Ankersmit Laboratory

for Diagnosis & Regeneration in Thoracic Diseases & Applied Immunology

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Mitochondrial iron chelation ameliorates cigarette smoke-induced bronchitis and emphysema in mice

Cloonan SM et al.

Nat Med. 2016 Jan 11. doi: 10.1038/nm.4021. [Epub ahead of print]

Introduction

COPD is linked to cigarette smoking and genetic determinants

Clinical phenotypes:

- Airway inflammation (chronic bronchitis)
- Destruction of lung tissue (emphysema)
- remodeling of the small airways

Pathogenesis:

- Aberrant Inflammatory
- Dysregulated cellular responses to cigarette smoke (CS)

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IRP2

Iron-responsive element-binding protein 2

- is increased in the lungs of individuals with COPD
- Located on 15q25

Function:

- IRP1 & IRP2 regulate cellular iron homeostasis
- Important physiological roles in duodenum, spinal cord and cns
- IRPs decrease iron storage and increase iron uptake by binding to iron-response elements (IREs)

Role of IRP2 in the response of the lung to CS??

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Results

I. Irp2-deficient mice resist experimental COPD

II. Identification of novel target pathways of IRP2 in the lung

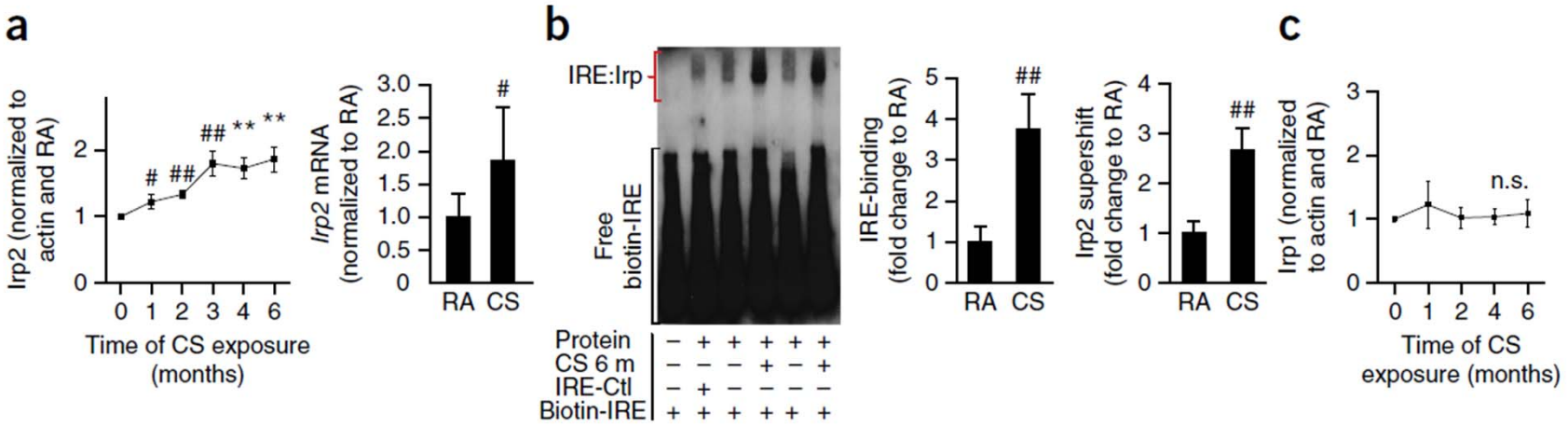
III. Irp2-/- mice resist CS-induced mitochondrial dysfunction

