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Planar cell polarity in organ formation

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The planar cell polarity (PCP) pathway controls a variety of morphological events across many species. During embryonic development, the PCP pathway regulates coordinated behaviour of groups of cells to direct morphogenetic processes such as convergent extension and collective cell migration. In this review we discuss the increasingly prominent role of the PCP pathway in organogenesis, focusing on the lungs, kidneys and heart. We also highlight emerging evidence that PCP gene mutations are associated with adult diseases.

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Introduction

Planar cell polarity (PCP) was originally identified in *Drosophila* through the study of mutant flies where PCP disruption can be readily observed in the disturbed arrangement of structures such as wing hairs, bristles on the abdomen or ommatidia in the eye. Since then research on PCP has broadened and it is now understood that the key group of 'core' proteins (*Vangl*, *Celsr*, *Frizzled*, *Dishevelled and Prickle*) which control PCP, operate more widely to regulate the coordinated behaviour of groups of cells by mediating cytoskeleton dynamics. This ability to regulate cytoskeletal organisation lies at the heart of the PCP pathway's roles in organ formation.

In this article we highlight key themes emerging from recent studies of the PCP pathway in mammalian organ development with an emphasis on three organs, the lungs, kidneys and heart. Finally we discuss the emerging role of this pathway in human disease.

The PCP pathway

The exact details of how planar polarity is controlled at the biochemical level are still not entirely clear and are discussed in other reviews [1,2••,3•]. In organ formation the most prominent view is that the PCP pathway is initiated when a Wnt ligand binds to a Frizzled (Fz) receptor at the cell surface and this triggers recruitment of Dishevelled (Dvl) to the cell membrane [4]. Subsequently Dvl recruits additional cytoplasmic proteins, such as Dishevelled associated activator of morphogenesis (Daam) proteins, which promote the activation of GTPases and enable cytoskeletal reorganisation via Rho Kinase (ROCK) [5]. This step of Dvl recruitment to the membrane appears to be a key event in PCP signalling. Interestingly, Seo *et al.*, have now shown that Vangl2 can act cell autonomously to promote recruitment of Dvl to the plasma membrane and activate PCP during convergent extension [6••]. The authors suggest that Vangl2 mediated recruitment of Dvl to the cell membrane ensures that this protein can be efficiently activated when PCP signalling is triggered, for example, by a Wnt ligand binding to Fz. Additionally, data from *Drosophila* indicate that PCP is regulated by the asymmetric distribution of different core PCP proteins at the cell membranes and that this is a pre-requisite to establishing planar polarity across fields of cells [3•]. This asymmetric distribution of PCP proteins is not always as prominent in vertebrate organogenesis, but has been observed in several organs including the cochlea, skin epidermis, heart and more recently in the papilla of the tongue and kidneys [7–10,11••]. The asymmetric distribution of PCP proteins may be triggered by one or more inputs, for example, a gradient of Wnt ligand, anisotropic strain caused by fluid flow or morphogenesis itself. In some organs JNK has been identified as an important intermediary in planar polarity output. However, small GTPases can both activate and be activated by JNK [12]; it is therefore not clear if this constitutes a separate downstream pathway that can directly trigger transcription of target genes via Jun family members or whether it is part of the same pathway that also leads to cytoskeletal modification via GTPases [13].

Collective cell migration and convergent extension

Some of the earliest studies of the PCP pathway in mammalian organ formation highlighted its role in skin and kidney development but there is now an increasing list of other organs for which the PCP pathway has been shown to be required, this includes the heart, lungs, eyes, testes, teeth and tongue among others [7,9,14•,15–19]. A recurrent theme in organogenesis is that the PCP pathway

drives changes to cell behaviours across groups of cells via cytoskeletal reorganisation. Two prominent morphogenetic processes controlled by PCP are collective cell migration and convergent extension, both of which have a key role in organ development (Figure 1a).

