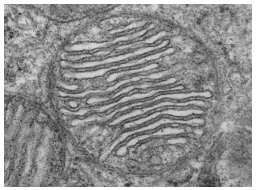
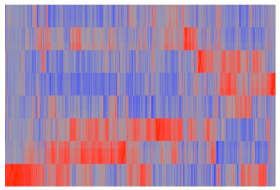
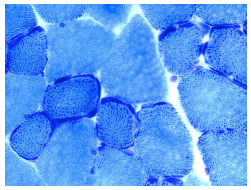
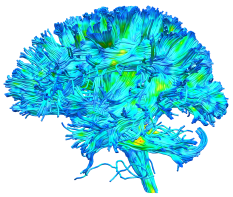
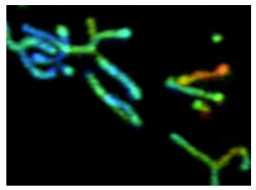
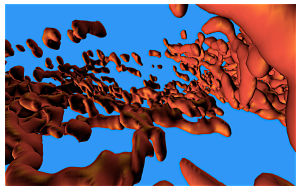
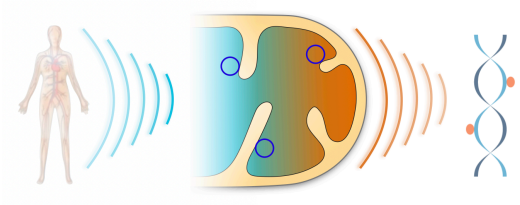





The **B**rain-Body **E**nergy **C**onservation Model of Aging



Martin Picard, Ph.D.
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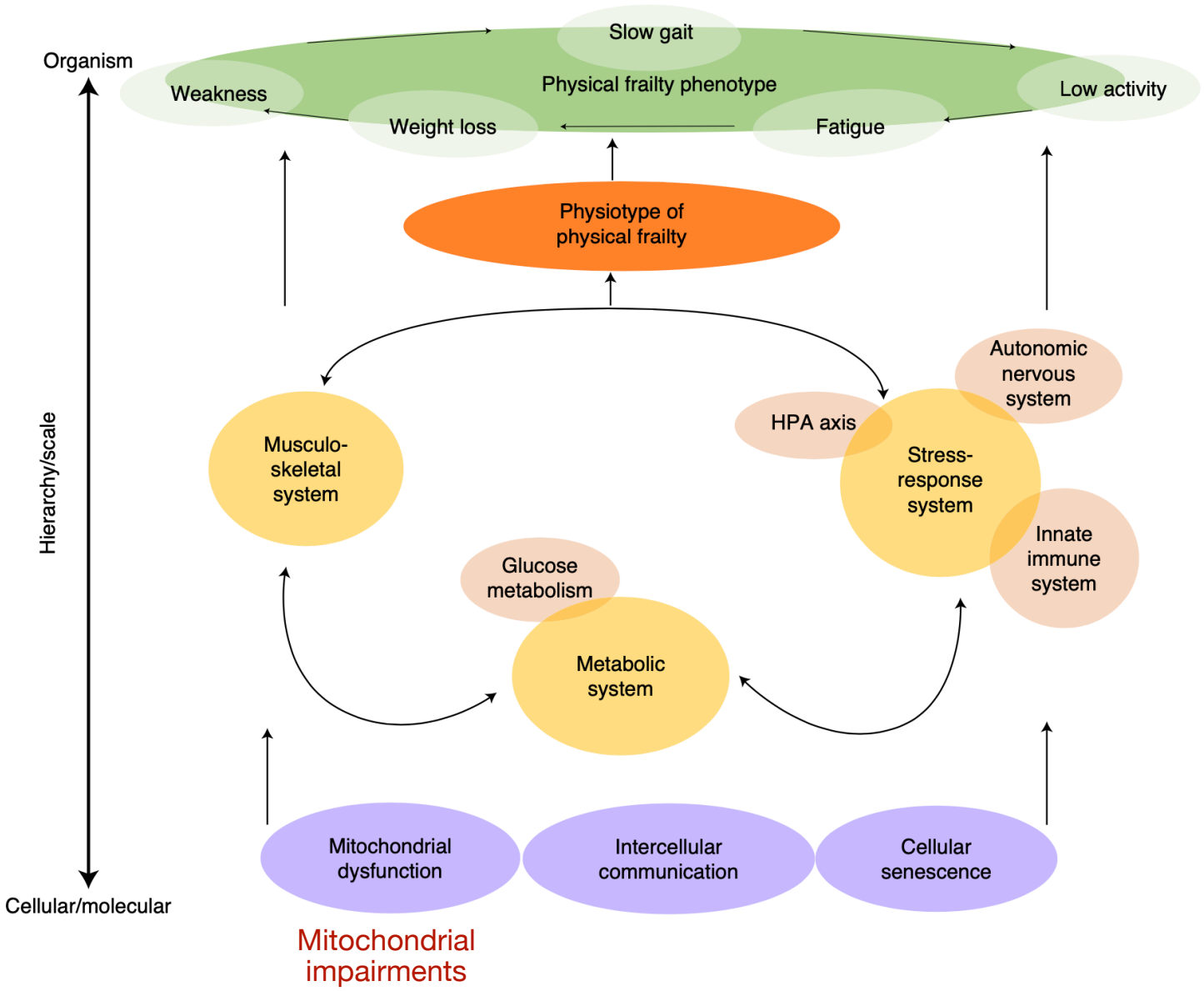
New York State Psychiatric Institute (NYSPI)

COLUMBIA
COLUMBIA UNIVERSITY
IRVING MEDICAL CENTER

NEW YORK STATE OF OPPORTUNITY.
New York State Psychiatric Institute

Energy and Aging



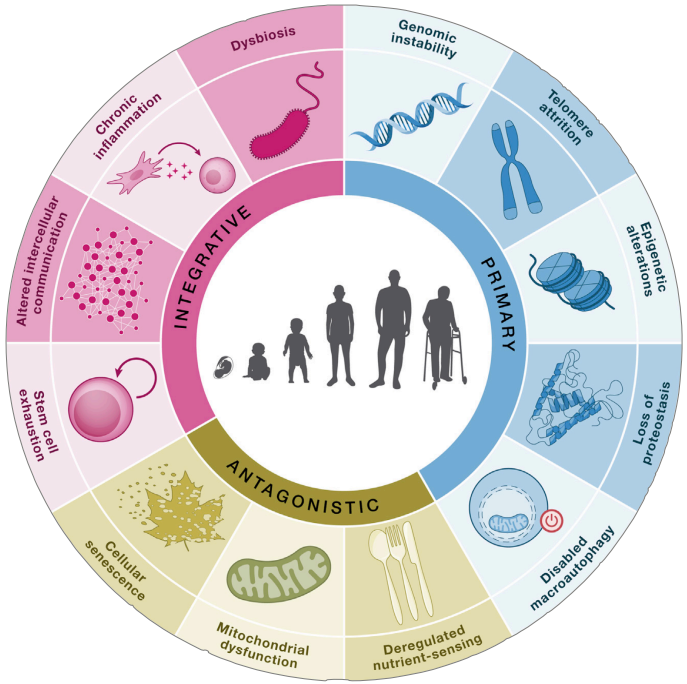
Fried et al. *Nat Aging* 2021

GeroScience
https://doi.org/10.1007/s11357-021-00365-7

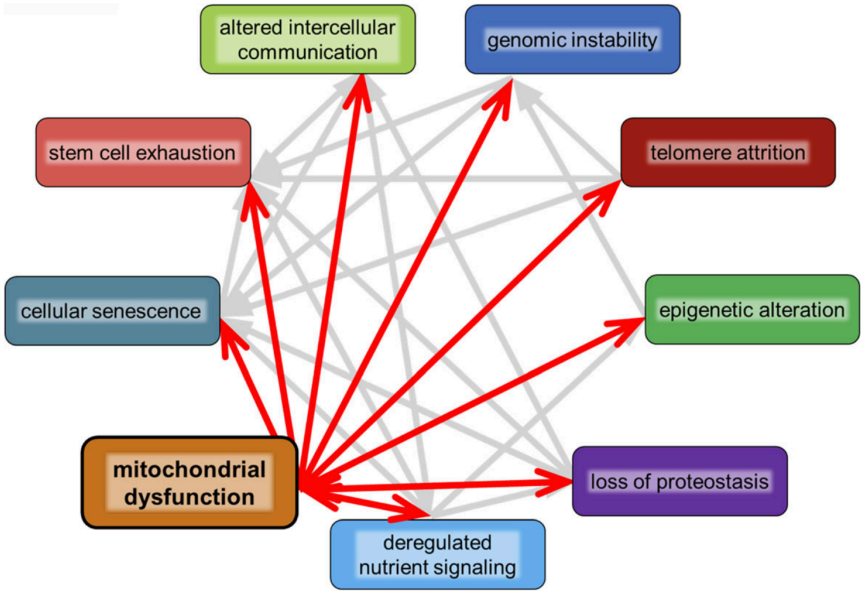
ORIGINAL ARTICLE

An energetics perspective on geroscience: mitochondrial protonmotive force and aging

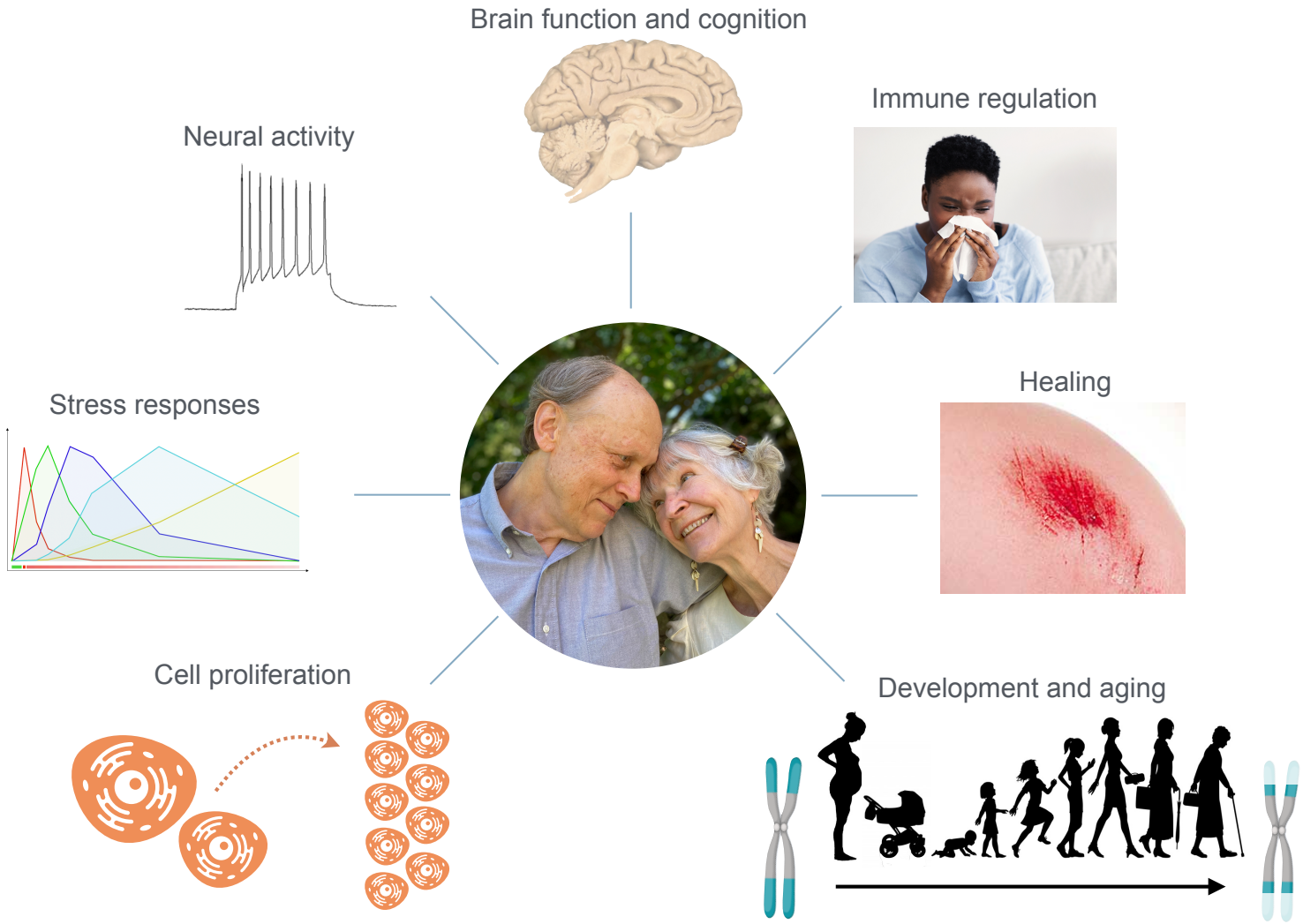
Brandon J. Berry · Matt Kaeberlein



Lopez-Otin et al. *Cell* 2023



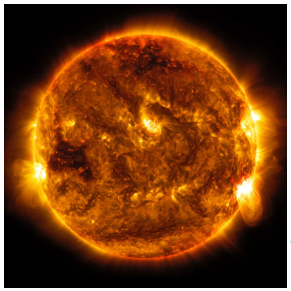
Berry and Karberlein. *GeroScience* 2021



BIOLOGY, PHYSIOLOGY, CONSCIOUSNESS, AGING

PSYCHOBIOLOGICAL ALLOSTATIC PROCESSES

Biochemistry 2022



Nuclear fusion
Quantum electrodynamics

Photons and heat

Oils and fats, proteins, carbohydrates

CO_2 + H_2O = $C_{17}H_{33}COOH$ + O_2

ENERGY STORED AS CHEMISTRY

Food

O_2

EATING and BREATHING

CO_2 H_2O

'Waste' products

Brain function and cognition

Neural activity

Immune regulation

Stress responses

Healing

Cell proliferation

Development and aging

ENERGY
+ Body heat

Electricity and Chemiosmosis
$\Delta\Psi m + \Delta pH$

Protons (H+)

