Index

Page numbers followed by an f denote a figure on the corresponding page.

A

A1, NOXA neutralization of, 203 ABC1, 160 ABC7, 160 ABT-737, 226, 226f Accidental cell death, 121 Acinus, 21 Actin cytoskeleton, 162, 165f Actin polymerization, 22 Active cell death, 1, 4-5 Active site, caspase, 11 Acute lymphoproliferative syndrome (ALPS), 95, 129 Acute myelogenous leukemia, 211 Acylation step of caspase cleavage, 12, 12f Adapter proteins, 5-6, 32-33, 34f Adaptive immune response, consequences of dying cells for, 169-170 Adenosine nucleotide transporter (ANT), 55, 56f Adenosine triphosphatase type 11C (ATP11C), 22, 23f AFR-BP1, 200 AIF (apoptosis-inducing factor), 54-55, 54f AIM2, 113, 113f AKT, 76-77, 79, 79f, 142, 196, 208 Alcoholic cirrhosis, 228 ALPS (acute lymphoproliferative syndrome), 95 Aminophospholipid translocase, 151 Amphibian metamorphosis, 186, 186f AMPK, 140, 142 Amylotrophic lateral sclerosis (ALS), 132

Annexin V, detecting phosphatidylserine by use of, 152-153, 152f-153f Anoctamin-6, 154 Anoikis, 198 BIM and BMF mediation of, 78 pathway of, 78f Antagonistic pleiotropy, 196, 196f Anthracyclines, 216 Anthrax, 112 Anti-apoptotic BCL-2 proteins BH3 profiling and, 226-227 cell proliferation and, 196-198 controlled by signaling, 79-80, 79f inactivation by NOXA, 203 inactivation by PUMA, 203 inhibition for cancer therapy, 226-227 models of BH3-only protein function in apoptosis, 71-73, 73f MOMP prevention by, 64-68, 66f-67f p53 sequestered by, 204-205, 205f Antibody diversity, 198 Antigen presentation, 169-170 AP-1, 97 APAF1 (apoptotic protease activating factor-1), 208, 213 caspase-9 activation, 47-48, 48f-49f CICD and, 52-53, 53f cytochrome c and, 48, 58–59, 146 domains of, 47-48, 48f effect of deletion in, 49, 50f, 99, 192 homologs, 56-59, 57f, 180, 182

264 INDEX

APAF1 (apoptotic protease activating factor-1) (Continued) in neuron selection, 187 NLRs (Nod-like receptors) and, 115-116, 115f vertebrate limb development and, 185 APAF1-related killer (ARK), 56-57, 57f-58f, 59, 182, 183f APAFs (apoptotic protease activating factors), 56-59, 57f, 80 APO-1, 89, 90f APO-2L, 90, 90f Apoptosis, 1 as an Achilles' heel of cancer, 209 bottom-up view of, 5-6 caspases involved in (see Caspase(s)) compensatory proliferation induced by, 176 connections to cell cycle, 195-197 cytotoxic lymphocyte induction of, 29-31, 29f-30f death receptor pathway, 89-102 in Drosophila metamorphosis, 182-183, 183f evolution of, 116 features of, 2, 3f "find-me" signals, 150-151, 151f HMGB1 oxidation in, 170, 171f importance in mammalian development, 192-193 inducers of, 8, 10 inhibition of inflammation, 168-169, 168f in nematode development, 180-181, 181f in neuron selection, 187-188 p53 and, 200, 202-208, 203f, 207f pathways, 5-10, 33f (see also specific pathways) as cancer cause, 212-214, 213f cross-talk, 10 death-receptor, 6, 8, 8f inflammasome, 8, 9f, 10 mitochondrial, 6, 7f sublethal engagement, 213, 213f phosphatidylserine externalization, 151-153 proliferation and, 195-198 removal of apoptotic cells, 10 selection in development and, 187-191 "stay-away" signals, 155 TRAIL and, 95-96 in vertebrates development, 184-187, 185f-186f Apoptosis-inducing factor (AIF), 54-55, 54f Apoptosomes, 48-49, 48f, 56-59, 57f-58f, 105 Apoptotic bodies, 2

Apoptotic protease activating factors (APAFs), 56-59, 57f, 80. See also APAF1 (apoptotic protease activating factor-1) APP. 90, 90f. 214 ARF, 199-200, 199f, 227 ARK (APAF1-related killer), 56-57, 57f-58f, 59, 182, 183f ASC, 106-107, 106f-107f NLRC4 binding, 112 NLRP2 and, 113 NLRP3 binding, 109, 110f, 111 ASNT (adenosine nucleotide transporter), 55, 56f ATG5, 183 ATG7, 141, 183 ATG13, 140, 142 Atherosclerosis, 114 ATM, 200, 207 ATP11C (adenosine triphosphatase type 11C), 22, 23f ATR, 200 Autoimmune diseases, 174, 195 Autoimmunity, 1 Autophagic cell death, 169 cancer and, 214 in Drosophila, 183-184, 183f features of, 2-3, 3f Autophagolysosomes, 139, 139f, 143, 143f Autophagosomes, 139, 139f, 141, 142f, 145f, 146, 183f Autophagy, 2, 137-147 cancer and, 214 canonical, 171, 173 in Drosophila, 164, 183-184, 184f mammalian, 140-141, 141f-142f mitochondria, removal of, 87-88, 87f-88f mitophagy, 143-144, 144f-145f, 146 pathway, 139-143 engagement of, 139-143 hierarchical action, 139, 140f as survival mechanism, 138-139 Autopods, 184, 185f

В

Bacterial sepsis, treated with caspase inhibitors, 228 Bacterial toxins, 83–84, 84F, 112 Baculovirus, 39, 41, 43–44 Baculovirus IPA repeat (BIR), 41–42, 43f BAD, 73f, 211

as growth factor signaling sensor, 77, 77f in neuron selection, 187 role in regulating glucose metabolism in mammals, 85 BAI1, 157, 158f, 162, 164f BAK, 99, 100f, 221-222 activation, 66f, 68-72, 72f anti-apoptotic proteins action on, 64-66, 66f BH domain organization, 62f calcium homeostasis and, 85 cancer therapy drugs to activate, 227 effect of deletion of, 192 as effector of MOMP, 62-64 inhibition, 66f mitochondrial dynamics and, 86 in neuron selection, 187 nonapoptotic cell death in intestines lacking, 147, 148f pharmacological inhibition of activation, 229-230 PUMA activation of, 203 structure of, 65f in vertebrate limb development, 185, 185f Basigin, 23, 23f BAX, 99, 100f, 221-222 activation, 68-72, 69f-72f anti-apoptotic proteins action on, 64-66 BH domain organization, 62f calcium homeostasis and, 85 cancer therapy drugs to activate, 227 effect of deletion of, 192 as effector of MOMP, 62-64, 63f mitochondrial dynamics and, 86 in neuron selection, 187 nonapoptotic cell death in intestines lacking, 147, 148f as p53 target, 203-205, 205f pharmacological inhibition of activation, 229-230 PUMA activation of, 203 structure of, 65f, 84f structure of activated, 69f-70f in vertebrate limb development, 185, 185f BCL-2 autophagy regulation, 142 BAD specificity for, 211 cell proliferation and, 197-198, 197f-198f constitutive expression of, 198 in lymphocyte selection, 190, 191f Venetoclax binding to, 226

