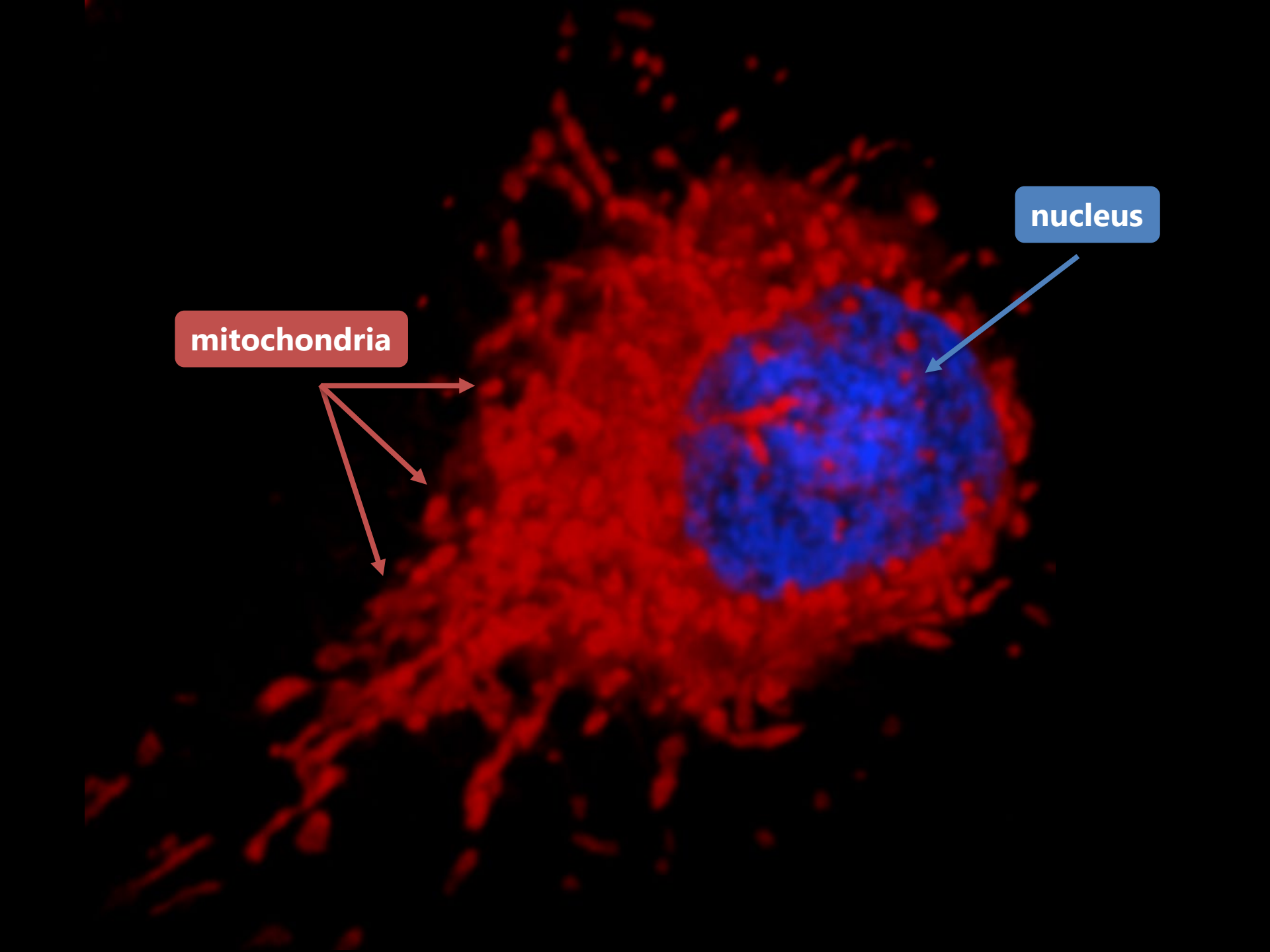
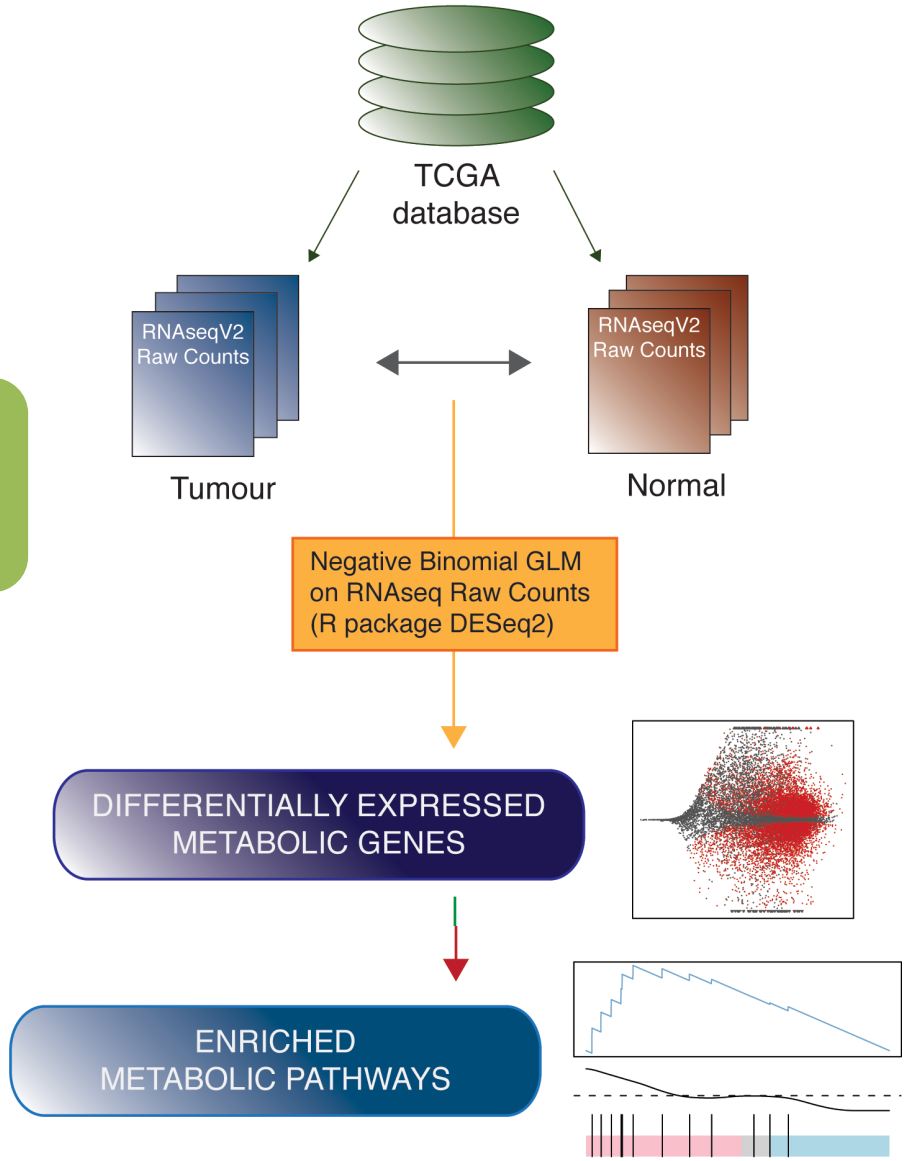
MITOCHONDRIAL DYSFUNCTION AND CANCER

Christian Frezza
MRC Cancer Unit

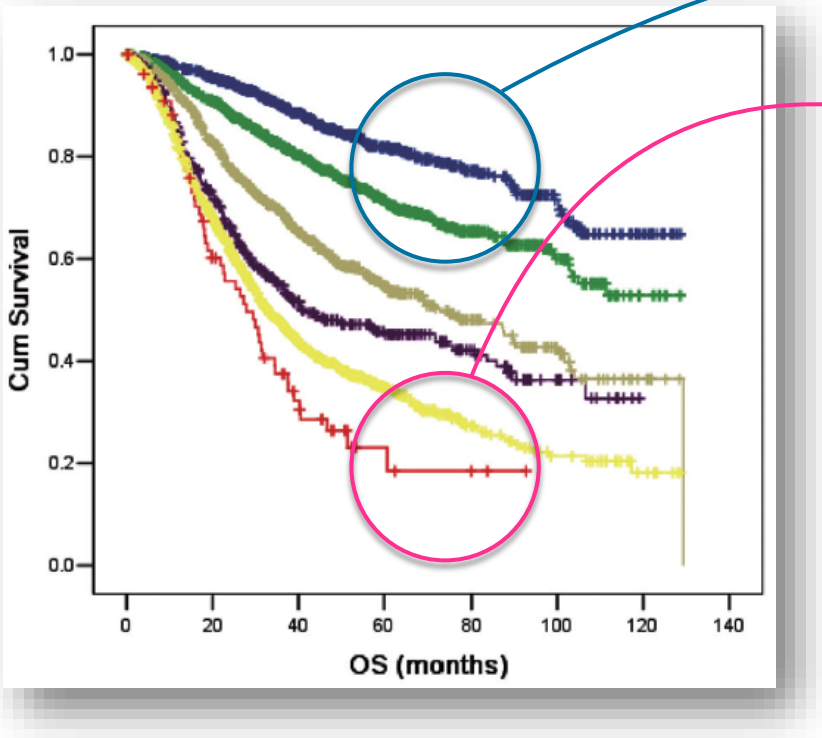

nucleus
mitochondria

METABOLIC LANDSCAPE OF CANCER

TCGA dataset
22 tumour types
>8000 patients



METABOLISM AND PATIENT OUTCOME



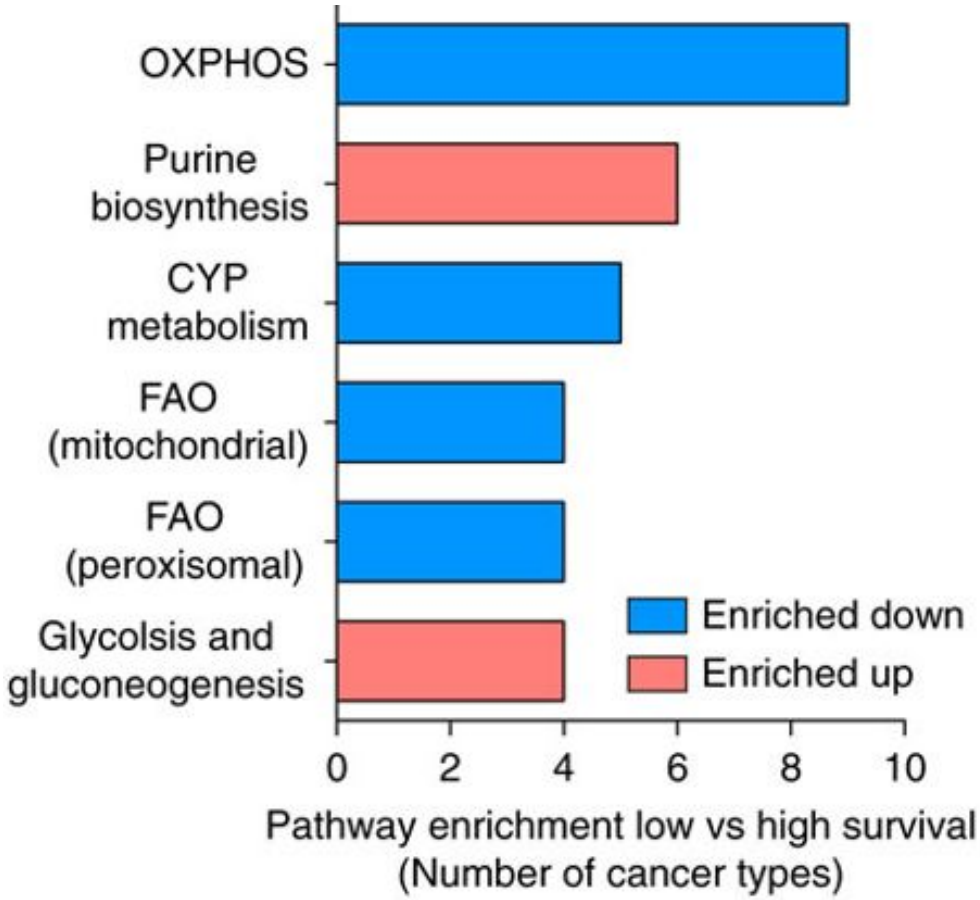
Low Survival

High Survival

Gene Set Enrichment Analysis

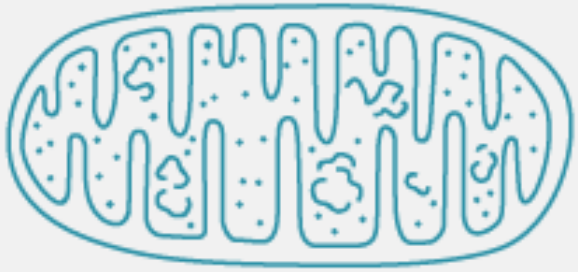
Metabolic Pathways linked to patient **survival**

