Title:	**The big and intricate dreams of little organelles: Embracing complexity in the study of membrane traffic**
Authors:	Allen P. Liu, Roberto J. Botelho and Costin N. Antonescu
Article Type:	Review

Monitoring Editor	Michael S. Marks
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Decision and Reviews

Dear Costin,

Thank you for taking the time recently to write your review "The big and intricate dreams of little organelles: Embracing complexity in the study of membrane traffic" for Traffic. I asked two colleagues who are experts in the field to review the paper and their verbatim comments are appended below. I share their enthusiasm and agree that this is a well-written and timely review that will be of interest to the readers of Traffic. I ask that you consider incorporating the additional papers suggested by referee 2 in your discussion, but this is not required for this paper to be accepted.

Thank you so much and congratulations for such a nice contribution to Traffic!

Sincerely,

Mickey Marks, Ph.D.
Co-Editor

Referee's Comments to the Authors

Referee: 1

Comments to the Author
This is a very well written and comprehensive review on an interesting and timely topic. The article clearly illustrates the extraordinary complexity and versatility of the biological systems and emphasizes the critical importance of combining reductionist and system biology approaches to better understand complex processes.

Referee: 2

Comments to the Author
The authors have sampled membrane trafficking studies to integrate with systems biology advances. The authors consider the field of organelle proteomics, high –content imaging, lipids relevant to membrane traffic, clathrin mediated endocytosis including heterogeneity of clathrin coated pits, transcription factor EB as an example of the regulation of organelle adaption as well as XBP1, computational modeling, cell migration, and cell division.
Figure 1 summarizes the interplay between organelle communications as it affects cell physiology. Figure2 compares organelle homogeneity, organelle heterogeneity and organelle adaptation to consider how these might impact cell physiology.
The authors' sample of the literature is indicated in 185 references.

Such a review may be encouraged. Certainly, the track record of using highly enriched populations of organelles have led to enormous discoveries for clathrin coated vesicles, ER, Golgi, phagosomes etc. The proteins uncovered in these studies for the first time have been transformative in membrane traffic mechanisms and other properties of these organelles. These past discoveries have been well described elsewhere and here the authors' eagerness to embrace the application of "approaches used by systems biologists to understand complex systems " is welcomed. Towards this goal, the mining of current large data sets by cell biologists who are talented in the tools and rigor of systems analysis, may be helpful to the authors' goal to "understand how little organelles can have big impact on cell physiology as a result of being key components within intricate cellular regulatory networks." Of potential additional relevance to those raised by the authors are several efforts to deduce protein interaction networks (e.g., PMID:28077563, PMID:27803151, PMID:25416956, PMID:26496610 that includes stoichiometry and abundances readily visualized for each bait prey interaction and vice versa) and large data sets for protein localization (e.g. PMID:28495876) as well as past applications of proximity-specific ribosome profiling to organelle dynamics (e.g., PMID: 25378625).

The review by the authors may be a welcomed step towards the indicated goal to integrate the impact of organelle dynamics on cell physiology.

Author Rebuttal

Dear Dr. Michael S. Marks,

We thank you very much for the enthusiastic and positive comments about our manuscript entitled, "The big and intricate dreams of little organelles: Embracing complexity in the study of membrane traffic" by Allen P. Liu, Roberto J. Botelho and myself for consideration for publication in Traffic. We are pleased to submit a revised version of this manuscript that incorporates the minor yet helpful suggestions provided by the reviewers.

We thank reviewer 1 for indicating that our manuscript is "a very well written and comprehensive review on an interesting and timely topic" and that "the article clearly illustrates the extraordinary complexity and versatility of the biological systems…".

We thank reviewer 2 for indicating that our manuscript "may be a welcomed step towards the indicated goal to integrate the impact of organelle dynamics on cell physiology." Importantly, we thank reviewer 2 for suggesting some additional studies that are worth discussing and citing in our manuscript. We have included a brief discussion of each of the important studies indicated. Specifically, we have now added a description of the databases and interaction maps that have been devised from the systematic study of protein and genetic interactions, as well as subcellular localizations (references 10-13, on page 3). Furthermore, we have also now included a brief discussion of the important study from Weissman & col. that describes the use of proximity biotinylation to resolve the spatial organization of translation of specific mRNAs (reference 20, page 3). Finally, we also include a brief description of the study which used a receptor-based strategy to systematically probe protein-protein and protein-drug interactions (reference 42, page 4).

In addition, we have included a very brief discussion and citation of two additional studies. First, we include a brief description of a recent study that used proximity-based biotinylation to resolve the distinct interactome of two G-protein coupled receptors during ligand-stimulated transit from the plasma membrane to endosomes (reference 33, page 4). Second, we also include an important study in yeast that systematically assessed protein localization to various compartments, and how these localizations were altered under various conditions (reference 40, page 4). Adding these brief passages does not change the conclusions of the manuscript, but provide the readers with some additional examples and perspectives of high content approaches to resolve the dynamic proteome of specific organelles.

We believe that this revised manuscript is improved relative to our initial submission, and that work will be of interest to a broad range of cell biology researchers, as well as researchers in other disciplines such as systems biology. We thank you for your consideration of our manuscript for publication in Traffic.

Sincerely,
Costin Antonescu