7. LITERATURVERZEICHNIS

Adjei,A.A. (2001). Blocking oncogenic Ras signaling for cancer therapy. J Natl. Cancer Inst. *93*, 1062-1074.

Alessi,D.R., Cuenda,A., Cohen,P., Dudley,D.T., and Saltiel,A.R. (1995). PD 098059 is a specific inhibitor of the activation of mitogen- activated protein kinase kinase in vitro and in vivo. J Biol. Chem. *270*, 27489-27494.

Aoki,K., Yoshida,T., Matsumoto,N., Ide,H., Sugimura,T., and Terada,M. (1997). Suppression of Ki-ras p21 levels leading to growth inhibition of pancreatic cancer cell lines with Ki-ras mutation but not those without Ki-ras mutation. Mol. Carcinog. *20*, 251-258.

Apolloni,A., Prior,I.A., Lindsay,M., Parton,R.G., and Hancock,J.F. (2000). H-ras but not K-ras traffics to the plasma membrane through the exocytic pathway. Mol. Cell Biol. *20*, 2475-2487.

Attwell,S., Roskelley,C., and Dedhar,S. (2000). The integrin-linked kinase (ILK) suppresses anoikis. Oncogene *19*, 3811-3815.

Baltimore,D. (1970). RNA-dependent DNA polymerase in virions of RNA tumour viruses. Nature *226*, 1209-1211.

Bar-Sagi,D. (2001). A Ras by any other name. Mol. Cell Biol. *21*, 1441-1443.

Barbacid,M. (1987). ras genes. Annu. Rev. Biochem. *56*, 779-827.

Bardeesy,N. and DePinho,R.A. (2002). Pancreatic cancer biology and genetics. Nat. Rev. Cancer *2*, 897-909.

Boettner,B. and Van Aelst,L. (2002). The RASputin effect. Genes Dev. *16*, 2033-2038.

Boice,J.A. and Fairman,R. (1996). Structural characterization of the tumor suppressor p16, an ankyrin- like repeat protein. Protein Sci. *5*, 1776-1784.

Bos,J.L. (1989). ras oncogenes in human cancer: a review. Cancer Res. *49*, 4682-4689.

Boudreau,N., Sympson,C.J., Werb,Z., and Bissell,M.J. (1995). Suppression of ICE and apoptosis in mammary epithelial cells by extracellular matrix. Science *267*, 891-893.

Bourne,H.R., Sanders,D.A., and McCormick,F. (1990). The GTPase superfamily: a conserved switch for diverse cell functions. Nature *348*, 125-132.

Brummelkamp,T.R., Bernards,R., and Agami,R. (2002). Stable suppression of tumorigenicity by virus-mediated RNA interference. Cancer Cell *2*, 243-247.

Caldas,C., Hahn,S.A., da Costa,L.T., Redston,M.S., Schutte,M., Seymour,A.B., Weinstein,C.L., Hruban,R.H., Yeo,C.J., and Kern,S.E. (1994). Frequent somatic mutations and homozygous deletions of the p16 (MTS1) gene in pancreatic adenocarcinoma. Nat. Genet. *8*, 27-32.

Cammett,T.J., Luo,L., and Peng,Z.Y. (2003). Design and characterization of a hyperstable p16INK4a that restores Cdk4 binding activity when combined with oncogenic mutations. J Mol. Biol. *327*, 285-297.

Chen,Q., Kinch,M.S., Lin,T.H., Burridge,K., and Juliano,R.L. (1994). Integrin-mediated cell adhesion activates mitogen-activated protein kinases. J Biol. Chem. *269*, 26602-26605.

Chin,L., Pomerantz,J., Polsky,D., Jacobson,M., Cohen,C., Cordon-Cardo,C., Horner,J.W., and DePinho,R.A. (1997). Cooperative effects of INK4a and ras in melanoma susceptibility in vivo. Genes Dev. *11*, 2822-2834.

Choy,E., Chiu,V.K., Silletti,J., Feoktistov,M., Morimoto,T., Michaelson,D., Ivanov,I.E., and Philips,M.R. (1999). Endomembrane trafficking of ras: the CAAX motif targets proteins to the ER and Golgi. Cell *98*, 69-80.

Coucouvanis,E. and Martin,G.R. (1995). Signals for death and survival: a two-step mechanism for cavitation in the vertebrate embryo. Cell *83*, 279-287.

Crespo,P. and Leon,J. (2000). Ras proteins in the control of the cell cycle and cell differentiation. Cell Mol. Life Sci. *57* , 1613-1636.

Crosland-Taylor,P.J. (1953). Nature Lond. *171*, 37.

