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Review

Dynamic length regulation of sensory stereocilia

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ABSTRACT

Stereocilia, the mechanosensory organelles of hair cells, are a distinctive class of actin-based cellular protrusions with an unparalleled ability to regulate their lengths over time. Studies on actin turnover in stereocilia, as well as the identification of several deafness-related proteins essential for proper stereocilia structure and function, provide new insights into the mechanisms and molecules involved in stereocilia length regulation and long-term maintenance. Comparisons of ongoing investigations on stereocilia with studies on other actin protrusions offer new opportunities to further understand common principles for length regulation, the diversity of its mechanisms, and how the specific needs of each cell are met.

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1. Introduction

Actin-based cellular protrusions such as microvilli, filopodia, and stereocilia serve a broad range of functions in eukaryotic cells. The length and lifespan of these cellular protrusions, often matched to their specific functions, depend on regulatory mechanisms acting on the protrusions' dominant structure- the core bundle of actin filaments. Although much has been revealed about the signaling mechanisms and assembly processes that initiate the formation of these structures, considerably less is known about their length regulation.

Stereocilia, the mechanosensory actin protrusions on the surface of hair cells, are the key players in the transduction of sound or motion into the electrical signals that underlie our senses of hearing and balance. Each stereocilium is supported by a rigid paracrystalline array of parallel, uniformly polarized and regularly crosslinked actin filaments. Stereocilia share many construction principles with the actin formations in microvilli and filopodia, yet different stereocilia in a single cell can be from 1 up to 120 μm in length, and in the hair cells of the mammalian organ of Corti they persist for the lifetime of the organism, as the hair cells are not replaced. In each hair cell, stereocilia are graded in length and organized into a characteristic staircase shape (Fig. 1). Also, each stereocilia bundle displays a tightly regulated size and shape that depends on the location of the hair cell within the tissue. For example, the vertebrate auditory epithelium displays a tonotopic gradient of stereocilia bundles with lengths inversely proportional to the frequency of sound the cell is tuned to detect. The overall

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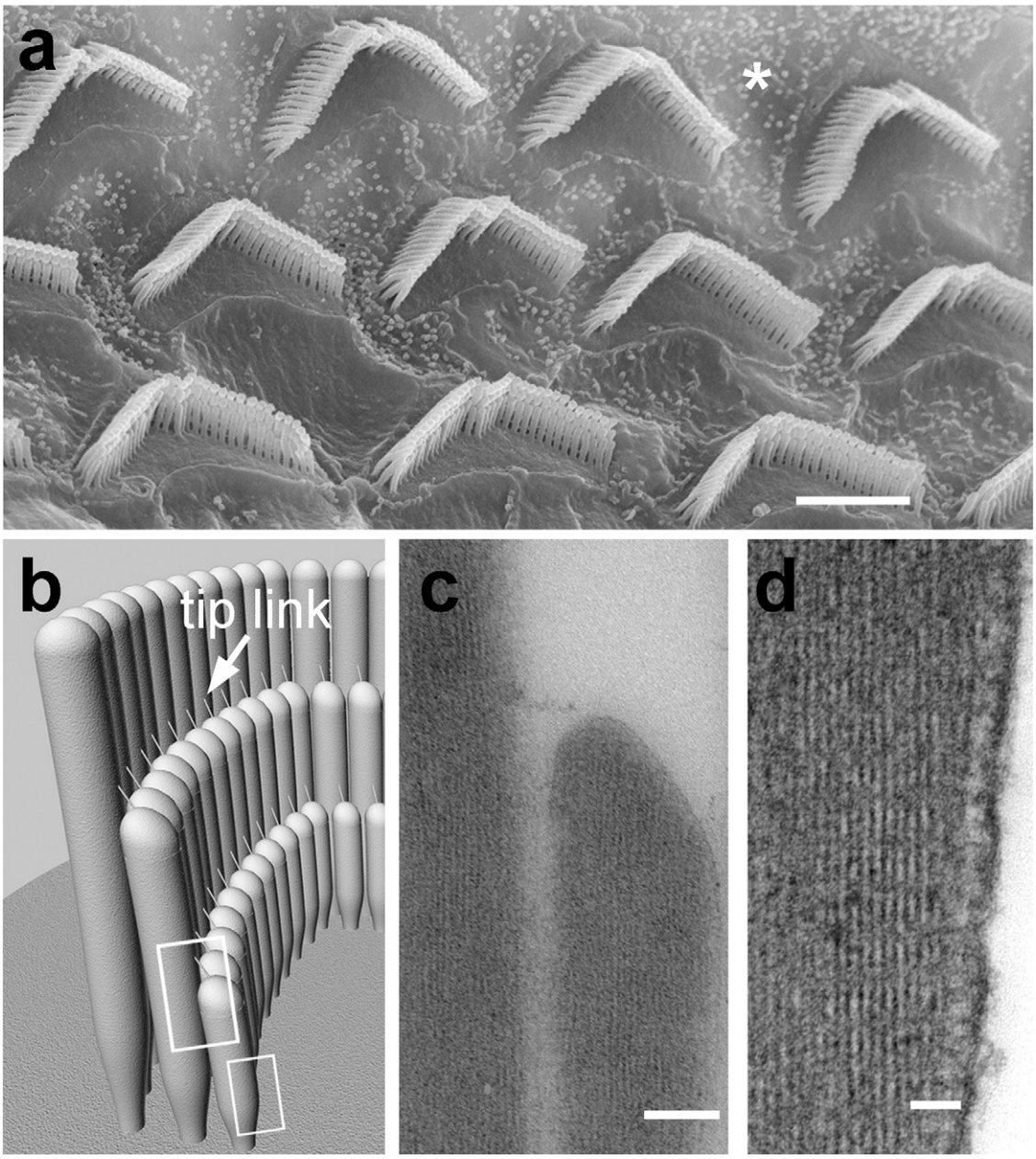

