Oncogenic Genes and Human Malignancy

PAUL LEBOWITZ, M.D.

Department of Internal Medicine and Division of Oncology, Comprehensive Cancer Center, Yale University School of Medicine, New Haven, Connecticut

Received April 19, 1983

All vertebrates possess a series of genes which are homologs of the oncogenic genes of acute transforming retroviruses. Two lines of evidence suggest that these genes may play a role in the development of human malignancy: (1) DNA from a variety of human tumors transforms NIH 3T3 mouse fibroblasts and the transforming genes from a number of carcinomas, sarcomas, and hematological malignancies have been identified as members of a family of genes, the ras family, closely related to the oncogenic genes of the Harvey and Kirsten murine sarcoma viruses; and (2) correlations exist between the chromosomal localizations of certain oncogenes and the chromosomal breakpoints in specific translocations and deletions in certain human malignancies. In three separate hematological malignancies, alterations in more than one oncogenic gene may be involved in the neoplastic process.

For many years our thinking about the etiology of malignancy has rested on two basic concepts. The most fundamental is that the malignant process probably involves multiple events: an initial change which makes a cell permissive for undergoing transformation to the malignant phenotype; the actual transformation, or oncogenic, event; and a series of subsequent steps which allow the malignancy to survive in the host, determine the specific phenotype of the transformed cell, and explain, at least in part, the diverse clinical behavior of seemingly similar malignancies in different individuals. The second basic concept is that the transformation step and probably all three steps leading to malignancy result from mutations or other alterations in cellular DNA.

Our understanding of the etiology of malignancy has taken a great leap forward in the past few years with the discoveries that the human genome contains specific genes which are potentially oncogenic and that these genes (oncogenes or onc genes) are homologs of the oncogenic genes of a number of RNA tumor viruses (retroviruses). Furthermore, recent studies suggest that mutations in or translocations or deletions of some of these genes may play a role in the development of certain human malignancies.

RETROVIRAL AND HUMAN ONCOGENIC GENES

Retroviruses are the etiological agents of a wide variety of spontaneous and induced malignancies of animals. These viruses fall into two broad groups: those that cause malignancy over months (chronic acting viruses, mostly leukemia viruses) and those that lead to malignancy within weeks (acute leukemia, lymphoma, sarcoma, and carcinoma viruses). Whereas members of the former group possess gag, env,
and pol genes (coding respectively for viral core and coat proteins and reverse transcriptase) which confer replication competence, members of the latter (except for RSV) contain large deletions in or lack one or more of these genes and are replication-defective. In place of the deleted sequences, and in RSV in addition to the replicatory genes, the acute acting viruses contain oncogenic genes which confer upon them the ability to cause acute malignancies in animals and transform fibroblasts and in some cases hematological precursors in tissue culture [1–3]. To date, about twenty acute acting viruses have been isolated. The oncogenic gene of each codes for an oncogenic protein (AEV is the sole exception, containing two separate oncogenes coding for two separate oncogenic proteins). On the basis of the following properties, four types of oncogenic proteins have been distinguished: the proteins of several avian sarcoma viruses (e.g., RSV), FeSV and AbLV, all of which bind to the inner aspect of the plasma membrane of transformed cells, serve as ATP-dependent protein kinases, and phosphorylate both their own tyrosine residues and those of certain cellular proteins [1,2]; the structurally similar ras proteins of Ha- and KiSV which are 21,000 daltons, also are associated with the inner aspect of the plasma membrane of transformed cells, but bind GTP and GDP rather than adenine nucleotides and appear only to autophosphorylate one of their own threonine residues [4]; the myc protein of AMV which is a nuclear protein with DNA-binding activity [5]; and the erb B protein of AEV which is a cytoplasmic glycoprotein [1,2]. Despite this information, the mechanism(s) by which these proteins induce malignancy remains unknown.

