MEMBRANE TRAFFICKING

Efficient recycling

DOI:
10.1038/nrm2345

How functional WNT proteins are made and how their secretion is regulated is becoming a focal point for the field of WNT signalling. Five reports now link the transmembrane protein Wntless (WLS) and the retromer complex in the WNT pathway.

To elucidate the mechanisms underlying retromer function in WNT-producing cells, the groups of Basler, Lin and Vincent generated a *Drosophila melanogaster* mutant of the VPS35 subunit of the retromer complex. They showed that loss of retromer activity causes a defect in the secretion of Wingless (a *D. melanogaster* WNT protein), which subsequently leads to a reduction in Wingless target-gene expression. This defect can be rescued by overexpression of WLS. WLS levels are substantially reduced in *vps35* mutants and biochemical evidence confirmed that WLS engages with the retromer complex.

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A connection between retromer function and MIG-14 (the *Caenorhabditis elegans* homologue of WLS) was also demonstrated in worms by the groups of Garriga and Korswagen. *mig-14* is expressed in WNT-producing cells and genetically interacts with retromer mutants. MIG-14 levels are significantly reduced in *vps-35* mutants; in the absence of the retromer complex, MIG-14 is targeted to lysosomes. Therefore, the retromer complex modulates MIG-14 trafficking.

Together, the five papers lead to the conclusion that the main function of retromer in WNT secretion is to maintain a steady supply of WLS protein in the Golgi. This function also seems to be conserved in mammalian cells.

WLS was found on the plasma membrane, in the *trans*-Golgi network and in vesicles in worms, flies and mammalian cells, and colocalizes with early endosome markers. The localization of WLS to early endosomes indicates that WLS might be internalized from the plasma membrane. Indeed, WLS was found to colocalize with subunits of the AP-2 complex, which is involved in clathrin-mediated endocytosis.

A function of endocytosis in WNT function was also suggested by the findings of Garriga and colleagues, which show that the *C. elegans dpy-23* gene encodes the μ subunit of the AP-2 clathrin adaptor complex and functions in several WNT-related processes. In *dpy-23* mutants, MIG-14 accumulates at or near the plasma membrane. By contrast, MIG-14 accumulates in intracellular compartments in *vps-35* mutants. These findings suggest that DPY-23/AP-2 and VPS-35 control WNT secretion by regulating MIG-14/WLS recycling.

Although there are some discrepancies between the different model organisms, all reports point to a model in which WLS accompanies WNT to the plasma membrane, where the two proteins would dissociate. Following dissociation from WNT, WLS is internalized through clathrin-mediated endocytosis and is returned to the Golgi in a retromer-dependent manner.

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ORIGINAL RESEARCH PAPERS Pan, C-L. *et al.* *C. elegans* AP-2 and retromer control Wnt signaling by regulating MIG-14/Wntless. *Dev. Cell* 7 Jan 2008 (doi: 10.1016/j.devcel.2007.12.001) | Belenkaya, T. Y. *et al.* The retromer complex influences Wnt secretion by recycling Wntless from endosomes to the trans-Golgi network. *Dev. Cell* 7 Jan 2008 (doi:10.1016/j.devcel.2007.12.003) | Yang, P-T. *et al.* Wnt signaling requires retromer-dependent recycling of MIG-14/Wntless in Wnt-producing cells. *Dev. Cell* 7 Jan 2008 (doi:10.1016/j.devcel.2007.12.004) | Franch-Marro, X. *et al.* Wingless secretion requires endosome-to-Golgi retrieval of Wntless/Evi/Sprinter by the retromer complex. *Nature Cell Biol.* 13 Jan 2008 (doi:10.1038/ncb1678) | Port, F. *et al.* Wingless secretion promotes and requires retromer-dependent cycling of Wntless. *Nature Cell Biol.* 13 Jan 2008 (doi:10.1038/ncb1687)
FURTHER READING Hausmann, G. *et al.* Helping Wingless take flight: how WNT proteins are secreted. *Nature Rev. Mol. Cell Biol.* **8**, 331–336 (2007)