Danilkovitch,A., Donley,S., Skeel,A., and Leonard,E.J. (2000). Two independent signaling pathways mediate the antiapoptotic action of macrophage-stimulating protein on epithelial cells. Mol. Cell Biol. *20* , 2218-2227.

Dannenberg,J.H., van Rossum,A., Schuijff,L., and te,R.H. (2000). Ablation of the retinoblastoma gene family deregulates G(1) control causing immortalization and increased cell turnover under growth- restricting conditions. Genes Dev. *14*, 3051-3064.

Darling,D.C. and Brickell,P.M. (1996) Labor im Fokus, Nukleinsäure-Blotting. Spektrum Akad. Verlag.

Downward,J. (2003). Targeting RAS signalling pathways in cancer therapy. Nat. Rev. Cancer *3*, 11-22.

Dudley,D.T., Pang,L., Decker,S.J., Bridges,A.J., and Saltiel,A.R. (1995). A synthetic inhibitor of the mitogen-activated protein kinase cascade. Proc. Natl. Acad. Sci. U. S. A *92*, 7686-7689.

Dyson,N. (1998). The regulation of E2F by pRB-family proteins. Genes Dev. *12*, 2245-2262.

Ehrhardt,A., Ehrhardt,G.R., Guo,X., and Schrader,J.W. (2002). Ras and relatives--job sharing and networking keep an old family together. Exp. Hematol. *30*, 1089-1106.

Elad,G., Paz,A., Haklai,R., Marciano,D., Cox,A., and Kloog,Y. (1999). Targeting of K-Ras 4B by S-trans,trans-farnesyl thiosalicylic acid. Biochim. Biophys. Acta *1452*, 228-242.

Ellis,C.A. and Clark,G. (2000). The importance of being K-Ras. Cell Signal. *12*, 425-434.

Fahraeus,R. and Lane,D.P. (1999). The p16(INK4a) tumour suppressor protein inhibits alphavbeta3 integrin- mediated cell spreading on vitronectin by blocking PKC-dependent localization of alphavbeta3 to focal contacts. EMBO J *18*, 2106-2118.

Fang,X., Jin,X., Xu,H.J., Liu,L., Peng,H.Q., Hogg,D., Roth,J.A., Yu,Y., Xu,F., Bast,R.C., Jr., and Mills,G.B. (1998). Expression of p16 induces transcriptional downregulation of the RB gene. Oncogene *16*, 1-8.

Fisher,G.H., Wellen,S.L., Klimstra,D., Lenczowski,J.M., Tichelaar,J.W., Lizak,M.J., Whitsett,J.A., Koretsky,A., and Varmus,H.E. (2001). Induction and apoptotic regression of lung adenocarcinomas by regulation of a K-Ras transgene in the presence and absence of tumor suppressor genes. Genes Dev. *15*, 3249-3262.

Fitzgerald,D.A. (2001). Integral Connections, Integrins mediate bidirectional transmembrane signaling. The Scientist *15*, 29.

Frisch,S.M. and Francis,H. (1994). Disruption of epithelial cell-matrix interactions induces apoptosis. J. Cell Biol. *124*, 619-626.

Frisch,S.M., Vuori,K., Kelaita,D., and Sicks,S. (1996). A role for Jun-N-terminal kinase in anoikis; suppression by bcl-2 and crmA. J Cell Biol. *135*, 1377-1382.

Frisch,S.M. and Ruoslahti,E. (1997). Integrins and anoikis. Curr. Opin. Cell Biol. *9*, 701-706.

Frisch,S.M. (2000). Anoikis. Methods Enzymol. *322*, 472-479.

Frisch,S.M. and Screaton,R.A. (2001). Anoikis mechanisms. Curr. Opin. Cell Biol. *13*, 555-562.

Frizelle,S.P., Grim,J., Zhou,J., Gupta,P., Curiel,D.T., Geradts,J., and Kratzke,R.A. (1998). Re-expression of p16INK4a in mesothelioma cells results in cell cycle arrest, cell death, tumor suppression and tumor regression. Oncogene *16*, 3087-3095.

Fujita,M., Norris,D.A., Yagi,H., Walsh,P., Morelli,J.G., Weston,W.L., Terada,N., Bennion,S.D., Robinson,W., Lemon,M., Maxwell,I.H., and Yohn,J.J. (1999). Overexpression of mutant ras in human melanoma increases invasiveness, proliferation and anchorage-independent growth in vitro and induces tumour formation and cachexia in vivo. Melanoma Res. *9*, 279-291.

