

Oncogenes: Clinical Relevance

U. R. Rapp, S. M. Storm, and J. L. Cleveland

The last 10 years have seen something of a revolution in experimental carcinogenesis, sparked by the discovery of oncogenes [1–3]. The first such gene and most of the ones that followed [1] have been isolated as part of the genome of a tumor-inducing retrovirus. Mostly obtained from birds and mice, these viral oncogenes are nearly identical to genes present in normal cells and, because of their high degree of evolutionary conservation, could be used directly to isolate their human counterparts.

What implicated these genes in chemically induced and natural tumors? First indications came from oncogene transduction experiments with retroviruses and chemically transformed mouse and rat cells [4–6]. The transduction experiments led to the isolation of new oncogene-carrying viruses [5, 7, 8], but proof of the supposition that cellular oncogenes were involved in chemical carcinogenesis came from another quarter. Gene transfer methods using transfection of chromosomal DNA had become more efficient [9, 10], and their application to the search for transforming genes in chemically transformed mouse cells was successful [11]. The advent of molecular cloning greatly accelerated the identification of transfected, focus-inducing DNA, thus leading to the following central findings.

DNA from transformed cells was active, while DNA from untransformed cells had very little or no activity. The transforming DNA was related to one of several groups of

known viral oncogenes, the *ras* oncogenes. Similar transforming DNA could be isolated from human tumor cell lines and biopsies, whereas normal control tissue was negative. Comparison of *ras* oncogene DNA from tumor and normal tissue revealed point mutations at specific codons in transforming *ras* genes, which increased their focus-forming activity [for a review see reference 12]. Thus, it was established that at least some chemically transformed cells and cells in natural tumors differed from their normal progenitors in the biological activity and primary structure of a class of cellular oncogenes, the *ras* family. Curiously, first experiments testing DNA from a wide variety of tumors yielded only transforming *ras* genes, even though the cells were known to harbor a fair number of other oncogenes previously identified in retroviruses. While this was sometimes looked upon as a blessing, indicative of the fact that all tumors were the result of one basic malfunction, other lines of investigation suggested otherwise. Activation of human oncogenes by translocation was discovered (*myc*, *abl*) [for a review see reference 13], and amplification of cellular oncogenes (*myc* family, *Ki-ras*) was observed in certain tumors [2, 14]. More recently, DNA transfection also led to identification of other, non-*ras*-related oncogenes [15–19], and thus it was established that a variety of cellular oncogenes were involved in the development of human tumors.

Was oncogene activation cause or consequence of tumor development? In animal systems, it could clearly be shown to occur as an early, presumably initiation, event [20, 21]. In human tumors, some changes, such

Laboratory of Viral Carcinogenesis, Division of Cancer Etiology, National Cancer Institute, National Institutes of Health

as oncogene amplification [22, 23] and perhaps activation by translocation [24], as well as at least two documented cases of mutational activation of *ras* genes, appeared to be late events [25, 26]. This does not exclude the possibility that other oncogenes had become active early in the same tumors; in fact, the combined data from *in vivo* carcinogenesis, animal models, and human pathology make it likely that oncogenes are involved in initiation, maintenance, and progression of human tumors [2, 3]. But the process of carcinogenesis is definitely more complex.

A major disappointment with tumor-derived *ras* genes was the observation that, as a rule, they were not able to induce in one step a fully transformed phenotype in the presumed progenitor cells. Inspiration again came from the tumor virus sector, where cooperation between two or more genes for transformation had previously been observed [27–29], and high-efficiency transformation of primary cells in culture with specific combinations of viral and tumor-derived oncogenes was accomplished [30–33]. While the *in vitro* experiments could only suggest what might be going on *in vivo*, owing to the artificial nature of culture conditions and the limited variety of cell types of which they allowed study, support for the

concept of cooperating oncogenes in natural settings came from work with retroviruses carrying multiple cell-derived oncogenes or a single oncogene in the company of a supposed helper gene [33]. In fact, it was work with a dual oncogene-carrying retrovirus that established the phenomenon of synergistic transformation *in vivo* [32, 34] consistent with its behavior *in vitro* [32, 34, 35].

However, the mere fact that certain combinations of oncogenes accelerate tumor induction in birds and mice does not directly address the question of the role of oncogene synergism in human tumor development, and to date there is no example of the isolation of multiple active oncogenes from a primary human tumor. Moreover, the true assay for the transforming potential of a tumor-derived oncogene, i.e., incorporation into tumor progenitor cells by gene replacement or at least addition, and implantation of these cells at various doses into their natural site, has yet to be performed. Nevertheless, it seems reasonable to expect that multiple, weakly transforming oncogenes, presumably activated successively, are involved in the development of perhaps the majority of human tumors.

What are cellular oncogenes and what is their normal role in cellular physiology? The

