# Literature Report

**Reporter: 陶奕**

**Date: 2021-10-21**

nature COMMUNICATIONS

Published: 09 September 2021

ARTICLE

Check for updates

https://doi.org/10.1038/s41467-021-25621-4 OPEN

# ORP1L mediated PI(4)P signaling at ER-lysosome-mitochondrion three-way contact contributes to mitochondrial division

Maxime Boutry[1] & Peter K. Kim[1,2]✉

# Author Information

## Peter K. Kim

**University of Toronto:**

2009 to present | Associate Professor (Biochemistry)

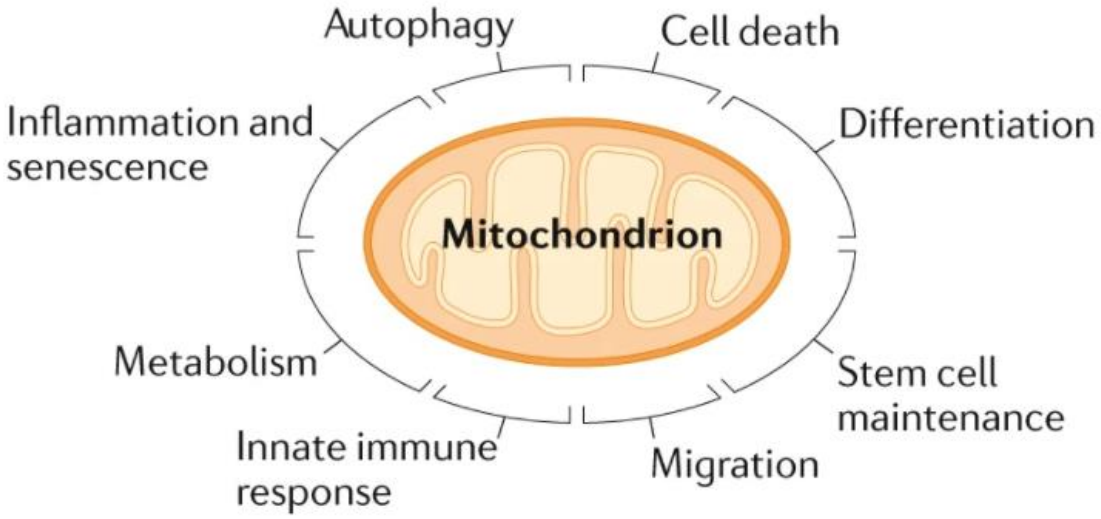
**The Hospital for Sick Children Research Institute:**

2009 to present | Senior Scientist (Cell Biology)

**Research direction:** Using high and super-resolution microscopy combined with genetic tools, they are studying the mechanisms that control these two organelles (Peroxisomes and Mitochondria that makings and breakings down fats) and how defects in these mechanisms lead to various diseases from genetic disorders to severe malnutrition.

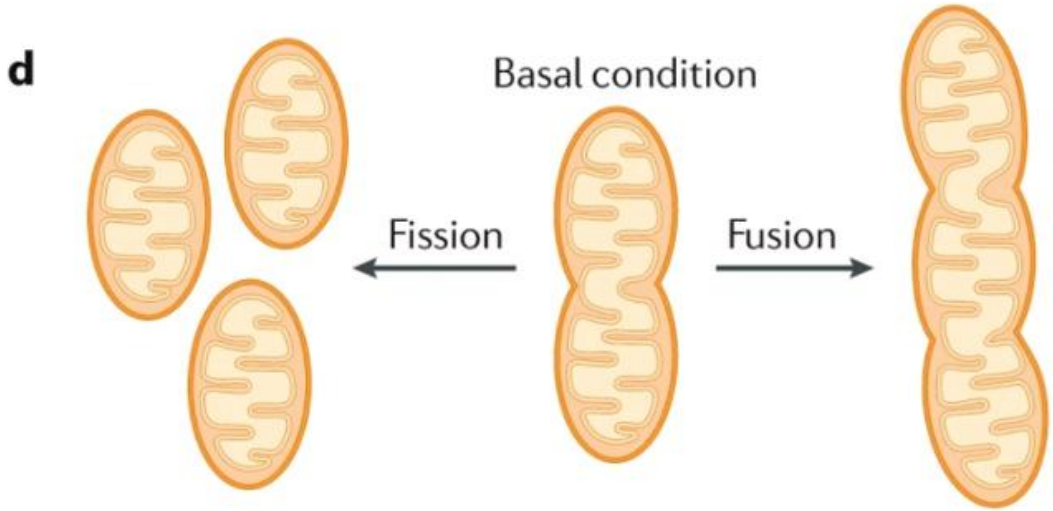
# Introduction

## 线粒体




✓ 调节无数细胞过程

## 线粒体动力学

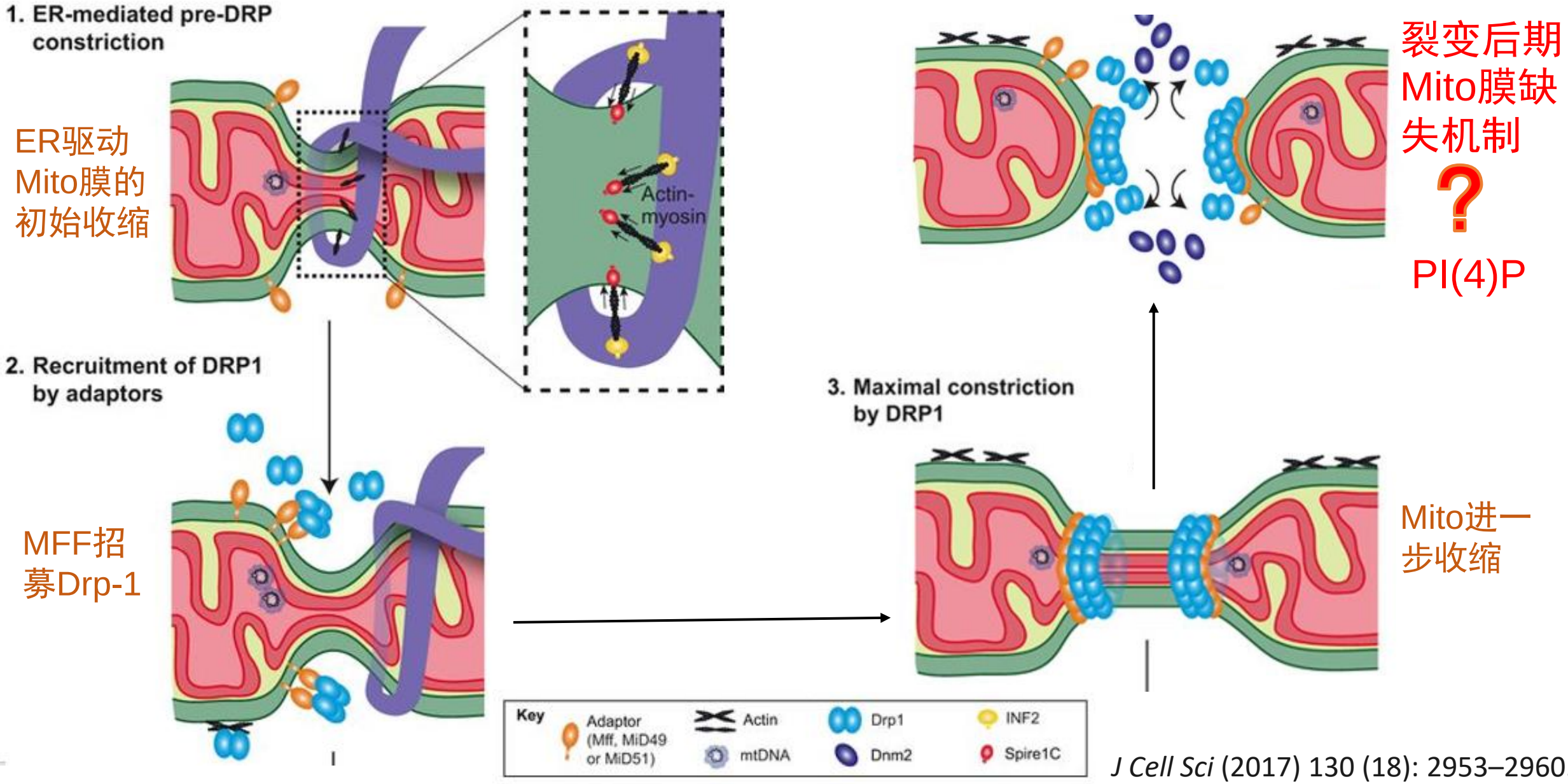



✓ 调节形态→平衡融合裂变过程→维持功能性网络→调节数量、大小、位置

*Nature Reviews Molecular Cell Biology* **volume 21**, pages204–224 (2020)

# Introduction

## 线粒体裂变——内质网的参与




ER驱动Mito膜的初始收缩

MFF招募Drp-1

裂变后期Mito膜缺失机制

?

PI(4)P

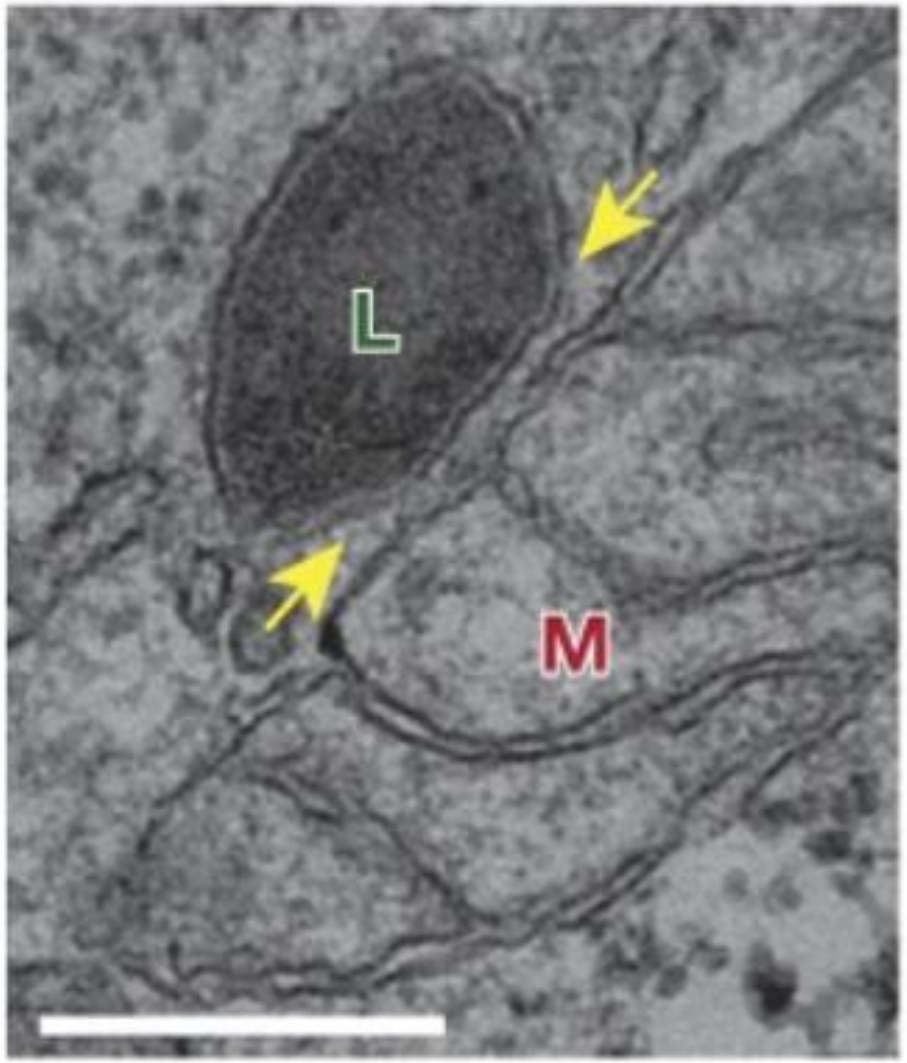
Mito进一步收缩

*J Cell Sci* (2017) 130 (18): 2953–2960.

