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Regulation of iron metabolism by sideroflexin 1

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Introduction

SIDEROFLEXINS

- SFXNs are conserved in eukaryote
- Mammalian SFXNs → 5 members (SFXN1-5)
- Mitochondrial carriers (SLC56)
- SFXN1 main function = serine transporter
- SFXN1 potentially involved in iron homeostasis → controversial

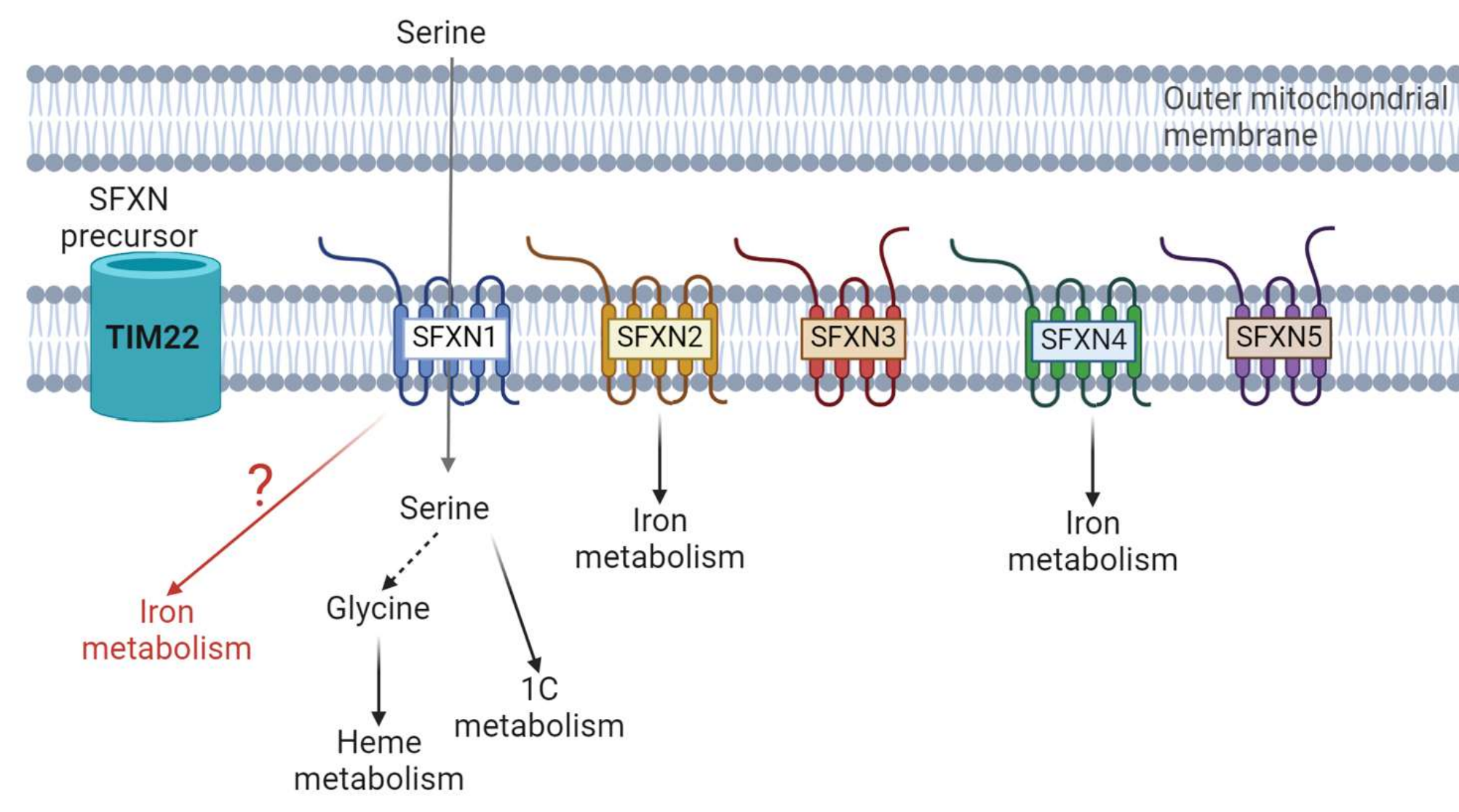


Fig 1. Functions of the mammalian sideroflexins (SFXN). Created with BioRender

FERROPTOSIS & signaling pathway

- Cell death driven by iron-dependent lipid peroxidation
- Ferroptosis is activated physiologically and pathologically
- Deregulation of iron homeostasis, ROS & glutathione metabolism trigger ferroptosis

