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Metabolic Alterations in Fumarate Hydratase Deficient Cells

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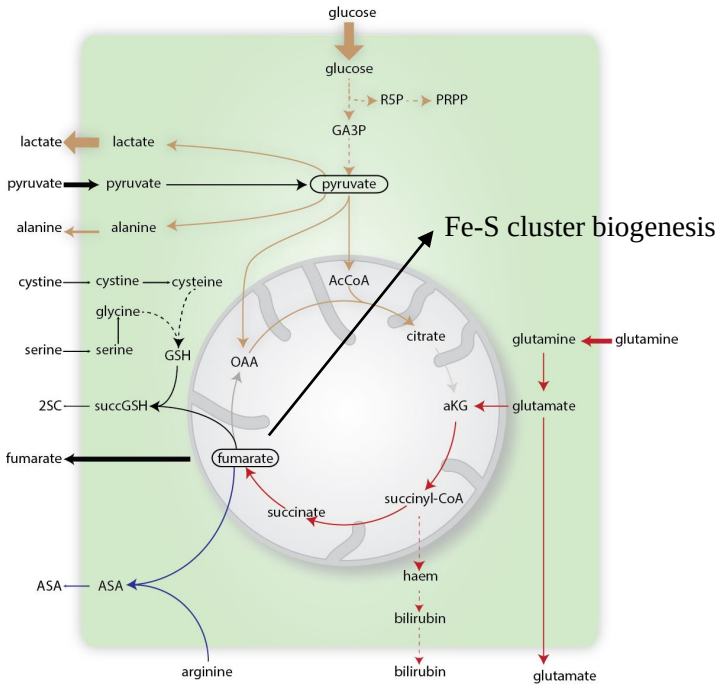
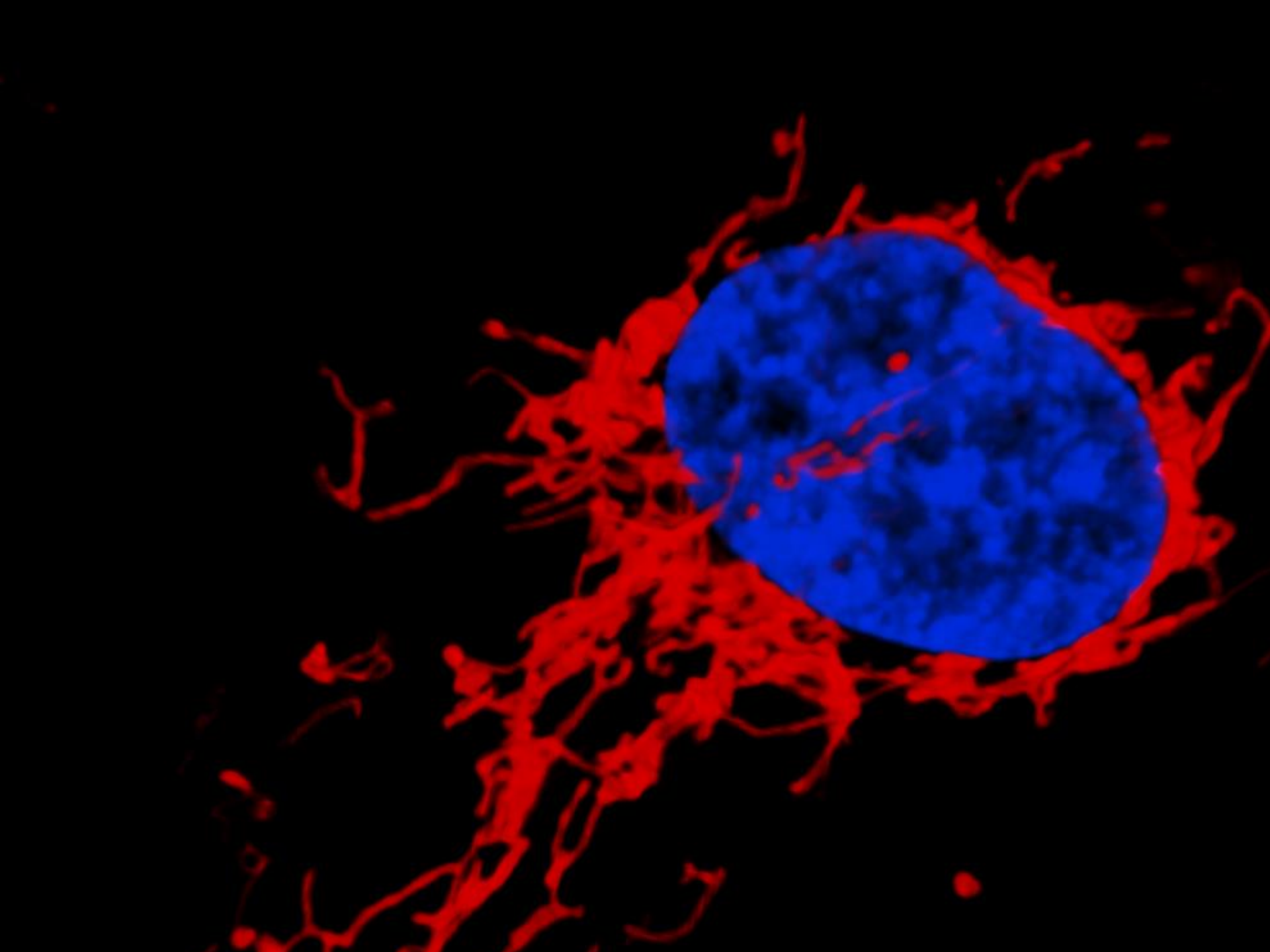
Metabolic Alterations in Fumarate Hydratase Deficient Cells

Graphical Abstract

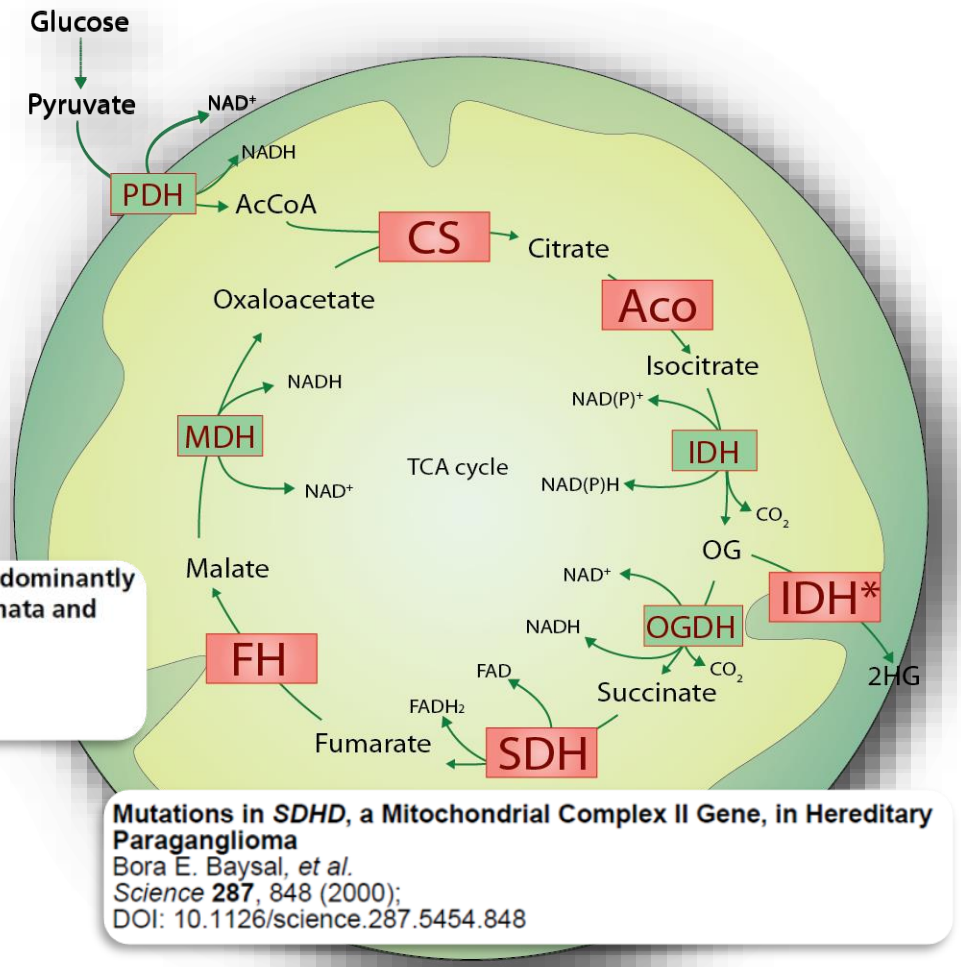


Abstract: Mutations of the tricarboxylic acid cycle (TCA cycle) enzyme fumarate hydratase (FH) cause the hereditary cancer syndrome Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC). FH-deficient renal cancers are highly aggressive and metastasise even when small, leading to an abysmal clinical outcome. How these cells survive without FH and how they become transformed is still under investigation. Today, I will show our data on the metabolic reprogramming triggered by the loss of FH, which induces, amongst various changes, the fumarate-mediated succination of the iron-sulfur-cluster proteins ISCU1, NFU1, and Bola1/3. Of note, this post translational modification leads to defects in iron-sulfur cluster biogenesis and complex I deficiency. These results could help to explain the profound alteration of mitochondrial metabolism in cells that lack FH.

Keywords: cancer metabolism, fumarate hydratase, mitochondria



TCA cycle and cancer



Germline mutations in *FH* predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer

The Multiple Leiomyoma Consortium

Published online: 25 Febrary 2002. DOI: 10.1038/ng849

Mutations in *SDHD*, a Mitochondrial Complex II Gene, in Hereditary Paraganglioma

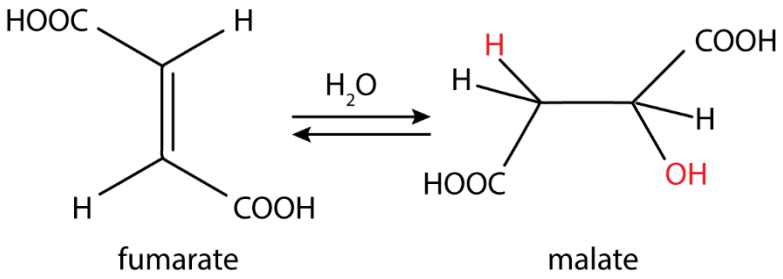
Bora E. Baysal, *et al.*

Science **287**, 848 (2000);

