Why does Caloric Restriction appear to extend lifespan?

RCCN Workshop: Nutrition and Aging Biology

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Molecular & Cellular Biology of Aging Research

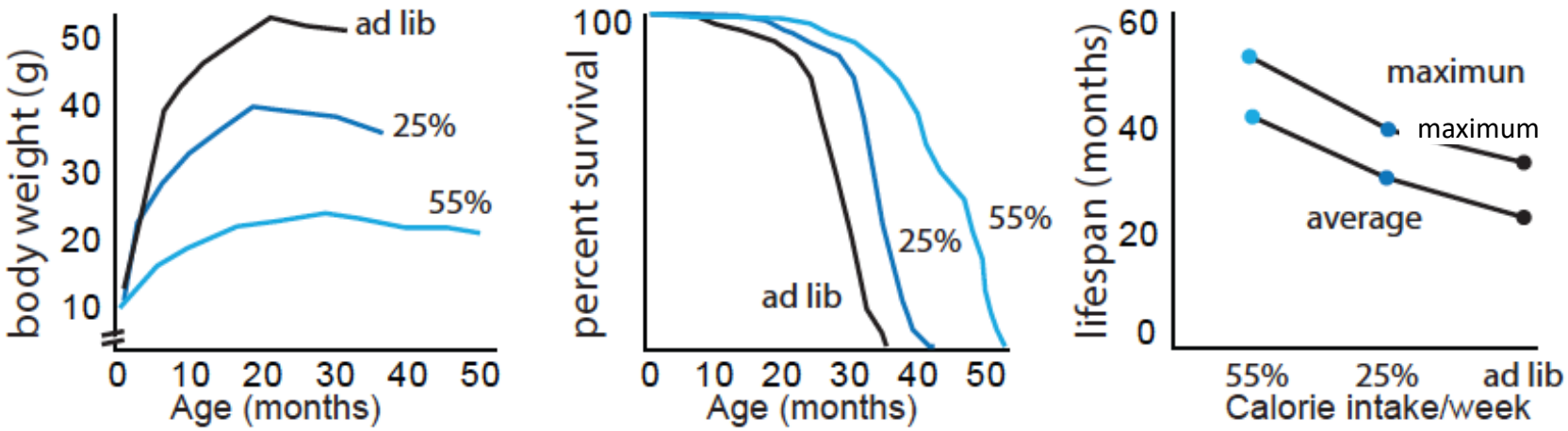
MCBAR

Anderson Lab

Metabolism of Aging Research Program

The University of Wisconsin Madison

Caloric/Energy Restriction Delays Aging in Mice



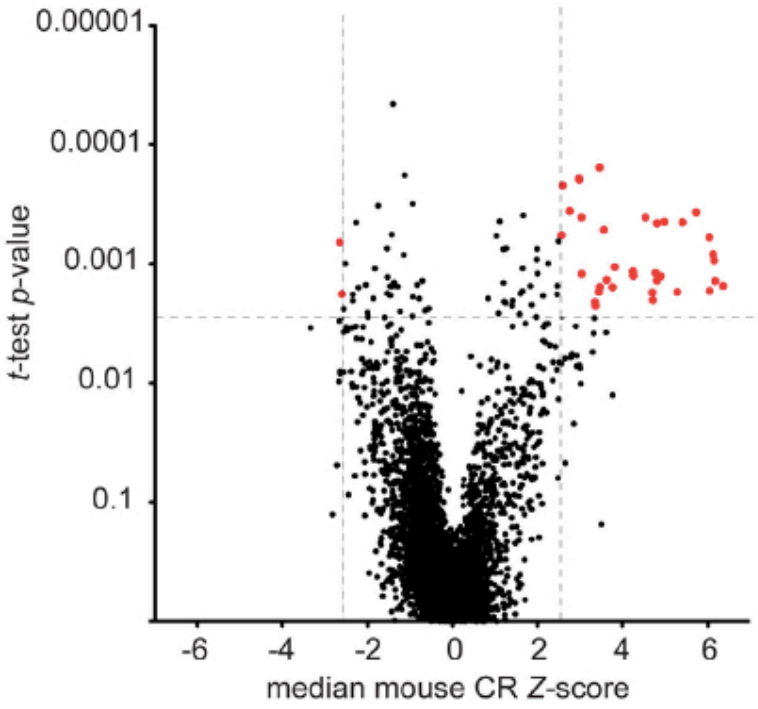
Inverse linear relationship between calorie intake and lifespan

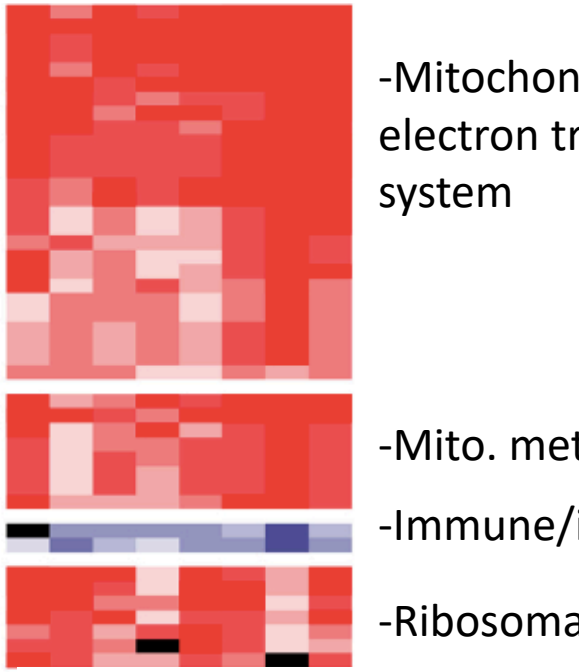
Processes involved in regulating longevity are nutrient and energy status sensitive

Weindruch et al PMID 3958810

Metabolic Reprogramming is a signature of CR

Brain. Inner Ear. Heart. Liver. Kidney. Adipose muscle.



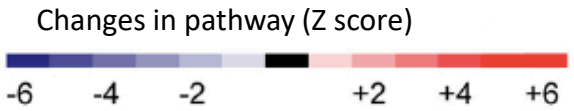


-Mitochondrial electron transport system

-Mito. metabolism

-Immune/inflamm.

-Ribosomal



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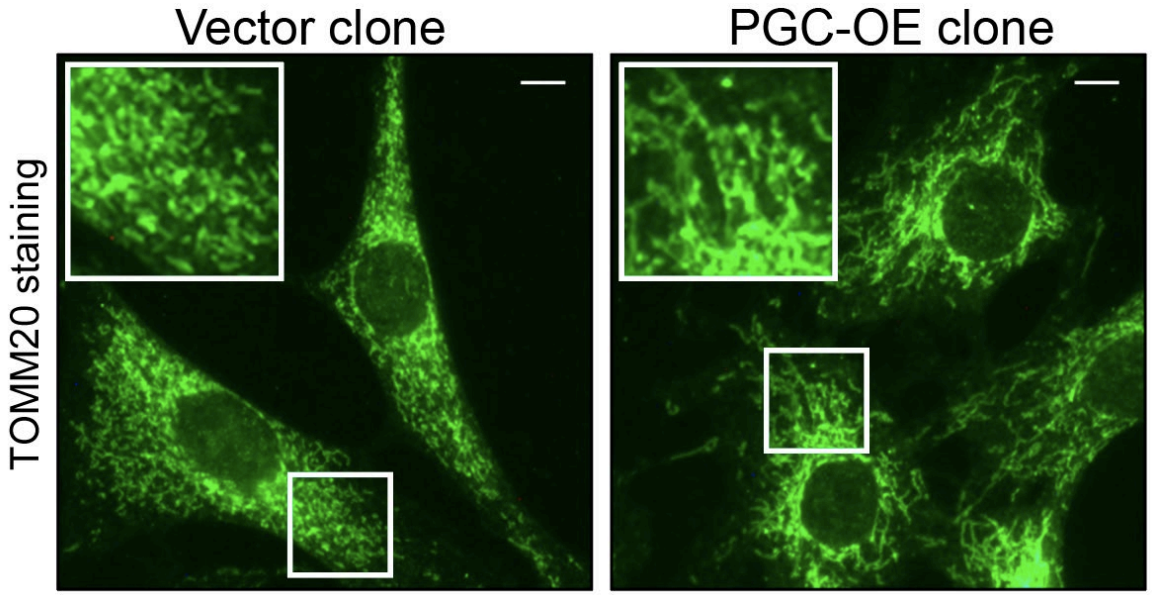
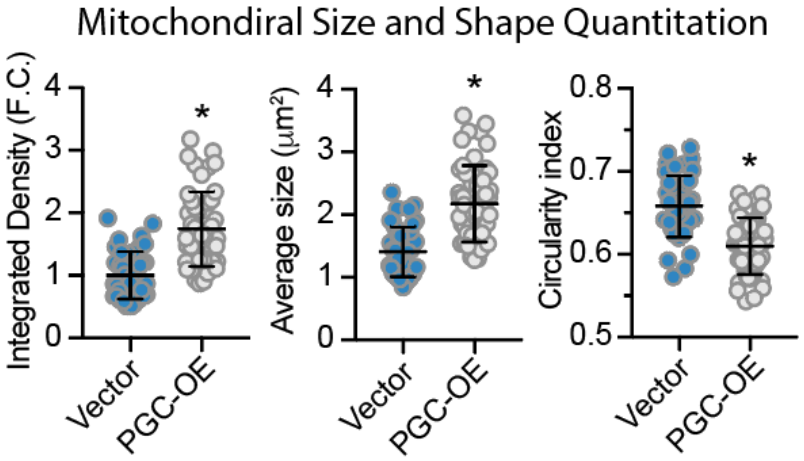
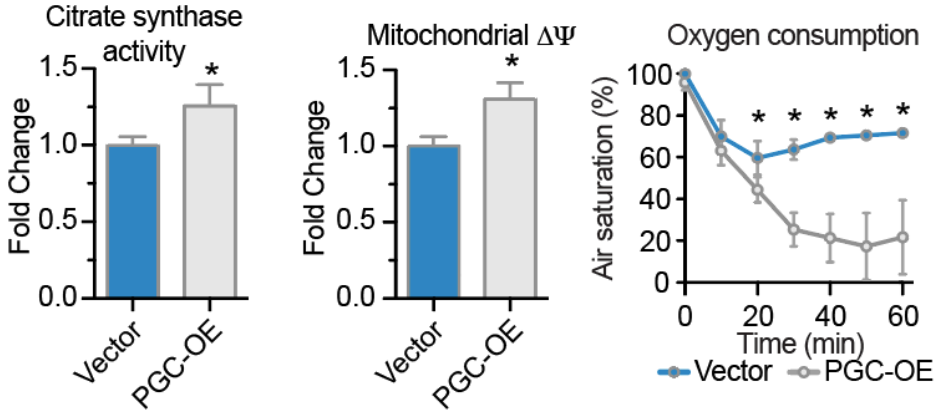
Energetic Processes are vital for maintained cellular, tissue, and organismal function…. OK, sure…

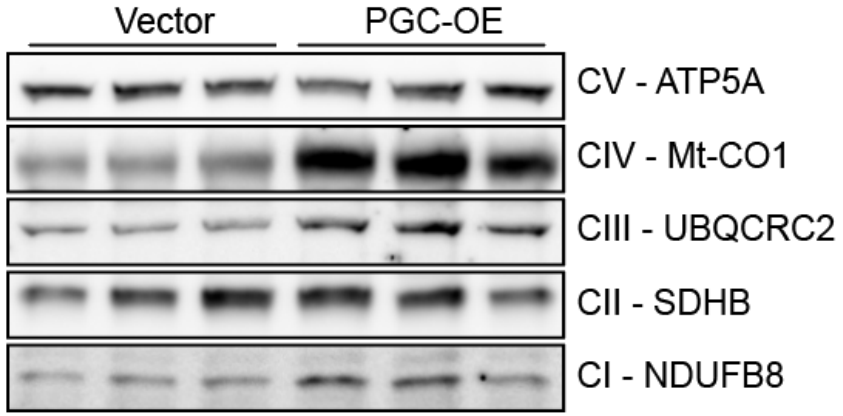
but metabolism influences everything

PGC-1a Directed Mitochondrial Activation









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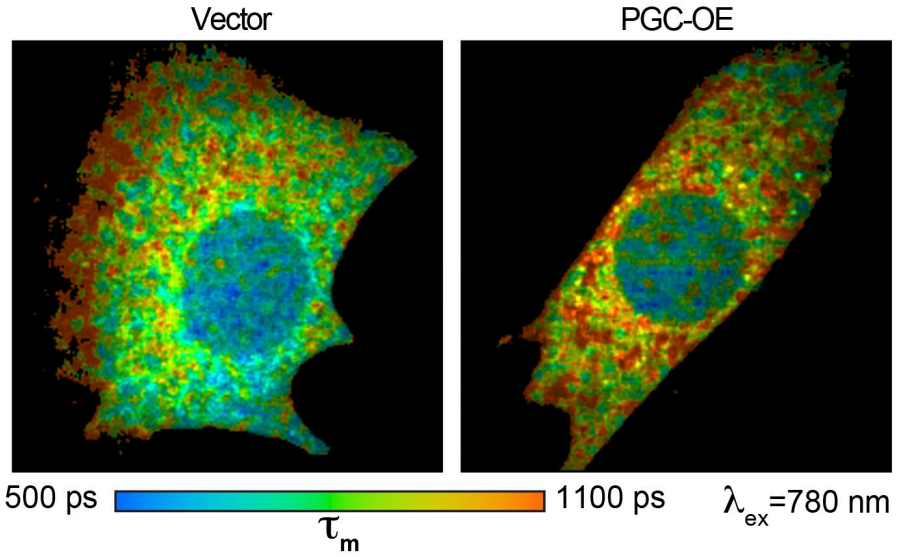
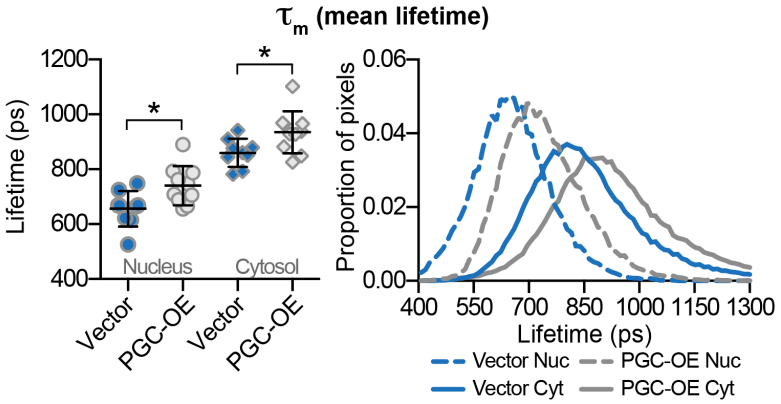
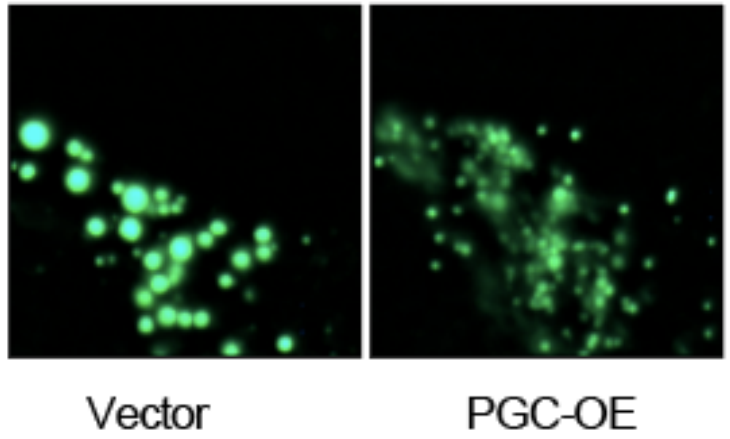
Mitochondrial Activation: Cellular Redox & Lipids

