

## 7. Literaturverzeichnis

1. Kerr, J. F., Wyllie, A. H. & Currie, A. R. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *Br. J. Cancer* **26**, 239-257 (1972).
2. Wyllie, A. H., Kerr, J. F. & Currie, A. R. Cell death: The significance of apoptosis. *Int. Rev. Cytol.* **68**, 251-306 (1980).
3. Alnemri, E. S. Human ICE/CED-3 protease nomenclature. *Cell* **87**, 171 (1996).
4. Budihardjo, I., Oliver, H., Lutter, M., Luo, X. & Wang, X. Biochemical pathways of caspase activation during apoptosis. *Annu Rev Cell Dev Biol* **15**, 269-290 (1999).
5. Cikala, M., Wilm, B., Hobmayer, E., Bottger, A. & David, C. N. Identification of caspases and apoptosis in the simple metazoan Hydra. *Curr Biol* **9**, 959-962 (1999).
6. Earnshaw, W. C., Martins, L. M. & Kaufmanns, S. H. Mammalian caspases: structure, activation, substrates, and functions during apoptosis. *Annu Rev Biochem* **68**, 383-424 (1999).
7. Thornberry, N. A. A combinatorial approach defines specificities of members of the caspase family and granzyme B. Functional relationships established for key mediators of apoptosis. *J. Biol. Chem.* **272** (1997).
8. Kidd, V. J., Lahti, J. M. & Teitz, T. Proteolytic regulation of apoptosis. *Cell & Developmental Biology* **11**, 191-201 (2000).
9. Wyllie, A. H., Kerr, J. F. & Currie, A. R. Glucocorticoid-induced thymocyte apoptosis is associated with endogenous endonuclease activation. *Nature* **284**, 555-556 (1980).
10. Liu, X., Zou, H., Slaughter, C. & Wang, X. DFF, a heterodimeric protein that functions downstream of caspase-3 to trigger DNA fragmentation during apoptosis. *Cell* **89**, 175-184 (1997).
11. Enari, M. A caspase-activated DNase that degrades DNA during apoptosis, and its inhibitor ICAD. *Nature* **391**, 43-50 (1998).
12. Sakahira, H., Enari, M. & Nagata, S. Cleavage of CAD inhibitor in CAD activation and DNA degradation during apoptosis. *Nature* **391**, 96-99 (1998).
13. Rao, L., Perez, D. & White, E. Lamin proteolysis facilitates nuclear events during apoptosis. *J. Cell Biol.* **135**, 1441-1455 (1996).
14. Kothakota, S. Caspase-3-generated fragment of gelsolin: effector of morphological change in apoptosis. *Science* **278**, 294-298 (1997).
15. Rudel, T. & Bokoch, G. M. Membrane and morphological changes in apoptotic cells regulated by caspase-mediated activation of PAK2. *Science* **276**, 1571-1574 (1997).
16. Buendia, B., Santa-Maria, A. & Courvalin, J. C. Caspase-dependent proteolysis of integral and peripheral proteins of nuclear membranes and nuclear pore complex proteins during apoptosis. *J Cell Sci* **112**, 1743-1753 (1999).
17. Hengartner, M. O. The biochemistry of apoptosis. *Nature* **407**, 770-776 (2000).
18. Muzio, M., Stockwell, B. R., Stennicke, H. R., Salvesen, G. S. & Dixit, V. M. An induced proximity model for caspase-8 activation. *J Biol Chem* **273**, 2926-2930 (1998).

19. Rodriguez, J. & Lazebnik, Y. Caspase-9 and APAF-1 form an active holoenzyme. *Genes Dev* **13**, 3179-3184 (1999).
20. Kumar, S. & Cakouros, D. Transcriptional control of the core cell-death machinery. *TRENDS Bioch Sci* **29**, 193-199 (2004).
21. Scadiffi, C., Medema, J. P., H., K. P. & E., P. M. FLICE is predominantly expressed as two functionally active isoforms, caspase-8/a and caspase-8/b. *J Biol Chem* **272**, 26953-26958 (1997).
22. Medema, J. P. et al. FLICE is activated by association with the CD95 death-inducing signalling complex (DISC). *EMBO J* **16**, 2794-2804 (1997).
23. Mitsiades, N., Poulaki, V., Tseleni-Balafouta, S., Koutras, D. A. & Stamenkovic, I. Thyroid carcinoma cells are resistant to FAS-mediated apoptosis but sensitive tumor necrosis factor-related apoptosis-inducing ligand. *Cancer Res* **60**, 4122-4129 (2000).
24. Sprick, M. R. et al. FADD/MORT1 and caspase-8 are recruited to TRAIL receptors 1 and 2 and are essential for apoptosis mediated by TRAIL receptor 2. *Immunity* **12**, 599-609 (2000).
25. Cryns, V. L. & Yuan, J. Y. Proteases to die for. *Genes Dev* **12**, 1551-1570 (1998).
26. Muzio, M. FLICE, a novel FADD-homologous ICE/CED-3-like protease, is recruited to the CD95 (Fas/Apo-1) death-inducing signaling complex. *Cell* **85**, 817-827 (1996).
27. Muzio, M., Salvesen, G. S. & Dixit, V. M. FLICE induced apoptosis in a cell-free system. Clavage of caspase zymogens. *J Biol Chem* **272**, 2952-2956 (1997).
28. Fernandes-Alnemri, T. et al. In vitro activation of CPP32 and Mch3 by Mch4, a novel human apoptotic cysteine protease containing two FADD-like domains. *Proc Natl Acad Sci* **93**, 7464-7469 (1996).
29. Nagata, S. & Golstein, P. The Fas death factor. *Science* **267**, 1449-1456 (1995).
30. Nagata, S. Apoptosis by death factor. *Cell* **88**, 355-365 (1997).
31. Griffith, T. S., Brunner, T., Fletcher, S. M., Green, D. R. & Ferguson, T. A. Fas ligand-induced apoptosis as a mechanism of immune privilege. *Science* **270**, 1189-1192 (1995).
32. Bellgrau, D. et al. A role of CD 95 ligand in preventing graft rejection. *Nature* **377**, 630-632 (1995).
33. Dockrell, D. et al. The expression of Fas ligand by macrophages and its upregulation by human immunodeficiency virus infection. *J Clin Invest* **101**, 2394-2405 (1998).
34. Oshimi, Y., Oda, S., Honda, Y., Nagata, S. & Miyazaki, S. Involvement of Fas ligand and Fas-mediated pathway in the cytotoxicity of human natural killer cells. *J Immunol* **157**, 2909-2915 (1996).
35. Sata, M. & Walsh, K. Oxidized LDL activates Fas-mediated endothelial cell apoptosis. *J Clin Invest* **102**, 1682-1689 (1998).
36. Fukuo, K. et al. Possible participation of Fas-mediated apoptosis in the mechanism of atherosclerosis. *Gerontology* **43**, 35-42 (1997).
37. Cai, W., Devaux, B. & Schaper, J. The role of Fas/APO 1 and apoptosis in the development of human atherosclerotic lesions. *Atherosclerosis* **131**, 177-186 (1997).
38. Geng, Y.-J., Henderson, L. E., Levesque, E. B., Muszynsky, M. & Libby, P. Fas is expressed in human atherosclerotic intima and promotes apoptosis of

