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Wnt Signalling: A Moving Picture Emerges From *van gogh*

Dispatch

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Recent studies on vertebrate homologues of the *van gogh*/*strabismus* (*vang*/*stbm*) gene, a key player in planar cell polarity signalling in *Drosophila*, show that *vang*/*stbm* is involved in patterning and morphogenesis during vertebrate gastrulation where it modulates two distinct Wnt signals.

Epithelial polarisation is an important part of the differentiation of a broad range of tissues. Epithelia can be polarised along the apical–basolateral axis and within the plane of the epithelia; this is commonly called planar cell polarity (PCP). In *Drosophila*, several genes are known to be required for the establishment of PCP. Many of these genes are either components of the Wingless (Wg) signal transduction pathway, such as *frizzled* (*fz*) and *dishevelled* (*dsh*), or genetically interact with this pathway, for example *flamingo* (*fmi*) and *van gogh*/*strabismus* (*vang*/*stbm*) (reviewed in [1,2]). While most of the genes involved in PCP are required cell-autonomously, *vang*/*stbm* and the Wg/Wnt receptor Fz play important roles in intercellular signalling. Three recent studies have analysed the function of vertebrate *vang*/*stbm* homologues in mouse, *Xenopus* and zebrafish, revealing interesting parallels between the regulation of PCP in *Drosophila* and the cellular rearrangements during vertebrate gastrulation [3–5].

During vertebrate gastrulation, the precisely coordinated movement of large populations of cells leads to the formation of the three germ layers, mesoderm, ectoderm and endoderm. A prominent cellular rearrangement during gastrulation is convergent extension, when mesodermal and ectodermal cells move to the dorsal side of the gastrula followed by an anterior–posterior extension of the forming body axis. The cellular basis for convergent extension has been well studied in amphibians and teleosts [6,7]. Cells undergoing convergent extension polarise along the medial–lateral axis leading to medial–lateral cell intercalations and elongation of the body axis (Figure 1A). However the molecular mechanisms underlying these cellular processes are only poorly understood.

Recent studies in *Xenopus* and zebrafish have shed some light on the role of Wg/Wnt signalling in regulating vertebrate gastrulation movements. In *Xenopus* cell polarisation during gastrulation is directly mediated by Dsh [8] and can be blocked by a dominant negative form of Dsh that specifically inhibits Wg/Wnt signalling during the establishment of *Drosophila* PCP

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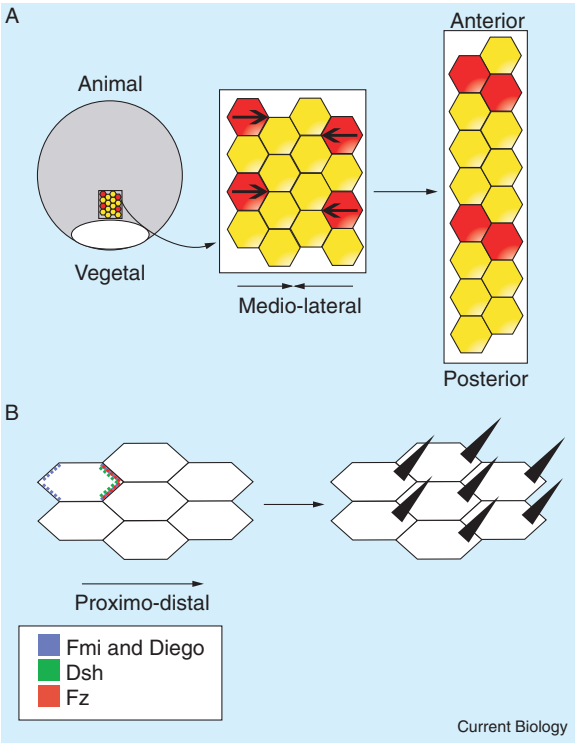

Figure 1. Schematic of the cellular mechanisms leading to convergent extension during vertebrate gastrulation and epithelial planar polarity in the *Drosophila* wing disc.

(A) Medial–lateral cell intercalations cause convergent extension movements during *Xenopus* and zebrafish gastrulation (see [3]). (B) Intracellular localisation of proteins involved in establishing epithelial planar cell polarity along the proximo–distal axis of the *Drosophila* wing disc is required for a polarised outgrowth of wing hairs (reviewed in [1]). Fmi, Flamingo; Fz, Frizzled; Dsh, Dishevelled.

[9]. Similarly in zebrafish, *silberblick(slb)/wnt11* mutants showing defective convergent extension movements during gastrulation can be rescued by overexpression of a mutant Dsh molecule that specifically activates the PCP pathway in *Drosophila* [10]. These observations suggest similarities between the signalling pathways which establish PCP in *Drosophila* and regulate vertebrate gastrulation movements.

Park and Moon [3] have tested this hypothesis by analysing the function of *vang*/*stbm*, a PCP specific gene in *Drosophila*, during vertebrate gastrulation. *Drosophila vang*/*stbm* encodes a novel protein with four transmembrane domains and a PDZ domain binding motif at the carboxyl terminus. Vang/Stbm acts both cell non-autonomously within the wing disc to establish PCP and cell-autonomously within the eye disc for PCP and photoreceptor cell fate specification [11,12]. Vang/Stbm can activate the Jun N-terminal kinase (JNK) cascade — a downstream mediator of *Drosophila* Wg/PCP signalling — in cultured mammalian cells, and can modulate activin-induced elongation of

Xenopus animal cap explants — a process that mimics convergent extension movements. Conversely, if *vang/stbm* is inhibited with morpholino antisense oligonucleotides in zebrafish, embryos have a phenotype reminiscent of reduced convergent extension movements. Together these findings strongly support the hypothesis that in vertebrate gastrulation, *vang/stbm* regulates convergent extension through the activation of JNK and therefore the Wnt/PCP signalling pathway (Figure 2A).