In the past few years DNA sequences bearing extensive homology to retrovirus oncogenes have been identified in cells from a wide variety of vertebrates, including man [1,2,6]. Furthermore, certain of the cellular homologs of viral oncogenes are active, serving as templates for synthesis of proteins that share immunological determinants with and are similar in size and, in certain cases, sequence to the respective viral oncogenes [1,2]. These findings have a number of important implications. (1) They suggest a cellular origin for the oncogenes of the acute acting viruses. Moreover, it seems likely that these viruses arose by recombinational events between chronic acting viruses and cellular oncogenic sequences. (2) The facts that cellular genes are highly conserved and that some are active suggest that they carry out important functions in normal cells. Indeed, there is some evidence to suggest that certain oncogenes may be involved in regulation of cell differentiation [7]. (3) The similarity of viral oncogenic proteins and their cellular counterparts taken together with the observation that virus-transformed cells express elevated levels of viral oncogenic proteins [1,2] raises the question if malignancy in the absence of viral infection may at least in some cases result from elevated levels of the cellular counterparts of viral oncogenic proteins, i.e., of normal cellular proteins. (4) Most important, the data suggest that all normal vertebrate cells harbor potentially oncogenic sequences. Indeed, cloned cellular homologs of the HaSV ras gene and the MoSV mos gene,

1Abbreviations for retroviruses and their oncogenic genes are as follows: Abelson murine leukemia virus: AbLV and abl; Snyder-Thelen feline sarcoma virus: FeSV and fes; Moloney murine sarcoma virus: MoSV and mos; avian erythroleukemia virus: AEV and erb A and B; avian myeloblastosis virus: AMV and myb; avian myelocytomatosis virus, strain 29: MC29 and myc; Harvey murine sarcoma virus: HaSV and rasH; Kirsten murine sarcoma virus: KiSV and rasK; simian sarcoma virus: SSV and sis; Rous avian sarcoma virus: RSV and src; avian leukemia virus: ALV, no oncogenic gene.

Abbreviations for human malignancies: Burkitt lymphoma: BL; acute myelogenous, promyelocytic, and lymphoblastic leukemias: AML, APL, and ALL; chronic myelogenous leukemia: CML.
linked at their 5'-end to viral activator sequences, transform mouse fibroblasts in culture [8,9].

HUMAN TRANSFORMING GENES (ACTIVATED ONCOGENIC GENES)

In contrast to the viral etiology of many animal malignancies, attempts to elucidate a viral role in human malignancies have been relatively disappointing. Despite intensive searches, viruses have been implicated in only four malignancies: BL and nasopharyngeal carcinoma, in which infection with Epstein-Barr (EB) virus is an important step in oncogenesis [10]; certain T cell lymphomas, in which a newly discovered retrovirus appears to be the etiological agent [11,12]; and certain cases of hepatocellular carcinoma occurring in patients who are chronic carriers of hepatitis B virus and suffer from chronic active hepatitis [13,14].

In an attempt to elucidate the mechanism by which malignancies of man and animals not associated with viruses might arise, Drs. Robert Weinberg and Geoffrey Cooper set out to test the hypothesis that malignancies contain altered or activated normal genes that are responsible for oncogenesis and can transmit the transformed phenotype. This approach was based upon an extensive body of evidence indicating that the cellular target of a wide variety of oncogenic agents is DNA and the possibility that under certain conditions the cellular homologs of viral oncogenes might become mutated or otherwise activated, setting off a chain of events leading to malignancy. In 1979, Shih et al. [15] and in 1980 Cooper et al. [16] showed that transfection of monolayers of NIH 3T3 mouse fibroblasts with high molecular weight DNA extracted from chemically induced tumors of mice led to the development of foci of morphologically transformed cells at greater than control rates. Moreover, tests for virus in the tumors were negative and DNA from primary transformants yielded secondary and tertiary transformants on further rounds of transfection of 3T3 cells. Subsequently, the 3T3 cell assay has been used to test a wide variety of animal and human malignancies and cell lines, derived from malignant tissue, for transforming genes. The human malignancies whose DNA has demonstrated transforming genes include carcinomas of the lung, colon, bladder, gall bladder, pancreas, breast and ovaries, B and T cell lymphomas, acute myeloid and lymphoid leukemias, neuroblastomas, and certain sarcomas [15,17-25]. The presence of human sequences in secondary and tertiary transformants, which contain only small amounts of the original transfecting DNA (usually only one gene), has supported the conclusion that in each of these cases transformation resulted from the acquisition of human transforming genes.

