

Index

A

- A20, 384
- AB204, 1133
- Acromesomelic dysplasia (AMD), 961, 969
- ACTA2, 778
- Activin
 - adipogenesis, 744
 - BAMBI binding, 60
 - cancer studies, 86
 - chondrocyte differentiation, 734
 - Cripto complex, 59–60
 - developmental expression, 61
 - Drosophila*
 - axon guidance, 505–506
 - neuroblast proliferation role, 505
 - neuromuscular junction, 502–505
 - neuronal remodeling, 506–507
 - epidermis development role, 661–663
 - erythropoiesis signaling, 842–843
 - female reproduction, 940
 - fibrosis role, 85–86
 - follistatin binding, 60
 - functions
 - adipocytes, 81
 - bone homeostasis, 83
 - erythropoiesis, 79
 - glucose homeostasis, 81–82
 - inflammation, 83–85
 - mouse models
 - activin β A, 61
 - activin β B, 61
 - activin C, 64, 68
 - activin E, 68
 - overview, 65–68
 - receptors, 68–69
 - Smads, 69
 - nervous system, 79–81
 - overview, 62–64
 - reproduction
 - female reproduction, 71, 73–77
 - hypothalamic–pituitary–gonadal axis, 70–72
 - male reproduction, 77–79
 - wound healing, 85
 - history of study, 51–52
 - liver and bile duct development, 698
 - male reproduction, 934, 936
 - mesoendoderm patterning, 584–585
 - nomenclature, 52
 - osteoblast differentiation, 726–727
 - pancreas development, 690
 - signaling
 - Drosophila* studies, 70
 - MAPK, 58–59
 - receptor types, 54–57
 - Smads, 57–58
 - skeletal development, 968
 - structure, 52, 54
 - therapeutic targeting
 - anemia, 88–89
 - cancer-induced cachexia, 88
 - inflammation, 89–90
 - muscular dystrophy, 88
 - obesity, 87–88
 - osteopenia, 89
 - prospects, 90
 - strategies, 87
 - Xenopus laevis* studies, 69–70
- Activin response element (ARE), 472
- Acute lymphoblastic leukemia (ALL), transforming growth factor- β signaling, 856
- Acute myeloid leukemia (AML), 855, 1044
- Acute promyelocytic leukemia (APL), transforming growth factor- β signaling, 855
- ADAM12, 231
- ADAM17 (TACE), 228, 306, 444, 451
- ADAMTS, 531, 1070
- Adipocyte, activin function, 80
- Adipogenesis
 - activin, 744
 - bone morphogenetic proteins, 739, 741–742
 - growth differentiation factors, 743–744
 - overview, 739–740
 - transforming growth factor- β , 742–743
- ADMP, 586–587, 596–597
- ADT-2, 531
- AER. *See* Apical epidermal ridge
- AGE-1, 529
- AIRE-1, 413
- Akt, 311, 350, 352, 358, 384, 428–430, 428–430, 430, 441, 453–455, 471–474, 478, 482, 560, 704, 1018, 1119
- ALK-1, 32, 110–111, 116, 123, 222–223, 227, 232–233, 273–274, 310, 352, 446, 470, 774, 776–778, 784–785, 791, 813–814, 816, 818–819, 1121, 1129

Index

- ALK-2, 32, 110–111, 116, 220–221, 233, 310, 381, 406, 408, 553, 668, 727, 735, 745, 813, 821, 827, 827, 930, 981, 1127–1128, 1134
- ALK-3, 32, 110–111, 123, 219–220, 227, 232, 273–274, 350, 352, 378, 381, 586–587, 843, 1068, 1124, 1130, 1133
- ALK-4, 32, 54–55, 57, 59, 110–111, 220, 222, 234, 274, 310, 548, 563, 738, 744, 842, 945
- ALK-5, 37, 110–111, 219, 222–223, 225, 273–274, 310, 350, 352, 381, 404, 470, 738, 774, 777–778, 790, 840, 944, 1036, 1072
- ALK-6, 110–111, 220, 224, 227, 273–274, 310, 350, 378, 587, 55, 57, 220, 222, 227, 234, 310, 548
- ALK-7, 580, 743, 842
- ALL. *See* Acute lymphoblastic leukemia
- Alp, 721, 725
- α 2-Macroglobulin, 187–188
- ALS. *See* Amyotrophic lateral sclerosis
- Alzheimer's disease, transforming growth factor- β studies, 913
- AMD. *See* Acromesomelic dysplasia
- AMH. *See* Anti-Müllerian hormone
- AML. *See* Acute myeloid leukemia
- Amnionless, 177
- AMSH, 387–388
- Amyotrophic lateral sclerosis (ALS), transforming growth factor- β studies, 913
- Anemia, activin therapeutic targeting, 88–89
- Angiogenesis, cancer, 1070–107
- ANGPTL4, 1049, 1054
- Anti-Müllerian hormone (AMH), 30, 34, 252, 269, 706, 931–932, 936, 940–943, 946
- Aortic aneurysm, 232–233, 786–787
- AP-1, 388, 696
- AP-2, 535
- APC, 41, 440–441, 444
- Apical epidermal ridge (AER), induction, 969–970
- APL. *See* Acute promyelocytic leukemia
- Apoptosis, transforming growth factor- β regulation in fibrosis, 1018–1020 signaling, 476–478 tumor suppression, 1041–1042
- ARC105, 340
- ARE. *See* Activin response element
- ARF-6, 535
- arf-6*, 535
- Arkadia. *See* RNF111
- Artery development, 768–770, 808 homeostasis and transforming growth factor- β signaling, 974–975 wall structure, 973–974
- ARTS, 478
- ASK1, 426
- Asthma, activin protection, 85
- Astrocyte, cell fate specification, 908–909
- ATF1, 1045
- ATF3, 314, 338, 473, 1041
- Atherosclerosis bone morphogenetic protein studies, 823 transforming growth factor- β signaling, 788–789
- Autophagy, transforming growth factor- β signaling, 479
- Axial patterning, vertebrates bone morphogenetic proteins mouse, 601–602 *Xenopus*, 598–600 zebrafish, 594–597 nodal signaling mouse, 601–602 *Xenopus*, 600–601 zebrafish, 597–598
- Axin, 443–444
- Axon guidance, transforming growth factor- β signaling, 909–910
- ## B
- Babo, 490, 501, 505
- Bacterial infection, transforming growth factor- β studies, 882
- Bam, 510
- BAMBI, 60, 112, 222, 305, 378, 381, 597, 671, 901, 936
- BAT3, transforming growth factor- β receptor signaling modulation, 225
- BAX, 1019
- B cell, transforming growth factor- β regulation activation and differentiation, 873–874 proliferation and survival, 873
- Bcl2, 364, 477
- BCL6, 1053
- BCR-ABL, 855, 1093
- BD. *See* Brachydactyly
- β -Catenin axial patterning in vertebrates, 594–595, 598, 600 epithelial–mesenchymal transition, 1012 hair follicle development role, 660–661 neural induction, 902 osteoblast differentiation, 722, 725
- Betaglycan, 59, 221–222, 275–276, 773
- BGLAP*, 339
- BGN. *See* Biglycan
- BID, 1019
- Biglycan (BGN), 185
- Bile duct, development, 695–698
- Bladder, development, 698–703
- BMPER, 587, 620–621, 817
- BMPs. *See* Bone morphogenetic proteins
- Bone development. *See* Skeletal development homeostasis activins, 83 catabolic bone diseases, 983–984

