8 References

1. Fang, S. and A.M. Weissman, A field guide to ubiquitylation. *Cell Mol Life Sci*, 2004. **61**(13): p. 1546-61.
2. Hershko, A. and A. Ciechanover, The ubiquitin system. *Annu Rev Biochem*, 1998. **67**: p. 425-79.
3. VanDemark, A.P. and C.P. Hill, Structural basis of ubiquitylation. *Curr Opin Struct Biol*, 2002. **12**(6): p. 822-30.
4. Pickart, C.M., Mechanisms underlying ubiquitination. *Annu Rev Biochem*, 2001. **70**: p. 503-33.
5. Breitschopf, K., et al., A novel site for ubiquitination: the N-terminal residue, and not internal lysines of MyoD, is essential for conjugation and degradation of the protein. *Embo J*, 1998. **17**(20): p. 5964-73.
6. Huibregtse, J.M., et al., A family of proteins structurally and functionally related to the E6-AP ubiquitin-protein ligase. *Proc Natl Acad Sci U S A*, 1995. **92**(7): p. 2563-7.
7. Borden, K.L. and P.S. Freemont, The RING finger domain: a recent example of a sequence-structure family. *Curr Opin Struct Biol*, 1996. **6**(3): p. 395-401.
8. Jackson, P.K., et al., The lore of the RINGs: substrate recognition and catalysis by ubiquitin ligases. *Trends Cell Biol*, 2000. **10**(10): p. 429-39.
9. Borden, K.L., RING domains: master builders of molecular scaffolds? *J Mol Biol*, 2000. **295**(5): p. 1103-12.
10. Ozkan, E., H. Yu, and J. Deisenhofer, Mechanistic insight into the allosteric activation of a ubiquitin-conjugating enzyme by RING-type ubiquitin ligases. *Proc Natl Acad Sci U S A*, 2005. **102**(52): p. 18890-5.
11. Hicke, L. and R. Dunn, Regulation of membrane protein transport by ubiquitin and ubiquitin-binding proteins. *Annu Rev Cell Dev Biol*, 2003. **19**: p. 141-72.
12. Muratani, M. and W.P. Tansey, How the ubiquitin-proteasome system controls transcription. *Nat Rev Mol Cell Biol*, 2003. **4**(3): p. 192-201.
13. Hochstrasser, M., Lingering mysteries of ubiquitin-chain assembly. *Cell*, 2006. **124**(1): p. 27-34.
14. Koegl, M., et al., A novel ubiquitination factor, E4, is involved in multiubiquitin chain assembly. *Cell*, 1999. **96**(5): p. 635-44.
15. Hoppe, T., Multiubiquitylation by E4 enzymes: 'one size' doesn't fit all. *Trends Biochem Sci*, 2005. **30**(4): p. 183-7.
16. Peng, J., et al., A proteomics approach to understanding protein ubiquitination. *Nat Biotechnol*, 2003. **21**(8): p. 921-6.
17. Johnson, E.S., et al., A proteolytic pathway that recognizes ubiquitin as a degradation signal. *J Biol Chem*, 1995. **270**(29): p. 17442-56.
18. Baboshina, O.V. and A.L. Haas, Novel multiubiquitin chain linkages catalyzed by the conjugating enzymes E2EPF and RAD6 are recognized by 26 S proteasome subunit 5. *J Biol Chem*, 1996. **271**(5): p. 2823-31.
19. Wu-Baer, F., et al., The BRCA1/BARD1 heterodimer assembles polyubiquitin chains through an unconventional linkage involving lysine residue K6 of ubiquitin. *J Biol Chem*, 2003. **278**(37): p. 34743-6.
20. Nishikawa, H., et al., Mass spectrometric and mutational analyses reveal Lys-6-linked polyubiquitin chains catalyzed by BRCA1-BARD1 ubiquitin ligase. *J Biol Chem*, 2004. **279**(6): p. 3916-24.
21. Thrower, J.S., et al., Recognition of the polyubiquitin proteolytic signal. *Embo J*, 2000. **19**(1): p. 94-102.

22. Passmore, L.A. and D. Barford, Getting into position: the catalytic mechanisms of protein ubiquitylation. *Biochem J*, 2004. **379**(Pt 3): p. 513-25.
23. Sun, L. and Z.J. Chen, The novel functions of ubiquitination in signaling. *Curr Opin Cell Biol*, 2004. **16**(2): p. 119-26.
24. Pickart, C.M., DNA repair: right on target with ubiquitin. *Nature*, 2002. **419**(6903): p. 120-1.
25. Welchman, R.L., C. Gordon, and R.J. Mayer, Ubiquitin and ubiquitin-like proteins as multifunctional signals. *Nat Rev Mol Cell Biol*, 2005. **6**(8): p. 599-609.
26. Varadan, R., et al., Structural properties of polyubiquitin chains in solution. *J Mol Biol*, 2002. **324**(4): p. 637-47.
27. Varadan, R., et al., Solution conformation of Lys63-linked di-ubiquitin chain provides clues to functional diversity of polyubiquitin signaling. *J Biol Chem*, 2004. **279**(8): p. 7055-63.
28. Gill, G., SUMO and ubiquitin in the nucleus: different functions, similar mechanisms? *Genes Dev*, 2004. **18**(17): p. 2046-59.
29. Johnson, E.S. and G. Blobel, Ubc9p is the conjugating enzyme for the ubiquitin-like protein Smt3p. *J Biol Chem*, 1997. **272**(43): p. 26799-802.
30. Rodriguez, M.S., C. Dargemont, and R.T. Hay, SUMO-1 conjugation in vivo requires both a consensus modification motif and nuclear targeting. *J Biol Chem*, 2001. **276**(16): p. 12654-9.
31. Johnson, E.S., Protein modification by SUMO. *Annu Rev Biochem*, 2004. **73**: p. 355-82.
32. Melchior, F., M. Schergaut, and A. Pichler, SUMO: ligases, isopeptidases and nuclear pores. *Trends Biochem Sci*, 2003. **28**(11): p. 612-8.
33. Hay, R.T., SUMO: a history of modification. *Mol Cell*, 2005. **18**(1): p. 1-12.
34. Zhang, H., H. Saitoh, and M.J. Matunis, Enzymes of the SUMO modification pathway localize to filaments of the nuclear pore complex. *Mol Cell Biol*, 2002. **22**(18): p. 6498-508.