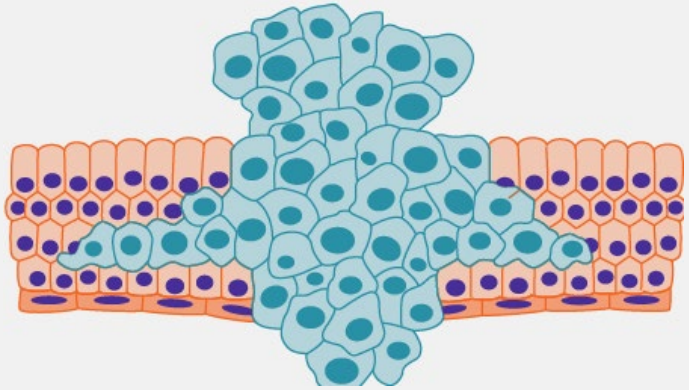
METABOLISM AND PATIENT OUTCOME



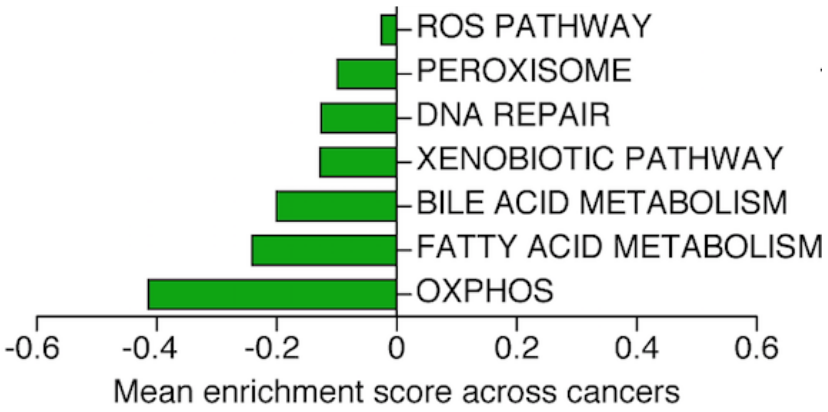
OXPHOS suppression

Cancer





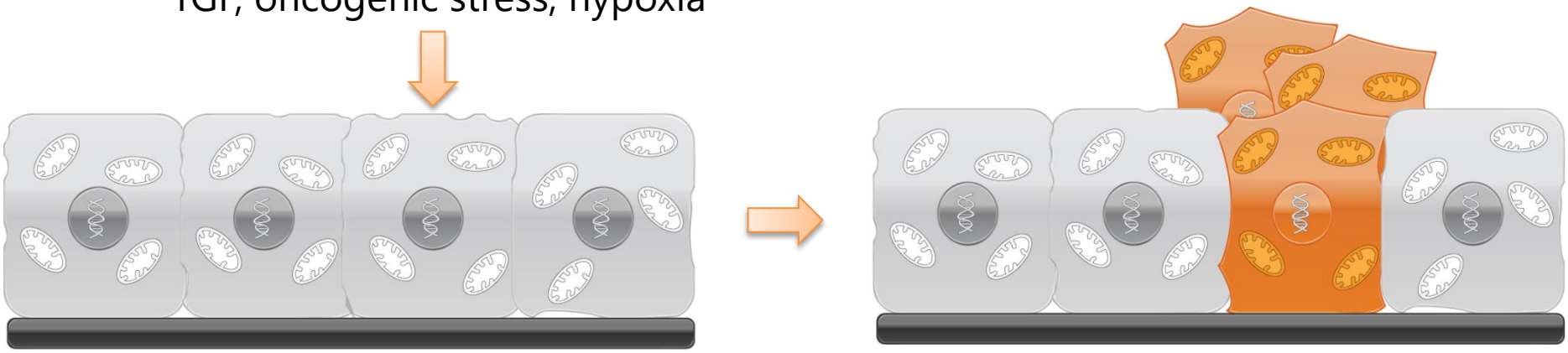
OXPHOS SUPPRESSION AND EMT



EMT: epithelial to mesenchymal transition

EPITHELIAL-TO-MESENCHYMAL TRANSITION (EMT)

TGF, oncogenic stress, hypoxia



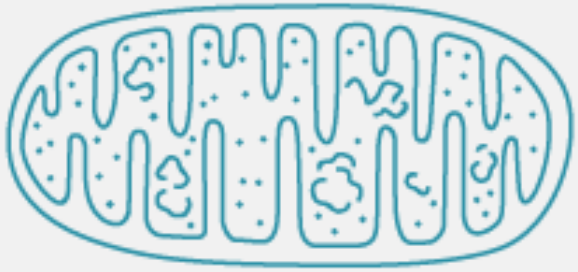
epithelial cell

mesenchymal cells

migration

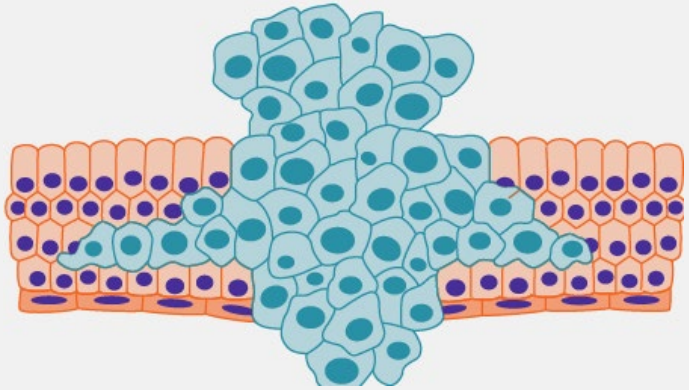
metastasis

OXPHOS suppression



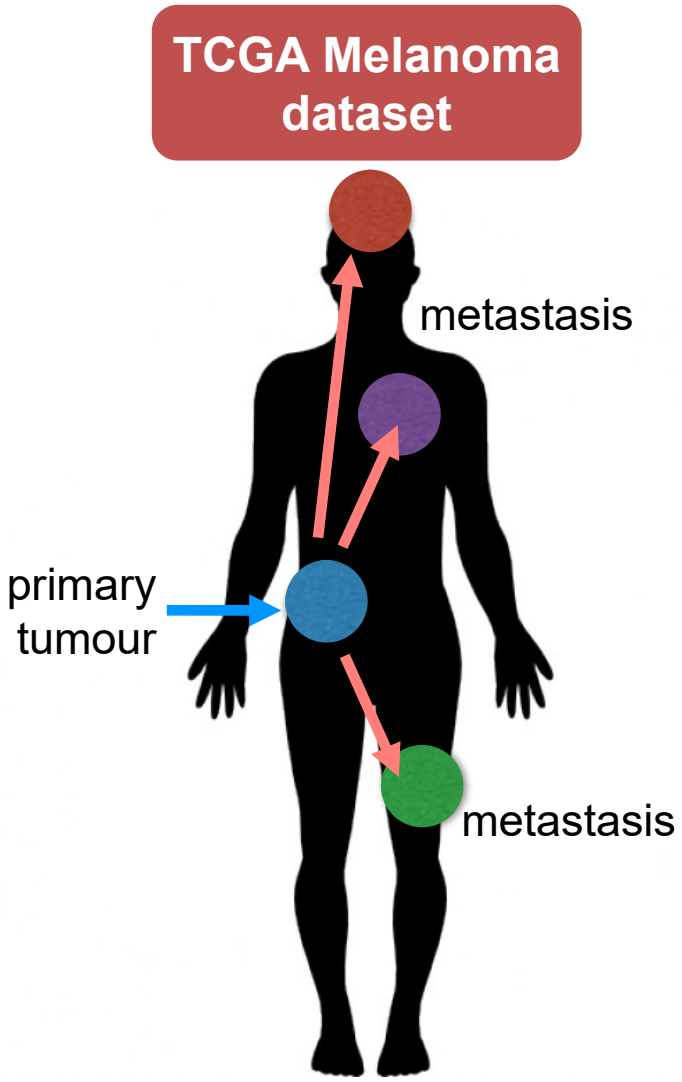
EMT

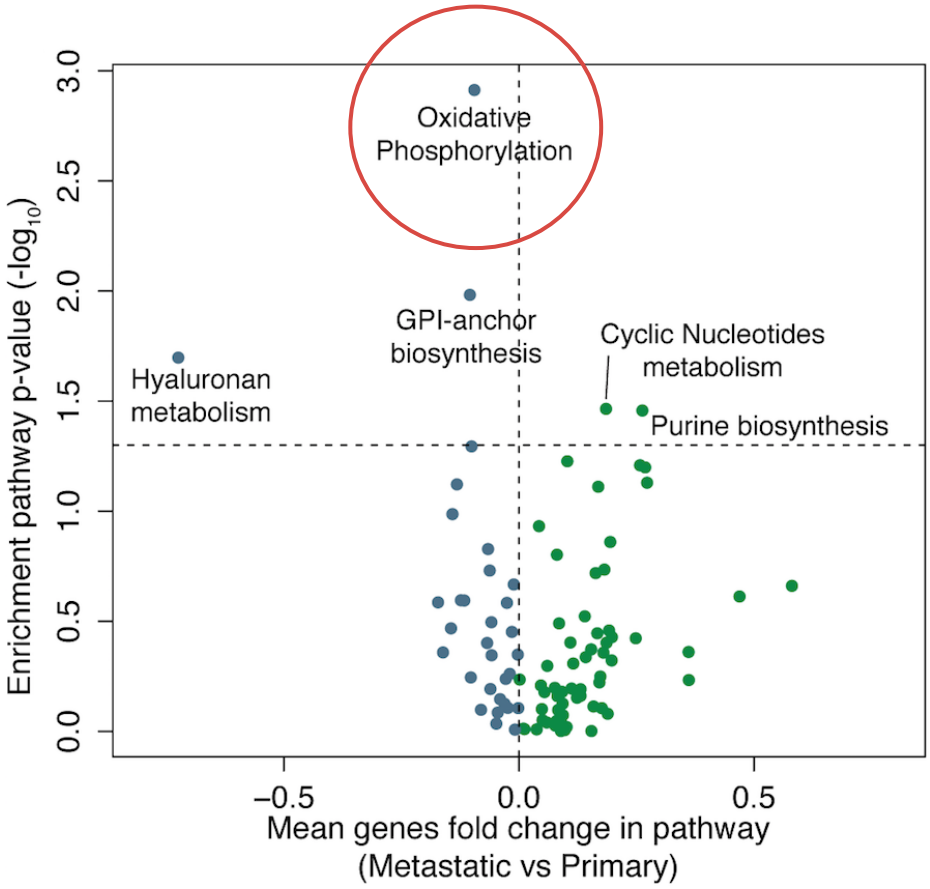
Cancer



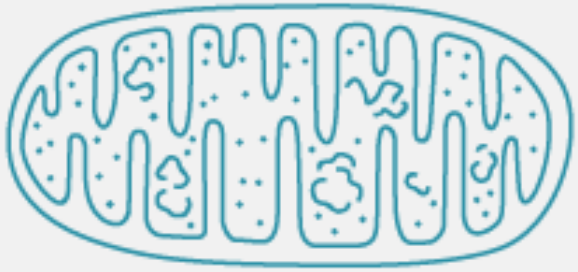
Metastasis

OXPHOS IS SUPPRESSED IN METASTATIC MELANOMA





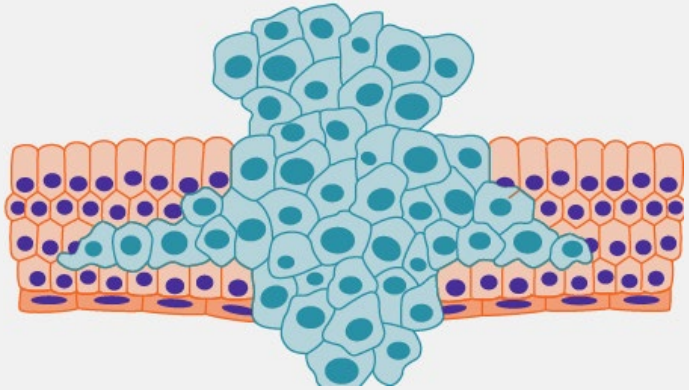
OXPHOS suppression



?

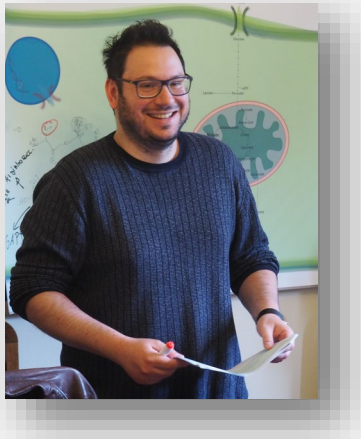
EMT

Cancer

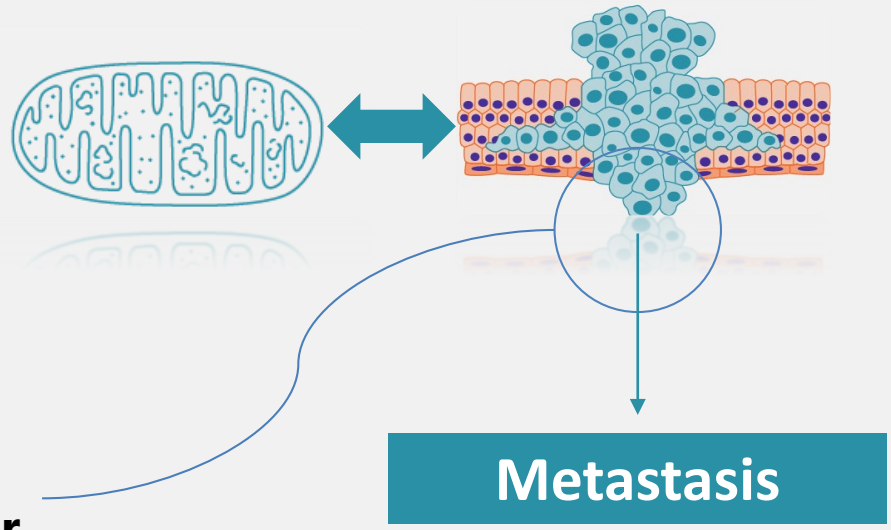


?

