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Differential Expression of the *ras* Gene Family in Mice

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We compared the expression of the *ras* gene family (H-*ras*, K-*ras*, and N-*ras*) in adult mouse tissues and during development. We found substantial variations in expression among different organs and in the amounts of the different transcripts originating from each gene, especially for the N-*ras* gene. The expression patterns were consistent with the reported preferential tissue activation of *ras* genes and suggested different cellular functions for each of the *ras* genes.

ras genes form a family of evolutionarily conserved genes present in eucaryotes from yeasts to primates (11, 15, 30, 35, 38). There are three members of the mammalian *ras* family, termed H-*ras*, K-*ras*, and N-*ras*. The first two genes were originally described as the transforming oncogenes of rat sarcoma Harvey and Kirsten viruses, respectively (10, 13). The third member of the family, N-*ras*, was first found in a human neuroblastoma cell line (39). *ras* oncogene activation, resulting from point mutations in the coding sequence, has been detected in a significant proportion of spontaneous and induced malignancies (44). One of the intriguing points is that the three genes encode very similar products, p21 proteins (15, 38). So the question arises as to why the genome contains three genes for essentially the same polypeptide. It is conceivable that some important differences among the three genes lie at the level which regulates gene expression.

The levels of expression of H-*ras* and K-*ras* genes in organs of adult mice and during development have been studied before (28, 29, 41). However, no data have been reported yet on the expression of the more recently cloned mouse N-*ras* gene (18), and a systematic analysis comparing the transcripts, RNA levels, and developmental expression of the three *ras* genes has never been carried out. We have undertaken these studies in a search for clues toward an understanding of *ras* gene family expression and preferential activation of a particular *ras* gene found in animal model systems for carcinogenesis.

Because *ras* genes have significant homology in the coding region, it was important to rule out any possible cross-hybridization among the probes used. The H-*ras* probe contains only coding sequences (460-base pair *Eco*RI fragment of plasmid BS9) (12). The K-*ras* probe (600-base-pair *Eco*RI-*Hin*dIII fragment of plasmid pY413) (14) and N-*ras* probe (600-base-pair *Bgl*II-*Rsa*I fragment of the 3′ region) (19) were essentially derived from the last coding exon (the more divergent between *ras* genes) (15) and 3′ untranslated regions. Lack of cross-hybridization was confirmed by Southern genomic blots hybridized with the three probes (data not shown). To obtain equal hybridization with all of the mRNAs, we chose probes for K-*ras* and N-*ras* with 3′ untranslated sequences that are contained in all of the transcripts, so that the signal intensity was not biased in favor of any one of the mRNAs.

Differential expression of *ras* genes in adult mouse tissues. mRNAs were extracted from organs of RF/J mice by the guanidine thiocyanate procedure (9, 37) and oligo(dT)-cellulose chromatography (24). The concentration of poly(A)$^+$ RNAs was measured by A_{260} and hybridization to [^{3}H]poly(U) as previously described (32). Three parallel dot blots were prepared for hybridization with each of the three *ras* probes. Since equal counts per minute were used for each probe (labeled to the same specific activity), the intensities obtained with each of them should be comparable. To confirm this, we included mouse genomic DNA in the blots as a control. The filters were hybridized to nick-translated probes in the presence of 50% formamide at 42°C as previously described (24), and the autoradiographs were analyzed by densitometry. There were clear differences in the total expression of the three *ras* genes in the organs screened (Table 1). The more salient features were as follows. (i) H-*ras* seemed to have a particular pattern of expression, whereas K-*ras* and N-*ras* were similar to each other. (ii) H-*ras* was expressed more in brain, muscle, and skin. (iii) K-*ras* was most prevalently expressed in gut, lung, and thymus. (iv) N-*ras* was expressed more in thymus and testis than in any other organ examined. (v) In skin, H-*ras* was the gene most prominently expressed, whereas in thymus K-*ras* and N-*ras* showed higher levels of expression. This last result is consistent with the preferential activation of *ras* genes reported in model systems of carcinogenesis. In recent studies, mouse skin papillomas or squamous cell carcinomas induced by carcinogens have repeatedly been found to contain activated H-*ras* but not K-*ras* or N-*ras* (2, 7, 34). Conversely, thymic lymphomas induced by *N*-nitroso-*N*-methylurea or γ radiation have been found to contain K-*ras* or N-*ras* but never H-*ras* (16; L. Diamond, I. Guerrero, and A. Pellicer, manuscript in preparation). This preferential activation may reflect biological selection of some tissues as targets for tumor development. Activating mutations may only contribute to develop a tumor when the altered *ras* gene is substantially expressed in the target tissue.