DOI: 10.1126/science.287.5454.848

mitochondrion

FH and HLRCC



fumarate malate

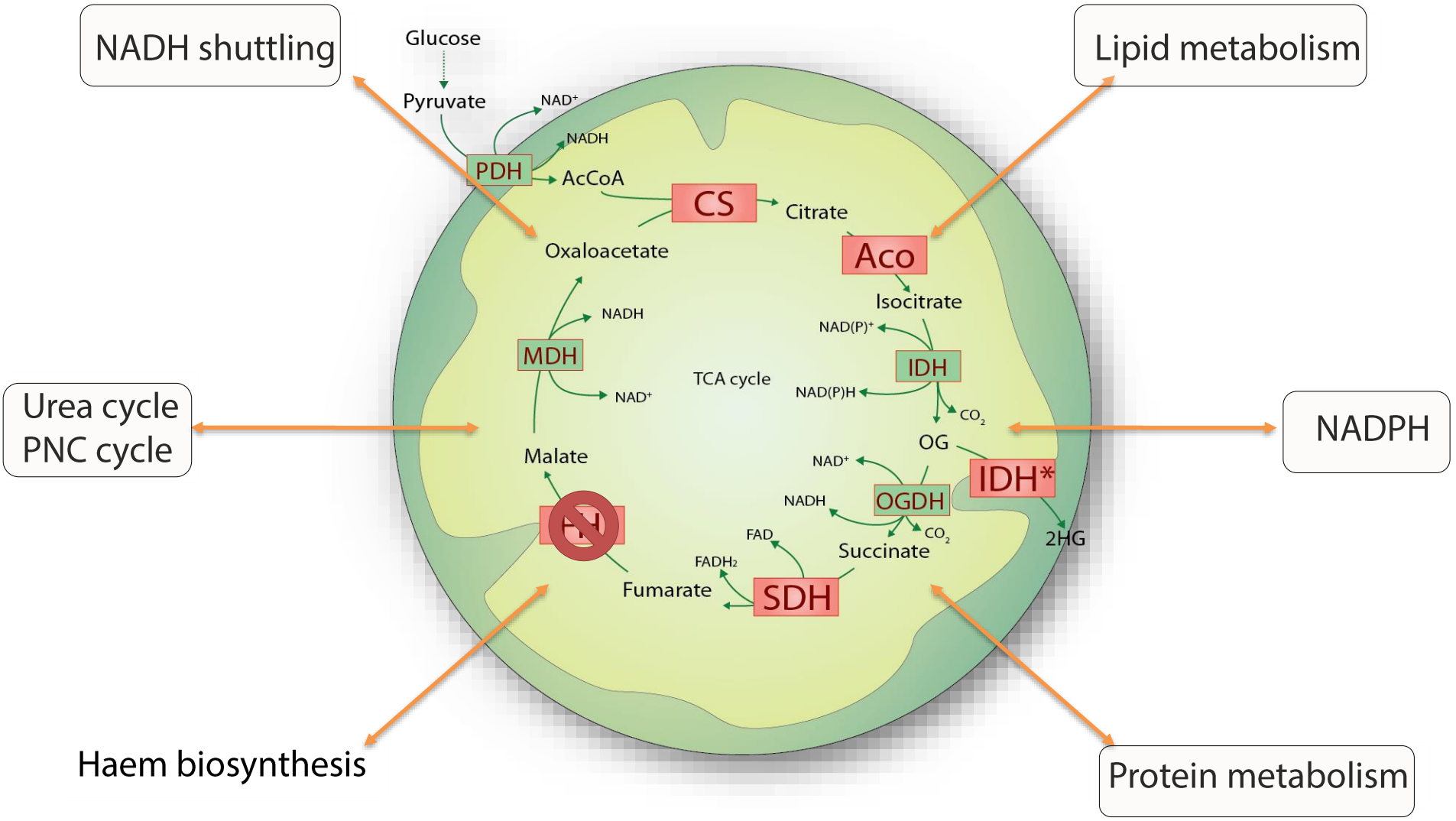
Hereditary Leiomyomatosis and renal cell cancer

- Skin fibroids
- Uterine fibroids
- Papillary type 2 renal cancer

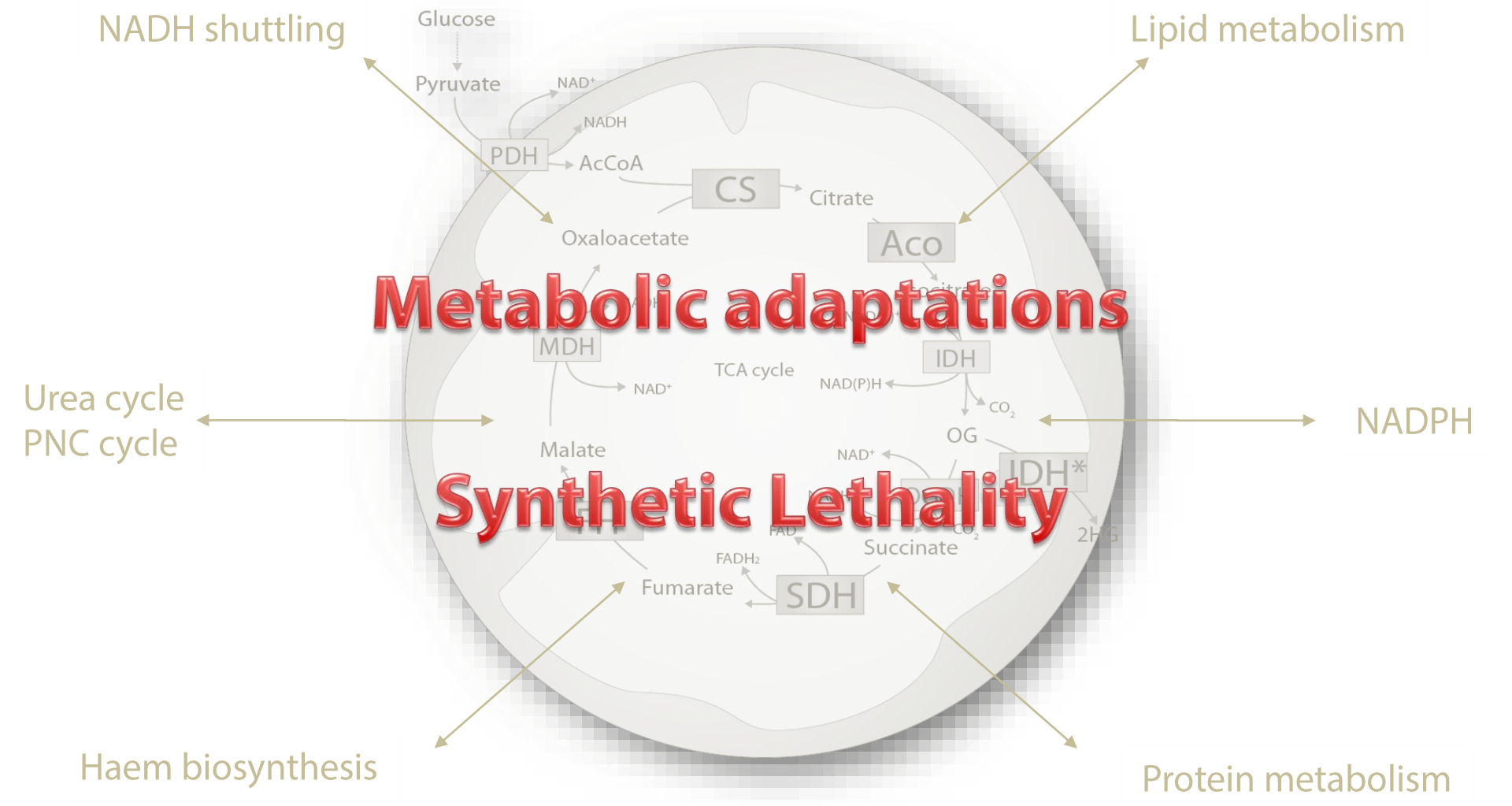
Unanswered questions:

- How do these cells survive without FH?
- Why loss of FH leads to cancer?

Metabolic adaptations in cancer cell

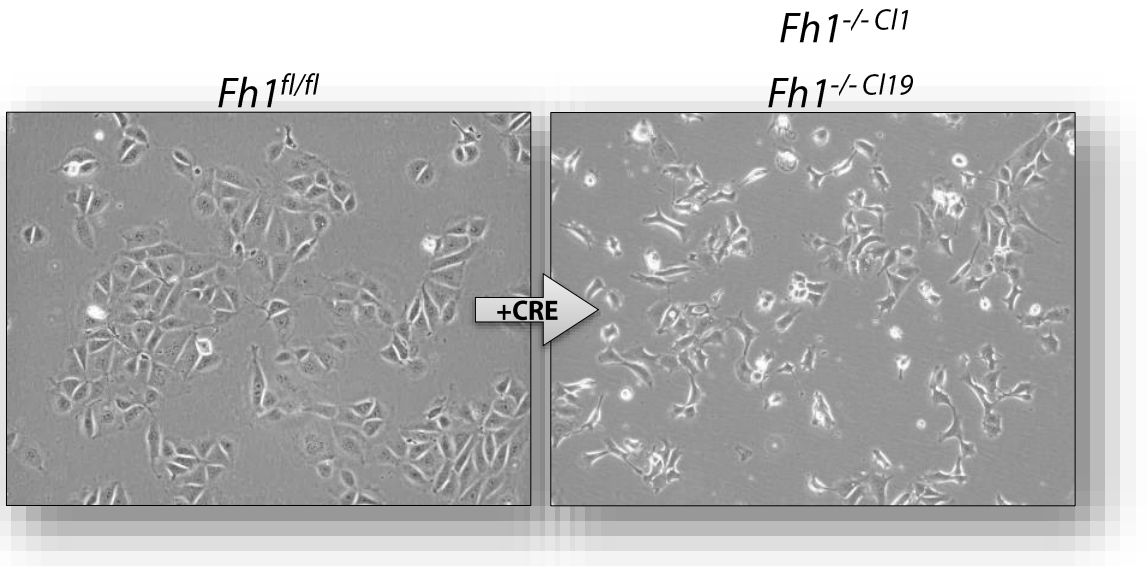


Metabolic adaptations in cancer cell

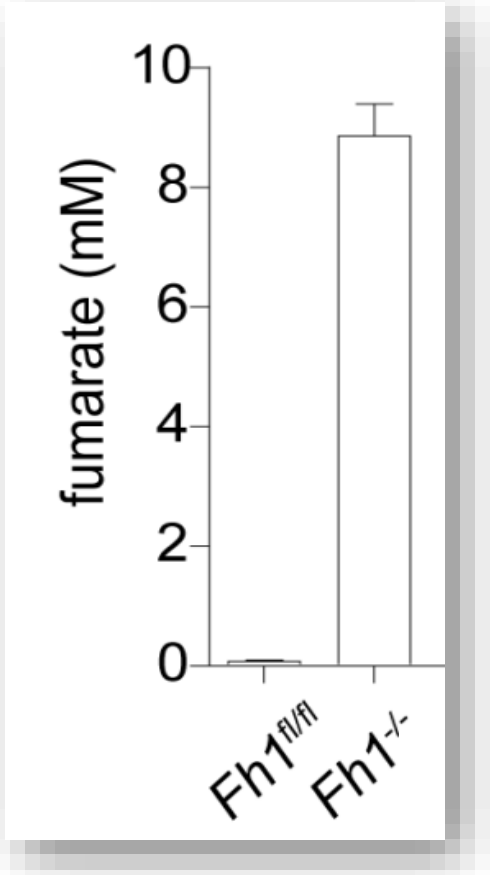


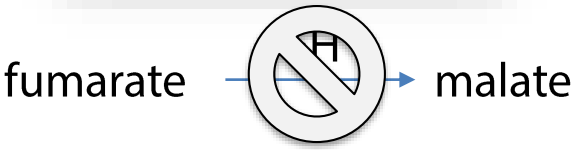
The model: Fumarate Hydratase deficient (*Fh1*$^{-/-}$) cells

