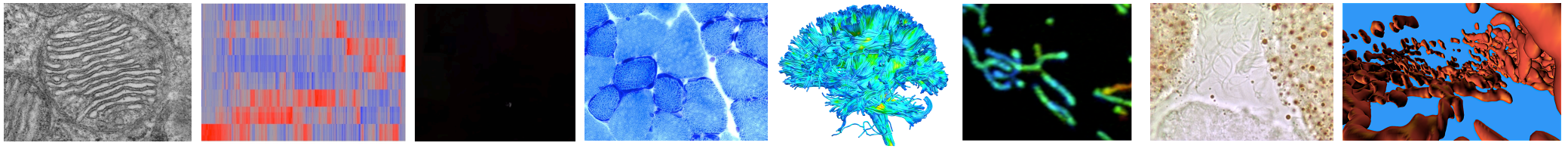
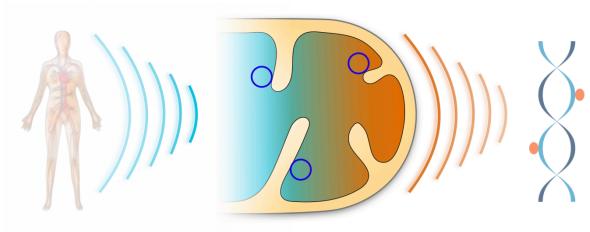


Energetic regulation of aging: What is the role of the brain?



Yale — Biology of Aging

Martin Picard, Ph.D.
Department of Psychiatry, Division of Behavioral Medicine
Department of Neurology, H. Houston Merritt Center
Robert N Butler Columbia Aging Center
Columbia Translational Neuroscience Initiative
New York State Psychiatric Institute (NYSPI)

COLUMBIA
COLUMBIA UNIVERSITY
IRVING MEDICAL CENTER

NEW YORK STATE OF OPPORTUNITY. New York State Psychiatric Institute

PART 1

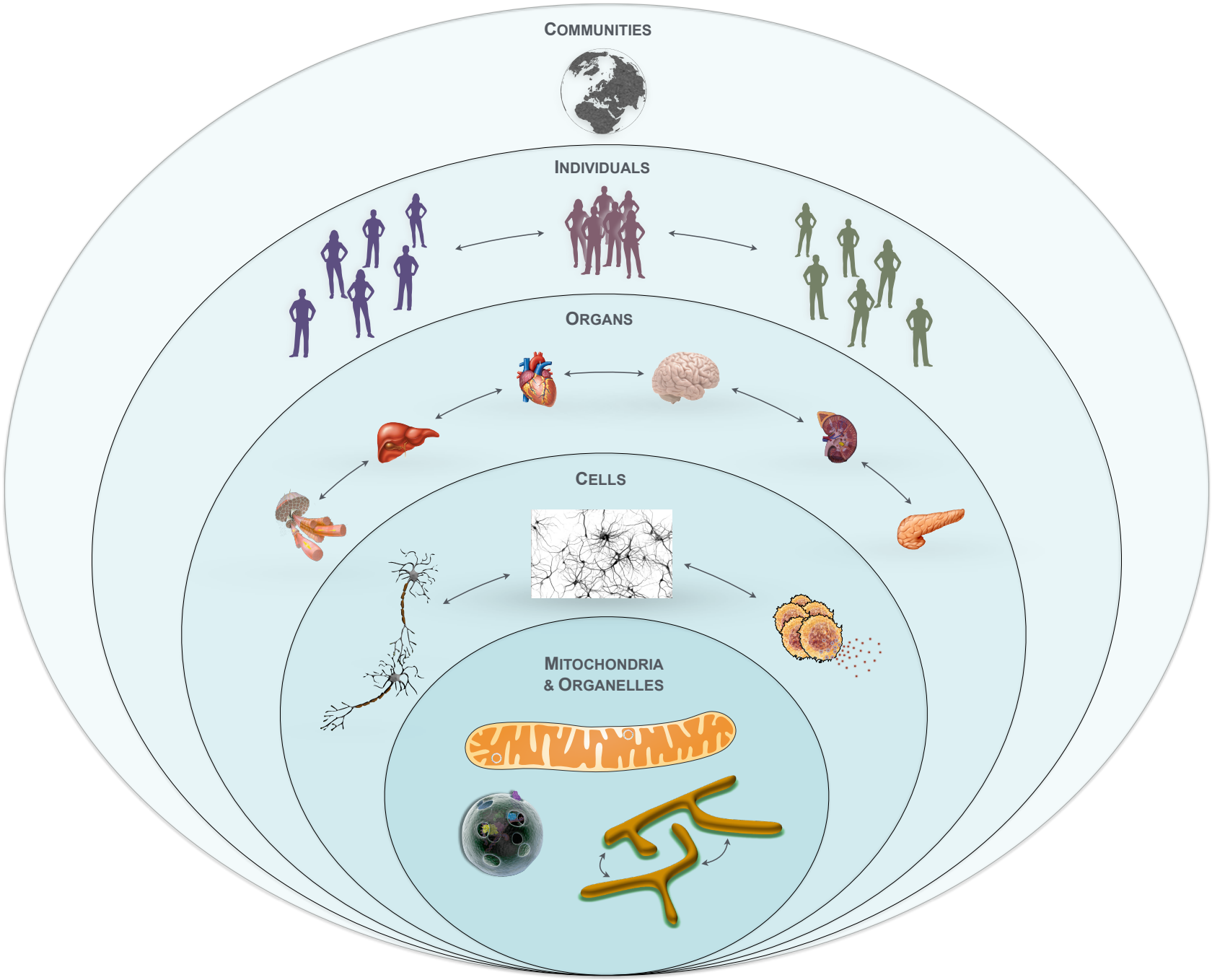
Mitochondrial Signal Transduction, Hair greying

PART 2

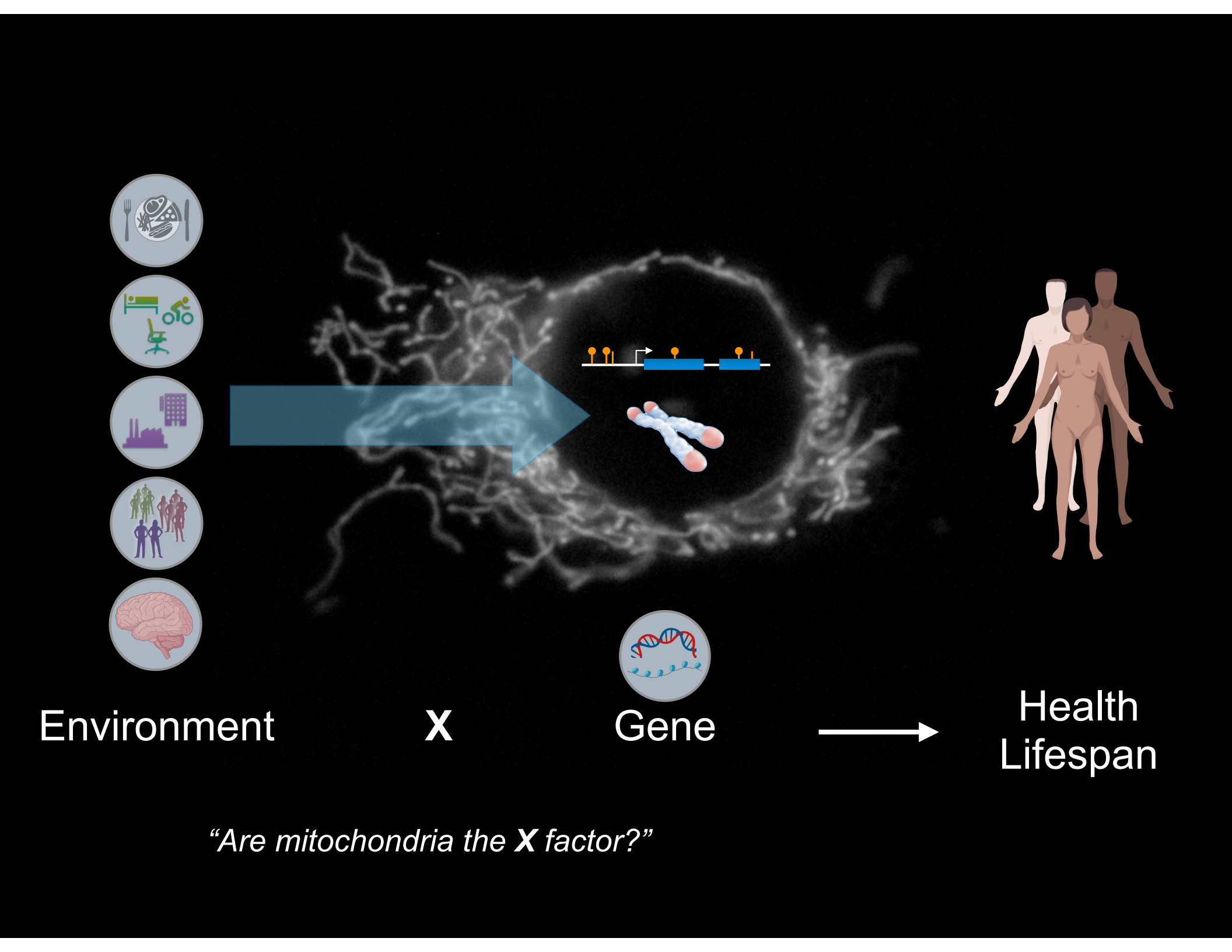
Energy, OxPhos defects, Hypermetabolism, Rate of aging

PART 3

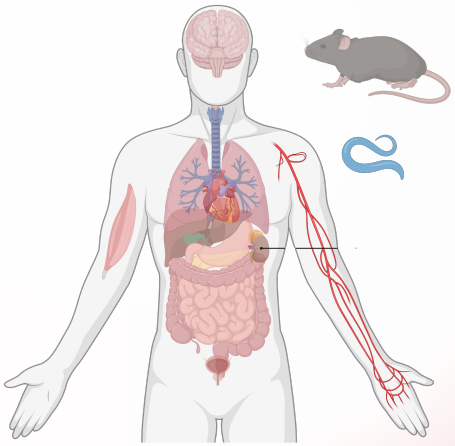
Somato-cognitive **E**nergy **C**onservation — **SEC**



Picard and Sandi.
Neurosci Biobehav Rev 2021


Environment
X
Gene
Health
Lifespan
"Are mitochondria the X factor?"

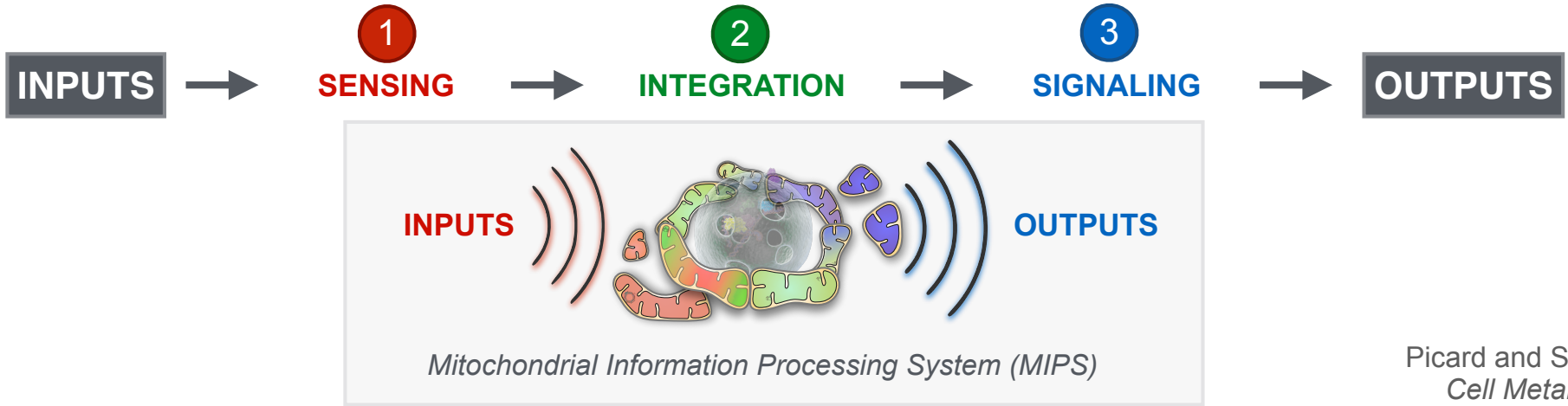
Multicellular organisms



INPUTS
- Peptide hormones
- Steroid & other hormones
- Nutrients levels
- Metabolites
- Ions
- Gases (e.g., O_2, NO)
- ATP/ADP (ΔGp)
- NAD(P)$^+$/NAD(P)H ratio
- mtDNA variations
- Others

OUTPUTS (mitochondrial, DIRECT)
- Metabolites
- Lipids
- DNA and RNA
- cf-mtDNA (whole, fragments)
- ATP (ΔGp)
- Ions
- ROS
- Gases
- Heat
- Steroid hormones
- Small peptides
- Others

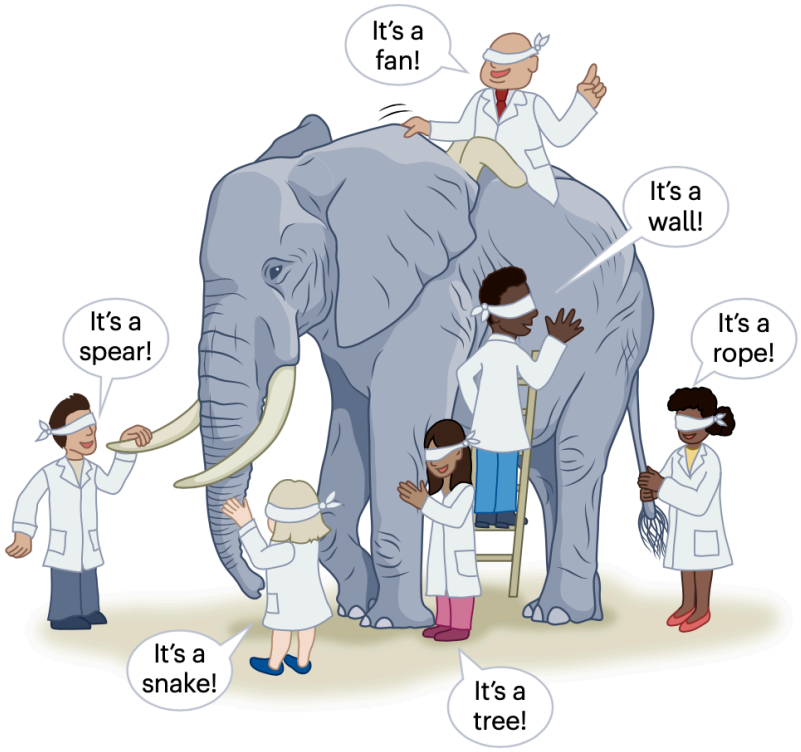
OUTPUTS (via nucleus, INDIRECT)
- Peptide hormones

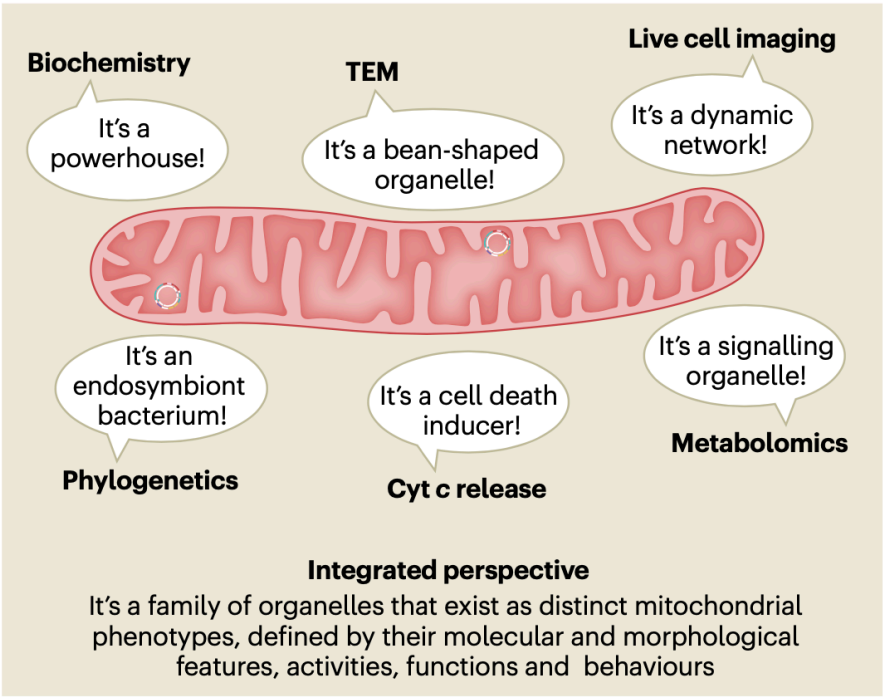


Picard and Shirihai.
Cell Metab 2022

Perspective https://doi.org/10.1038/s42255-023-00783-1

Multifaceted mitochondria: moving mitochondrial science beyond function and dysfunction

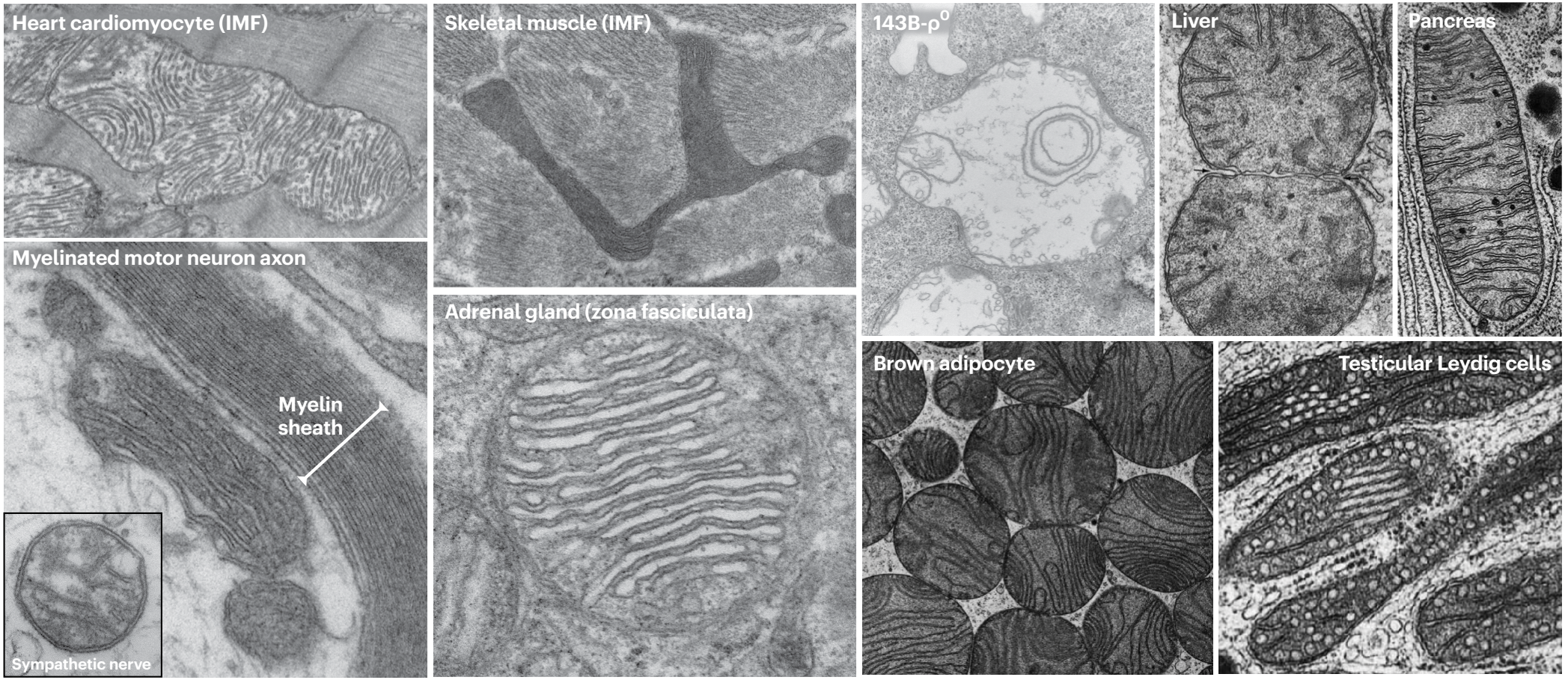


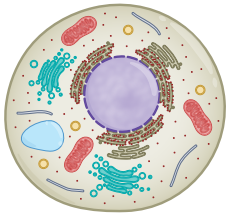


A catalogue of mitochondrial *functions*

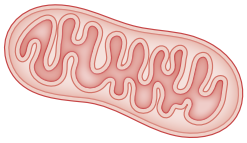
Monzel, Enriques, Picard. *Nat Metab* 2023

Different mitochondria types (mitotypes)



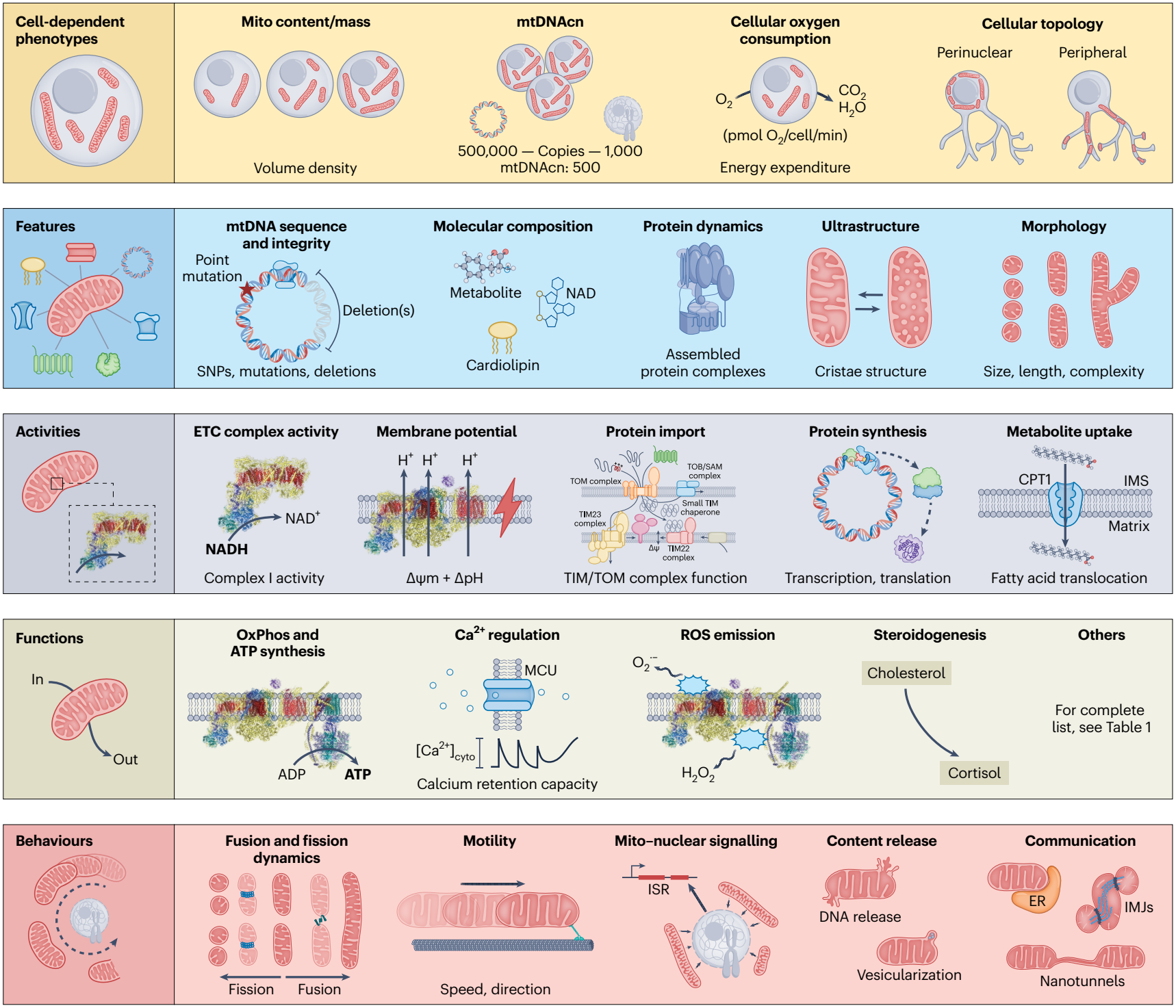


Cell types and subtypes



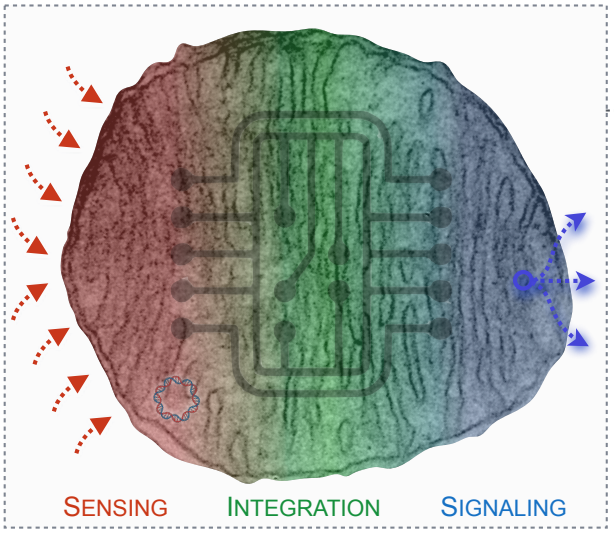
Mitochondrial phenotypes

Monzel et al.
Nat Metab 2023

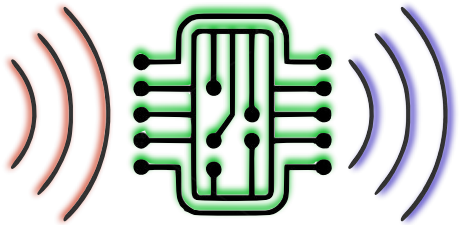

Cell-dependent phenotypes
Mito content/mass
Volume density
mtDNAcn
500,000 — Copies — 1,000
mtDNAcn: 500
Cellular oxygen consumption
O2
CO2
H2O
(pmol O2/cell/min)
Energy expenditure
Cellular topology
Perinuclear
Peripheral
Features
mtDNA sequence and integrity
Point mutation
Deletion(s)
SNPs, mutations, deletions
Molecular composition
Metabolite
NAD
Cardiolipin
Protein dynamics
Assembled protein complexes
Ultrastructure
Cristae structure
Morphology
Size, length, complexity
Activities
ETC complex activity
NAD+
NADH
Complex I activity
Membrane potential
H+ H+ H+
Δψm + ΔpH
Protein import
TOM complex
TOB/SAM complex
Small TIM chaperone
TIM23 complex
Δψ
TIM22 complex
TIM/TOM complex function
Protein synthesis
Transcription, translation
Metabolite uptake
CPT1
IMS
Matrix
Fatty acid translocation
Functions
In
Out
OxPhos and ATP synthesis
ADP
ATP
Ca2+ regulation
MCU
[Ca2+]cyto
Calcium retention capacity
ROS emission
O2·−
H2O2
Steroidogenesis
Cholesterol
Cortisol
Others
For complete list, see Table 1
Behaviours
Fusion and fission dynamics
Fission
Fusion
Motility
Speed, direction
Mito–nuclear signalling
ISR
Content release
DNA release
Vesicularization
Communication
ER
IMJs
Nanotunnels