- cytokine-primed human vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol* **17**, 2200-2208 (1997).
39. Dong, C., Wilson, J. E., Winters, G. L. & McManus, B. M. Human transplant coronary artery disease: pathological evidence for Fas-mediated apoptotic cytotoxicity in allograft arteriopathy. *Lab Invest* **74**, 921-931 (1996).
  40. Sata, M. & Walsh, K. TNFalpha regulation of Fas ligand expression on the vascular endothelium modulates leukocyte extravasation. *Nat Med* **4**, 415-420 (1998).
  41. Sata, M., Suhara, T. & Walsh, K. Vascular endothelial cells and smooth muscle cells differ in expression of Fas and Fas ligand and in sensitivity to Fas ligand-induced cell death. *Arterioscler Thromb Vasc Biol* **20**, 309-316 (2000).
  42. Imanishi, T. et al. Transition of apoptotic resistant vascular smooth muscle cells to apoptotic sensitive state is correlated with downregulation of c-FLIP. *J Vasc Res* **37**, 523-531 (2000).
  43. Boyle, J. J., Bowyer, D. E., Weissberg, P. L. & Bennett, M. R. Human blood-derived macrophages induce apoptosis in human plaque-derived vascular smooth muscle cells by Fas-ligand/Fas interactions. *Arterioscler Thromb Vasc Biol* **21**, 1402-1407 (2001).
  44. Walford, G. & Loscalzo, J. Nitric oxide in vascular biology. *J Thromb Haemost* **1**, 2112-2118 (2003).
  45. Boyle, J. J., Weissberg, P. L. & Bennett, M. R. Human macrophage-induced vascular smooth muscle cell apoptosis requires NO enhancement of Fas/Fas-L interactions. *Arterioscler Thromb Vasc Biol* **22**, 1624-1630 (2002).
  46. Hayden, M. A., Lange, P. A. & Nakayama, D. K. Nitric oxide and cyclic Guanosin monophosphate stimulate apoptosis via activation of the Fas-FasL pathway. *J Surg Res* **101**, 183-189 (2001).
  47. Bennett, M. R. et al. Cell surface trafficking of Fas: a rapid mechanism of p53-mediated apoptosis. *Science* **282**, 290-293 (1998).
  48. Moncada, S., Palmer, R. M. & Higgs, E. A. Nitric oxide: physiology, pathophysiology, and pharmacology. *Pharmacol Rev* **43**, 109-142 (1991).
  49. Jun, C. D. et al. Synergistic cooperation between phorbol ester and IFN-gamma for induction of nitric oxide synthesis in murine peritoneal macrophages. *J Immunol* **153**, 3684-3690 (1994).
  50. Boyle, J. J., Weissberg, P. L. & Bennett, M. R. Tumor necrosis factor-alpha promotes macrophage-induced vascular smooth muscle cell apoptosis by direct and autocrine mechanisms. *Arterioscler Thromb Vasc Biol* **23**, 1553-1558 (2003).
  51. Messmer, U. K. & Brune, B. Nitric oxide-induced apoptosis: p53-dependent and p53-independent signalling pathways. *Biochem J* **319**, 299-305 (1996).
  52. So, H. S. et al. Nitric oxide inhibits c-Jun N-terminal kinase 2 (JNK2) via S-Nitrosylation. *Biochem Biophys Res Com* **247**, 809-813 (1998).
  53. Jun, C. D. et al. Overexpression of protein kinase C isoforms protects RAW 264.7 macrophages from nitric oxide-induced apoptosis: involvement of c-Jun N-terminal kinase/stress-activated protein kinase, p38 kinase, and CPP-32 protease pathways. *J Immunol* **162**, 3395-3401 (1999).
  54. Ding, A. H., F., N. C. & Stuehr, D. J. Release of reactive nitrogen intermediates and reactive oxygen intermediates from mouse peritoneal macrophages.

