

Index

a

- A-kinase anchoring protein (AKAP) 371, 374, 432ff., 436ff., 454
 - isoforms 438
 - signal transduction 437
- Abelson (Abl) tyrosine kinase 513ff.
 - activation 515, 517
 - autoinhibition 516
 - functions 517f.
 - inactivation 517
 - interaction partners 515f.
 - medical importance 517
 - oncogenic activation 518
 - regulation 517
 - substrate selection 515f.
 - structure 513, 517
- acetylome 57
- activation function 1 (AF-1 function) 265
- activation function 2 (AF-2 function) 263
- activation loop 424f., 428, 482, 484, 511, 676
- activation segment 424
- adapter protein 24, 497ff.
- adenomatosis polyposis coli (APC) 719, 737, 740, 765, 770ff.
- adenylyl cyclase (AC) 352ff., 400
 - formation of cAMP 371ff.
 - inhibition 355
 - regulation 355ff.
 - stimulation 355
 - structure 354
 - types 371f.
- adrenaline 12f.
- Akt kinase *see* protein kinase B
- allostery 34, 162
- alternative reading frame (ARF) protein 570, 743, 746
- alternative splicing 209ff., 215
 - regulation 211, 214
- AMP-activated protein kinase (AMPK) 766
- anaphase-promoting complex (APC) 76, 684
 - mitotic APC 684, 702
 - nonmitotic APC 684, 702
 - substrates 76, 702
 - subunits 684
- antagonistic ligand 505
- anti-oncogene 741f.
- antigen-presenting cell (APC) 618
- antigrowth signal 728
- apoptogenic protein 792
- apoptosis 388, 567, 590, 631, 707, 709, 741, 744, 769, 777ff.
 - evasion 726, 729
 - links to cellular signaling pathways 795ff.
 - mitochondrial pathway 789ff.
 - PI3 kinase/Akt kinase pathway 796
- apoptosis-inducing factor (AIF) 792
- apoptosome 785, 791
- apoptotic pathway 778
 - extrinsic pathway 779
 - intrinsic pathway 779
- aporeceptor complex 282
- Arg finger 549
- arrestin 317ff., 363ff.
- ataxia telangiectasia and Rad3-related (ATR) sensor kinase 707
 - functions 709
- ataxia telangiectasia mutated (ATM) sensor kinase 707ff.
 - ATM interactions 708
 - function 708
- atypical protein kinase (aPK) 419
- autocrine signaling 14f.
- autocrine stimulation 727
- autoinhibition 428, 484, 492
- autoinhibitory sequence element 424
- autophagosomal pathway 64
- autoprocessing 96

b

- B-cell receptor (BCR) 531, 618ff.
 - structure 619f.
- bacterial transcription 133
- basal transcription apparatus 139
- Bcl-2 family 786ff.
 - antiapoptotic Bcl-2 members 787
 - BH3-only proteins 788f.
 - domains 787
 - proapoptotic Bcl-2 members 787f.
- bistability 120
- bone morphogenetic protein (BMP) 633, 635, 637
- branching 114
- bromodomain 185, 193

c

- C-helix 423
- c-jun-terminal kinase (JNK) 574f., 582f., 588ff.
 - input signals 589
 - signal entry points 589
 - substrates 590f.
- C-terminal domain (CTD) 132, 142f., 146ff.
- Ca²⁺ 381ff., 450ff., 563
 - activation of proteins 395
 - as signal molecule 394ff.
 - channels 381, 385, 388ff.
 - concentration 391
 - distribution 383
 - influx 388f.
 - oscillations 391f.
 - receptors 394
 - release 381ff., 388f.
 - removal 390
 - sensor 396, 400
 - storage 381ff., 390
- Ca²⁺/calmodulin-dependent protein kinase (CaMK) 455ff.
 - function 455
 - multifunctional CaMK 456
 - substrates 456
- Ca²⁺-binding protein 395f.
- Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) 456ff.
 - activation 457ff.
 - autoinhibition 458
 - Ca²⁺/calmodulin binding 458
 - deactivation 460
 - holoenzyme 458
 - memory function 460f.
 - phosphorylation 458
 - structure 457ff.
 - substrate binding 460
 - subunits 459
- calcineurin 461, 467ff.
 - regulatory function 467
 - subunit structure 467
- calmodulin 352, 355, 357, 372, 383, 382, 396ff., 467
 - binding 398
 - structure 397
 - substrate activation 398f.
 - target proteins 399f.
- cAMP responsive element (CRE) 174f.
- cancer 718ff.
 - acquired capabilities 726
 - altered DNA methylation 718f.
 - altered histone modification 720
 - hallmarks 725
 - initiation 723
 - micro RNAs 720
- cancer gene 721
 - drivers 721f.
 - passengers 721f.
- capping 210, 215
- carcinogenesis 722
- caretaker gene 741f.
- caspase 777, 779ff.
 - activation 783, 785
 - caspase cascade 791
 - control by inhibitor proteins 785
 - domains 782
 - effector caspases 780ff.
 - gatekeeper 786
 - inhibitors 786
 - initiator caspases 780ff.
 - maturation 784
 - mechanism 781f.
 - properties 780
 - regulation 783
 - substrates 786
- caspase recruitment domain (CARD) 783
- catalytic domain 541
- β-catenin 770ff.
 - activation 772
 - downregulation 772
- Cbl protein 77
- CDK inhibitor (CKI) 666, 668, 671ff., 744
 - function 672
 - p21^{CIP1} 673f.
 - p27^{KIP1} 672, 677
 - regulation 672f.
- CDK-activating kinase (CAK) 141f.
- CDK-cyclin complex 674