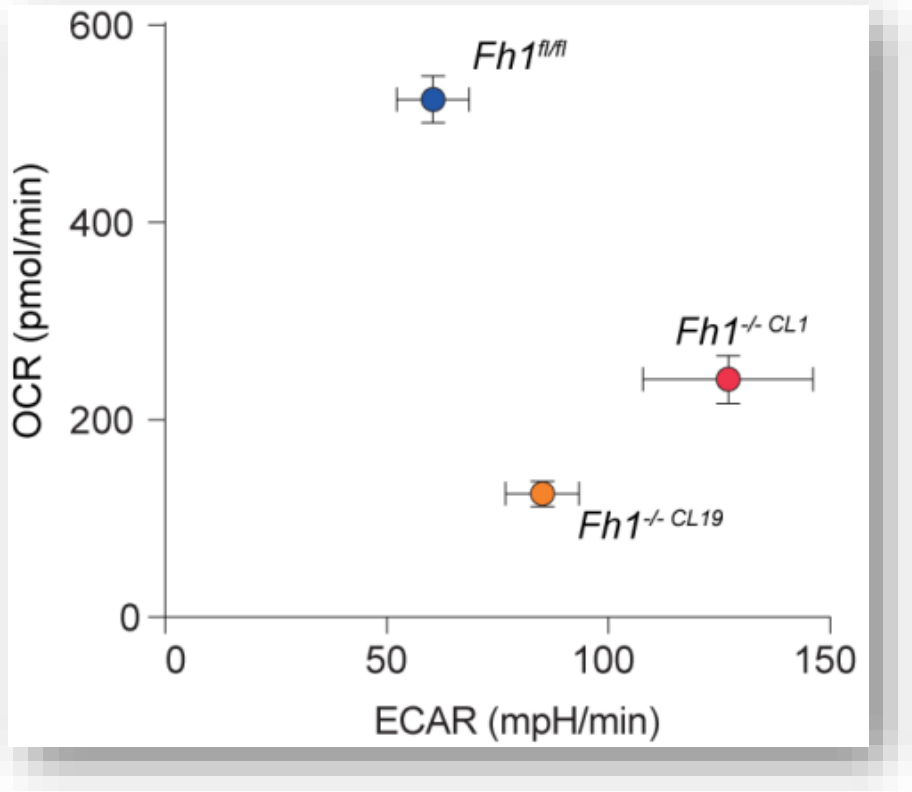
epithelial kidney cells



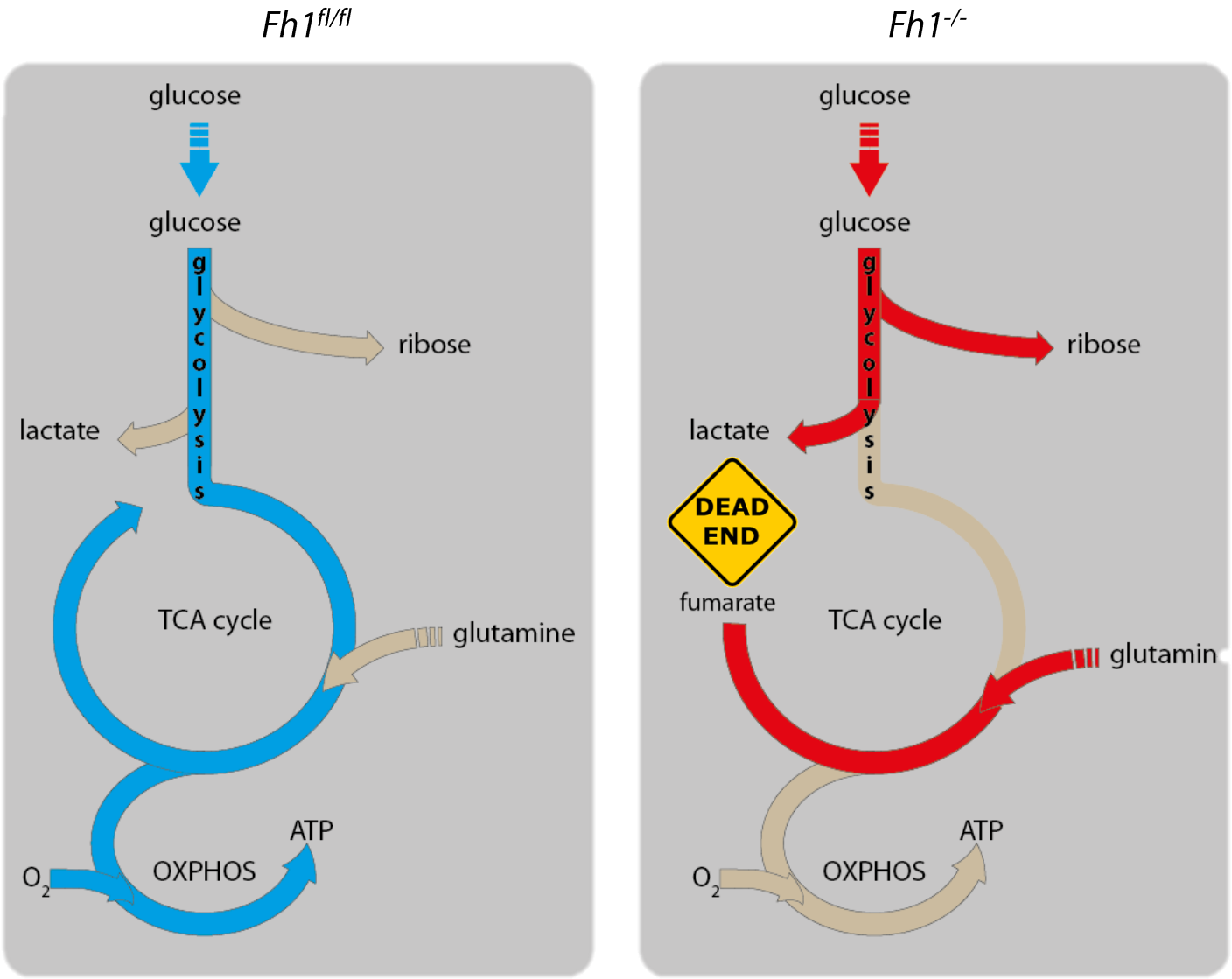
Metabolic profile of Fh1-deficient cells



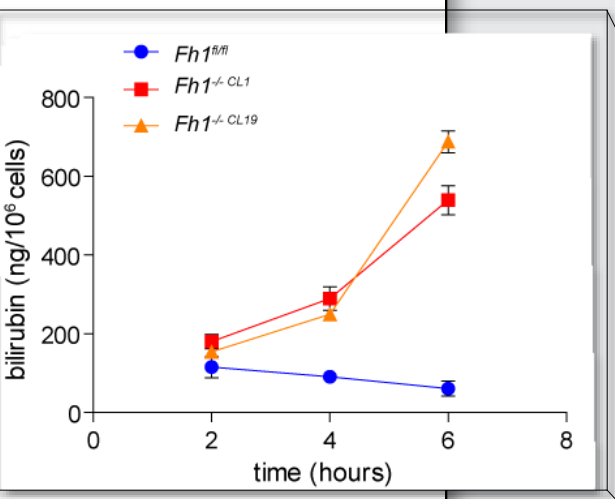


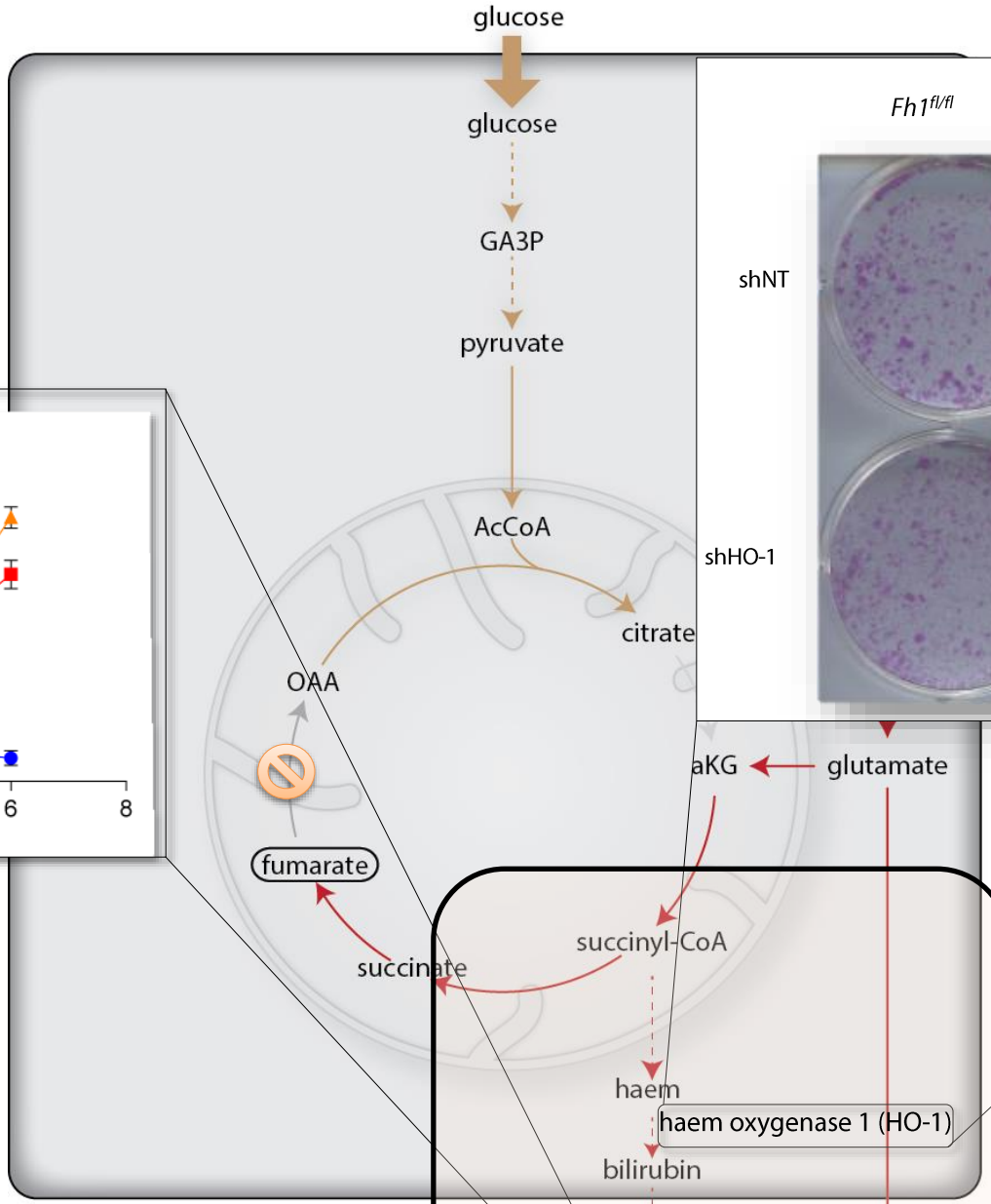


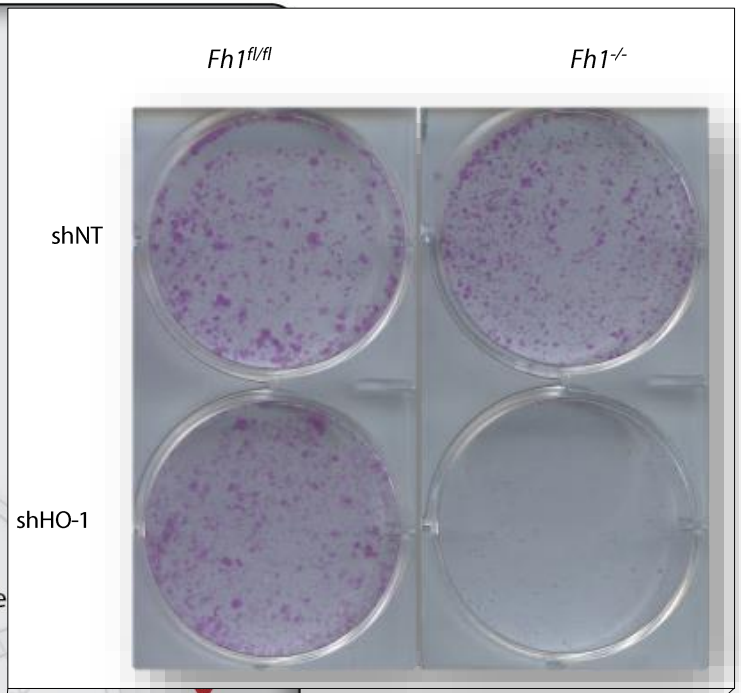
Metabolic diversions in *Fh1*$^{-/-}$ cells