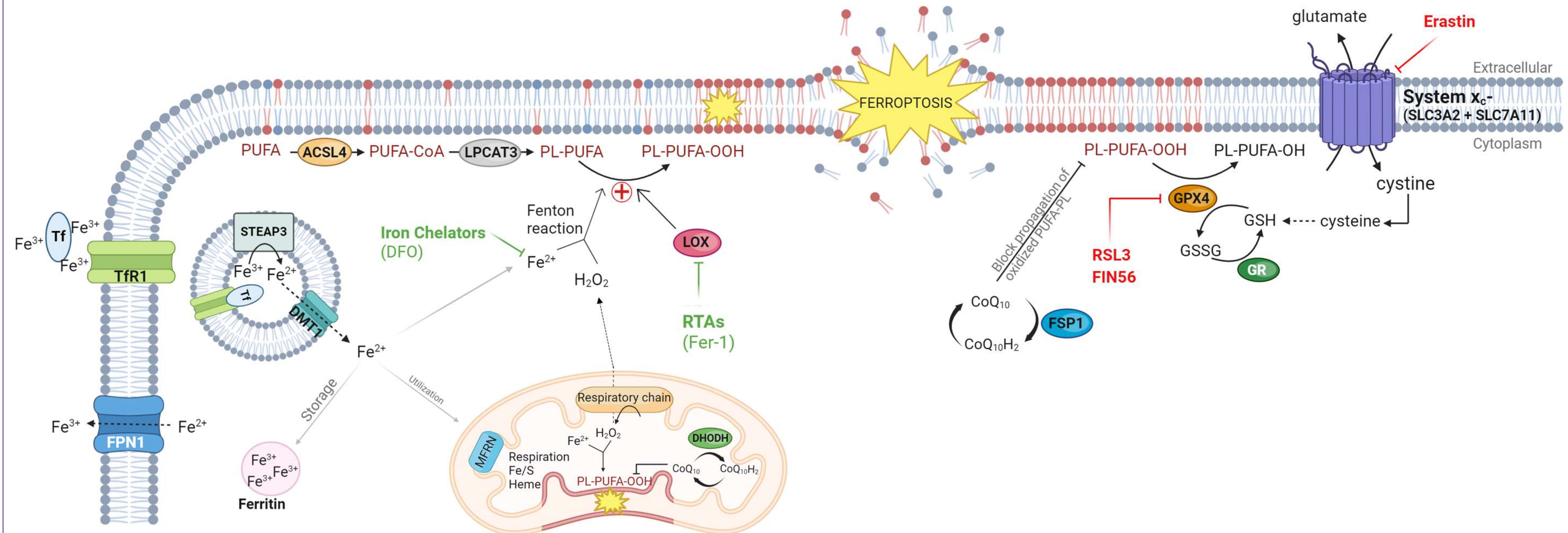
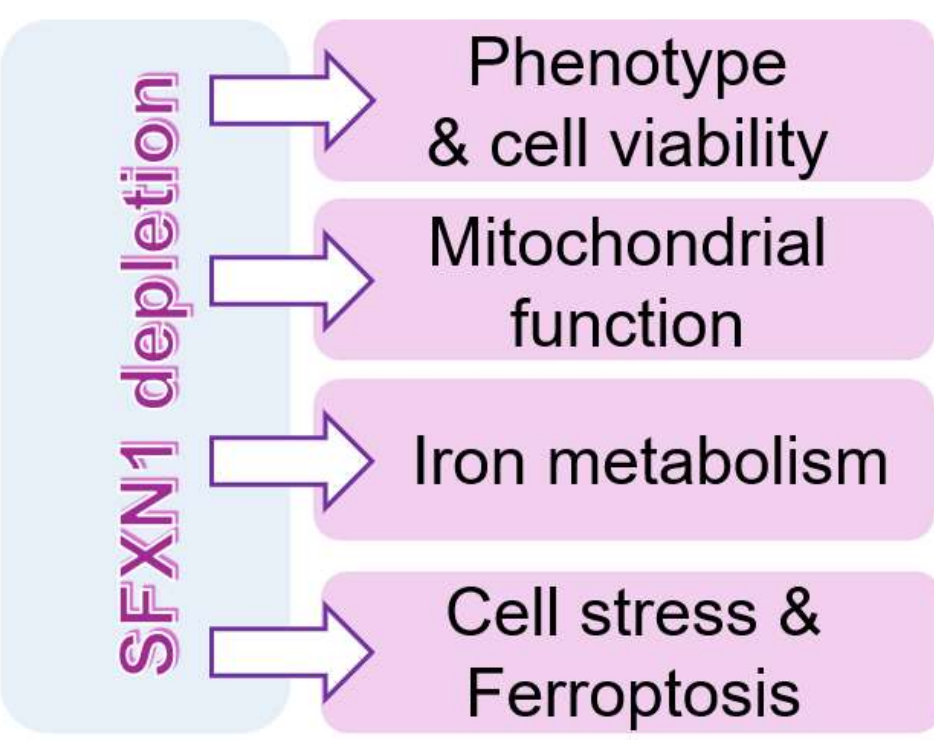


Fig 2. Mechanisms of ferroptosis. Ferroptosis inducers (red) and ferroptosis suppressors (green) are shown. Created with BioRender

Consequences of SFXN1 depletion on iron metabolism and ferroptosis ?

