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·Review·

Planar cell polarity genes, *Celsr1–3*, in neural development

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Abstract: *flamingo* is among the 'core' planar cell-polarity genes, protein of which belongs to a unique cadherin subfamily. In contrast to the classic cadherins, composed of several extracellular cadherin repeats, one transmembrane domain and one cytoplasmic segment linked to catenin binding, *Drosophila* Flamingo has seven transmembrane segments and a cytoplasmic tail with no catenin-binding sequence. In *Drosophila*, Flamingo has pleotropic roles in controlling epithelial polarity and neuronal morphogenesis. Three mammalian orthologs of *flamingo*, *Celsr1–3*, are widely expressed in the nervous system. Recent work has shown that Celsr1–3 play important roles in neural development, such as in axon guidance, neuronal migration, and cilium polarity. *Celsr1–3* single-gene knockout mice exhibit different phenotypes, but there are cooperative interactions among these genes.

Keywords: planar cell polarity; Celsr genes; neural development

1 Introduction

flamingo is one member of the "core" planar cell polarity (PCP) genes, whose function has been well studied in flies. Based on its symmetric expression on adjacent cells, it is proposed that Flamingo propagates PCP signaling, which eventually regulates the uniform organization of epithelial cells[1-3]. Further studies have shown that Flamingo is involved in the development of many organs during embryogenesis, in which it probably cooperates with other PCP members[1,2,4,5] or acts independently of the PCP pathway[6,7], and the involvement of Flamingo in this process has been discussed recently[8]. *Celsr1–3* (Celsr: cadherin, EGF-like, LAG-like, and seven-pass receptor) are three orthologs of *flamingo* in mammals. Using transgenic animal models, it has been shown that *Celsr1–3* play a crucial role in many aspects of neural development.

2 PCP

PCP, also termed tissue polarity, designates the uniform organization of epithelial cells in the plane of the epithelial sheet, perpendicular to the apical-basal axis of single cells. Basic PCP regulatory mechanisms are best studied in *Drosophila*, and are highly conserved in vertebrates, in which PCP genes are involved in several processes such as convergent extension, neural tube closure, gastrulation, neurulation, inner ear development, and ciliogenesis[3,9-11].

PCP is readily observed in the epithelia of the *Drosophila* wing, which are covered by a quasi-crystalline array of hexagonal cells, each of which elaborates a single distally-directed actin-rich hair. This pattern is controlled by a set of signaling molecules that includes upstream factors, PCP core components and PCP effectors[3]. Initially, a long-range signal establishes the direction of polarity, and the factors involved form the "upstream group" of PCP signaling

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components, which includes Dachsous, Atrophin and Widerborst. They provide a long-range or "global" patterning cue along the axis of the tissue, and regulate the asymmetric subcellular localization of the core PCP proteins along the proximal/distal axis of the cell. The core PCP group, composed of Frizzled, Dishevelled, Flamingo/Starry night, Strabismus/Van Gogh, Prickle and Diego, participates in establishing the planar polarity of individual cells. These PCP proteins form membrane-associated signaling complexes whose subcellular localization, stoichiometry and distribution are crucial for normal PCP signaling. Among them, Frizzled, Dishevelled and Diego form one complex which becomes specifically enriched at the distal side of wing cells, while Strabismus and Prickle form another that is enriched at the proximal side. This asymmetric subcellular localization is mediated by a feedback loop between the two complexes, which propagates molecular polarity from cell to cell[12]. Flamingo is symmetrically localized on the distal and proximal sides, possibly stabilizing both complexes through homophilic interactions and promoting adhesion between neighboring cell surfaces (Fig. 1).

In the PCP signaling pathway, Frizzled, Van Gogh and Flamingo are required early in development and are the only components needed for intercellular polarity signaling. In contrast, the cytoplasmic components, Dishevelled and Diego, are not needed for intercellular communication, but are required for the cell-cell propagation of polarity, most likely by promotion of intracellular asymmetry[15].

