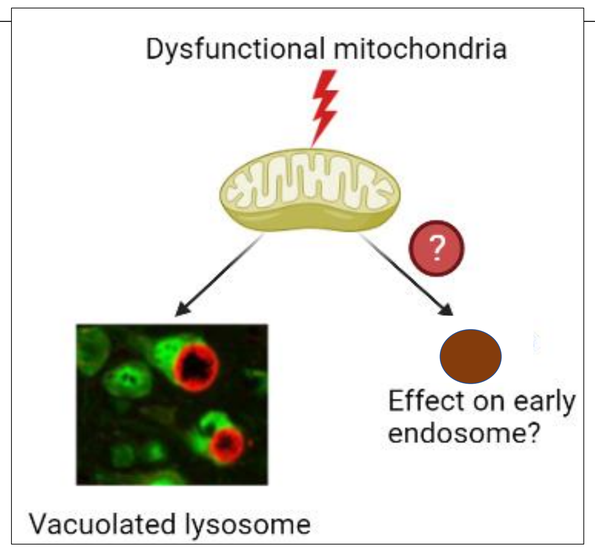
Mitochondrial dysfunction: The endocytic pathway connection

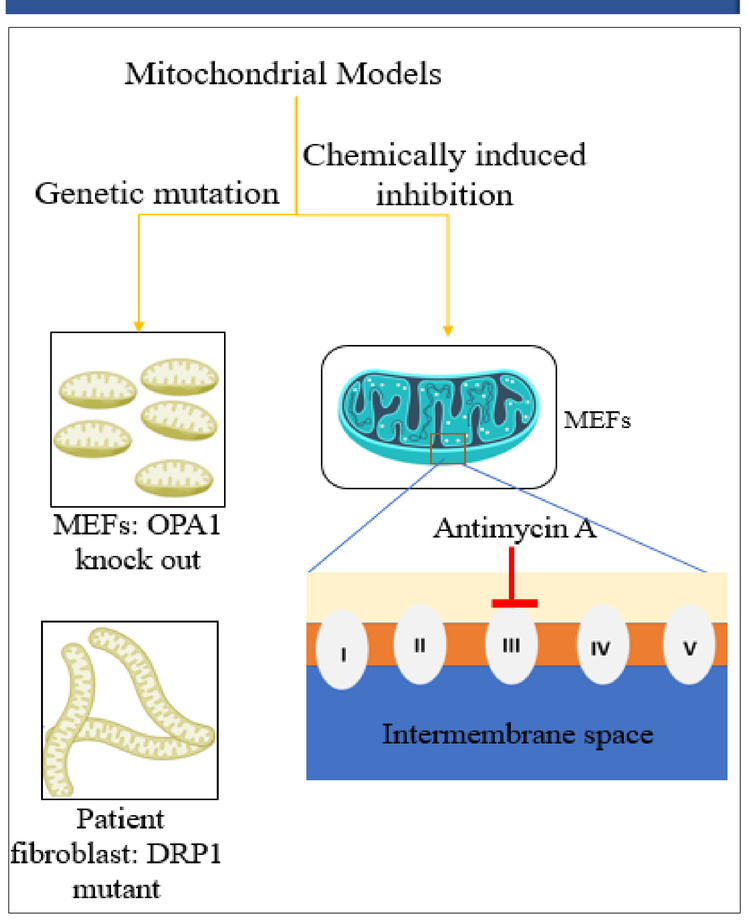
Anjali Vishwa [1,2,3] , Kiran Todkar, Julie Demers-Lamarche, Mathieu Ouellet (Cell lines), Marc Germain
1. Département de Biologie médicale et Groupe de Recherche en Signalisation Cellulaire, UQTR
2. Centre d'excellence en recherche sur les maladies orphelines - Fondation Courtois (CERMO-FC)
3. Réseau Intersectoriel de recherche en Santé de l'Université du Québec (RISUQ)

Introduction



- Mitochondria play a key role in the regulation of metabolism, cell signalling, apoptosis and immunity, while mutations affecting mitochondrial function generally cause neurological or muscular pathologies.
- To exert their roles, mitochondria interact with different organelles. Among the organelles interacting with mitochondria, endosomes are required for the delivery of extracellular and cytoplasmic material to lysosomes for degradation.
- In this context, the interaction between endosomes and mitochondria has been proposed to promote the trafficking of endocytosed material and endosomal maturation, but the underlying mechanisms remain elusive.

