Index

A

AAV. See Adeno-associated virus ABCA5, 120 ABR. See Auditory brainstem response AC6, 63 ACAN, 276 ACOT7, 120 ADAM10, 303 Adeno-associated virus (AAV) channelrhodopsin delivery for optogenetic cochlear implant, 330-331 gene therapy vectors, 310-311 Adenovirus channelrhodopsin delivery for optogenetic cochlear implant, 331 gene therapy vectors, 310 ADE 117 ADGRV1, 61-63, 65, 71, 119, 122, 155-156 ADNSHL. See Autosomal dominant nonsyndromic hearing loss Age-related hearing loss (ARHL) animal models, 276-279 cochlear efferent protective functions, 183-184 dementia association, 279-280 epidemiology, 224-226, 272-273 genome-wide association studies, 273-276 hidden hearing loss, 236 overview, 271-272 pathology, 272-273 prospects for study, 279 treatment and prevention, 280-281 ALDOB/C, 119 Alport syndrome, epidemiology, 223 Alström syndrome, 47 Aminoglycoside-induced hearing loss epidemiology, 224 hair cell entry, 257-259 hidden hearing loss, 237 macrophage response, 288 mechanisms, 259-260 otoprotection BLB drug transport modulation, 260 cell death pathway targeting, 262 challenges, 263-264 drug discovery cell lines, 261 zebrafish, 261 GV1001, 262 hydrogen therapy, 262 MET channel blocking, 260

ototoxic drug design, 261 strategies, 260 ototoxin tracking in inner ear, 255-257 overview, 253-255 Ankle link, hair bundle, 61-63 ANXA5, 120 ARHL. See Age-related hearing loss ARNSHL. See Autosomal recessive nonsyndromic hearing loss ATOH1, 280 Atoh1, 310, 313-314 ATP2B2, 64, 119-120, 123 Auditory brainstem response (ABR), hidden hearing loss diagnosis, 242-243 AUT00063, 280 Autosomal dominant nonsyndromic hearing loss, (ADNSHL), epidemiology, 220 Autosomal recessive nonsyndromic hearing loss (ARNSHL), epidemiology, 219-220

В

Bardet–Biedl syndrome (BBS), 47 Basilar membrane (BM), length and cochlear frequency tuning, 15, 19, 24 Bazooka, 50–51 BBS. *See* Bardet–Biedl syndrome BDNF, 315–316 BM. *See* Basilar membrane BOR syndrome. *See* Branchio-oto-renal syndrome Branchio-oto-renal (BOR) syndrome, epidemiology, 223 Bullae, evolution, 5

С

CALB1, 120 CAPZA1, 116 CAPZA2, 116 CAPZB, 116, 124 Carbonic anhydrase, 120 CCL2, 291 CD1, 84 CD2, 69–70, 84 CD3, 69, 84 CDH23, 68–71, 93, 104, 119, 122, 156 CDHR15, 155 CDHR23, 155 *Celsr*, 43 CGRP, 183 Channelrhodopsin, 327–329

Index

Charcot-Marie-Tooth disease, 236-237 CHARGE syndrome, 220 Chudley-McCullough syndrome (CMCS), 52 CI. See Cochlear implant CIB2, 84-85, 106 Cimetidine, 258 Cisplatin-induced hearing loss hair cell entry, 257-259 mechanisms, 259-260 otoprotection BLB drug transport modulation, 260 cell death pathway targeting, 262 challenges, 263-264 drug discovery cell lines, 261 zebrafish, 261 GV1001, 262 hydrogen therapy, 262 MET channel blocking, 260 ototoxic drug design, 261 strategies, 260 ototoxin tracking in inner ear, 255-257 overview, 253-255 CKB, 119 Clarin-1, 156 Clathrin, 122 CLIC5, 65, 116 CLRN1, 104 CMCS. See Chudley-McCullough syndrome CMV. See Cytomegalovirus Cochlear implant (CI) indications, 325-326 optogenetics electrical stimulation comparison, 333-334 microLEDs, 332-333 overview, 327 prospects, 334 tuning, 327-329 overview, 325-327 virus vectors for channelrhodopsin delivery to cochlea adeno-associated virus, 330-331 adenovirus, 331 biosafety, 331-332 lentivirus, 331 overview, 329-330 Cochlear synaptopathy gene therapy, 316 hidden hearing loss, 237-239 Collagen, gene mutations in hearing loss, 223 Connexins ATP release, 201 calcium signaling in development, 201-206 domains, 193 expression in cochlea, 196-197 gap junctions in cochlea, 194-196 gene therapy, 317-318 genes, 193 mouse models of nonsyndromic deafness, 199-201 mutations and hereditary hearing loss, 197-199