BCL-2 homology (BH) domains, 61, 62f BCL-2 proteins, 6, 7f, 61-88. See also specific proteins amphibian metamorphosis and, 186 antagonistic pleiotropy regulated by, 196 anti-apoptotic BH3 profiling and, 226-227 cell proliferation and, 196-198 controlled by signaling, 79-80, 79f inactivation by NOXA, 203 inactivation by PUMA, 203 inhibition for cancer therapy, 226-227 models of BH3-only protein function in apoptosis, 71-73, 73f MOMP prevention by, 64-68, 66f-67f p53 sequestered by, 204-205, 205f bacterial toxin and, 83-84, 84f BH domains, 61, 62f BH3-only proteins BAX and BAK activation, 68-72 MOMP and apoptosis promoted by, 66-73 as stress sensors, 74-79 BID as protease sensor, 75, 76f BIM and BAD as growth factor signaling sensors, 75-77, 76f-77f BIM and BMF as anoikis mediators, 78 BOK regulation, 73-74, 74f mitochondrial pathway of apoptosis, 61-88 MOMP and, 220-222, 221f-222f in nonhuman animals, 80-82, 81f-82f roles in cells, 84-88 apoptosis, 61-84 calcium regulation, 85 mitochondrial dynamics, 85-86, 87f removal of mitochondria, 87-88, 88f viral, 82-83, 82f-83f BCL-xL, 226 Beclin-1, 87-88, 88f, 140, 141f, 142-143, 214 β1-GP1, 155, 156f BH3 mimetics, 209-210, 209f, 226, 226f BH3 profiling, 210-212, 210f-211f, 226-227 BH3-only proteins, 226 autophagy and, 142-143 BAX and BAK activation, 68-72 BH3 profiling, 210-212, 210f-211f EGL1, 180-181, 181f in lymphocyte selection, 189-191, 191f mammalian breast development and, 186 MOMP and apoptosis promoted by, 66-73 in neuron selection, 187

266 INDEX

BH3-only proteins (Continued) as stress sensors, 74-79 BID as protease sensor, 75, 76f BIM and BAD as growth factor signaling sensors, 75-77, 76f-77f BIM and BMF as anoikis mediators, 78 vertebrate limb development and, 185 BID, 99-100, 100f activation by caspase-1, 114 BAX/BAK activation, 68-69, 71f caspase-2 and, 116 as p53 target, 203 pathway for cleavage and activation of, 76f as protease sensor, 75 structure of, 75f BIM, 101, 209 anoikis mediated by, 78 BAX/BAK activation, 68-69, 71f, 73f as growth factor signaling sensor, 75-77 in lymphocyte selection, 189-191, 191f mammalian breast development and, 186 in neuron selection, 187 in vertebrate limb development, 185, 185f "Bind-me" signals bridging molecule recognition of, 155-156, 156f-157f on dying cells, 151, 153 in other animals, 159-160, 161f phagocyte receptors for, 157-159, 158f-159f BIR (baculovirus IPA repeat), 41-42, 43f Bistability in cell death pathways, 220-223 BCL-2 proteins and MOMP, 220-222, 221f-222f caspase activation and inhibition, 222-223 in Drosophila, 224, 224f in nematodes, 223, 223f Blebbing, plasma membrane, 2, 21-22, 22f BMF anoikis mediated by, 78 mammalian breast development and, 186 in vertebrate limb development, 185, 185f BNIP3, 87, 88f, 144 BOK, 208 effect if deketuib if, 192 as effector of MOMP, 63 regulation of, 73-74, 74f Bone morphogenetic proteins (BMPs), 184-185 BR-C, 182-183, 183f Bridging molecules binding to dying cells, 155-156, 156f-157f phagocyte receptors for, 157-159, 158f-159f

Buffy, 81, 86 Button experiment, 230–231, 231f

С

CAD (caspase-activated DNase), 20-21, 21f, 24, 166, 213-214, 214f Cadherins, 174 Caenorhabditis elegans BCL-2 proteins, 80-81, 81f-82f "bind-me" signals, 159-160, 161f caspase activation, 56-57, 57f caspases in, 14, 24-25, 25f, 36 cell death in development, 179-182, 180f-182f developmental plan, 179-180, 180f engulfment in, 162 mitochondrial fragmentation, 86 neurosecretory motor neuron (NMN) pathway of apoptosis in nematodes, 223, 223f p53 protein, 207, 207f Calcineurin, 136 Calcium activation of NADPH oxidase, 133, 134f, 135f lymphocyte selection and, 189, 191f mitochondrial permeability transition (MPT) and, 135, 136f Calcium homeostasis, role of BCL-2 proteins in, 85 Calcium pyrophosphate dihydrate (CPPD), 110 Calpain, 134, 135f Calreticulin, 215-216 exposure on surface of dying cells, 151, 159, 170 immunogenic cell death and, 170 LRP1 interaction, 159-159 Cancer, 1-2, 195-216 apoptosis as an Achilles' heel of, 209-210 apoptotic pathways as cause of, 212-214, 213f autophagic cell death and, 214 autophagy and, 214 BH3 profiling, 210-212, 210f-211f collateral tissue damage during therapy, 212 defective p53 and, 201-202 drugs promoting cell death, 225, 226f, 227f, 228 eliminated by p53, 202 entosis, 215 ferroptosis and, 214-215 as gene therapy risk, 224-225 iatrogenic, 213-214 immunogenic cell death, 215-216