The transforming genes from certain of these malignancies have been identified by nucleic acid hybridization analysis (Southern blot analysis) of either cloned transforming genes or DNA from secondary or tertiary transformants. Transforming genes from two bladder carcinoma cell lines (EJ and T24, both probably derived from the same original tumor) have been identified as homologs of the ras\textsuperscript{Ha} gene [26-28] whereas the transforming gene from one bladder carcinoma has been identified as the homolog of the ras\textsuperscript{Ki} gene [Barbacid M: personal communication]. Similarly, transforming genes from three lung carcinoma cell lines have been identified as homologs of the ras\textsuperscript{Ha} and ras\textsuperscript{Ki} genes [26,29,30]. In addition, single pancreatic and gall bladder carcinomas have demonstrated ras\textsuperscript{Ki} transforming genes [Barbacid M: personal communication]. Transforming genes from the remaining malignancies have not shown homology to any viral oncogene probes under stringent hybridization conditions. However, recent studies [29,31] have shown that the cloned
transforming genes from the HL60 APL and SK-N-SH neuroblastoma cell lines hybridize to \( ras^{\text{Ha}} \) and \( ras^{\text{Ki}} \) genes under non-stringent conditions and to each other under stringent conditions. Moreover, transforming genes from single colon carcinoma, fibrosarcoma, and BL cell lines and from leukemic cells from one patient with AML bear homology to the cloned HL60 transforming gene [31]. These results suggest that the \( ras \) family of genes contains an additional related member, designated \( ras^{N} \), and that the transforming genes in the above six malignancies are \( ras^{N} \) genes. It is striking that all human transforming genes identified to date belong to the \( ras \) family. Whether this reflects a selection inherent in the 3T3 cell assay or activation of these genes in a wide variety of malignancies is not known. It also seems quite remarkable that more than one member of the \( ras \) family can serve as the transforming gene in bladder, lung, and colon carcinomas. Thus, activation of any one of the endogenous \( ras \) genes may be capable of initiating the oncogenic process in these and, likely, other malignancies. Finally, the transforming genes of certain malignancies, e.g., breast and ovarian carcinomas and certain lymphomas, have not demonstrated homology to any of the known oncogenes. It thus seems almost certain that additional cellular oncogenes exist and will require identification in the future.

Characterization of human transforming genes has been carried to the nucleotide level in four cases: the \( ras^{\text{Ha}} \) genes of the EJ bladder carcinoma [32-34] and HS 242 lung carcinoma [30] cell lines, the \( ras^{\text{Ki}} \) gene of the Calu-1 lung carcinoma [35], and the \( ras^{\text{N}} \) gene of the SK-N-SH neuroblastoma cell lines [36]. In the EJ and Calu-1 cell lines, single point mutations in the twelfth codon of the \( ras^{\text{Ha}} \) and \( ras^{\text{Ki}} \) genes have been identified whereas, in the HS 242 and SK-N-SH lines, point mutations in the 61st codon of the \( ras^{\text{Ha}} \) and \( ras^{\text{N}} \) genes have been found. (Although the three cellular \( ras \) genes differ to some extent in nucleotide sequence, they code for p21 ras proteins with similar amino acid sequences, including glycine and glutamine in positions 12 and 61, respectively). It has been suggested that these mutations, resulting in single amino acid substitutions in the respective \( ras \) proteins, are responsible not only for the acquisition of transforming activity, but also are involved in the development of malignancy in vivo. The mutations at position 12 in the transforming genes of the EJ and Calu-1 lines are especially interesting in that the predicted substitutions of the amino acids valine and cysteine for glycine would be expected to alter the helical structure of the normal \( ras^{\text{Ha}} \) and \( ras^{\text{Ki}} \) proteins, respectively, reducing their flexibility and presumably altering their function. It is also noteworthy that in the EJ cell line there is no amplification of the transforming gene and the amount of p21 ras protein synthesized is not significantly increased [26,32,33]. Thus, if the activated \( ras^{\text{Ha}} \) gene was involved in the development of the EJ bladder carcinoma, it was the qualitative alteration rather than increased quantity of the protein that was critical.