- Comparison of activating cytokines and evidence for independent production. *J Immunol* **141**, 2407-2412 (1988).
55. Drapier, J. C. & Hibbs, J. B. J. Differentiation of murine macrophages to express nonspecific cytotoxicity for tumor cells results in L-arginine-dependent inhibition of mitochondrial iron-sulfur enzymes in the macrophage effector cells. *J Immunol* **140**, 2829-2838 (1988).
56. Stuehr, D. J. & Marletta, M. A. Induction of nitrite/nitrate synthesis in murine macrophages by BCG infection, lymphokines, or interferon-gamma. *J Immunol* **139**, 18-25 (1987).
57. Ankarcona, M., Dypbukt, J. M., Brune, B. & Nicotera, P. Interleukin-1 beta-induced nitric oxide production activates apoptosis in pancreatic RINm5F cells. *Exp Cell Res* **213**, 172-177 (1994).
58. Geng, Y.-J., Wu, Q., Muszynski, M., Hansson, G. & Libby, P. Apoptosis of vascular smooth-muscle cells induced by in vitro stimulation with interferon-gamma, tumor necrosis factor-alpha, and interleukin-1-beta. *Arterioscler Thromb Vasc Biol* **16**, 19-27 (1996).
59. Gross, A. et al. Caspase cleaved Bid targets mitochondria and is required for cytochrome c release, while Bcl-XL prevents this release but not tumor necrosis factor-R1/Fas death. *J Biol Chem* **274**, 1156-1163 (1999).
60. Stoka, V. et al. Lysosomal protease pathways to apoptosis. Cleavage of Bid, not pro-caspases, is the most likely route. *J Biol Chem* **276**, 3149-3157 (2001).
61. Heibein, J. A. et al. Granzyme B-mediated cytochrome c release is regulated by the Bcl-2 family members Bid and Bax. *J Exp Med* **192**, 1391-1402 (2000).
62. Marzo, I. et al. Caspases disrupt mitochondrial membrane barrier function. *FEBS Lett* **427**, 198-202 (1998).
63. Saikumar, P. et al. Apoptosis: definition, mechanisms, and relevance to disease. *Amer J Med* **107**, 489-506 (1999).
64. Goldstein, J. C., Waterhouse, N. J., Juin, P., Evan, G. I. & Green, D. R. The coordinate release of cytochrome c during apoptosis is rapid, complete and kinetically invariant. *Nat Cell Biol* **2**, 156-162 (2000).
65. Srinivasula, S. M., Ahmad, M., Fernandes-Alnemri, T. & Alnemri, E. S. Autoactivation of procaspase-9 by Apaf-1-mediated oligomerization. *Mol Cell* **1**, 949-957 (1998).
66. Jiang, X. & Wang, X. Cytochrome c promotes caspase-9 activation by inducing nucleotide binding to Apaf-1. *J Biol Chem* **275**, 31199-31203 (2000).
67. Cain, K. et al. Apaf-1 oligomerizes into biologically active ~700-kDa and inactive ~1.4-MDa apoptosome complexes. *J Biol Chem* **275**, 6067-6070 (2000).
68. Cain, K., Brown, D. G., Langlais, C. & Cohen, G. M. Caspase activation involves the formation of the apoptosome, a large (~700 kDa) caspase-activating complex. *J Biol Chem* **274**, 22686-22692 (1999).
69. Green, D. R. & Kroemer, G. The pathophysiology of mitochondrial cell death. *Science* **305**, 626-629 (2004).
70. Susin, S. A. et al. Bcl-2 inhibits the mitochondrial release of a apoptogenic protease. *J Exp Med* **184**, 1331-1341 (1996).
71. Kroemer, G. The proto-oncogene Bcl-2 and its role in regulating apoptosis. *Nat Med* **3**, 614-620 (1997).
72. Wei, M. C. et al. Proapoptotic Bax and Bak: a requisite gateway to mitochondrial dysfunction and death. *Science* **292**, 727-730 (2001).

73. Breckenridge, D. G. & Xue, D. Regulation of mitochondrial membrane permeabilization by Bcl-2 family proteins and caspases. *Curr Opin Cell Biol* **16**, 647-652 (2004).
74. Liu, X., Kim, C. N., Yang, J., Jemmerson, R. & Wang, X. Induction of apoptotic program in cell-free extracts: requirement for dATP and cytochrome c. *Cell* **86**, 147-157 (1996).
75. Du, C., Fang, M., Li, Y., Li, L. & Wang, X. Smac, a mitochondrial protein that promotes cytochrome c-dependent caspase activation. *Cell* **102**, 33-42 (2000).
76. Susin, S. A. et al. Molecular characterization of mitochondrial apoptosis-inducing factor. *Nature* **397**, 441-446 (1999).
77. Kim, R. Recent advances in understanding the cell death pathways activated by anticancer therapy. *Cancer* **103**, 1551-1560 (2005).
78. Henry-Mowatt, J., Dive, C., Martinou, J. C. & James, D. Role of mitochondrial membrane permeabilization in apoptosis and cancer. *Oncogene* **23**, 2850-2860 (2004).
79. Wang, X. et al. Bcl-XL disrupts death-inducing signal complex formation in plasma membrane induces by hypoxia/reoxygenation. *FASEB J* **18**, 1826-1833 (2004).
80. Luo, X., Budihardjo, I., Zou, H., Slaughter, C. & Wang, X. Bid, A Bcl-2 interacting protein, mediates cytochrome c release from mitochondria in response to activation of cell surface death receptors. *Cell* **94**, 481-490 (1998).
81. Heinrich, M. et al. Cathepsin D links TNF-induced acid sphingomyelinase to Bid-mediated caspase-9 and -3 activation. *Cell Death Differ* **11**, 550-563 (2004).
82. Waterhouse, N. J. et al. A central role for Bid in granzyme B-induced apoptosis. *J Biol Chem* **280**, 4476-4482 (2005).
83. Deng, Y., Ren, X., Yang, L., Lin, Y. & Wu, X. A NK-dependent pathway is required for TNF $\alpha$ -induced apoptosis. *Cell* **115**, 61-70 (2003).
84. Cartron, P. F. et al. Nonredundant role of Bax and Bak in Bid-mediated apoptosis. *Mol Cell Biol* **23**, 4701-4712 (2003).
85. Kuwana, T. Bid, Bax, and lipids cooperate to form supramolecular openings in the outer mitochondrial membrane. *Cell* **111**, 331-342 (2002).
86. Kuwana, T. BH3 domains of BH3-only proteins differentially regulate Bax-mediated mitochondrial membrane permeabilization both directly and indirectly. *Mol Cell* **17**, 525-535 (2005).
87. Cartron, P. F. The first alpha helix of Bax plays a necessary role in its ligand-induced activation by the BH3-only proteins Bid and PUMA. *Mol Cell* **16**, 807-818 (2004).
88. Chen, L. Differential targeting of pro-survival Bcl-2 proteins by their BH3-only ligands allows complementary apoptotic functions. *Mol Cell* **17**, 393-403 (2005).
89. Boucher-Hayes, L., Lartigue, L. & Newmeyer, D. D. Mitochondria: pharmacological manipulation of cell death. *J Clin Invest* **115**, 2640-2647 (2005).
90. Turk, B., Turk, V. & Turk, D. Structural and functional aspects of papain-like cysteine proteinases and their protein inhibitors. *Biol Chem* **387**, 141-150 (1997).
91. Brzin, J., Popovic, T. & Turk, V. Human cystatin, a new protein inhibitor of cysteine proteinases. *Biochem Biophys Res Com* **118**, 103-109 (1984).