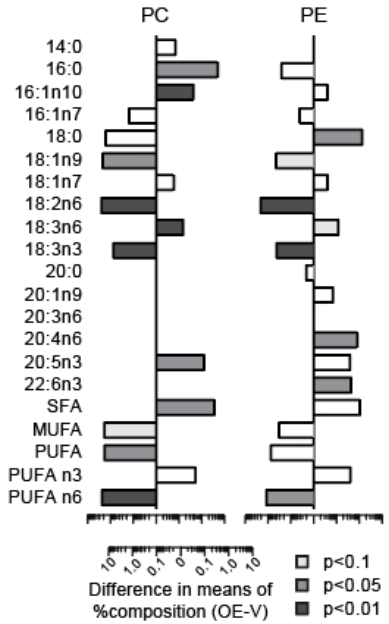
Metabolic imaging redox

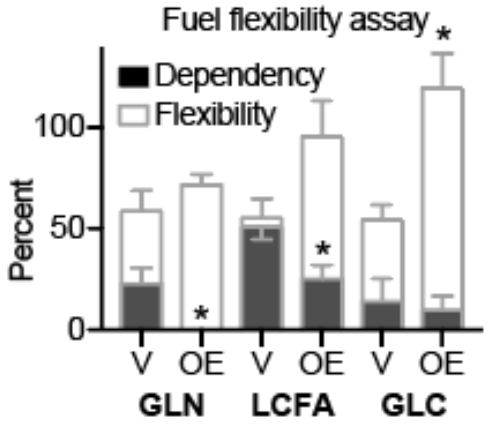


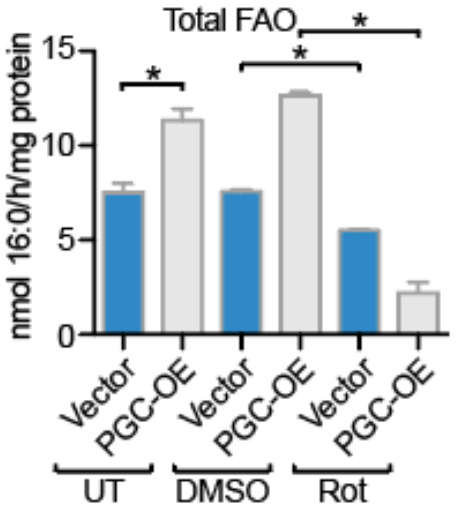


Lipid droplet detection Bodipy

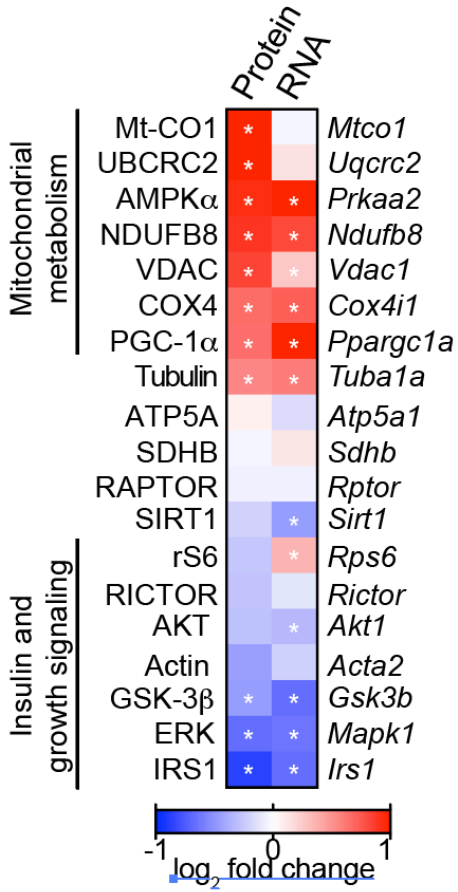




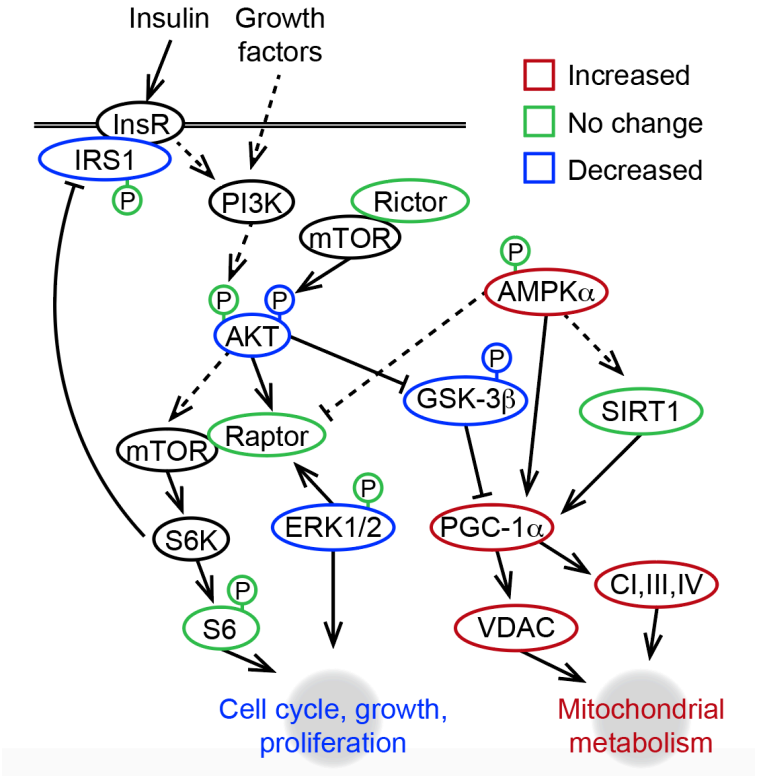




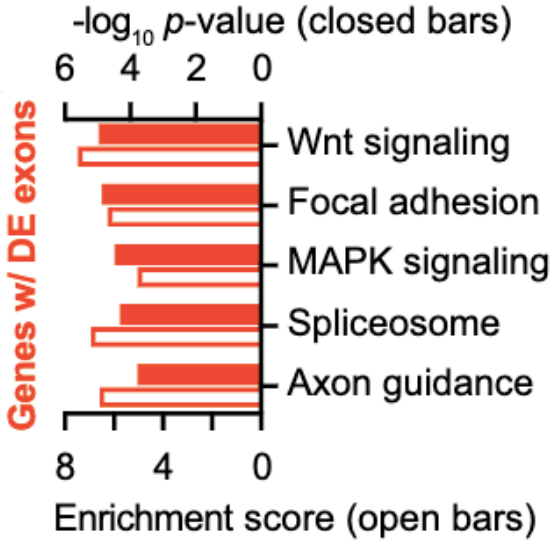
Mitochondrial Activation: Growth Signaling Regulation



Regulation by abundance



Regulation by PTM



Regulation by splicing

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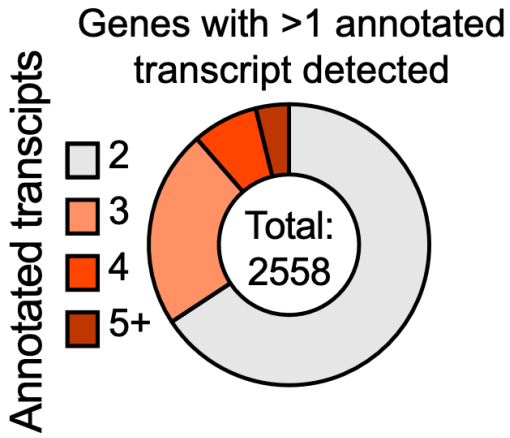
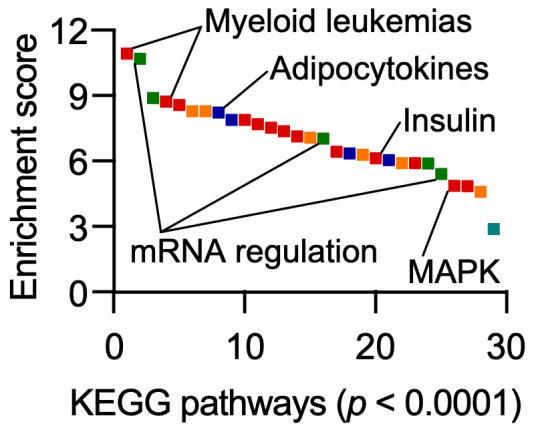
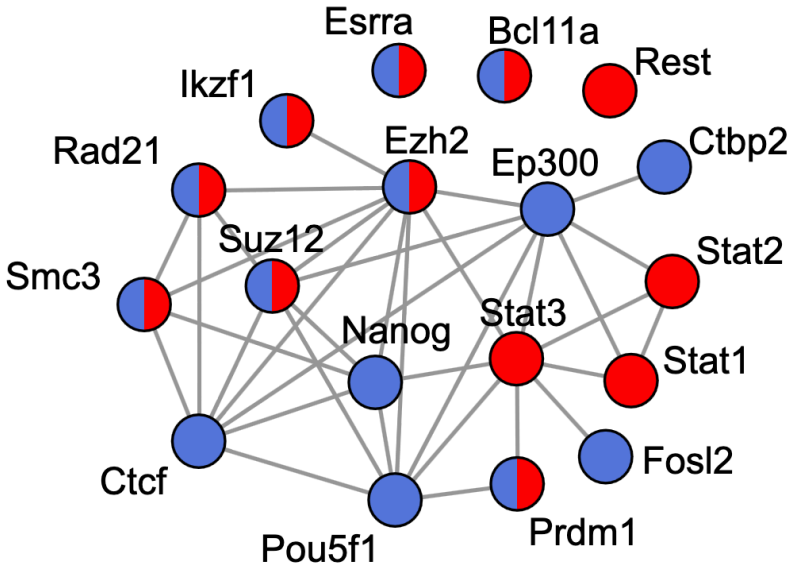
Mitochondrial Activation: RNA Processing & Chromatin Remodeling

