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Manuscript #	E22-09-0421R
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Current Stage	Under Review
Title	Interaction of the sorting nexin 25 homolog Snazarus with Rab11 balances endocytic and secretory transport and maintains the ultrafiltration diaphragm in nephrocytes
Running Title	Snz counteracts Rab11 in nephrocytes
Manuscript Type	Article
Nominations	N/A
Database deposition	None
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Abstract	Proper balance of exocytosis and endocytosis is important for the maintenance of plasma membrane lipid and protein homeostasis. This is especially critical in human podocytes and the podocyte-like Drosophila nephrocytes that both use a delicate diaphragm system with evolutionarily conserved components for ultrafiltration. Here we show that the sorting nexin 25 homolog Snazarus (Snz) binds to Rab11 and localizes to Rab11-positive recycling endosomes in Drosophila nephrocytes, unlike in fat cells where it is present in plasma membrane/lipid droplet/ER contact sites. Loss of Snz leads to redistribution of Rab11 vesicles from the cell periphery and increases endocytic activity in nephrocytes. These changes are accompanied by defects in diaphragm protein distribution that resemble those seen in Rab11 gain-of-function cells. Of note, co-overexpression of Snz rescues diaphragm defects in Rab11 overexpressing cells, whereas snz knockdown in Rab11 overexpressing nephrocytes or simultaneous knockdown of snz and tbc1d8b encoding a Rab11 GAP lead to massive expansion of the lacunar system that contains mislocalized diaphragm components: Sns and Pyd/ZO-1. We find that loss of Snz enhances while its overexpression impairs secretion, which, together with genetic epistasis analyses, suggest that Snz counteracts Rab11 to maintain the diaphragm via setting the proper balance of exocytosis and endocytosis.
Highlight Summary for TOC	We report a novel function of the sorting nexin 25 homolog Snazarus in larval garland nephrocytes, the highly endocytic, podocyte-like cells of Drosophila. We propose a model in which Snz negatively regulates exocytosis via its interaction with Rab11, thus contributing to the maintenance of membrane balance in the endosomal system of nephrocytes.
Tweet	N/A
Monitoring Editor	Assigned
Subject Categories	Membrane Traffic/endocytic trafficking, Membrane Traffic/exocytosis and regulated exocytosis, Membrane Traffic/inter-organelle trafficking, Membrane Traffic/trafficking in specialized cell types, Microscopy/electron microscopy (including cryo-EM, FIB-SEM), Microscopy/light microscopy (including superresolution methods), Model and Experimental Organisms/files, Organelles - Membrane Bound/endosomes, lysosomes, and multivesicular bodies, Organelles - Membrane Bound/organelle contact sites, Organelles - Membrane Bound/secretory organelles
Reviews and Decision Letter from Another Journal	No editor's disposition letter or peer reviewers' comments from another journal are included.
Questions to Ensure Reproducibility of Data	Please refer to the complete MBOC Author Submission Checklist at www.ascb.org/files/mboc-checklist.pdf when answering these questions. I. Data Presentation: This manuscript meets the applicable requirements listed in Section I. II. Methodology and Statistics : This manuscript meets the applicable requirements listed in Section II. III. Reagents and Model Systems: This manuscript meets the applicable requirements listed in Section III. IV. Data Accessibility: This manuscript meets the applicable requirements listed in Section IV.
Open Review	Yes

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Manuscript Items

1. Author Cover Letter [PDF \(277KB\)](#)
2. "Rebuttal Letter" [PDF \(465KB\)](#)
3. Merged File containing manuscript text and 6 Figure files. [PDF \(20339KB\)](#)
 - a. Article File [PDF \(360KB\)](#) [Small PDF \(352KB\)](#)
 - b. Figure 1 [PDF \(14116KB\)](#)
Loss of Snz enhances endocytic activity in nephrocytes
 - c. Figure 2 [PDF \(1085KB\)](#)
Snz colocalizes with and binds to Rab11 in nephrocytes
 - d. Figure 3 [PDF \(1423KB\)](#) [Small PDF \(208KB\)](#)
Snz modulates Rab11 activity for the proper maintenance of nephrocyte diaphragm (ND) integrity
 - e. Figure 4 [PDF \(1241KB\)](#) [Small PDF \(178KB\)](#)
Snz and Rab11 control the depth of lacunar channels in nephrocytes
 - f. Figure 5 [PDF \(835KB\)](#) [Small PDF \(118KB\)](#)
Snz is a negative regulator of exocytosis
 - g. Figure 6 [PDF \(1285KB\)](#) [Small PDF \(195KB\)](#)
Snz is a negative regulator of Rab11-mediated recycling in Drosophila nephrocytes
4. Video - Supplementary movie V1 [Video](#)
Live imaging of control nephrocytes pulse-chase labeled with Avidin-Texas Red endocytic tracer.
5. Video - Supplementary movie V2 [Video](#)
Live imaging of vps39 knockdown nephrocytes pulse-chase labeled with Avidin-Texas Red endocytic tracer.
6. Video - Supplementary movie V3 [Video](#)
Live imaging of snz knockdown nephrocytes pulse-chase labeled with Avidin-Texas Red endocytic tracer.
7. Supplementary figure S1 [PDF \(1527KB\)](#) [Small PDF \(192KB\)](#)
Loss of snz enhances endocytic activity in nephrocytes and it does not affect lysosomal degradation
8. Supplementary figure S2 [PDF \(571KB\)](#) [Small PDF \(122KB\)](#)
Localization of Snz in nephrocytes
9. Supplementary Figure S3 [PDF \(964KB\)](#) [Small PDF \(141KB\)](#)
Snz and Rab11 control nephrocyte diaphragm (ND) integrity and intracellular ND protein deposits
10. Supplementary table S1 [PDF \(107KB\)](#) [Small PDF \(111KB\)](#)
Results of quantification and statistical analysis
11. Supplemental Material [PDF \(89KB\)](#) [Small PDF \(88KB\)](#)
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