92. Turk, V. & Bode, W. The cystatins: protein inhibitors of cysteine proteinase. *FEBS Lett* **285**, 213-219 (1991).
93. Turk, V. & Bode, W. Human cysteine proteinases and their inhibitors, stefins and cystatins. *Japan Scientific Societies Press*, 47-59 (1994).
94. Zettergren, J. G., Peterson, L. L. & Wuepper, K. D. Keratolinin: the soluble substrate of epidermal transglutaminase from human and bovine tissue. *Proc Natl Acad Sci* **81**, 238-242 (1984).
95. Takahashi, M., Tezuka, T. & Katunuma, N. Phosphorylated cystatin alpha is a natural substrate of epidermal transglutaminase for formation of skin cornified envelope. *FEBS Lett* **308**, 79-82 (1992).
96. Steinert, P. M. & Marekov, L. N. Direct evidence that involucrin is a major early isopeptide cross-linked component of the keratinocyte cornified cell envelope. *J Biol Chem* **272**, 2021-2030 (1997).
97. Pennacchio, L. A. et al. Progressive ataxia, myoclonic epilepsy and cerebellar apoptosis in cystatin B-deficient mice. *Nat Genet* **20**, 251-258 (1998).
98. Barret, A. J. et al. Cysteine proteinase inhibitors of the cystatin superfamily. In: *proteinase Inhibitors*, Elsevier, Amsterdam, 515-568 (1986).
99. Abrahamson, M., Barret, A. J., Salvesen, G. & Grubb, A. Isolation of six cysteine proteinase inhibitors from human urine. *J Biol Chem* **261**, 11282-11289 (1986).
100. Alvarez-Fernandez, M., Barret, A. J., Gerhartz, B., Dando, P. M. & Abrahamson, M. Inhibition of mammalian legumain by some cystatins is due to a novel second reactive site. *J Biol Chem* **274**, 19195-19203 (1999).
101. Shi, G.-P. et al. Cystatin c deficiency in human arteriosclerosis and aortic aneurysms. *J Clin Invest* **104**, 1191-1197 (1999).
102. Salvesen, G., Parkes, C., Abrahamson, M., Grubb, A. & Barret, A. J. Human low Mr kininogen contains three copies of a cystatin sequence that are divergent in structure and in inhibitory activity for cysteine proteinases. *Biochem J* **234**, 429-434 (1986).
103. Parkes, C. Calpastatins. In: *proteinase Inhibitors*, Elsevier, Amsterdam, 571-587 (1986).
104. Arthur, J. S., Elce, J. S., Hegadorn, C., Williams, K. & Greer, P. A. Disruption of the murine calpain small subunit gene, *Capn4*: calpain is essential for embryonic development but not for cell growth and division. *Mol Cell Biol* **20**, 4474-4481 (2000).
105. Zimmerman, U. J. P., Boring, L., Pak, J. H., Mukerjee, N. & Wang, K. K. The calpain small subunit is essential: its inactivation results in embryonic lethality. *IUBMB Life* **50**, 63-68 (2000).
106. Fukui, I., Tanaka, K. & Murachi, T. Extracellular appearance of calpain and calpastatin in the synovial fluid of the knee joint. *Biochem Biophys Res Com* **162**, 559-566 (1989).
107. Newcomb, J. K., Ike, B. R., Zhao, X., Banik, N. L. & Hayes, R. L. Altered calpastatin protein levels following traumatic brain injury in rat. *J Neurotrauma* **16**, 1-11 (1999).
108. Pontremoli, S. et al. Characterization of calpastatin defect in erythrocytes from patients with essential hypertension. *Biochem Biophys Res Com* **157**, 867-874 (1988).

