

Preface

ALONG WITH THE OTHER SENSES, HEARING CONTRIBUTES to the survival of individuals and species. However, during the course of hominid evolution it became, through the development of language and music, the major sense by which individuals communicate. In humans, hearing is linked intimately to cognitive function. The first genes for nonsyndromic and syndromic forms of deafness were discovered just over 20 years ago. Ever since, our understanding of how the inner ear works, how it develops, and of the multiple causes of deafness has increased at a considerable pace. With 112 genes for nonsyndromic deafness already identified (hereditaryhearingloss.org) and the technologies now available, the inner ear is firmly within the molecular domain. The paucity of material available for analysis is, thanks to the genetic approach, no longer a limiting factor and we are already at a point where it is realistic to think that therapies bespoke for certain forms of deafness will become available in the near future. Molecules that underlie auditory transduction, the conversion of sounds into electrical signals, or the amplification of nanometer scale displacements of the cochlear partition, have now been identified. As a result, we have a better understanding of the mechanisms that underlie sharp frequency tuning in the auditory system, how temporal information is encoded in the cochlea and transmitted to the brain, and how the latter can provide top-down control of sound processing.

In this volume, we bring together a series of brief reviews by experts in the field that summarize recent findings and suggest avenues for future advances. The volume starts with a functional perspective on how hearing has evolved by Christine Köppl and Geoff Manley, a chapter that considers when and why features unique to the mammalian cochlea, ranging from the endolymphatic potential through to the loss of a capacity for hair-cell regeneration, have appeared. Christopher Shera and Karolina Charaziak then ask why otoacoustic emissions, a by-product of auditory amplification, have longer than expected delays in the human ear, and Dolores Bozovic reviews progress in understanding the cellular and biophysical basis of active hair-bundle motion, a process that likely contributes to the amplification of sounds. Next, Mireille Montcouquiol and Matthew Kelley discuss how the cochlea develops and how the hair bundles of the sensory hair cells that are so critical for cochlear function become correctly polarized, and the editors then review the molecular structure of the different link types that are associated with the mechanosensory hair bundle and the critical roles they play in hair-bundle function and development, all of which were revealed by the study of deafness genes. Next there are two chapters focusing on the hair cell's mechano-electrical transduction complex: David Corey, Nurunisa Akyuz, and Jeffrey Holt discuss the transmembrane channel-like proteins TMC1 and TMC2 and recent evidence indicating these proteins form the ion-conducting pore of the long-sought-after mechano-electrical transduction channel, while Christopher Cunningham and Ulrich Müller critically appraise the roles of all the proteins that are thus far known to be associated with the complex. Jocelyn Krey and Peter Barr-Gillespie then present a consensus proteome for the vestibular hair bundles of different species, an invaluable data set that reveals how much we still need to learn about the way in which the hair bundle forms and functions.

Moving on from the mechanosensory hair bundle, Jon Sellon, Roozbeh Ghaffari, and Dennis Freeman review recent advances in understanding the mechanical properties and functions of the tectorial membrane, a prominent extracellular matrix that lies atop the organ of Corti. Walter Marcotti and colleagues extensively discuss the function and dysfunction of the inner hair cell afferent synapses, the synapses that relay information with extraordinary temporal precision to the central nervous system, and Jonathan Ashmore reviews recent findings about prestin and the electromotile properties of the cochlear outer hair cells, the cells that are critically involved in amplification in

Preface

mammals, highlighting outstanding issues. Paul Fuchs and Amanda Lauer then describe and discuss the efferent system that can control the outer hair cell activity and provide protection from noise and aging, and Fabio Mammano reviews how the connexins of the inner ear, mutations in which are a very prevalent cause of human hereditary hearing loss, play key roles in both the development and the maintenance of cochlear function. Abraham Sheffield and Richard Smith follow to present the epidemiology of deafness, discussing the genetic, environmental, and other causes of a sensory deficit that affects many worldwide, and Gabriel Corfas and colleagues review causes, diagnoses, and possible therapies for hidden hearing loss, a problem in which patients present with normal audiometric thresholds but have difficulties hearing in noisy environments. Finally, to conclude on the many causes of deafness, Corné Kros and Peter Steyger discuss the mechanisms underlying the ototoxic side effects of the aminoglycoside antibiotics and the anticancer reagent cisplatin and possible strategies for preventing the loss of hair cells caused by these otherwise invaluable compounds, and Mike Bowl and Sally Dawson review what is known about the causes of, and possible therapies for, age-related hearing loss, a sensory deficit that affects a large percentage of the population.

The final four chapters of this volume move on to emerging therapies. Mark Warchol reviews how the macrophage population in the inner ear interacts with the hair cells and the afferent neurons following injury to influence their repair and survival, Amanda Janesick and Stefan Heller address the issue of hair-cell regeneration, asking if there is a stem cell population in the avian hearing organ and where it is located, and Lawrence Lustig and Omar Akil discuss the most recent advances in cochlear gene therapy and the approaches that are being currently explored. Last, Tobias Dombrowski, Vladan Rankovic, and Tobias Moser review progress in redesigning and potentially improving, using optogenetics, one of the most successful cures for deafness that has been developed thus far, the cochlear implant.

In progressing from cochlear evolution through to the latest therapeutic strategies for preventing or treating deafness, we hope the reader gains a broad overview of the field and of the specific questions that need to be, and are being, addressed at this point in time. We are immensely grateful to all the authors for their time and efforts, to those in our laboratories and elsewhere who helped us review the articles, and to the staff at Cold Spring Harbor Laboratory Press, Barbara Acosta, Richard Sever, Diane Schubach, and Denise Weiss, for their patience and guidance.

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