35. Sen, R. and D. Baltimore, Multiple nuclear factors interact with the immunoglobulin enhancer sequences. *Cell*, 1986. **46**(5): p. 705-16.
36. Sen, R. and D. Baltimore, Inducibility of kappa immunoglobulin enhancer-binding protein Nf-kappa B by a posttranslational mechanism. *Cell*, 1986. **47**(6): p. 921-8.
37. Cross, S.L., et al., Functionally distinct NF-kappa B binding sites in the immunoglobulin kappa and IL-2 receptor alpha chain genes. *Science*, 1989. **244**(4903): p. 466-9.
38. Griffin, G.E., et al., Activation of HIV gene expression during monocyte differentiation by induction of NF-kappa B. *Nature*, 1989. **339**(6219): p. 70-3.
39. May, M.J. and S. Ghosh, Rel/NF-kappa B and I kappa B proteins: an overview. *Semin Cancer Biol*, 1997. **8**(2): p. 63-73.
40. Ghosh, S., M.J. May, and E.B. Kopp, NF-kappa B and Rel proteins: evolutionarily conserved mediators of immune responses. *Annu Rev Immunol*, 1998. **16**: p. 225-60.
41. Hayden, M.S. and S. Ghosh, Signaling to NF-kappaB. *Genes Dev*, 2004. **18**(18): p. 2195-224.
42. Chen, F.E., et al., Crystal structure of p50/p65 heterodimer of transcription factor NF-kappaB bound to DNA. *Nature*, 1998. **391**(6665): p. 410-3.
43. Ghosh, G., et al., Structure of NF-kappa B p50 homodimer bound to a kappa B site. *Nature*, 1995. **373**(6512): p. 303-10.
44. Muller, C.W., et al., Structure of the NF-kappa B p50 homodimer bound to DNA. *Nature*, 1995. **373**(6512): p. 311-7.
45. Plaksin, D., P.A. Baeuerle, and L. Eisenbach, KBF1 (p50 NF-kappa B homodimer) acts as a repressor of H-2Kb gene expression in metastatic tumor cells. *J Exp Med*, 1993. **177**(6): p. 1651-62.

46. Zhong, H., et al., The phosphorylation status of nuclear NF-kappa B determines its association with CBP/p300 or HDAC-1. *Mol Cell*, 2002. **9**(3): p. 625-36.
47. Fan, C.M. and T. Maniatis, Generation of p50 subunit of NF-kappa B by processing of p105 through an ATP-dependent pathway. *Nature*, 1991. **354**(6352): p. 395-8.
48. Palombella, V.J., et al., The ubiquitin-proteasome pathway is required for processing the NF-kappa B1 precursor protein and the activation of NF-kappa B. *Cell*, 1994. **78**(5): p. 773-85.
49. Xiao, G., E.W. Harhaj, and S.C. Sun, NF-kappaB-inducing kinase regulates the processing of NF-kappaB2 p100. *Mol Cell*, 2001. **7**(2): p. 401-9.
50. Mordmuller, B., et al., Lymphotoxin and lipopolysaccharide induce NF-kappaB-p52 generation by a co-translational mechanism. *EMBO Rep*, 2003. **4**(1): p. 82-7.
51. Rice, N.R., M.L. MacKichan, and A. Israel, The precursor of NF-kappa B p50 has I kappa B-like functions. *Cell*, 1992. **71**(2): p. 243-53.
52. Naumann, M., et al., NF-kappa B precursor p100 inhibits nuclear translocation and DNA binding of NF-kappa B/rel-factors. *Oncogene*, 1993. **8**(8): p. 2275-81.
53. Solan, N.J., et al., RelB cellular regulation and transcriptional activity are regulated by p100. *J Biol Chem*, 2002. **277**(2): p. 1405-18.
54. Wulczyn, F.G., M. Naumann, and C. Scheidereit, Candidate proto-oncogene bcl-3 encodes a subunit-specific inhibitor of transcription factor NF-kappa B. *Nature*, 1992. **358**(6387): p. 597-9.
55. Lenardo, M. and U. Siebenlist, Bcl-3-mediated nuclear regulation of the NF-kappa B trans-activating factor. *Immunol Today*, 1994. **15**(4): p. 145-7.
56. Kitamura, H., et al., MAIL, a novel nuclear I kappa B protein that potentiates LPS-induced IL-6 production. *FEBS Lett*, 2000. **485**(1): p. 53-6.
57. Baeuerle, P.A. and T. Henkel, Function and activation of NF-kappa B in the immune system. *Annu Rev Immunol*, 1994. **12**: p. 141-79.
58. Pahl, H.L., Activators and target genes of Rel/NF-kappaB transcription factors. *Oncogene*, 1999. **18**(49): p. 6853-66.
59. Kopp, E.B. and S. Ghosh, NF-kappa B and rel proteins in innate immunity. *Adv Immunol*, 1995. **58**: p. 1-27.
60. Chen, C.C. and A.M. Manning, Transcriptional regulation of endothelial cell adhesion molecules: a dominant role for NF-kappa B. *Agents Actions Suppl*, 1995. **47**: p. 135-41.
61. Wissink, S., et al., NF-kappa B/Rel family members regulating the ICAM-1 promoter in monocytic THP-1 cells. *Immunobiology*, 1997. **198**(1-3): p. 50-64.
62. Courtois, G. and T.D. Gilmore, Mutations in the NF-kappaB signaling pathway: implications for human disease. *Oncogene*, 2006. **25**(51): p. 6831-43.
63. Baldwin, A.S., Jr., The NF-kappa B and I kappa B proteins: new discoveries and insights. *Annu Rev Immunol*, 1996. **14**: p. 649-83.
64. Verma, I.M., et al., Rel/NF-kappa B/I kappa B family: intimate tales of association and dissociation. *Genes Dev*, 1995. **9**(22): p. 2723-35.
65. DiDonato, J., et al., Mapping of the inducible IkappaB phosphorylation sites that signal its ubiquitination and degradation. *Mol Cell Biol*, 1996. **16**(4): p. 1295-304.
66. Whiteside, S.T., et al., I kappa B epsilon, a novel member of the I kappa B family, controls RelA and cRel NF-kappa B activity. *Embo J*, 1997. **16**(6): p. 1413-26.
