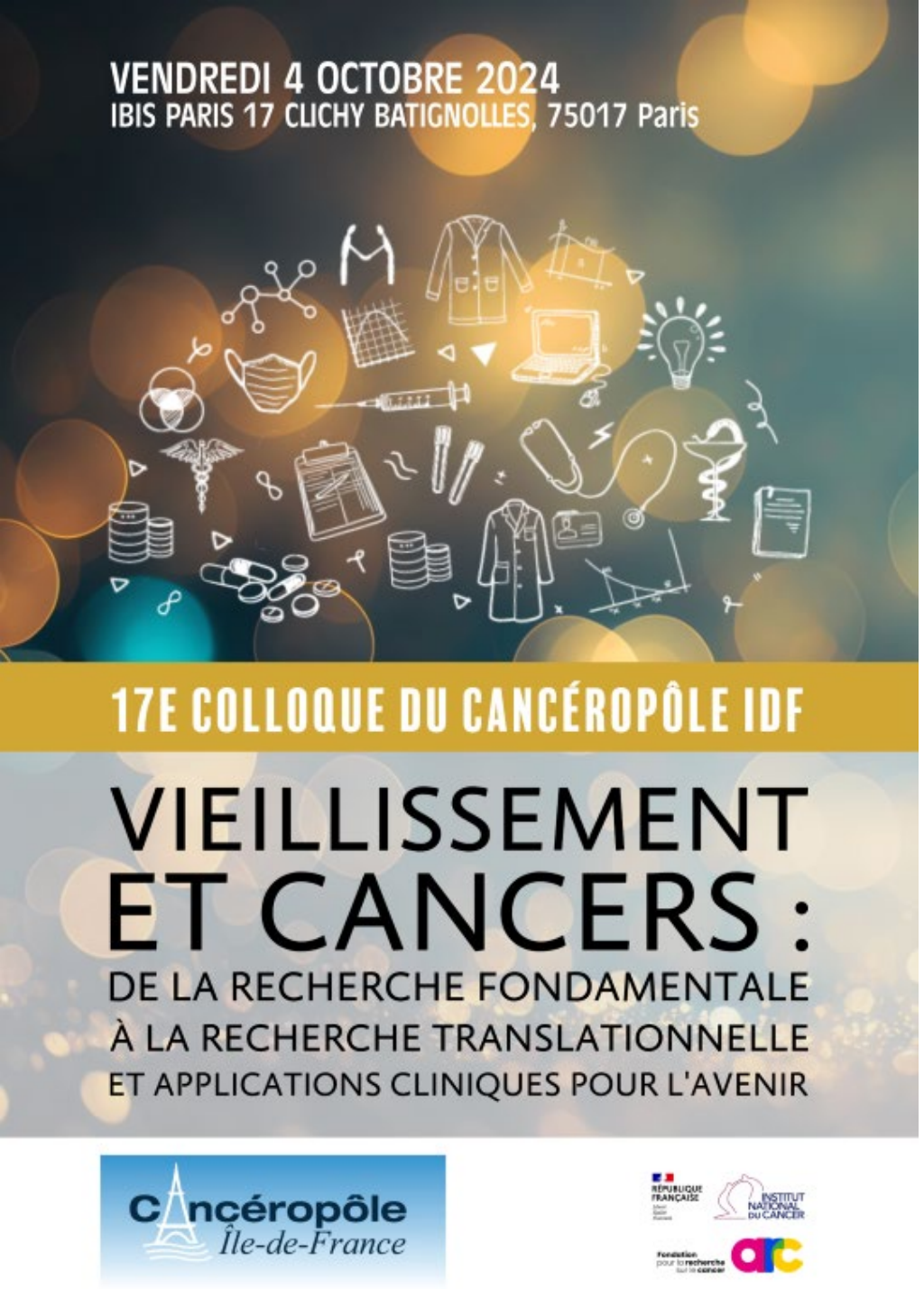
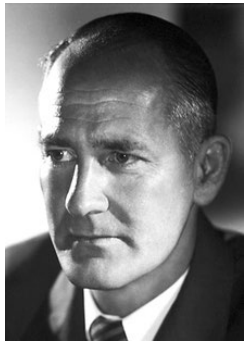


On the mechanism of metformin

Raphaël Rodriguez, PhD, FRSC

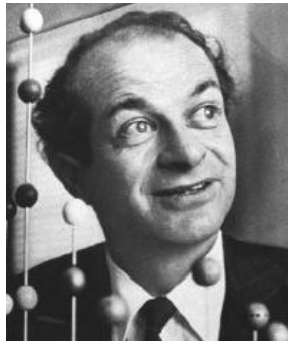
Genetic *vs* non-genetic control of cell identity