The downstream components of PCP signaling consist of tissue-specific effectors such as the small GTPases of the RhoA family, Dishevelled-associated activator (Daam1) and c-Jun N-terminal kinase (JNK) that upon activation lead to a variety of cellular responses including cytoskeletal rearrangements[3]. Using domineering nonautonomy function assay, it was suggested that *inturned*, *fuzzy*, and *multiple wing hairs* are downstream genes from the *frizzled*/PCP signaling pathway[16].

In *Drosophila*, another example of planar polarity is

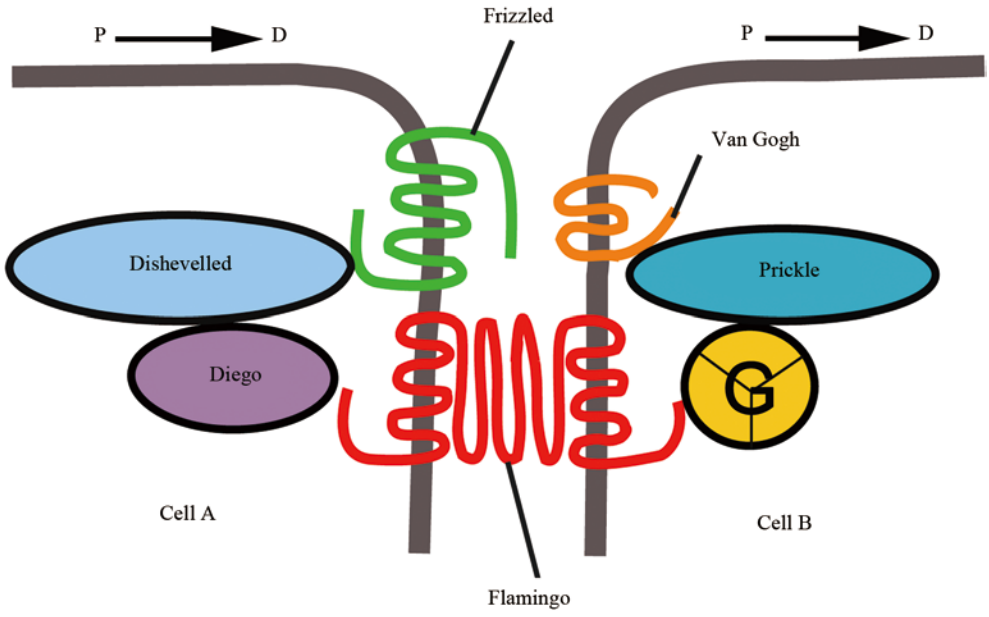

Fig. 1. Model of different planar cell polarity (PCP) proteins expression on two adjacent cells. On the adjacent cells, Flamingo is symmetrically located on the distal membrane (D) of Cell A and the proximal membrane (P) of Cell B. The Frizzled orthologs Fzd3 and Fzd6 are expressed on the distal side of Cell A, and interact with Flamingo through Dishevelled and Diego, whereas the Van Gogh ortholog Vangl2, on the proximal membrane of Cell B, interacts with Flamingo through Prickle. Flamingo acts as a bridge to propagate cell-cell polarity. Provided by Andre Goffinet and adapted from models of PCP signaling in *Drosophila*[13,14].

