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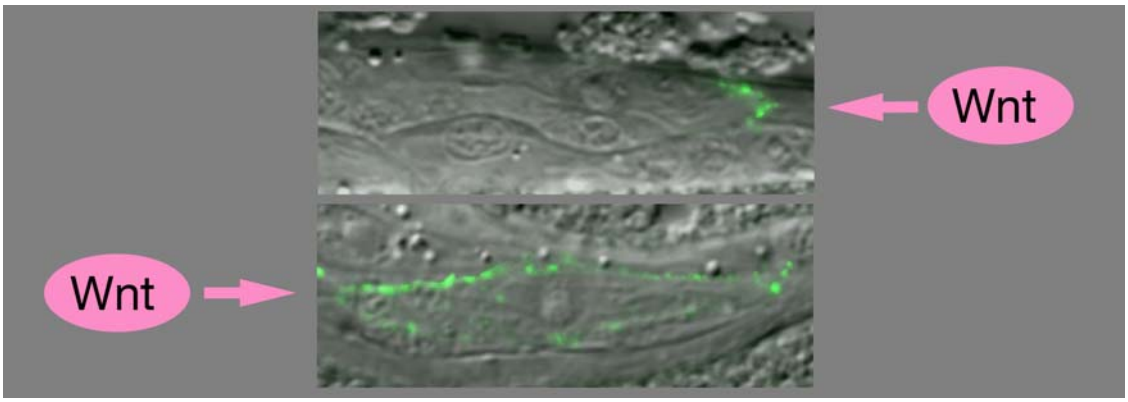
Off to one side: Determination of cell polarity by Wnt signaling

March 8, 2006 - Cellular polarity is a criterion in many forms of asymmetric cell division, the process by which a cell divides to produce daughter cells of different types. Communication between cells often dictates where, when and how cells become polarized and subsequently divide, but the means by which these molecular communiqués actually get the work done has remained obscure. The question of whether the Wnt signaling pathway functions as an essential positional cue in establishing cell polarity has been a particular teaser.

Now, in a study published in the March issue of the journal *Developmental Cell*, Hitoshi Sawa (Team Leader; Laboratory for Cell Fate Division) and colleagues from Kobe University and at the University of North Carolina at Chapel Hill (USA) have revealed that Wnt signals can determine the polarity of both embryonic and postembryonic cells in the nematode *C. elegans*. These findings stand in contrast to previous studies in which misexpression of Wnt proteins suggested that Wnt signals may only need to be present, while other signals actually effect the polarization.

The collaborators looked first at the four-cell stage nematode development, in which messages from one signaling cell to its responding neighbor (the EMS cell) result in the responder's polarization, thereby enabling it to divide asymmetrically into daughter cells with distinct developmental fates. Two factors expressed in the signaling cell, MOM-2 and MES-1, were known to play roles both in the mitotic spindle orientation and polarization of the EMS cell itself and to send one of its daughters down the path to an endodermal fate, but it was not clear whether this was a result of MES-1 or the Wnt signal MOM-2.



Localization of LIN-17/Frizzled receptor. Upper panel: LIN-17::GFP localization in wild type where LIN-44 is expressed posterior to the T cell. Lower panel: LIN-17::GFP localization in lin-44 mutants with ectopic LIN-44 expression anterior to the T cell. Anterior is to the left.

The team devised a series of tests in which a pair of altered signaling cells (one lacking MOM-2, the other lacking MES-1) were placed on either side of a responding cell allowing them to study the effects on endoderm development, which normally occurs in a responder exposed to both signals. In their initial experiments, endodermal development proceeded as usual, so they next tested placing the Wnt factor MOM-2 and the (non-Wnt) MES-1 cells in different positions relative to each other, and found that the orientation of the mitotic spindle (a cytoskeletal structure that pulls the chromosomes of a dividing cell apart) was consistently oriented in line with the source of the Wnt signal.

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Wnt signaling had also been known to play some role in the establishment of polarity in postembryonic cells, but here again, they faced the question of whether a Wnt factor (this time, LIN-44) serves only in a permissive capacity in the regulation of polarity, or whether it acts as a true positional determinant. By ectopically expressing LIN-44 and examining the effects on asymmetric cell division of T cells found in the worm's tail, Sawa et al hoped to find evidence of Wnt's true function. In normal development, LIN-44 is usually expressed in cells posterior to the T cells; the polarity of these cells is often reversed when this factor is absent. By misexpressing LIN-44 in cells anterior to T cells the authors observed strong enhancement of the polarity reversal phenotype in lin-44 mutants. Once more, the position of the Wnt signal source was shown to play a critical role in determining cellular sidedness, this time at a postembryonic phase of development. Sawa et al further showed that the Wnt signal determines the polarized localization of the Wnt receptor LIN-17/Frizzled in the T cell, indicating that its polarizing effect in these cells is direct.

This work provides solid evidence that, more than being a downstream actor, Wnt signaling plays a director's role in orientating the polarity of cells in the roundworm, at both embryonic and postembryonic stage. Kota Mizumoto, a scientist in the Sawa lab and one of the study's authors, hopes that by "working out the molecular mechanisms of polarity establishment in *C. elegans* we will be able to shed light on the unidentified role of the Wnt signaling pathway in other organisms, especially in mammals."

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