Beadle, Tatum

1941

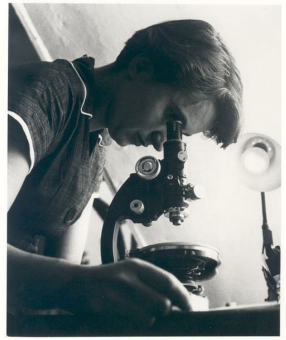
Genes control biochemical processes



Pauling

1949

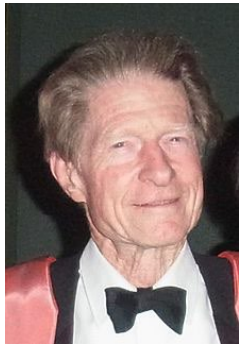
Gene mutation cause Sickle cell anemia



Franklin, Crick…

1953

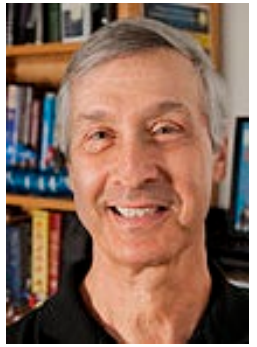
DNA structure

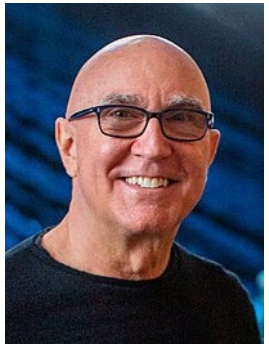


Gurdon

1962

Cell differentiation does not require gene restriction





Allis ***Schreiber***

1996

Identification of HATs and HDACs

Yamanaka

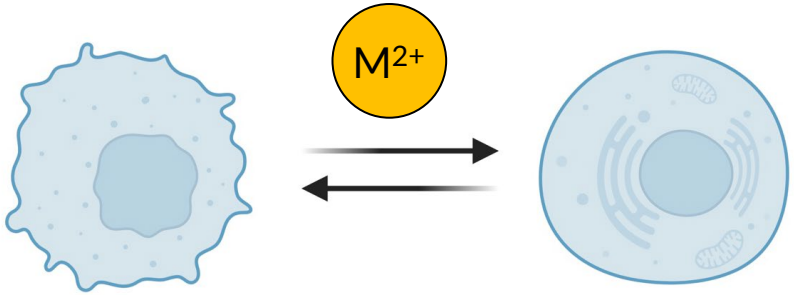
2006

Mature cells give rise to stem cells

Liu

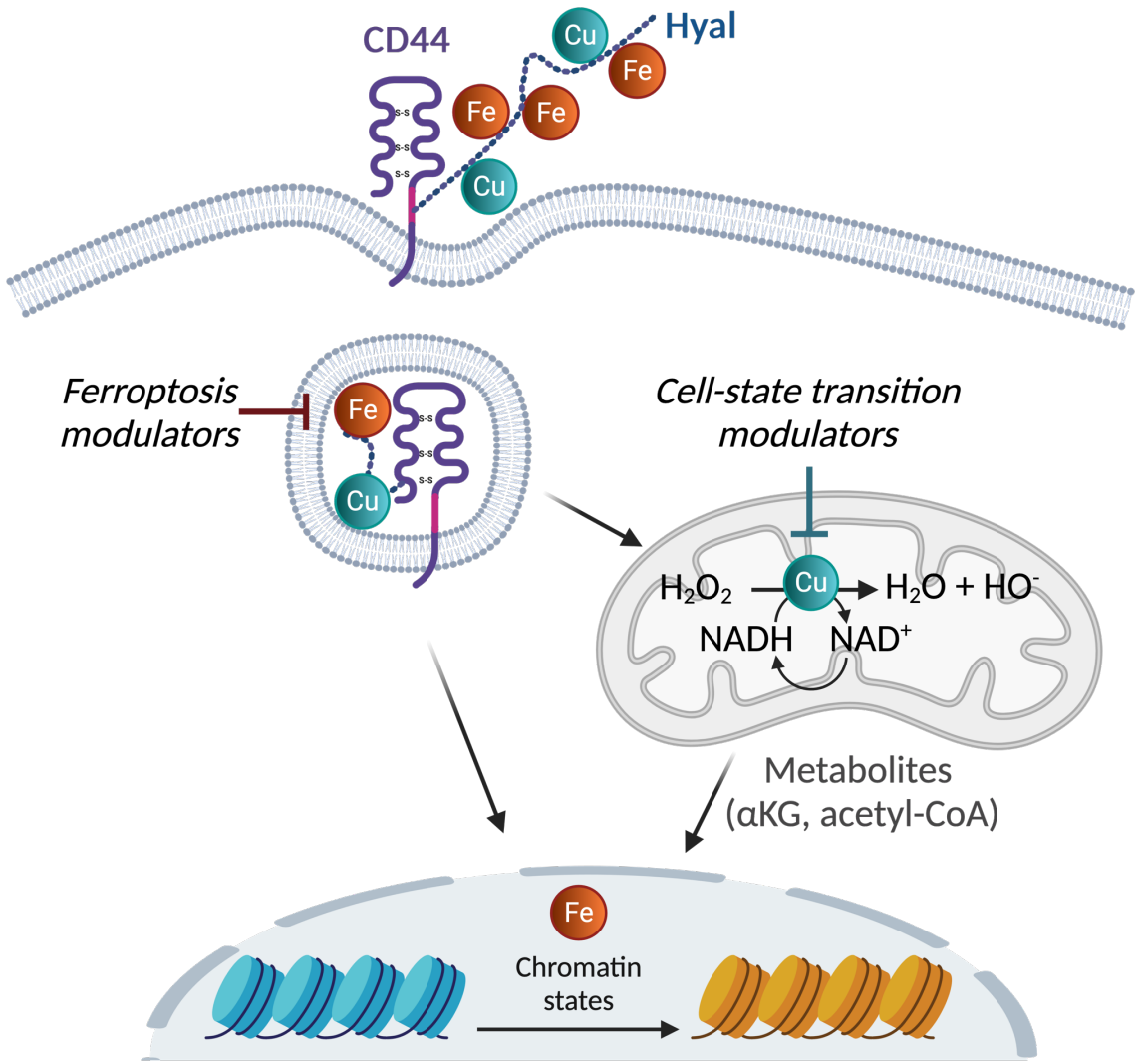
2021

Genome editing corrects Sickle cell anemia



State 1 State 2

Metal signaling in biomedicine



- Development
  (e.g., hematopoiesis)
- Immunity
  (e.g., immune cell activation)
- Cancer
  (e.g., tumor seeding, metastasis, drug tolerance)

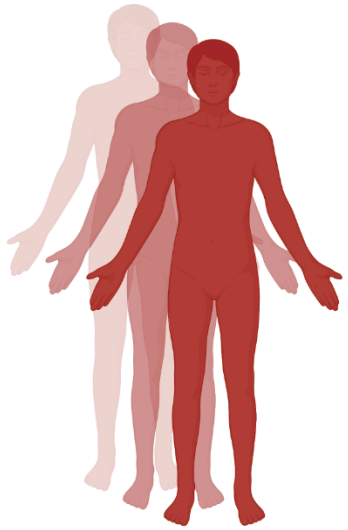
Salinomycin kills cancer stem cells by sequestering iron in lysosome
Mai et al **2017**

CD44 regulates epigenetic plasticity by mediating iron endocytosis
Müller et al **2020**

A druggable copper-signalling pathway that drives inflammation
Solier et al **2023**

Activation of lysosomal iron triggers ferroptosis in cancer
Cañeque et al (under revision, *Res. Sq. 2024)*

Mitochondrial copper(II) increases in inflammatory macrophages



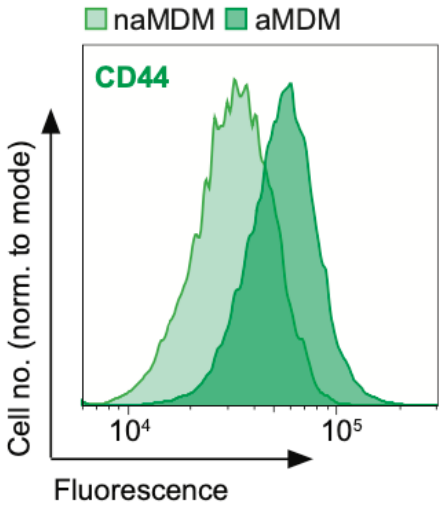
Monocytes
(negative sorting)