model of BCL-2 protein interactions in MOMP predicting outcome in patients, 222, 222f necroptosis and, 214 "primed for death" status of, 210-212 rarity, reasons for, 195 therapies designed to trigger apoptosis, 174 tumor suppressors, 198-199, 208 Canonical autophagy, 171, 173 CARD. See caspase-recruitment domains (CARDs) Cardiac glycosides, 216 Caspase-1, 169, 228. See also Inflammatory caspases activation, 36-37 by inflammasomes, 104-106, 105f by NLRs, 110-113, 110f by TLRs, 107 ASC and, 106-107, 106f BID activation by, 114 CARD domain, 107 domain structure, 14f fibrils in inflammasomes, 107, 107f, 108f gasdermin D activation by, 114 inhibition of, 43 noncanonical secretion and, 114 pyroptosis, 37, 38f Caspase-2, 228. See also Initiator caspases action on a tumor suppressor, 208 activation of, 31, 38, 116-120, 117f, 119f CDK1 and, 147 domain structure, 14f functions of, 38 p53 activation by, 205-206, 206f Caspase-3, 13. See also Executioner caspases acinus cleavage by, 21 activation of, 29 blockage of XIAP inhibition of, 52f deficient mice, 25, 26f DNA fragmentation and, 20-21, 21f domain structure of, 14f inhibition of, 42, 43f mice deficient in, 49, 50f mutations in human cancers, 208 in neuron selection, 187 substrate preference, 15, 17, 17f Caspase-4. See also Inflammatory caspases adapterless activation of, 103-104 caspase-1 activation, 37 domain structure, 14f pyroptosis, 37

Caspase-5. See also Inflammatory caspases adapterless activation of, 103-104 caspase-1 activation, 37 domain structure, 14f pyroptosis, 37 Caspase-6, 13. See also Executioner caspases activation of, 29 cleavage of lamins by, 21 domain structure of, 14f substrate preference, 17f Caspase-7, 13. See also Executioner caspases acinus cleavage by, 21 activation of, 27-29, 28f, 37 blockage of XIAP inhibition of, 52f domain structure of, 14f structures of inactive and active, 27, 28f substrate preference, 15, 17, 17f Caspase-8. See also Initiator caspases activation of, 31, 35, 105 death effector domain (DED), 92, 93f in death receptor pathway of apoptosis, 92-96, 94f, 98-102, 100f-101f deficiency and embryonic lethality, 192 domain structure, 14f FLIP interaction with, 35 inhibition of, 43 MALT heterodimer with, 35 mutations in human cancers, 208 necroptosis inhibition by, 127-129, 128f RIPK1 cleaved by, 12/8f, 127-128 Caspase-9, 182, 208, 213. See also Initiator caspases activation of, 31, 34, 35f, 105 amphibian metamorphosis and, 186 blockage of XIAP inhibition of, 52f deficient mice, 25 domain structure, 14f effect of deletion in, 192 IAP-binding sequence, 59, 60f inhibition of, 42 mice deficient in, 49, 50f in mitochondrial pathway of apoptosis, 47-49, 47f, 49f in neuron selection, 187 suicide switch in engineered T cells, 225f vertebrate limb development and, 185 Caspase-10. See also Initiator caspases DISC, 93 domain structure, 14f

268 INDEX

Caspase-11 adapterless activation of, 103-104 caspase-1 activation, 37 pyroptosis, 37 Caspase-12, 37 Caspase(s), 11–26. See also specific caspases activation, 27-38 adapterless, 103-104 ASC and, 106-107, 106f caspase-2, 38 death folds and, 32-33, 34f death receptor pathway, 89 by dimerization, 34-35, 35f by dimerization with other molecules, 35-36 in Drosophila, 57-58, 58f executioner caspases, 27-29, 28f by induced proximity, 103-104, 225 by inflammasomes, 104-106, 105f inflammatory caspases, 36-37, 38f initiator caspases, 31-32, 32f, 34 LPS, 104, 105f, 111 by mitochondria, 47-49, 47f-49f, 51 in nematodes, 56-57, 57f in other animals, 36, 38-39, 39f active site, 11 bistability in activation and inhibition, 222-223 caspase-12 and beyond, 38-39, 39f CED3, 180-181, 181f-182f cleavage sites, 11, 15-17, 15f, 18f, 19t in Drosophila metamorphosis, 182, 183f-184f executioner, 5-6, 6f, 8, 8f inhibition, 39-43 cancer therapy and, 214 synthetic, 40-41, 40f-41f viral, 39-43 initiator, 5-6, 6f, 8, 8f as killers, 24-26, 25f-26f LPC production and, 150, 151f mechanism of action, 11-13, 12f mitochondrial effects of executioner caspases, 23 - 24in nematodes, 180-181, 181f-182f in neuron selection, 187 nuclear events mediated by, 20-21, 21f in other animals, 14, 15f PGE₂ production and, 176 pharmacologic inhibition, 228, 229f plasma membrane events caused by, 21-22, 22f-23f

prodomain structure, 13, 14f substrate for executioner caspases, 18, 20 substrate preferences, 15-17, 17f-18f, 19t types of, 13 Caspase-activated DNase (CAD), 20-21, 21f, 24, 166, 213-214, 214f Caspase-independent cell death (CICD), 52-55, 53f-54f Caspase-recruitment domains (CARDs), 33, 47-48, 47f-49f, 56, 57f, 91, 91f of ASC, 106-107, 106f-107f of caspase-2, 116-117 LPS binding to, 104 of NLRC4, 112 Cavitation, 185-186, 186f C3b, 156, 157f, 158 CD31, 154, 154f CD36, 158, 160, 183 CD47, 154, 154f CD68, 158 CD91, 158 CD95, 89, 90f, 228 apoptosis triggered by, 91-95, 94f death domain (DD), 92f defects and acute lymphoproliferative disease, 129 defects in signaling, 95, 96f FADD and, 92-93, 92f, 95-96 ischemia-reperfusion injury and, 136 p53 induction of expression of, 203 CDC50A, 22, 23f CDK1 (cyclin-dependent kinase 1), 147 CD95-L, 90, 90f, 91, 95, 98, 129 CED1, 159, 161f, 162, 163f, 184 CED2, 162 CED3, 14, 15f, 25, 25f, 36, 56-57, 57f, 164, 180–181, 181f–182f CED4, 56-57, 57f, 80-81, 81f-82f, 86, 180-181, 181f-182f CED5, 162 CED6, 162, 163f CED7, 163f CED8, 151 CED9, 57, 80-81, 81f-82f, 86 CED10, 162, 163f CED12, 162 Cell cycle, 118-120, 119f, 195 Cell death. See also Apoptosis; Necroptosis accidental, 121 active, 1, 4-5

