

7. LITERATURVERZEICHNIS

J.M.Adams and S.Cory, The Bcl-2 protein family: arbiters of cell survival, *Science* 281:1322 (1998).

E.S.Alnemri, D.J.Livingston, D.W.Nicholson, G.Salvesen, N.A.Thornberry, W.W.Wong, and J.Yuan, Human ICE/CED-3 protease nomenclature, *Cell* 87:171 (1996).

B.Antonsson, F.Conti, A.Ciavatta, S.Montessuit, S.Lewis, I.Martinou, L.Bernasconi, A.Bernard, J.J.Mermod, G.Mazzei, K.Maundrell, F.Gambale, R.Sadoul, and J.C.Martinou, Inhibition of Bax channel-forming activity by Bcl-2, *Science* 277:370 (1997).

B.Antonsson, S.Montessuit, S.Lauper, R.Eskes, and J.C.Martinou, Bax oligomerization is required for channel-forming activity in liposomes and to trigger cytochrome c release from mitochondria, *Biochem.J.* 345 Pt 2:271-8.:271 (2000).

J.D.Ashwell, N.A.Berger, J.A.Cidlowski, D.P.Lane, and S.J.Korsmeyer, Coming to terms with death: apoptosis in cancer and immune development, *Immunol.Today* 15:147 (1994).

M.Baba, H.Iishi, and M.Tatsuta, Transfer of bcl-xs plasmid is effective in preventing and inhibiting rat hepatocellular carcinoma induced by N-nitrosomorpholine, *Gene Ther.* 8:1149 (2001).

A.Bardelli, P.Longati, D.Albero, S.Goruppi, C.Schneider, C.Ponzetto, and P.M.Comoglio, HGF receptor associates with the anti-apoptotic protein BAG-1 and prevents cell death, *EMBO J.* 15:6205 (1996).

R.C.Bargou, C.Wagener, K.Bommert, M.Y.Mapara, P.T.Daniel, W.Arnold, M.Dietel, H.Guski, A.Feller, H.D.Royer, and B.Dorken, Overexpression of the death-promoting gene bax-alpha which is downregulated in breast cancer restores sensitivity to different apoptotic stimuli and reduces tumor growth in SCID mice, *J.Clin.Invest* 97:2651 (1996).

M.A.Bean, B.R.Bloom, R.B.Herberman, L.J.Old, H.F.Oettgen, G.Klein, and W.D.Terry, Cell-mediated cytotoxicity for bladder carcinoma: evaluation of a workshop, *Cancer Res.* 35:2902 (1975).

M.V.Blagosklonny, P.Giannakakou, W.S.el Deiry, D.G.Kingston, P.I.Higgs, L.Neckers, and T.Fojo, Raf-1/bcl-2 phosphorylation: a step from microtubule damage to cell death, *Cancer Res.* 57:130 (1997).

L.H.Boise, M.Gonzalez-Garcia, C.E.Postema, L.Ding, T.Lindsten, L.A.Turka, X.Mao, G.Nunez, and C.B.Thompson, bcl-x, a bcl-2-related gene that functions as a dominant regulator of apoptotic cell death, *Cell* 74:597 (1993).

H.K.Bojes, X.Feng, J.P.Kehrer, and G.M.Cohen, Apoptosis in hematopoietic cells (FL5.12) caused by interleukin-3 withdrawal: relationship to caspase activity and the loss of glutathione, *Cell Death.Differ.* 6:61 (1999).

C.Brenner, H.Cadiou, H.L.Vieira, N.Zamzami, I.Marzo, Z.Xie, B.Leber, D.Andrews, H.Duclohier, J.C.Reed, and G.Kroemer, Bcl-2 and Bax regulate the channel activity of the mitochondrial adenine nucleotide translocator, *Oncogene* 19:329 (2000).

J.Bruggen, J.Fogh, and C.Sorg, Tumor production in the nude mouse, fibrinolytic activity and cross-reactivity with antimelanoma sera of various human tumor cell lines, *J.Cancer Res.Clin.Oncol.* 102:141 (1981).

L.Campos, J.P.Rouault, O.Sabido, P.Oriol, N.Roubi, C.Vasselon, E.Archimbaud, J.P.Magaud, and D.Guyotat, High expression of bcl-2 protein in acute myeloid leukemia cells is associated with poor response to chemotherapy, *Blood* 81:3091 (1993).

C.Cande, I.Cohen, E.Daugas, L.Ravagnan, N.Larochette, N.Zamzami, and G.Kroemer, Apoptosis-inducing factor (AIF): a novel caspase-independent death effector released from mitochondria, *Biochimie* 84:215 (2002).

T.E.Carey, T.Takahashi, L.A.Resnick, H.F.Oettgen, and L.J.Old, Cell surface antigens of human malignant melanoma: mixed hemadsorption assays for humoral immunity to cultured autologous melanoma cells, *Proc.Natl.Acad.Sci.U.S.A* 73:3278 (1976).

B.S.Chang, A.J.Minn, S.W.Muchmore, S.W.Fesik, and C.B.Thompson, Identification of a novel regulatory domain in Bcl-X(L) and Bcl-2, *EMBO J.* 16:968 (1997).

D.T.Chao and S.J.Korsmeyer, BCL-2 family: regulators of cell death, *Annu.Rev.Immunol.* 16:395-419.:395 (1998).