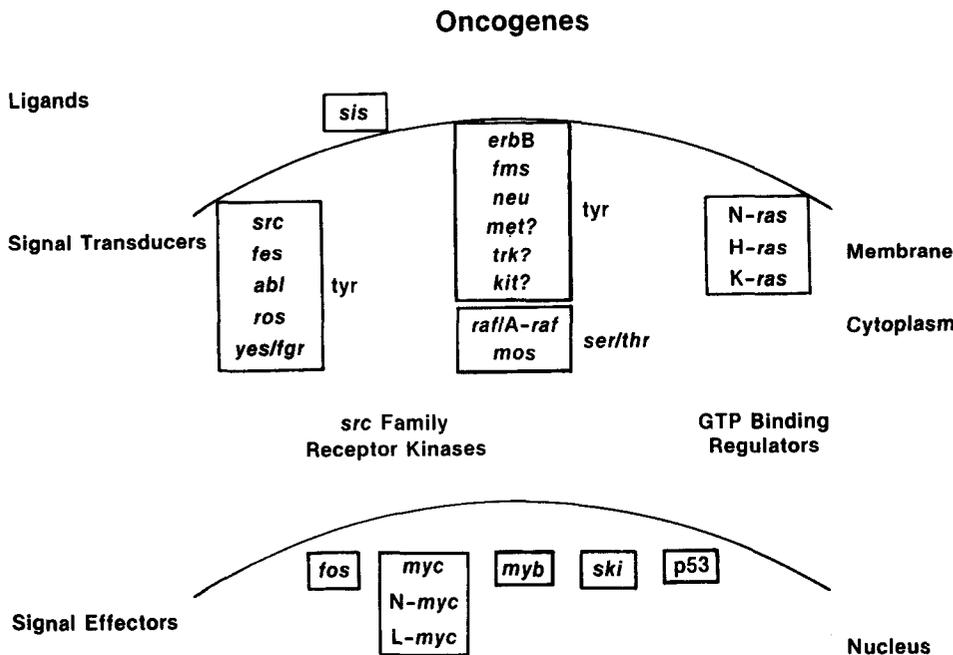


Fig. 1. Schematic representation of oncogenes grouped in the cell according to their amino acid sequence relatedness, cellular location, and posi-

tion in the signal transduction pathway of growth factors

Table 1. Human oncogene map**Chromosome**

1. *N-ras*, *c-SK*, *NGF*
2. *fos*, *N-myc*
3. *raf-1*
4. *raf-2*, *IL-2*
5. *fms*
6. *myb*, *c-Ki-ras-1*
7. *ERV3*, *erb-B*, *A-raf-2* *met*
8. *myc*, *mos*
9. *abl*
- 10.
11. *c-Ha-ras-1*
12. *c-Ki-ras-2*, *int-1*
13. *RB-1* (retinoblastoma)
- 14.
15. *fes* (*fps*), *ERV2*
- 16.
17. *erb-A1*, *erb-A2*
18. *ERV1*
- 19.
20. *src*
- 21.
22. *sis* (PDGF)
- X. *c-Ha-ras-2*, *A-raf-1*

functions of several such genes have recently been identified [36–38] or approximated [34, 39–42]. Figure 1 shows a compilation of the best-studied oncogenes according to their location in the cell, sequence relatedness, enzymatic activity, and known or presumed function in the signal transduction pathway of growth factors [34, 43]. Table 1 gives the chromosomal locations of oncogenes in humans. Briefly, there are three major functional groups: ligands [*sis* = platelet-derived growth factor (PDGF) gene-derived], receptors, and cytoplasmic transmitters (two large families, *src* and *ras*) and genes for nuclear proteins, at least one of which (*myc*) appears to function as a central relay for growth factor signal transduction [34, 39–41]. The largest superfamily of known oncogenes is the *src* family, which contains transmembrane receptors [*erbB*, derived from the epidermal growth factor (EGF) receptor; *fms*, related to the colony-stimulating factor (CSF)-1 receptor; and *neu*, *met*, and *trk*, derived from receptors for unknown ligands], and both membrane-associated (*src*, a form of *abl*) and cytoplasmic protein kinases (*c-raf*, *A-raf*, and *mos*). In general, these kin-

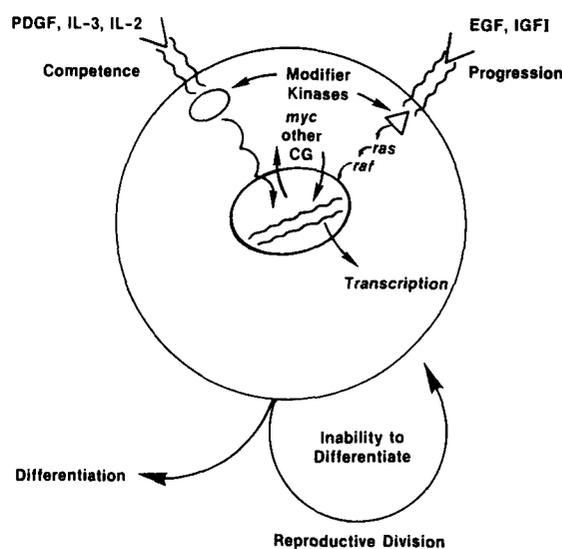


Fig. 2. Schematic representation of proto-oncogenes involved in the signal transduction pathways of growth factors. *PDGF*, platelet-derived growth factor; *IL-3*, *IL-2*, interleukin 3 and 2; *EGF*, epidermal growth factor; *IGF-1*, insulin-like growth factor 1; *CG*, “competence” genes; \approx , receptors

ases have specificity for tyrosine, with the exception of the *raf* family and *mos*, which have associated kinase activity specific for serine and threonine [44]. The second, growing cytoplasmic/membrane-associated family is the *ras* family, which appears to have to do with cyclic nucleotide metabolism and guanosine triphosphate (GTP) binding [12].

