

Index

A

AC. *See* Adenylate cyclase
Adenylate cyclase (AC), sperm signaling, 278
ADPKD. *See* Autosomal-dominant polycystic kidney disease
Agouti-related peptide (AgRP), 259
AgRP. *See* Agouti-related peptide
AHI1, 351
AKAPs. *See* Protein kinase A–anchoring proteins
AKT, cilia signaling, 128–131
AKT1, 265
ALR13b, 232
Alstrom syndrome, 230, 257, 259–260, 355
AMPK, 265
ANKS6, 225, 229
Annulus
 migration, 119–121
 structure, 119
Arl3, 101
ARL13B, 101, 155
Autosomal-dominant polycystic kidney disease (ADPKD)
 cilia-dependent cyst activation
 animal models, 244–245
 cyst formation in other ciliopathies, 247
 PC1 regulation, 251
 physiological function, 245
 prospects for study, 251–252
 signaling
 β 1-integrin, 249
 cyclic AMP, 248
 Hedgehog signaling, 245, 247–248
 Lkb1, 248
 mitogen-activated protein kinase, 249
 mTOR, 248–249
 platelet-derived growth factor, 249
 ciliary dysfunction in cyst formation, 243–244
 gene mutations, 242–244
 mechanosensor hypothesis for polycystins in cilia, 249–251
 overview, 241
Axoneme
 central pair structure, 12–13
 dynein
 arms
 assembly in axonemal superstructure, 35–36
 composition, 32–34, 37

cytoplasmic preassembly and trafficking of complexes, 34–35
dysfunction consequences, 38–39
motor function and regulation, 36, 38
prospects for study, 39
bending mechanism, 11–12
intermediate chain and light chain complexes, 12
isoform distribution, 12
nucleotide-induced structural change, 5
structure and arrangement, 4, 10–11
electron microscopy, 8–9
exceptional motile cilia, 6–8
microtubule doublet
 linkers, 13
 structure, 3, 6–10
9+2 structure, 3, 6, 9, 126
prospects for study, 13–14
radial spoke structure, 12–13
structural overview, 1–6

B

Bardet–Biedl syndrome (BBS), 230, 247, 257, 259–260, 354–355
Basal body (BB)
 amplification, 184–186
 assembly
 dynamics, 185, 187
 evolution, 188
 molecular control, 187–188
 ciliary beat orientation, 191–192
 docking and ciliogenesis
 actin cytoskeleton role, 188–190
 assembly, 190–191
 docking, 190
BBS. *See* Bardet–Biedl syndrome
BBS10, 264
BBS12, 264
BBSome, intraflagellar transport protein roles in transport, 79–80
 β -Arrestin, 168, 174
 β 1-Integrin, cilia-dependent cyst activation signaling, 249
Bitter taste receptor (T2R), 175
Bld10p, 48
BLD12, 48
BMPs. *See* Bone morphogenetic proteins
Bone morphogenetic proteins (BMPs), cilia signaling, 134–135