Recently, Dhar and colleagues and we [unpublished results] have probed the structure of the eleventh and twelfth codons of the \( ras^{\text{Ha}} \) gene in 15 bladder carcinomas and peripheral leukocytes from 35 normal individuals. We were able to do this by direct Southern blotting since the normal sequence at this site, GCCGGC, is recognized and cleaved by the enzymes Hpa II and Msp I, whereas sequences with mutations in the CCGG tetranucleotide are resistant to these enzymes. All samples contained the normal sequence in the first two positions of the twelfth codon. Thus, mutations in the codon for amino acid 12 of the \( ras^{\text{Ha}} \) gene are not essential for the development of bladder carcinoma and occur fairly infrequently.

A final transforming gene sequenced is one derived from a chicken B cell lym-
phoma induced by ALV [37]. It is unrelated to the oncogene of any known virus and has been designated Blym. From its sequence Blym codes for a protein of about 65 amino acids with significant homology to transferrin. This is of great interest since transferrin is a mitogen and a requirement for many cells growing in serum-free medium, and its level and that of its membrane-associated receptor are increased in proliferating normal and tumor cells. Blym is also of potential importance for human malignancy since at least certain murine and human lymphoid neoplasms contain similar, if not identical, stage-specific transforming genes [20].

KARYOTYPIC ABNORMALITIES AT ONCOGENE LOCI

It has been known for some time that specific chromosomal abnormalities exist in certain human malignancies. These include translocations in certain hematological malignancies (e.g., BL, AML, APL, CML, and ALL) and deletions in certain solid tumors and hematological malignancies (e.g., ovarian carcinoma, Wilm's tumor, menigioma, and ALL). Until recently, the significance of these abnormalities was unknown. However, many of the human genes related to viral oncogenes have been localized to specific chromosomes (rasN, rasHa, and rasKi to chromosomes 1, 11, and 12 [38–41], respectively; myb to chromosome 6 [42]; mos [43] and myc [43–45] to chromosome 8; abl to chromosome 9 [46]; fes to chromosome 15 [46]; src to chromosome 20 [47]; and sis to chromosome 22 [48]) and striking correlations have been noted between the localizations of certain of the oncogenes and the sites of breakage of chromosomes involved in specific translocations and deletions. Moreover, in two cases, entire oncogenes are translocated to new sites. The following summarizes our current knowledge of several of these translocations and deletions.

Reciprocal translocations involving chromosome 22 (the Philadelphia chromosome) and chromosomes 9, 12, 17, or 19 are present in malignant cells in approximately 90 percent of patients with CML. The 9;22 translocation is most common. In most cases of the 9;22 translocation examined to date, the breakpoint in chromosome 9 lies within band q34 [49] (q refers to the long arm and p to the short arm of each chromosome), the site of the abl gene. Moreover, in at least certain cases the translocation involves transfer of the entire abl gene to band q11 on chromosome 22 [50]. To date, no gene has been assigned to band q11; in fact, only one known oncogene, sis, has been identified on chromosome 22 and its location is not known. Since chromosome 22 is the common denominator in all the translocations in CML and since the clinical picture is essentially the same in patients with the 9;12;17; and 19;22 translocations, future efforts must be directed toward examination of the structure and expression of genes located on chromosome 22, especially abl and sis.

