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Wnt Moves Beyond the Canon

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Abstract

A secreted protein associated with the metastasis of a melanoma harnesses cell adhesion proteins and the cytoskeleton to direct cell motility.

The cellular signaling pathways that respond to Wnts, a highly conserved family of secreted proteins, control numerous and different animal developmental processes, particularly those that govern cell fate and patterning. Often, components of Wnt signaling pathways malfunction and foster deadly cancers (1). Although intensely studied, much about Wnt signaling remains enigmatic. Whereas most signaling events that target gene expression in response to Wnt are referred to as canonical pathways (the more commonly observed sequence of molecular events), non-canonical Wnt signaling often targets the cytoskeleton. On page 365 of this issue, Witze *et al.* (2) advance our understanding of a non-canonical Wnt signaling pathway (Wnt5a) that promotes the invasive migration of melanoma cancer cells. Their findings advance our understanding of cancer metastasis and highlight the diversity of mechanisms through which Wnt signals influence cells.

The canonical Wnt signaling pathway was deduced from genetic studies in the fruit fly *Drosophila melanogaster* and is widely conserved in other animals (1). Wnt binds to Frizzled, its transmembrane receptor, prompting cytosolic Dishevelled proteins to prevent the otherwise constitutive proteolytic destruction of another cytosolic protein, β -catenin. Stabilized β -catenin then transits to the nucleus, where it converts transcriptional repressors called T cell factors into activators, driving the expression of target genes that specify cell fate. By contrast, one cannot so easily summarize noncanonical Wnt signaling. The best-understood example was discovered in *Drosophila*, where it polarizes epithelial cells along a common axis (3, 4). This planar cell polarity requires the canonical Wnt signaling components Frizzled and Dishevelled as well as proteins that do not participate in the canonical pathway. Although related signaling pathways that respond to Wnt influence cell migration during early vertebrate embryogenesis (gastrulation), the full extent of their conservation remains unclear. More recently, genetic studies in the nematode *Caenorhabditis elegans* have identified non-canonical Wnt signaling pathways that bear little or no resemblance to the one that controls planar cell polarity (5–9). The only unifying theme is that all of these examples somehow differ from the canon.

Nevertheless, a shared feature of many noncanonical Wnt pathways is their targeting of the cytoskeleton, with important implications for cancer. For example, expression of noncanonical Wnt5a correlates with metastatic melanoma invasiveness in humans, and exposure to Wnt5a, but not other Wnts, promotes invasiveness in melanoma cell lines (10).

Witze *et al.* investigated how Wnt5a polarizes the cytoskeleton to promote directional motility in cultured melanoma cells. They show that this response is permissive, requiring an independent directional cue (a chemokine). Dispersed cells within a chemokine gradient require exposure to Wnt5a for polarization and migration, but exposure to Wnt5a alone has little effect.

To understand this noncanonical and permissive response, Witze *et al.* used fixed- and live-cell imaging to examine the localization and movement of proteins within single cells shortly after exposure to Wnt5a. They examined several proteins, including a melanoma cell adhesion molecule previously implicated in metastatic melanoma (11), a Frizzled receptor, and cytoskeletal components (actin microfilaments and a nonmuscle myosin, together called actomyosin). In response to Wnt5a, all of these proteins become polarized in overlapping bands within the trailing edge of migrating cells (see the figure). Polarized bands of actomyosin contract to lift the trailing edge and, together with cell process extensions at the leading edge, promote migration toward a chemokine source. Multiple pulses of these transient polarizations occur within single cells over time.

In exploring the signaling pathway that mediates this Wnt5a response, Witze *et al.* discovered that actin microfilaments and the cell adhesion protein depend on each other for polarized localization and that both are required for myosin polarization. Like some other noncanonical Wnt pathways, the cytosolic proteins Dishevelled and Protein Kinase C are required. But in contrast to noncanonical pathways that influence actin through the small guanosine triphosphatase (GTPase) RhoA, Wnt5a acts through RhoB, which controls the movement of intracellular vesicles called endosomes. Furthermore, the authors observed an enrichment of multivesicular bodies at the polarized cell edge, and polarization required both the GTPase Rab4 (known to regulate multivesicular body formation) and dynamin (known to control the formation of endosomes at the cell surface). Witze *et al.* also found that polarization of the cell adhesion protein occurs by its transit through the Golgi. The authors conclude that Wnt5a polarizes cells by promoting the recycling of membrane components to specific surface sites. The concurrent or subsequent recruitment of actomyosin and other factors to these sites defines the trailing edge of the cell and thus the direction of migration.

This admirably integrated view of both cell surface and actomyosin polarization raises important questions. For instance, it's not clear how polarization of the membrane and cytoplasm are coupled, or how different proteins are targeted to the same sites. Also, how does Wnt5a signaling interface with the graded chemokine to ensure that polarization occurs at cell surfaces distal to the chemokine source? Intriguingly, Witze *et al.* observed that some responding melanoma cells polarized in the opposite (proximal) direction. Both distal and proximal polarizations require Wnt5a, with a preponderance of distal events promoting migration toward the chemokine source. Thus, the chemokine and Wnt5a are more tightly coupled to the same axis than they are to the same direction along that axis.

It is interesting to compare Wnt5a to other noncanonical Wnt signals that polarize single cells. One common theme is a requirement for actin. Actin microfilaments and myosin are required for planar cell polarity in *Drosophila* (3), and microfilaments are required in four-

cell-stage *C. elegans* embryos for the Wnt-mediated induction of an asymmetric cell division that segregates endoderm from meso-derm (6). However, planar cell polarity acts through RhoA (8), whereas Wnt5a acts through RhoB. Furthermore, the *C. elegans* Wnt signal that segregates endoderm from mesoderm acts instructively and requires a permissive signal (a tyrosine kinase) (12), in contrast to the permissive action of Wnt5a in the presence of an instructive chemokine signal. Once again, noncanonical Wnt pathways present a bewildering mix of similarities and differences. Appropriately, the Wnt field is evolving toward the use of individual pathway names based on key molecules and properties, and away from the historical distinction between canonical and noncanonical. Presumably, as we learn to speak more clearly about different Wnt pathways, we also will come to better understand their different molecular mechanisms of action.

Acknowledgments

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Figure. Directing cell movement

Exposure of a melanoma cell to Wnt5a and a gradient of the chemokine CXCL12 polarizes the localization of the cell adhesion protein MCAM and the cytoskeleton (actomyosin) to overlapping regions that are distal to the Golgi, promoting migration toward the chemokine source. Wnt5a stimulates a noncanonical signaling pathway to elicit this response.