Fukazawa,H., Noguchi,K., Murakami,Y., and Uehara,Y. (2002). Mitogen-activated protein/extracellular signal-regulated kinase kinase (MEK) inhibitors restore anoikis sensitivity in human breast cancer cell lines with a constitutively activated extracellular-regulated kinase (ERK) pathway. Mol. Cancer Ther. *1*, 303-309.

Furth,M.E., Aldrich,T.H., and Cordon-Cardo,C. (1987). Expression of ras proto-oncogene proteins in normal human tissues. Oncogene *1*, 47-58.

Gjertsen,M.K., Buanes,T., Rosseland,A.R., Bakka,A., Gladhaug,I., Soreide,O., Eriksen,J.A., Moller,M., Baksaas,I., Lothe,R.A., Saeterdal,I., and Gaudernack,G. (2001). Intradermal ras peptide vaccination with granulocyte-macrophage colony- stimulating factor as adjuvant: Clinical and immunological responses in patients with pancreatic adenocarcinoma. Int. J Cancer *92*, 441-450.

Grossmann,J., Walther,K., Artinger,M., Kiessling,S., and Scholmerich,J. (2001). Apoptotic signaling during initiation of detachment-induced apoptosis ("anoikis") of primary human intestinal epithelial cells. Cell Growth Differ. *12*, 147-155.

Grossmann,J. (2002). Molecular mechanisms of "detachment-induced apoptosis--Anoikis". Apoptosis. *7*, 247-260.

Guerrero,S., Casanova,I., Farre,L., Mazo,A., Capella,G., and Mangues,R. (2000). K-ras codon 12 mutation induces higher level of resistance to apoptosis and predisposition to anchorage-independent growth than codon 13 mutation or proto-oncogene overexpression. Cancer Res. *60*, 6750-6756.

Hahn,W.C. and Weinberg,R.A. (2002). Modelling the molecular circuitry of cancer. Nat. Rev. Cancer *2*, 331-341.

Hall,P.A., Coates,P.J., Ansari,B., and Hopwood,D. (1994). Regulation of cell number in the mammalian gastrointestinal tract: the importance of apoptosis. J Cell Sci. *107 (Pt 12)*, 3569-3577.

Harada,H., Nakagawa,K., Iwata,S., Saito,M., Kumon,Y., Sakaki,S., Sato,K., and Hamada,K. (1999). Restoration of wild-type p16 down-regulates vascular endothelial growth factor expression and inhibits angiogenesis in human gliomas. Cancer Res. *59*, 3783-3789.

Harvey,J.J. (1964). An unidentified virus which causes the rapid production of tumors in mice. Nature *204*, 1104-1105.

Hilger,R.A., Scheulen,M.E., and Strumberg,D. (2002). The Ras-Raf-MEK-ERK pathway in the treatment of cancer. Onkologie. *25*, 511-518.

Hingorani,S.R. and Tuveson,D.A. (2003). Ras redux: rethinking how and where Ras acts. Curr. Opin. Genet. Dev. *13*, 6-13.

Hostein,I., Robertson,D., DiStefano,F., Workman,P., and Clarke,P.A. (2001). Inhibition of signal transduction by the Hsp90 inhibitor 17-allylamino- 17-demethoxygeldanamycin results in cytostasis and apoptosis. Cancer Res. *61*, 4003-4009.

Howe,A.K., Aplin,A.E., and Juliano,R.L. (2002). Anchorage-dependent ERK signaling--mechanisms and consequences. Curr. Opin. Genet. Dev. *12*, 30-35.

Hruban,R.H., Goggins,M., Parsons,J., and Kern,S.E. (2000). Progression model for pancreatic cancer. Clin. Cancer Res. *6*, 2969-2972.

Hynes,R.O. (1992). Integrins: versatility, modulation, and signaling in cell adhesion. Cell *69*, 11-25.

Janssen,K.P., el Marjou,F., Pinto,D., Sastre,X., Rouillard,D., Fouquet,C., Soussi,T., Louvard,D., and Robine,S. (2002). Targeted expression of oncogenic K-ras in intestinal epithelium causes spontaneous tumorigenesis in mice. Gastroenterology *123*, 492-504.

Jemal,A., Thomas,A., Murray,T., and Thun,M. (2002). Cancer statistics, 2002. CA Cancer J Clin. *52*, 23-47.

Johnson,L., Greenbaum,D., Cichowski,K., Mercer,K., Murphy,E., Schmitt,E., Bronson,R.T., Umanoff,H., Edelmann,W., Kucherlapati,R., and Jacks,T. (1997). K-ras is an essential gene in the mouse with partial functional overlap with N-ras. Genes Dev. *11*, 2468-2481.

