Walk This Way: Moving neurons communicate with surrounding cells

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The planar cell polarity pathway (PCP) is a mechanism of communicating polarity cues by cell-to-cell contact. The components of this pathway are conserved among vertebrates and invertebrates allowing for their study in model organisms such as optically clear zebrafish embryos. Mechanisms that establish the stereotypical position of planar cell polarity proteins in static epithelial cells have been well studied. However, little is known about the role of planar cell polarity signaling in motile cells such as migrating neurons in the developing embryo. Scientists in the Moens Laboratory (Basic Sciences Division) set out to investigate whether planar cell polarity signaling was required for the movement of the facial branchiomotor neurons (FBMNs) in zebrafish embryos. The results of their study were recently published in *PLOS Genetics*.

To begin, PCP signaling was altered within the FBMNs in several different ways to evaluate the effect on migration. A dominant-negative PCP-specific component of the Wnt pathway, called Dvl-DEP, was expressed exclusively in the FBMNs themselves. When this construct was expressed, fluorescently labeled neurons stayed near their origin and did not migrate out of rhombomere (segment) 4 as they would have in wild type animals. Additionally, specific loss of expression of the PCP gene Vangl2 in FBMNs also prevented migration. It was previously shown that PCP signaling requires inter-cellular communication, so the authors investigated whether PCP signaling components need to be expressed in cells surrounding the migrating FBMNs. Wild-type FBMNs were transplanted into fish expressing the dominant-negative mutant PCP protein Dvl-DEP in
rhombomere 4. In contrast to neurons transplanted into wild-type hosts, the neurons transplanted into Dvl-DEP r4 mutant hosts failed to migrate out of r4. Thus, expression of PCP components is required within the FBMNs as well as in the cells of the migratory environment.

In order to visualize PCP proteins within cells in their native environment, the scientists turned to spinning disc confocal microscopy. Mosaic expression of fluorescently labeled PCP proteins allowed researchers to visualize polarized PCP protein localization within single, young FBMNs in r4 as well as in cells of the floorplate beneath them. While monitoring migrating FBMNs, a weak but detectable accumulation of the PCP protein Vangl2 was observed at the tips of filopodia prior to retraction. Filopodia are dynamic protrusions of migrating cells that contribute to physical movement. Given the lack of migration in PCP mutant neurons and embryos, as well as the accumulation of Vangl2 at retracting tips, the scientists characterized the effects of mutating PCP components on filopodial dynamics. Filopodia of FBMNs in vangl2 mutant animals were longer lived while filopodia in a fzd3a mutant were shorter lived. These effects on filopodia stability disappeared when FBMNs were dissected out of embryos and monitored in vitro. Thus, expression of Vangl2 and Fzd3a in the FBMNs and in cells in their environment is required for normal filopodial dynamics.

In order to further characterize the role of PCP signaling in epithelial cells in the environment, transplant experiments placing wild-type neurons into mutant hosts were carried out. Wild-type FBMNs transplanted into vangl2 mutant hosts had short lived filopodia while the wild-type FBMN filopodia in fzd3a mutant hosts were longer lived. This is the opposite effect than observed from neurons that originated in vangl2 and fzd3a mutant hosts. This led the scientists to conclude that there is an antagonistic relationship between Vangl2 and Fzd3a on filopodia stability, such that Fzd3a and Vangl2 in surrounding epithelial cells activate the intracellular activities of Vangl2 and Fzd3a, respectively. Therefore, Vangl2 protein in wild-type neurons transplanted into vangl2 mutant hosts can be activated by environmental Fzd3a and destabilize filopodia, which is consistent with the appearance of longer-lived filopodia in vangl2 negative mutant neurons.

While this is the first description of an antagonistic relationship between Vangl2 and Fzd3a in moving cells, it fits in with previous studies of these proteins. For example, it has been observed that Vangl1 and Fzd6 in metastatic breast cancer cells localize to exclusive locations on the cell surface and that preventing expression of either one inhibits cell movement\(^2\). Together, these multiple lines of evidence suggest a mechanism whereby polarity cues are communicated to migrating cells through interactions between planar polarity proteins to ensure that cells move in a specific direction.


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