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Cell Biology: Function Guides Form of Auditory Sensory Cells

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Mechanosensory bundles on auditory sensory cells are composed of stereocilia that grow in rows of decreasing height. This pattern depends on the specification of the eventual tallest row, then the assignment of distinct molecular identities to the shorter rows. Mechanotransduction refines and maintains row identity, thus instructing the form of the bundle.

The bundles of stereocilia on sensory hair cells that detect sound in the inner ear are beautiful, probably because of their visual symmetry. Their function, however, depends to a greater degree on molecular asymmetry. It works like this: several of these actin-based protrusions grow to form a bundle on top of auditory sensory cells. The stereocilia are arranged in tall, medium, and short rows, each of a particular height. Force-sensitive ion channels housed in the tips of the stereocilia in shorter rows are then connected to the sides of stereocilia in the next taller row by extracellular linkages. As the taller row is pushed backwards by sound energy, the channel opens and ions flood in, depolarizing the cell. This is mechanotransduction — conversion of physical movement into neuronal signals. Tiered rows of stereocilia are required for proper mechanotransduction because the bundle shape influences its function. Two recent studies by Tadenev *et al.* [1] and Krey *et al.* [2] (the latter in this issue of *Current Biology*) provide exciting new insights into stereocilia bundle morphogenesis. The data in these papers define key proteins that are required to establish the molecular asymmetry between the stereocilia rows and the findings reveal how mechanotransduction itself influences these proteins to refine bundle form (Figure 1).

The stereocilia bundle emerges during late embryonic mouse development from much thinner microvilli that initially cover the entire surface of the hair cell. A subset of these protrusions elongate and widen to become stereocilia, while the remainder are resorbed [3]. By the time the mouse is born, the tiered arrangement of stereocilia is evident, though still immature and unrefined. Within a few days of birth, the bundle starts to acquire mechanotransduction currents [4], which seem to affect stereocilia development [2,5]. In the chicken, it has long been understood that stereocilia have two periods of elongation separated by a widening phase [6]. A significant advance in the new studies [1,2] is the demonstration that mouse stereocilia development follows a similar progression and is coordinated with the onset of mechanotransduction. As ion flux increases, elongation pauses while stereocilia widen [2]. Several different proteins are essential for the bundle to develop to its normal dimensions, presumably contributing to and coordinating growth and mechanotransduction. In particular, a group of five proteins — Myo15a, Eps8, Whrn, GPSM2, and GNAI — appears to be essential to promote the elongation of the tallest row and provide molecular asymmetry to the bundle [7–11].

A key insight from the Tadenev *et al.* [1] study is that GPSM2, GNAI, and Whrn arrive after Myo15a and Eps8 to specify what will become the tallest row of the bundle from a group of similar microvilli. Multiple lines of evidence support this view. First, the authors performed an ambitious genetic analysis, which showed that double mutants lacking combinations of the five proteins were almost indistinguishable from any of the single mutants. This is strong evidence that these proteins are united in a common mission to facilitate growth of the tallest row (row 1). Each protein eventually localizes to the tip of row 1 stereocilia where they are positioned to direct elongation, but the order of their arrival is highly informative. Myo15a and Eps8 are first on the scene. This pair is initially present at the tips of stereocilia in all rows, suggesting a general role in elongation. Next, GPSM2, GNAI and Whrn more selectively target row 1 tips and together they reinforce Myo15a and Eps8 localization. As Myo15a and Eps8 are stabilized at row 1 tips, their levels decrease in shorter stereocilia to produce a highly asymmetric localization pattern between rows.

When GPSM2 or GNAI are deleted, row 1 identity is diluted as the remaining row 1 proteins now appear equally in all rows. Intriguingly, other proteins that are typically restricted to row 2 tips likewise find their way to row 1 tips [1]. Thus, the failure to reinforce row 1's distinct molecular identity results in all stereocilia settling into an intermediate, undifferentiated state, perhaps similar to the unrefined bundle observed at birth.

Krey *et al.* [2] further advance our understanding of stereocilia bundle development by considering the impact of mechanotransduction on morphogenesis. At first glance, mutant mice lacking components of the mechanotransduction channel have normal-looking bundles. However, closer inspection reveals notable differences, including extra rows of stereocilia, along with changes in both length and width [2,5,12,13]. The work of Krey *et al.* [2] provides a much more detailed understanding of the molecular events that follow loss of mechanotransduction. These authors report that row 2 proteins can now be found in row 1 in mechanotransduction mutants. Shifting the localization of row 2 proteins is not so