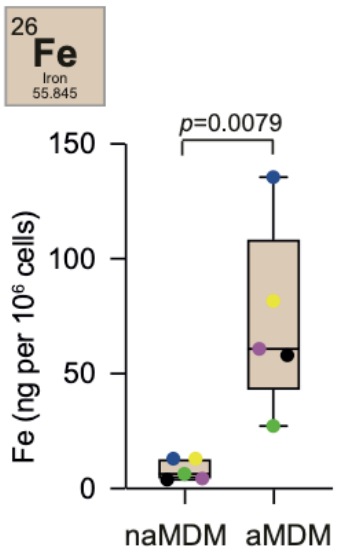
GM-CSF

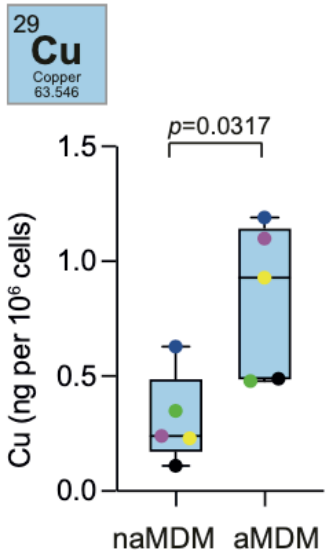
Non-activated
Monocyte-derived
Macrophages
(**naMDM**)

LPS, IFNγ

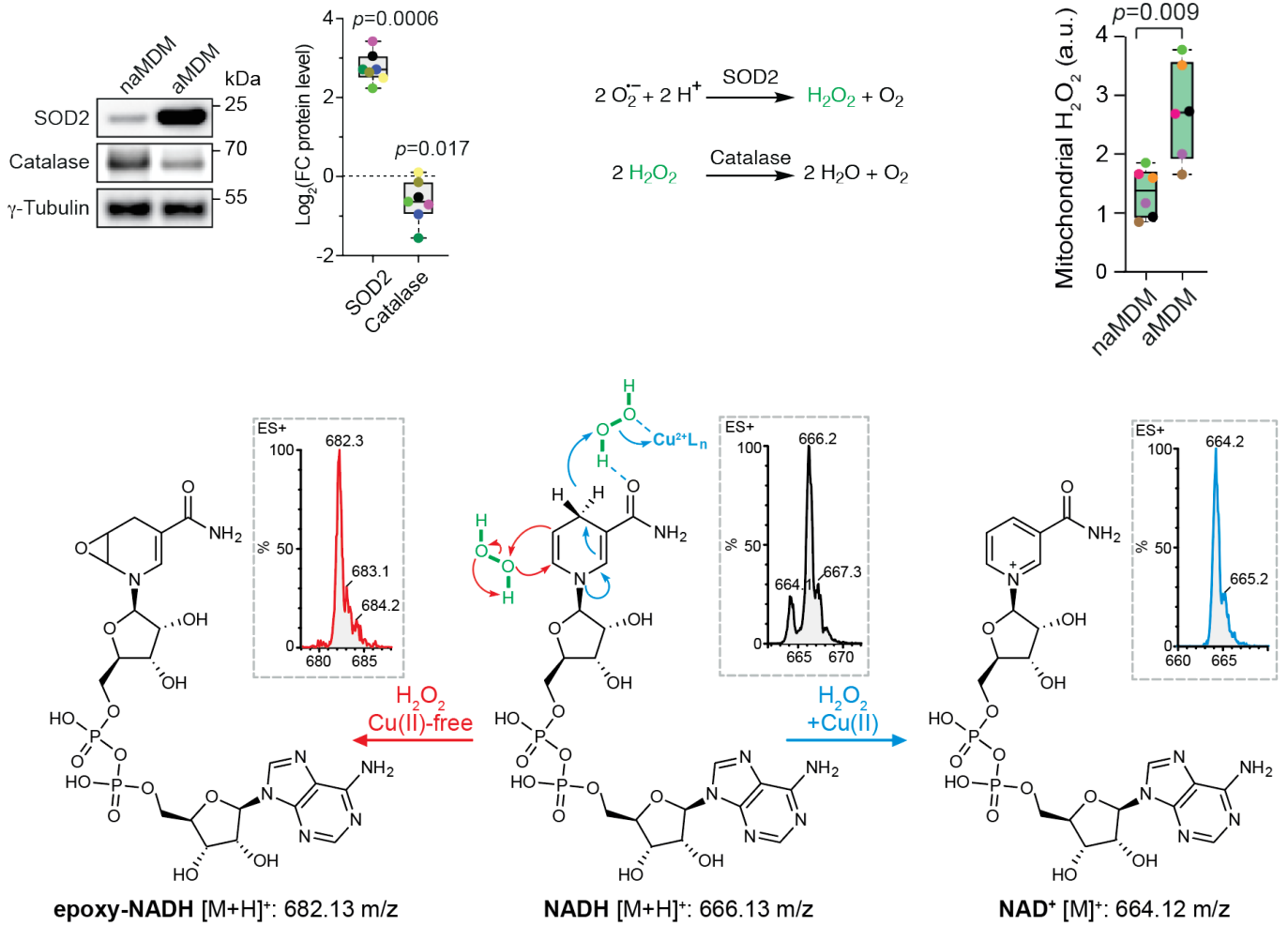
Activated
Macrophages
(**aMDM**)





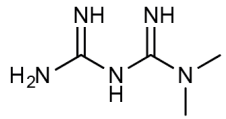


Mitochondrial copper(II) regulates metabolism

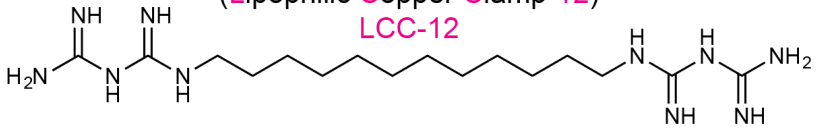


Mitochondrial copper(II) is druggable

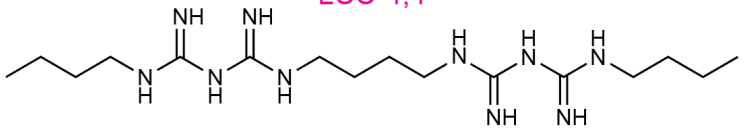
Metformin (Met)

