

Dihydroceramide desaturase regulates the compartmentalization of Rac1 for neuronal oxidative stress



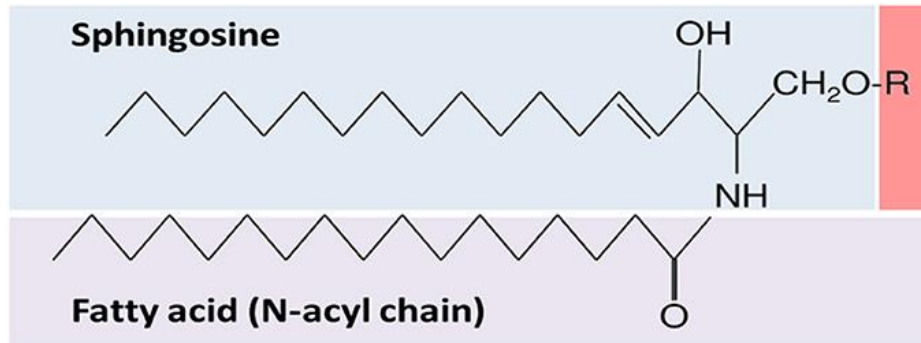
Fei-Yang Tzou (鄒飛洋), Tsu-Yi Su, Wan-Syuan Lin, Han-Chun Kuo, Yu-Lian Yu, Yu-Han Yeh,
Chung-Chih Liu, Ching-Hua Kuo, Shu-Yi Huang, and **Chih-Chiang Chan (詹智強)***

Cell Reports, Volume 35, Issue 2, 108972

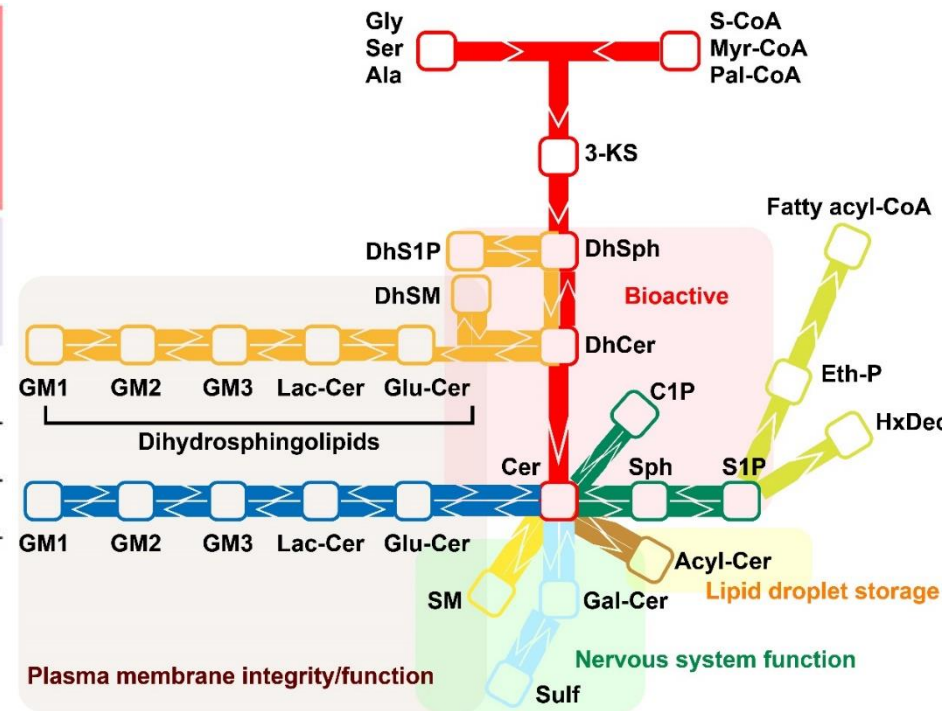
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2022/11/12