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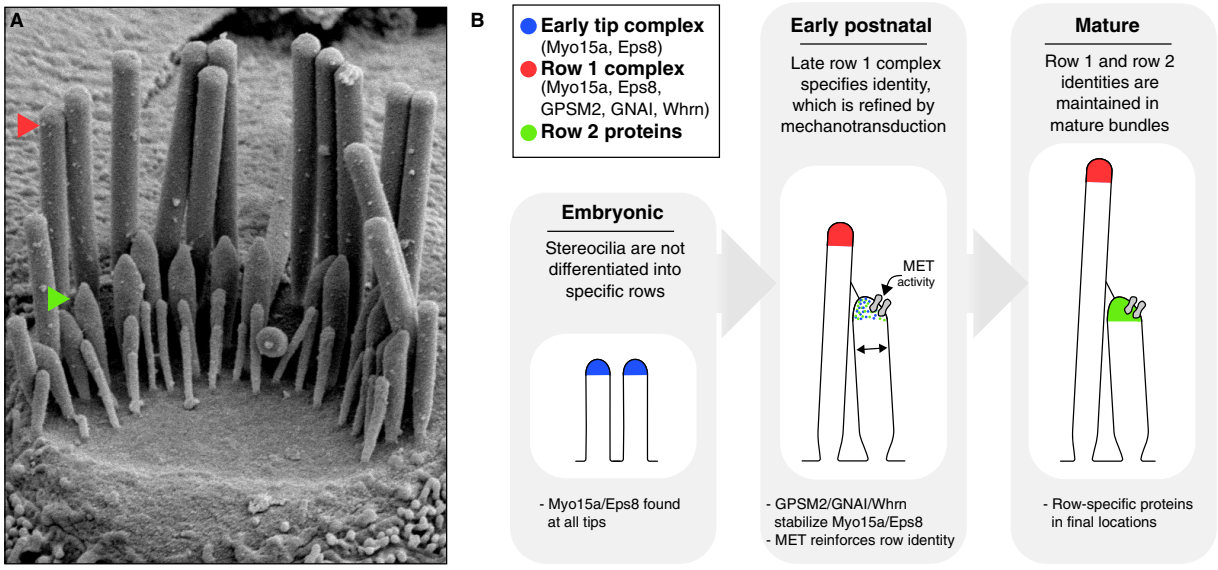

Figure 1. Morphological development of auditory stereocilia bundles.
(A) Mature inner hair cell stereocilia bundle. The tallest stereocilia are in row 1 (red arrowhead) and mechanotransduction channels are at the tips of stereocilia in row 2 (green arrowhead). (B) Schematic of row 1 and row 2 specification and growth. Stereocilia differentiate from microvilli-like protrusions. Embryonic stereocilia are short and lack an obvious height gradient but have Myo15a and Eps8 at their tips. Around birth, GPSM2/GNAI/Whrn specify row 1 tips, further enriching Myo15a/Eps8. Concurrently, mechanotransduction (MET) activity at row 2 stereocilia tips promotes row identity by reinforcing sorting of row-specific complexes. Following stereocilia widening, row 1 elongates further. Mature stereocilia have fixed dimensions and maintain the polarized localization of row 1 and row 2 complexes.

surprising since they may be ordinarily enriched by mechanotransduction channels, themselves at row 2 but not row 1 tips [14]. Interestingly, row 1 proteins are also mislocalized in the absence of mechanotransduction. For example, Myo15a and Eps8, which typically define row 1 stereocilia, are more abundantly localized to row 2 stereocilia in mechanotransduction mutants.
Even more intriguing is that the authors find that simply blocking the mechanotransduction channel causes a similar loss of row identity, suggesting that ion flux is a relevant upstream signal in this pathway. Thus, bundle development is a dynamic process with feedback from function guiding the ultimate form of the bundle through the sorting of proteins to either row 1 or row 2 stereocilia tips.

The overall molecular framework guiding stereocilia bundle morphogenesis is now clearer than ever. Nevertheless, many fascinating questions remain to challenge the field. For example, how does ion influx through channels at row 2 stereocilia tips change the localization of proteins at row 1 tips? Another missing piece of the puzzle relates to how row-specific proteins and mechanotransduction regulate the actin core of stereocilia to change their shape. The mechanism coupling these processes must use ion influx to regulate actin-binding proteins and is at the heart of coordinating form with function. Hopefully future studies will address these knowledge gaps.

The processes that build the bundle may also be involved in its maintenance. Certainly, it is well known that mechanotransduction regulates the length of row 2 stereocilia. When the extracellular links that connect to the mechanotransduction channels are lost, or the mechanotransduction channel is simply blocked, then row 2 stereocilia rapidly shorten [15,16]. In mature stereocilia, actin turnover is more evident in row 2 tips than elsewhere in stereocilia, perhaps reflecting repair following the transient loss of mechanotransduction [17–19]. A better appreciation of the connections between mechanotransduction function and stereocilia form promises to shed new light on both the development and maintenance of these remarkable and unique cellular protrusions.

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Marine Life Cycle: A Polluted *Terra Incognita* Is Unveiled

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Teleost fishes have a biphasic life cycle, with pelagic larvae dispersing in the open ocean and juveniles or adults living in reef or coastal environments. A recent study reveals that fish larvae concentrate in a specific oceanic compartment, the surface slicks, which are polluted by microplastics that can be ingested by most larvae.

Because we are terrestrial mammals of macroscopic size we very often neglect the incredible diversity of the living world around us. This diversity culminates in the sea, from which most metazoan phyla originate. But we also often forget that the diversity of animal forms must be extended to their ontogenic stages, and, again, this is particularly true for marine animals [1]. The vast majority of marine animals, including teleost fishes, exhibit a biphasic life cycle with one (or several) larval planktonic stages and juvenile/adult stages that occur in a different ecological niche [2,3]. The existence of two distinct phases during the life cycle ensures the dispersion of individuals due to oceanic currents that convey these pelagic stages. It also reduces the predation level, which could be very high in coastal environments, such as coral reefs, and ensures access to a large food source in plankton [4].

A large number of studies have addressed the entry of larval fish to their juvenile environments, often called settlement or recruitment [5]. In the case of coral reef fishes, this step is easy to recognize as it corresponds with the passing of the reef crest and the selection of an adequate microhabitat. In pelagic fishes, this step is less easy to follow, but

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