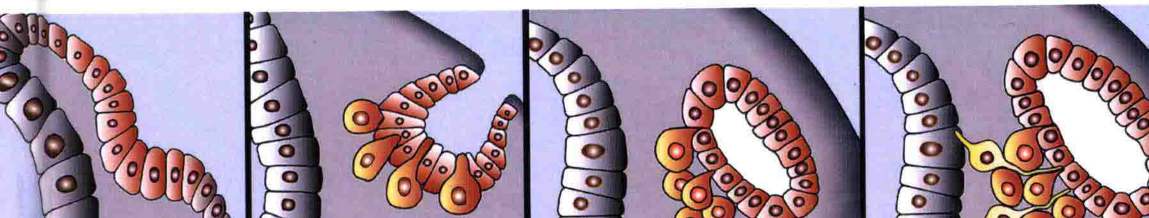
FOURTH EDITION

Development of Auditory and Vestibular Systems



Edited by

Raymond Romand
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DEVELOPMENT OF AUDITORY AND VESTIBULAR SYSTEMS

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CHAPTER

1

Early Development of the Vertebrate Inner Ear

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OUTLINE

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SUMMARY

The auditory and vestibular receptors of vertebrates are located in the inner ear and connected to the brain by the VIIIth cranial nerve. The inner ear is a complex and integrated system, damage to which causes hearing and/or balance impairment. Understanding the genetic, cellular, and molecular bases of inner ear development will enhance our understanding of adult inner ear physiology and pathology. Cells of the sensory receptors have a common embryonic origin in the ectodermal otic placode. The three main otic lineages of sensory hair cells, non-sensory support cells, and spiral and vestibular neurons have common otic progenitors. Apoptosis, proliferation, autophagy, and cell differentiation processes interact during early otic development to generate the structures and functionally distinct cell types of the adult inner ear. Groundbreaking work has begun to delineate the signaling networks that regulate early inner ear development, and this will be discussed in detail in this chapter.

1. THE ADULT INNER EAR

1.1 Anatomy of the Adult Inner Ear

The mammalian inner ear is formed by fluid-filled canals and cavities, named the membranous labyrinth, that are encased within the bony labyrinth and located inside the temporal bone (Fig. 1.1A). The auditory (hearing) and vestibular (balance) organs are located in the inner ear, and they are connected to the brain by the fibers of the VIIIth cranial nerve. The cochlear, or hearing part, is divided into the three parallel helical scalas, tympanic, vestibular, and media, filled with lymph (Fig. 1.1A–C). The organ of Corti is located inside the scala media. This is the sensory receptor, where the hair cells transform the mechanical input elicited by sounds into an electrochemical signal (Hudspeth, 2008). The organ of Corti is formed by two main types of functional cells: sensory hair cells and non-sensory support cells (Fig. 1.1D–F). The hair cells are the sensory receptor cells and possess a set of sterocilia in their apical surface that allow mechanotransduction. There are two types of hair cells that exhibit specific functions: the inner hair cells (IHC) and the outer hair cells (OHC), which are arranged in one and three rows, respectively. IHC and OHC rows are separated by support pillar cells that form the tunnel of Corti. Deiters', Hensen's, and Claudius's cells are other specialized non-sensory support cells that participate in ionic and metabolic cochlear homeostasis (Forge and Wright, 2002; Lefebvre and Van De Water, 2000).

The bipolar auditory neurons of the spiral ganglion are connected to the hair cells and convey the encoded sound information to the central nervous system (Nayagam et al., 2011; Raphael and Altschuler, 2003) (Fig. 1.1G–I). The dendritic ends of type I neurons connect to the IHCs, whereas those of the type II innervate the OHCs. The axons of the spiral neurons leave the spiral ganglion and pass through the base of the modiolus to form the cochlear division of the cochleo-vestibular nerve toward the cochlear nuclei in the brainstem. Sound information progresses in a complex, multisynaptic, parallel, and ascendant pathway from the cochlea through the brainstem nuclei to the auditory cortex (Webster et al., 1992). The tonotopic organization present in the cochlea is maintained along the pathway up to the auditory cortex. Neurons from the superior olivary complex at the brainstem also contact hair cells in a centrifugal control mechanism of the auditory pathway.

The spiral ligament and the stria vascularis form the lateral wall, and both are central to hearing physiopathology (Fig. 1.1J–L). The stria vascularis is a three-layered vascular epithelium that regulates intracochlear ion transport and maintains the endocochlear potential. The intermediate cells of the stria vascularis are melanocyte-like cells (Murillo-Cuesta et al., 2010; Patuzzi, 2011; Takeuchi et al., 2000).