67. Brockman, J.A., et al., Coupling of a signal response domain in I kappa B alpha to multiple pathways for NF-kappa B activation. *Mol Cell Biol*, 1995. **15**(5): p. 2809-18.
68. Brown, K., et al., Control of I kappa B-alpha proteolysis by site-specific, signal-induced phosphorylation. *Science*, 1995. **267**(5203): p. 1485-8.
69. Scheidereit, C., IkappaB kinase complexes: gateways to NF-kappaB activation and transcription. *Oncogene*, 2006. **25**(51): p. 6685-705.

70. Senftleben, U., et al., Activation by IKKalpha of a second, evolutionary conserved, NF-kappa B signaling pathway. *Science*, 2001. **293**(5534): p. 1495-9.
71. Xiao, G., A. Fong, and S.C. Sun, Induction of p100 processing by NF-kappaB-inducing kinase involves docking IkappaB kinase alpha (IKKalpha) to p100 and IKKalpha-mediated phosphorylation. *J Biol Chem*, 2004. **279**(29): p. 30099-105.
72. Janssens, S. and J. Tschopp, Signals from within: the DNA-damage-induced NF-kappaB response. *Cell Death Differ*, 2006. **13**(5): p. 773-84.
73. Huang, T.T., et al., Sequential modification of NEMO/IKKgamma by SUMO-1 and ubiquitin mediates NF-kappaB activation by genotoxic stress. *Cell*, 2003. **115**(5): p. 565-76.
74. Hay, R.T., Modifying NEMO. *Nat Cell Biol*, 2004. **6**(2): p. 89-91.
75. Chen, Z.J., L. Parent, and T. Maniatis, Site-specific phosphorylation of IkappaBalpha by a novel ubiquitination-dependent protein kinase activity. *Cell*, 1996. **84**(6): p. 853-62.
76. DiDonato, J.A., et al., A cytokine-responsive IkappaB kinase that activates the transcription factor NF-kappaB. *Nature*, 1997. **388**(6642): p. 548-54.
77. Mercurio, F., et al., IKK-1 and IKK-2: cytokine-activated IkappaB kinases essential for NF-kappaB activation. *Science*, 1997. **278**(5339): p. 860-6.
78. Zandi, E., et al., The IkappaB kinase complex (IKK) contains two kinase subunits, IKKalpha and IKKbeta, necessary for IkappaB phosphorylation and NF-kappaB activation. *Cell*, 1997. **91**(2): p. 243-52.
79. Woronicz, J.D., et al., IkappaB kinase-beta: NF-kappaB activation and complex formation with IkappaB kinase-alpha and NIK. *Science*, 1997. **278**(5339): p. 866-9.
80. Zandi, E., Y. Chen, and M. Karin, Direct phosphorylation of IkappaB by IKKalpha and IKKbeta: discrimination between free and NF-kappaB-bound substrate. *Science*, 1998. **281**(5381): p. 1360-3.
81. Ling, L., Z. Cao, and D.V. Goeddel, NF-kappaB-inducing kinase activates IKK-alpha by phosphorylation of Ser-176. *Proc Natl Acad Sci U S A*, 1998. **95**(7): p. 3792-7.
82. Li, Q., et al., Severe liver degeneration in mice lacking the IkappaB kinase 2 gene. *Science*, 1999. **284**(5412): p. 321-5.
83. Li, Z.W., et al., The IKKbeta subunit of IkappaB kinase (IKK) is essential for nuclear factor kappaB activation and prevention of apoptosis. *J Exp Med*, 1999. **189**(11): p. 1839-45.
84. Beg, A.A., et al., Embryonic lethality and liver degeneration in mice lacking the RelA component of NF-kappa B. *Nature*, 1995. **376**(6536): p. 167-70.
85. Alcamo, E., et al., Targeted mutation of TNF receptor I rescues the RelA-deficient mouse and reveals a critical role for NF-kappa B in leukocyte recruitment. *J Immunol*, 2001. **167**(3): p. 1592-600.
86. Hu, Y., et al., Abnormal morphogenesis but intact IKK activation in mice lacking the IKKalpha subunit of IkappaB kinase. *Science*, 1999. **284**(5412): p. 316-20.
87. Sil, A.K., et al., IkappaB kinase-alpha acts in the epidermis to control skeletal and craniofacial morphogenesis. *Nature*, 2004. **428**(6983): p. 660-4.
88. Tang, E.D., et al., A role for NF-kappaB essential modifier/IkappaB kinase-gamma (NEMO/IKKgamma) ubiquitination in the activation of the IkappaB kinase complex by tumor necrosis factor-alpha. *J Biol Chem*, 2003. **278**(39): p. 37297-305.
89. Yang, F., et al., The zinc finger mutation C417R of I-kappa B kinase gamma impairs lipopolysaccharide- and TNF-mediated NF-kappa B activation through inhibiting phosphorylation of the I-kappa B kinase beta activation loop. *J Immunol*, 2004. **172**(4): p. 2446-52.
90. Makris, C., J.L. Roberts, and M. Karin, The carboxyl-terminal region of IkappaB kinase gamma (IKKgamma) is required for full IKK activation. *Mol Cell Biol*, 2002. **22**(18): p. 6573-81.

91. Janeway, C.A., Jr. and R. Medzhitov, Innate immune recognition. *Annu Rev Immunol*, 2002. **20**: p. 197-216.
92. Barton, G.M. and R. Medzhitov, Toll-like receptor signaling pathways. *Science*, 2003. **300**(5625): p. 1524-5.
93. Kopp, E. and R. Medzhitov, Recognition of microbial infection by Toll-like receptors. *Curr Opin Immunol*, 2003. **15**(4): p. 396-401.
94. Takeda, K., T. Kaisho, and S. Akira, Toll-like receptors. *Annu Rev Immunol*, 2003. **21**: p. 335-76.
95. Adachi, O., et al., Targeted disruption of the MyD88 gene results in loss of IL-1- and IL-18-mediated function. *Immunity*, 1998. **9**(1): p. 143-50.
96. Janssens, S. and R. Beyaert, Functional diversity and regulation of different interleukin-1 receptor-associated kinase (IRAK) family members. *Mol Cell*, 2003. **11**(2): p. 293-302.
97. Qian, Y., et al., IRAK-mediated translocation of TRAF6 and TAB2 in the interleukin-1-induced activation of NFkappa B. *J Biol Chem*, 2001. **276**(45): p. 41661-7.