Three translocations (2;8, 14;8, and 22;8) have been identified in both African and non-African BL cell lines and in certain cases of ALL. The 14;8 translocation is most common in BL and has been studied most extensively. As noted, chromosome 8 harbors two oncogenic genes, myc and mos, at bands q24 and q22 [43–45], respectively. Although no oncogene has been assigned to chromosome 14, this chromosome does contain the gene for the immunoglobulin heavy chain mu at band q32 [51]. In certain BL lines, myc sequences have been identified on chromosome 14 at q32 adjacent to mu heavy chain sequences [44,45], and mu sequences have been found on chromosome 8 [45]. Thus, the translocation is reciprocal. Although the significance of this translocation in BL is not clear, it is noteworthy that analogous translocations involving myc and immunoglobulin genes occur in mouse plasmacy-
etiology molecular certain to 
quences bring to shown 
tion the mechanisms cogenes 
ALL, respectively, 
abi the human pre-B 
event associated with 

Thus, amplification 
breakpoints 
chromosome 
chromosome 

current 
cultured 
cellular 
volved 

Although correlations between the chromosomal locations of oncogenes and breakpoints in translocations and deletions in the aforementioned malignancies are striking, there are no data yet which directly demonstrate that the indicated oncogenes play a role in the development of the cited malignancies. However, two mechanisms by which translocations may result in malignancy seem plausible. On the one hand, an oncogene may undergo an alteration in sequence during translocation possibly resulting in altered function and malignancy. Alternatively, as has been shown for ALV-induced lymphomas of chickens [60], translocation of an oncogene to a new location or insertion of a new DNA sequence adjacent to an oncogene may bring the oncogene under the control of proximate strong promoter or activator sequences leading to increased expression and possibly to malignancy.

MULTIPLE ONCOGENIC HITS IN 
THE DEVELOPMENT OF MALIGNANCY

Multiple hit theories of malignancy have been based on the observation that certain agents induce malignancies whereas others promote induction and on the need to invoke one or more environmental events as well as one inherited mutation in the etiology of familial malignancies. There is now accumulating evidence at the molecular level which also suggests that multiple events are involved in the genesis of certain malignancies.

For the HL60 APL cell line, current data suggest that at least two steps were involved in the leukemogenic process: one step involving the rasN transforming gene [31] and a second step involving amplification and enhanced expression of the cellular myc gene [61]. Amplified myc sequences have been identified not only in cultured HL60 cells, but also in leukemic cells obtained directly from the patient. Thus, amplification did not develop as a by-product of long-term culture. Amplification of myc sequences has not yet been demonstrated in other myeloid leukemias and so it may be restricted to APL or rare patients like the HL60 patient. A second malignancy which seemingly results from multiple oncogenic hits is BL. Current evidence suggests three oncogenic events: infection by EB virus [10], a subsequent event involving the rasN transforming gene [31], and, likely, a third event associated with the translocation of myc to chromosome 14 [44,45]. Finally, in the human pre-B cell leukemia line SMS-SB, both vigorous expression of the cellular abl gene and a transforming gene distinct from abl have been implicated [62].
The apparent involvement of multiple steps in the malignant process in these malignancies resembles that described in certain B cell lymphomas of chickens. At least three steps appear to be important in development of this malignancy: infection with ALV, integration of the ALV provirus immediately upstream of the cellular \textit{myc} gene and downstream promotion of \textit{myc} expression [60], and some action of the \textit{Blym} transforming gene [37].