The vestibular part of the inner ear contains the balance receptors, which are formed by specialized balance mechanoreceptor hair cells, similar to those of the organ of Corti, and organized into several sensory organs. The three *cristae* are located at the base of the semicircular canals and detect angular acceleration, whereas the two *maculae* detect linear acceleration and gravity (Goldberg, 1991; Highstein and Fay, 2004) (Fig. 1.1).

Hearing loss and balance impairment are consequences of adult inner ear injury. Understanding the genetic, cellular, and molecular bases of inner ear development is the first step in unraveling adult inner ear physiology and pathology.

1.2 Comparative Anatomy of the Adult Inner Ear

The auditory sensory organs have been highly modified along the phylogenetic tree (Fritzsch et al., 2013) (Fig. 1.2) but in contrast the vestibular sensory organs are highly comparable among species. The cochlea is absent

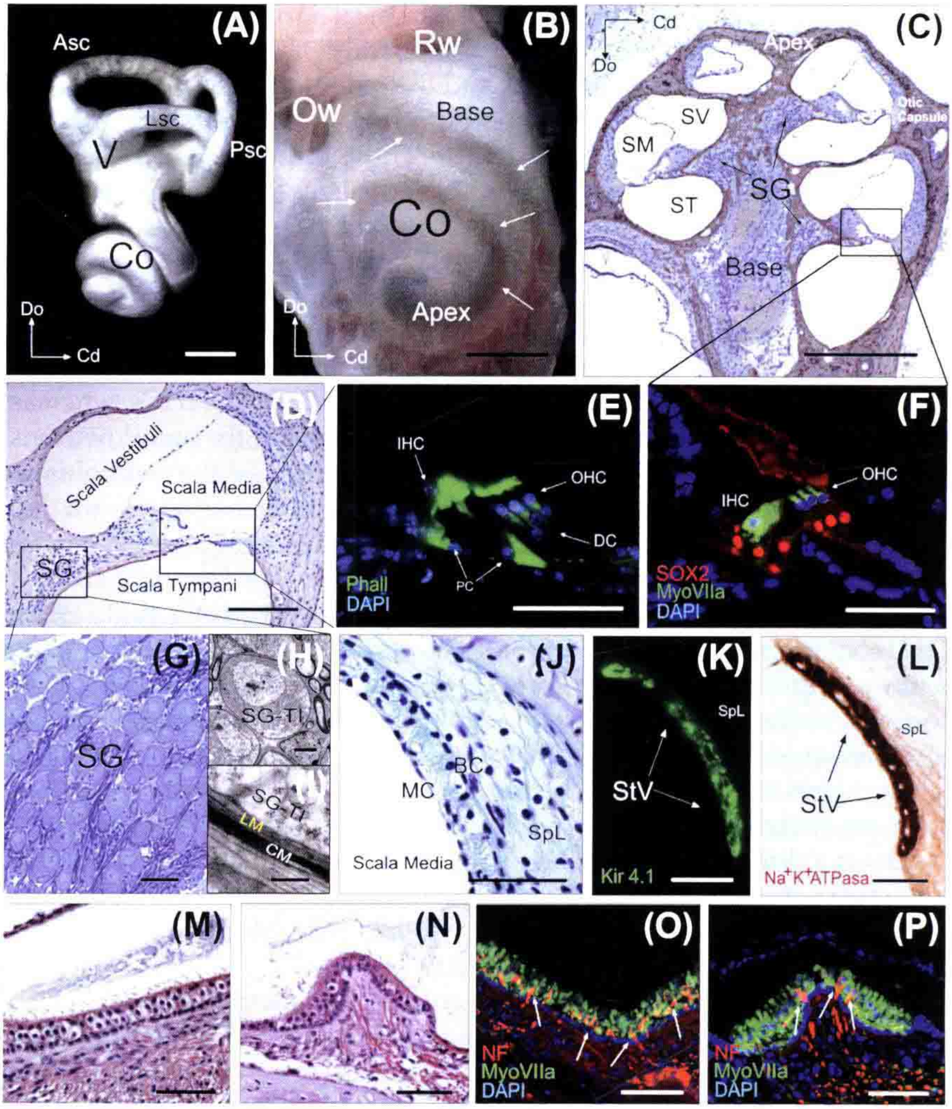

FIGURE 1.1 **Anatomy of the adult mouse inner ear.** (A) Lateral view of paint-filled inner ear. Abbreviations are: Co, cochlea; V, vestibule; Asc, Lsc, and Psc, anterior, lateral, and posterior semicircular canals; Do, dorsal; Cd, caudal. (B) Lateral view of a whole-mounted cochlea showing the pigmented stria vascularis (arrows) in the lateral wall and the round (RW) and oval (OW) windows. (C) Midmodiolar section of the cochlea and the surrounding osseous otic capsule showing the three fluid-filled scales: the scala vestibuli (SV), the scala media (SM) with the auditory receptor (black box), and the scala tympani (ST). (D) Detail of a cochlear turn highlighting the spiral ganglion (SG, left black box) and the auditory receptor (organ of Corti, right black box). (E) Phalloidin histochemistry (Phal) of the organ of Corti, labeling F-actin in the stereocilia and cuticular plate of hair cells (IHC, OHC), the reticular lamina, and pillar cells. (F) Detail of organ of Corti, showing the myosin (MyoVIIa) expression at the hair cells and the SOX2 expression at the supporting cells. (G) Semi-thin section showing a detail of the spiral ganglion (SG). (H) Electron micrograph of a spiral ganglion neuron type I (SG-TI). (I) Detail of the external compact (CM) and internal loose (LM) myelin sheaths in a SG type I neuron.