nutrient supply to organ of Corti, 196 overview of cochlear function, 191–194 Convergence and extension, cochlear outgrowth, 42 CREATE, 330 CRISPR/Cas9, gene therapy, 319–320 CSC-L1, 80 CSC-L2, 80 *CtBP2*, 149 CTR1, 258 CX3CL1, 289, 291 CX3CR1, 289, 291 CX3CR1, 289, 291 Cytomegalovirus (CMV), 227

D

Dapl, 49 Dchs1, 43 DCTN1, 121 DCTN2, 121 Deafness, epidemiology age-related hearing loss, 224-226, 272-273 aminoglycoside-induced hearing loss, 224 infectious hearing loss, 227-228 noise-induced hearing loss, 228-229 nonsyndromic hearing loss autosomal dominant nonsyndromic hearing loss, 220 autosomal recessive nonsyndromic hearing loss, 219-220 X-linked nonsyndromic hearing loss, 220 otosclerosis, 226 overview, 217-218 syndromic hearing loss Alport syndrome, 223 branchio-oto-renal syndrome, 223 Jervell and Lange-Nielsen syndrome, 222 mitochondrial diseases, 223 overview, 220-222 Pendred syndrome, 222 Stickler syndrome, 222-223 Treacher Collins syndrome, 223 Usher syndrome, 222 Waardenburg syndrome, 222 Dementia, age-related hearing loss association, 279-280 DFNB7, 80 DFNB11, 80 DFNB48, 84 DFNB84, 64 DIAPH1, 44 Dlg, 51 Dsh1, 43, 46 Dsh2, 43, 46 DSTN, 117 Dvl, 50 Dynein, 121

Ε

EF1α, 312 Efferent innervation, cochlea

Index

acetylcholine inhibition, 175, 178-181, 184 aging effects, 179-180 auditory nerve responses and otoacoustic emissions lateral olivocochlear afferents, 180-181 noise responses, 181-182 quiet responses, 180 development and maturation, 179 electrophysiology, 177-179 GABA inhibition, 179 modulation, 179 overview, 175-176 pathology, 184 perceptual effects hearing in noise, 182 mutant mouse strain studies, 183 selective attention, 182-183 perceptual learning role, 184 prospects for study, 184-185 protective functions age-related hearing loss, 183-184 noise, 183 ultrastructure, 176-177 EFR. See Envelope following response EGFR, 303 Endocochlear potential (EP), evolution, 8-10 Envelope following response (EFR), hidden hearing loss diagnosis, 243 EP. See Endocochlear potential Eps8, 52 EPS8L2, 116 Esketamine, hidden hearing loss management, 246 ESPN-1, 69 ESPNL, 69 ESRRG, 276 Evolution, cochlea bony invasions, 7 bullae, 5 coiling, 6-7 endocochlear potential, 8-10 hair cells, 7-8 impedance matching between middle and inner ear, 3-5 lagenar macula loss, 10 length, 6-7, 11 organ of Corti, 7 phylogenetic tree of mammals, 2-3 pinnae, 5-6 regenerative capacity loss, 10-11 EYA1, 223

F

Fat, 43 FBXO2, 121 FDPS, 120 FGF-2, 303 FGF3, 44 FOX11, 44 Frz, 43, 46 FSCN1, 117 FSCN2, 116–117 *Fz*, 49–50

G

GAKIN, 51 Gap junctions. See Connexins GAPDH, 119 GDI1, 121 GDI2, 121 Gene therapy applications hair-cell regeneration, 313-315 hidden hearing loss and cochlear synaptopathy, 316 spiral ganglion neuron preservation and regeneration, 315-316 CRISPR/Cas9, 319-320 deafness treatment GIB2, 317-318 TMC1, 318-319 Usher syndrome, 317-318 VGLUT3, 317 delivery to cochlea, 312-313 genetic regulatory elements, 311-312 vectors, 310-311 GFAP, 315 GJB2, 197-201, 203, 219-221, 317-318 GJB3, 198 GJB4, 198 GJB6, 198 GLI3, 44 Gpsm2-LGN cytoskeletal remodeling, 52-53 hair bundle, control of movement and shape, 47 - 49inner hair cell function, 52 GPX1, 119 GPX2, 119 GPX4, 119 GRM7, 275 GSN, 116-117 GV1001, 262