We then performed Northern experiments so as to resolve the different mRNAs corresponding to the different *ras* genes. The poly(A)$^+$ RNAs were fractionated on a 1.2% agarose–formaldehyde gel, blotted onto nitrocellulose (24), and hybridized as described above. Figure 1 shows the result

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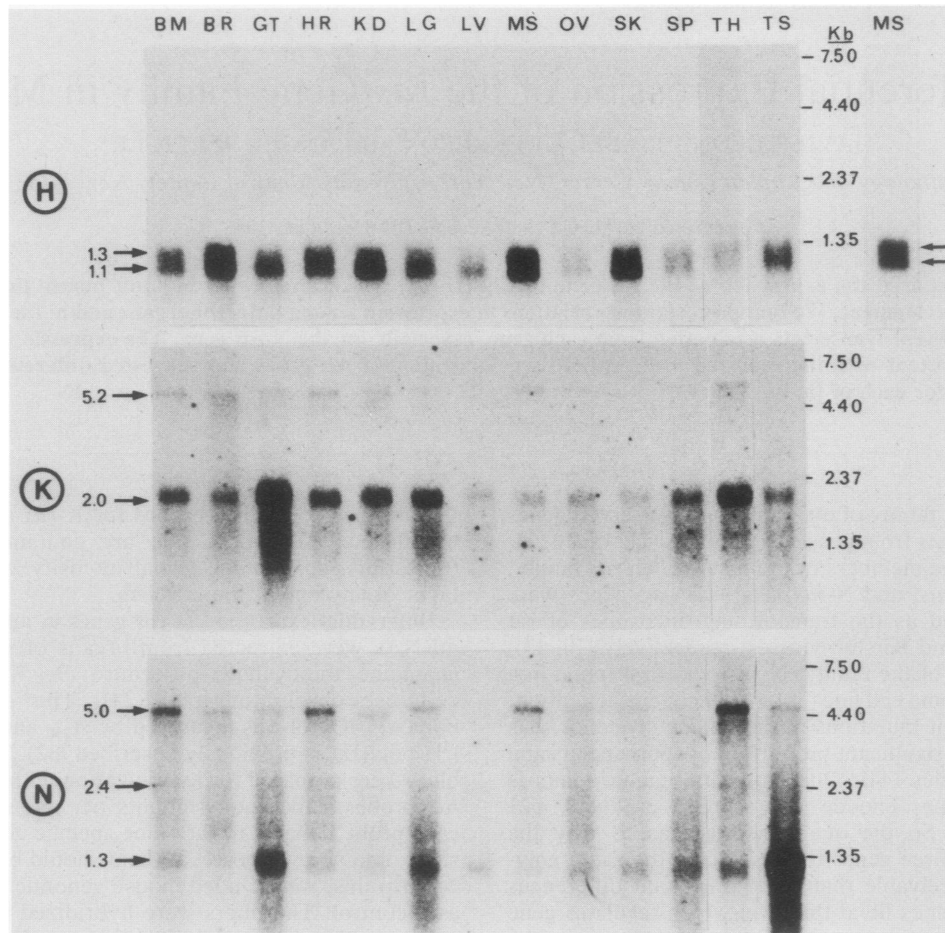

FIG. 1. Transcripts of *ras* genes in adult mouse tissues. Poly(A)$^+$ RNAs (4 μg per lane) from several organs were analyzed by Northern blotting, and the filter was consecutively hybridized with N-*ras* (N), K-*ras* (K), and H-*ras* (H) ^{32}P-labeled probes as described in the text. Marker sizes (MS) in kilobases (Kb) are indicated on the right. Sizes of *ras* transcripts are indicated with arrows at the left. The samples were: bone (femur containing bone marrow) (BM), brain (BR), gut (GT), kidney (KD), heart (HR), lung (LG), liver (LV), skeletal muscle (MS), ovary (OV), skin (SK), spleen (SP), thymus (TH), and testis (TS). A shorter exposure of muscle RNA hybridized with the H-*ras* probe is added at the right of panel H for a better appreciation of the two H-*ras* transcripts.