Electrons

TCA Cycle

Beta Oxidation

Carbon substrates

Electron transport chain

O_2 H_2O

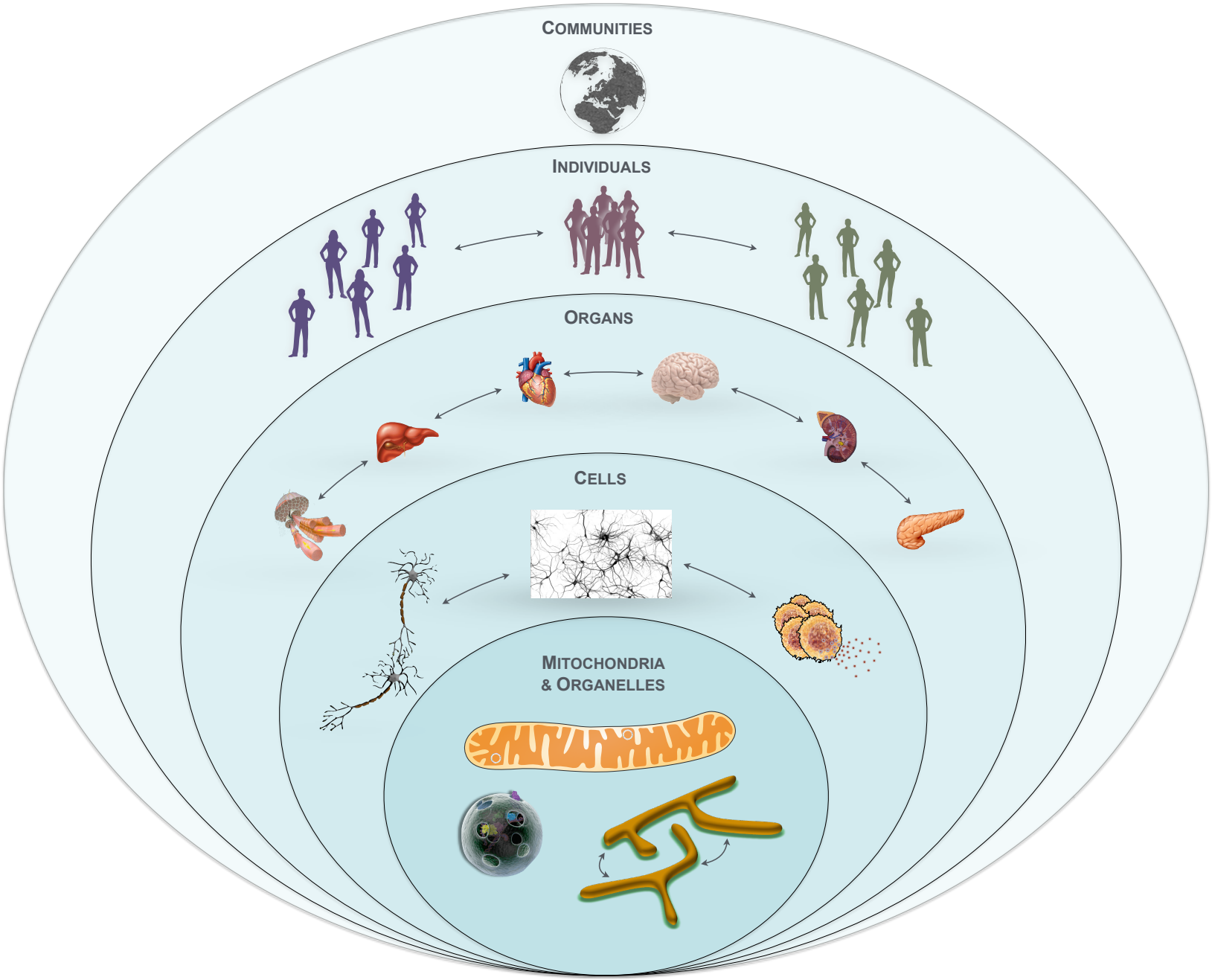
ATP

mtDNA

BIOLOGY, PHYSIOLOGY, CONSCIOUSNESS, AGING
PSYCHOBIOLOGICAL ALLOSTATIC PROCESSES

CHEMICAL ENERGY TRANSFORMED INTO ELECTROCHEMICAL FORCE

Biochemistry 2022

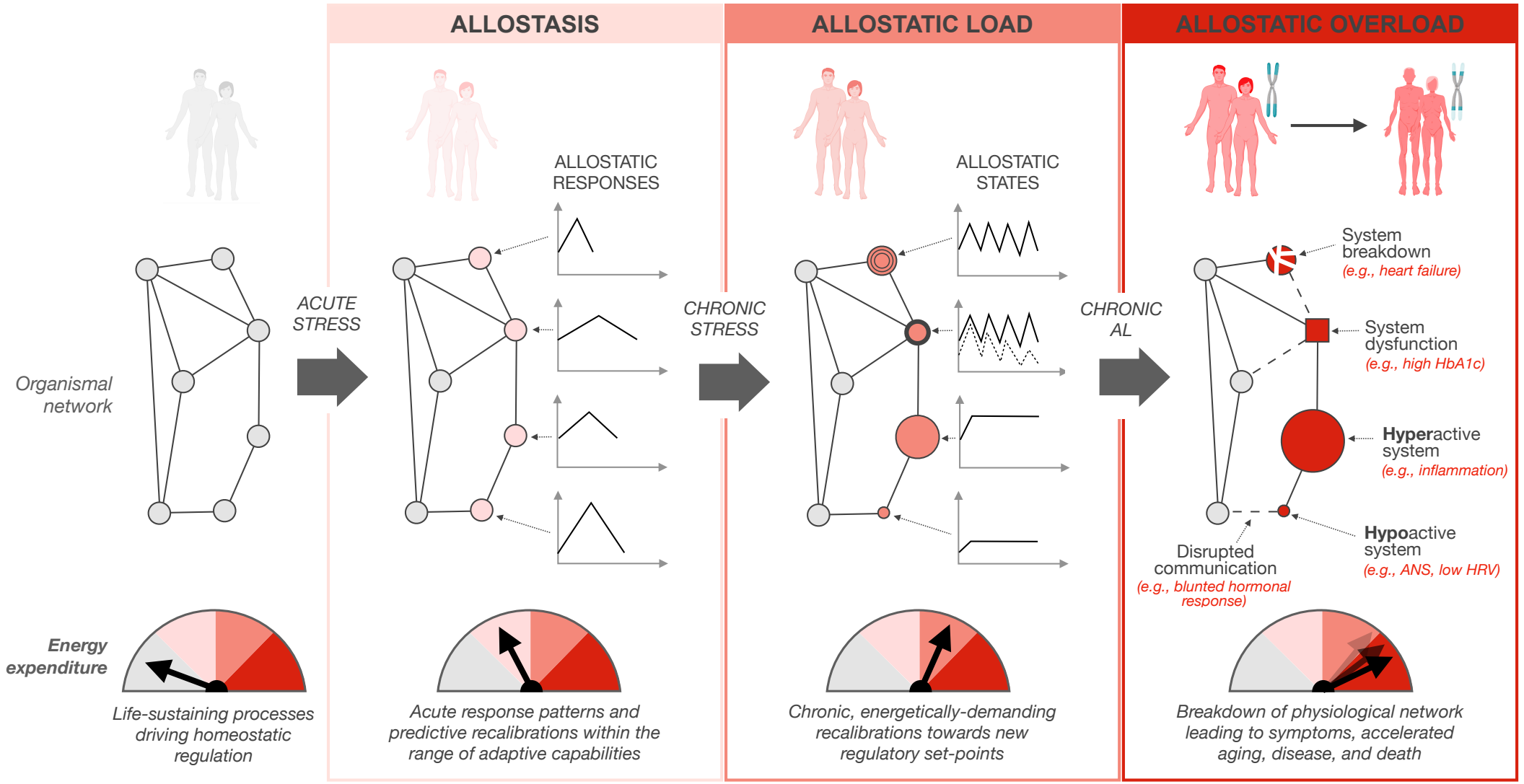


Picard and Sandi. *Neurosci Biobehav Rev* 2021

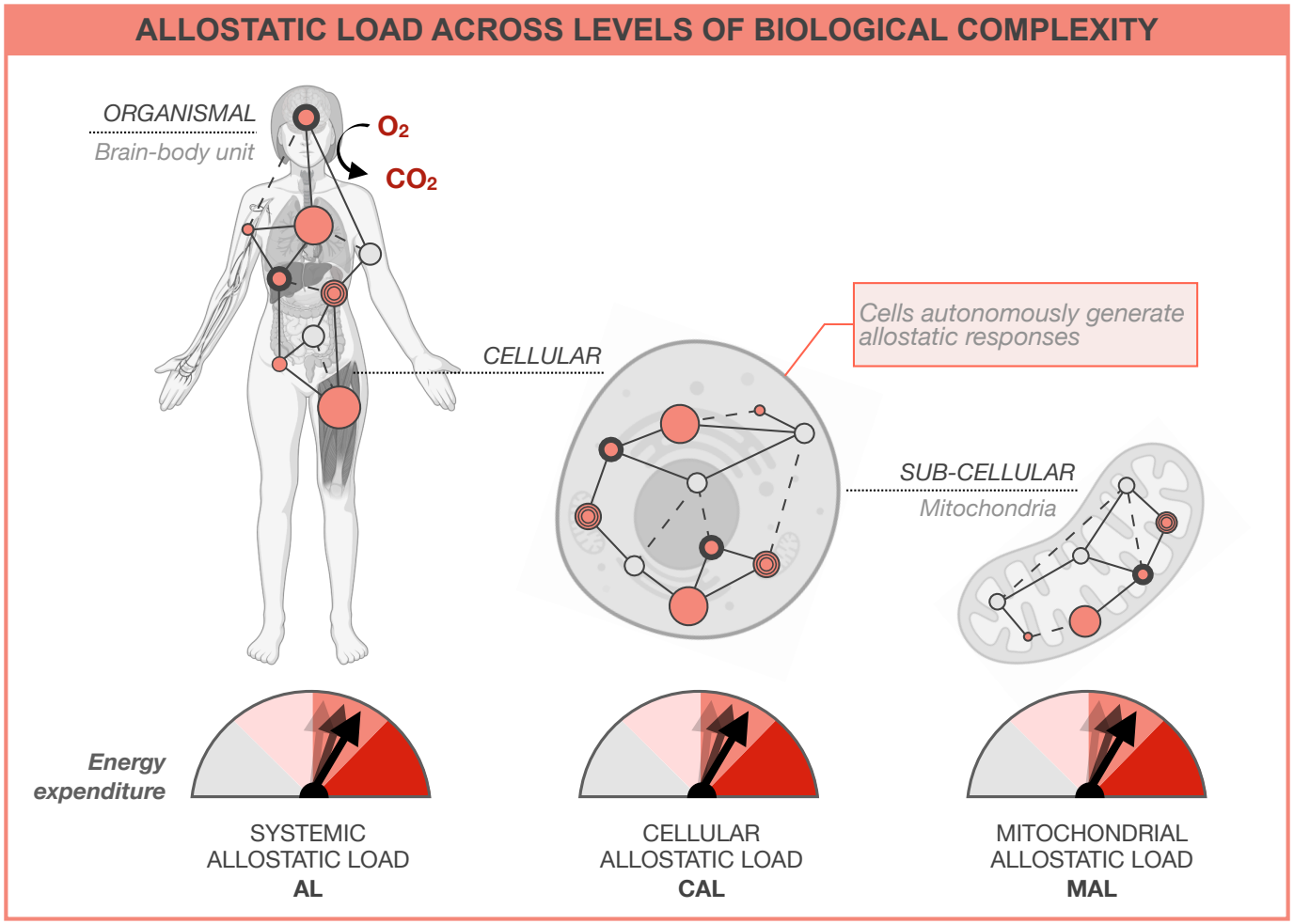
Energetic principles of human health

Energetic principles of human health

1. Energy distribution across physiological networks



Bobba-Alves et al. *Psychoneuroendocrinol* 2022



Bobba-Alves et al. *Psychoneuroendocrinol* 2022

Energetic principles of human health

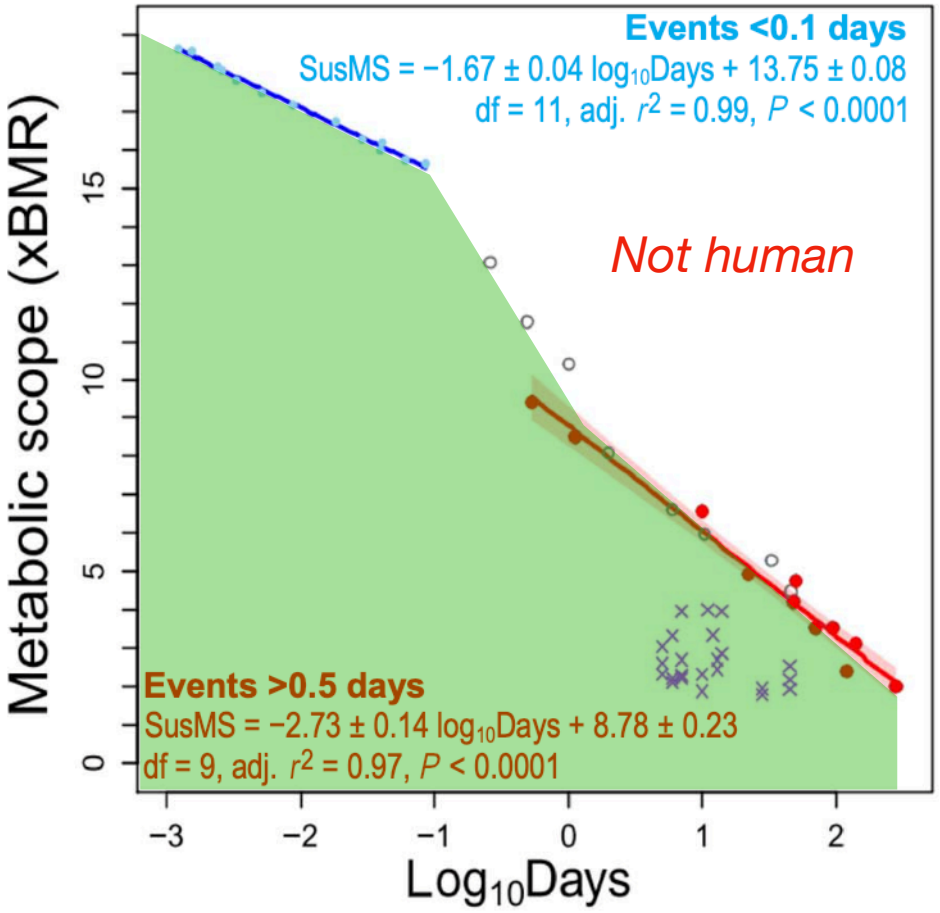
1. **Energy is distributed** across physiological networks

Energetic principles of human health

1. **Energy is distributed** across physiological networks

2. **Total energy transformation capacity is limited**

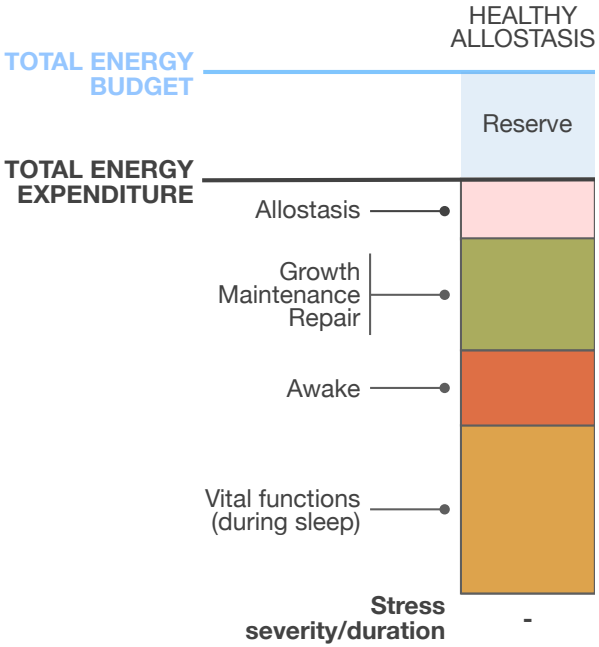
Limit to human energy transformation capacity

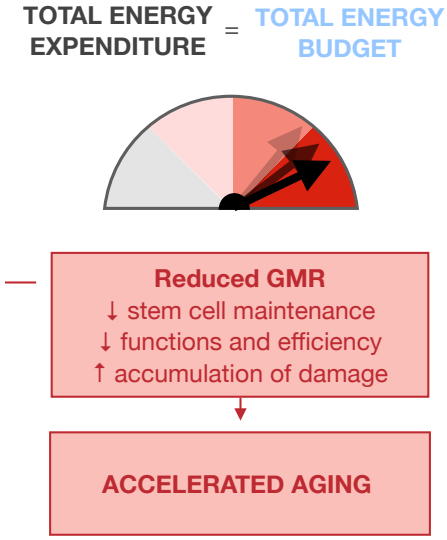


SusMS: maximum Sustained Metabolic Scope

Thurber et al. *Sci Adv* 2019

Partitioning of energetic resources in humans





Bobba-Alves et al. *Psychoneuroendocrinol* 2022

Bioenergetic principles of health

1. Energy is distributed across physiological networks

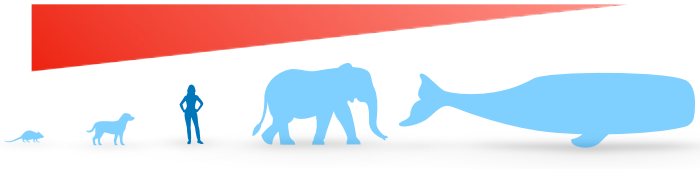
2. Total energy transformation **capacity is limited**

3. Sustained **hypermetabolism promotes damage**

Damage accumulation

Energy flow ➡ entropy production ➡ decay and finite lifespan

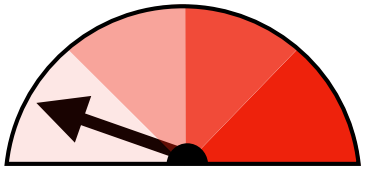
HYPERMETABOLISM



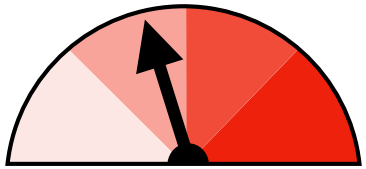
Seconds | **Years / Decades** | **Centuries**

Hypermetabolism is an increase in the amount of energy needed to sustain one's life over time

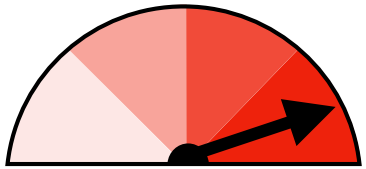
What happens to cellular energy demand/consumption with increasing cellular age?



HYPOmetabolism



NORMOmetabolism



HYPERmetabolism

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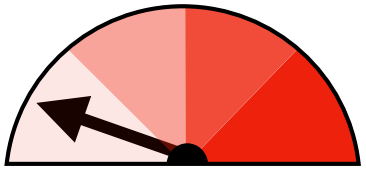
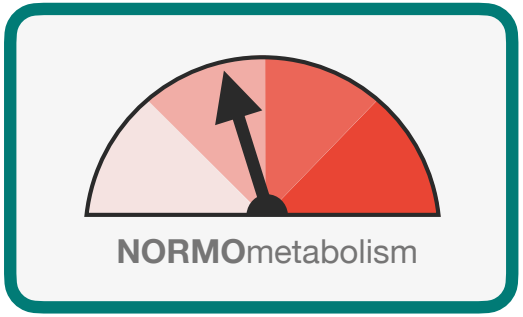
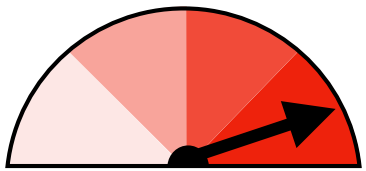


HYPOmetabolism



NORMOmetabolism



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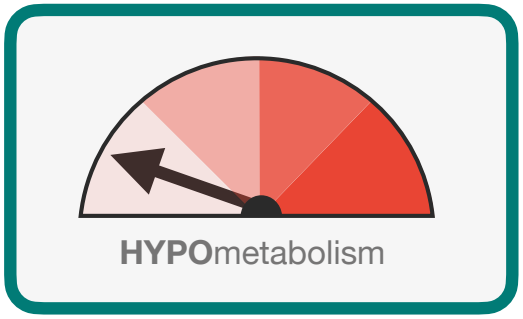

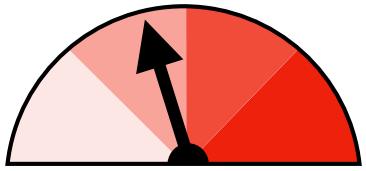

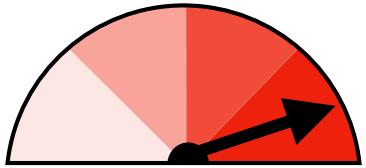

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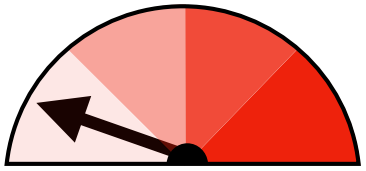
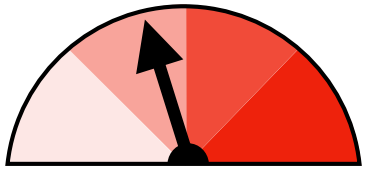
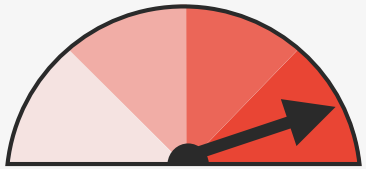