# Introduction

## 线粒体裂变——溶酶体的参与

Ly定位于Mito分裂部位形成膜接触




Ly在裂变中的作用

?

新见解：后期提供PI(4)P…

*Nature* **volume 554**, pages382–386 (2018)

# Introduction

## 线粒体—溶酶体接触：Rab7

- 小GTP酶
- Ly功能重要调节因子

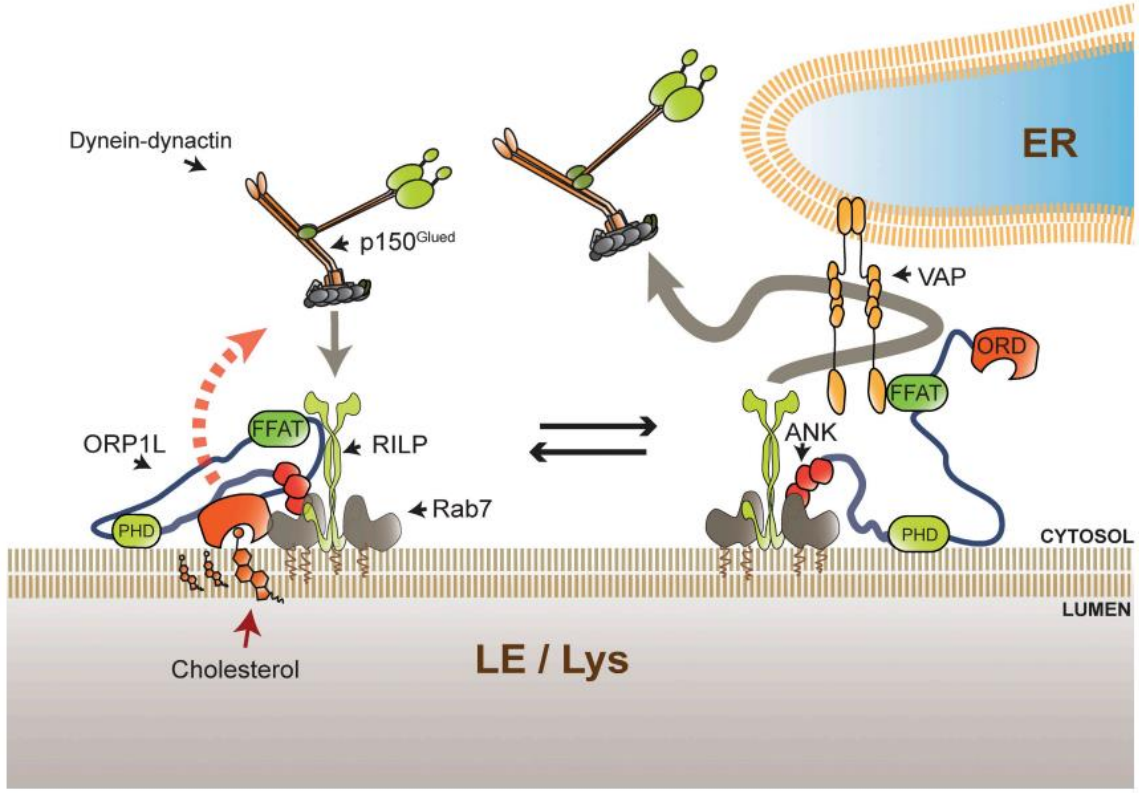
- 非活性：细胞质GDP结合态
- 活性：GTP结合态（定位于Ly）

促进Ly-Mito接触　　水解促进解离

介导溶酶体募集到线粒体分裂位点 ？

ER募集

## 内质网—溶酶体接触：Rab7与ORP1L结合

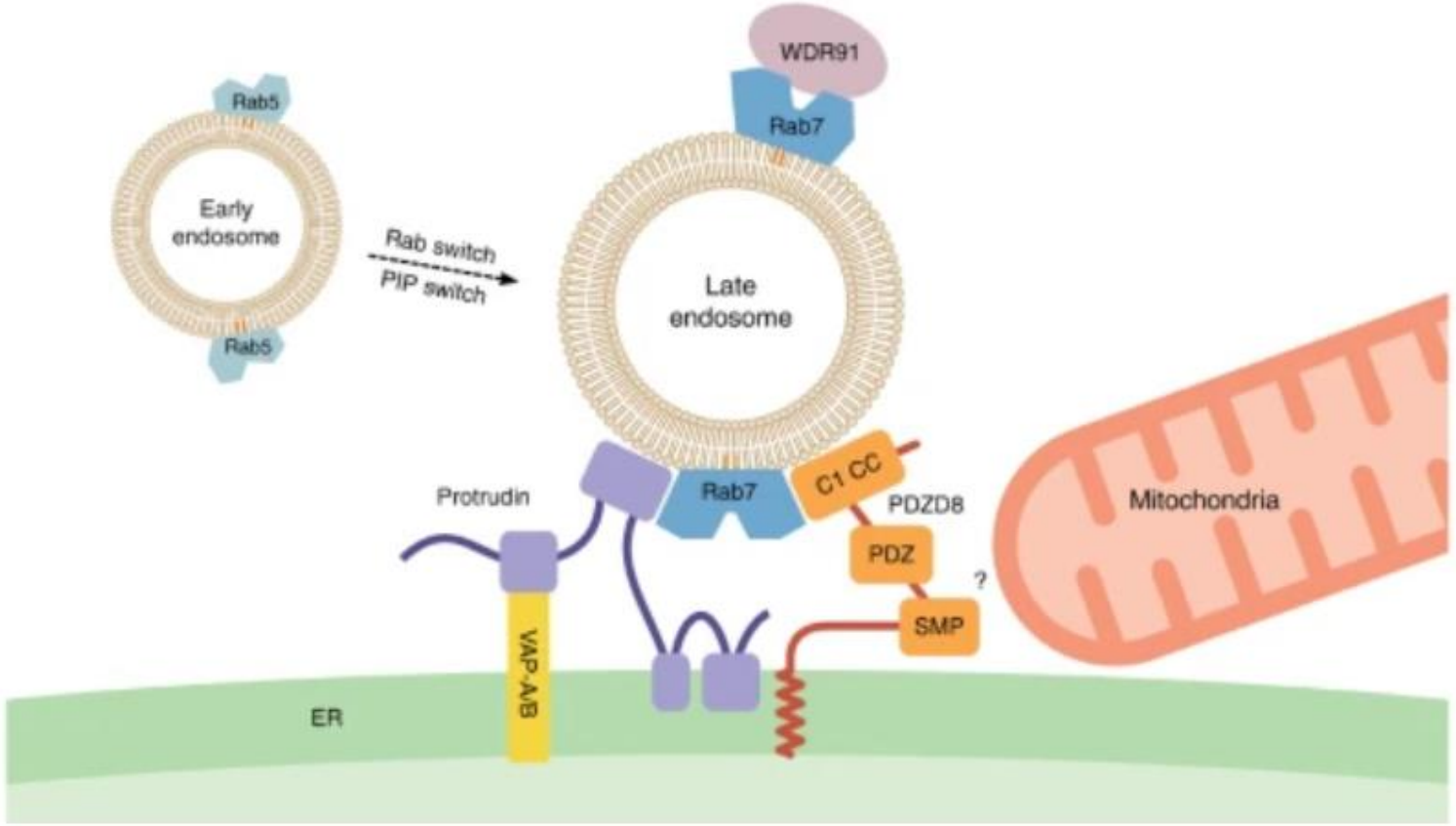



✓ 增加了分裂过程中形成三向接触的可能性。

*J Cell Biol* (2009) 185 (7): 1209–1225.

# Introduction

## ER-Ly和ER-Mito接触位点紧密相连




线粒体裂变的
三向接触模型

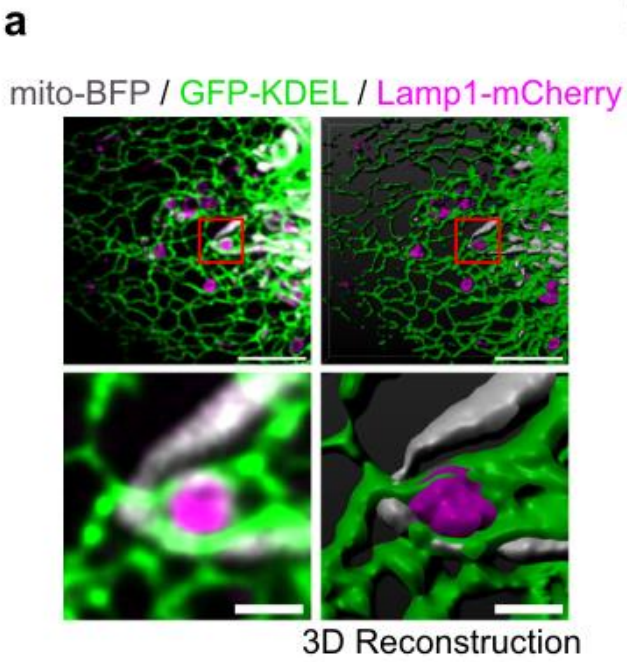
验证真实性
对问题的新见解

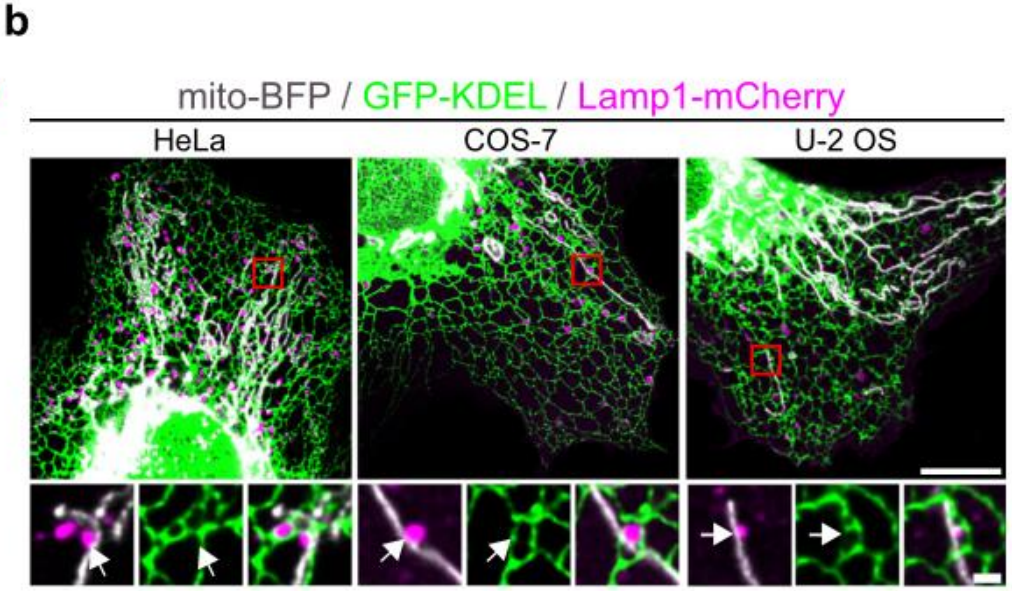
这种接触是否有助于线粒体裂变 ？ 是

*Nature Communications* **volume 11:** 3645 (2020)