autophagic, 2-3, 3f, 169, 183-184, 183f, 214 bistability in pathways, 220-223 caspase-independent cell death (CICD), 52-55, 53f-54f consequences, 149-177 definition of, 9 in development, 179-193 as essential, 1-2 immunogenic, 215-216 limiting, 228-230 nonapoptotic pathways, 121-148 reasons for, 1-2 types of, 2-4, 3f-4f Cell death by design, 224-228 drugs promoting cell death, 225, 226f, 227f, 228 suicide switches, 224-225, 225f Cell division and stochastic death, 218f Cellular states, models of death and, 217-220 Centrosomes aberrant, 205-206, 206f caspase-2 activation, 119, 119f PIDD localization to, 118-119, 118f CEP-1, 207, 207f CES1, 180-181, 181f Chk1, 200 Chk2, 200 Chloroquine, 214 Cholesterol management, 166, 167f Chromatin condensation, 21 Chromatin fragmentation. See DNA fragmentation Chronic hepatitis, 228 Chronic lymphoblastic leukemia, 17p-deleted, 226 CIAPs, 96-97, 227 CICD (caspase-independent cell death), 52-55, 53f-54f Cisplatin, 215 c-Jun amino-terminal kinase (JNK), 77, 97 Clearance of dying cells "bind-me" signals, 151, 153 bridging molecules, binding of, 155-156, 156f-157f in C. elegans, 159-160, 161f "clear-me" process, 166 disease and, 173-174, 174f "don't-eat-me" signals, 153-155 in Drosophila, 160, 161f "eat-me" signals, 160, 162, 163f-165f engulfment promotion of cell death, 162, 164, 166 entosis, 174-175, 175f

"find-me" signals, 150-151, 151f LC3-associated, 170-173, 172f-173f, 175, 175f phagocyte receptors, role of, 157-159, 158f-159f "tether and tickle" model, 156-157 waste management, 149-150, 166, 167f "Clear-me" process, 166 Cleft palate, 192 c-Myc, 212, 215 Cnidaria, 36 Colicins, 83, 84f Combinatorial peptide libraries, identifying caspase specificity with, 15-17 Compensatory proliferation, 176-177, 176f Complement proteins, 156, 157f, 158 Cornification, 4 CPPD (calcium pyrophosphate dihydrate), 110 C1q, 156, 157f, 158 CRKII, 162 Croquemort, 160, 161f, 183-184 Cross talk, 10 Cross-priming, 216 Cyclin-dependent kinase 1 (CDK1), 147 Cyclophilin D, 55-56, 56f, 135-136, 229 Cyclosporin A, 136, 229 CYLD, 98, 98f, 128 Cysteine protease, 11 Cystine, 137, 138f, 204 Cystine/glutamate antiporter, 137, 138f Cytochrome c, 6, 7f, 48-49, 49f, 61, 116, 192, 210 APAF1 activation, 48, 58-59, 146 MOMP and, 50-51, 50f Cytokines. See also specific molecules adaptive immune response and, 170 caspase-1 processing of precursors, 36-37 innate immune system and, 167-169 Cytokinesis, failure of, 119f, 120 Cytoskeleton anoikis and, 78 rearrangement of the actin, 162, 165f Cytotoxic lymphocytes, 29-31, 29f-30f, 216

D

DAI, 124, 125f Damage-associated molecular patterns (DAMPs), 106 as "find-me" signals, 150–151 as maturation signals to dendritic cells, 170

270 INDEX

Damage-associated molecular patterns (DAMPs) (Continued) NLRs and, 109, 109f oxaliplatin-induced production of, 215 release by dying cells, 150-151, 167 Damm, 14, 15f Darwin, Charles, 231 DBorg1, 81 DBorg2, 81 DCP1, 14, 15f, 36 Deacylation step of caspase cleavage, 12, 12f Death, definition of, 9 Death domain, 90-92, 91f-92f, 96, 98, 117 Death effector domains (DEDs), 32-33, 91-94, 91f, 93f-94f, 102 Death fold, 32-33, 34f, 109 Death ligands, 89-91, 90f-91f Death receptor pathway of apoptosis, 6, 8, 8f, 89-102 CD95-induced pathway, 91-95, 94f mitochondrial pathway engaged by, 99-101 in nonhuman animals, 102 sublethal engagement of, 213, 213f TNFR1 and, 96-99 TRAIL and, 95-96 triggers of, 8, 10 Death receptors, 6 necroptosis caused by, 123-124, 124f in other animals, 102 p53 induction of expression of, 203 as subset of the tumor necrosis factor receptor family, 89-91, 90f-91f Death-inducing signaling complex (DISC), 93, 105, 128 Death-receptor-mediated engagement of necroptosis, 228 DeBCL, 81, 86 Decapentaplegic, 176 Decay, 14, 15f Dendritic cells, 150, 168-170, 171f-172f Deubiquitinase (DUB), 128 Development, cell death in, 1, 45, 179-193 bistability in cell death pathways, 223-224 in Drosophila, 182-184, 183f-184f, 224, 224f importance in mammals, 192-193 in nematodes, 179-182, 180f-182f selection, 187-191 lymphocytes, 188–191, 190f–191f negative selection, 189-191, 190f-191f neurons, 187-188, 188f

in vertebrates, 184-187, 185f-186f Developmental signals, mitochondrial pathway and, 8 **DFADD**, 102 DFF45, 20. See also iCAD Diablo, 51 DIAP1 (Drosophila IAP1), 41-43, 42f, 57, 58f, 59, 59f DIAP inhibitors, 182 Digits in the vertebrate limb, development of, 184-185, 184f-185f Dimerization activation of initiator caspases by, 34-35, 35f initiator caspases can be activated by dimerization with other molecules, 35-36 Diphtheria toxin, 83, 84f Direct activator/derepressor model, 72-73, 73f, 221–222, 221f DISC (death-inducing signaling complex), 93, 105, 128 Disease cell death as component of, 1 clearance and, 173-174, 174f inflammasomes in, 114-115 necroptosis and, 131-132, 132f DNA, cleavage of, 2 DNA damage apoptosis triggered by, 133 autophagy caused by, 143 p53 induction by, 200-201, 200f, 207, 207f DNA fragmentation, 18, 20-21, 21f, 54, 54f, 166 DNA fragmentation factor of 40 kDa (DFF40), 20. See also CAD DNA repair, 132 DNAse II, 166 DNFA5, 122-123 DOCK180, 162, 165f Domain structure of caspases, 13, 14f "Don't-eat-me" signals on cells, 153-155 DR3 (death receptor 3), 89, 90, 90f DR4 (death receptor 4), 89, 90f DR5 (death receptor 5), 89, 90f, 96, 203 DR6 (death receptor 6), 89, 90, 90f, 214 DRAM, 146 Draper, 162, 164, 184 Dredd, 36, 37, 102 Drice, 14, 15f, 36, 182, 183f Dronc, 25f, 36, 41, 56-57, 58f, 59, 182, 183f