C

- CA. *See* Central apparatus
cAMP. *See* Cyclic AMP
CapZIP, 190
CatSper, sperm signaling, 277–278, 281, 284
Cby1, 93, 103
CCDC14, 302
CCDC39, 35
CCDC40, 35
CCDC78, 188
CCDC103, 35
CCDC151, 302, 372
CCNO, multiciliated cell specification and differentiation regulation, 184–185, 188
Cdc123, 93
Cdc41, 93
CDH23, 350
CDH1, 348
Celsr, 189
Central apparatus (CA)
 assembly, 47–49
 composition, 45–47
 functions, 49–51
 pathology, 51–52
 prospects for study, 52
 structure, 43–45
Central pair (CP), structure, 12–13
Centriole
 cell-cycle changes, 111–112
 cilium relationship, 112
 elongation before axoneme assembly, 112, 114
 hedgehog response regulation, 149
 sperm
 giant centrioles, 115–117
 specialized centrioles, 115
Centriole and spindle-associated protein (CSAP), 23
CEP63, 187–188
CEP78, 350
Cep83, 93–94, 102
Cep89, 93
Cep123, 93
CEP162, 121–122, 187
CEP164, 83–94, 102, 190
CEP250, 350
Cep290, 95, 97, 104, 118, 121, 227
Cerl2, 207–209
CFAP54, 52
CG42699, 122
CHD. *See* Congenital heart disease
CIB2, 350
Cilia-dependent cyst activation. *See* Autosomal-dominant polycystic kidney disease
Ciliary nephronophthisis (NPHP), 95–97, 102
CLRN1, 348–350
C-MYB, multiciliated cell specification and differentiation regulation, 184
CNGK. *See* Cyclic nucleotide-gated potassium channel
Cogan syndrome, 227–228
Congenital heart disease (CHD)
 cilia and signaling
 cell polarity specification and polarized cell migration, 332–333
 ciliopathy-associated congenital heart disease, 335–336
 development role, 326–328
 gene mutations, 334–335
 left–right patterning, 333–334
 Sonic hedgehog, 329
 transforming growth factor- β , 332
 Wnt, 329, 332
 development of cardiovascular system, 324–325
 four-chamber perturbation, 324, 326
 overview, 323–324
 prospects for study, 336–337
CP. *See* Central pair
CP110, 93, 150, 190–191
CPC1, 46–47, 51
CPLANE, 150
Craniofacial ciliopathies. *See also* specific diseases
 ciliary dysfunction sensitivity, 310
 development
 cranial neural crest cells, 313–315
 facial ectoderm, 315–316
 neuroectoderm, 315
 overview, 312–313
 pharyngeal endoderm, 316
 signaling in cilia
 Hedgehog signaling, 316–318
 Wnt, 318–319
 overview, 309–310
 pairwise combination of phenotypes, 311
 prospects for study, 319–320
 tables of diseases, 312–313
CSAP. *See* Centriole and spindle-associated protein
Cyclic AMP (cAMP)
 cilia-dependent cyst activation signaling, 248
 sperm signaling, 278
Cyclic nucleotide-gated potassium channel (CNGK), sperm signaling, 276, 279–280
Cyclin D1, 292

D

- DAAM1, 188, 190
DEUP1, 187–188
Dishevelled, 189, 192–193, 205
Diversin, 189
DNAH1, 302
DNAH5, 302
DNAH11, 303
DNAJB13, 121