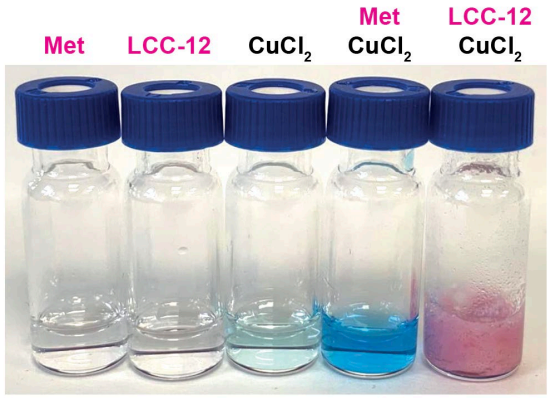


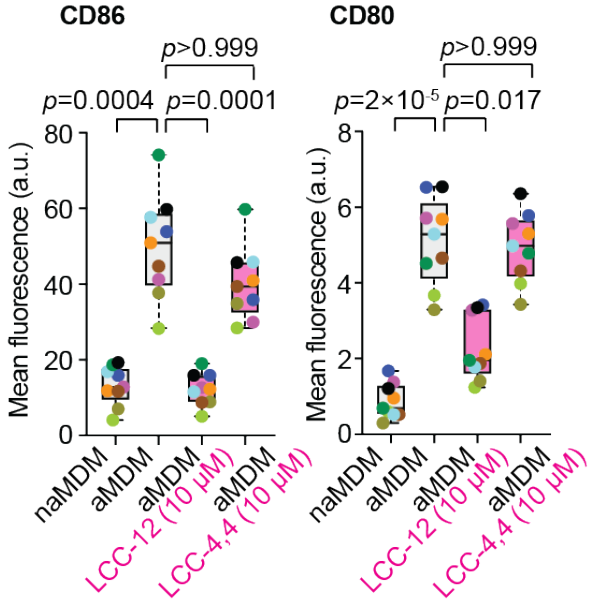
(Lipophilic Copper Clamp-12)
LCC-12



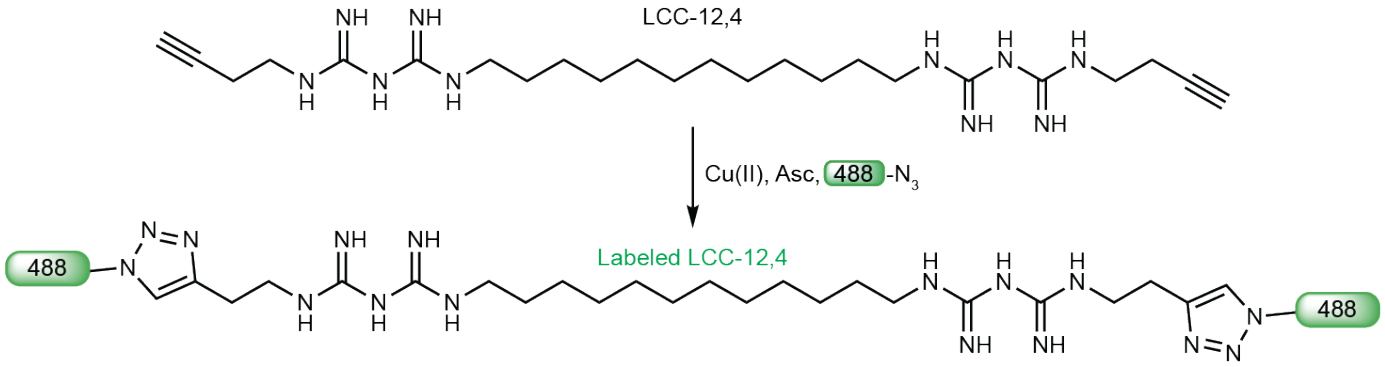
(Lipophilic Copper Clamp-4,4)
LCC-4,4

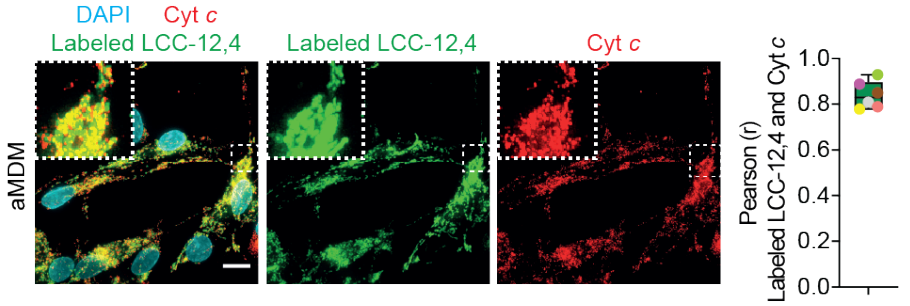