- defects, 981–983
 - inhibins, 83
 - signaling, 979–981
 - Bone morphogenetic proteins (BMPs)
 - adipogenesis, 739, 741–742
 - BAMBI binding, 60
 - cancer studies
 - overview, 123
 - stroma effects, 124
 - therapeutic targeting, 124–125
 - tumor promotion, 124
 - tumor suppression, 123–124
 - chondrocyte differentiation, 727–731
 - chordin modulation, 170–171
 - Drosophila* signaling
 - early axial patterning, 492–495
 - late embryogenesis roles, 495–496
 - neuromuscular junction, 502–505
 - non-wing imaginal disc signaling, 501–502
 - pupal wing development, 499–500
 - transcriptional responses in wing disc, 498–499
 - fat tissue function, 117–118
 - gradients, 809
 - hair follicle development role, 119–120
 - hematopoietic stem cell signaling, 843
 - heterodimers, 183
 - iron homeostasis, 120–121
 - kidney development role, 121
 - modulation strategies
 - extracellular environment, 1120–1123
 - receptor and effectors, 1121, 1124–1126
 - modulators of signaling, 112–113
 - muscle function, 116–117
 - myoblast differentiation, 735
 - neural induction and patterning, 899–906
 - noggin binding, 169–170
 - nomenclature, 33–34, 108, 807–808
 - osteoblast differentiation, 720–724
 - overview, 30, 32, 107–108
 - processing, 108–109, 808–809
 - receptors. *See also specific receptors*
 - coreceptors, 810–812
 - signaling, 111, 812–813, 965, 1117–1119
 - tetrameric complexes, 812
 - types, 109–111, 809–810
 - skeletal function
 - development, 114–115, 967–970
 - differentiation of osteoblasts and chondrocytes, 115–116
 - tooth development, 118–119
 - stem cell function, 121–122
 - structure, 108–109
 - target genes, 111–112
 - therapeutic applications
 - fibrosis, 1129–1130
 - heterochromatosis, 1130
 - heterotopic ossification, 1127–1128
 - iron deficiency anemia, 1130
 - myocardial infarction, 1132
 - orthopedics and craniofacial settings, 1124, 1127
 - prospects, 1133–1134
 - spinal cord injury, 1131–1132
 - stroke, 1131
 - vascular disease, 1128–1129
 - tissue distribution, 113
 - vascular system function, 122–123
 - vertebrate development
 - dorsal convergence, 615
 - dorsoventral patterning
 - expression regulation, 588–591
 - gradients, 587, 592–593
 - ligands and receptors, 585–587
 - tail and trunk patterning, 593–594
 - epidermis development, 655–657
 - extracellular regulators
 - BMPER, 620–621
 - Cerberus, 622–623
 - chordin, 616, 618–619
 - Crescent, 619
 - Follistatin, 621–622
 - Gremlin, 622
 - Noggin, 621–622
 - overview, 603–606, 616–617
 - Sizzled, 619–620
 - Tomoregulin, 623–624
 - Tsg, 520
 - feather development, 664–665
 - hair follicle
 - development role, 658–659
 - expression, 659
 - left–right patterning, 603–606, 613–614
 - joint formation, 731–732
 - kidney development, 699–703
 - lens differentiation, 671–672
 - lung development, 705–707
 - mammary gland development, 684–686
 - pancreas development, 691
 - prostate gland development, 689
 - salivary gland development, 692
 - tooth development, 669–670
 - Brachydactyly (BD), 961, 970–971
 - Brk, 498
 - Brorin, 175
 - Brorin-like, 175
 - BTG proteins, 388
- C**
- c-Abl, 423
 - Caenorhabditis elegans*, transforming growth factor- β family
 - aging and longevity regulation, 536

Index

- Caenorhabditis elegans*, transforming growth factor- β family (*Continued*)
dauer pathway, 525, 527–529
fat metabolism regulation, 536–537
history of study, 524–525
overview, 523–524
reproductive system, 926–927
signaling pathways, 525–526
Sma/Mab pathway
 alternative signaling, 538
 body size regulation, 530–532
 cell fate specification
 ectoderm, 533
 mesoderm, 532–533
 innate immunity role, 532
 overview, 530
 receptor trafficking, 533–536
UNC-129 signaling, 537
Calpain, transforming growth factor- β activation, 145
Camurati–Engelmann disease (CED), 40, 961, 981–982
Cancer
 activin studies, 86
 angiogenesis, 1070–1073
 autocrine mitogens, 1047–1048
 bone morphogenetic protein studies
 overview, 123
 stroma effects, 124
 therapeutic targeting, 124–125
 tumor promotion, 124
 tumor suppression, 123–124
 cachexia, activin therapeutic targeting, 88
 desmoplasia, 1068–1070
 epithelial–mesenchymal transition, 42, 1050–1052
 epithelial–stromal interactions, 1066–1068
 I-Smad dysfunction, 393
 immune evasion role of transforming growth factor- β , 1045
 immune response
 adaptive immunity, 1074–1076
 innate immunity, 1076–1079
 overview, 1073–1074
 inhibin studies, 86–87
 macrophage effects of transforming growth factor- β , 1047
 metastasis and transforming growth factor- β , 1053–1054
 microenvironment and mitogenic signals, 1048–1050
 natural killer cell effects of transforming growth factor- β , 1046–1047
 T cell effects of transforming growth factor- β , 1045–1046
 therapeutic properties, 1054–1055
 transforming growth factor- β studies
 cancer stem cell maintenance, 1092–1093
 cell proliferation inhibition, 1091
 chemotherapy resistance, 1093–1094
 epithelial–mesenchymal transition, 1092
 expression levels and responsiveness, 1090–1091
 extracellular matrix regulation, 1091–1092
 genetic and epigenetic alterations in tumor suppression escape
 receptor complex, 1042–1043
 signaling mediators, 1043–1044
 receptor defects, 231–232
 therapeutic targeting
 adjunctive therapy, 1104–1105
 applications, 1095–1096
 clinical trials, 1101–1104
 immunotherapy, 1105–1106
 prospects, 1106–1107
 signaling blockers, 1096–1099
 toxicity monitoring and prevention, 1100–1101
 tumor immunosurveillance suppression, 1094–1095
 tumor suppression
 apoptosis induction, 1041–1042
 cell differentiation regulation, 1041
 cytostatic program, 1039–1041
 paracrine signals, 1042
 selective failure of antitumor response, 1044–1045
 tumor initiation, 1052–1053
Cardiac fibrosis. *See* Fibrosis
Cardiac valves
 aortic valve disease, 783–784
 cushion formation, 780, 782
 transforming growth factor- β signaling in development, 782–783
Cardiovascular disease, transforming growth factor- β signaling gene defects, 775–776
Cartilage oligomeric matrix protein (COMP), 188–189
Cathepsin D, transforming growth factor- β activation, 145
CBF1, 445
Cbl-b, 387
CBP, 18, 359, 440, 687, 977, 1006
CCM. *See* Cerebral cavernous malformation
CCM1, 781
CCN proteins, 180
CD31, 1048
CD44, 224, 1092
CD69, 872
CD103, 872
CD109, 223
CD133, 1053
Cdc25A, 475
Cdc25a, 358
Cdc42, 229, 383, 430–432, 504
CDH1, 339
CDK2, 354, 355, 473, 475, 1039

- CDK4, 354–355, 473, 553, 1039–1040
CDK6, 473, 553, 1039
CDK8, 355, 415, 471, 355, 415, 447
CDK9, 471
CDKN1A, 35, 473
CDKN2B, 342, 475
CDMP-1, 969
C/EBPs, 718, 945, 739, 743
 C/EBP α , 339
 C/EBP β , 1040–1041, 1044, 1106
CED. *See* Camurati–Engelmann disease
Cell differentiation. *See also specific cells*
 history of study, 12–13
 transforming growth factor- β functional overview,
 37–38
Cell fate
 mapping in fibrosis, 1014–1016
 neural development
 astrocyte, 908–909
 microglia, 909
 neurons
 forebrain, 906–907
 hindbrain, 907
 midbrain, 907
 olfactory epithelium, 908
 retina, 908
 oligodendrocyte, 909
 specification in *Caenorhabditis elegans*
 ectoderm, 533
 mesoderm, 532–533
Cellular senescence, transforming growth factor- β
 regulation in fibrosis, 1018–1020
 signaling, 479–482
Cerberus, 177–178, 280, 579, 622–623, 900
Cerebral cavernous malformation (CCM), bone
 morphogenetic protein studies, 823
Cerl-2, 178
cGKI, transforming growth factor- β receptor signaling
 modulation, 226
CHIP, 356
Chondrocyte
 differentiation roles
 activins, 734
 bone morphogenetic proteins, 115–116,
 727–731
 transforming growth factor- β , 732–734
 growth differentiation factors and joint formation,
 731–732
Chordin, 170–171, 174, 285–288, 495, 616, 618–619
Chordin-like, 174, 560
CHRDL1, 174
CHRDL2, 174–175
Chronic myeloid leukemia (CML), transforming growth
 factor- β signaling, 852–853, 855
Chronic obstructive pulmonary disease (COPD),
 1021–1023
CK1, 440, 449
CK2.3, 1124
CKGF domain, 248, 250–251
CLIC4, 353
c-Met, 1050
CML. *See* Chronic myeloid leukemia
c-Myc, 480, 546, 1040
CNTF, 908
Coco, 178
Collagen
 accumulation and transforming growth factor- β
 signaling in fibrosis, 1004–1010
 transforming growth factor- β family binding, 188
COMP. *See* Cartilage oligomeric matrix protein
Connective tissue growth factor (CTGF), 180, 455, 659,
 725, 788, 1024, 1050
COPD. *See* Chronic obstructive pulmonary disease
CoREST, 342
CREB, 16, 432, 440
CREB1, 1047
Crescent, 172, 592, 619
CRIM1, 176, 504
CRIPTO, 580, 583
Cripto, 59–60, 222–223, 275–276
CRISPR-Cas9, 792
CRM1, 381
Crossveinless-2, 175–176
CRYPTIC, 609, 611
CSFR1, 980
c-Ski, 226, 389, 28
CtBB, 367, 383
CTGF. *See* Connective tissue growth factor
CTLA-4, 1105
CV-2, 494–495
CXCL1, 1067
CXCL12, 558, 1048
CXCL5, 1067
CXCR3, 1046
CXCR4, 1046–1047
Cyclin A, 873