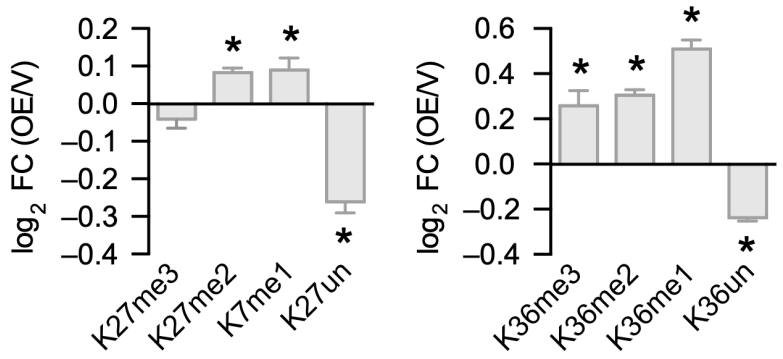
RNA Processing

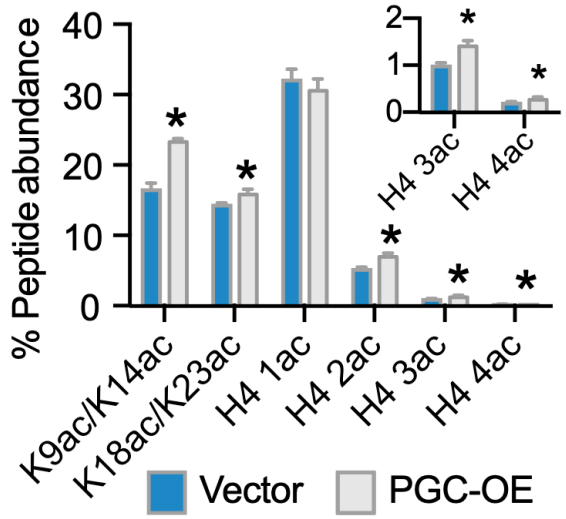




Chromatin Remodeling

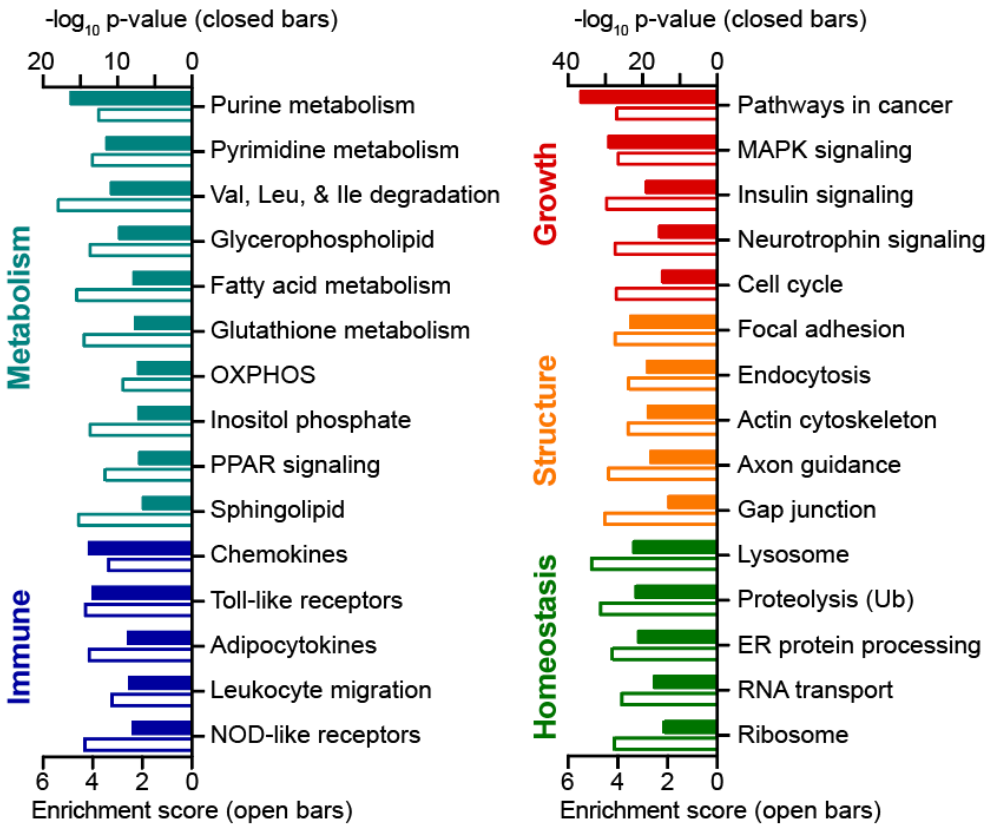






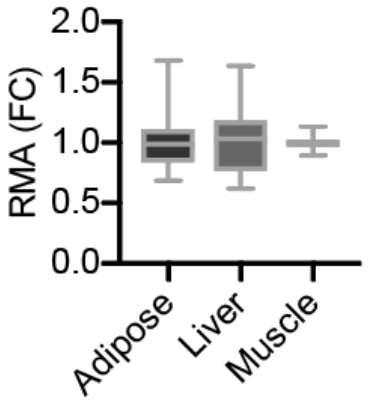
Extensive Cellular Networks are linked to Metabolism

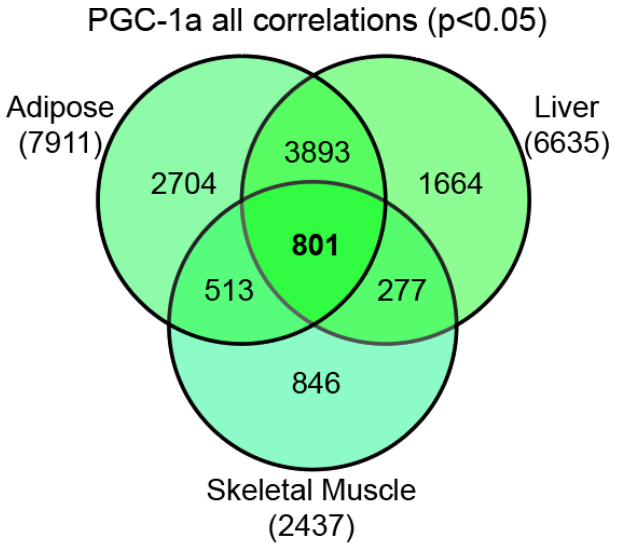
PGC-1a in vitro

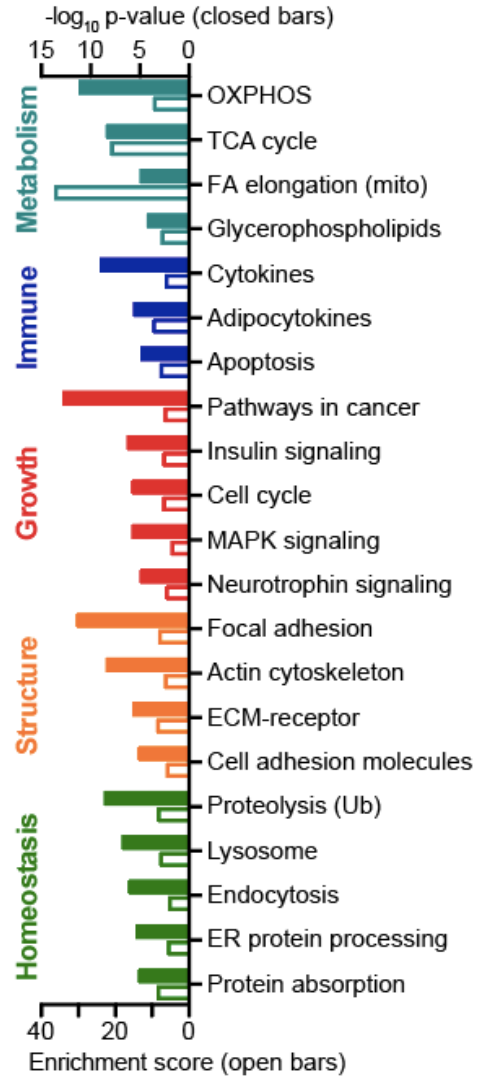


11K unique transcripts;
PGC-1a OE >5K DE

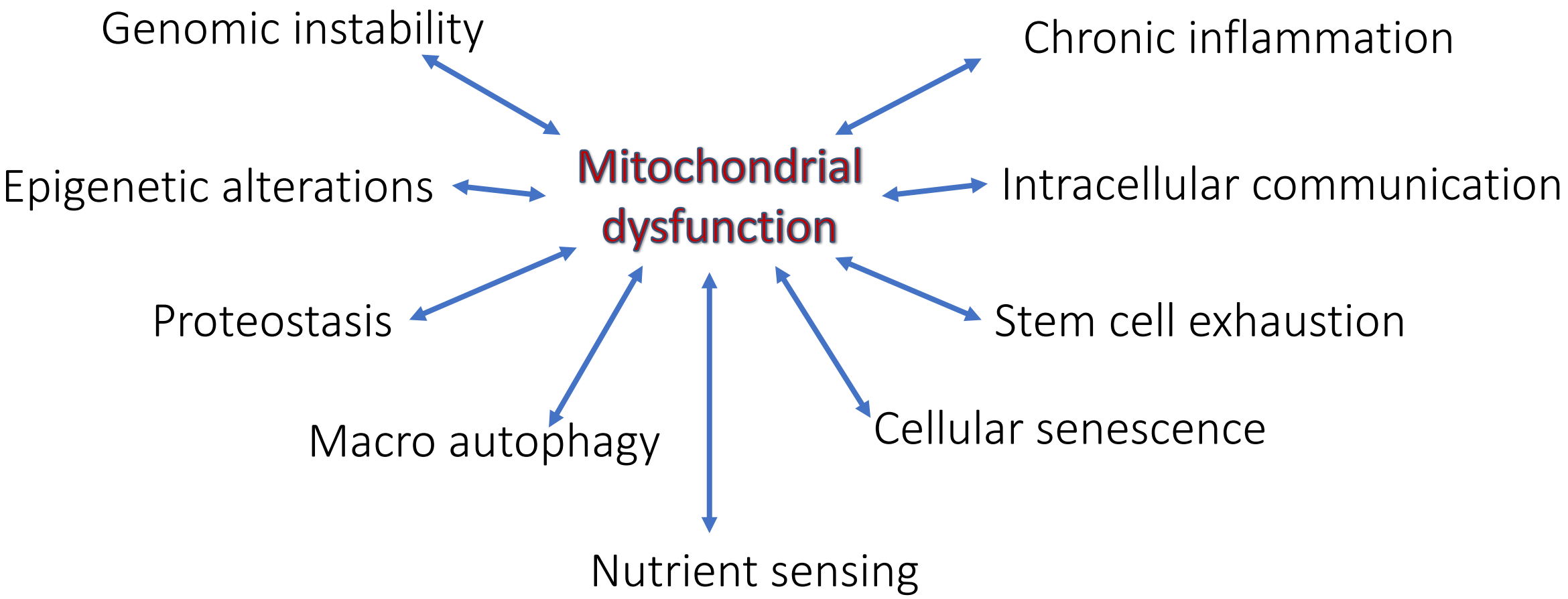
PGC-1a in vivo





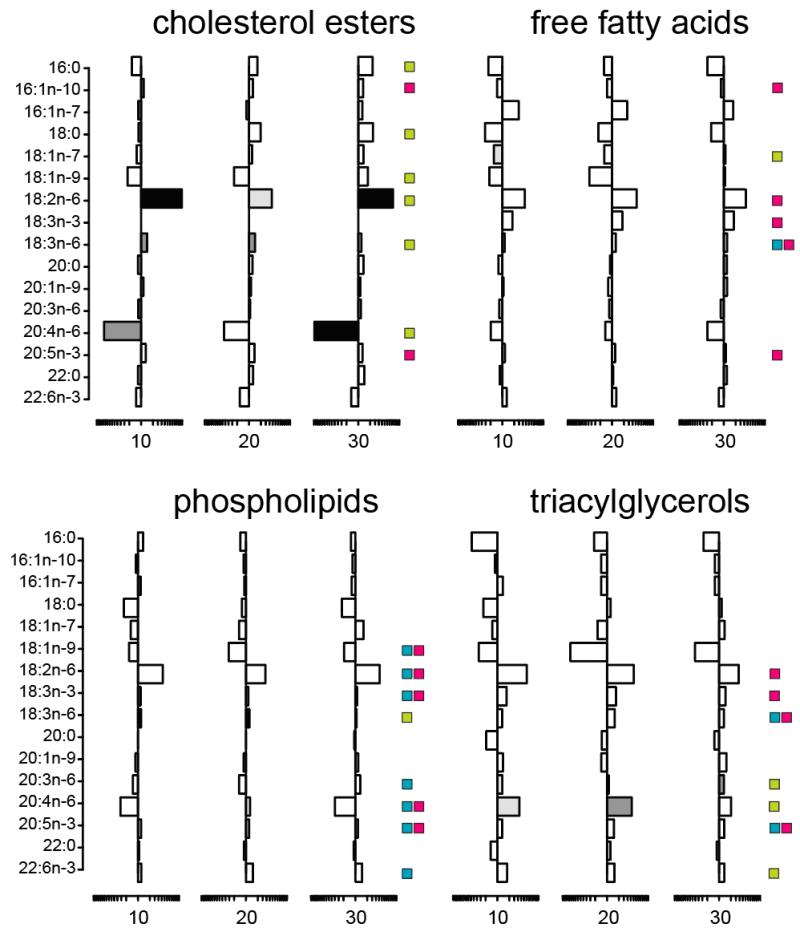


Metabolic connections to Hallmarks of Aging



Mouse Aging & CR Impact Circulating & Central Lipids

Circulating Lipids



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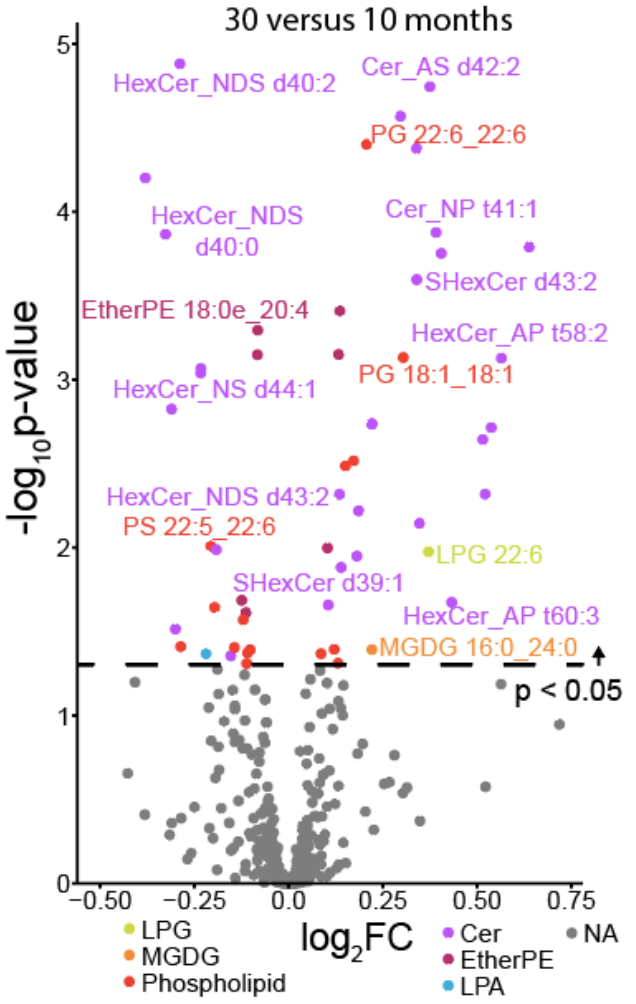
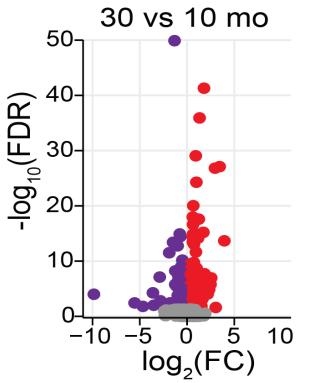
Brain Aging Lipidomics