98. Takaesu, G., et al., Interleukin-1 (IL-1) receptor-associated kinase leads to activation of TAK1 by inducing TAB2 translocation in the IL-1 signaling pathway. *Mol Cell Biol*, 2001. **21**(7): p. 2475-84.
99. Cao, Z., et al., TRAF6 is a signal transducer for interleukin-1. *Nature*, 1996. **383**(6599): p. 443-6.
100. Lomaga, M.A., et al., TRAF6 deficiency results in osteopetrosis and defective interleukin-1, CD40, and LPS signaling. *Genes Dev*, 1999. **13**(8): p. 1015-24.
101. Wang, C., et al., TAK1 is a ubiquitin-dependent kinase of MKK and IKK. *Nature*, 2001. **412**(6844): p. 346-51.
102. Takaesu, G., et al., TAB2, a novel adaptor protein, mediates activation of TAK1 MAPKKK by linking TAK1 to TRAF6 in the IL-1 signal transduction pathway. *Mol Cell*, 2000. **5**(4): p. 649-58.
103. Shim, J.H., et al., TAK1, but not TAB1 or TAB2, plays an essential role in multiple signaling pathways in vivo. *Genes Dev*, 2005. **19**(22): p. 2668-81.
104. Chen, G. and D.V. Goeddel, TNF-R1 signaling: a beautiful pathway. *Science*, 2002. **296**(5573): p. 1634-5.
105. Hsu, H., J. Xiong, and D.V. Goeddel, The TNF receptor 1-associated protein TRADD signals cell death and NF-kappa B activation. *Cell*, 1995. **81**(4): p. 495-504.
106. Hsu, H., et al., TNF-dependent recruitment of the protein kinase RIP to the TNF receptor-1 signaling complex. *Immunity*, 1996. **4**(4): p. 387-96.
107. Hsu, H., et al., TRADD-TRAF2 and TRADD-FADD interactions define two distinct TNF receptor 1 signal transduction pathways. *Cell*, 1996. **84**(2): p. 299-308.
108. Devin, A., et al., The distinct roles of TRAF2 and RIP in IKK activation by TNF-R1: TRAF2 recruits IKK to TNF-R1 while RIP mediates IKK activation. *Immunity*, 2000. **12**(4): p. 419-29.
109. Wu, C.J., et al., Sensing of Lys 63-linked polyubiquitination by NEMO is a key event in NF-kappaB activation [corrected]. *Nat Cell Biol*, 2006. **8**(4): p. 398-406.
110. Ea, C.K., et al., Activation of IKK by TNFalpha requires site-specific ubiquitination of RIP1 and polyubiquitin binding by NEMO. *Mol Cell*, 2006. **22**(2): p. 245-57.
111. Li, H., et al., Ubiquitination of RIP is required for tumor necrosis factor alpha-induced NF-kappaB activation. *J Biol Chem*, 2006. **281**(19): p. 13636-43.
112. Zhou, H., et al., Bcl10 activates the NF-kappaB pathway through ubiquitination of NEMO. *Nature*, 2004. **427**(6970): p. 167-71.
113. Sebban, H., S. Yamaoka, and G. Courtois, Posttranslational modifications of NEMO and its partners in NF-kappaB signaling. *Trends Cell Biol*, 2006. **16**(11): p. 569-77.

114. Mellman, I. and R.M. Steinman, Dendritic cells: specialized and regulated antigen processing machines. *Cell*, 2001. **106**(3): p. 255-8.
115. Thery, C. and S. Amigorena, The cell biology of antigen presentation in dendritic cells. *Curr Opin Immunol*, 2001. **13**(1): p. 45-51.
116. Janeway, C.A., Jr., Travers P., Walport M., Shlomichik M.J., *Immunobiology - the immune system in health and disease*. sixth ed. 2005: Garland Science Publishing.
117. Reiner, S.L. and R.A. Seder, T helper cell differentiation in immune response. *Curr Opin Immunol*, 1995. **7**(3): p. 360-6.
118. Griffiths, G.M., The cell biology of CTL killing. *Curr Opin Immunol*, 1995. **7**(3): p. 343-8.
119. Garcia, K.C., et al., An alphabeta T cell receptor structure at 2.5 A and its orientation in the TCR-MHC complex. *Science*, 1996. **274**(5285): p. 209-19.
120. Pitcher, L.A. and N.S. van Oers, T-cell receptor signal transmission: who gives an ITAM? *Trends Immunol*, 2003. **24**(10): p. 554-60.
121. Kim, P.W., et al., A zinc clasp structure tethers Lck to T cell coreceptors CD4 and CD8. *Science*, 2003. **301**(5640): p. 1725-8.
122. Zamoyska, R., CD4 and CD8: modulators of T-cell receptor recognition of antigen and of immune responses? *Curr Opin Immunol*, 1998. **10**(1): p. 82-7.
123. Greenwald, R.J., G.J. Freeman, and A.H. Sharpe, The B7 family revisited. *Annu Rev Immunol*, 2005. **23**: p. 515-48.
124. Schwartz, R.H., T cell anergy. *Annu Rev Immunol*, 2003. **21**: p. 305-34.
125. Sancho, D., et al., Regulation of microtubule-organizing center orientation and actomyosin cytoskeleton rearrangement during immune interactions. *Immunol Rev*, 2002. **189**: p. 84-97.
126. Monks, C.R., et al., Three-dimensional segregation of supramolecular activation clusters in T cells. *Nature*, 1998. **395**(6697): p. 82-6.
127. van Der Merwe, P.A. and S.J. Davis, Immunology. The immunological synapse--a multitasking system. *Science*, 2002. **295**(5559): p. 1479-80.
128. He, H.T., A. Lellouch, and D. Marguet, Lipid rafts and the initiation of T cell receptor signaling. *Semin Immunol*, 2005. **17**(1): p. 23-33.
129. Douglass, A.D. and R.D. Vale, Single-molecule microscopy reveals plasma membrane microdomains created by protein-protein networks that exclude or trap signaling molecules in T cells. *Cell*, 2005. **121**(6): p. 937-50.
130. Lin, J., M.J. Miller, and A.S. Shaw, The c-SMAC: sorting it all out (or in). *J Cell Biol*, 2005. **170**(2): p. 177-82.