Dynein, axoneme

 arms

 assembly in axonemal superstructure, 35–36

 composition, 32–34, 37

 cytoplasmic preassembly and trafficking of complexes, 34–35

 dysfunction consequences, 38–39

 motor function and regulation, 36, 38

 prospects for study, 39

 bending mechanism, 11–12

 intermediate chain and light chain complexes, 12

 isoform distribution, 12

 nucleotide-induced structural change, 5

 structure and arrangement, 4, 10–11

DYXCI, 302

E

EGF. *See* Epidermal growth factor

EHD1, 93

EHD3, 93

Ellis–van Revland syndrome, 156

Epidermal growth factor (EGF), cilia signaling, 133

EVC, 156

Evolution

 basal body, 188

 cilia

 eukaryote divergence

 evolution after, 374–375

 evolution before, 375–377

 last eukaryotic common ancestor, 370–371

 motility, 372–373

 overview, 369–370

 trafficking, assembly, and signaling, 373–374

 tubulins, 371–372

 radial spoke, 60–62

F

FAP59, 35

FAP172, 35

FAP221, 51

FBB18, 34

Fbf1, 93

FGF. *See* Fibroblast growth factor

Fibroblast growth factor (FGF), cilia signaling, 133

FLTP, 190

FSCN2, 348

FTO, 258, 263–264

G

GC. *See* Guanylate cyclase

Gdf1, 207

GEMC1, multiciliated cell specification and differentiation regulation, 183–184

GLI1, 151, 153

GLI2, 151, 153, 155

GLI3, 153, 155, 317

GPCRs. *See* G-protein-coupled receptors

G-protein-coupled receptors (GPCRs). *See also specific ligands*

 cholangiocyte cilia signaling, 172–173

 cilia localization impact, 175–176

 ciliary localization, 168

 hedgehog signaling modulation, 171

 motile cilia signaling, 175

 neuron cilia signaling, 173–175

 olfactory receptor signaling, 167–170

 opsin signaling, 169–171

 overview of signaling, 165–167

 renal cilia signaling, 171–172

Guanylate cyclase (GC), sperm signaling, 274, 276, 278–279

H

HARS, 350

HCN. *See* Hyperpolarization-activated and cyclic nucleotide-gated channel

HDAC6, 20

Hedgehog signaling. *See also specific proteins*

 centriole and basal body protein regulation of response, 149

cilia

 cell lineage determination of primary cilia in mouse embryo, 156–158

 cell-type-specific differences and signaling modulation, 155–156

 gene mutation effects, 147–149, 154–155

 pathway switching control, 153–154

 requirement for signaling in all vertebrate tissues, 150–151

 cilia-dependent cyst activation, 245, 247–248

 craniofacial ciliopathies, 316–318

 developmental patterning, 144–145

 G-protein-coupled receptors in signaling modulation, 171

 intraflagellar transport protein regulation, 79, 154–155

 peripheral cilia in metabolic regulation and obesity, 264–265

Hepatocyte growth factor (HGF), cilia signaling, 133

HGF. *See* Hepatocyte growth factor

HSP40, 60, 62

Hydin, 46–47

Hyperpolarization-activated and cyclic nucleotide-gated channel (HCN), sperm signaling, 276–277

I

IFT. *See* Intraflagellar transport

IGF-1. *See* Insulin-like growth factor 1

- Inpp5e, 94
Insulin-like growth factor 1 (IGF-1), cilia signaling, 132–133
Intraflagellar transport (IFT)
history of study, 73–75
IFT-A complex
architecture, 82
protein functions in complex formation and stability, 82–83
IFT-B complex
architecture
IFT-B1, 75–76
IFT-B2, 76–78
protein functions
BBSome transport, 79–80
formation and stability, 78
Hedgehog signaling regulation, 79, 154–155
membrane protein sorting at cilium, 80–81
transport of motility factors, 78–79
tubulin dimer and microtubule binding, 81–82
turnaround at ciliary tip, 80
motor protein interactions with IFT complexes, 84–85
overview, 71–73, 127
photoreceptor sensory cilia, 343, 347
prospects for study, 85
protein nomenclature, 74
Sonic hedgehog signal transduction in mouse embryo, 145–146, 149
train formation and IFT-A/IFT-B complex interactions, 83
- INVS*, 225
IQCB1, 227
IRX3, 264
- J**
JBTS4, 228
JBTS6, 228
JBTS7, 228
JBTS10, 230
Joubert syndrome, 228, 247, 353
- K**
KAP3, 145
Kif17, 101
KIF3, 145, 149
Kinesin-1, 20
Kinesin-2, 127
KISS1R, 175
KLP1, 46–47
- L**
Last eukaryotic common ancestor. *See Evolution*
LCA5, 348
- Left–right asymmetry**
cilia-driven fluid flow in mouse embryo, 203–205
clockwise rotation of mouse node cilia, 206–207
congenital heart disease and cilia role in patterning, 334
fluid flow in symmetry breaking
calcium flux, 208
Cerl2 messenger RNA asymmetry in flow sensing, 208–209
immotile colia as flow sensor, 207–208
overview, 203
planar cell polarity, 205
prospects for study, 209
- Leptin**, 258–259, 262
- LKB1**, 248, 265
- LRP2**, 334
- LRRC50**, 3
- M**
- MAK**, 348
- MAPK**. *See Mitogen-activated protein kinase*
- MC4R**. *See Melanocortin 4 receptor*
- MCC**. *See Mucociliary clearance; Multiciliated cell*
- MCIDAS**, multiciliated cell specification and differentiation regulation, 183–184, 187
- MCKD**. *See Medullary–cystic kidney disease*
- MEC-17/ATAT1**, 18, 20
- Meckel–Gruber syndrome (MKS)**, 229–230, 247, 353–354
- Medullary–cystic kidney disease (MCKD)**, 214, 223
- Melanocortin 4 receptor (MC4R)**, 258–259
- Microtubule doublet (MTD)**
linkers, 13
structure, 3, 6–10
- Mitogen-activated protein kinase (MAPK)**
cilia-dependent cyst activation signaling, 249
cilium signaling, 128–130
- MKS**. *See Meckel–Gruber syndrome*
- MKS complex**, 95, 103
- MORM syndrome**, 355
- MTD**. *See Microtubule doublet*
- mTOR**, cilia-dependent cyst activation signaling, 248–249
- MUC1***, 223
- Mucociliary clearance (MCC)**
cilium
beat frequency, 299–300
regulation, 299–300
structure, 297–299
- components
mucous layer, 295, 297
overview, 295–296
periciliary layer, 297
surfactant, 297
- measurement