TABLE 1. Expression of *ras* genes in adult mouse tissues[a]

Tissue	Relative RNA level		
	H-*ras*	K-*ras*	N-*ras*
Bone and bone marrow	+ +	+ +	+ + +
Brain	+ + + +	+ +	+ +
Gut	+ +	+ + +	+ + +
Heart	+ + +	+ +	+ +
Kidney	+ + +	+ +	+
Lung	+ +	+ +	+ + +
Liver	+	+	+
Skeletal muscle	+ + + +	+	+ +
Ovary	+	+	+ +
Skin	+ + + +	+	+ +
Spleen	+ +	+ +	+ + +
Thymus	+ +	+ + +	+ + + +
Testis	+ + +	+ +	+ + + +

[a] Three parallel dot blots (0.8 μg of poly(A)$^+$ RNA per dot) were hybridized, as described in the text, with each of the *ras* probes and exposed for 24 h. The data represent densitometric measurements of the resulting autoradiographs. Values were normalized to 100 for the highest level of expression (N-*ras* in testis). The symbols correspond to the following densitometric values: +, 10 to 25; + +, 26 to 50; + + +, 51 to 75; + + + +, 76 to 100.

of this analysis, in which the same filter was sequentially hybridized with the three *ras* probes and stripped to ensure that the differences of the relative RNA levels in the same organ for each gene were real. We repeated the experiment, changing the order of probe hybridization and using RNAs from two independent RNA extractions, and the same relative levels were observed. The three mouse *ras* genes had several transcripts in the different organs (Fig. 1). H-*ras* had two transcripts of approximately 1.3 and 1.1 kilobases (kb). To our knowledge, these two H-*ras* transcripts have not yet been described, and the larger one seemed to be less prevalent in gut, kidney, lung, and liver. K-*ras* had two transcripts of about 5.2 and 2 kb, the smaller transcript being much more abundant than the larger one, especially in gut. N-*ras* had three transcripts of approximately 5, 2.4, and 1.3 kb, although the 2.4-kb message was present in low amounts in every organ analyzed. The pattern of N-*ras* expression was the most complex, showing a wide variation between the proportions of the 5- and 1.3-kb transcripts. Densitometry revealed that the two extreme examples are brain, where the signal corresponding to the large message represented about 90% of the total N-*ras* transcript, and testis, where it accounted for only 5%.

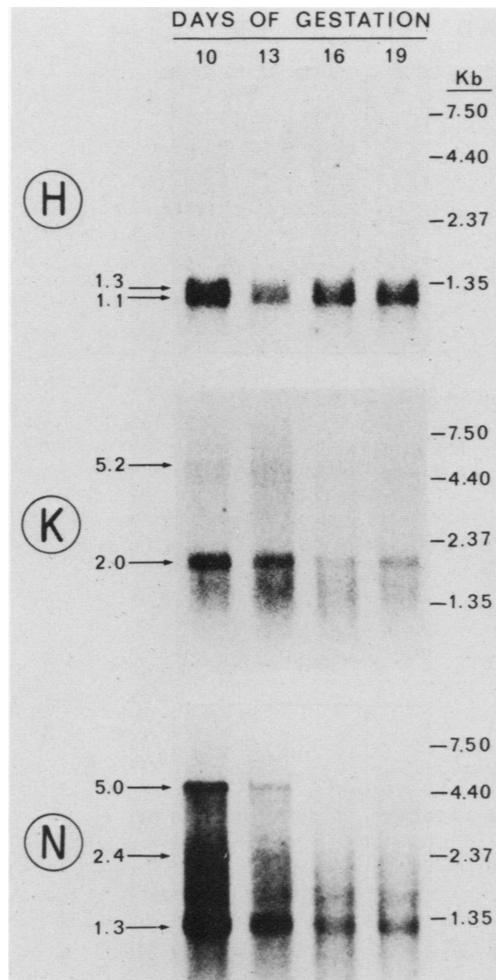

FIG. 2. Expression of *ras* genes during mouse prenatal development. Poly(A)$^+$ RNAs (4 μg per lane) were extracted from embryos or fetuses at 10, 13, 16, or 19 days of gestation and analyzed by Northern blotting. The filters were sequentially hybridized with N-*ras* (N), K-*ras* (K), and H-*ras* (H) ^{32}P-labeled probes as described in the text. Marker sizes in kilobases (Kb) are indicated on the right. Sizes of *ras* transcripts are indicated with arrows on the left.