HYPOmetabolism

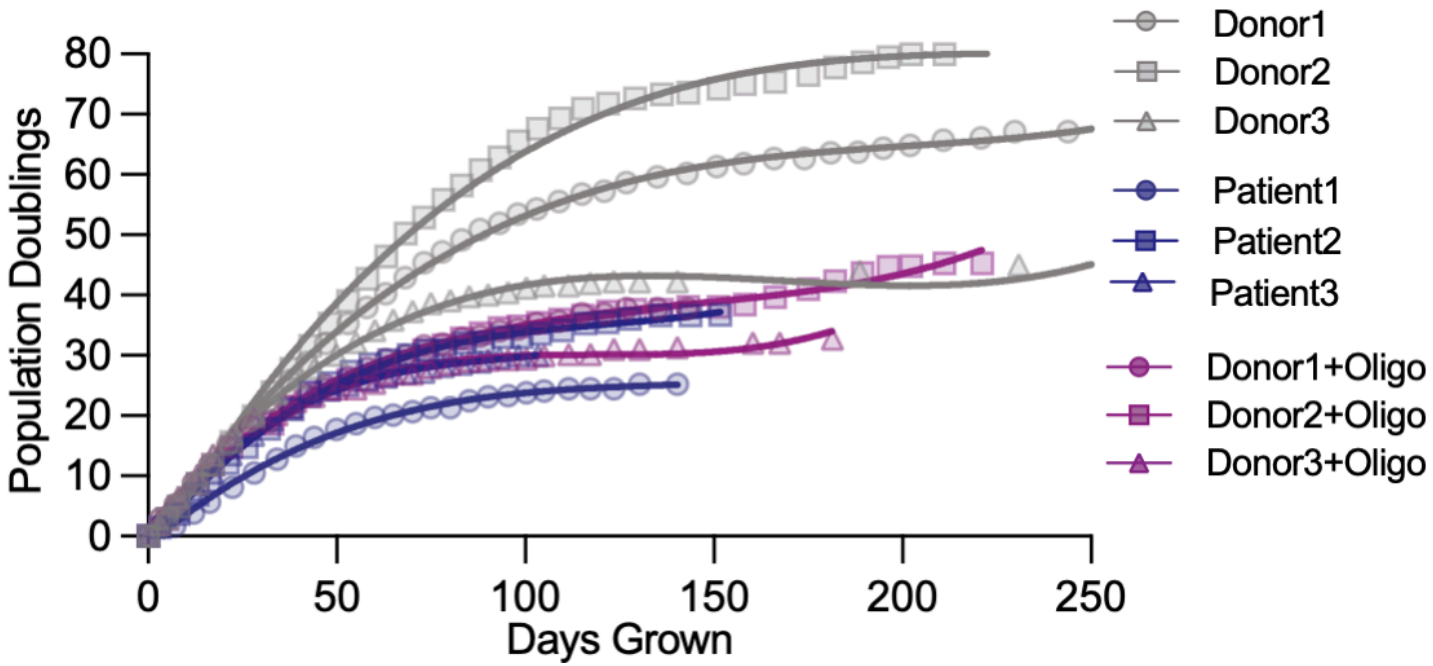


NORMOmetabolism



HYPERmetabolism

Cellular quiescence/senescence decrease division rate by >90-95%



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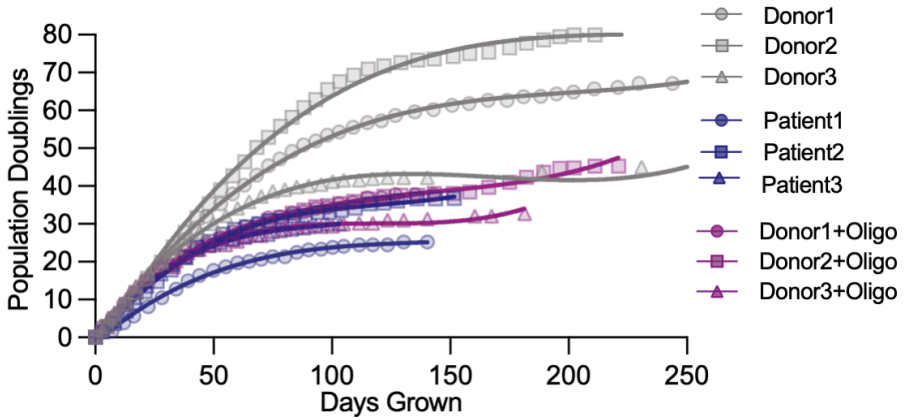
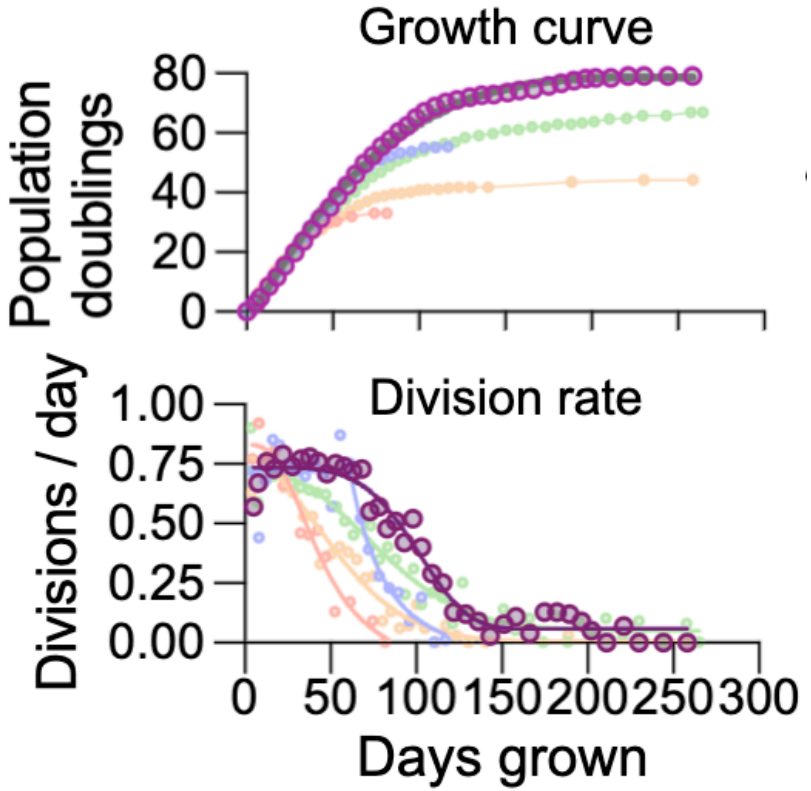
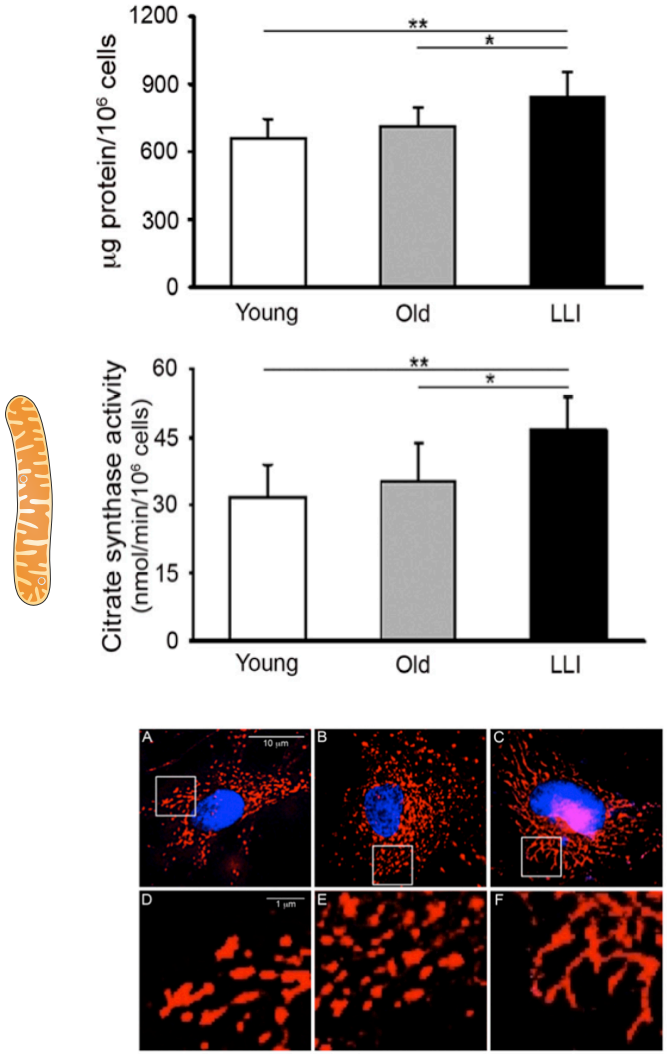




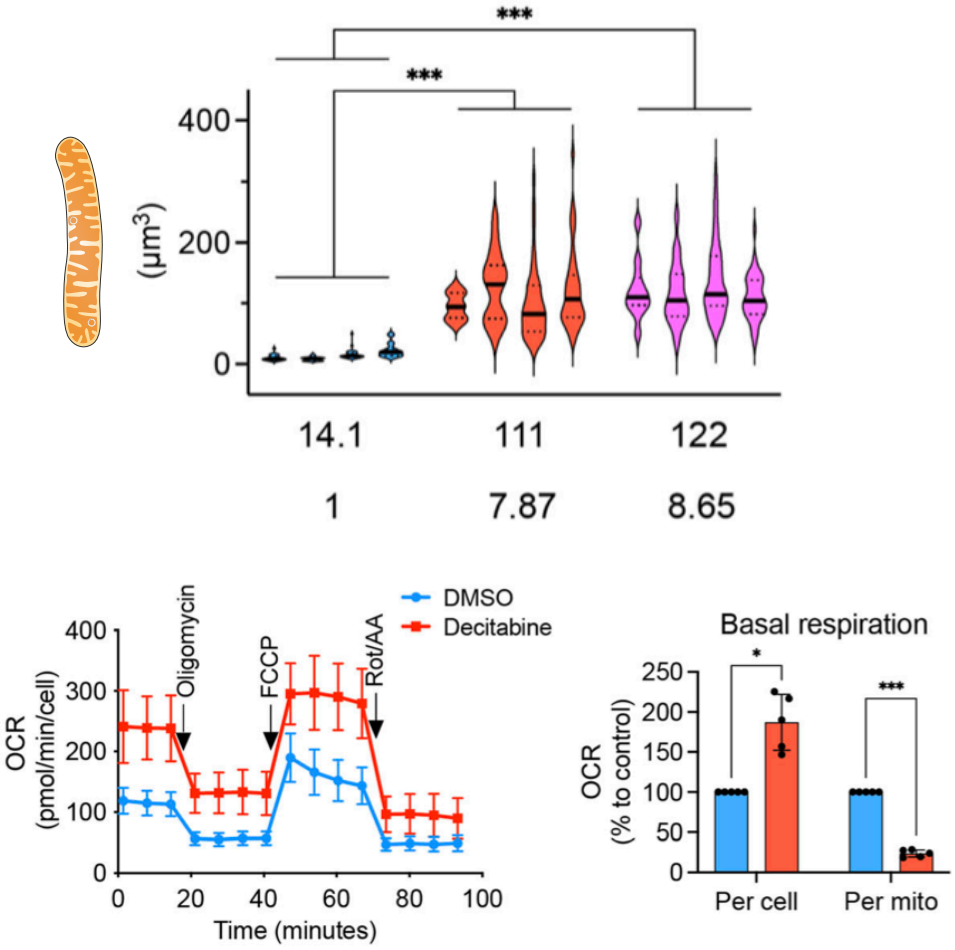
Slower division = less DNA replication, less protein synthesis, less telomerase activity, less mitochondrial biogenesis, … **ENERGY SAVINGS?**

More proteins, and **more** hyperfused mitochondria in fibroblasts from old individuals



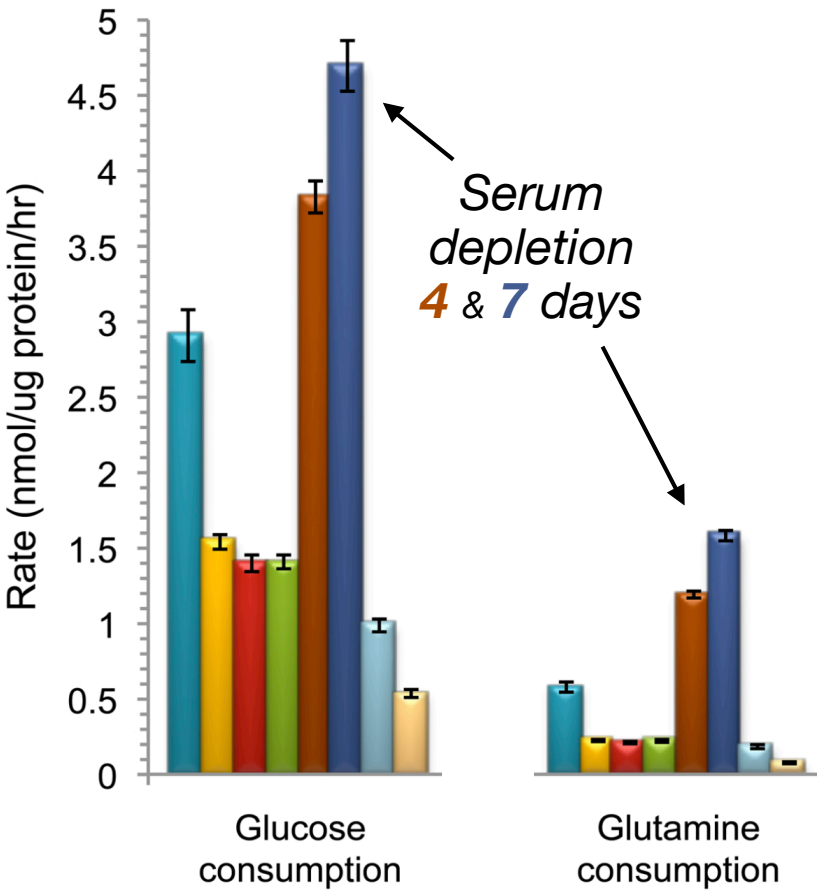
Sgarbi et al. *Aging* 2014

Increased mitochondrial mass, mtDNAcn, and basal respiration in senescent fibroblasts