- overview, 300–301
variables, 301–302
- overview, 291–292
- primary ciliary dyskinesia, 302–303
- prospects for study, 303
- respiratory tract
- cell types in lower respiratory tract
 - ciliated cells, 294–295
 - secretory cells, 294
 - development, 292
 - structure, 293–294
- Multiciliated cell (MCC)
- ciliary beat orientation
 - basal body organization, 191–192
 - beat regulation, 194–195
 - hydrodynamic forces, 194
 - polarization by planar cell polarity pathway, 192–194
 - ciliogenesis. *See* Basal body
 - mammalian epithelia, 182
 - overview, 181–182
 - prospects for study, 195
 - specification and differentiation
 - downstream effectors, 184–185
 - GEMC1 regulation, 183–184
 - MCIDAS regulation, 183–184
 - Notch inhibition, 182–183
- MYO7A, 350
- N**
- NDK5, 60–61
- NEK8, 229
- Nephronophthisis (NPHP)
- cilia-dependent cyst activation, 247
 - clinical presentation, 224–225
 - diagnosis, 226
 - differential diagnosis, 226
 - extrarenal manifestations
 - Alstrom syndrome, 230
 - Bardet–Biedl syndrome, 230
 - Cogan syndrome, 227–228
 - congenital heart disease, 229
 - Joubert syndrome, 228
 - liver involvement, 228–229
 - Meckel–Gruber syndrome, 229–230
 - oral-facial-digital syndrome type 1, 230
 - overview, 226–227
 - Senior–Løken syndrome, 227
 - skeletal phenotypes and polydactyly, 229
 - Usher syndrome, 230–231
- genetics, 231
- genotype–phenotype correlations, 215–223
- model organisms, 231–232
- overview, 214, 223
- pathology, 225–226
- therapy and prognosis, 225
- type 1 disease, 231
- type 2 disease, 224
- Neuropeptide Y (NPY), 173
- NF- κ B. *See* Nuclear factor- κ B
- NHE. *See* Sodium/proton exchanger
- Nmyc, 292
- Nodal, 207–208
- Notch, multiciliated cell specification and differentiation regulation, 182–183
- NPHP. *See* Ciliary nephronophthisis; Nephronophthisis
- NPHP1, 228, 231
- NPHP2, 228–229
- NPHP3, 228–229, 232, 244
- NPHP4, 189, 228, 231
- NPHP5, 227
- NPHP6, 227
- NPHP7, 231
- NPHP9, 244
- NPY. *See* Neuropeptide Y
- Nubp1, 190
- Nuclear factor- κ B (NF- κ B), cilia signaling, 134
- O**
- Obesity
- ciliopathies with obesity
 - conditional mutants in mice, 260
 - LEPR mutations, 262
 - mouse models, 260–261
 - neuron involvement, 260, 262–263
 - overview, 259–260
 - genetic predisposition, 258
 - leptin–melanocortin pathway regulation of energy homeostasis, 258–259
 - pathophysiology, 258
 - peripheral cilia in metabolic regulation and obesity, 264–265
 - prospects for study, 265–266
 - RPBRIPL studies, 263–264
- ODA proteins, 34
- ODF2, 191
- Odf2, 93
- OFD1. *See* Oral-facial-digital syndrome type 1
- Olfactory receptor, signaling, 167–170
- Opsins, vision signaling, 169–171
- Oral-facial-digital syndrome type 1 (OFD1), 93, 150, 230, 355–356
- P**
- Patched1, 127–128, 143, 153–154
- PCD. *See* Primary ciliary dyskinesia
- PCDH15, 350
- PCP. *See* Planar cell polarity