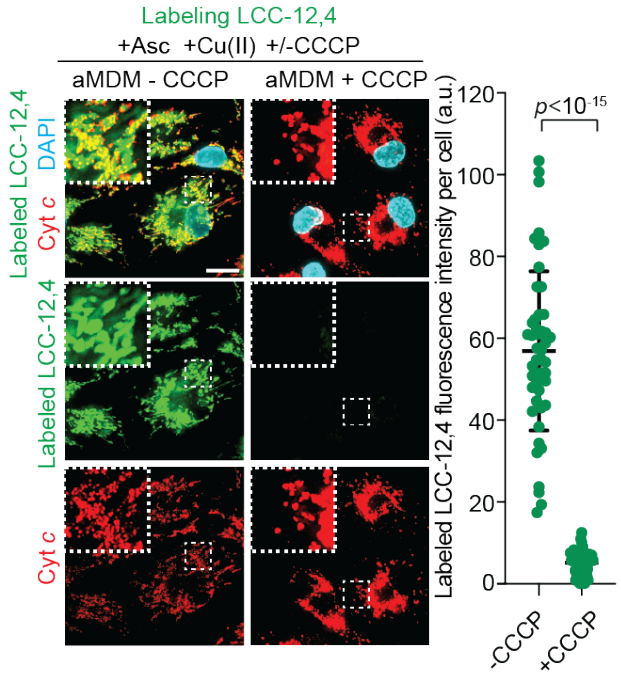


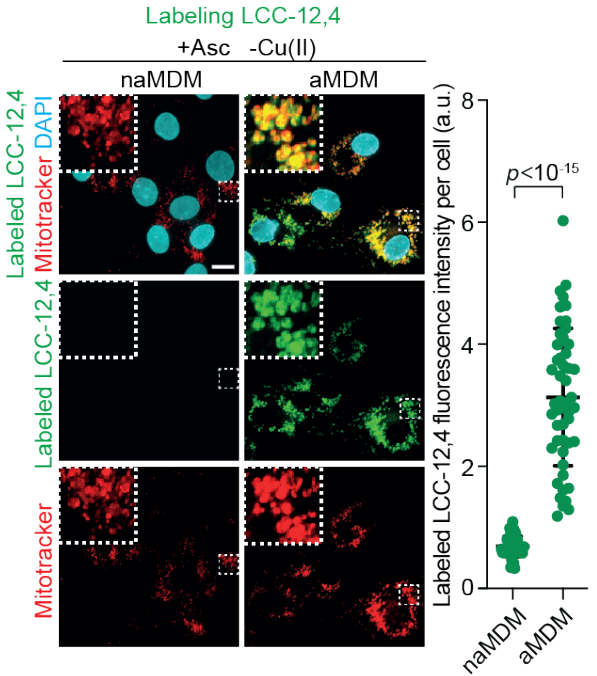


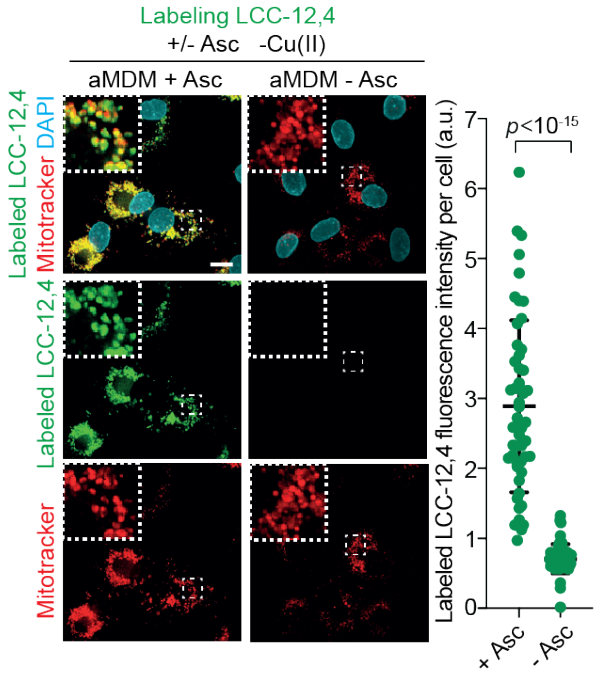
Mitochondrial copper(II) is druggable



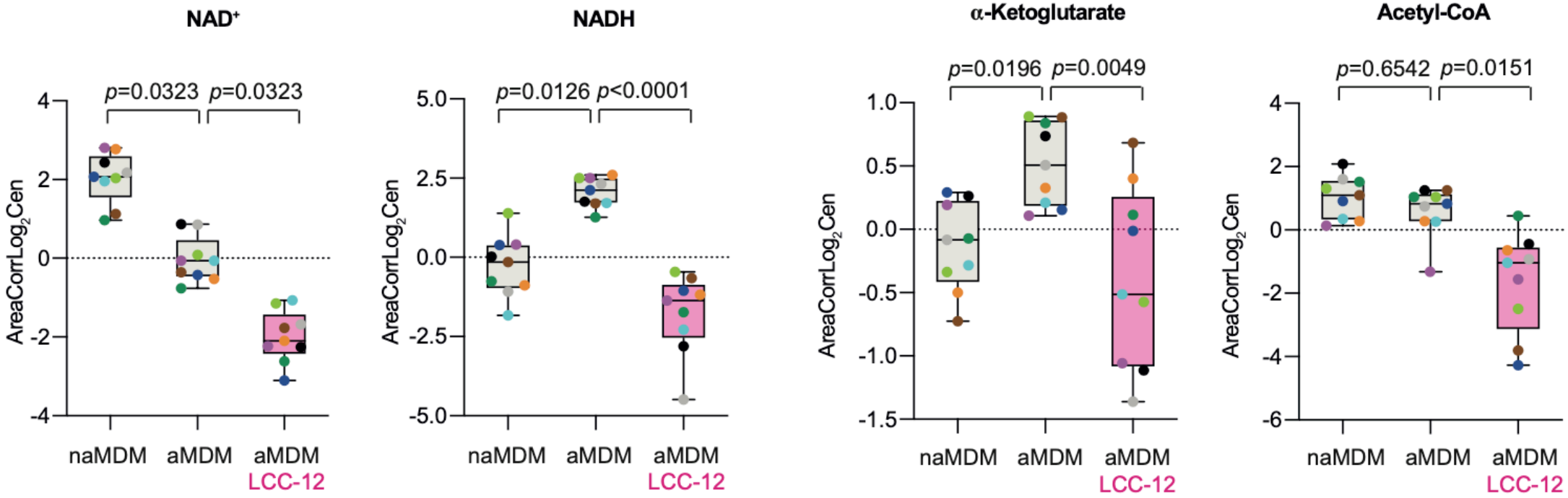




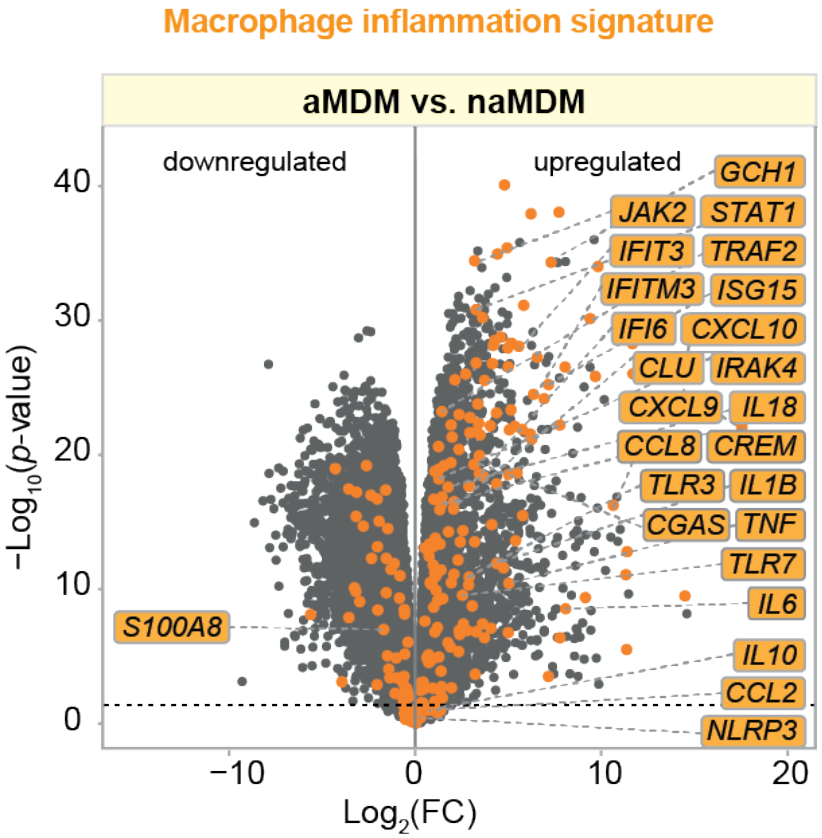