109. Nakayama, J., Yoshizawa, T., Yamamoto, N. & Arinami, T. Mutation analysis of the calpastatin gene (CAST) in patients with Alzheimer's disease. *Neurosci Lett* **320**, 77-80 (2002).
110. Mouatt-Prigent, A., Karlsson, J. O., Yelnik, J., Agid, Y. & Hirsch, E. C. Calpastatin immunoreactivity in the monkey and human brain of control subjects and patients with Parkinson's disease. *J Comp Neurol* **419**, 175-192 (2000).
111. Scheer, J. M., Romanowski, M. J. & Wells, J. A. A common allosteric site and mechanism in caspases. *Proc Natl Acad Sci* **103**, 7595-7600 (2006).
112. Methot, N. et al. Differential efficacy of caspase inhibitors on apoptosis markers during sepsis in rats and implication for fractional inhibition requirements for therapeutics. *J Exp Med* **199**, 199-207 (2004).
113. Valentino, K. L., Gutierrez, M., Sanchez, R., Winship, M. J. & Shapiro, D. A. First clinical trial of a novel caspase inhibitor: anti-apoptotic caspase inhibitor, IDN-6556, improves liver enzymes. *Int J Clin Pharmacol Ther* **41**, 441-449 (2003).
114. Rudolphi, K., Gerwin, N., Verzijl, N., van der Kraan, P. & van den Berg, W. Pralnacasan, an inhibitor of interleukin-1beta converting enzyme, reduces joint damage in two murine models of osteoarthritis. *J Osteoarthritis Cartilage* **11**, 738-746 (2003).
115. Bhoola, K. D., Figueroa, C. D. & Worthy, K. Bioregulation of kinins: kallikrein, kininogen, and kininases. *Pharmacol Rev* **44**, 1-80 (1992).
116. Kitamura, N. et al. Structure organization of the kininogen gene and a model for its evolution. *J Biol Chem* **260**, 8610-8617 (1985).
117. Zhang, J.-C. et al. Two-chain high molecular weight kininogen induces endothelial cell apoptosis and inhibits angiogenesis: partial activity within domain 5. *FASEB J* **14**, 2589-2600 (2000).
118. Colman, R. W. Role of the light chain of high molecular weight kininogen in adhesion, cell-associated proteolysis and angiogenesis. *Biol Chem* **382**, 65-70 (2001).
119. Cugno, M. et al. Parallel reduction of plasma levels of high and low molecular weight kininogen in patients with cirrhosis. *Thromb Haemost* **82**, 1428-1432 (1999).
120. Chao, J., Swain, C., Chao, S., Xiong, W. & Chao, L. Tissue distribution and kininogen gene expression after acute phase inflammation. *Biochim Biophys Acta* **964**, 329-339 (1988).
121. Poblete, M. T. et al. Tissue kallikrein and kininogen in human sweat glands and psoriatic skin. *Br J Dermatol* **124**, 236-241 (1991).
122. Richoux, J. P. et al. The kallikrein-kinin system in the rat hypothalamus. *Histochemistry* **96**, 229-243 (1991).
123. Figueroa, C. D. et al. Immunolocalization of high (HK) and low (LK) weight kininogens on isolated human neutrophils. *Blood* **79**, 754-759 (1992).
124. Chao, J., Simson, J. A., Chung, P., Chen, L. M. & Chao, L. Regulation of kininogen gene expression and localization in the lung after monocrotaline-induced pulmonary hypertension in rats. *Proc Soc Exp Biol Med* **203**, 243-250 (1993).
125. Iwai, N., Matsunaga, M., Kita, T., Tei, M. & Kawai, C. Detection of low molecular weight kininogen messenger RNA in human kidney. *J Hypertens* **6 (Suppl)**, 399-400 (1988).

126. Kakizuka, A., Kitamura, N. & Nakanishi, S. Localization of DNA sequences governing alternative mRNA production of rat kininogen genes. *J Biol Chem* **263**, 3884-3892 (1988).
127. Kitagawa, H., Kitamura, N., Hayashida, H., Miyata, T. & Nakanishi, S. Differing expression patterns and evolution of the rat kininogen gene family. *J Biol Chem* **262**, 219-2198 (1987).
128. Moreau, T., Gutman, N., el Moujahed, A., Esnard, F. & Gauthier, F. Relationship between the cysteine-proteinase-inhibitory function of rat T kininogen and the release of immunoreactive kinin upon trypsin treatment. *Eur J Biochem* **159**, 341-346 (1986).
129. Okamoto, H., Yayama, K., Shibata, H., Nagaoka, M. & Takano, M. Kininogen expression by rat vascular smooth muscle cells: stimulation by lipopolysaccharide and angiotensin II. *Biochim Biophys Acta* **1404**, 329-337 (1998).
130. Oza, N. B., Schwartz, J. H., Goud, H. D. & Levinsky, N. G. Rat aortic smooth muscle cells in culture express kallikrein, kininogen, and bradykininase activity. *J Clin Invest* **85**, 597-600 (1990).
131. Lattion, A. L. et al. The high-molecular-mass kininogen deficient rat expresses all kininogen mRNA species, but does not export the high-molecular-mass kininogen synthesized. *FEBS Lett* **239**, 59-64 (1988).
132. Carey, D. J. Control of growth and differentiation of vascular cells by extracellular matrix proteins. *Annu Rev Physiol* **53**, 161-177 (1991).
133. Kavurma, M. M., Bhindi, R., Lowe, H. C., Chesterman, C. & Khachigian, L. M. Vessel wall apoptosis and atherosclerotic plaque instability. *J Thromb Haemost* **3**, 465-472 (2005).
134. de Boer, O. J., Becker, A. E. & van der Wal, A. C. T lymphocytes in atherogenesis-functional aspects and antigenic repertoire. *Cardiovasc Res* **60**, 78-86 (2003).
135. Boyle, J. J. Macrophage activation in atherosclerosis: pathogenesis and pharmacology of plaque rupture. *Curr Vasc Pharmacol* **3**, 63-68 (2005).
136. Hansson, G. K. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* **352**, 1685-1695 (2005).
137. Hansson, G. K., Holm, J. & Jonasson, L. Detection of activated T lymphocytes in the human atherosclerotic plaque. *Am J Pathol* **135**, 169-175 (1989).
138. Kolodgie, F. D. et al. Pathologic assessment of the vulnerable human coronary plaque. *Heart* **90**, 1385-1391 (2004).
139. Stoneman, V. E. & Bennett, M. R. Role of apoptosis in atherosclerosis and its therapeutic implications. *Clin Sci* **107**, 343-354 (2004).
140. Lutgens, E. Biphasic pattern of cell turnover characterizes the progression from fatty streaks to ruptured human atherosclerotic plaques. *Cardiovasc Res* **41**, 473-479 (1999).
141. Geng, Y.-J. & Libby, P. Evidence for apoptosis in advanced human atheroma: colocalization with interleukin-1beta converting enzyme. *Am J Pathol* **147**, 251-266 (1995).
142. Son, B.-K. et al. Statins protect human aortic smooth muscle cells from inorganic phosphate-induced calcification by restoring Gas6-Axl survival pathway. *Circ Res* **98**, 1024-1031 (2006).