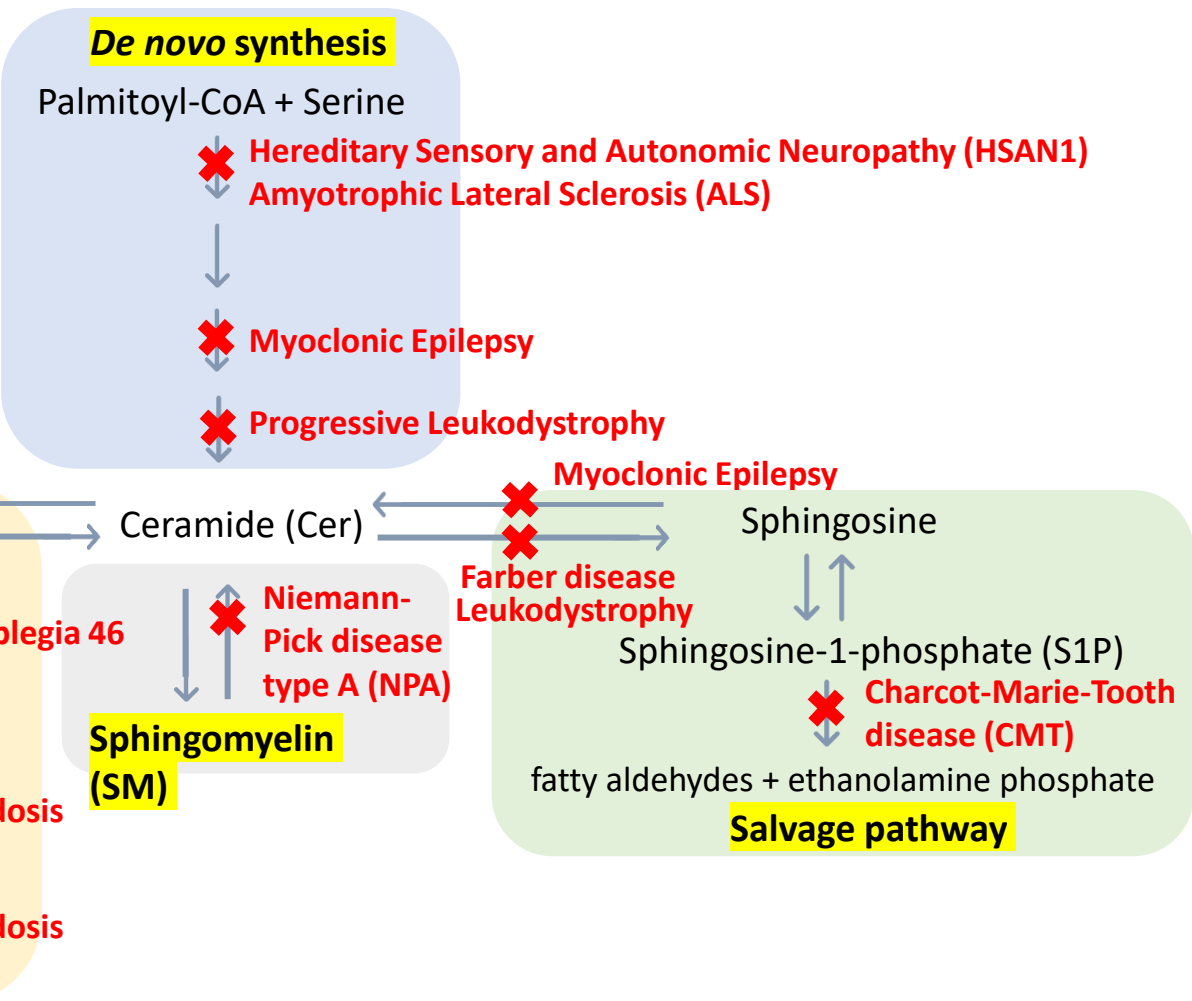
Sphingolipids have complex structures and diverse functions



Substituent (R)	Sphingolipid
H	Ceramides
Phosphocholine	Sphingomyelins
Sugar (s)	Glycosphingolipids
- Single sugar (glucose or galactose)	- Cerebrosides
- Lactose (disaccharide)	- Lactosylceramides
- Oligosaccharide	- Gangliosides
- Sugar + sulfate	- Sulfatides



SLs enzymes variants associate with neurological diseases



Dihydroceramide desaturase deficiency leads to systemic neuropathy and hypomyelinating leukodystrophy

JCI The Journal of Clinical Investigation

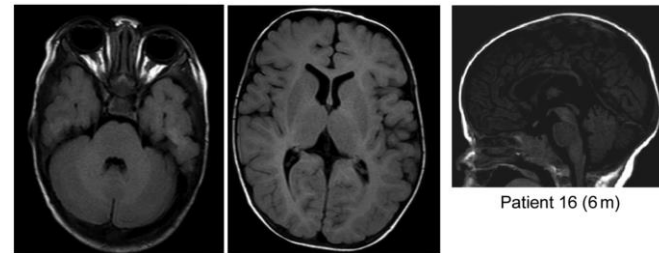
DEGS1-associated aberrant sphingolipid metabolism impairs nervous system function in humans



(Karsai *et al.*, *J Clin Invest.*, 2019)