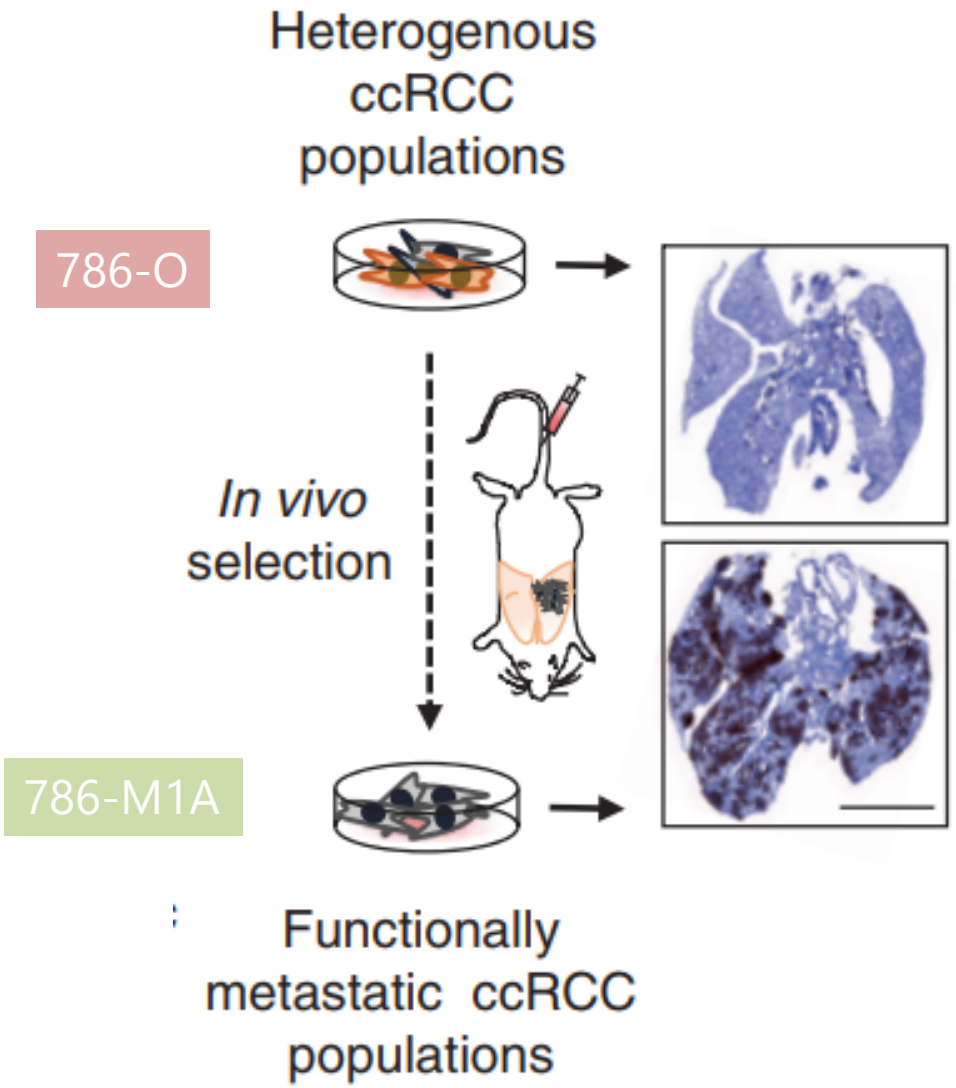
Metastasis



MARCO SCIACOVELLI
Metastatic renal cancer

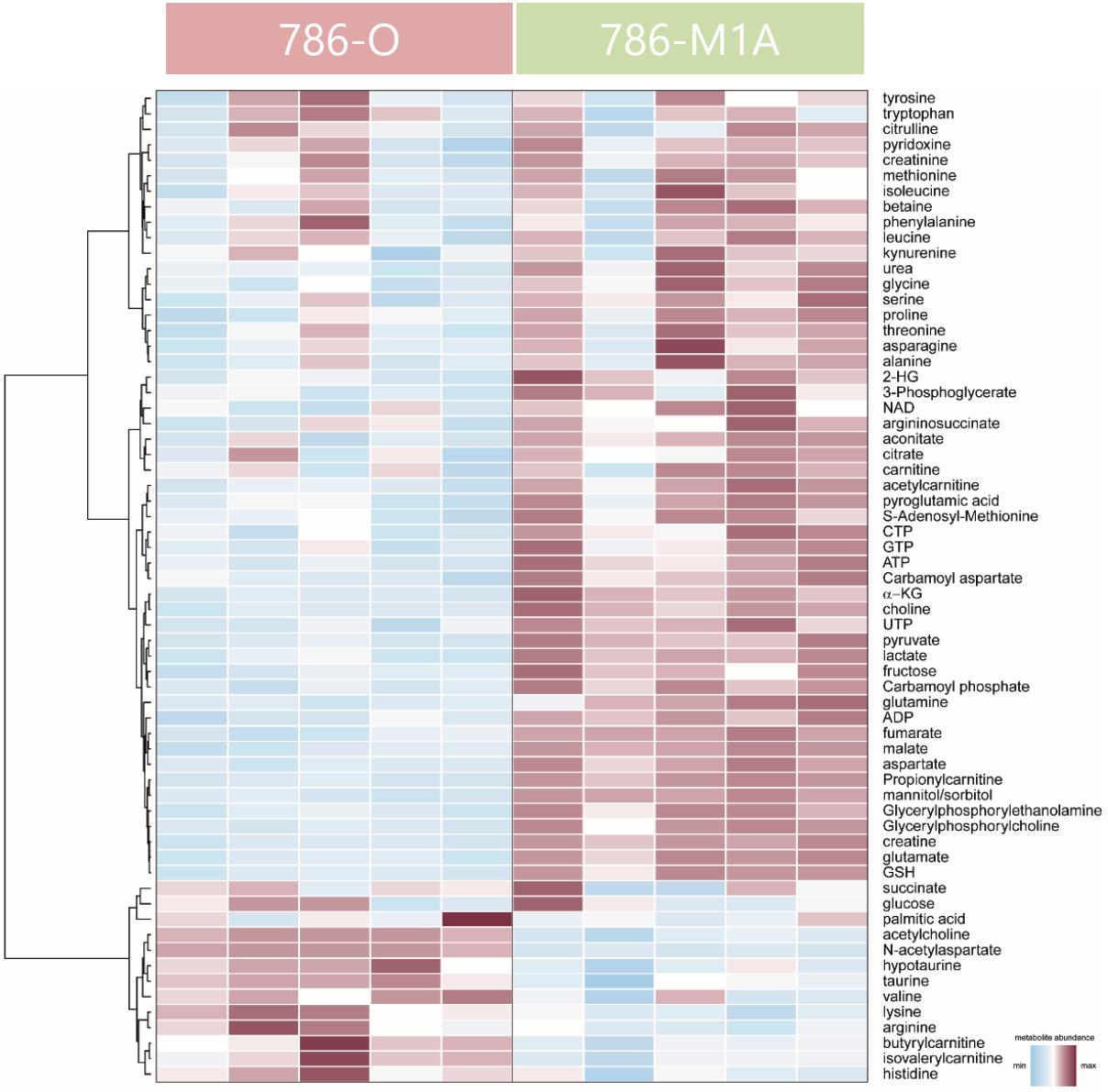


MODELS OF CLEAR CELL RENAL CANCER (ccRCC)



Adapted from Vanharanta et al.2012
Rodrigues et al.2018

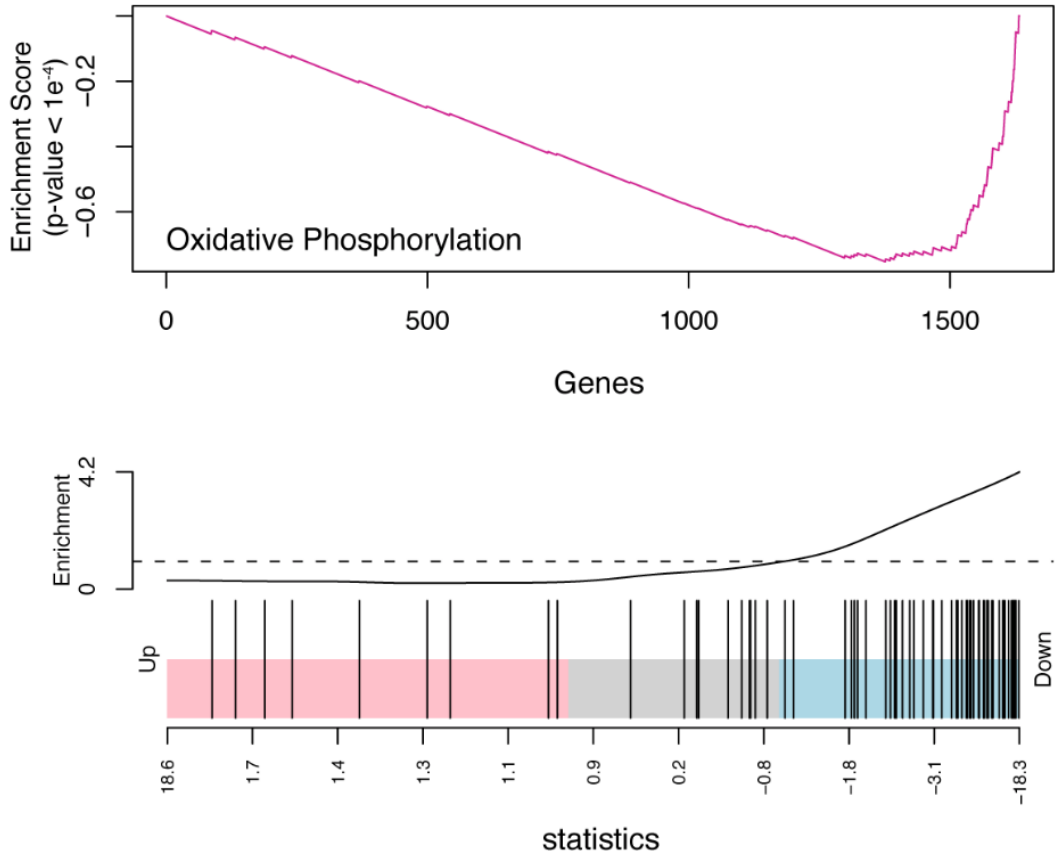
METABOLIC SIGNATURE OF METASTATIC ccRCC



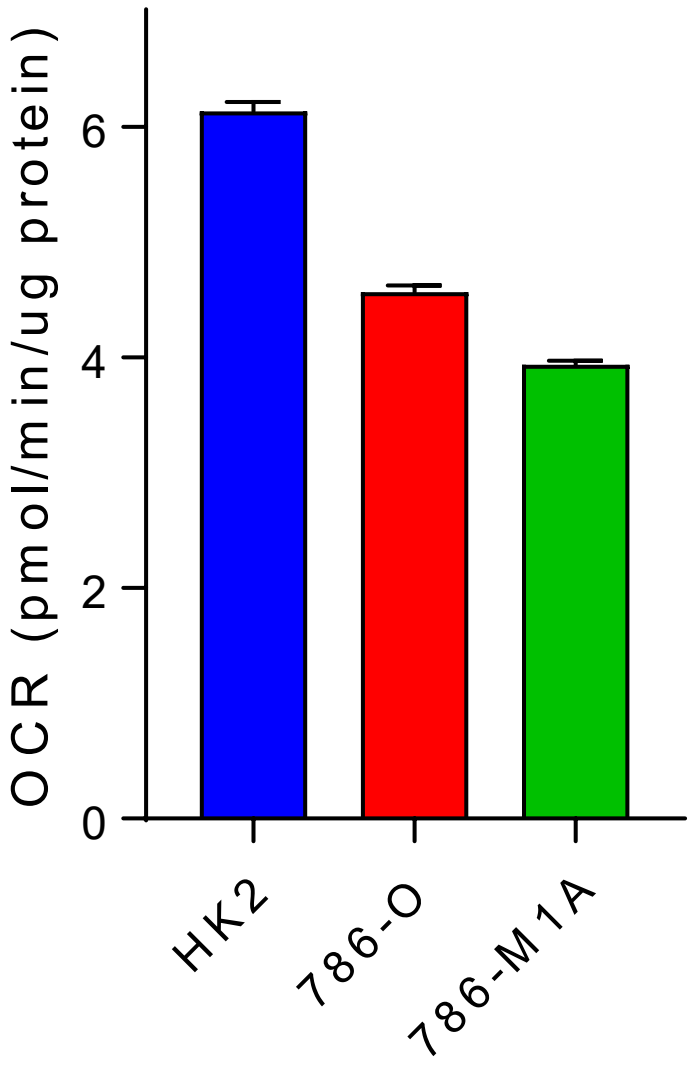
Liquid Chromatography Mass Spectrometry

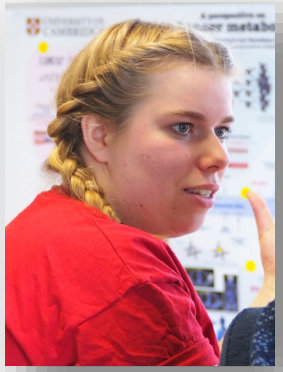
OXPHOS IS SUPPRESSED IN METASTATIC ccRCC