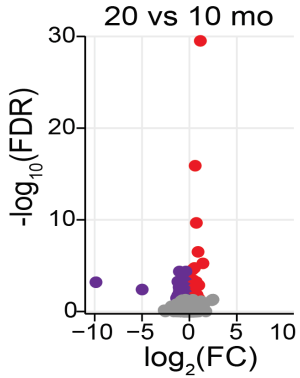


Mac Anderson & Timothy Rhoads

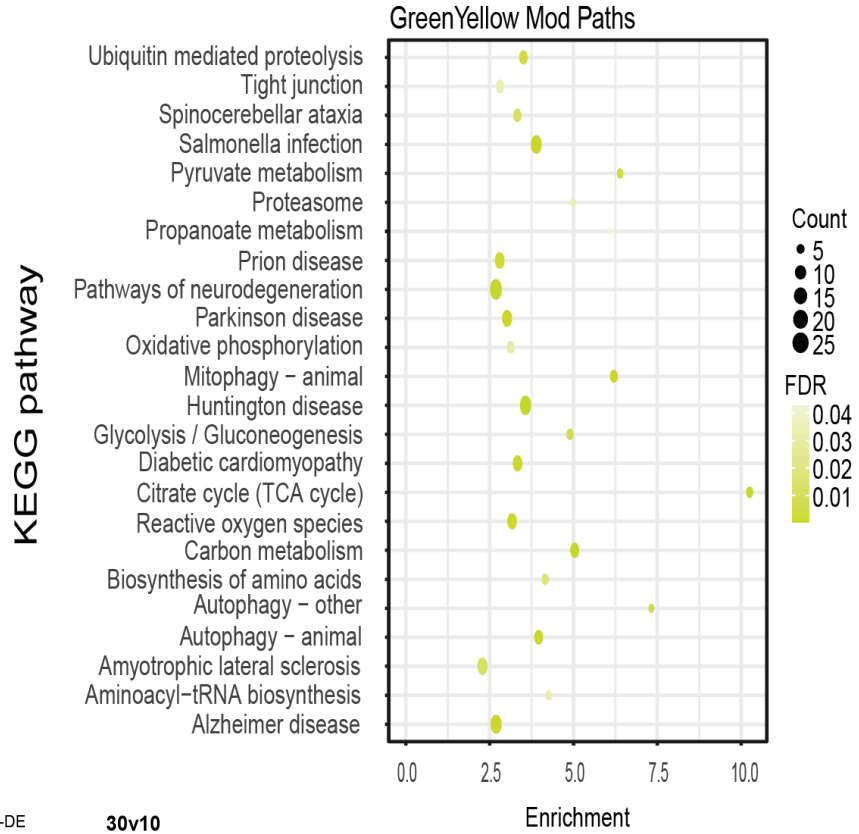
MOUSE

Mouse Brain Aging Molecular Signatures of Metabolism

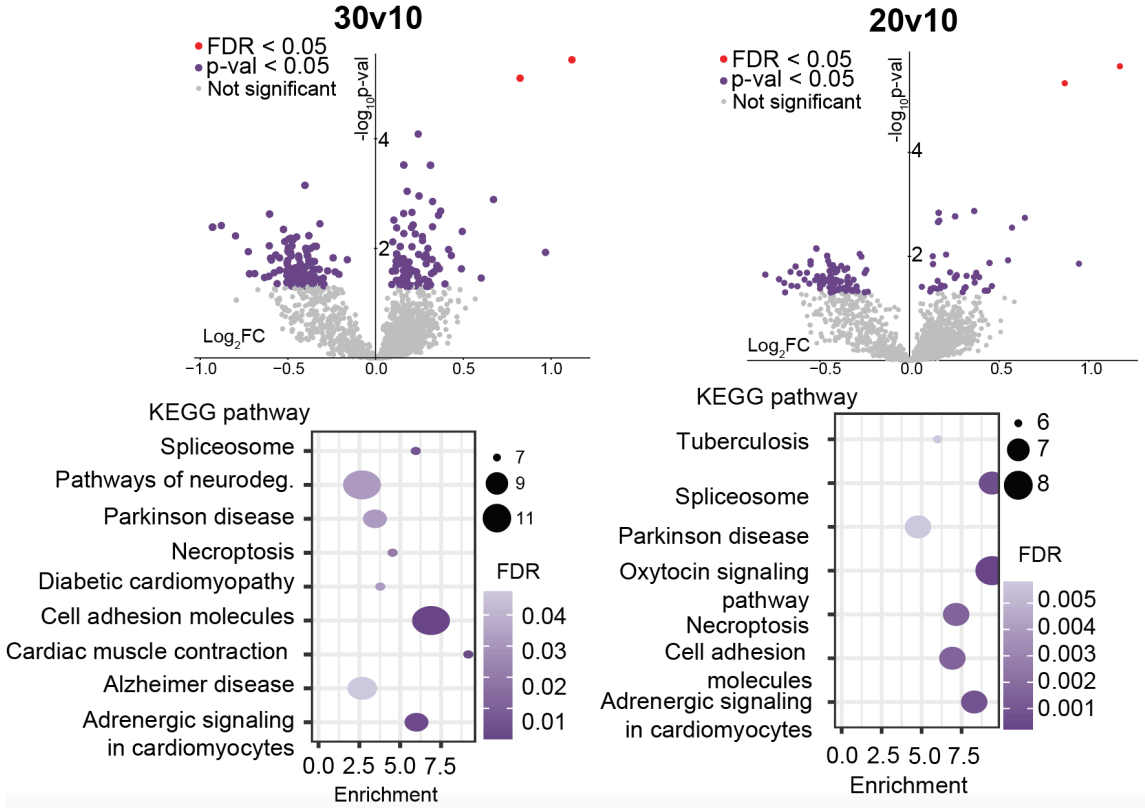


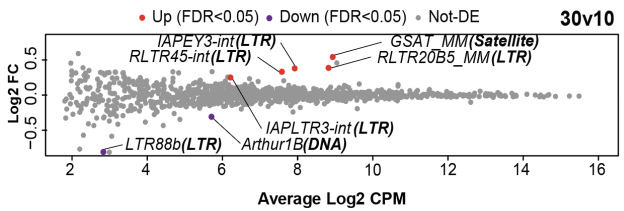


Aging Transcriptome



Aging Proteome



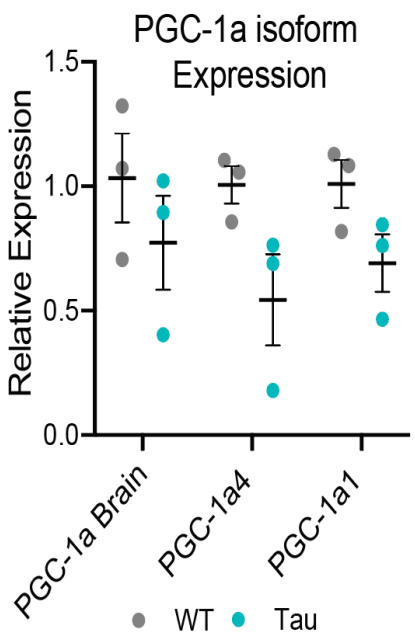


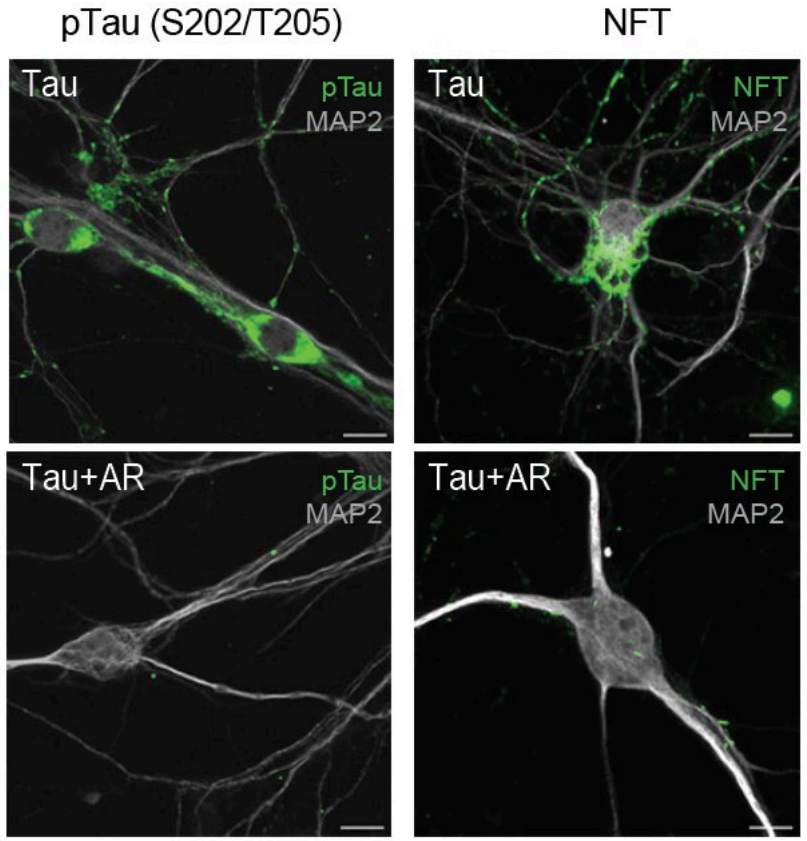
Transposons

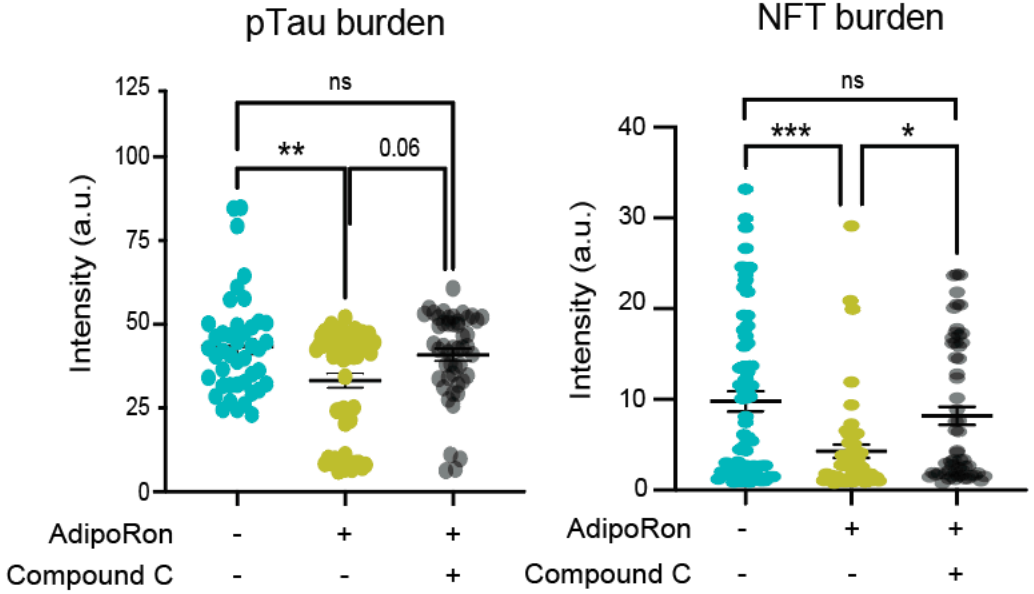
Dylan Souder and Timothy Roads

Tauopathy is Rescued by CR-like Metabolic Stimulation

Primary neurons with hTauP301S
NF seeded – 10 days growth



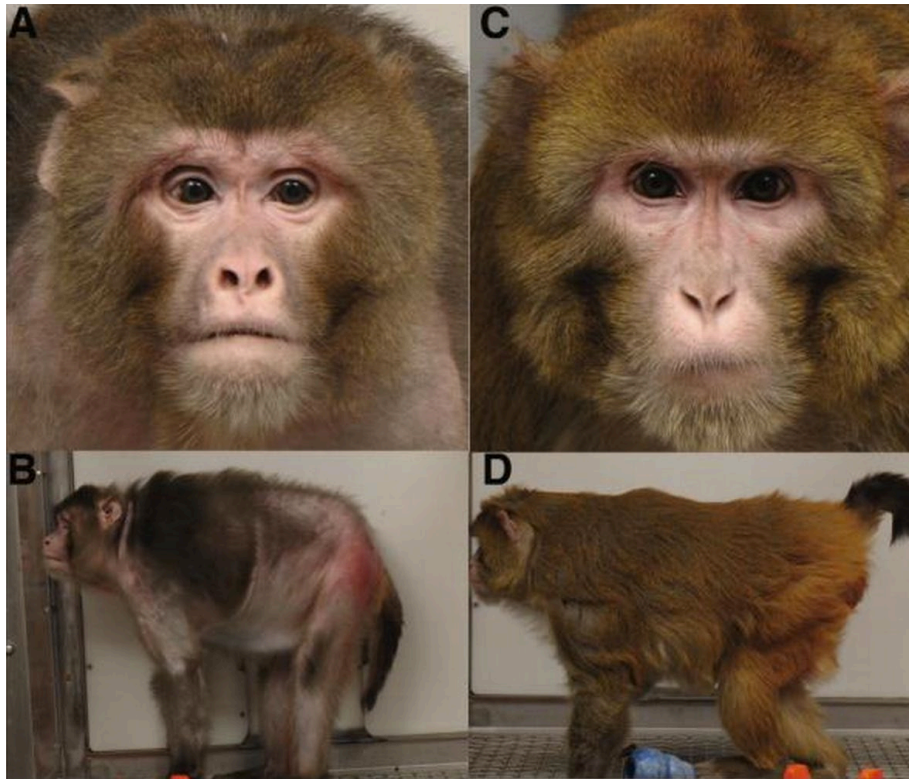




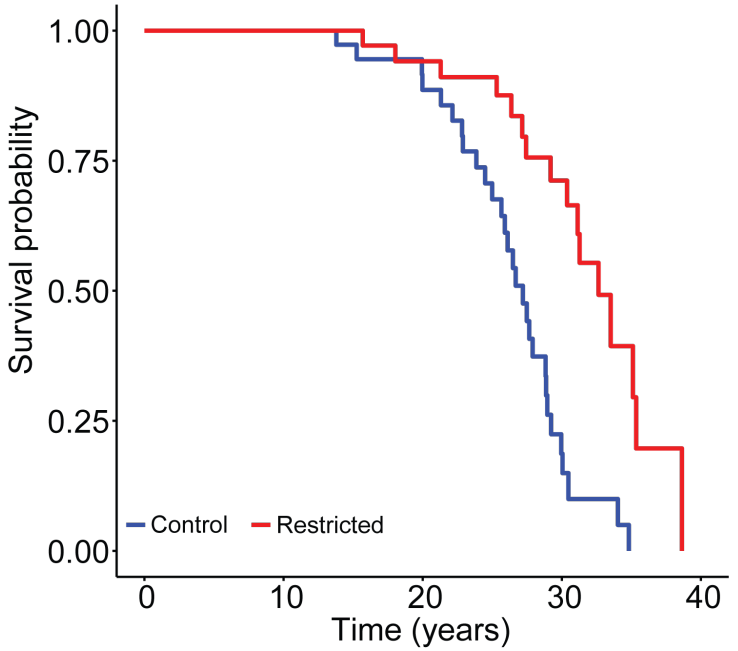
Dendritic complexity
Autophagy activation
Lipid Mobilization
Electrophysiology restoration

Eric McGregor

Caloric Restriction Improves Survival in Monkeys (NHPs)