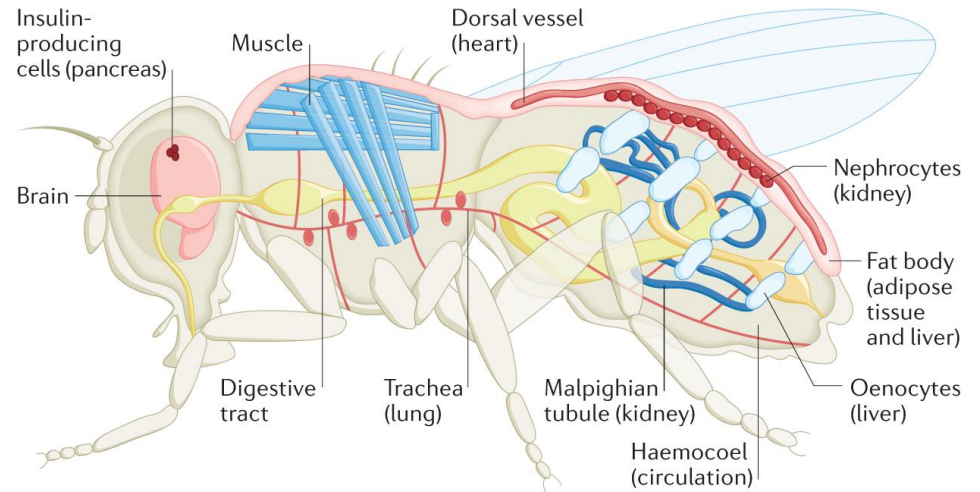
JCI The Journal of Clinical Investigation

Loss of the sphingolipid desaturase DEGS1 causes hypomyelinating leukodystrophy



(Pant *et al.*, *J Clin Invest.*, 2019)

Let's Fly!



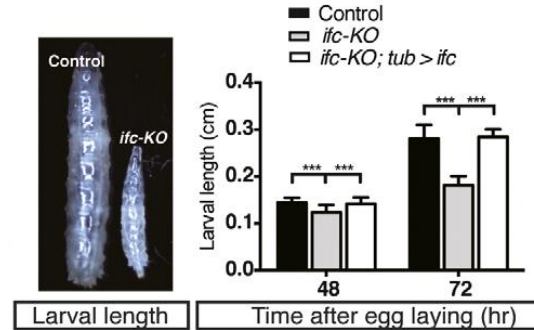
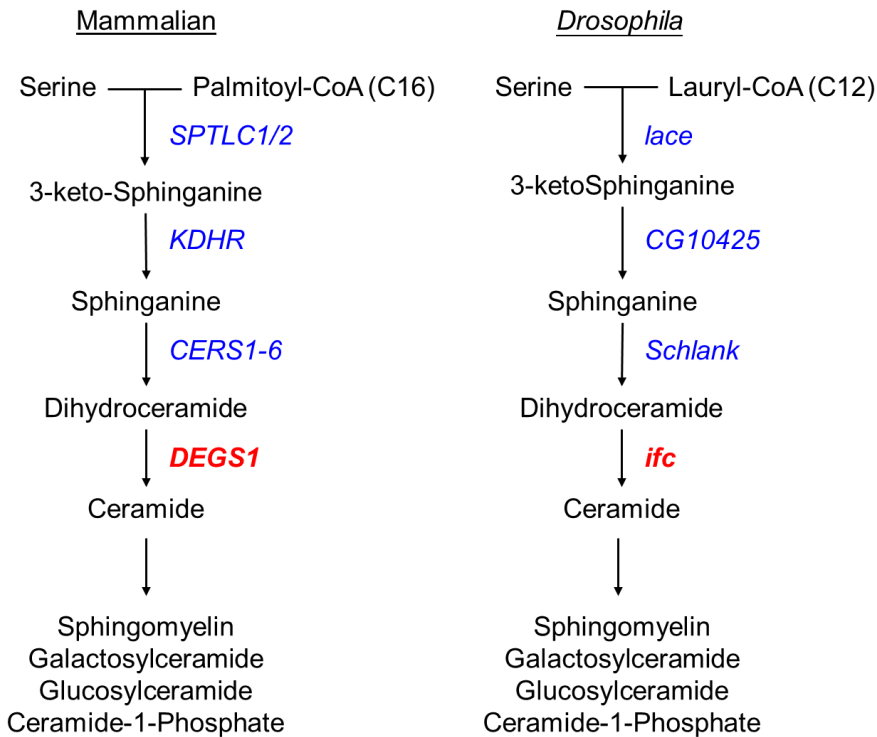
- ✓ Physiological functions are conserved
- ✓ Gene functions are conserved
- ✓ Shorter lifespan, large number of embryos
- ✓ Low cost and less ethical concerns
- ✓ **High genetic tractability**
(mutant alleles, RNAi, (human) cDNA...)