Mitochondrial **I**nformation **P**rocessing **S**ystem — **MIPS**

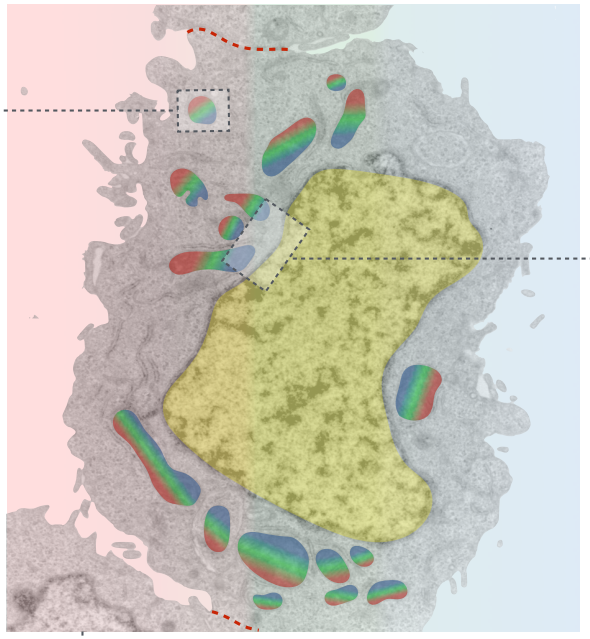
Signal transducing mitochondrion

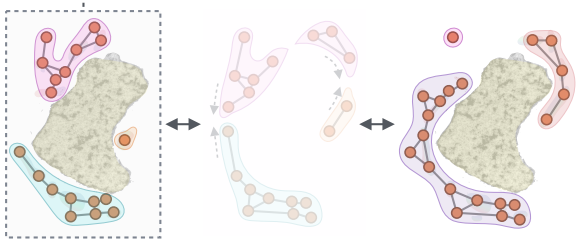


Incoming data *Outgoing data*

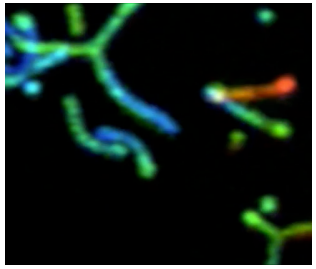


"Mitochondria are the processor of the cell"

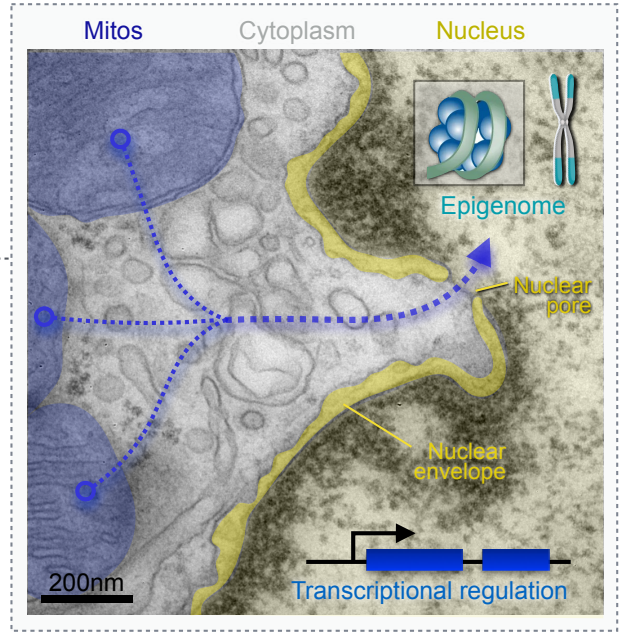


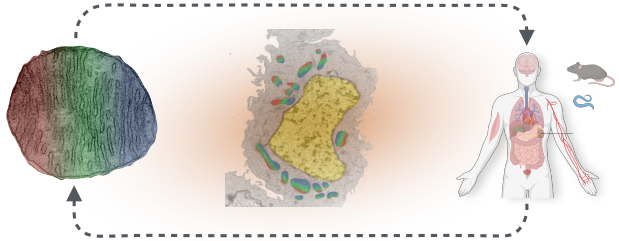


Dynamic remodeling of mito networks



Mito-nuclear unit





SEC theory of aging

Picard and Shirihai. *Cell Metab* 2022

PART 1

Mitochondrial Signal Transduction, Hair greying

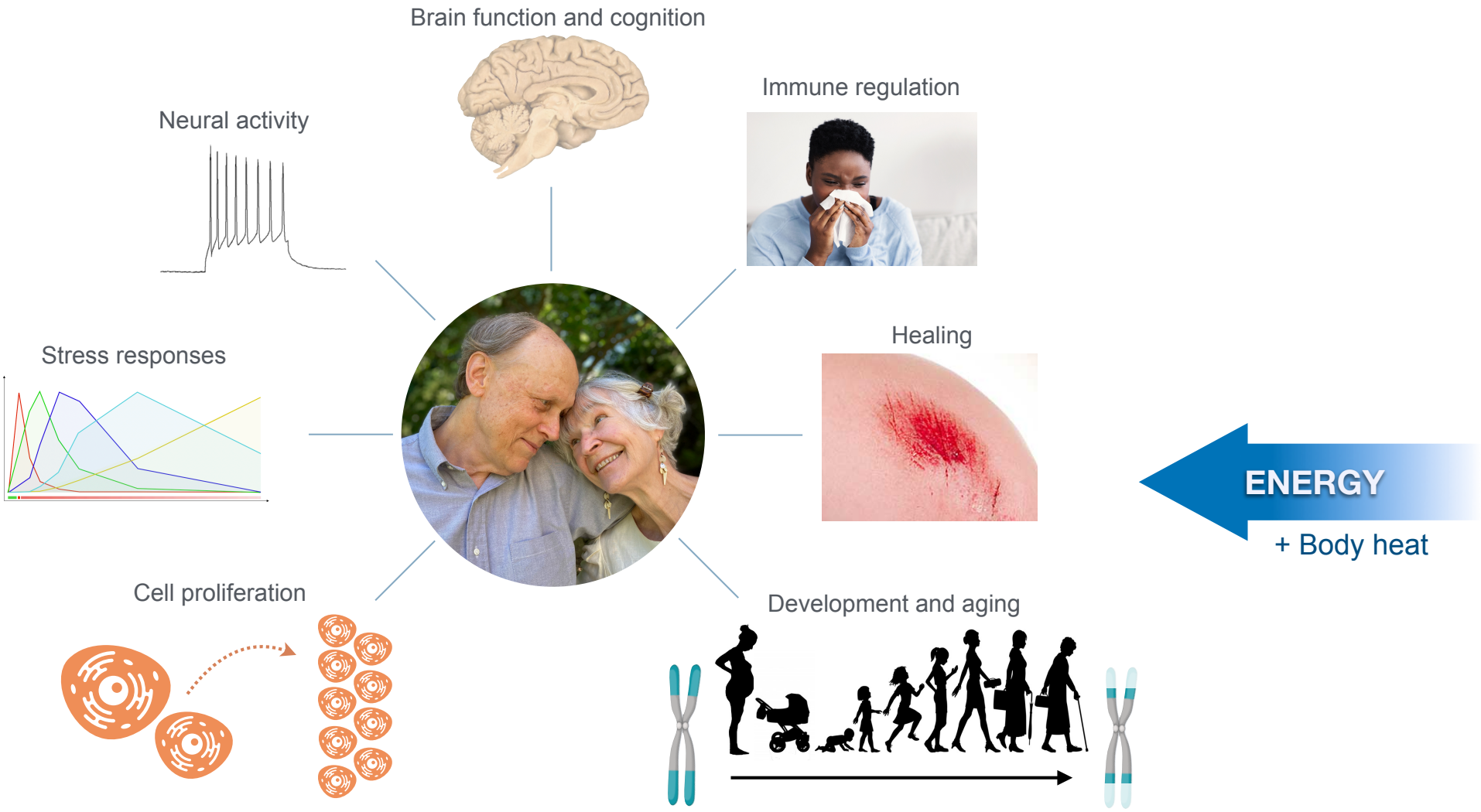
PART 2

Energy, OxPhos defects, Hypermetabolism, Rate of aging

PART 3

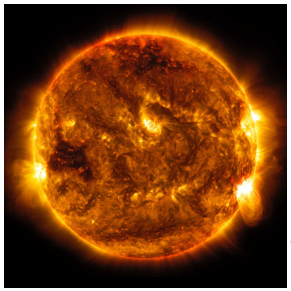
Somato-cognitive **E**nergy **C**onservation — **SEC**

What costs energy?



BIOLOGY, PHYSIOLOGY, COGNITION, CONSCIOUSNESS

PSYCHOBIOLOGICAL ALLOSTATIC PROCESSES



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

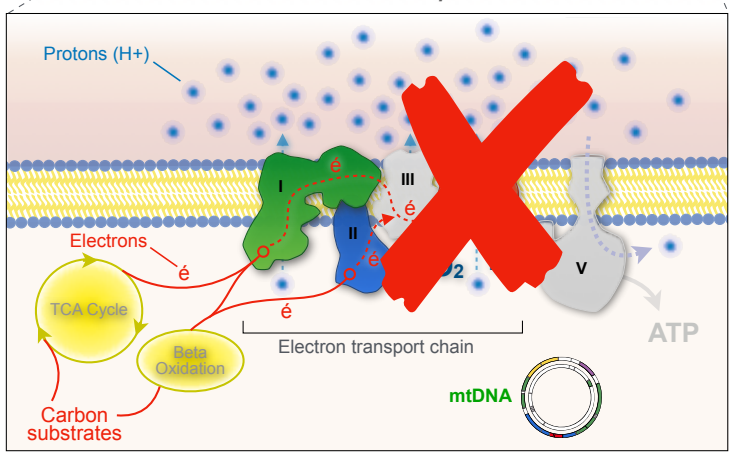
Development and aging

ENERGY

+ Body heat

PHYSIOLOGY, COGNITION, CONSCIOUSNESS
PSYCHOBIOLOGICAL ALLOSTATIC PROCESSES

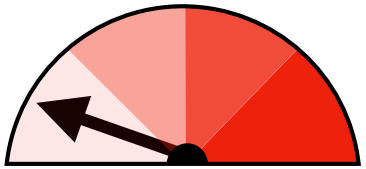
Electricity and Chemiosmosis
$\Delta\Psi m + \Delta pH$



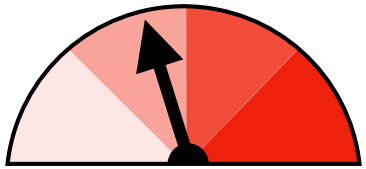
CHEMICAL ENERGY TRANSFORMED INTO
ELECTROCHEMICAL FORCE

Biochemistry 2022

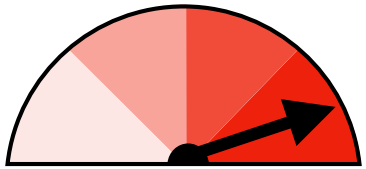
How do OxPhos defects influence cellular energy demand / expenditure?



HYPOmetabolism

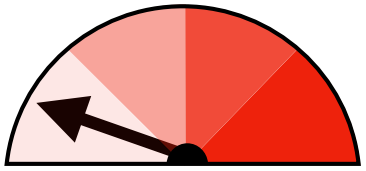


NORMOmetabolism

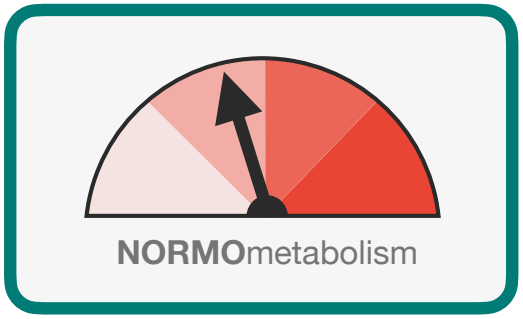


HYPERmetabolism

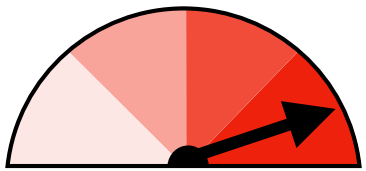
How do OxPhos defects influence cellular energy demand / expenditure?



HYPOmetabolism



NORMOmetabolism



HYPERmetabolism

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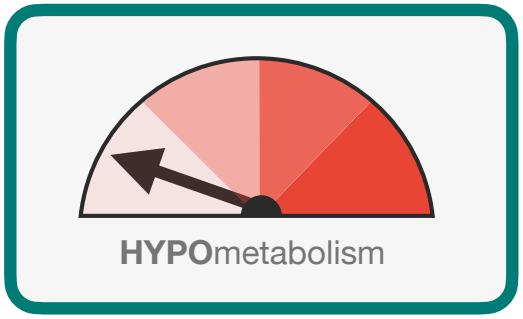

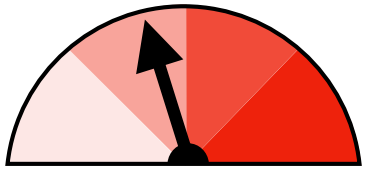

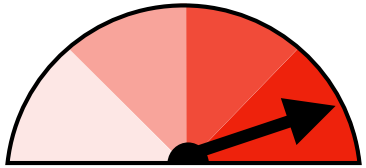

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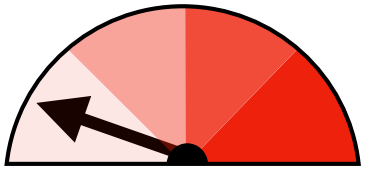
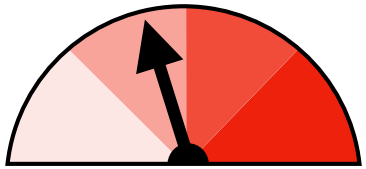
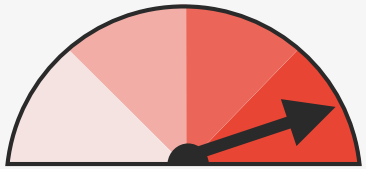


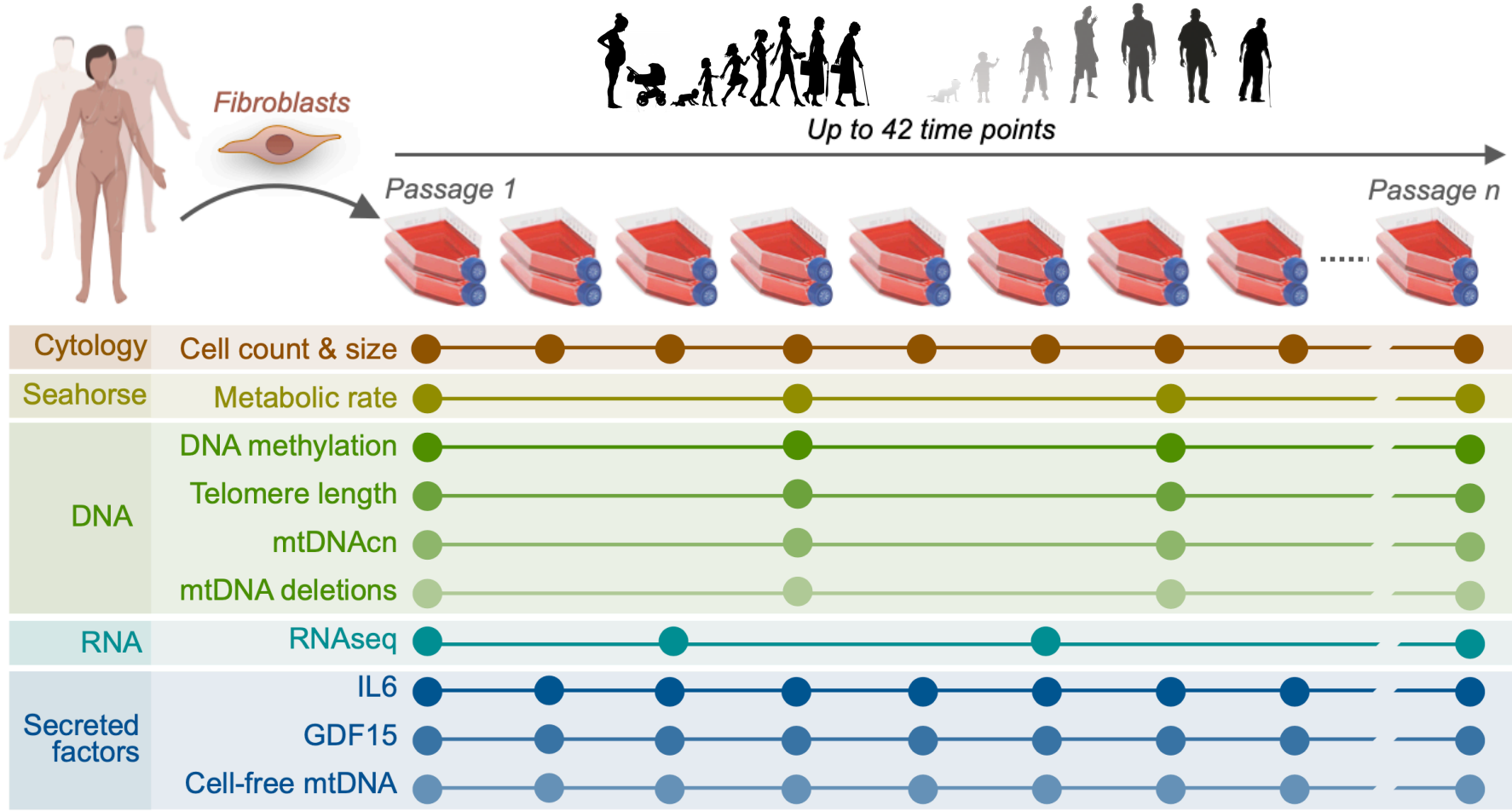
HYPOmetabolism

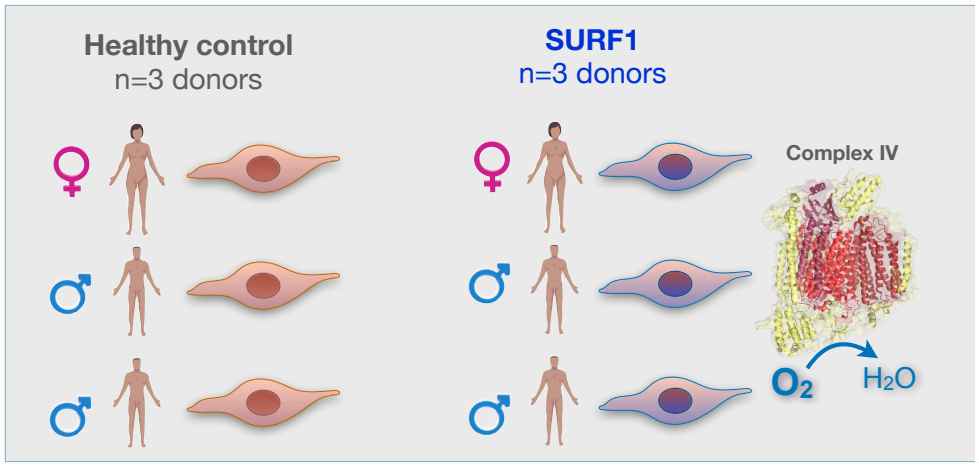


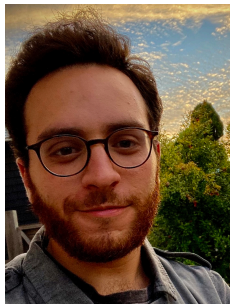
NORMOmetabolism



HYPERmetabolism



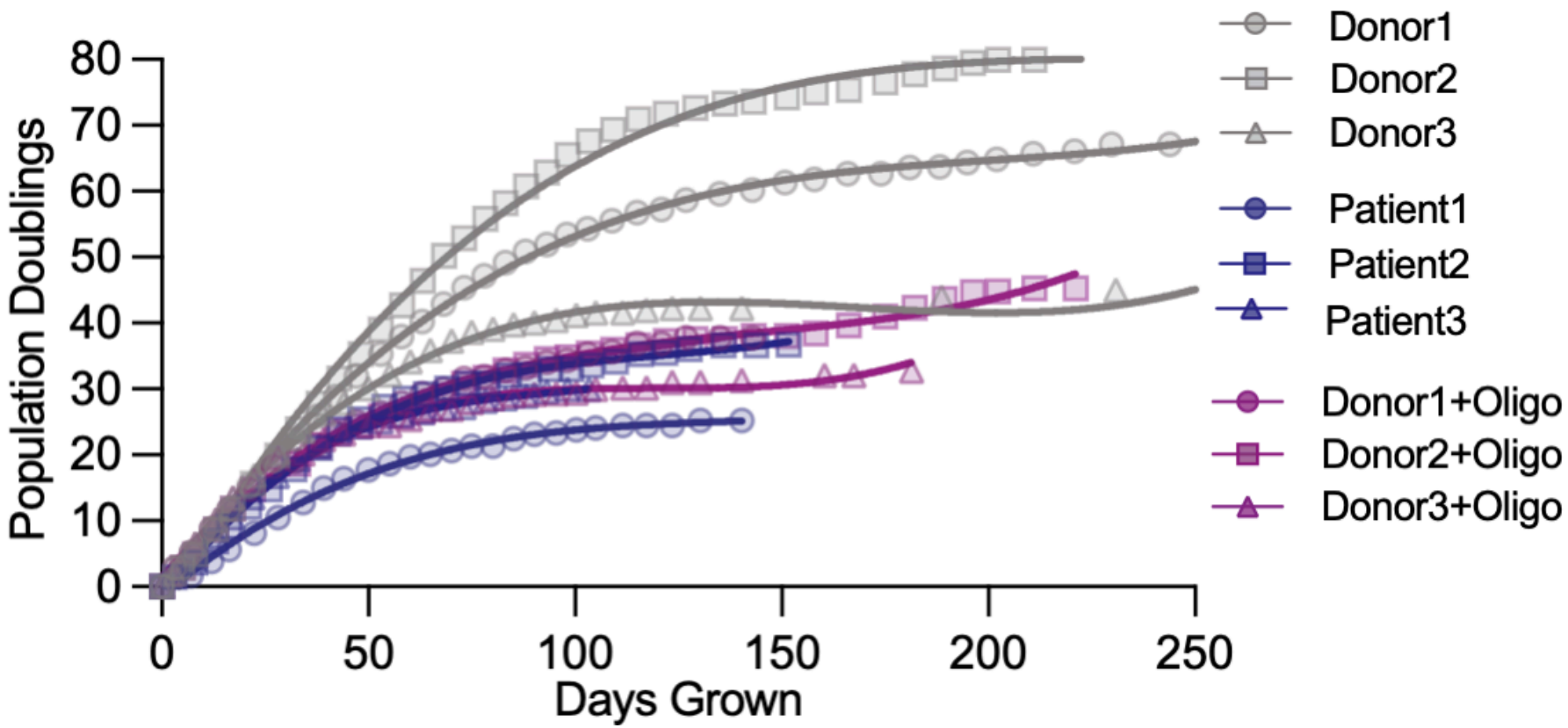




Gabriel Sturm

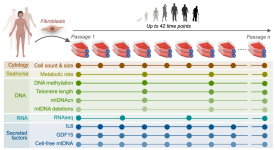
Sturm et al. *Commun Biol* 2023

OxPhos defects **reduce** cell division rate by 32-48%

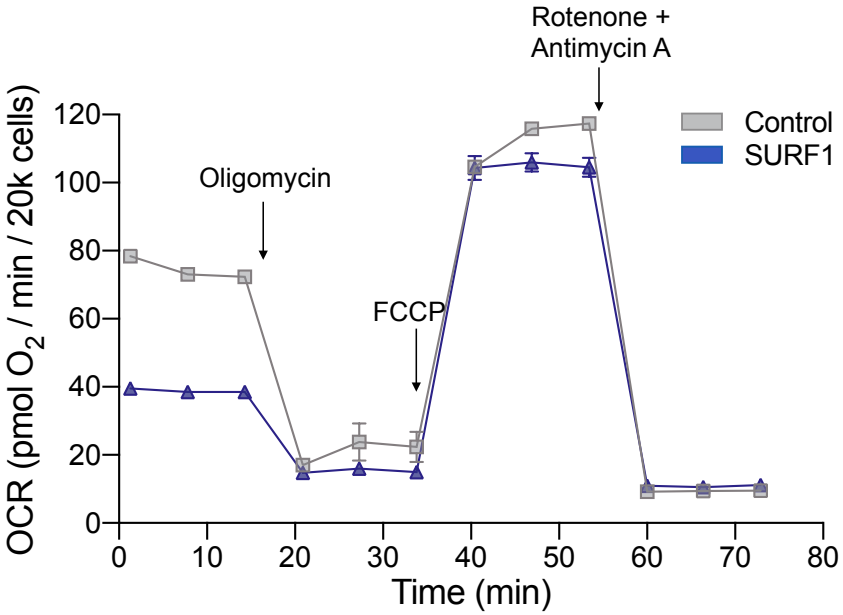


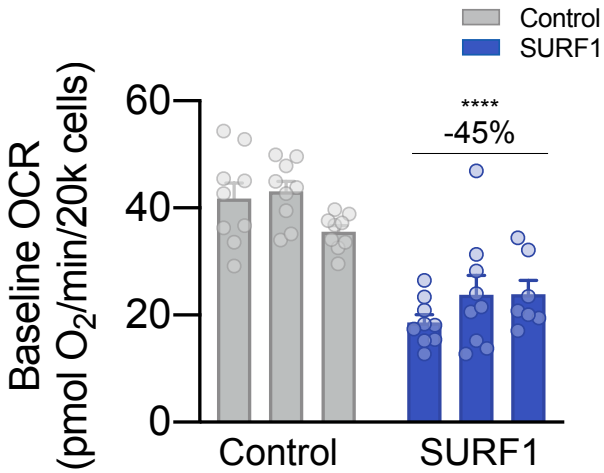
Slower division = less DNA replication, less protein synthesis, less telomerase activity, less mitochondrial biogenesis, … **ENERGY SAVINGS?**