PCP mediated convergent extension has been particularly well studied in neural tube closure. Initiation of this event requires convergent extension and mutations in core PCP pathway genes have been shown to disrupt the closure process [20]. The PCP pathway is also required for later stages of neural tube closure where the apical surface of neuroepithelial cells constricts, allowing the cells to become more cone shaped, thus facilitating bending of the tissue required to close the neural tube [20]. Loss of PCP function is associated with neural tube closure defects that result in spina bifida or the severe closure defect, craniorachischisis [20]. Galea and colleagues have now discovered another important link between the PCP pathway and neural tube closure by showing that conditional deletion of *Vangl2* in the surface ectoderm throughout neurulation leads to altered biomechanics resulting in caudal spina bifida [21••].

PCP and cytoskeleton polarisation

Morphogenesis, mediated by the actomyosin network, is critical to precisely shape organs for optimal function. In non-muscle cells actomyosin structures are not always polarised, for example in stress fibres, actin is bundled but not polarised. However, for certain functions, one of which is collective cell migration, the actomyosin network must be polarised, therefore it is not surprising that the PCP pathway plays a role in this process [22,23•]. In migrating cells, polarised features of the actin cytoskeleton include generation of an actin meshwork at the leading edge of the cell, where actin filaments are arranged with the barbed (plus) ends immediately adjacent to the plasma membrane, rapid actin polymerisation at the plus ends helps to propel the cell forwards [24] (Figure 1b). Studies of organ development have also linked the PCP pathway with another constituent of the cytoskeleton, microtubules. Investigations have revealed that microtubules provide a key network through which directional information required for PCP function can be relayed [25]. It appears that microtubules are particularly important for vesicular trafficking of PCP proteins, to facilitate their asymmetric distribution. The microtubule network is also polarised in migrating cells; the centrosome is oriented to a position between the nucleus and the leading edge of the cell and the microtubules are organised with their minus ends towards the centrosome and their plus ends towards the plasma membrane (Figure 1b) [24]. In addition, cilia are comprised of microtubules and it has been recognised for some time that there is a close relationship between the PCP pathway and cilia [26–29]. There are two major types of cilia, primary (non-motile) and motile. Cilia motility depends on the arrangement of microtubules within the appendage and PCP signalling is required for the directional beating of multiple motile cilia in a number of organs [30].

Primary cilia extend from the surface of most mammalian cells and are important for a number of processes including regulation of the cell cycle and transduction of some signalling pathways. Although there is evidence of a strong connection between the PCP pathway and primary cilia, for example, PCP related phenotypes are observed in cilia mutants, this connection is still not entirely clear [31]. Interestingly, one recent investigation in kidneys indicates that PCP contributes to organ formation independently from the primary cilia [11••].

PCP and branching morphogenesis

Two organs where there has been considerable focus on the role of the PCP pathway are the lungs and kidneys. Both of these organs develop by branching morphogenesis, a process that requires extensive cell migration and morphogenesis to generate and precisely shape an arborized network of tubes with a large surface area. Perturbation of the PCP pathway in the lungs and kidneys impairs tissue morphogenesis and results in fewer and misshapen tubes. In fact analysis of mice with mutations in core PCP genes shows similar tubule defects in a number of structures generated by branching morphogenesis suggesting that PCP is uniformly required for this process (Figure 2). In fact recent studies indicate that PCP can contribute to the formation of tubular organs in several ways (see below).

Lung

Lung development initiates by outpouching from the foregut endoderm at embryonic day (E) 9.5 in mouse and week 4 of human gestation. The initial bud grows out into the surrounding mesoderm and divides to form the primordial lung buds. The network of airways is then generated from these initial buds by branching morphogenesis. Subsequent to this, the gas-exchanging region of the lungs is generated from the distal ends of the small airways. Cells at the distal tips of the airways begin to differentiate into specialised alveolar epithelial cells (ATI and ATII) and at the same time the tissue thins and airspaces widen to form air sacs. Finally the alveoli form by thinning of the air sac walls and repeated sub divisions (septation) to generate a large surface area optimised for gas exchange.

Mouse mutants of the PCP genes *Vangl2*, *Celsr1* and *Scribble* all have fewer and misshapen airways [32,33]. Both phalloidin and non-muscle IIA staining revealed significant changes to the distribution of the actin-myosin cytoskeleton from an early stage of lung development (E11.5), indicating that perturbation of the PCP pathway impairs tissue morphogenesis and this disrupts the