IV. IRP2 promotes CS-induced mitochondrial iron loading

V. IRP2 and CS increase lung COX activity and expression

VI. Targeting mitochondrial iron in experimental COPD

IRP2 is pathogenic in experimental COPD



CS = cigarette smoke
RA = room air
IRE = Irp2 expression

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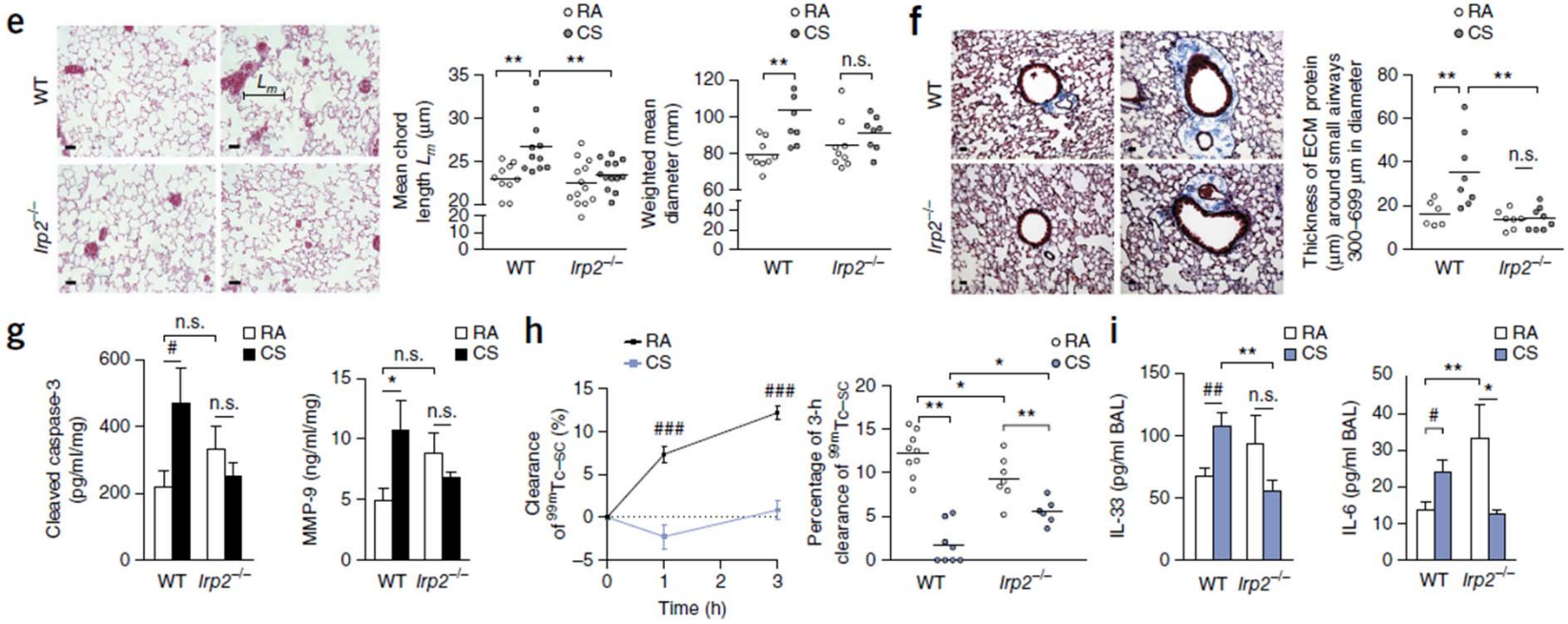
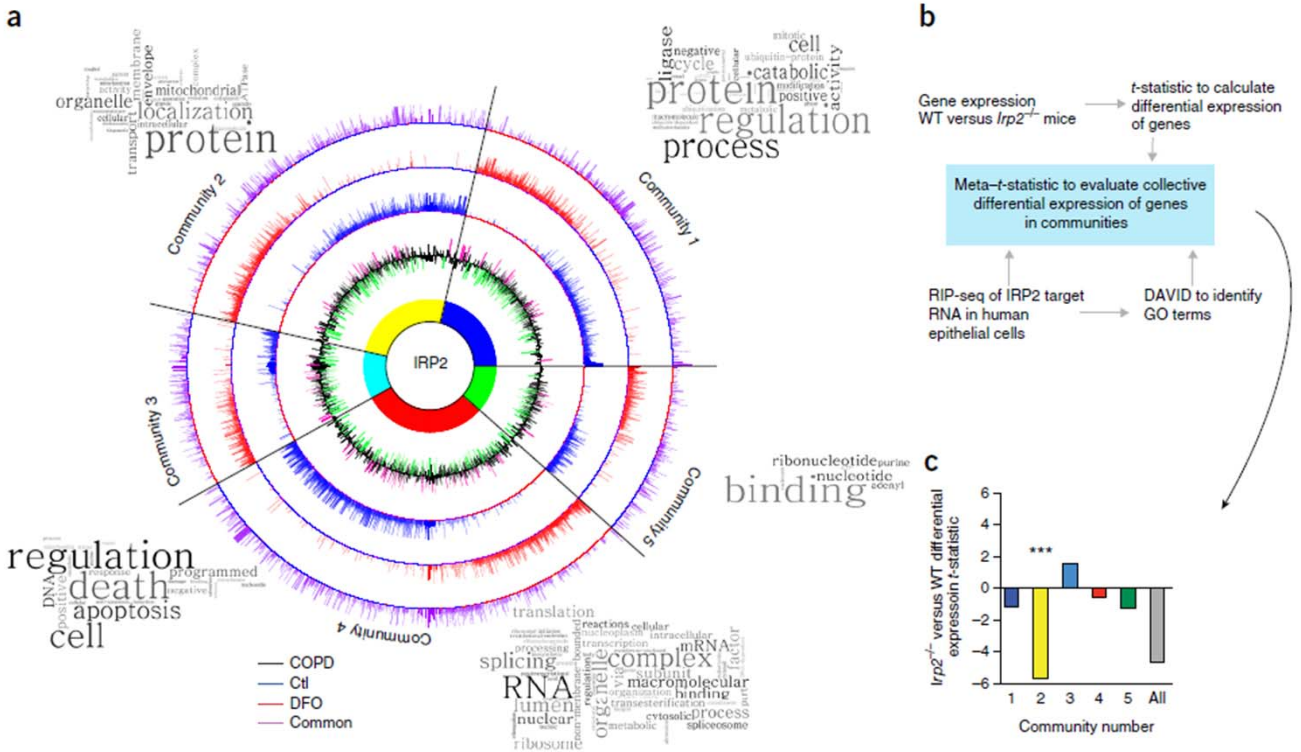
I. Irp2-deficient mice resist experimental COPD