D.B.Chappell, T.Z.Zaks, S.A.Rosenberg, and N.P.Restifo, Human melanoma cells do not express Fas (Apo-1/CD95) ligand, *Cancer Res.* 59:59 (1999).

D.Chatterjee, Z.Han, J.Mendoza, L.Goodglick, E.A.Hendrickson, P.Pantazis, and J.H.Wyche, Monocytic differentiation of HL-60 promyelocytic leukemia cells correlates with the induction of Bcl-xL, *Cell Growth Differ.* 8:1083 (1997).

A.M.Chinnaiyan and V.M.Dixit, The cell-death machine, *Curr.Biol.* 6:555 (1996).

M.F.Clarke, I.J.Apel, M.A.Benedict, P.G.Eipers, V.Sumantran, M.Gonzalez-Garcia, M.Doedens, N.Fukunaga, B.Davidson, J.E.Dick, and ., A recombinant bcl-x s adenovirus selectively induces apoptosis in cancer cells but not in normal bone marrow cells, *Proc.Natl.Acad.Sci.U.S.A* 92:11024 (1995).

G.M.Cohen, Caspases: the executioners of apoptosis, *Biochem.J.* 326:1 (1997).

M.Colombel, F.Vacherot, S.G.Diez, E.Fontaine, R.Buttyan, and D.Chopin, Zonal variation of apoptosis and proliferation in the normal prostate and in benign prostatic hyperplasia, *Br.J.Urol.* 82:380 (1998).

J.L.Cordell, B.Falini, W.N.Erber, A.K.Ghosh, Z.Abdulaziz, S.MacDonald, K.A.Pulford, H.Stein, and D.Y.Mason, Immunoenzymatic labeling of monoclonal antibodies using immune complexes of alkaline phosphatase and monoclonal anti-alkaline phosphatase (AAPAAP complexes), *J.Histochem.Cytochem.* 32:219 (1984).

S.P.Cregan, A.Fortin, J.G.MacLaurin, S.M.Callaghan, F.Ceconni, S.W.Yu, T.M.Dawson, V.L.Dawson, D.S.Park, G.Kroemer, and R.S.Slack, Apoptosis-inducing factor is involved in the regulation of caspase-independent neuronal cell death, *J.Cell Biol.* 158:507 (2002).

P.T.Daniel, T.Wieder, I.Sturm, and K.Schulze-Osthoff, The kiss of death: promises and failures of death receptors and ligands in cancer therapy, *Leukemia* 15:1022 (2001).

E.Daugas, D.Nochy, L.Ravagnan, M.Loeffler, S.A.Susin, N.Zamzami, and G.Kroemer, Apoptosis-inducing factor (AIF): a ubiquitous mitochondrial oxidoreductase involved in apoptosis, FEBS Lett. 476:118 (2000).

G.Del Poeta, A.Venditti, M.I.Del Principe, L.Maurillo, F.Buccisano, A.Tamburini, M.C.Cox, A.Franchi, A.Bruno, C.Mazzone, P.Panetta, G.Suppo, M.Masi, and S.Amadori, The amount of spontaneous apoptosis detected by bax/bcl-2 ratio predicts outcome in acute myeloid leukemia (AML), Blood .: (2002).

G.Del Poeta, A.Venditti, M.I.Del Principe, L.Maurillo, F.Buccisano, A.Tamburini, M.C.Cox, A.Franchi, A.Bruno, C.Mazzone, P.Panetta, G.Suppo, M.Masi, and S.Amadori, Amount of spontaneous apoptosis detected by Bax/Bcl-2 ratio predicts outcome in acute myeloid leukemia (AML), Blood 101:2125 (2003).

Q.L.Deveraux and J.C.Reed, IAP family proteins--suppressors of apoptosis, Genes Dev. 13:239 (1999).

M.G.Dole, R.Jasty, M.J.Cooper, C.B.Thompson, G.Nunez, and V.P.Castle, Bcl-xL is expressed in neuroblastoma cells and modulates chemotherapy-induced apoptosis, Cancer Res. 55:2576 (1995).

M.G.Dole, M.F.Clarke, P.Holman, M.Benedict, J.Lu, R.Jasty, P.Eipers, C.B.Thompson, C.Rode, C.Bloch, Nunez, and V.P.Castle, Bcl-xS enhances adenoviral vector-induced apoptosis in neuroblastoma cells, Cancer Res. 56:5734 (1996).

M.W.Ealovega, P.K.McGinnis, V.N.Sumantran, M.F.Clarke, and M.S.Wicha, bcl-xs gene therapy induces apoptosis of human mammary tumors in nude mice, Cancer Res. 56:1965 (1996).

J.Eberle, K.Krasagakis, C.Garbe, and C.E.Orfanos, Proliferation and morphology of melanoma cells and benign human melanocytes under varying culture conditions, Melanoma Res. 3:107 (1993).

J.Eberle, L.F.Fecker, J.U.Bittner, C.E.Orfanos, and C.C.Geilen, Decreased proliferation of human melanoma cell lines caused by antisense RNA against translation factor eIF-4A1, Br.J.Cancer 86:1957 (2002).

L.Eckhart, W.Declercq, J.Ban, M.Rendl, B.Lengauer, C.Mayer, S.Lippens, P.Vandenabeele, and E.Tschachler, Terminal differentiation of human keratinocytes and stratum corneum formation is associated with caspase-14 activation, J.Invest Dermatol. 115:1148 (2000).