Н

Hair bundle active bundle motion bifurcation theory, 34–36 biophysical models, 33–34 overview, 28–30 calcium feedback, 32 components actin and actin-associated proteins, 116–118 adhesion molecules, 119 antioxidant proteins, 119 chaperones, 119 consensus proteome, 114–116 glycocalyx, 123–124

Index

Hair bundle (Continued) ion channels, 120 lipid metabolism proteins, 120 lipids, 123 membrane-associated proteins, 120 metabolic enzymes, 119-120 microtubules and axonemes, 120-121 otolithic membrane and extracellular matrix, 121 protein complexes, 122-123 coupled arrays, 36-37 Gpsm2-LGN and PAR complex control of movement and shape, 47-49links ankle links, 61-63 kinocilial links, 69-70 overview of types, 59-60 prospects for study, 71, 73 shaft connectors, 63-65 tip links, 67-69, 72 top connectors, 65-67 transient lateral links, 70-71 macrophage interactions birds, 292 regeneration studies, 292-294 zebrafish, 292, 294 molecular motors in adaptation, 31-32 nonlinear mechanics, 28, 34 planar cell polarity and orientation, 46-47 protein synthesis and turnover, 121 signaling, 121-122 trafficking, 122 transduction complex gating, 30-31 Hair-cell regeneration avian model historical perspective, 299-300 mitotic and nonmitotic regeneration, 300-302 modes of regeneration, 304-305 prospects, 305-306 stem cells, 302-304 gene therapy, 313-315 macrophage studies, 292-294 HARMONIN. See USH1C Hath1, 315 HCN1, 95 HHL. See Hidden hearing loss Hidden hearing loss (HHL) diagnosis auditory brainstem response, 242-243 envelope following response, 243 middle ear muscle reflex, 243 etiology aging, 235 aminoglycoside antibiotics, 237 noise, 235–236 peripheral neuropathy, 236-237 gene therapy, 316 mechanisms cochlear synaptopathy, 237-239 demyelination, 240-241

hair cell dysfunction, 240, 242 overview, 233–235 prospects for study, 246 treatment efferent feedback modulation, 244–246 neurotrophins, 244 HO-1, 291 Hopf bifurcation, hair bundle, 34–36 HSP70, 119 HSP90, 119 Huperzine A, 280

I

Ift20, 43 Ift25, 43 Ift88, 43 IGF-1, 303 IHC. See Inner hair cell Inner hair cell (IHC) afferent synapses development functions in pre-hearing cochlea, 146 morphological changes, 144-146 excitatory postsynaptic current drivers, 152 exocytosis mechanisms calcium channels, 149-152 ribbon synapses, 147-149 gene discoveries otoferlin, 154-155 Usher proteins, 155-156 VGLUT3, 155 overview, 141-144 prospects for study, 156 spiral ganglion afferent fibers type I, 152-154 type II, 154 evolution, 7-8 mechanoelectrical transduction. See Mechanoelectrical transduction, hair cells mosaic in cochlea, 45-46 TMC1/2 function binding partners CIB2, 84-85 LHFPL5, 84 PCDH15, 83-84 TMIE, 84 TOMT, 85 conductance, 88-89 discovery, 79-80 expression and localization, 80-82 gating, 88 mechanoelectrical transduction, current mediation, 82-83 molecular structure, 85-88 pore formation, 87 Ins, 51 ISG20, 276

Index

J

Jervell and Lange–Nielsen syndrome (JLNS), epidemiology, 222 JLNS. See Jervell and Lange–Nielsen syndrome

Κ

KCNE1, 222 *KCNJ10*, 44 *KCNQ1*, 222 *KCNQ4*, 89, 220 *Khc-73*, 51 *Kif3a*, 43 Kinocilial link, hair bundle, 69–70

L

Lagenar macula, loss in evolution, 10 LDHA, 119 Lentivirus channelrhodopsin delivery for optogenetic cochlear implant, 331 gene therapy vectors, 310 LHFPL5, 84, 96–98