Fig. 1. Hair cell stereocilia appear in a precisely regulated staircase pattern of rows of increasing length. (a) Scanning electron micrograph showing a top view of stereocilia bundles on the apical surface of the inner ear sensory epithelium in the rat cochlea. The asterisk indicates an area on the surface of a non-sensory cell, which displays normal microvilli much shorter than stereocilia. Bar = 5 μm (b) A side view cartoon of a cochlear hair cell. Every bundle in the mammalian cochlea has three rows of stereocilia with rigorously defined lengths. Each stereocilia has a tip-link connecting it to its neighbor in the next shortest row. (c) A thin section electron micrograph showing a cross-section of the upper region of two stereocilia in a rat hair cell, as indicated by the large rectangle in (b). Notice that the tip of the shorter stereocilia is tented due to tip link tension, and that the actin filaments closely match the prolate profile of the membrane. Bar = 150 nm (d) A thin section electron micrograph of the tapered base region of a frog hair cell stereocilium. Notice that the filaments terminate immediately on the plasma membrane. Bar = 50 nm.

organization gives the impression of an array of 'strings' organized like a piano, with a systematic increase in length from one end of the instrument to the other. Although stereocilia are exquisitely sensitive to mechanical vibration, orderly structured, and easily damaged by over-stimulation, many are maintained in proper working order for a lifetime. The precision and range of operation of the stereocilia length regulation machinery in hair cells is a challenging but excellent system for asking the general cell biology question: How can the length of an organelle or cytoskeletal ensemble be controlled?

Like other actin protrusions, stereocilia structure and properties emerge largely from the intrinsic and extrinsic factors modulating the structure and dynamic properties of the actin core. Factors intrinsic to the actin core include (1) molecules that influence the rate of actin polymerization and depolymerization at the plus and minus ends of the actin filaments, respectively; (2) crosslinking within the actin core; and (3) the action of myosin motors and their binding partners. Factors extrinsic to the actin core, such as plasma membrane tension, interstereociliary links, and overlying extracellular structures, also influence stereocilia lengths and actin dynamics. We do not yet have a completely integrated molecular understanding of the architecture, dynamics, function, and renewal of these specialized cellular structures. However, several pieces of this complex system are being unraveled in mouse model and over-