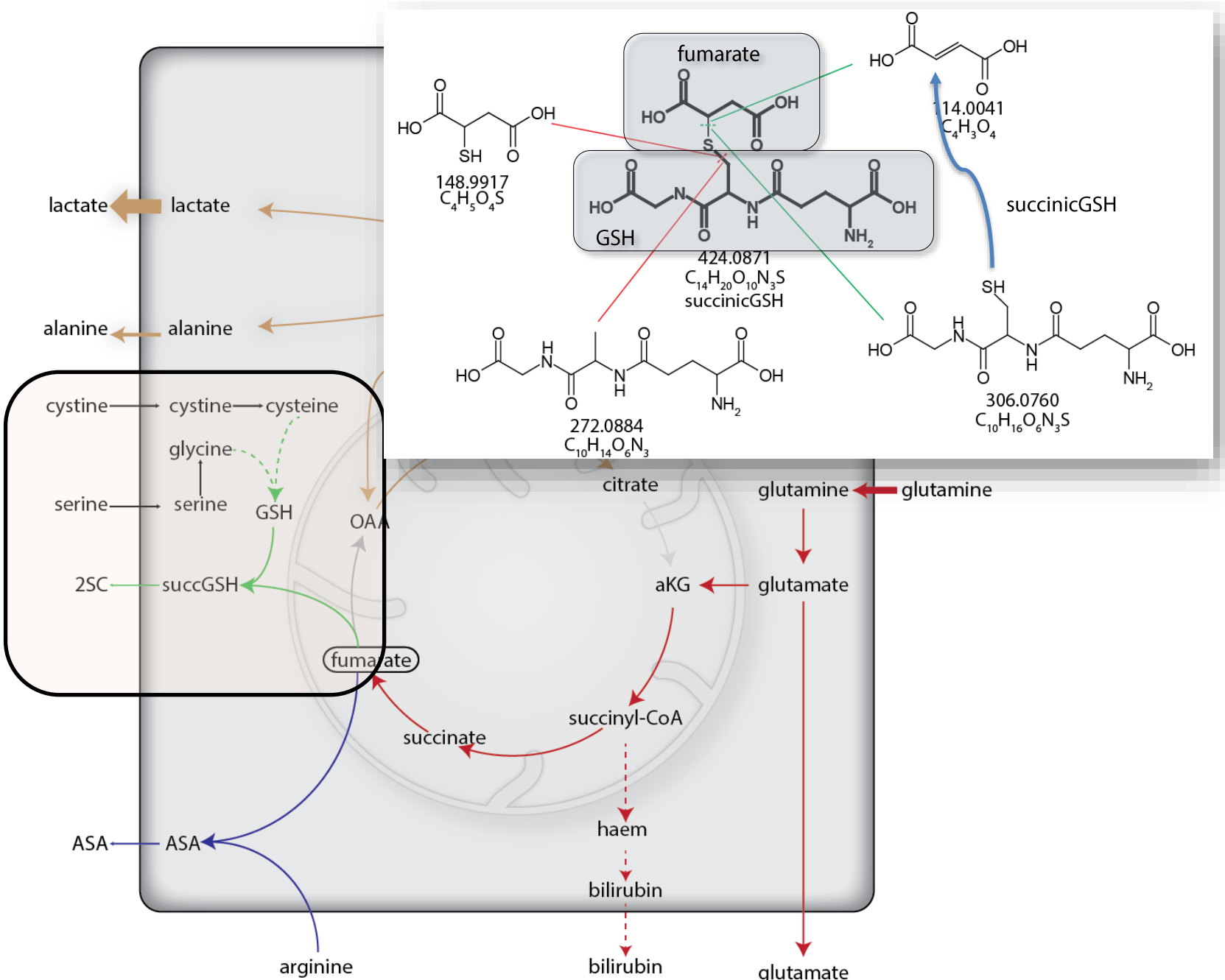
Heam biosynthesis pathways in Fh1-deficient cells



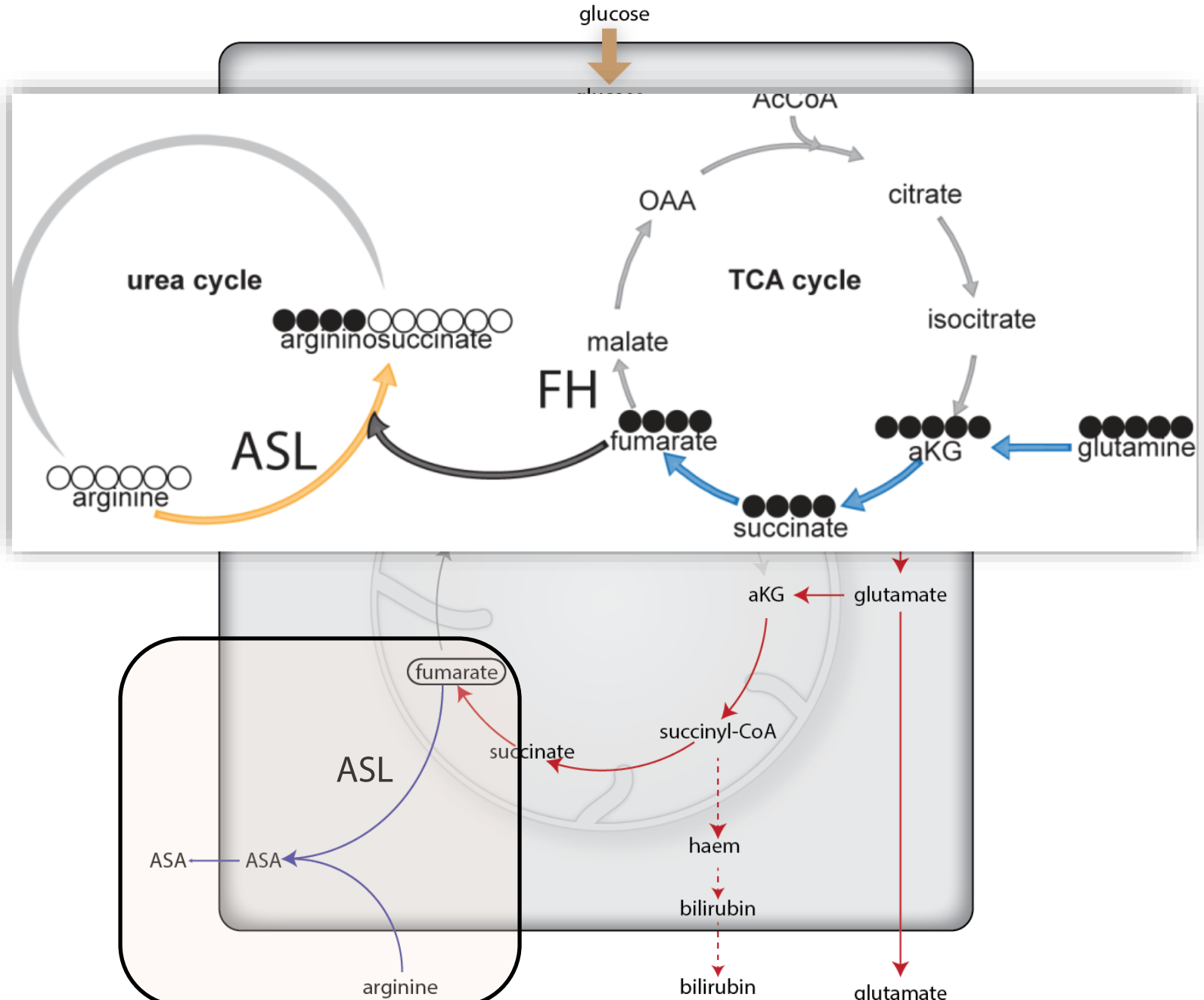




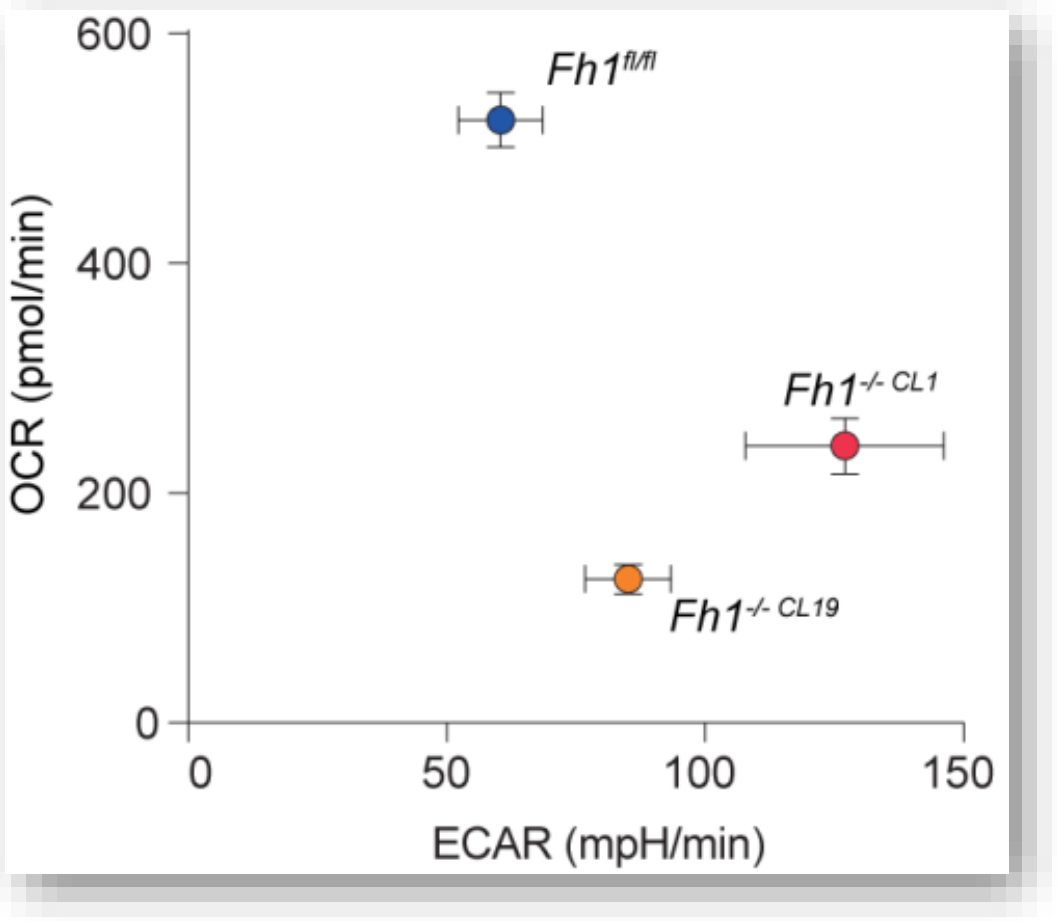
Fumarate leads to succination of glutathione