Taken together, these results indicated that, although the p21 proteins encoded by the three *ras* genes are structurally similar (15, 38), the expression level of each gene and the amounts of the different transcripts present in adult mice showed a high degree of variation depending upon the organ. Therefore, we studied the RNA levels during mouse pre- and postnatal development to determine how far back this differential expression could be traced.

Expression of *ras* genes during mouse development. For studies of RNA levels during fetal development, pregnant mice were sacrificed at day 10, 13, 16, or 19 of pregnancy, whole fetuses were used for poly(A)$^+$ RNA extraction, and Northern blot experiments were performed as described above. Expression of K-*ras* and N-*ras* was higher at day 10 and decreased toward the end of pregnancy (day 19) (Fig. 2). The same transcripts described for adult mice were seen during fetal development, and the ratios among the transcripts did not change significantly during development. These results demonstrated an important differential expression of *ras* genes during prenatal development. However, these samples represent a mixture of RNA species coming from many different embryonic tissues. We then studied the postnatal development of individual organs.

Mice were sacrificed 5, 10, 15, 20, 25, or 30 days after birth. Eight organs were used for total RNA extraction: brain, gut, kidney, liver, skin, spleen, thymus, and testis. Figure 3 shows the corresponding Northern blots hybridized with the *ras* probes. We stained gels before transfer with ethidium bromide to check the amount and integrity of 28S and 18S ribosomal RNAs. H-*ras* displayed a slightly increased level in gut, kidney, and testis throughout development (Fig. 3). It is noteworthy that H-*ras* expression in brain was high during postnatal development into adulthood. For K-*ras*, there was increased expression in testis at days 15 to 25, but there was a decrease later, in contrast to the corresponding pattern with H-*ras* and N-*ras*. K-*ras* also showed an increase toward days 20 to 30 in gut. For N-*ras* there was some decrease in expression during postnatal development in brain and kidney. Interestingly, N-*ras* showed a large increase in expression in testis, which was mostly limited to the small 1.3-kb transcript. This transcript reached its usual high levels in adults (Fig. 1) at the time of testicular maturation, around 20 days of age. This last result has some resemblance with the reported appearance of a new transcript for the proto-oncogene c-*abl* in mouse testes (33), although in N-*ras* it is not a new RNA but a marked increase of the 1.3-kb transcript.

The experiments reported here clearly showed that the *ras* genes are regulated in a complex manner. The three *ras* genes were expressed in all of the samples analyzed, which is consistent with the notion that all *ras* genes might be expressed in all cells. Differences in expression occurred through pre- and postnatal development, and certain adult tissues preferentially expressed one member of the family over the others. Assuming that these differences in expression correlate with the levels of gene product, our results are in agreement with the current thought that the cellular functions of the p21s encoded by H-*ras*, K-*ras*, and N-*ras* are indeed different, as their products seem to be required in different amounts and at different times in a tissue-specific manner. Although p21 seems to be involved in cell proliferation (23, 27), in this study we showed that H-*ras* is also expressed in mouse brain and muscle at its highest levels, where cell division is minimal. This suggests a role for *ras* genes which is not restricted to proliferation. Similar results were observed in *Drosophila melanogaster*, in which D-*ras* genes are highly expressed in brain cortex and ganglia (36). Also, high levels of *ras* protein were found in rat brain (43) and nervous tissue of the mollusc *Aplysia* sp. (42). These findings are consistent with recent observations demonstrating that *ras* genes are able to induce differentiation of neuronal cell lines (3, 20, 31) and erythroid precursor cells (21, 45).