D
DAB2, 229, 1106
Dab2, 470
DAF-1, 525
DAF-2, 529, 537
DAF-3, 525, 527–529
daf-3, 529
DAF-4, 525
daf-4, 525
DAF-5, 529
daf-5, 528–529
DAF-7, 527, 529, 537
Daf-7, 927
daf-7, 525, 536–537

Index

- DAF-8, 525, 527
daf-1, 524–525, 527
DAF-11, 529
daf-12, 529
DAF-14, 525, 527
DAF-16, 529, 536–537
DAF-18, 529
DAN, 177
Dan proteins, structures, 280–284
Dante, 178
Dapper2, transforming growth factor- β receptor
 signaling modulation, 225
Dauer pathway, 525, 527–529
Daw, 490, 492, 505–509
DAXX, 1041
Daxx, 362
DBL-1, 525, 530–532, 533, 538
dbl-1, 525
DC. *See* Dendritic cell
DCN. *See* Decorin
DDX proteins, 317
DDX5, 36
DEAF-1, 413
DEANRI, 552–553
Decorin (DCN), 184–185
Delta, 248, 444
Dendritic cell (DC), transforming growth factor- β
 regulation, 874–876
 cancer studies, 1095
 stiff skin syndrome pathology, 978
Dental stem cells, transforming growth factor- β family
 functions, 563–564
Desmoplasia, cancer, 1068–1070
Diabetes type 1, transforming growth
 factor- β studies, 881
Dicer, 35
Diffuse intrinsic pontine glioma, 233
Dilp2, 508
DKK1, 579
Dkk1, 596, 599, 668
Dkk3, 599
Dkk4, 668
DLC1, 354
Dll, 501–502
DMH2, 1133
Dorsoventral patterning, vertebrates
 bone morphogenetic protein signaling
 expression regulation, 588–591
 gradients, 587, 592–593
 ligands and receptors, 585–587
 tail and trunk patterning, 593–594
 nodal tail and trunk patterning, 593–594
DPC4, 16, 409
DPC4, 476
Dpp, 186, 188, 440, 443, 490, 492–496, 498, 509–511,
 532, 777, 901, 927–928
 gradient
 formation models, 496–497
 modifiers, 497
 imaginal disc signaling, 501–502
 tissue growth regulation, 499
DPY30, 342
DRAG-1, 533
drag-1, 532
Drm, 178
Drosophila transforming growth factor- β family
 signaling
 activins
 axon guidance, 505–506
 neuroblast proliferation role, 505
 neuromuscular junction, 502–505
 neuronal remodeling, 506–507
 bone morphogenetic proteins
 early axial patterning, 492–495
 late embryogenesis roles, 495–496
 neuromuscular junction, 502–505
 non-wing imaginal disc signaling, 501–502
 pupal wing development, 499–500
 transcriptional responses in wing disc, 498–499
 core components, 489–492
Dpp
 gradient
 formation models, 496–497
 modifiers, 497
 tissue growth regulation, 499
Gbb in wing growth and patterning, 497–498
hormonal control of development, 509
innate immunity, 509–510
Mad integration of cross-pathway signals, 500–501
metabolic homeostasis, 507–509
prospects for study, 512, 514
reproductive system, 927–928
tissue homeostasis, 510–513
wing imaginal disc signaling, 496
Ductal morphogenesis, overview, 683–684
DYNLRB1, 311
- E**
- EAE. *See* Experimental autoimmune encephalitis
EC. *See* Endothelial cell
Ecdysone, 509
Ectoderm, development, 655–657
Ectodin, 179
Ectodysplasin A (EDA), 659
Ectodysplasin A receptor (EDAR), 659
EDA. *See* Ectodysplasin A
EDAR. *See* Ectodysplasin A receptor
EFN-4, 533
EGE. *See* Epidermal growth factor
EGFR, 385
EGLN3, 84

- eIF4E, 475
- Embryonic stem cell (ESC)
 - overview, 545–546
 - transforming growth factor- β family
 - functions, 38
 - signaling
 - human cells, 549–550
 - mouse cells, 547–549
- Emilin1, 189
- EMT. *See* Epithelial–mesenchymal transition
- EndMT. *See* Endothelial-to-mesenchymal transition
- Endoglin, 222, 275, 773–774, 776, 783, 789, 813, 816–817, 824–825, 827, 848
- Endoglycosidase, transforming growth factor- β
 - activation, 147
- Endometriosis, 946–947
- Endothelial cell (EC)
 - bone morphogenetic proteins and metabolism, 825
 - mural cell interplay, 778–779
 - transforming growth factor- β signaling, 774, 776–777
- Endothelial-to-mesenchymal transition (EndMT), 779–782, 782, 1052
- Epidermal growth factor (EGF), transforming growth factor- β synergism, 27
- Epidermis
 - bone morphogenetic protein signaling in
 - development, 655–657
 - overview of development, 657–658
 - Smads in development, 660
 - stem cells and hair cycling, 660–661
 - transforming growth factor- β and activin in
 - development, 661–663
- Epithelial–mesenchymal transition (EMT)
 - cancer, 42, 1050–1052, 1092
 - definition, 1011, 1016–1017
 - developmental function, 1012–1013
 - ductal morphogenesis, 684
 - epiblast, 653–654
 - epithelial organogenesis, 652–653
 - eye, 671–672
 - fibrosis studies, 1013
 - gastrointestinal tract development, 693–695
 - history of study, 13–14
 - kidney development, 702
 - liver and bile duct, 695–698
 - lung development, 706–707
 - mammary gland, 688
 - mTORC role, 454
 - neural crest, 654–655
 - Notch signaling, 445
 - pancreas, 689
 - pathway, 1011–1012
 - PI3K-Akt signaling, 428–429
 - prospects for study, 673
 - RhoA role, 431
 - transforming growth factor- β
 - fibrosis, 41
 - induction of family members, 423–424
 - isoform functions, 39
 - signaling, 39, 213
 - Wnt signaling, 441
- Epithelium
 - mesenchymal-epithelial interaction, 658, 684
 - transforming growth factor- β family in
 - differentiation, 651–652
- EPO. *See* Erythropoietin
- ERK, 422–425, 548, 555
 - transforming growth factor- β /Smad cross talk
 - activation of MAPK signaling, 452–453
 - cooperative interactions, 450–451
 - downregulation of transforming growth factor- β signaling, 451–452
 - overview, 450
- Erythropoiesis, activin function and therapeutic targeting, 79, 88–89
- Erythropoietin (EPO), 79
- ESC. *See* Embryonic stem cell
- E-selectin-ligand-1, 141
- Esophagus, differentiation, 693–695
- EVI1, 855–856
- Evolution, transforming growth factor- β family
 - CKGF domain, 248, 250
 - deuterosome emergence, 250–251
 - overview, 247–249
 - phylogenetic trees, 251–252
 - procomplex structure and function
 - biosynthesis and latency, 255–256
 - conformational change in transforming growth factor- β activity regulation, 261–262
 - growth factor binding partner competition, 260
 - prodomain diversity, 262
 - prodomain–growth factor complex structure, 256–260
 - transforming growth factor- β release from prodomain, 260–261
 - prodomain, 252, 255
 - prospects for study, 288
 - sequence alignment, 253–254
 - three-dimensional structures
 - antagonists
 - chordin, 285–288
 - Dan, 280–284
 - follistatin, 284–286
 - Nbl1, 283
 - noggin, 278, 280–281
 - overview, 278–279
 - sclerostin, 280–283
 - coreceptors, 274–278
 - family members, 262–266
 - growth factor–receptor complexes, 267, 269–274
 - receptor ectodomains, 265, 267–268

Index

Experimental autoimmune encephalitis (EAE), 881
EZH2, 871

F

Fanconi anemia, transforming growth factor- β
signaling, 851–852

FAP, 1048

FAST1, 311, 472

FAST2, 552

FBN1, 787

Fbxw7, 850

Feather, development, 663–665

Female reproduction, transforming growth factor- β
signaling

ovarian function, 938–943

overview, 935

pathology, 946–947

pregnancy, 943–946

FGF. *See* Fibroblast growth factor

Fibrillin, 40, 141–142, 190, 978–979

Fibroblast growth factor (FGF)

axial patterning in vertebrates, 601

FGF2, 549–550, 555–556, 698, 701, 1050

FGF7, 556

FGF8, 585, 594–595

FGF10, 556, 671

FGF18, 556

Fibrodysplasia ossificans progressiva (FOP), 233, 779,
820–822, 962, 981

Fibromodulin (FMOD), 186

Fibrosis

activin role, 85–86

bone morphogenetic protein therapeutic targeting,
1129–1130

cardiac fibrosis, 790–791

cell fate mapping, 1014–1016

collagen accumulation and transforming growth
factor- β signaling, 1004–1010

epithelial–mesenchymal transition

definition, 1011, 1016–1017

developmental function, 1012–1013

fibrosis studies, 1013

pathway, 1011–1012

fibroblast proliferation and apoptosis regulation,
1016–1020

I-Smad dysfunction, 392

integrins

extracellular matrix stiffness interplay in
transforming growth factor- β activation
and stromal expansion, 1002–1003