Fumarate leads to reversal of Argininosuccinate Lyase

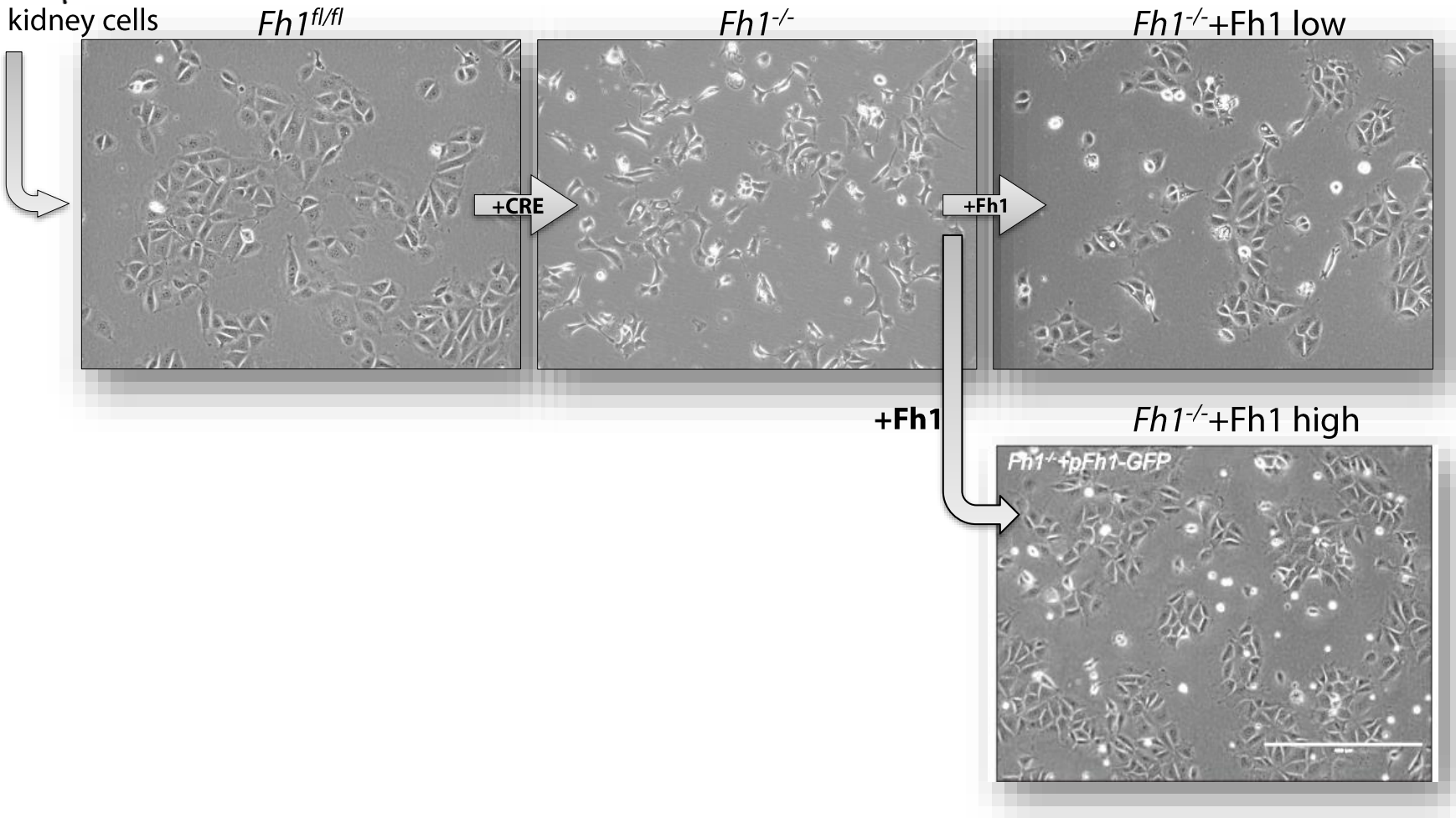


Mitochondrial dysfunction in Fh1-deficient cells

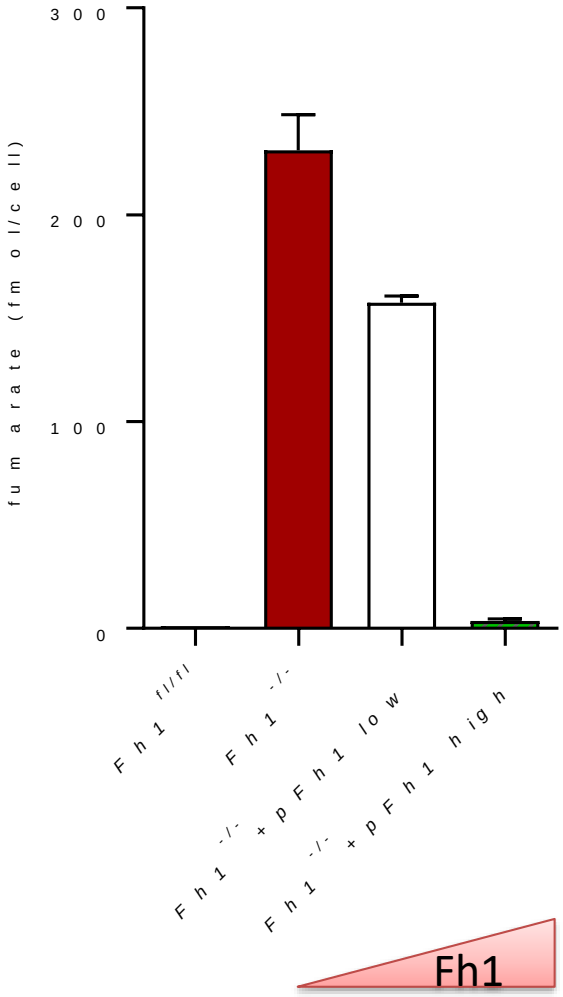


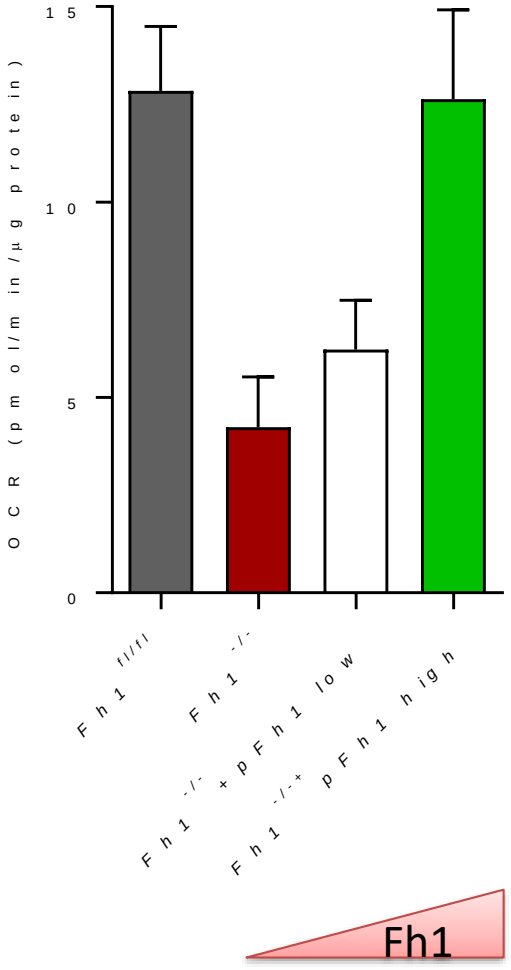
The models: *Fh1*$^{-/-}$ rescue cells

epithelial kidney cells

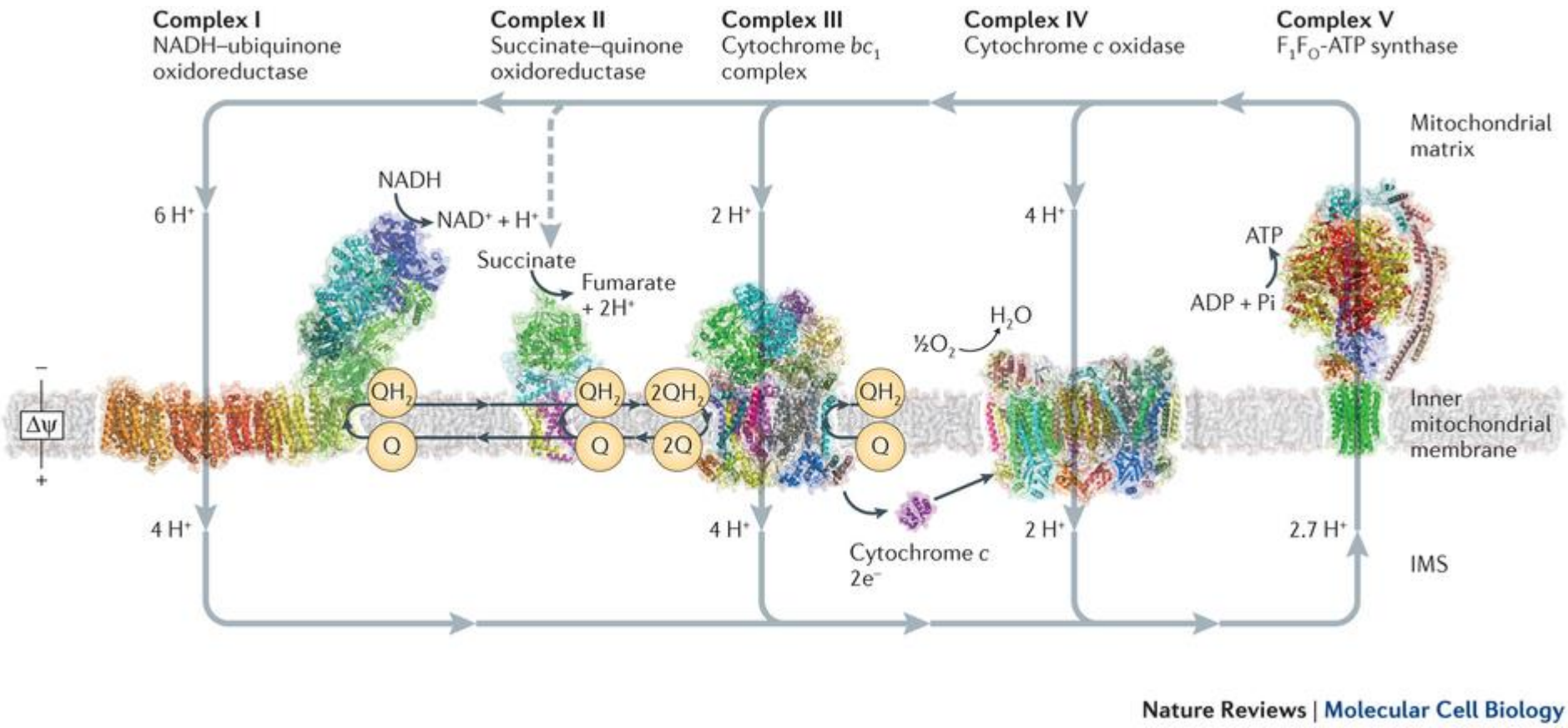


Fh1-rescue restores fumarate levels and respiration



