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Review

Line up and listen: Planar cell polarity regulation in the mammalian inner ear

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ABSTRACT

The inner ear sensory organs possess extraordinary structural features necessary to conduct mechanosensory transduction for hearing and balance. Their structural beauty has fascinated scientists since the dawn of modern science and ensured a rigorous pursuit of the understanding of mechanotransduction. Sensory cells of the inner ear display unique structural features that underlie their mechanosensitivity and resolution, and represent perhaps the most distinctive form of a type of cellular polarity, known as planar cell polarity (PCP). Until recently, however, it was not known how the precise PCP of the inner ear sensory organs was achieved during development. Here, we review the PCP of the inner ear and recent advances in the quest for an understanding of its formation.

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1. Introduction

Fields across which cells are oriented with stunning precision are a recurring theme in biology and have riveted scientists for centuries. To understand the biological mechanism that generates the regular alignment of cuticular hairs and bristles in *Drosophila melanogaster*, Gubb and Garcia-Bellido exploited the power of fruit-fly genetics and identified a small set of genes that constitute conserved components of what is now termed the planar cell polarity (PCP) pathway, which governs the genesis of this reiterative pattern of uniformly oriented structures [1]. Planar cell polarity refers to the coordinated orientation of cells in the two-dimensional plane of a cell sheet. It is now well known that the PCP pathway operates in both invertebrates and vertebrates, orchestrating complex tissue movements and patterning events in different types of tissues during development. During evolution, intrinsic differences in morphogenetic processes between invertebrates and vertebrates and among different types of tissues have led to variations in the ways in which the PCP pathway has been deployed. However, in many systems showing PCP features, PCP signaling functions as a crucial biological switch-board integrating long-range signals with local ones to precisely orient diverse subcellular structures or entire cell populations along a specific axis. Among the finest model

Abbreviations: PCP, planar cell polarity; CE, convergent extension; AJ, adherens junction; IHC, inner hair cell; OHC, outer hair cell; IPH, inner phalangeal cell; IPC, inner pillar cell; OPC, outer pillar cell; DC, Deiters' cell; IFT, intraflagellar transport.

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systems in which to study the exquisite capacities and detailed mechanics of the PCP signaling pathway in vertebrates are the sensory epithelia of the inner ear. This review will therefore focus on the role of PCP signaling in the development of the fine cellular architecture of the mammalian inner ear—the basis of its extraordinary operational capabilities for hearing and balance.

2. PCP of the inner ear

2.1. The inner ear—a marvel in miniature

The mammalian inner ear detects and processes both auditory and positional information over a considerable range with remarkable sensitivity and resolution. It contains precisely organized fields of mechanosensory hair cells, intervening supporting cells and neurons that are functionally arranged in fluid-filled chambers to produce three types of highly specialized sensory epithelia (Fig. 1A): (a) the organ of Corti that detects auditory signals; (b) the maculae of the utricle and the saccule that detect linear acceleration in the horizontal and vertical planes respectively; (c) the cristae of the semicircular canals that sense angular acceleration.

Despite the differences in the appearance of the inner ear sensory organs, they all comprise spatially organized ensembles of sensory cells each sensitive to different modalities of mechanical stimuli. Strikingly, they all share a common feature and exhibit perhaps the most distinctive forms of vertebrate PCP, which are described in greater detail in the following sections. These epithelia have now become established model systems to elucidate the molecular mechanisms responsible for the generation of planar polarity in vertebrates.

2.2. PCP in the cochlea

The sensory organ within the mammalian cochlea is the organ of Corti that runs along the entire length of the snail-shaped cochlea. Typically, the mammalian organ of Corti comprises three rows of outer hair cells (OHCs), a single row of inner hair cells (IHCs) and several types of interdigitating non-sensory supporting cells (Fig. 1B). The IHCs are located towards the center of the cochlear spiral and are described as being "medial". In contrast, the OHCs are on the outer periphery of the cochlear spiral, away from the center, and are hence described as "lateral". Each hair cell in the organ of Corti has on its lumenal surface a set of actin-rich stereocilia to form a hair bundle. The stereocilia function by pivoting at their bases in response to sound stimuli. Stereocilia are graded in height and are arranged in multiple tightly packed rows with the shorter rows positioned closer to the center of the apical surface. The stereocilia form a bilaterally symmetrical "V"-shaped descending staircase (Fig. 1B and C). The cochlear hair bundle also transiently contains a single primary cilium, the kinocilium, which is eccentrically positioned near the tallest stereocilia at the vertex of the "V"-shaped hair bundle and is physically linked to adjacent stereocilia. Individual hair cells are therefore intrinsically polarized. Furthermore, all the sensory hair cells show precise and identical orientations of their "V"-shaped hair bundles with the vertices aligned in the medial-to-lateral direction (planar polarity axis), producing an ordered array of sensors endowed with directional sensitivity to mechanical stimulation (Fig. 1C, lower panel).