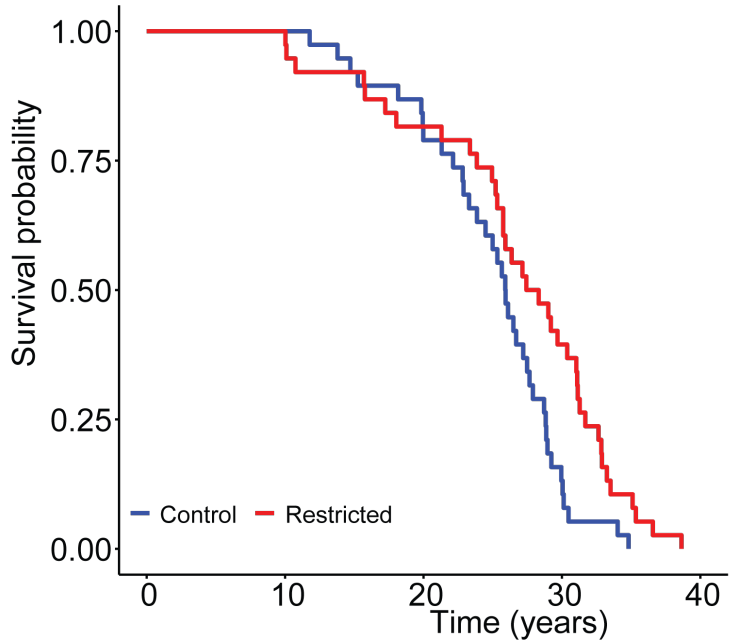


Age-related survival



Hazard ratio = 4.432 (p = 0.003)

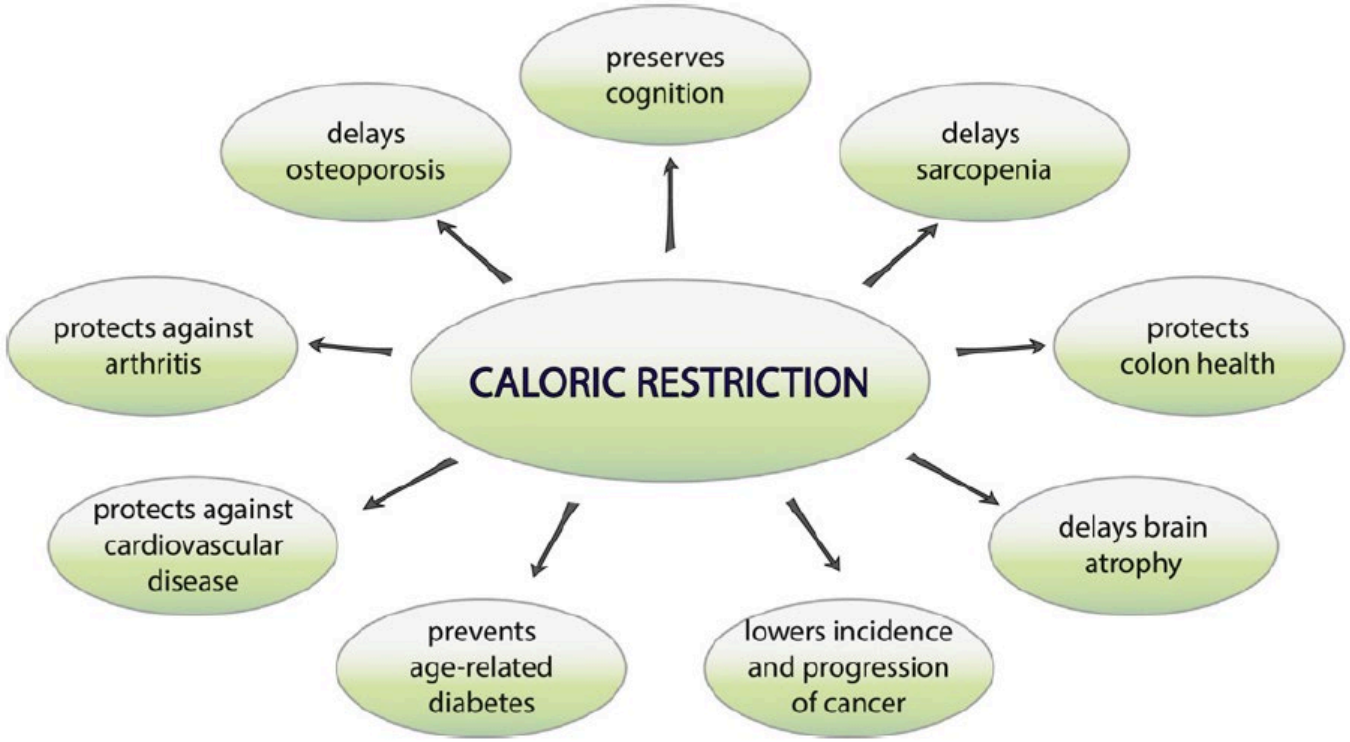
All-cause survival



Hazard ratio = 1.828 (p = 0.013)

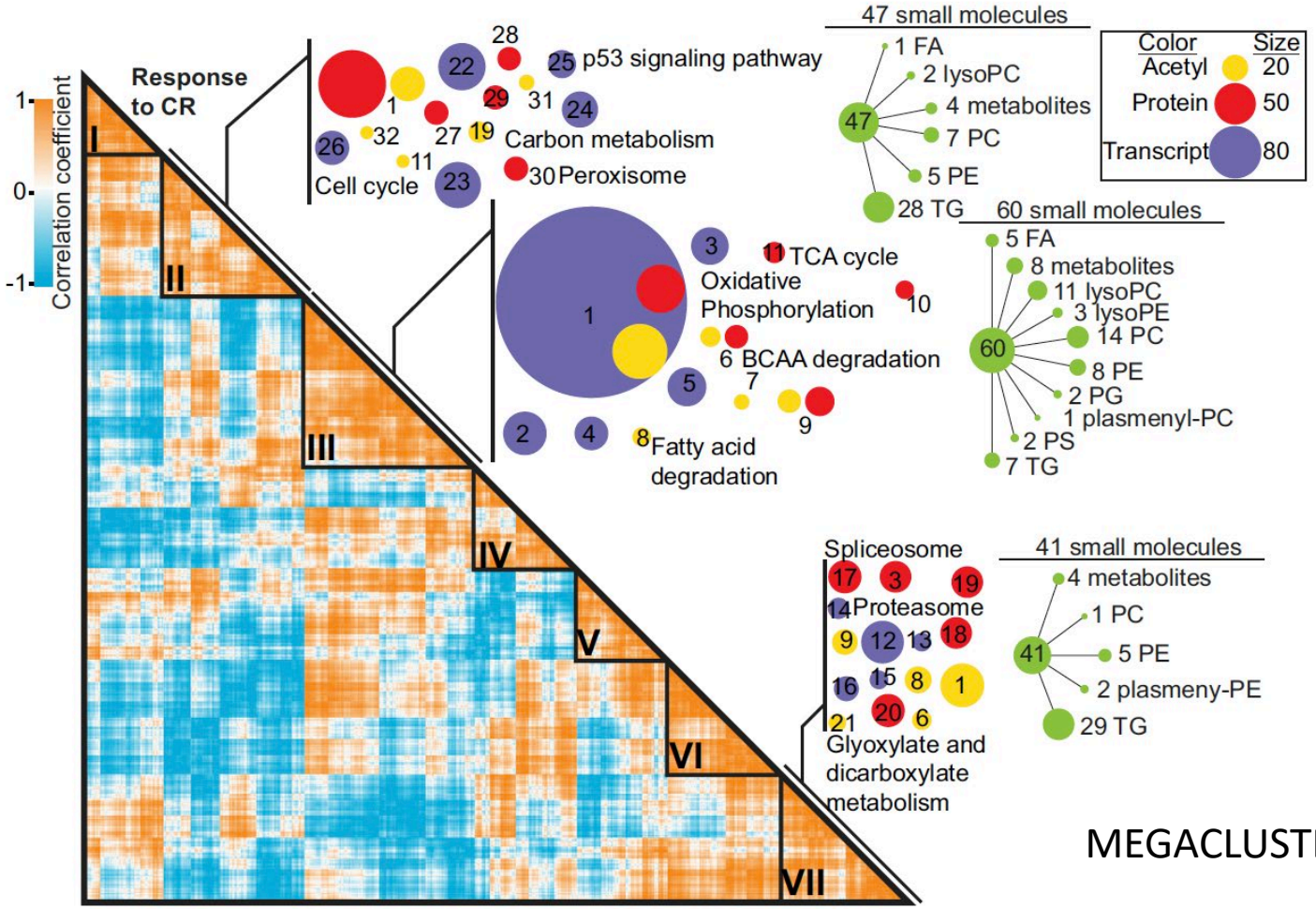
- 76 monkeys recruited to the study and monitored for 30 years
- Adult onset (8-14 years of age) males & females
- 30% CR from baseline food intake

CR Impacts Multiple Age-Related Diseases & Disorders



Q1. What creates shared vulnerability to a host of seemingly unrelated diseases and disorders?
Q2. What is CR changing to delay aging and onset of age-related conditions?

Highly Coordinated NHP Hepatic CR Metabolic Response



MEGACLUSTERS

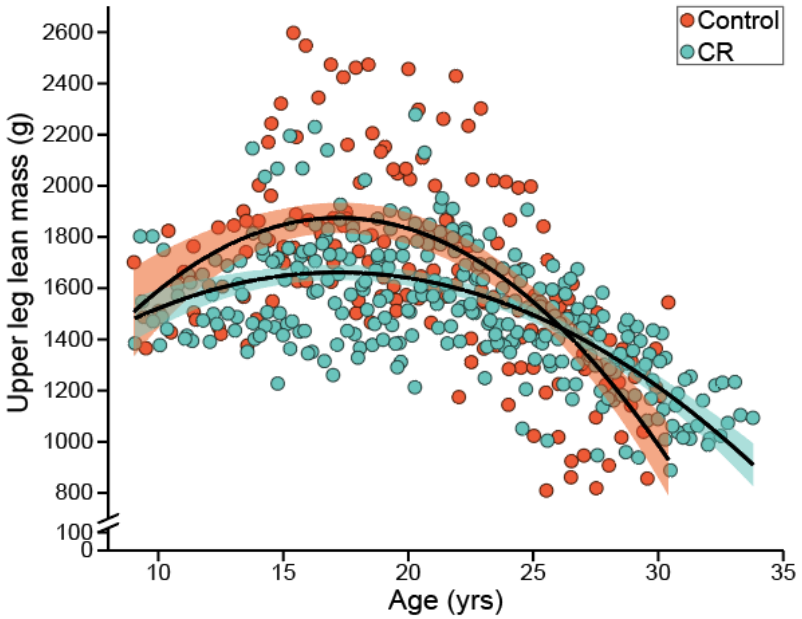
Correlation plot (Pearson)

Caloric restriction implements a program that changes metabolism - how energy is derived, stored, used, and shared. This program can be detected across all platforms & pathways, influencing many cellular processes

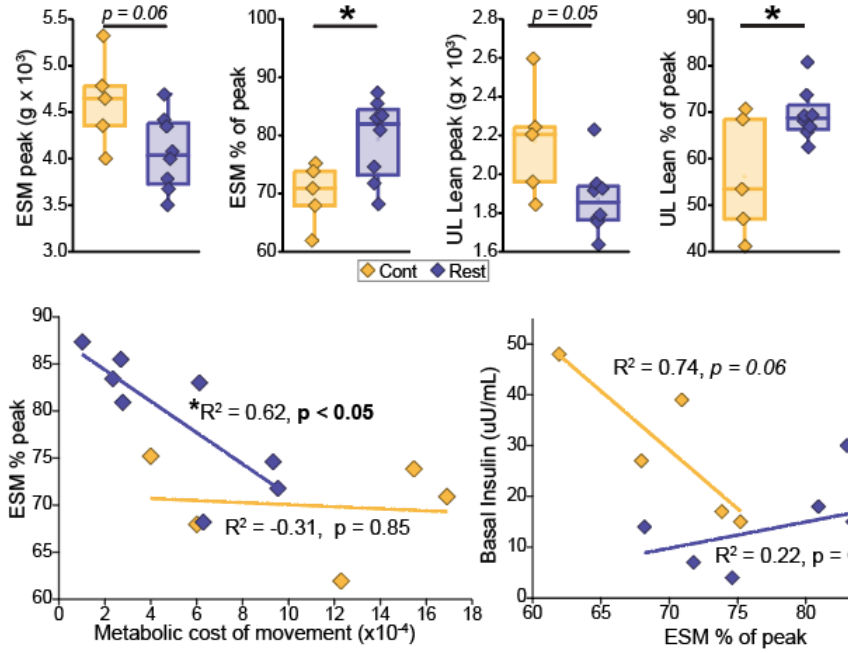
PMC:5844481

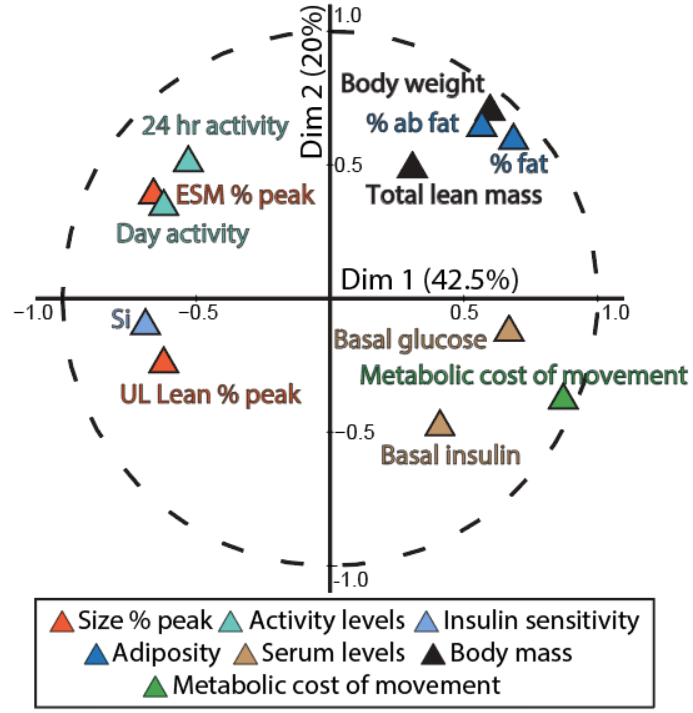
CR Delays Sarcopenia (Mass & Function) In NHPs