R.E.Ellis, J.Y.Yuan, and H.R.Horvitz, Mechanisms and functions of cell death, Annu.Rev.Cell Biol. 7:663-98.:663 (1991).

M.Enari, H.Sakahira, H.Yokoyama, K.Okawa, A.Iwamatsu, and S.Nagata, A caspase-activated DNase that degrades DNA during apoptosis, and its inhibitor ICAD, Nature 391:43 (1998).

E.Engidawork, T.Gulesserian, R.Seidl, N.Cairns, and G.Lubec, Expression of apoptosis related proteins in brains of patients with Alzheimer's disease, Neurosci.Lett. 303:79 (2001).

R.Eskes, S.Desagher, B.Antonsson, and J.C.Martinou, Bid induces the oligomerization and insertion of Bax into the outer mitochondrial membrane, Mol.Cell Biol. 20:929 (2000).

- W.Fang, J.J.Rivard, D.L.Mueller, and T.W.Behrens, Cloning and molecular characterization of mouse bcl-x in B and T lymphocytes, *J.Immunol.* 153:4388 (1994).
- C.Fleury, M.Pampin, A.Tarze, and B.Mignotte, Yeast as a model to study apoptosis?, *Biosci.Rep.* 22:59 (2002).
- A.Fraser and G.Evan, A license to kill, *Cell* 85:781 (1996).
- J.S.Fridman, M.A.Benedict, and J.Maybaum, bcl-X(S)-induced cell death in 3T3 cells does not require or induce caspase activation, *Cancer Res.* 59:5999 (1999).
- J.S.Fridman, J.Parsels, A.Rehemtulla, and J.Maybaum, Cytochrome c depletion upon expression of Bcl-XS, *J.Biol.Chem.* 276:4205 (2001).
- P.Gazzaniga, A.Gradilone, R.Vercillo, O.Gandini, I.Silvestri, M.Napolitano, L.Albonici, A.Vincenzoni, M.Gallucci, L.Frati, and A.M.Agliano, Bcl-2/bax mRNA expression ratio as prognostic factor in low-grade urinary bladder cancer, *Int.J.Cancer* 69:100 (1996).
- D.J.Giard, S.A.Aaronson, G.J.Todaro, P.Arnestein, J.H.Kersey, H.Dosik, and W.P.Parks, In vitro cultivation of human tumors: establishment of cell lines derived from a series of solid tumors, *J.Natl.Cancer Inst.* 51:1417 (1973).
- R.J.Gilbert, J.L.Jimenez, S.Chen, I.J.Tickle, J.Rossjohn, M.Parker, P.W.Andrew, and H.R.Saibil, Two structural transitions in membrane pore formation by pneumolysin, the pore-forming toxin of *Streptococcus pneumoniae*, *Cell* 97:647 (1999).
- M.Gonzalez-Garcia, I.Garcia, L.Ding, S.O'Shea, L.H.Boise, C.B.Thompson, and G.Nunez, bcl-x is expressed in embryonic and postnatal neural tissues and functions to prevent neuronal cell death, *Proc.Natl.Acad.Sci.U.S.A* 92:4304 (1995).
- M.Gossen and H.Bujard, Tight control of gene expression in mammalian cells by tetracycline-responsive promoters, *Proc.Natl.Acad.Sci.U.S.A* 89:5547 (1992).
- M.Gossen and H.Bujard, Efficacy of tetracycline-controlled gene expression is influenced by cell type: commentary, *Biotechniques* 19:213 (1995).
- M.L.Gougeon, Programmed cell death in HIV infection: dysregulation of BCL-2 and Fas pathways and contribution to AIDS pathogenesis, *Psychoneuroendocrinology* 22 Suppl 1:S33-9.:S33 (1997).
- D.A.Grillot, R.Merino, and G.Nunez, Bcl-XL displays restricted distribution during T cell development and inhibits multiple forms of apoptosis but not clonal deletion in transgenic mice, *J.Exp.Med.* 182:1973 (1995).
- D.A.Grillot, R.Merino, J.C.Pena, W.C.Fanslow, F.D.Finkelman, C.B.Thompson, and G.Nunez, bcl-x exhibits regulated expression during B cell development and activation and modulates lymphocyte survival in transgenic mice, *J.Exp.Med.* 183:381 (1996).
- D.A.Grillot, M.Gonzalez-Garcia, D.Ekhterae, L.Duan, N.Inohara, S.Ohta, M.F.Seldin, and G.Nunez, Genomic organization, promoter region analysis, and chromosome localization of the mouse bcl-x gene, *J.Immunol.* 158:4750 (1997).