# Results

## 1. ER、Ly和Mito形成三向接触参与线粒体分裂。

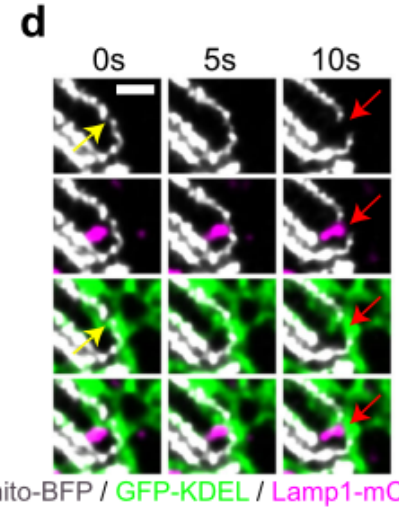



3-way contacts

| Outcome | n = 100 events |
|---|---|
| Untethering | 86 % |
| Remain tethered | 11 % |
| Mitochondrial division | 3 % |

n=20 cells




e

n=30 cells

| Mitochondrial division | n = 73 events |
|---|---|
| ER at division | 100 % |
| Lysosome at division | 58.9 % |

| Mitochondrial division marked by lysosome | n = 43 events |
|---|---|
| ER at division | 100 % |

f

Recruitment at mitochondrial division site

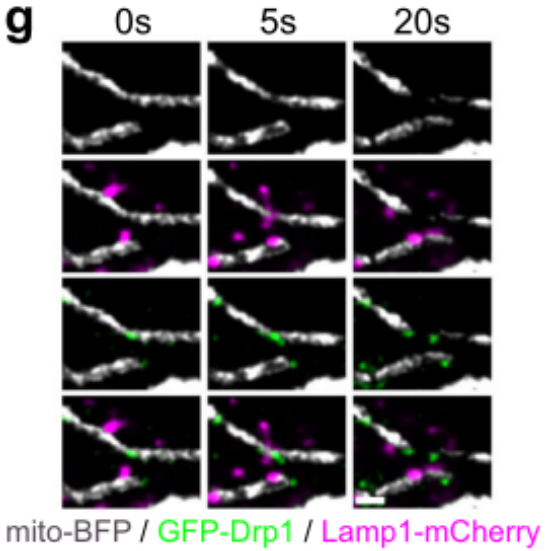
| Sequence | n = 33 events |
|---|---|
| ER then lysosome | 90.9 % |
| Lysosome then ER | 9.1 % |

- 溶酶体有可能是在内质网最初收缩线粒体后被招募到分裂位点。

# Results

## 1. ER、Ly和Mito形成参与线粒体分裂的三向接触。

g




h

n=22 cells

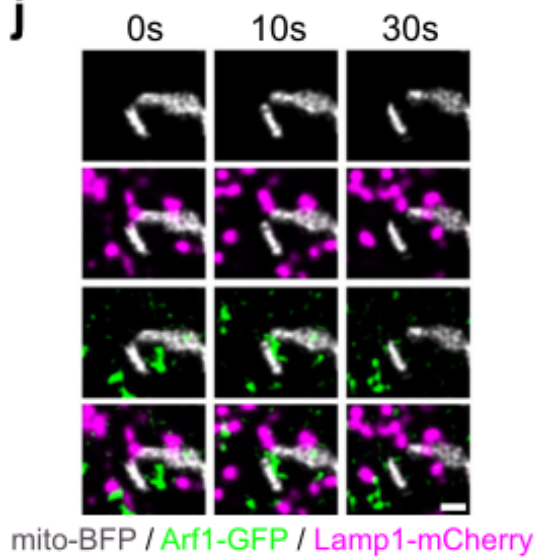
| Mitochondrial division | n = 69 events |
|---|---|
| Drp1 at division | 97.1 % |
| Lysosome at division | 60.8 % |

i

Recruitment at mitochondrial division site

| Sequence | n = 36 events |
|---|---|
| Drp1 then lysosome | 69.5 % |
| Lysosome then Drp1 | 22.2 % |
| Same time | 8.3 % |

j




k

n=25 cells

| Mitochondrial division | n = 81 events |
|---|---|
| Arf1 at division | 53.1 % |
| Lysosome at division | 59.2 % |
| Both at division | 37 % |

l

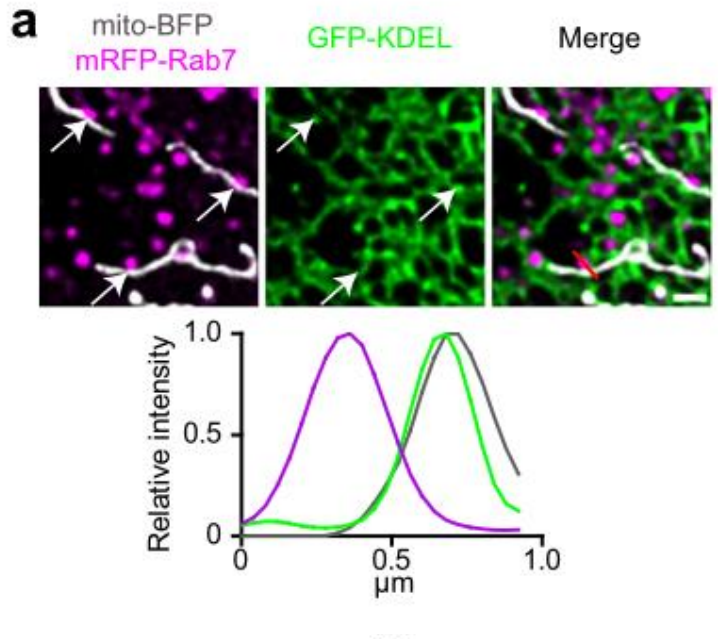
Recruitment at mitochondrial division site

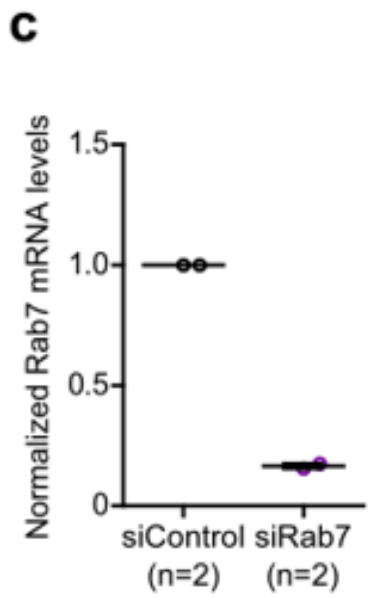
| Sequence | n = 27 events |
|---|---|
| Arf1 then lysosome | 11.1 % |
| Lysosome then Arf1 | 77.8 % |
| Same time | 11.1 % |