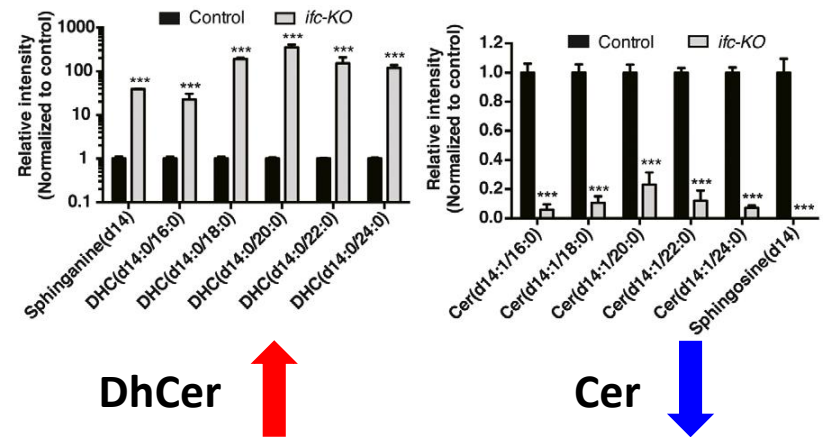
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Dihydroceramide desaturase is responsible for the insertion of C4-5 double bond of ceramides

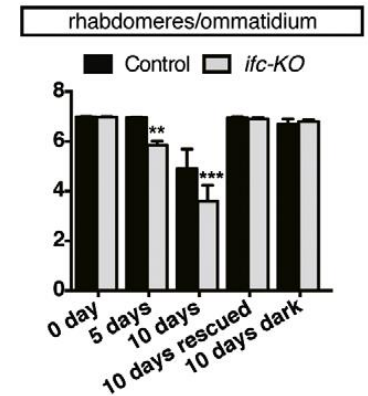
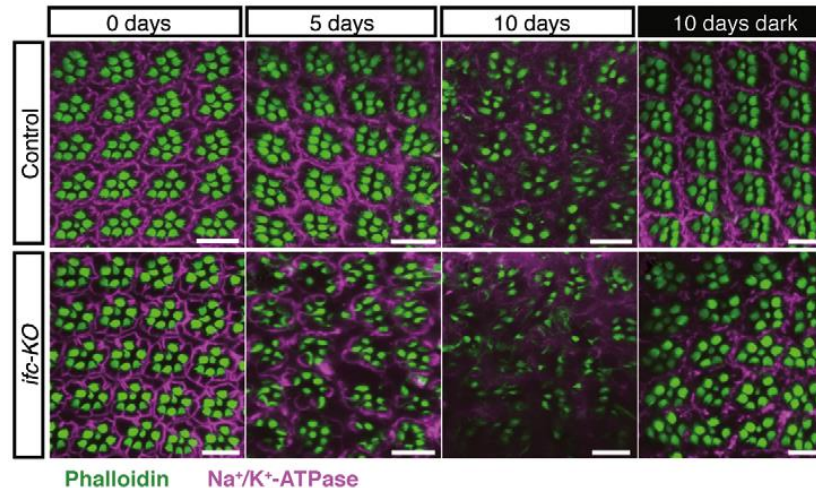
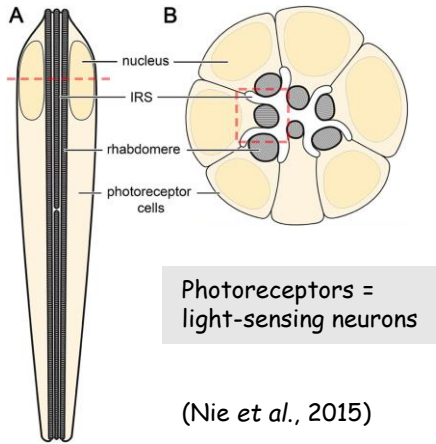


Lethality rescue	<i>tub-Gal4</i>
UAS- <i>ifc</i>	+++
UAS- <i>ifc</i> -mCherry	+++
UAS- <i>DEGS1</i>	++

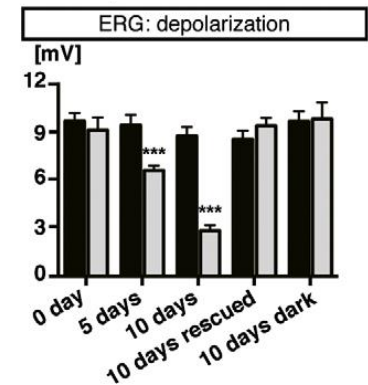
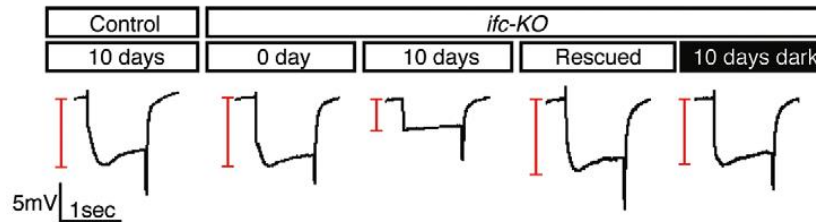
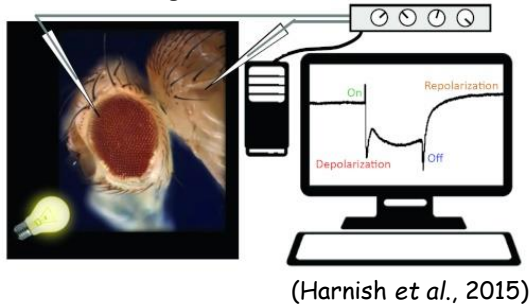