Bioenergetic recalibrations to OxPhos defects

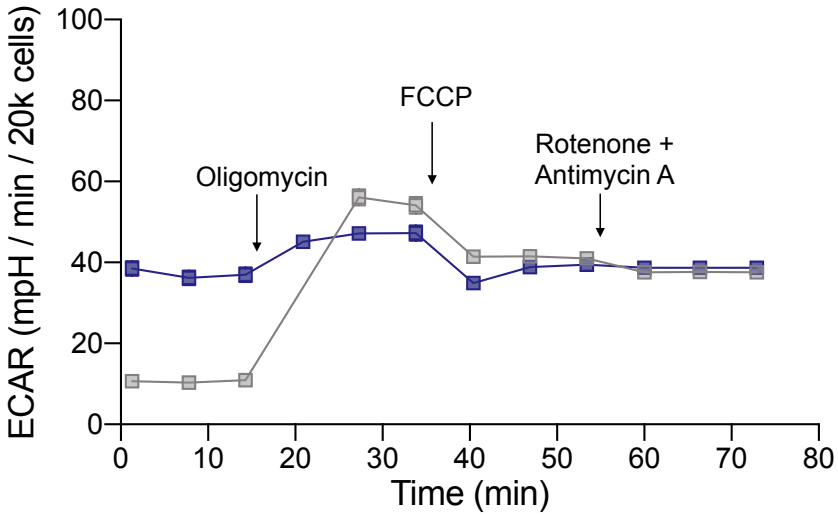


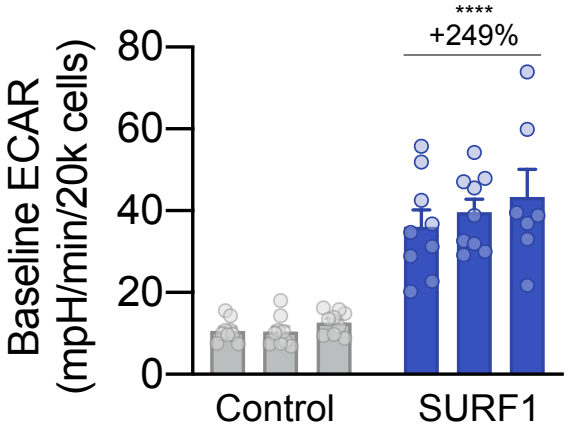
OCR





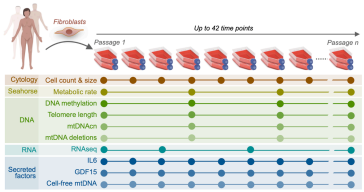
ECAR

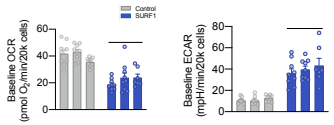




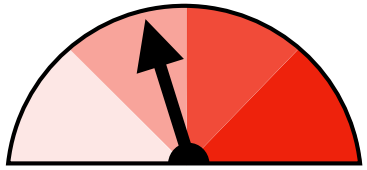
Sturm et al. *Commun Biol (2023)*

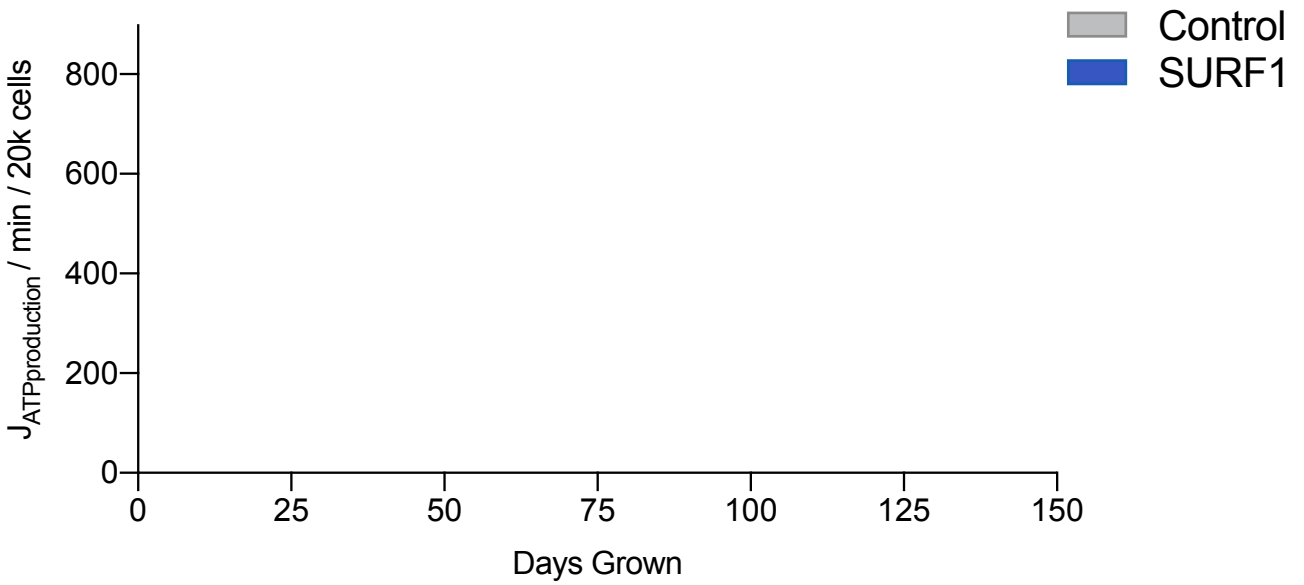
Lifespan trajectories of energy expenditure





Total energy consumption

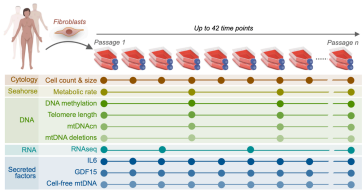


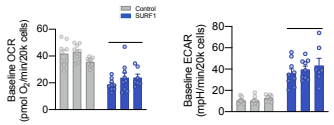


Method from Mookerjee et al. *JBC* 2017

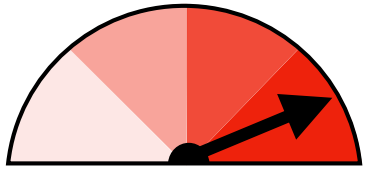
Sturm et al. *Commun Biol (2023)*

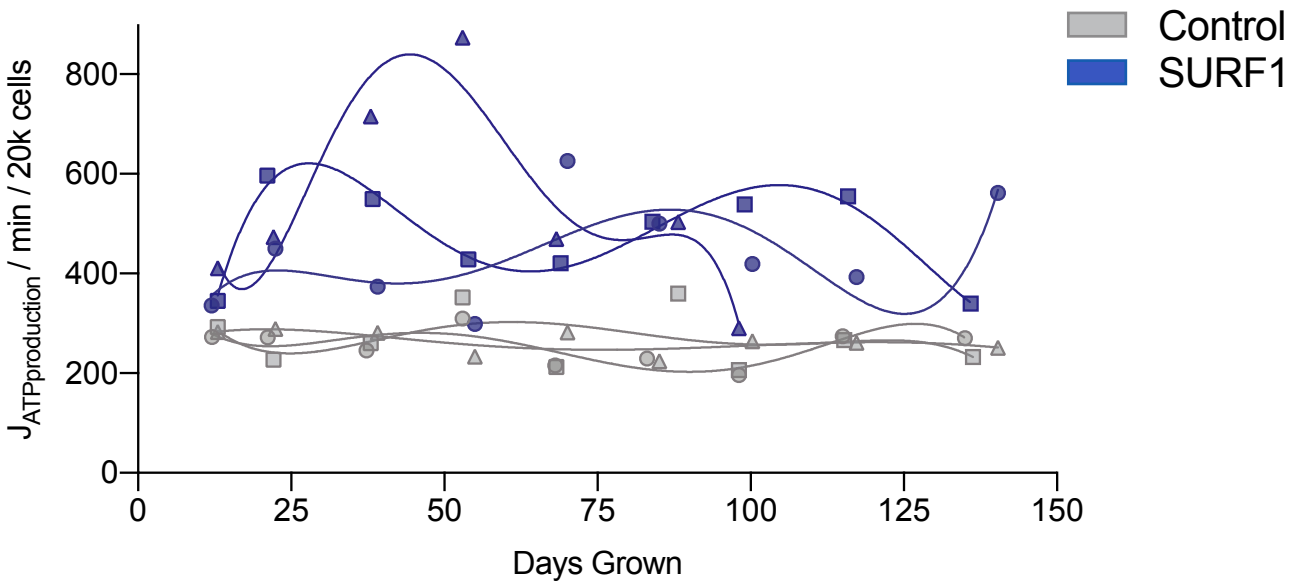
Lifespan trajectories of energy expenditure





Total energy consumption

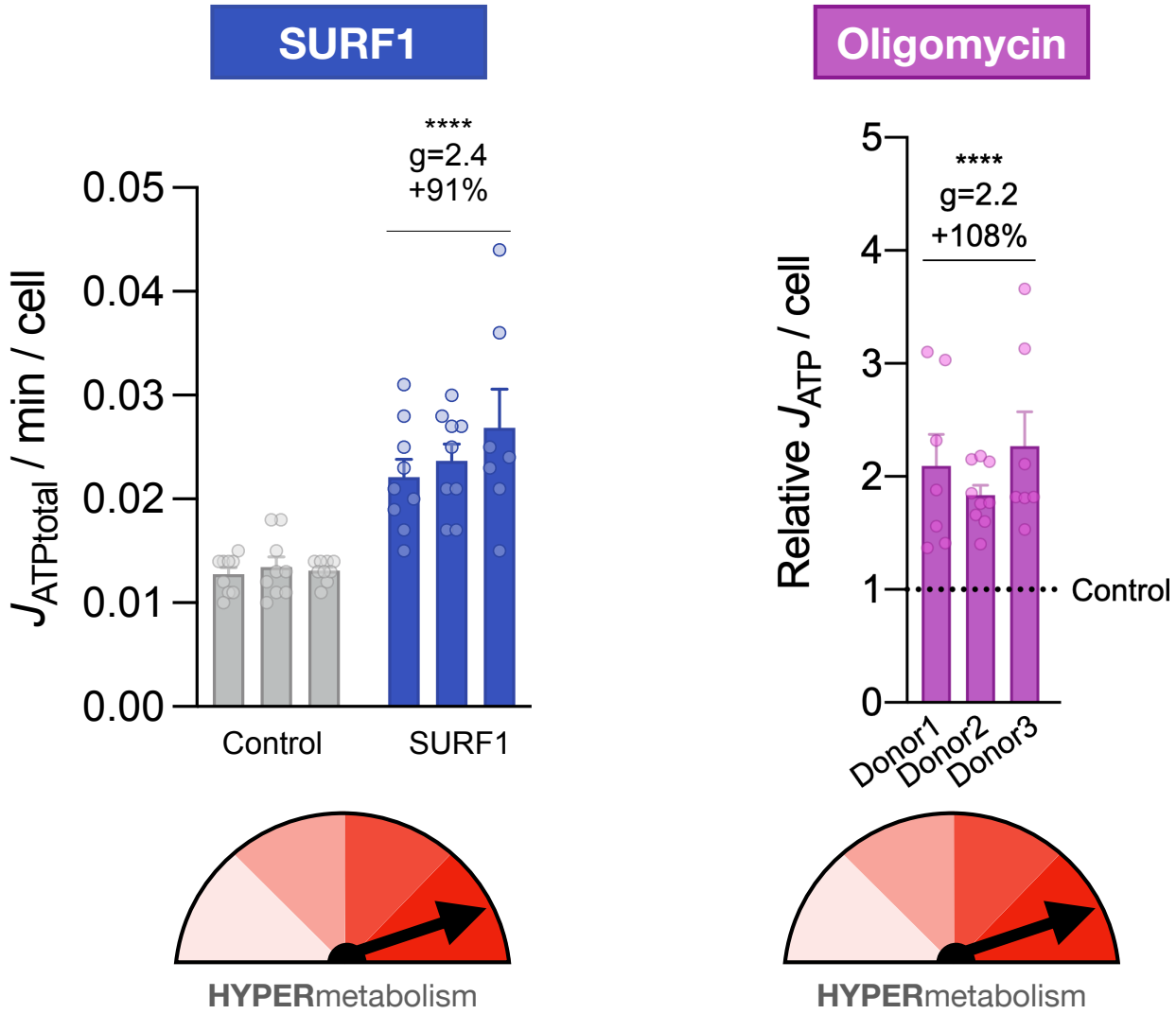




Method from Mookerjee et al. *JBC* 2017

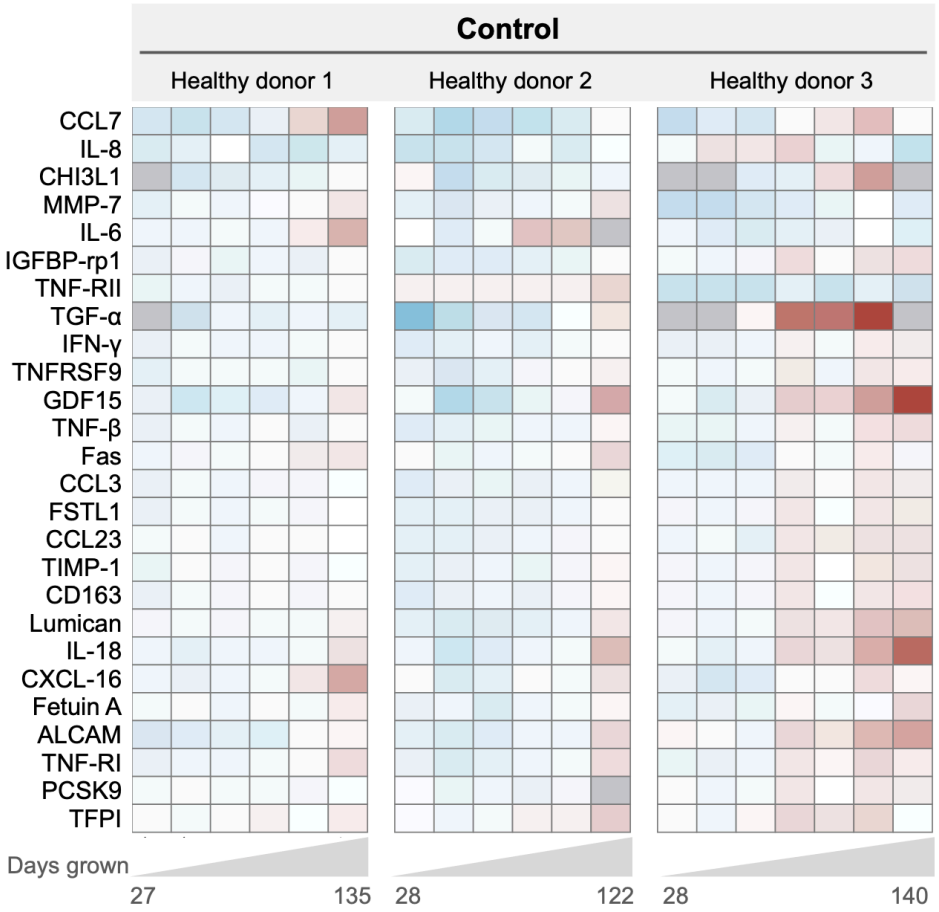
Sturm et al. *Commun Biol (2023)*

OxPhos-deficient cells are hypermetabolic

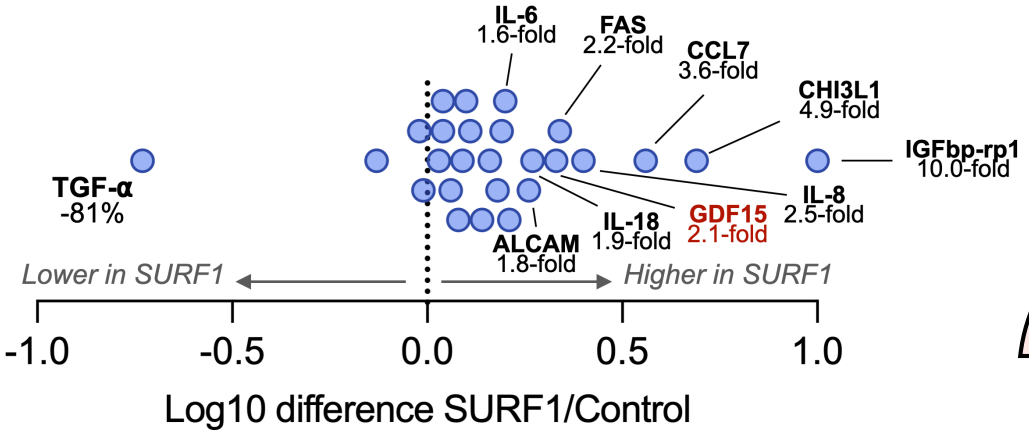


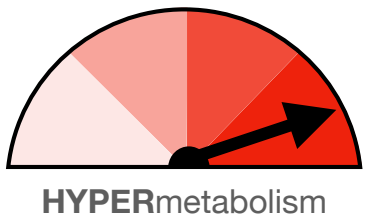
Sturm et al. *Commun Biol (2023)*

OxPhos defects increase cytokine release

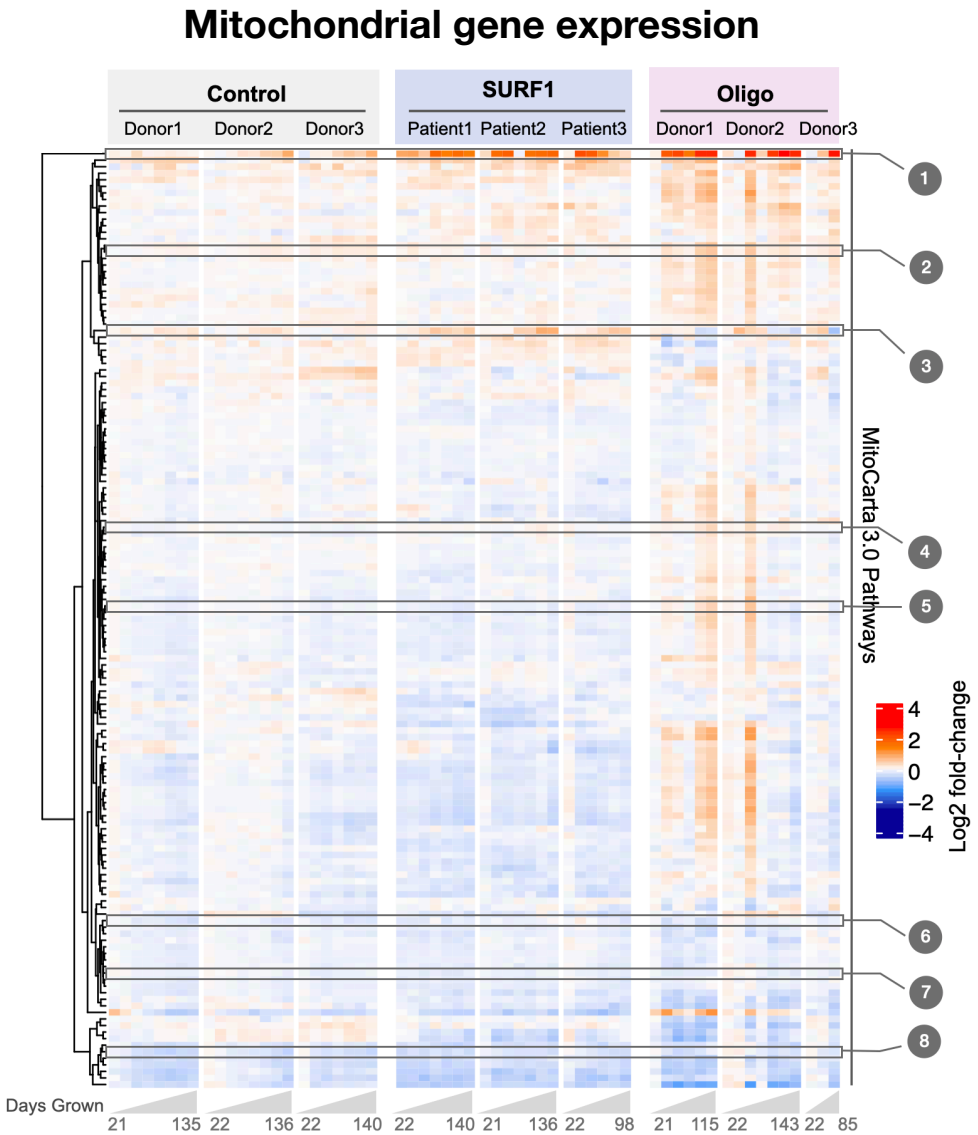


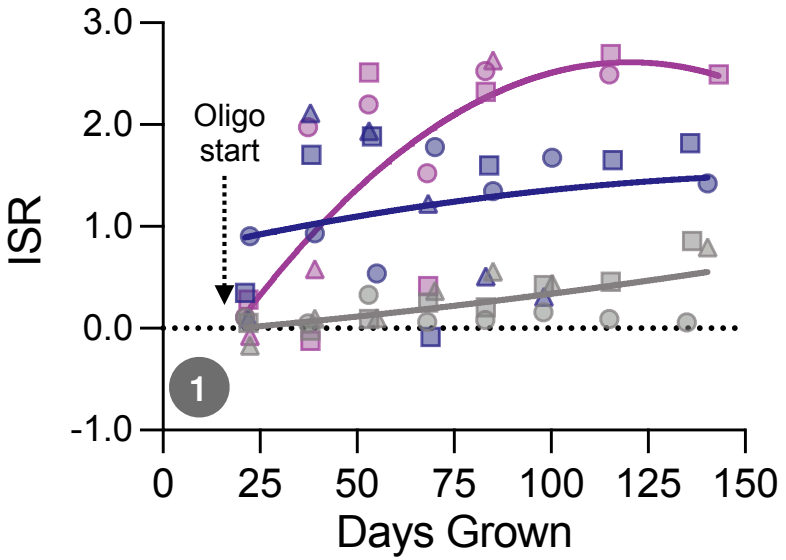
Maximum cytokine levels across the lifespan

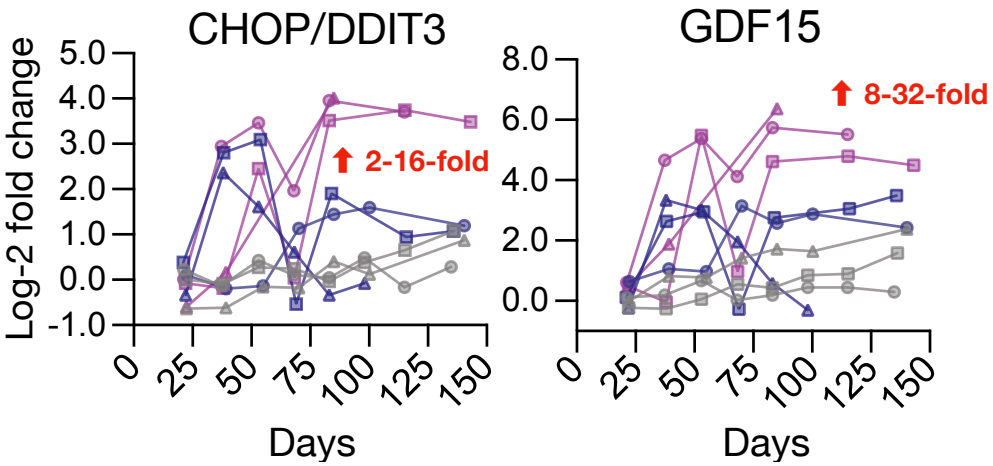




OxPhos defects cause a time-dependent activation of the integrated stress response (ISR)