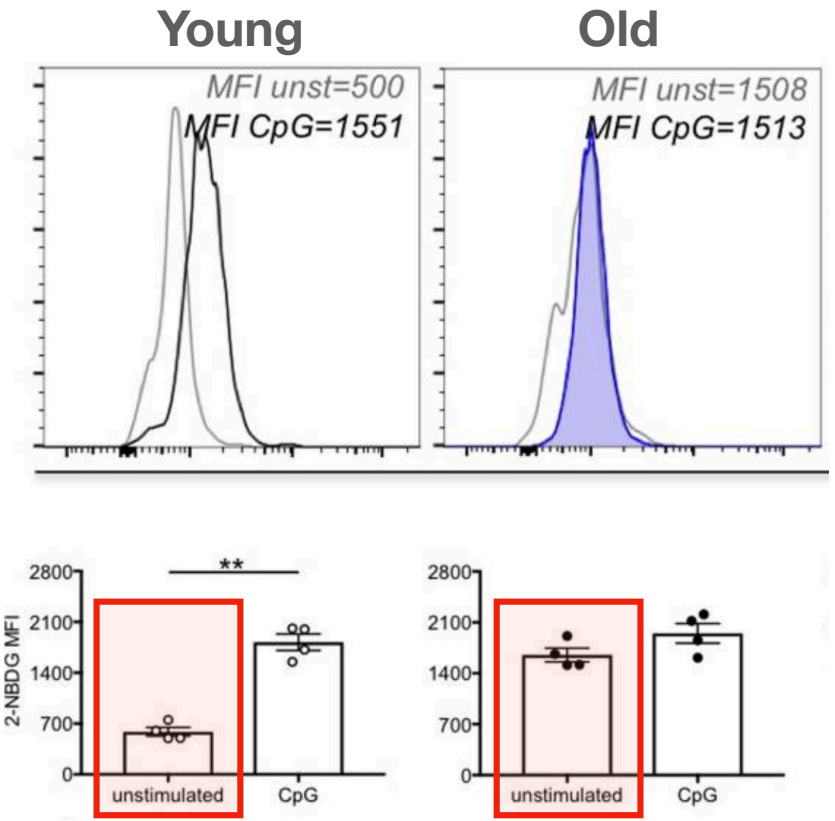
Kim et al. *Life Sci Alli* 2023

Increased glucose and glutamine consumption in quiescent fibroblasts

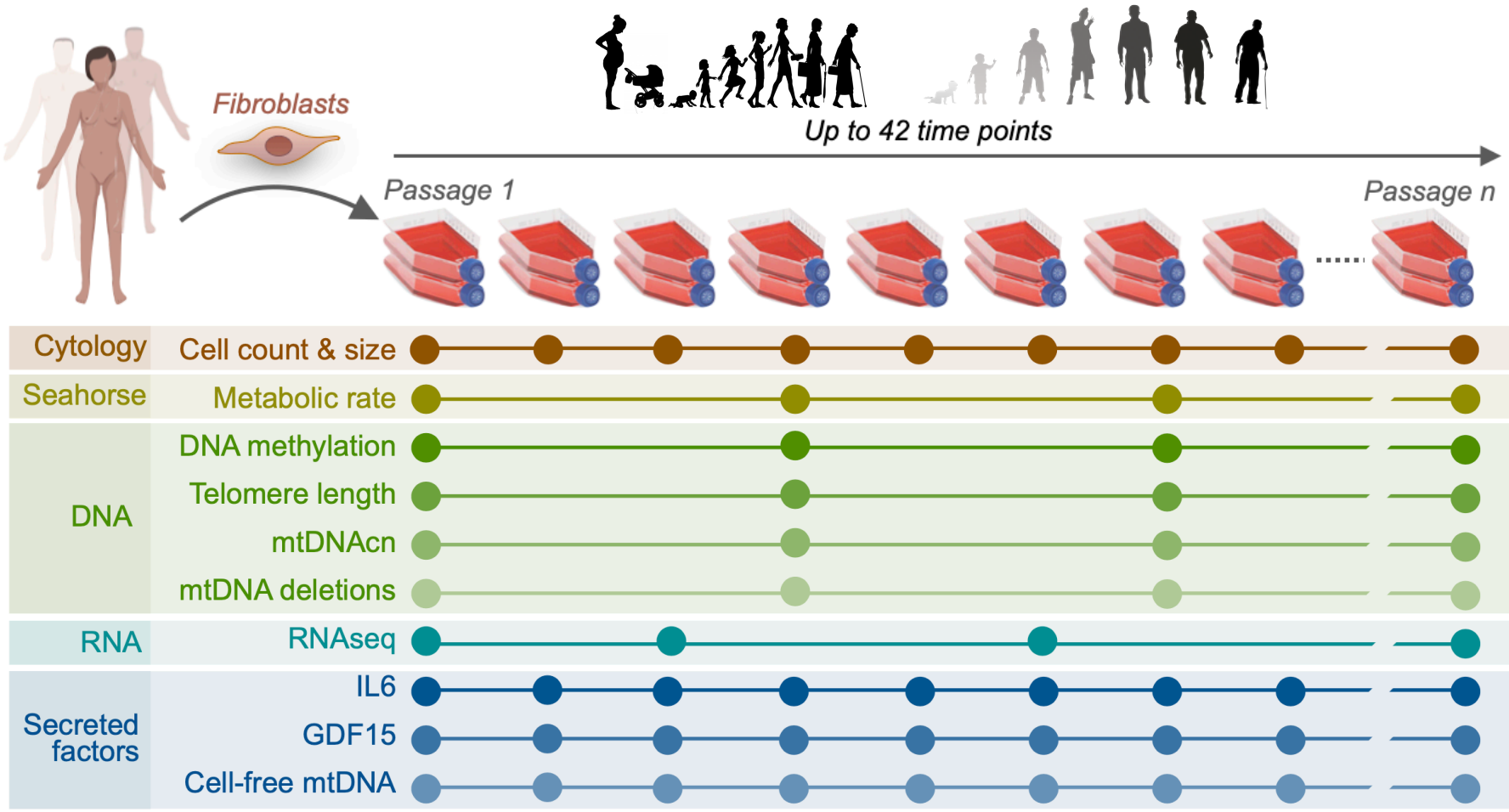


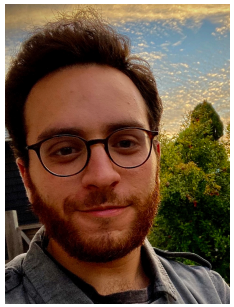
Lemons et al. *Plos Biol* 2010

Increased glucose consumption in human B cells from aged individuals



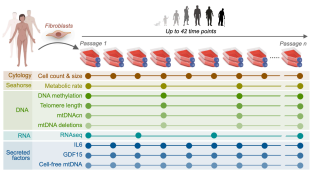
Frasca et al. *Plos One* 2019



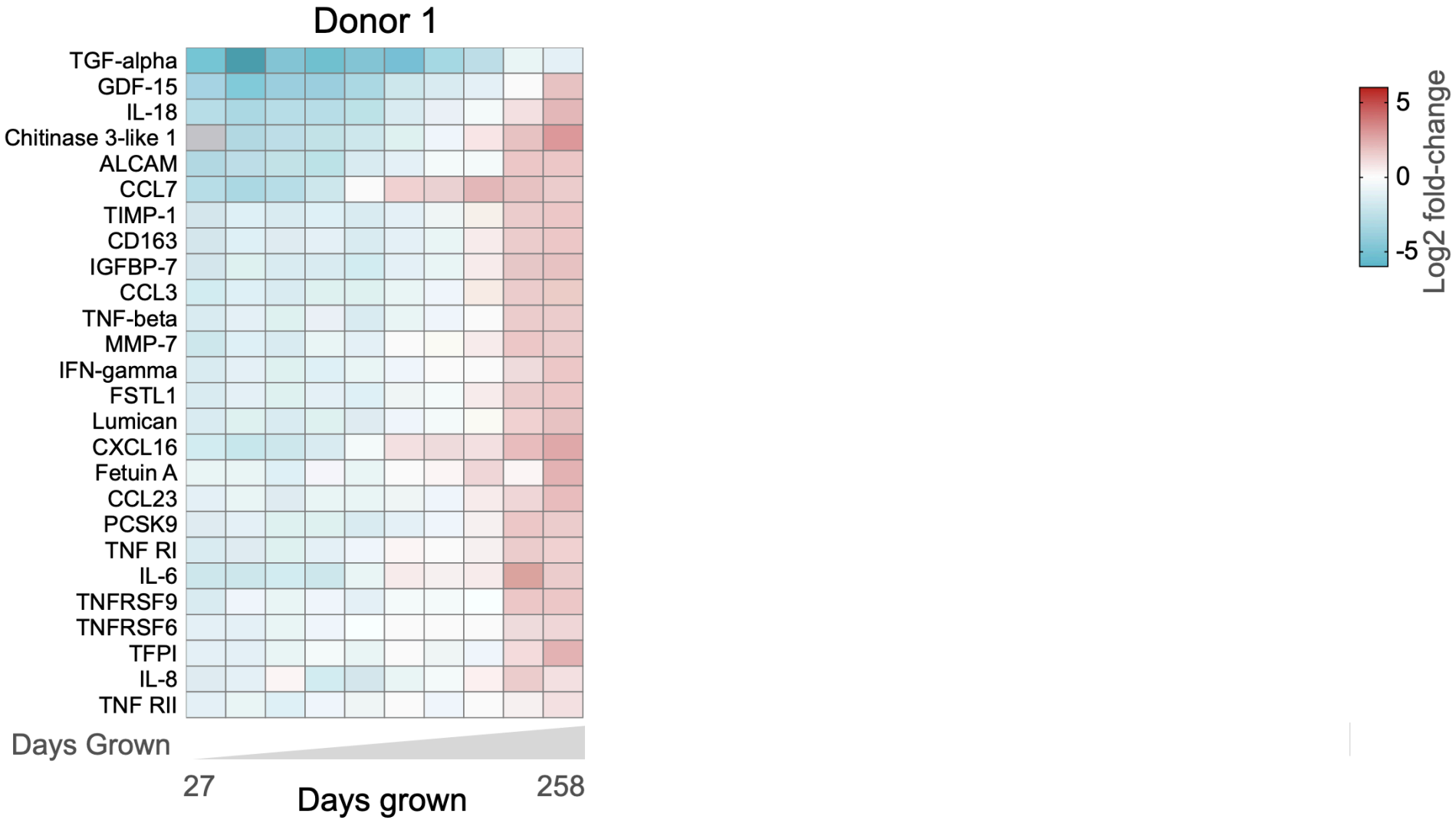


Gabriel Sturm

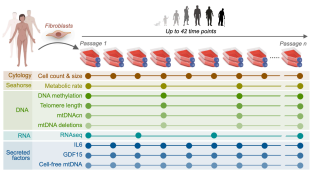
Sturm et al. *Commun Biol* 2023



Increased protein secretion (SASP)



Protein concentration ⬆ >30-fold


Fibroblasts
Up to 42 time points
Passage 1
Passage n
Cytology
Cell count & size
Senhorne
Metabolic rate
DNA
DNA methylation
Telomere length
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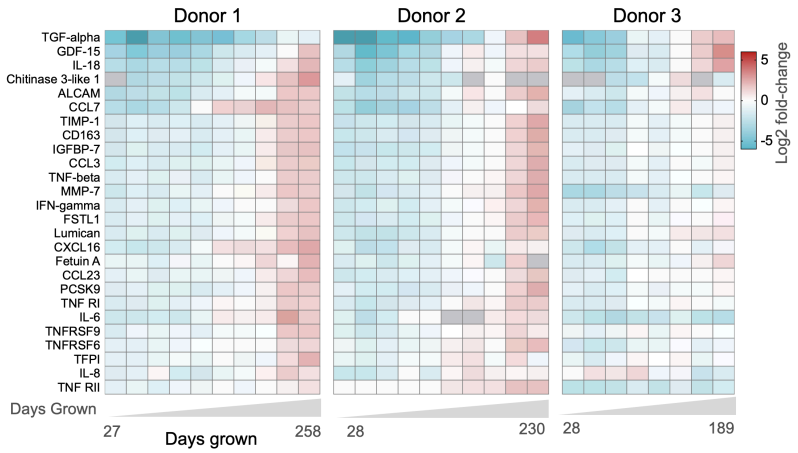
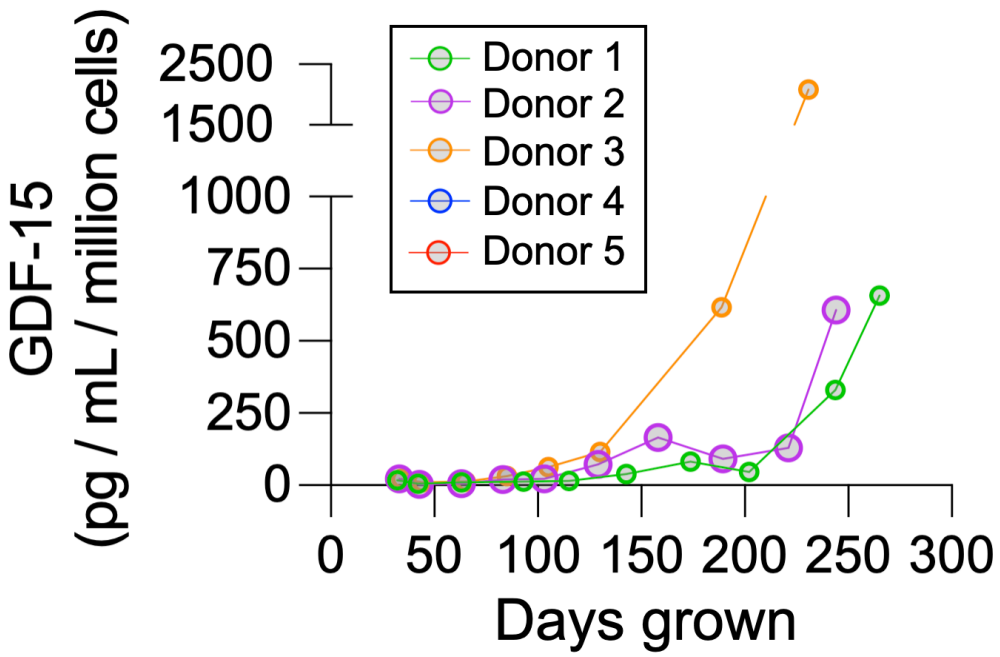
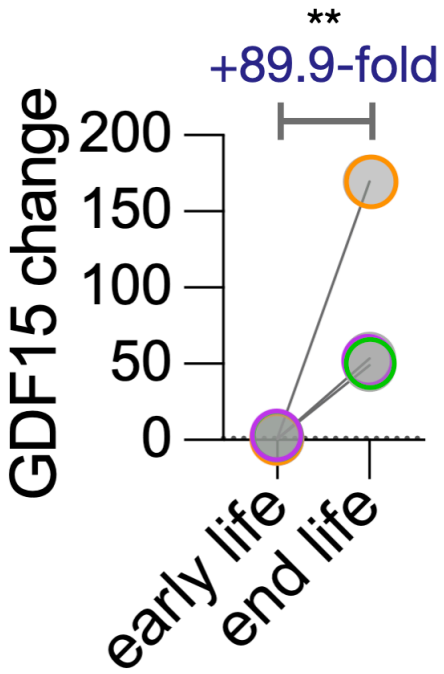
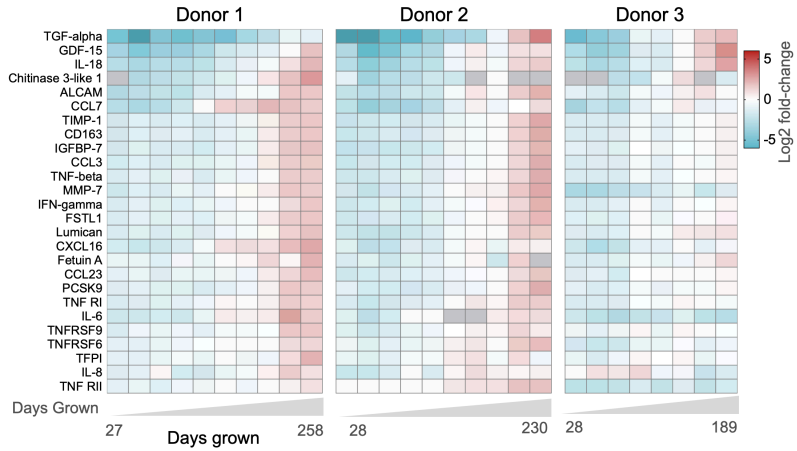
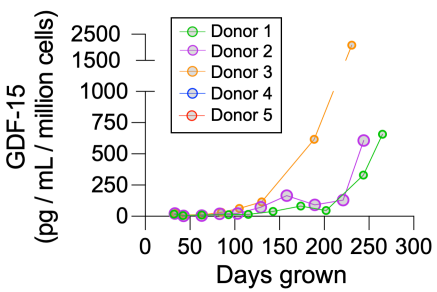
mtDNA deletions
RNA
RNAseq
Secreted factors
IL6
GDF15
Cell-free mtDNA

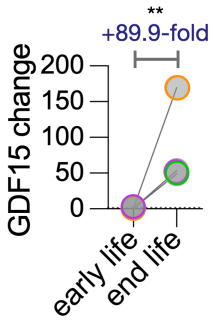

Donor 1
Donor 2
Donor 3
TGF-alpha
GDF-15
IL-18
Chitinase 3-like 1
ALCAM
CCL7
TIMP-1
CD163
IGFBP-7
CCL3
TNF-beta
MMP-7
IFN-gamma
FSTL1
Lumican
CXCL16
Fetuin A
CCL23
PCSK9
TNF RI
IL-6
TNFRSF9
TNFRSF6
TFPI
IL-8
TNF RII
Days Grown
27
258
28
230
28
189
Days grown
5
0
-5
Log2 fold-change

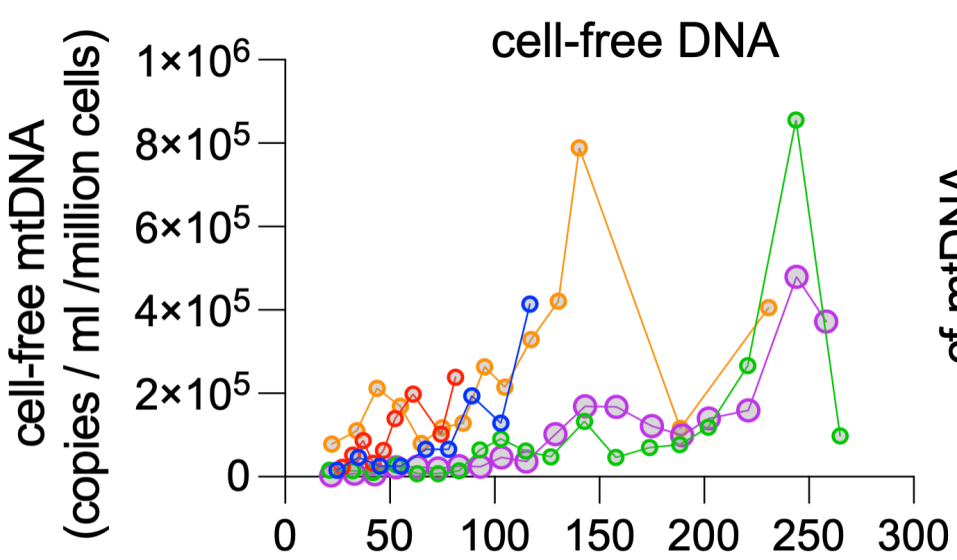

GDF-15
(pg / mL / million cells)
2500
1500
1000
750
500
250
0
Donor 1
Donor 2
Donor 3
Donor 4
Donor 5
0
50
100
150
200
250
300
Days grown