- CDK1-cyclin B 700f.
- CDK2-cyclin E 687, 710
- CDK4-cyclin D1 685f
- CDK4/6-cyclin D 685
- structures 675
- CDK8 module 145
- cell cycle 661ff.
 - checkpoints 665f.
 - control points 663
 - external control 663
 - key elements 666ff.
 - phases 661f.
 - regulation by proteolysis 681
 - S phase entry 684ff.
- cell cycle control 661ff.
 - antimitogenic signals 665
 - cyclin-dependent protein kinases 667
 - effectors 705
 - external cell cycle control 664f.
 - intrinsic control mechanisms 662f.
 - mitogenic signals 664
 - principles 661ff.
- cell proliferation 567, 697
- dysregulation 730
- cell signaling 1ff.
- ceramide 402
 - formation 403
 - function 403
- chaperone 177, 283
- cholera toxin 332f.
- cholesterol membrane anchor 95
- chromatin-binding domain 192
- chromatin modification 151, 159, 177, 182, 215
- chromatin remodeling 180f.
- chromatin structure 175ff., 214
- chromosomal instability (CIN) 717
- chronic myelogenous leukemia (CML) 735f.
 - treatment 736
- CIP/KIP family 672
- citrullination 61f.
- coactivator 153, 256, 271ff.
- conventional protein kinase (ePK) 419
- core promoter 137f.
- coregulator 153, 173, 269f.
- corepressor 153, 256, 274
- covered promoter 178f.
- CRE-binding (CREB) protein 174f., 432
- CREB-binding protein (CBP) 174f., 636
- cross regulation 47
- crosstalk 114, 194f., 279, 300
- Cullin-RING ligase 73ff.
 - examples 75
 - regulation 73
 - structure 73
 - substrate recognition 74
- cyclic ADP-ribose (CADP-ribose) 387
- cyclic AMP (cAMP) 352, 371ff., 433ff.
 - compartmentalization 374
 - degradation 353, 371ff.
 - formation 353, 371ff.
 - targets 372ff.
- cyclic GMP (cGMP) 375ff.
 - targets 377f.
- cyclin 667ff.
 - D-type cyclins 685
 - degradation 671
 - expression 671
 - functions 670
 - oncogenic activation 737
 - phosphorylation 671
 - regulation 670
 - subcellular distribution 671
 - types 669
- cyclin D 685f.
 - control of translation 696
 - regulation 686
 - stability 696
 - transcriptional control 695
- cyclin-dependent protein kinase (CDK) 148, 666ff.
 - activation 669
 - activation loop phosphorylation 676
 - inhibitory phosphorylation 677
 - phase-specific activation 680
 - phosphorylation 676
 - regulation 675, 678f., 705
 - structural basis of regulation 674
 - substrates 679ff.
- cyclin E 687
 - control 687
 - multiple regulation 688
- cysteine-rich domain (CRD) 650
- cytidine methylation 199
- cytokine 593ff.
 - classification 594
 - function 595
 - structure 595
- cytokine-binding homology region (CHR) 597
- cytokine receptor 593ff.
 - activation 596ff., 599, 601
 - classification 596
 - cytokine binding 599, 601
 - domains 597
 - downstream effectors 598
 - general features 596

- isoforms 599
- non-signaling subunits 599
- oligomeric structure 598f.
- shared β -chain receptors 603f.
- shared γ -chain receptors 603
- signaling subunits 599
- structure 596ff.
- cytokine receptor signaling 598, 615f.
- regulation 615f.
- cytoplasmic tyrosine kinase *see* Non-RTK

d

- damage-regulated autophagy modulator (DRAM) 766
- Darwinian evolution 722
- Dbl homology (DH) domain 541f.
- death domain (DD) 648ff., 783
- death effector domain (DED) 783
- death inducing signaling complex (DISC) 784, 793ff.
- death platform 783f.
- death receptor-triggered apoptosis 792ff.
- degron 73f.
- denitrosylation 412
- desensitization 300, 318, 345f.
 - heterologous desensitization 315
 - homologous desensitization 315f.
- deubiquitination 81
- diacylglycerol (DAG) 357f., 378f., 393, 401, 450ff., 503, 563
 - formation 382, 401f.
 - function 382, 401f.
- direct repeat 155
- DNA-binding domain 154, 173
- DNA-binding motif 154f.
- DNA-binding protein 167ff.
 - activity control 167f.
- DNA damage 702ff., 711, 762
 - recognition 707
 - response 708
- DNA damage checkpoints 702ff., 741, 777
 - components 703ff.
 - G₁DNA damage checkpoint 710f.
 - organization 703ff.
 - protein kinases 708
- DNA double-strand break (DSB) 706
- DNA element 149, 155, 170
- DNA methylation 197ff., 200ff., 718f.
 - biological functions 202f.
 - types 200
- DNA methyltransferase (DNMT) 200f.
- DNA replication 699ff.
 - checkpoints 702ff.
 - control 699
 - initiation 700
 - replication components 699
- dual lipidation 95
- dual-specificity phosphatase (DUSP) 581f.

e

- 4E-binding protein (4E-BP) 223ff.
- EF-hand 396f.
- EGF receptor (EGFR) 481, 504, 513, 555, 614
 - oncogenic activation 734
 - signaling 504f.
- EGFR kinase 486
 - activation 486
- electrical signaling 4
- β -element 296f.
- elongation 132, 135, 146ff., 202, 204, 216
- elongation factor 326
- endocrine cell 13
- endocrine signaling 13f.
- endocytosis 506
- endonuclease G (endoG) 792
- energy metabolism 568
- enhanceosome 159f.
- epidermal growth factor (EGF) 481
- ErbB network 125
- ERK pathway 586ff.
 - activation 587
 - input signals 586f.
 - substrates 587
- erythropoietin (EPO) 593f.
- erythropoietin receptor (EPOR) 598, 606
- estrogen receptor (ER) 252, 264, 276f., 279f., 285f.
 - nongenomic functions 287
 - signal transmission 285
- eukaryotic initiation factor-2 (eIF-2) 226f.
 - control by phosphorylation 228
- eukaryotic transcription 131ff.
 - basic features 132ff.
 - components 131, 134
 - elementary steps 135f.
- external signal 5, 7, 15, 19
 - reception 15
- extracellular messenger 3
- extracellular regulated kinase (ERK) 438, 573ff., 577, 588

f

- farnesylation 93f.
- Fas/CD95 signaling pathway 793ff.
- feedback loop 117

feedback regulation 504
 ferritin 220f.
 fibroblast growth factor (FGF) 480
 fibroblast growth factor receptor (FGFR) 480f.
 fibroblast growth factor receptor substrate (FRS) 497
 focal adhesion kinase (FAK) 626ff.
 furin 647