The most prominent of the nuclear genes are *myc*, *fos*, and *myb*, which have all been shown to be growth-factor-regulated in expression [39, 45–47] and might in turn mediate growth factor signals [40, 41]. Another illustration of the growth factor connection of oncogenes is to be found in Fig. 2, which places various genes in a scheme built on earlier observations made by others [48, 49] in the course of study of growth regulation of BALB 3T3 fibroblasts. Under certain conditions, these cells require sequentially two qualitatively distinct ligands – PDGF, which was called a competence factor, followed by EGF, a progression factor – before they enter S-phase. Treatment of cells with PDGF induces a set of “competence” or early G1 genes, [48] to which belong oncogenes such as *myc* and *fos* and *R-fos* [50], at least one of which can partially [40] or completely [41], presumably depending on dose, replace the cell’s need for the inducing fac-

Table 2. Human tumors frequently associated with a specific oncogene

Burkitt's lymphoma	<i>c-myc</i>
CML	<i>abl</i>
Neuroblastoma	<i>N-myc</i>
Lung carcinoma	<i>c-raf-1</i>
Stomach cancer	<i>c-raf-1</i> (sporadic?)

tor. On the basis of experiments in growth factor abrogation [41], oncogene synergism [32, 34, 51], and the relationship of *ras* and *raf* oncogenes [43, 52, 53], the latter two were placed in the progression pathway of growth regulation, with *raf* located downstream of *ras*. One possibility for connecting the two pathways, consistent with the observed synergisms and the enzymatic activity of *raf* as well as with properties of *myc*, is the activation of *myc* by *raf* via phosphorylation [43, 54].

Thus, the conclusion from the above findings is that oncogenes are relevant to human oncology. Their deregulated function presumably causes the loss of growth control in malignant cells. Does this knowledge help us in diagnosis or treatment of clinical cancer? The answer is no, or not yet. Although there are a few types of human tumors in which a specific oncogene is consistently involved (presumably activated), such as chronic myelocytic leukemia (CML) [55, 56], Burkitt's lymphoma [13, 57–59], and perhaps lung and stomach cancer [18, 43, 60; Table 2), most tumors appear to be variably associated with a variety of oncogenes, if they yield activated oncogenes at all. There is some hope, however, that with the isolation of additional oncogenes and improved histological typing, a list of preferred oncogenes may be emerging which is typical for certain tumors. It is likely to be a list of genes rather than a single one because, as indicated in Fig. 2, oncogenes appear to belong in signal transmission pathways from cell surface to the nucleus, where presumably each pathway involves the agency of multiple oncogene products, any one of which may be able to deregulate the chain. In any case, there is some hope that different tumor types may be distinguishable on the basis of oncogene profiles, which would provide a set of functional rather than structural tumor markers.

What might be the consequence of identifying such markers? So far, there is no evidence that oncogene typing would be useful for early diagnosis or treatment of tumors, except for certain familial cases of retinoblastoma, where the DNA probe that is being used, however, is not an oncogene probe but a RFLP probe. Using such probes, the presence of a predisposing retinoblastoma chromosome 13 (Table 1) in one case was detected in amniocentesis material, and early surgery on the infant probably saved his life [61].

There are also familial cases of renal carcinoma which may involve *raf* and *myc* oncogenes [43, 62], and other rare familial tumors associated with distinct chromosomal abnormalities [24] for which a similar approach may become applicable in the future. Moreover chromosomal site changes or specific gene changes involved in hereditary cancer may also occur in sporadic tumors of the same type, and their identification may thus become important for establishing tumor-specific (onco)-gene profiles in individual patients. Another example of the clinical use of oncogene- or oncogene-related DNA probes is a breakpoint specific probe characterizing the translocation that activates the *abl* oncogene in CML. Current technology allows detection of translocation-positive CML cells in cell mixtures at the level of 1%, and this probe is therefore presently being evaluated in clinical trials to determine the effect of various treatment regimens at the level of the target cell.

Oncogene probes have also become clinically useful for diagnosis of unrelated genetic diseases. For example, the *raf-2* pseudogene is currently the closest RFLP marker for Huntington's chorea [63], and the active *met* oncogene probe is used to help in the diagnosis of people with a predisposition to cystic fibrosis [64–66]. Thus, oncogene probes are today clinical tools important for diagnosis and treatment of certain human tumors as well as for diagnosis of two of the four most common noncancerous human hereditary diseases. Moreover, we are only beginning to explore what other consequences of specific oncogene expression in tumors might be exploited in the future. To list a few ongoing investigations: (a) Production of transforming growth factors by tu-

Table 3. *raf* oncogenes

2 active genes in man: <i>c-raf-1</i> and <i>A-raf-1</i>
<i>c-raf-1</i> on chromosome 3p25; site altered in several epithelial neoplasias
Gene expressed in many tissues
<i>A-raf-1</i> on chromosome Xp21
Gene expressed in select tissues
Genes encode 74- and 69-kd cytosolic proteins with associated serine/threonine kinase activity
Function in signal transduction downstream of <i>ras</i>
Oncogenic activation can be achieved by truncation
Both genes have pseudogenes: <i>c-raf-2</i> and <i>A-raf-2</i>
<i>c-raf-2</i> marks Huntington's chorea

mors and excretion in urine are being studied and may become of diagnostic and/or prognostic value [67]. (b) We are determining the possibility of immunity induction to altered oncogenes in cancer patients. (c) There is some hope that expression of specific oncogene constellations in a cell will alter their physiology such that they now differ from their normal progenitors predictably in sensitivity to metabolic poisons or other cell regulators.

Since at least some growth factor receptors are cellular oncogenes and some tumor cells show autocrine secretion, efforts are under way to develop receptor-blocking agents in order to stop or slow down cancer cell growth. Unfortunately, cancer-specific receptors have yet to be identified, and we already know that tumor cells can become receptor-independent by switching to oncogenes capable of intracellular mitogen signal transmission [40, 41]. It is therefore especially worthwhile to focus on modes of inactivation of intracellular oncogenes, particularly those such as *raf* which are located at the effector end of the growth factor signal transduction chain. Indeed, there is preliminary evidence suggesting that *raf* protein kinase activity is regulated at the level of the protein, thus providing us with a target site to which to fit a downregulating agent.