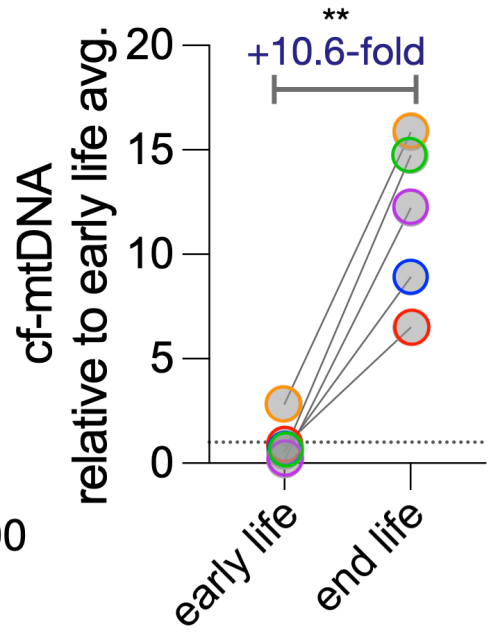

**
+89.9-fold
GDF15 change
200
150
100
50
0
early life
end life





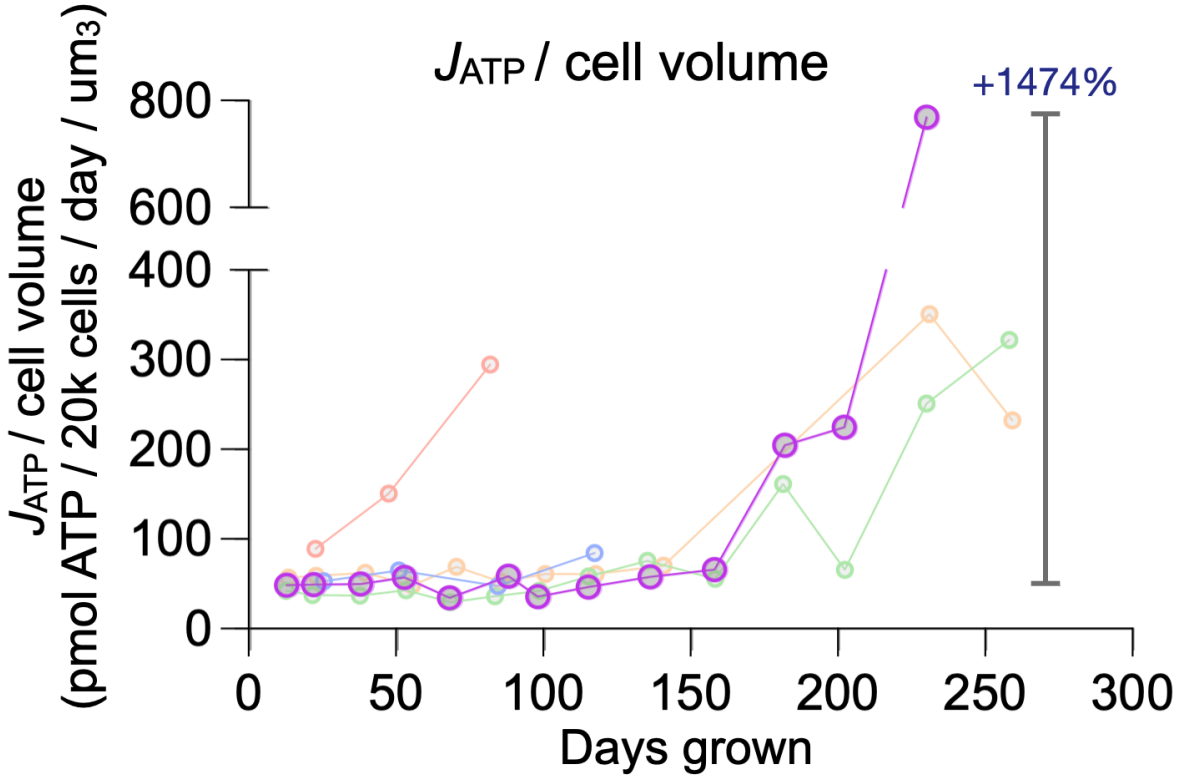


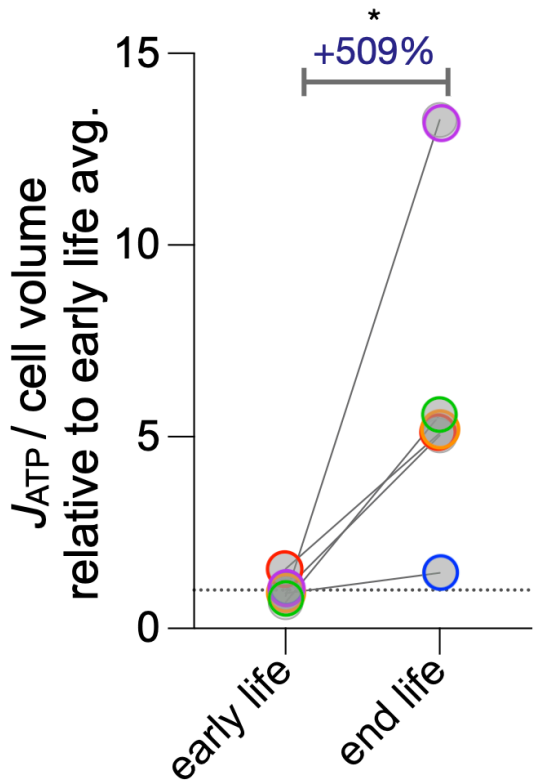


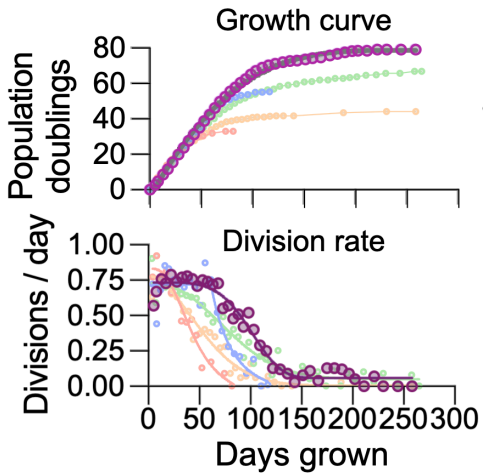


Secretion of protein & DNA ⬆ >10-90-fold

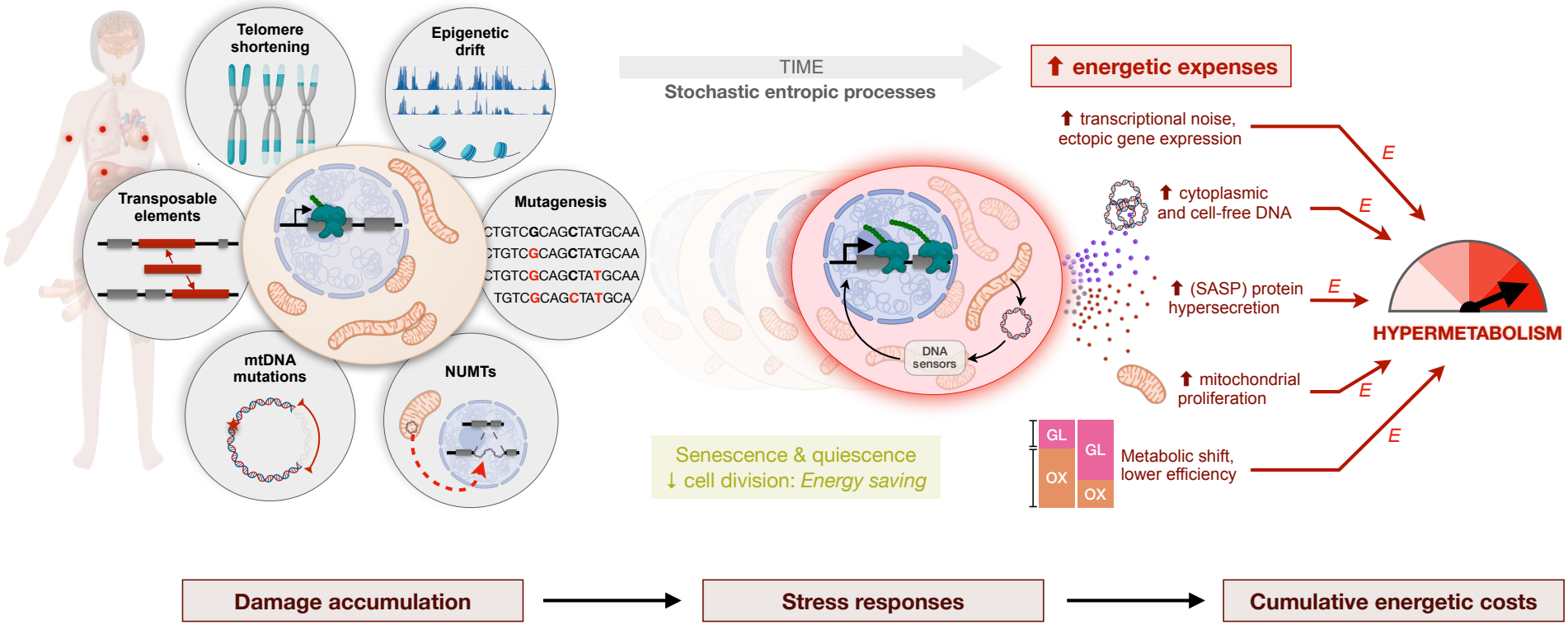
Aging human fibroblasts are HYPERmetabolic







Senescence costs
(a lot of) **energy**



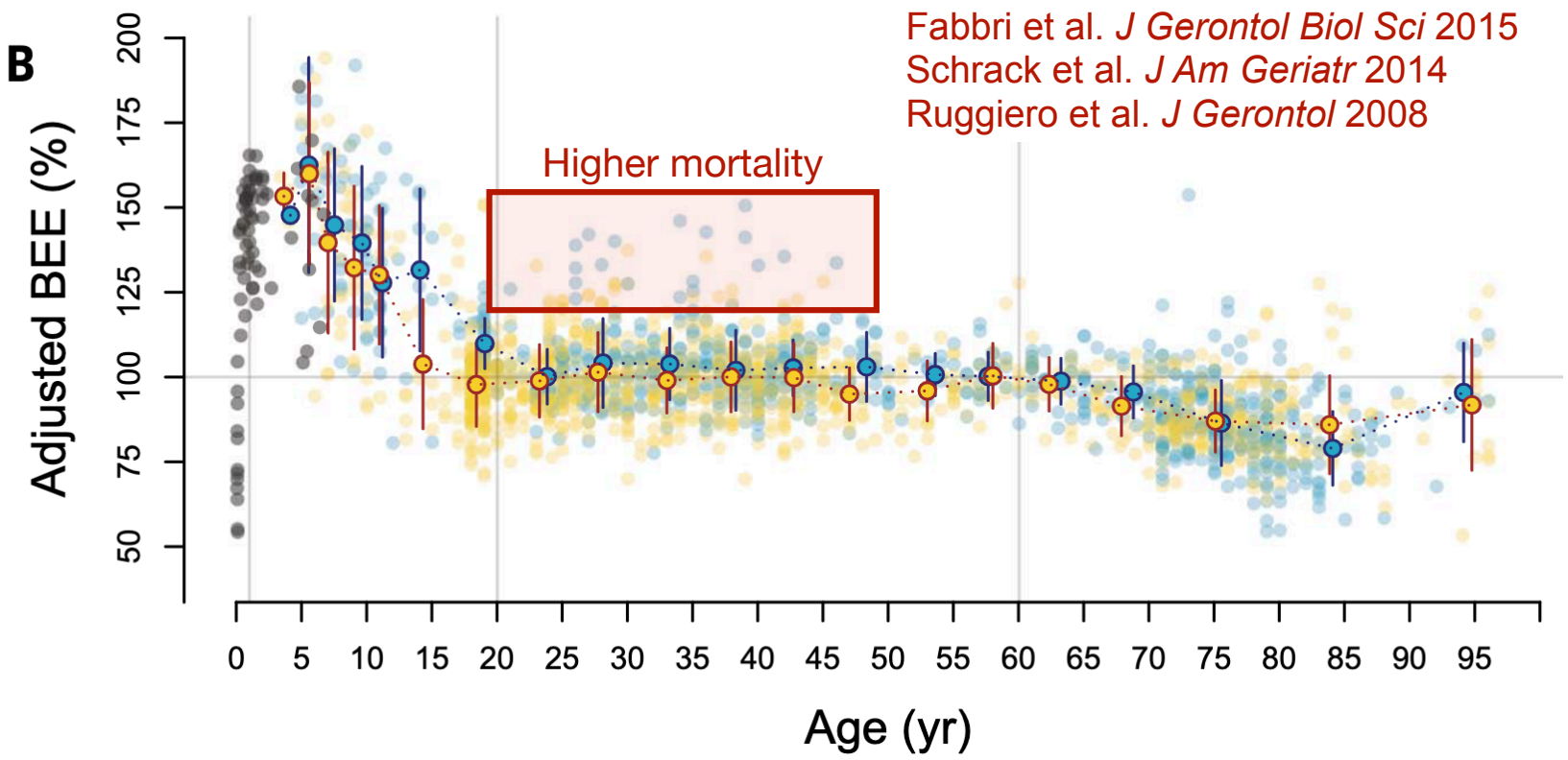
Aging (senescent) cells become **hypermetabolic**

Shaulson, Cohen, Picard. *Preprint* (osf.io/zuey2)

Aging (senescent) cells become **hypermetabolic**

But the whole body does not

In fact, whole body energy expenditure **declines with age**



Pontzer et al. *Science* 2021

Aging (senescent) cells become **hypermetabolic**

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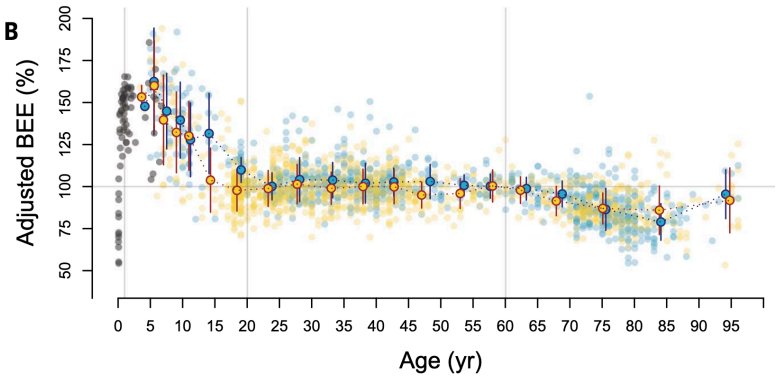
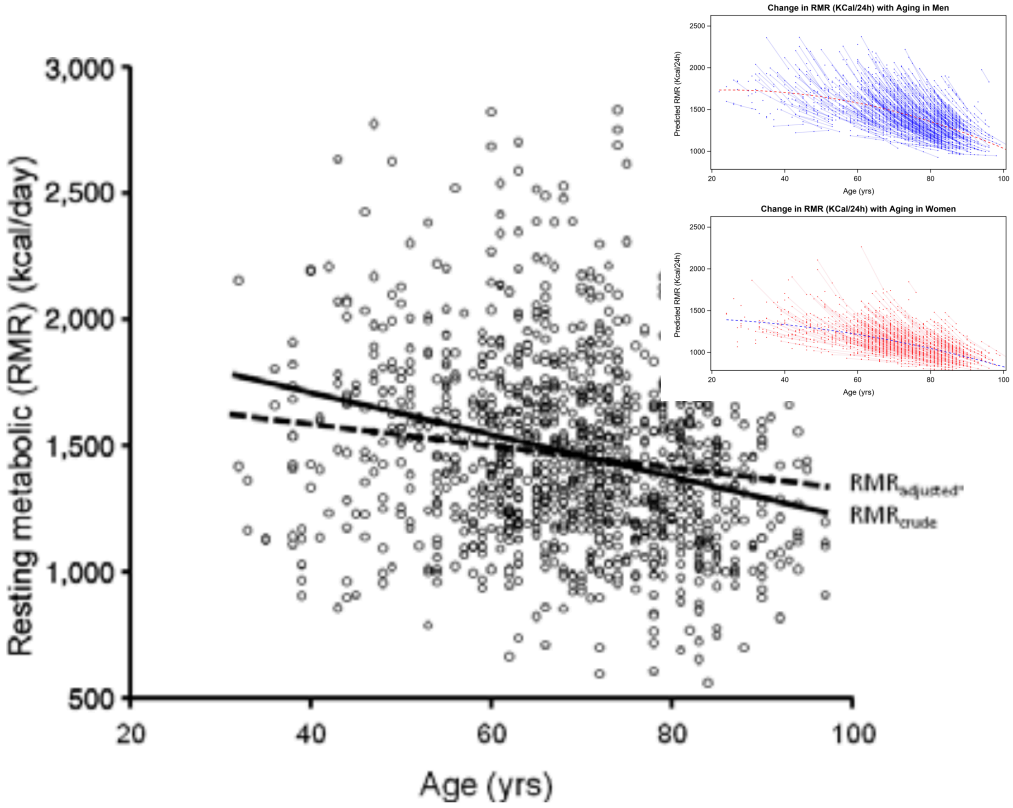
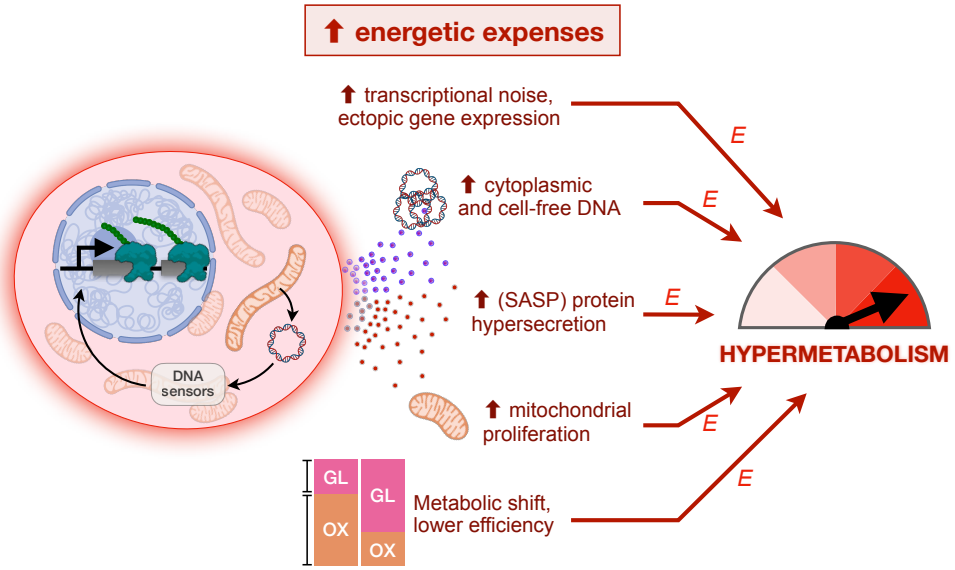




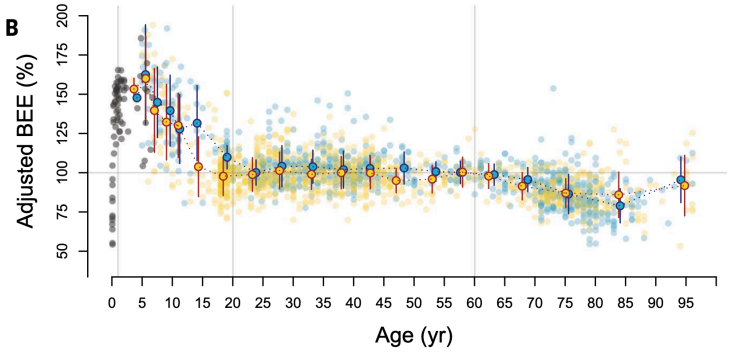
Ferrucci et al. *JAGS* 2012

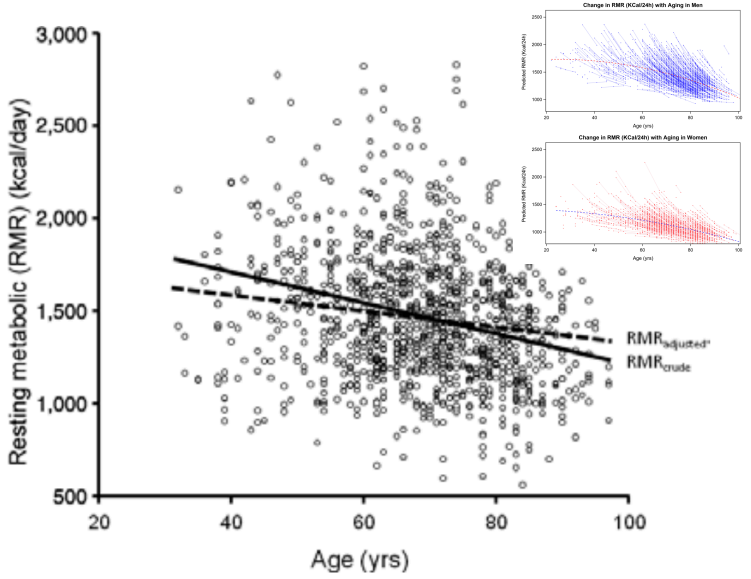
Energetic paradox ?