the arrangement of photoreceptors in the compound eye that is composed of 800 subunits, the ommatidia. All ommatidia are organized into two chiral forms relative to the dorsoventral midline (the equator), one in the dorsal and one in the ventral half, showing mirror symmetry. Each ommatidium contains eight photoreceptors (R cells), which form an asymmetric trapezoid. The relative position of the R3 and R4 cells within each ommatidium mainly accounts for the planar arrangement, whereby R3 cells are closer to the equator and R4 cells are closer to the poles, and the cell fate specification of the R3 and R4 photoreceptors is the key to ommatidial polarity[17]. As in epithelial cells, in the eye, Frizzled/Diego are enriched on the apical, polar side of the R3 cell and absent from the equatorial side of R4, while Strabismus shows the reverse pattern[18]. Flamingo is first enriched at the equatorial cell borders of R3/R4 and later upregulated in R4 cells[19]. Consistently, Frizzled specifies R3 cell fate, Strabismus determines *R4* cell fate, and Flamingo is required in both R3 and R4 cells. In the fly epithelium, PCP signaling activates distinct effectors to rearrange the cytoskeleton, leading to localized actin polymerization[20]. Studies on PCP signaling in the *Drosophila* eye focused on the differential specification of R3 and R4 photoreceptor cells, and several transcription factors have been identified to be downstream of PCP signaling. For example, Fos is required to specify R3 cell fate, whereas the ETS factors Yan and Pnt seem to be PCP-dependent R3/R4 determinants[21].

3 Flamingo and neuronal morphogenesis

Functional neuronal connections depend on the outgrowth and target selection of axons, dendritic branching and synapse formation. Studies in *Drosophila* show that Flamingo is widely implicated in these processes. During development, the dendrites of a subclass of multiple dendritic neurons grow towards the dorsal midline, and show minimal overlap with their contralateral counterparts after crossing the midline. A proper level of Flamingo expression in these neurons is required for the formation of normal dendritic fields and the competition between the dendrites of homologous neurons[6]. With physical or genetic ablation of neighboring or contralateral homologous neurons, overextension of dendrites occurs only when the homologous neurons are ablated. Dendritic overgrowth can be seen in the *flamingo* mutants and this phenotype can be rescued by neuronal expression of *flamingo*, indicating that Flamingo functions autonomously in this process[6]. Single-neuron analysis revealed that Flamingo limits the extension of one or more dorsal dendrites without grossly affecting the lateral branches[22]. Further work showed that Flamingo acts probably through two different mechanisms to regulate dendritic field formation[23]. At the initial stage, the "overgrowth" phenotype in the *flamingo* mutant can be rescued by neuronal expression of full-length and truncated Flamingo without extracellular cadherin repeats. However, the "overlap" phenotype at the later stage can be rescued by full-length but not truncated Flamingo. Together, these results indicate that the initial inhibition of dendritic growth by Flamingo is probably through an unidentified ligand, in which process Flamingo functions as a receptor, and the late avoidance of dendritic overlap is probably through Flamingo-mediated dendro-dendritic interactions.

Using a mosaic genetic screen, *flamingo* has been found to regulate axonal projection in addition to suppressing dendritic overextension[24]. Flamingo overexpression in the mushroom body results in loss of the dorsal branches of axons. This occurs probably through axonal retraction, because the initial development of the axonal projection is normal. The function of Flamingo in regulating axon-axon and axon-target interactions is best studied in the developing *Drosophila* eye, as shown in the work of Hakeda-Suzuki *et al.*[25]. In each ommatidium, the axons of R1–R8 photoreceptor cells terminate in different layers of the optic lobe: R1–R6 synapse in the lamina, R7 terminates in the M6 layer of the medulla, and R8 in the more superficial M3 layer. Flamingo is required for the layer-specific targeting of axons, a process mediated by a pathway distinct from that used in establishing ommatidial polarity[26,27]. In the *flamingo* mutant, the axons of R8 fail to innervate their appropriate targets, but the axons of R1–R7 approach their specific layers normally. This defect in R8 axons can be rescued by restoring Flamingo function in the eye.

In *flamingo* mosaic flies, R8 growth cones are irregularly spaced and overlap widely. In the axonal targeting of R8 neurons, Flamingo-mediated axon-axon inhibitory interaction probably guides target selection. This process is different from the PCP pathway because the axons of R1–R8 project normally in mutants for *frizzled*, *strabismus* and *prickle*, the other core PCP gene members. Interestingly, Flamingo also guides R1–R6 target selection and this is a non-cell-autonomous process[28]. Using single cell manipulation, the axons with defective Flamingo function show normal targeting, whereas their immediately neighboring axons display mis-targeting. Furthermore, Flamingo overexpression in a single cell results in targeting errors in its neighboring cells, but this overexpression in the target neurons that contact R cell axons has no effect on R cell target choice[28]. These studies suggest that Flamingo functions as a short-range, homophilic signal, passing between specific R cell growth cones to influence their choice of postsynaptic partners.