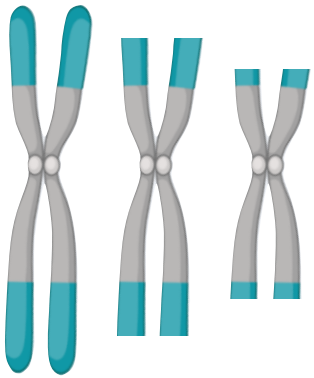


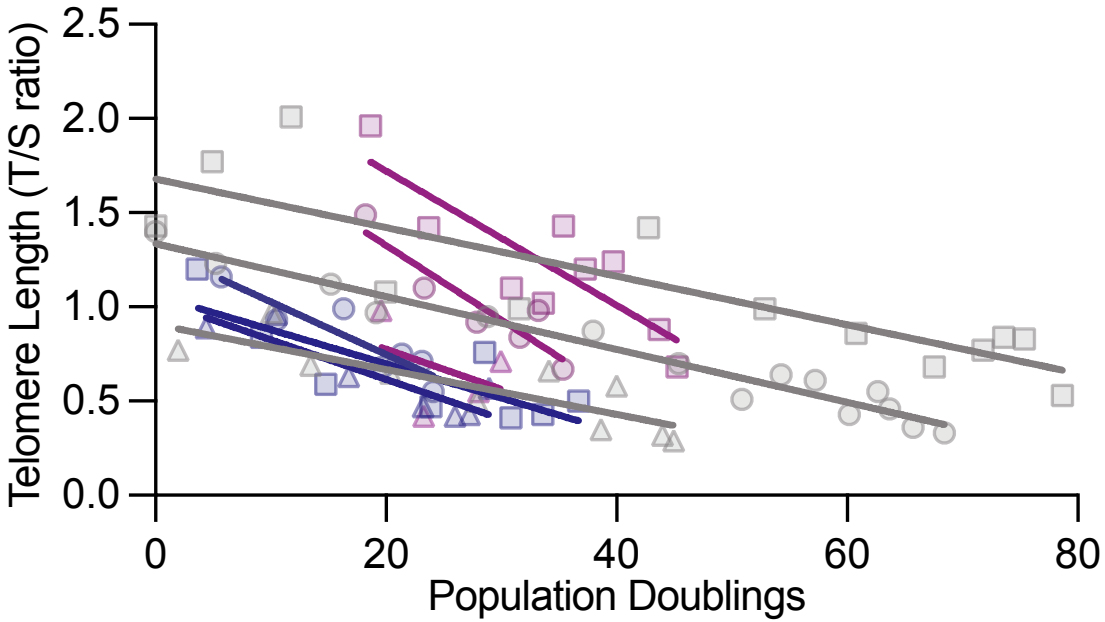


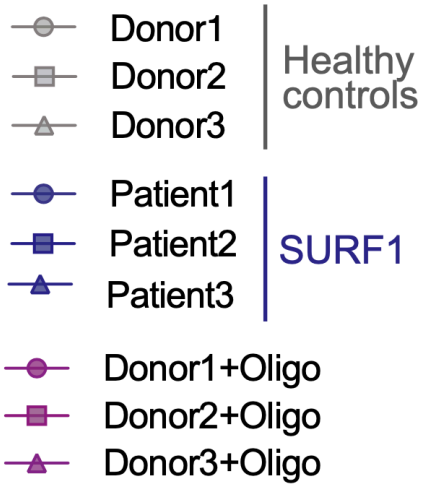


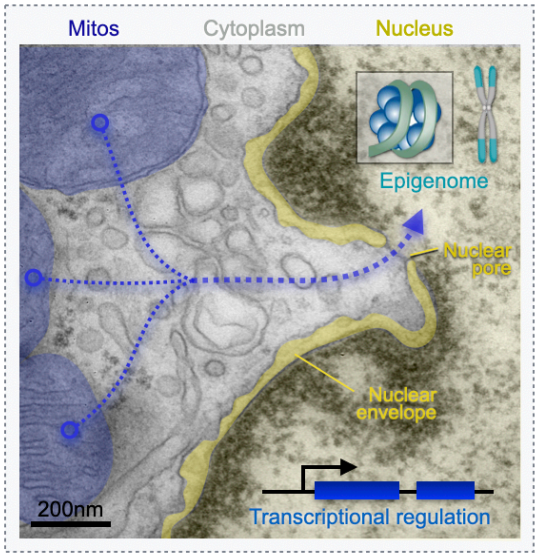
Sturm et al. *Commun Biol (2023)*

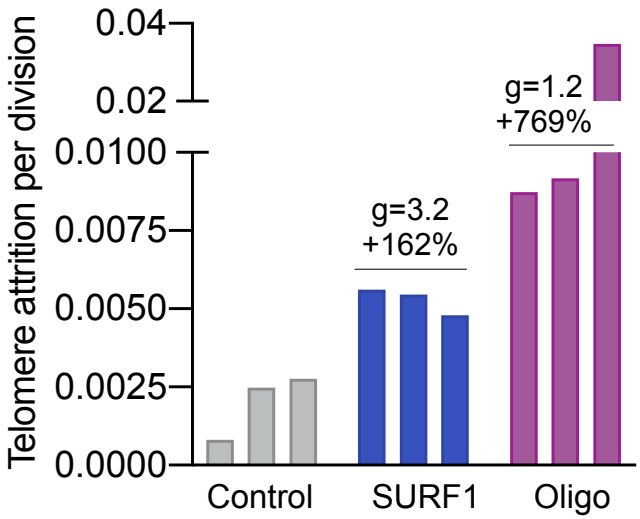
OxPhos defects accelerate telomere shortening rate

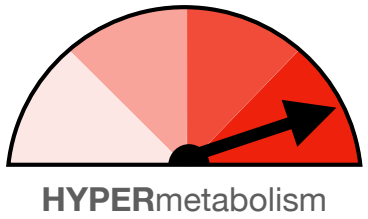






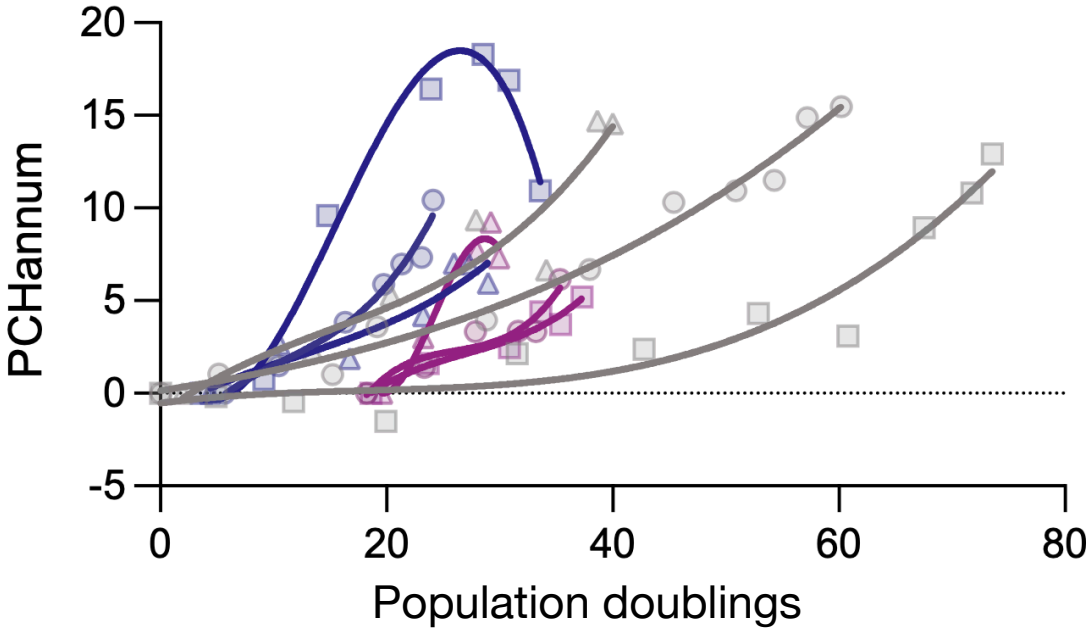


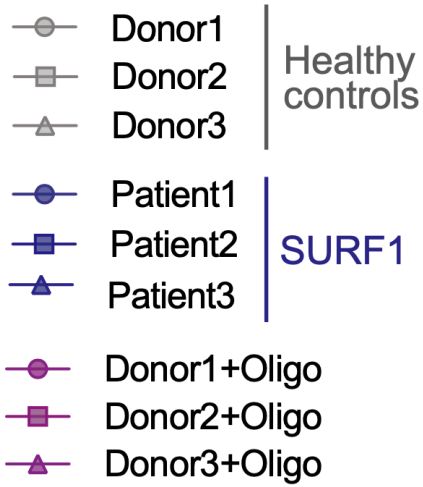


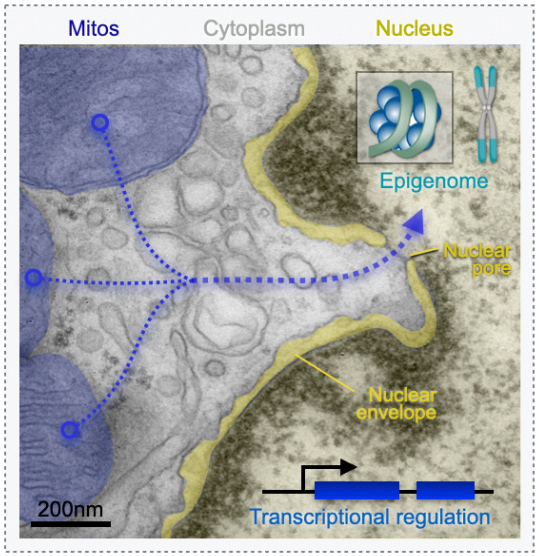


Jue Lin, Elissa Epel
Gabriel Sturm

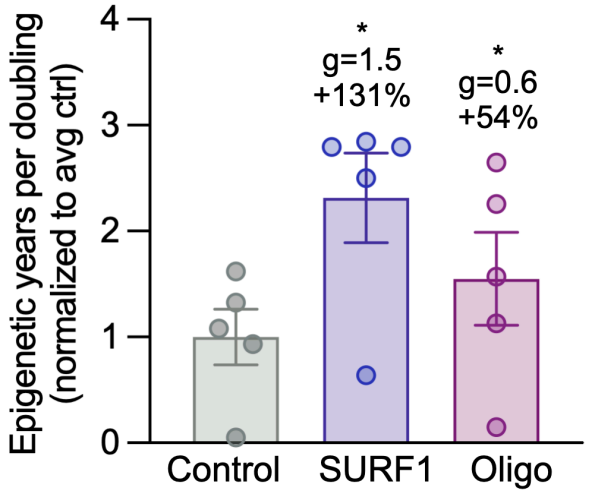
OxPhos defects accelerate epigenetic aging DNA methylation clocks





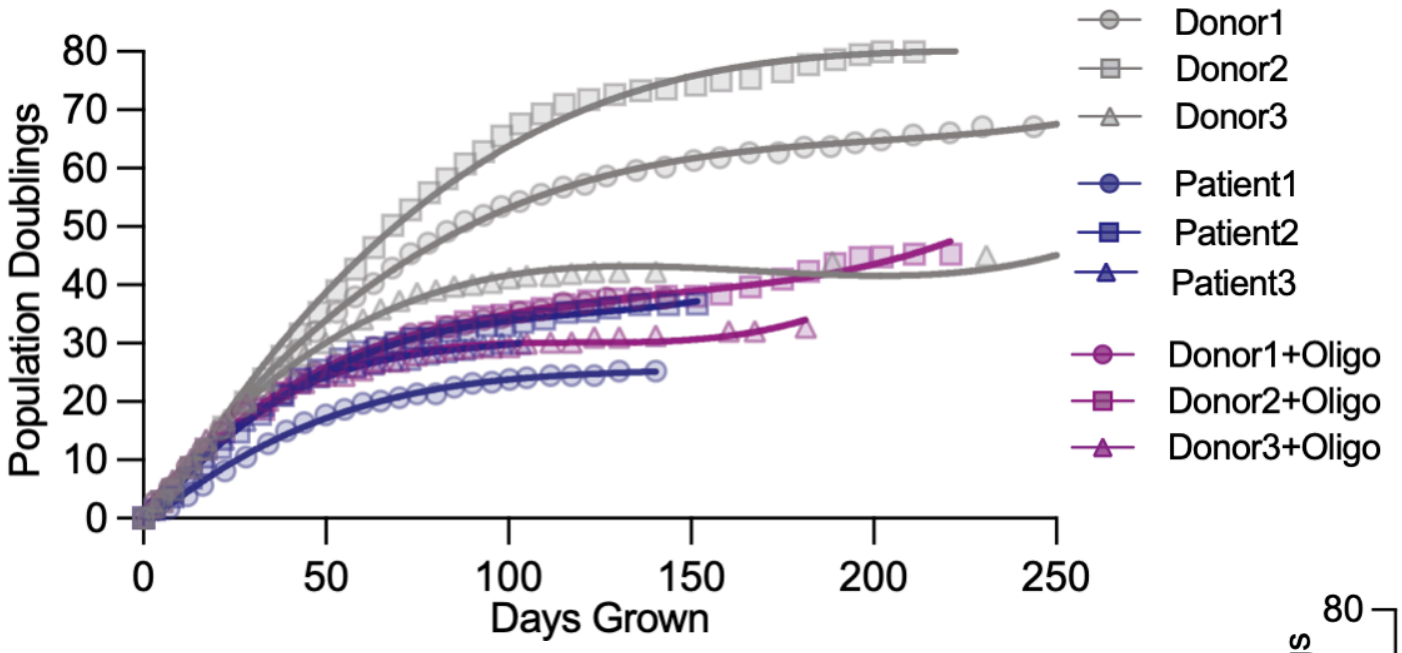


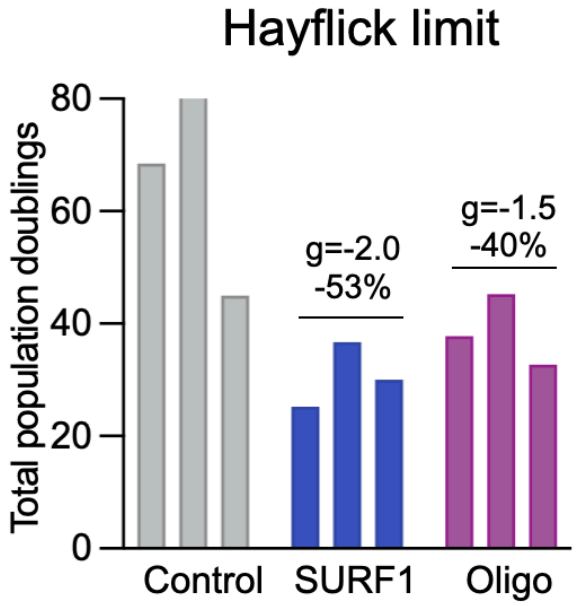
Average rate of epigenetic aging



Steve Horvath, Morgan Levine.
Albert Higgins-Chen
Gabriel Sturm

Hypermetabolic cells have a reduced Hayflick limit





Gabriel Sturm

scientific **data**

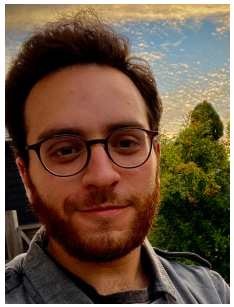
OPEN

DATA DESCRIPTOR

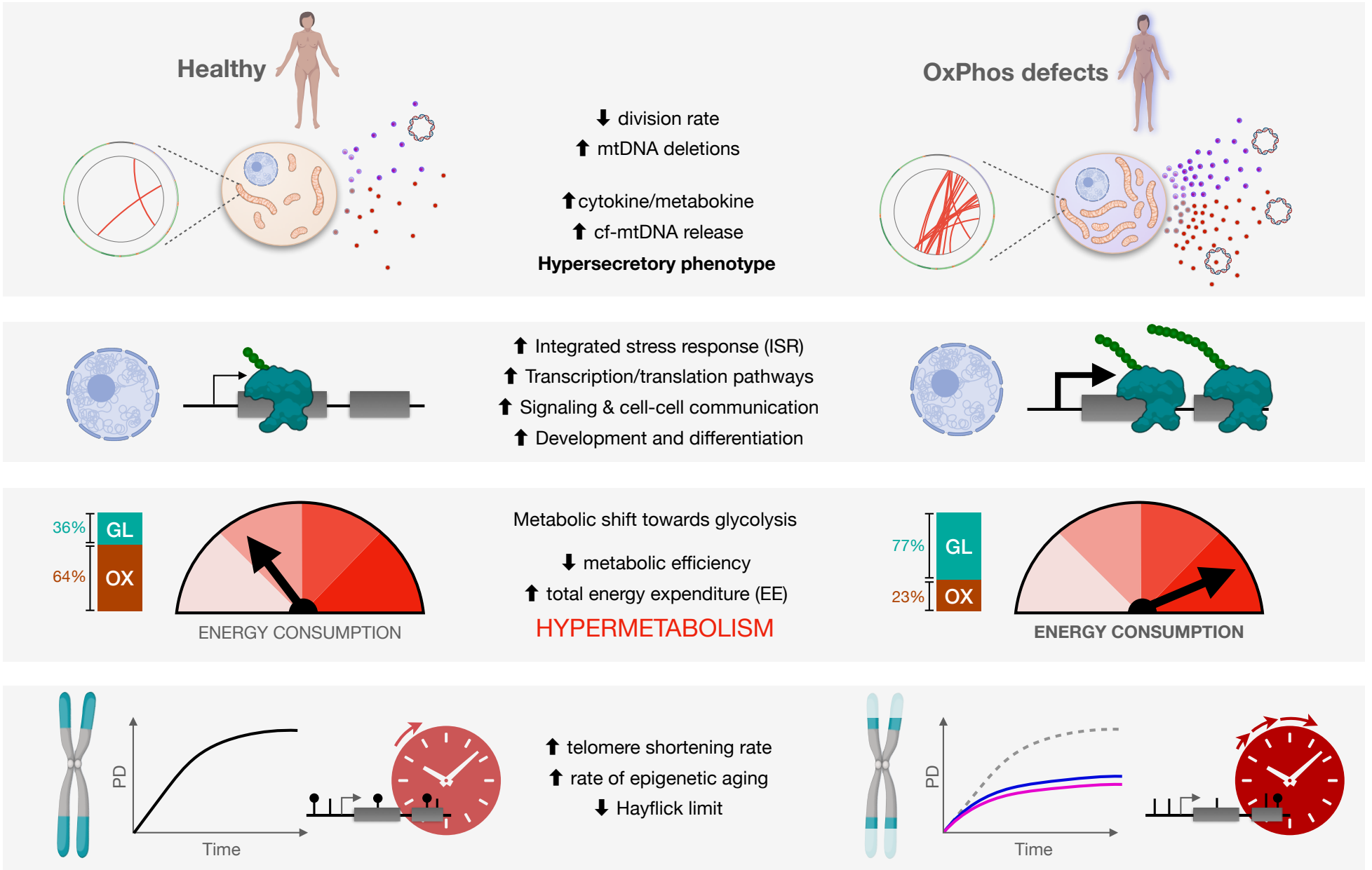
A multi-omics longitudinal aging dataset in primary human fibroblasts with mitochondrial perturbations

Gabriel Sturm[1,2], Anna S. Monzel[1], Kalpita R. Karan[1], Jeremy Michelson[1], Sarah A. Ware[3], Andres Cardenas[4], Jue Lin[2], Céline Bris[5,6], Balaji Santhanam[7], Michael P. Murphy[8], Morgan E. Levine[9,10], Steve Horvath[10,11], Daniel W. Belsky[12], Shuang Wang[13], Vincent Procaccio[5,6], Brett A. Kaufman[3], Michio Hirano[14] & Martin Picard[1,14,15] ✉

Aging is a process of progressive change. To develop biological models of aging, longitudinal datasets with high temporal resolution are needed. Here we report a multi-omics longitudinal dataset for cultured primary human fibroblasts measured across their replicative lifespans. Fibroblasts were sourced from both healthy donors (n = 6) and individuals with lifespan-shortening mitochondrial disease (n = 3). The dataset includes cytological, bioenergetic, DNA methylation, gene expression, secreted proteins, mitochondrial DNA copy number and mutations, cell-free DNA, telomere length, and whole-genome sequencing data. This dataset enables the bridging of mechanistic processes of aging as outlined by the "hallmarks of aging", with the descriptive characterization of aging such as epigenetic age clocks. Here we focus on bridging the gap for the hallmark mitochondrial metabolism. Our dataset includes measurement of healthy cells, and cells subjected to over a dozen experimental manipulations targeting oxidative phosphorylation (OxPhos), glycolysis, and glucocorticoid signaling, among others. These experiments provide opportunities to test how cellular energetics affect the biology of cellular aging. All data are publicly available at our webtool: https://columbia-picard.shinyapps.io/shinyapp-Lifespan_Study/

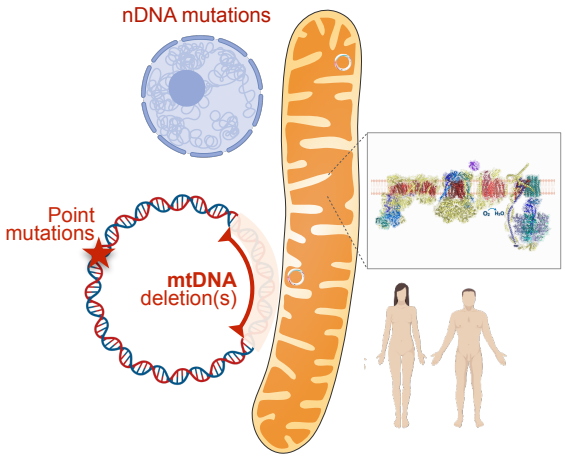


Gabriel Sturm



Sturm et al. *Commun Biol (2023)*

In vivo — OxPhos defects trigger hypermetabolism and shorten lifespan in humans



System-level & physiological

- Cori cycle
- Increased heart rate
- Increased ventilation
- Stress and anxiety
- Hyperkinetic cardioresp. system
- Drug metabolism
- Others

Tissue-level, circulating

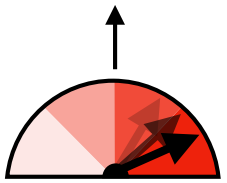
- Circulating metabokines
- Inter-cellular signaling
- Metabolic shift towards anabolism
- Catecholamines
- Circulating metabolites
- Immune alterations
- Angiogenesis

Cell-autonomous

- Mito biogenesis
- Integrated Stress Response (ISR)
- Secretion
- Maintenance
- DNA instability
- Others

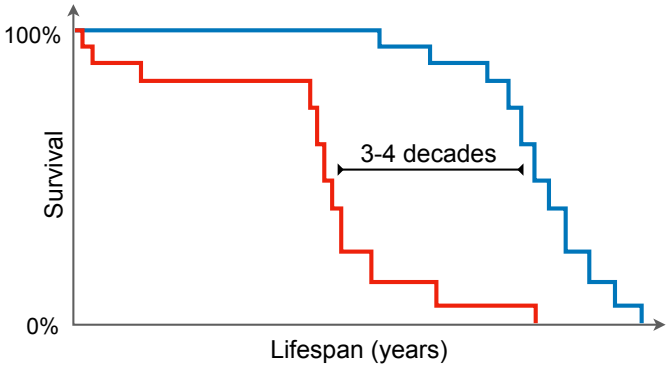
Pathogenesis

- Chronic fatigue
- Low BMI
- Alcohol intolerance
- Blunted cytokine production to LPS
- Susceptibility to infections
- Elevated lactate
- Excess sleep
- Short stature

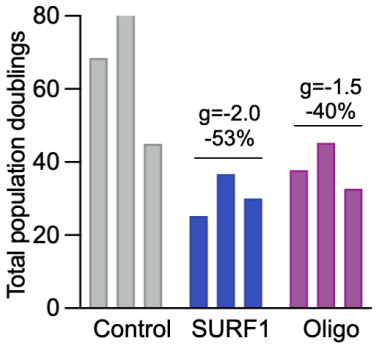


HYPERMETABOLISM

Premature death



Hayflick limit



Sercel et al. (BioRxiv)

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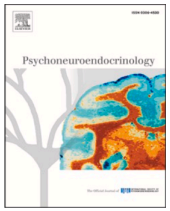
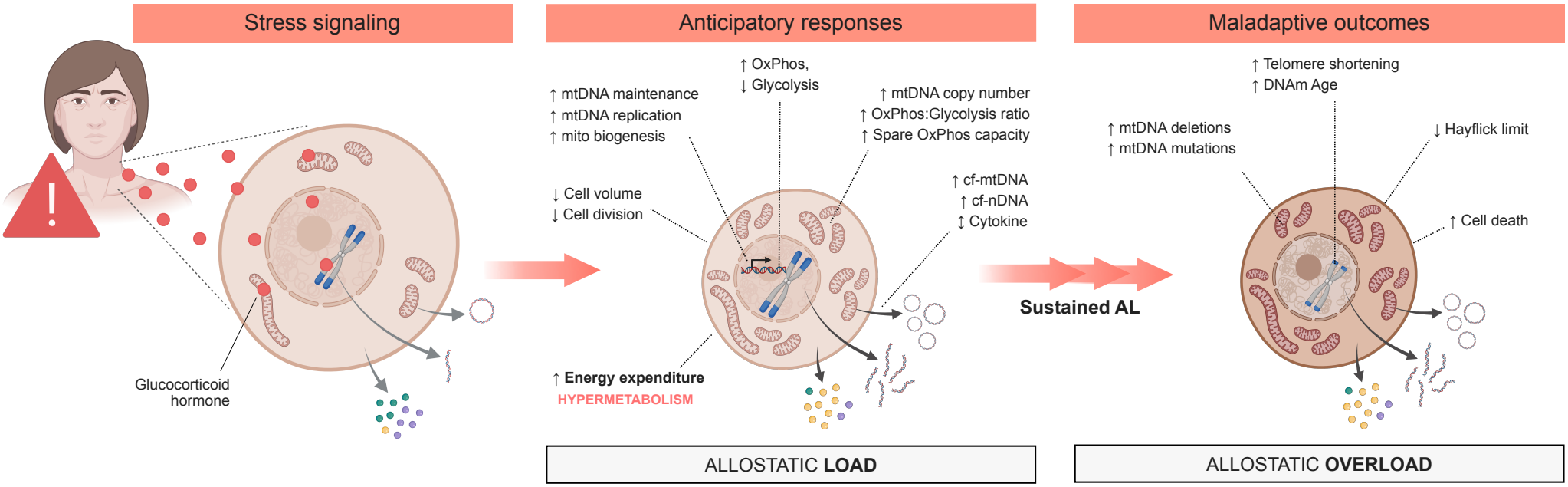
journal homepage: www.elsevier.com/locate/psyneuen



Natalia Bobba-Alves

Cellular allostatic load is linked to increased energy expenditure and accelerated biological aging



Glucocorticoid signaling increases energy expenditure by **60%**

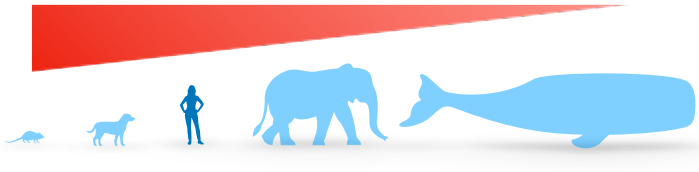
And accelerates cellular aging by **10-40%**

Bobba-Alves et al. *PNEC* 2023

Rate of living hypothesis?

