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Review Article

Insight into planar cell polarity

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ABSTRACT

Planar cell polarity or PCP refers to a uniform cellular organization within the plan, typically orthogonal to the apico-basal polarity axis. As such, PCP provides directional cues that control and coordinate the integration of cells in tissues to build a living organism. Although dysfunctions of this fundamental cellular process have been convincingly linked to the etiology of various pathologies such as cancer and developmental defects, the molecular mechanisms governing its establishment and maintenance remain poorly understood. Here, we review some aspects of invertebrate and vertebrate PCPs, highlighting similarities and differences, and discuss the prevalence of the non-canonical Wnt signaling as a central PCP pathway, as well as recent findings on the importance of cell contractility and cilia as promising avenues of investigation.

Contents

Abbreviations: AB, apico-basal polarity; AML, acute myeloid leukemia; CE, convergence extension; CLL, chronic lymphocytic leukemia; COPII, coat protein complex II; dpc, days post coïtum; Dvl, disheveled; ER, endoplasmic reticulum; Fz, frizzled receptor; JNK, jun kinase; MEF, mouse embryonic fibroblast; PAPC, paraxial protocadherin; PCP, planar cell polarity; TGN, trans-golgi-network

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Introduction

Most of the cells of multicellular organisms are polarized. The best described cell polarity process is apico-basal (AB) polarity, which characterizes epithelial and endothelial cells, and is discussed by others in this series of reviews. Nevertheless, the most widespread, and paradoxically the less well characterized form of polarity is planar cell polarity (PCP). Typically orthogonal to the AB polarity axis, PCP refers to a uniform cellular organization within the plan. Thus, PCP provides directional cues that control and coordinate the integration of cells in a tissue. As such, PCP is essential for multicellularization as it establishes a mutually coordinated planar polarization between contacting cells [1]. Although it is anticipated that PCP has to be established and maintained throughout the life cycle of an organism, its contribution is most obvious – and therefore most investigated – during the process of embryonic development, during which dynamic cellular rearrangements and tissue formation occur [1]. PCP is less studied in adult animals in normal conditions even though its role in hair alignment was demonstrated in adult mice [2]. Developmental studies in lower vertebrates (*Xenopus laevis*, *Danio rerio*) and in mice have revealed a potential contribution of PCP at the morula and blastocyst stages [3], but the most prominent aspects are observed at the gastrulation stage during the patterning of the proximal–distal and antero–posterior axis, and at later stages of development. During the embryonic development of vertebrates, alterations of PCP lead to typical and dramatic phenotypes used as read-outs of its dysfunctions, such as defects of embryonic left-right patterning [4,5], convergent extension (CE) [6] and associated neural tube closure, misorientation of hair bundles in inner ear sensory cells [7–9] and defects of organogenesis [10–12]. Even though a direct link between PCP and human diseases is more difficult to establish, the contribution of alterations of this developmental process to the etiology of cystic kidney diseases [13] and cancer [14–17] has now been well established. In those cases, it is believed that loss of PCP perturbs tissue organization and dynamic cellular processes, leading to uncontrolled migration or division of cells or group of cells [18–20]. Whereas the importance of PCP in normal physiology and diseases leaves no doubt, and that a growing number of PCP genes have been identified over the last 20 years, little is known about the molecular mechanisms governing PCP initiation and maintenance. Here, we have chosen to summarize the accumulated knowledge about the mechanisms of mammalian PCP and to discuss some of their most intriguing aspects.

Lessons from drosophila

Genetic studies in invertebrates, especially in *Drosophila melanogaster*, have allowed the initial characterization of PCP and the identification of three sets of genes involved in this process recently reviewed by Axelrod and col. [21]. The so called "core PCP", a highly evolutionary conserved module, comprises a set of genes required to prime the establishment of PCP, as demonstrated by the inactivation of these genes in Drosophila and vertebrates (Table 1). The encoded core PCP proteins belong to various protein families, from ligands (Wnts) to receptors (Celsr1, Frizzled, Vangl, Fat) and intracellular proteins (Disheveled, Scrib, Prickle). These proteins are asymmetrically localized within and between cells forming an epithelial sheet. For example, in the Drosophila wing, whereas the atypical cadherin Flamingo (Celsr1 in vertebrates) is localized both at the distal and proximal sides of cells, the other core PCP members are each localized at either one side or the other (Fig. 1). Indeed, Van Gogh (also known as Strabismus in Drosophila, or Vangl in vertebrates) and Prickle accumulate at the distal side of the cell [22]; in contrast Frizzled (Fz) [23], Diego (Inversin) [24] and Disheveled (Dvl) [25] segregate at the proximal side. Such an asymmetric localization of core PCP proteins is considered sufficient to initiate a local cellular spatial organization through cell–cell contacts [22,26,27]. Propagation of this local organization through the tissue appears to be dependent on a second set of genes known as the "global module" [28–30]. In Drosophila, this module includes Four-jointed, a Golgi ectokinase, and two atypical cadherins: Fat and Daschous. Orientation cues propagated by these molecules are not based on their asymmetric cellular localization but rather on the modulated affinity between Fat and Daschous. Indeed, Fat and Daschous form heterodimers regulated by Four-jointed through phosphorylation [31,32]. Under the action of a currently undefined morphogenic gradient, Daschous and Four-jointed are expressed in opposing gradients throughout the tissue [33]. This would convert tissue-wide expression gradients into subcellular gradients of Fat within each cell [28,33]. The third and last set of PCP components includes genes responsible for the translation of the orientation cues into cellular polarized outputs that vary according to one specific tissue. Obviously, proteins involved in cytoskeletal organization are well represented in this set of PCP proteins, especially those affecting the contractile actin meshwork such as Rho1 and Drok (respectively RhoA and Rock in vertebrates) [34–38]. In Drosophila, the hierarchy between these different sets of genes remains unclear [1,21,39,40]. Recent work suggests that, in the wing, the establishment of PCP mainly results from the propagation of the plane of orientation of cell division from a few initial organized cells [41,42]. Interestingly, in these studies, it has been proposed that contraction at the wing hinge leads to an anisotropic tension along the proximal–distal axis [41], which might provide orientation cues contributing to core PCP asymmetrical localization as well as to establish the orientation of the cell division axis [42]. Indeed, these orientation cues overlap with the global module function governed by Fat–Daschous signaling, which regulates nuclear shuttling of the transcriptional factor Yorkie [43,44]. Interestingly, YAP, the vertebrate homolog of Yorkie, was shown to have an acto-myosin contractility-sensitive nuclear localization driven by external mechanical forces [45,46]. Although this mechanism is conserved in Drosophila [47], its potential contribution to PCP directional cues has to be clarified.

Similarities and differences with vertebrate PCP

Vertebrate core PCP members

In vertebrates, information on PCP has mainly been gathered from studies focusing on embryonic development, a period during