g

G_{βγ}-complex 342ff., 441
 – effectors 344
 – function 342
 – signaling 343f.
 – structure 342
 G_{βγ}dimer 441
 G-domain 325
 G₁ phase 661ff., 81ff.
 – G₁ checkpoints 405
 – G₁ entry 694
 – G₁ progression 672, 684ff., 694
 – G₁/S transition 667, 672, 674, 677, 679, 687, 697f., 712
 G₂ phase 661, 663, 666, 669
 – G₂/M checkpoint 712
 – G₂ checkpoints 705
 – G₂/M transition 663, 667, 677, 680, 400
 G protein 305, 310, 330
 – effectors 352ff.
 – membrane association 345
 – structure 337ff.
 – switch function 337ff.
 G protein-coupled receptor (GPCR) 301ff., 344, 380, 391, 451f., 541, 569
 – activation 302, 310
 – classification 304
 – desensitization 315, 318
 – downregulation 315
 – interacting proteins 313
 – ligand binding 309
 – oligomerization 319
 – phosphorylation 314ff.
 – regulation 312ff.
 – signaling 311f., 363ff.
 – structure 305, 307
 – subfamilies 302ff.
 G protein-coupled receptor kinase (GRK) 313, 316f., 349
 – membrane attachment 317
 G protein-coupled signal transmission pathway 291ff.

gap junction 3f.
 GDI dissociation factor (GDF) 545
 gene expression 129ff., 197
 – basic steps 129ff.
 – regulation 129ff.
 general transcription factor (GTF) 131, 134, 137, 139, 143
 genetic imprinting 203
 genetic instability 717
 genomic signaling 251, 254f., 281
 genotoxic stress 749
 geranylation 93f.
 glucocorticoid receptor (GR) 260
 glucocorticoid response element (GRE) 280
 glutathione 405f., 412ff.
 glycogen phosphorylase 53
 glycolysis 767
 glycosyl-phosphatidyl-inositol (GPI) anchor 98f.
 Gp130 receptor 601f.
 Grb2-associated binder (Gab) 499
 growth factor 476f., 530
 growth factor receptor 476, 578
 growth factor receptor binding protein 497
 growth hormone (GH) 593f.
 growth hormone receptor (GHR) 598
 GTP analog 324
 GTP hydrolysis 340ff., 548ff.
 – by Ras 549
 – mechanism 548f.
 – stimulation by GAPs 548
 GTPase 23f., 336
 – crosstalk 543
 – functions 321
 – inhibition 324
 – linkage 543
 – superfamily 321, 326
 – switch function 321, 323
 GTPase activating protein (GAP) 117f., 323, 524, 535ff., 541ff.
 – activity 540
 – catalytic domains 541
 – domain structure 539f.
 – regulation 540
 guanine nucleotide dissociation inhibitor (GDI) 323, 349, 535, 537f., 544f.
 guanine nucleotide exchange factor (GEF) 117f., 120, 320, 323, 351, 374, 535ff., 541ff., 546, 566
 – activation of GTPases 543
 – catalytic domain 541ff.
 – Dbl homology (DH) domain 541f.
 – multivalency 542

guanylyl cyclase 375ff.
 – ligands 376
 – soluble guanylyl cyclases 377
 guanylyl cyclase receptor 376f.

h

heat shock protein (Hsp) 283f.
 Hect domain enzyme 69ff.
 Hedgehog (Hh) protein 95f.
 heme-regulated eIF-2 kinase (HRI) 227f.
 hemoglobin (Hb) 410
 – R-state 410f.
 – T-state 410f.
 heterotrimeric G protein 326ff.
 – activation 328, 333ff.
 – characterization 332
 – classification 328ff.
 – conformational changes 339
 – functional cycle 334ff.
 – $G_{\beta\gamma}$ -complex 342ff.
 – $G_{\beta\gamma}$ signaling 343f.
 – in supramolecular complexes 337
 – inactive ground state 334
 – novel G protein cycle 350
 – receptor-independent functions 350ff.
 – structure 327f., 337ff.
 – subfamilies 329ff.
 histone acetylation 182, 184
 histone acetyltransferase (HAT) 55f., 184,
 191, 693
 – regulation 185
 – substrates 185
 histone arginine methylation 189
 histone deacetylase (HDAC) 153, 163f.,
 186
 histone deacetylation 185
 histone demethylase (HDM) 58ff., 188
 histone lysine methylation 188
 histone methylation 186, 201
 histone methyltransferase (HMT) 58f., 188
 histone modification 176, 183, 196, 202,
 720
 – crosstalk 193ff.
 – dynamics 198
 – epigenetics 197
 histone modification code 196
 histone modification patterns 196
 histone phosphorylation 190f.
 histone ubiquitination 192
 histone variant 180
 hnRNP 214
 hormone 2, 7ff., 170, 251ff.
 – biosynthesis 7

– chemical nature 8ff.
 – degradation 7
 – modification 7
 – reception 8
 – regulation of protein synthesis 226
 – secretion 8
 – storage 8
 – transport 8
 hormone agonist 11ff.
 hormone analog 11f.
 hormone antagonist 11f.
 hormone binding 288
 hormone derivative 13
 hormone-responsive element (HRE) 251,
 255f., 258f., 261
 Hub protein 122f.
 – characteristics 124
 – functions 124
 hybrid oncoprotein 736
 hydrophilic messenger 369
 hydrophobic messenger 369
 hypermethylation 719
 hypoxia-induced transcription factor
 (HIF) 738

i

immunophilin 283
 immunoreceptor tyrosine activation motif
 (ITAM) 619f.
 inhibitor of apoptosis (IAP) 786
 inhibitor protein 35, 435
 initiation factor 326
 initiation region (INR) 138, 141
 INK4 protein 674, 678
 inositol messenger 380
 – formation 381
 – function 381
 inositol phosphate 378
 – formation 380
 inositol phospholipid 378ff.
 inositol trisphosphate (ITP₃) 378ff., 3825ff.,
 391
 inositol trisphosphate receptor 385f.
 insulin 223ff.
 insulin receptor 423
 insulin receptor kinase (IRK) 484
 insulin receptor substrate (IRS) 495, 498
 – regulation 498
 – signaling 496
 integrin 623ff.
 – downstream signaling 626, 628
 – inside-out signaling 624f.
 – integrin signaling 624f., 628