How does Vang/Stbm regulate cell movement during fish and frog gastrulation? In *Drosophila*, membrane localisation of Dsh is a key process in the establishment of PCP in the wing [13], and presumably leads to the formation of a signalling complex, including Fz, Fmi and Diego, required for the outgrowth of a hair at the distal tip of the cell [14–17] (Figure 1B). To see if Vang/Stbm is localised to the membrane, Park and Moon [3] generated an anti-Vang/Stbm antibody and found that Vang/Stbm protein is localised to the plasma membrane and that Dsh also translocates to the membrane in the presence of Vang/Stbm. Furthermore, in coimmunoprecipitation experiments they showed that Vang/Stbm binds to Dsh directly. This implies that Vang/Stbm affects cell movements by localising Dsh to the membrane, thereby activating the PCP pathway.

In addition to its role in regulating cell movements during gastrulation, Vang/Stbm also appears to modulate the patterning of anterior neural tissues. When *vang/stbm* RNA is overexpressed in zebrafish embryos, anterior neural markers are expanded, while inhibiting *vang/stbm* with morpholino antisense oligonucleotides reduces the expression of forebrain specific genes. The ability of Vang/Stbm to activate anterior neural markers is reminiscent of known antagonists of canonical Wnt signalling such as Frizbee and Dickkopf [18]. Therefore, Park and Moon tested if Vang/Stbm can interfere with canonical Wnt signalling through GSK3 and β-catenin (reviewed in [19]). They found that Wnt1-induced β-catenin dependent transcription in cultured cells is blocked by *vang/stbm* expression showing that Vang/Stbm can inhibit canonical Wnt signalling in anterior patterning during gastrulation (Figure 2B).

Many questions remain about the role of Vang/Stbm in Wnt signalling which will hopefully be answered by looking at Vang/Stbm on a cellular level in the embryo. Which cells of the gastrula actually require Vang/Stbm? And as *vang/stbm* expression is ubiquitous during gastrulation, how is Vang/Stbm regulated to influence cell fate or motility? A key obstacle in analysing the function of Vang/Stbm is that general gain- and loss-of-function assays affect both patterning and cellular rearrangements during gastrulation. As changes in patterning of the gastrula can have profound effects on cell movements, it will be necessary to define experimental conditions in which the function of Vang/Stbm in patterning and cell movements can be separately analysed.

Additional opportunities for understanding Vang/Stbm function should arise from the recent work of Kibar *et al.* [4] and Murdoch *et al.* [5] showing that the mouse

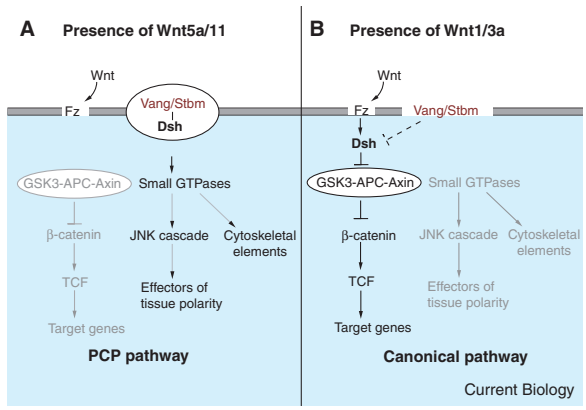

Figure 2. Model of roles of Vang/Stbm in Wg/Wnt signal transduction.

(A) In response to Wnt5a or Wnt11, Dsh is recruited to the membrane via Vang/Stbm leading to an activation of the planar cell polarity pathway. The classification of Wnts is reviewed in [18]. (B) In the presence of Wnt1 or Wnt3a, the interaction of Dsh and Vang/Stbm is prevented by an unknown mechanism and Dsh is free to activate the canonical pathway; here, Vang/Stbm potentially inhibits the canonical pathway. Vang/Stbm, Van Gogh/Strabismus; Fz, Frizzled; Dsh, Dishevelled.

Loop-tail (*Lp*) locus encodes Vang/Stbm. The *Lp* locus has now been known for nearly half a century as a semi-dominant mutation in which heterozygous mice have a looped tail while homozygous embryos have a characteristic open neural tube phenotype. Through genetic mapping of the *Lp* locus and positional cloning, the groups found mutations in two independent alleles of *vang/stbm* that lead to alterations in conserved amino acids. The observation that mutations in the *vang/stbm* gene might cause an open neural tube phenotype is particularly interesting in light of recent findings in *Xenopus*, showing that Dsh/PCP signalling is involved in regulating proper convergent extension of the neural plate [20]. The *Lp* mutant might therefore represent a very useful tool for addressing the role of Wg/Wnt PCP signalling in vertebrate neural plate/tube morphogenesis.

The finding that the genetic pathway which establishes PCP in *Drosophila* has significant overlap with the signalling pathway which regulates gastrulation movements in vertebrates is another example of how similar genetic pathways can be used in very different developmental systems. Further studies on the genetic and cellular regulation of *Drosophila* PCP and vertebrate gastrulation movements will help to uncover the common mechanism that underlies tissue morphogenesis during development.

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