Jost,M., Huggett,T.M., Kari,C., and Rodeck,U. (2001). Matrix-independent survival of human keratinocytes through an EGF receptor/MAPK-kinase-dependent pathway. Mol. Biol. Cell *12*, 1519-1527.

Kamb,A., Gruis,N.A., Weaver-Feldhaus,J., Liu,Q., Harshman,K., Tavtigian,S.V., Stockert,E., Day,R.S., III, Johnson,B.E., and Skolnick,M.H. (1994a). A cell cycle regulator potentially involved in genesis of many tumor types. Science *264*, 436-440.

Kamb,A., Shattuck-Eidens,D., Eeles,R., Liu,Q., Gruis,N.A., Ding,W., Hussey,C., Tran,T., Miki,Y., Weaver-Feldhaus,J., and . (1994b). Analysis of the p16 gene (CDKN2) as a candidate for the chromosome 9p melanoma susceptibility locus. Nat. Genet. *8*, 23-26.

Kato,K., Hitomi,Y., Imamura,K., and Esumi,H. (2002). Hyperstable U1snRNA complementary to the K-ras transcripts induces cell death in pancreatic cancer cells. Br. J Cancer *87*, 898-904.

Kawada,M., Fukazawa,H., Mizuno,S., and Uehara,Y. (1997). Inhibition of anchorage-independent growth of ras-transformed cells on polyHEMA surface by antisense oligodeoxynucleotides directed against K- ras. Biochem. Biophys. Res. Commun. *231*, 735-737.

Khwaja,A., Rodriguez-Viciana,P., Wennstrom,S., Warne,P.H., and Downward,J. (1997). Matrix adhesion and Ras transformation both activate a phosphoinositide 3-OH kinase and protein kinase B/Akt cellular survival pathway. EMBO J *16*, 2783-2793.

Kinzler,K.W. and Vogelstein,B. (1996). Lessons from hereditary colorectal cancer. Cell *87*, 159-170.

Kirsten,W.H. and Mayer,L.A. (1967). Morphologic responses to a murine erythroblastosis virus. J. Natl. Cancer Inst. *39*, 311-335

Kita,K., Saito,S., Morioka,C.Y., and Watanabe,A. (1999). Growth inhibition of human pancreatic cancer cell lines by anti-sense oligonucleotides specific to mutated K-ras genes. Int. J Cancer *80*, 553-558.

Klein,W.M., Hruban,R.H., Klein-Szanto,A.J., and Wilentz,R.E. (2002). Direct correlation between proliferative activity and dysplasia in pancreatic intraepithelial neoplasia (PanIN): additional evidence for a recently proposed model of progression. Mod. Pathol. *15*, 441-447.

Koera,K., Nakamura,K., Nakao,K., Miyoshi,J., Toyoshima,K., Hatta,T., Otani,H., Aiba,A., and Katsuki,M. (1997). K-ras is essential for the development of the mouse embryo. Oncogene *15*, 1151-1159.

Krimpenfort,P., Quon,K.C., Mooi,W.J., Loonstra,A., and Berns,A. (2001). Loss of p16Ink4a confers susceptibility to metastatic melanoma in mice. Nature *413*, 83-86.

Laemmli,U.K. (1970). Cleavage of structural proteins during the assembly of the head of bacteriophage T4. Nature *227*, 680-685.

Le Gall,M., Chambard,J.C., Breittmayer,J.P., Grall,D., Pouyssegur,J., and Obberghen-Schilling,E. (2000). The p42/p44 MAP kinase pathway prevents apoptosis induced by anchorage and serum removal. Mol. Biol. Cell *11*, 1103-1112.

Lee,K.Y., Ladha,M.H., McMahon,C., and Ewen,M.E. (1999). The retinoblastoma protein is linked to the activation of Ras. Mol. Cell Biol. *19*, 7724-7732.

Leon,J., Guerrero,I., and Pellicer,A. (1987). Differential expression of the ras gene family in mice. Mol. Cell Biol. *7*, 1535-1540.

Li,Y., Nichols,M.A., Shay,J.W., and Xiong,Y. (1994). Transcriptional repression of the D-type cyclin-dependent kinase inhibitor p16 by the retinoblastoma susceptibility gene product pRb. Cancer Res. *54*, 6078-6082.

Liggett,W.H., Jr. and Sidransky,D. (1998). Role of the p16 tumor suppressor gene in cancer. J Clin. Oncol. *16*, 1197-1206.

Lin,T.H., Chen,Q., Howe,A., and Juliano,R.L. (1997). Cell anchorage permits efficient signal transduction between ras and its downstream kinases. J Biol. Chem. *272*, 8849-8852.