One possible level of regulation might occur by differential usage of polyadenylation signals (6). Mouse N-*ras* is known to produce its three transcripts by this mechanism (17, 19). Previous reports have shown that 3′ untranslated sequences play a role in the stability of the transcripts (40, 25) and are important for transcriptional regulation (4, 5). The 5.2-kb K-*ras* and 5-kb N-*ras* transcripts have long 3′ untranslated regions (around 4.5 kb) (14, 17), among the largest so far described, suggesting a role in gene regulation. Differential tissue expression by alternative usage of polyadenylation sites has also been reported for other genes (1, 8, 22, 26).

In conclusion, demonstration of a diversified pattern of expression among organs and through developmental stages may reflect differences in the functions of the three *ras*

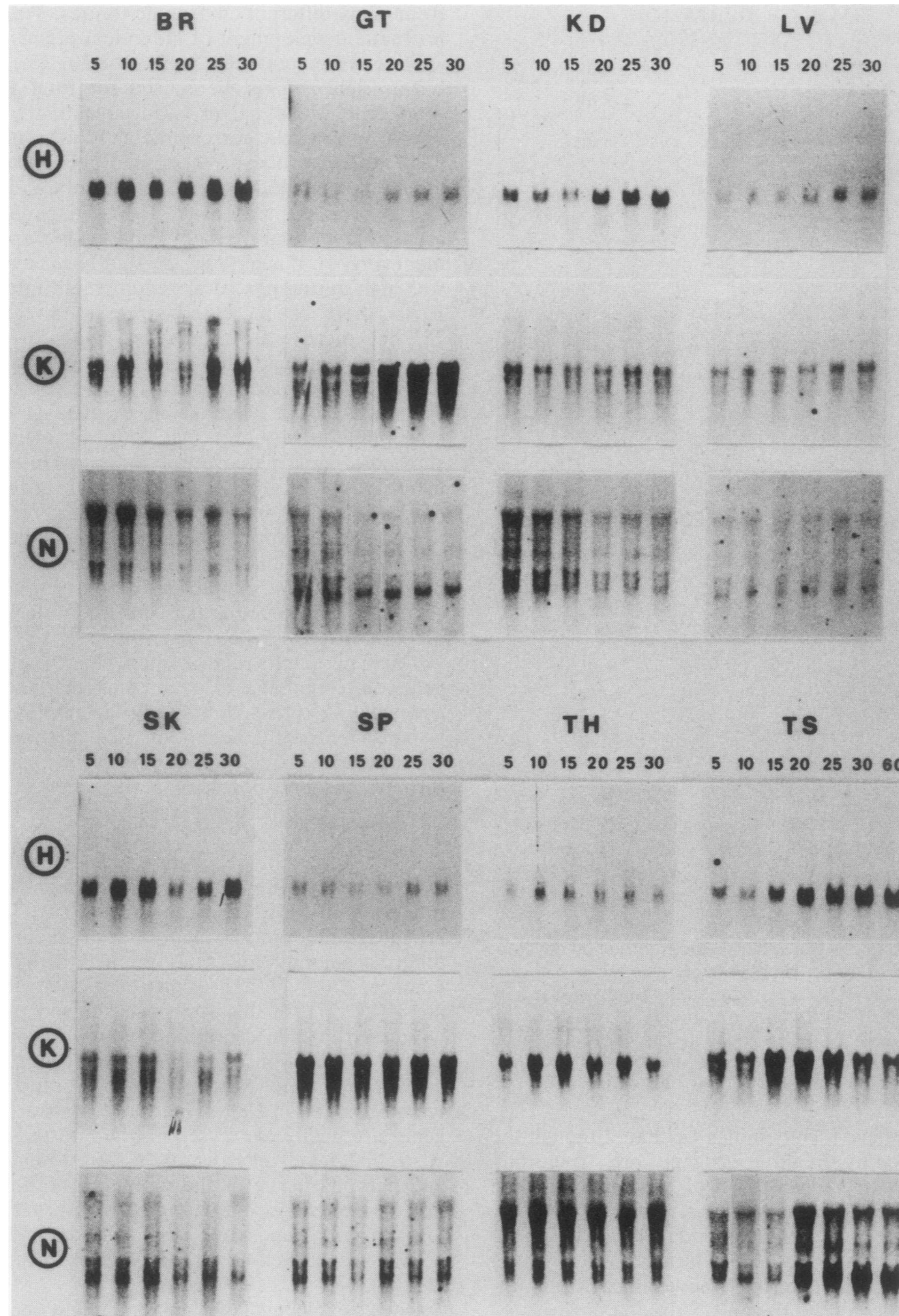

FIG. 3. Expression of *ras* genes during mouse postnatal development. Total RNAs from different organs were isolated from mice of ages 5, 10, 15, 20, 25, and 30 days as indicated (for testis, an extra point of 60 days was also analyzed). The RNAs (18 μg per lane) were analyzed by Northern blotting as described in the text. The filters were sequentially hybridized with N-*ras* (N), K-*ras* (K), and H-*ras* (H) ^{32}P-labeled probes. Organ abbreviations are as in the legend to Fig. 1.

products. Additionally, differential tissue expression provides some explanation for preferential activation of particular *ras* genes in animal model systems of carcinogenesis.