Methodology

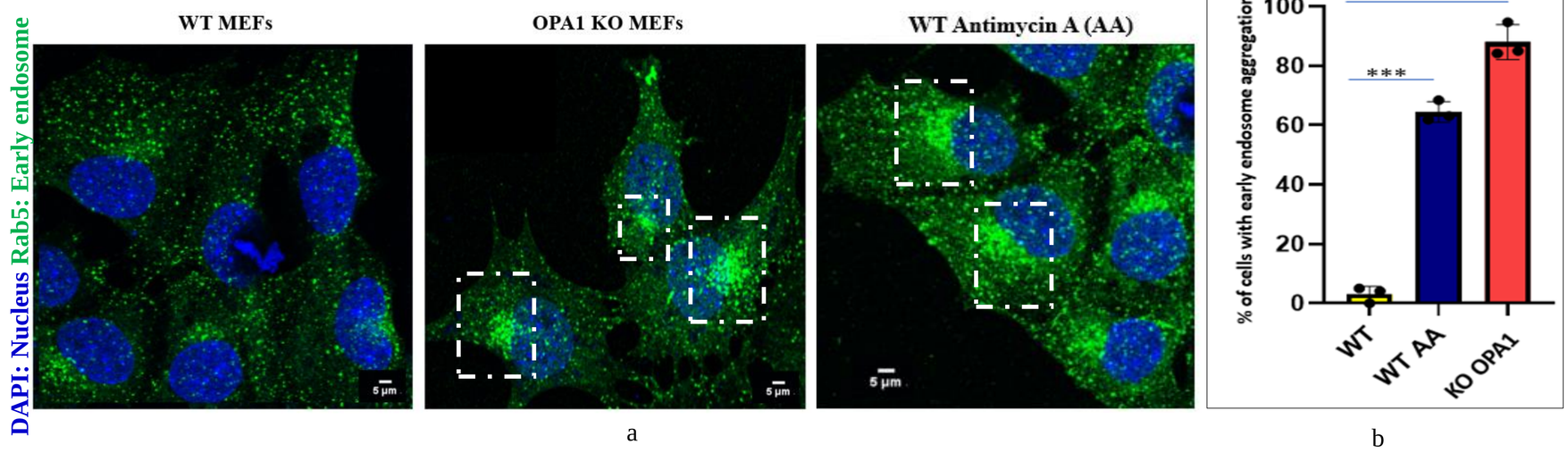


Hypothesis

Mitochondrial impairment affects the endocytic pathway

Results

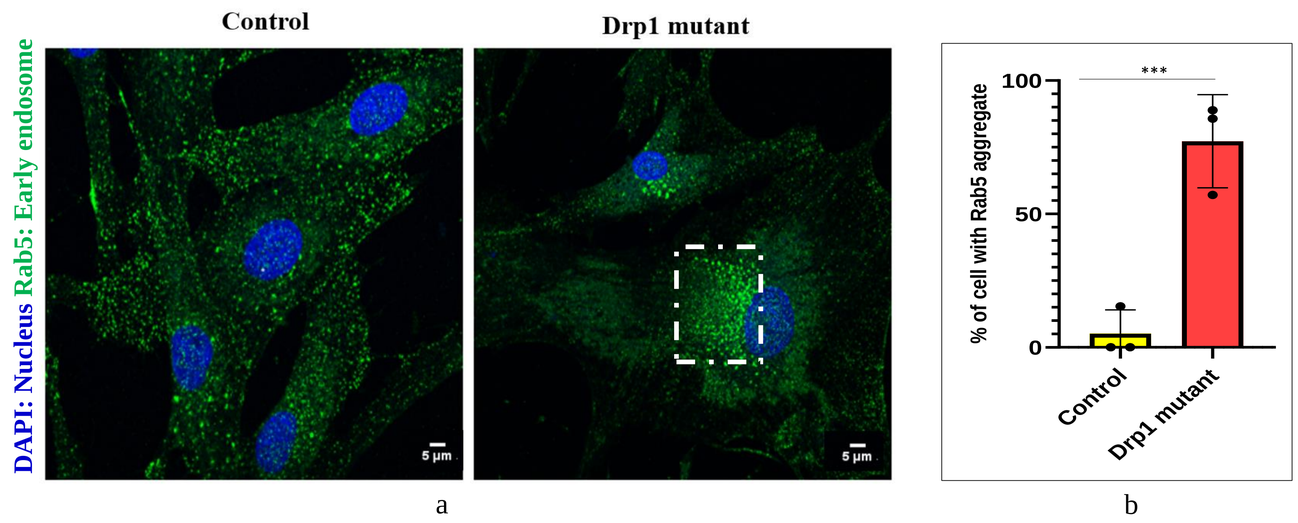
1. Mitochondrial dysfunction cause aggregation of early endosome in the perinuclear region in mouse embryonic fibroblast (MEFs)