REFERENCES

1. Weiss A, Teich NM, Varmus H, et al: RNA Tumor Viruses: The Molecular Biology of Tumor Viruses, Part III. Cold Spring Harbor Monograph 106. Cold Spring Harbor, New York, 1982
2. Bishop JM: Oncogenes. Scientific American 246:68–78, 1982
3. Coffin JM, Varmus HE, Bishop JM, et al: Proposal for naming host cell-derived inserts in retrovirus genomes. J Virol 40:953–957, 1981
4. Shih TY, Papageorge A, Stokes PE, et al: Guanine nucleotide binding and autophosphorylating activities associated with the p21^{\text{src}} protein of Harvey murine sarcoma virus. Nature 287:686–691, 1980
5. Donner P, Greiser-Wilke K, Moelling K: Nuclear localization and DNA binding of the transforming gene product of avian myelocytomatosis virus. Nature 296:262–266, 1982
6. Spector DH, Varmus HE, Bishop JM: Nucleotide sequences related to the transforming gene of avian sarcoma virus are present in DNA of uninfected vertebrates. Proc Natl Acad Sci USA 75:4102–4106, 1978
7. Muller R, Slamon DJ, Trembly JM, et al: Differential expression of cellular oncogenes during pre and postnatal development of the mouse. Nature 299:640–644, 1982
8. Chang EH, Furth ME, Scolnick EM, et al: Tumorigenic transformation of mammalian cells induced by a normal human gene homologous to the oncogene of Harvey murine sarcoma virus. Nature 297:479–484, 1982
9. Blair DG, Oskarsson PJ, Wood TG, et al: Activation of the transforming potential of a normal cell sequence: A molecular model for oncogenesis. Science 212:941–943, 1981
10. Schnipper LE: The Epstein-Barr virus and human lymphoproliferative disorders. Progress in Hematology 12:275–297, 1981
11. Poiesz BS, Ruscetti FW, Gazdar AF, et al: Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T cell lymphoma. Proc Natl Acad Sci USA 77:7415–7419, 1980
12. Gallo RC, Wong-Stahl FW: Retroviruses as etiologic agents of some animal and human leukemias and lymphomas and as a tool for elucidating the molecular mechanism of leukemogenesis. Blood 60:545–557, 1982
13. Blumberg BS, London WJ: Hepatitis B virus and the prevention of primary hepatocellular carcinoma. New Eng J Med 304:782–784, 1981
14. Shafritz DA, Shouval D, Sherman HI, et al: Integration of hepatitis B virus DNA into the cellular genome of liver cells in chronic liver disease and hepatocellular carcinoma. New Eng J Med 305:1067–1073, 1981
15. Shih C, Shilo B, Goldfarb MP, et al: Passage of phenotypes of chemically transformed cells via transfection of DNA and chromatin. Proc Natl Acad Sci USA 76:5714–5718, 1979
16. Cooper GM, Okenquist S, Silverman L: Transforming activity of DNA of chemically transformed and normal cells. Nature 284:418–421, 1980
17. Krontivis JG, Cooper GM: Transforming activity of human tumor DNAs. Proc Natl Acad Sci USA 78:1181–1185, 1981
18. Shih C, Paddy LC, Murray M, et al: Transforming genes of carcinomas and neuroblastomas introduced into mouse fibroblasts. Nature 290:261–264, 1981
19. Lane MA, Sainten A, Cooper GM: Activation of related transforming genes in mouse and human mammary carcinomas. Proc Natl Acad Sci USA 78:5185–5189, 1981
20. Lane MA, Sainten A, Cooper GM: Stage-specific transforming genes of human and mouse B and T lymphocyte neoplasms. Cell 28:873–880, 1982
21. Murray MJ, Shilo B, Shih C, et al: Three different human tumor cell lines contain different oncogenes. Cell 25:355–361, 1981
22. Pulciani S, Santos E, Lauver AV, et al: Oncogenes in human tumor cell lines: Molecular cloning of a transforming gene from bladder carcinoma cells. Proc Natl Acad Sci USA 79:2845–2849, 1982
23. Marshall CJ, Hall A, Weiss RA: A transforming gene present in human sarcoma cell lines. Nature 299:171–173, 1982
24. Pulciani S, Santos E, Lauver AV, et al: Oncogenes in solid human tumors. Nature 300:539–542, 1982
25. Perucho M, Goldfarb M, Shimizu K, et al: Human tumor-derived cell lines contain common and different transforming genes. Cell 27:467–476, 1981
