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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

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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[1]) 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 oncogenic proteins [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,

[1]Abbreviations for retroviruses and their oncogenic genes are as follows: Abelson murine leukemia virus: AbLV and *abl;* Snyder-Theilen feline sarcoma virus: FeSV and *fes;* Moloney murine sarcoma virus: MoSV and *mos;* avian erythroblastosis 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 ras^{Ha}; Kirsten murine sarcoma virus: KiSV and ras^{Ki}; simian sarcoma virus: SSV and *sis;* Rous avian sarcoma virus: RSV and *src;* avian leukosis 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*^{Ha} gene [26–28] whereas the transforming gene from one bladder carcinoma has been identified as the homolog of the *ras*^{Ki} gene [Barbacid M: personal communication]. Similarly, transforming genes from three lung carcinoma cell lines have been identified as homologs of the *ras*^{Ha} and *ras*^{Ki} genes [26,29,30]. In addition, single pancreatic and gall bladder carcinomas have demonstrated *ras*^{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*^{Ha} and *ras*^{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*^{Ha} genes of the EJ bladder carcinoma [32–34] and HS 242 lung carcinoma [30] cell lines, the *ras*^{Ki} gene of the Calu-1 lung carcinoma [35], and the *ras*^{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*^{Ha} and *ras*^{Ki} genes have been identified whereas, in the HS 242 and SK-N-SH lines, point mutations in the 61st codon of the *ras*^{Ha} and *ras*^{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*^{Ha} and *ras*^{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*^{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*^{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*^{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, meningioma, 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 (*ras*^{N}, *ras*^{Ha}, and *ras*^{Ki} 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-

tomas [45,52]. Furthermore, *myc* expression is increased in some mouse plasmacytomas [53,54] and may be increased in certain BL lines [55,56].

The final translocation of interest is an 8;21 translocation seen in certain patients with AML. The breakpoint on chromosome 8 in this translocation lies at band q22 [43] containing the *mos* gene. However, it is not known whether the *mos* gene remains on chromosome 8 or is transferred to chromosome 21. It is also not known whether *mos* expression is turned on.

Two deletions are of interest, involving, respectively, the ras^{Ha} gene located at band p13 of chromosome 11 [40] and the *myb* gene located at band q24 of chromosome 6 [42]. The former is important because individuals who lack p13 are aniridic and are at risk to develop Wilm's tumor [57]. In addition, one patient with Wilm's tumor has been identified with a deletion of p13 in tumor cells, but a normal chromosome 11 in other tissues [58]. The second deletion occurs in about 6 percent of patients with ALL and involves loss of bands q21 to q25 of chromosome 6 [59], including the *myb* gene. Alteration of ras^{Ha} and *myb* expression in Wilm's tumor and ALL, respectively, has not been reported.

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 ras^{N} 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 ras^{N} 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 *myc* gene and downstream promotion of *myc* expression [60], and some action of the *Blym* transforming gene [37].

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