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LITERATURE CITED

1. **Amara, S. G., R. M. Evans, and M. G. Rosenfeld.** 1984. Calcitonin/calcitonin gene-related peptide transcription unit: tissue-specific expression involves selective use of alternative polyadenylation sites. Mol. Cell. Biol. **4**:2151–2160.
2. **Balmain, A., M. Ramsden, G. T. Bowden, and J. Smith.** 1984. Activation of the mouse cellular Harvey-*ras* gene in chemically induced benign skin papillomas. Nature (London) **307**:658–660.
3. **Bar-Sagi, D., and J. R. Feramisco.** 1985. Microinjection of *ras* oncogene protein into PC12 cells induces morphological differentiation. Cell **42**:841–848.
4. **Battistuzzi, G., M. D'Urso, D. Toniolo, G. M. Persico, and L. Luzzatto.** 1985. Tissue-specific levels of human glucose-6-phosphate dehydrogenase correlate with methylation of specific sites at the 3′ end of the gene. Proc. Natl. Acad. Sci. USA **82**:1465–1469.
5. **Bellard, M., G. Dretzen, F. Bellard, J. S. Kaye, S. Pratt-Kaye, and P. Chambon.** 1986. Hormonally induced alterations of chromatin structure in the polyadenylation and transcription termination regions of the chicken ovalbumin gene. EMBO J. **5**:567–574.
6. **Birnstiel, N. L., M. Busslinger, and K. Strub.** 1985. Transcription termination and 3′ processing: the end is in site! Cell **41**:349–359.
7. **Bizub, D., A. W. Wood, and A. M. Skalka.** 1986. Mutagenesis of the Ha-*ras* oncogene in skin tumors of mice induced by polycyclic aromatic hydrocarbons. Proc. Natl. Acad. Sci. USA **83**:6048–6052.
8. **Capetanaki, Y. G., J. Ngai, C. N. Flytzanis, and E. Lazarides.** 1983. Tissue-specific expression of two mRNA species transcribed from a single vimentin gene. Cell **35**:411–420.
9. **Chirgwin, J. M., A. E. Przybyla, R. J. MacDonald, and W. J. Rutter.** 1979. Isolation of biologically active ribonucleic acid from sources enriched in ribonuclease. Biochemistry **18**:5294–5299.
10. **DeFeo, D., M. A. Gonda, H. A. Young, E. H. Chang, D. R. Lowy, E. M. Scolnick, and R. W. Ellis.** 1981. Analysis of two divergent rat genomic clones homologous to the transforming gene of Harvey murine sarcoma virus. Proc. Natl. Acad. Sci. USA **78**:3328–3332.
11. **DeFeo-Jones, D., E. M. Scolnick, R. Koller, and R. Dahr.** 1983. *ras*-Related gene sequences identified and isolated from *Saccharomyces cerevisiae*. Nature (London) **306**:707–709.
12. **Ellis, R. W., D. DeFeo, J. M. Maryak, H. A. Young, T. Y. Shih, E. H. Chang, D. R. Lowy, and E. M. Scolnick.** 1980. Dual evolutionary origin for the rat genetic sequences of Harvey murine sarcoma virus. J. Virol. **36**:408–420.
13. **Ellis, R. W., D. DeFeo, T. Y. Shih, M. A. Gonda, H. A. Young, N. Tsuchida, D. R. Lowy, and E. Scolnick.** 1981. The P21 *src* genes of Harvey and Kirsten sarcoma viruses originate from divergent members of a family of normal vertebrate genes. Nature (London) **292**:506–511.
14. **George, D. L., A. F. Scott, S. Trusko, B. Glick, E. Ford, and D. J. Dorney.** 1985. Structure and expression of amplified K-*ras* gene sequences in Y1 mouse adrenal tumor cells. EMBO J. **4**:1199–1203.
15. **Gibbs, J. B., I. S. Sigal, and E. M. Scolnick.** 1985. Biochemical properties of normal and oncogenic *ras* p21. Trends Biochem. Sci. **10**:350–353.
16. **Guerrero, I., P. Calzada, A. Mayer, and A. Pellicer.** 1984. A molecular approach to leukemogenesis: mouse lymphomas contain an activated c-*ras* oncogene. Proc. Natl. Acad. Sci. USA **81**:202–205.
17. **Guerrero, I., A. Villasante, V. Corces, and A. Pellicer.** 1985. Loss of the normal N-*ras* allele in a mouse thymic lymphoma induced by a chemical carcinogen. Proc. Natl. Acad. Sci. USA **82**:7810–7814.
18. **Guerrero, I., A. Villasante, P. D'Eustachio, and A. Pellicer.** 1984. Isolation, preliminary characterization, and chromosomal localization of the activated mouse N-*ras* gene from a carcinogen-induced thymic lymphoma. Science **225**:1041–1043.