In addition, Flamingo is reported to regulate synaptogenesis and to prevent axonal and synaptic degeneration in *Drosophila*[29]. In normal larvae, the intersegmental nerves travel towards dorsal muscles showing a "beads-on-a-string" pattern of synapses extending along the surface of these muscles. In *flamingo* mutants, a dramatic number of ectopic synapses are found "*en passant*" and synaptic proteins accumulate in the segmental nerves. Neuronal expression of *flamingo* can rescue these abnormal "*en passant*" synapses. Electrophysiological studies showed that the functions of these synapses in the *flamingo* mutants are maintained in early development but are gradually lost. Axon degeneration of these motor neurons is suggested by morphological studies, but the precise contribution of Flamingo to this phenotype is not known.

4 Mammalian *Celsr1–3* and neural development

The three Celsr protein sequences are >50% identical in their extracellular and transmembrane segments but differ in their cytoplasmic portions. In mice, expression of *Celsr1* is initiated on embryonic day 7.5 in the primitive streak and that of *Celsr2* and *Celsr3* about one day later[30]. At early stages, all three Celsr genes are broadly expressed in the neuroepithelium. In the mouse forebrain, distinct expression patterns of *Celsr1–*3 become evident after the pre-plate stage[31]. *Celsr1* mRNA is expressed mainly in the ventricular zone but not in the marginal zone, *Celsr2* in all layers of the cerebral cortex, and *Celsr3* widely in postmigratory neurons in most regions, particularly the olfactory bulb, telencephalon, dorsal thalamus and hippocampus. The expression patterns are maintained after birth. In some regions, such as olfactory epithelium and the vomeronasal organ, all three Celsr genes are co-expressed. The expression of *Celsr1* and *Celsr3* peaks at birth and abates gradually, while *Celsr2* mRNA expression remains high at maturity.

Two mouse mutants of *Celsr1* have been identified in an ethylnitrosourea mutagenesis screen[32], and revealed to be single-point mutations in the second exon of *Celsr1*. Homozygous mutants exhibit severe neural tube defects which are associated with defective convergent extension. In this process, the polarized meso- and neuroectodermal cells move medially and intercalate with other neighboring cells, eventually leading to extension of the developing tissue along the anterior-posterior axis. PCP signaling is a key mediator of mediolateral intercalation and related cell behaviors[9,10]. Mutation of some other PCP genes, such as *Vangl2*, double *Fz3* and *Fz6*, and two of the three *Dishevelled* homologs (*Dvl1* and *Dvl2*), also results in a convergent extension defect, generating a shorter body axis and open neural tube[32-36].

Celsr2 protein is distributed in both the dendrites and axons of embryonic and postnatal neurons such as hippocampal and cortical pyramidal cells, and cerebellar Purkinje cells[30]. Using siRNA *in vitro*, Shima and colleagues found that *Celsr2* regulates dendritic maintenance and growth[37]. Knocking down *Celsr2* expression reduces the length of apical dendrites and the numbers of basal dendrites of pyramidal neurons and Purkinje cells, probably due to dendritic retraction as shown by time-lapse analysis. Rescue of the siRNA-induced phenotype indicates that the EGF-HRM domain of Celsr2 is associated with

dendritic retraction, and probably does not signal via a cadherin repeat-mediated homophilic interaction.