131. Lin, J. and A. Weiss, T cell receptor signalling. *J Cell Sci*, 2001. **114**(Pt 2): p. 243-4.
132. Zhang, W., et al., LAT: the ZAP-70 tyrosine kinase substrate that links T cell receptor to cellular activation. *Cell*, 1998. **92**(1): p. 83-92.
133. Zhang, W., R.P. Trible, and L.E. Samelson, LAT palmitoylation: its essential role in membrane microdomain targeting and tyrosine phosphorylation during T cell activation. *Immunity*, 1998. **9**(2): p. 239-46.
134. Costello, P.S., et al., The Rho-family GTP exchange factor Vav is a critical transducer of T cell receptor signals to the calcium, ERK, and NF-kappaB pathways. *Proc Natl Acad Sci U S A*, 1999. **96**(6): p. 3035-40.
135. Herndon, T.M., et al., ZAP-70 and SLP-76 regulate protein kinase C-theta and NF-kappa B activation in response to engagement of CD3 and CD28. *J Immunol*, 2001. **166**(9): p. 5654-64.
136. Isakov, N. and A. Altman, Protein kinase C(theta) in T cell activation. *Annu Rev Immunol*, 2002. **20**: p. 761-94.
137. Schmitz, M.L. and D. Krappmann, Controlling NF-kappaB activation in T cells by costimulatory receptors. *Cell Death Differ*, 2006. **13**(5): p. 834-42.

138. Kane, L.P., J. Lin, and A. Weiss, It's all Rel-ative: NF-kappaB and CD28 costimulation of T-cell activation. *Trends Immunol*, 2002. **23**(8): p. 413-20.
139. Schulze-Luehrmann, J. and S. Ghosh, Antigen-receptor signaling to nuclear factor kappa B. *Immunity*, 2006. **25**(5): p. 701-15.
140. Kane, L.P., et al., Akt-dependent phosphorylation specifically regulates Cot induction of NF-kappa B-dependent transcription. *Mol Cell Biol*, 2002. **22**(16): p. 5962-74.
141. Lee, K.Y., et al., PDK1 nucleates T cell receptor-induced signaling complex for NF-kappaB activation. *Science*, 2005. **308**(5718): p. 114-8.
142. Hehner, S.P., et al., Tyrosine-phosphorylated Vav1 as a point of integration for T-cell receptor- and CD28-mediated activation of JNK, p38, and interleukin-2 transcription. *J Biol Chem*, 2000. **275**(24): p. 18160-71.
143. Hehner, S.P., et al., Vav synergizes with protein kinase C theta to mediate IL-4 gene expression in response to CD28 costimulation in T cells. *J Immunol*, 2000. **164**(7): p. 3829-36.
144. Jain, J., C. Loh, and A. Rao, Transcriptional regulation of the IL-2 gene. *Curr Opin Immunol*, 1995. **7**(3): p. 333-42.
145. Khoshnan, A., et al., The NF-kappa B cascade is important in Bcl-xL expression and for the anti-apoptotic effects of the CD28 receptor in primary human CD4+ lymphocytes. *J Immunol*, 2000. **165**(4): p. 1743-54.
146. Ullman, K.S., et al., Transmission of signals from the T lymphocyte antigen receptor to the genes responsible for cell proliferation and immune function: the missing link. *Annu Rev Immunol*, 1990. **8**: p. 421-52.
147. Monks, C.R., et al., Selective modulation of protein kinase C-theta during T-cell activation. *Nature*, 1997. **385**(6611): p. 83-6.
148. Bi, K., et al., Antigen-induced translocation of PKC-theta to membrane rafts is required for T cell activation. *Nat Immunol*, 2001. **2**(6): p. 556-63.
149. Sun, Z., et al., PKC-theta is required for TCR-induced NF-kappaB activation in mature but not immature T lymphocytes. *Nature*, 2000. **404**(6776): p. 402-7.
150. Villalba, M., et al., Translocation of PKC[theta] in T cells is mediated by a nonconventional, PI3-K- and Vav-dependent pathway, but does not absolutely require phospholipase C. *J Cell Biol*, 2002. **157**(2): p. 253-63.
151. Thome, M., The immunological synapse and actin assembly: a regulatory role for PKC theta. *Dev Cell*, 2003. **4**(1): p. 3-5.
152. Matsumoto, R., et al., Phosphorylation of CARMA1 Plays a Critical Role in T Cell Receptor-Mediated NF-kappaB Activation. *Immunity*, 2005. **23**(6): p. 575-85.
153. Sommer, K., et al., Phosphorylation of the CARMA1 Linker Controls NF-kappaB Activation. *Immunity*, 2005. **23**(6): p. 561-74.
154. Egawa, T., et al., Requirement for CARMA1 in antigen receptor-induced NF-kappa B activation and lymphocyte proliferation. *Curr Biol*, 2003. **13**(14): p. 1252-8.
155. Hara, H., et al., The MAGUK family protein CARD11 is essential for lymphocyte activation. *Immunity*, 2003. **18**(6): p. 763-75.
156. Ruland, J., et al., Bcl10 is a positive regulator of antigen receptor-induced activation of NF-kappaB and neural tube closure. *Cell*, 2001. **104**(1): p. 33-42.
157. Ruland, J., et al., Differential requirement for Malt1 in T and B cell antigen receptor signaling. *Immunity*, 2003. **19**(5): p. 749-58.
158. Ruefli-Brasse, A.A., D.M. French, and V.M. Dixit, Regulation of NF-kappaB-dependent lymphocyte activation and development by paracaspase. *Science*, 2003. **302**(5650): p. 1581-4.
159. Fanning, A.S. and J.M. Anderson, Protein modules as organizers of membrane structure. *Curr Opin Cell Biol*, 1999. **11**(4): p. 432-9.

160. Dimitratos, S.D., et al., Signaling pathways are focused at specialized regions of the plasma membrane by scaffolding proteins of the MAGUK family. *Bioessays*, 1999. **21**(11): p. 912-21.
161. Bertin, J., et al., CARD11 and CARD14 are novel caspase recruitment domain (CARD)/membrane-associated guanylate kinase (MAGUK) family members that interact with BCL10 and activate NF-kappa B. *J Biol Chem*, 2001. **276**(15): p. 11877-82.