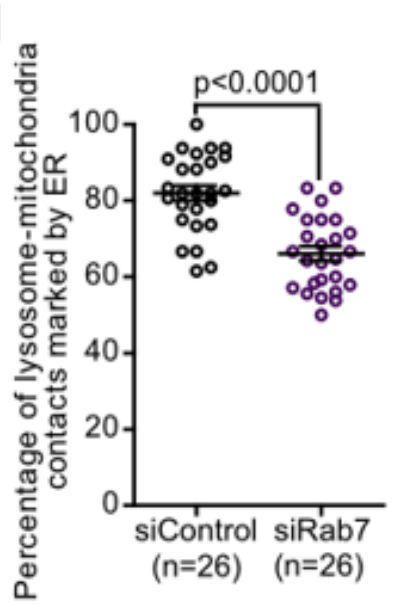
- 在Drp1募集后分裂过程的后期阶段，在线粒体分裂位点形成三向接触。

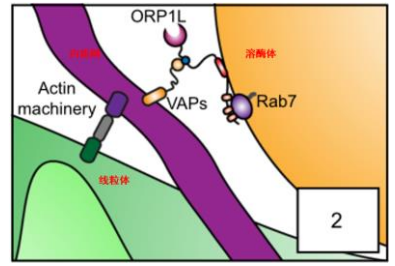
# Results

## 2. Rab7介导Ly、Mito和ER之间三向接触子集的形成。

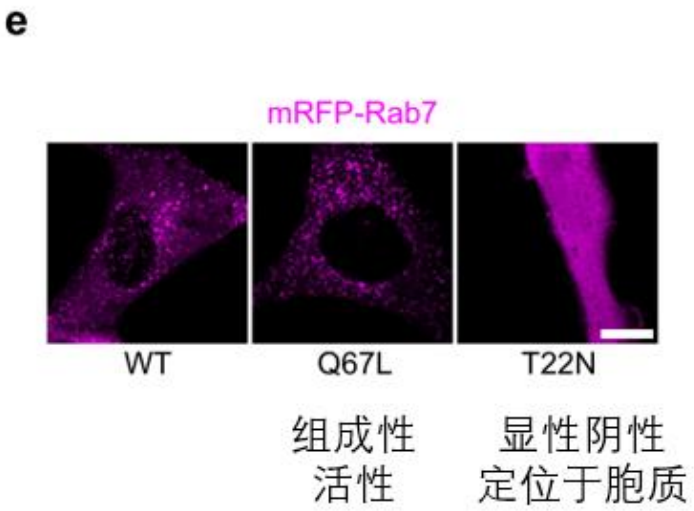


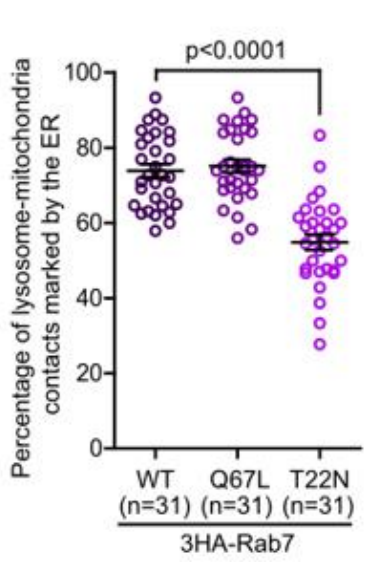



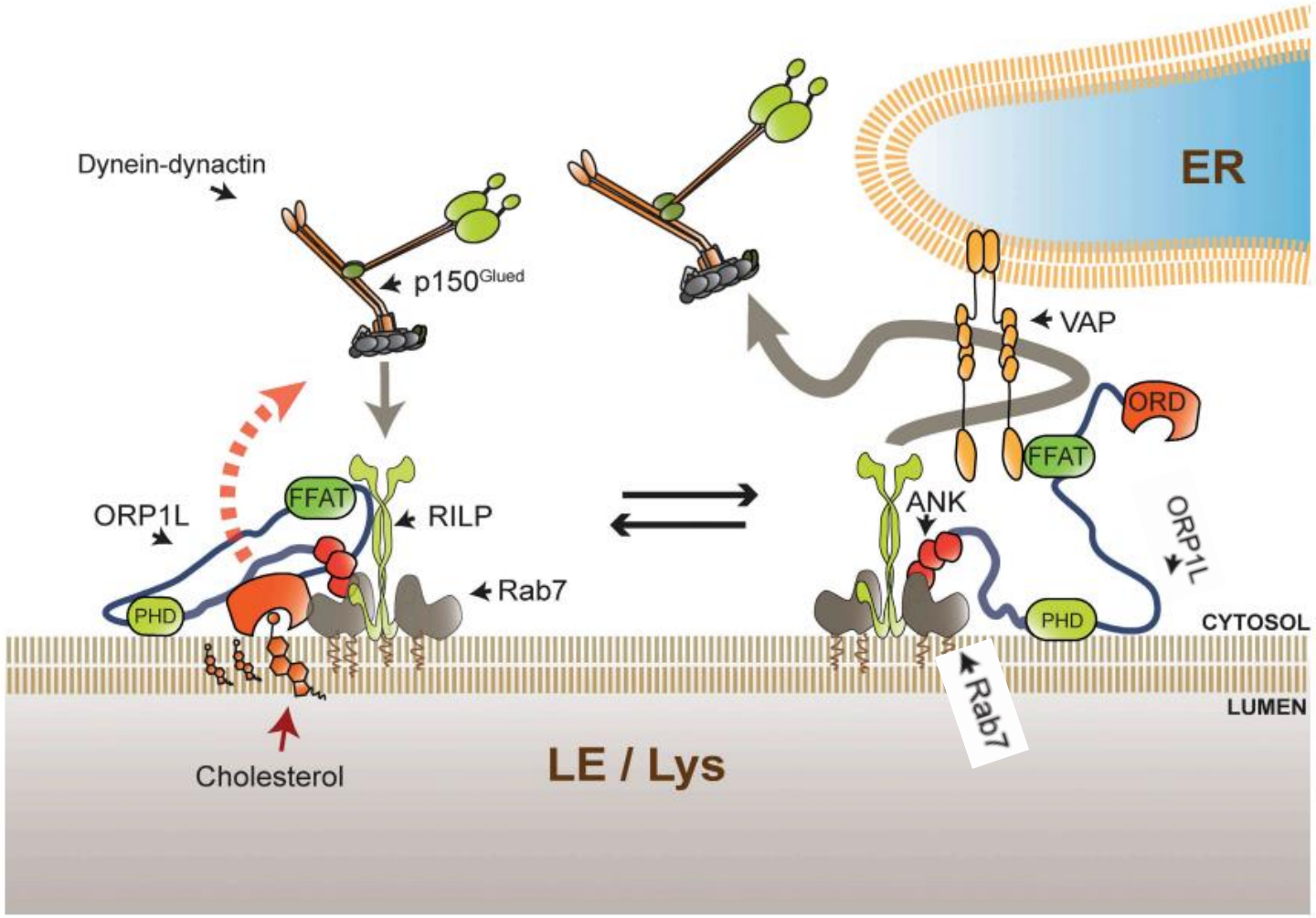

- Rab7是三种细胞器之间形成三向接触子集所需要的。




- 溶酶体定位的Rab7积极促进溶酶体、线粒体和内质网之间三向接触的形成。

# Results

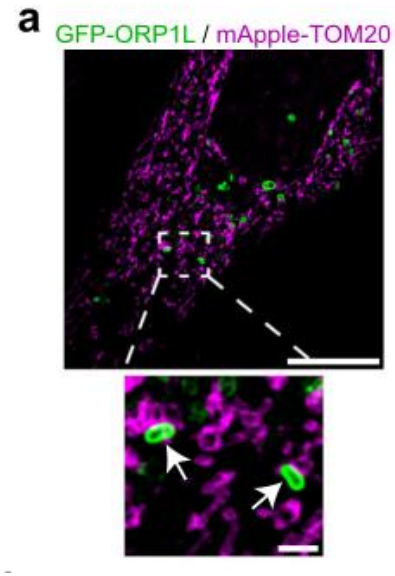


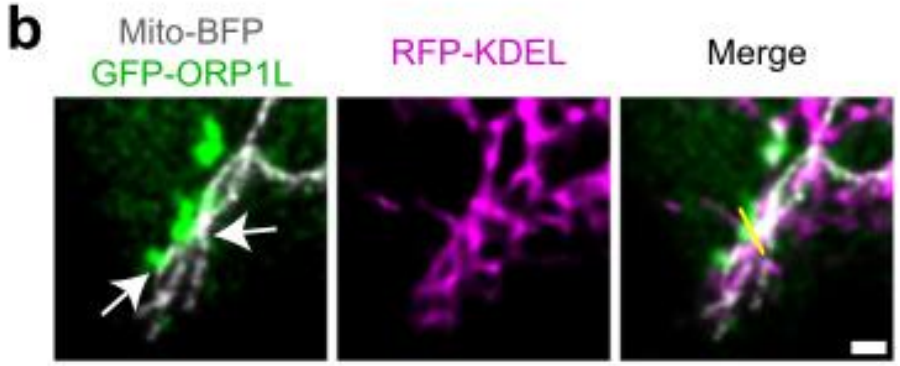

ORP1L通过与Rab7结合的锚蛋白重复结构域被招募到溶酶体中，它会与内质网驻留的VAPs蛋白相互作用，以帮助建立内质网溶酶体接触。

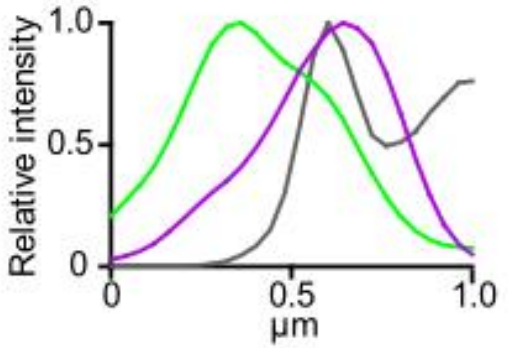
*J Cell Biol* (2009) 185 (7): 1209–1225.