METHODS

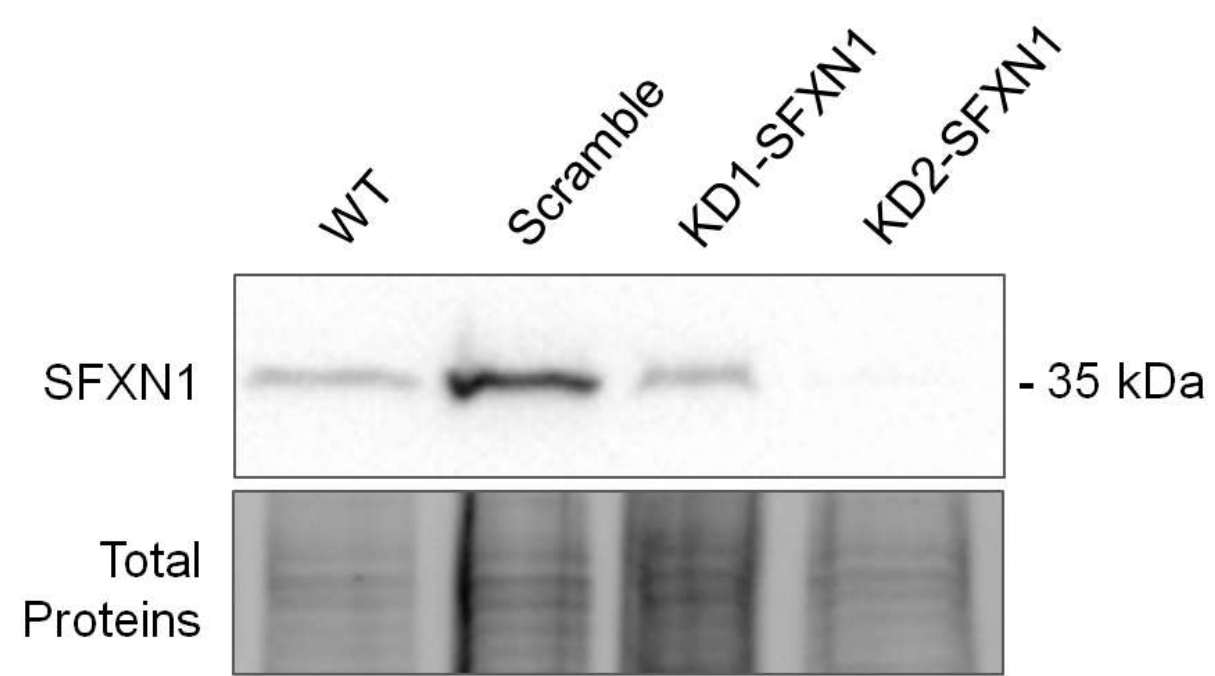
Scientific questions



Cellular model

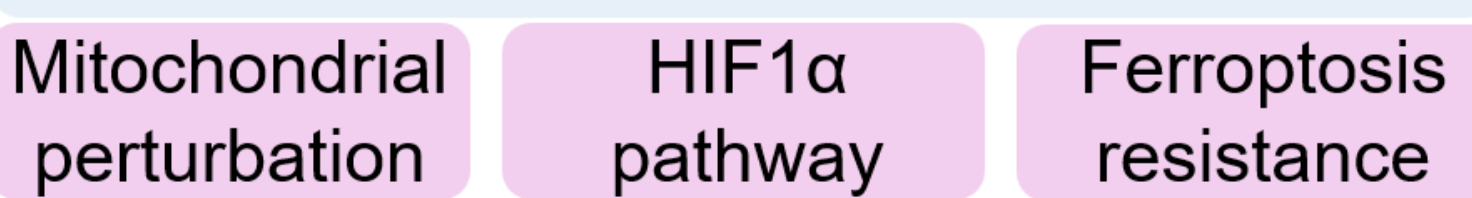
- HT1080 cancer cells (fibrosarcoma) sensitive to ferroptosis inducers
- Stable knockdown of SFXN1 (KD1 & KD2 – SFXN1) → 2 different shRNA targeting SFXN1 transcripts
- shRNA-Scramble as control

Verification by western-blot



CONCLUSION

SFXN1 depletion



Perspectives



Molecular & cellular pathways

Open questions :

- Does SFXN1 depletion allows ferroptosis resistance through the regulation of ROS formation and/or iron homeostasis and/or oxidative stress response ?
- What are the signaling pathways allowing the induction of HIF1α during SFXN1 depletion ?

References:
Kory N et al. 2018. SFXN1 is a mitochondrial serine transporter required for one-carbon metabolism. Science. doi: 10.1126/science.aat9528. PMID: 30442778; PMCID: PMC6300058.