- A.Gross, J.M.McDonnell, and S.J.Korsmeyer, BCL-2 family members and the mitochondria in apoptosis, *Genes Dev.* 13:1899 (1999).
- A.Gross, BCL-2 proteins: regulators of the mitochondrial apoptotic program, *IUBMB.Life* 52:231 (2001).
- R.Grover and G.D.Wilson, Bcl-2 expression in malignant melanoma and its prognostic significance, *Eur.J.Surg.Oncol.* 22:347 (1996).
- M.Hahne, D.Rimoldi, M.Schroter, P.Romero, M.Schreier, L.E.French, P.Schneider, T.Bornand, A.Fontana, D.Lienard, J.Cerottini, and J.Tschopp, Melanoma cell expression of Fas(Apo-1/CD95) ligand: implications for tumor immune escape, *Science* 274:1363 (1996).
- A.J.Hale, C.A.Smith, L.C.Sutherland, V.E.Stoneman, V.L.Longthorne, A.C.Culhane, and G.T.Williams, Apoptosis: molecular regulation of cell death, *Eur.J.Biochem.* 236:1 (1996).
- J.S.Han, G.Nunez, M.S.Wicha, and M.F.Clarke, Targeting cancer cell death with a bcl-XS adenovirus, *Springer Semin.Immunopathol.* 19:279 (1998).
- M.H.Harris and C.B.Thompson, The role of the Bcl-2 family in the regulation of outer mitochondrial membrane permeability, *Cell Death.Differ.* 7:1182 (2000).
- E.Heere-Ress, C.Thallinger, T.Lucas, H.Schlagbauer-Wadl, V.Wacheck, B.P.Monia, K.Wolff, H.Pehamberger, and B.Jansen, Bcl-X(L) is a chemoresistance factor in human melanoma cells that can be inhibited by antisense therapy, *Int.J.Cancer* 99:29 (2002).
- M.Hernberg, J.P.Turunen, K.von Boguslawsky, T.Muhonen, and S.Pyrhonen, Prognostic value of biomarkers in malignant melanoma, *Melanoma Res.* 8:283 (1998).
- S.W.Hetts, To die or not to die: an overview of apoptosis and its role in disease, *JAMA* 279:300 (1998).
- W.Hillen and C.Berens, Mechanisms underlying expression of Tn10 encoded tetracycline resistance, *Annu.Rev.Microbiol.* 48:345-69.:345 (1994).
- B.Holzmann, J.M.Lehmann, H.W.Ziegler-Heitbrock, I.Funke, G.Riethmuller, and J.P.Johnson, Glycoprotein P3.58, associated with tumor progression in malignant melanoma, is a novel leukocyte activation antigen, *Int.J.Cancer* 41:542 (1988).
- M.R.Hussein, A.K.Haemel, and G.S.Wood, Apoptosis and melanoma: molecular mechanisms, *J.Pathol.* 199:275 (2003).
- M.D.Jacobson, M.Weil, and M.C.Raff, Programmed cell death in animal development, *Cell* 88:347 (1997).
- L.Jia, M.G.Macey, Y.Yin, A.C.Newland, and S.M.Kelsey, Subcellular distribution and redistribution of Bcl-2 family proteins in human leukemia cells undergoing apoptosis, *Blood* 93:2353 (1999).
- R.W.Johnstone, A.A.Ruefli, and S.W.Lowe, Apoptosis: a link between cancer genetics and chemotherapy, *Cell* 108:153 (2002).

- N.Joza, S.A.Susin, E.Daugas, W.L.Stanford, S.K.Cho, C.Y.Li, T.Sasaki, A.J.Elia, H.Y.Cheng, L.Ravagnan, K.F.Ferri, N.Zamzami, A.Wakeham, R.Hakem, H.Yoshida, Y.Y.Kong, T.W.Mak, J.C.Zuniga-Pflucker, G.Kroemer, and J.M.Penninger, Essential role of the mitochondrial apoptosis-inducing factor in programmed cell death, *Nature* 410:549 (2001).
- J.F.Kerr, A.H.Wyllie, and A.R.Currie, Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics, *Br.J.Cancer* 26:239 (1972).
- J.F.Kerr, A.H.Wyllie, and A.R.Currie, Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics, *Br.J.Cancer* 26:239 (1972).
- S.Kharbanda, P.Pandey, L.Schofield, S.Israels, R.Roncinske, K.Yoshida, A.Bharti, Z.M.Yuan, S.Saxena, R.Weichselbaum, C.Nalin, and D.Kufe, Role for Bcl-xL as an inhibitor of cytosolic cytochrome C accumulation in DNA damage-induced apoptosis, *Proc.Natl.Acad.Sci.U.S.A* 94:6939 (1997).
- M.Krajewska, S.Krajewski, J.I.Epstein, A.Shabaik, J.Sauvageot, K.Song, S.Kitada, and J.C.Reed, Immunohistochemical analysis of bcl-2, bax, bcl-X, and mcl-1 expression in prostate cancers, *Am.J.Pathol.* 148:1567 (1996).
- S.Krajewski, S.Tanaka, S.Takayama, M.J.Schibler, W.Fenton, and J.C.Reed, Investigation of the subcellular distribution of the bcl-2 oncogene: residence in the nuclear envelope, endoplasmic reticulum, and outer mitochondrial membranes, *Cancer Res.* 53:4701 (1993).
- P.H.Krammer, CD95's deadly mission in the immune system, *Nature* 407:789 (2000).
- G.Kroemer, The proto-oncogene Bcl-2 and its role in regulating apoptosis, *Nat.Med.* 3:614 (1997).
- G.Kroemer and J.C.Reed, Mitochondrial control of cell death, *Nat.Med.* 6:513 (2000).
- U.K.Laemmli, Cleavage of structural proteins during the assembly of the head of bacteriophage T4, *Nature* 227:680 (1970).
- U.Leiter, R.M.Schmid, P.Kaskel, R.U.Peter, and G.Krahn, Antiapoptotic bcl-2 and bcl-xL in advanced malignant melanoma, *Arch.Dermatol.Res.* 292:225 (2000).
- H.Li, H.Zhu, C.J.Xu, and J.Yuan, Cleavage of BID by caspase 8 mediates the mitochondrial damage in the Fas pathway of apoptosis, *Cell* 94:491 (1998).
- L.Y.Li, X.Luo, and X.Wang, Endonuclease G is an apoptotic DNase when released from mitochondria, *Nature* 412:95 (2001).
- P.Li, D.Nijhawan, I.Budihardjo, S.M.Srinivasula, M.Ahmad, E.S.Alnemri, and X.Wang, Cytochrome c and dATP-dependent formation of Apaf-1/caspase-9 complex initiates an apoptotic protease cascade, *Cell* 91:479 (1997).
- S.K.Liao, P.B.Dent, and P.B.McCulloch, Characterization of human malignant melanoma cell lines. I. Morphology and growth characteristics in culture, *J.Natl.Cancer Inst.* 54:1037 (1975).
- L.Lindenboim, J.Yuan, and R.Stein, Bcl-xS and Bax induce different apoptotic pathways in PC12 cells, *Oncogene* 19:1783 (2000).