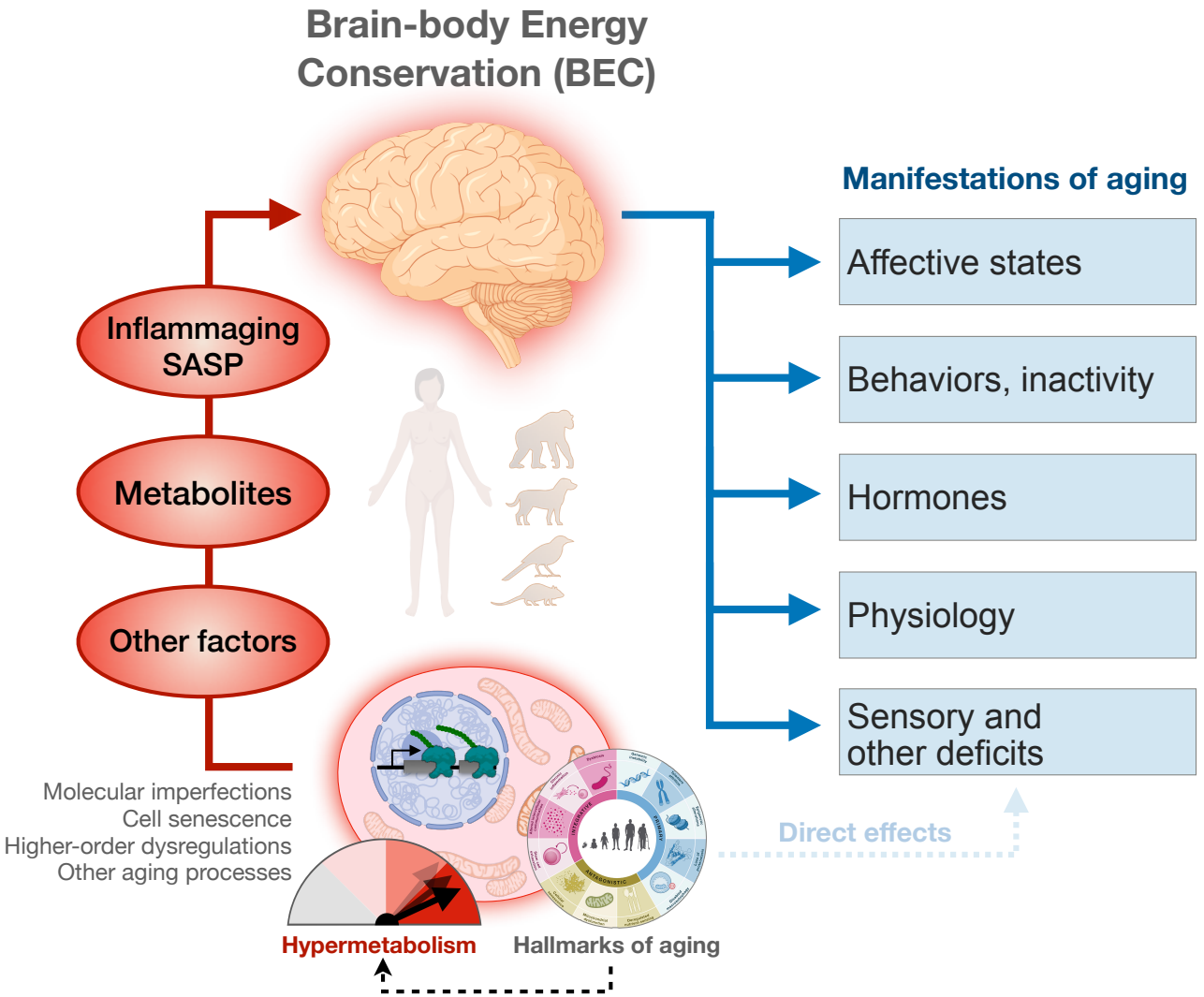
CELLULAR HYPERMETABOLISM



WHOLE-BODY HYPOMETABOLISM

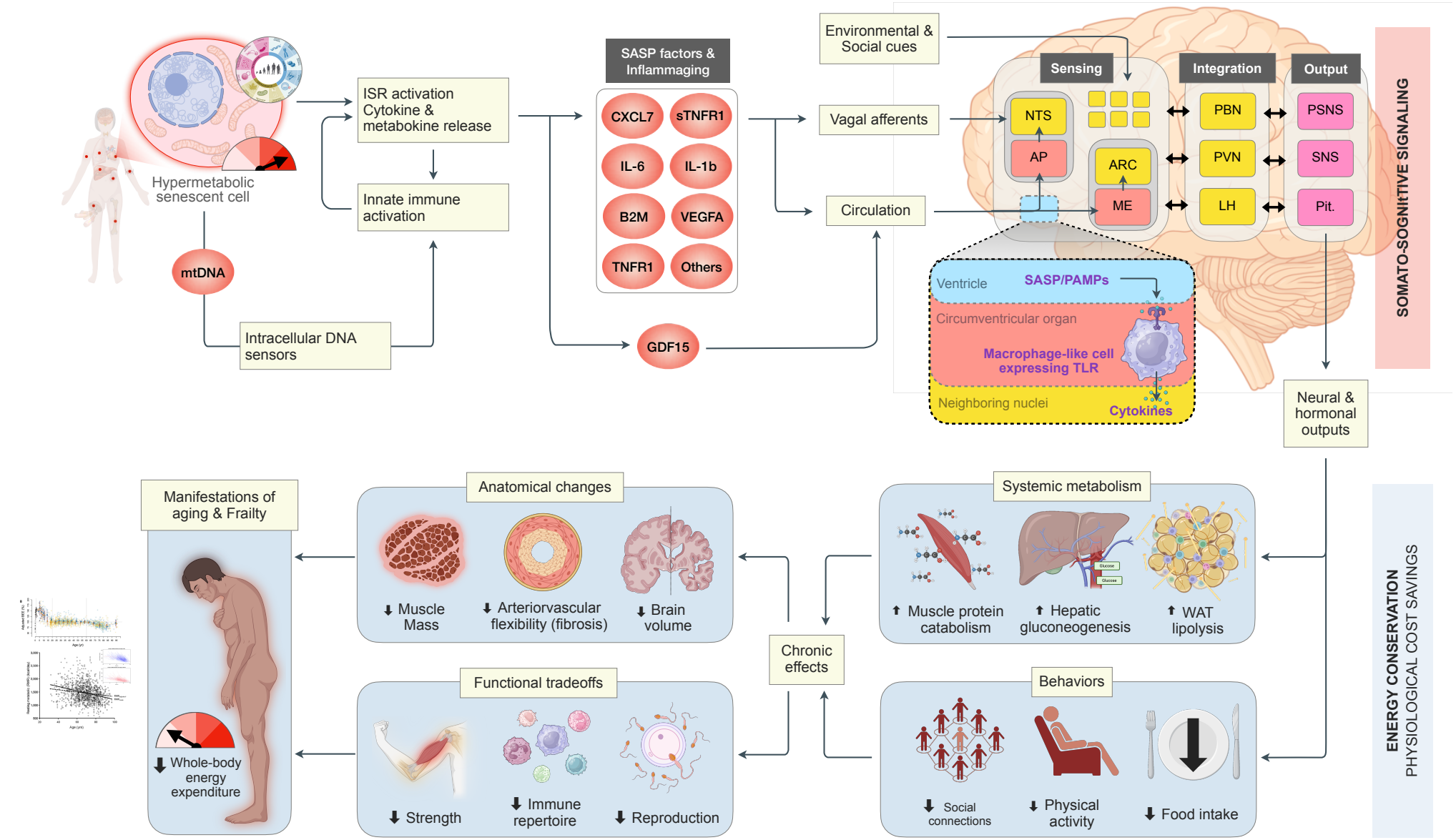






Shaulson, Cohen, Picard. *Preprint* (osf.io/zuey2)

Brain-body energy conservation (BEC)



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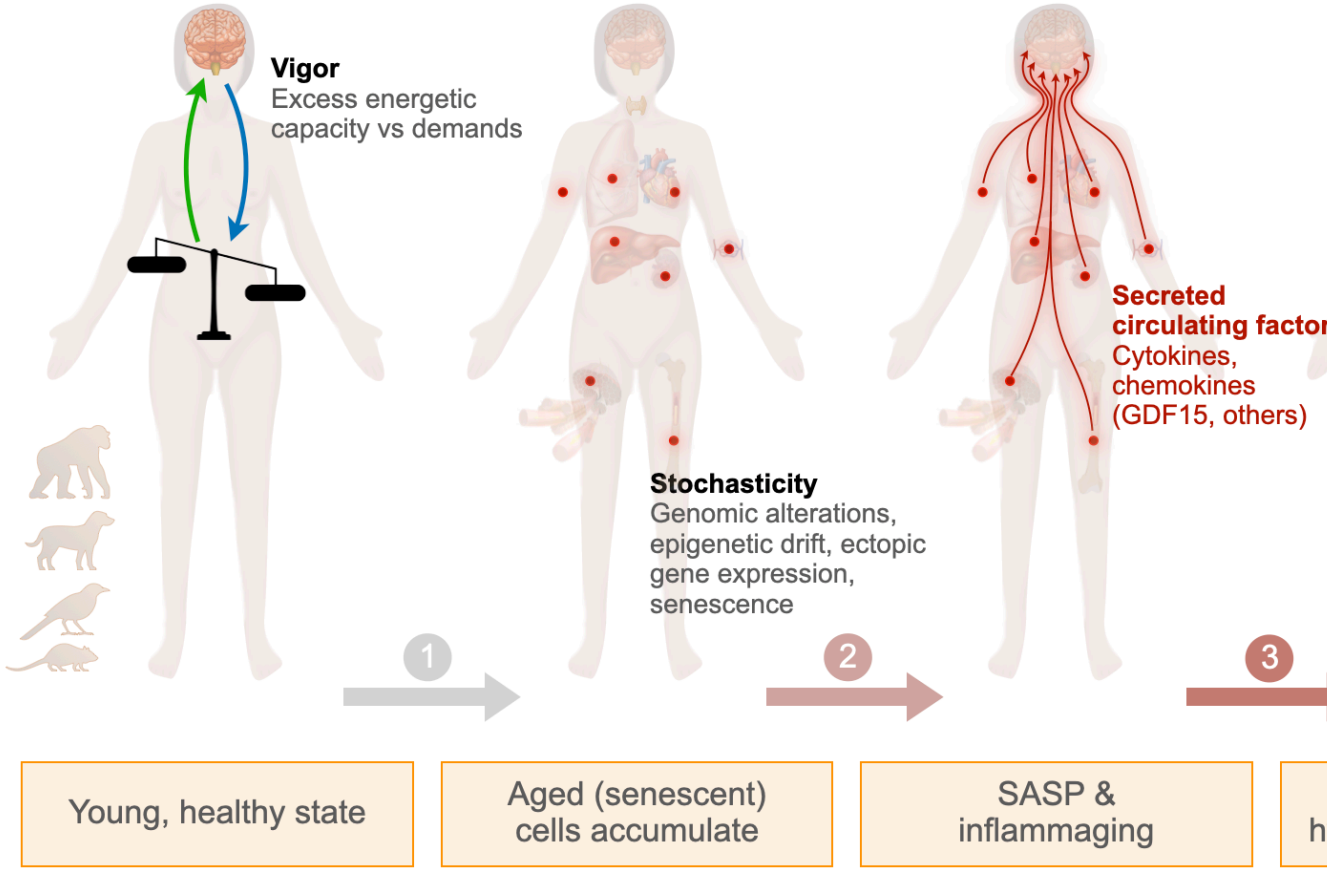

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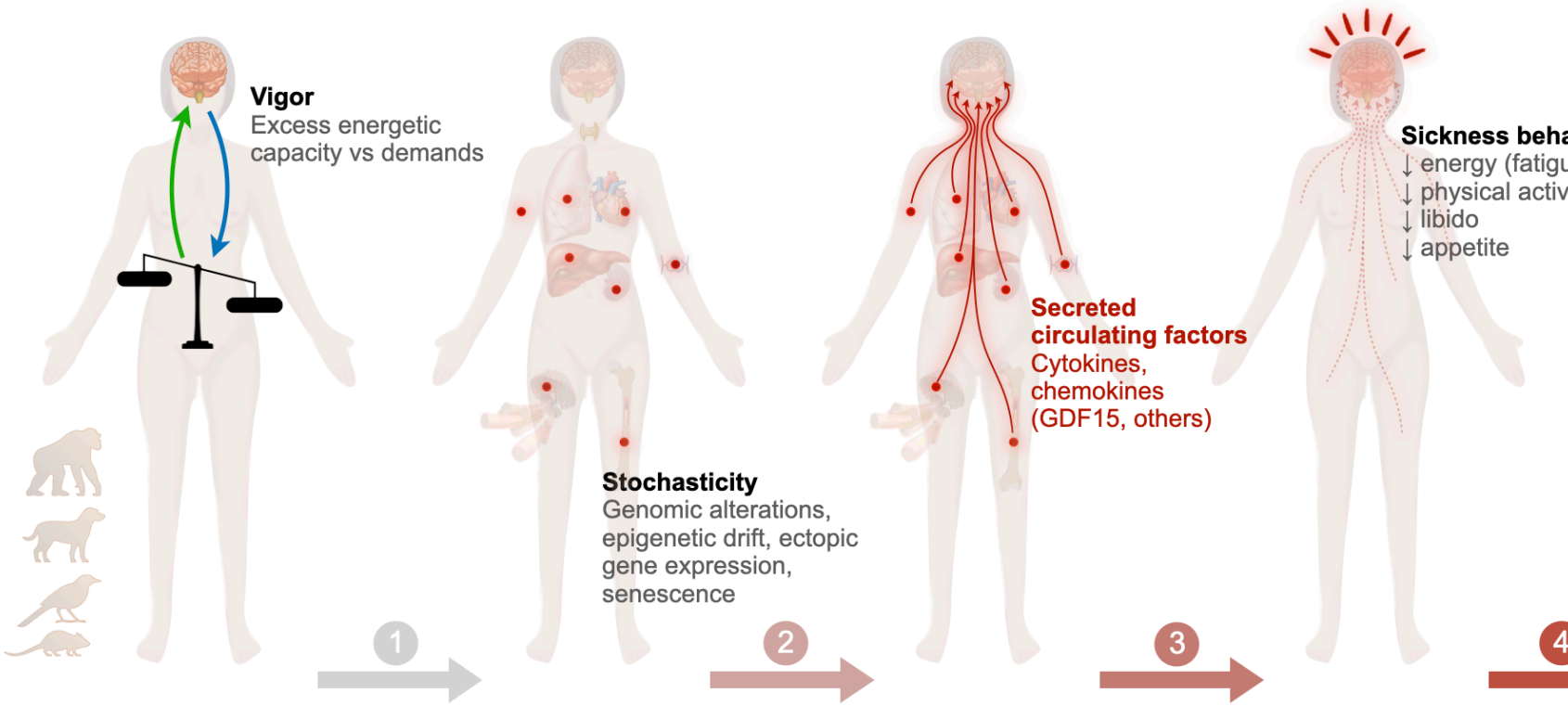

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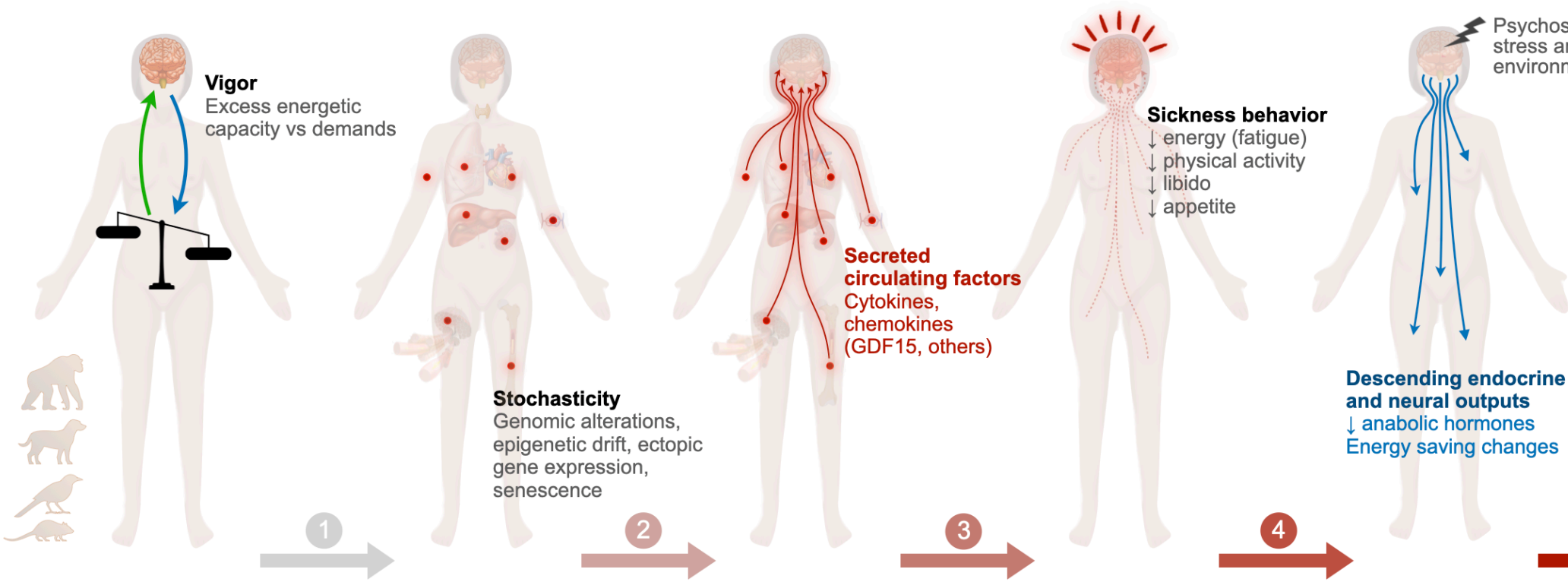

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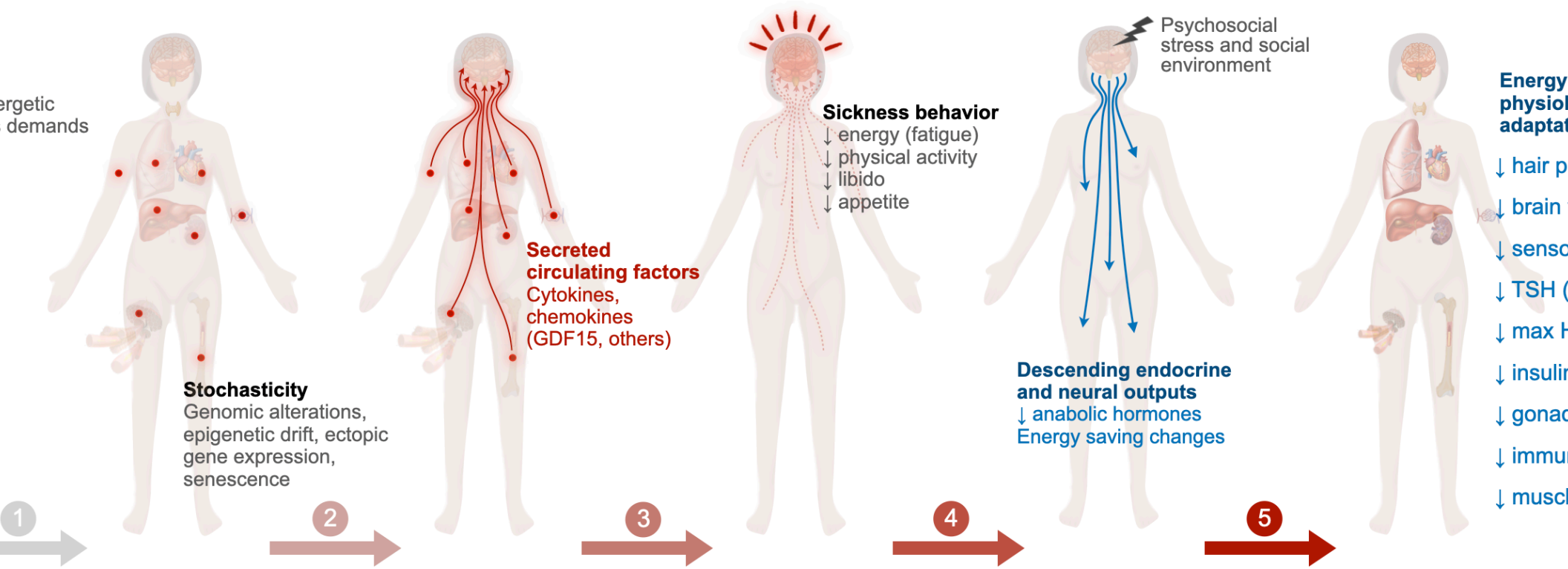