Lionetto,R., Pugliese,V., Bruzzi,P., and Rosso,R. (1995). No standard treatment is available for advanced pancreatic cancer. Eur. J Cancer *31A*, 882-887.

Lowy,D.R. and Willumsen,B.M. (1993). Function and regulation of ras. Annu. Rev. Biochem. *62*, 851-891.

Lu,X., Xu,T., Qian,J., Wen,X., and Wu,D. (2002). Detecting K-ras and p53 gene mutation from stool and pancreatic juice for diagnosis of early pancreatic cancer. Chin Med J (Engl.) *115*, 1632-1636.

Macaluso,M., Russo,G., Cinti,C., Bazan,V., Gebbia,N., and Russo,A. (2002). Ras family genes: an interesting link between cell cycle and cancer. J Cell Physiol *192*, 125-130.

Malumbres,M. and Pellicer,A. (1998). RAS pathways to cell cycle control and cell transformation. Front Biosci. *3*, d887-d912.

Mani,S., Wang,C., Wu,K., Francis,R., and Pestell,R. (2000). Cyclin-dependent kinase inhibitors: novel anticancer agents. Expert. Opin. Investig. Drugs *9*, 1849-1870.

Maniatis,T., Fritsch, E.F., and Sambrook,J. (1989). Molecular Cloning – A Laboratory Manual. Cold Spring Harbor Lab.

Marciano,D., Ben Baruch,G., Marom,M., Egozi,Y., Haklai,R., and Kloog,Y. (1995). Farnesyl derivatives of rigid carboxylic acids-inhibitors of ras- dependent cell growth. J Med Chem. *38*, 1267-1272.

Marom,M., Haklai,R., Ben Baruch,G., Marciano,D., Egozi,Y., and Kloog,Y. (1995). Selective inhibition of Ras-dependent cell growth by farnesylthiosalisylic acid. J Biol. Chem. *270*, 22263-22270.

Martin,D.A., Siegel,R.M., Zheng,L., and Lenardo,M.J. (1998). Membrane oligomerization and cleavage activates the caspase-8 (FLICE/MACHalpha1) death signal. J Biol. Chem. *273*, 4345-4349.

Matsushime,H., Quelle,D.E., Shurtleff,S.A., Shibuya,M., Sherr,C.J., and Kato,J.Y. (1994). D-type cyclin-dependent kinase activity in mammalian cells. Mol. Cell Biol. *14*, 2066-2076.

McFall,A., Ulku,A., Lambert,Q.T., Kusa,A., Rogers-Graham,K., and Der,C.J. (2001). Oncogenic Ras blocks anoikis by activation of a novel effector pathway independent of phosphatidylinositol 3-kinase. Mol. Cell Biol. *21*, 5488-5499.

Meredith,J.E., Jr., Fazeli,B., and Schwartz,M.A. (1993). The extracellular matrix as a cell survival factor. Mol. Biol. Cell *4*, 953-961.

Meyer,M., Maly,K., Uberall,F., Hoflacher,J., and Grunicke,H. (1991). Stimulation of K+ transport systems by Ha-ras. J Biol. Chem. *266*, 8230-8235.

Michael,D. and Oren,M. (2002). The p53 and Mdm2 families in cancer. Curr. Opin. Genet. Dev. *12*, 53-59.

Michieli,P., Li,W., Lorenzi,M.V., Miki,T., Zakut,R., Givol,D., and Pierce,J.H. (1996). Inhibition of oncogene-mediated transformation by ectopic expression of p21Waf1 in NIH3T3 cells. Oncogene *12*, 775-784.

Mitchell,P.J., Perez-Nadales,E., Malcolm,D.S., and Lloyd,A.C. (2003). Dissecting the contribution of p16(INK4A) and the Rb family to the Ras transformed phenotype. Mol. Cell Biol. *23*, 2530-2542.

Mohiuddin,M., Ahmed,M.M., and Venkatasubbarao,K. (1996). C-Ki-ras mutations in peripheral blood of pancreatic cancer patients: a marker for early tumor metastasis. Int. J Radiat. Oncol. Biol. Phys. *34*, 161-166.

Mulcahy,L.S., Smith,M.R., and Stacey,D.W. (1985). Requirement for ras proto-oncogene function during serum-stimulated growth of NIH 3T3 cells. Nature *313*, 241-243.

Mullis,K.B. and Faloona,F.A. (1987). Specific synthesis of DNA in vitro via a polymerase-catalyzed chain reaction. Methods Enzymol. *155*, 335-350.

Niv,H., Gutman,O., Kloog,Y., and Henis,Y.I. (2002). Activated K-Ras and H-Ras display different interactions with saturable nonraft sites at the surface of live cells. J Cell Biol. *157*, 865-872.