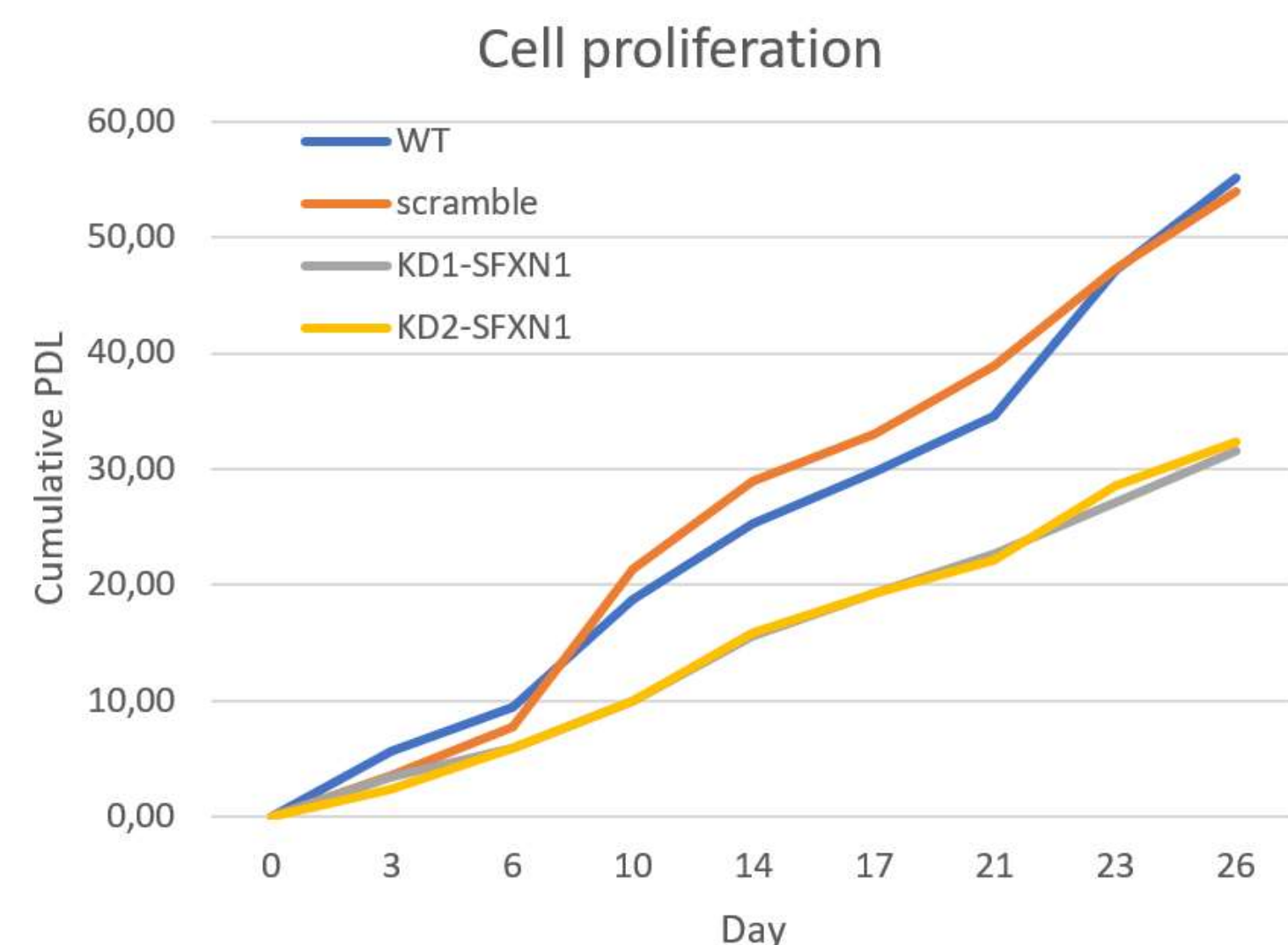
Acoba MG et al. 2021. The mitochondrial carrier SFXN1 is critical for complex III integrity and cellular metabolism. Cell Rep. doi: 10.1016/j.celrep.2021.108869. PMID: 33730581; PMCID: PMC8048093.

Tifoun N et al. 2021. Insights into the Roles of the Sideroflexins/SLC56 Family in Iron Homeostasis and Iron-Sulfur Biogenesis. Biomedicine. doi: 10.3390/biomedicine9020103. PMID: 33494450; PMCID: PMC7911444.

Stockwell BR. 2022. Ferroptosis turns 10 : Emerging mechanisms, physiological functions, and therapeutic applications. Cell. doi: 10.1016/j.cell.2022.06.003. PMID: 35803244; PMCID: PMC9273022.