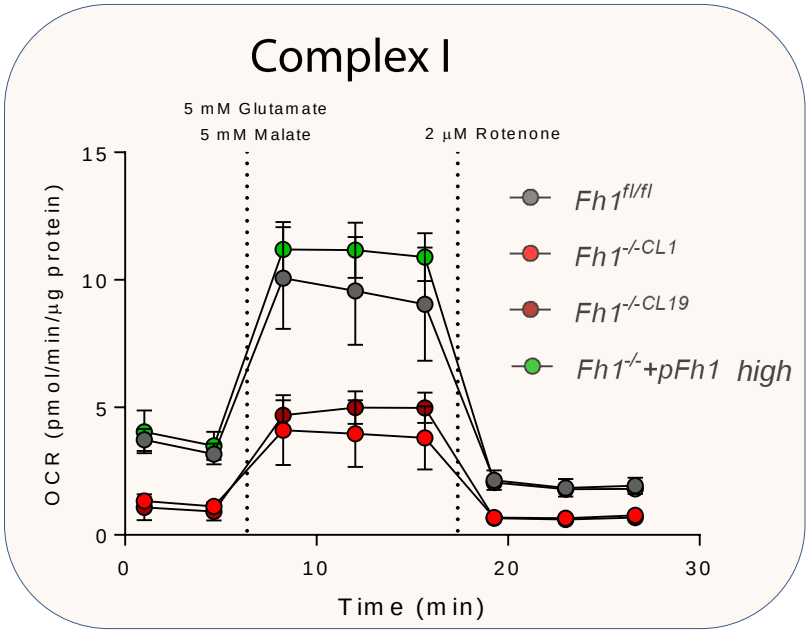


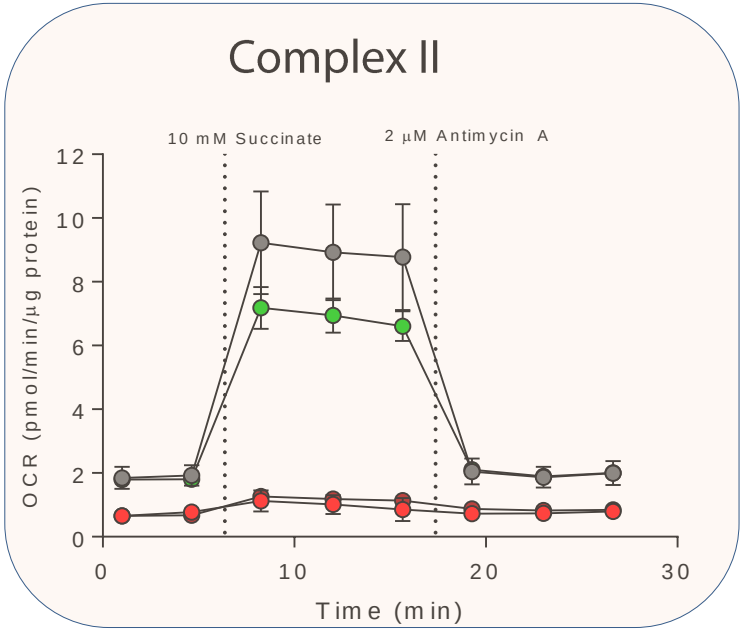
Assessing respiratory chain activity

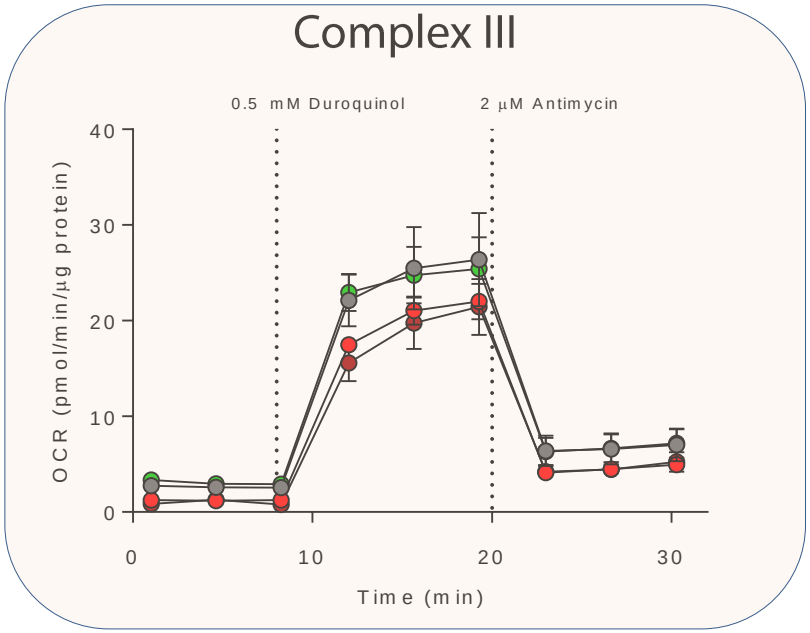


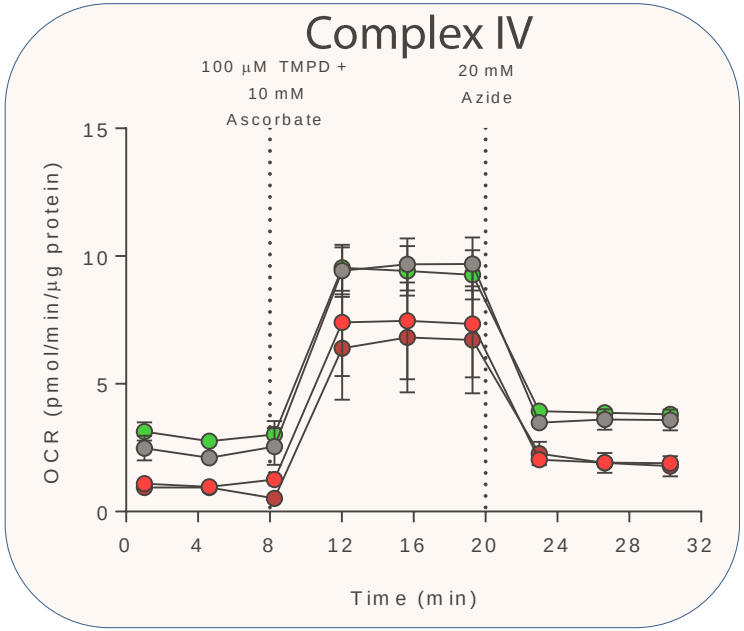
Nature Reviews | Molecular Cell Biology

Respiratory chain activity in Fh1-deficient cells

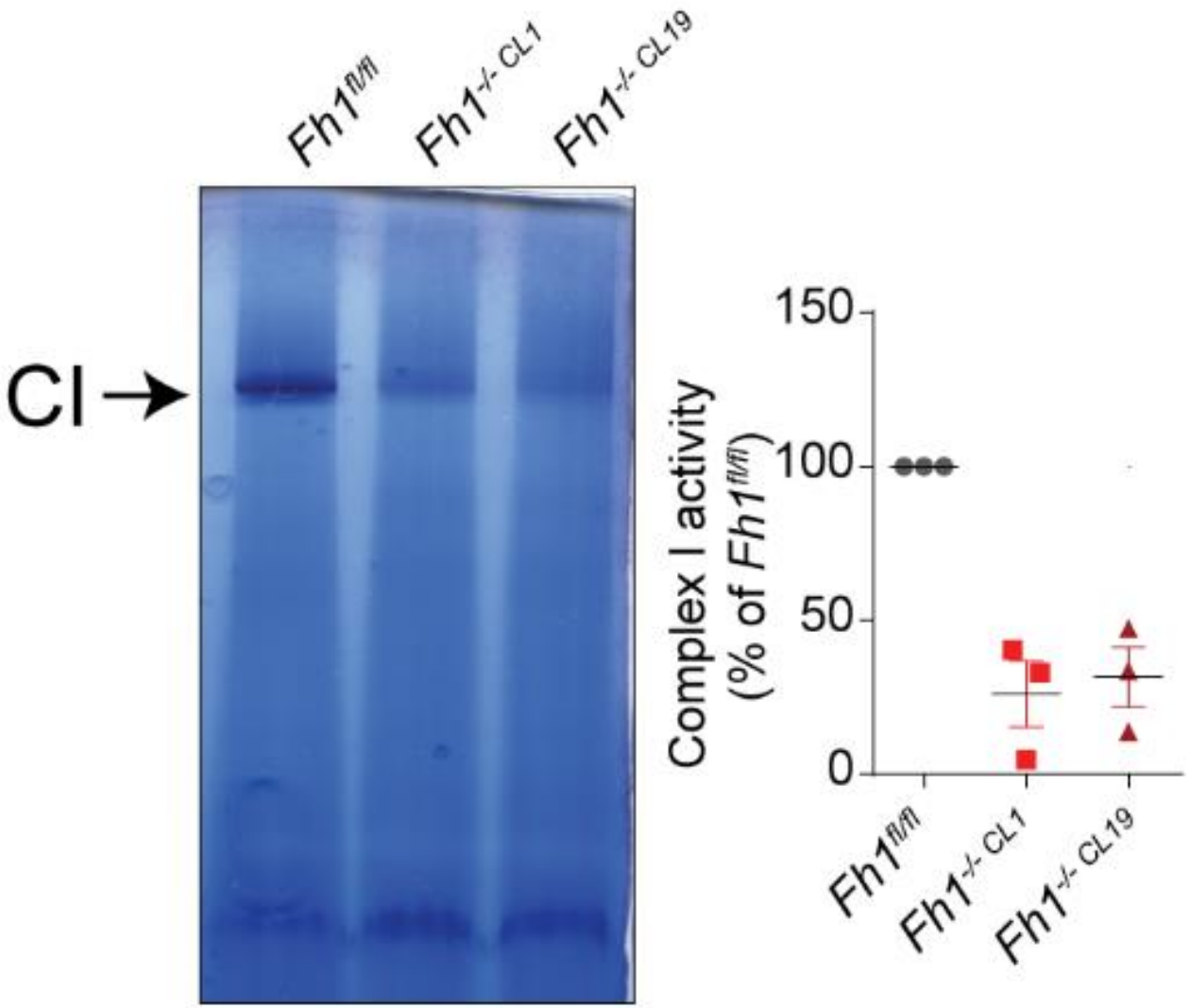




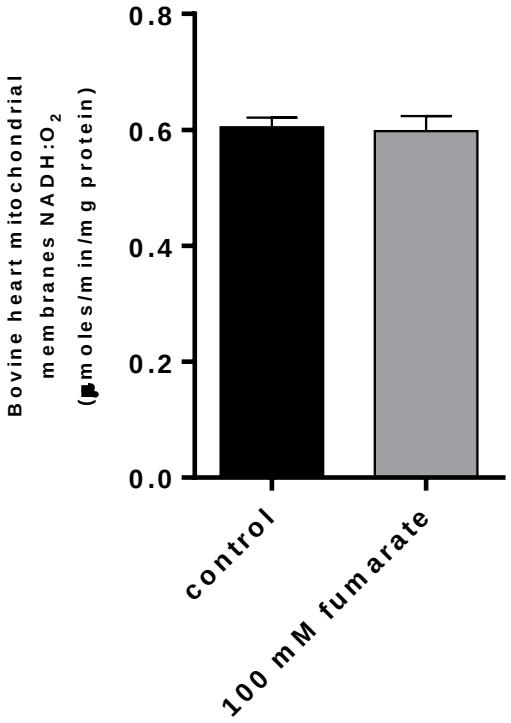


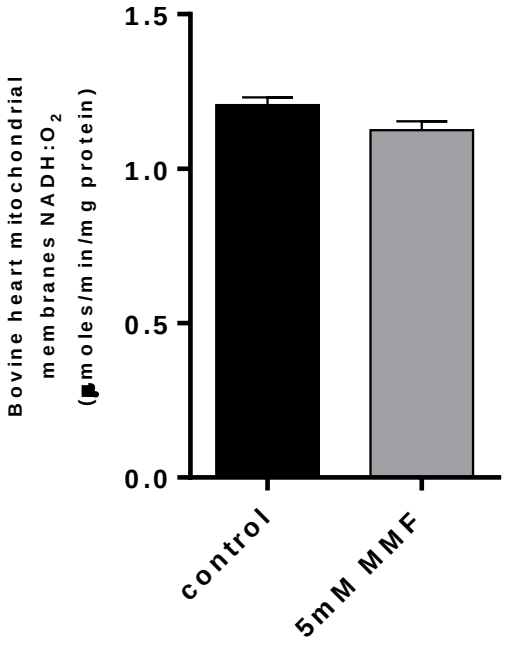