Many of the techniques and approaches discussed above are being used in our laboratory to evaluate the role of *raf* oncogenes in lung carcinoma, the most common tumor of Western man.

The general properties of *raf* oncogenes are summarized in Table 3. *c-raf-1* was first implicated in lung cancer because of its chromosomal map position at 3p25, a site that is

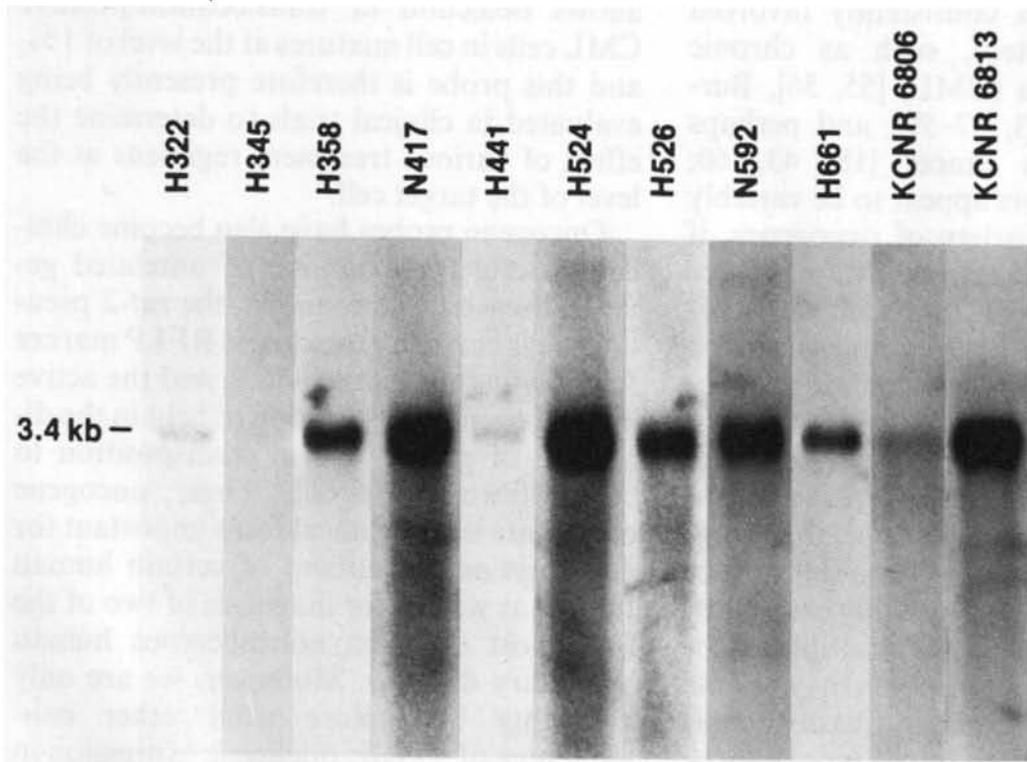


Fig. 3. Expression of *c-raf-1* in human lung cancer cell lines. Poly(A)⁺mRNA from the indicated small-cell lung cancer cell lines was purified and

analyzed using Northern blot procedures for *c-raf-1* RNA. The size of the *c-raf* RNA is shown in kilobases (*kb*)

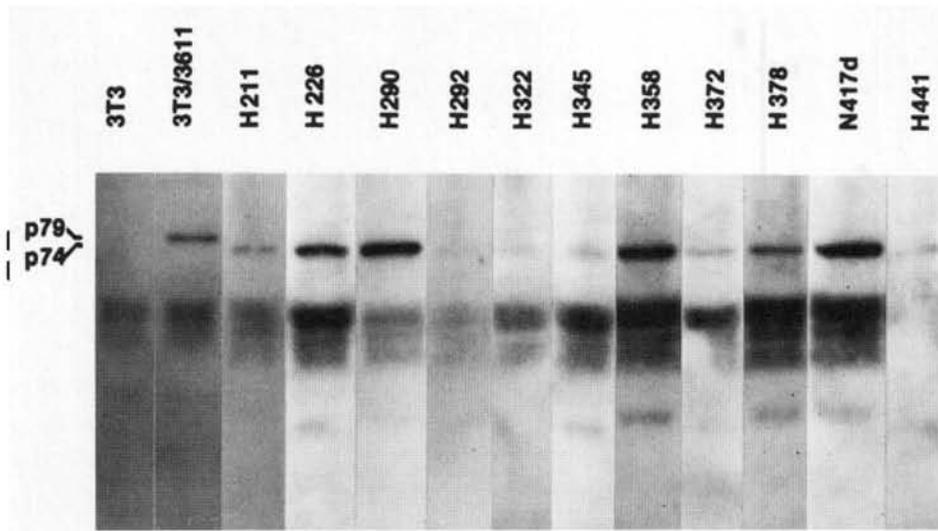


Fig. 4. Western analysis of *c-raf* proteins in human lung cancer cell lines. Unlabeled extracts of cells were affinity-purified using *c-raf* C-terminal specific anti-SP63 antibody. The extracts were electrophoresed, blotted, and reacted with anti-SP63 serum and ^{125}I protein A. As a negative control,

c-raf immunoprecipitates from mouse 3T3 cells were reacted with anti-p15 *gag* serum and ^{125}I protein A. For comparison of levels of *raf*, 3T3 cells transformed by *v-raf* (3T3/3611) are shown. Sizes of proteins are indicated in kilodaltons (*kd*)