RESULTS

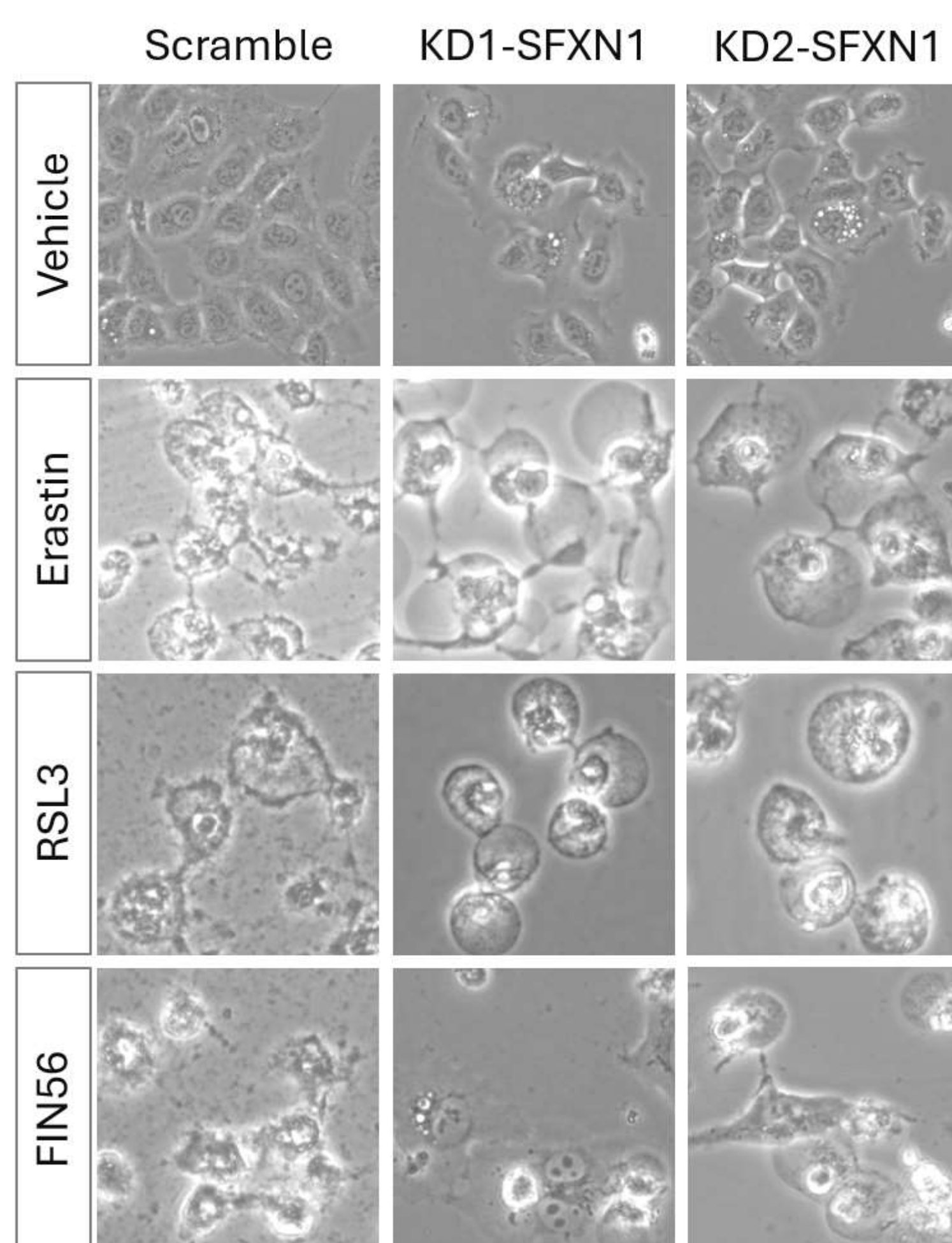
Cellular phenotype



- KD cells proliferated slowly in full medium compared to control cells
- Test the viability and cytotoxicity (stress oxidant condition)

Ferroptosis sensibility

Cellular morphology

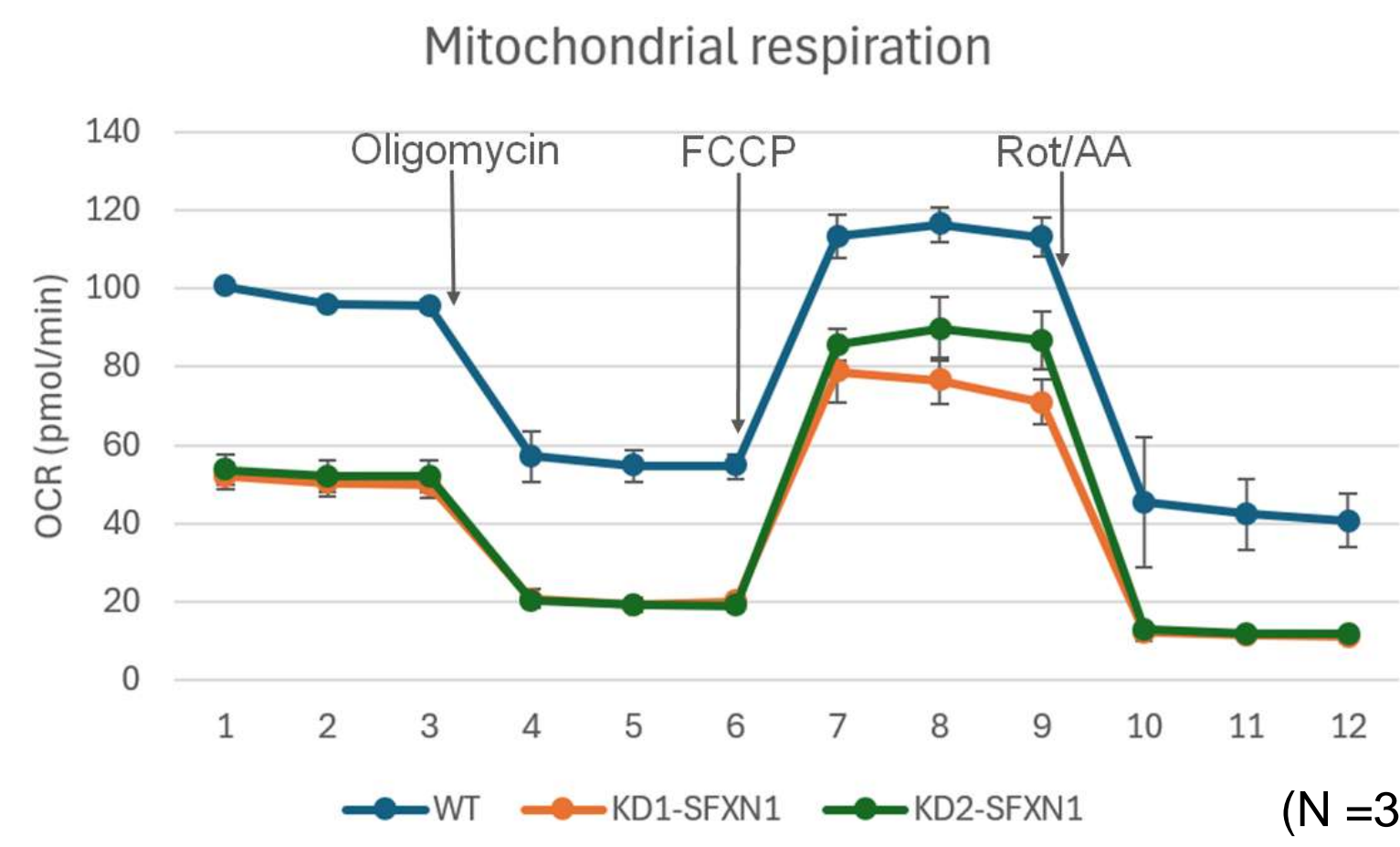


24H treatment with 10µM of erastin, 1µM of RSL3 or 5µM of FIN56

- Delay of ferroptosis, KD cells appear to be resistant (or less sensitive to ferroptosis inducers)
- What are the mechanism allowing this resistance ?