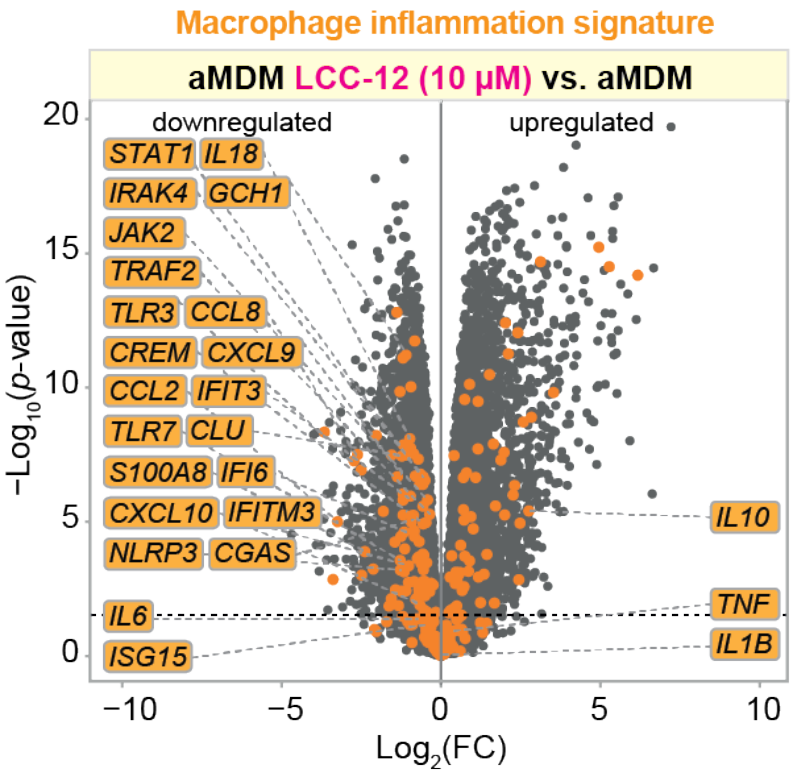


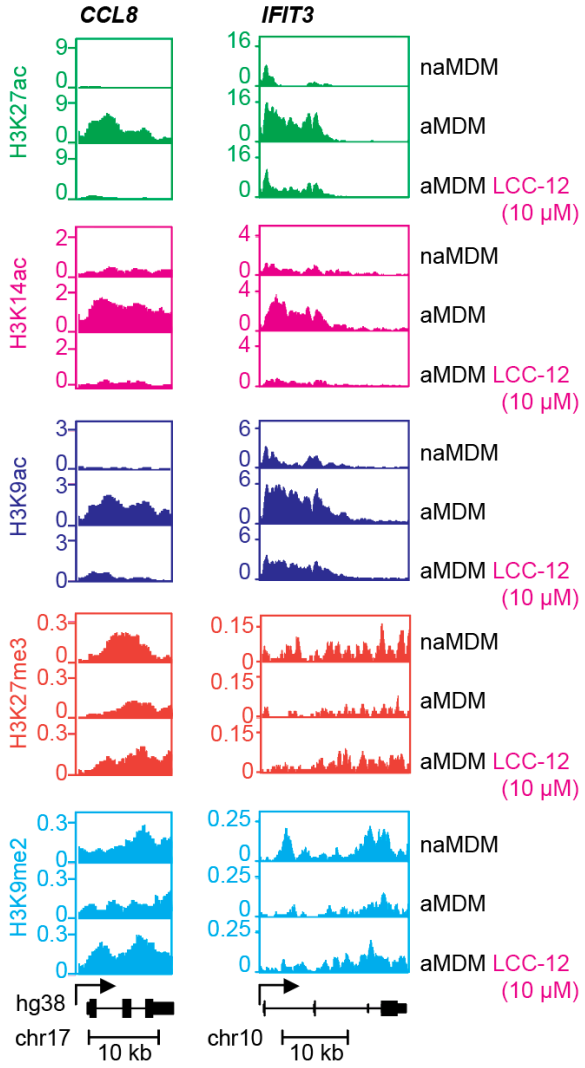
Mitochondrial copper(II) inactivation alters metabolism



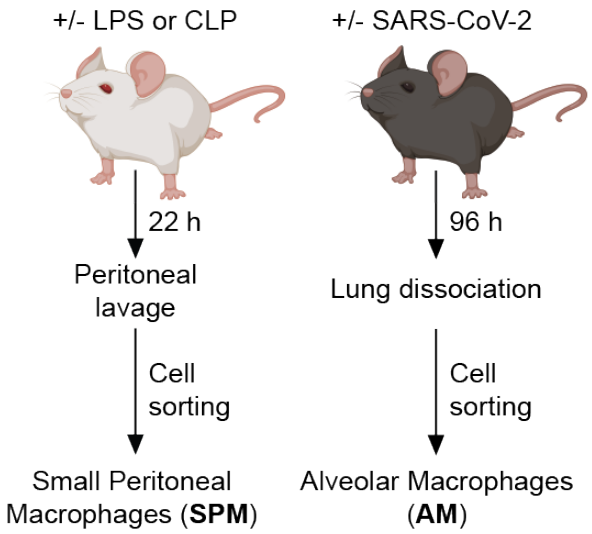
Mitochondrial copper(II) inactivation represses transcription