mechanical force in transforming growth
factor- β activation, 1003–1004

tissue stiffness and fibrosis progression, 1010–1011

organs affected, 1001

pulmonary fibrosis

epithelial activation, 1020–1021

transforming growth factor- β role
evidence, 1020

signaling in integration of immunity and
stromal signaling, 1021–1023

therapeutic targets, 1023–1035

transforming growth factor- β role, 40–41

Fibulin proteins, 189–190

FK506, 786

FKBP, 809, 909

FKBP10, 1008

FKBP12, 16, 217, 225, 306, 404, 406, 1037

FLIP, 478

Flk1, 441

FMOD. *See* Fibromodulin

FOG1, 729

Follicle-stimulating hormone (FSH), 70–77, 934, 940

Follistatin, 621–622

activin binding, 60

domain, 162

mouse engineering, 61, 64

myoblast differentiation, 738–739

osteoblast differentiation, 726–727

structure, 284–286

transforming growth factor- β interactions, 162

FOP. *See* Fibrodysplasia ossificans progressiva

4EBP1, 475

FOXA1, 332

FOXA2, 552–553, 582

FoxG1, 1044

FoxH1, 336, 338, 458, 472, 581, 583

FoxN1, 666

FoxO, 35, 338, 453, 472, 738, 849, 1044, 1053

Foxp3, 39, 870

Fresolimumab, 1097, 1099, 1101

FSH. *See* Follicle-stimulating hormone

FSP1, 124, 779

F-spondin, transforming growth factor- β activation, 147

FSTL, 60, 77–78, 81–82, 162, 167–168

FSTL1, 77–78, 162, 167–168, 284

FSTL3, 284–285

FSTL4, 284

FSTL5, 284

EXR2, 555

G

GADD34, 217, 363, 382

GADD45 β , 425, 477, 1041

GAL4, 383

Galunisertib. *See* LY2157299

GARP, 140–141, 872, 967, 1107

GASPI, 671

Gastrulation, nodal signaling, 577–580

GATA, 339

GATA-3, 659, 870–871

- GATA4, 729
GATA5, 729
GATA6, 338, 729
Gbb, 490, 495, 497–499, 502, 505, 509–510
GCN5, 340
GDFs. *See* Growth and differentiation factors
GDNF, 699, 907
GEF-H1, 672–673
GFAB, 455, 555, 908, 912
GIPC, 813
GLAST, 555
Gli, 449, 903
Gli1, 564
Gli2, 449, 729
Gli3, 729
Glypicans, 186–187
Gonad development, transforming growth factor- β
 signaling, 931–934
Granulocyte, transforming growth factor- β
 regulation, 878
Grb2, 217, 423
GREM1, 560
Gremlin, 178–179, 560, 622
GRK2, 354
Growth and differentiation factors (GDFs)
 adipogenesis, 743–744
 GDF-1
 left–right patterning in vertebrates, 610
 mesoendoderm patterning, 584–585
 GDF-3, 32, 182, 263, 743
 GDF-5, 224, 263, 275, 670, 746, 969–971, 1132
 GDF-6, 731–732, 746
 GDF-7, 689, 732, 746, 910
 GDF-8, 390, 743–744, 984, 1132
 GDF-8. *See* Myostatin
 GDF-9, 32
 GDF-9, 75, 111, 263, 938–939, 941, 947
 GDF-9B, 32
 GDF-10, 744
 GDF-11, 34, 262, 536, 671, 843
 GDF-15, 262
 nomenclature, 33–34
 overview, 30, 32
 structure, 31–32
GRP78, 59–60
GSK3, 355–356, 429, 471, 500, 550, 553
GSK3 β , 364, 384, 386, 430, 440, 442–444, 449, 454,
 453, 556
Gut microbiota, transforming growth factor- β studies, 880
- H**
- Hair follicle
 bone morphogenetic proteins
 development role, 119–120, 658–659
 expression, 659
 epidermis stem cells and hair cycling, 660–661
 Hair follicle stem cell (HFSC), transforming growth
 factor- β family functions, 556–557
HBE, 578
HDACs. *See* Histone deacetylases
Hedgehog, 448–450
Hematopoietic stem cell (HSC)
 bone morphogenetic protein signaling, 843
 lineage-based commitment, 843–845
 Smad signaling, 841–842
 transforming growth factor- β
 family functions, 557–560
 signaling
 aging, 845–847
 niche, 847–848
 normal cells, 839–841
 quiescence, 848–850
 stemness signaling cross talk, 850–851
Heparan sulfate proteoglycans (HSPGs), 169, 174, 186
Hepatitis, 882–883
Hepatocyte growth factor (HGF), 1042
HER2, 450
Hereditary hemorrhagic telangiectasia (HHT), 232, 962
 bone morphogenetic protein
 signaling defects, 813–814
 therapeutic targeting, 1129
 genetic modifiers, 824
 mouse models, 819–820
 second hit hypothesis, 824
 transforming growth factor- β signaling overview,
 784–786
HERP, 445
HES, 445
Heterochromatosis, bone morphogenetic protein
 therapeutic targeting, 1130
Heterotopic ossification, 981, 1127–1128
Hex, 385
Hex, 582
HFE2, 1130
HFSC. *See* Hair follicle stem cell
HGF. *See* Hepatocyte growth factor
HHT. *See* Hereditary hemorrhagic telangiectasia
Hic-5, 387
HIF-1, 693
HIF1 α , 1008
HIPK1, 911
Hippo, 313, 446–448, 552
Histone deacetylases (HDACs), 385
HIV. *See* Human immunodeficiency virus
HMGA2, 338, 1092
HNF1 α , 696–697
HNF4, 696–697
HNF4A, 338
Hnk-1, 654
Hoxb7, 702
HP1, 332

Index

- HP1 γ , 552
HSC. *See* Hematopoietic stem cell
HSF1, 1069
HSP47, 1006, 1008–1009
Hsp90, transforming growth factor- β receptor signaling modulation, 225
HSPB1, 1052
HSPGs. *See* Heparan sulfate proteoglycans
Human immunodeficiency virus (HIV), 883
Hypoxia
 bone morphogenetic protein studies, 825–826
 vascular endothelial growth factor induction, 770
- I**
- IBD. *See* Inflammatory bowel disease
ICAM-1, 823, 1093
Id proteins, 473, 706
 Id1, 391, 548, 1041, 1046, 1051, 1134
 Id2, 385, 909
 Id3, 548, 1134
 Id4, 909
IDH, 1104
Idiopathic pulmonary arterial hypertension (IPAH), 220, 233
IFN- γ . *See* Interferon- γ
IGF-1, 556, 737–738
IGFBP3. *See* Insulin-like growth factor- β -binding protein 3
IKK, 422, 427, 456–458
IL-1. *See* Interleukin-1
IL-4. *See* Interleukin-4
IL-6. *See* Interleukin-6
IL-8. *See* Interleukin-8
IL-10. *See* Interleukin-10
IL-11. *See* Interleukin-11
IL-12. *See* Interleukin-12
IL-13. *See* Interleukin-13
IL-17. *See* Interleukin-17
IL-21. *See* Interleukin-21
IL-22. *See* Interleukin-22
IL-23. *See* Interleukin-23
IL-25. *See* Interleukin-25
IMC-TR1, 1099
Induced pluripotent stem cell (iPSC)
 bone morphogenetic protein studies, 122
 overview, 546
 transforming growth factor- β
 differentiation role, 551–553
 family signaling, 550–551
Inflammation
 activin modulation
 adipose tissue, 84
 chronic lung disease, 85
 macrophages, 83–84
 therapeutic targeting, 89–90
 I-Smad dysfunction, 392–393
Inflammatory bowel disease (IBD), transforming growth factor- β studies, 880
Influenza, 882
INHA, 734
Inhibins
 betaglycan coreceptor, 59
 cancer studies, 86–87
 developmental expression, 61
 functions
 bone homeostasis, 83
 glucose homeostasis, 82
 mouse models
 knockout mice, 69
 overview, 65–68
 overview, 62–64
 reproduction
 female reproduction, 71, 73–77, 938
 hypothalamic–pituitary–gonadal axis, 70–72
 male reproduction, 77–79, 934
 history of study, 51–52
 nomenclature, 52
 osteoblast differentiation, 726–727
 structure, 31–32, 52, 54
Insulin-like growth factor- β -binding protein 3 (IGFBP3), 180
Integrins
 fibrillin interactions and transforming growth factor- β overactivation, 978–979
 fibrosis studies
 extracellular matrix stiffness interplay in transforming growth factor- β activation and stromal expansion, 1002–1003
 mechanical force in transforming growth factor- β activation, 1003–1004
 tissue stiffness and fibrosis progression, 1010–1011
 transforming growth factor- β
 activation, 142–144
 receptor signaling modulation, 224
 release from prodomain, 260–261
Interferon regulatory factors (IRFs), 409, 411
Interferon- γ (IFN- γ), 870, 880, 1078
Interleukin-1 (IL-1), 871, 1047
Interleukin-4 (IL-4), 871, 1022
Interleukin-6 (IL-6), 871, 876, 909, 1047
Interleukin-8 (IL-8), 1047
Interleukin-10 (IL-10), 871, 876, 909, 1047
Interleukin-11 (IL-11), 1049
Interleukin-12 (IL-12), 871, 876
Interleukin-13 (IL-13), 1022
Interleukin-17 (IL-17), 1023
Interleukin-21 (IL-21), 871
Interleukin-22 (IL-22), 871
Interleukin-23 (IL-23), 871