INDEX 271

Drosophila ARK, 56-57, 57f-58f autophagy in, 164 BCL-2 proteins, 81 "bind-me" signals, 160, 161f caspase activation in, 57-58, 58f caspases in, 14, 15f, 25, 25f, 36, 37 compensatory proliferation in, 176 developmental apoptosis in, 224, 224f dFADD, 102 DIAP1, 41-43, 42f, 57, 58f, 59, 59f Dredd, 102 Dronc, 56-57, 58f, 59 engulfment in, 162 metamorphosis, 145, 182-184, 183f-184f mitochondrial fragmentation, 86 p53-like protein, 206-207, 207f DUB (deubiquitinase), 128 Dying cells. See also Clearance of dying cells adaptive immune response and, 169–170 "bind-me" signals on, 151, 153 innate immune response induced by, 166-169 loss of "don't-eat-me" signals, 154 as signals, 10 Dynein motor complexes, 78

E

E74, 182-183, 183f E93, 182-183, 183f "Eat-me" signals, 160, 162, 163f-165f Ecdysone, 182-183, 183f, 224 Echinoderm, caspases in, 36 EGL1, 81, 81f-82f, 86, 180-181, 181f, 207 ELMO, 162, 165f Embryo implantation, 187 Endopeptidases, 11, 30 Endoplasmic reticulum-associated degradation (ERAD), 74, 74f Endosymbiosis, 45, 83 Engulfment. See also Phagocytosis cell death promoted by, 162, 164, 166 "eat-me" signals, 160, 162, 163f-165f entosis, 174-175, 175f Entosis, 174-175, 175f, 187, 215 Epithelial cells, entosis and, 174 ERAD (endoplasmic reticulum-associated degradation), 74, 74f Erastin, 227 ERK, 77

E3-ubiquitin ligase, 42, 200 Evolution, 231 Excitotoxicity, 133, 134f Executioner caspases, 5-6, 6f, 8, 8f activation of, 27-29, 28f active sites of, 27 ATP11C cleavage by, 22 CED3 as, 164 Drice, 182, 183f induce production of the "find-me" signal LPC, 151f inhibition of, 42 key substrates for, 18, 20 as killer, 24-25 mitochondrial effects of, 23-24 pharmacologic inhibition of, 214 phospholipase A₂ activation by, 212 proforms of, 27-29, 28f structure of, 13-14, 14f-15f

F

FADD (FAS-associated death domain protein), 92-93, 92f-94f, 95-96, 98, 100f, 128-129, 128f deficiency and embryonic lethality, 192 dFADD, 102 hypothetical connection between autophagy and necrosis, 146, 147f RIPK1 binding, 129, 131 Fas, 89, 90f Fas-L, 90, 90f, 229f FBW7, 79 Ferroptosis, 137, 138f cancer and, 214-215 ferrostatins, 229 induced pharmacologically, 227-228 p53 sensitizes cells for, 204, 214 Ferrostatins, 229 "Find-me" signals, 150-151, 151f FK506, 225 FK-binding proteins (FKBPs), 225 FLICE-like inhibitory protein (FLIP), 35, 93-95, 94f, 97.99 deficiency and embryonic lethality, 192 FLIPs, 95 necroptosis inhibition by, 127-129, 128f v-FLIP, 95 Flippase, 22-23, 23f FOIP200, 140, 141f

Follicular lymphoma, 198 Form, created by death, 179 FOXO3a, 76, 76f

G

Gas6, 155, 156f, 157, 158f, 168 Gasdermin D, 104, 105f, 111, 114, 123 Gasdermin E, 122–123 Gelsolin, 22 Gene therapy, 224-225 Genetic engineering, introduction of suicide switches and, 224-225, 225f Glutamate, neuron necrosis and, 133 Glutathione, 137, 138f, 204, 215 Glycogen synthase kinase, 79-80, 79f Gout, 110, 110f, 114 GPX4, 137, 138f, 228 Graft rejection, 173 Granzyme B, 30-31, 30f, 43 Granzymes, 30-31, 30f Grim, 59, 60f, 224 Growth factor signaling BIM and BAD as sensors for, 75-76, 76f-77f MVL-1 stability regulated by, 79-80, 79f GULP, 162, 163f

Н

Heart attacks, 134 Hermaphrodite-specific neurons (HSNs) cell death, 180–181, 181f Herpes viruses v-FLIP, 95 Hid, 59, 60f, 182, 183f, 207, 224 High-mobility group protein B1 (HMGB1), 167, 170, 171f HLH2, 180–181, 181f HLH3, 180–181, 181f Homeostasis, cell death essential to, 1 Homeostatic proliferation, 177 HRK, 187, 211 Human genome, 230 Hydroxyl radicals, 24

I

IAP-binding sequences, 59, 60f IAPs caspase inhibited by, 223 inhibition of, 51

by caspase, 223 in Drosophila apoptosis, 59, 59f ICAD, 20, 21f, 24, 166, 213 Immune checkpoints, 216 Immune system development, 187, 188-191, 190f, 191f Immunogenic cell death, 215-216 Induced proximity model, 31, 103-104 Infection, cell death induced by, 8, 9f, 10 Inflammasomes, 8, 9f, 10 activation, 166, 169 AIM2, 113, 113f ASC and, 106-107, 106f-107f caspase-1 activation by, 104-106, 105f in disease, 114-115 general structures of, 107f NLRs (Nod-like receptors) and, 109-116 disease and, 114-115 NLRC4, 111-112, 112f NLRP1, 112-113, 113f NLRP2, 113 NLRP3, 109-111, 110f, 114-115 noncanonical, 104 PAMP/DAMP triggering formation of, 106 TLRs (Toll-like receptors) induction of, 107-108 triggers of, 10 Inflammation cell death effect on, 169, 169f inhibition by apoptotic cells, 168-169, 168f necrosis and, 150 response in apoptosis, 2 Inflammatory caspases function in secretion and cell death, 36-37 structure of, 13, 14f Inhibitor of apoptosis protein, 39, 41-44, 42f-44f Initiator caspases, 5-6, 6f, 8, 8f activated by induced proximity, 225 activation of, 31-32, 32f, 34 by dimerization, 34–35, 35f by dimerization with other molecules, 35-36 inactive form, 31 structure of, 13-14, 14f-15f Innate immune system, impact of dying cells on, 166-169 Inositol (1,4,5)-triphosphate (IP3), 85 Integrins, 157, 158f Intein, 118 Interleukin-1, 36-37, 104, 114, 115, 169 Interleukin-18, 36-37, 104, 114, 115, 169

