cessful liver transplantation from a living donor to her son. N Engl J Med 1990; 322:1505-1507

10. Todo S, Nery J, Yanaga K, Podesta L, Gordon RD, Starzl TE: Extended preservation of human liver grafts with UW solution. JAMA 1989; 261:711-714

11. Donovan JP, Zetterman RK, Burnett DA, Sorrell MF: Preoperative evaluation, preparation, and timing of orthotopic liver transplantation in the adult. Semin Liv Dis 1989; 9:168-175

12. Dickson ER, Grambsch PM, Fleming TR, Fisher LD, Langworthy A: Prognosis in primary biliary cirrhosis: Model for decision making. Hepatology 1989; 10:1-7

13. Markus BH, Dickson ER, Grambsch PM: Efficacy of liver transplantation in patients with primary biliary cirrhosis. N Engl J Med 1989; 320:1709-1713

14. Wiesner RH, Grambsch PM, Dickson ER, et al: Primary sclerosing cholangitis: Natural history, prognostic factors, and survival analysis. Hepatology 1989; 10:430-436

15. O'Grady JG, Alexander GJM, Hayllar KM, Williams R: Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989; 97:439-445

16. Macleod AM, Thomson AW: FK 506: An immunosuppressant for the 1990s? Lancet 1991; 337:25-27

17. Starzl TE, Van Thiel D, Tzakis AG, et al: Orthotopic liver transplantation for alcoholic cirrhosis. JAMA 1988; 260:2542-2544

18. Demetris AJ, Todo S, Van Thiel DH, et al: Evaluation of hepatitis B virus liver disease after hepatic replacement: Practical and theoretical considerations. Am J Pathol 1990; 137:667-676

19. Read AE, Donegan E, Lake J, et al: Hepatitis C in patients undergoing liver transplantation. Ann Intern Med 1991; 114:282-284

20. O'Grady JG, Polson RJ, Rolles K, et al: Liver transplantation for malignant disease: Results in 93 consecutive patients. Ann Surg 1988; 207:373-379

Molecular Genetics in the Cancer Clinic

THE INCORPORATION OF modern molecular approaches into research on clinical problems is now extensive. Indeed, one can hardly read a medical journal these days without at least a general understanding of the various techniques in molecular biology. This is arguably as true for investigations of the neoplastic diseases as it is anywhere, perhaps reflecting a relatively early appreciation that malignant neoplasms are, in essence, genetic disorders. Many results of "basic" research on the molecular mechanisms of oncogenesis are rapidly approaching the point of clinical application in the diagnosis and management of human cancer. This work is thus of more than passing concern to physicians who care for patients in their practice with cancer. The literature in this discipline is vast and often minutely focused, however, and so is not always readily accessible to interested clinicians. In this issue of the journal, Koeffler and colleagues have distilled from this mass of information a usefully concise and current summary of the genetic lesions that have been identified in human tumors.[1] They also touch on many of the ideas that these findings have prompted regarding molecular mechanisms in the pathogenesis of cancer. Several of the models that the authors discuss are particularly useful in their generality. I wish to illustrate this point by reviewing some important related findings published too recently for inclusion in their article.

Chromosomal Translocations in Oncogenesis

The finding of a given chromosomal translocation (at the cytogenetic level) in multiple independent specimens of the same tumor type is strong circumstantial evidence for participation of the associated genes in the origin or progression phase of tumorigenesis. Molecular analysis of such recurrent translocations is a venerable, and still fruitful, approach to the isolation of novel genes involved in oncogenesis. This has been particularly true for the lymphoid neoplasms, where one partner in the translocation is frequently an immunoglobulin or T-cell receptor *(TCR)* gene. These can serve as a toehold from which it is possible to "walk" across a cloned translocation break point to the candidate proto-oncogene.

