already specific clinical-molecular correlations are emerging. For example, amplification of the c-myb gene has been found in acute myelogenous leukemia and amplification of the N-myc gene in human neuroblastoma cells has been associated with rapid tumor progression and poor prognosis. Soon, knowledge of the DNA changes in specific neoplasms may assume equal importance with respect to diagnosis and prognosis as the exact histologic or cytologic classification of the neoplasm.

From the type of studies reviewed in this and subsequent issues of the Journal may come a detailed understanding of the molecular mechanisms in neoplasia. Much work will be required and many confusing aspects of initial studies will demand resolution but the probability of ultimate success of this approach can be judged by the enormous impact that modern molecular biology has had—in just a few years—on understanding human genetic diseases, of which the thalassemias are one example. Those involved in the care of patients with neoplastic disease may anticipate the opportunity of devising and applying new therapeutic strategies that are based on a fundamental understanding of the genetic mechanisms involved.

REFERENCES

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