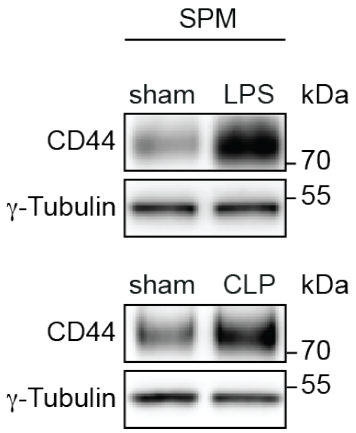


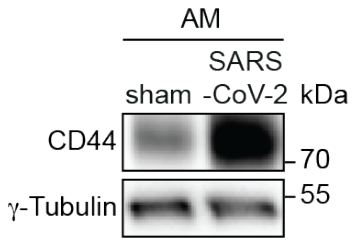


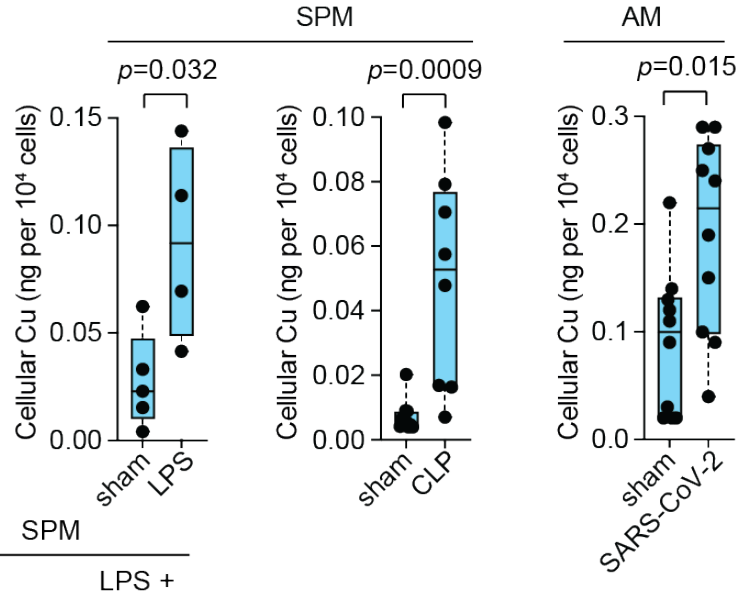


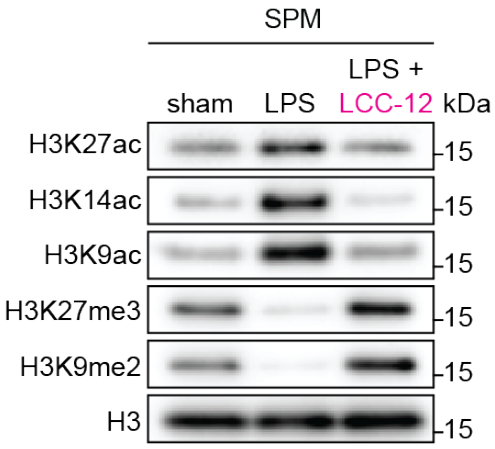
Mitochondrial copper(II) inactivation reduces inflammation