frequently altered in small-cell lung cancer [43, 60, 68]. Expression of *c-raf-1* was therefore determined in lung cancer cell lines and biopsy material by Northern blotting (Fig. 3), Western blotting (Fig. 4), and immunohistochemistry with *raf*-specific antibodies, a highly sensitive technique applicable to biopsy material (data not shown). *c-raf-1* RNA and protein of normal size are expressed in the majority of lung tumors of all histological types, whereas they are low or undetectable in normal lung (unpublished results). Thus, *c-raf-1*, sporadically amplified *myc* family genes [2], and occasionally occurring mutation-activated *Ki-ras* oncogenes [12, 69, 70] are candidate components of the machinery that drives the uncontrolled growth of these tumors. But how can we determine whether *raf* is an "activated" oncogene in these cells, given the fact that it is of normal size? Work with full-length, normal *c-raf-1* cDNA has suggested that while amino terminal truncation of the molecule is a common structural change typical of several transforming versions of the gene, high-level expression of the normal gene may also facilitate transformation. The levels of *c-raf-1* protein in lung tumor cells are well within the range observed in *c-raf-1* cDNA transformed mouse cells (unpublished results). Nevertheless, because of the lack of telltale

signs of oncogenic activation, it remains to be determined whether *raf* oncogene and also *myc* gene functions play a role in the maintenance of the transformed phenotype of lung tumor cells.

Assuming that *c-raf-1* is involved in lung carcinoma, is there evidence to suggest that *raf* transformed cells are more sensitive than control cells to potential negative growth regulators? We have examined the effects of a variety of substances in ongoing experiments and observed inhibitory actions of two reagents, the C-kinase activator TPA on *raf* transformed mouse cells and hydrocortisone for transformed rat, but not control cells (Fig. 5 a, b). These are preliminary data, and there may exist other agents, more suitable for clinical application, which are more effective, but these experiments serve to illustrate that there is a basis for the hope that tumor cells may have an altered or increased sensitivity to (negative) growth modulators.

To evaluate further the effects of potential negative growth regulators experimentally in vivo, we have developed an animal model system for the induction of lung carcinoma (Fig. 6). Transplacental treatment with ethylnitrosourea of NFS (female) mated with AKR (male) mice, followed by promotion with butylated hydroxytoluene (BHT), results in rapid tumor development, starting at

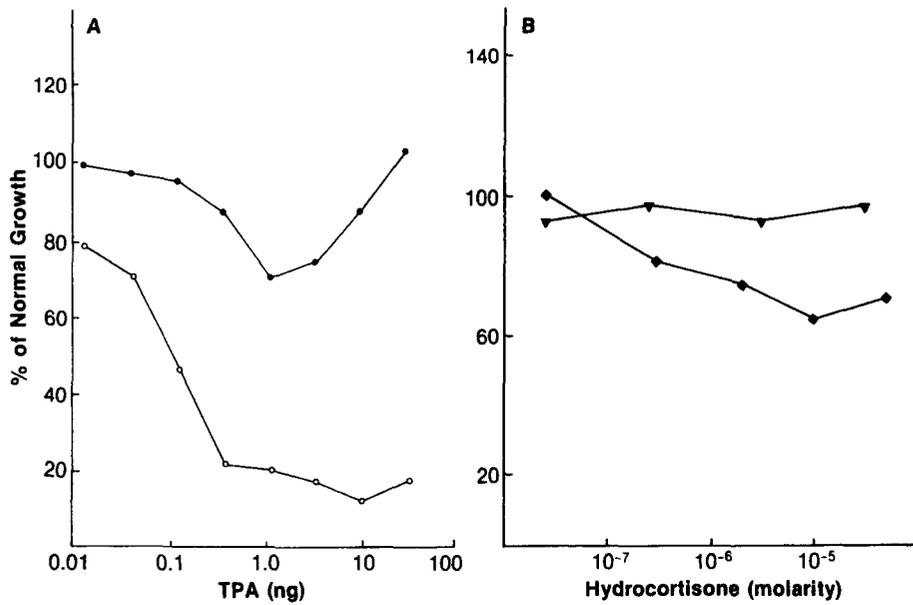


Fig. 5 a, b. Growth inhibition of mouse NIH/3T3 (a) and rat FRE3A (b) *raf*-transformed cells with TPA (a) and hydrocortisone (b), respectively; subconfluent cultures of control (●, ▼) and *v-raf* transformed (○, ◆) cells were treated with the dose of TPA and hydrocortisone indicated, and after 4 days were pulsed with [¹²⁵I] IdUrd for the last 24 h to determine levels of DNA synthesis. In-

corporation of [¹²⁵I] IdUrd is expressed in terms of percent normal growth of untreated control cultures. A minor fraction of flat revertant cells present in the transformed parent culture is resistant to growth arrest by hydrocortisone. On microscopic inspection of LTR-*raf* transformed rat cells treated with 10⁻⁵ molar hydrocortisone only flat revertants were apparent (data not shown)