26. Der CJ, Krontiris JG, Cooper GM: Transforming genes of human bladder and lung carcinoma lines are homologous to the ras genes of Harvey and Kirsten sarcoma viruses. Proc Natl Acad Sci USA 79:3637–3640, 1982
27. Parada LF, Tabin CJ, Shih C, et al: Human EJ bladder carcinoma oncogene is homolog of Harvey sarcoma ras gene. Nature 297:474–478, 1982
28. Santos E, Tronick SR, Aaronson SA, et al: T24 human bladder carcinoma oncogene is an activated form of the normal human homolog of Balb and Harvey MSV transforming genes. Nature 298:343–347, 1982
29. Shimizu K, Goldfarb M, Suard Y, et al: Three human transforming genes are related to the viral ras oncogenes. Proc Natl Acad Sci USA 80:2112–2116, 1983
30. Yuasa Y, Srivastava SK, Dunn CY, et al: Acquisition of transforming properties by alternative point mutations within c-bas/has human proto-oncogene. Nature 303:775–779, 1983
31. Murray M, Cunningham JM, Parada LF, et al: The HL60 transforming sequence: A ras oncogene co-existing with altered myc genes in hematopoietic tumors. Cell, in press
32. Tabin CJ, Bradley SM, Bargmann CI, et al: Mechanism of activation of a human oncogene. Nature 300:143–149, 1983
33. Reddy EP, Reynolds RK, Santos E, et al: A point mutation is responsible for the acquisition of transforming properties by the T24 human bladder carcinoma oncogene. Nature 300:149–152, 1982
34. Taparowsky E, Suard Y, Fasano O, et al: Activation of the human H-ras gene. Nature 300:762–765, 1983
35. Shimizu K, Birnbaum D, Ruley MA, et al: The structure of the K-ras gene of the human lung carcinoma cell line Calu-1. Nature, in press
36. Taparowsky E, Shimizu K, Goldfarb M, et al: Structure and activation of the N-ras gene. Cell, in press
37. Goubin G, Goldman DS, Luce J, et al: Molecular cloning and nucleotide sequence of a transforming gene detected by transfection of chicken B-cell lymphoma DNA. Nature 302:114–119, 1982
38. Ryan JJ, Barker PE, Ruddle FH: Chromosomal assignment of a family of human oncogenes. Cell 42:2189, 1983
39. McBride OW, Swan DC, Santos E, et al: Localization of the normal allele of T24 human bladder carcinoma oncogene to chromosome 11. Nature 300:773–774, 1982
40. deMartinville B, Giacolone J, Francke U, et al: Oncogene from human EJ bladder carcinoma is located on the short arm of chromosome 11. Science 219:498–501, 1983
41. Sakaguchi AY, Naylor SL, Storrs TB, et al: Human c-Ki ras proto-oncogene on chromosome 12. Science 219:1081–1083, 1983
42. Dalla-Favera R, Franchini G, Martinotti S, et al: Chromosomal assignment of the human homologs of feline sarcoma virus and avian myeloblastosis virus onc genes. Proc Natl Acad Sci USA 79:4714–4717, 1982
43. Neel BG, Jharwar SC, Chaganti RS, et al: Two human c-onc genes are located on the long arm of chromosome 8. Proc Natl Acad Sci USA 79:7842–7846, 1982
44. Dalla-Favera R, Bregni M, Erickson J, et al: Human c-myc onc gene is located in the region of chromosome 8 that is translocated in Burkitt lymphoma cells. Proc Natl Acad Sci USA 79:7824–7827, 1982
45. Taub R, Kirsch I, Morton C, et al: Translocation of the c-myc gene into the immunoglobulin heavy chain locus in Burkitt lymphoma and murine plasmacytoma cells. Proc Natl Acad Sci USA 79:7837–7841, 1982
46. Heisterkamp N, Groffen J, Stephenson JR, et al: Chromosomal localization of human cellular homologues of two viral oncogenes. Nature 299:747–749, 1982
47. Sakaguchi AY, Naylor SL, Storrs TB: A sequence homologous to Rous sarcoma virus v-src is on human chromosome 20. Prog Nucleic Acid Res Mol Biol, in press
48. Dalla-Favera R, Gallo RC, Giallongo A, et al: Chromosomal localization of the human homolog (c-sis) of the simian sarcoma virus onc gene. Science 218:686–687, 1982
49. Rowley JD: A new consistent chromosomal abnormality in chronic myelogenous leukemia identified by quinacrine fluorescence and Giemsa staining. Nature 243:290–293, 1973
50. de Klein A, van Kessel AG, Gросveld G, et al: A cellular oncogene is translocated to the Philadelphia chromosome in chronic myelogenous leukemia. Nature 300:765–767, 1982
ONCOGENIC GENES AND HUMAN MALIGNANCY