Mitochondrial function & morphology

Mitochondrial respiration by Seahorse

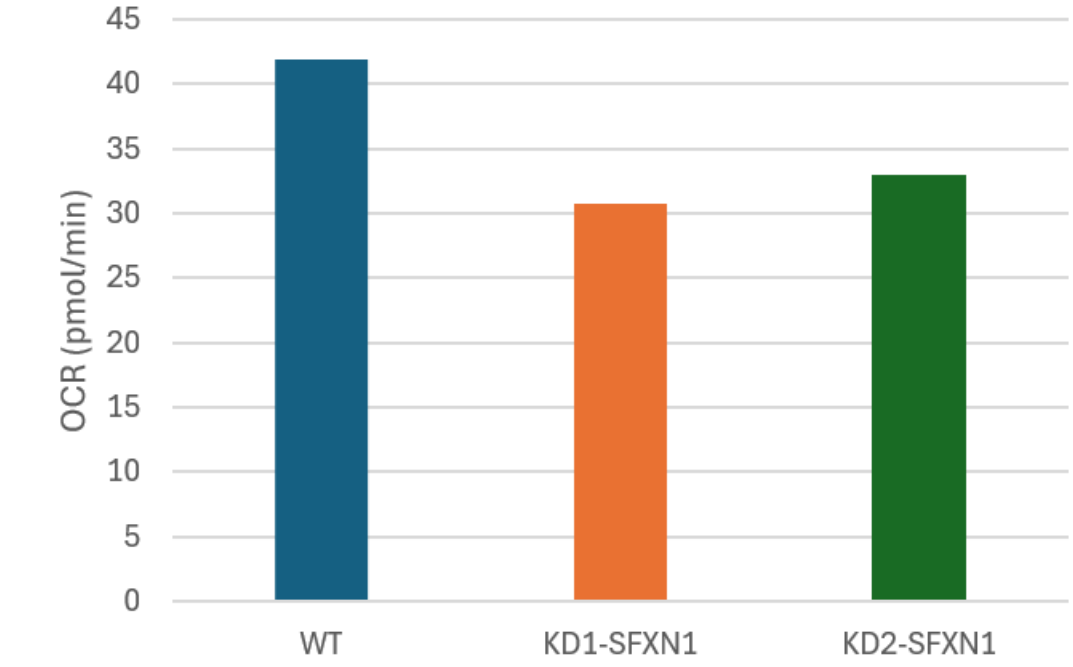


- Oligomycin inhibits ATP synthase
- FCCP uncoupling agent = disrupts mitochondrial membrane potential
- Rotenone / Antimycin (Rot/AA) inhibits complex I and III

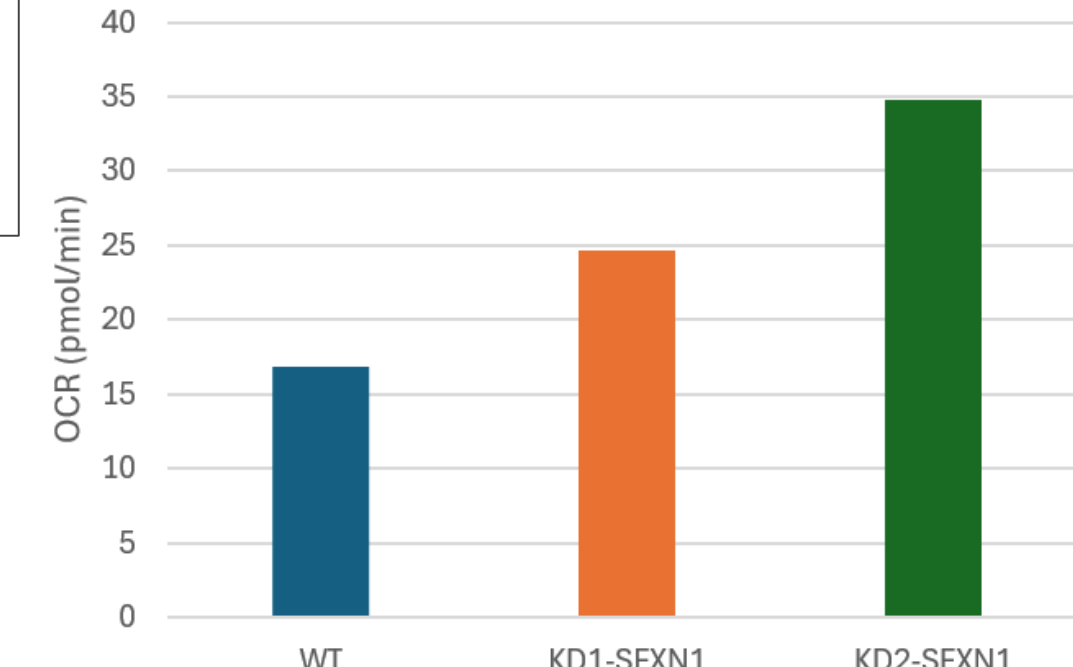
- SFXN1 depletion seems to decrease the mitochondrial respiration
- Decrease of ATP production
- Increase of spare capacity

→ Mitochondrial function alteration results from a disorganization of respiratory complexes ? Problem with complex activity ? Alteration of mitochondrial morphology ?