ECM protein = extracellular matrix protein around the small airways
MMP-9 = matrix metalloproteinase 9 expression
BAL = Bronchoalveolar lavage

II. Identification of novel target pathways of IRP2 in the lung



DAVID = Database for Annotation, Visualization and Integrated Discovery

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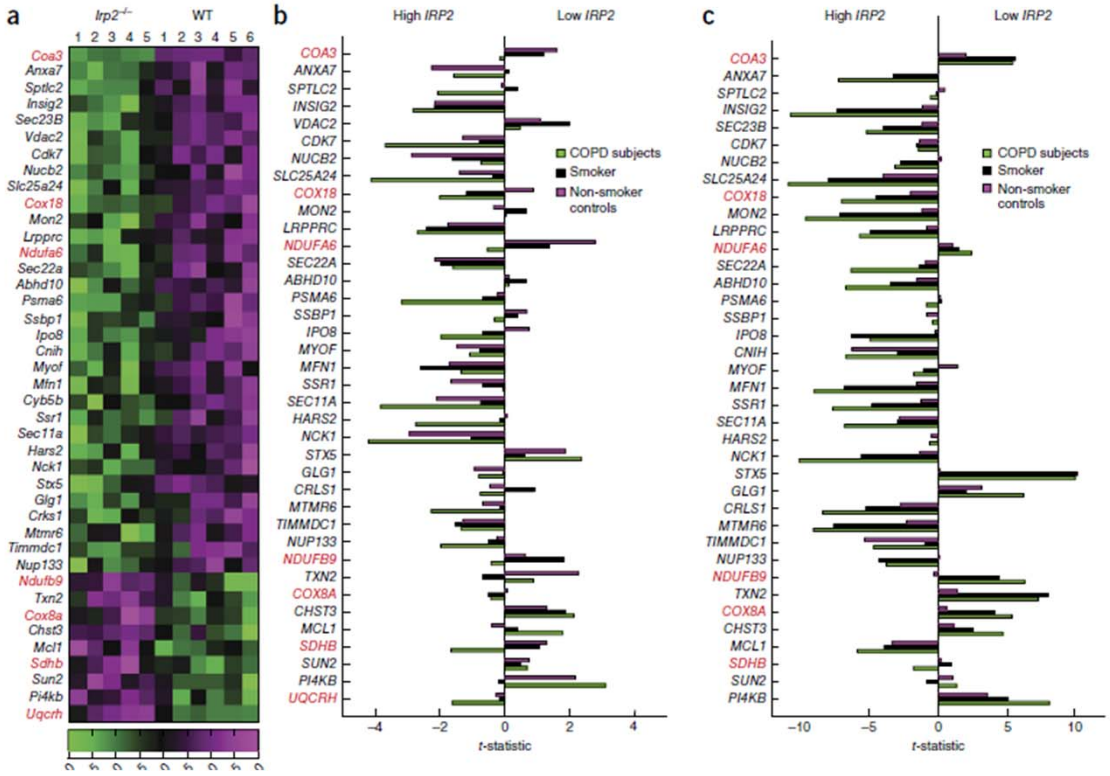
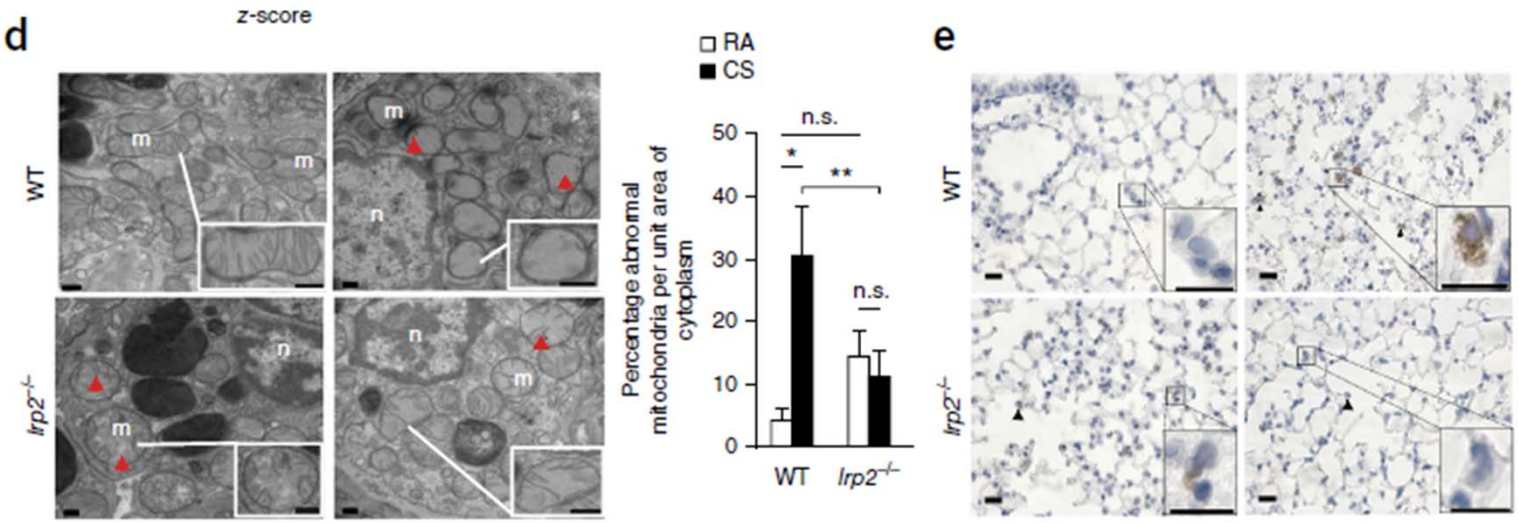
III. IRP2-/- mice resist CS-induced mitochondrial dysfunction (red)