The elaborate patterning and intricate polarity of the hair bundle are morphogenetic readouts of a very complex developmental program that controls hair cell maturation. Terminal differentiation of the organ of Corti begins near the base of the cochlea, and extends toward the apex. Concurrently, another maturational wave advances from the medial to the lateral side of the epithelium. The formation of the highly polarized stereociliary bundles follows the differentiation gradients of hair cells. Initially, a single primary cilium is present on all epithelial cells in the center of the apical surface and is surrounded by microvilli of uniform height. Subsequently, this primary cilium, known as the kinocilium on hair cells, begins to migrate towards the lateral side of the apical surface, and thus becomes asymmetrically positioned. This movement is concomitant with a graded enlargement of microvilli. In the cochlea, this process results in the production of descending stereociliary staircases with a defined "V"-shaped orientation. The expansion of the cuticular plate, which comprises a dense network of cross-linked actin filaments and associated proteins, and anchorage of core filaments from the stereocilia in the actin meshwork of the apical cytoplasm, proceed concurrently with the maturation of stereocilia on the lumenal surface. The basal body that nucleates and lies at the base of the kinocilium is located just below the apical plasma membrane in the fonticulus, an actin-free hole in the cuticular plate. The kinocilia in the cochlear hair cells are lost prior to the onset of hearing.

The PCP of the cochlea also manifests in another form, known as convergent extension (CE). CE originally described a process in which the elongation of the body axis occurs by narrowing of mesodermal and neuroectodermal tissues along one axis and a concomitant lengthening of the body axis in a perpendicular direction during gastrulation and neurulation [2–4]. The cells in the field become highly polarized along the mediolateral axis during CE, manifesting a fundamental process of PCP. A vast body of evidence has now shown that the PCP signaling pathway governs both CE and the coordinated orientation of epithelial cells. The development of epithelial PCP in the organ of Corti occurs concomitantly with cellular rearrangements characteristic of CE. The mature organ of Corti is elongated from a shorter and thicker primordium. It is noteworthy that, although there is substantial circumstantial evidence in favor of a CE-like process mediating cochlear extension, cochlear CE has not been formally demonstrated.

2.3. PCP in the vestibular system

The vestibular sensory organs also exhibit an alternating arrangement of sensory hair cells and supporting cells with each hair cell being surrounded by a rosette of supporting cells (Fig. 1D–G). In addition, the sensory hair cells of the vestibule also show distinct intrinsic polarity, and all of the hair cells in each of the vestibular sensory organs are coordinately oriented. The orientation of vestibular hair cells is similarly manifested by the polarity of the stereociliary bundle and the location of the kinocilium, although the shape of hair bundles is different. The hair bundles in the cristae (Fig. 1D and E) show uniform alignment towards one side of the epithelia. In the macular sensory organs of the utricle (Fig. 1F and G) and saccule, the stereociliary bundles are coordinately oriented along the mediolateral axis of the epithelia. Strikingly, the hair cells on either side of a line of polarity reversal in the macular sensory organs have opposite orientations. In the utricle (Fig. 1F and G) and the saccule, hair cells are all oriented toward or away from, respectively, the corresponding line of polarity reversal.

3. The vertebrate PCP signaling pathway

The generation of planar polarity in any tissue presents two important challenges: first, to polarize individual cells in the field and second, to ensure that all the cells in the field are aligned along the correct axis and perfectly with respect to each other. Based on data accrued over the last decade from several model systems, it has become amply clear that conceptually, PCP signaling comprises at least three regulatory modules to accomplish coordinated alignment of all the cells in a given field: (1) directional cues for the