Translocations with gene deregulation. As noted by Koeffler and associates, juxtaposition of the c-*myc* locus with the immunoglobulin heavy chain *(IGH)* gene (as in Burkitt's lymphoma) may be regarded as the prototype of situations in which proto-oncogenes suffer deregulation as a consequence of translocation.[1] In instances such as these, the cognate oncoprotein gene products are inappropriately expressed, but they are not physically altered. Several recently described cases of this pathogenic mechanism have made for interesting additions to the list of cellular functions that are apparently oncogenic when corrupted in this context. For example, *BCL2*—a gene "activated" by translocation to the *IGH* locus in most follicular malignant lymphomas—encodes a mitochondrial protein somehow involved in governing B-lymphocyte lifespan[2,3]; overexpression of *BCL2* protein in association with the translocation seems to block programmed cell death in this lineage. This leads in turn to a pathologically expanded B-cell population by decreased attrition rather than increased proliferation.[2,3]

The *BCL1* gene, yet another gene sometimes juxtaposed with the *IGH* locus in lymphoid malignant diseases, codes for a member of the cyclin protein family.[4] Several of the cyclins are known to be intimately connected with the regulation of cell-cycle progression in eukaryotes. The *BCL1* locus is also amplified (without known translocation) in a number of nonlymphoid tumor types.[4] The exact role of *BCL1* deregulation in tumorigenesis is by no means clear at present. It is an intuitively appealing notion, however, that cyclin function could sustain derangement in neoplastic cells, leading to the loss of a normal control of proliferation.

A recurrent translocation of T-cell acute leukemia situates a *TCR* locus adjacent to a so-called homeobox *(HOX)* protein gene.[5] The many *HOX* family proteins appear to figure prominently in regulating cell type-specific differentiation during development. Here, too, nothing is certain regarding detailed pathogenic mechanisms of tumorigenesis supported by the translocation. It is interesting to suggest, though, that this is a case where the abrogation of normal differentiation (perhaps an interfering effect of the inappropriately expressed *HOX* protein), rather than a loss of proliferation control per se, is the root cause of neoplasia.[3,6]

Translocation with protein alteration. Chromosomal translocation can also lead to the synthesis of a functionally abnormal and pathogenic fusion protein; the *BCR/ABL* products in acute lymphocytic and chronic myelogenous leukemias[7] are discussed by Koeffler and co-workers as models for this mechanism of neoplastic change.[1] As another example, the breakpoint of the t(15;17) translocation of acute promyelocytic leukemia occurs in the retinoic acid-receptor-α locus *(RAR)*.[3,8] This is intriguing because retinoic acid and its analogues are known to be potent inducers of differentiation in primitive myeloid cells.[3,8] The translocation event leads to the formation of a protein in which aminoterminal sequences of *RAR* are replaced with those of a previously undescribed gene designated *MYL*.[8] While the *MYL/RAR* fusion protein, like the parent *RAR* protein, can mediate the regulation of gene expression by retinoic acid, its function in this respect is clearly abnormal.[8] It is possible that the *MYL/RAR* fusion protein acts in an inhibitory way in promyelocytic leukemia cells by outcompeting normal *RAR* molecules. The latter would otherwise affect progress along the myeloid differentiation pathway.[3,8] It has recently been found that administering all-*trans*-retinoic acid induces complete remission in a large proportion of patients with acute pro-

myelocytic leukemia who have the *MYL/RAR* translocation.[9] It remains to be determined whether this reflects augmented in vivo function of *MYL/RAR* protein, of normal *RAR* protein, or neither of these.

Tumor Suppressor Genes

Retinoblastoma. Koeffler and associates discuss retinoblastoma *(RB)* as a paradigm for the isolation of tumor suppressor genes connected with an inherited susceptibility to cancer. The genetic basis of familial retinoblastoma was understood first at the clinicoepidemiologic level, next at the cytogenetic level, and finally, with the cloning of the *RB* gene, at the molecular level.[6] Subsequent studies of this disorder have led to a key realization: a tumor suppressor gene involved in a heritable cancer-prone diathesis can also be important in sporadic (nonfamilial) tumorigenesis. This result is of considerable practical importance because sporadic cancers are much more common than familial ones. Interestingly, these sporadic tumors are often of histologic types different from those found in the inherited cases.