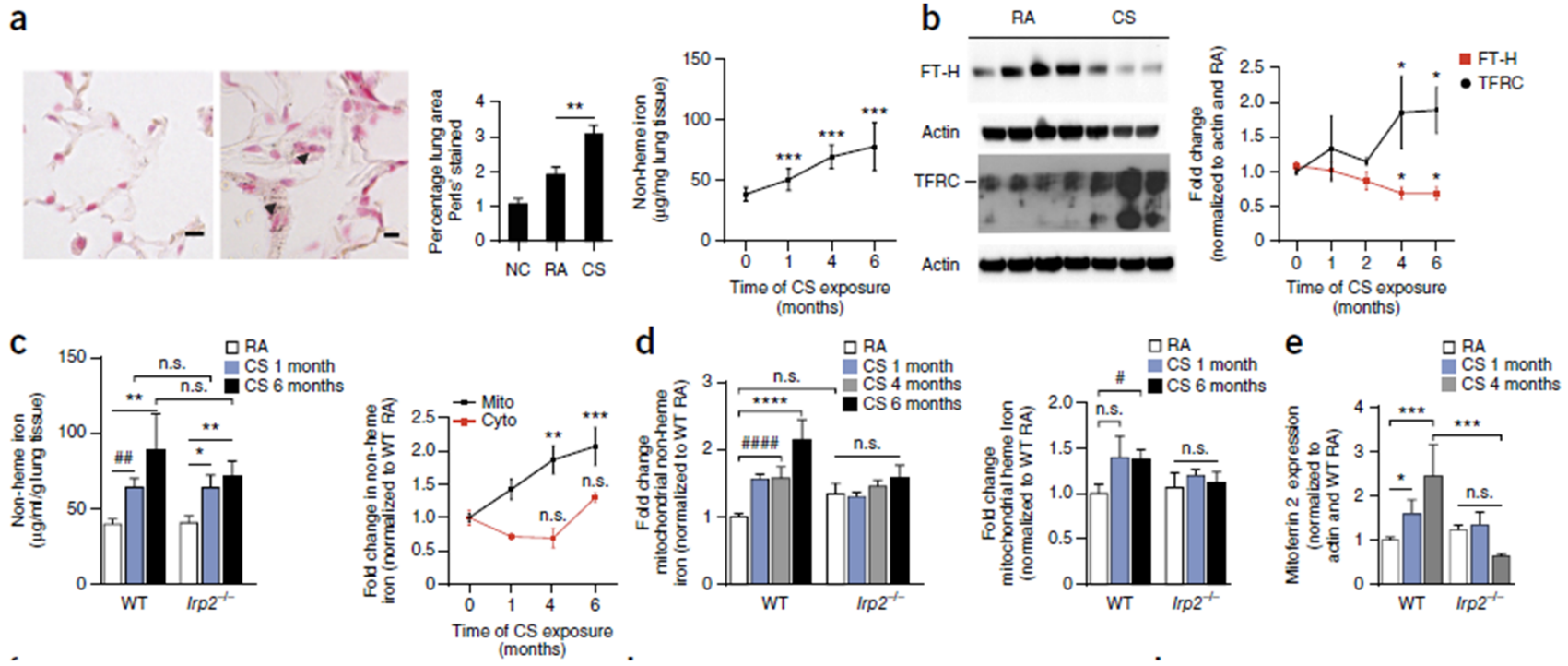
Red: Genes encoding for subunits and factors important for COX assembly
-> see result V.

a) gene expression in lung tissue b) gene expression in blood c) cohorts of humans with COPD relative to high or low IRP2 expression