786-M1A vs 786-O



OXPHOS IS SUPPRESSED IN METASTATIC ccRCC

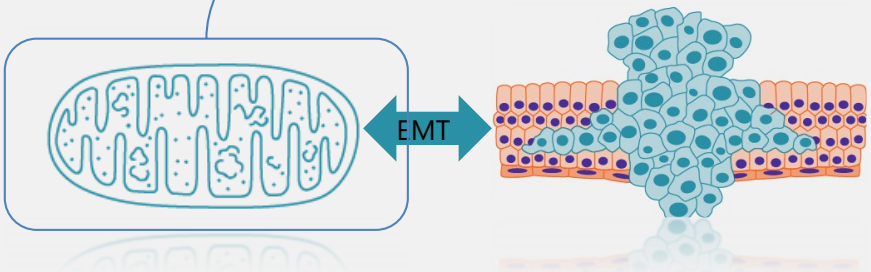




CHRISTINA SCHMIDT

FH deficient renal cancers

MARCO SCIACOVELLI



FH MUTATIONS CAUSE HLRCC

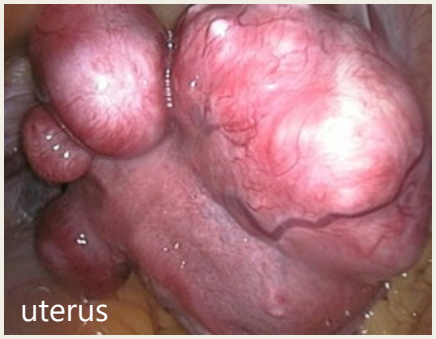
HLRCC

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

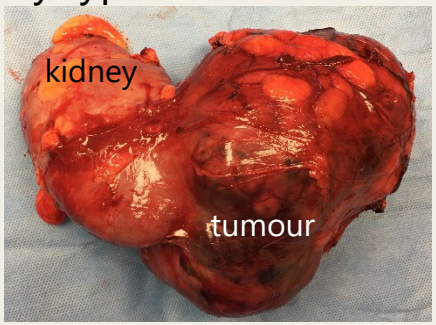
The Multiple Leiomyoma Consortium

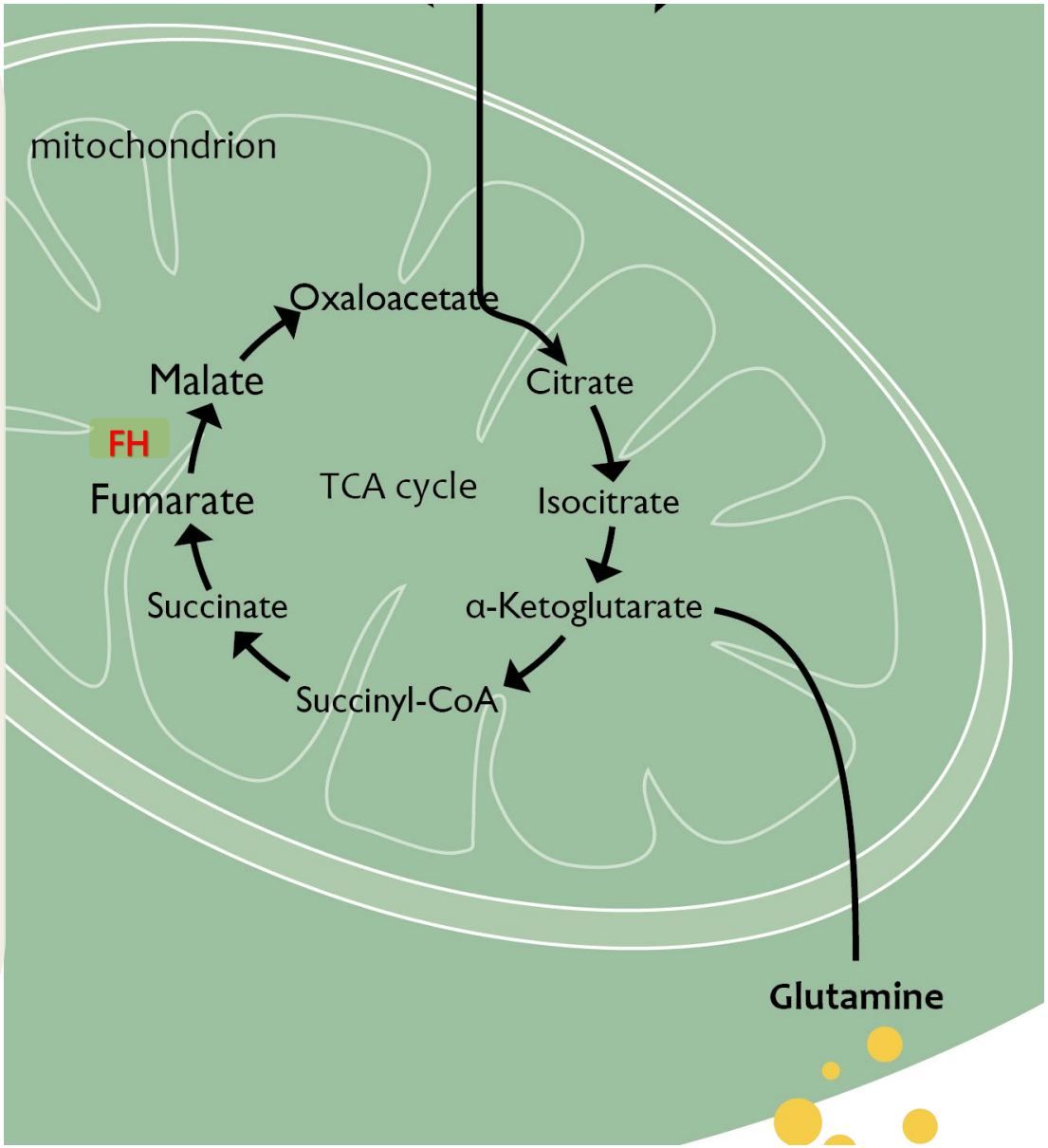
Published online: 25 Febrary 2002, DOI: 10.1038/ng849

- Benign tumours of the skin and uterus

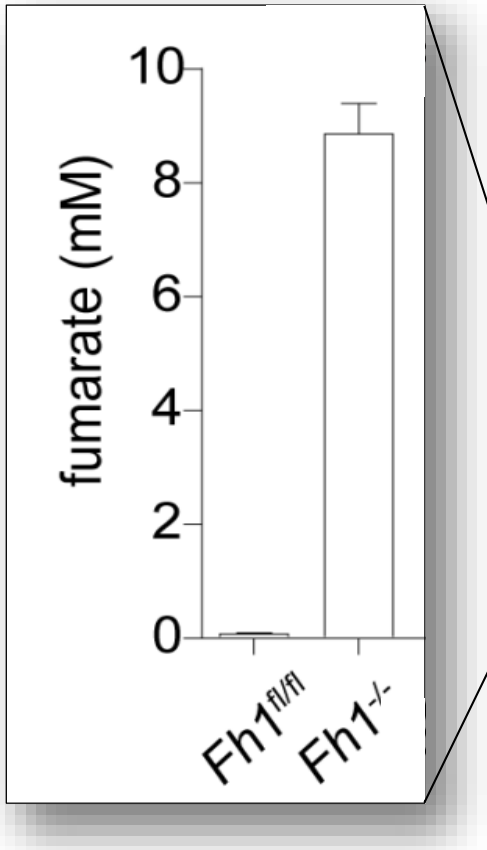


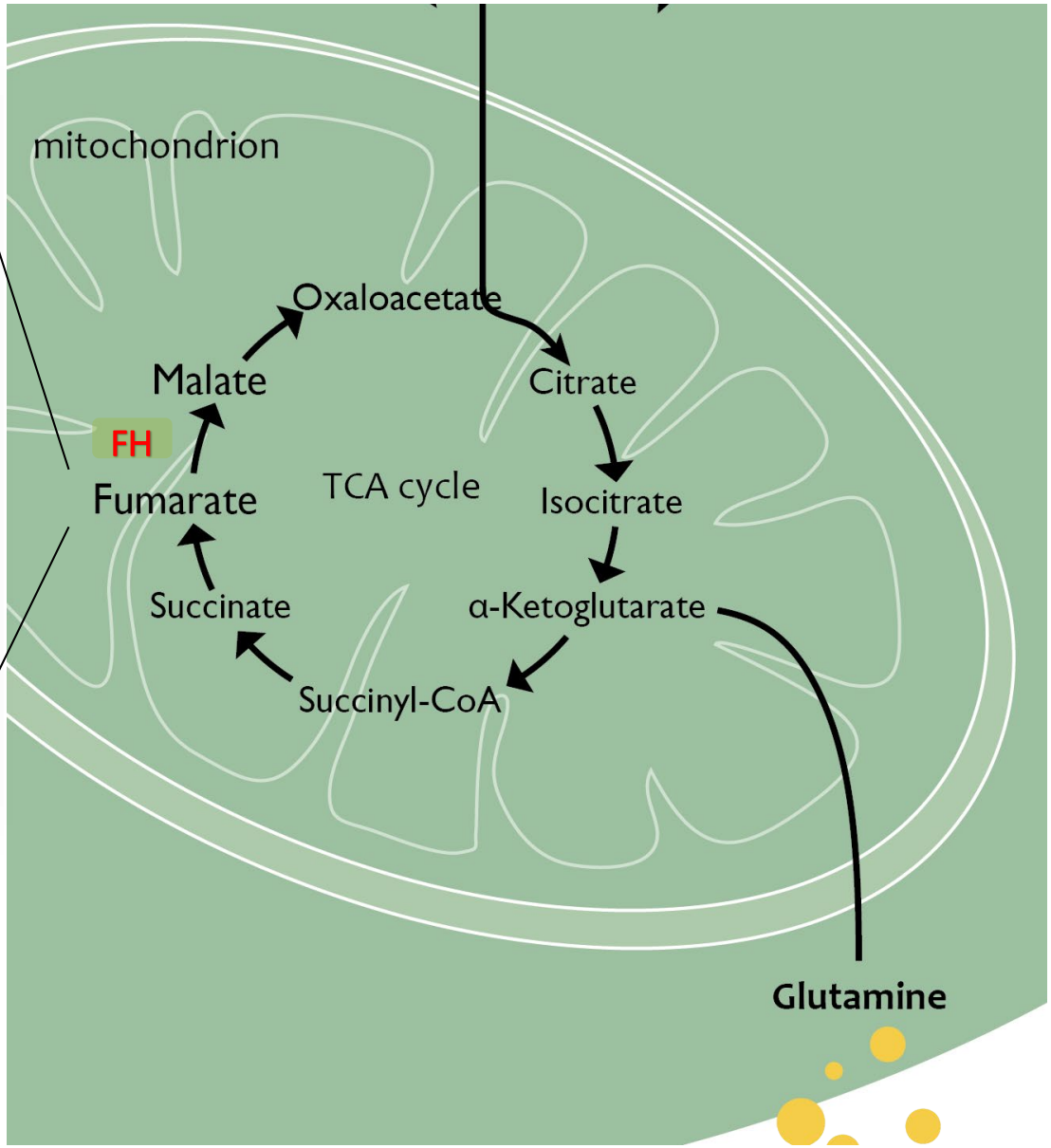
- Papillary type 2 renal cell carcinoma



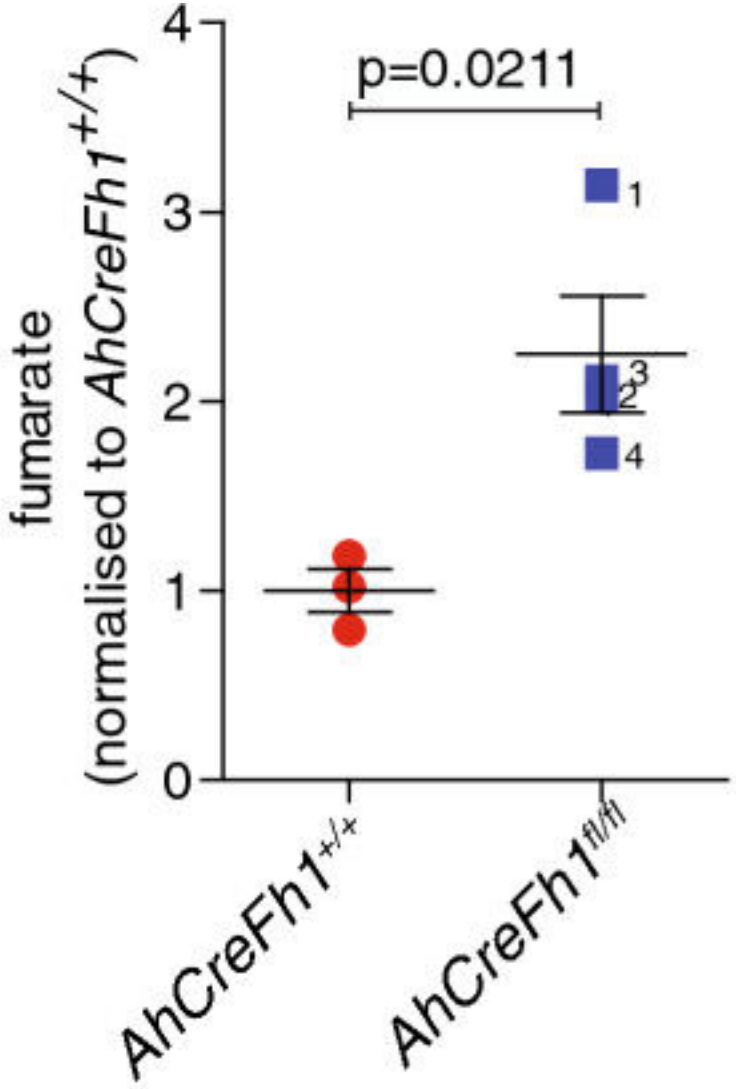


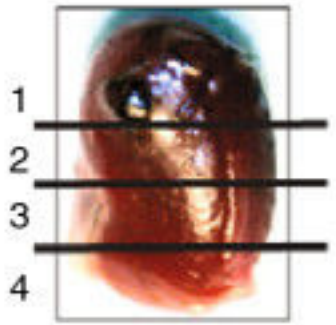
FUMARATE ACCUMULATES IN FH-DEFICIENT CELLS



