Caloric restriction induces unique transcriptional responses between adipose depots in rhesus monkeys

Josef Clark
Biology of Aging T32 - Scholars Symposium
May 8, 2019
The U.S. is Aging!

Population 65 years and older by size and percent of total population

Sources: U.S. Census Bureau, decennial census of population, 1900 to 2000; 2010 Census Summary File 1.
Healthy Life Expectancy - U.S.


1990 - 2010

Males
Change in Life Expectancy + 4.2

Females
Change in Healthy Life Expectancy + 2.7

Salomon, et al., 2012
Prevalence of diseases that cause deaths in U.S.

https://vizhub.healthdata.org/gbd-compare/
Theories of Aging

Lopez-Otin et al., 2013
Caloric restriction (CR) delays aging

WNPRC Longitudinal Study

Adapted from Colman et al., 2009

Colman et al., 2014
UW Rhesus Longevity Study Design

Year: 0 5 10 15 20 25

Diet: Control CR

Animals moved to Control or CR diet
Open Question:

How does CR change the transcriptional program of distinct White Adipose Depots?
## Biometric data

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<tbody>
<tr>
<td>Age (y)</td>
<td>24.7 ± 2.3</td>
<td>24.7 ± 1.3</td>
<td>0.97</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>13.5 ± 1.2</td>
<td>10.1 ± 1.5</td>
<td>0.01</td>
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<tr>
<td>Fat (%)</td>
<td>36 ± 6.2</td>
<td>18.3 ± 6.3</td>
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<tr>
<td>Lean (%)</td>
<td>64 ± 6.2</td>
<td>81.7 ± 6.3</td>
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<tr>
<td>Abd (%TotFat)</td>
<td>46.9 ± 4.1</td>
<td>41 ± 7.2</td>
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<td>Insulin sensitivity</td>
<td>2.1 ± 0.6</td>
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![Biometric data diagram](image)
Adipose Depot transcriptomes - *Very* similar, yet distinct

SubQ
149

13823

472 Visceral
Exclusive gene expression means **Low** expression.
~3% of genes differentially expressed between depots

SubQ
149

Visceral
13823

472

Unsig

Up in SubQ (p<0.05)

Up in Vis (p<0.05)
DE genes define the depots

SubQ
149

Visceral
472

13823

Unsig
Orange: Up in SubQ (p<0.05)
Blue: Up in Visceral (p<0.05)

Log2(Visceral/SubQ)

Log2(SubQ/Visceral)

Phenylalanine metabolism
Biosynthesis of unsaturated fatty acids
GPI-anchor biosynthesis
Fatty acid metabolism
ECM-receptor interaction
Hypertrophic cardiomyopathy (HCM)
Dilated cardiomyopathy (DCM)
Transcriptional misregulation in cancer
Proteoglycans in cancer
Focal adhesion
Cell adhesion molecules (CAMs)
Pathogenic Escherichia coli infection
Complement and coagulation cascades
Signaling in pluripotency of stem cells
Melanogenesis
Hippo signaling pathway
Axon guidance
Rap1 signaling pathway
PI3K-Akt signaling pathway
Human papillomavirus infection

Visceral
SubQ

Enrichment Ratio

0
10
5
0
5
Adipose depots differentially respond to CR

Gene overlap

SubQ Sig. genes

Visceral Sig. genes

361

1881

SubQ adipose tissue

Visceral adipose tissue

R vs. C Log₂ Fold Change

Average Log₂ Expression

R vs. C Log₂ Fold Change

Average Log₂ Expression

p ≥ 0.05

p < 0.05
Adipose depots differentially respond to CR
Depot shared CR-responsive Pathways

Pathway overlap
SubQ Sig. pathways
Visceral Sig. pathways

RNA processing
Immune/inflammation
Proteostasis
General metabolism
Miscellaneous

Ubiquitin-mediated proteolysis

Ribosome
Spliceosome
Proteasome
RNA Degradation
Protein export

Energy and amino acid metabolism, detoxification, and inflammation pathways
Oxidative phosphorylation
Neurodegenerative diseases (electron transport chain) and diabetes
Depot unique CR-responsive Pathways

Pathway overlap

SubQ Sig. pathways

Visceral Sig. pathways

RNA processing
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Protein export
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RNA Degradation

Visceral NES

Energy and amino acid metabolism, detoxification, and inflammation pathways
Oxidative phosphorylation
Neurodegenerative diseases (electron transport chain) and diabetes

Subcutaneous nominal enrichment score
Graft vs host disease
Autoimmune thyroid disease
Calcium signaling pathway
Steroid hormone biosynthesis
Glycerolipid metabolism
Allograft rejection
Starch/sucrose metabolism
Pyrimidine metabolism
RNA polymerase
Prostate cancer
Thyroid cancer
Complement and coagulation cascade
Valine, leucine, isoleucine degradation
Arrhythmogenic right ventricular cardiomyopathy
Tight junction
Nucleotide excision repair
Butanoate metabolism
Tryptophan metabolism
Base excision repair
Hypertrophic cardiomyopathy
Dilated cardiomyopathy
Nod-like receptor signaling pathway
Glycolysis/gluconeogenesis
Hematopoietic cell lineage
Leishmania infection
Apoptosis

Visceral nominal enrichment score
CR-induced RNA Processing

Genes quantified

14626

1999

Genes with multiple isoforms

SubQ R vs. C Log2 FC

Transcript

Visceral R vs. C Log2 FC

Transcript

Exons

Corresponding Genes

Count

11000

9000

7000

5000

3000

10734

5240

4476

3030

156

129

SubQ p < 0.05

Visceral p < 0.05

SubQ p < 0.1

Visceral q < 0.1

3802

1438

1592

SubQ genes with exon changes

Visceral genes with exon changes
CR-induced RNA Processing

Genes quantified

14,626

1,999

Genes with multiple isoforms

SubQ R vs. C Log2 FC

Visceral R vs. C Log2 FC

Transcript

Count

SubQ vs. Visceral

SubQ with exon changes

Visceral genes with exon changes

SubQ genes with exon changes

SubQ Vis

Arrhythmogenic right ventricular cardiomyopathy (ARVC)

ABC transporters

Dilated cardiomyopathy (DCM)

Hypertrophic cardiomyopathy (HCM)

Platelet activation

Phosphatidylinositol signaling system

Inositol phosphate metabolism

Focal adhesion

ECM–receptor interaction

Protein digestion and absorption

Avg Log2 FC

-1.5 0 1.5
CR changes transcriptional programs of adipose depots
Acknowledgements

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