III. Irp2-/- mice resist CS-induced mitochondrial dysfunction



IV. Irp2 promotes CS-induced mitochondrial iron loading



NC = negative control, FT-H = ferritin heavy chain, TFRC = transferrin receptor
Actin was used as a loading control

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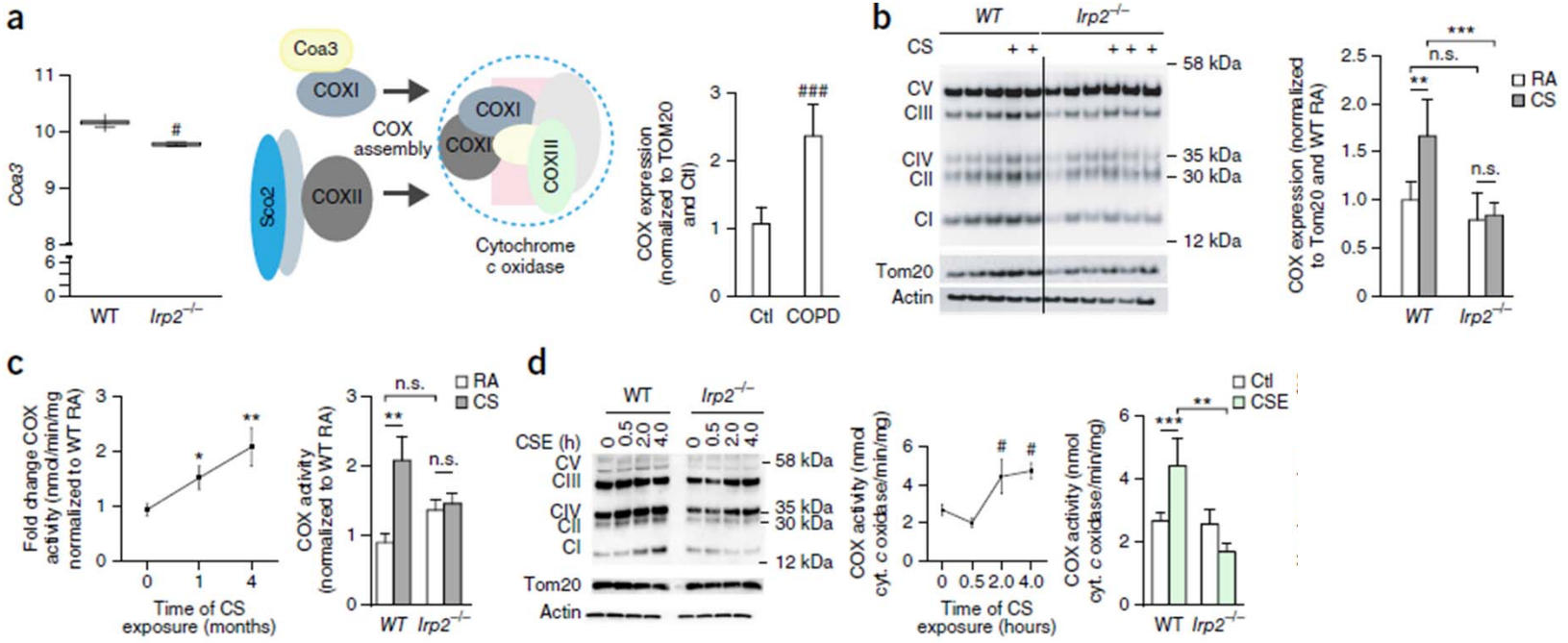
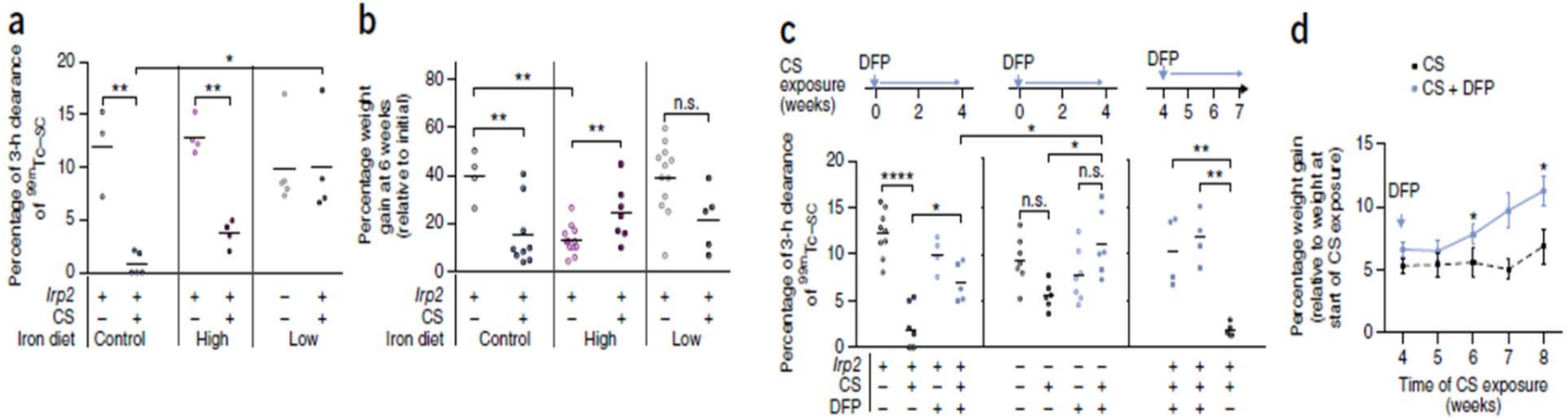
V. IRP2 and CS increased lung COX activity and expression