Ischemia-reperfusion injury, 133–137, 135f–136f, 138f, 229

J

JNK, 101, 189, 191f Just So Stories (Kipling), 45

Κ

Kaposi sarcoma virus vBCL-2, 83f Kipling, Rudyard, 45 *KRAS*, 215

L

Lactadherin, 155, 156f Lactoferrin, 155 Lamins, 21 LC3, 141, 142f LC3-associated phagocytosis and clearance, 170-173, 172f-173f LE bodies, 173, 174f Leukemia, 211-212 Leukotriene-B4, 169 Li-Fraumeni syndrome, 201 Limb development, in vertebrates, 184-185, 184f-185f Linker cell, 180, 180f Lipid peroxidase, 228 Liver diseases, RIPK3 and, 131-132 LOX1, 158 LPS, caspase activation by, 104, 105f, 111 LRP1, 158, 162 LXR (liver X receptor), 166, 167f Lymphoaccumulative disease, 95, 96f Lymphocytes apoptosis and selection, 188-191, 190f-191f cytotoxic, 29-31, 29f-30f, 216 Lymphoma, 204, 226 Lysosomes, 139, 141, 146, 162, 165f, 166

М

Macrophages, 150, 169, 171, 173, 177 inflammatory response and, 169, 169f recruitment by "find-me" signals, 150, 151f, 155 TGF-β production by, 168 TIM4 deficient mice and, 157–158 tingible body macrophage (TBM), 155, 155f

in wound healing, 176 Major histocompatibility complex (MHC) molecules, 169 MALT, 35 Mammalian autophagy, 140-142, 141f-142f Mammalian breast, 185-186 Mannose-binding lectin (MBL), 155-156, 156f MAP kinases, 77 MCL-1, 66, 67f, 68, 77, 226 mammalian breast development and, 186 NOXA neutralization of, 211 stability regulation by growth factor receptor signaling, 79-80, 79f TCTP binding to, 200 MDM2, 199-200, 204-205, 205, 206f, 223, 227 Mer, 157-158, 158f, 168, 168f Metamorphosis, 179, 224 amphibian, 186, 186f in Drosophila, 145, 182-184, 183f-184f Metastasis, 214 MFGE8, 155, 156f, 157, 158f MFN2, 144 MHC (major histocompatibility complex) molecules, 169 Michelangelo, 179 Milk fat globulin-E8, 155, 156f "Minority MOMP," 213, 213f Mitochondria autophagy of, 143-144, 144f-145f, 146 fragmentation of, 86 functions of, 45 necrosis, role in, 135 NLRP3 inflammasome and, 111 origins of, 45-47, 46f removal of, 87-88, 87f-88f Mitochondrial dynamics, influenced by BCL-2 proteins, 85-86, 87f Mitochondrial outer membrane permeabilization (MOMP), 6, 49-56, 60, 228 BAX and BAK as effectors of, 62-64, 63f-64f, 68-72, 71f BH3 profiling and, 210f-211f bistability and, 220-222 caspase-independent cell death (CICD), 52-55, 53f-54f cytochrome c release, 50-51, 50f death receptor signaling, 99-100, 100f-101f direct activator/derepressor model, 221-222, 221f minority, 213, 213f

274 INDEX

Mitochondrial outer membrane permeabilization (MOMP) (Continued) mitochondrial permeability transition, 55-56, 56f in neuron selection, 187 neutralization model, 220-223, 221f p53 and, 203, 205, 205f pharmacological inhibition of activation, 229-230 prevention by anti-apoptotic BCL-2 proteins, 64-66, 66f-67f promotion by BH3-only proteins, 66-73 BAX and BAK activation, 68-72 direct activator/derepressor model, 72-73, 73f neutralization model, 72, 72f protein release with, 51-52, 52f Mitochondrial pathway of apoptosis, 6, 7f, 45-60 amphibian metamorphosis and, 186 apoptosomes in animals, 56-59, 57f-58f BCL-2 protein family, 61-88 cancer therapy and, 211 caspase activation, 47-49, 47f-49f, 51 caspase-independent cell death (CICD), 52-55, 53f-54f death receptor signaling engagement of, 99-101 disruption of mitochondrial outer membrane, 49-51 importance in mammalian development, 192 mitochondrial outer membrane permeabilization (MOMP), 49-56, 50f, 52f, 60 mitochondrial permeability transition, 55-56, 56f in neuron selection, 187-188 triggers of, 8 in vertebrate limb development, 185 Mitochondrial permeability transition (MPT), 55-56, 56f, 135-136, 136f, 229 Mitofusin-2, 86 Mitophagy, 143-144, 144f-145f, 146 Mitotic catastrophe, 147-148, 148f MLKL (mixed-lineage kinase domain-like protein), 125-127, 126f, 129, 132, 151 development in deficient mice, 193 inhibition by necrosulfonamide, 229 Models of death, cellular states and, 217-220 MOMP. See Mitochondrial outer membrane permeabilization Morphological changes associated with apoptosis, 2. 3f

Mouse double minute 2 (MDM2), 199–200, 204–205, 205, 206f, 223, 227 MPT (mitochondrial permeability transition), 55–56, 56f, 135–136, 136f, 229 MTOR, 140, 142, 143f MULE, 80, 200 Mutations, cancer and, 195, 199, 201, 208, 213 Myc, 195–197, 196f–197f, 201, 204, 208–209

Ν

NACHT domain, 48, 48f-49f, 115, 115f NAD⁺, 132–133 NADPH, 137 NADPH oxidase, 133-134, 134f135f NAIP 112 Natural killer cells, 29 Navitoclax, 226 NDUFS1, 24, 170 Necroptosis, 123-137 cancer and, 214 death receptors and, 123-124, 124f, 228 disease and, 131-132, 132f importance in mammalian development, 192-193 inflammation induction, 169 inhibition by caspase-8 and FLIP, 127-129, 128f ischemia-reperfusion injury, 136 MLKL and, 125-127, 126f necrostatins, 228-229 pharmacologic induction of, 227 phosphatidylserine exposure, 151 priming T-cell responses, 170 as protective, 132 as recent evolutionary invention, 127 suicide switch engineering and, 225 TRIF and, 24, 125f Necrosis, 122f. See also Necroptosis autophagy in stressed cells is blocked, 143 cell death, 122-137 compensatory proliferation and, 176-177 DAMPs released by, 150-151, 167 excitotoxicity, 133, 134f features of, 3-4, 4f inflammation and, 150, 167 ischemia-reperfusion injury, 133-137, 135f-136f linker cell death by, 180, 180f mitochondria role in, 135 neuronal, 133