- outside-in signaling 624f., 627
- structure 624
- integrin-linked kinase (ILK) 626f.
- interaction domain 41, 43, 61f., 103f., 490
 - classification 44
 - modification-specific interaction domain 41
 - regulatory interaction domain 43
 - versatility and variability 46
- interaction network 122f.
 - modularity 126
 - redundancy 126f.
 - robustness 126f.
- intercellular signaling 1ff.
 - principal mechanisms 3
 - regulation 7f.
 - steps 5ff.
 - tools 3ff.
- interferon (IFN) 593f., 596
- interferon (IFN)- β gene 159f.
- interleukin (IL) 593f., 603
- interleukine-2 (IL-2) 595, 603f.
- interleukine-2 receptor (IL-2R) 603f., 606ff.
- intracellular messenger 4
- intracellular messenger substance *see* second messenger
- intracellular pathway 6
- intracellular signaling 1f., 292, 573ff.
 - aberrant activation 728
 - basics 15ff.
 - components 19
 - molecular tools 18ff.
- intronic miRNA 241
- iron regulatory protein (IRP) 220f.
- iron-responsive element (IRE) 220f.

j

- JAK/STAT pathway 608ff., 612, 614f.
- Janus kinase (Jak kinase) 604, 608f.
 - coupling of other receptor types 610
 - kinase regulation 609
 - nuclear functions 610
 - pseudokinase domain 609
- JNK module 591
- juxtamembrane autoinhibition 484

k

- kinase suppressor of Ras (KSR) 560, 584
- kindlin 625f.

l

- layered network 124ff.
- leukocyte inhibitory factor (LIF) 595
- leukocyte inhibitory factor receptor (LIFR) 602

- ligand binding 262, 309
 - activation function-2 263
 - promiscuous ligand binding 265
 - switch function 264
- linker for activation of T lymphocytes (LAT) 500, 623
- lipid anchor 90, 112
 - examples 91
 - structure 91
 - switch function 96f.
- local mediator 15
- long noncoding RNA (lncRNA) 231
- lysine acetylation 277
 - regulatory functions 57
- lysine acetyltransferase (KAT) 55f., 184
- lysine demethylase (KDM) 58ff., 188f.
- lysine methylation 58ff., 188, 277
- lysine methyltransferase (KMT) 58f., 188
- lysophosphatidic acid (LPA) 403f.
- lysosomal pathway 64

m

- M phase 661, 666, 669, 680ff., 686f., 699ff.
 - control 701
 - progression 702
- major histocompatibility complex (MHC) 618
- MAP/ERK kinase (MEK) 575ff., 579
- MAPK kinase (MAPKK, MAP2K) 575, 577, 579
- MAPK multiprotein complex 575, 583, 585f., 590
- MAPK pathways 573ff., 588ff., 626
 - components 575ff.
 - feedback loops 580
 - major MAPK pathways of mammals 586
 - organization 575ff.
 - p38 pathway 588ff.
 - regulation by inhibitory proteins 583
 - regulation by MAPK phosphatase 581ff.
 - regulation by protein phosphatases and inhibitors 579ff.
 - scaffolding 583ff.
- MAPK phosphatase (MKP) 581ff.
- MAPK/ERK pathway 118, 121, 555, 560
- MAPK-activated protein kinase 1 (MAPKAP-K1) 588
- MAPKK kinase (MAPKKK, MAP3K) 575, 577, 579, 591
- mediator 134, 139, 143f., 150, 158, 273
 - function 144
 - structure 144f.
- mediator complex 143ff.
 - regulatory roles 145

- MEK kinase (MEKK) 556, 559, 565, 575f.
 - membrane anchor 345
 - membrane-associated messenger 26
 - messenger ribonucleoprotein (mRNP) 216
 - metal ion center 410
 - methyl CpG-binding protein (MBP) 201
 - microRNA (miRNA) 229ff., 233ff.
 - biogenesis 233, 236, 239
 - cancer 243, 720ff.
 - functions 240
 - mature miRNA 239
 - processing 235f.
 - regulation 238ff., 242, 244
 - regulatory functions 240
 - targets 241
 - transcription 234, 239
 - microsatellite instability (MSI) 717
 - miRNA-induced silencing complex (miRISC) 229
 - formation 235
 - mitochondrial apoptosis-induced channel (MAC) 791
 - mitogen-activated protein kinase (MAPK) 107, 118, 287, 363f., 425, 501, 503, 532, 573ff., 577, 587
 - atypical MAPKs 575
 - conventional MAPKs 574
 - mitogenic signal 694
 - moderator of nongenomic activity of ER (MNAR) 287
 - modular signaling complex 31
 - regulation 33
 - signal-directed assembly 33
 - specificity 33
 - variability 33
 - monomeric GTPase 535, 539
 - GTPase-activating proteins 539ff.
 - guanine nucleotide exchange factors 541ff.
 - Ras family 545
 - mRNA 131
 - mRNA circularization 217f.
 - multisite protein modification 42f.
 - multivalent scaffold 436
 - Myc transcription factor 737ff.
 - cooperation with other transcription factors 738
 - regulation of Myc transcription 739
 - transcriptional targets 739
 - myristic acid anchor 92
 - myristoylation 91f.
 - myristoyl-electrostatic switch 97
 - myristoyl-ligand switch 97
- n**
- N-end rule 74
 - natriuretic peptide receptor (NPR) 376f.
 - natural killer (NK) cells 603
 - negative feedback 117ff., 505, 560, 580
 - nerve growth factor (NGF) 480
 - network 115
 - network structure 121
 - NFκB pathway 85ff., 652
 - canonical pathway 87
 - noncanonical pathway 87
 - nicotinic acid adenine dinucleotide phosphate (NAADP) 387f.
 - nitric oxide (NO) 375, 404ff., 564
 - reactivity 405f.
 - signal transduction 405
 - synthesis 406
 - targets 410
 - toxic action 413
 - nitrosative stress 413f.
 - nitrosylation 409ff.
 - nitrosylation of hemoglobin 410
 - nitrosylation of metal centers 409
 - physiological functions 409
 - NO-sensitive guanylyl cyclase 409
 - NO-synthase (NOS) 404, 406f., 412
 - activation 408
 - cofactors 407
 - forms 407
 - eNOS 408
 - iNOS 409
 - nNOS 408
 - substrates 407
 - non-G protein signaling 349
 - non-genomic signaling 251, 254f., 257
 - non-genotoxic stress 749, 763
 - non-Smad signaling pathway 636
 - nonreceptor protein tyrosine phosphatase (PTPN) 519, 521, 523
 - autoinhibition 523
 - nonreceptor tyrosine-specific protein kinase (non-RTK) 507ff., 593f., 598, 601, 623, 626, 735
 - activation 604
 - autophosphorylation 604
 - binding of signaling proteins 606
 - domains 508
 - function 507ff.
 - oncogenic nonreceptor tyrosin kinases 735
 - phosphorylation 605f.
 - structure 507ff.
 - Notch extracellular truncation (NEXT) 646f.
 - Notch intracellular domain (NICD) 647f.