L.Lindenboim, C.Borner, and R.Stein, Bcl-x(S) can form homodimers and heterodimers and its apoptotic activity requires localization of Bcl-x(S) to the mitochondria and its BH3 and loop domains, *Cell Death.Differ.* 8:933 (2001).

X.Liu, C.N.Kim, J.Yang, R.Jemmerson, and X.Wang, Induction of apoptotic program in cell-free extracts: requirement for dATP and cytochrome c, *Cell* 86:147 (1996).

X.Liu, H.Zou, C.Slaughter, and X.Wang, DFF, a heterodimeric protein that functions downstream of caspase-3 to trigger DNA fragmentation during apoptosis, *Cell* 89:175 (1997).

A.Lockshin, B.C.Giovanella, P.D.De Ipolyi, L.J.Williams, Jr., J.T.Mendoza, S.O.Yim, and J.S.Stehlin, Jr., Exceptional lethality for nude mice of cells derived from a primary human melanoma, *Cancer Res.* 45:345 (1985).

M.Loeffler, E.Daugas, S.A.Susin, N.Zamzami, D.Metivier, A.L.Nieminan, G.Brothers, J.M.Penninger, and G.Kroemer, Dominant cell death induction by extramitochondrially targeted apoptosis-inducing factor, *FASEB J.* 15:758 (2001).

H.K.Lorenzo, S.A.Susin, J.Penninger, and G.Kroemer, Apoptosis inducing factor (AIF): a phylogenetically old, caspase-independent effector of cell death, *Cell Death.Differ.* 6:516 (1999).

J.Lotem and L.Sachs, Regulation of bcl-2, bcl-XL and bax in the control of apoptosis by hematopoietic cytokines and dexamethasone, *Cell Growth Differ.* 6:647 (1995).

X.Luo, I.Budihardjo, H.Zou, C.Slaughter, and X.Wang, Bid, a Bcl2 interacting protein, mediates cytochrome c release from mitochondria in response to activation of cell surface death receptors, *Cell* 94:481 (1998).

J.C.Martinou and D.R.Green, Breaking the mitochondrial barrier, *Nat.Rev.Mol.Cell Biol.* 2:63 (2001).

L.M.Martins, I.Iaccarino, T.Tenev, S.Gschmeissner, N.F.Totty, N.R.Lemoine, J.Savopoulos, C.W.Gray, C.L.Creasy, C.Dingwall, and J.Downward, The serine protease Omi/HtrA2 regulates apoptosis by binding XIAP through a reaper-like motif, *J.Biol.Chem.* 277:439 (2002).

I.Marzo, C.Brenner, N.Zamzami, S.A.Susin, G.Beutner, D.Brdiczka, R.Remy, Z.H.Xie, J.C.Reed, and G.Kroemer, The permeability transition pore complex: a target for apoptosis regulation by caspases and bcl-2-related proteins, *J.Exp.Med.* 187:1261 (1998).

D.K.Miller, The role of the Caspase family of cysteine proteases in apoptosis, *Semin.Immunol.* 9:35 (1997).

A.J.Minn, L.H.Boise, and C.B.Thompson, Bcl-x(S) antagonizes the protective effects of Bcl-x(L), *J.Biol.Chem.* 271:6306 (1996).

A.J.Minn, P.Velez, S.L.Schendel, H.Liang, S.W.Muchmore, S.W.Fesik, M.Fill, and C.B.Thompson, Bcl-x(L) forms an ion channel in synthetic lipid membranes, *Nature* 385:353 (1997).

A.J.Minn, C.S.Kettlun, H.Liang, A.Kelekar, M.G.Vander Heiden, B.S.Chang, S.W.Fesik, M.Fill, and C.B.Thompson, Bcl-xL regulates apoptosis by heterodimerization-dependent and -independent mechanisms, *EMBO J.* 18:632 (1999).

T.Miyashita and J.C.Reed, Tumor suppressor p53 is a direct transcriptional activator of the human bax gene, *Cell* 80:293 (1995).

C.R.Morales-Ducret, R.M.van de, D.P.LeBrun, and B.R.Smoller, bcl-2 expression in primary malignancies of the skin, *Arch.Dermatol.* 131:909 (1995).