2nd law of thermodynamics

HYPERMETABOLISM

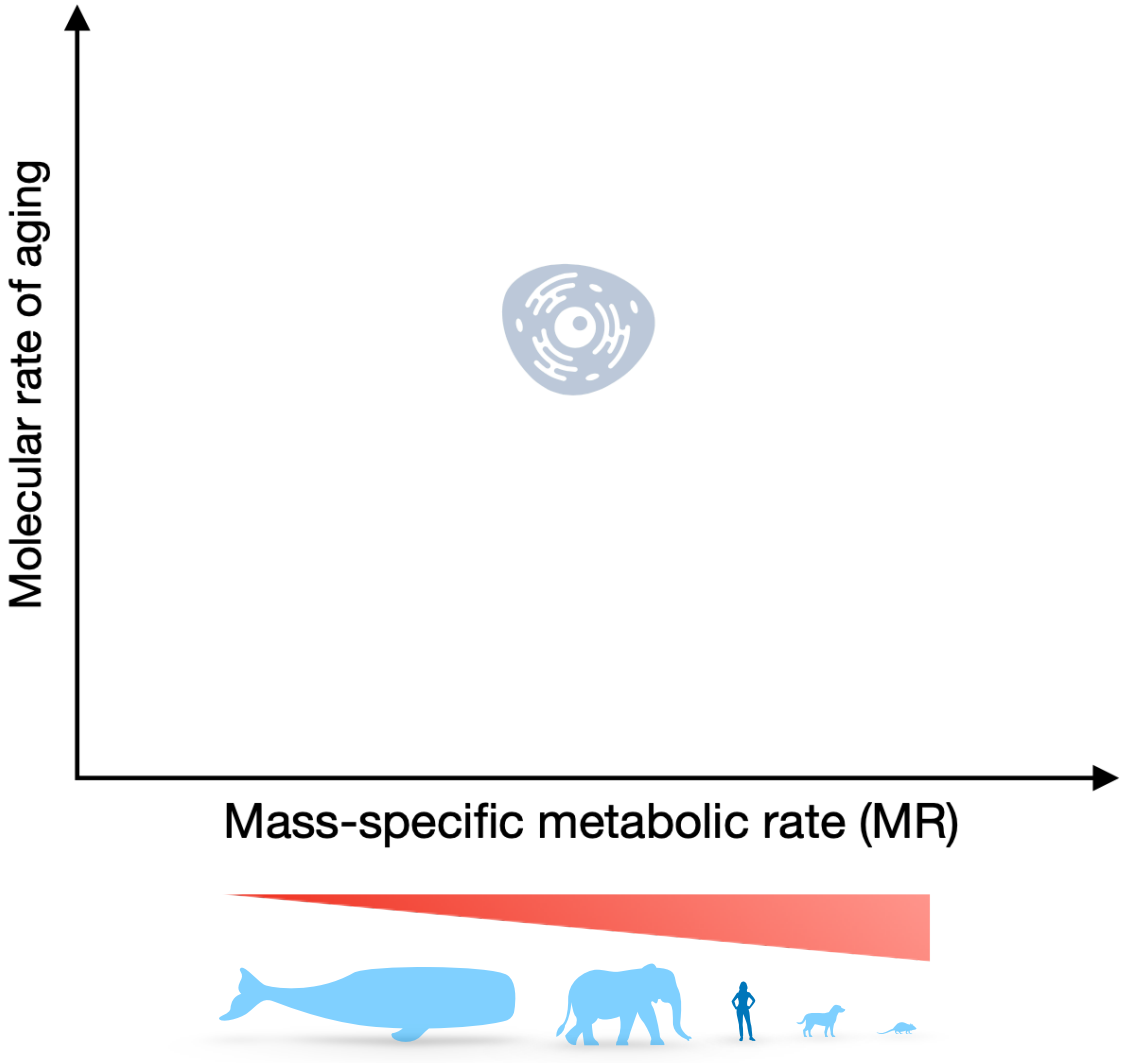


Seconds

Years / Decades

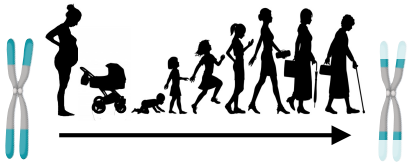
Centuries

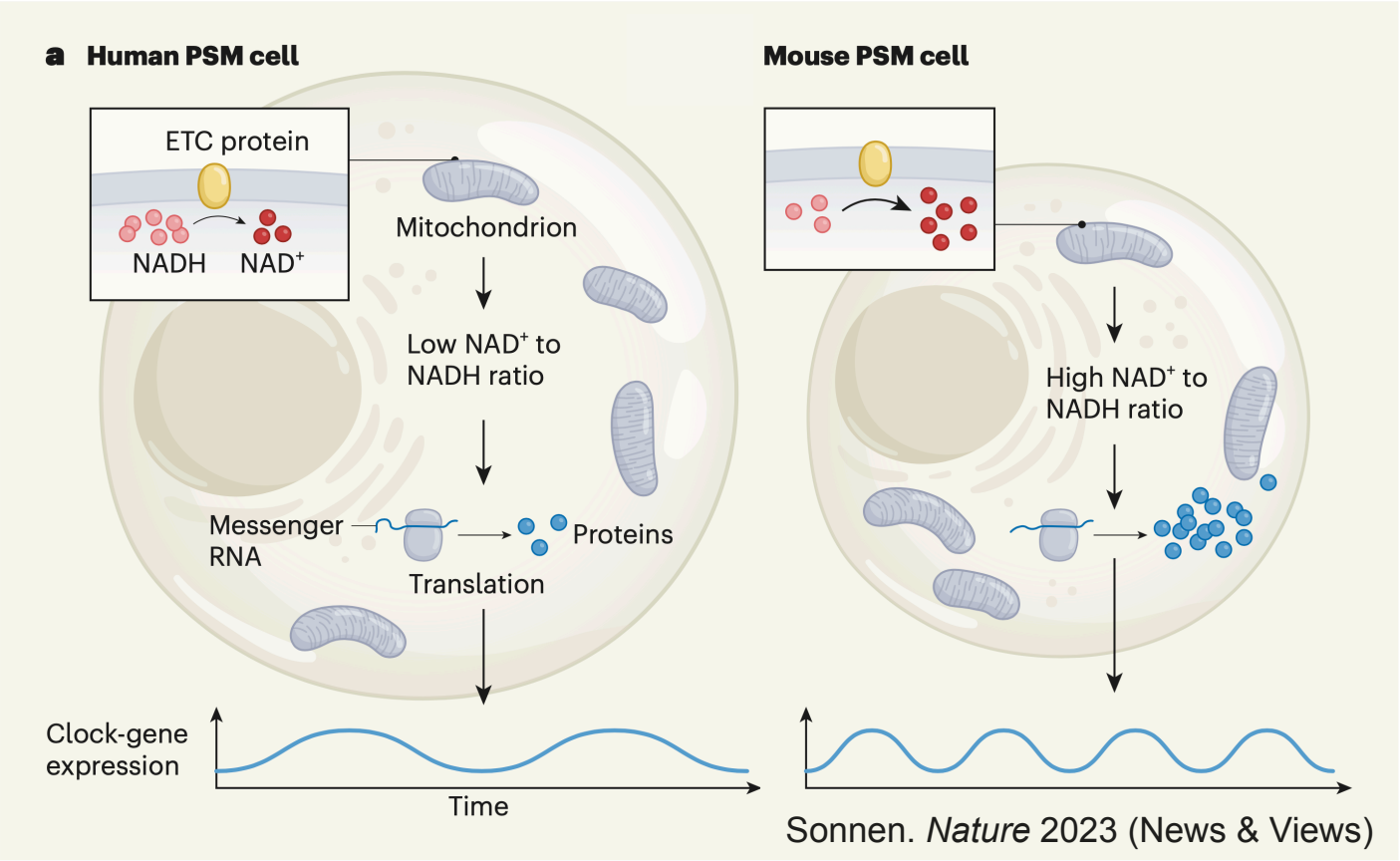
Scaling of metabolic rate (MR) & rate of aging



Sturm, Kempes et al. (BioRxiv)

What sets the pace of aging ?

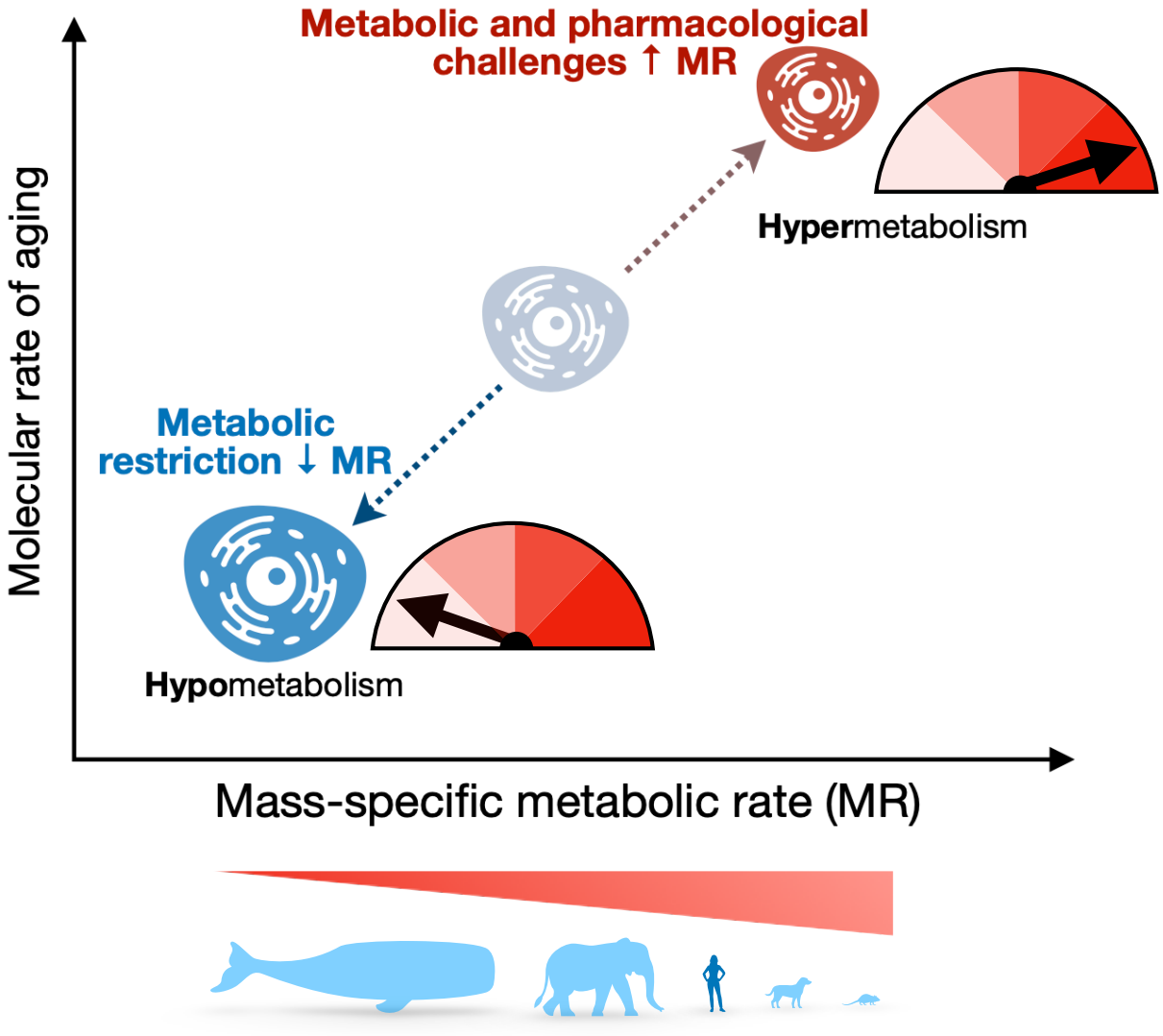




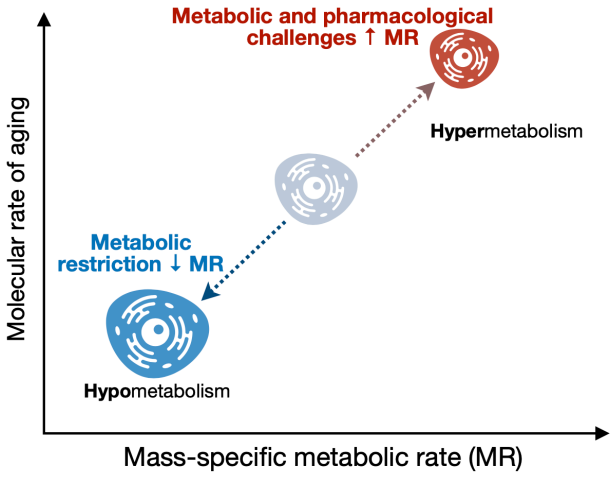
The **rate** of development can be altered by manipulating **mitochondrial energy metabolism**

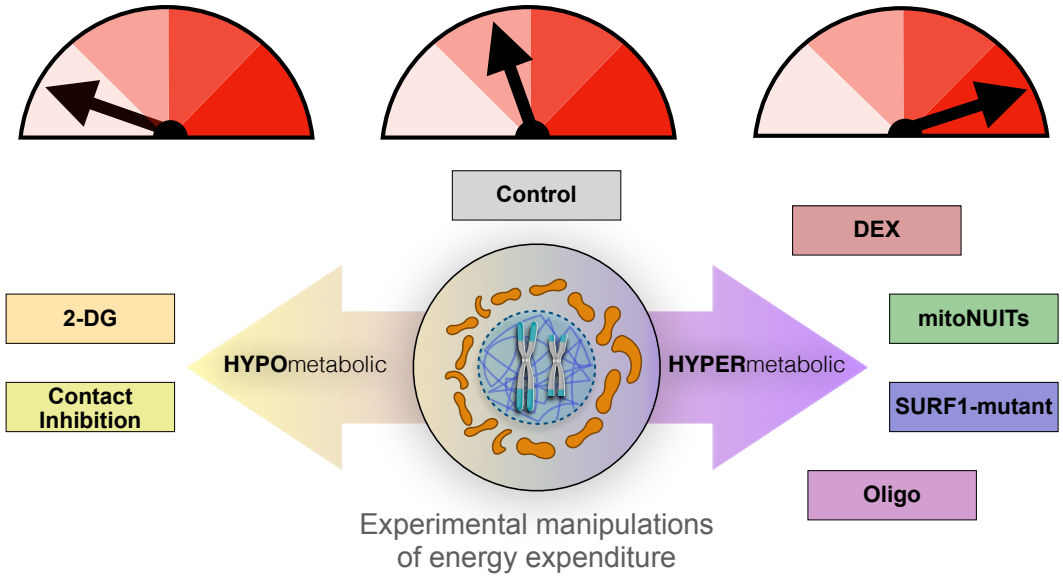
(Presomitic mesoderm) Diaz-Cuadros et al. *Nature* 2023
(Neuronal development) Iwata et al. *Science* 2023

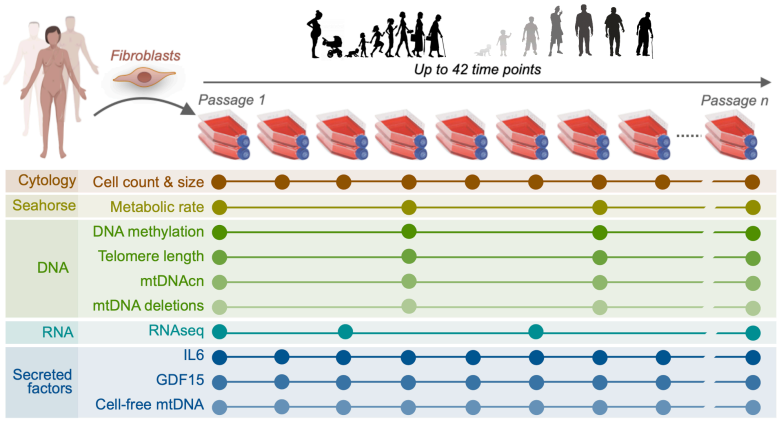
Scaling of metabolic rate (MR) & rate of aging

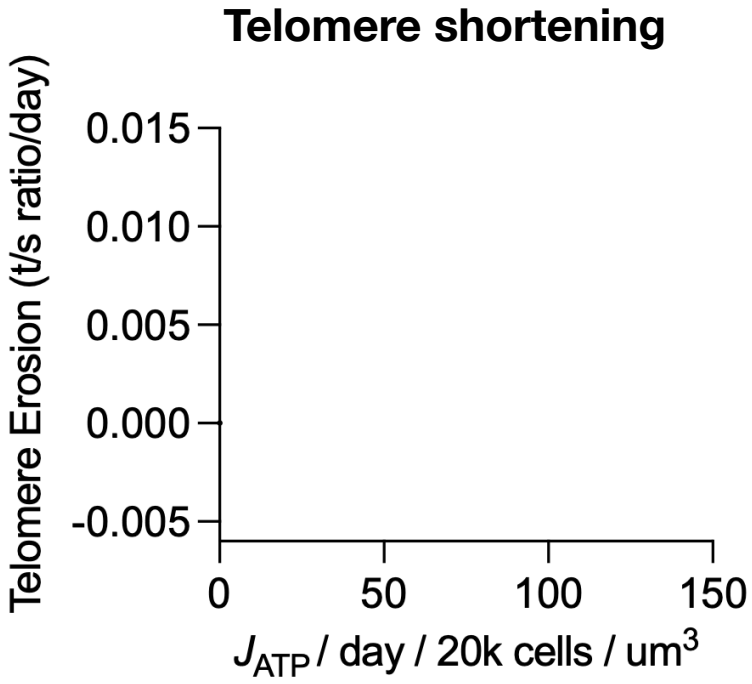


Sturm, Kempes et al. (BioRxiv)

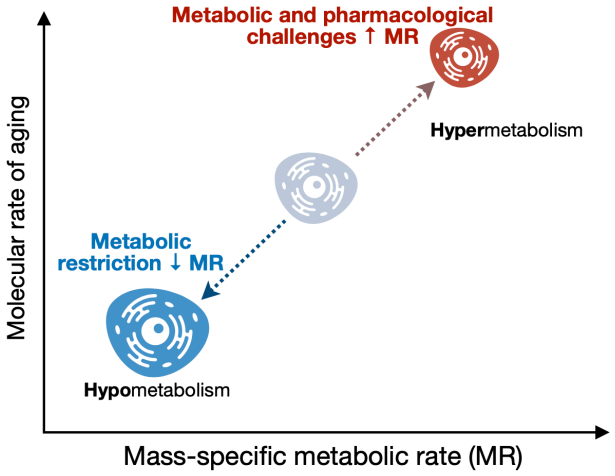


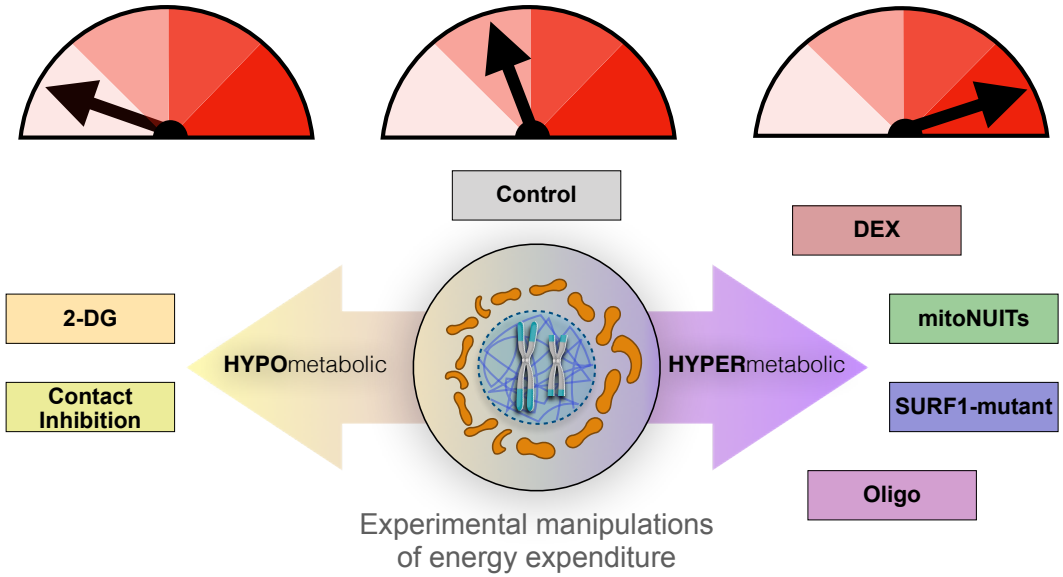


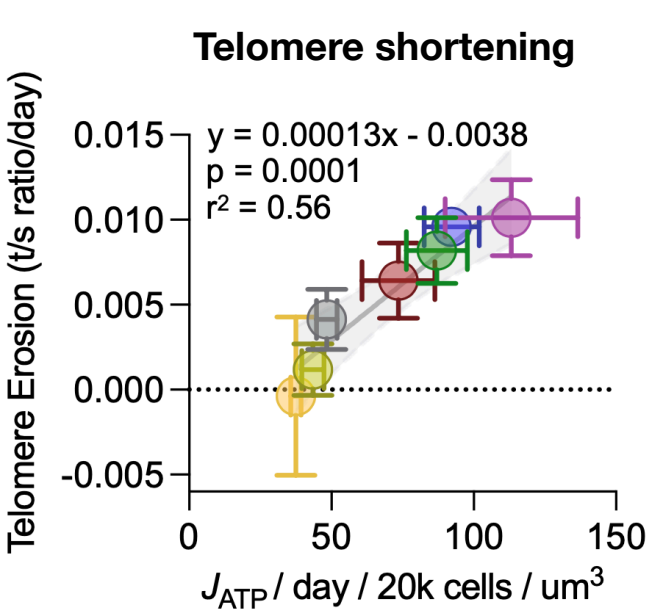


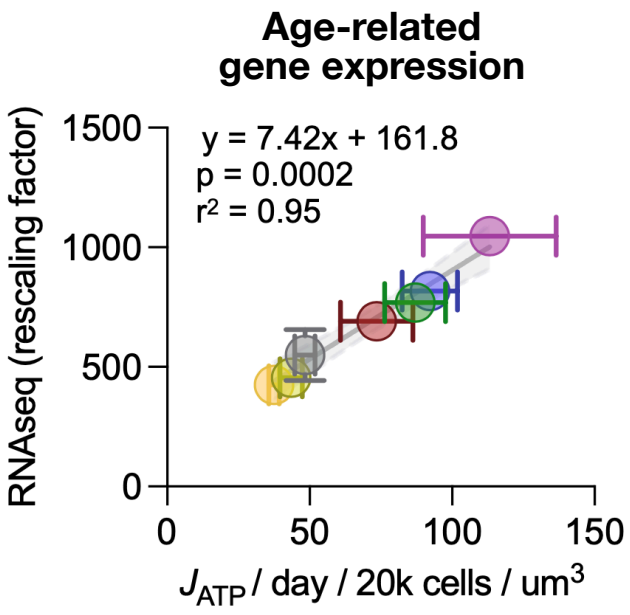


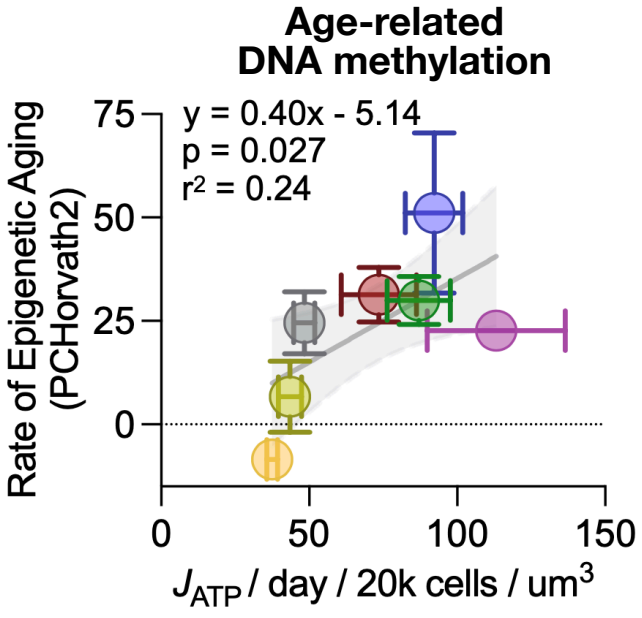
Sturm, Kempes et al. (BioRxiv)









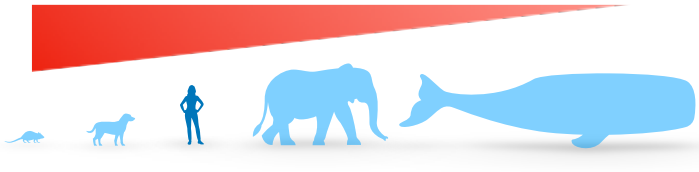


Sturm, Kempes et al. (BioRxiv)

Rate of living hypothesis?