- Interleukin-25 (IL-25), 880
Intestinal stem cell, transforming growth factor- β family functions, 560
Intestine, differentiation, 693–695
IPA. *See* Idiopathic pulmonary arterial hypertension
iPSC. *See* Induced pluripotent stem cell
IRAK1, 384
IRE-1, 1009
IRF4, 871
Iron deficiency anemia, bone morphogenetic protein therapeutic targeting, 1130
ISTH0036, 1097
ISTH0047, 1097, 1101
- J**
- Jab1, 366, 386–387
JAGGED1, 1049
JAK, 854
Jak-Stat, 432, 455–456, 471
JMJD3, 342, 458
JNK, 363–364, 366, 383, 425–428, 450, 452, 478, 494, 699, 720, 722, 728, 910, 1041
JPS. *See* Juvenile polyposis syndrome
Juvenile hormone, 509
Juvenile polyposis syndrome (JPS), 232
- K**
- Kallikreins, transforming growth factor- β activation, 145–146
KCB, 176–177
Keratoacanthoma, 1100
Kidney, development, 698–703
Kielin, 176
Kielin/chordin-like protein, 113
KLF2, 550, 781–782, 872
KLF4, 546, 548, 551, 578, 781–782
KLF6, 702
KLF15, 946
KLRG1, 869–870
KRAS, 41
- L**
- Lag1, 445
Lag-2, 444
LAP. *See* Latency-associated peptide
Large latent complex (LLC)
 extracellular matrix interactions, 139–140
 overview, 31, 40, 136
Latency-associated peptide (LAP), 559
 functional overview, 30–31, 135
 history of study, 8
 transforming growth factor- β interactions, 136–137, 772
- Lats1, 446
Lats2, 446, 448
LDN-193189, 1121, 1130, 1133–1134
LDS. *See* Loeys–Dietz syndrome
LEF, 440, 444, 472, 1012
LEF1, 314, 384, 659, 668
Lefty proteins, 32, 34, 181–182, 583
 Lefty1, 378, 598, 612
 Lefty2, 378, 597–598, 611
Left–right patterning, vertebrates
 lateral plate mesoderm
 asymmetry transfer, 610–611
 transforming growth factor- β family signaling, 611–615
 organizer specification, 608–609
 overview, 602
 symmetry breakage
 mechanisms, 602, 608
 transforming growth factor- β family, 609–610
Leiomyoma. *See* Uterine fibroid
Leishmania, 883
Lens, differentiation, 671–672
Leukemia inhibitory factor (LIF), 121–122, 441, 444, 450, 547–548, 550, 908, 1053
Leuprolide acetate, 947
LH. *See* Luteinizing hormone
LIF. *See* Leukemia inhibitory factor
LIMK, 655
LIMK1, 229, 431–432
Liver, development, 695–698
LLC. *See* Large latent complex
Lmx1a, 904
Loeys–Dietz syndrome (LDS), 40, 232–233, 786, 962, 973, 976–977
LON-2, 531–532
Losartan, 975
LOX, 1009, 1070
LOXL1, 1009
LOXL2, 1006, 1009
LOXL4, 1067
Lrp5, 440, 444
Lrp6, 440, 444
LTBP
 functional overview, 40, 135
 isoforms, 138
 LTBP-1, 783, 1003–1004
 LTBP-4, 787
 release, 260–261
 structure, 137–138, 258, 260
 transforming growth factor- β interactions, 135–139, 190
Lumican, 186
Lung, development, 703–707
Luteinizing hormone (LH), 70–77, 934
LY2109761, 1100
LY2157299, 1094, 1097–1099, 1102–1103

Index

- LY2382770, 1097, 1102
LY3022859, 1097, 1102
Lymphatic system
 development, 770–771
 endothelium and transforming growth factor- β
 signaling, 777–778
 vascular remodeling defects, 818
LYVE-1, 777
- M**
- Mab. *See* Sma/Mab
Macrophage
 bone morphogenetic proteins in differentiation,
 824–825
 cancer and effects of transforming growth factor- β ,
 1047
 transforming growth factor- β regulation, 876–878
Mad, 57–75, 443, 457, 489–491, 493, 500–501, 504
Male reproduction, transforming growth factor- β
 signaling, 934, 936–938
Mammary gland, development, 684–688
MAN1, 353
MAPK, 15–16, 18–19, 58–59, 228, 310, 311, 350,
 354–355, 363–366, 383, 450–453, 471
 adipogenesis, 741–742
 aneurysm and activation, 976
 apoptosis signaling, 1041–1042
 craniofacial development signaling, 972
 epithelial–mesenchymal transition, 654
 lung development, 704–705
 osteoblast differentiation, 720, 724
Marfan syndrome (MFS), 40, 232–233, 783, 787, 791,
 962, 975–976
Mast cell, transforming growth factor- β regulation, 878
Matrilin-3, 188
Matrix GLA protein (MGP), 189
Matrix metalloproteinases (MMPs), transforming
 growth factor- β activation, 145
MBT. *See* Midblastula transition
MCP-1, 1076
MDM2, 729
MDS. *See* Myelodysplastic syndromes
MED12, 226, 1094
Medea, 489
MEF2, 719
MEK, 385
MEK1, 450
MEKK1, 426
MEKK4, 426
Meprin, 1008
Mesenchymal–epithelial transition (MET), 652, 684,
 689, 1013
Mesenchymal stem cell (MSC), 560–563, 717–718, 741
Mesoendoderm specification
 activins in patterning, 584–585
 GDF-1 in patterning, 584–585
 nodal signaling, 577–583
 tissue patterning mechanisms, 583–584
 transforming growth factor- β family components,
 580–581
MET, 1093
MET. *See* Mesenchymal–epithelial transition
MFS. *See* Marfan syndrome
MGP. *See* Matrix GLA protein
MH1 domain, 18
Microglia, cell fate specification, 909
MicroRNA
 Smads
 expression regulation, 315–319
 maturation, 389
 transforming growth factor- β
 receptor expression control, 219–221
 regulation, 36, 319
Midblastula transition (MBT), 586, 594
MIP, 1047
Mix2, 440
Mixl1, 581, 583
Mixl1, 552
Miz-1, 473, 1040, 1044
MKK3, 383, 452–453
MKK6, 452
MKP2, 1041
MLK2, 426
MLK3, 426
MMP13, 983
MMPs. *See* Matrix metalloproteinases
Monocyte, transforming growth factor- β regulation,
 876–878
MPK38, 387
Mrf4, 719
MRTE, 1012
MS. *See* Multiple sclerosis
MSC. *See* Mesenchymal stem cell
Mst1, 446
Mst2, 446
Msx1, 665
Msx2, 666
MTMR4, 353
mTOR, 453, 739, 871
mTORC, 453–454
Mucosal immunity, transforming growth factor- β
 regulation
 gut barrier development, 879–880
 inflammatory bowel disease, 880
 microbiome, 880
Müllerian-inhibiting substance. *See* Anti-Müllerian
 hormone
Multiple sclerosis (MS), transforming growth factor- β
 studies, 881
Multiple synostosis syndrome, 962
Mural cell, endothelial cell interplay, 778–779

