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CELL SIGNALLING

Dynamic redistribution

Although intensively studied, much about Wnt signalling remains enigmatic. Witze *et al.* report a cell-autonomous mechanism that allows the non-canonical WNT5a pathway to control cell orientation, polarity and directional movement by the redistribution of adhesion receptors.

Most of the signalling events that target gene expression in response to Wnt are referred to as canonical pathways, whereas non-canonical Wnt signalling often targets the cytoskeleton, with important implications for cancer. Witze *et al.* investigated how WNT5a polarizes the cytoskeleton to promote directional motility in cultured melanoma cells. In response to WNT5a, several proteins, including actin, myosin IIb, a melanoma cell-adhesion molecule (MCAM) and a Frizzled receptor, become polarized in overlapping regions within the trailing edge of migrating cells. These structures of Wnt-mediated receptor-actin-myosin polarity (W-RAMP) form within 30 minutes of WNT5a treatment, and mediate membrane contraction to lift the trailing edge. Polarization in dispersed cells is driven by exposure to WNT5a in the presence of a chemokine source, suggesting that WNT5a functions permissively in conjunction with other factors that confer cues for positional orientation.

So what is the signalling pathway that mediates this response? Actin microfilaments and MCAM depend on each other for polarized localization and are both required for myosin recruitment to the structure. In contrast to non-canonical Wnt pathways that influence actin through the small GTPase RhoA, the authors found that WNT5a signals to the W-RAMP structure through RAB4 (which controls the movement of endosomes) and RhoB (which regulates multivesicular body (MVB) formation). They also observed an enrichment of MVBs at the polarized cell edge and found that the polarized structure moves from one end of the cell to another on a timescale of minutes. These results suggest that dynamic movement and intracellular translocation of MCAM is mediated through the internalization of MCAM and trafficking to late endosome compartments. Whether this occurs through a linear pathway with WNT5a upstream of RAB4, or through parallel pathways involving convergence between WNT5a and endosomal effectors remains to be investigated.

These findings highlight the diversity of mechanisms through which Wnt signals influence cells and advance our understanding of cancer metastasis.

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ORIGINAL RESEARCH PAPER Witze, E. S. *et al.* Wnt5a control of cell polarity and directional movement by polarized redistribution of adhesion receptors. *Science* **320**, 365–369 (2008)