2nd law of thermodynamics

HYPERMETABOLISM

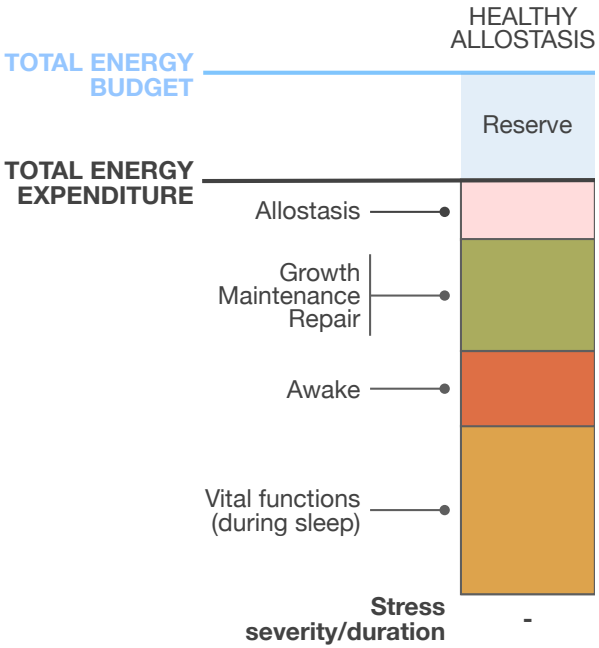


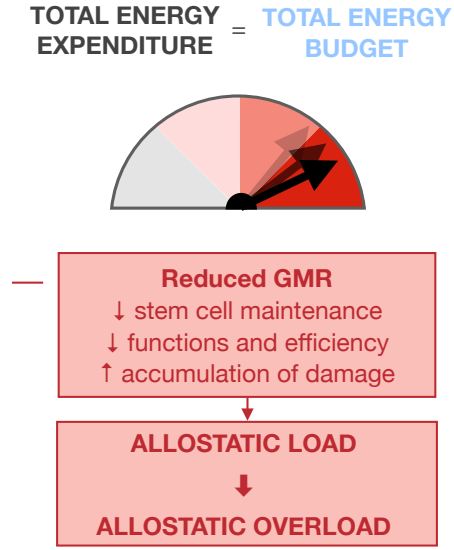
Seconds

Years / Decades

Centuries

Human aging and lifespan determined by partitioning of limited energetic resources ?





Bobba-Alves et al. The energetic cost of allostasis and allostatic load. *Psychoneuroendocrinol* 2022

PART 1

Mitochondrial Signal Transduction, Hair greying

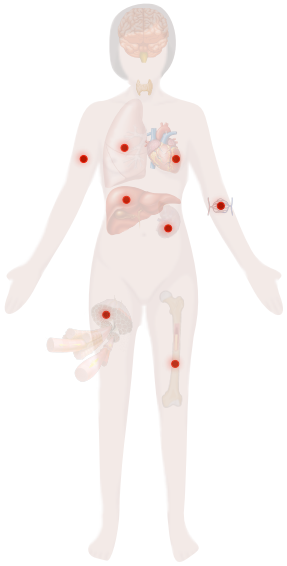
PART 2

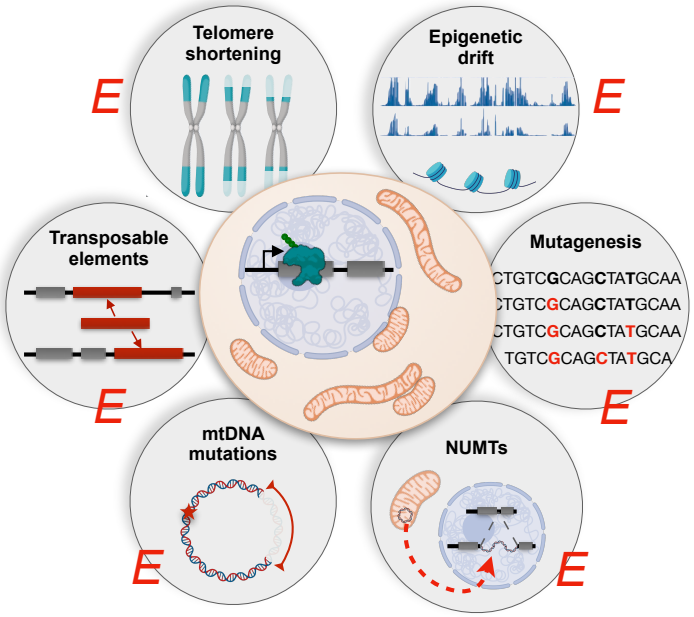
Energy, OxPhos defects, Hypermetabolism, Rate of aging

PART 3

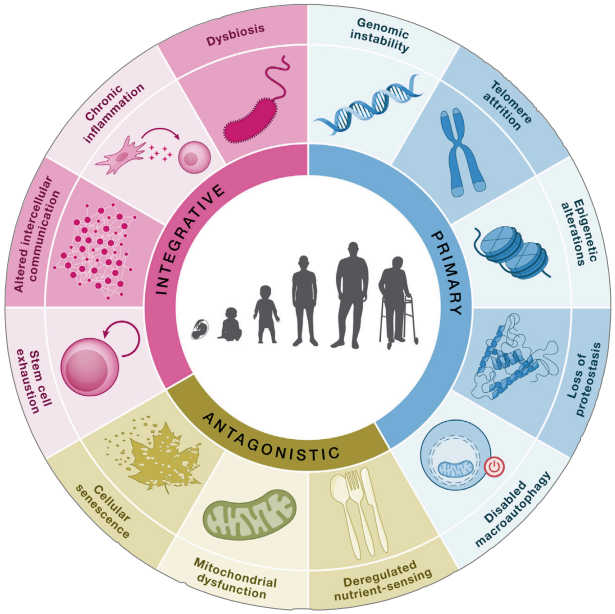
Somato-cognitive **E**nergy **C**onservation — **SEC**

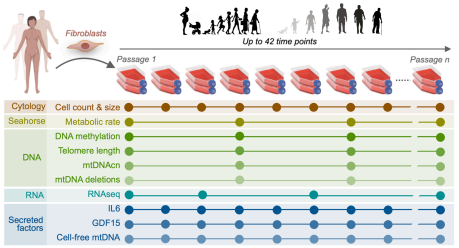
The imperfection of life as (costly) driver of cellular aging



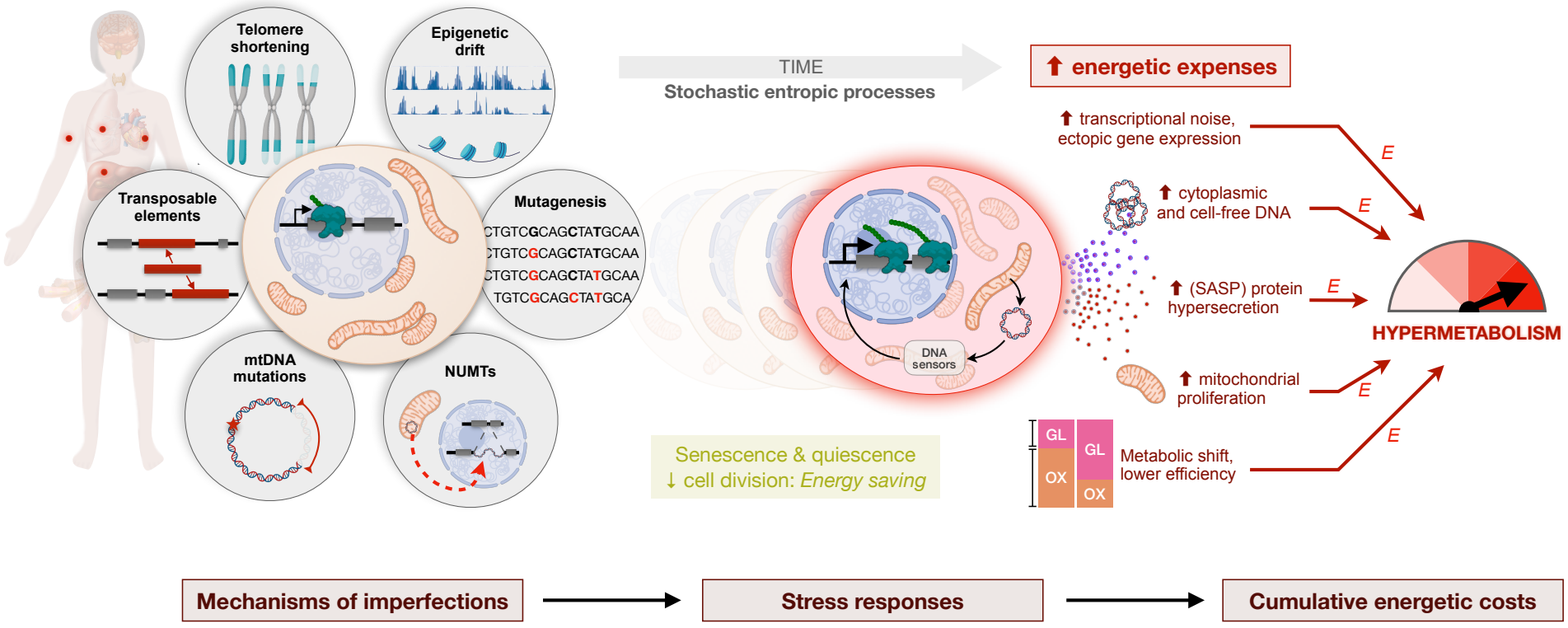


Mechanisms of imperfections





Lopez-Otin et al. *Cell* 2023



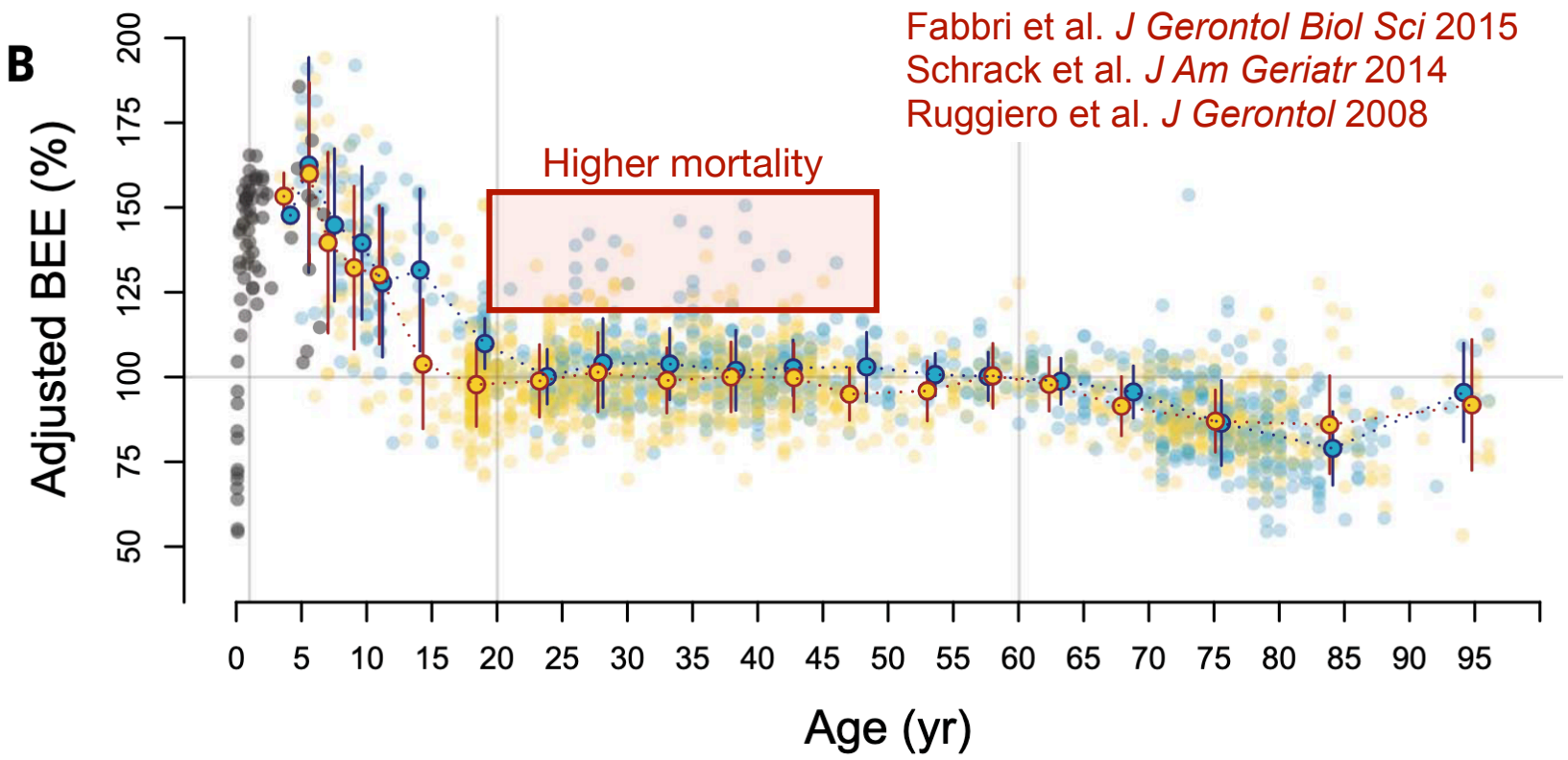
Aging (senescent) cells become **hypermetabolic**

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**

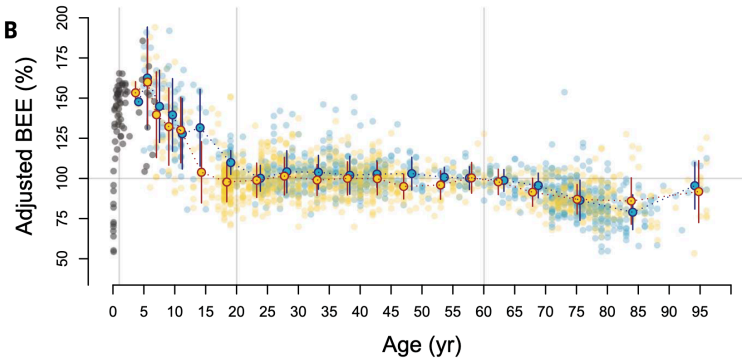


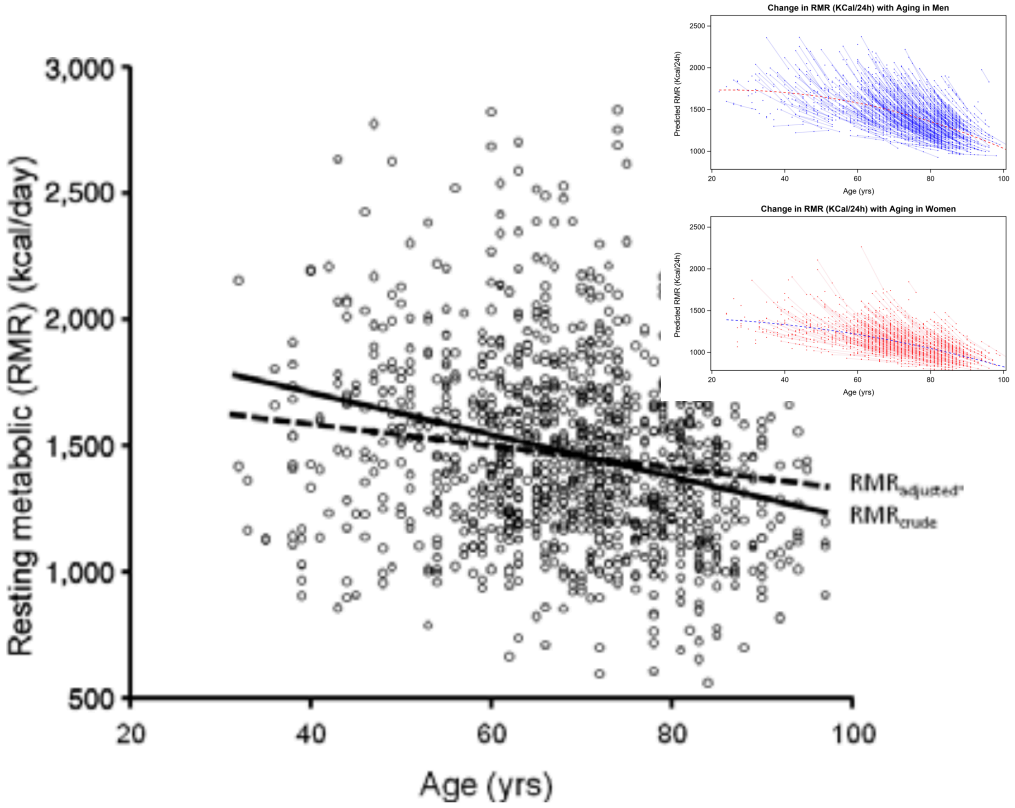
Pontzer et al. *Science* 2021

Aging (senescent) cells become **hypermetabolic**

But the whole body does not

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

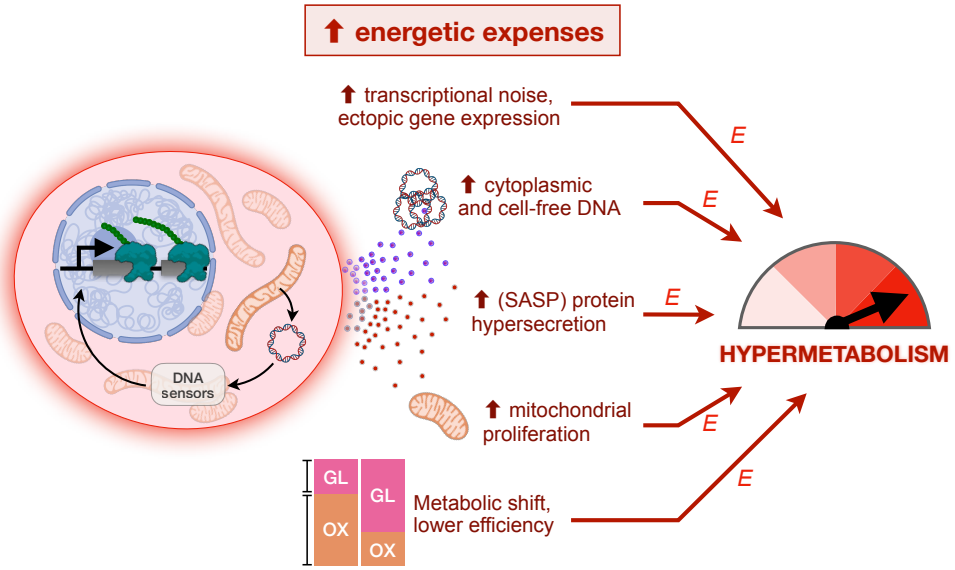




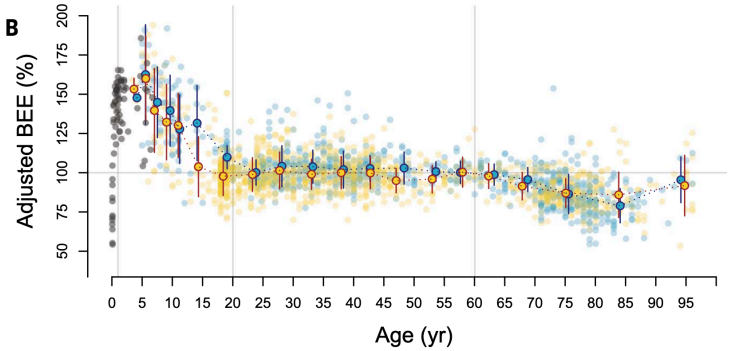
Ferrucci et al. *JAGS* 2012

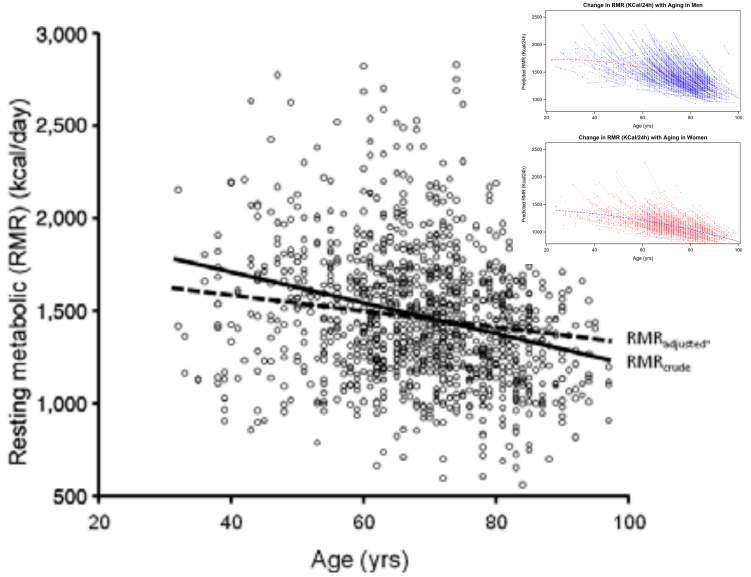
Energetic paradox ?