143. Littlewood, T. D. & Bennett, M. R. Apoptotic cell death in atherosclerosis. *Curr Opin Lipidol* **14**, 469-475 (2003).
144. Greenhalgh, R. M., Mannick, J. A. & Powell, J. T. The cause and management of aneurysms. London, UK: *WB Saunders* (1990).
145. Pschyrembel. Klinisches Wörterbuch. *de Gruyter* **258**. (1998).
146. O'Gara, P. T. Aortic aneurysm. *Circulation* **107**, e43-e45 (2003).
147. Wills, A., Thompson, M. M., Crowther, M., Sayer, R. D. & Bell, P. F. Pathogenesis of abdominal aortic aneurysms: cellular and biological mechanisms. *Eur J Vasc Endovasc Surg* **12**, 391-400 (1996).
148. Wassef, M. et al. Pathogenesis of abdominal aortic aneurysms: a multidisciplinary research program supported by the National Heart, Lung and Blood Institute. *J Vasc Surg* **34**, 730-738 (2001).
149. Zhang, J. et al. Expressions of matrix metalloproteinases in human abdominal aortic aneurysm. *Chin J Exp Surg* **16**, 26-27 (1999).
150. Newman, K. M. et al. Cellular localization of matrix metalloproteinases in the abdominal aortic aneurysm wall. *J Vasc Surg* **20**, 814-820 (1994).
151. Zhang, J. et al. Effects of inflammatory infiltration on the formation of abdominal aortic aneurysms. *Chin J Surg* **37**, 177-179 (1999).
152. Koch, A. E., Haines, G. K. & Pearce, W. H. Human abdominal aortic aneurysms: Immunophenotypic analysis suggesting an immune-mediated response. *Am J Pathol* **137**, 1199-1215 (1990).
153. Henderson, L. E. et al. Death of smooth muscle cells and expression of mediators of apoptosis by T lymphocytes in human abdominal aortic aneurysms. *Circulation* **99**, 96-104 (1999).
154. Lopez-Candales, A. et al. Decreased vascular smooth muscle cell density in medial degeneration of human abdominal aortic aneurysms. *Am J Pathol* **150**, 993-1007 (1997).
155. Galis, Z., Muszynski, M. & Sukhova, G. K. Cytokine-stimulated human vascular smooth muscle cells synthesize a complement of enzymes required for extracellular matrix digestion. *Circ Res* **75**, 181-189 (1994).
156. Curci, J. A. & Thompson, R. W. Adaptive cellular immunity in aortic aneurysms: cause, consequence, or context? *J Clin Invest* **114**, 168-171 (2004).
157. Woessner, J. Matrix metalloproteinases and their inhibitors in connective tissue remodelling. *FASEB J* **5**, 2145-2154 (1991).
158. Brophy, C. M., Reilly, J. M., Smith, G. J. & Tilson, M. D. The role of inflammation in nonspecific abdominal aortic aneurysm disease. *Ann Vasc Surg* **5**, 229-233 (1991).
159. Beckman, E. N. Plasma cell infiltrates in atherosclerotic abdominal aortic aneurysms. *Am J Clin Pathol* **85**, 21-24 (1986).
160. Koch, A., Kunkel, S. L. & Pearce, W. H. Enhanced production of the chemotactic cytokines interleukin-8 and monocyte chemoattractant protein-1 in human abdominal aortic aneurysms. *Am J Pathol* **142**, 1423-1431 (1993).
161. Hance, K. A., Tataria, M., Ziorin, S. J., Lee, J. K. & Thompson, R. W. Monocyte chemotactic activity in human abdominal aortic aneurysms: role of elastin degradation peptides and the 67-kD cell surface elastin receptor. *J Vasc Surg* **35**, 254-261 (2002).

162. Newman, K. M., Jean-Claude, J., Lil, H., Ramey, W. & Tilson, M. Cytokines that activate proteolysis are increased in abdominal aortic aneurysms. *Circulation* **90** (II), 224-227 (1994).
163. Szekanecz, Z., Shah, M., Pearce, W. H. & Koch, A. Human atherosclerotic abdominal aortic aneurysms produce interleukin (IL)-6 and interferon-gamma but not IL-2 and IL-4: The possible role of IL-6 and interferon-gamma in vascular inflammation. *Agents and Actions* **42**, 159-162 (1994).
164. Walton, L. J. Inhibition of prostaglandin E2 synthesis in abdominal aortic aneurysms: implications for smooth muscle cell viability, inflammatory processes, and the expansion of abdominal aortic aneurysms. *Circulation* **100**, 48-54 (1999).
165. Miller, F. J. Oxidative stress in human abdominal aortic aneurysms: a potential mediator of aneurysmal remodeling. *Arterioscler Thromb Vasc Biol* **22**, 560-565 (2002).
166. Powell, J. T. & Brady, A. R. Detection, management, and prospects for the medical treatment of small abdominal aortic aneurysms. *Arterioscler Thromb Vasc Biol* **24**, 241-245 (2004).
167. Damas, J. The Brown Norway rats and the kinin system. *Peptides* **17**, 859-872 (1996).
168. Damas, J. & Adam, A. The relationship between kininogens and kallikreins in Brown Norway deficient rat plasma. *Mol Physiol* **8**, 307-316 (1985).
169. Hayashi, I., Hoshiko, S., Makabe, O. & Oh-ishi, S. A point mutation of alanine 163 to threonine is responsible for the defective secretion of high molecular weight kininogen by the liver of Brown Norway Katholiek rats. *J Biol Chem* **268**, 17219-17224 (1993).
170. Colman, R. W., Bagdasarian, A. & Talamo, R. C. Williams trait. Human kininogen deficiency with diminished levels of plasminogen proactivator and prekallikrein associated with abnormalities of the Hageman factor-dependent pathways. *J Clin Invest* **56**, 1650-1662 (1975).
171. Colman, R. W. Structure-function correlates of human high molecular weight kininogen. *Braz J Med Biol Res* **27**, 1839-1853 (1994).
172. Kaschina, E. et al. Genetic kininogen deficiency contributes to aortic aneurysm formation but not to atherosclerosis. *Physiol Genomics* **19**, 41-49 (2004).
173. Schecke, J. H., Lehmann, K. E., R., B. I., Unger, T. & Funke-Kaiser, H. Quantitative real-time RT-PCR data analysis: current concepts and the novel "gene expression's CT difference" formula. *J Mol Med* **84**, 901-910 (2006).
174. Al-Fakhri, N. et al. Induction of apoptosis in vascular cells by plasminogen activator inhibitor-1 and high molecular weight kininogen correlates with their anti-adhesive properties. *Biol Chem* **384**, 423-435 (2003).
175. Barros, N. M. et al. High molecular weight kininogen as substrate for cathepsin B. *Biol Chem* **385**, 551-555 (2004).
176. Motta, G., Shariat Madar, Z., Mahdi, F., Sampaio, C. & Schmaier, A. Assembly of high molecular weight kininogen and activation of prekallikrein on cell matrix. *Thromb Haemost* **86**, 840-847 (2001).
177. Guicciardi, M. E. et al. Cathepsin B contributes to TNF-alpha-mediated hepatocyte apoptosis by promoting mitochondrial release of cytochrome c. *J Clin Invest* **106**, 1127-1137 (2000).

