Animals have vastly different regenerative capabilities

Skin shedding and tissue regeneration in African spiny mice (Acomys)

Genetic experiments in regenerative mammals

Define limits of mammalian regeneration

Dissect molecular/cellular mechanisms

Determine relevance to real human diseases

Understand consequences (CANCER)
Does more regeneration mean more cancer?

The liver is an exceptionally regenerative organ.

BUT even the liver has its limits.

Chronic liver injury leads to cirrhosis and cancer.

Genetic diseases, Hepatitis C, Drug/Autoimmune/Alcohol.

Is chromatin state plasticity a factor in regeneration?
Do chromatin remodelers influence regeneration?

Arid1a turns on in aging liver

Mice without Arid1a have improved liver regeneration

Arid1a deficient mice sustain less necrosis
Loss of ARID1A blocks biliary injury

Improved regeneration occurs after equal levels of injury

The same is true for hepatectomy and DDC injuries

Human ARID1A overexpression blocks liver proliferation
LKO livers show reduced maturation

GSEA analysis of RNA-seq at baseline:
Increased differentiation in WT mice
Suppressed differentiation in LKO mice

Do chromatin remodelers influence regeneration?

Arid1a is enriched on promoters of hepatic lineage genes
Arida loss restricts C/ebpa access

Dual transcriptional effects regulate injury/regeneration

Working model
Arid1a restricts tissue repair in other tissues.

Normal mouse ear

Arid1a deficient mouse ear

Image by Peng Yi and Douglas Melton

Arid1a restricts physiologic beta-cell expansion and its suppression potentiates regeneration.

Jen-Chieh Chuang

B-cell loss leads to diabetes.
Arid1α is highly expressed in pancreatic islets

Arid1α IHC

Ibrahim Nassour

Arid1α is suppressed during physiological β-cell expansion

High fat diet 50%
Pancreatectomy
Pregnancy

Arid1α deletion in whole pancreas leads to β-cell expansion during development
Global adult deletion of Arid1a does not affect β-cell mass or glucose clearance at basal state

Loss of Arid1a protects against Type 1 diabetes

β-cell specific Arid1a deletion after STZ could reduce the development of diabetes, modeling a therapeutic approach
Arid1a loss mediates increased proliferation in β-cells

Islet transcriptome reveals increase NRG/EGF signaling in Arid1a KO

Arid1a deficient β-cells are more sensitive to EGF
EGFR inhibition abrogates increase in proliferation and receptor phosphorylation after Arid1a KD in β-cell lines.

EGFR inhibition in vivo abolishes anti-diabetic effect of Arid1a loss.

ErbB family of receptors.
Conclusions

1. Regeneration can be improved through changes in single genes.
2. *Arid1a* loss leads to increased regenerative capacity in multiple tissues.
3. Using these models, determine how regenerative capacity impacts organ function, aging, and cancer.

Acknowledgements