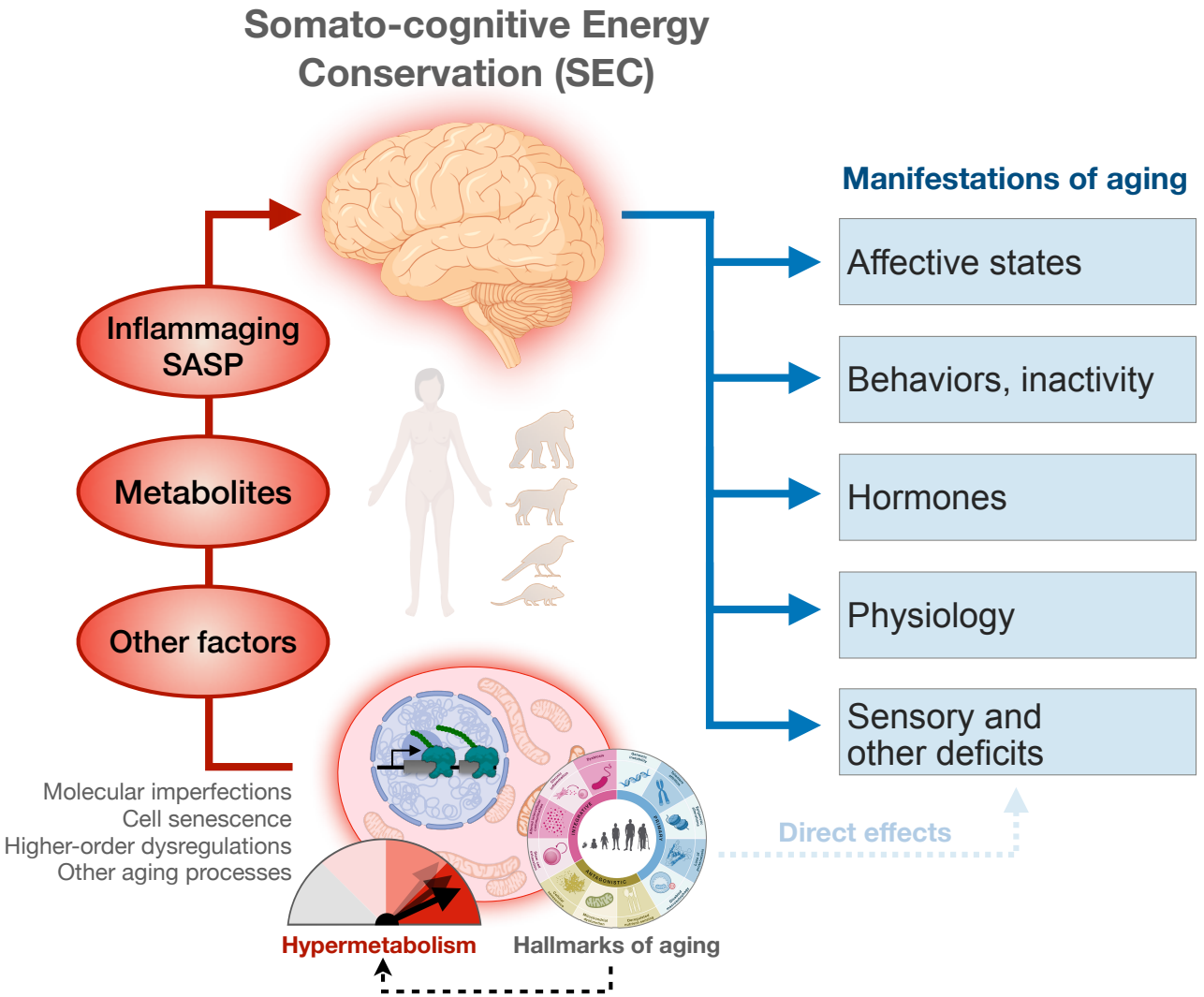
CELLULAR HYPERMETABOLISM



WHOLE-BODY HYPOMETABOLISM

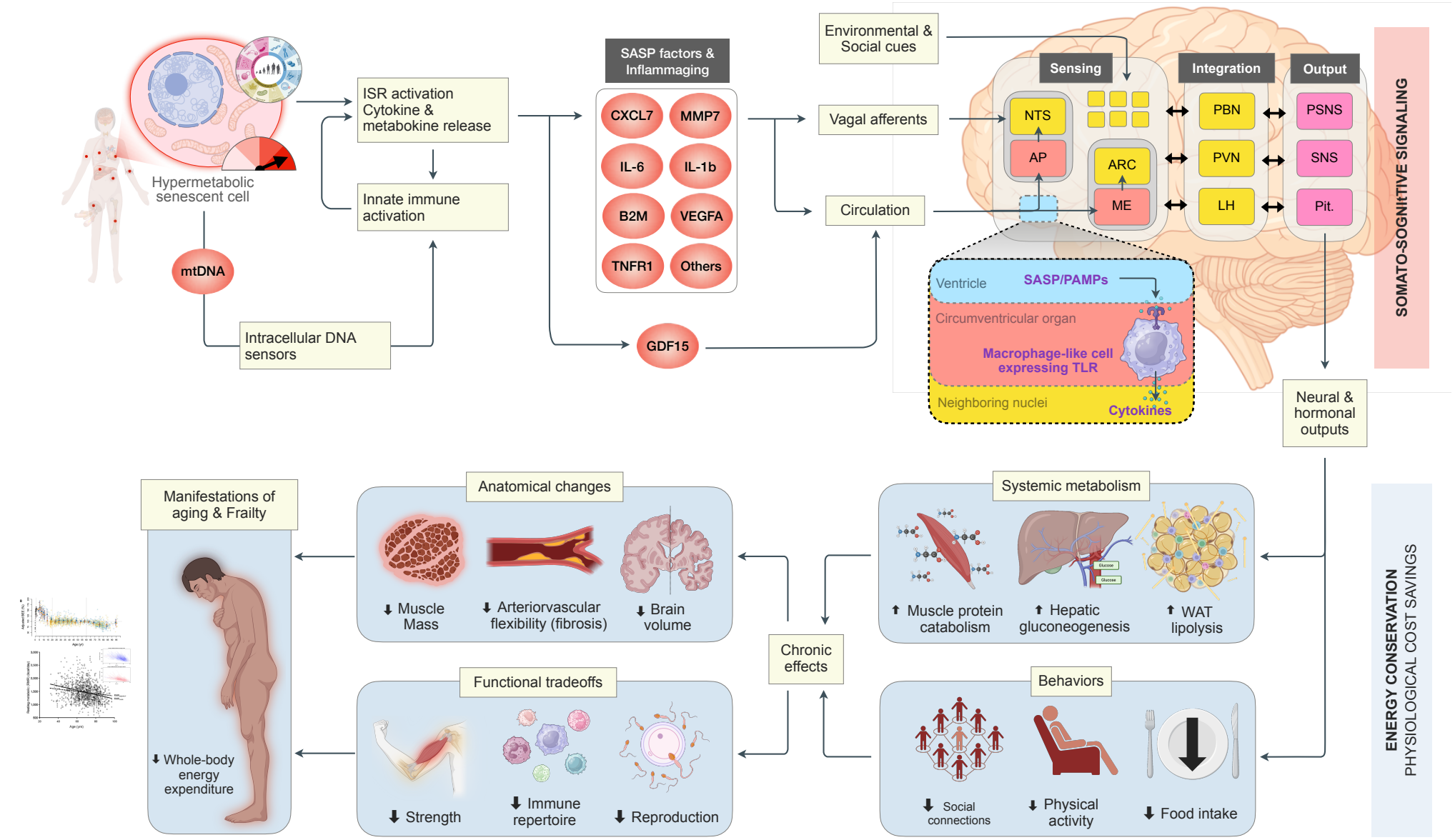






Shaulson, Cohen, Picard. *Preprint* (osf.io/zuey2)

Somato-cognitive energy conservation (SEC)



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

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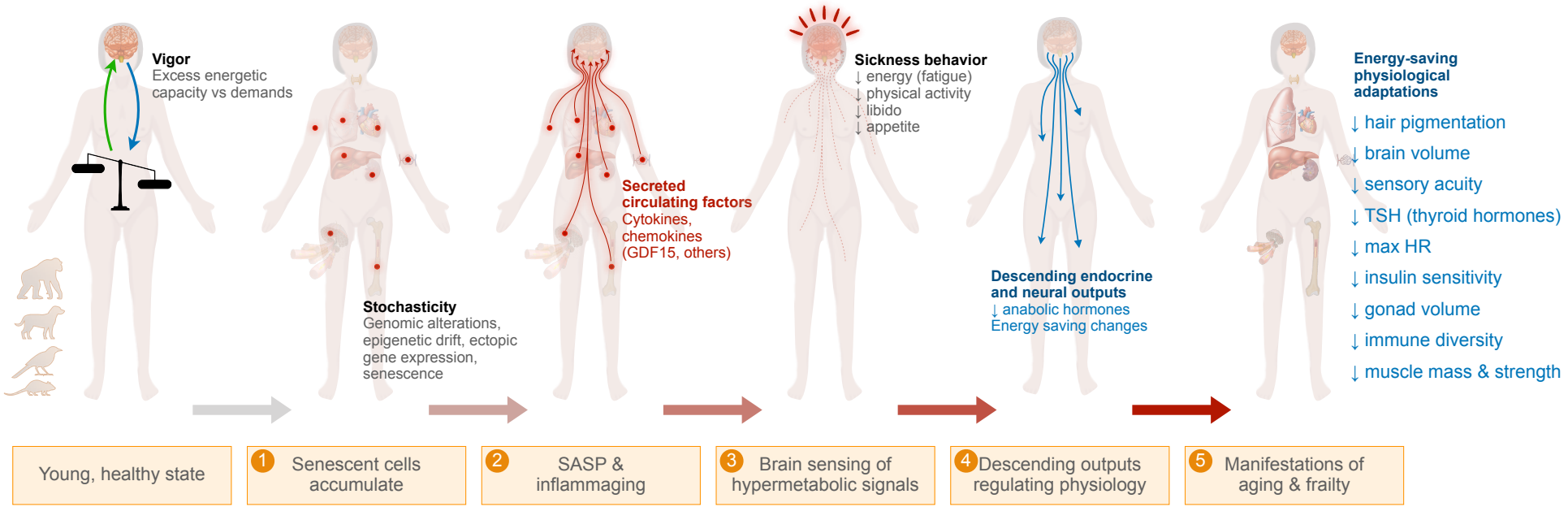
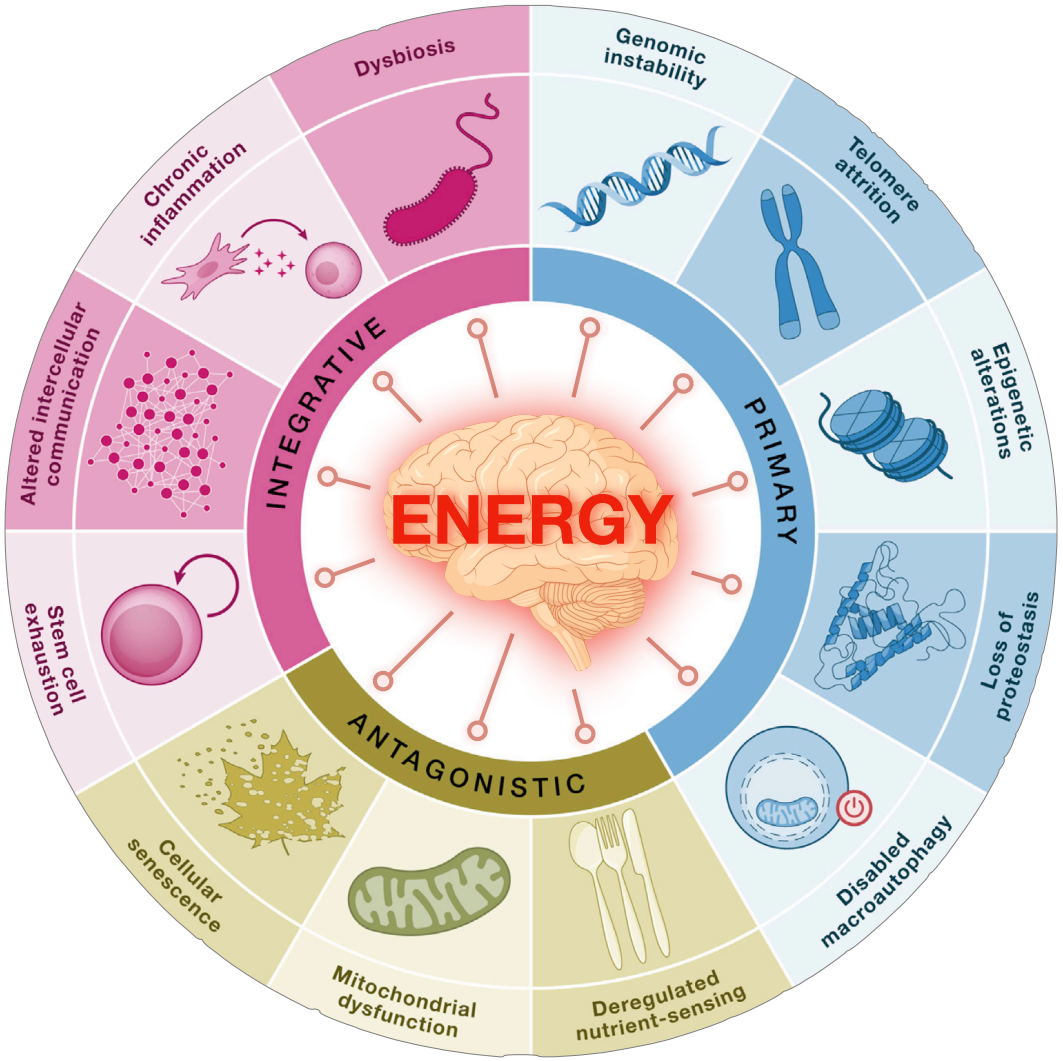


Shaulson, Cohen, Picard. *Preprint* (osf.io/zuey2)

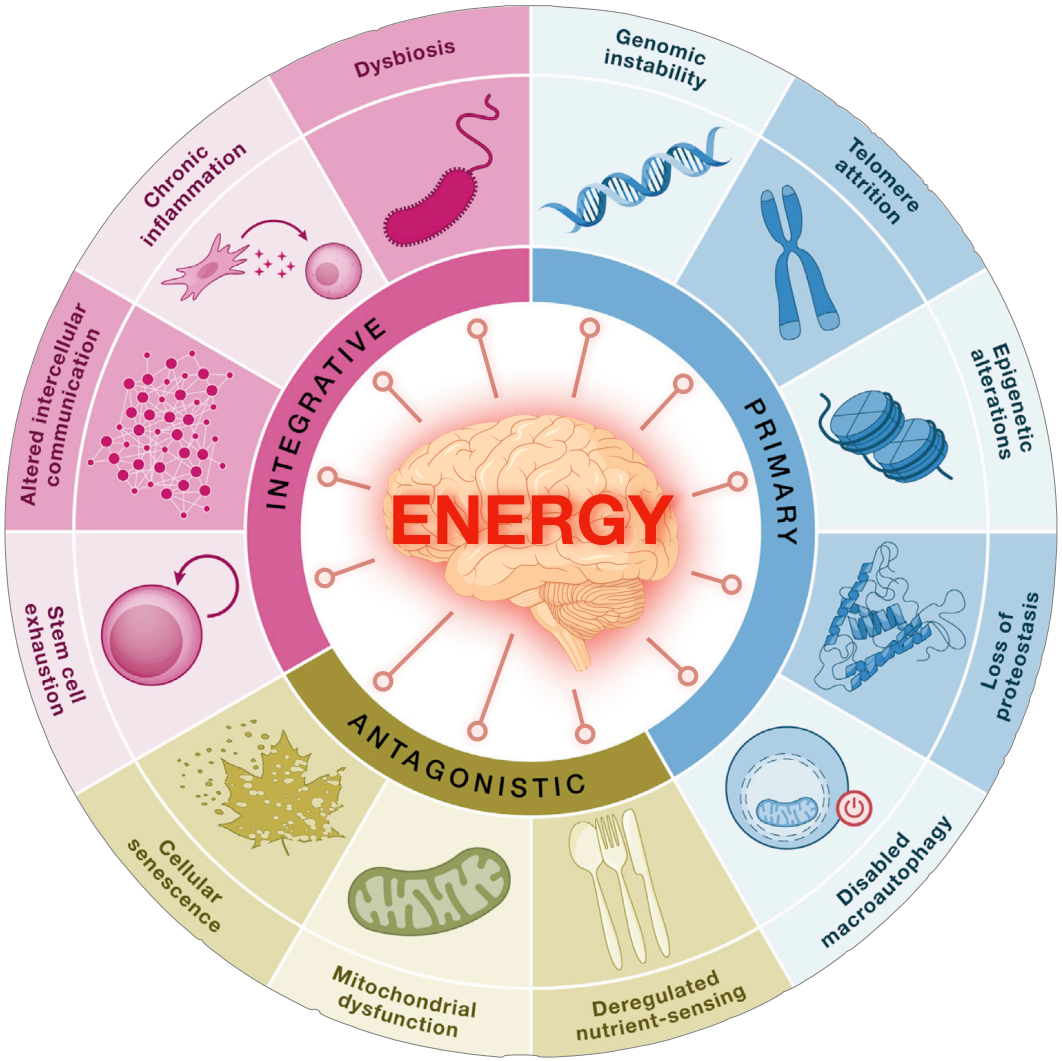
Is the shared factor among hallmarks of aging ENERGY ?

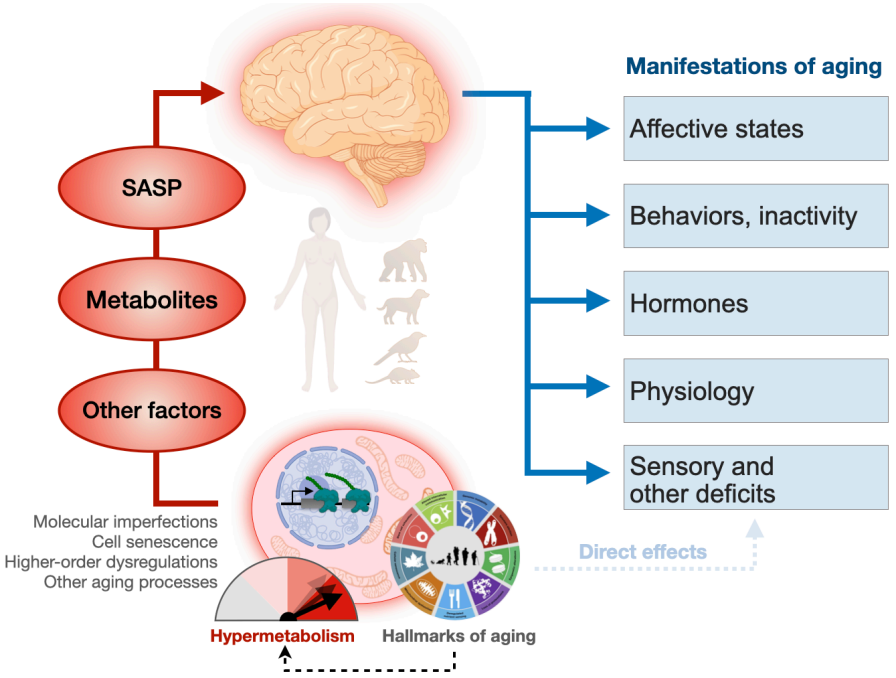
Do the hallmarks physically intersect in the BRAIN ?



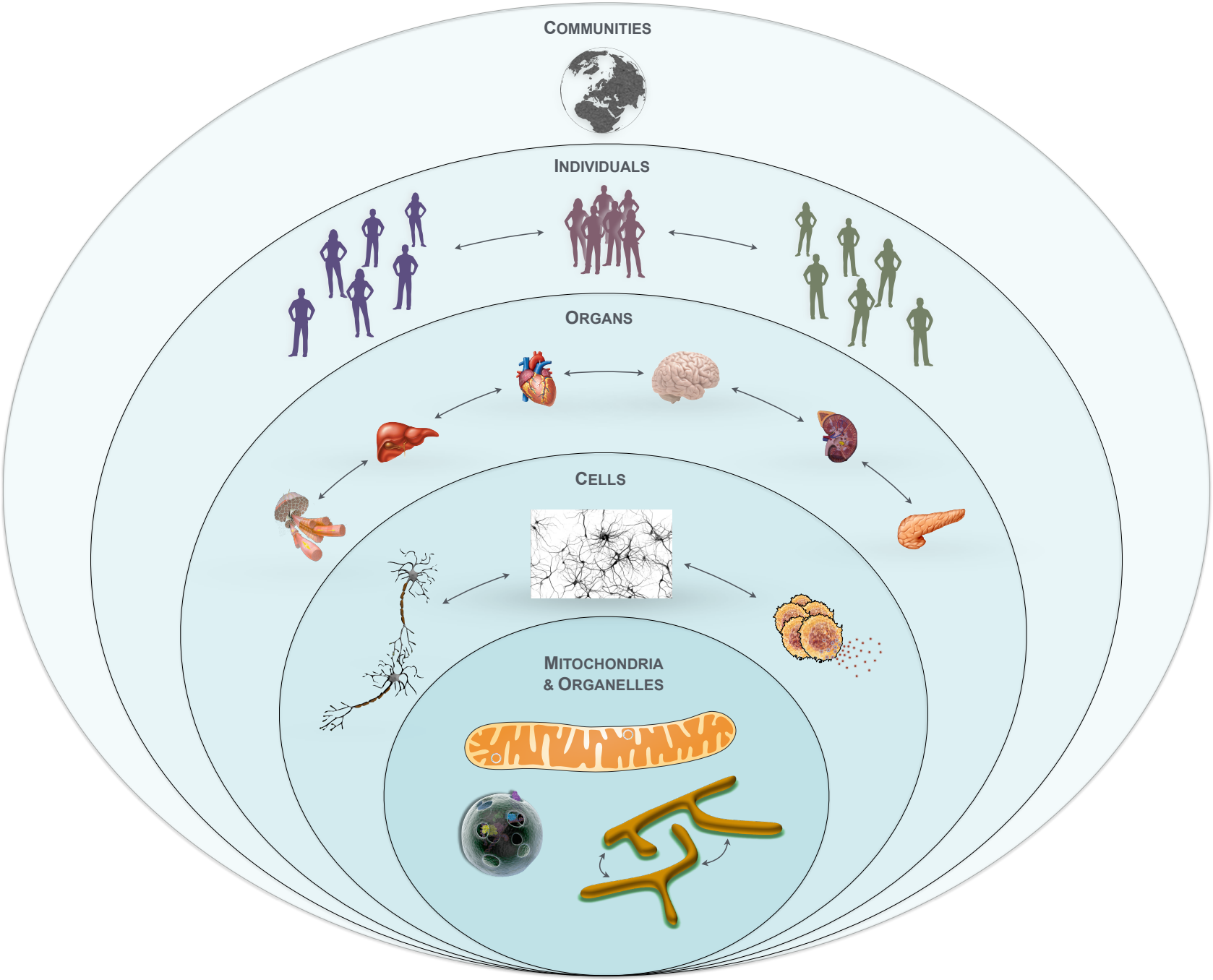
Lopez-Otin et al. *Cell* 2023

Somato-cognitive energy conservation (SEC)

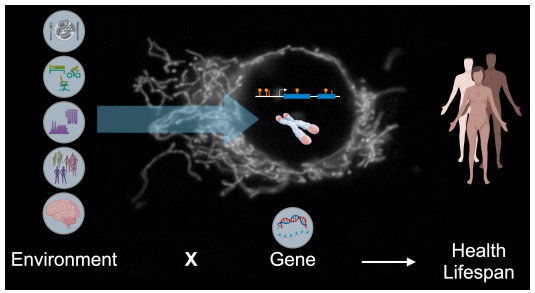


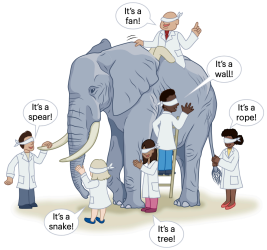


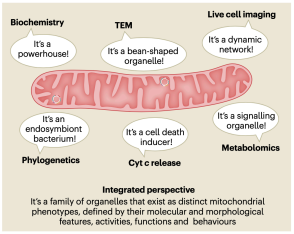
Shaulson, Cohen, Picard. *Preprint* (osf.io/zuey2)

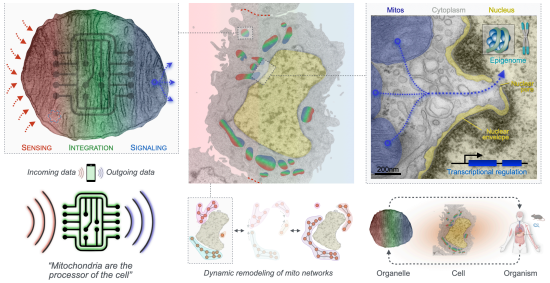

COMMUNITIES
INDIVIDUALS
ORGANS
CELLS
MITOCHONDRIA
& ORGANELLES

PART 1









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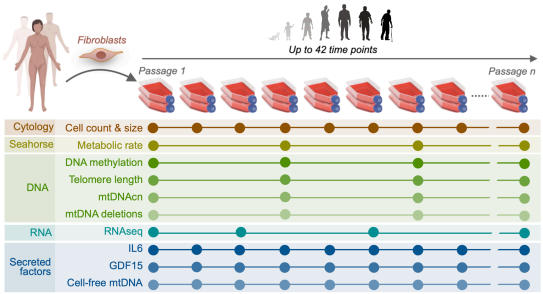

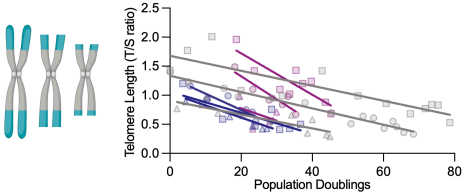

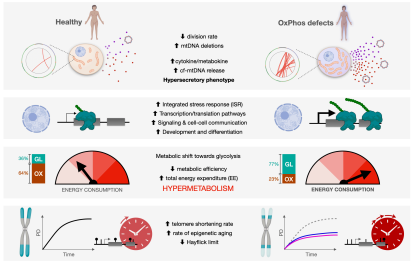

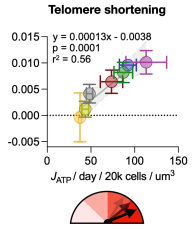

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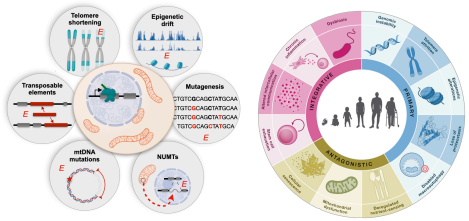

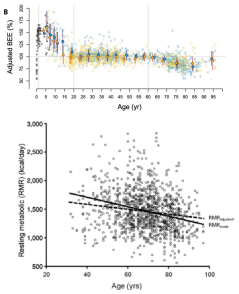

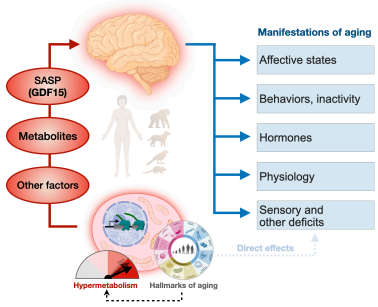

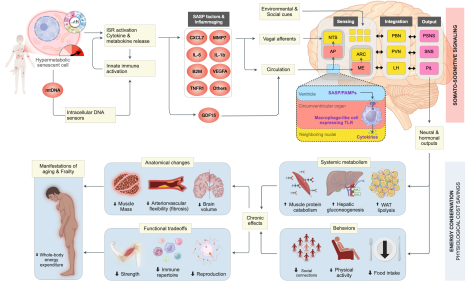

Mitochondrial PsychoBiology Lab

Linking molecular processes within mitochondria with the human experience

OUR RESEARCH

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Alan Cohen
Dan Belsky
Linda Fried
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BASZUCKI
BRAIN RESEARCH FUND