INDEX 275

PARP and, 132-133 PGE₂ production, 176-177 phosphatidylserine exposure, 151, 153 secondary, 122-123, 122f, 150 Necrostatins, 123, 228-229 Necrosulfonamide, 229 Necrotic cells, removal of cells, 10 Negative selection in self-nonself discrimination, 189-191, 190f-191f Negative-feedback regulation, 219-220 Nematodes. See also Caenorhabditis elegans BCL-2 proteins, 80-81, 81f-82f caspase activation, 56-57, 57f cell death in development, 179-182, 180f-182f developmental plan, 179-180, 180f lack of caspase-inhibitory IAP proteins, 43 p53 protein, 207, 207f NEMO, 97 Nerve growth factor, 187 Neural tube, closure of, 192 Neuroblastoma, 208 Neurons, selecting, 187-188, 188f Neuroplastin, 23, 23f Neurosecretory motor neuron (NMN) pathway of apoptosis in nematodes, 223, 223f Neurosecretory motor neuron (NMN) sister cell death, 180-181, 181f Neurotrophism model, 187 Neutralization model, 72, 72f, 220-221, 221f Neutrophils, 150, 155, 169, 169f NF-κB (nuclear factor-κB), 97-99, 118, 128, 129, 170 NHE-1, 80 NIX, 87, 87f, 144 NLRC4 inflammasome, 111-112, 112f NLRP1 inflammasome, 112–113, 113f NLRP3 inflammasome, 109-111, 110f, 114-115 NLRs (Nod-like receptors), 109-116, 166 APAF1 and, 115-116, 115f disease and, 114-115 NLRC4, 111-112, 112f NLRP1, 112-113, 113f NLRP2, 113 NLRP3, 109-111, 110f, 114-115 Nonapoptotic cell death pathways, 121-148 accidental cell death, 121 autophagic cell death (type II cell death), 137-147 mitotic catastrophe, 147-148, 148f necrosis (type III cell death), 122-137

Noncanonical secretion, 114 Nox, 133 NOXA, 80 MCL-1 neutralization, 203, 211 as p53 target, 203 Nuclear events mediated by caspase cleavage of specific substrates, 20–21, 21f Nuclear factor-κB. See NF-κB Nuclease, 20 Nucleotide exchange factor, 162 Nucleus changes in apoptosis, 2 Nutlin-3, 227, 227f

0

Omi, 51–52, 52f, 59, 60f, 99, 227 On the Origin of Species (Darwin), 231 Oncogenes, 175, 195, 199, 201, 208–209, 212 Oxaliplatin, 215

Р

p35, 43, 44 p53, 119, 223 activation, 199-201, 199f-200f by caspase-2, 205-206, 206f by DNA damage, 200-202, 200f, 207, 207f by ribosomal protein imbalance, 201 apoptosis and, 200, 202-208, 203f, 207f cytosolic p53, 204-205 in Drosophila, 206-207, 207f in nematodes, 207, 207f nuclear p53, 202-204 ARF and, 199-200, 199f cancer and, 199, 201-202 cytosolic, 204-205, 205f defective, 201-202 gene mutation, 199 induced apoptosis in other animals, 206-208, 207f MDM2 induction by, 199-201 mitochondrial outer membrane permeabilization (MOMP) and, 203, 205, 205f nuclear, 202-204, 205f p53-MDM2 feedback loop, 199f regulation by ATM, 207 stabilization of, 227 targets of, 202-204, 202f BAX, 203-205, 205f

276 INDEX

p53 (Continued) BID, 203 death receptors, 203-204 ferroptosis, 204, 214 genes encoding pro-apoptotic proteins, 203, 203f MDM2, 199 NOXA, 203 PUMA, 203, 205, 205f p21-activated kinase (PAK), 22 Pancreatic islets, Myc in, 197, 197f Pancreatitis, RIPK3 and, 132 Paracaspase, 35 Parasite, 1 Parkin, 144, 144f, 146 PARP1 (poly(ADP-ribose) polymerase 1), 132-133 Passive cell death, 4 Pathogen-associated molecular patterns (PAMPs), 106, 116, 167, 170 LTRs and, 107-108, 108f as maturation signals to dendritic cells, 170 NLRC4 inflammasome and, 112 NLRs and, 109, 109f Pattern-recognition receptors (PRRs), 109, 166. See also NLRs (Nod-like receptors); TLRs Perforin, 30, 30f Peritonitis, 132 Permeability transition pore (PTP), 55-56, 56f, 135 Persister cells, 217-218 PGE₂ (prostaglandin E₂), 176–177 Phagocytic cells, 149-150 receptors for "bind-me" signals and bridging molecules, 157-159, 158f-159f recruitment by "find-me" signals, 150-151 SIRPa receptor, 154, 154f Phagocytosis apoptotic body removed by, 2 "bind-me" signals, 151, 153 "don't-eat-me" signals and, 153-155 "eat-me" signals, 160, 162, 163f-165f engulfment promotion of cell death, 162, 164, 166 engulfment-promoted cell death, 162, 164, 166 LC3-associated (LAP), 170-173, 172f-173f, 175, 175f "tether-and-tickle" model, 156-157 Phagolysosome, 165f, 166 Phagophore, 139, 141, 142f Phagosome, 162, 165f, 166, 171, 172f-173f

Pharmacological approaches to making cells die, 225-228 Phosphatase and tensin homolog (PTEN), 208 Phosphatidylserine, 22-23, 23f, 166 as "bind-me" signal, 151, 153 bridging molecules binding to, 155, 156f detection of, 152-153, 152f-153f externalization of, 160 phagocyte receptors for, 157-158, 158f Phosphoinositide 3-kinase (PI3K), 139 Phospholipase A2, 150, 151f, 176, 212 Phospholipid derivative lysophosphatidylcholine (LPC), 150 PIDD, 117-120, 117f, 205-206, 206f PIDDosome, 117, 117f Pin-1, 205, 205f PINK1, 144, 144f, 146 Plasma membrane events caused by caspases, 21-22, 22f-23f Pleiotropy, antagonistic, 196, 196f Poly(ADP-ribose) polymerase 1 (PARP1), 132-133 Potassium in ischemia-reperfusion injury, 134 NLRP3 inflammasome and, 111 Poxviruses, inhibitors of caspases, 43 PPARy (peroxisome proliferator-activated receptor y), 166, 167f, 168, 168f, 174 Procaspases, 13 Pro-death signal strength expected relationship to cell death per unit time, 219 observable relationship to cell death per unit time, 220 Prodomain, of caspases, 13, 14f Programmed cell death, 1-2, 179 Proliferation apoptosis and, 195-198 compensatory, 176-177, 176f homeostatic, 177 Prostaglandin E2 (PGE2), 176-177, 212-213 Proteases, 5. See also Caspase(s) BID as sensor of, 75 serine, 30 thiol. 11 Protein-S, 155, 156f PRRs. See pattern-recognition receptors Pseudogout, 110, 114 Pseudokinase, 125, 126f PTEN (phosphatase and tensin homolog), 208 PTP (permeability transition pore), 55-56, 56f, 135