a b

Figure 1: Impact of mitochondria functional loss in early endosome structure. **a**) Cells were tagged with **Rab5** (early endosome) and **DAPI** (nucleus). The boxed areas indicate cells with aggregated early endosome in the perinuclear region. **b)** Quantification of early endosome aggregation.

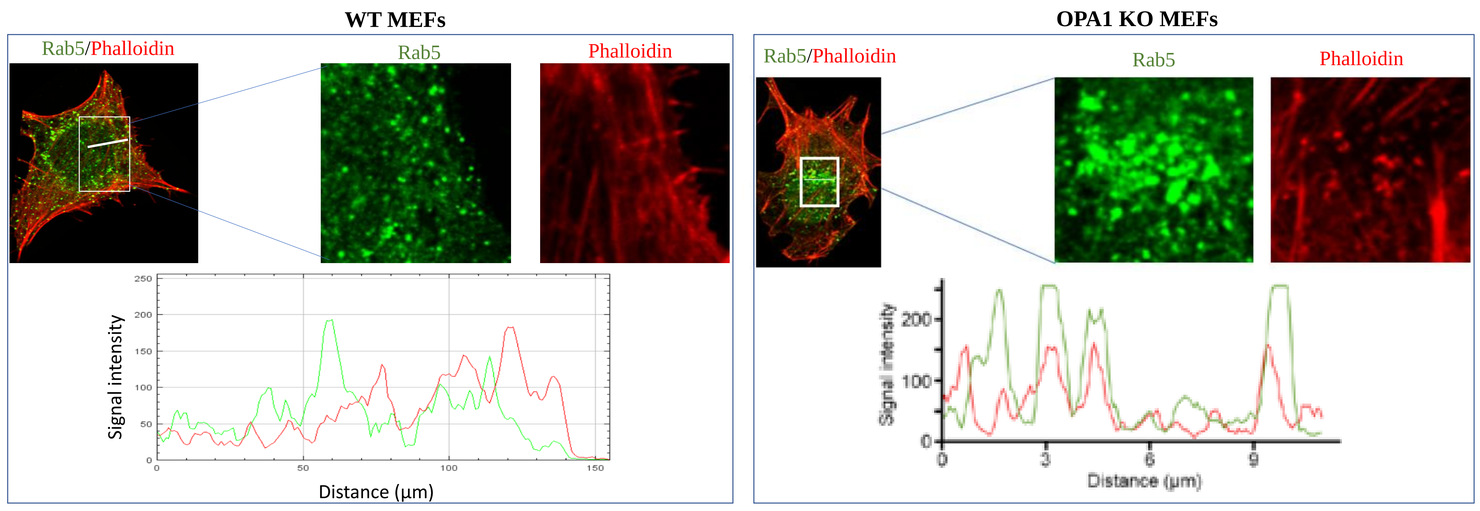
2. Mitochondrial dysfunction cause aggregation of early endosome in the perinuclear region in patient cells with a Drp1 mutation



a b

Figure 2: Impact of mitochondria functional loss in early endosome structure in primary fibroblasts mutant for the mitochondrial fission protein DRP1 **a**) Control and DRP1 mutant cells were tagged with **Rab5** (early endosome) and **DAPI** (nucleus). The boxed areas indicate cells with aggregated early endosome in the perinuclear region **b**) Quantification of early endosome aggregation.