178. Foghsgaard, L. et al. Cathepsin B acts as a dominant execution protease in tumor cell apoptosis induced by tumor necrosis factor. *J Cell Biol* **153**, 999-1010 (2001).
179. Guicciardi, M. E., Miyoshi, H., Bronk, S. F. & Gores, G. J. Cathepsin B knockout mice are resistant to tumor necrosis factor- $\alpha$ -mediated hepatocyte apoptosis and liver injury: implications for therapeutic applications. *Am J Pathol* **159**, 2045-2054 (2001).
180. Liu, N. et al. NF- $\kappa$ B protects from the lysosomal pathway of cell death. *EMBO J* **22**, 5313-5322 (2003).
181. Manders, E. M. M., Verbeek, F. J. & Aten, J. A. Measurement of co-localization of objects in dual-color confocal images. *J Microsc* **169**, 375-382 (1993).
182. Schwartz, S. M., Campbell, G. R. & Campbell, J. H. Replication of smooth muscle cells in vascular disease. *Circ Res* **58**, 427-444 (1986).
183. Ishitani, R. & Chuang, D. M. Glyceraldehyde-3-phosphate dehydrogenase antisense oligodeoxynucleotides protect against cytosine arabinonucleoside-induced apoptosis in cultured cerebellar neurons. *Proc Natl Acad Sci* **93**, 9937-9941 (1996).
184. Ishitani, R., Tanaka, M., Sunaga, K., Katsube, N. & Chuang, D. M. Nuclear localization of overexpressed glyceraldehyde-3-phosphate dehydrogenase in cultured cerebellar neurons undergoing apoptosis. *Mol Pharmacol* **53**, 701-707 (1998).
185. Yang, M. H., Yoo, K. H., Yook, Y. J., Park, E. Y. & Jeon, J. O. The gene expression profiling in murine cortical cells undergoing programmed cell death (PCD) induced by serum deprivation. *J Biochem Mol Biol* **40**, 277-285 (2007).
186. Michel, J.-B. Anoikis in the cardiovascular system. *Arterioscler Thromb Vasc Biol* **23**, 2146-2154 (2003).
187. Asakura, S., Hurley, R. W., Skorstengaard, K., Ohkubo, I. & Mosher, D. F. Inhibition of cell adhesion by high molecular weight kininogen. *J Cell Biol* **116**, 465-476 (1992).
188. Chavakis, T. et al. Different mechanisms define the anti-adhesive function of high molecular weight kininogen in integrin- and urokinase-dependent interactions. *Blood* **96**, 514-522 (2000).
189. Kidd, V. J., Lahti, J. M. & Teitz, T. Proteolytic regulation of apoptosis. *Semin Cell Dev Biol* **11**, 191-201 (2000).
190. Perlman, H., Maillard, L., Krasinski, K. & Walsh, K. Evidence for the rapid onset of apoptosis in medial smooth muscle cells following balloon injury. *Circulation* **95**, 981-987 (1997).
191. Keogh, S. A., Walczak, H., Boucher-Hayes, L. & Martin, S. Failure of Bcl-2 to block cytochrome c redistribution during TRAIL-induced apoptosis. *FEBS Lett* **471**, 93-98 (2000).
192. Arriola, E. L., Rodriguez-Lopez, A. M., Hickman, J. A. & Chresta, C. M. Bcl-2 overexpression results in reciprocal downregulation of Bcl-X(L) and sensitizes human testicular germ cell tumours to chemotherapy-induced apoptosis. *Oncogene* **18**, 1457-1464 (1999).
193. Beale, P. J., Rogers, P., Boxall, F., Sharp, S. Y. & Kelland, L. R. Bcl-2 family protein expression and platinum drug resistance in ovarian carcinoma. *Br J Cancer* **82**, 436-440 (2000).