(Jung and Liu *et al.*, *EMBO Rep.*, 2017)

Activity-dependent degeneration of *ifc*-KO eyes in morphology and function



Electroretinograms (ERG)



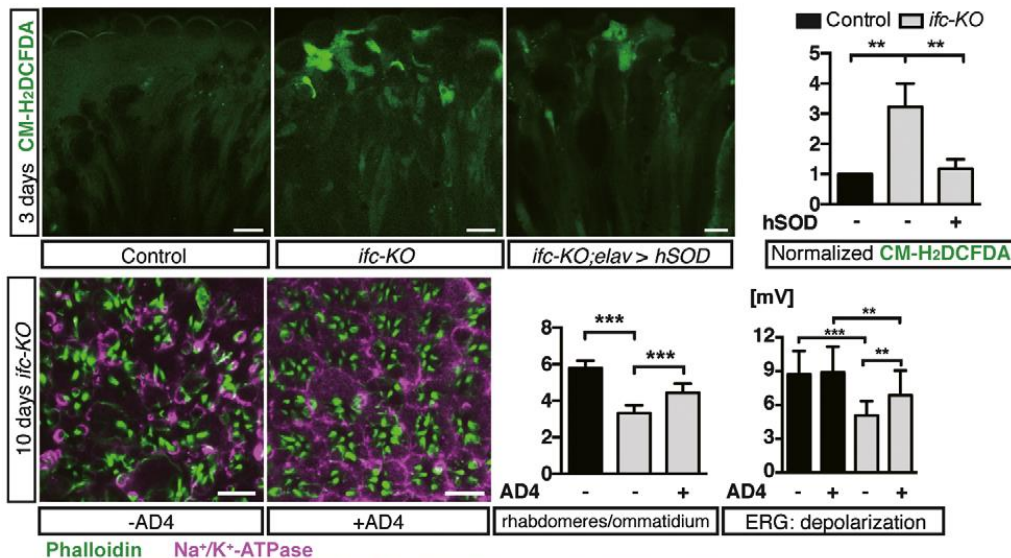
(Jung and Liu et al., *EMBO Rep.*, 2017)

Oxidative stress is a hallmark of *ifc*-KO and patient fibroblast with *DEGS1* variants, but the mechanism remained unknown