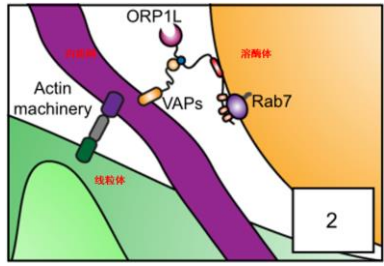
# Results

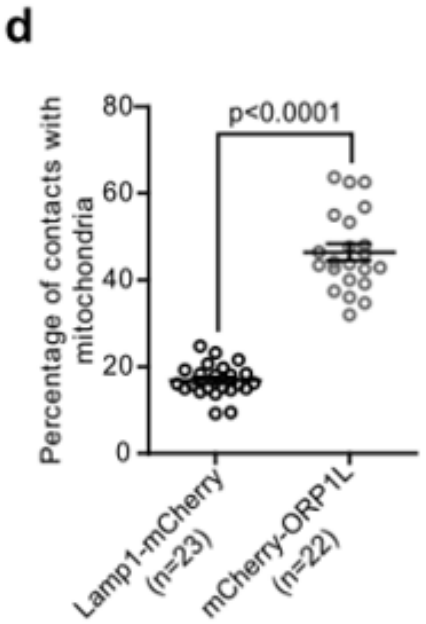
## 3. ORP1L介导Rab7依赖性ER-Ly-Mito接触。

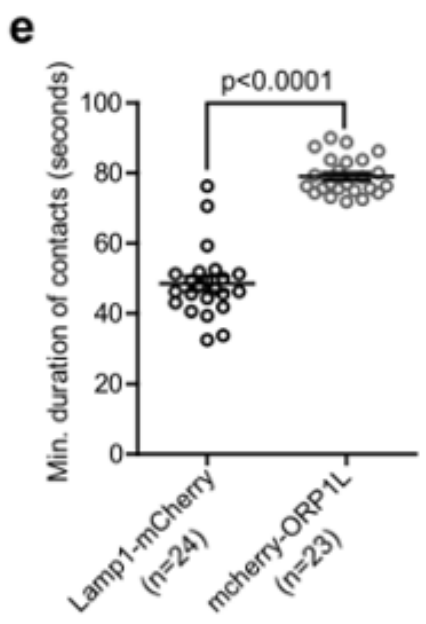


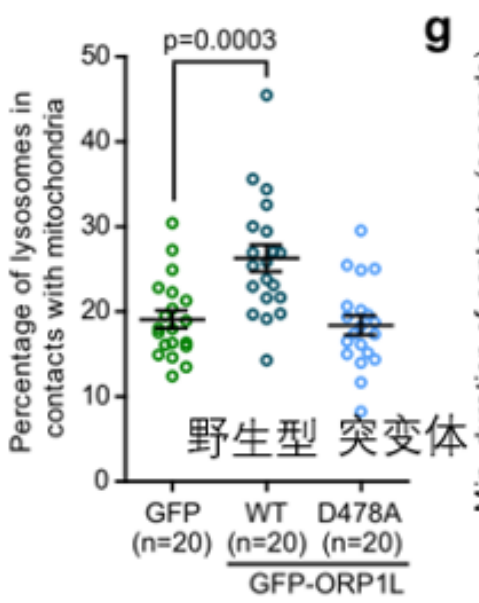



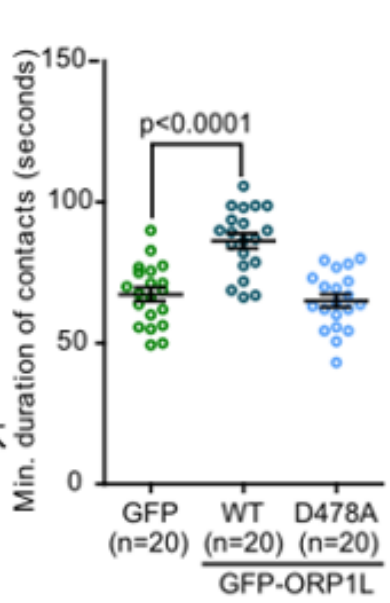



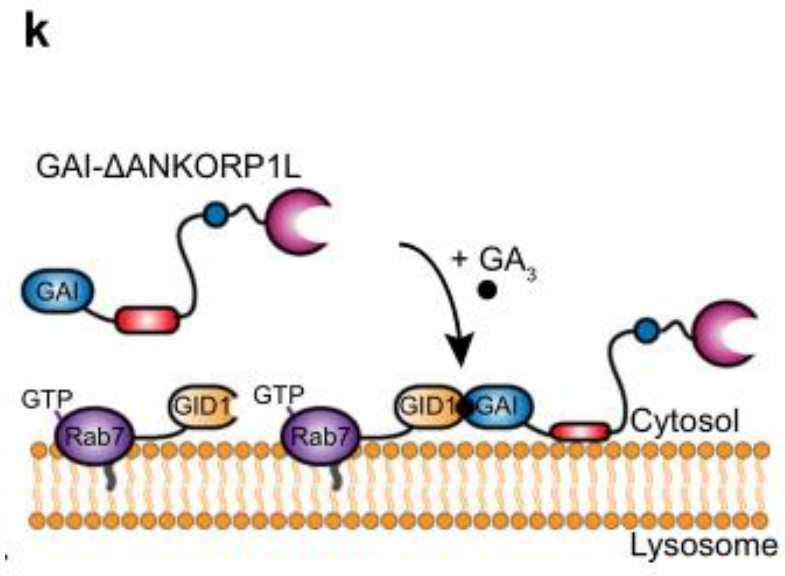



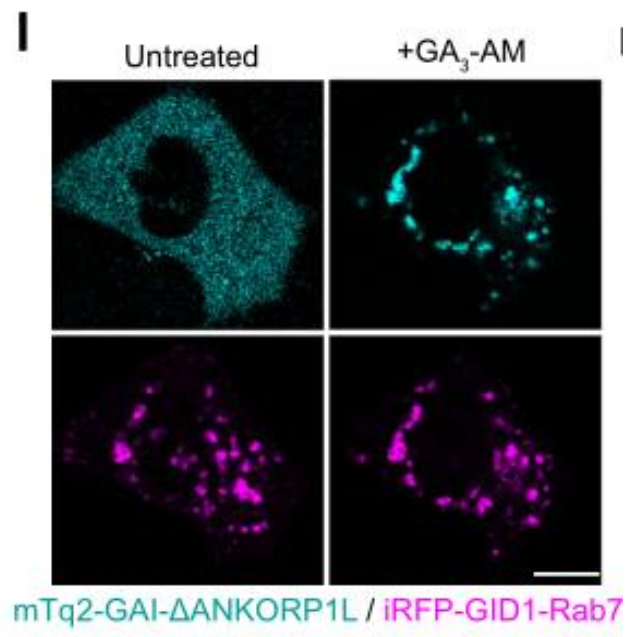



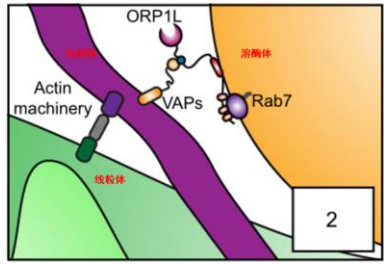

- ORP1L过表达可增加溶酶体与线粒体接触的频率和持续时间。
- ORP1L的过度表达以内质网依赖的方式介导溶酶体-线粒体接触。

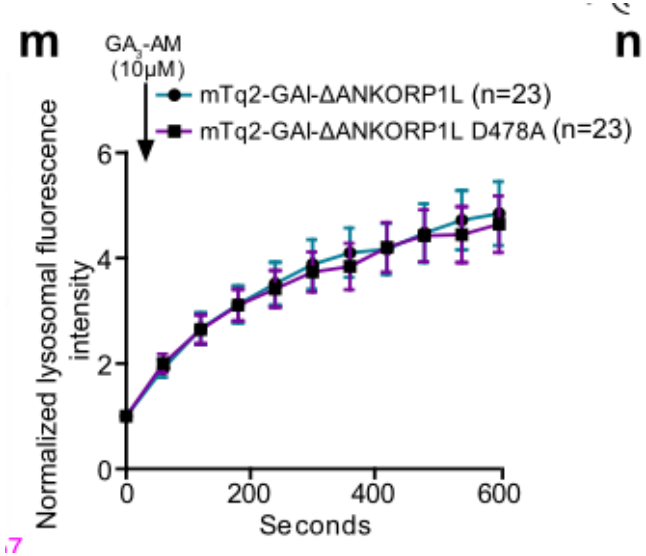
# Results

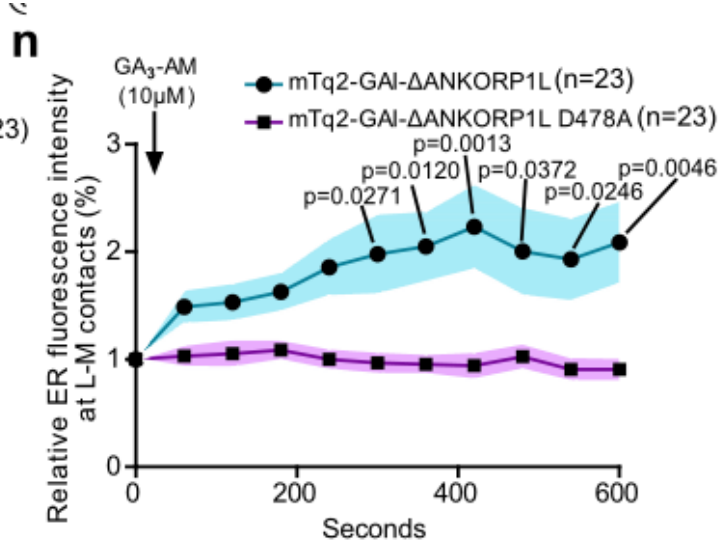
## 3. ORP1L介导Rab7依赖性ER-Ly-Mito接触。



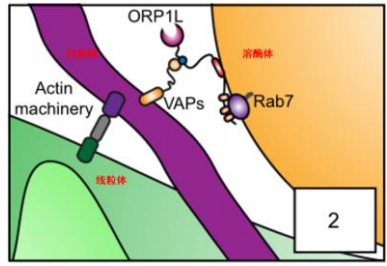



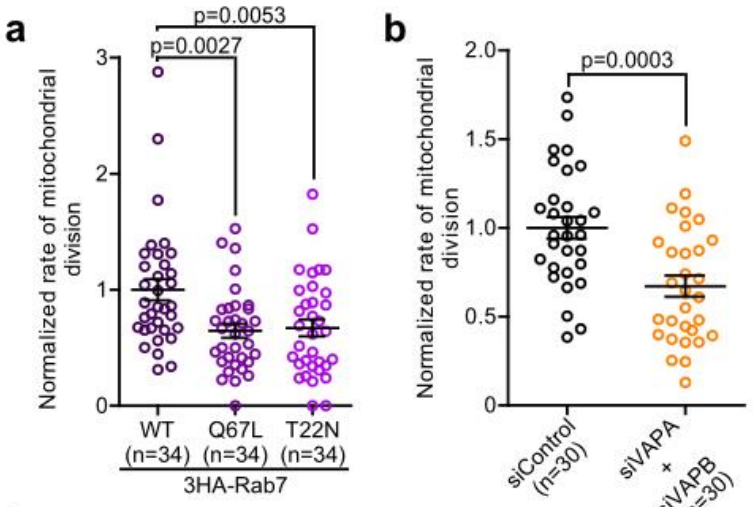



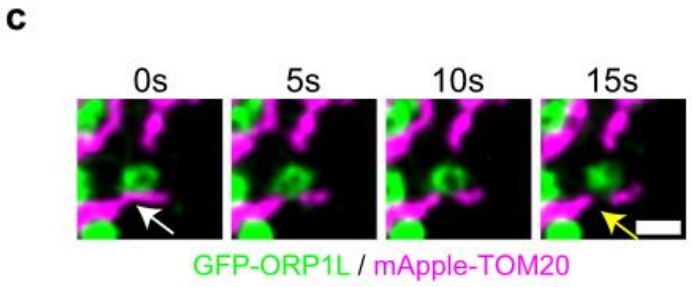

- Rab7-ORP1L-VAPs调节内质网、溶酶体和线粒体之间三向接触子集的形成。

# Results

## 4. Rab7-ORP1L-VAPs调节线粒体分裂。



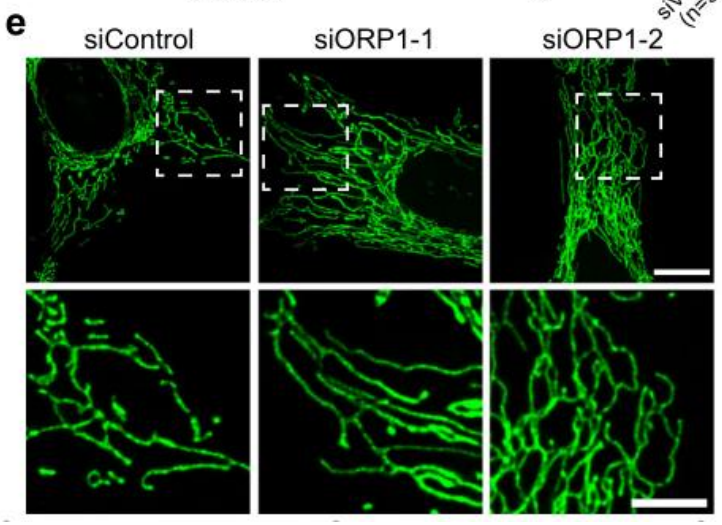



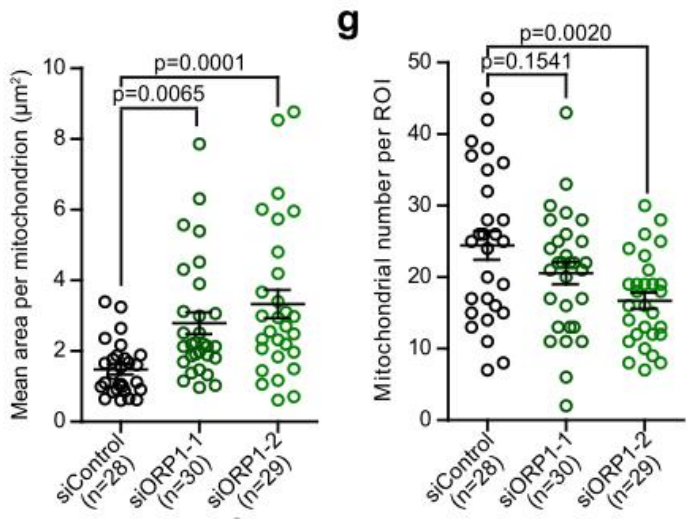



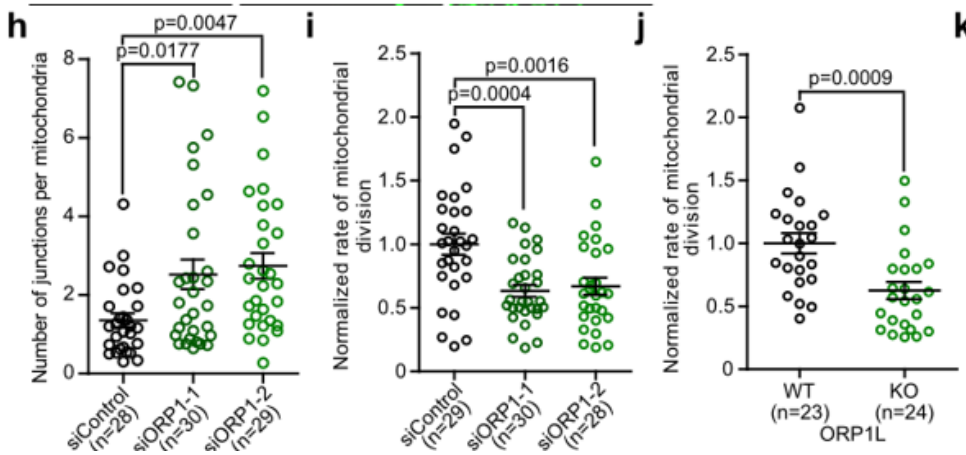

d

n=24 cells

| Mitochondrial division | n = 74 events |
|---|---|
| ORP1L at division | 58.1 % |