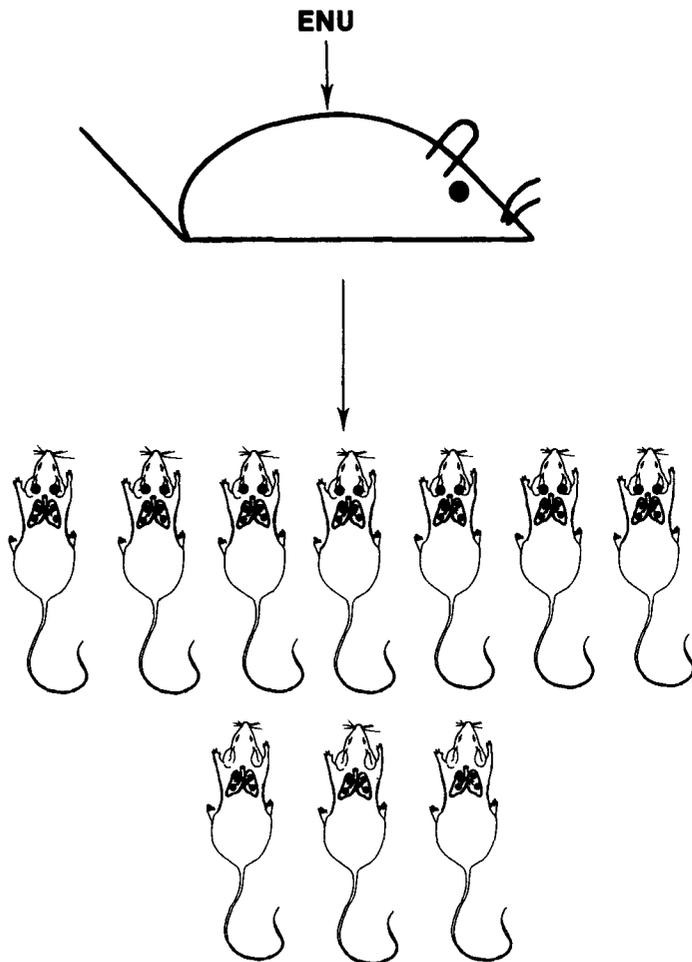


Fig. 6. Induction of lung adenocarcinoma and lymphoma in mice treated with ethylnitrosourea (ENU). Pregnant NFS females (mated with AKR males) were injected transplacentally with ENU, and weanling-age F1 mice were promoted with weekly injections of butylated hydroxytoluene (BHT). The incidence of tumor induction in F1 mice is shown diagrammatically; about 70% of animals develop a T-cell lymphoma and nearly 100% develop lung adenocarcinoma

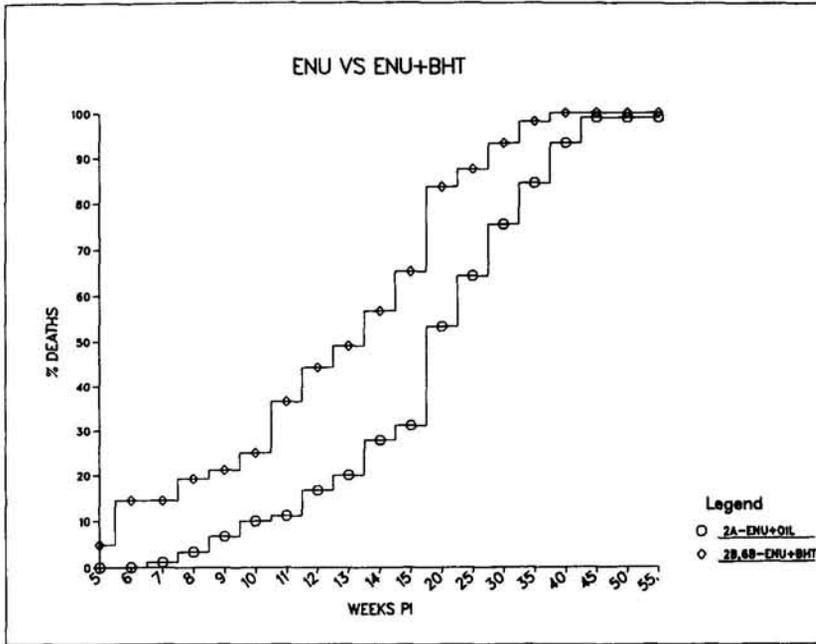


Fig. 7. Mortality curves for NFS \times AKR F1 mice treated in utero with ENU (\circ) and mice treated with ENU followed by weekly promotion with BHT (\diamond). Fifty percent of mice treated with ENU + BHT died with a mean latency of 13 weeks, whereas those treated with ENU alone died with a mean latency of 20 weeks. Vaccinations with control proteins were ineffective