fly photoreceptors

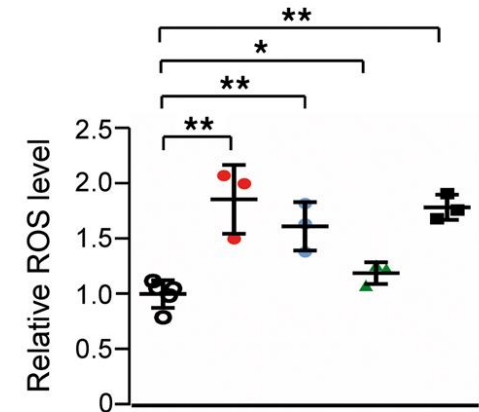
Patient Fibroblasts

H2DCF: reactive oxygen species (ROS) probe



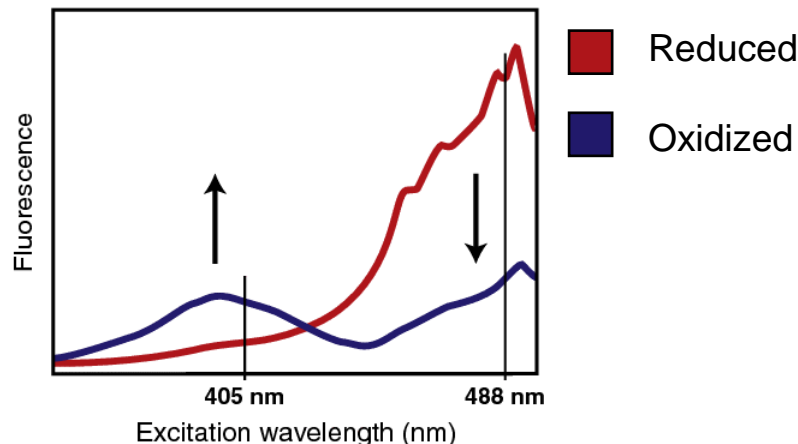
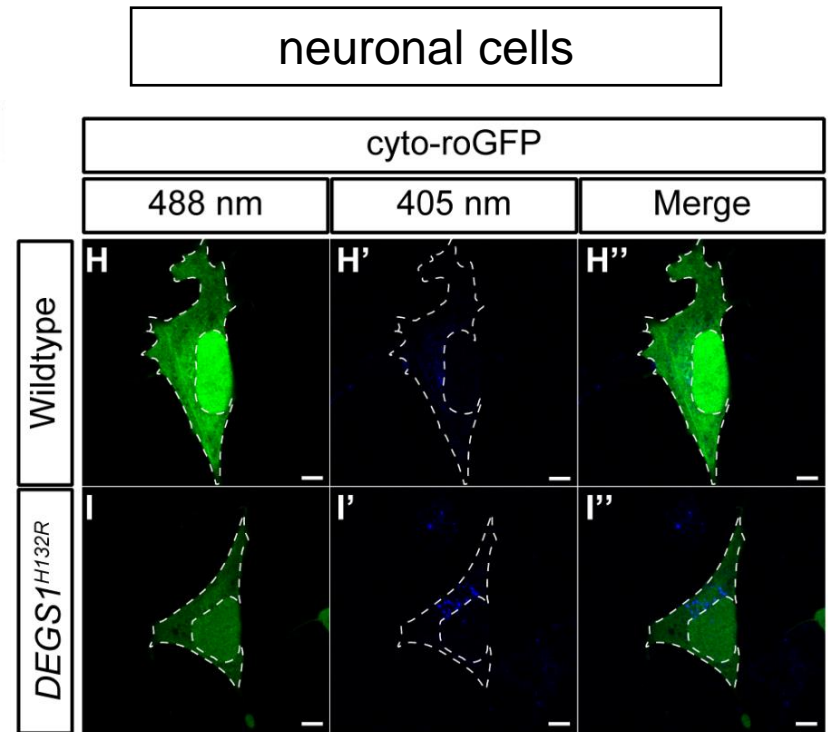
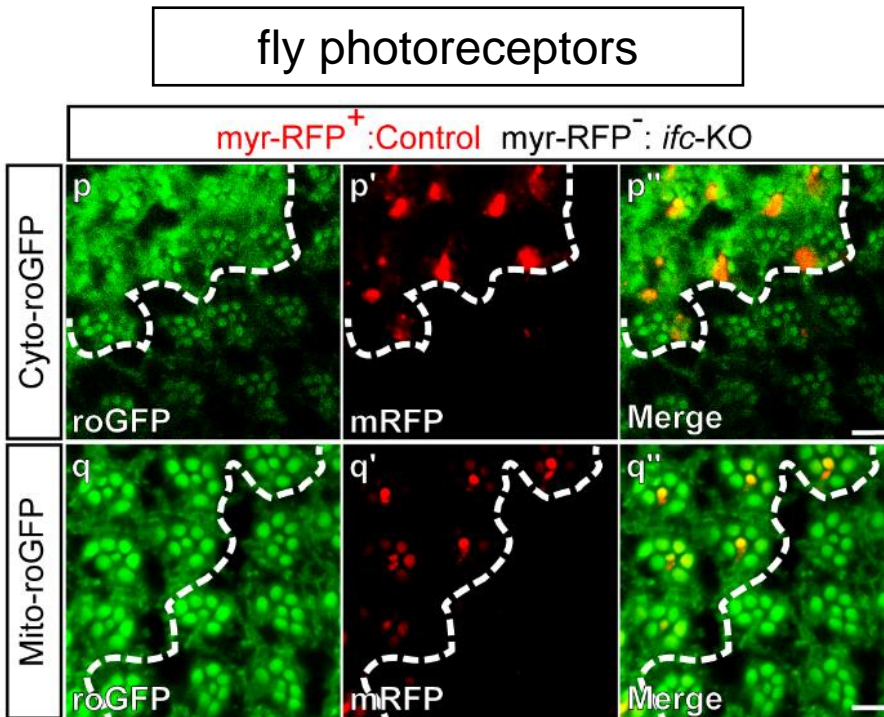
(Jung and Liu *et al.*, *EMBO Rep.*, 2017)

- Control fibroblasts
- P4 (p.Leu114Profs*11/p.Asn255Ser)
- P7 (n.Asn255Ser)
- ▲ P9 (p.Asn113Asp)
- Antimycin



(Pant *et al.*, *J Clin Invest.*, 2019)