- Pde6d, 101
PDGF. *See* Platelet-derived growth factor
PF proteins, 45–50
Phosphoinositide 3-kinase (PI3K), cilia signaling, 128–130
Phospholipase C (PLC), cilia signaling, 129–130
Photoreceptor sensory cilia (PSC)
functional overview, 341–342
outer segment components, 343
protein transport
intraflagellar transport, 343, 347
membrane protein transport, 347
photoactivated protein diffusion, 347
retinal ciliopathies
Alstrom syndrome, 355
Bardet–Biedl syndrome, 354–355
genetic modifiers, 351–352, 355–356
Joubert syndrome, 353
Meckel–Gruber syndrome, 353–354
MORM syndrome, 355
nonsyndromic retinal degeneration
genes, 344–346
sensory function defects, 349–350
structural disruption, 348–349
oral-facial-digital syndrome, 355–356
phenotypic spectrum, 355–356
Senior–Løken syndrome, 353
short-rib thoracic dysplasia, 355
Usher syndrome, 350, 353
structure, 342–343
PI3K. *See* Phosphoinositide 3-kinase
PKA. *See* Protein kinase A
PKD1, 232, 242–243
PKD1, 349, 374
PKD2, 232, 242–243
PKD2, 208, 349, 374
Pkd111, 208
Pkd2l1, 175
Planar cell polarity (PCP), 189, 192–194, 205
Platelet-derived growth factor (PDGF)
cilia-dependent cyst activation signaling, 249
cilia signaling, 129–132
PLC. *See* Phospholipase C
PLK4, 187
Polycystic kidney disease. *See* Autosomal-dominant polycystic kidney disease
Prickle, 189, 205
Primary ciliary dyskinesia (PCD)
dynein arm dysfunction, 39
gene mutations, 302–303
PROM1, 348
Protein kinase A (PKA), 153, 173
Protein kinase A–anchoring proteins (AKAPs),
RSP3 as, 60
PRPH2, 348, 356
PSC. *See* Photoreceptor sensory cilia
- R**
- Radial spoke (RS)
assembly, 62–63
evolution, 60–62
functions
axoneme stability maintenance, 65–66
chemical signaling, 65
mechanical feedback and coordination
of molecular motors, 64–65
planar waveform generation, 64
morphology, 58
mutants, 63
outer doublet connections, 63
periodicity, 58
prospects for study, 66
proteins
Chlamydomonas, 58–60
organization, 60
structure, 12–13, 59
Receptor tyrosine kinase signaling. *See specific ligands*
ROM1, 348
RP1, 348, 356
RPBRIPL, 263–264
Rpgrip1l, 96–97, 103–104, 257–258
RPIL1, 348
RS. *See* Radial spoke
RSPH1, 302–303
RSPH19, 302
RSPH4A, 302
- S**
- SAS4*, 149
SAS-6, 187
Senior–Løken syndrome (SLS), 227, 353
SHH. *See* Sonic hedgehog
Short-rib thoracic dysplasia (SRTD), 355
SIRT2, 20
Slo3, 283
SLS. *See* Senior–Løken syndrome
SMADs, cilia signaling, 134–136
SMO. *See* Smoothened
Smoothened (SMO), 127–128, 143, 151, 247, 264
Sodium/proton exchanger (NHE), sperm signaling, 276, 280
Sonic hedgehog (SHH)
cilia signaling, 127–128
congenital heart disease and cilia signaling, 329
craniofacial ciliopathies, 316–318
developmental patterning, 145
intraflagellar transport and signal transduction
in mouse embryo, 145–146, 149
Sox9, 292
SPAG1, 302
Spag16L, 52
Spag17, 51