PUMA, 68, 203, 205, 205f, 208 P2X purinoceptor 7 (P₂X₇), 111 PyD domain of AIM2, 113 of ASC, 106, 107f, 109, 113 of NLRP3, 109 Pyrin domain, 91f Pyroptosis, 8, 37, 38f, 103, 108, 114

R

RAC1, 162, 165f RAGE (receptor for advanced glycation end products), 167 RAIDD, 117-119, 117f Reactive oxygen species (ROS), 55, 133, 136-137, 144, 146, 170, 214 Reaper, 59, 60f, 182, 183f, 207, 224 Regulatory T cells (T_{reg}), 170 Removal of cells, 10 Reperfusion. See Ischemia-reperfusion injury Retinal detachment, 132 Rheostat model, 66, 67f RHOG, 162, 164f Ribosomal protein imbalance, p53 induced by, 201 RING domain, 42 RIP-homology interaction motif (RHIM), 124, 125f RIPK1, 96-97, 98, 98f, 123-124, 170, 216 caspase-8 cleavage of, 127-128, 128f hypothetical connection between autophagy and necrosis, 146, 147f pharmacological inhibition by necrostatins, 228 two faces of, 129-131, 130f RIPK3, 124, 124f, 125f, 136 activation, 129, 131 cancer metastasis and, 214 caspase-8-FLIP dimer cleavage of, 128 development in deficient mice, 193 hypothetical connection between autophagy and necrosis, 146, 147f inhibitors, 228-229 MLKL activation by, 127 ROCK1 kinase, 22, 22f, 174-175 ROS. See Reactive oxygen species Rotenone, 111

S

Sabotage, 5 Scavenger receptors, 158, 159f Scramblase, 23, 23f, 127, 152 Secondary necrosis, 122-123, 122f, 150 Selection in vertebrate development, 187-191 lymphocytes, 188-191, 190f-191f negative selection, 189-191, 190f-191f neurons, 187-188, 188f Self-nonself discrimination in the immune system, 187, 188-191, 190f-191f Serine protease, 30 Serpins, 43 Shigella flexneri, 114 Short hairpin (shRNA), 202 Sickle, 59, 60f, 207 SIRPa, 154, 154f Skin, cornification process in, 4 SLE (systemic lupus erythematosus), 173-174, 174f Sloughing of dead cells, 149 Smac, 51-52, 52f, 59, 60f, 99, 227 Smac-mimetic drugs, 227 SOCS1 (suppressor of cytokine signaling 1), 168, 168f SP-A, 156, 156f SP-D, 156, 156f Sphingosine-1-phosphate, 150 Stabilin-2, 157, 158f, 162 "Stay-away" signal, 155 Step function, 219 Stress, 1, 8 Stress sensors, BH3-only proteins as, 74-79 BID as protease sensor, 75 BIM and BAD as growth factor signaling sensors, 75-76, 76g-77g BIM and BMF as anoikis mediators, 78 Strica, 36 Suicide, 1-2, 5, 46, 123 Suicide switches, 224-225 Superoxides, 24 Suppressor of cytokine signaling 1 (SOCS1), 168, 168f Survival mechanism, autophagy as, 138-139 System Xc⁻, 204, 215, 227 Systemic lupus erythematosus (SLE), 173-174, 174f

Т

Tail-spike cell, death of, 181–182, 182f T-cell receptors, 189 T-cell responses to tumors, 215–216 TCTP (translationally controlled tumor protein), 200

278 INDEX

"Tether and tickle" model, 156-157 TGF-β (transforming growth factor beta), 168, 168f, 170, 172f, 185 Thiol proteases, 11 Thrombospondin-1, 155, 156f Thyroid hormone, 186 TIM4, 157-158, 158f Tingible body macrophages, 155, 155f TIR-domain-containing adapter-inducing interferon (TRIF), 124, 125f TLRs (Toll-like receptors), 107, 166-167, 168f TMEM16F, 23, 154 TNF. See Tumor necrosis factor TNFR. See Tumor necrosis factor receptor TNF-receptor-associated factor-2 (TRAF-2), 96 Toll-like receptors (TLRs), 107, 166-167, 168f TORC1, 140, 142 TORC2, 140 Toxins, bacterial, 83-84, 84f, 112 TRA1, 181, 181f TRADD (tumor necrosis factor receptor type 1-associated death domain), 96, 98, 98f, 100f TRAF-2 (TNF-receptor-associated factor-2), 96 TRAIL (TNF-related apoptosis-inducing ligand), 90, 90f, 97-99, 203-204 apoptosis and, 95-96 receptors, 89, 90f Transcription, bistability at level of, 223-224 Transferrin, 137, 138f Transforming growth factor beta (TGF-β) family, 168, 168f, 170, 172f, 185 Translationally controlled tumor protein (TCTP), 200 Transthyretin-like protein 52 (TTR-52), 159, 161f TRIF (TIR-domain-containing adapter-inducing interferon), 124, 125f TRIO, 162, 164f TSC1/2, 142 Tumor necrosis factor (TNF) as death ligand, 89, 90f, 96, 98f necrosis induced by, 123-124 signaling for NF-kB, antiapoptosis, and inflammation, 97f structure, 91f Tumor necrosis factor (TNF) family death ligands, 89-91, 90f-91f death receptors, 89–91, 90f–91f

Tumor necrosis factor receptor (TNFR), 89, 90f, 91f, 128 apoptotic signaling by, 96–99 necroptosis caused by, 123–124, 124f Tumor-suppressor proteins, 198–199, 208. See also p53 Type I cell death. See Apoptosis Type II cell death. See Autophagic cell death Type III cell death. See Necroptosis; Necrosis Tyrosine phosphatases, 154

u

ULK1, 139–140, 141f, 171 Unfolded proteins, 214 Uric acid, 110, 110f, 150, 167 UVRAG, 143

V

Vacuoles, in autophagic cell death, 3 Venetoclax, 226 Vertebrate development, cell death in, 184–187, 185f–186f Viral BCL-2 proteins, 82–83, 82f–83f Viruses apoptosis induced by cytotoxic lymphocytes, 29–30, 29f caspase inhibitors, 39–43 necroptosis as defense against, 132 Voltage-dependent anion channel (VDAC), 55, 56f VPS34, 139–140, 141f, 143, 171

W

Waste management, 149–152, 166, 167f WD domain, 48, 49f, 56–58, 57f West Nile virus, 132 WIPI2, 140–141 Wound healing, 176

Х

Xc⁻, 204, 215, 227 XIAP, 41–43, 43f, 51–52, 52f, 99–100, 227 Xjr8, 151

Ζ

Z-DNA-binding protein 1 (ZBP1), 124, 125f