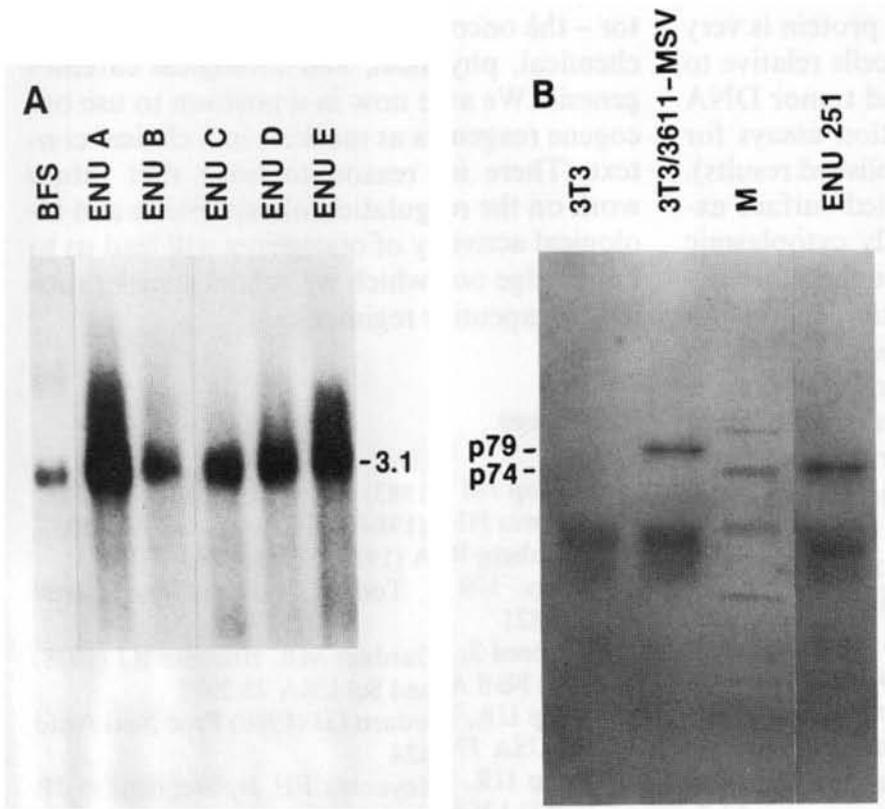


Fig. 8 a, b. Expression of *c-raf-1* mRNA (a) and protein (b) in ENU-induced lung adenocarcinoma and lymphoma. a Levels of *c-raf-1* poly(A)+mRNA (5.0 μ g) isolated from three T-lymphomas (ENU A–C) and two lung adenocarcinoma (ENU D and E) were compared to levels found in a murine T-cell line, BFS. b Western analysis of levels of *c-raf-1* protein in an ENU-induced lymphoma

(ENU 251) compared to those found in *v-raf* 3611-MSV transformed mouse fibroblast cells. p79 is the size (in kd) of the *gag-v-raf* fusion protein of 3611-MSV, whereas p74 is the size of *c-raf*. M, 14 C molecular weight standards. As a negative control, *c-raf* immunoprecipitates from mouse 3T3 cells were reacted with p15 *gag* antibody and [125 I] protein A

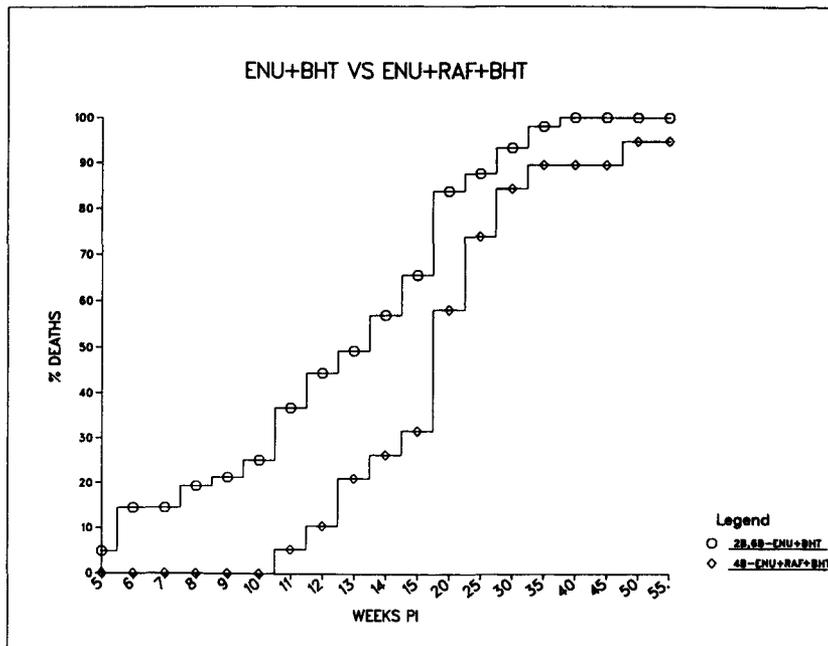


Fig. 9. Mortality curves of NFS \times AKR F1 mice treated with ENU + BHT (\circ), and of those treated with ENU + BHT and vaccinated weekly with purified *v-raf* protein (\diamond)

5 weeks of age (Fig. 7). Two types of tumors result – lung adenocarcinoma (80%–100%) and T-cell lymphomas (60%–70%). Expression of *c-raf-1* RNA and protein is very high in both types of tumor cells relative to control tissue (Fig. 8 a, b), and tumor DNA is positive in DNA transfection assays for focus-forming activity (unpublished results). Live cell fluorescence suggested surface expression of the predominantly cytoplasmic *raf* protein in tumor cells. We therefore decided to test whether induction of an immune response to *raf* oncogene protein in these mice would affect tumor development, and observed significant effect of *raf* protein vaccination on the BHT-promoted early phase of tumor incidence, whereas no long-term protection was achieved (Fig. 9).

The *raf* oncogene may not be the best choice for study of the potentials of immune modulation of tumor growth, since it is predominantly located in the cytoplasm of cells [43]. Receptor-related oncogenes which become structurally altered in tumors may be more promising. However, the rules on how to induce a cellular immune response, which is presumably the critical element in host defense against tumor growth, are only becoming established. It may be that intracellular antigens are in fact more efficient in triggering a cytotoxic T-cell response [71]. In any case, the experiments with *raf* serve to illuminate some of the strategies for control of

tumor growth that may hold promise for the future.

In the last 10 years, a common denominator – the oncogenes – has been identified for chemical, physical, and biological carcinogenesis. We are now in a position to use oncogene reagents as markers in a clinical context. There is reason to hope that future work on the regulation of expression and biological activity of oncogenes will lead us to knowledge on which we can base new rational therapeutic regimens.