Complex I activity in *Fh1*$^{-/-}$ cells

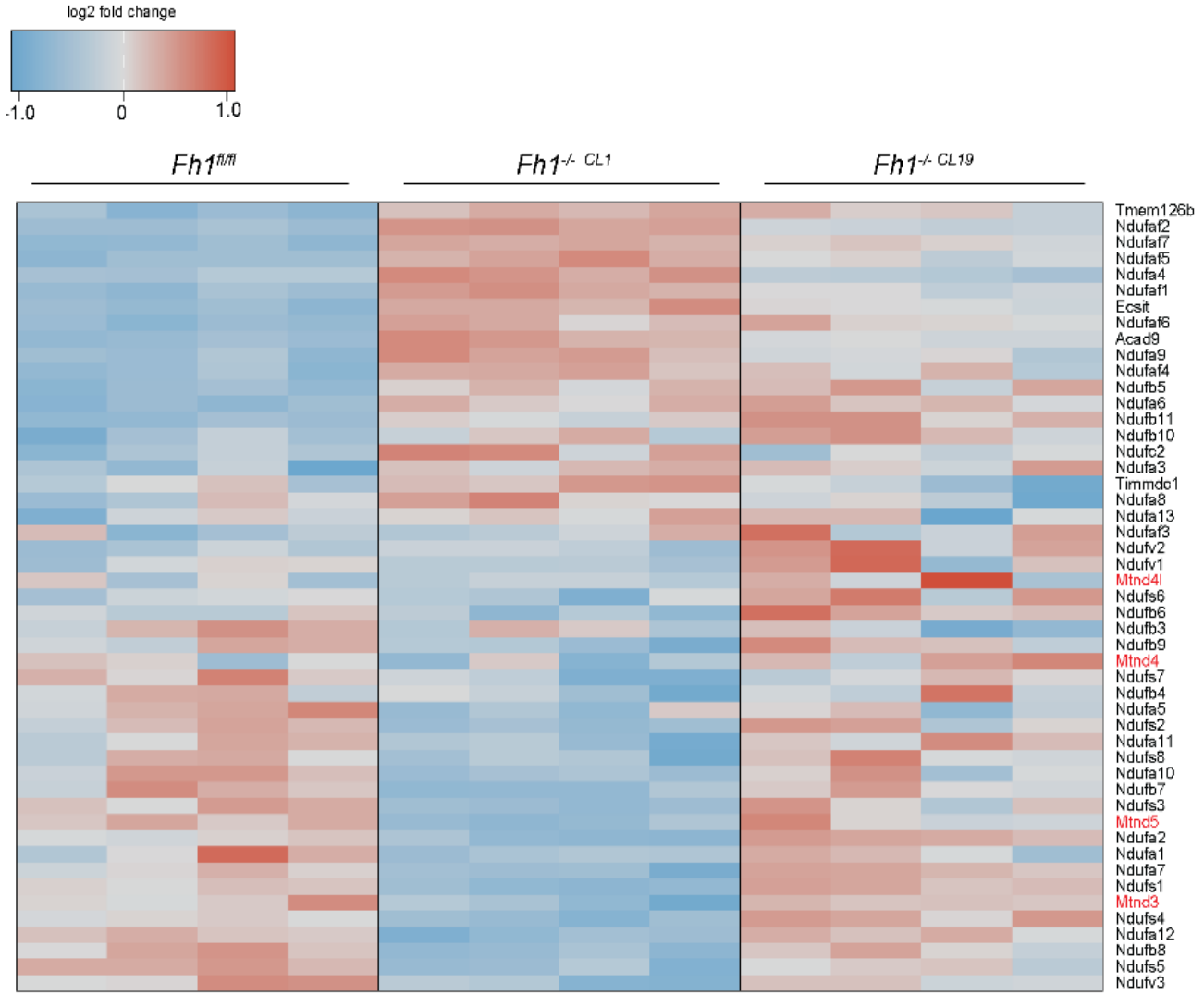


Fumarate does not affect Complex I

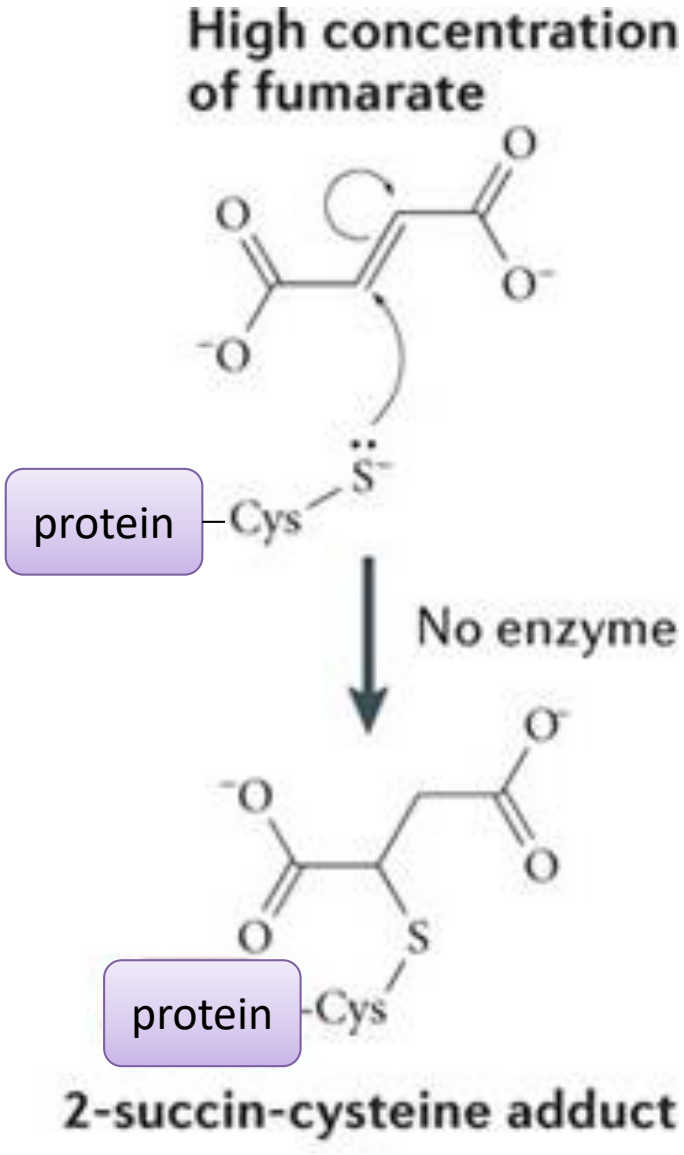




Complex I levels are not decreased in *Fh1*$^{-/-}$ cells

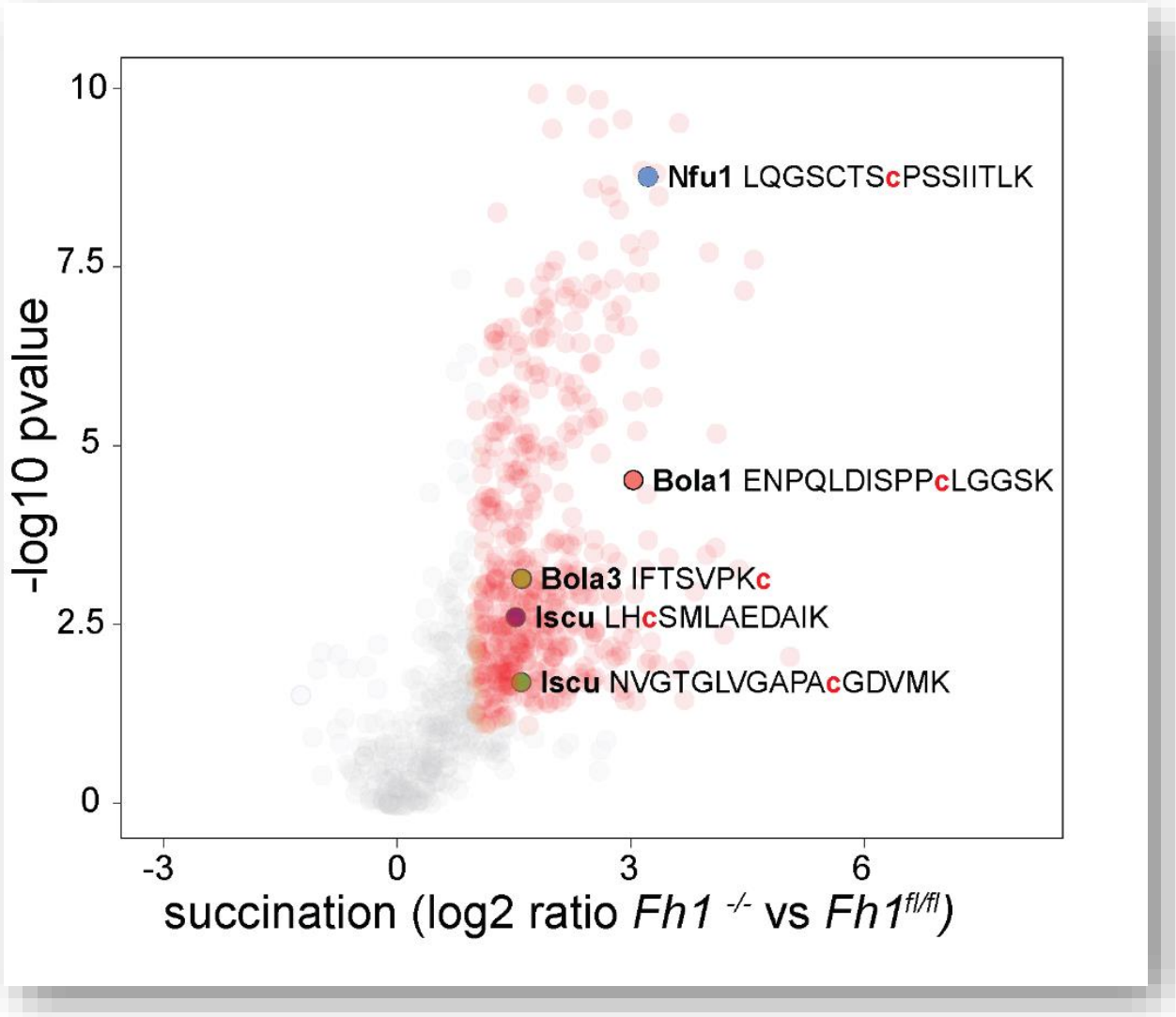


Protein succination and fumarate accumulation

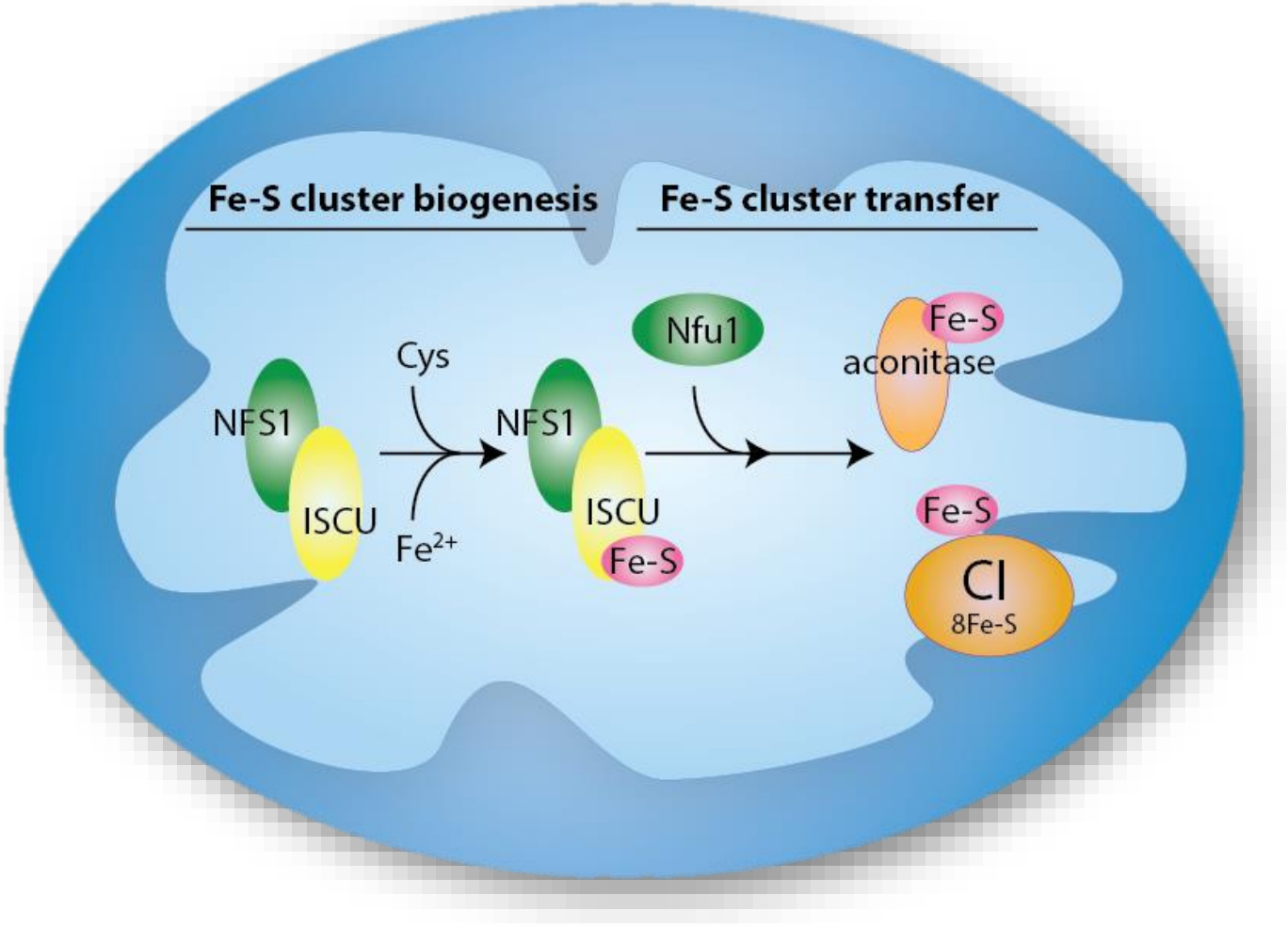


Nature Reviews Cancer **12**, 564-571 (August 2012)