- Muscular dystrophy, activin therapeutic targeting, 88
MYC, 473
MyD88, 878
Myelodysplastic syndromes (MDS), transforming growth factor- β signaling, 854–855
Myeloproliferative neoplasms, transforming growth factor- β signaling, 854
Myf5, 738
MYH11, 788
Myoblast differentiation
 bone morphogenetic proteins, 735
 follistatin, 738–739
 myostatin, 738
 overview, 734–735
 Smads, 739
 transforming growth factor- β , 735–738
Myocardial infarction, bone morphogenetic protein therapeutic targeting, 1132
MyoD, 339, 385, 719, 738
MYOG, 339
Myogenin, 738
Myoglianin, 490, 505
Myostatin, 390, 743–744, 984, 1132
 functional overview, 34
 myoblast differentiation, 738
- N**
- Nail, morphogenesis, 666
NANOG, 342, 578
Nanog, 458, 546–549
Natural killer (NK) cell
 cancer and effects of transforming growth factor- β , 1046–1047
 transforming growth factor- β regulation, 876
Nbl1, 280, 283
NBL1. *See* DAN
Ndfip1, 870
NDP. *See* Norrie
Ndr1, 583–584, 597
Ndr2, 583–584, 597
Ndst1, 705
Neddd4L, 357
NEDD8, 218
NELL1, 741
NEMO, 456
Neogenin, 276
Nerve growth factor (NGF), 909
Neural development
 cell death and survival, 911–912
 cell fate specification
 astrocyte, 908–909
 microglia, 909
 neurons
 forebrain, 906–907
 hindbrain, 907
 midbrain, 907
 olfactory epithelium, 908
 retina, 908
 oligodendrocyte, 909
 induction, 899–902
 migration and axon guidance, 909–910
 patterning, 902–906
 synaptogenesis and plasticity, 910–911
 Neural injury, transforming growth factor- β family on repair, 912
 Neural stem cell (NSC), transforming growth factor- β family functions, 554–556
 Neuromuscular junction (NMJ), *Drosophila*, 502–505
 Neuropilin, transforming growth factor- β activation, 147
 Neuropilin-1 (NRP1), 223
 NF- κ B. *See* Nuclear factor- κ B
 NFI-C, 670
 NGF. *See* Nerve growth factor
 NIS793, 1099
 Nitric oxide synthase (NOS), 1077
 Nivolumab, 1102
 NK cell. *See* Natural killer cell
 NKG2D, 1046–1047, 1078
 Nkx2.1, 705–706
 Nkx3.2, 718, 729
 NMJ. *See* Neuromuscular junction
 Nodal, 331, 336, 342
 pregnancy signaling, 945
 vertebrate development
 antagonists, 623–624
 axial patterning
 mouse, 601–602
 Xenopus, 600–601
 zebrafish, 597–598
 dorsal convergence, 615–616
 left–right patterning, 607, 611–614
 mesoendoderm specification, 577–580
 overview, 576
 tail and trunk patterning, 593–594
 NOG, 971
 Nog, 732
 Noggin, 169–170, 278, 280–281, 555, 560, 621–622, 724, 1131
 Norrie (NDP), 180
 NOS. *See* Nitric oxide synthase
 Notch, 248, 444–446
 left–right patterning in vertebrates, 610
 osteoblast differentiation, 722
Nox, 1042
Nrf2, 694, 1094
NRP1. *See* Neuropilin-1
 NSC. *See* Neural stem cell
 Nuclear factor- κ B (NF- κ B), 42, 392–393, 429, 456–458, 874
 NuRD, 343

Index

O

OA. *See* Osteoarthritis
Obesity, activin therapeutic targeting, 87–88
Occludin, transforming growth factor- β receptor signaling modulation, 224
Ocn, 721
OCT4, 336, 578
Oct4, 444, 458, 546–551, 595
OFC11. *See* Orofacial cleft 11
OI. *See* Osteogenesis imperfecta
Olfactory epithelium, cell fate specification, 908
Olig1, 909
Olig2, 909
Oligodendrocyte, cell fate specification, 909
Omb, 498
ONT1, 172
Ont1, 592
OPG. *See* Osteoprotegerin
Orofacial cleft 11 (OFC11), 963, 972
OSR1, 431
Osteoarthritis (OA), transforming growth factor- β studies, 732–734, 983
Osteoblast
 development overview, 720
 differentiation roles
 activins, 726–727
 bone morphogenetic proteins, 720–724
 follistatin, 726–727
 inhibins, 726–727
 transforming growth factor- β , 724–726
Osteoblast, bone morphogenetic proteins in differentiation, 115–116
Osteocalcin, 735
Osteogenesis imperfecta (OI), 984
Osteopenia, activin therapeutic targeting, 89
Osteopontin, 385
Osteoporosis, 983–984
Osteoprotegerin (OPG), 979–980
Osx, 722
OTUB1, 358
Ovol1, 457
OVOL2, 688

P

p15, 36, 473, 475, 480, 1039–1040, 1045, 1091
p16, 482
p21, 36, 473, 475, 480, 556, 1039–1040, 1044, 1091
p27, 36, 1040
p107, 18
p300, 18, 340, 359
p38 MAPK, 450, 452, 425–428, 443, 482, 563, 1120
p53, 124, 338, 361, 480, 729
p57, 475, 558, 846, 1040
p68, 480
p70, 1041

PAH. *See* Pulmonary arterial hypertension
PAI-1, 17, 35, 1008
PAK1, 431
PAK2, 431–432
Palate, differentiation and fusion, 666–669
Pancreas, development, 689–691
Par6, 229, 430
Parasitic infection, transforming growth factor- β studies, 883–884
Parathyroid hormone (PTH), 725
Parkinson's disease, transforming growth factor- β studies, 913
PARP, 313
PARP-1, 359, 363, 1051
Patched, 102
Pax7, 738
PCP. *See* Planar cell polarity
PDCD4, 477
PDGF. *See* Platelet-derived growth factor
PECAM1, 779
PEMPA1, 1054
PENK. *See* Proenkephalin
Pent, 497
PFP. *See* Pore-forming protein
PFR. *See* Phalanx-forming region
PGC. *See* Primordial germ cell
PGC1, 741
Phalanx-forming region (PFR), 970
Phospholipase C (PLC), 440
PI3K, 229, 311, 350, 352, 358, 384, 428–430, 428–430, 430, 441, 453–455, 471–474, 478, 482, 1018
PIAS, 313
PIAS1, 362
PIC. *See* Preinitiation complex
PICK1, 310
Pin1, 313
Pituitary gland, differentiation, 692
Pitx2, 602, 612, 614
PKA. *See* Protein kinase A
PKC. *See* Protein kinase C
PKG, 356
PKR, 578
Planar cell polarity (PCP), 610, 615–616
Plasmin, transforming growth factor- β activation, 145
Platelet-derived growth factor (PDGF), 476, 659, 1003, 1022, 1024, 1048, 1050, 1076
 transforming growth factor- β modulation, 6, 37, 224, 233
PLC. *See* Phospholipase C
PLOD2, 1008
Plum, 506
PLX-2, 533
PML-RAR α , 855
POH. *See* Progressive osseous heteroplasia
POMC. *See* Proopiomelanocortin
Pore-forming protein (PFP), 1045

- POU2F1, 338
Pou5f3, 595
PP1, 382
PP2A, 314
PP2C, 226
PPAR γ , 562–563, 718
PPM proteins, 314
PPM1A, 352–353, 471
PRDC, 179, 281, 283–284
Prdm1, 553
Prdm14, 553
Preeclampsia, bone morphogenetic protein studies, 823–824
Pregnancy, transforming growth factor- β signaling, 943–946
Preinitiation complex (PIC), 332, 340–341
Primordial germ cell (PGC)
 development in mammals, 928, 930–931
 knockout mouse studies, 929–930
 transforming growth factor- β family functions, 553–554
PrKX, 367
PRMT1, 227, 367, 387
Proenkephalin (PENK), 80
Progressive osseous heteroplasia (POH), 981
Proopiomelanocortin (POMC), 80
Prostate gland, development, 688–689
Protein kinase A (PKA), 432, 449, 457, 697
Protein kinase C (PKC), 471, 1089
PROX1, 777, 818
Proximal symphalangism, 963, 971
Prx1, 724
PS1, 446
PSG1, transforming growth factor- β activation, 147
PTCH1, 449
PTCH2, 449
PTEN, 352, 364, 441, 453–454, 529, 556, 704
PTH. *See* Parathyroid hormone
PTH1R, 229
PTH1LH, 1054
PTPN14, 824
PU.1, 336
Pulmonary arterial hypertension (PAH)
 bone morphogenetic protein signaling defects, 814
 genetic modifiers, 824
 mouse models, 820
 second hit hypothesis, 824
 transforming growth factor- β signaling overview, 786, 1128
Pulmonary fibrosis. *See* Fibrosis
Punt, 489–490, 494
- R**
Rac, 430–431, 502
RANBP3, 311, 353
RANKL, 723, 979–980
RANTES, 1069
Ras, 451–452
RB1CC1, 386
Reactive oxygen species (ROS), transforming growth factor- β activation, 147
RelA, 457
Retina, cell fate specification, 908
Retinal epithelium, formation, 672–673
RGMs, 113, 223, 275–277
Rheumatoid arthritis, transforming growth factor- β studies, 880–881
RhoA, 229, 383, 430–431, 778
RhoB, 430
RME-1, 535
rme-1, 535
RNA polymerase II, 332
RNF11, 387–388
RNF12, 386–387
RNF111, 357, 366, 385–386
ROCK, 432
ROCK2, transforming growth factor- β receptor signaling modulation, 226
Ron, 1050
Ror2, transforming growth factor- β receptor signaling modulation, 224–225
ROS. *See* Reactive oxygen species
RSK, 1047
RUNX2, 338–339
Runx2, 562, 722, 724
RUNX3, 475–476
- S**
S100A4, 1048
Sal, 498
Salivary gland, development, 691–692
 gastrointestinal tract development, 694–695
 liver and bile duct development, 698
SARA, 229, 309, 406–409, 470
SASP. *See* Senescence-associated secretory phenotype
Sax, 490, 497, 928
SB431542, 389, 684
SB505124, 1106
Scarring. *See* Fibrosis
SCF proteins, 356, 558
Sclerosteosis, 963
Sclerostin (SOST), 179, 280–283, 980, 982–983
SCP proteins, 314, 355
 SCP1, 471
 SCP2, 471
 SCP3, 471
 SCP4, 353
Scw, 490, 492–494, 505
Scx, 719
SDF-1, 1047