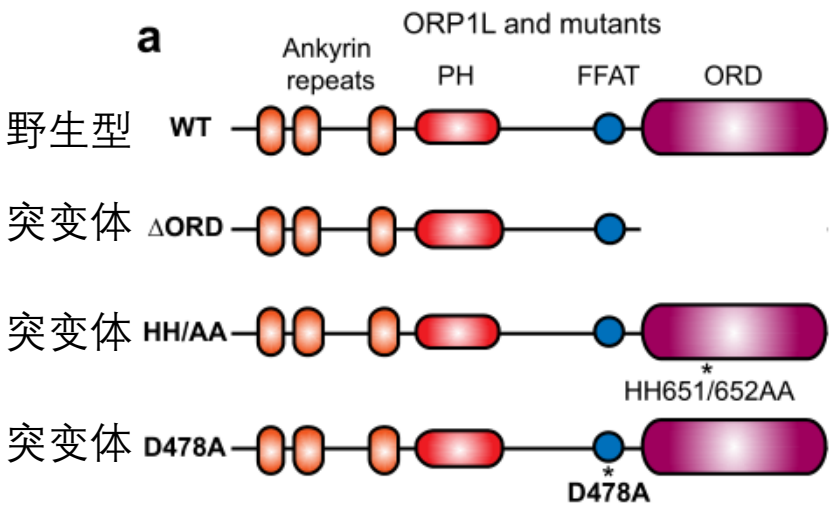




- Rab7和VAPs都是线粒体分裂所必需的。

- Rab7-ORP1L-VAPs相互作用是线粒体有效分裂所必需的。

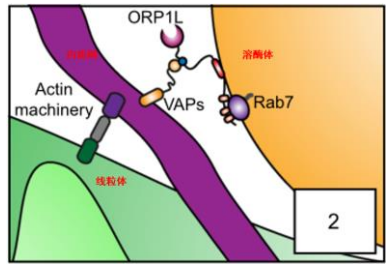
# Results

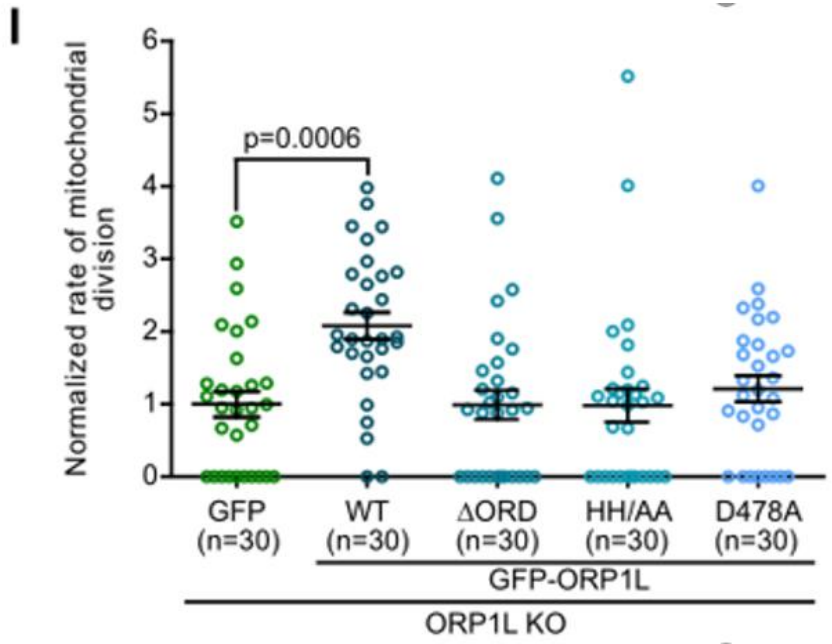
## 5. ORP1L脂质转运域是线粒体分裂所必需的。




k

| ORP1L mutants | Loss of function |
|---|---|
| ΔORD | Lipid transfer |
| HH/AA | PI(4)P extraction |
| D478A | VAPs binding |