Skeletal Muscle aging
Longitudinal measures



Cross-sectional measures



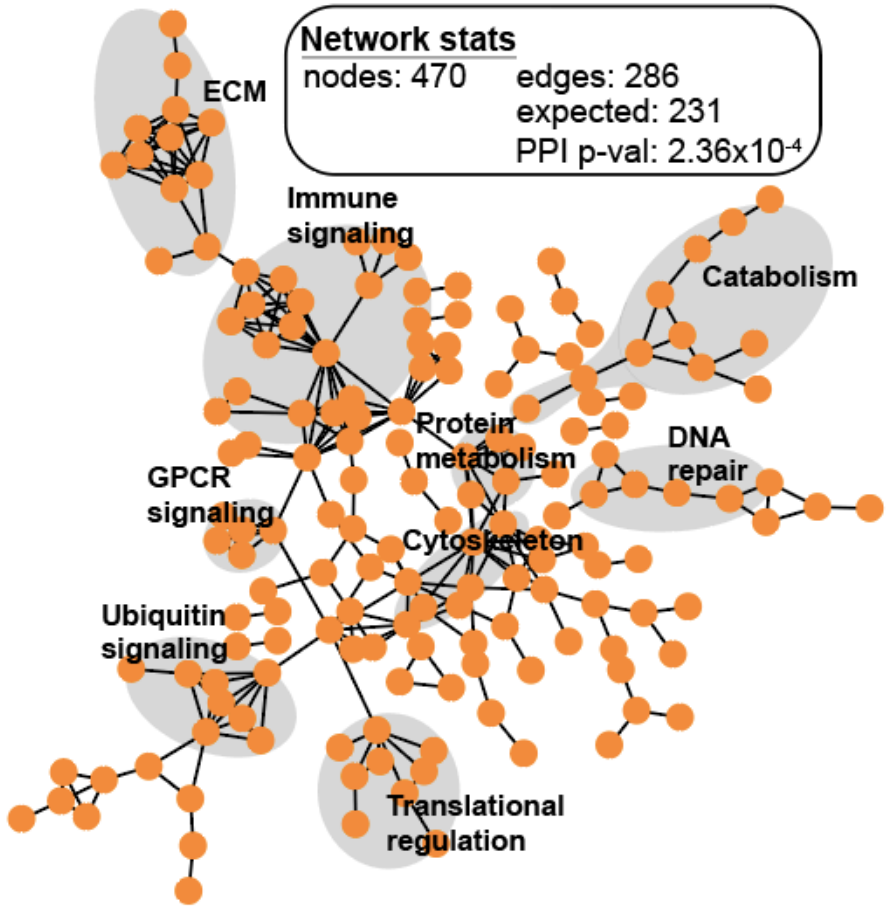


MFA analysis shows linked parameters during aging

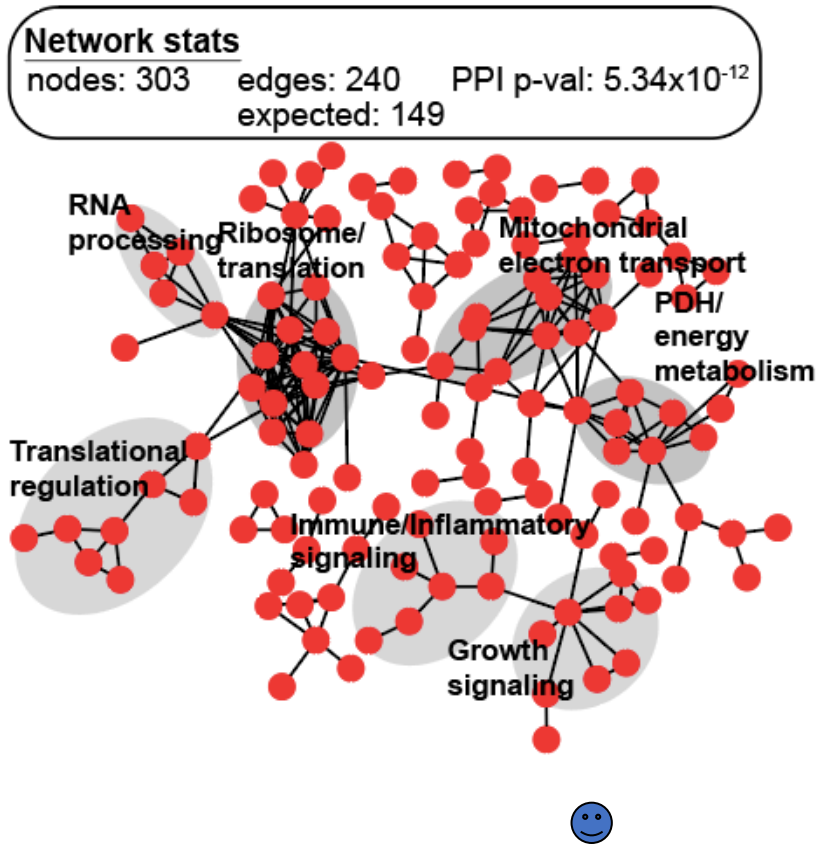
PMC:7047532

NHP Skeletal muscle Sex Dimorphic CR response metabolism, growth, & repair

Males



Females



Tim Rhoads & Mike Polewski

SMN
UW Madison
Skeletal Muscle Network

Translational Implications:
Two-year Clinical Trial: NIH/NIA CALERIE Study

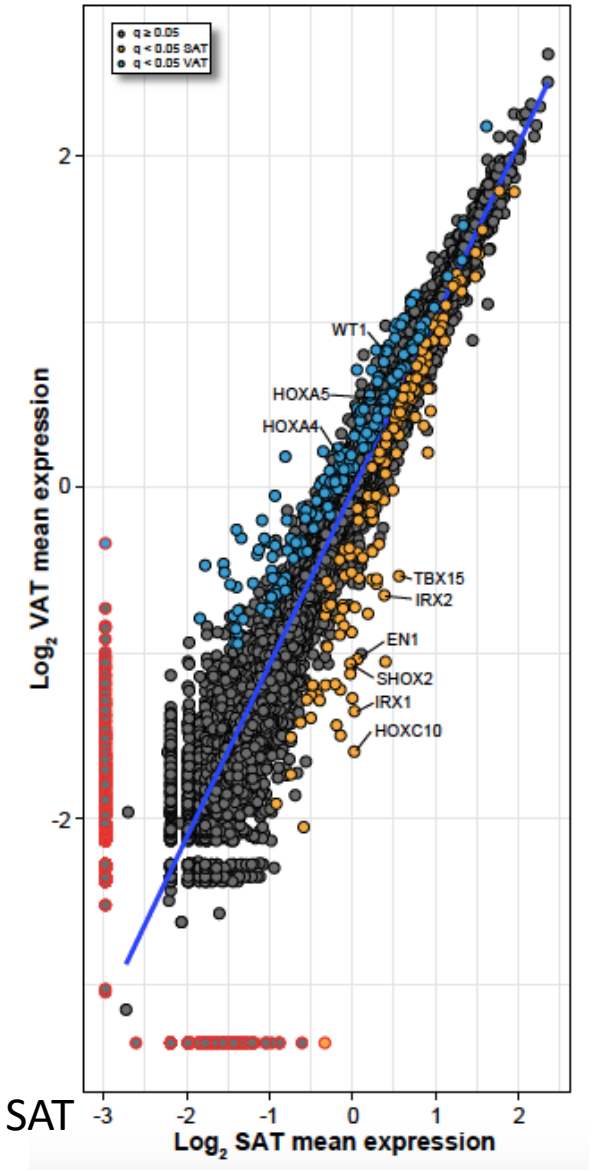
HUMAN CR	MONKEY CR
• Lower bodyweight	✓
• Lower adiposity	✓
• Lower circulating glucose	✓
• Lower circulating insulin	✓
• Improved insulin sensitivity	✓
• Lower risk factors for CVD	✓

3 locations, n=220 (145 CR; 75 Control)

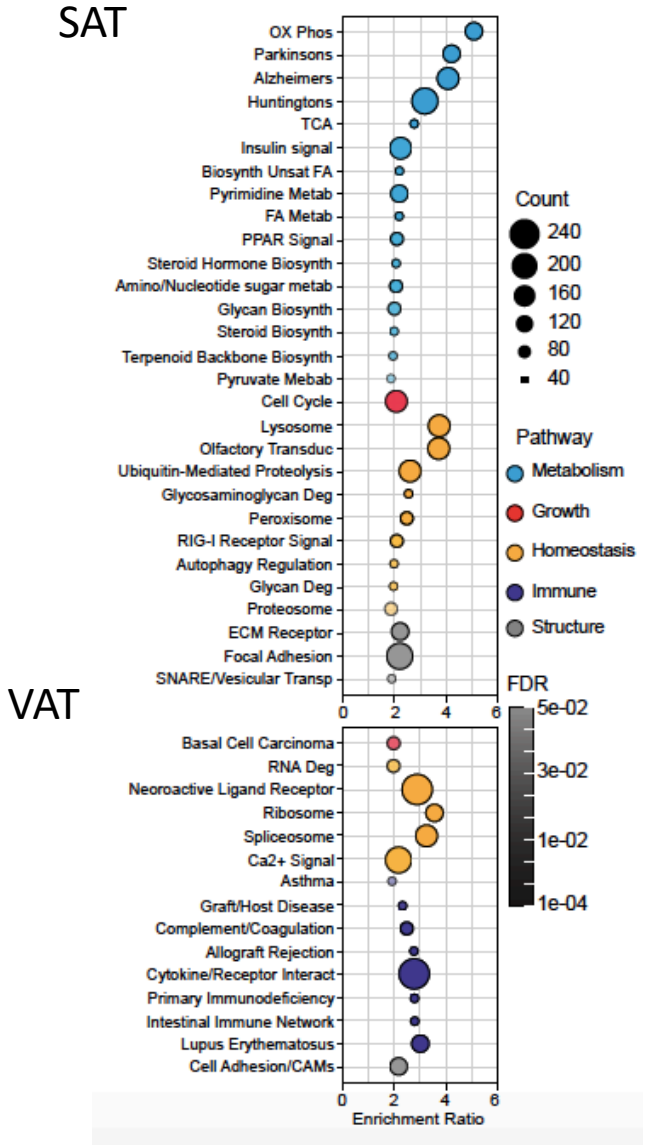
non-obese adults (BMI 22-28kg/m^2), 21-50 years old

NHP Adipose Tissue transcriptome Depot specificity

Gene expression by Adipose Tissue Depot

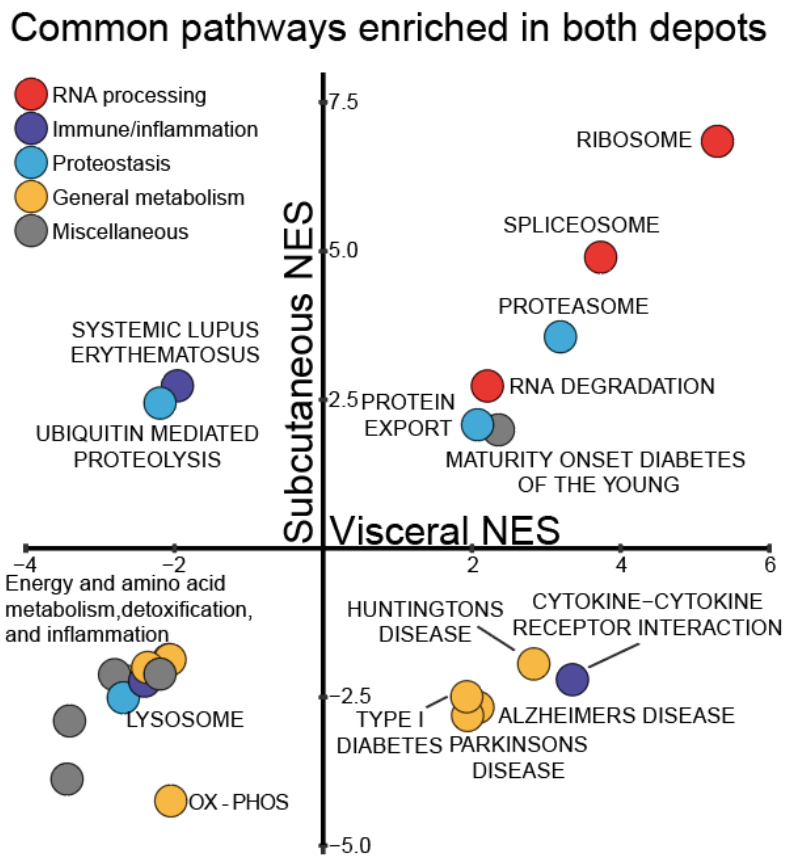


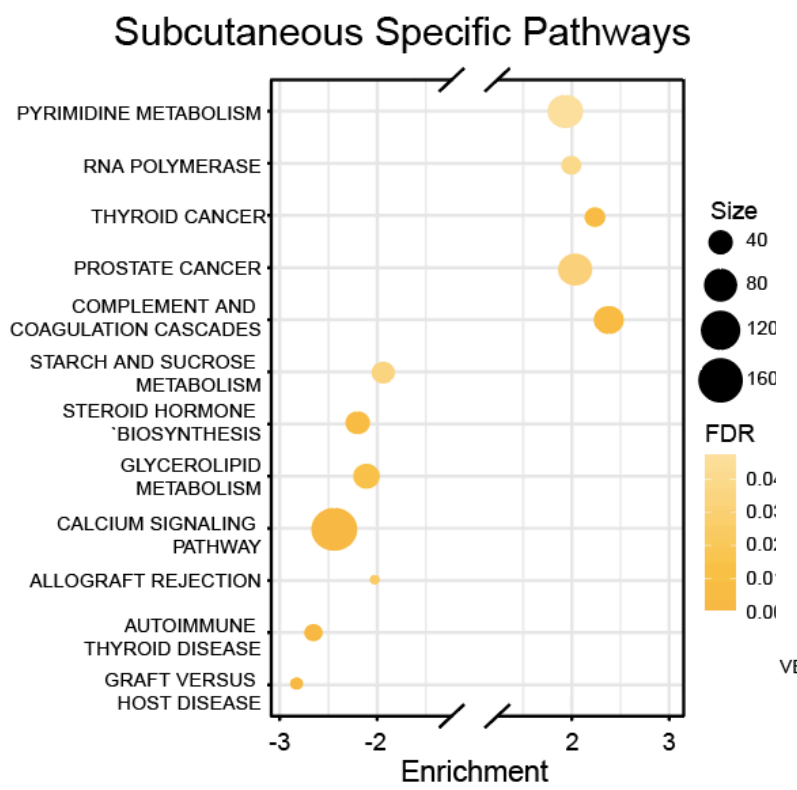
Enriched pathways by Adipose Tissue Depot

