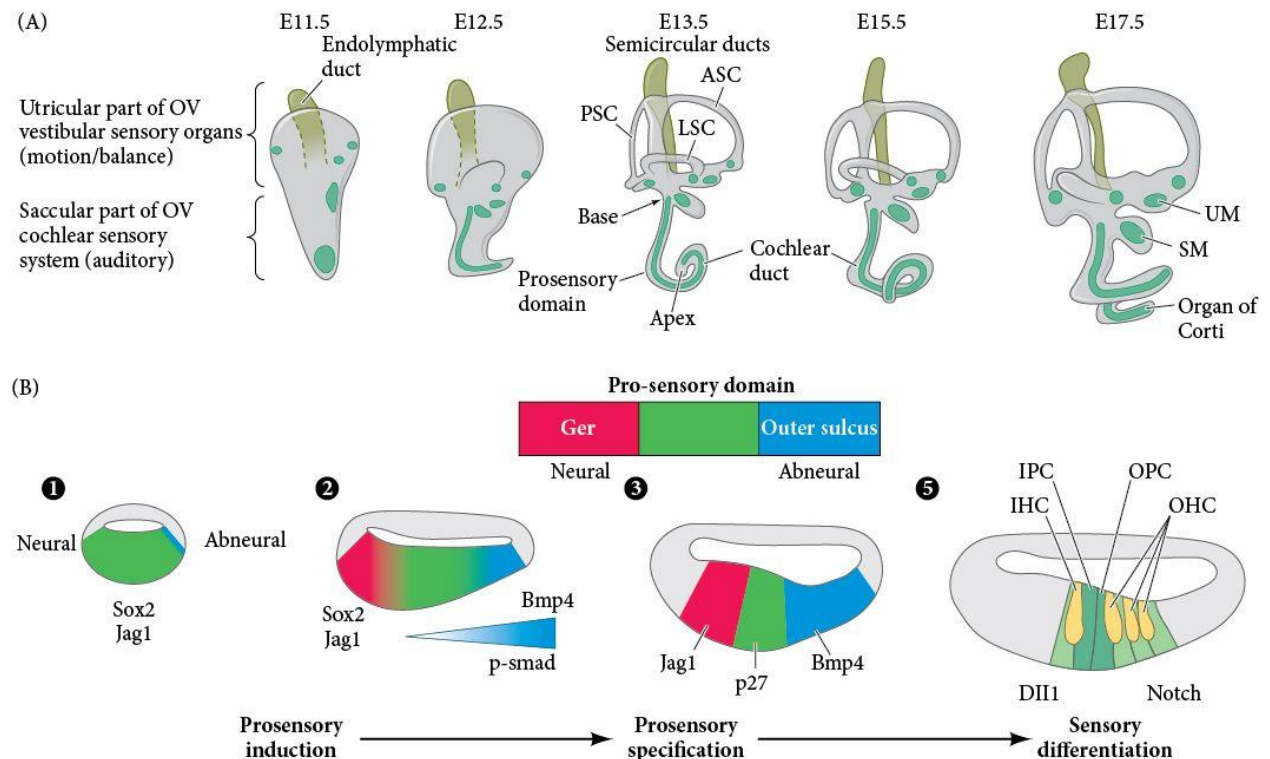


# Cell Fate Determination in the Organ of Corti of the Mouse Ear

The cochlear duct grows out from the medial and ventral walls of the developing otocyst. Three domains become specified within the cochlea along the neural (closest to neural tube) to abneural (farthest from neural tube) axis. The hair cell generating prosensory domain is flanked on either side by non-sensory domains. On the neural side, the non-sensory Kölliker's organ will develop into the greater epithelial ridge of the inner sulcus, while on the abneural side lies the non-sensory cell domain that will give rise to the outer sulcus (Figure 1). Over the course of cochlear development, a wave of cell cycle exit progresses from the apex or tip of the cochlea to its base (Ruben 1967). Typically, during developmental events the timing of cell cycle exit is linked to the cell's subsequent differentiation. However, it appears that differentiation in the cochlea shows a temporal incongruity with the onset of cell cycle exit, wherein it is the last cells exiting the cell cycle at the base of the cochlear duct that first start to differentiate, and this inverse wave of differentiation proceeds to cells at the apex (the first post-mitotic cells). Although Wnt signaling and p27 are suspected to be involved in the regulation of cell cycle exit and differentiation in the cochlea (see Chen and Segil 1999; Lee et al. 2006; Laine et al. 2007; Schimmang and Pirvola 2013), the field has yet to produce a modeled mechanism to account for the uncoupled timing of these two processes.



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**Figure 1** Differentiation of the mammalian cochlea. (A) Diagrams show the developmental progression of the inner ear. (ASC, LSC, and PSC, anterior, lateral, and posterior semicircular canals; IPC, inner pillar cell; OPC, outer pillar cell; SM, saccular macula; UM, utricular macula.) Labeled lines (b1–b5) correspond to the section diagrams shown in (B). (B) Drawings depict the development of the organ of

Corti. Initially the entire cochlear epithelium will express Sox2 and Jag1. Later, however, this pattern becomes refined into three domains (the greater epithelial ridge [GER], the prosensory, and the outer sulcus domains), largely defined by the abneural-derived gradient of Bmp4. p27 upregulation within the prosensory domain triggers cell cycle exit. However, final sensory organ differentiation requires lateral inhibition by Notch-Delta1 cell-to-cell signaling. It should be noted that the prosensory domain is also under the influence of dynamic Fgf, Wnt, and Shh signaling (not shown).

The sensory and non-sensory epithelium of the cochlea is specified along the neural-abneural axis by the dynamic intrinsic expression of Fgfs, Wnts, and Bmps, as well as the extrinsic Shh signaling from the newly formed cochleovestibular ganglion. Although more targeted analysis of the embryonic cochlea is required to confirm the role of these different signaling pathways, a generalized model is emerging. Initially, a neural oriented gradient of Fgf10 promotes prosensory cell specification, whereas the opposing abneural expression of Bmps specifies non-sensory fates, such as the outer sulcus (see Figure 1). In fact, intermediate concentrations of Bmp4 support prosensory fates, while higher concentrations induce the sulcus fate (Ohyama et al. 2010). As development proceeds, another non-sensory structure appears (Kölliker's organ) in a domain where Fgf10 expression becomes concentrated, and the prosensory domain is now sandwiched between the outer sulcus and Kölliker's organ. Further subdivision of the prosensory domain (the future organ of Corti) into hair cells and support cells is specified by different Fgf and Wnt gradients. Interestingly, the transient expression of Shh from the cochlear-vestibular ganglion provides yet another asymmetric morphogen signal that promotes the development of the Kölliker's organ (reviewed by Groves and Fekete 2012). Finally, the precise alternating positions of each hair cell with a supportive adjacent cell is built through a mechanism of Notch-mediated lateral inhibition (Eddison et al. 2000; Daudet and Lewis 2005; Daudet et al. 2009). A cell in the prosensory domain begins to express the transmembrane ligands for the Notch receptor (such as Delta1 and Serrate2), which results in two outcomes: the cell differentiates into a hair cell, and the Notch pathway becomes activated in adjacent cells, repressing the hair cell fate while promoting a supportive cell identity. In summary, it is the remarkable symphony of these many different signals that orchestrate the construction of the inner ear so that we may hear the sounds around us.

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