Celsr3 mutant mice have defects in several major axonal tracts, a phenotype similar to that of *Fzd3* mutant mice[38,39]. In both mutants, commissural spinal cord axons fail to turn rostrally after crossing the midline[40-42]; thalamocortical, corticofugal and subcerebral axons are unable to traverse the ventral telencephalon to reach their targets, and the development of some commissures is defective. Both mutants have nearly identical phenotypes, suggesting that these proteins function together in a common axon guidance mechanism. *In situ* hybridization studies showed that the expression patterns of *Celsr3* and *Fzd3* are very similar in mouse during development of the central nervous system, although *Fzd3* expression is wider[43]. In *Ceslr3* conditional knockout mice, we found that *Ceslr3* is required in both projecting axons and guidepost cells for axonal pathfinding[44-46]. When *Celsr3* is removed from the guidepost cells of the basal forebrain using Dlx5/6-Cre, corticofugal and thalamic axons fail to navigate the internal capsule for innervating their targets. Inactivation of *Celsr3* in the projection neurons, such as in *Celsr3|Emx1* (*Celsr3f/-;Emx1-Cre/+;* f, floxed) mice, leads to defects of corticospinal tract and anterior commissure development. This mimics the *flamingo* function in regulating tissue polarity as suggested. In addition, it is reported that Celsr3 is also involved in monoaminergic projections in the midbrain, which work together with the other core planar cell polarity components such as Frizzled3 and Vangl2[47]. In a word, *Celsr3* is involved in most axonal projections and its roles are similar to other core PCP genes in steering brain wiring.

5 Cooperative actions of *Celsr1*–3 in neural development

Although the expression patterns of *Celsr1–3* are different, their roles are closely related to some processes in neural development, such as dendritic development, neuronal migration and the planar organization of ependymal cilia.

Using gene-silencing and coculture assay, Celsr3 and Celsr2 were shown to play opposing roles in neurite growth[37,48]. This functional difference is most probably attributed to a single amino-acid difference in the transmembrane domain. Celsr2-Celsr2 or Celsr3-Celsr3 homophilic interactions activate their respective signaling pathways, enhancing or suppressing neurite growth respectively. Celsr2 has a stronger activity in stimulating calcium release than Celsr3, and this difference results in the activation of distinct sets of second messenger-dependent enzymes, that mediate contrasting effects on neurite growth.

Recently, it was reported that *Celsr1–3* work together to regulate facial branchiomotor neuron (FBM) migration[49]. *Celsr1* is expressed in FBM neuron precursors and the floor plate, but not in FBM neurons, which helps to specify the direction of FBM neuron migration in a non-cell autonomous manner. In *Celsr2*-/- mutants, the initiation of FBM neuron migration is normal but these neurons fail to reach their final destination. This defect is enhanced in double *Celsr2* and *Celsr3* mutants, suggesting that *Celsr2* and *Celsr3* control the ability of FBM neurons to migrate.

This cooperative action is also found in the planar organization of ependymal cilia regulated by *Celsr2* and *Celsr3*[50]. *Celsr2*-deficient mice show defective cerebrospinal fluid dynamics and hydrocephalus, and the polarity of ependymal cilia is disrupted. This phenotype is much worse in *Celsr2* and *Celsr3* double mutants. In these mutants, the membrane distribution of Vangl2 and Fzd3 is disturbed, which suggests that *Celsr2* and *Celsr3* affect ciliary function via the planar cell polarity signaling pathway.

6 Summary and prospects

Evidence is accumulating that *Celsr1–3* play important roles in multiple processes during neural development. Single-*Celsr* knockout mice show different phenotypes, such as the failure of axonal projections in *Celsr3*-/-[38], abnormal organization of ependymal cilia in *Celsr2*-/-[50], and improper neuronal migration in *Celsr1*-/-[49]. However, double or triple mutants of *Celsr1–3* enhance the phenotype of individual mutants. This indicates that individual Celsr1–3 genes focus on a particular process during neural

development, in which the others show redundancy. So far, the exact signaling pathways of Celsr1–3 involved in different neural processes remain unknown, as are the mechanisms by which Celsr1–3 affect each other. Generating antibodies against Celsr1–3 and screening the genes differentially expressed in these mutants will be useful for elucidating these issues.

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