Olson,M.F., Paterson,H.F., and Marshall,C.J. (1998). Signals from Ras and Rho GTPases interact to regulate expression of p21Waf1/Cip1. Nature *394*, 295-299.

Ortega,S., Malumbres,M., and Barbacid,M. (2002). Cyclin D-dependent kinases, INK4 inhibitors and cancer. Biochim. Biophys. Acta *1602*, 73-87.

Parmryd,I., Adler,J., Patel,R., and Magee,A.I. (2003). Imaging metabolism of phosphatidylinositol 4,5-bisphosphate in T-cell GM1-enriched domains containing Ras proteins. Exp. Cell Res. *285*, 27-38.

Plath,T., Detjen,K., Welzel,M., von Marschall,Z., Murphy,D., Schirner,M., Wiedenmann,B., and Rosewicz,S. (2000). A novel function for the tumor suppressor p16(INK4a): induction of anoikis via upregulation of the alpha(5)beta(1) fibronectin receptor. J Cell Biol. *150*, 1467-1478.

Polakowska,R.R., Piacentini,M., Bartlett,R., Goldsmith,L.A., and Haake,A.R. (1994). Apoptosis in human skin development: morphogenesis, periderm, and stem cells. Dev. Dyn. *199*, 176-188.

Prior,I.A. and Hancock,J.F. (2001). Compartmentalization of Ras proteins. J Cell Sci. *114*, 1603-1608.

Prior,I.A., Muncke,C., Parton,R.G., and Hancock,J.F. (2003). Direct visualization of Ras proteins in spatially distinct cell surface microdomains. J Cell Biol. *160*, 165-170.

Puviani,M., Marconi,A., Cozzani,E., and Pincelli,C. (2003). Fas ligand in pemphigus sera induces keratinocyte apoptosis through the activation of caspase-8. J Invest Dermatol. *120*, 164-167.

Qiu,R.G., Chen,J., Kirn,D., McCormick,F., and Symons,M. (1995a). An essential role for Rac in Ras transformation. Nature *374*, 457-459.

Qiu,R.G., Chen,J., McCormick,F., and Symons,M. (1995b). A role for Rho in Ras transformation. Proc. Natl. Acad. Sci. U. S. A *92*, 11781-11785.

Qiu,R.G., Abo,A., McCormick,F., and Symons,M. (1997). Cdc42 regulates anchorage-independent growth and is necessary for Ras transformation. Mol. Cell Biol. *17*, 3449-3458.

Rebollo,A., Pérez-Sala,D., and Martinez,A.C. (1999). Bcl-2 differentially targets K-, N-, and H-Ras to mitochondria in IL-2 supplemented or deprived cells: Implications in prevention of apoptosis. Oncogene. *18*, 4930-4939.

Renshaw,M.W., Ren,X.D., and Schwartz,M.A. (1997). Growth factor activation of MAP kinase requires cell adhesion. EMBO J *16*, 5592-5599.

Reuther,G.W. and Der,C.J. (2000). The Ras branch of small GTPases: Ras family members don't fall far from the tree. Curr. Opin. Cell Biol. *12*, 157-165.

Rocco,J.W. and Sidransky,D. (2001). p16(MTS-1/CDKN2/INK4a) in cancer progression. Exp. Cell Res. *264*, 42-55.

Roitt,I.M., Brostoff,J., and Male,D.K. (1993). Kurzes Lehrbuch der Immunologie, 3. Aufl., Thieme Verlag.

Rosen,K., Rak,J., Leung,T., Dean,N.M., Kerbel,R.S., and Filmus,J. (2000). Activated Ras prevents downregulation of Bcl-X(L) triggered by detachment from the extracellular matrix. A mechanism of Ras-induced resistance to anoikis in intestinal epithelial cells. J Cell Biol. *149*, 447-456.

Rosewicz,S., Detjen,K., Kaiser,A., Prosenc,N., Cervos-Navarro,J., Riecken,E.O., and Haller,H. (1994). Bombesin receptor gene expression in rat pancreatic acinar AR42J cells: transcriptional regulation by glucocorticoids. Gastroenerology. *107*, 208-218.

Rosewicz,S. and Wiedenmann,B. (1997). Pancreatic carcinoma. Lancet *349*, 485-489.

Ruas,M. and Peters,G. (1998). The p16INK4a/CDKN2A tumor suppressor and its relatives. Biochim. Biophys. Acta *1378*, F115-F177.

Rytomaa,M., Martins,L.M., and Downward,J. (1999). Involvement of FADD and caspase-8 signalling in detachment-induced apoptosis. Curr. Biol. *9*, 1043-1046.