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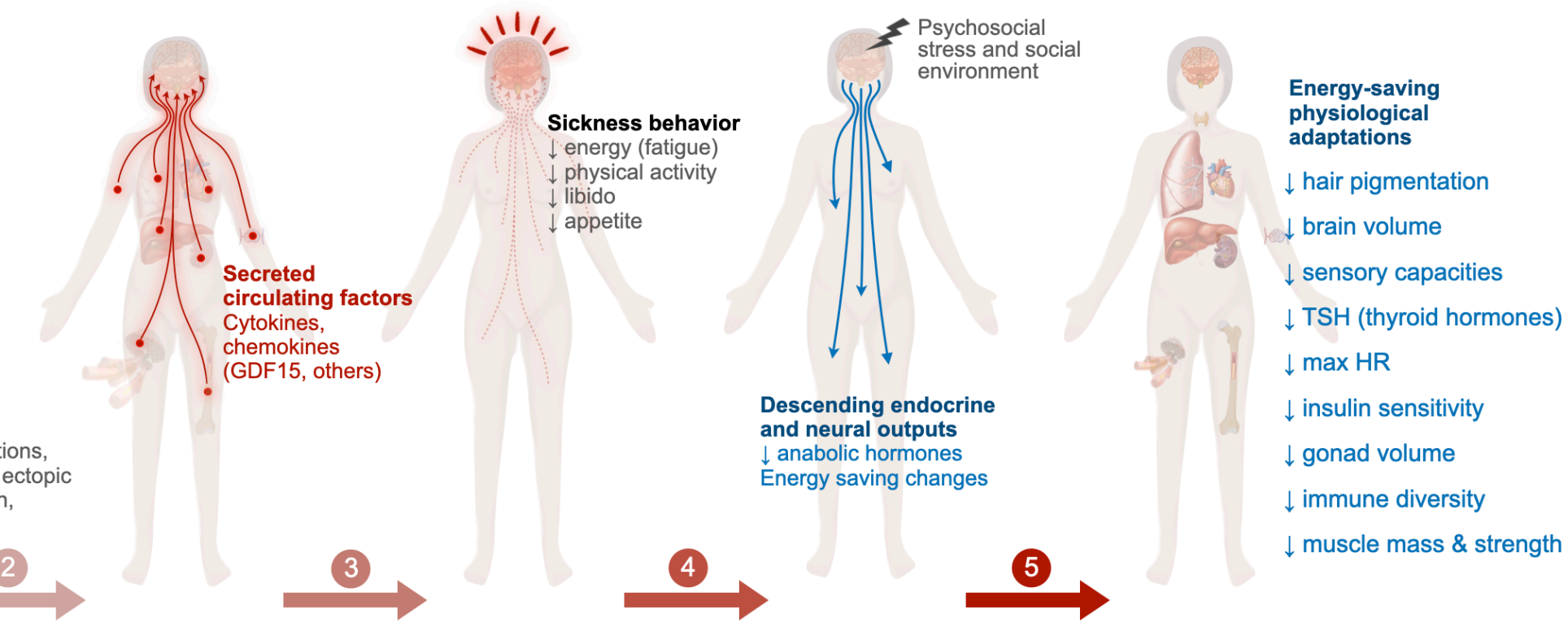

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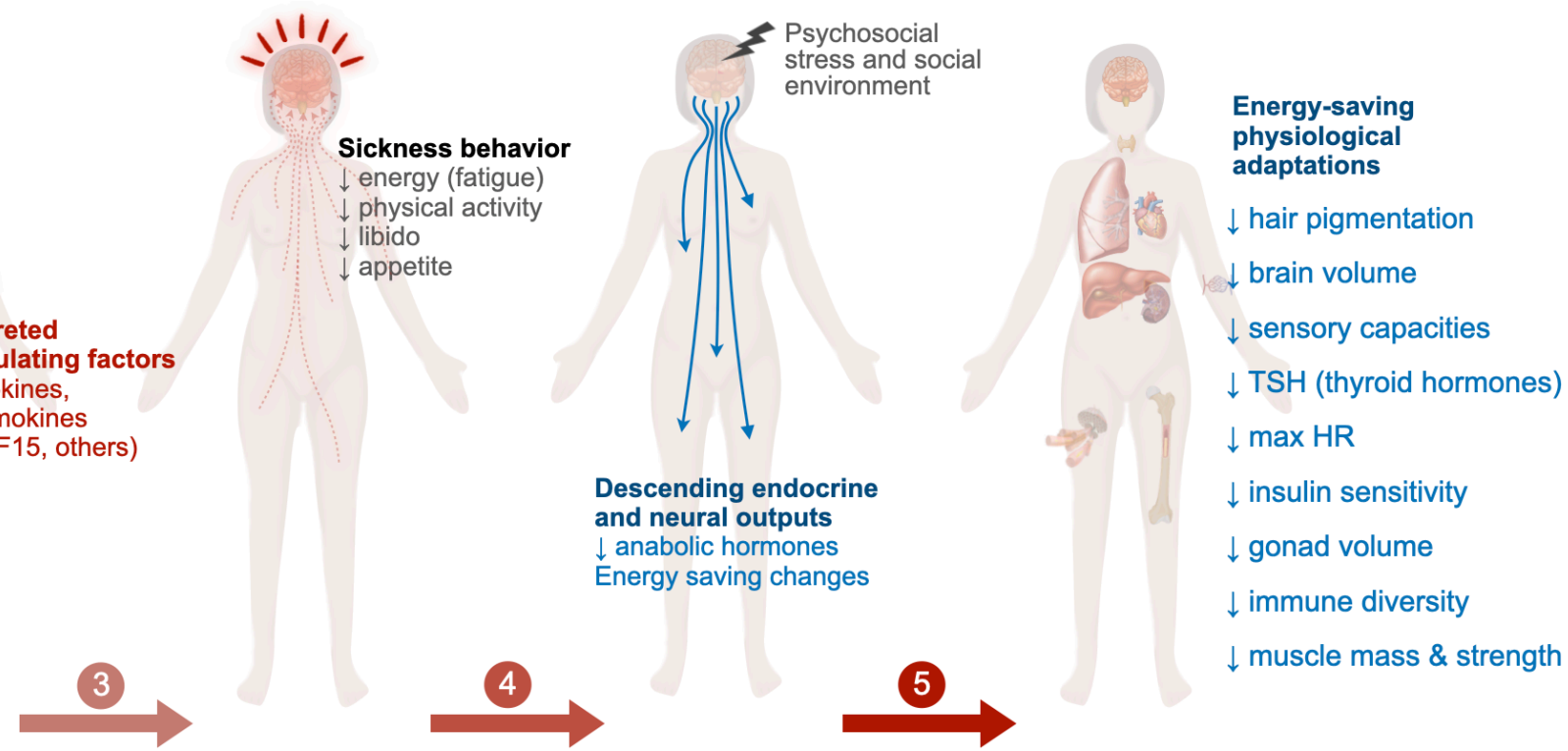

Shaulson, Cohen, Picard. *Preprint* (osf.io/zuey2)

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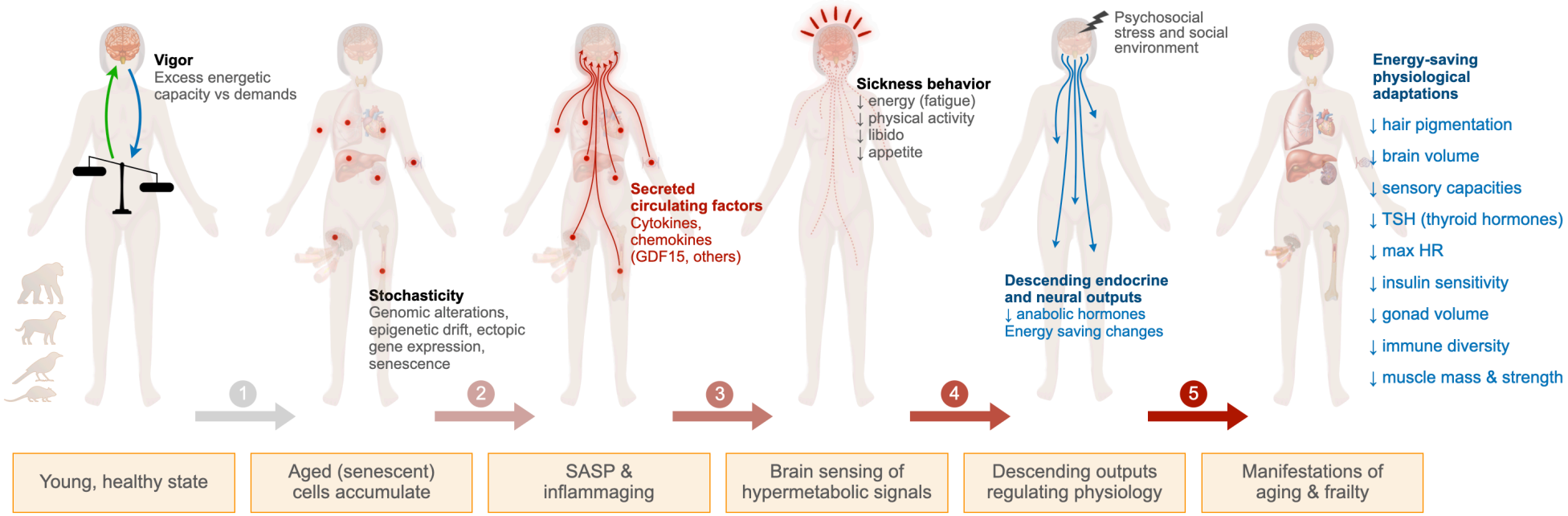
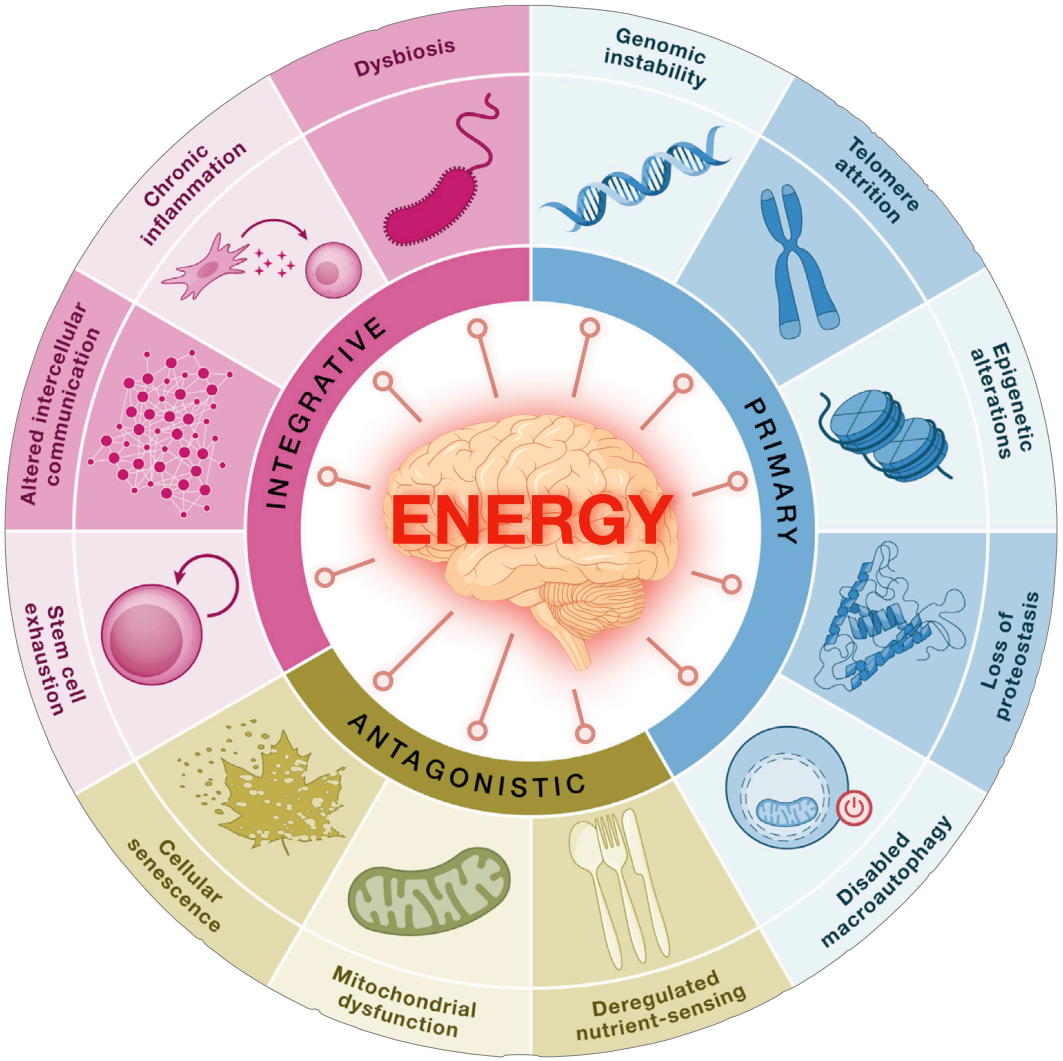


Organelle-to-organism bioenergetic principles of human aging can inform holistic health-promoting interventions

Shaulson, Cohen, Picard. *Preprint* (osf.io/zuey2)

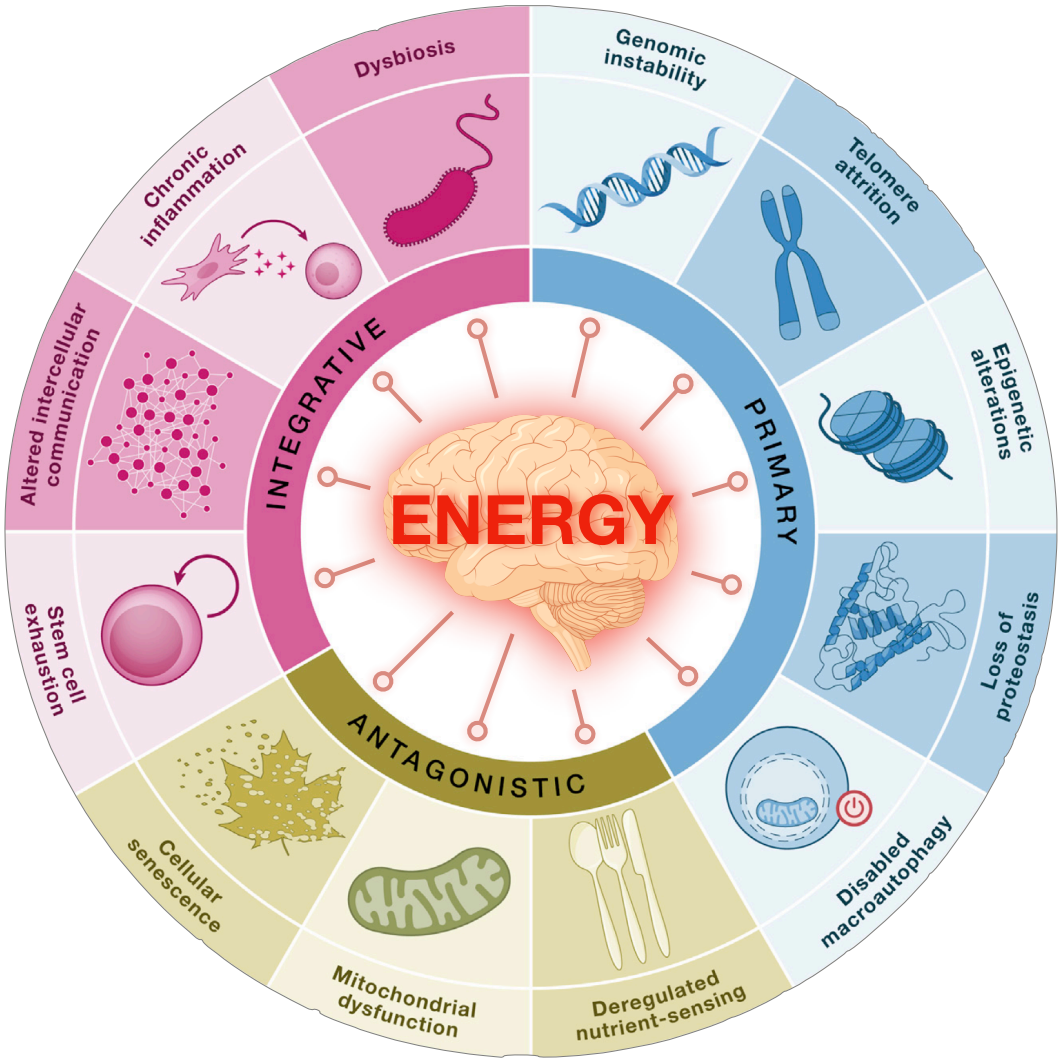
Is the common factor or intersection point ENERGY ?

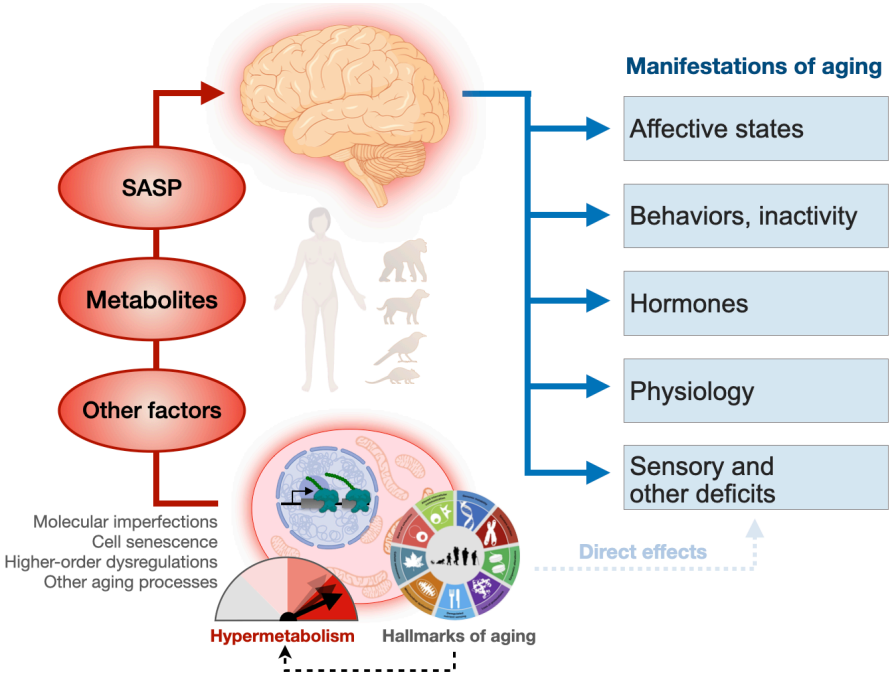
Do the hallmarks physically intersect in the BRAIN ?