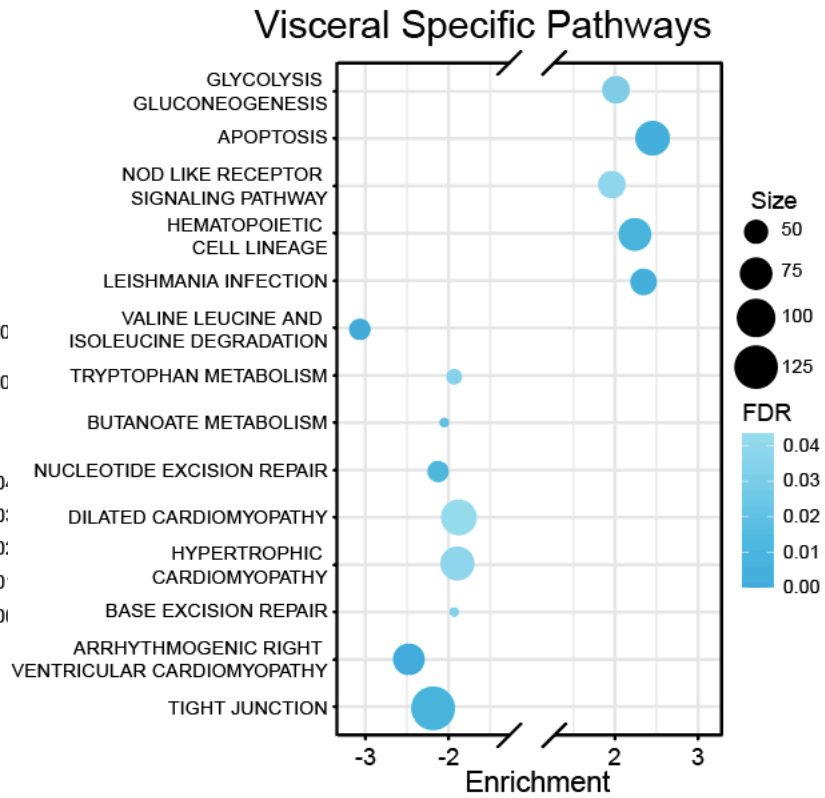


Josef Clark & Tim Rhoads

Adipose CR: response is Depot Specific

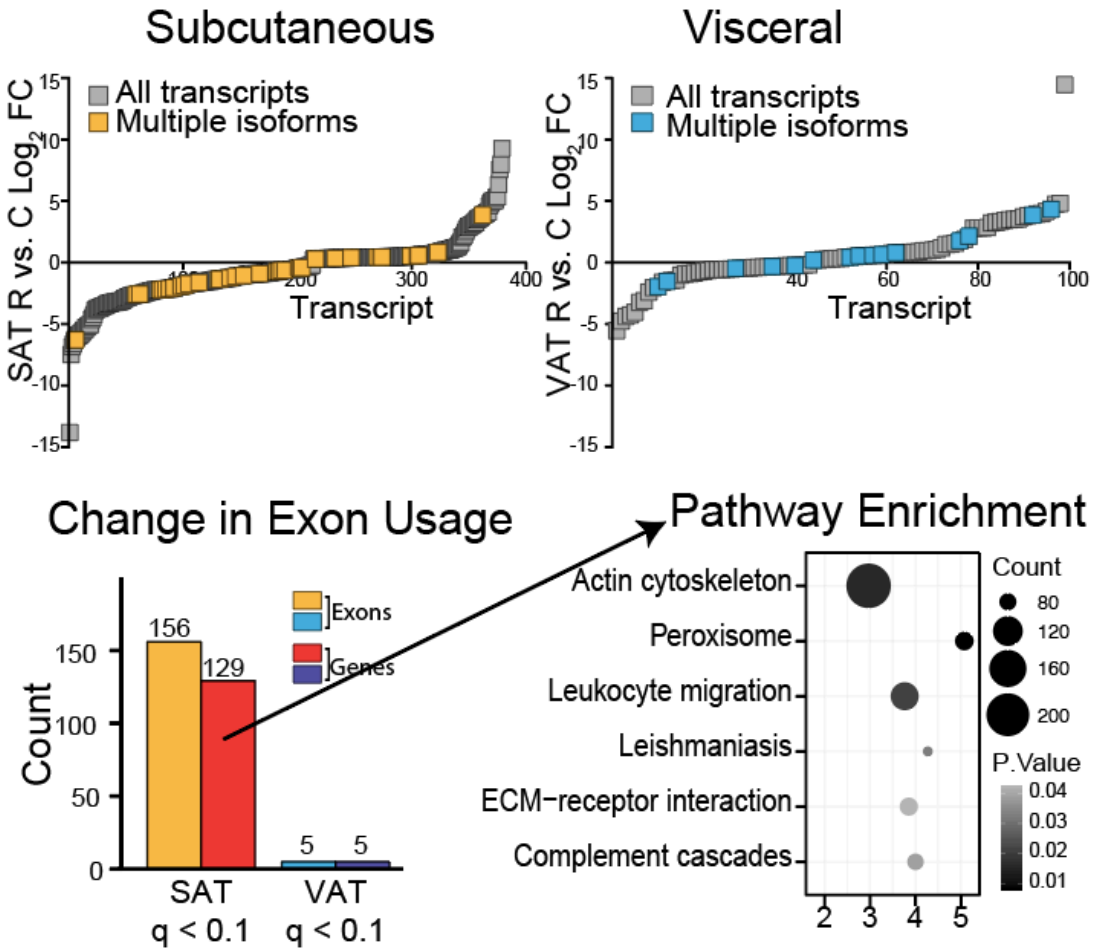


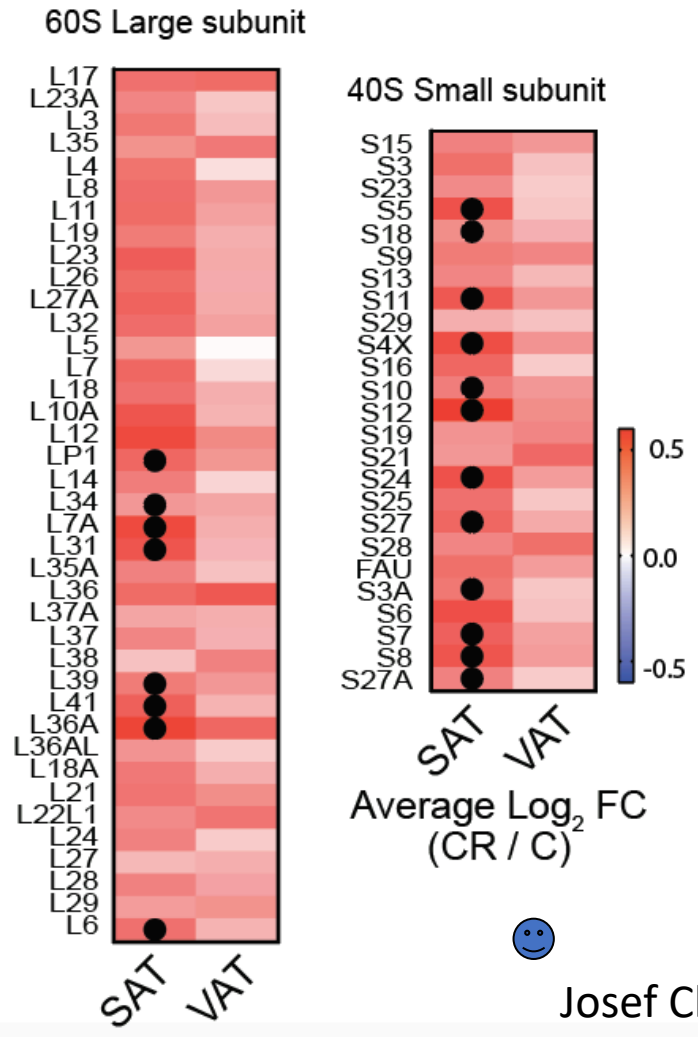




Josef Clark & Tim Rhoads

Adipose CR: RNA Processing & Ribosomal Rearranging





Josef Clark & Tim Rhoads

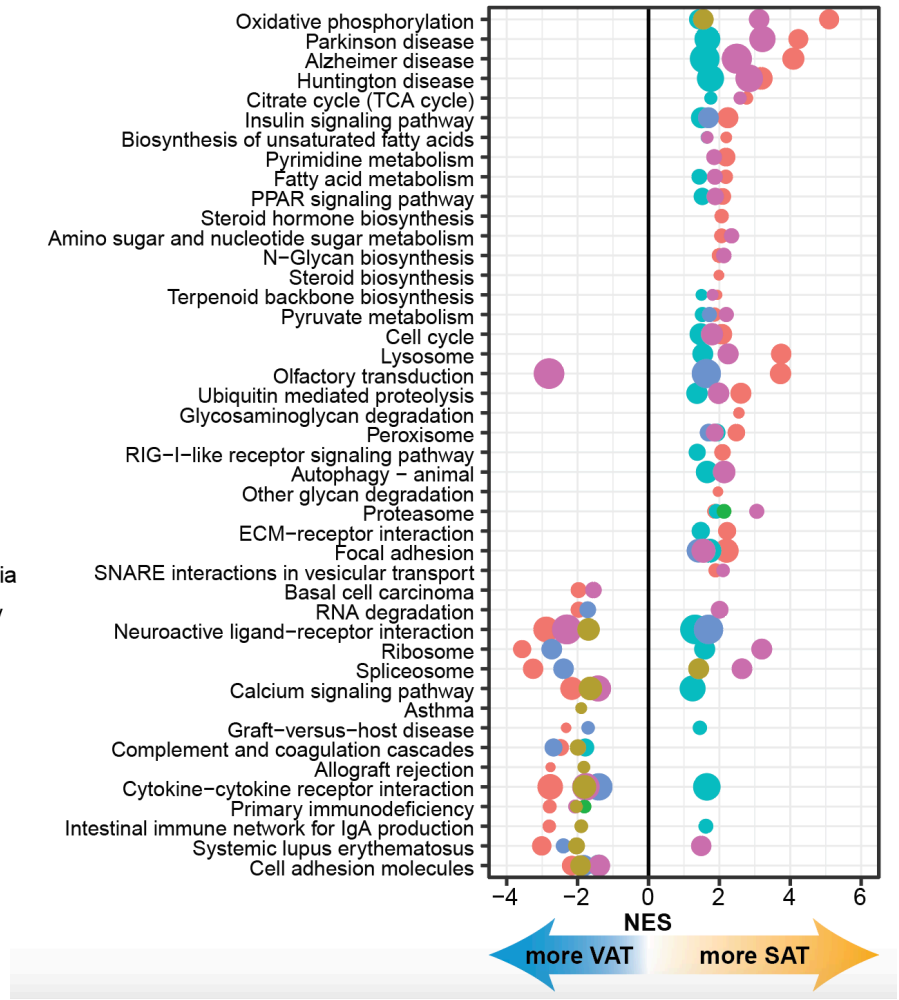
Monkey & Human Adipose are highly similar

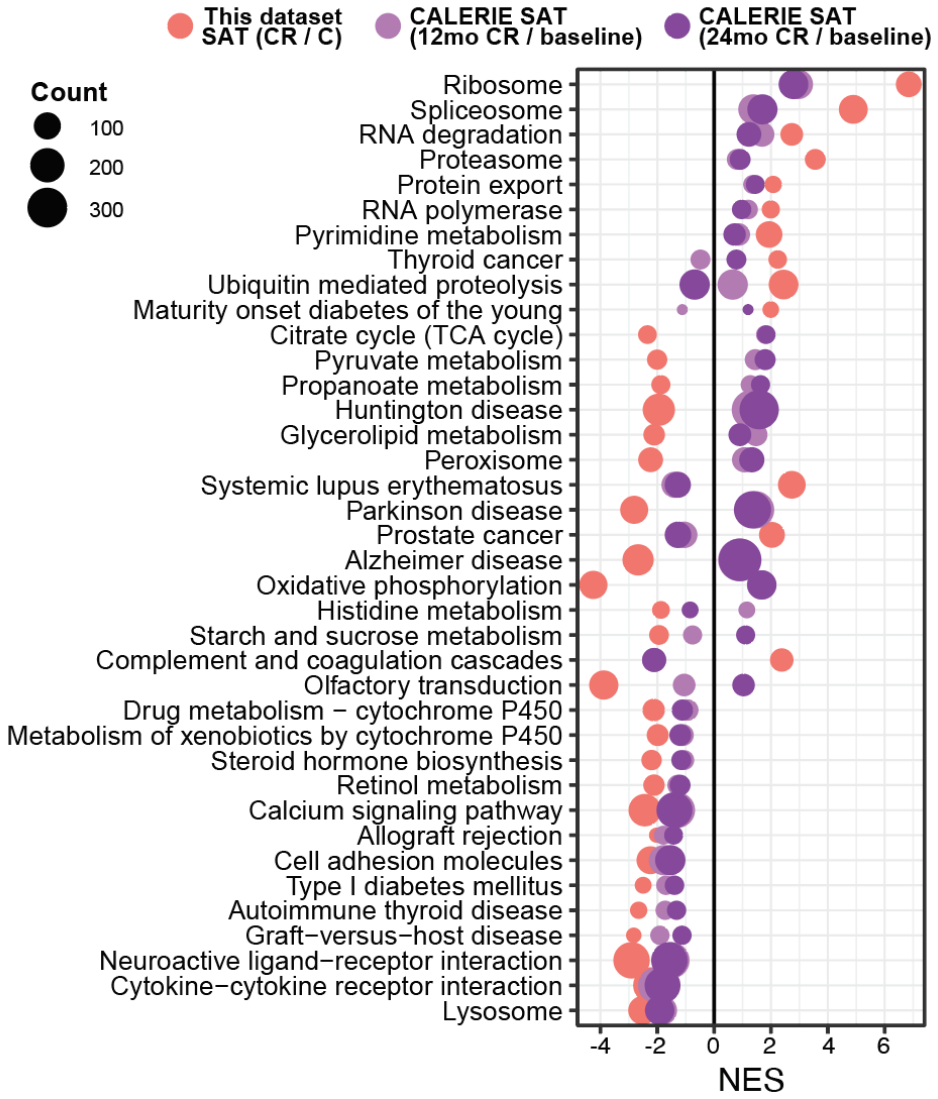
Depot specificity
Matched

Response to CR
Matched

Dataset	Sequencing technology	Species	Participant details
This dataset	RNAseq	M. mulatta	control diet
GSE186466	RNAseq	H. sapiens	cancer / cachexia
GSE213058	RNAseq	H. sapiens	morbid obesity
GSE73108	Microarray	H. sapiens	obesity
GSE73439	Microarray	H. sapiens	normal
GSE78721	Microarray	H. sapiens	normal