Index

- Senescence. *See* Cellular senescence
Senescence-associated secretory phenotype (SASP),
482, 1020
SERPINE1, 35
Serrate, 444
SetDB1, 545
Sexual differentiation, transforming growth factor- β
signaling, 931–934
Sfrp5, 172
Shc, 423
Shh. *See* Sonic Hedgehog
SHIP, 477–478
Shprintzen–Goldberg syndrome (SGS), 963, 977–978
SHS. *See* Shprintzen–Goldberg syndrome
SIK, 382
Sildenafil, 1129
SIP1, 36, 316, 655, 1024, 1051
SIRT1, 366
Sizzled, 171–172, 592, 619–620
Skeletal development. *See also* Bone morphogenetic
proteins
bone morphogenetic proteins, 114–115, 967–970
chondrogenesis regulation, 968–969
craniofacial development and defects, 972–973
digit malformations, 970–971
growth plate defects, 969
limb formation and digit patterning signaling,
969–970
longitudinal bone growth regulation, 968–969
overview, 967–968
SKI, 40, 340
Ski, 413, 448
SKIL, 340–341, 1120
SLC. *See* Small latent complex
SLE. *See* Systemic lupus erythematosus
SLRP proteins, 183–184
Slug, 1024
SMA. *See* Smooth muscle actin
SMA-2, 525, 530
sma-2, 525, 530
SMA-3, 525, 530
sma-3, 525, 530
SMA-4, 525, 530
sma-4, 525, 530
SMA-6, 525
SMA-9, 530–533
SMA-10, 530–531
Smads
activation by receptors
complexes, 307–309
phosphorylated R-Smad dissociation, 408–409
recruitment by SARA, 406–407
type I receptor interaction, 407–408
activin
mouse models of function, 69
signaling, 57–58
bone morphogenetic protein signaling, 111, 116, 812
Caenorhabditis elegans, 527–529
cancer defects, 1043–1044
classification, 307
epidermis development, 660
hematopoietic stem cell signaling, 841–842
heteromeric Smad assembly
R-Smad structure comparison with interferon
regulatory factors, 409, 407
Smad4 structure, 409
structural basis, 409–410
history of study, 15–19
I-Smads
dysregulation in disease
cancer, 393
fibrosis, 392
inflammation, 392–393
wound healing, 392–393
expression regulation, 388–389
functions
Smad6, 389–390
Smad7, 390–392
non-Smad signaling pathways, 383–385
overview, 377–378
prospects for study, 394
R-Smad complex formation interference,
382–383
stability regulation, 385–387
structures, 378–379
transcriptional regulation of signaling, 383
type I receptor
binding regulation by posttranslational
modifications, 387–388
effector recruitment, 381–382
interactions, 380–381
intracellular movement, 310–312
microRNA expression regulation, 315–319
myoblast differentiation, 739
posttranslational modifications
acetylation, 313
ADP-ribosylation, 313
I-Smads
acetylation, 366–367
methylation, 367
overview, 363–365
phosphorylation, 367
ubiquitylation, 364, 366
overview, 349–350, 367–368
phosphorylation/dephosphorylation, 313–314
R-Smads
acetylation, 359
ADP-ribosylation, 359
dephosphorylation, 352–353
linker region phosphorylation, 353–355
overview, 350–351
phosphorylation, 350, 352, 356

- sumoylation, 358–359
 - ubiquitylation/deubiquitylation, 356–358
 - Smad4
 - ADP-ribosylation, 363
 - overview, 359–360
 - phosphorylation, 359, 361
 - sumoylation, 362–363
 - ubiquitylation, 361–362
 - sumoylation, 313
 - ubiquitylation, 312–313
 - presentation to transforming growth factor- β receptors, 308–310
 - SMAD3, 40
 - Smad3, 853
 - SMAD4, 41
 - Smad7, 35
 - structure of DNA complexes, 333–335
 - target gene regulation
 - coactivator interactions, 340–342
 - corepressor interactions, 342–343
 - DNA binding of Smad complexes and posttranslational modification regulation, 333–335
 - overview, 314, 316, 331–333
 - prospects for study, 343
 - transcription factor interactions
 - R-SMADs, 340
 - SMAD1/5, 339
 - SMAD2/3, 336–339
 - SMAD4, 340
 - transcription regulation
 - DNA binding, 411–413
 - Ski, 413
 - Smad linker interactions, 413–415
 - transforming growth factor- β receptor signaling
 - components, 299–301
 - overview, 227–229
 - Sma/Mab pathway
 - alternative signaling, 538
 - body size regulation, 530–532
 - cell fate specification
 - ectoderm, 533
 - mesoderm, 532–533
 - innate immunity role, 532
 - overview, 530
 - receptor trafficking, 533–536
 - Small latent complex (SLC), 30–31, 136
 - SMARCA4, 341
 - SMC. *See* Smooth muscle cell
 - SMO, 449
 - SMOC1, 284
 - SMOC2, 284
 - Smooth muscle actin (SMA), 1010, 1069–1070
 - Smooth muscle cell (SMC), vasculature, 776–779, 781, 786, 788–789, 808, 817, 973–975
 - Smurf proteins, 356–358, 363–364, 415, 443, 451
 - Smurf1, 877
 - Smurf2, 877
 - SNAIL, 1051
 - Snail, 477, 654
 - Snail1, 1024
 - SnoN, 357, 389, 413, 444, 448, 456, 475, 528, 777
 - Sog, 494–495, 500
 - Sonic Hedgehog (Shh), 670, 903, 1012
 - Sos1, 217
 - SOST. *See* Sclerostin
 - SOSTDC1, 179–180
 - Sox2, 336, 444, 458, 546–551, 555, 564, 578
 - Sox4, 477
 - Sox9, 654
 - Sox17, 582, 584
 - Sox32, 582, 584
 - Sp1, 388
 - Sp100, 413
 - SPARC, 1070
 - Spinal cord injury, bone morphogenetic protein therapeutic targeting, 1131–1132
 - SPPI, 339
 - SPSB1, transforming growth factor- β receptor signaling modulation, 225
 - Srw, 492
 - STAT, 17
 - STAT5, 687–688
 - Stem cell. *See also specific cells*
 - bone morphogenetic protein function, 121–122
 - overview, 543–546
 - Stiff skin syndrome, 963, 978
 - STK11, 361
 - Stomach, differentiation, 693–695
 - STRAP, 225, 305, 388
 - Stroke, bone morphogenetic protein therapeutic targeting, 1131
 - SUMO-1, 362
 - Syndecans, 187
 - Systemic lupus erythematosus (SLE), transforming growth factor- β studies, 881–882
- ## T
- TAB2, 384, 878
 - TAB3, 384, 878
 - TACE. *See* ADAM17
 - TACS. *See* Tumor-associated collagen signature
 - tag-68, 525
 - TAGLN, 778
 - TAK1, 16, 18, 228–229, 366, 383–384, 425–428, 453, 457, 668, 812, 818, 977, 1041
 - Tax, 856
 - TAZ, 311, 446–448, 551–552
 - T-bet, 391