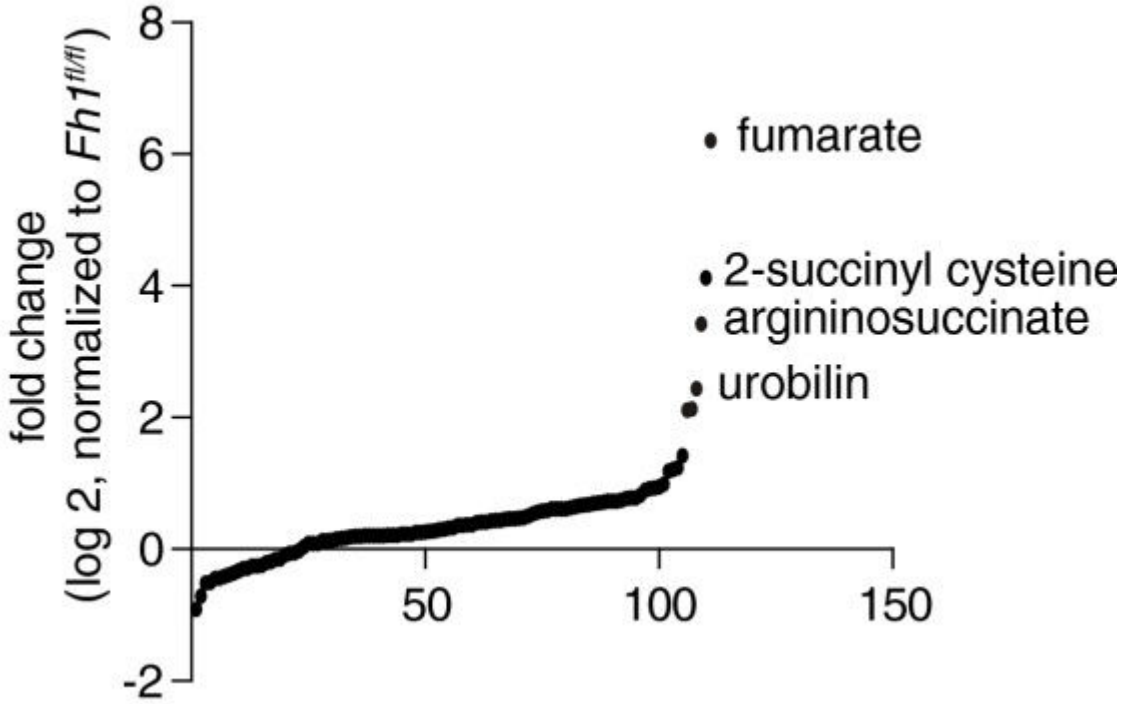


FH1-DEFICIENT MOUSE MODEL: THE KIDNEY

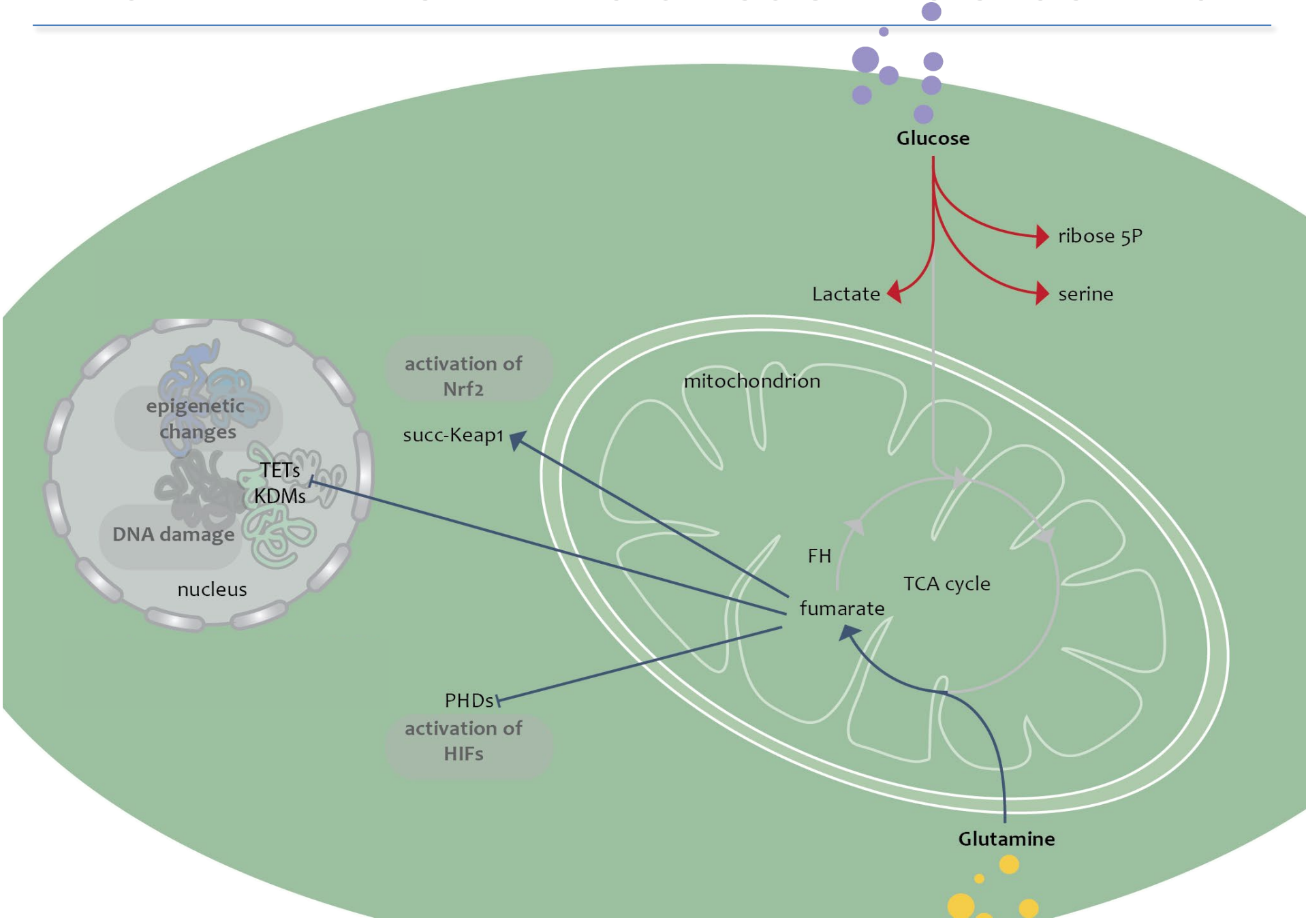




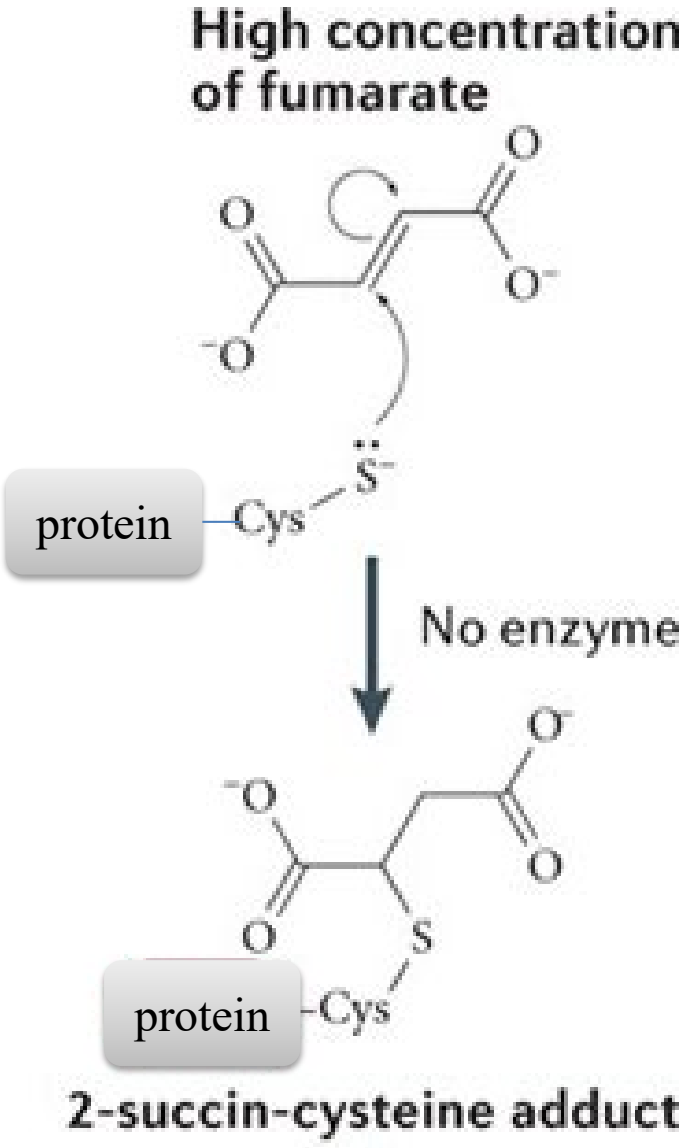
FH1-DEFICIENT MOUSE MODEL: URINE



FUMARATE ACTIVATES ONCOGENIC CASCADES



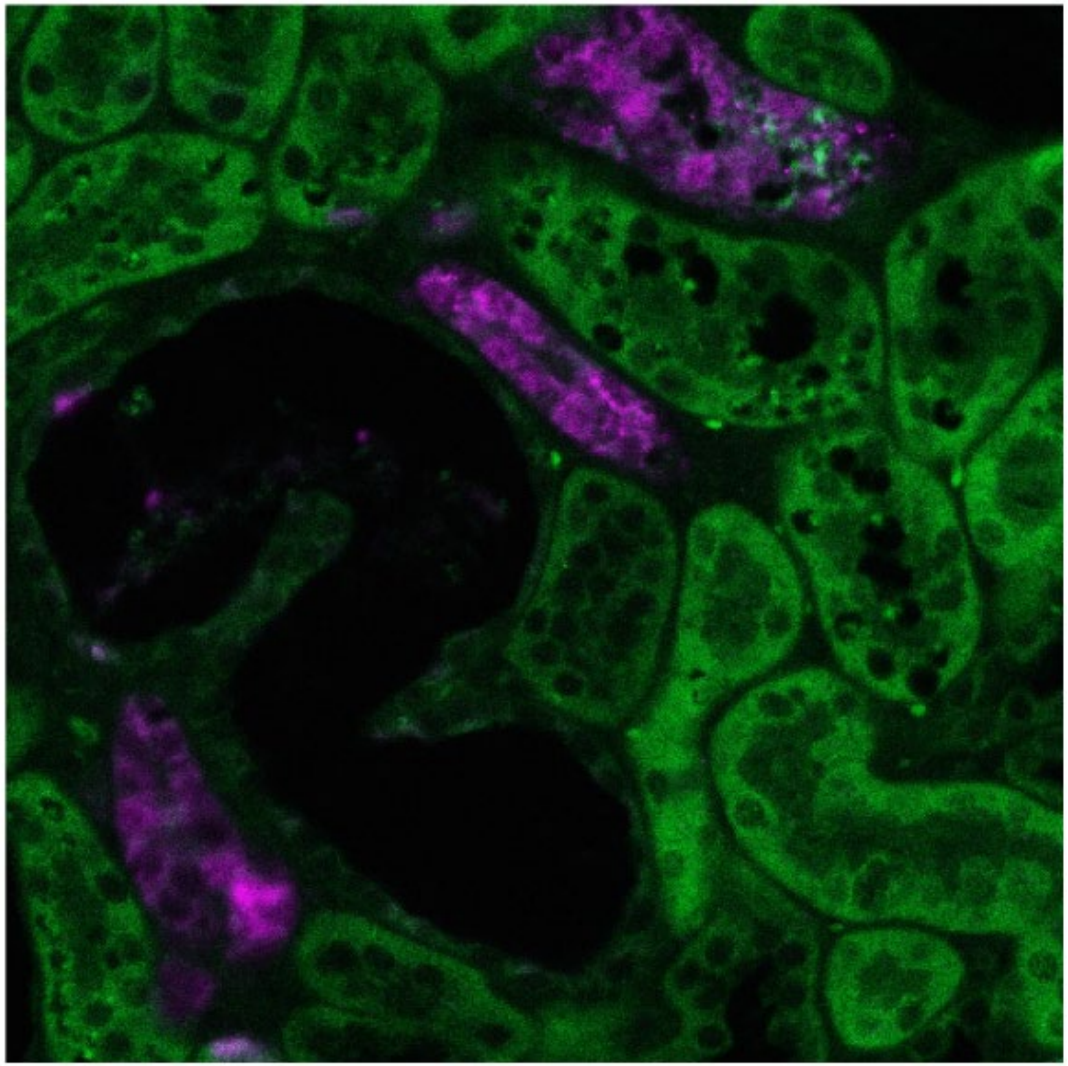
FUMARATE CAUSES PROTEIN SUCCINATION



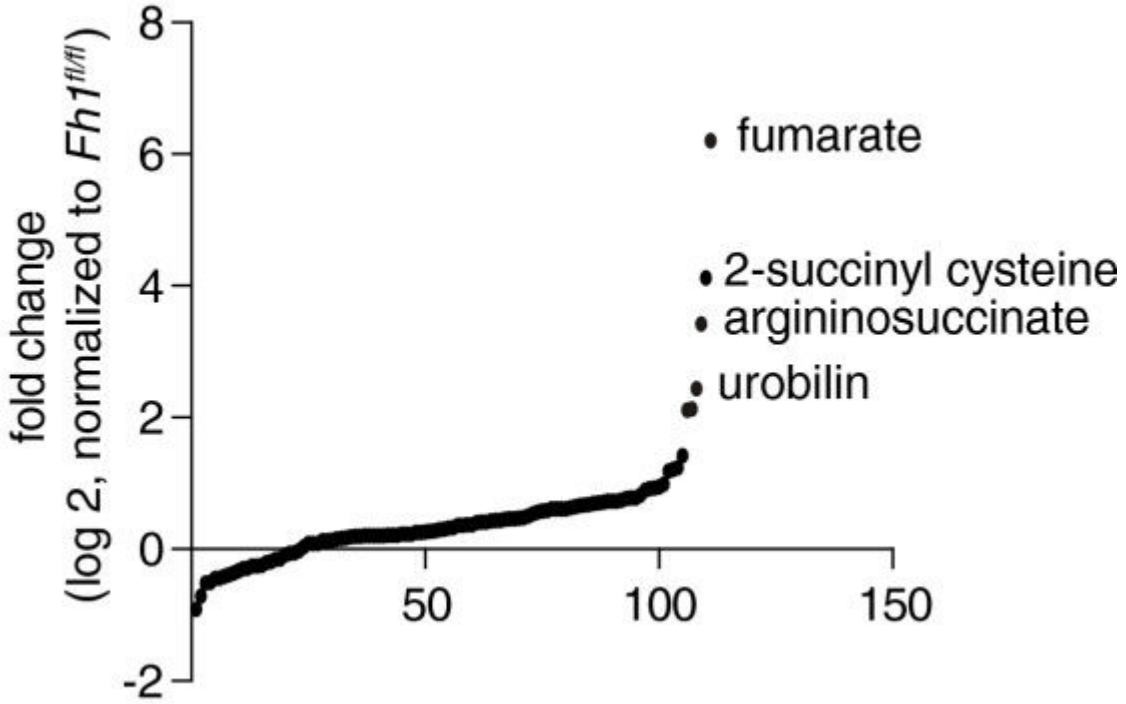
SUCCINATION IS A MARKER OF FH LOSS

Fh1-deficient mouse kidney