19. **Guerrero, I., A. Villasante, L. Diamond, J. W. Berman, E. W. Newcomb, J. J. Steinberg, R. Lake, and A. Pellicer.** 1986. Oncogene activation and surface markers in mouse lymphomas induced by radiation and nitrosomethylurea. Leuk. Res. **10**:851–858.
20. **Guerrero, I., H. Wong, A. Pellicer, and D. E. Burstein.** 1986. Activated N-*ras* gene induces neuronal differentiation of PC-12 rat pheochromocytoma cells. J. Cell. Physiol. **129**:71–76.
21. **Hankins, W. D., and E. M. Scolnick.** 1981. Harvey and Kirsten sarcoma viruses promote the growth and differentiation of erythroid precursor cells in vitro. Cell **26**:91–97.
22. **Helfman, D. M., S. Cheley, E. Kuissmanen, L. A. Finn, and Y. Yamawaki-Kataoka.** 1986. Nonmuscle and muscle tropomyosin isoforms are expressed from a single gene by alternative RNA splicing and polyadenylation. Mol. Cell. Biol. **6**:3582–3595.
23. **Lumpkin, C. K., J. E. Knepper, J. S. Butel, J. R. Smith, and O. M. Pereira-Smith.** 1986. Mitogenic effects of the proto-oncogene and oncogene forms of c-H-*ras* DNA in human diploid fibroblasts. Mol. Cell. Biol. **6**:2990–2993.
24. **Maniatis, T., E. F. Fritsch, and J. Sambrook.** 1982. Molecular cloning: a laboratory manual. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York.
25. **Meijlink, F., T. Curran, A. D. Miller, and I. Verma.** 1985. Removal of a 67-base-pair sequence in the noncoding region of protooncogene *fos* converts it to a transforming gene. Proc. Natl. Acad. Sci. USA **82**:4987–4991.
26. **Milcarek, C., and B. Hall.** 1985. Cell-specific expression of secreted versus membrane forms of immunoglobulin gamma 2b mRNA involves selective use of alternative polyadenylation sites. Mol. Cell. Biol. **5**:2514–2520.
27. **Mulcahy, L. S., M. R. Smith, and D. W. Stacey.** 1985. Requirement for *ras* proto-oncogene function during serum-stimulated growth of NIH 3T3 cells. Nature (London) **313**:241–243.
28. **Müller, R., D. J. Slamon, E. D. Adamson, J. M. Tremblay, D. Müller, M. J. Cline, and I. M. Verma.** 1983. Transcription of c-*onc* genes c-*ras*^{Ki} and c-*fms* during mouse development. Mol. Cell. Biol. **3**:1062–1069.
29. **Müller, R., D. J. Slamon, J. M. Tremblay, M. J. Cline, and I. Verma.** 1982. Differential expression of cellular oncogenes during pre- and postnatal development of the mouse. Nature **299**:640–644.
30. **Neuman-Silberberg, F. S., E. Schejter, F. M. Hoffman, and B. Shilo.** 1984. The Drosophila *ras* oncogenes: structure and nucleotide sequence. Cell **37**:1027–1033.
31. **Noda, M., M. Ko, A. Ogura, D. Liu, T. Amano, T. Takano, and Y. Ikawa.** 1985. Sarcoma viruses carrying *ras* oncogenes induce differentiation-associated properties in a neuronal cell line. Nature (London) **318**:73–75.
32. **Pfeifer-Ohlsson, S., A. S. Goustin, J. Rydnert, T. Wahlstrom, L. Bjersing, D. Stehelin, and R. Ohlsson.** 1984. Spatial and temporal pattern of cellular *myc* oncogene expression in developing human placenta: implications for embryonic cell proliferation. Cell **38**:585–596.
33. **Ponzetto, C., and D. J. Wolgemuth.** 1985. Haploid expression of a unique c-*abl* transcript in the mouse male germ line. Mol. Cell. Biol. **5**:1791–1794.
34. **Quintanilla, M., K. Brown, M. Ramsden, and A. Balmain.** 1986. Carcinogen-specific mutation and amplification of Ha-*ras* during mouse skin carcinogenesis. Nature (London) **322**:78–80.
35. **Reymond, C. D., R. H. Gomer, M. C. Medhy, and R. A. Firtel.** 1984. Developmental regulation of a Dictyostelium gene encoding a protein homologous to mammalian *ras* protein. Cell **39**:141–148.
36. **Segal, D., and B.-Z. Shilo.** 1986. Tissue localization of *Drosophila melanogaster ras* transcripts during development. Mol. Cell. Biol. **6**:2241–2248.
37. **Setzer, D. R., M. McGoogan, J. H. Nunberg, and R. T. Schimke.** 1980. Size heterogeneity in the 3′ end of dihydrofolate reductase messenger RNAs in mouse cells. Cell **22**:361–370.
38. **Shih, T. Y., and M. O. Weeks.** 1984. Oncogenes and cancer: the