162. Gaide, O., et al., Carma1, a CARD-containing binding partner of Bcl10, induces Bcl10 phosphorylation and NF-kappaB activation. *FEBS Lett*, 2001. **496**(2-3): p. 121-7.
163. Wang, L., et al., Card10 is a novel caspase recruitment domain/membrane-associated guanylate kinase family member that interacts with BCL10 and activates NF-kappa B. *J Biol Chem*, 2001. **276**(24): p. 21405-9.
164. McAllister-Lucas, L.M., et al., Bimp1, a MAGUK family member linking protein kinase C activation to Bcl10-mediated NF-kappaB induction. *J Biol Chem*, 2001. **276**(33): p. 30589-97.
165. Wang, D., et al., A requirement for CARMA1 in TCR-induced NF-kappa B activation. *Nat Immunol*, 2002. **3**(9): p. 830-5. Epub 2002 Aug 5.
166. Pomerantz, J.L., E.M. Denny, and D. Baltimore, CARD11 mediates factor-specific activation of NF-kappaB by the T cell receptor complex. *Embo J*, 2002. **21**(19): p. 5184-94.
167. Jun, J.E., et al., Identifying the MAGUK protein Carma-1 as a central regulator of humoral immune responses and atopy by genome-wide mouse mutagenesis. *Immunity*, 2003. **18**(6): p. 751-62.
168. Gaide, O., et al., CARMA1 is a critical lipid raft-associated regulator of TCR-induced NF-kappa B activation. *Nat Immunol*, 2002. **3**(9): p. 836-43.
169. Wang, D., et al., CD3/CD28 costimulation-induced NF-kappaB activation is mediated by recruitment of protein kinase C-theta, Bcl10, and IkappaB kinase beta to the immunological synapse through CARMA1. *Mol Cell Biol*, 2004. **24**(1): p. 164-71.
170. Zhang, Q., et al., Inactivating mutations and overexpression of BCL10, a caspase recruitment domain-containing gene, in MALT lymphoma with t(1;14)(p22;q32). *Nat Genet*, 1999. **22**(1): p. 63-8.
171. Willis, T.G., et al., Bcl10 is involved in t(1;14)(p22;q32) of MALT B cell lymphoma and mutated in multiple tumor types. *Cell*, 1999. **96**(1): p. 35-45.
172. Srinivasula, S.M., et al., CLAP, a novel caspase recruitment domain-containing protein in the tumor necrosis factor receptor pathway, regulates NF-kappaB activation and apoptosis. *J Biol Chem*, 1999. **274**(25): p. 17946-54.
173. Koseki, T., et al., CIPER, a novel NF kappaB-activating protein containing a caspase recruitment domain with homology to Herpesvirus-2 protein E10. *J Biol Chem*, 1999. **274**(15): p. 9955-61.
174. Streubel, B., et al., T(14;18)(q32;q21) involving IGH and MALT1 is a frequent chromosomal aberration in MALT lymphoma. *Blood*, 2003. **101**(6): p. 2335-9.
175. Dierlamm, J., et al., The apoptosis inhibitor gene API2 and a novel 18q gene, MLT, are recurrently rearranged in the t(11;18)(q21;q21) associated with mucosa-associated lymphoid tissue lymphomas. *Blood*, 1999. **93**(11): p. 3601-9.
176. Akagi, T., et al., A novel gene, MALT1 at 18q21, is involved in t(11;18) (q21;q21) found in low-grade B-cell lymphoma of mucosa-associated lymphoid tissue. *Oncogene*, 1999. **18**(42): p. 5785-94.
177. Morgan, J.A., et al., Breakpoints of the t(11;18)(q21;q21) in mucosa-associated lymphoid tissue (MALT) lymphoma lie within or near the previously undescribed gene MALT1 in chromosome 18. *Cancer Res*, 1999. **59**(24): p. 6205-13.

178. Lucas, P.C., et al., Bcl10 and MALT1, independent targets of chromosomal translocation in malt lymphoma, cooperate in a novel NF-kappa B signaling pathway. *J Biol Chem*, 2001. **276**(22): p. 19012-9.
179. Uren, A.G., et al., Identification of paracaspases and metacaspases: two ancient families of caspase-like proteins, one of which plays a key role in MALT lymphoma. *Mol Cell*, 2000. **6**(4): p. 961-7.
180. Wegener, E., et al., Essential role for IkappaB kinase beta in remodeling Carma1-Bcl10-Malt1 complexes upon T cell activation. *Mol Cell*, 2006. **23**(1): p. 13-23.
181. Che, T., et al., MALT1/paracaspase is a signaling component downstream of CARMA1 and mediates T cell receptor-induced NF-kappaB activation. *J Biol Chem*, 2004. **279**(16): p. 15870-6.
182. Thome, M., CARMA1, BCL-10 and MALT1 in lymphocyte development and activation. *Nat Rev Immunol*, 2004. **4**(5): p. 348-59.
183. Sun, L., et al., The TRAF6 ubiquitin ligase and TAK1 kinase mediate IKK activation by BCL10 and MALT1 in T lymphocytes. *Mol Cell*, 2004. **14**(3): p. 289-301.
184. Bradley, J.R. and J.S. Pober, Tumor necrosis factor receptor-associated factors (TRAFs). *Oncogene*, 2001. **20**(44): p. 6482-91.
185. Darnay, B.G., et al., Activation of NF-kappaB by RANK requires tumor necrosis factor receptor-associated factor (TRAF) 6 and NF-kappaB-inducing kinase. Identification of a novel TRAF6 interaction motif. *J Biol Chem*, 1999. **274**(12): p. 7724-31.
186. Ye, H., et al., Distinct molecular mechanism for initiating TRAF6 signalling. *Nature*, 2002. **418**(6896): p. 443-7.
187. Deng, L., et al., Activation of the IkappaB kinase complex by TRAF6 requires a dimeric ubiquitin-conjugating enzyme complex and a unique polyubiquitin chain. *Cell*, 2000. **103**(2): p. 351-61.
188. Lamothe, B., et al., Site-specific Lys-63-linked tumor necrosis factor receptor-associated factor 6 auto-ubiquitination is a critical determinant of I kappa B kinase activation. *J Biol Chem*, 2007. **282**(6): p. 4102-12.
189. Ea, C.K., et al., TIFA activates IkappaB kinase (IKK) by promoting oligomerization and ubiquitination of TRAF6. *Proc Natl Acad Sci U S A*, 2004. **101**(43): p. 15318-23.
