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ARTICLE

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# SNX3-retromer requires an evolutionary conserved MON2:DOPEY2:ATP9A complex to mediate Wntless sorting and Wnt secretion

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Wntless transports Wnt morphogens to the cell surface and is required for Wnt secretion and morphogenic gradients formation. Recycling of endocytosed Wntless requires the sorting nexin-3 (SNX3)-retromer-dependent endosome-to-Golgi transport pathway. Here we demonstrate the essential role of SNX3-retromer assembly for Wntless transport and report that SNX3 associates with an evolutionary conserved endosome-associated membrane remodelling complex composed of MON2, DOPEY2 and the putative aminophospholipid translocase, ATP9A. In vivo suppression of *Ce-mon-2*, *Ce-pad-1* or *Ce-tat-5* (respective MON2, DOPEY2 and ATP9A orthologues) phenocopy a loss of SNX3-retromer function, leading to enhanced lysosomal degradation of Wntless and a Wnt phenotype. Perturbed Wnt signalling is also observed upon overexpression of an ATPase-inhibited TAT-5(E246Q) mutant, suggesting a role for phospholipid flippase activity during SNX3-retromer-mediated Wntless sorting. Together, these findings provide in vitro and in vivo mechanistic details to describe SNX3-retromer-mediated transport during Wnt secretion and the formation of Wnt-morphogenic gradients.

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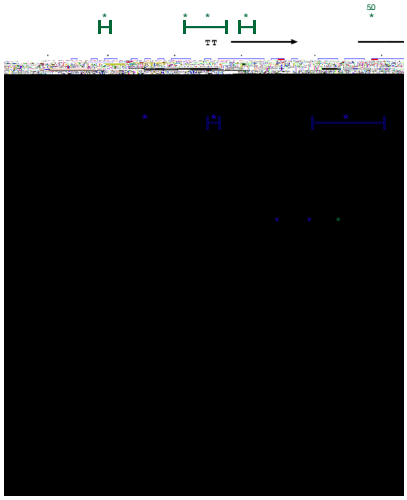

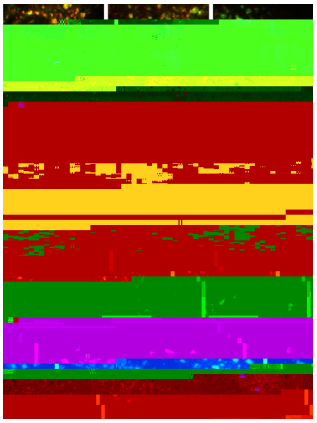

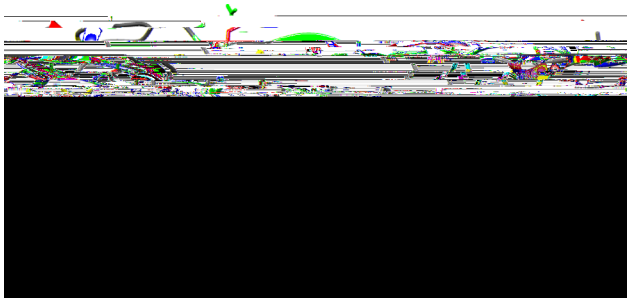

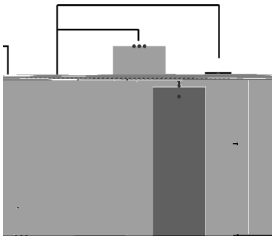

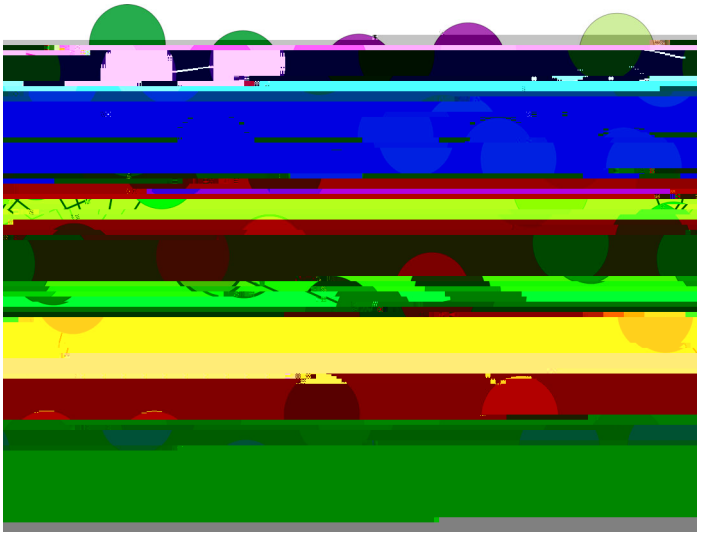

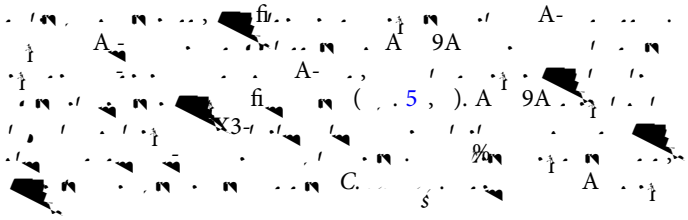

## Discussion

[redacted]

## Methods

**Cell culture**. [redacted]

**Immunofluorescence analysis**. [redacted]

**Immunoprecipitation and western blotting analysis**. [redacted]

53. [illegible] *J. Biol. Chem.* **291**, 15727–15739 (2016).
54. [illegible], A. A. & [illegible] *Cell. Logist.* **6**, 1228791 (2016).
55. [illegible]