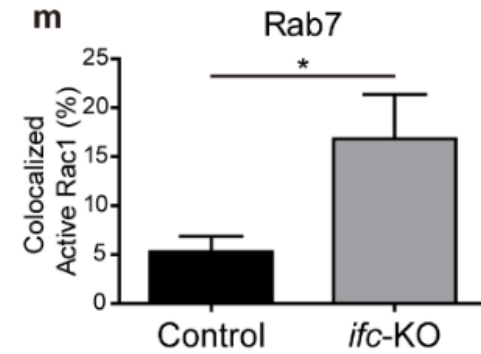
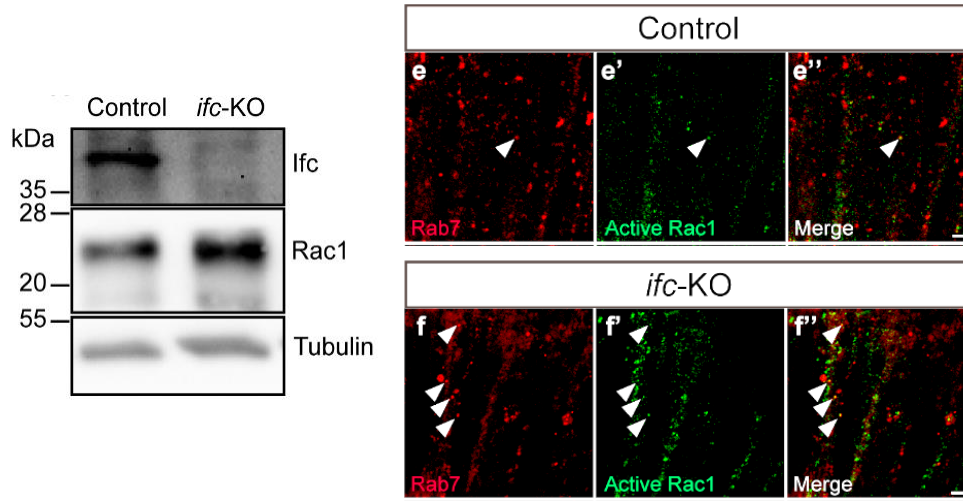
Loss-of-*ifc* induced cytosolic oxidative stress



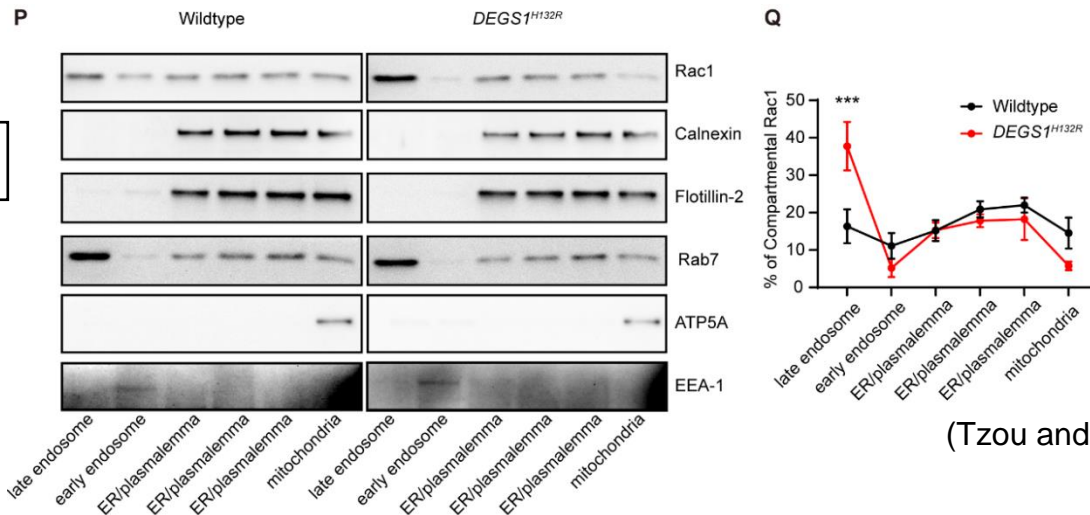
(Tzou and Su *et al.*, *Cell Rep.*, 2021)

Loss-of-*ifc* led to increased level of Rac1 in the endolysosomal compartments

fly photoreceptors



neuronal cells



(Tzou and Su *et al.*, *Cell Rep.*, 2021)

Dihydroceramide regulates the binding of active-Rac1 to membrane of distinct subcellular compartments