194. Chang, F. et al. Signal transduction mediated by the Ras/Raf/Mek/ERK pathway from cytokine receptors to transcription factors: potential targeting for therapeutic intervention. *Leukemia* **17**, 1263-1293 (2003).
195. Chang, Y. H. et al. Activation of caspase-8 and Erk-1/2 in domes regulates cell death induced by confluence in MDCK cells. *J Cell Physiol* **211**, 174-182 (2006).
196. Villedieu, M. et al. Anticancer and chemosensitizing effects of 2,3-DCPE in ovarian carcinoma cell lines: Link with ERK activation and modulation of p21 WAF1/CIP1, Bcl-2 and Bcl-XL expression. *Gynecol Ocol*, (article in press) (2007).
197. Allan, L. A. et al. Inhibition of caspase-9 through phosphorylation at Thr 125 by ERK MAPK. *Nat Cell Biol* **5**, 647-654 (2003).
198. Xia, Z. Opposing effects of ERK and JNK-p38 AP kinases on apoptosis. *Science* **270**, 1326-1331 (1995).
199. Erhardt, P., Schremser, E. J. & Cooper, G. M. B\_Raf inhibits programmed cell death downstream of cytochrome c release from mitochondria by activating the Mek/Erk pathway. *Mol Cell Biol* **19**, 5308-5315 (1999).
200. Le Gall, M. et al. The p42/p44 MAP kinase pathway prevents apoptosis induced by anchorage and serum removal. *Mol Cell Biol* **11**, 1103-1112 (2000).
201. Wang, X., Martindale, J. L., Liu, Y. & Holbrook, N. J. The cellular response to oxidative stress: influences of mitogen-activated protein kinase signalling pathways on cell survival. *Biochem J* **333**, 291-300 (1998).
202. MacKeigan, J. P., Collins, T. S. & Ting, J. P. MEK inhibition enhances paclitaxel-induced tumor apoptosis. *J Biol Chem* **275**, 38953-38956 (2000).
203. Barlas, A., Okamoto, H. & Greenbaum, L. M. T-kininogen--the major plasma kininogen in rat adjuvant arthritis. *Biochem Biophys Res Com* **129**, 280-286 (1985).
204. Dendorfer, A., Wellhöner, P., Braun, A., Roscher, A. A. & Dominiak, P. Synthesis of kininogen and degradation of bradykinin by PC12 cells. *Br J Pharmacol* **122**, 1585-1592 (1997).
205. van Iwaarden, F., de Groot, P. G., Sixma, J. J., Berrettini, M. & Bouma, B. N. High-molecular weight kininogen is present in cultured human endothelial cells: localization, isolation, and characterization. *Blood* **71**, 1268-1276 (1988).
206. Müller-Esterl, W. et al. Human plasma kininogens are identical with alpha-cysteine proteinase inhibitors. Evidence from immunological, enzymological and sequence data. *FEBS Lett* **182**, 310-314 (1985).
207. Desmazes, C., Gauthier, F. & Lalmanach, G. Cathepsin L, but not cathepsin B, is a potential kininogenase. *Biol Chem* **382**, 811-815 (2001).
208. Karlsrud, T. S., Buo, L., Aasen, A. O. & Johansen, H. T. Quantification of kininogens in plasma. A functional method based on the cysteine proteinase inhibitor activity. *Thromb Res* **82**, 265-273 (1996).
209. Reddigari, S. R. et al. Human high molecular weight kininogen binds to human umbilical vein endothelial cells via its heavy and light chains. *Blood* **81**, 1306-1311 (1993).
210. Krijanovski, Y. et al. Characterization of molecular defects of Fitzgerald trait and another novel high-molecular-weight kininogen-deficient patient: insights into structural requirements for kininogen expression. *Blood* **101**, 4430-4436 (2003).

211. Abrahamson, M., Barret, A. J., Salvesen, G. & Grubb, A. Isolation of six cysteine proteinase inhibitors from human urine. *J Biol Chem* **261**, 11282-11289 (1986).
212. Takeyabu, K. Cysteine proteinases and cystatin C in bronchoalveolar lavage fluid from subjects with subclinical emphysema. *Eur Respir J* **12**, 1033-1039 (1998).
213. Skaleric, U., Babnik, J., Curin, V., Lah, T. & Turk, V. Immunochemical quantiation of cysteine prteinase inhibitor cystatin C in inflamed human gingiva. *Arch Oral Biol* **34**, 301-305 (1998).
214. Daugherty, A., Manning, M. W. & Cassis, L. A. Angiotenin II promotes atherosclerotic lesions and aneurysms in apolipoprotein E-deficient mice. *J Clin Invest* **105**, 1605-1612 (2000).
215. Habashi, J. P. et al. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mous model of marfan syndrome. *Science* **312**, 117-121 (2006).
216. Nishimoto, M., Takai, S. & Fukumoto, H. Increased local angiotensin II formation in aneurysmal aorta. *Life Sci* **71**, 2195-2205 (2002).
217. Fatini, C., Pratesi, G. & Sofi, F. ACE DD genotype: a predisposing factor for abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* **29**, 227-232 (2005).
218. Slowik, A., Borratynska, A. & Pera, J. II genotype of the angiotensin converting enzyme gene increases the risk for subarachnoid hemorrhage from ruptured aneurysm. *Stroke* **35**, 1594-1597 (2004).
219. Takeuchi, K., Yamamoto, K. & Kataoka, S. High incidence of angiotensin I converting enzyme genotype II in Kawasaki disease patients with coronary aneurysm. *Eur J Pediatr* **156**, 266-268 (1997).
220. Hackam, D. G., Thiruchelvam, D. & Redelmeier, D. A. Angiotensin-converting enzyme inhibitors and aortic rupture: a population-based case-control study. *Lancet* **368**, 659-665 (2006).
221. Huang, W., Gelas, F. A. & Osborne-Pellegrin, M. J. Protection of the arterial internal elastic lamina by inhibition of the renin-angiotensin system in the rat. *Circ Res* **82**, 879-890 (1998).
222. Liao, S. et al. Suppression of experimental abdominal aortic aneurysms in the rat by treatment with angiotensin-converting enzyme inhibitors. *J Vasc Surg* **33**, 1057-1064 (2001).
223. Golub, L. M., Lee, H. M. & Ryan, M. E. Minocycline reduces gingival collagenolytic activity during diabetes. Preliminary observations and a proposed new mechanism of action. *J Periodontal Res* **18**, 516-526 (1983).
224. Thompson, R. W., Liao, S. & Curci, J. A. Therapeutic potential of tetracycline derivates to supress the growth of abdominal aortic aneurysms. *Adv Dent Res* **12**, 159-165 (1998).
225. Petrinc, D., Liao, S. & Holmes, D. R. Doxycycline inhibition of aneurysmal degeneration in an elastase-induced rat model of abdominal aortic aneurysm: preservation of aortic elastin associated with suppressed production of 92 kD gelatinase. *J Vasc Surg* **26**, 336-346 (1996).
226. Prall, A. K., Longo, G. M. & Mayhan, W. G. Doxycycline in patients with abdominal aortic aneurysms and in mice: comparison of serum levels and effect on aneurysm growth in mice. *J Vasc Surg* **35**, 923-929 (2002).

227. Steinmetz, E. F., Buckley, C. & Thompson, R. W. Prospects for the medical management of abdominal aortic aneurysms. *Vasc Endovasc Surg* **37**, 151-163 (2003).
228. Investigators, T. P. A. T. Propranolol for small abdominal aortic aneurysms: Results of a randomized trial. *J Vasc Surg* **35**, 72-79 (2002).