p21 *ras* genes. Cancer Invest. **2**:109–123.
39. **Shimizu, K., M. Goldfarb, M. Perucho, and M. Wigler.** 1983. Isolation and preliminary characterization of the transforming gene of a human neuroblastoma cell line. Proc. Natl. Acad. Sci. USA **80**:383–387.
40. **Simcox, A. A., C. M. Cheney, E. P. Hoffman, and A. Shearn.** 1985. A deletion of the 3′ end of the *Drosophila melanogaster* hsp70 gene increases stability of mutant mRNA during recovery from heat shock. Mol. Cell. Biol. **5**:3397–3402.
41. **Slamon, D. J., and M. J. Cline.** 1984. Expression of cellular oncogenes during embryonic and fetal development of the mouse. Proc. Natl. Acad. Sci. USA **81**:7141–7145.
42. **Swanson, M. E., A. M. Elste, S. N. Greenberg, J. H. Schwartz, T. H. Aldrich, and M. E. Furth.** 1986. Abundant expression of *ras* proteins in *Aplysia* neurons. J. Cell. Biol. **103**:485–492.
43. **Tanaka, T., N. Ida, H. Shimada, C. Waki, D. J. Slamon, and M. J. Cline.** 1986. Organ-specific expression of *ras* oncoproteins during growth and development of the rat. Mol. Cell. Biochem. **70**:97–104.
44. **Varmus, H. E.** 1984. The molecular genetics of cellular oncogenes. Annu. Rev. Genet. **18**:553–612.
45. **Waneck, G. L., L. Keyes, and N. Rosenberg.** 1986. Abelson virus drives the differentiation of Harvey virus-infected erythroid cells. Cell **44**:337–344.