51. Kirsch IR, Morton CC, Nakahara K, et al: Human immunoglobulin heavy chain genes map to a region of translocations in malignant B lymphocytes. Science 216:301-303, 1982
52. Harris LJ, D'Eustachio P, Ruddle FH, et al: DNA sequence associated with chromosome translocations in mouse plasmacytomases. Proc Natl Acad Sci USA 79:6622-6626, 1982
53. Marcu KB, Harris LJ, Stanton LW, et al: Transcriptionally active c-myc oncogene is contained within NIARD, a DNA sequence associated with chromosome translocations in B-cell neoplasia. Proc Natl Acad Sci USA 80:519-523, 1983
54. Mushinski JF, Bauer SR, Potter M, et al: Increased expression of myc-related oncogene mRNA characterizes most Balb/c plasmacytomases induced by pristane or Abelson murine leukemia virus. Proc Natl Acad Sci USA 80:1073-1077, 1983
55. Erikson J, Ar-Rushdi A, Drwinga HL, et al: Transcriptional activation of the translocated c-myc oncogene in Burkitt lymphoma. Proc Natl Acad Sci USA 80:820-824, 1983
56. Maguire RT, Robins TS, Thorgeirsson SS, et al: Expression of cellular myc and mos genes in undifferentiated B cell lymphomas of Burkitt and non-Burkitt types. Proc Natl Acad Sci USA 80:1947-1950, 1983
57. Francke U, Holmes LB, Atkins L, et al: Aniridia-Wilm's tumor association: Evidence for specific deletion of 11p13. Cytogenet Cell Genet 24:185-192, 1979
58. Kaneko Y, Egnes MC, Rowley JD: Interstitial deletion of short arm of chromosome 11 limited to Wilm's tumor cells in a patient without aniridia. Cancer Res 41:4577-4578, 1981
59. The Third International Workshop on Chromosomes in Leukemia: Chromosomal abnormalities in acute lymphoblastic leukemia: Structural changes in 234 cases. Cancer Genet Cytogenet 4:101-110, 1981
60. Neel BG, Hayward WS, Robinson HL, et al: Avian leukosis virus-induced tumors have common proviral integration sites and synthesize discrete new RNAs: Oncogenesis by promoter insertion. Cell 23:323-334, 1981
61. Dalla-Favera R, Wong-Stahl F, Gallo RC: Onc gene amplification in promyelocytic leukemia cell line HL60 and primary leukemic cells of the same patient. Nature 299:61-63, 1982
62. Ozanne B, Wheeler T, Zack J, et al: Transforming gene of a human leukemia cell is unrelated to the expressed tumor virus-related gene of the cell. Nature 299:744-747, 1982