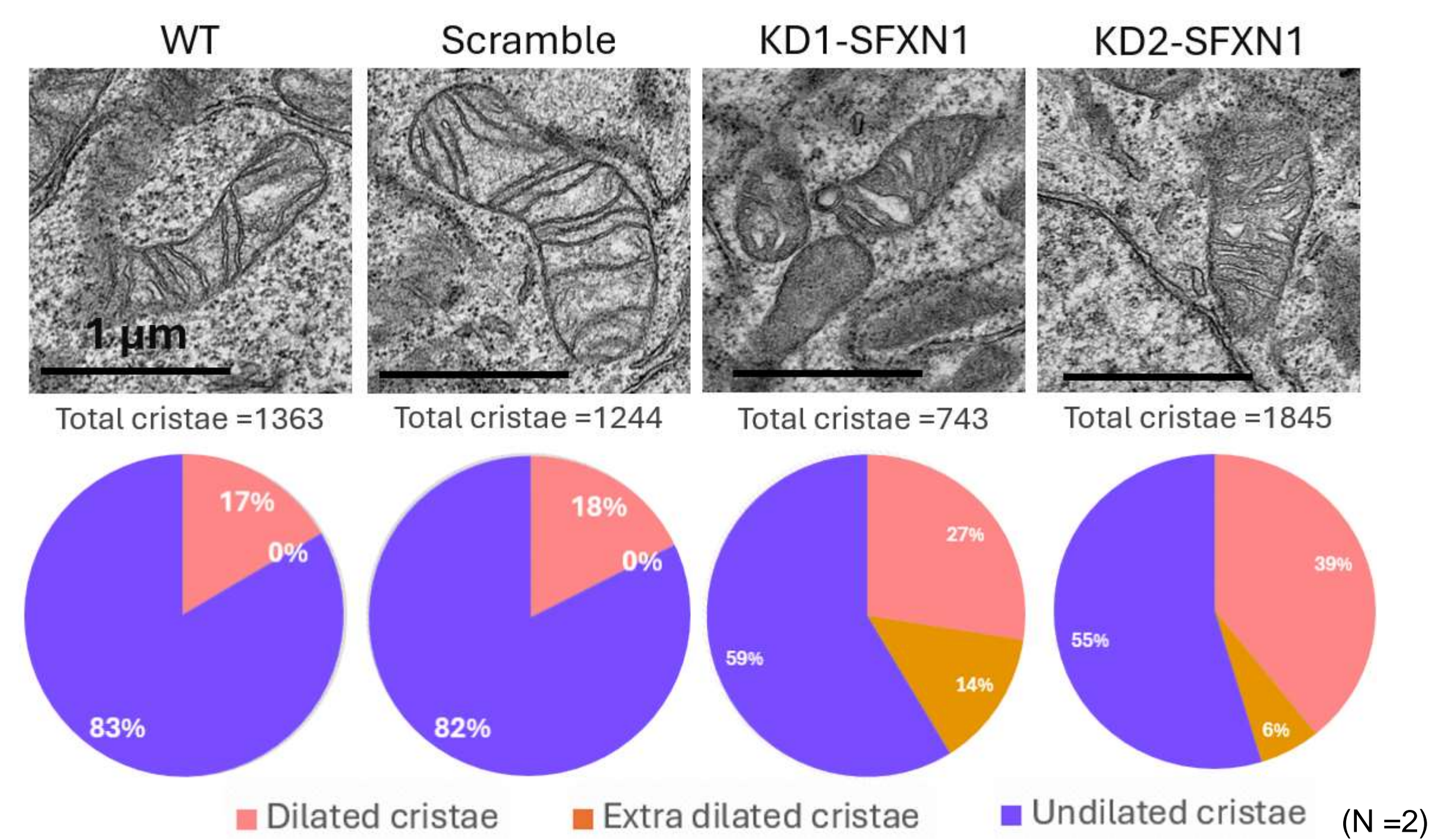
ATP Production



Spare Respiratory Capacity



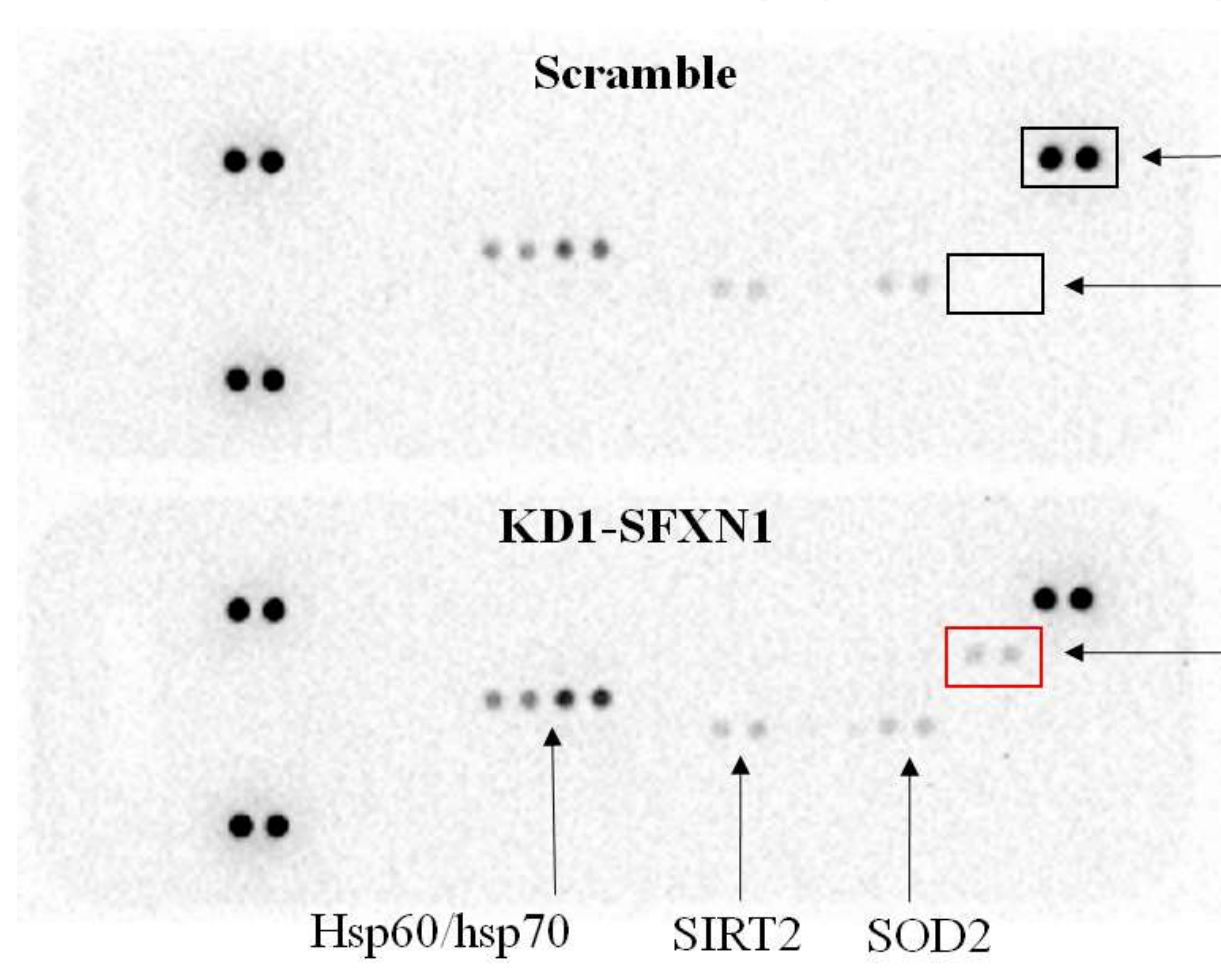
Mitochondrial morphology by TEM



- Altered cristae morphology in KD cells
- Test mitochondrial biogenesis and mitochondrial network
- Investigate the composition of the complexes maintaining cristae junctions