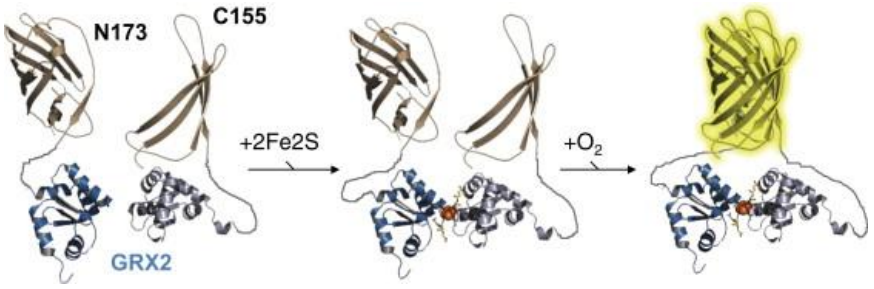
Fe-S cluster biogenesis proteins are succinated in *Fh1*$^{-/-}$ cells



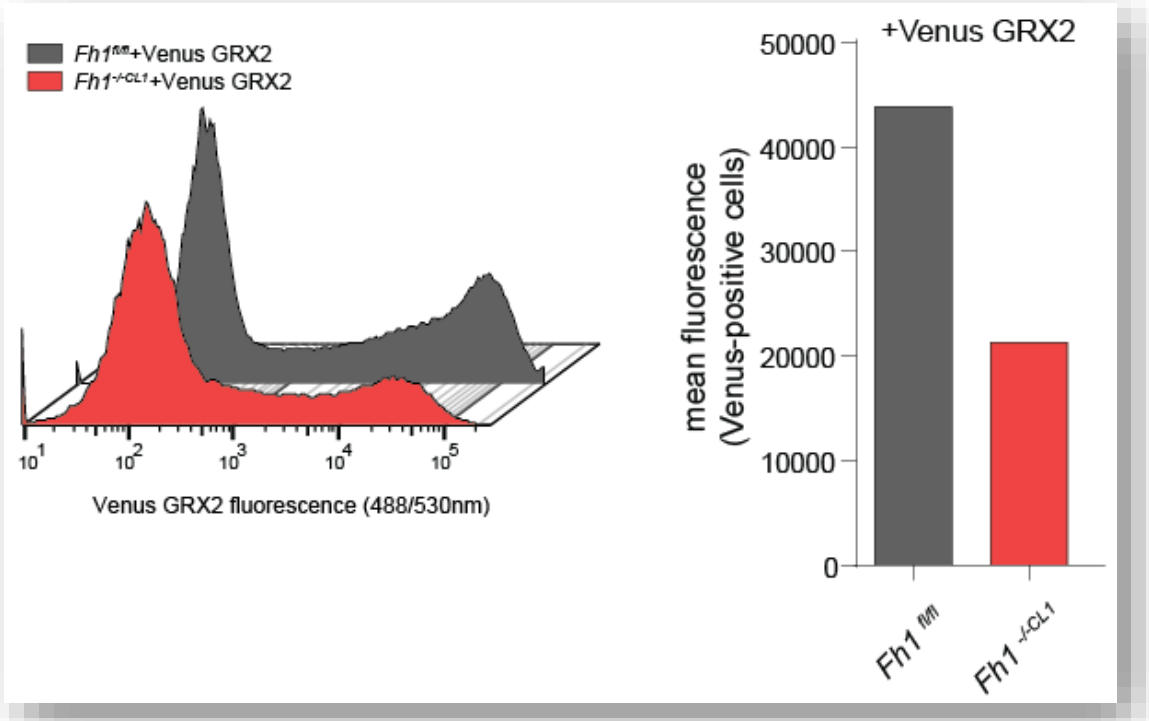
Fe-S cluster proteins and respiratory chain



Fe-S are decreased in Fh1-deficient cells



Hoff et al 2009



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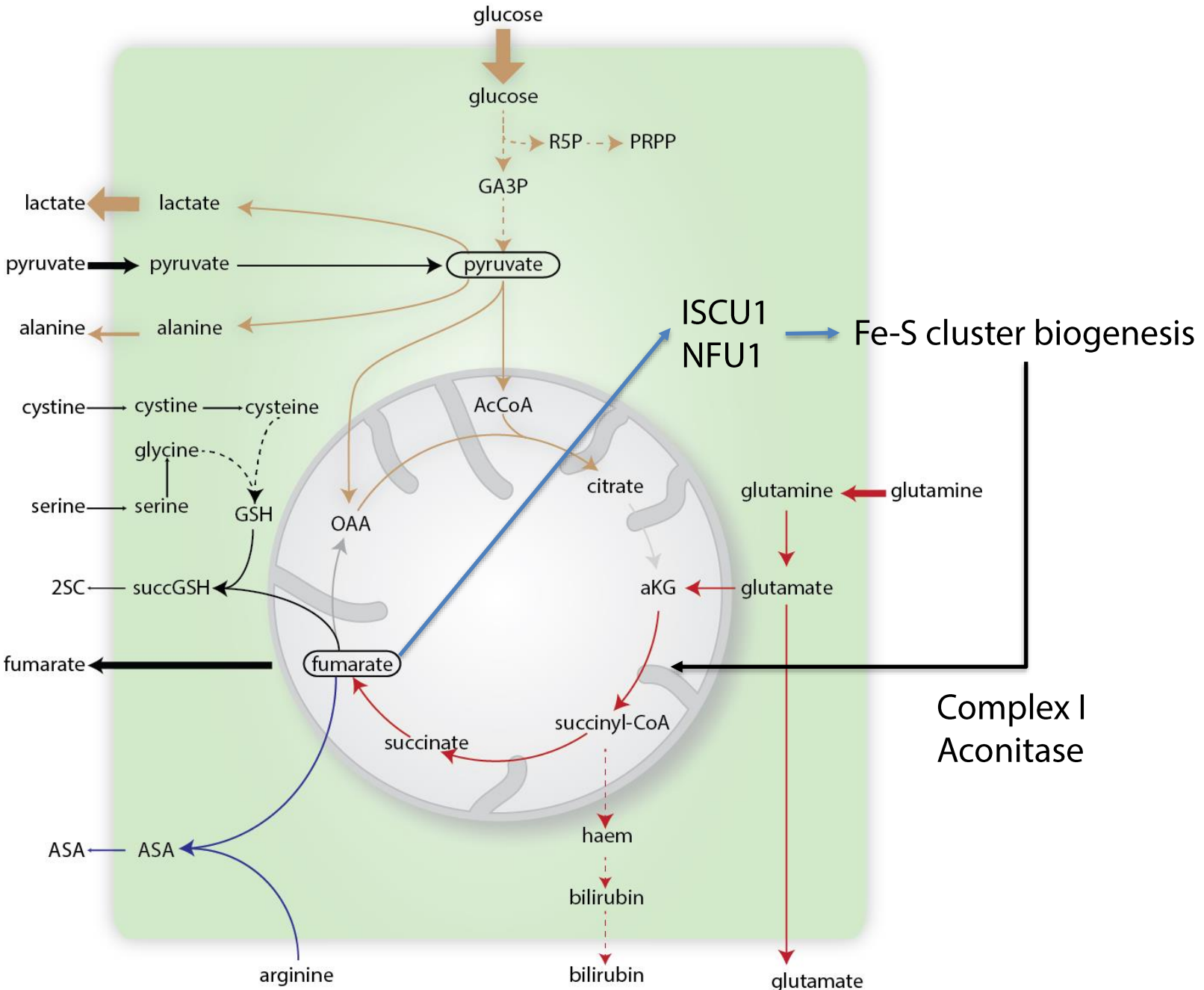

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