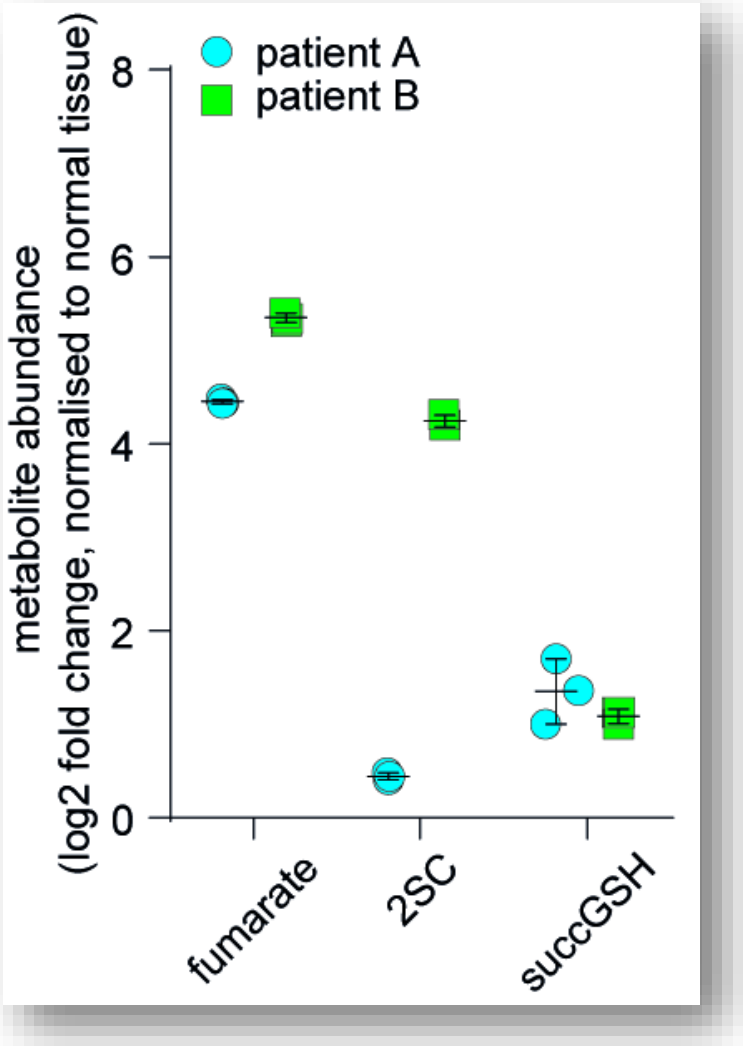
Green: FH
Magenta: 2SC



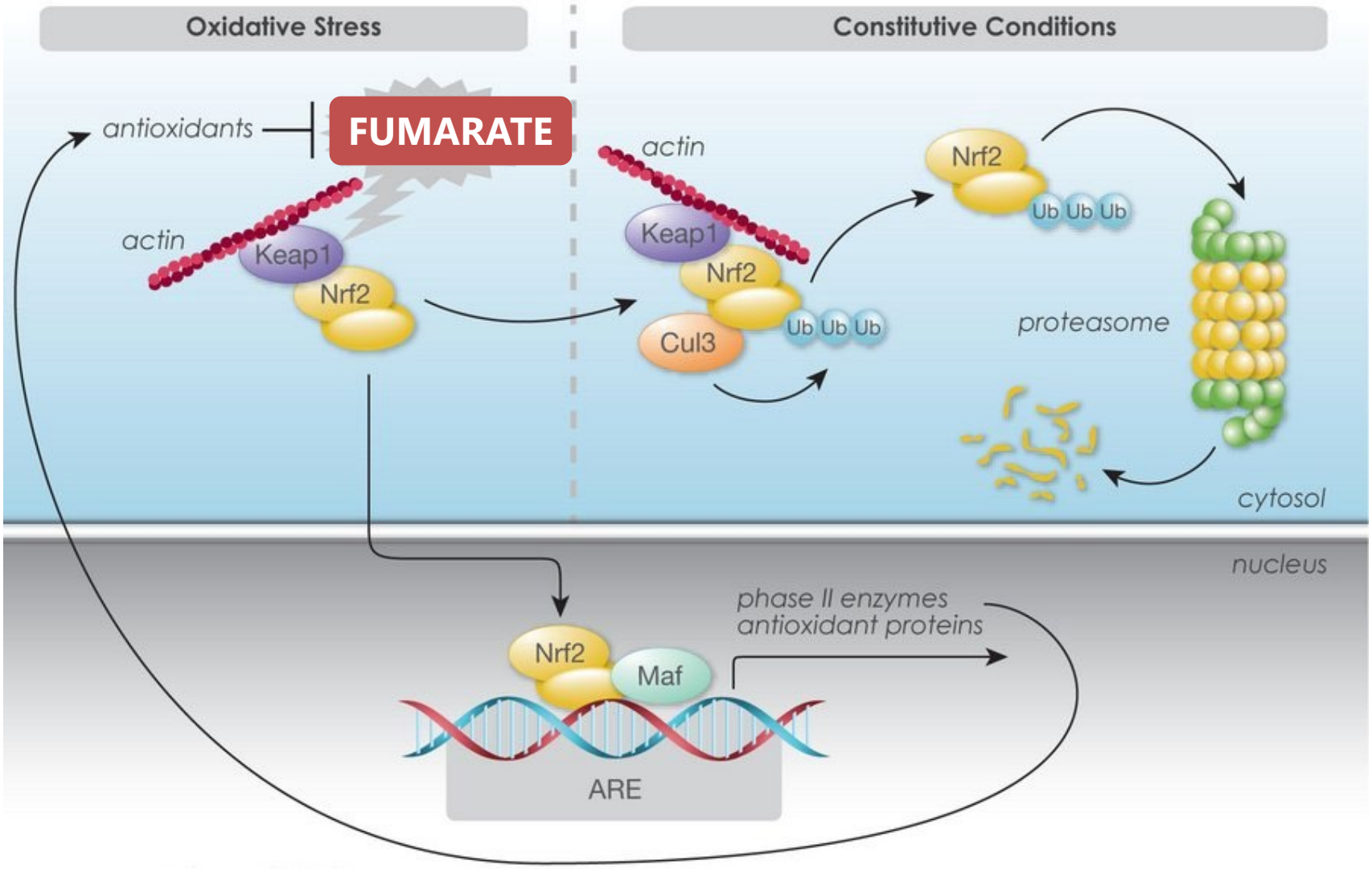
FH1-DEFICIENT MOUSE MODEL: URINE



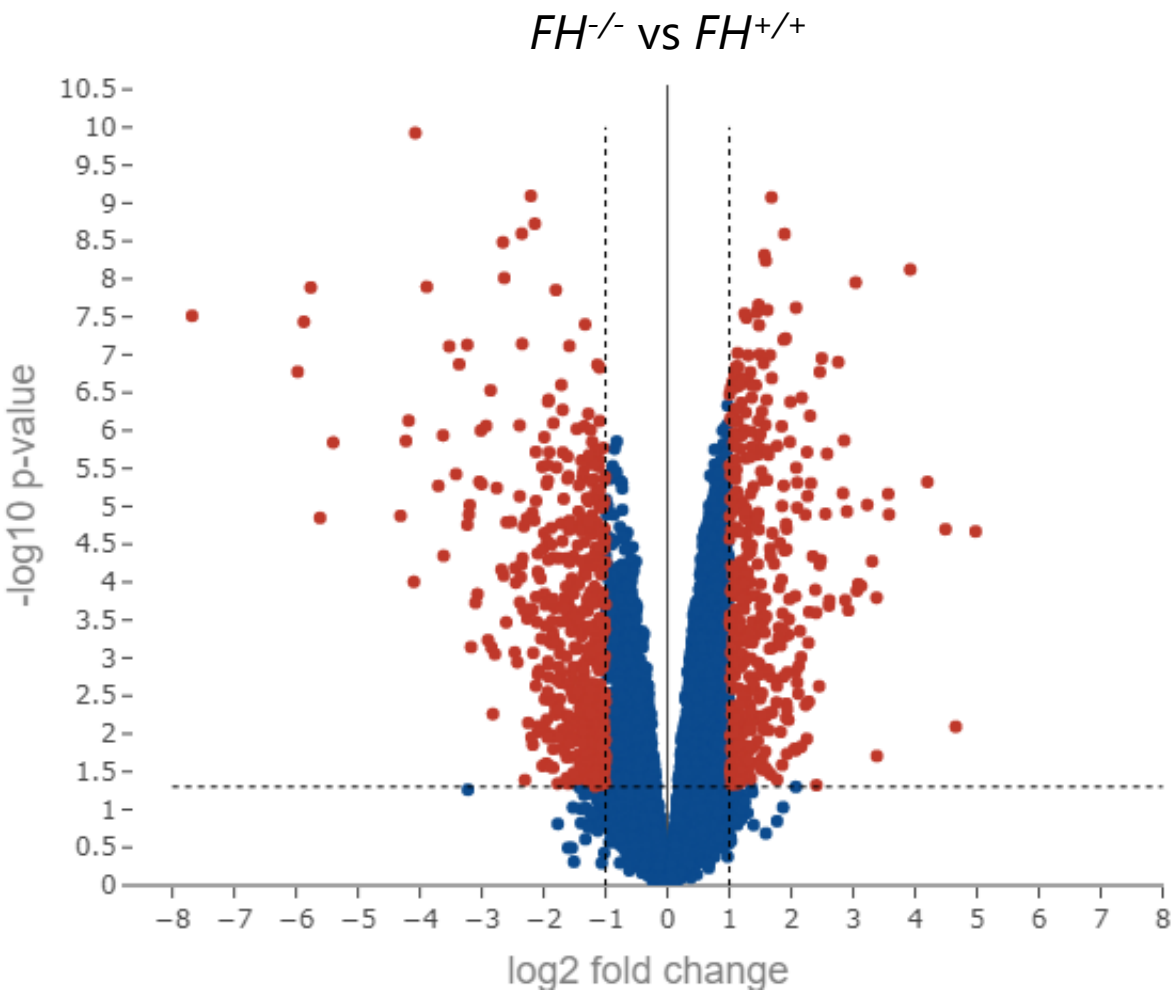
FUMARATE-DEPENDENT SIGNATURE IN HLRCC

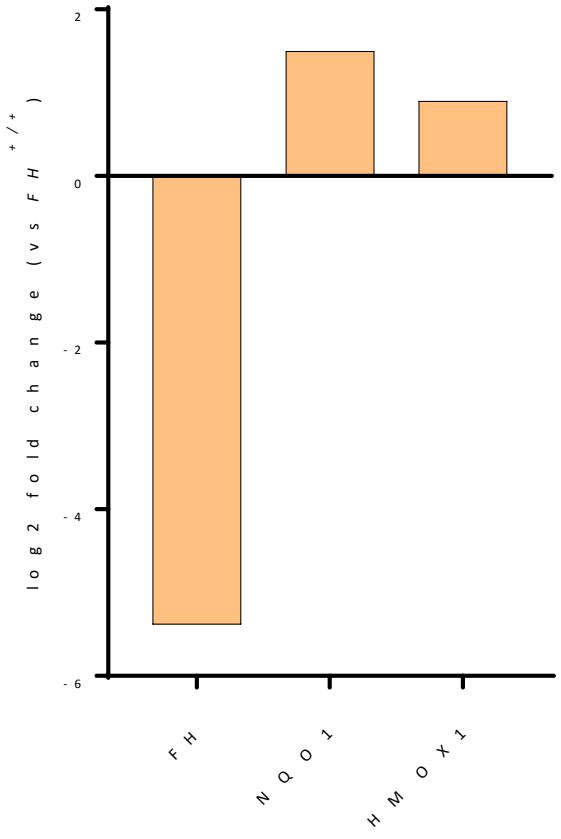


REGULATION OF NRF2 STABILITY

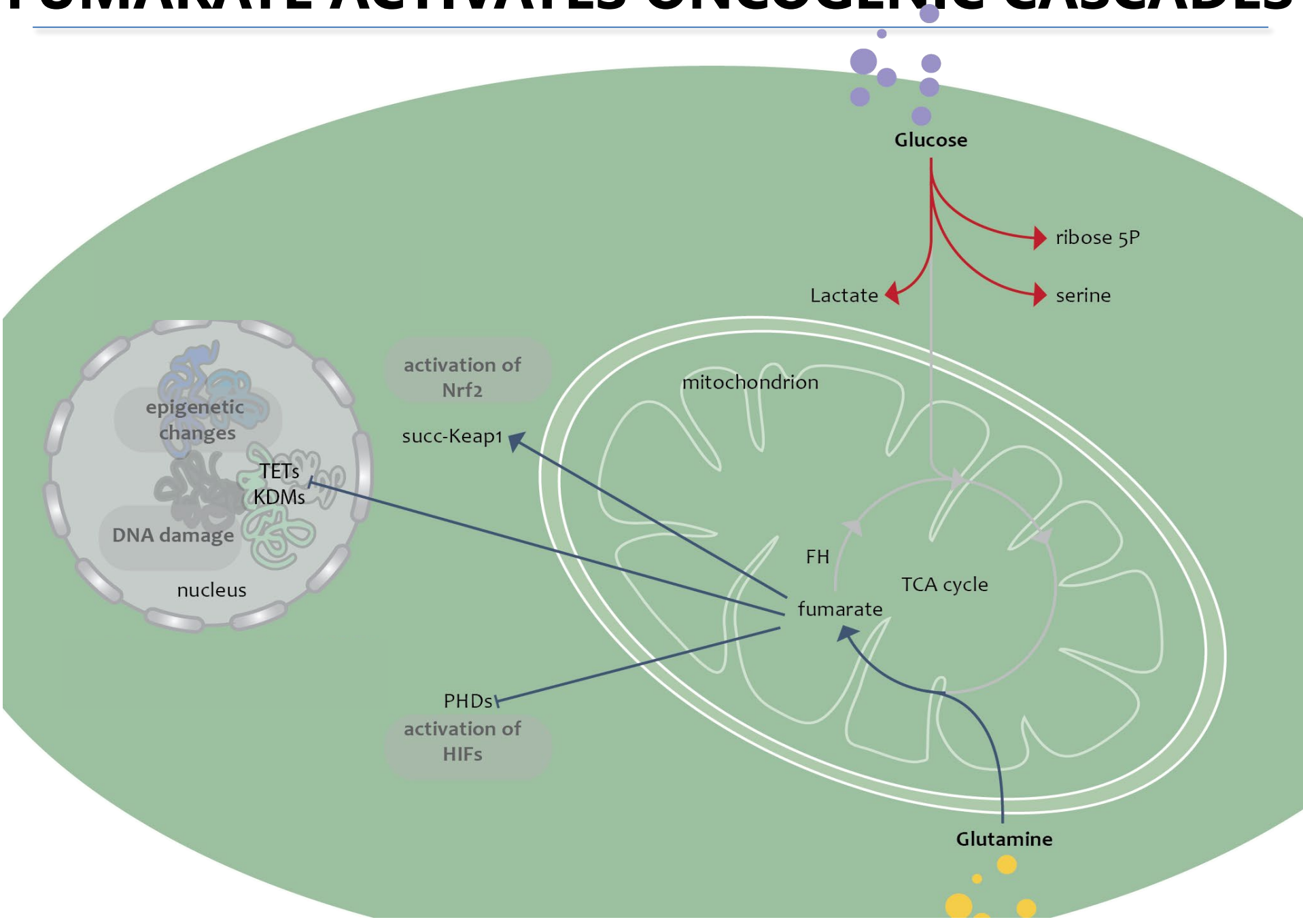


NRF2 SIGNATURE IN FH-DEFICIENT CELLS

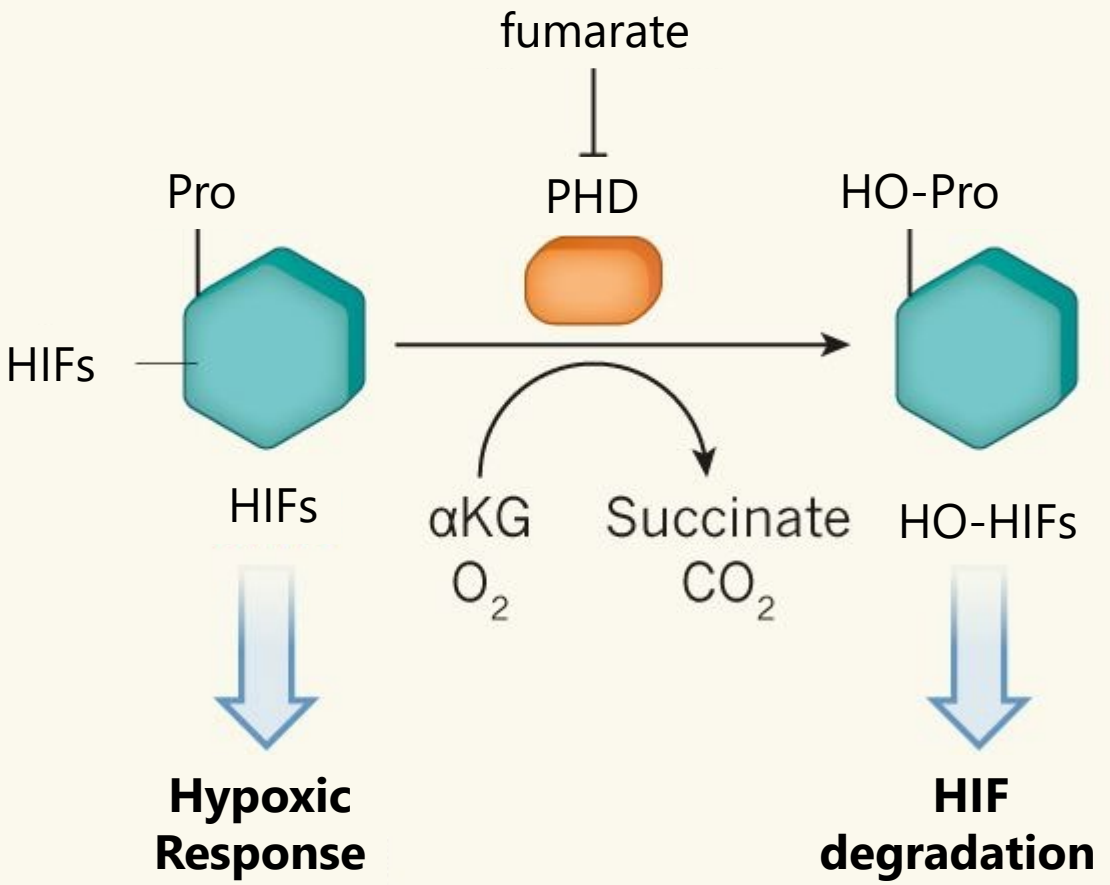