Neurofibromatosis and familial adenomatous polyposis. Two additions have been made to the list of cloned human tumor suppressor genes provided in the article[1]: *NF1*, associated with type I neurofibromatosis,[10,11] and *APC*, associated with adenomatous polyposis coli (also known as familial adenomatous polyposis).[12,13] Each of these disorders confers heritable susceptibility to specific tumors. In contrast to *RB*, where the position of the gene could be inferred initially from karyotypic studies, the *NF1* gene chromosome assignment (17q11.2) was educed by genetic linkage analysis of affected families (subsequent identification of patients with translocations in this area further refined the localization) (reviewed by Marshall[6]). The finding of mutations in exonic (messenger RNA-encoding) gene sequences in this region in patients with neurofibromatosis, but not in normal subjects, positively identified the *NF1* gene.[6] Sequence analysis revealed that the *NF1* gene product has significant structural homology to *gap*—the *ras*-associated guanosine triphosphatase-activating protein discussed in the article.[1] Models proposed for the function of *NF1* and for its dysfunction in neurofibromatosis-associated tumors[6] are analogous for those noted for *gap*.[1]

Previous cytogenetic and linkage analyses had localized the gene for susceptibility to familial adenomatous polyposis *(APC)* to chromosome 5 at band q21.[6] This chromosomal locus was noted by Koeffler and colleagues in two connections[1]: heterozygosity at 5q21 in sporadic colorectal carcinomas is frequently lost, and this is the location of the putative colorectal tumor suppressor gene *MCC*. It had been cautiously suggested that *MCC* might itself be the gene *(APC)* associated with familial adenomatous polyposis. It is now evident, however, that *APC* is distinct from (but closely adjacent to) *MCC*.[12,13] It appears that, while both of these genes can be altered in sporadic colorectal carcinomas, only *APC* is abnormal in the germ line of families with familial adenomatous polyposis. Nothing is yet known about the functions of these genes.

p53 Tumor suppressor gene and familial cancer. The p53 locus has provided an interesting twist to studies on the genetics of heritable neoplasia: here it was the understanding of a gene that prompted the search for a disease, rather than the reverse. A number of results—reviewed by Koeffler and colleagues[1]—had strongly indicated that the normal p53 gene product functions as a tumor suppressor. By analogy with retinoblastoma, it was therefore reasonable to postulate that inherited mutations in the p53 gene are the basis of other familial cancer-prone disorders. This has been found to be the case. In two studies, families fitting the clinical criteria for the Li-Fraumeni syndrome—a rare but well-described condition predisposing to certain tumors including breast carcinoma, sarcoma, and glioma—were shown to carry germ-line mutations in p53.[14,15] In a third study, germ-line mutation of p53 was found in a boy with an ependymoma who was from a cancer-prone family. This tumor and those of several of his relatives had not been strongly associated previously with the Li-Fraumeni syndrome.[16] To reconcile these results, it is tempting to speculate that the various mutant p53 alleles present in different cancer-prone families might predispose to distinct tumor types. It is also interesting to consider the possibility that some germ-line mutations of p53 (and other tumor suppressor genes as well) may have less severe phenotypic effects than others. Such a situation might account for families wherein cancer seems to be frequent or to strike the relatively young but not so dramatically as in the prototypic cancer-prone diseases noted earlier. Recent laboratory evidence supports this concept of mutation-specific differences in the biologic properties of different p53 alleles.[17]

Future Prospects

For information about tumor genetics to be most useful in clinical practice, the respective molecular analyses would ideally be done with the speed and reliability of present hospital laboratory tests (or nearly so). Recent technologic advances and the development of molecular diagnostics as a clinical specialty make this goal conceivable. The polymerase chain reaction method—discussed by Koeffler and colleagues in connection with tumor *ras* gene mutations—is especially noteworthy in this regard as it has decreased the time scale of some manipulations from days or weeks to hours. As a current example, by using the polymerase chain reaction, the presence of the Philadelphia translocation in a specimen can now be assessed overnight; this is sufficiently rapid to permit inclusion of the result in the selection of initial therapy for a newly diagnosed case of acute lymphoblastic leukemia.[18] Other breakthroughs are likely to follow in the foreseeable future. As readers of the article will appreciate, this is indeed a time when both oncologists and basic molecular biologists can share in the excitement and optimism as the genetic mechanisms of cancer become better understood.