Μ

Macrophage, inner ear cochlea organ of Corti, 287 supporting tissues, 287-288 injury response cell survival influences, 291-292 recruitment, 290-291 sensory region, 288-289 spiral ganglion, 289 origin and distribution, 286 overview, 285-286 vestibular organs, 289 hair cell interactions birds, 292 regeneration studies, 292-294 zebrafish, 292, 294 MAGUK, 51 Math1, 314 Mechanoelectrical transduction, hair cells channels mechanosensitive channel criteria, 95-96 pore-forming subunits, 96-104 functions CIB2, 106 LHFPL5, 96-98 PIP₂, 107 TMC1/2, 101-104 TMIE, 98-101 TOMT, 106-107 overview, 93-95 TMC and current mediation, 82-83 Meckel-Gruber syndrome (MKS), 47 MELAS, 223

MEMR. See Middle ear muscle reflex MERRF, 223 MIDD, 223 Middle ear muscle reflex (MEMR), hidden hearing loss diagnosis, 243 MKS. See Meckel-Gruber syndrome MT-RNR1, 224 Mud, 50 Myh10, 44 MYO1C, 116, 122 MYO1H, 116, 122 MYO3B, 116 MYO5A, 116 MYO6, 64-65, 71, 116-117 MYO7A, 33, 62, 104, 106, 116, 122, 124 MYO15A, 116

Ν

Nectin1, 45–46 Nectin3, 45–46 NF-κB. See Nuclear factor-κB Noise-induced hearing loss cochlear efferent protective functions, 183 epidemiology, 228–229 hidden hearing loss, 235–236 macrophage response, 288 NOX3, 259 NPTN, 66, 119 NT3, 244, 315–316 Nuclear factor-κB (NF-κB), 196 NUDC, 121 NUMA, 50

0

OAE. See Otoacoustic emission OCT1, 258-259 OCT2, 258-259 OHC. See Outer hair cell Optogenetics. See Cochlear implant Organ of Corti development, 42 evolution, 7 **OSBP**, 120 **OTOA**, 66 Otoacoustic emission (OAE) delay comparison between species, 15-16, 21-25 frequency tuning and delay, 17-19 tuning ratio noninvasive estimation, 21 species invariance, 19-21 units for reporting, 16-17 Otoferlin, 154-155 Otosclerosis, epidemiology, 226 Outer hair cell (OHC) afferent synapses development functions in pre-hearing cochlea, 146 morphological changes, 144-146

Index

Outer hair cell (OHC) (Continued) excitatory postsynaptic current drivers, 152 exocytosis mechanisms calcium channels, 149-152 ribbon synapses, 147-149 gene discoveries otoferlin, 154-155 Usher proteins, 155-156 VGLUT3, 155 overview, 141-144 prospects for study, 156 spiral ganglion afferent fibers type I, 152-154 type II, 154 electromotility antiporter activity, 168-169 genetics human, 169-170 mouse, 169 mechanisms, 167-168 overview, 165-167 pharmacology, 169 prestin evolution, 170 membrane topology, 171-172 structure, 170-171 prospects for study, 172 evolution, 7-8 mechanoelectrical transduction. See Mechanoelectrical transduction, hair cells mosaic in cochlea, 45-46

Р

P21-activated kinase (PAK), 50 PAICS, 120 PAK. See P21-activated kinase Pallster-Hall syndrome (PHS), 44-45 Par3, 50-51 Par6, 50 PAX3, 222 PCDH15, 67-70, 83-84, 88, 93, 103-104, 119, 122 PCDH20, 276 PCP. See Planar cell polarity PDZD7, 62, 124 PEBP1, 120 Pendred syndrome, epidemiology, 222 Peripheral neuropathy, hidden hearing loss, 236-237 PFK, 119 PGK1, 119 PHS. See Pallster-Hall syndrome PI4KA, 120 PIEZO2, 62, 70, 79, 95, 99 Pinnae, evolution, 5-6 Pins, 50-51 PIP₂, 64-65 PIP₃, 64 PIPK2, 120 PITPNA, 120