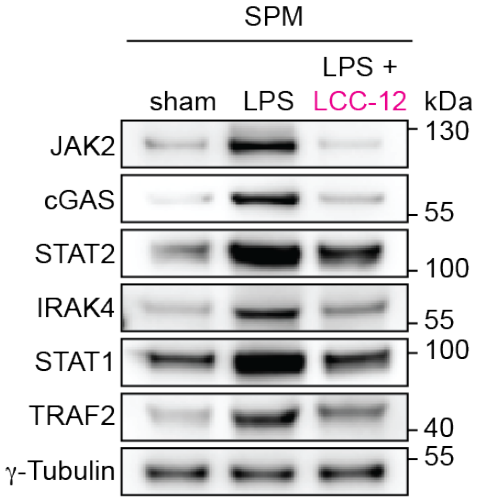




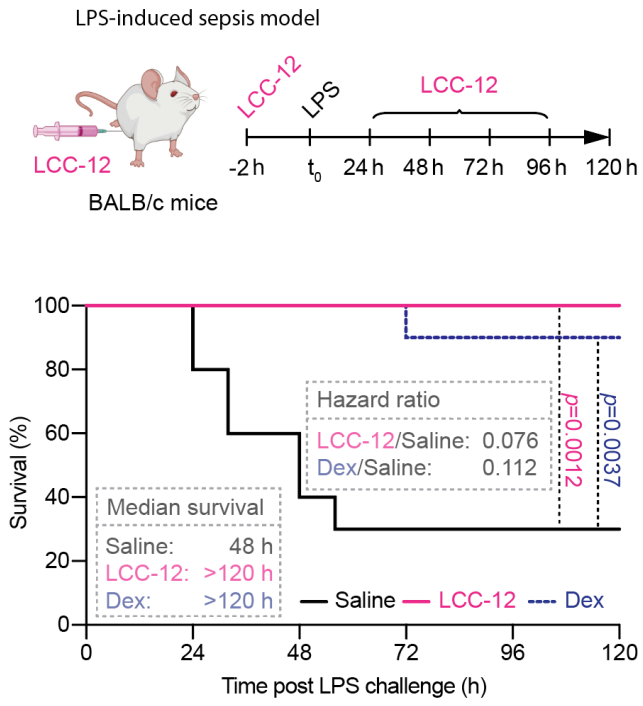


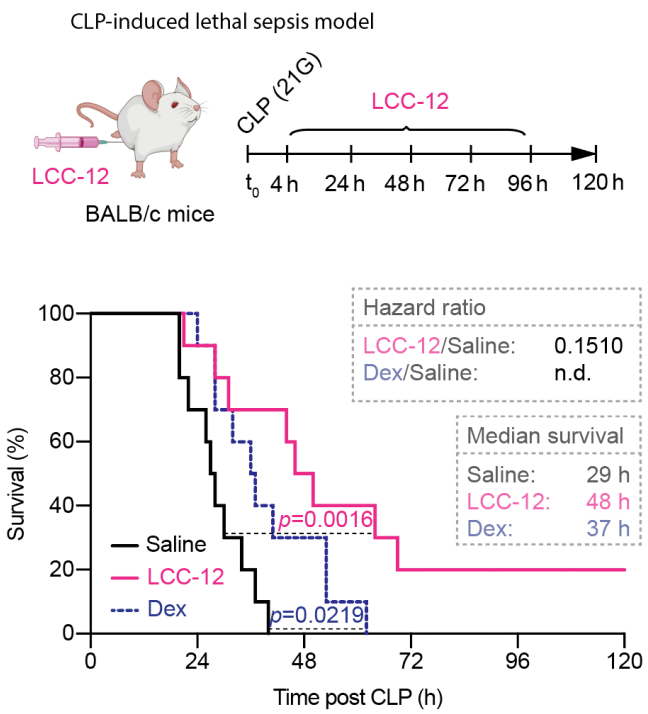


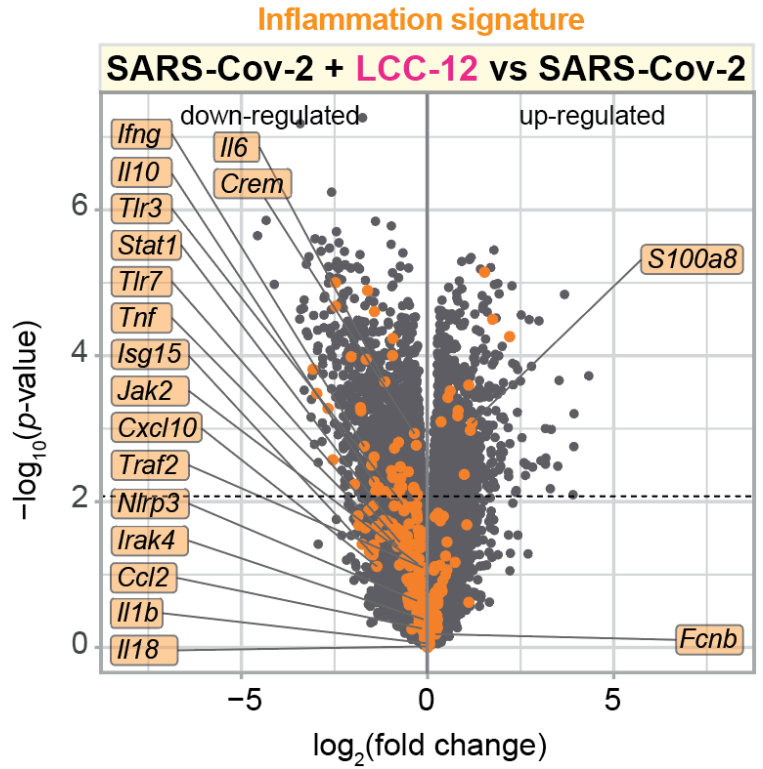




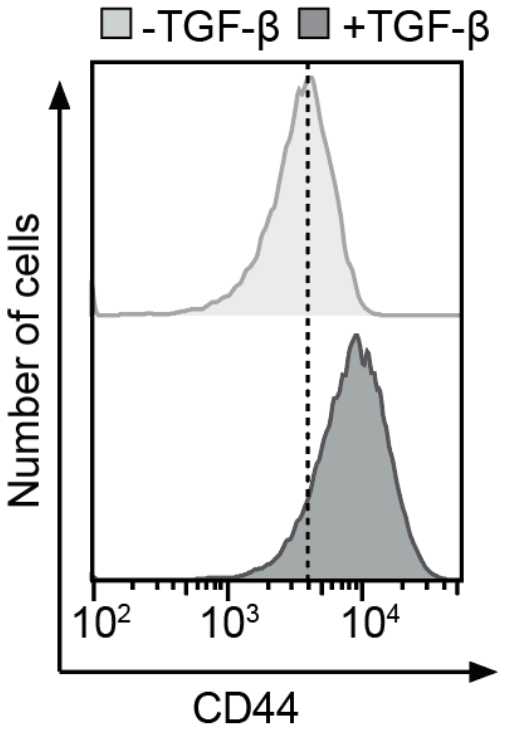
Mitochondrial copper(II) inactivation prevents sepsis

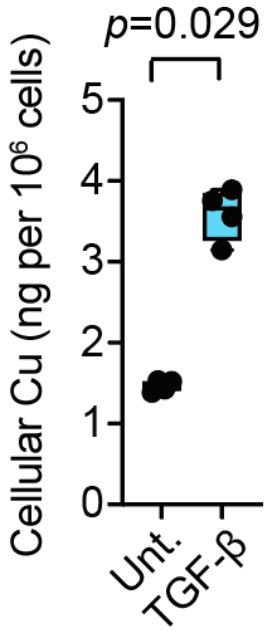


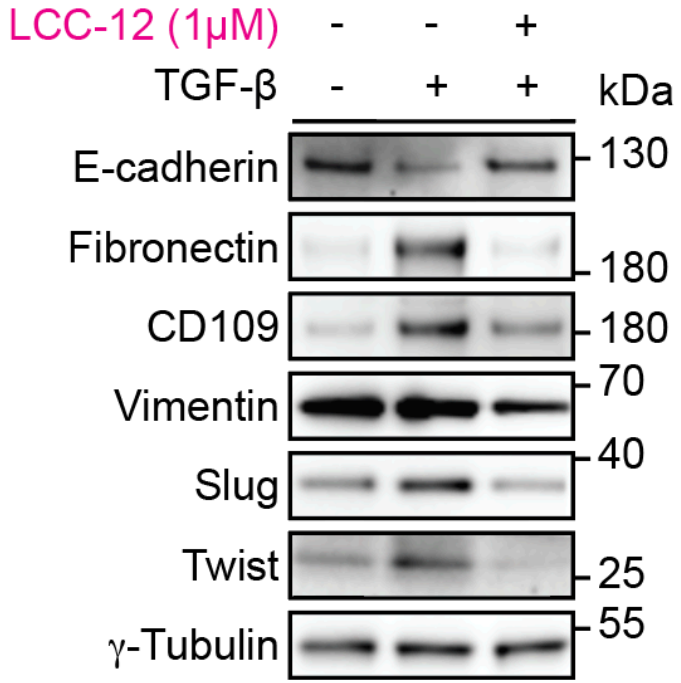




Mitochondrial copper(II) inactivation blocks cell-state transition in cancer







Remarks

- CD44 regulates cell-state transitions by mediating metal uptake
- Redox-active metals orchestrate metabolic and epigenetic programs in cancer and immunity
- Mitochondrial copper(II) are druggable
- Cancer metastasis and acute inflammation are similar molecular diseases
- Controlling cell-state transitions confers therapeutic benefits
- Role of copper in aging ?

The who and the how

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