Notch receptor 642ff.
 – activation 644, 646
 – domain organization 644f.
 – downstream signaling 646
 – function 643
 – ligands 643f.
 – processing 644
 – structure 643
 nuclear factor of activated T cells (NF-AT) 468f.
 nuclear receptor (NR) 251ff.
 – AF-2 function 263
 – coactivator 271f.
 – coregulator 269f.
 – corepressors 274
 – cytoplasmic functions 284
 – DNA-binding elements 258, 260f.
 – domains 270
 – ligand-binding domain 261ff., 267
 – ligand-dependent translocation 281
 – ligands 252ff., 275
 – lipidation 278
 – long-range actions 279
 – nongenomic functions 284ff.
 – principles of signaling by NR 254ff.
 – regulation of signaling 274ff.
 – signaling 251ff.
 – specificity 280
 – structure 257ff., 266
 – subcellular localization 280
 – sumoylation 278
 – transactivation function 265
 – transcription activation 269
 – transcription repression 269
 – transcriptional regulation 268
 – ubiquitination 278
 nuclear translocation 283
 nucleosome remodeler 181
 nucleotide exchange 542

O

oncogene 715ff., 722, 729ff.
 – activation 730ff.
 – functions 733ff.
 – oncogene products 734
 – structural changes 730
 oncogene Mdm2 756ff.
 – control of Mdm2 function 759
 – control of p53 756
 – downregulation of Mdm2 by ARF 758
 – p53 independent functions of Mdm2 759
 – regulation of Mdm2 757
 oncogenic fusion protein 731f.

oncogenic receptor tyrosine kinase 734f.
 – ErbB2/neu receptor 734f.
 oncogenic stress 749, 762
 oncogenic transcription factors 737
 oncoprotein 546, 744
 open promoter 178f.
 orphan nuclear receptor 257, 268

P

P-tyrosine-binding (PTB) domain 493
 – subgroups 493
 p130Cas 500
 p38 module 591
 p38MAPK pathway 589
 – input signals 589
 – signal entry points 589
 – substrates 590f.
 palindromic sequence 155
 palmitic acid anchor 92
 palmitoylation 92f.
 paracrine signaling 14f.
 pathogen-associated molecular pattern (PAMP) 653f.
 PDGF receptor (PDGF-R) 489f., 513, 518, 555
 peptidyl arginine deaminase (PADs) 61
 peroxisome proliferator activator receptor (PPAR) 263, 266
 peroxynitrite 413
 pertussis toxin (PTX) 333, 361
 Philadelphia translocation 735
 phosducin 346f.
 phosphatase and tensin homolog (PTEN) 445f.
 phosphatidylinositol (PtdIns) 378ff.
 phosphatidylinositol-3,4,5-triphosphate (PtdIns(3,4,5)P₃) 392f., 444
 phosphodiesterase (PDE) 354, 372, 437
 phosphoinositide 392ff.
 phosphoinositide-3 kinase (PI3K) 439ff., 452, 492, 500, 566, 620
 – activation 441f.
 – classification 440
 – properties 440
 phosphoinositide-dependent protein kinase (PDK) 443f., 452f.
 phospholipase 358
 phospholipase A₂ 588
 phospholipase C (PLC) 357ff., 380, 401, 566
 – activation 360f.
 – domains 359f.
 – PLC-β 358ff., 394
 – PLC-γ 362, 394f., 492, 501ff., 620, 623
 – PLC-δ 362