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ERIC H. RADANY, MD, PhD
Department of Radiation Oncology and the G.W. Hooper Research Foundation
University of California, San Francisco
San Francisco, California

REFERENCES

1. Koeffler HP, McCormick F, Denny C, Miller CW: Molecular mechanisms of cancer. West J Med 1991 Nov; 155:505-514

2. Korsmeyer SJ, McDonnell TJ, Nunez G, Hockenberry D, Young R: Bcl-2: B cell life, death and neoplasia. Curr Topics Microbiol Immunol 1990; 166:203-207

3. Sawyers CL, Denny CT, Witte ON: Leukemia and the disruption of normal hematopoiesis. Cell 1991; 64:337-350

4. Withers DA, Harvey RC, Faust JB, Melnyk O, Carey K, Meeker TC: Characterization of a candidate *bcl-1* gene. Mol Cell Biol 1991; 11:4846-4853

5. Hatano M, Roberts CW, Minden M, Crist WM, Korsmeyer SJ: Deregulation of a homeobox gene, HOX11, by the t(10;14) in T cell leukemia. Science 1991; 253: 79-82

6. Marshall CJ: Tumor suppressor genes. Cell 1991; 64:313-326

7. Kurzrock R, Gutterman JU, Talpaz M: The molecular genetics of Philadelphia chromosome-positive leukemias. N Engl J Med 1988; 319:990-998

8. Pandolfi PP, Grignani F, Alcalay M, et al: Structure and origin of the acute promyelocytic leukemia myl/RAR α cDNA and characterization of its retinoid-binding and transactivation properties. Oncogene 1991; 6:1285-1292

9. Warrell RP Jr, Frankel SR, Miller WH, et al: Differentiation therapy of acute promyelocytic leukemia with tretinoin (all-*trans*-retinoic acid). N Engl J Med 1991; 324:1385-1393

10. Wallace MR, Marchuk DA, Andersen LB, et al: Type 1 neurofibromatosis gene: Identification of a large transcript disrupted in three NF1 patients. Science 1990; 249:181-186

11. Cawthon RM, Weiss R, Xu GF, et al: A major segment of the neurofibromatosis type 1 gene: cDNA sequence, genomic structure, and point mutations. Cell 1990; 62:193-201 [published erratum Cell 1990; 62:608]

12. Nishisho I, Nakamura Y, Miyoshi Y, et al: Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients. Science 1991; 253:665-669

13. Groden J, Thliveris A, Samowitz W, et al: Identification and characterization of the familial adenomatous polyposis coli gene. Cell 1991; 66:589-600

14. Srivastava S, Zou ZQ, Pirollo K, Blatner W, Chang EH: Germ-line transmission of a mutated p53 gene in a cancer-prone family with Li-Fraumeni syndrome. Nature 1990; 348:747-749

15. Malkin D, Li FP, Strong LC, et al: Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 1990; 250:1233-1238

16. Metzger AK, Sheffield VC, Duyk G, Daneshvar L, Edwards MS, Cogen PH: Identification of a germ-line mutation in the p53 gene in a patient with an intracranial ependymoma. Proc Natl Acad Sci USA 1991; 88:7825-7829

17. Halevy O, Michalovitz D, Oren M: Different tumor-derived p53 mutants exhibit distinct biological activities. Science 1990; 250:113-115

18. Maurer J, Janssen JWG, Thiel E, et al: Detection of chimeric BCR-ABL genes in acute lymphoblastic leukaemia by the polymerase chain reaction. Lancet 1991; 337:1055-1058