Rytomaa,M., Lehmann,K., and Downward,J. (2000). Matrix detachment induces caspase-dependent cytochrome c release from mitochondria: inhibition by PKB/Akt but not Raf signalling. Oncogene *19*, 4461-4468.

Sage,J., Mulligan,G.J., Attardi,L.D., Miller,A., Chen,S., Williams,B., Theodorou,E., and Jacks,T. (2000). Targeted disruption of the three Rb-related genes leads to loss of G(1) control and immortalization. Genes Dev. *14*, 3037-3050.

Sandig,V., Brand,K., Herwig,S., Lukas,J., Bartek,J., and Strauss,M. (1997). Adenovirally transferred p16INK4/CDKN2 and p53 genes cooperate to induce apoptotic tumor cell death. Nat. Med *3*, 313-319.

Scheele,J.S., Rhee,J.M., and Boss,G.R. (1995). Determination of absolute amounts of GDP and GTP bound to Ras in mammalian cells: comparison of parental and Ras-overproducing NIH 3T3 fibroblasts. Proc. Natl. Acad. Sci. U. S. A *92*, 1097-1100.

Scheffzek,K., Ahmadian,M.R., and Wittinghofer,A. (1998). GTPase-activating proteins: helping hands to complement an active site. Trends Biochem. Sci. *23*, 257-262.

Schneider,G. and Schmid,R.M. (2003). Genetic alterations in pancreatic carcinoma. Mol. Cancer *2*, 15.

Schutte,M., Hruban,R.H., Geradts,J., Maynard,R., Hilgers,W., Rabindran,S.K., Moskaluk,C.A., Hahn,S.A., Schwarte-Waldhoff,I., Schmiegel,W., Baylin,S.B., Kern,S.E., and Herman,J.G. (1997). Abrogation of the Rb/p16 tumor-suppressive pathway in virtually all pancreatic carcinomas. Cancer Res. *57*, 3126-3130.

Senderowicz,A.M. and Sausville,E.A. (2000). Preclinical and clinical development of cyclin-dependent kinase modulators. J Natl. Cancer Inst. *92*, 376-387.

Serrano,M., Hannon,G.J., and Beach,D. (1993). A new regulatory motif in cell-cycle control causing specific inhibition of cyclin D/CDK4. Nature *366*, 704-707.

Serrano,M., Gomez-Lahoz,E., DePinho,R.A., Beach,D., and Bar-Sagi,D. (1995). Inhibition of ras-induced proliferation and cellular transformation by p16INK4. Science *267*, 249-252.

Serrano,M. (1997). The tumor suppressor protein p16INK4a. Exp. Cell Res. *237*, 7-13.

Shapiro,H. (1988). Flow Cytometry. Alan Liss, New York.

Sharpless,N.E., Bardeesy,N., Lee,K.H., Carrasco,D., Castrillon,D.H., Aguirre,A.J., Wu,E.A., Horner,J.W., and DePinho,R.A. (2001). Loss of p16Ink4a with retention of p19Arf predisposes mice to tumorigenesis. Nature *413*, 86-91.

Sherr,C.J. and Roberts,J.M. (1995). Inhibitors of mammalian G1 cyclin-dependent kinases. Genes Dev. *9*, 1149-1163.

Sherr,C.J. (2001). The INK4a/ARF network in tumour suppression. Nat. Rev. Mol. Cell Biol. *2*, 731-737.

Shields,J.M., Pruitt,K., McFall,A., Shaub,A., and Der,C.J. (2000). Understanding Ras: 'it ain't over 'til it's over'. Trends Cell Biol. *10*, 147-154.

Spandidos,D.A., Sourvinos,G., Tsatsanis,C., and Zafiropoulos,A. (2002). Normal ras genes: their onco-suppressor and pro-apoptotic functions (review). Int. J Oncol. *21*, 237-241.

Stacey,D. and Kazlauskas,A. (2002). Regulation of Ras signaling by the cell cycle. Curr. Opin. Genet. Dev. *12*, 44-46.

Stacey,D.W. and Kung,H.F. (1984). Transformation of NIH 3T3 cells by microinjection of Ha-ras p21 protein. Nature *310*, 508-511.

Su,Z., Lebedeva,I.V., Gopalkrishnan,R.V., Goldstein,N.I., Stein,C.A., Reed,J.C., Dent,P., and Fisher,P.B. (2001). A combinatorial approach for selectively inducing programmed cell death in human pancreatic cancer cells. Proc. Natl. Acad. Sci. U. S. A *98*, 10332-10337.