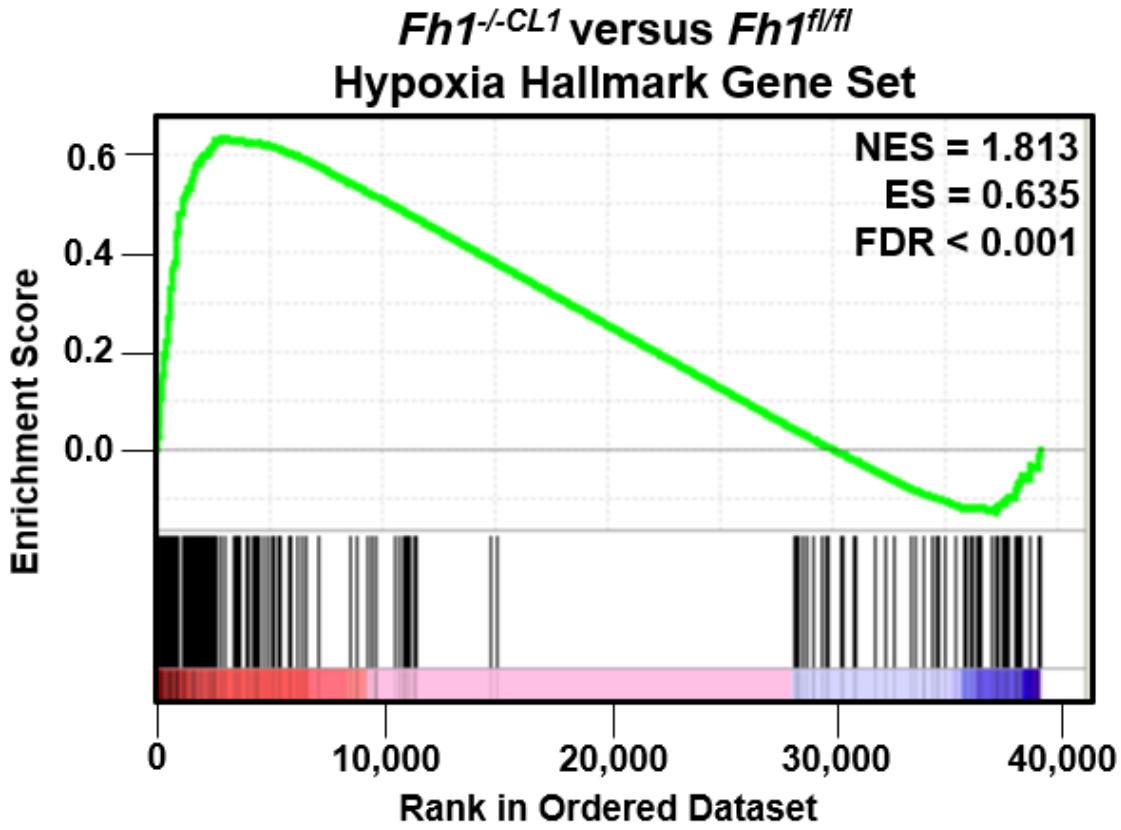
FUMARATE ACTIVATES ONCOGENIC CASCADES



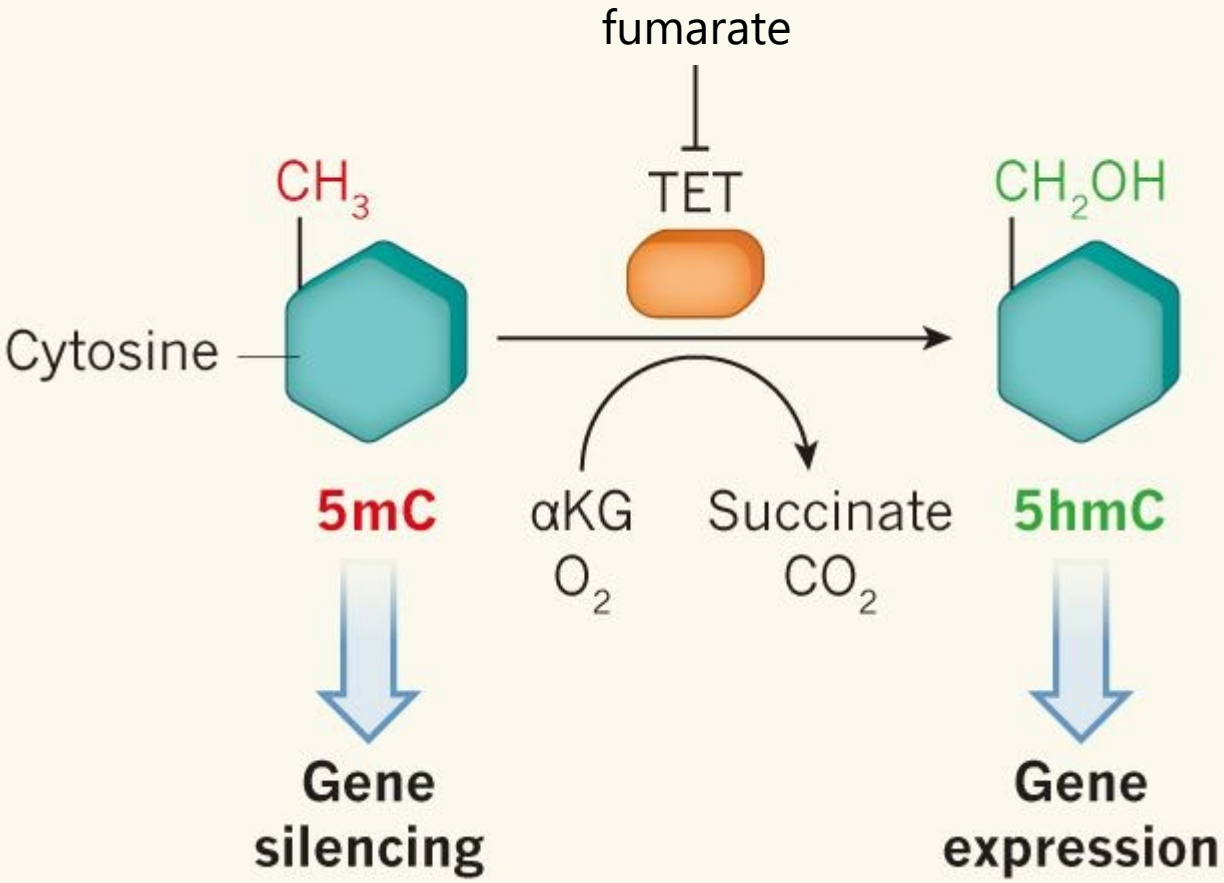
FUMARATE INHIBITS PROLYL HYDROXYLASES



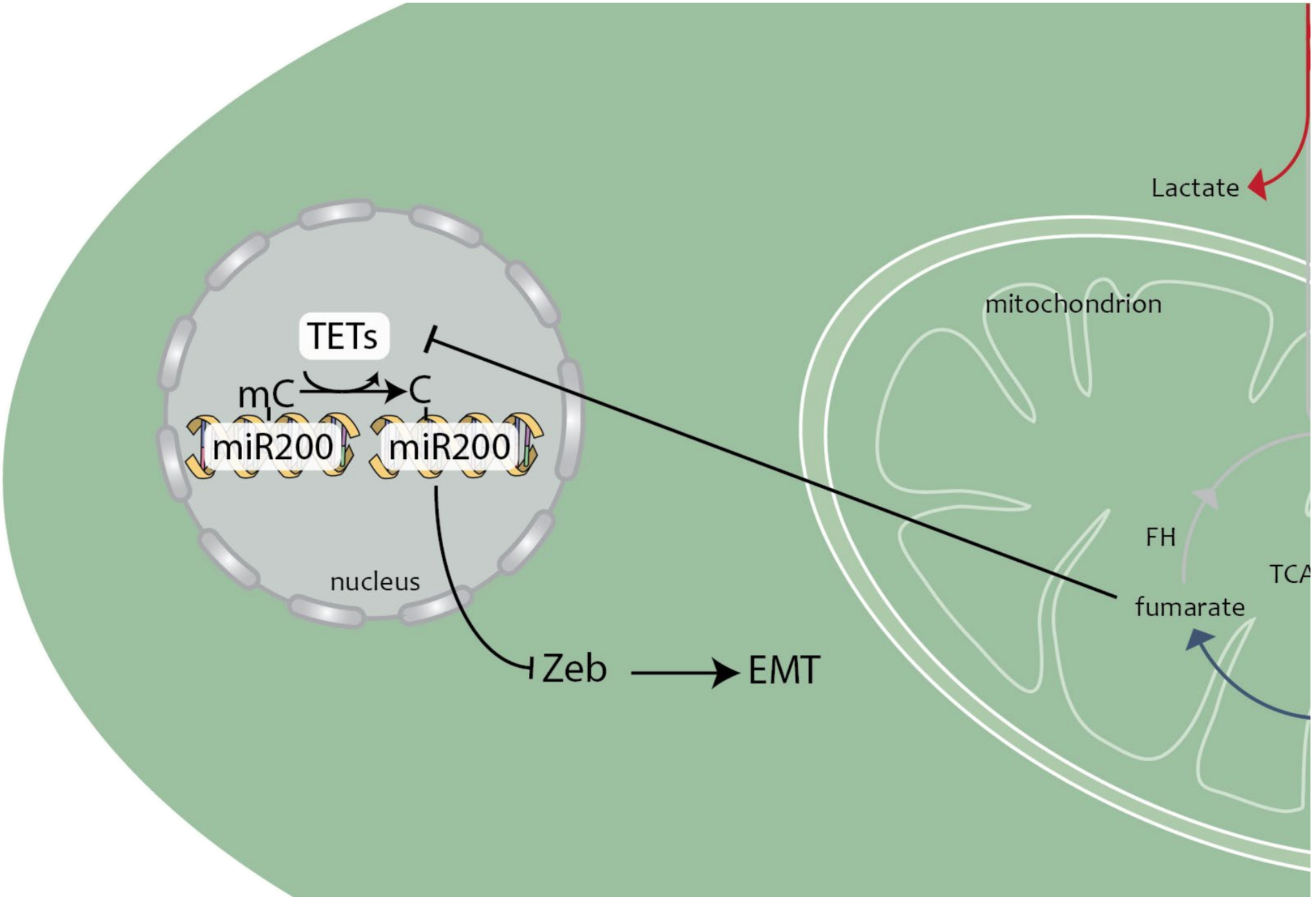
PSEUDOHYPOXIA IN FH1-DEFICIENT CELLS



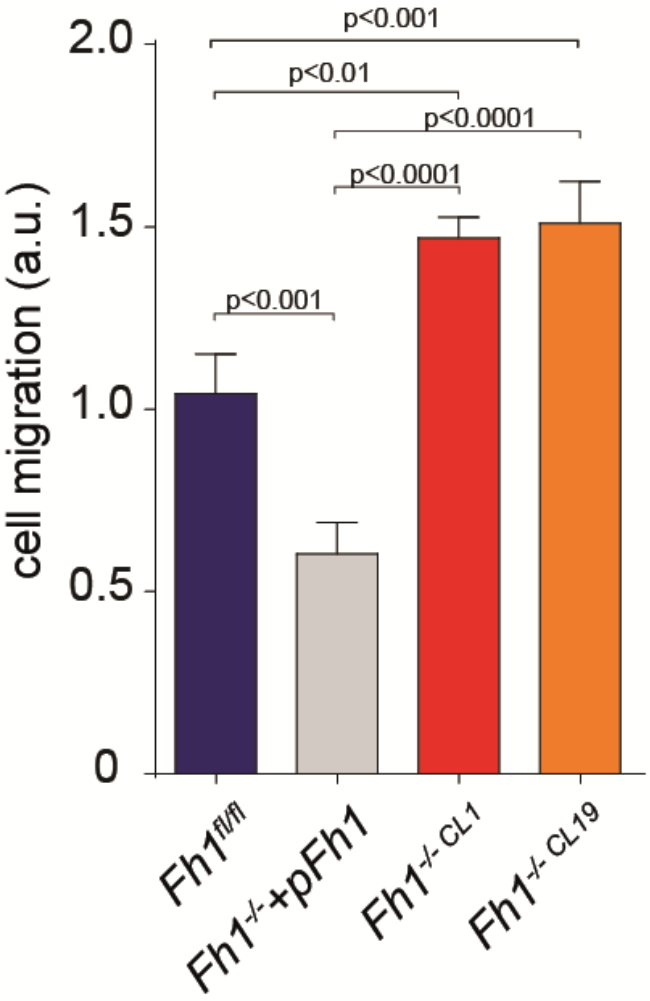
FUMARATE INHIBITS DNA DEMETHYLASES

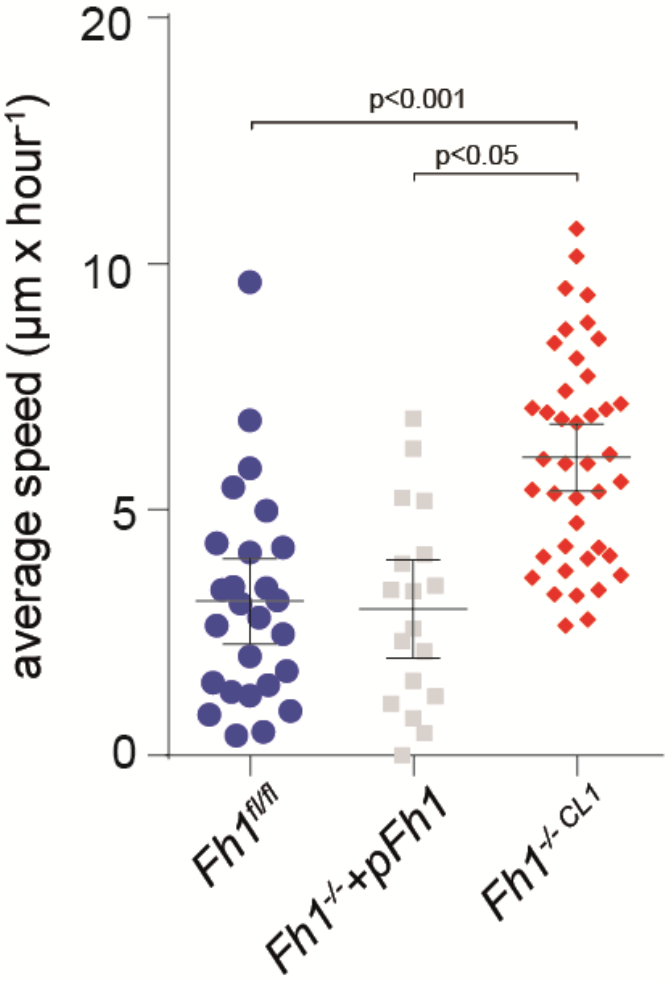


FUMARATE SUPPRESSES *MIR200* AND DRIVES EMT