S.Motoyama, M.Kitamura, S.Saito, Y.Minamiya, H.Suzuki, R.Saito, K.Terada, J.Ogawa, and H.Inaba, Bcl-2 is located predominantly in the inner membrane and crista of mitochondria in rat liver, *Biochem.Biophys.Res.Commun.* 249:628 (1998).

V.Muller-Wieprecht, C.Riebeling, A.Stooss, C.E.Orfanos, and C.C.Geilen, Bcl-2 transfected HaCaT keratinocytes resist apoptotic signals of ceramides, tumor necrosis factor alpha and 1 alpha, 25-dihydroxyvitamin D(3), *Arch.Dermatol.Res.* 292:455 (2000).

K.B.Mullis and F.A.Faloona, Specific synthesis of DNA in vitro via a polymerase-catalyzed chain reaction, *Methods Enzymol.* 155:335-50.:335 (1987).

P.Navarro, A.M.Valverde, R.Conejo, M.Benito, and M.Lorenzo, Inhibition of caspases rescues brown adipocytes from apoptosis downregulating BCL-XS and upregulating BCL-2 gene expression, *Exp.Cell Res.* 246:301 (1999).

M.Nguyen, D.G.Millar, V.W.Yong, S.J.Korsmeyer, and G.C.Shore, Targeting of Bcl-2 to the mitochondrial outer membrane by a COOH-terminal signal anchor sequence, *J.Biol.Chem.* 268:25265 (1993).

O.I.Olopade, M.O.Adeyanju, A.R.Safa, F.Hagos, R.Mick, C.B.Thompson, and W.M.Recant, Overexpression of BCL-x protein in primary breast cancer is associated with high tumor grade and nodal metastases, *Cancer J.Sci.Am.* 3:230 (1997).

Z.N.Oltvai, C.L.Milliman, and S.J.Korsmeyer, Bcl-2 heterodimerizes in vivo with a conserved homolog, Bax, that accelerates programmed cell death, *Cell* 74:609 (1993).

C.E.Orfanos, C.Garbe, Therapie der Hautkrankheiten, Springer, Berlin-Heidelberg-New York, S 856:881 (2001).

J.A.Ortiz-Rey, C.Alvarez-Alvarez, I.Anton-Badiola, P.Miguel-Fraile, and A.Fuente-Buceta, Human Meissner corpuscles express Bcl-2 but not Bax protein, *Neurosci.Lett.* 329:240 (2002).

G.Packham, E.L.White, C.M.Eischen, H.Yang, E.Parganas, J.N.Ihle, D.A.Grillot, G.P.Zambetti, G.Nunez, and J.L.Cleveland, Selective regulation of Bcl-XL by a Jak kinase-dependent pathway is bypassed in murine hematopoietic malignancies, *Genes Dev.* 12:2475 (1998).

F.Pettersson, A.G.Dagleish, R.P.Bissonnette, and K.W.Colston, Retinoids cause apoptosis in pancreatic cancer cells via activation of RAR-gamma and altered expression of Bcl-2/Bax, *Br.J.Cancer* 87:555 (2002).

E.Pisha, H.Chai, I.S.Lee, T.E.Chagwedera, N.R.Farnsworth, G.A.Cordell, C.W.Beecher, H.H.Fong, A.D.Kinghorn, D.M.Brown, and ., Discovery of betulinic acid as a selective inhibitor of human melanoma that functions by induction of apoptosis, *Nat.Med.* 1:1046 (1995).

A.Plettenberg, C.Ballaun, J.Pammer, M.Mildner, D.Strunk, W.Weninger, and E.Tschachler, Human melanocytes and melanoma cells constitutively express the Bcl-2 proto-oncogene in situ and in cell culture, *Am.J.Pathol.* 146:651 (1995).

A.G.Porter, P.Ng, and R.U.Janicke, Death substrates come alive, *Bioessays* 19:501 (1997).

M.Priault, B.Chaudhuri, A.Clow, N.Camougrand, and S.Manon, Investigation of bax-induced release of cytochrome c from yeast mitochondria permeability of mitochondrial membranes, role of VDAC and ATP requirement, *Eur.J.Biochem.* 260:684 (1999).

M.Raisova, M.Bektas, T.Wieder, P.Daniel, J.Eberle, C.E.Orfanos, and C.C.Geilen, Resistance to CD95/Fas-induced and ceramide-mediated apoptosis of human melanoma cells is caused by a defective mitochondrial cytochrome c release, *FEBS Lett.* 473:27 (2000).

M.Raisova, A.M.Hossini, J.Eberle, C.Riebeling, T.Wieder, I.Sturm, P.T.Daniel, C.E.Orfanos, and C.C.Geilen, The Bax/Bcl-2 ratio determines the susceptibility of human melanoma cells to CD95/Fas-mediated apoptosis, *J.Invest Dermatol.* 117:333 (2001).

J.A.Ramsay, L.From, and H.J.Kahn, bcl-2 protein expression in melanocytic neoplasms of the skin, *Mod.Pathol.* 8:150 (1995).

L.Ravagnan, T.Roumier, and G.Kroemer, Mitochondria, the killer organelles and their weapons, *J.Cell Physiol* 192:131 (2002).

J.C.Reed, S.Kitada, S.Takayama, and T.Miyashita, Regulation of chemoresistance by the bcl-2 oncprotein in non-Hodgkin's lymphoma and lymphocytic leukemia cell lines, *Ann.Oncol.* 5 Suppl 1:61-5.:61 (1994).