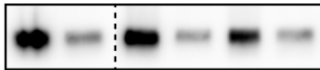
Reconstitute Organelles

neuronal cells

Membrane raft

DhCer ↑ GTP-Rac ↓

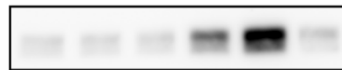
Cer	-	+	-
dhCer	-	-	+
Rac1	GTP	GDP	GTP



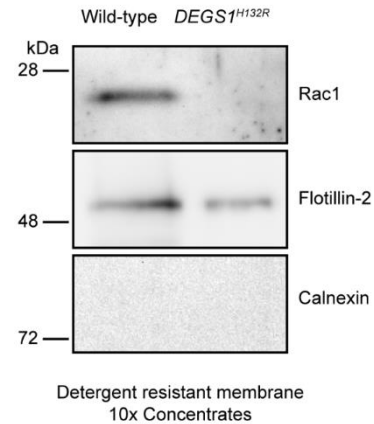
Autophagosomes

DhCer ↑ GTP-Rac ↑

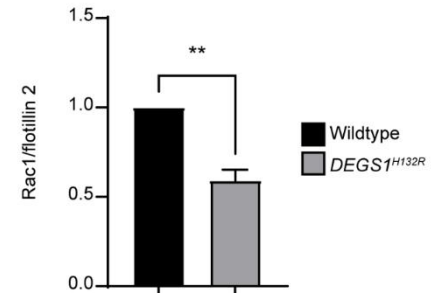
Cer	-	+	-
dhCer	-	-	+
Rac1	GTP	GDP	GTP



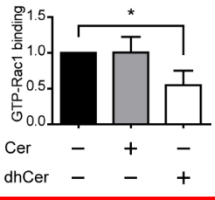
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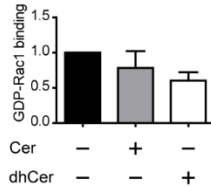
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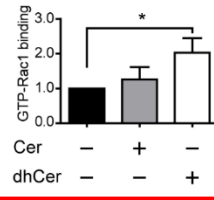
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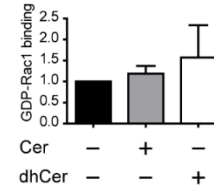
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E



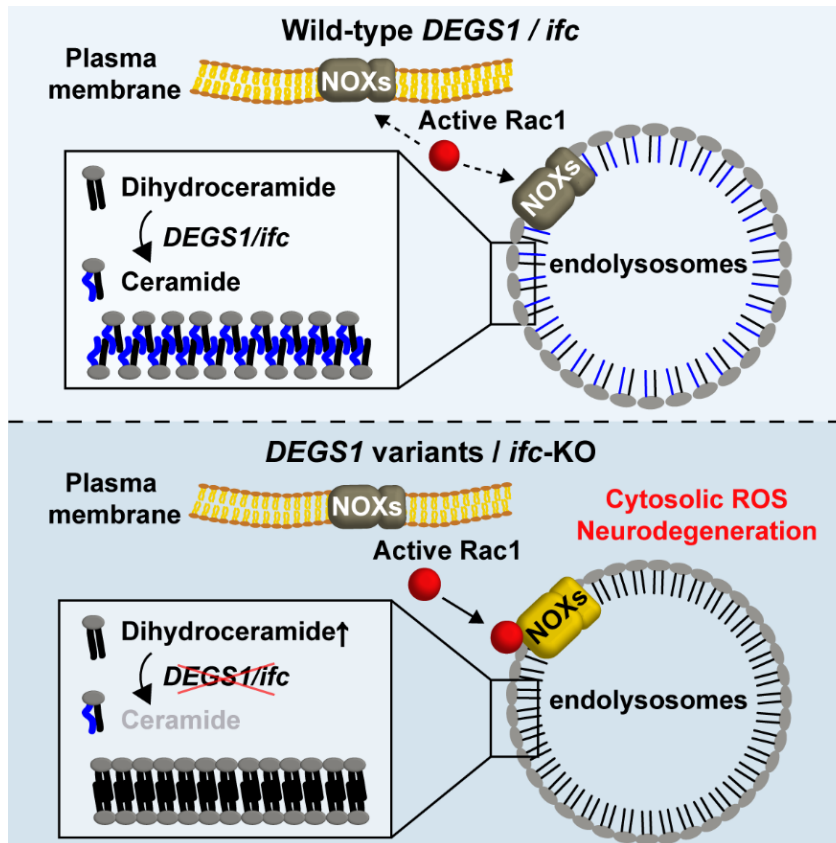
F



GTP-Rac1: active form of Rac1
GDP-Rac1: inactive form of Rac1

(Tzou and Su *et al.*, *Cell Rep.*, 2021)

Summary



- Lack of dihydroceramide desaturase activity induces **cytoplasmic ROS**
- **Rac1-NADPH** oxidase-elicited ROS mediates leukodystrophy-related neuronal death
- *DEGS1/ifc* defects cause mislocalization of Rac1 to the **endolysosomes**
- Dihydroceramide alters **binding affinity** of active Rac1 to reconstituted organelle membranes

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科技龍