190. Bidere, N., et al., Caspase-8 regulation by direct interaction with TRAF6 in T cell receptor-induced NF-kappaB activation. *Curr Biol*, 2006. **16**(16): p. 1666-71.
191. Su, H., et al., Requirement for caspase-8 in NF-kappaB activation by antigen receptor. *Science*, 2005. **307**(5714): p. 1465-8.
192. Shinohara, H., et al., PKC beta regulates BCR-mediated IKK activation by facilitating the interaction between TAK1 and CARMA1. *J Exp Med*, 2005. **202**(10): p. 1423-31.
193. Sato, S., et al., Essential function for the kinase TAK1 in innate and adaptive immune responses. *Nat Immunol*, 2005. **6**(11): p. 1087-95.
194. Liu, H.H., et al., Essential role of TAK1 in thymocyte development and activation. *Proc Natl Acad Sci U S A*, 2006. **103**(31): p. 11677-82.
195. Wan, Y.Y., et al., The kinase TAK1 integrates antigen and cytokine receptor signaling for T cell development, survival and function. *Nat Immunol*, 2006. **7**(8): p. 851-8.
196. Lobry, C., et al., Negative feedback loop in T cell activation through IkappaB kinase-induced phosphorylation and degradation of Bcl10. *Proc Natl Acad Sci U S A*, 2007. **104**(3): p. 908-13.
197. Zeng, H., et al., Phosphorylation of Bcl10 negatively regulates T cell receptor-mediated NF-{kappa}B activation. *Mol Cell Biol*, 2007.
198. Ishiguro, K., et al., Bcl10 is phosphorylated on Ser138 by Ca2+/calmodulin-dependent protein kinase II. *Mol Immunol*, 2007. **44**(8): p. 2095-100.
199. Thome, M. and R. Weil, Post-translational modifications regulate distinct functions of CARMA1 and BCL10. *Trends Immunol*, 2007.

200. Sagaert, X., et al., The pathogenesis of MALT lymphomas: where do we stand? *Leukemia*, 2007. **21**(3): p. 389-96.
201. Bertoni, F. and E. Zucca, Delving deeper into MALT lymphoma biology. *J Clin Invest*, 2006. **116**(1): p. 22-6.
202. Roy, N., et al., The c-IAP-1 and c-IAP-2 proteins are direct inhibitors of specific caspases. *Embo J*, 1997. **16**(23): p. 6914-25.
203. Hu, S., et al., CIAP2 inhibits anigen receptor signaling by targeting Bcl10 for degredation. *Cell Cycle*, 2006. **5**(13): p. 1438-42.
204. Hu, S., et al., cIAP2 is a ubiquitin protein ligase for BCL10 and is dysregulated in mucosa-associated lymphoid tissue lymphomas. *J Clin Invest*, 2006. **116**(1): p. 174-81.
205. Baens, M., et al., Selective expansion of marginal zone B cells in Emicro-API2-MALT1 mice is linked to enhanced IkappaB kinase gamma polyubiquitination. *Cancer Res*, 2006. **66**(10): p. 5270-7.
206. Zhou, H., M.Q. Du, and V.M. Dixit, Constitutive NF-kappaB activation by the t(11;18)(q21;q21) product in MALT lymphoma is linked to deregulated ubiquitin ligase activity. *Cancer Cell*, 2005. **7**(5): p. 425-31.
207. Maes, B., et al., BCL10 mutation does not represent an important pathogenic mechanism in gastric MALT-type lymphoma, and the presence of the API2-MLT fusion is associated with aberrant nuclear BCL10 expression. *Blood*, 2002. **99**(4): p. 1398-404.
208. Ye, H., et al., Strong BCL10 nuclear expression identifies gastric MALT lymphomas that do not respond to H pylori eradication. *Gut*, 2006. **55**(1): p. 137-8.
209. Ye, H., et al., BCL10 expression in normal and neoplastic lymphoid tissue. Nuclear localization in MALT lymphoma. *Am J Pathol*, 2000. **157**(4): p. 1147-54.
210. Liu, H., et al., T(11;18)(q21;q21) is associated with advanced mucosa-associated lymphoid tissue lymphoma that expresses nuclear BCL10. *Blood*, 2001. **98**(4): p. 1182-7.
211. Ngo, V.N., et al., A loss-of-function RNA interference screen for molecular targets in cancer. *Nature*, 2006. **441**(7089): p. 106-10.
212. Guiet, C. and P. Vito, Caspase recruitment domain (CARD)-dependent cytoplasmic filaments mediate bcl10-induced NF-kappaB activation. *J Cell Biol*, 2000. **148**(6): p. 1131-40.
213. Fornerod, M., et al., CRM1 is an export receptor for leucine-rich nuclear export signals. *Cell*, 1997. **90**(6): p. 1051-60.
214. Wen, W., et al., Identification of a signal for rapid export of proteins from the nucleus. *Cell*, 1995. **82**(3): p. 463-73.
215. la Cour, T., et al., Analysis and prediction of leucine-rich nuclear export signals. *Protein Eng Des Sel*, 2004. **17**(6): p. 527-36.
216. Henderson, B.R. and A. Eleftheriou, A comparison of the activity, sequence specificity, and CRM1-dependence of different nuclear export signals. *Exp Cell Res*, 2000. **256**(1): p. 213-24.
217. Kudo, N., et al., Leptomycin B inhibition of signal-mediated nuclear export by direct binding to CRM1. *Exp Cell Res*, 1998. **242**(2): p. 540-7.
218. Xu, L. and J. Massague, Nucleocytoplasmic shuttling of signal transducers. *Nat Rev Mol Cell Biol*, 2004. **5**(3): p. 209-19.
219. Nakagawa, M., et al., MALT1 contains nuclear export signals and regulates cytoplasmic localization of BCL10. *Blood*, 2005. **106**(13): p. 4210-6.
220. Wilkinson, K.D., Ubiquitination and deubiquitination: targeting of proteins for degradation by the proteasome. *Semin Cell Dev Biol*, 2000. **11**(3): p. 141-8.
221. Amerik, A.Y. and M. Hochstrasser, Mechanism and function of deubiquitinating enzymes. *Biochim Biophys Acta*, 2004. **1695**(1-3): p. 189-207.