Index

- T cell
 cancer and effects of transforming growth factor- β ,
 1045–1046
 cancer studies, 1074
 transforming growth factor- β regulation
 differentiation, 870–872
 overview, 39
 peripheral homeostasis, 868–870
 thymic development, 866–868
 tolerance, 872–873
- TCE, 384, 440, 444, 1012
- Tcf3, 598
- TCF4, 472
- TCPTP, 217–218
- Tctex2 β , transforming growth factor- β receptor
 signaling modulation, 226
- TEAD, 336, 552
- TEL-AML1, 856
- Tenascin-X, 189
- Tenocyte, differentiation, 745–746
- TEW-7197, 1097
- TFE3, 17, 388
- TGF- β . *See* Transforming growth factor- β
- THBS1, 1089
- Thymus, transforming growth factor- β in development,
 866–868
- Thyroid gland, development, 692
- Tie-2, 117
- TIEG1, 388–389, 477
- TIF1 γ , 361–362, 846
- TIFIG γ , 341
- tig-2*, 525, 538
- tig-3*, 525, 538
- TIMP3, 1008
- Tist2, 665
- Tkv, 490, 497, 928
- Tld, 492, 494, 500
- TLL, 171
- TLR, transforming growth factor- β receptor signaling
 modulation, 225
- Tlr, 500
- TMEFF1, 169, 557, 662
- TNF- α . *See* Tumor necrosis factor- α
- Tob2, 388
- Tolerance, transforming growth factor- β regulation
 fetal–maternal tolerance, 878–879
 T cells, 872–873
- Tollip, 382
- Tolloid, 618–619s
- Tomoregulin, 623–624
- Tooth, development, 669–671
- TRAF4, 228, 452, 457
- TRAF6, 228, 306–307, 310, 366, 383–384, 390, 425, 427,
 452, 871, 878, 977, 1041
- Transforming growth factor- β (TGF- β)
 activation of latent complex
 deglycosylases, 146
 evolutionary perspective, 148–149
 F-spondin, 147
 integrins, 142–144
 neuropilin, 147
 physicochemical factors, 147–148
 postactivation bioavailability, 148–152
 proteases, 145–146
 PSG1, 147
 TSP-1, 146–147
- adipogenesis, 742–743
- Caenorhabditis elegans*. *See* *Caenorhabditis elegans*,
 transforming growth factor- β family
- chondrocyte differentiation, 732–734
- epidermis development, 661–663
- evolution. *See* Evolution, transforming growth
 factor- β family
- extracellular matrix regulation of bioavailability,
 966–967
- feather development, 664–665
- functional overview
 cell differentiation control, 37–38
 cell proliferation control, 36–37
 gene expression control, 35–36
 immune function, 39–40
 wound healing, 38–39
- historical perspective
 background, 1–2
 complementary DNA cloning, 7
 discovery, 2
 function identification, 11–14
 growth inhibition studies, 5–6
 isoforms, 9–10
 latency studies, 7–8
 purification and characterization
 Moses laboratory, 3–5
 Sporn/Roberts laboratory, 2–3
- receptor studies
 complementary DNA cloning, 14–15
 identification, 5
 recombinant protein expression, 8–9
 SMAD pathway, 15–19
 superfamily members, 10–11
- kidney development, 703
- liver and bile duct development, 696–697
- lung development, 703–705, 707
- mammary gland development, 686–688
- myoblast differentiation, 735–738
- osteoblast differentiation, 724–726
- palate differentiation and fusion, 666–668
- pancreas development, 690
- pituitary gland differentiation, 692
- processing, 135–139
 processing, 135–139, 255–256
- prostate gland development, 688–689
- salivary gland development, 691–692

- superfamily members
 - nomenclature complexity, 32–34
 - phylogenetic tree, 33
 - polypeptide organization, 31
 - types, 28–29
- thyroid gland development, 692
- Transforming growth factor- β receptors
 - activation, 301, 305
 - cross-talk with other signaling pathways
 - ERK
 - activation of MAPK signaling, 452–453
 - cooperative interactions, 450–451
 - downregulation of transforming growth factor- β signaling, 451–452
 - overview, 450
 - Hedgehog, 448–450
 - Hippo, 446–448
 - Jak-Stat, 455–456
 - Notch, 444–446
 - nuclear factor- κ B/IKK, 456–458
 - overview, 439–440
 - PI3K-Akt pathway, 453–455
 - pluripotency and lineage-specific transcription factors, 458
 - prospects for study, 458–459
 - Wnt
 - development and tissue homeostasis role, 440–441
 - direct physical interactions, 442–444
 - overview, 440
 - reciprocal regulation of expression of pathway ligands and antagonists, 441
 - transcription complex convergence, 444
 - endocytosis, 229–231
 - history of study, 5, 14–15
 - kinases
 - type I receptor activation, structural basis, 404, 406
 - type II receptor kinase domain structure, 403–405
 - microRNA control of expression, 219–221
 - mutation in disease
 - aortic aneurysm, 232–233
 - cancer, 231–232
 - diffuse intrinsic pontine glioma, 233
 - fibrodysplasia ossificans progressiva, 233
 - hereditary hemorrhagic telangiectasia, 232
 - idiopathic pulmonary arterial hypertension, 233
 - juvenile polyposis syndrome, 232
 - Loeys–Dietz syndrome, 232–233
 - Marfan syndrome, 232–233
 - non-Smad signaling
 - ERK activation, 422–425
 - Jak-Stat, 432
 - JNK activation, 425–428
 - overview, 421–422, 1038
 - p38 MAPK activation, 425–428
 - PI3K-Akt pathway, 428–430
 - prospects for study, 432–433
 - protein kinase A, 432
 - Rho-like GTPases, 430–432
 - TAK1 activation, 425–428
 - pleiotropic pathways, 1036–1039
 - posttranslational modification
 - neddylation, 218–219, 305
 - overview, 302
 - phosphorylation, 217–218, 301, 303, 471–472
 - sumoylation, 218, 305
 - ubiquitylation, 218–219, 303
 - protein interaction overview, 304–306
 - proteolysis of T β R1, 306–307
 - signaling. *See also* Smads
 - apoptosis, 476–478
 - autophagy, 479
 - cell dormancy, 478–479
 - cell proliferation effects
 - promotion, 476
 - suppression, 472–476
 - cell-surface protein modulation
 - CD44, 224
 - integrins, 224
 - occludin, 224
 - platelet-derived growth factor, 224
 - Ror2, 224–225
 - TrkC, 224
 - VE-cadherin, 223–224
 - cellular senescence, 479–482
 - context-dependent regulation, 468–470
 - coreceptor regulation
 - BAMBI, 222
 - betaglycan, 221–222
 - CD109, 223
 - Cripto, 222–223
 - endoglin, 222
 - neuropilin-1, 223
 - RGMs, 223
 - cytoplasmic protein modulation
 - BAT3, 225
 - cGKI, 226
 - Dapper2, 225
 - FKBP12, 225
 - Hsp90, 225
 - ROCK2, 226
 - SPSB1, 225
 - STRAP, 225
 - Tctex2 β , 226
 - TLR, 225
 - YAP65, 225
 - Drosophila*. *See Drosophila* transforming growth factor- β family signaling
 - feedback mechanisms, 226–227
 - nuclear shuttling protein modulation, 226
 - overview, 470–471, 546–547, 773, 960, 964–966, 1088–1090

Index

- Transforming growth factor- β receptors (*Continued*)
 Smad versus non-Smad pathways, 227–229
 transcription factors, 472
 Smad activation
 phosphorylated R-Smad dissociation, 408–409
 recruitment by SARA, 406–407
 type I receptor interaction, 407–408
 therapeutic targeting, 233–234
 types, 234–235
TRIM33, 312–313, 361–362, 601, 668, 688, 728
Trim33, 552
TRIP-1, 306
TrkC, transforming growth factor- β receptor
 signaling modulation, 224
Trypanosoma cruzi, 883
TSC-22, 306, 388
Tsg, 492, 494, 520, 592
TSK. *See* Tsukushi
TSP-1, transforming growth factor- β activation, 146–147
tsp-21, 533
Tsukushi (TSK), 185–186
Tumor necrosis factor- α (TNF- α), 880, 909
Tumor-associated collagen signature (TACS), 1069
Twist, 1024, 1051
TWSG1, 172–174
- U**
- UBC9, 313, 362
UbcH7, 379
UBE2O, 387
UCP-1, 563, 739, 741
UNC-5, 537–538
UNC-6, 537
UNC-40, 537
UNC-129, 533, 537–539
unc-129, 525, 537
Unfolded protein response (UPR), 1009–1010, 1025
UPR. *See* Unfolded protein response
USAG-1, 119, 282, 556
USP15, 358, 366, 382, 1048
Uterine fibroid, 947
- V**
- Valvular heart disease. *See* Cardiac valves
Van Buchem disease (VBD), 963, 982–983
Vascular development, overview, 768–770, 808
Vascular endothelial growth factor (VEGF)
 angiogenesis, 770, 777
 cancer angiogenesis, 1070–1073
 hypoxia induction, 770
 inhibitors, 785
 smooth muscle cell effects, 778
 vascular remodeling, 768
VBD. *See* Van Buchem disease
VCAM-1, 823
VE-cadherin, transforming growth factor- β receptor
 signaling modulation, 223–224
Ved, 596
VEGF. *See* Vascular endothelial growth factor
VegT, 600
Vent, 596, 599
VEPH1, 309
Vg1, 623–624, 653
Viral infection, transforming growth factor- β
 studies, 882–883
Vox, 596
VU5350, 1133
- W**
- WFIKKN1, 168–169
WFIKKN2, 168–169
Wg, 440, 444, 501
Williams syndrome, 783
Wise, 179
Wit, 489–490, 502, 928
WNK1, 354
Wnt, 248, 251, 280, 563
 transforming growth factor- β /Smad cross talk
 development and tissue homeostasis role,
 440–441
 direct physical interactions, 442–444
 overview, 440
 reciprocal regulation of expression of pathway
 ligands and antagonists, 441
 transcription complex convergence, 444
Wnt11, 699
Wound healing
 activin function, 85
 history of study, 11–12
 I-Smad dysfunction, 392–393
 transforming growth factor- β functional overview,
 38–39
Wsp, 504
WWP1, 356, 364, 382
WWP2, 364
- X**
- XBP-1, 10099
Xcr, 611
Xnr3, 182
XPA089, 1097
XPA681, 1097
- Y**
- YAP, 415, 446–448, 551–552
YAP65, 225, 388
Yki, 500
- Z**
- ZEB1, 316, 701, 1024
ZEB2. *See* SIP1
ZNF451, 342