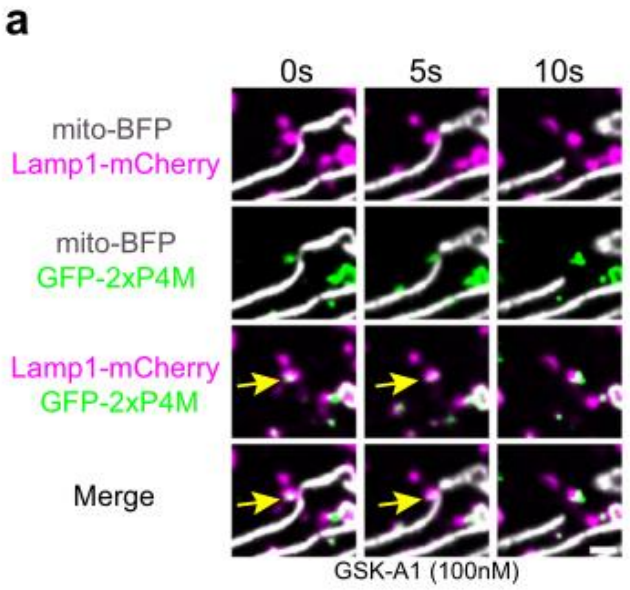


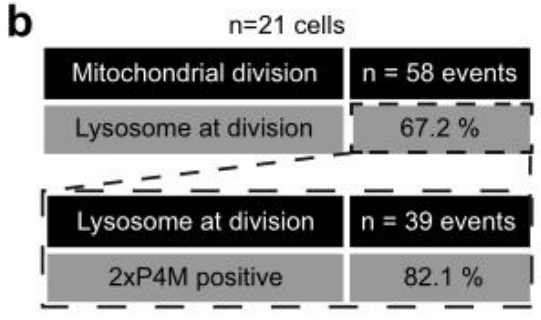



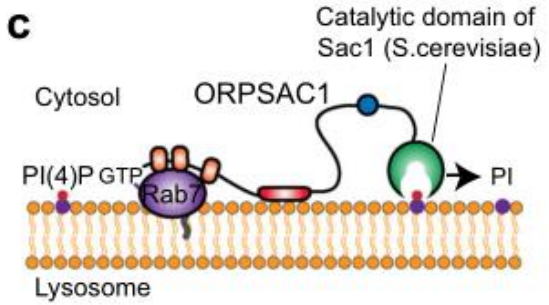

- ORP1L的脂质转移域是线粒体分裂所必需的。

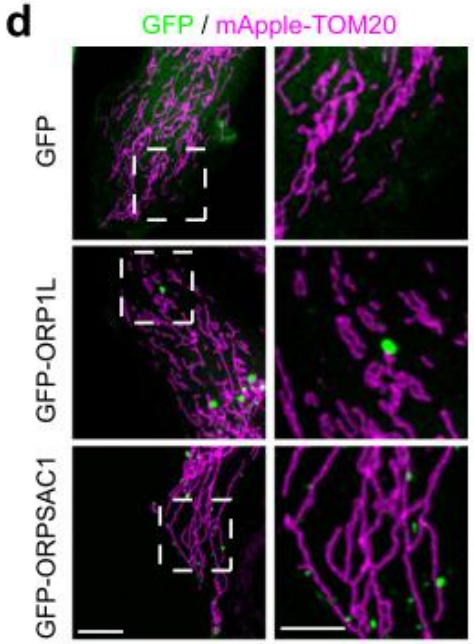
# Results

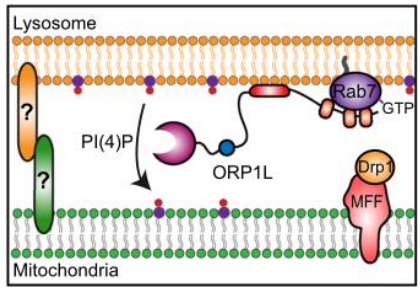
## 6. 线粒体分裂需要溶酶体PI(4)P。

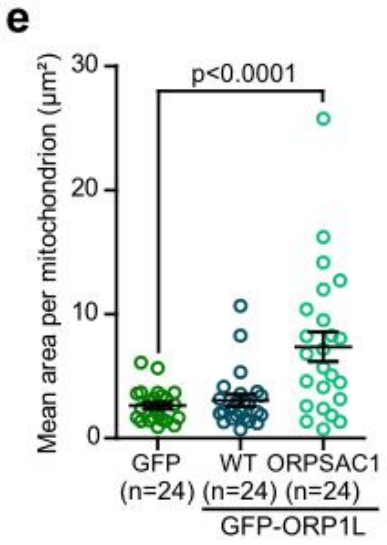


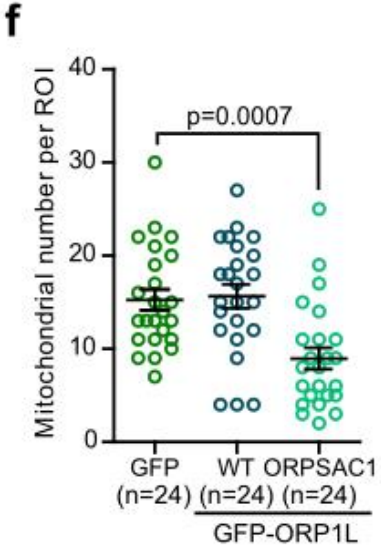



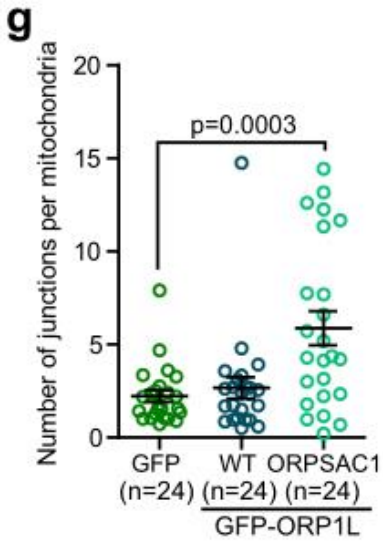



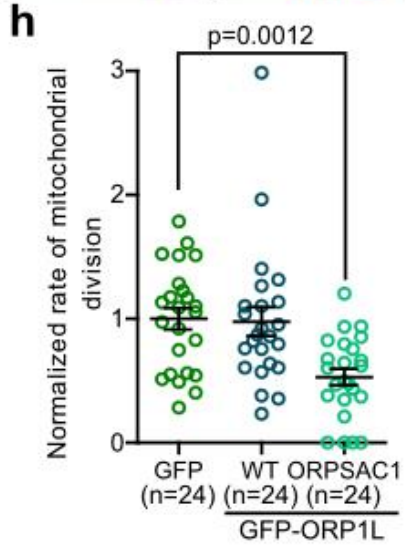



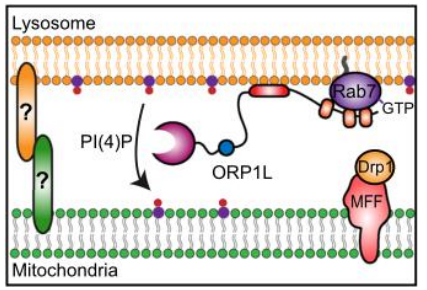



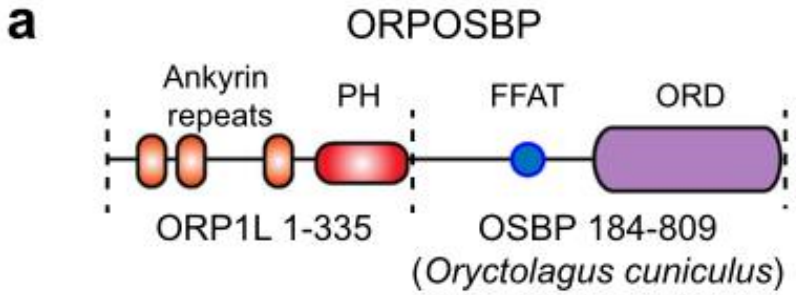



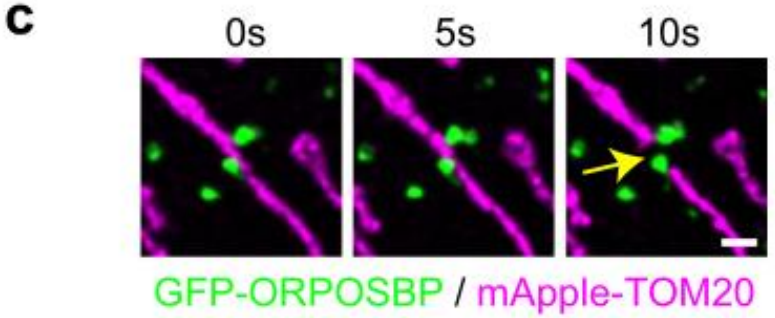

- 溶酶体膜上PI(4)P的特异性缺失会损害线粒体分裂。
- 溶酶体PI(4)P在线粒体分裂中起着关键作用，并提示ORP1L在这个过程中介导PI(4)P的转移。

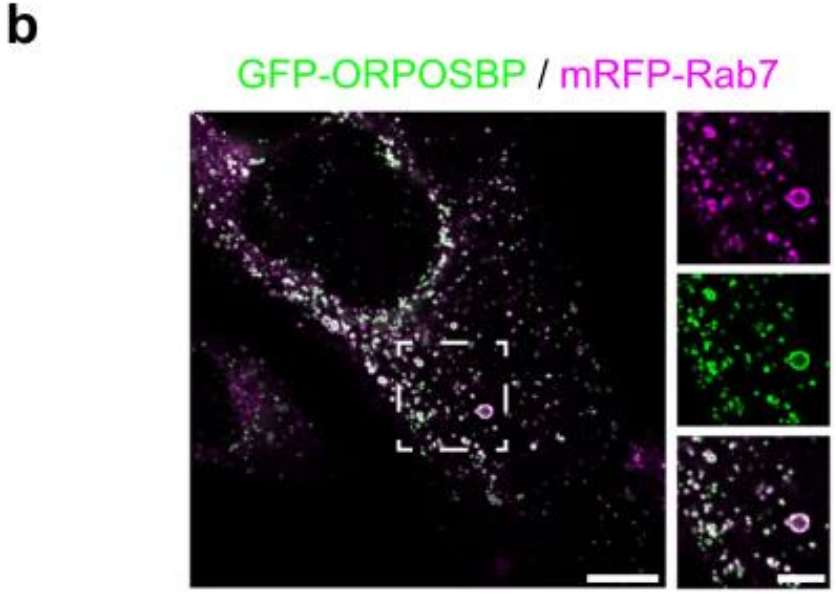
# Results

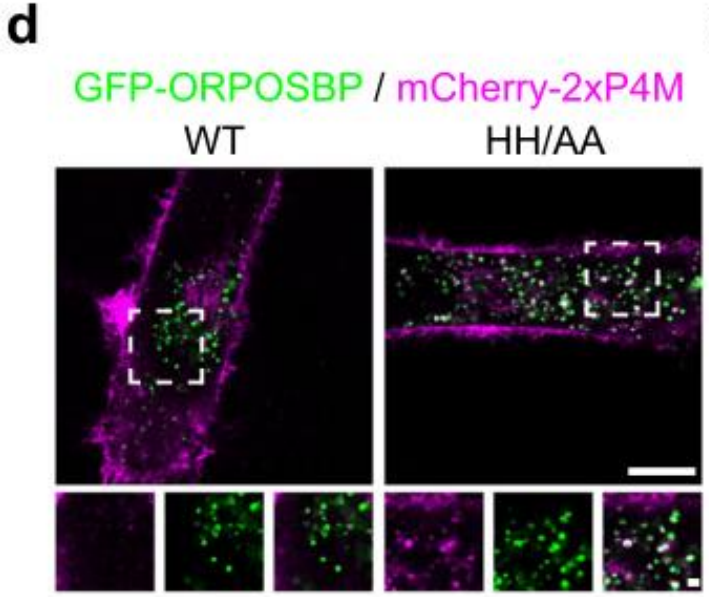
## 7. 从溶酶体恢复PI(4)P转移可挽救ORP1L缺失细胞的线粒体形态。

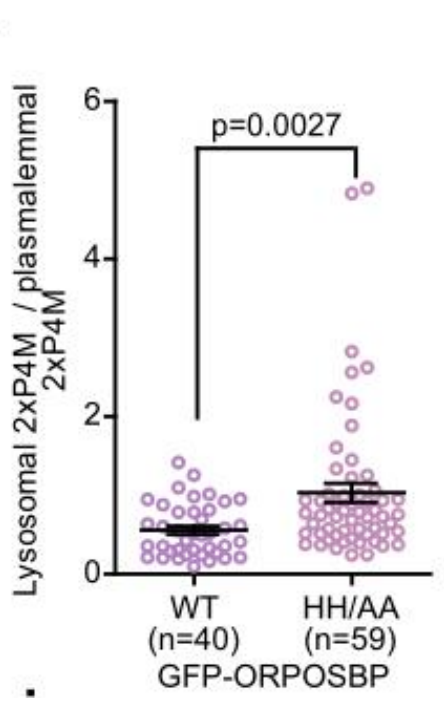


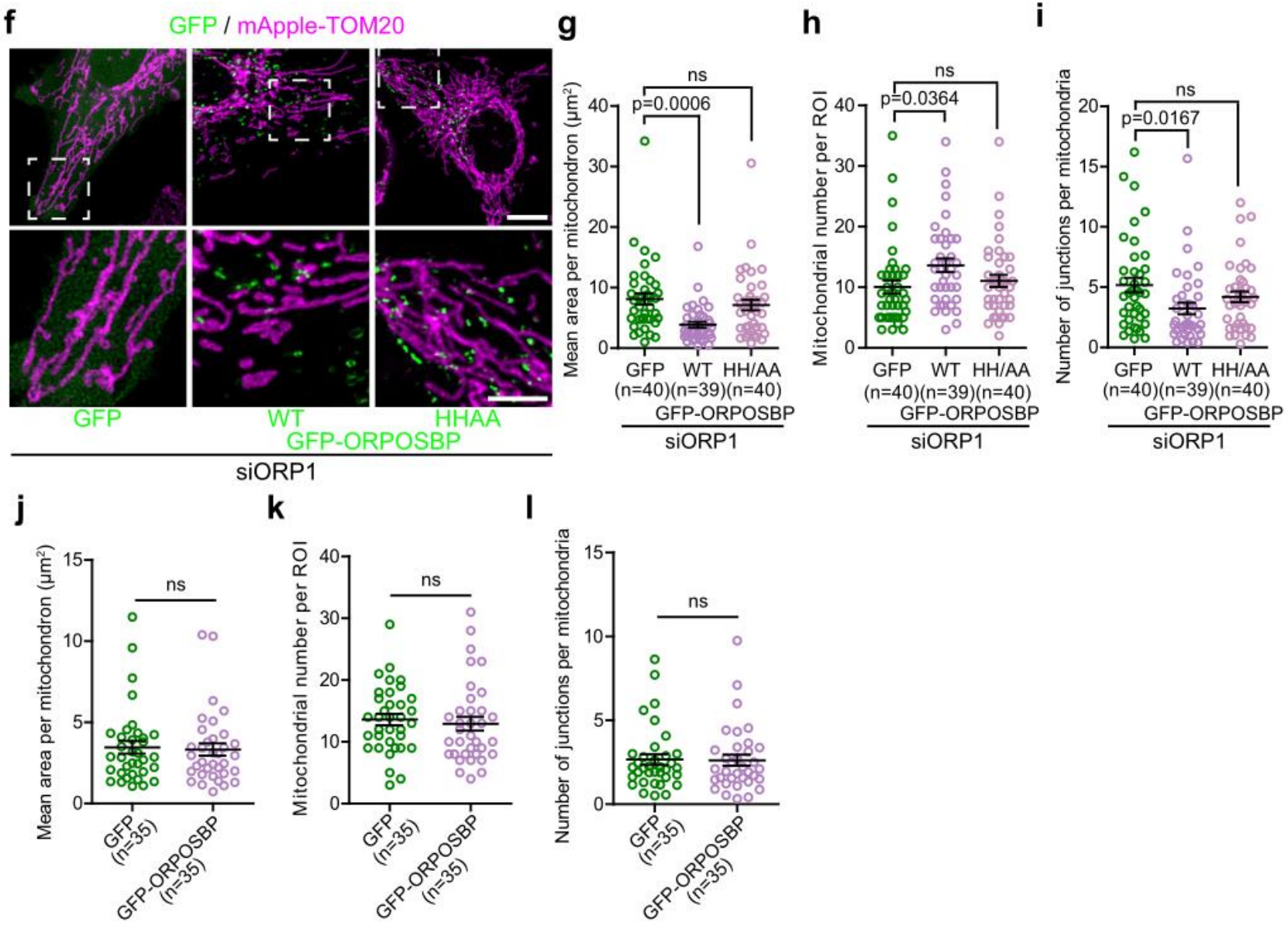