222. Krappmann, D. and C. Scheidereit, A pervasive role of ubiquitin conjugation in activation and termination of IkappaB kinase pathways. *EMBO Rep*, 2005. **6**(4): p. 321-6.
223. Chen, Z.J., Ubiquitin signalling in the NF-kappaB pathway. *Nat Cell Biol*, 2005. **7**(8): p. 758-65.
224. Noels, H., et al., A Novel TRAF6 binding site in MALT1 defines distinct mechanisms of NF-kappaB activation by API2middle dotMALT1 fusions. *J Biol Chem*, 2007. **282**(14): p. 10180-9.
225. King, C.G., et al., TRAF6 is a T cell-intrinsic negative regulator required for the maintenance of immune homeostasis. *Nat Med*, 2006. **12**(9): p. 1088-92.
226. Yamamoto, M., et al., Key function for the Ubc13 E2 ubiquitin-conjugating enzyme in immune receptor signaling. *Nat Immunol*, 2006. **7**(9): p. 962-70.
227. Cannons, J.L., E.M. Bertram, and T.H. Watts, Cutting edge: profound defect in T cell responses in TNF receptor-associated factor 2 dominant negative mice. *J Immunol*, 2002. **169**(6): p. 2828-31.
228. Arch, R.H., R.W. Gedrich, and C.B. Thompson, Tumor necrosis factor receptor-associated factors (TRAFs)--a family of adapter proteins that regulates life and death. *Genes Dev*, 1998. **12**(18): p. 2821-30.
229. Kopp, E.B. and R. Medzhitov, The Toll-receptor family and control of innate immunity. *Curr Opin Immunol*, 1999. **11**(1): p. 13-8.
230. Yeh, W.C., et al., Early lethality, functional NF-kappaB activation, and increased sensitivity to TNF-induced cell death in TRAF2-deficient mice. *Immunity*, 1997. **7**(5): p. 715-25.
231. Nakano, H., et al., Targeted disruption of Traf5 gene causes defects in CD40- and CD27-mediated lymphocyte activation. *Proc Natl Acad Sci U S A*, 1999. **96**(17): p. 9803-8.
232. Tada, K., et al., Critical roles of TRAF2 and TRAF5 in tumor necrosis factor-induced NF-kappa B activation and protection from cell death. *J Biol Chem*, 2001. **276**(39): p. 36530-4.
233. Sun, L., et al., The TRAF6 ubiquitin ligase and TAK1 kinase mediate IKK activation by BCL10 and MALT1 in T lymphocytes. *Mol Cell*, 2004. **14**(3): p. 289-301.
234. Zhou, H., et al., Bcl10 activates the NF-kappaB pathway through ubiquitination of NEMO. *Nature*, 2004. **427**(6970): p. 167-71.
235. Zhang, S.Q., et al., Recruitment of the IKK signalosome to the p55 TNF receptor: RIP and A20 bind to NEMO (IKKgamma) upon receptor stimulation. *Immunity*, 2000. **12**(3): p. 301-11.
236. Tegethoff, S., J. Behlke, and C. Scheidereit, Tetrameric oligomerization of IkappaB kinase gamma (IKKgamma) is obligatory for IKK complex activity and NF-kappaB activation. *Mol Cell Biol*, 2003. **23**(6): p. 2029-41.
237. McAllister-Lucas, L.M., et al., CARMA3/Bcl10/MALT1-dependent NF-kappaB activation mediates angiotensin II-responsive inflammatory signaling in nonimmune cells. *Proc Natl Acad Sci U S A*, 2007. **104**(1): p. 139-44.
238. Chen, Y., et al., B cell lymphoma 10 is essential for FcepsilonR-mediated degranulation and IL-6 production in mast cells. *J Immunol*, 2007. **178**(1): p. 49-57.
239. Klemm, S., et al., The Bcl10-Malt1 complex segregates Fc epsilon RI-mediated nuclear factor kappa B activation and cytokine production from mast cell degranulation. *J Exp Med*, 2006. **203**(2): p. 337-47.
240. Ye, R.D., Regulation of nuclear factor kappaB activation by G-protein-coupled receptors. *J Leukoc Biol*, 2001. **70**(6): p. 839-48.
241. Klemm, S., et al., Bcl10 and Malt1 control lysophosphatidic acid-induced NF-kappaB activation and cytokine production. *Proc Natl Acad Sci U S A*, 2007. **104**(1): p. 134-8.

242. Wang, D., et al., Bcl10 plays a critical role in NF-kappaB activation induced by G protein-coupled receptors. *Proc Natl Acad Sci U S A*, 2007. **104**(1): p. 145-50.
243. Cummings, R., et al., Protein kinase Cdelta mediates lysophosphatidic acid-induced NF-kappaB activation and interleukin-8 secretion in human bronchial epithelial cells. *J Biol Chem*, 2004. **279**(39): p. 41085-94.
244. Shahrestanifar, M., X. Fan, and D.R. Manning, Lysophosphatidic acid activates NF-kappaB in fibroblasts. A requirement for multiple inputs. *J Biol Chem*, 1999. **274**(6): p. 3828-33.
245. Grabiner, B.C., et al., CARMA3 deficiency abrogates G protein-coupled receptor-induced NF-{kappa}B activation. *Genes Dev*, 2007. **21**(8): p. 984-96.
246. Gross, O., et al., Card9 controls a non-TLR signalling pathway for innate anti-fungal immunity. *Nature*, 2006. **442**(7103): p. 651-6.
247. Sagaert, X., et al., MALT1 and BCL10 aberrations in MALT lymphomas and their effect on the expression of BCL10 in the tumour cells. *Mod Pathol*, 2006. **19**(2): p. 225-32.
248. Ye, H., et al., High incidence of t(11;18)(q21;q21) in Helicobacter pylori-negative gastric MALT lymphoma. *Blood*, 2003. **101**(7): p. 2547-50.
249. Ye, H., et al., MALT lymphoma with t(14;18)(q32;q21)/IGH-MALT1 is characterized by strong cytoplasmic MALT1 and BCL10 expression. *J Pathol*, 2005. **205**(3): p. 293-301.
250. Kuo, S.H., et al., Nuclear expression of BCL10 or nuclear factor kappa B predicts Helicobacter pylori-independent status of early-stage, high-grade gastric mucosa-associated lymphoid tissue lymphomas. *J Clin Oncol*, 2004. **22**(17): p. 3491-7.