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Review

Hair cell development: Commitment through differentiation

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ABSTRACT

The perceptions of sound, balance and acceleration are mediated through the vibration of stereociliary bundles located on the lumenal surfaces of mechanosensory hair cells located within the inner ear. In mammals, virtually all hair cells are generated during a relatively brief period in embryogenesis with any subsequent hair cell loss leading to a progressive and permanent loss of sensitivity. In light of the importance of these cells, considerable effort has been focused on understanding the molecular genetic pathways that regulate their development. The results of these studies have begun to elucidate the signaling molecules that regulate several key events in hair cell development. In particular, significant progress has been made in the understanding of hair cell commitment, survival and differentiation. In addition, several aspects of the development of the stereociliary bundle, including its elongation and orientation, have recently been examined. This review will summarize results from each of these developmental events and describe the molecular signaling pathways involved.

1. Introduction

Mechanosensory hair cells located within the inner ear act as the primary transducers of auditory and vestibular stimuli. In response to selective pressures to perceive small movements or pressure waves, hair cells have developed a unique group of specializations that is most obviously illustrated by the presence of a stereociliary bundle, a group of modified microvilli, located at the lumenal surface. Even the most subtle of movements of the individual stereocilia results in the opening of mechanosensory transduction channels and a subsequent influx of positively charged ions (reviewed in Eatock and Hurley, 2003). The resulting depolarization of the cell results in changes in the rate of tonic release of neurotransmitter from the base of the cell and subsequent changes in the rate of neural activity in the neurons that synapse with those hair cells. Considering the important role of these cells, it is not surprising that their loss results in significant deficits in hearing and balance.

Despite the importance of mechanosensory hair cells, our understanding of the factors that regulate the specification and differentiation of these cells is still fairly limited. However, recent progress has resulted in striking advances in several different aspects of hair cell formation, in particular the commitment of cells to develop as hair cells and subsequent development of the stereociliary bundle. In this review, I will discuss the timing of hair cell commitment and differentiation, using the mouse as a model system, and then present a brief overview of some of the more recent work on several different aspects of hair cell development. Unfortunately, time and space limitations will prevent an exhaustive discussion of all aspects of hair cell development. Readers are directed to recent reviews by Whitlon (2004), Fritzsch and Beisel (2004) and Barald and Kelley (2004), for further information.

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2. Hair cell development—an extended process

The mouse otic placode involutes to form the otocyst around embryonic day 8.5 (E8.5). The first sign of cochlear development, the ventral outgrowth of the cochlear duct, occurs around E11. Hair cell development begins in the vestibular system around E12 and in the cochlea around E13 (reviewed in Barald and Kelley, 2004). Among the earliest definitive markers of developing hair cells are two unconventional Myosins, Myosin VI (Myo6) and Myosin VIIa (Myo7a) (Hasson et al., 1997; Sahly et al., 1997; Montcouquiol and Kelley, 2003). In fact, in the cochlea, the first Myo6-positive cells are present at E13, suggesting that Myo6 is turned on soon after, or concomitant with, hair cell commitment (Montcouquiol and Kelley, 2003). While the first indications of hair cell development are present during the early embryonic period, hair cells do not become functional for another 4 to 5 days, based on studies in the vestibular system (Geleoc and Holt, 2003), and it is postnatal day 14 (P14) before the onset of hearing. Therefore, in some cases, hair cell maturation may take nearly 3 weeks. During this time period, several distinct events must occur. First, the progenitor cells that will develop as hair cells must become committed to a hair cell fate. Following commitment, developing hair cells become dependent on a specific group of transcription factors for their continued survival. At the same time, each developing hair cell must assemble the unique structural and molecular components of the stereociliary bundle and then place that bundle in the appropriate location on the lumenal surface of each cell. Concomitant with, or soon after, the development of the bundle, each developing hair cell must express several unique channel molecules that are required for the cell to maintain homeostasis and to respond to a nearly constant influx of positively charged ions. Further, each hair cell must attract and synapse with ingrowing neurites, both afferent inputs from the developing vestibulo-acoustic nerve and efferent fibers from the hindbrain (reviewed in Simmons, 2002). Finally, subsets of hair cells, such as cochlear outer hair cells, go through an extended period of differentiation that continues through the postnatal period, and includes the development of unique cellular aspects, such as electromotility.

Recently, the development of functional aspects of hair cells was examined in two series of studies, one examining vestibular hair cells Geleoc and Holt (2003) and Geleoc et al. (2004) and the second examining development of cochlear hair cells (Marcotti et al., 2003a,b). For the vestibular studies, mouse utricular hair cells were examined between E15 and the early postnatal period. At E15, stereociliary bundles were short with no apparent tip-links, anatomical structures that are believed to be associated with the transduction channels. Moreover, physical deflection of the bundles on 11 E15 and four E16 hair cells failed to elicit any transduction currents, nor did these cells take up FM1-43, a dye that enters hair cells through the transduction channels (Gale et al., 2001; Meyers et al., 2003). In contrast, by E17, stereociliary bundles on developing utricular hair cells had elongated to develop a morphology that appeared much more consistent with their mature form. In addition, tip-links were identified in the spaces between individual stereocilia, and hair cells were able to take up FM1-43, suggesting the presence of active transduction apparatus. Further, by E17 or E18, most utricular hair cells had developed a resting membrane potential that was below −50 mV, as well as key electrophysiological properties that are required for hair cell transduction. These results demonstrate a rapid onset of hair cell function between E15 and E17 in utricular hair cells; however, it is important to consider that despite this rapid onset, fully mature hair cell characteristics are not attained until the postnatal period. While a similar study examining both electrophysiological and anatomical aspects of development has not been conducted for hair cells located in other sensory epithelia, the development of inner and outer hair cell membrane properties has been examined (Marcotti et al., 2003a,b). As was observed for vestibular hair cells, cochlear hair cells develop many functional properties long before the onset of hearing. The basis for the early and rapid onset has not been determined, but Marcotti et al. (2003a,b) and Geleoc et al. (2004) suggest that the onset of increased receptor potentials could play a role in the recruitment and stabilization of synaptic contacts with in growing neurites.

3. Hair cell commitment

The molecular control of hair cell commitment has been studied most extensively in the mouse cochlea, although valuable insights have also been gained from studies on the avian auditory system during both initial development and regeneration. However, for reasons of clarity, the discussion presented here will be restricted to the mouse cochlea. More thorough reviews of hair cell commitment and regeneration, including avian systems, can be found in Stone and Rubel (2000) and Kelley (2002).

Prior to E12, the floor of the cochlear duct is comprised of actively proliferating epithelial cells. The floor of the duct will ultimately give rise to three distinct regions, the organ of Corti and the inner and outer sulci. Although the morphology of cells throughout the floor of the duct appears homogenous at E12, cells that will give rise to the organ of Corti are already positive for the transcription factor Sox2 (Kiernan et al., 2005b) (Fig. 1). Based on presumed differences in developmental potential, the region of the duct that will give rise to the organ of Corti has been termed the prosensory domain. Although specific functional studies have not been conducted, it seems likely that there is a close overlap between the prosensory domain and expression of Sox2 (Kiernan et al., 2005b). Beginning on E12, cells located within the prosensory domain at the apex of the cochlear spiral begin to leave the cell cycle and become permanently postmitotic. As development proceeds through E13 and E14, a wave of terminal mitosis extends from apex to base within the prosensory domain (Ruben, 1967). The factors that specify the wave of terminal mitoses are not fully understood; however, a key regulator of this event is expression of the cell cycle inhibitor, $p27^{kip1}$ (Chen and Segil,