- PLC- ϵ 362f.
- stimulation 359, 361
- types 359ff.
- phosphorylated protein 52
 - interactions 52
 - properties 52
- phosphorylation 171ff., 190f., 223, 276ff., 300, 314, 316, 450, 465, 528, 641
 - activating phosphorylation 559
 - inhibitory phosphorylation 559
- phosphotyrosine-binding (PTB) domain 348, 495
- PI3K/Akt pathway 439ff., 796f.
 - regulation of apoptosis 797
- piwi-interacting RNA (piRNA) 230f.
- PKC-interacting protein 453
- platelet-derived growth factor (PDGF) 482, 489
- pleckstrin homology (PH) domain 360
- poly(A)-binding protein (PABP) 219
- polyadenylation 210
- poly-ubiquitin linkage 82f., 87
- positive feedback 119f., 504, 581
- postsynaptic density (PSD) 460
- posttranslational modification (PTM) 23, 27, 29, 31, 36ff., 51, 58, 95, 103, 108ff., 117, 149, 152, 165, 170, 176, 272, 274, 276ff., 281, 301, 464, 490, 502, 536, 579, 608, 640, 739
 - allosteric and conformational functions 38
 - antagonistic action 49
 - chemical nature 37ff.
 - classes 37
 - convergent recognition 50
 - dynamic nature 38
 - multisite PTM 47
 - mutually exclusive PTM 48
 - recognition of PTMs 38
 - regulation of intramolecular interactions 49
 - regulatory PTMs 38
- PPAR-RXR complex 266f.
- pre-mRNA 209, 212
- pre-mRNA processing 209ff., 215
- preinitiation complex (PIC) 135, 148, 150, 204, 215
- prenylation 94
- prenyl anchor 93
- procaspase 786
- promoter 132, 138, 177
 - promoter types 178f.
- proteasome 78ff.
 - activator 80
 - structure 79
 - substrate delivery 80
- protein arginine methylation 61f.
- protein arginine methyltransferase (PRMT) 58, 189
- protein degradation pathway 63f.
- protein inhibitor of activated STATs (PIAS) 615ff.
- protein kinase 51, 53, 148, 227, 417
 - activation 429
 - amino acid specificity 418f.
 - characteristics 417
 - classification 417
 - conserved amino acids 421
 - control of activity 427, 429
 - inactivation 429
 - inhibitors 428
 - reaction 421f.
 - regulation 420ff.
 - structural elements 422ff.
 - structure 417, 420ff.
 - substrate binding 425ff.
 - substrate specificity 426
 - targeting 431
- protein kinase A (PKA) 372f., 422, 431ff.
 - activation 433
 - domains 434
 - phosphorylation site 434
 - regulation 373, 431ff., 435f.
 - structure 432
 - substrate specificity 432
 - subunits 432f.
- protein kinase B (PKB) 442ff.
 - activation 443, 445
 - domains 442f.
 - inhibition of apoptosis 444
 - phosphorylation 443
 - promotion of cell survival 444, 446
 - regulation of cellular metabolism 445
 - stimulation of protein synthesis 444
 - signaling 443ff.
- protein kinase C (PKC) 378f., 381, 395, 401ff., 438, 447ff.
 - activation 449ff.
 - autoinhibition 450
 - C1 domain 448ff.
 - C2 domain 448, 450
 - classification 447
 - cofactors 450
 - functions 451, 454
 - phosphorylation 452
 - receptors 453
 - regulation 450ff.
 - stimulation by phorbol esters 449
 - structure 447

- subfamilies 447
- substrates 454f.
- protein lysine acetylation 55
 - enzymes 56
 - general aspects 55
 - regulation by protein lysine acetylation 55
 - regulatory functions 57f.
- protein methylation 58ff.
- protein modification 39ff., 45
- protein phosphatase (PP) 417ff., 461ff.
 - targeting 431
- protein phosphatase 2A (PP2A) 465
 - C-terminal methylation 466
 - subunit structure 466
- protein phosphatase 2B (PP2B) *see* calcineurin
- protein phosphatase I (PPI) 464
- protein phosphorylation 51ff., 112, 419, 430
 - allosteric functions 53
 - general aspects 51f.
 - organization of signaling pathways 54
- protein S-nitrosylation 410ff.
 - regulatory functions 410
 - selectivity 410
 - target proteins 412
- protein tyrosine phosphatase (PTP) 504, 519ff., 608, 614, 617
 - activity 527
 - classification 520
 - functions 519f.
 - mechanism 520, 522
 - negative regulation 526
 - oncogenic functions 526
 - oxidation 528ff.
 - positive regulation 526f.
 - regulation of cell signaling 525ff.
 - subcellular localization 532
 - structure 520
 - tumor suppression 526f.
- protein tyrosine phosphatase activator (PTPA) 465
- proteolysis 78, 528, 681ff., 779ff.
- proto-oncogene 731f.
- PTEN phosphatase 446

r

- R-Ras protein 561
- Rab family 569
- Raf kinase 555, 565
 - activation 557f.
 - domains 557
 - formation of heterodimers 559
 - formation of homodimers 559
 - inactive state 558
 - isoforms 556
 - oncogenic activation 561
 - phosphorylation 559
 - regulation 557f., 560
 - structure 557
- Raf-1 kinase inhibitory protein (RKIP) 583
- Ral GTPase 562
- Ran family 570
- Rap GEF 562
- Rap GTPase 562
 - regulation 563
- Ras exchange motif (REM) 553f.
- Ras-GAP 552
- Ras-GEF 553
 - activation 553
 - regulation 554
 - structure 553
- Ras gene 546
- Ras nanocluster 551
- Ras pathway 441
- Ras protein 326, 501, 545ff.
 - domains 548
 - downstream effectors 565
 - effector loop 548
 - effector molecules 564
 - input signals 562ff.
 - membrane localization 551
 - oncogenic mutations 550f., 567
 - properties 545
 - reception of signals 562
 - structure 547f.
 - transforming mutants 550
 - transmission of signals 562
- Ras signal transduction 552f., 555
 - GTPase activating proteins 552
 - Guanine nucleotide exchange factors 553
 - Raf kinase 555
- Ras signaling pathway 566, 737
 - oncogenic activation 737
- Ras superfamily 535ff., 545, 568
 - crosstalk among members 538
 - structural organization 537
- reactive oxygen species (ROS) 413, 529, 531, 582
- receptor 15, 19, 252ff.
 - classification by signaling activity 632
 - interaction between hormone and receptor 21f.
 - intracellular receptor 21
 - membrane-bound receptor 20
 - transmembrane receptor 21
- receptor activity 22
- regulation 300