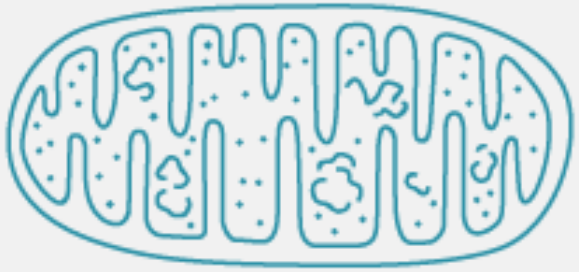


FH LOSS DRIVES CELL MIGRATION





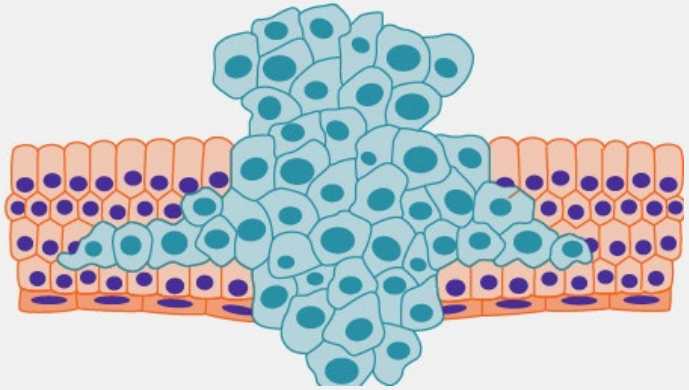
FH loss



Fumarate

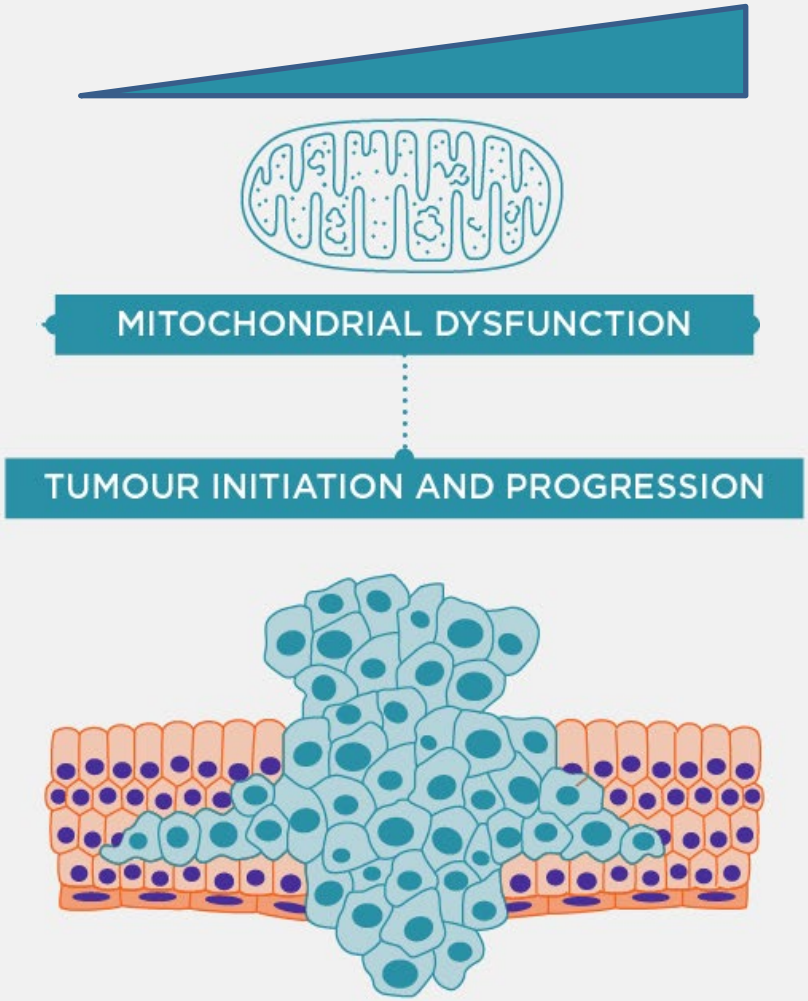
EMT
HIF
NRF2

cancer



Metastasis

MITOCHONDRIAL DYSFUNCTION AND CANCER



Key Collaborators:

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Sakari Vanharanta

University of Heidelberg
Julio Saez Rodriguez

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