Count
100
200
300





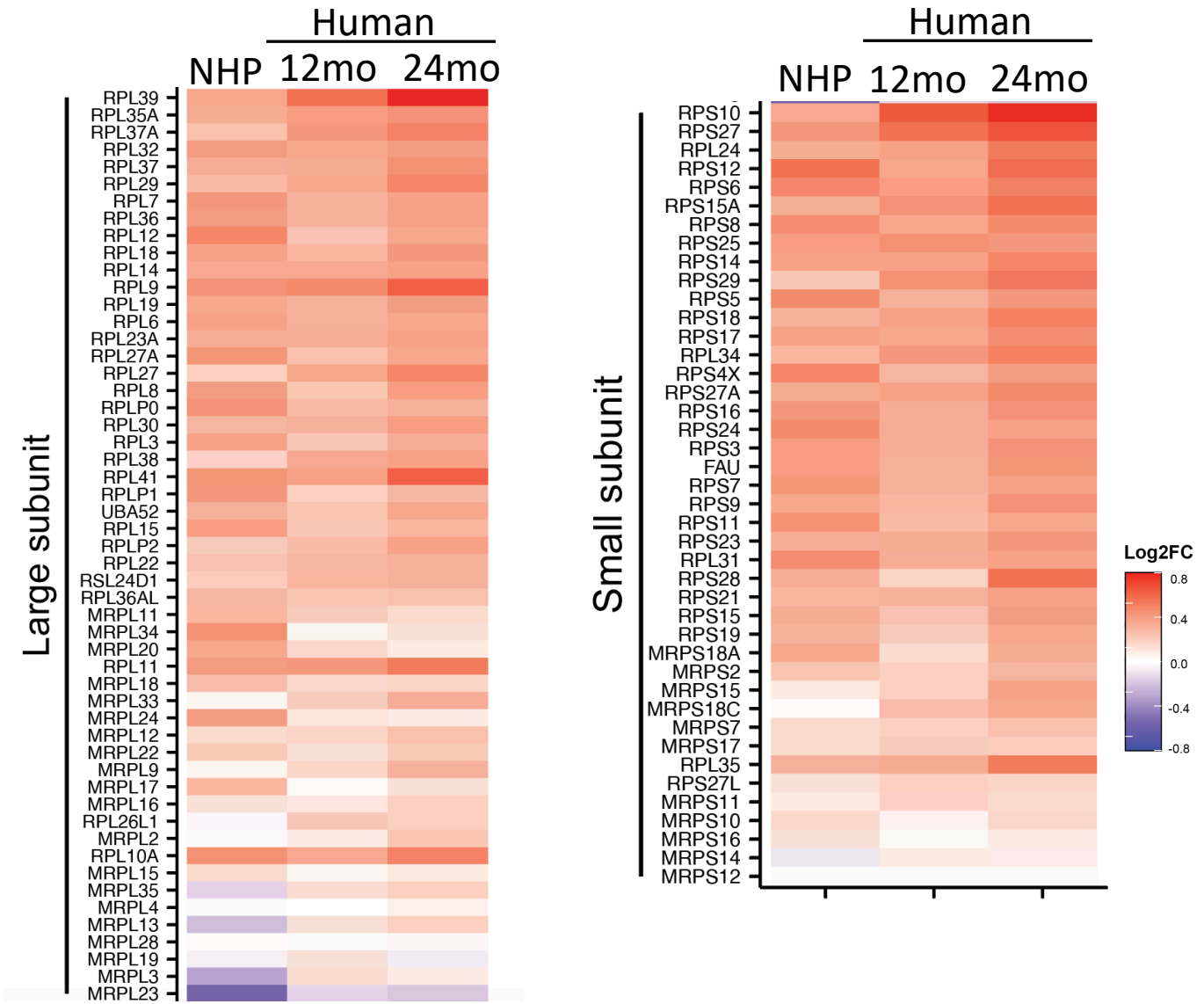
Josef Clark, CALERIE Daniel Belsky

Ribosomal Rearranging with Human CR

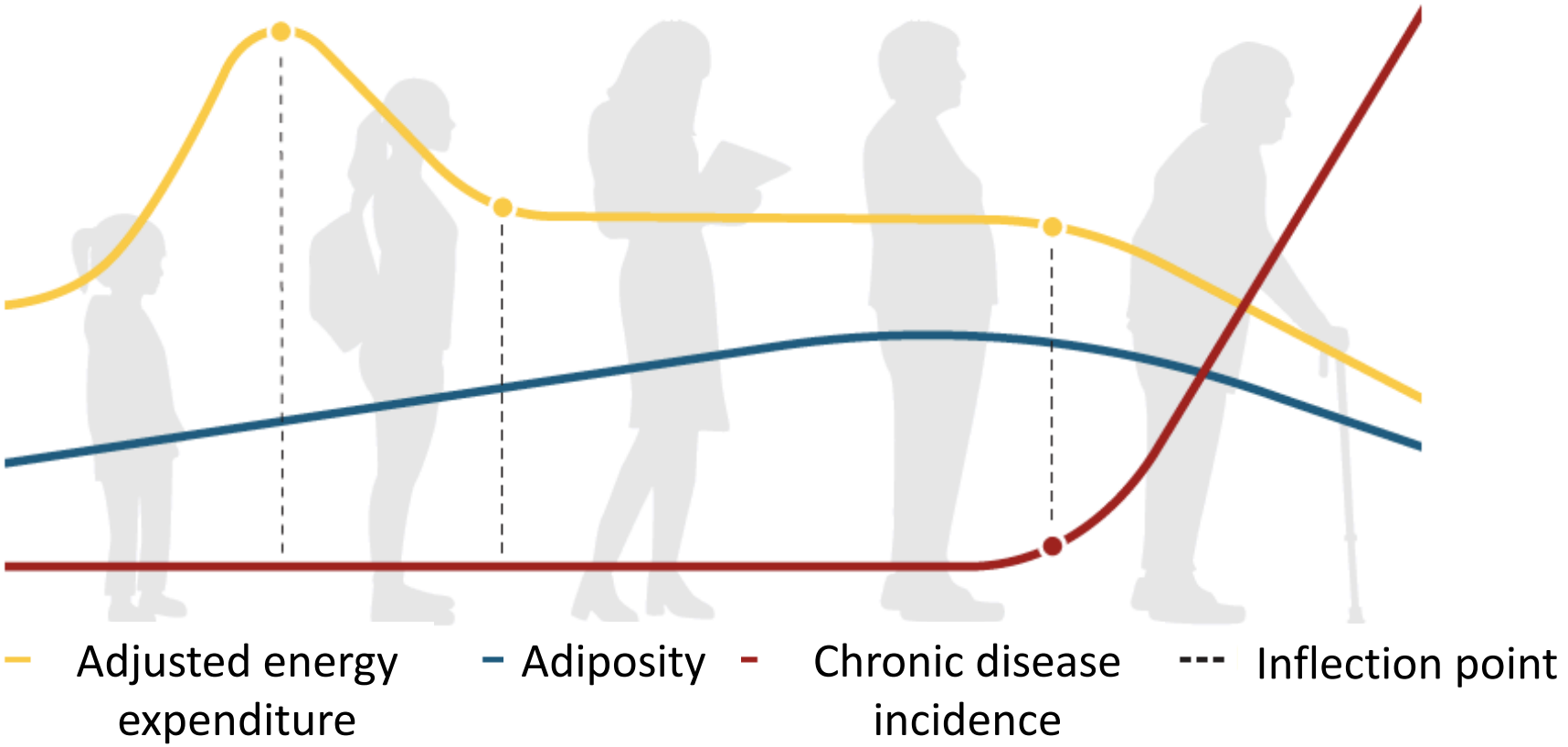
Subcutaneous Adipose Tissue

NHP (Monkeys)
Lifelong CR
vs
12mo CR people
(CALERIE)

24mo CR people
(CALERIE



Metabolism of Aging & Disease Vulnerability



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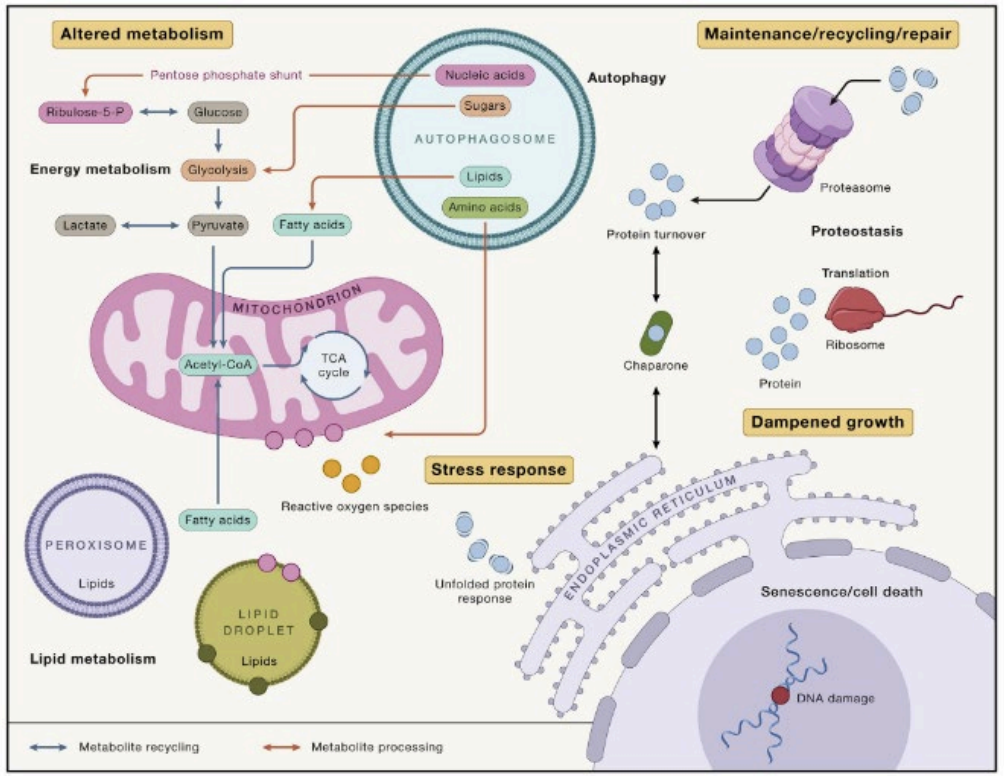
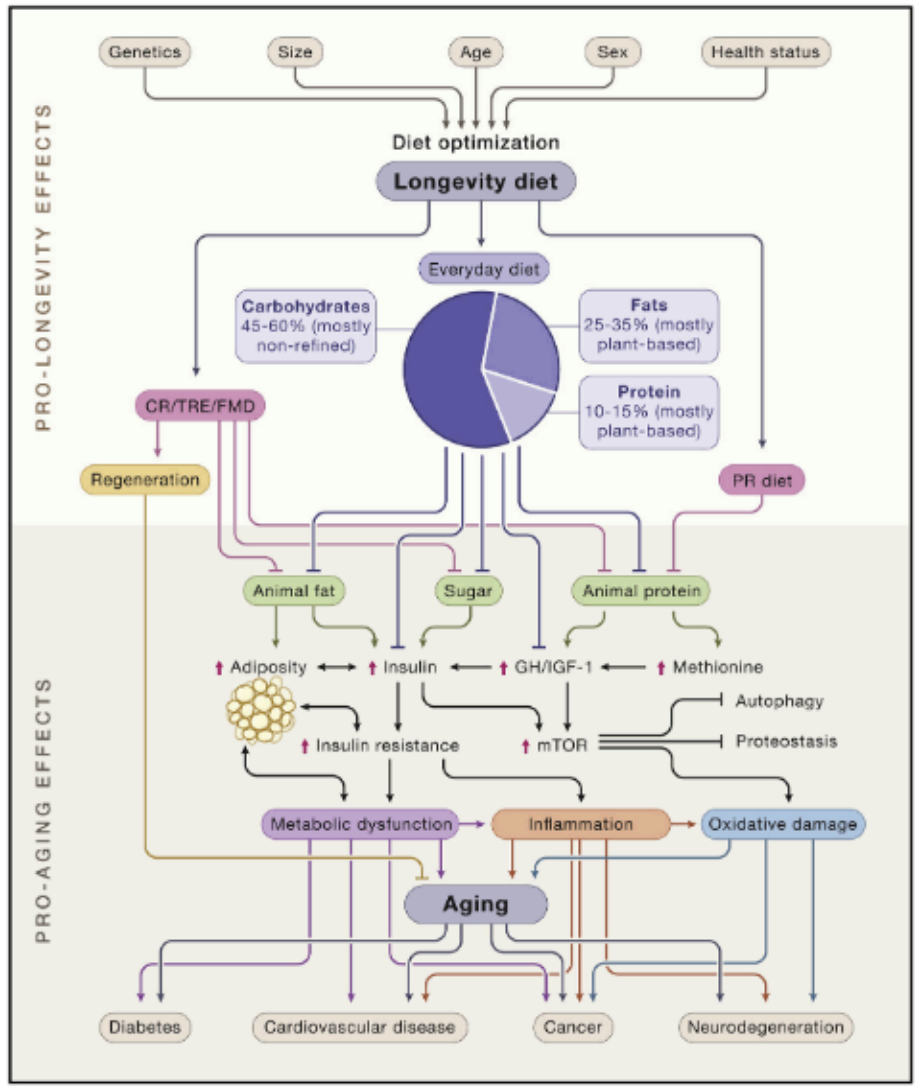
HUMAN

Metabolism & Nutrition in Longevity & Disease



PMC9089818



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