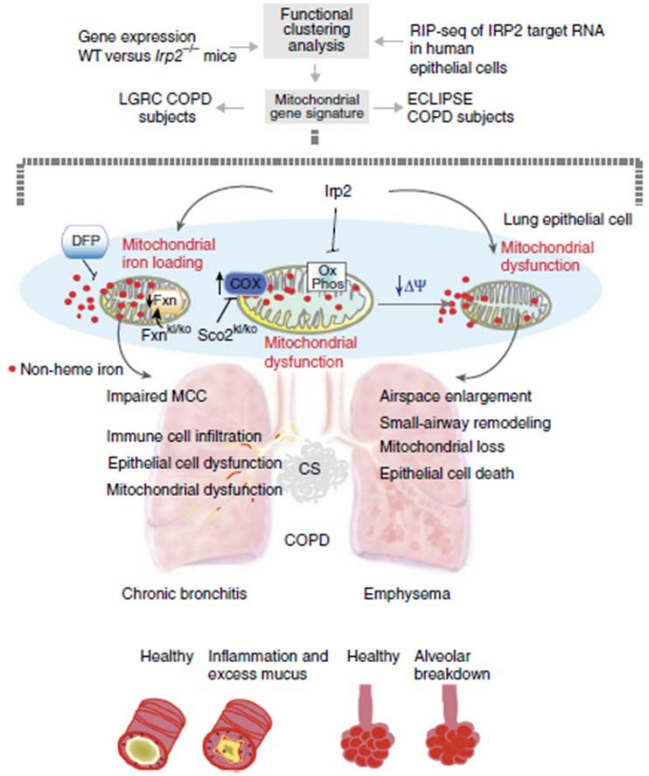
Coa3 = COX assembly factor 3, Ctl = Control, CI-CV = OxPhos complexes
CSE = cigarette smoke exposure

VI. Targeting mitochondrial iron in experimental COPD



DFP = Deferiprone, iron chelator

Conclusion



- Irp2 promotes mitochondrial dysfunction in experimental COPD by regulating mitochondrial iron loading

- Mitochondrial iron chelation alleviates established COPD

- Potential novel therapeutic approach for COPD