- receptor-activity modifying protein (RAMP) 313
 - receptor for activated protein kinase C (RACK) protein 453f.
 - receptor for 9-*cis*-retinoic acid (RXR) 262f., 266
 - receptor interaction domain (RID) 271
 - receptor phosphorylation 300
 - receptor protein tyrosine phosphatase (PTPR) 519, 521ff.
 - receptor recycling 300
 - receptor tyrosine kinase (RTK) 474f., 541, 554, 563, 569, 593, 614
 - activation 479f., 485
 - adapter proteins 494
 - autoinhibition 483ff.
 - autophosphorylation 478, 483, 487, 494
 - classification 475ff.
 - coupling of effectors 487
 - dimerization 480
 - disfunction in disease 506
 - domains 475, 477
 - downstream effectors 494ff., 500f.
 - downstream signaling 485
 - endocytosis 506
 - function 474ff.
 - heterodimerization 481f.
 - inhibition 505
 - kinase domain 482
 - ligand binding 477ff.
 - negative regulation 505
 - receptor dimerization 477
 - signal transmission 474
 - signaling network 501f.
 - structure 474ff.
 - trafficking 506
 - ubiquitination 506
 - recognition element (RE) 150ff., 156, 161f.
 - clustering 159
 - selection 161
 - sequence 161
 - recognition sequence 155
 - recoverin 400
 - regulated intermembrane proteolysis (RIP) 643
 - regulator of G protein signaling (RGS) 314, 327, 336, 342, 346ff.
 - regulatory circuit 116
 - regulatory GTPase 320ff., 340
 - regulatory transcription factor 166, 258
 - replication stress 707
 - repression 275
 - repressor 164, 169, 222
 - retinoblastoma protein (Rb) 687ff., 743ff.
 - apoptosis 744
 - control by phosphorylation 690
 - domain structure 689
 - functions 689
 - hyperphosphorylated Rb 690
 - hypophosphorylated Rb 690
 - in cancer 743ff.
 - inactivation 744
 - tumor suppressor function 743
 - retinoid 10
 - Rho/Rac family 568, 589
 - rhodopsin 305f., 337
 - structure 306
 - ribosomal S6 kinase (RSK) 588
 - RING domain enzyme 71ff.
 - RNA-dependent protein kinase (PKR) 427
 - RNA-induced silencer complex (RISC) 233, 237
 - RNA interference (RNAi) 209ff., 233, 243
 - RNA polymerase 135, 137, 146f.
 - RNA processing 209ff.
 - RNA-recognition motif (RRM) 213
 - RNA silencing 229ff., 245
 - basics 230ff.
 - componenets 232
 - RNA-specific eIF-2 kinase (PKR) 228f.
 - ryanodine receptor 381, 385f.
- S**
- S-adenosyl-L-methionine (SAM) 61
 - S6 kinase phosphorylation 226
 - S-nitroso-glutathione (GSNO) 412, 414
 - S phase 661, 663f., 669, 684, 699ff.
 - scaffold
 - as allosteric regulators 108
 - as signaling enzymes 108
 - organization of feedback loops 107
 - organization of signaling circuits 105
 - organization of signaling complexes 107f.
 - targets of regulation 107
 - scaffold protein 24, 103ff., 314
 - general aspects 103
 - Scr homology and collagen (Shc) protein 499
 - second messenger 25, 352, 357, 369ff., 541
 - formation 370
 - function 370
 - general properties 369ff.
 - types 369f.
 - senescence 741f., 747ff., 766, 769f.
 - sequence-specific transcription factor 134, 150f., 153, 169, 205
 - sequential signaling 106

- Ser/Thr-phosphate-specific protein phosphatase (PSP) 461
- Ser/Thr-phosphorylation 54, 496f.
- Ser/Thr-specific protein kinase 417ff., 447, 631ff.
- Ser/Thr-specific protein phosphatase 461ff.
 - classification 462
 - function 462f.
 - inhibitors 464
 - regulation 462, 464
 - structure 462
- signal dampening 496f.
- signal-directed inhibitory modification 17
- signal processing 6
 - in signaling paths and signaling networks 108ff.
- signal recognition particle (SRP) 326
- signal-regulated transcription factor 167
- signal switching 319
- signal transduction network 165
- signal transmission 473ff., 535ff.
- signaling 103ff., 251ff.
 - by nuclear receptors 251ff.
 - organization 103ff.
 - spatial control 111f.
 - specificity 109
 - temporal control 113
 - via ion channels 292
 - via transmembrane receptors 291
- signaling circuit 105f., 116
- signaling complex 109
 - PTM-induced formation 109
- signaling enzyme 23f., 34ff.
- signaling modul 27, 30f.
 - differential use 31
 - subtypes 31
- signaling network 108ff., 501
- signaling pathway
 - architecture 113
 - malfunction 715ff.
- signaling protein 16, 284, 298
 - activation 16f.
 - catalytic domain 28
 - clustering 112
 - deactivation 16f.
 - function 29
 - interaction domain 28
 - isoforms 18
 - lipidation 90ff.
 - modular structure 27, 29f.
 - mutations 729
 - properties 27
 - regulatory domain 28
 - regulatory modifications 38
 - unstructured section 30
 - variability 18
- silencing 190, 198
- silencing mediator for retinoic and thyroid hormone receptors (SMRT) 274
- Skp1-Cullin-F-box complex (SCF complex) 75, 682f.
 - proteolysis 682
 - structure 75
 - substrate 75, 683
 - subunits 683
- Smad anchor for receptor activation (SARA) 638
- Smad protein 636ff.
 - activation 638
 - classification 636
 - DNA binding 640
 - domains 636
 - expression 641
 - I-Smad 631, 636f., 639ff.
 - phosphorylation 638
 - R-Smad 631, 634, 636ff., 640f.
 - transcriptional regulation 640
- Smad protein signaling 631ff.
 - regulation 640
- small GTPase 535, 537ff., 541f., 565, 568, 570
- small interfering RNA (siRNA) 229ff., 237, 243ff.
 - applications 246f.
 - functions 246f.
 - posttranscriptional silencing 246
 - processing 243
 - sources 243
- small noncoding RNA (sncRNA) 231
- small ubiquitin-related modifier (SUMO) 88f.
 - regulation 89
- solenoid 176
- sphingomyelin 402
- sphingomyelinase 402
- sphingosine 403
- spliceosome 211
- splicing 214
- SR protein 213f.
- Src homolog 2 (SH2) domain 491ff.
- Src tyrosine kinase 508ff., 608
 - activation 511ff.
 - domains 509
 - inactive state 509, 511
 - regulation 509f.
 - signal transduction pathways 514
 - structure 509f.
- STAT protein 611