Sperm

- annulus, 119–121
- guidance to egg, 271–273
- signaling
 - fish sperm, 279–280
 - mammalian sperm
 - calcium clearance, 283–284
 - CatSper, 281, 283
 - compartmentalization and supramolecular structures, 284–285
 - intracellular pH regulation, 284
 - mouse versus human sperm, 282
 - overview, 280
 - potassium channels, 283
 - prospects for study, 285
 - sea urchin sperm
 - adenylate cyclase, 278
 - amplification, 278–279
 - CatSper, 277–278
 - cyclic nucleotide-gated potassium channel, 276, 279
 - guanylate cyclase, 274, 276, 278–279
 - hyperpolarization-activated and cyclic nucleotide-gated channel, 276–277
 - overview, 274–275
 - recovery, 278
 - sodium/proton exchanger, 276
 - specialized centrioles and cilia, 115–117
- SRTD. *See* Short-rib thoracic dysplasia
- SSTR3, 174–175
- SUFU, 158

T

- T2R. *See* Bitter taste receptor
- TAK1, 134
- Talpid3, 150
- Tctex-1, 133
- TF. *See* Transition fiber
- TGF- β . *See* Transforming growth factor β
- TGR5, 173
- Tie receptors, 133
- Transforming growth factor β (TGF- β)
 - cilia signaling, 133–137
 - congenital heart disease and cilia signaling, 332
- Transition fiber (TF)
 - architecture, 92–93
 - ciliary gate diseases, 102–104
 - functions, 93–94
 - overview, 91–92

Transition zone (TZ)

- architecture, 94–96
- ciliary gate diseases, 102–104
- ciliogenesis role, 97–98
- cilium compartmentalization, 114–115
- migration
 - centriole formation and ciliogenesis, 112–113

cytoplasmic ciliogenesis

- annulus in mammalian sperm, 119–121
- axoneme exposure to cytoplasm, 117–118
- ciliary gate elasticity, 122
- Drosophila* spermatids, 118–119
- motor-driven versus exchange-driven

migration, 121

- Drosophila* spermatocytes, 117–119

overview, 91–92

protein trafficking role

- membrane proteins, 100–102
- soluble proteins, 98–100

TTBK2, 94, 150, 190

TTC8, 355

TTL. *See* Tubulin tyrosine ligase

Tubulin

cilia evolution, 371–372

posttranslational modification

acetylation of K40

cilia disassembly role, 20

motor-driven motility role, 20–21

overview, 17–20

detyrosination, 21

glutamylation

ciliary assembly and microtubule stability role, 23

motility role, 22–23

negative length regulation of cilia, 23–24

overview, 21–22

glycation, 24–25

overview, 17

prospects for study, 25

Tubulin tyrosine ligase (TTL), 21–25

TULP1, 348

TULP3, 83, 154–155, 158

TZ. *See* Transition zone

U

UMOD, 223

Unc119b, 101

USH1C, 350

USH1G, 350

USH2A, 348–350

Usher syndrome, 230–231

V

Vangl, 189, 205

Vangl1, 192

Vangl2, 192

W

WNT

cilia signaling, 128

congenital heart disease and cilia signaling, 329, 332

craniofacial ciliopathies, 318–319