References

1. Bishop JM (1983) *Ann Rev Biochem* 52:301
2. Varmus HE (1984) *Ann Rev Genet* 18:553
3. Weinberg RA (1985) *Science* 230:770
4. Rapp UR, Todaro GJ (1978) *Science* 201:821
5. Rasheed S, Gardner MB, Huebner RJ (1978) *Proc Natl Acad Sci USA* 75:2972
6. Rapp UR, Todaro GJ (1980) *Proc Natl Acad Sci USA* 77:624
7. Rapp UR, Reynolds FH Jr, Stephenson JR (1983) *J Virol* 45:914
8. Rapp UR et al. (1983) *Proc Natl Acad Sci USA* 80:4218
9. Graham FL, van der Eb AJ (1973) *Virology* 52:456
10. Shih C et al. (1979) *Proc Natl Acad Sci USA* 76:5714
11. Parada LF, Weinberg RA (1983) *Mol Cell Biol* 3:2298

12. Barbacid M (1986) Human Oncogenes. In: Devita, Hellman, Rosenberg (eds) Important advances in oncology. Lippincott, Philadelphia, pp 3-22
13. Klein G (1983) Cell 32:311
14. Alitalo K et al. (1983) Proc Natl Acad Sci USA 80:1707
15. Cooper CS et al. (1984) Nature 311:29
16. Schechter AL et al. (1984) Nature 312:513
17. Fukui M et al. (1985) Proc Natl Acad Sci USA 81:5954
18. Shimizu K et al. (1985) Proc Natl Acad Sci USA 82:5641
19. Martin-Zanca D, Hughes SH, Barbacid M (1986) Nature 319:743
20. Sukumar S, Notario V, Martin-Zanca D, Barbacid M (1983) Nature 306:658
21. Balmain A, Ramsden M, Bowden GT, Smith J (1984) Nature 307:658
22. Kohl NE et al. (1983) Cell 35:359
23. Brodeur GM et al. (1984) Science 224:1121
24. Rowley JD (1980) Ann Rev Genet 14:17
25. Tainsky MA, Cooper CS, Giovanella BC, Vande Woude GF (1984) Science 225:643
26. Albino AP et al. (1984) Nature 308:69
27. Houweling A, van den Elsen PJ, van der Eb AJ (1980) Virology 105:537
28. Rassoulzadegan M et al. (1982) Nature 300:713
29. van den Elsen PJ et al. (1982) Gene 18:175
30. Land H, Parada LF, Weinberg RA (1983) Nature 304:596
31. Ruley HE (1983) Nature 304:602
32. Rapp UR et al. (1985) J Virol 55:23
33. Graf T et al. (1986) In: Genetics, cell differentiation and cancer, 7th Annual Bristol-Myers Symposium on Cancer Research
34. Rapp UR et al. (1985) In: Haveman K, Sorenson GD, Gropp C (eds) Peptide hormones in lung cancer. Springer, Berlin Heidelberg New York Tokyo, p 221 (Recent results in cancer research, vol 99)
35. Blasi E et al. (1985) Nature 318:667
36. Waterfield MD et al. (1983) Nature 304:35
37. Doolittle RF et al. (1983) Science 221:275
38. Downward J et al. (1984) Nature 307:521
39. Kelly K, Cochran BH, Stiles CD, Leder P (1983) Cell 35:603
40. Armelin HA et al. (1984) Nature 310:655
41. Rapp UR et al. (1985) Nature 317:434
42. Sherr CJ et al. (1985) Cell 41:665
43. Rapp UR, Cleveland JL, Bonner TI (1986) In: Curran, Reddy, Skalka (eds) The oncogene handbook
44. Moelling K et al. (1984) Nature 312:558
45. Greenberg ME, Ziff EB (1984) Nature 311:433
46. Muller R, Bravo R, Burckhardt J (1984) Nature 312:20
47. Kruijer W et al. (1984) Nature 312:711
48. Pledger WJ, Stiles CD, Antoniades HN, Scher CD (1977) Proc Natl Acad Sci USA 74:4481
49. Cochran BH, Reffel AC, Stiles CD (1983) Cell 33:939
50. Cochran BH, Zullo J, Verma IM, Stiles CD (1984) Science 226:1080
51. Cleveland JL et al. (1986) J Cell Biochem 30:195
52. Smith MR, DeGudicibus SJ, Stacey DW (1986) Nature 320:540
53. Huleihel M et al. (1986) Mol Cell Biol 6:2655
54. Rapp UR, Bonner TI, Cleveland JL (1985) In: Gallo, Stehelin, Varnier (eds) Retroviruses and human pathology. Humana, New Jersey, p 449
55. Heisterkamp N et al. (1983) Nature 306:239
56. Groffen J et al. (1984) Cell 36:93
57. Battey J et al. (1983) Cell 34:779
58. Adams JM et al. (1983) Proc Natl Acad Sci USA 80:1982
59. Dalla-Favera R et al. (1982) Proc Natl Acad Sci USA 79:7824
60. Bonner TI et al. (1984) Science 223:71
61. Cavenee WK et al. (1986) In: Cold Spring Harbor Symp Quant Biol Vol LI:829
62. Drabkin HA et al. (1985) Proc Natl Acad Sci USA 82:6980
63. Gusella JF et al. (1986) In: Cold Spring Harbor Symp Quant Biol
64. Knowlton RG et al. (1985) Nature 318:380
65. White R et al. (1985) Nature 318:382
66. Wainwright BJ et al. (1985) Nature 318:384
67. Sherwin SA et al. (1983) Cancer Res 43:403
68. Whang-Peng J et al. (1982) Science 215:181
69. Shimizu K et al. (1983) Nature 304:497
70. Capon DJ et al. (1983) Nature 304:507
71. Townsend ARM et al. (1986) Cell 44:959