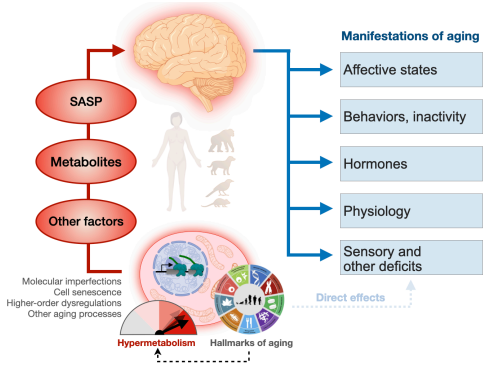
Modified from
Lopez-Otin et al. *Cell* 2023

Brain-body energy conservation (BEC)





Predictions of the BEC model



1. Frailty (loss of functions) is a pro-survival strategy (cancer cachexia), so people who can develop/sustain frailty should live longer (women vs men)

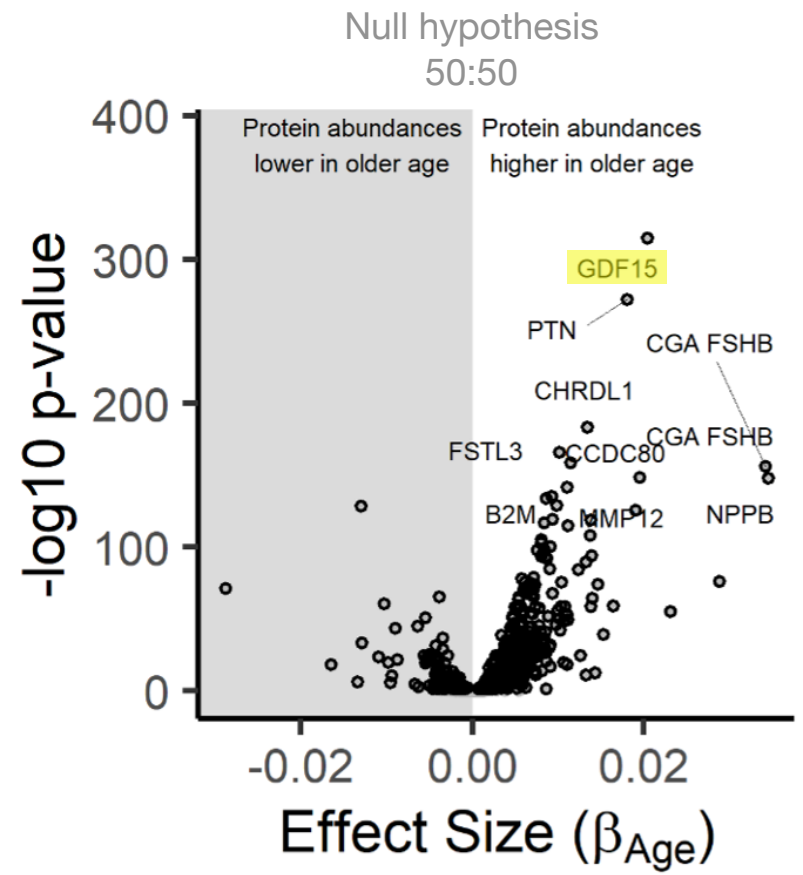
2. Costly processing of sensory information may be down regulated to conserve energy (sensory deficits)

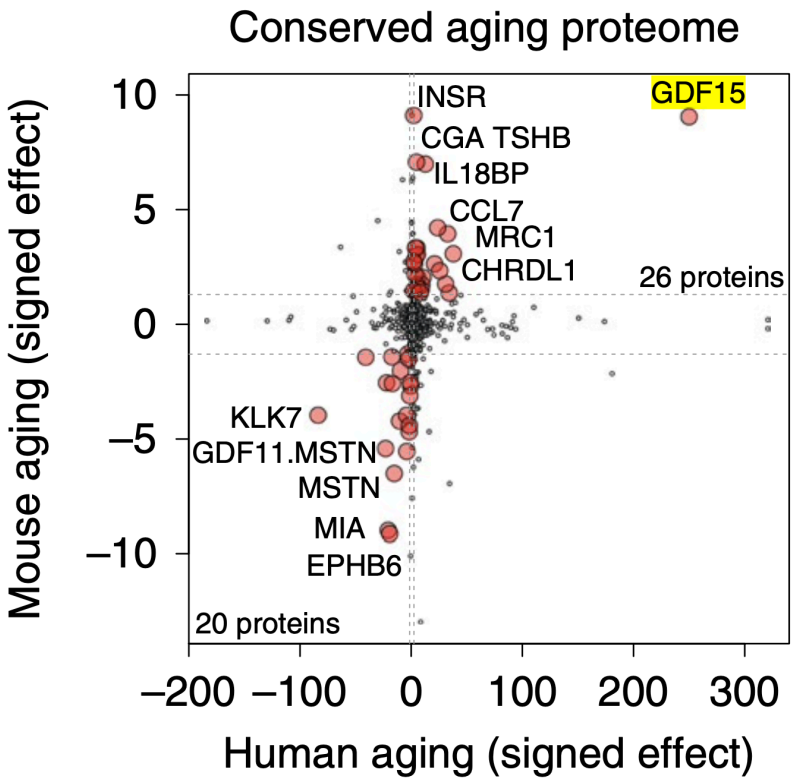
3. Torpor and energy conservation prolong healthspan/lifespan (Biorxiv 2024)

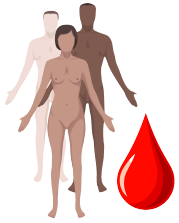
4. Chronic life stress and social isolation promotes cellular hypermetabolism, systemic signals of hypermetabolism (cytokines), and morbidity / accelerated physiological aging (Snyder Mackler et al. *Science* 2020)

5. Hormones should exist to convey somatic hypermetabolism to the brain (GDF15, other cytokines) (Monzel et al. *Life Metab* 2024)

GDF15 is the most significantly upregulated protein in human aging



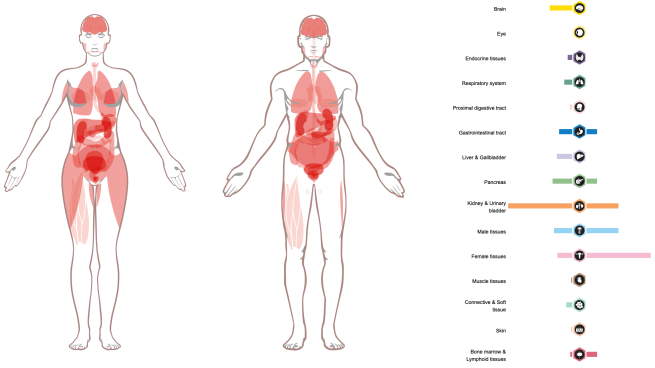




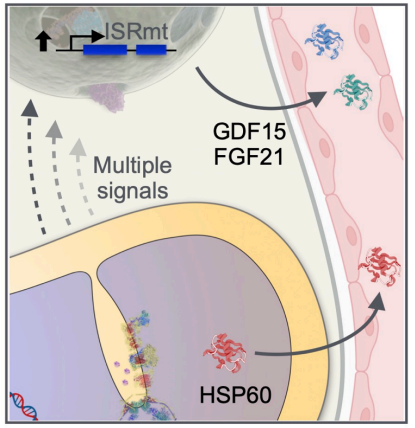
Tanaka et al. *Aging Cell* 2020

Lehallier et al. *Nature* 2019

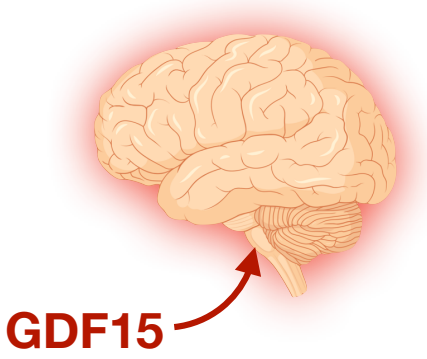
What does GDF15 mean to the organism?



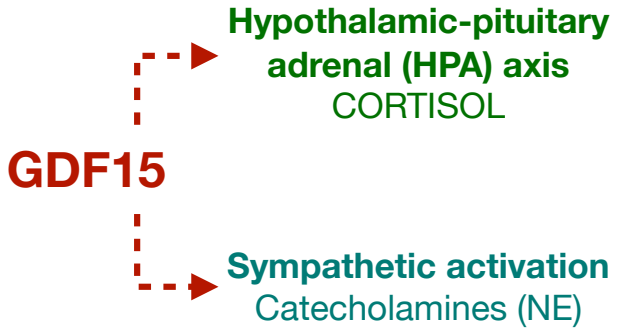
Expressed in >90% of somatic tissues



Triggered by mito OxPhos defects (ISR)



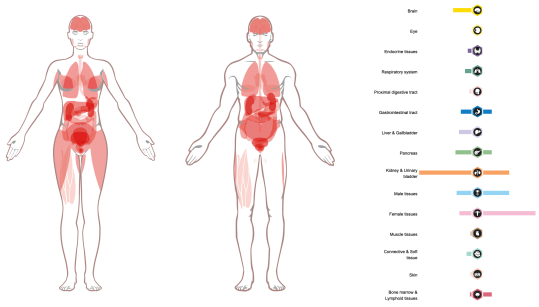
Signals on the brainstem, energy conservation



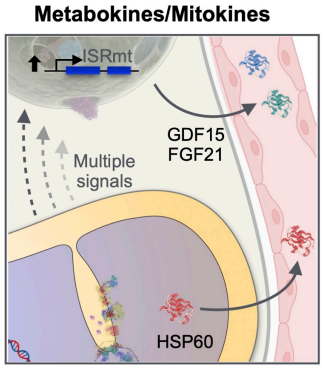
Activates canonical stress axes

Lockhart et al. *Endocr Rev* 2020

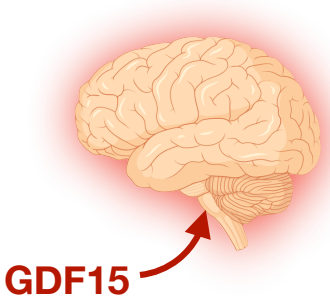
What does GDF15 mean to the organism?



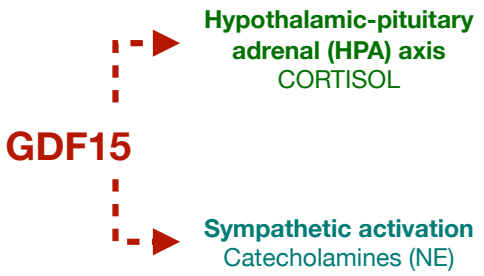
Expressed in >50% somatic tissues



Triggered by cellular stressors (ISR)

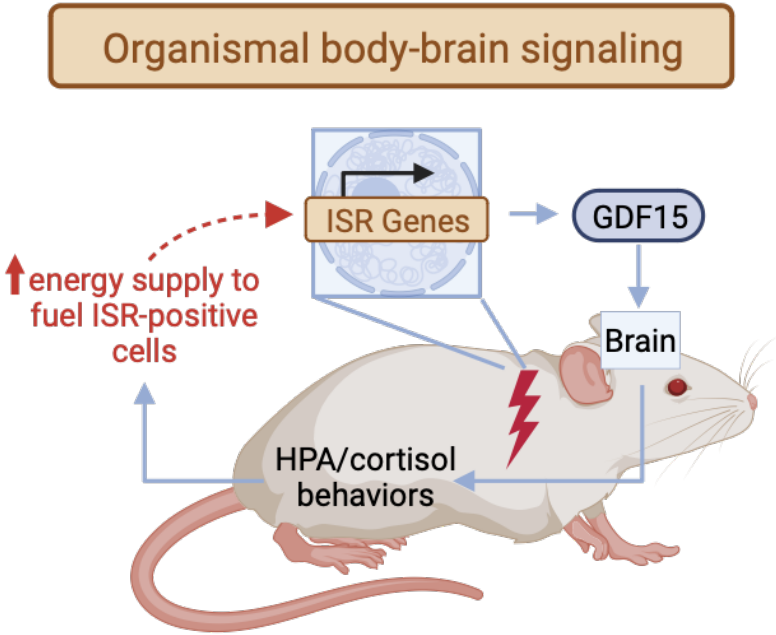


Signals on the brainstem, energy conservation



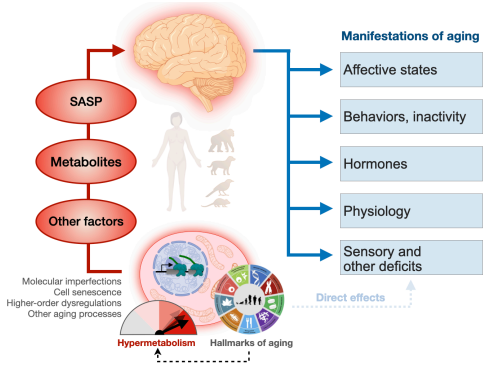
Activates canonical stress axes

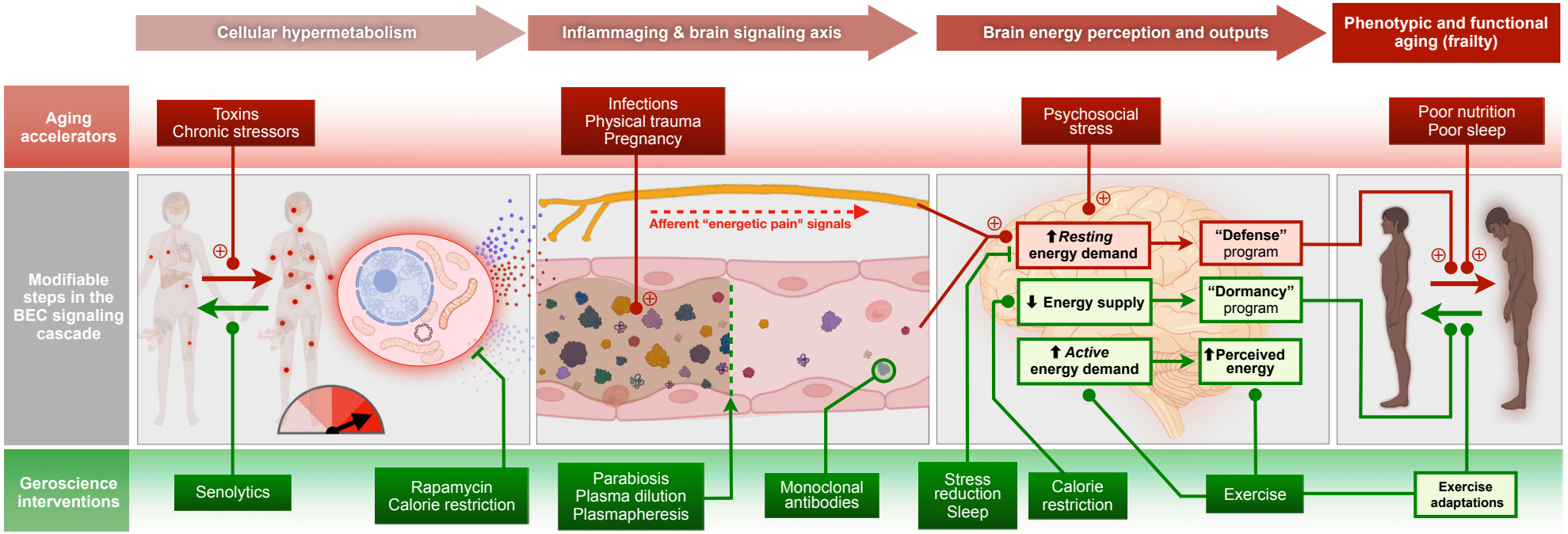
Psychological stress transiently increases GDF15 in humans

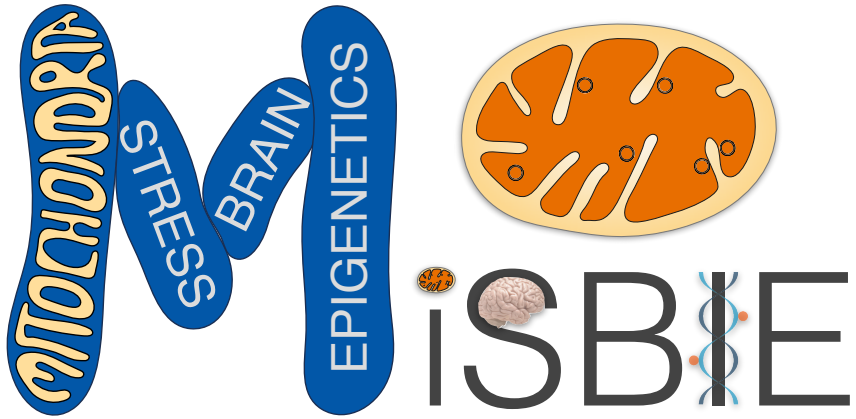


Monzel et al. *Life Metab* 2024

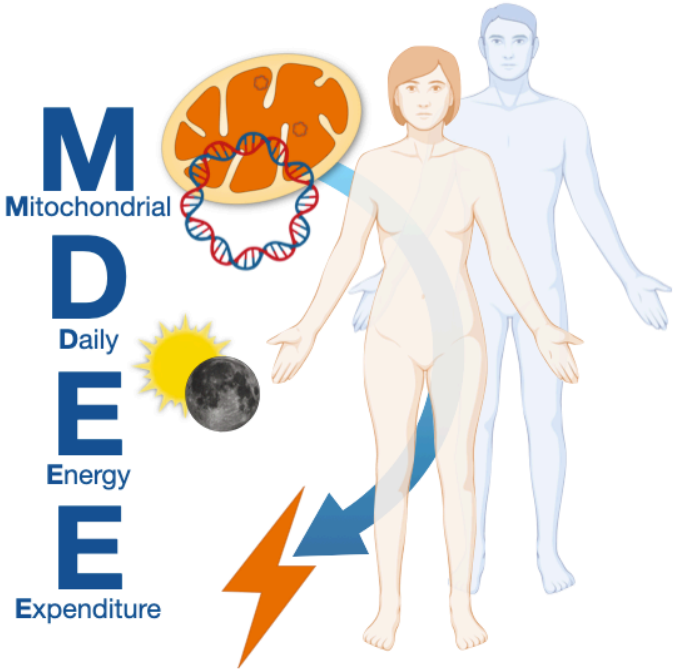
Predictions of the BEC model







Mitochondrial **S**tress, **B**rain **I**maging, and **E**pigenetics — **MiSBIE**



Mitochondrial **D**aily **E**nergy **E**xpenditure — **MDEE**

Evan Shaulson

Alan Cohen

Brain-body energy conservation (BEC)

Feedback welcome

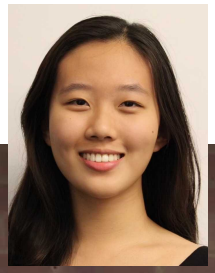
Thank you to:
- Matthew Yousefzadeh
- Jonathan Wanagat
- Robert Musci
- Judyann McNamara
- Will Fountain
- Judith Carroll
- Columbia Science of Health (SOH) group

Preprint: osf.io/zuey2

Mitochondrial PsychoBiology Lab

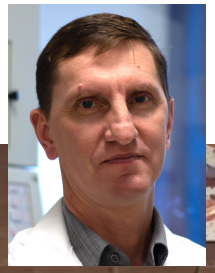
Linking molecular processes within mitochondria with the human experience

OUR RESEARCH







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NIH National Institute of Mental Health
NIH National Institute of General Medical Sciences
NIH National Institute on Aging

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The Nathaniel Wharton Fund nwf

Brain-body energy conservation (BEC)