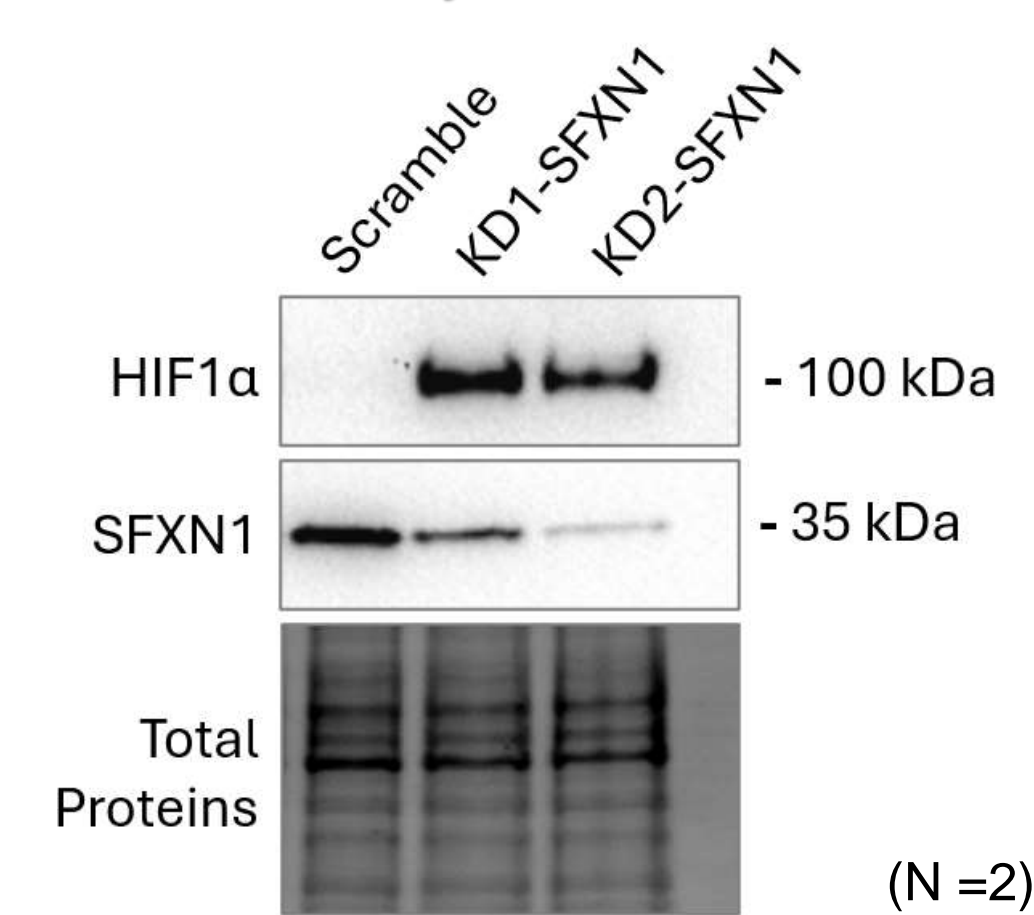
HIF1α is induced upon SFXN1 depletion

Proteome Profiler Array (cell stress kit)



- Same results with KD2-SFXN1

HIF1α by western-blot



- HIF1α seems to be upregulated in KD cells
- Iron can regulate HIF1α, so does SFXN1 can regulate HIF1α through iron ?