Sweeney,E.A., Inokuchi,J., and Igarashi,Y. (1998). Inhibition of sphingolipid induced apoptosis by caspase inhibitors indicates that sphingosine acts in an earlier part of the apoptotic pathway than ceramide. FEBS Lett. *425*, 61-65.

Takuwa,N. and Takuwa,Y. (2001). Regulation of cell cycle molecules by the Ras effector system. Mol. Cell Endocrinol. *177*, 25-33.

Tang,K.S., Guralnick,B.J., Wang,W.K., Fersht,A.R., and Itzhaki,L.S. (1999). Stability and folding of the tumour suppressor protein p16. J Mol. Biol. *285*, 1869-1886.

Temin,H.M. and Mizutani,S. (1970). RNA-dependent DNA polymerase in virions of Rous sarcoma virus. Nature *226*, 1211-1213.

Trahey,M. and McCormick,F. (1987). A cytoplasmic protein stimulates normal N-ras p21 GTPase, but does not affect oncogenic mutants. Science *238*, 542-545.

Ulsh,L.S. and Shih,T.Y. (1984). Metabolic turnover of human c-rasH p21 protein of EJ bladder carcinoma and its normal cellular and viral homologs. Mol. Cell Biol. *4*, 1647-1652.

Urban,T., Ricci,S., Grange,J.D., Lacave,R., Boudghene,F., Breittmayer,F., Languille,O., Roland,J., and Bernaudin,J.F. (1993). Detection of c-Ki-ras mutation by PCR/RFLP analysis and diagnosis of pancreatic adenocarcinomas. J. Natl. Cancer Inst. *85*, 2008-2012.

Vlahos,C.J., Matter,W.F., Hui,K.Y., and Brown,R.F. (1994). A specific inhibitor of phosphatidylinositol 3-kinase, 2-(4- morpholinyl)-8-phenyl-4H-1-benzopyran-4-one (LY294002). J Biol. Chem. *269*, 5241-5248.

Voice,J.K., Klemke,R.L., Le,A., and Jackson,J.H. (1999). Four human ras homologs differ in their abilities to activate Raf-1, induce transformation, and stimulate cell motility. J Biol. Chem. *274*, 17164-17170.

Wahrman,M.Z., Gagnier,S.E., Kobrin,D.R., Higgins,P.J., and Augenlicht,L.H. (1985). Cellular and molecular changes in 3T3 cells transformed spontaneously or by DNA transfection. Tumour. Biol. *6*, 41-56.

Watzinger,F. and Lion,T. (1999). K-RAS (Kirsten rat sarcoma 2 viral oncogene homolog). Atlas Genet. Cytogenet. Oncol. Haematol.

Way,D., Smith,S., Sivendran,S., Chie,L., Kanovsky,M., Brandt-Rauf,P.W., Chung,D.L., Michl,J., and Pincus,M.R. (2002). A protein kinase C inhibitor induces phenotypic reversion

of ras- transformed pancreatic cancer cells and cooperatively blocks tumor cell proliferation with an anti- ras peptide. Cancer Chemother. Pharmacol. *49*, 429-437.

Weng,Z., Xin,M., Pablo,L., Grueneberg,D., Hagel,M., Bain,G., Muller,T., and Papkoff,J. (2002). Protection against anoikis and down-regulation of cadherin expression by a regulatable beta-catenin protein. J Biol. Chem. *277*, 18677-18686.

Wickstrom,E. (2001). Oligonucleotide treatment of ras-induced tumors in nude mice. Mol. Biotechnol. *18*, 35-55.

Windham,T.C., Parikh,N.U., Siwak,D.R., Summy,J.M., McConkey,D.J., Kraker,A.J., and Gallick,G.E. (2002). Src activation regulates anoikis in human colon tumor cell lines. Oncogene *21*, 7797-7807.

Wolff,B. and Naumann,M. (1999). INK4 cell cycle inhibitors direct transcriptional inactivation of NF- kappaB. Oncogene *18*, 2663-2666.

Yan,J., Roy,S., Apolloni,A., Lane,A., and Hancock,J.F. (1998). Ras isoforms vary in their ability to activate Raf-1 and phosphoinositide 3-kinase. J Biol. Chem. *273*, 24052-24056.

Yang,R., Gombart,A.F., Serrano,M., and Koeffler,H.P. (1995). Mutational effects on the p16INK4a tumor suppressor protein. Cancer Res. *55*, 2503-2506.

Yang,R., Serrano,M., Slater,J., Leung,E., and Koeffler,H.P. (1996). Analysis of p16INK4a and its interaction with CDK4. Biochem. Biophys. Res. Commun. *218*, 254-259.