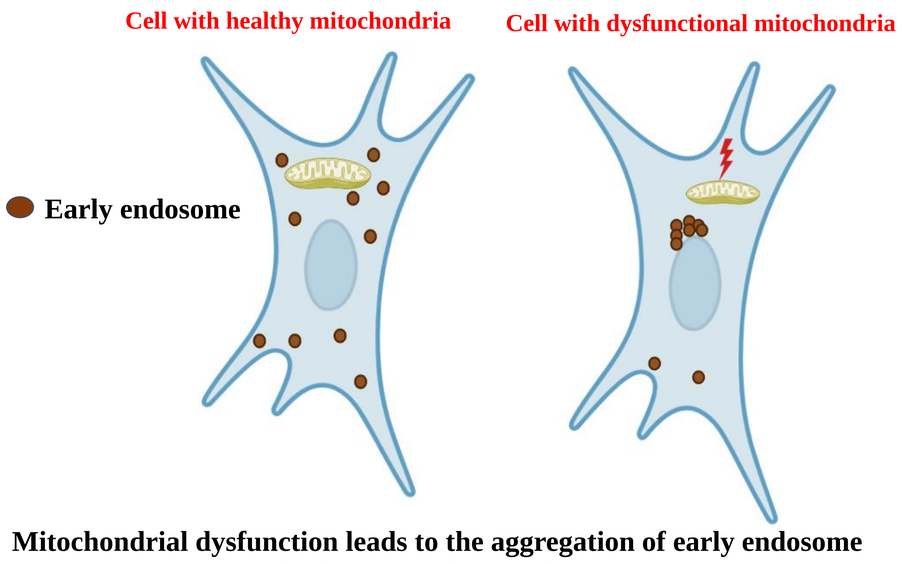
3. Actin plays a role in driving early endosomal aggregation in perinuclear region



a b

Figure 3: Early endosomes colocalise with actin patches in cells with dysfunctional mitochondria:
WT and OPA1 KO MEFs were tagged with **Rab5** (early endosome) and **phalloidin** (actin). Line scans (bottom) showing colocalization between Rab5 and phalloidin were performed in Fiji.

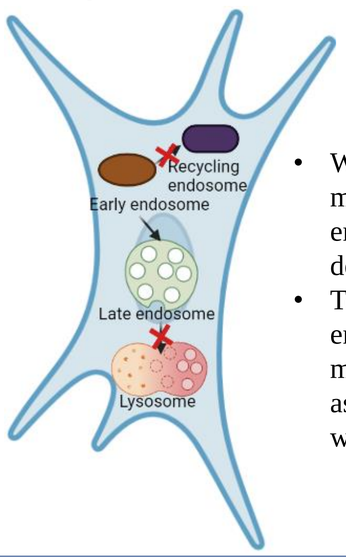
Conclusion



Mitochondrial dysfunction leads to the aggregation of early endosome in the perinuclear region.

Future experiments

Structural impairment in the early endosome in mitochondrial dysfunctioned cell could affect the endocytic pathway



- We will determine the consequence of mitochondrial dysfunction on early endosome function by measuring dextran and transferrin uptake.
- To study the mechanism of the early endosome aggregation in cells with mitochondrial dysfunction, the association between the two organelles will be analysed.

References

1. Demers-Lamarche, J., Guillebaud, G., Tlili, M., Todkar, K., Bélanger, N., Grondin, M., Nguyen, A.P., Michel, J. and Germain, M., 2016. Loss of mitochondrial function impairs lysosomes. *Journal of biological chemistry*, *291*(19), pp.10263-10276

2. Paul, S., Saha, D., & Binukumar, B. K. (2021). Mitochondrial Dysfunction and Mitophagy Closely Cooperate in Neurological Deficits Associated with Alzheimer's Disease and Type 2 Diabetes. *Molecular Neurobiology*, 1-15.