X.Roucou, M.Prescott, R.J.Devenish, and P.Nagley, A cytochrome c-GFP fusion is not released from mitochondria into the cytoplasm upon expression of Bax in yeast cells, *FEBS Lett.* 471:235 (2000).

M.C.Saenz-Santamaria, N.S.McNutt, J.K.Bogdany, and C.R.Shea, p53 expression is rare in cutaneous melanomas, *Am.J.Dermatopathol.* 17:344 (1995).

M.Sattler, H.Liang, D.Nettesheim, R.P.Meadows, J.E.Harlan, M.Eberstadt, H.S.Yoon, S.B.Shuker, B.S.Chang, A.J.Minn, C.B.Thompson, and S.W.Fesik, Structure of Bcl-xL-Bak peptide complex: recognition between regulators of apoptosis, *Science* 275:983 (1997).

C.Scaffidi, S.Fulda, A.Srinivasan, C.Friesen, F.Li, K.J.Tomaselli, K.M.Debatin, P.H.Krammer, and M.E.Peter, Two CD95 (APO-1/Fas) signaling pathways, *EMBO J.* 17:1675 (1998).

S.L.Schendel, Z.Xie, M.O.Montal, S.Matsuyama, M.Montal, and J.C.Reed, Channel formation by antiapoptotic protein Bcl-2, *Proc.Natl.Acad.Sci.U.S.A* 94:5113 (1997).

- T.W.Sedlak, Z.N.Oltvai, E.Yang, K.Wang, L.H.Boise, C.B.Thompson, and S.J.Korsmeyer, Multiple Bcl-2 family members demonstrate selective dimerizations with Bax, Proc.Natl.Acad.Sci.U.S.A 92:7834 (1995).
- E.Selzer, H.Schlagbauer-Wadl, I.Okamoto, H.Pehamberger, R.Potter, and B.Jansen, Expression of Bcl-2 family members in human melanocytes, in melanoma metastases and in melanoma cell lines, Melanoma Res. 8:197 (1998).
- L.Serrone and P.Hersey, The chemoresistance of human malignant melanoma: an update, Melanoma Res. 9:51 (1999).
- L.Sevilla, C.Aperlo, V.Dulic, J.C.Chambard, C.Boutonnet, O.Pasquier, P.Pognonec, and K.E.Boulukos, The Ets2 transcription factor inhibits apoptosis induced by colony-stimulating factor 1 deprivation of macrophages through a Bcl-xL-dependent mechanism, Mol.Cell Biol. 19:2624 (1999).
- J.W.Sheridan, C.J.Bishop, and R.J.Simmons, Biophysical and morphological correlates of kinetic change and death in a starved human melanoma cell line, J.Cell Sci. 49:119-37.:119 (1981).
- S.Shimizu, M.Narita, and Y.Tsujimoto, Bcl-2 family proteins regulate the release of apoptogenic cytochrome c by the mitochondrial channel VDAC, Nature 399:483 (1999).
- S.Shimizu, A.Konishi, T.Kodama, and Y.Tsujimoto, BH4 domain of antiapoptotic Bcl-2 family members closes voltage-dependent anion channel and inhibits apoptotic mitochondrial changes and cell death, Proc.Natl.Acad.Sci.U.S.A 97:3100 (2000).
- S.Shimizu and Y.Tsujimoto, Proapoptotic BH3-only Bcl-2 family members induce cytochrome c release, but not mitochondrial membrane potential loss, and do not directly modulate voltage-dependent anion channel activity, Proc.Natl.Acad.Sci.U.S.A 97:577 (2000).
- S.Shimizu, Y.Matsuoka, Y.Shinohara, Y.Yoneda, and Y.Tsujimoto, Essential role of voltage-dependent anion channel in various forms of apoptosis in mammalian cells, J.Cell Biol. 152:237 (2001).
- N.Shiraiwa, N.Inohara, S.Okada, M.Yuzaki, S.Shoji, and S.Ohta, An additional form of rat Bcl-x, Bcl-xbeta, generated by an unspliced RNA, promotes apoptosis in promyeloid cells, J.Biol.Chem. 271:13258 (1996).
- S.Shuman, Novel approach to molecular cloning and polynucleotide synthesis using vaccinia DNA topoisomerase, J.Biol.Chem. 269:32678 (1994).
- A.Sierra, B.Lloveras, X.Castellsague, L.Moreno, M.Garcia-Ramirez, and A.Fabra, Bcl-2 expression is associated with lymph node metastasis in human ductal breast carcinoma, Int.J.Cancer 60:54 (1995).
- A.Srinivasan, F.Li, A.Wong, L.Kodandapani, R.Smidt, Jr., J.F.Krebs, L.C.Fritz, J.C.Wu, and K.J.Tomaselli, Bcl-xL functions downstream of caspase-8 to inhibit Fas- and tumor necrosis factor receptor 1-induced apoptosis of MCF7 breast carcinoma cells, J.Biol.Chem. 273:4523 (1998).
- Z.Z.Su, M.T.Madireddi, J.J.Lin, C.S.Young, S.Kitada, J.C.Reed, N.I.Goldstein, and P.B.Fisher, The cancer growth suppressor gene mda-7 selectively induces apoptosis in human

breast cancer cells and inhibits tumor growth in nude mice, Proc.Natl.Acad.Sci.U.S.A 95:14400 (1998).