PITPNB, 120 PKA. See Protein kinase A PKC. See Protein kinase C PKD1, 95 PKD2, 95 Planar cell polarity (PCP) gene mutations and cochlear effects, 43-44 hair bundle orientation, 46-47 oriented cell division and hair cell planar cell polarity, 50 - 51PLS1, 116-117 POU3F4, 44, 220 **PPIB**, 120 Presbycusis. See Age-related hearing loss Prestin evolution, 170 membrane topology, 171-172 outer hair cell electromotility role, 167-169 structure, 170-171 Prickle, 51 Protein kinase A (PKA), 63 Protein kinase C (PKC), 50, 63 PTK7, 44 PTPRO, 64-65, 71, 123

R

Rab11, 52 *Rac1*, 43 RDX, 65, 116 Regeneration. *See* Hair-cell regeneration RHO, 121 Ribbon synapse, hair cell, 147–149 RIBEYE, 149, 156 RSPH4A, 121 Rubella, 227

S

Saddle node of invariant circle (SNIC) bifurcation, hair bundle, 35-36 SANS, 104 SERCA, 201 Shaft connector, hair bundle, 63-65 SIX1, 223 SIX5, 223 SKP1A, 121 SLC9A3R2, 117 SLC9A9, 120 SLC26A3, 168 SLC26A4, 170, 221-222 SLC26A5. See Prestin SLC26A6, 168 SLC26A7, 168 SNAP25, 148 SNARE, 147-148 SNIC bifurcation. See Saddle node of invariant circle bifurcation SOD1, 119

Index

Sorcs2, 52 ST3GAL5, 123 STARD10, 120 Stbm, 51 Stickler syndrome, epidemiology, 222–223 STRC, 66–67, 73, 119–220 Synapsin, 176

Т

TECTA, 121 Tecta, 131, 134, 136 **TECTB**, 121 Tectb, 131, 136-137 Tectorial membrane (TM) electrokinetics, 133-134 longitudinal coupling via traveling waves, 135-138 physical properties, 131-133 porosity, 131-132 radial fibrillar structure, 134 structure and morphology, 129-131 wave mechanics, 134-135 Tip link, hair bundle, 67-69, 72 TM. See Tectorial membrane TMC1 binding partners CIB2, 84-85 LHFPL5, 84 PCDH15, 83-84 TMIE, 84 TOMT, 85 discovery, 79-80 expression and localization, 80-82, 101, 103 gene therapy, 318-319 hair cell function conductance, 88-89 gating, 88 mechanoelectrical transduction current mediation, 82-83, 103 pore formation, 87 mutations, 103-104 structure, 85-88, 102 superfamily, 80 TMC2 binding partners CIB2, 84-85 LHFPL5, 84 PCDH15, 83-84 TMIE, 84 TOMT, 85 expression and localization, 80-82, 101, 103 hair cell function conductance, 88-89 gating, 88 mechanoelectrical transduction, current mediation, 82-83, 103 pore formation, 87 mutations, 103-104 structure, 85-88, 102

superfamily, 80 TMEM16, 80, 85-87, 257 TMHS. See LHFPL5 TMIE, 84, 98-101 TOMT, 85, 106-107 Top connector, hair bundle, 65-67 TORCH, 227 Treacher Collins syndrome, epidemiology, 223 TRIOBP, 275 TRPA1, 87, 95, 258 **TRPC3**, 95 **TRPC6**, 95 **TRPM1**, 95 TRPM6, 95 **TRPM7**, 95 TRPML3, 89, 95 TRPN1, 70, 95, 258-259 TRPV4, 95, 258 **TRPV6**, 95 TUBA, 120 TUBB, 120 Tuning ratio. See Otoacoustic emission TWF2, 117, 124

U

UBA1, 121 USH1C, 62–63, 68, 71, 104, 106, 122 USH1D, 155 USH1F, 155 USH1G, 69, 71 USH1J, 85 USH2A, 61, 63, 122, 155 USH2C, 155 USH3A, 156 Usher syndrome epidemiology, 222 gene therapy, 317–318

V

Vangl2, 43, 46, 50 VEZTn62 VGLUT3, 155, 317 VLGR1, 61, 119

W

Waardenburg syndrome (WS), epidemiology, 222 *WFS1*, 44, 220 WHIRLIN, 104, 106, 318 WHRN, 62–63 WNT, 303, 314 *Wnt5a*, 43 WS. *See* Waardenburg syndrome

Х

XBP-1, 237 XIRP2, 116