- acetylation 615
 - activation 612f.
 - function 612
 - signaling function 614
 - structure 612
 - unphosphorylated STATs 615
 - steroid hormone 9f., 254, 258, 276, 281
 - steroid hormone receptor 256, 258, 281f.
 - sumoylation 89, 641
 - suppressor of cytokine signaling (SOCS) 119, 505, 608, 616f.
 - synaptic scaffold 105
- t**
- T-cell receptor (TCR) 618ff.
 - activation 621f.
 - signaling 621
 - structure 618ff.
 - subunits 619
 - T₃ hormone 251, 253f., 259, 263, 275f., 281, 284, 288f.
 - talin 625f.
 - TATA box 138, 140
 - TATA box binding protein (TBP) 138, 140f.
 - TATA box binding protein associated factor (TAF) 140f.
 - TATA box binding protein-related factor (TRF) 141
 - tetradecanoyl phorbol acetate (TPA) 447, 449, 451
 - TFIID 139ff., 204
 - TFIIH 141ff.
 - enzymatic activities 141f.
 - subunit structure 142
 - thrombin 302, 308
 - thyroid hormone receptor-activation protein (TRAP) complex 273, 275
 - tissue hormone 15
 - TNF cytokine 651
 - Toll IL-1 receptor (TIR) 653, 657
 - Toll-like receptor (TLR) 583
 - activation 655f.
 - adapter-mediated downstream signaling 657
 - adapters 656
 - domains 654
 - extracellular TLRs 654
 - intracellular TLRs 654
 - ligand binding 655f.
 - signaling 653ff., 658
 - structure 654
 - transactivation domain 157f.
 - transcription 129ff., 215
 - activation 152, 161, 187, 256, 268
 - activator 165, 169
 - coregulators 153
 - initiation 149
 - proteins 133
 - regulation 129ff., 149ff., 163, 175ff. 203
 - repression 152, 163f., 268
 - steps 132
 - transcription factor 158, 162, 204, 279, 374
 - classification 165f.
 - control 165ff.
 - modular structure 152
 - repression mechanisms 164
 - transcription factor E2F 691ff., 745f.
 - activation 691
 - classes 692
 - control by Rb 691f.
 - repression 691
 - transcription regulator 170
 - transcriptional activator 172
 - transducin 331, 338f.
 - transforming growth factor β (TGF β) 632ff.
 - function 633
 - growth regulatory effects 642
 - regulation 640
 - subfamilies 633
 - transforming growth factor β (TGF β) receptor 631f., 634ff.
 - activation 634f.
 - domains 635
 - phosphorylation 635f.
 - structure 635
 - regulation of signaling 639
 - translation
 - control 218f., 222f.
 - initiation 217, 223ff.
 - mRNA-specific control 219f., 222
 - regulation 209ff., 217ff.
 - regulation via eIF-2 226ff.
 - repression 223, 236, 238
 - transmembrane adapter protein (TRAP) 623
 - transmembrane receptor 291, 441, 473ff., 631ff.
 - aberrant activation 728
 - activation 292
 - classification 291
 - downstream targets 300
 - extracellular domain 294
 - function 299
 - intracellular domain 298f.
 - ligand binding 294
 - signal transmission 473ff.
 - signaling 291, 293

- structure 291, 294ff.
 - regulation of activity 300
 - transmembrane domain 296ff.
 - transmembrane signaling 291
 - transnitrosylation 412
 - tumor cell 715ff.
 - characteristics 715, 723
 - epigenetic changes 717ff.
 - genetic changes 716
 - insensitivity to antigrowth signals 728
 - large-scale changes 717
 - mutation 715
 - physiologic changes 725ff.
 - self-sufficiency in growth signals 727
 - small-scale changes 717
 - tumor evolution 725
 - tumor necrosis factor (TNF) 87, 594, 778f.
 - tumor necrosis factor receptor (TNFR) 589, 614, 648ff.
 - activation of NF κ B pathways 652f.
 - apoptosis 795
 - biological functions 650
 - domains 649f.
 - downstream signaling 652
 - ligands 649f.
 - receptor activation 652
 - recruitment of adapter proteins 652
 - structure 650
 - tumor promoter 447, 449
 - tumor suppressor 633, 679, 688, 743
 - tumor suppressor gene 715ff., 722, 741ff.
 - classes 742
 - functions 741ff.
 - tumor suppressor protein 742
 - tumor suppressor protein p53 747ff.
 - aberrant destabilization 770
 - acetylation 755
 - activation 747, 750, 762
 - apoptotic genes 766, 798
 - apoptosis 797f.
 - biochemical properties 751ff.
 - control by Mdm2 756ff.
 - cousins of p53 751
 - domains 752
 - function 749ff.
 - genes regulated by p53 760
 - inactivation 748, 751
 - induction of miRNA 768
 - interaction partners 761
 - metabolic regulation 767
 - methylation 755
 - neddylation 756
 - negative feedback between p53 and Mdm2 757
 - p53 recognition element 760
 - phosphorylation 753, 758
 - posttranscriptional modifications 753f., 760
 - repression 757, 765, 767
 - selection of target genes 760
 - stabilization 750
 - structure 751ff.
 - sumoylation 756
 - targets 763ff.
 - transcription-independent induction of apoptosis 799
 - tumorigenic mutations 770
 - ubiquitination 756
 - tumorigenesis 203, 715ff.
 - Tyr-phosphorylation 54, 495
 - Tyr-specific protein phosphatase SHP-2 501
 - tyrosine kinase (TK) 299, 473ff., 593
 - activity 473ff.
 - domains 473, 481f.
- u**
- ubiquitin 65ff.
 - activation 68
 - degradation 78ff.
 - transacylation 68
 - transfer 68
 - ubiquitin-binding domain (UBD) 82, 84f., 193
 - ubiquitin conjugation 66ff., 82f., 85
 - E1 enzyme 66ff.
 - E2 enzyme 66ff.
 - E3 enzyme 66ff., 73
 - multiplicity 81
 - nonproteolytic functions 81ff.
 - ubiquitin-like protein 88
 - ubiquitin modification 62ff.
 - ubiquitin pathway 671
 - ubiquitin-protein ligase 69
 - regulation 69
 - structure 69
 - ubiquitin receptor 84f.
 - ubiquitination 66ff., 82, 192, 278, 301, 506, 641
- w**
- Wnt/ β -catenin signaling 770ff.
- x**
- X-linked severe combined immunodeficiency disease (X-SCID) 603
- z**
- zeta-associated protein 70 (ZAP70) 621f.