V.N.Sumantran, M.W.Ealovega, G.Nunez, M.F.Clarke, and M.S.Wicha, Overexpression of Bcl-XS sensitizes MCF-7 cells to chemotherapy-induced apoptosis, Cancer Res. 55:2507 (1995).

S.A.Susin, N.Zamzami, M.Castedo, T.Hirsch, P.Marchetti, A.Macho, E.Daugas, M.Geuskens, and G.Kroemer, Bcl-2 inhibits the mitochondrial release of an apoptogenic protease, J.Exp.Med. 184:1331 (1996).

S.A.Susin, H.K.Lorenzo, N.Zamzami, I.Marzo, B.E.Snow, G.M.Brothers, J.Mangion, E.Jacotot, P.Costantini, M.Loeffler, N.Larochette, D.R.Goodlett, R.Aebersold, D.P.Siderovski, J.M.Penninger, and G.Kroemer, Molecular characterization of mitochondrial apoptosis-inducing factor, Nature 397:441 (1999).

S.A.Susin, E.Daugas, L.Ravagnan, K.Samejima, N.Zamzami, M.Loeffler, P.Costantini, K.F.Ferri, T.Irinopoulou, M.C.Prevost, G.Brothers, T.W.Mak, J.Penninger, W.C.Earnshaw, and G.Kroemer, Two distinct pathways leading to nuclear apoptosis, J.Exp.Med. 192:571 (2000).

Y.Suzuki, Y.Imai, H.Nakayama, K.Takahashi, K.Takio, and R.Takahashi, A serine protease, HtrA2, is released from the mitochondria and interacts with XIAP, inducing cell death, Mol.Cell 8:613 (2001).

S.Tanaka, K.Saito, and J.C.Reed, Structure-function analysis of the Bcl-2 oncoprotein. Addition of a heterologous transmembrane domain to portions of the Bcl-2 beta protein restores function as a regulator of cell survival, J.Biol.Chem. 268:10920 (1993).

L.Tang, V.A.Tron, J.C.Reed, K.J.Mah, M.Krajewska, G.Li, X.Zhou, V.C.Ho, and M.J.Trotter, Expression of apoptosis regulators in cutaneous malignant melanoma, Clin.Cancer Res. 4:1865 (1998).

Y.Tsujimoto, L.R.Finger, J.Yunis, P.C.Nowell, and C.M.Croce, Cloning of the chromosome breakpoint of neoplastic B cells with the t(14;18) chromosome translocation, Science 226:1097 (1984).

Y.Tsujimoto and S.Shimizu, Bcl-2 family: life-or-death switch, FEBS Lett. 466:6 (2000).

Y.Tsujimoto and S.Shimizu, VDAC regulation by the Bcl-2 family of proteins, Cell Death.Differ. 7:1174 (2000).

M.E.Verhaegh, C.J.Sanders, J.W.Arends, and H.A.Neumann, Expression of the apoptosis-suppressing protein Bcl-2 in non-melanoma skin cancer, Br.J.Dermatol. 132:740 (1995).

A.M.Verhagen, J.Silke, P.G.Ekert, M.Pakusch, H.Kaufmann, L.M.Connolly, C.L.Day, A.Tikoo, R.Burke, C.Wrobel, R.L.Moritz, R.J.Simpson, and D.L.Vaux, HtrA2 promotes cell death through its serine protease activity and its ability to antagonize inhibitor of apoptosis proteins, J.Biol.Chem. 277:445 (2002).

H.P.Vosberg, The polymerase chain reaction: an improved method for the analysis of nucleic acids, Hum.Genet. 83:1 (1989).

P.Weinmann, K.Bommert, M.Y.Mapara, B.Dorken, and R.C.Bargou, Overexpression of the death-promoting gene bax-alpha sensitizes human BL-41 Burkitt lymphoma cells for surface IgM-mediated apoptosis, Eur.J.Immunol. 27:2466 (1997).

B.Weiss, A.Jacquemin-Sablon, T.R.Live, G.C.Fareed, and C.C.Richardson, Enzymatic breakage and joining of deoxyribonucleic acid. VI. Further purification and properties of polynucleotide ligase from Escherichia coli infected with bacteriophage T4, J.Biol.Chem. 243:4543 (1968).

T.Wieder, C.E.Orfanos, and C.C.Geilen, Induction of ceramide-mediated apoptosis by the anticancer phospholipid analog, hexadecylphosphocholine, J.Biol.Chem. 273:11025 (1998).

L.Xerri, P.Parc, P.Brousset, D.Schlaifer, J.Hassoun, J.C.Reed, S.Krajewski, and D.Birnbaum, Predominant expression of the long isoform of Bcl-x (Bcl-xL) in human lymphomas, Br.J.Haematol. 92:900 (1996).

L.Xerri, J.Hassoun, E.Devillard, D.Birnbaum, and F.Birg, BCL-X and the apoptotic machinery of lymphoma cells, Leuk.Lymphoma 28:451 (1998).

K.Xie, B.Wang, Q.Shi, J.L.Abruzzese, Q.Xiong, and X.Le, Mouse models of metastatic pancreatic adenocarcinoma, Int.J.Pancreatol. 29:25 (2001).

H.Yamaguchi, K.Inokuchi, and K.Dan, The study for loss of bcl-xs expression as a prognostic factor in acute myeloid leukemia, Leuk.Res. 26:1119 (2002).