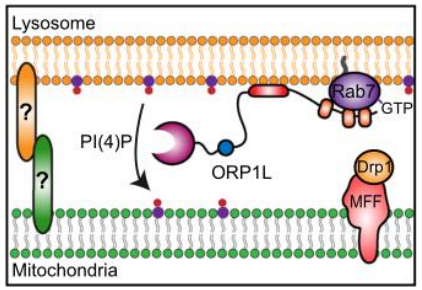



# Results

## 7. 从溶酶体恢复PI(4)P转移可挽救ORP1L缺失细胞的线粒体形态。

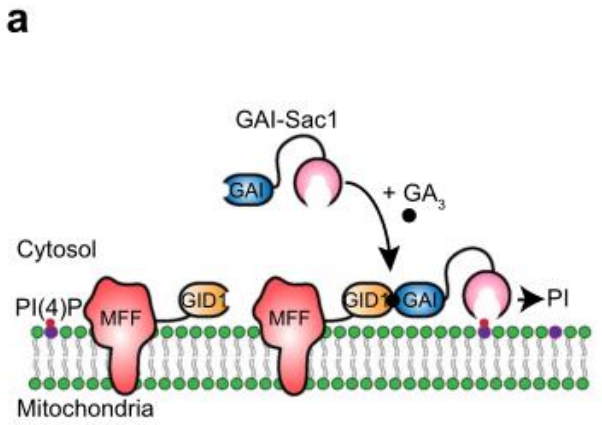


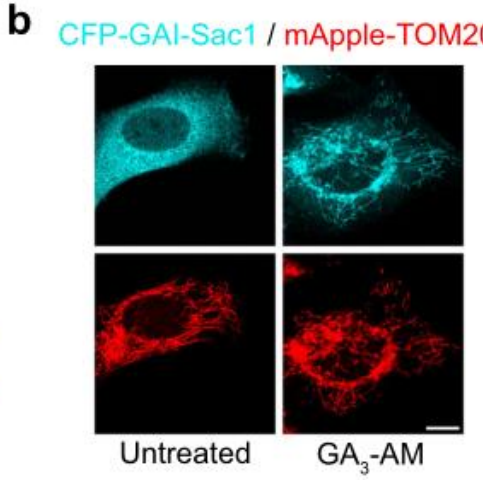



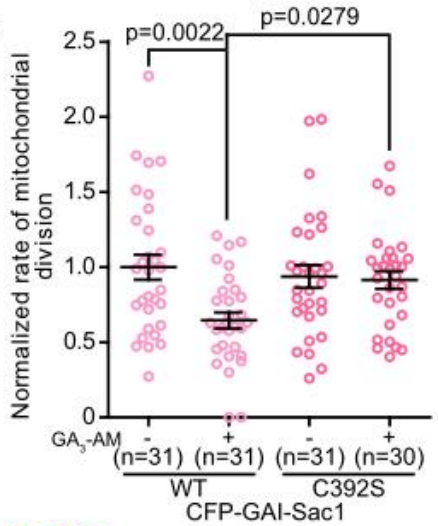

- ORP1L介导PI(4)P从溶酶体转移以促进线粒体分裂。

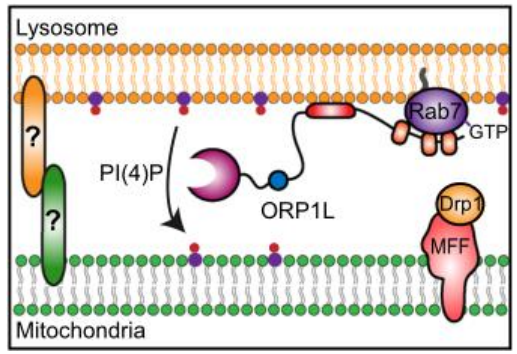
# Results

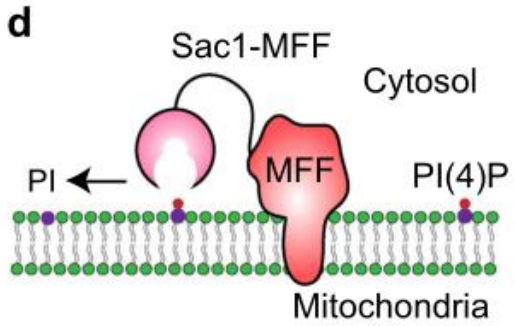
## 8. PI(4)P磷酸酶Sac1向线粒体的募集损害了它们的分裂。

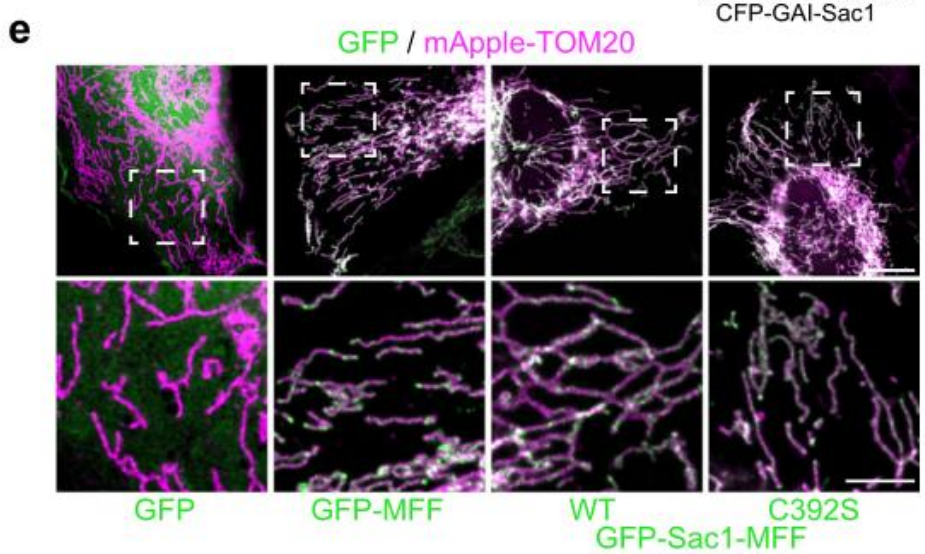


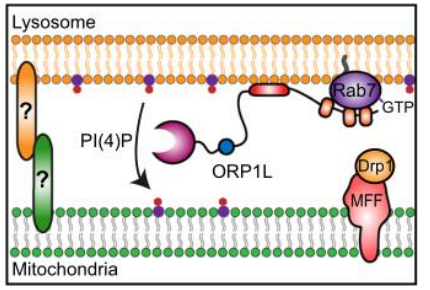



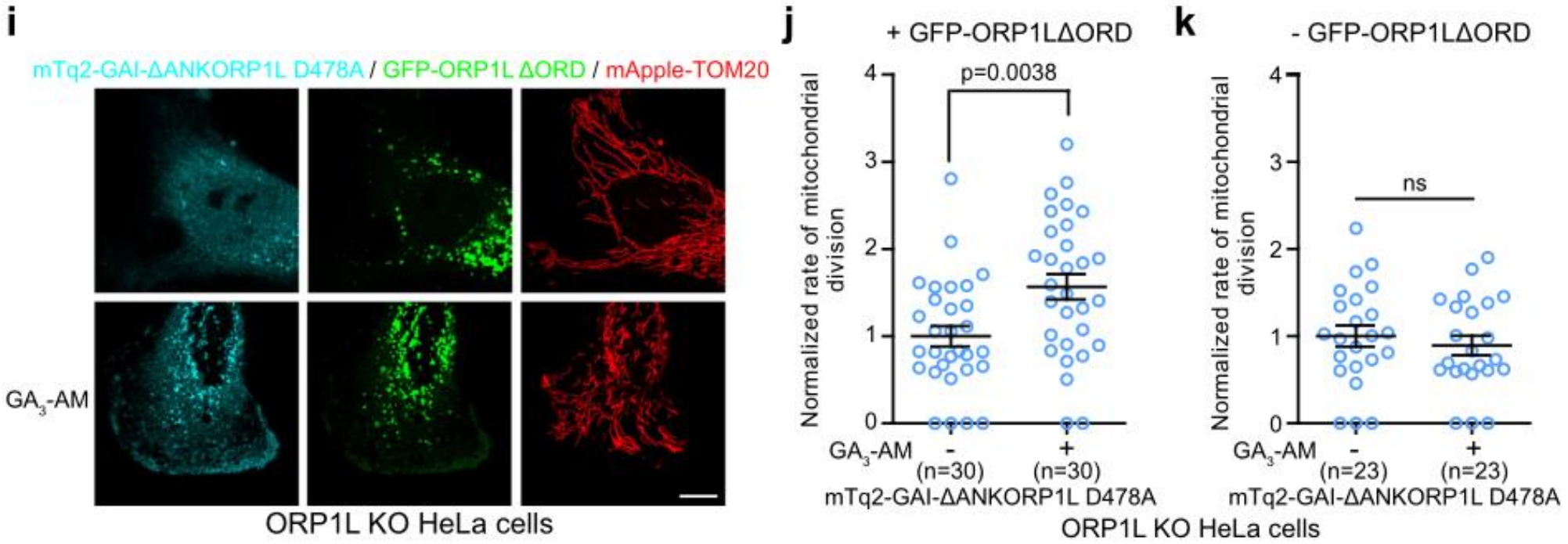




- 溶酶体PI(4)P的受体应该在线粒体上，PI(4)P在线粒体分裂位点是必需的，在分裂过程中起着关键作用。

# Results

## 9. VAPs非依赖性ORP1L脂质转运足以挽救ORP1L KO细胞的线粒体分裂。

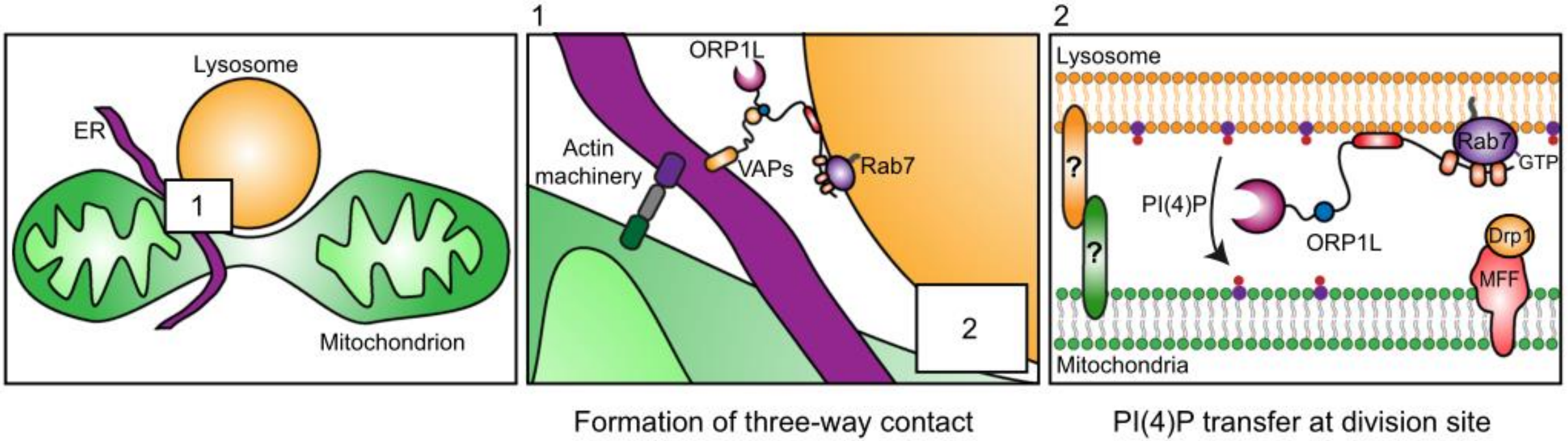



- ORP1L可以在不与VAPs结合的情况下转移脂质，从而进一步支持ORP1L在线粒体分裂期间作为PI(4)P转运蛋白在溶酶体-线粒体接触处的作用。

# Discussion

- 参与线粒体分裂的各种细胞器协同作用，并表明PI(4)P是分裂过程的关键参与者。




- ✓ ER-Ly-Mito三向接触
- ✓ ER将Ly募集到Mito裂变部位：Rab7-ORP1L-VAPs相互作用
- ✓ ORP1L介导PI(4)P信号：将PI(4)P从Ly转移到Mito分裂位点，完成膜断裂