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The Meckel-Gruber Syndrome protein TMEM67 (meckelin) regulates basal body planar polarization and non-canonical Wnt signalling via Wnt5a and ROR2

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Objective:
Ciliopathies are a group of developmental disorders that manifest with multi-organ anomalies. Mutations in *TMEM67* have been reported in human ciliopathies that include Meckel-Gruber and Joubert syndromes. In this study we describe multi-organ developmental abnormalities in the *Tmem67*$^{tm1Dgen/H1}$ knockout mouse that closely resemble those of *Wnt5a* and *Ror2* knockout mice.

Methods:
We used anatomical assessment, immunofluorescence confocal microscopy and biochemical methods to determine mutant phenotypes at the organismal, cellular and molecular levels.

Results:
Tmem67$^{-/-}$ mutant phenotypes include pulmonary hypoplasia, ventricular septal defects, shortening of the body longitudinal axis, limb abnormalities, and cochlear hair cell stereociliary bundle orientation and basal body/kinocilium positioning defects. The basal body/kinocilium complex was often uncoupled from the hair bundle, suggesting aberrant basal body migration. TMEM67 (meckelin) is essential for phosphorylation of the non-canonical Wnt receptor ROR2 (receptor tyrosine kinase-like orphan receptor 2) upon Wnt5a stimulation. ROR2 interacts with the intracellular C-terminal domain of TMEM67 and co-localizes with TMEM67 at the ciliary transition zone. The N-terminal domain of TMEM67 preferentially binds to Wnt5a in an *in vitro* binding assay. *Tmem67* mutant embryonic lungs in *ex vivo* culture failed to respond to Wnt5a stimulation of epithelial morphogenesis. However, stimulating the non-canonical Wnt pathway downstream of the receptor by activating RhoA resulted in an elicited response and the rescue of lung hypoplasia phenotypes.

Conclusion:
Our data suggest that TMEM67 is a novel receptor that has a major role in non-canonical Wnt signalling by Wnt5a and ROR2. We propose that this signalling ensures correct basal body positioning.

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