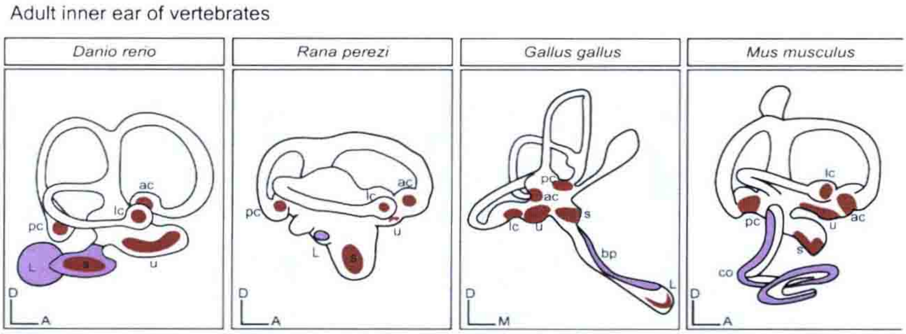

FIGURE 1.2 **Comparative anatomy of the adult inner ear of different vertebrates.** Schematic view of the inner ear of *Danio rerio*, *Rana perezi*, *Gallus gallus*, and *Mus musculus*. The scheme shows the cochlear and vestibular parts, as well as the sensory areas: crista (anterior, AC, posterior, PC, and lateral, LC), macula (utricle, U, and saccule, S), basilar papilla (BP), lagena (L), and organ of Corti (Co).

in fish and amphibians, and its functions have been replaced by alternative auditory organs, the saccule and lagena, respectively. The saccule has a vestibular function in birds and mammals, whereas the functions of the lagena in birds are only now beginning to be understood (Mahmoud et al., 2013), and it is not present at all in placental and marsupial mammals. Even in invertebrates, hearing is mediated by a mechanosensory organ, the Johnston's organ, which presents some developmental genetic similarities to that of vertebrates (Senthilan et al., 2012), although the sensory neurons themselves have mechanosensitive cilliary specializations, as is discussed in detail in Chapter 2.

2. DEVELOPMENT OF THE INNER EAR

The early development of the inner ear is very similar among all vertebrates. The sensory and supporting cells of the inner ear and the spiral ganglion neurons develop from the ectodermal embryonic otic placode (Fig. 1.3). The cells for the spiral ligament, otic capsule, and modiolus

(J) Detail of the marginal (MC) and basal (BC) cells in the stria vascularis. The spiral ligament (SpL) is close to the otic capsule. (K–L) Immunostaining showing the expression of Kir4.1, a K^+ channel related to the production of the endocochlear potential (K), and Na^+K^+ATPase (L) expression in the stria vascularis (StV). (M–N) Sensory epithelium of the vestibular inner ear, a detail of the utricular macula and the cristae gross anatomy. (O–P) Detail of the macula (O) and cristae ampullaris (P) showing the myosin VIIa expression (green, labeling sensory hair cells) and neurofilament expression (red, labeling macula and cristae nerve fibers). Arrows show the afferent calyx of type I hair cells. **Scale bars:** A-C, K, 0.5 mm; D, 100 μm; E,F,J,L,M, 50 μm; G, 30 μm; H, 5 μm; I, 0.1 μm; J,K,L,M,N,O,P, 50 μm.