The Nathaniel Wharton Fund

NIH National Institute of Mental Health

NIH National Institute of General Medical Sciences

NIH National Institute on Aging

Downloadable presentation slides

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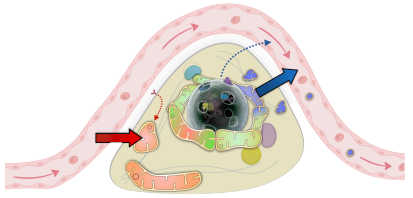
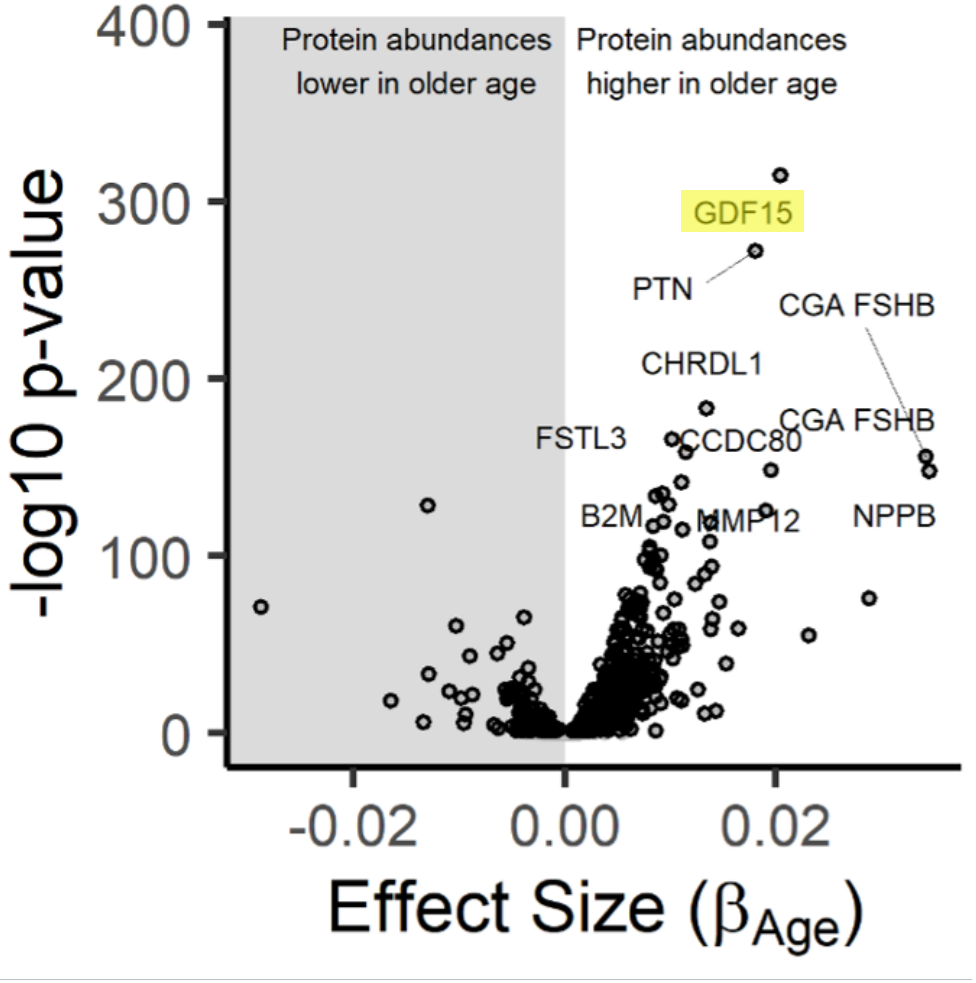
IRVING MEDICAL CENTER

MITOCHONDRIAL
PSYCHOBIOLOGY LAB

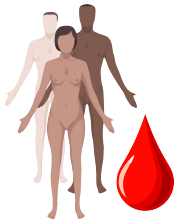
MITOCHONDRIA STRESS BRAIN EPIGENETICS
MiSBiE

UPregulation of most signaling proteins in human aging

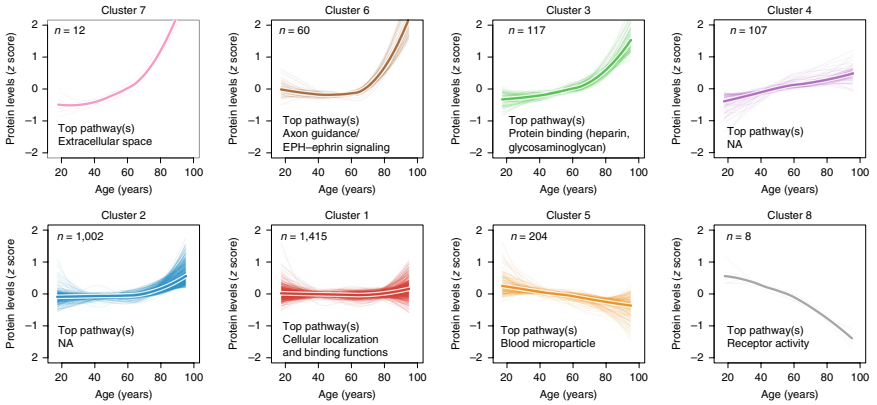


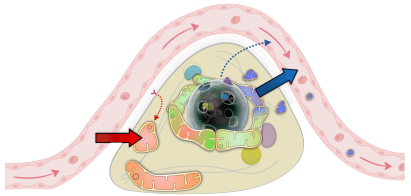


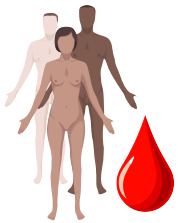
Null hypothesis: 50:50

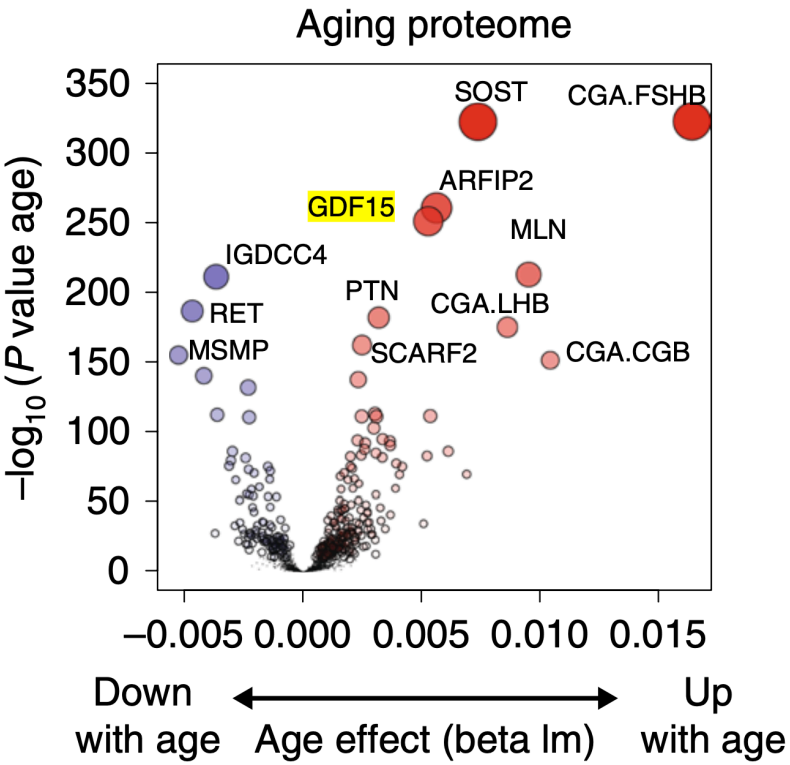


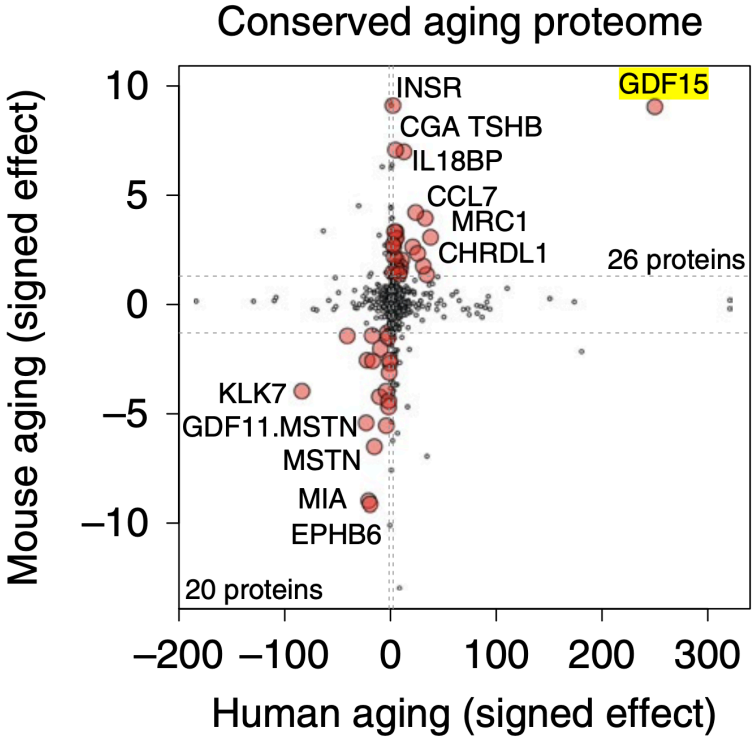
Luigi Ferrucci and colleagues
Tanaka et al. *Aging Cell* 2020







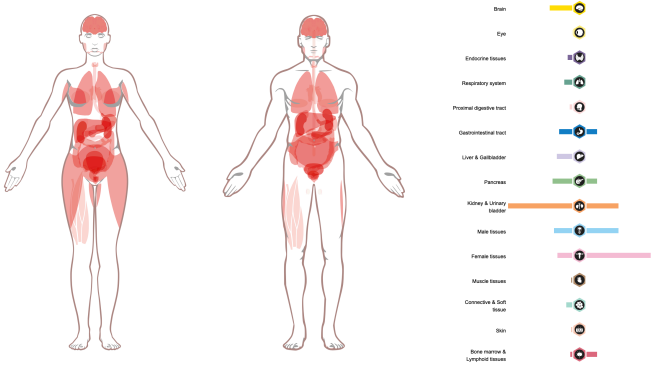




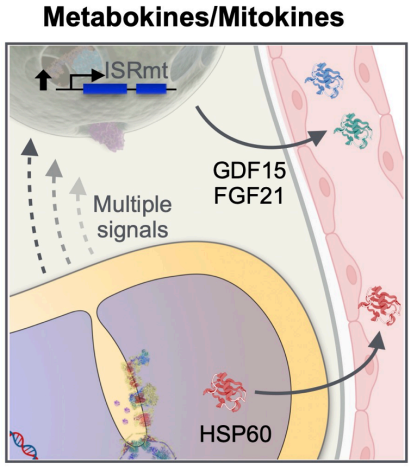
Lehallier et al. *Nature* 2019

What does GDF15 mean to the organism?

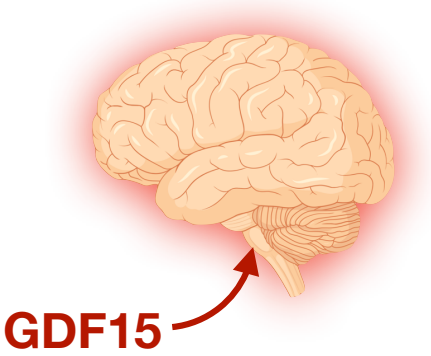
What does GDF15 mean to the organism?



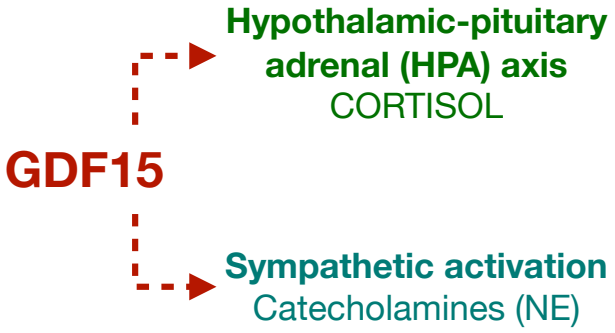
Expressed in >50% of somatic tissues



Triggered by cellular stressors (ISR)



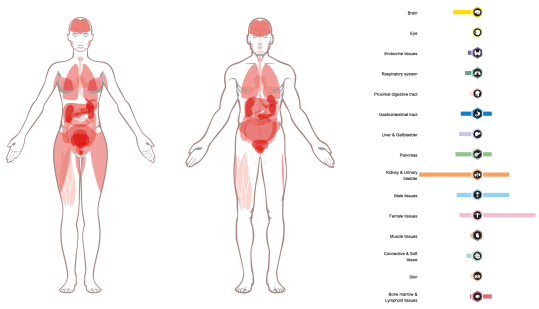
Signals on the brainstem



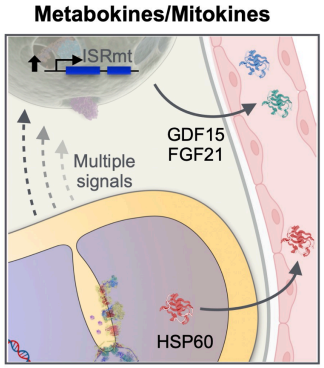
Activates canonical stress axes

Lockhart et al. *Endocr Rev* 2020

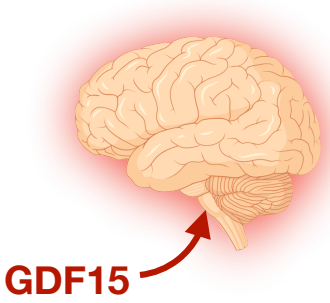
What does GDF15 mean to the organism?



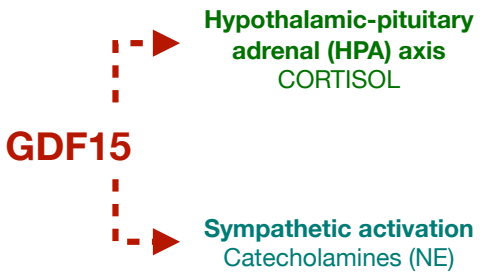
Expressed in >50% somatic tissues



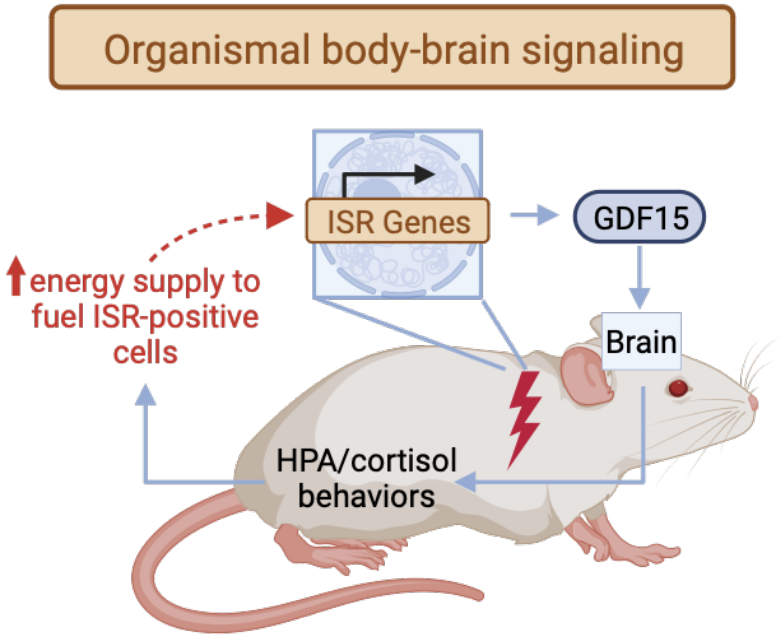
Triggered by cellular stressors (ISR)



Signals on the brainstem

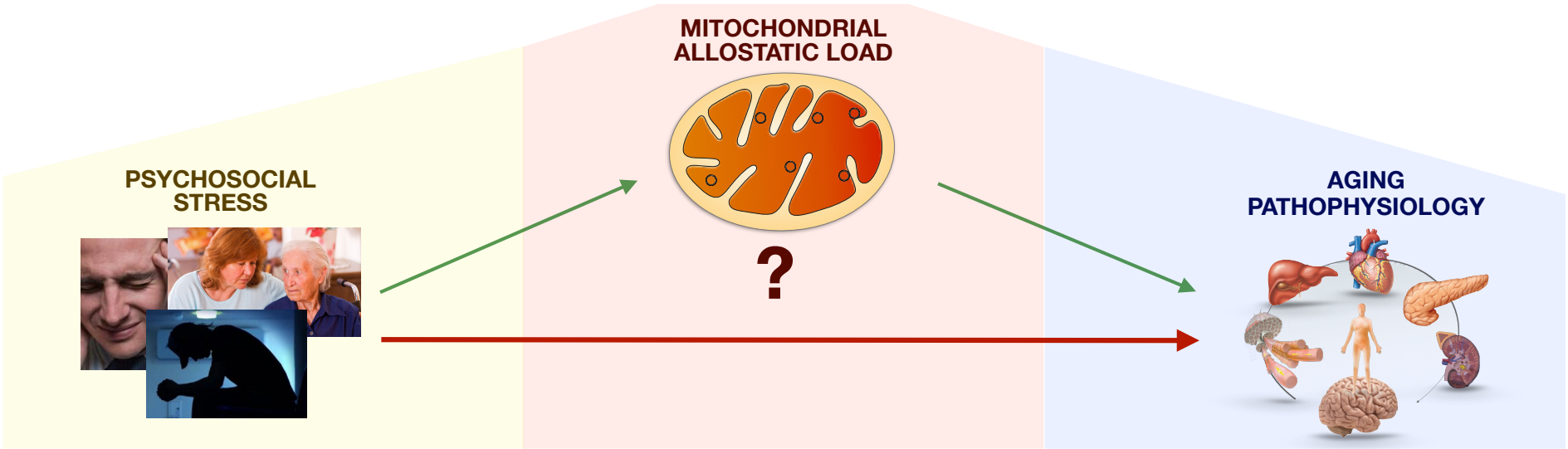


Activates canonical stress axes

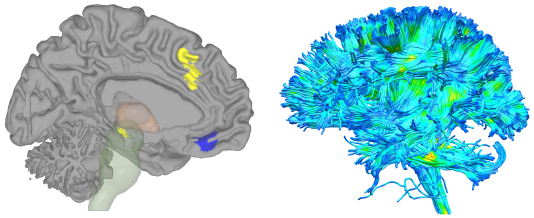


Monzel et al. *Life Metab* (in press)

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

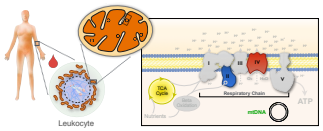


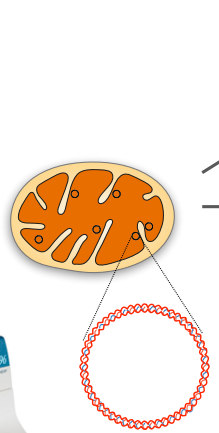
Mitochondrial **S**tress, **B**rain **I**maging, and **E**pigenetics — **MiSBIE**

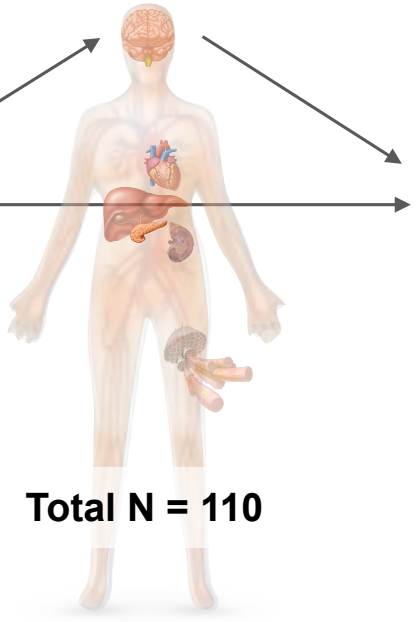


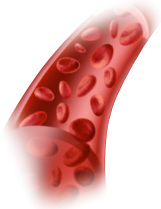
Brain structure and function
Neuropsychological function

mtDNA heteroplasmy
Mitochondrial OxPhos
Lymphocytes, Monocytes,
Neutrophils, Platelets





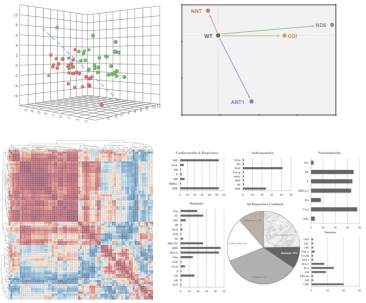




Total N = 110

Disease biomarkers
Stress reactivity
Energy expenditure

e.g., GDF15, Lactate,
Pyruvate, Alanine, etc.

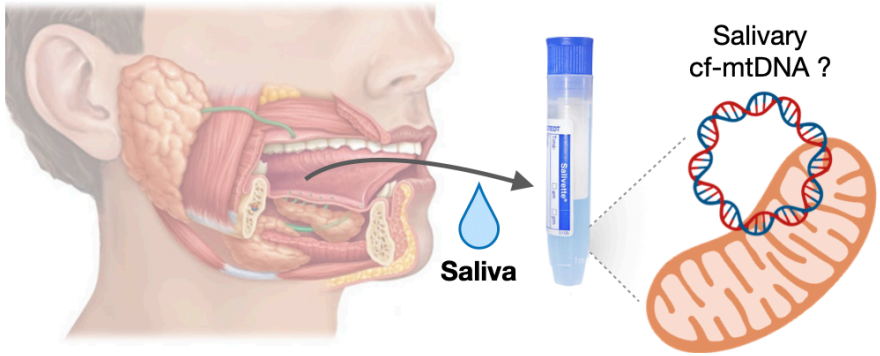


- **Healthy controls** (n = 70)
- **mtDNA defects**
  - **3243A>G (group A)** (n = 20)
  - **3243A>G (group B)** (n = 5)
  - **Single deletion** (n = 15)

MITOCHONDRIA STRESS BRAIN EPIGENETICS MiSBIE

Stress hormones & metabolites are detectable in saliva

Can we quantify cf-mtDNA and other "mitokines" in human saliva?



If so: this would make possible epidemiological and high-temporal resolution timecourse studies of GDF15

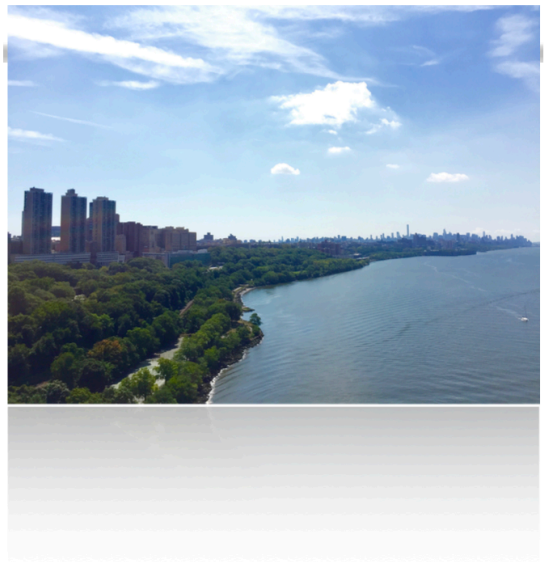
Shannon Rausser

Caroline Trumpff

The MiSBIE Study

Mitochondrial **S**tress **B**rain **I**maging and **E**pigenetics

Investigating the link between the mind and the body



COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

MiSBIE

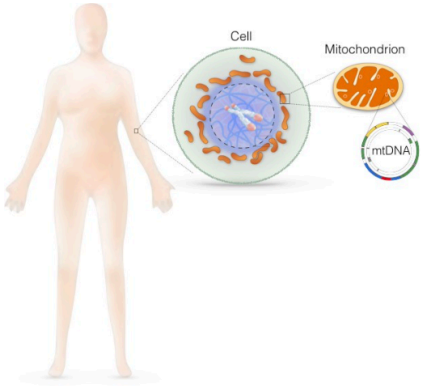
Understanding Mitochondrial Disease

Researchers are just starting to understand the factors that influence aging and the progression of various diseases. Life stress can change the function of the body and influence the development of certain age-related diseases, such as cardiovascular disease and neurodegeneration.

The goal of the MiSBIE study is to understand how an individual's life experience and emotions affect physical health, psychological functioning, and disease risk.

Each cell of the body contains hundreds of mitochondria, which have their own DNA: mitochondrial DNA (mtDNA). Mitochondria produce energy and signals enabling cells to function normally. The MiSBIE study investigates the link between mitochondria, brain function, and different organs to understand their interaction, and *the person as a whole*.

This study also aims to understand the behavior of genes, whether they are turned "on" or "off". This is called "epigenetics" and is measured in DNA from different cells.



Columbia University Medical Center

The MiSBIE study is a research study taking place at the College of Physicians and Surgeons at the **Columbia University Medical Center (CUMC)**, a leading medical institution of care and research.

The partnering Department of Neurology and Department of Psychiatry have a long history of clinical care and research in studying the effects of stress on the body and in mitochondrial disease.

CUMC is located at 168th Street and Broadway in Upper Manhattan, by the Hudson River in New York City, NY.

COLUMBIA UNIVERSITY
MEDICAL CENTER

The MiSBIE Study

A two-day visit

This research includes two visits of about 8 hours each. Participants stay overnight at a nearby hotel.

Breakfast and lunch are provided.

Transport

Would you need to travel to NYC? If so, the MiSBIE Team will arrange your travel and reimburse your expenses associated with the study.

Study tests

On Day 1, participants undergo a laboratory evaluation. Saliva and blood samples, and a small clip of hair are collected. Heart rate and blood pressure are monitored. Participants also complete a medical exam with a doctor.

On Day 2, magnetic resonance imaging (MRI, *picture above*) is used to safely measure brain activity, participants complete questionnaires on an iPad, and meet with a neuropsychologist.

Participants also collect saliva at home.

Confidentiality

All results and biological samples are kept **strictly confidential**.

Compensation

Participants who complete the study receive a compensation of $599.

Eligibility

You are eligible if you are a woman or man between the ages of 18 and 60, and willing to visit Columbia University Medical Center (CUMC) for a two-day visit.

We are recruiting individuals with the following mtDNA mutations:

- m.3243A>G (MELAS)
- Single, large scale deletion (CPEO)

The MiSBIE Team

The MiSBIE team is a group of caring clinicians and researchers from academic disciplines including mitochondrial medicine, physiology, neuroscience, epigenetics, and psychology.

For more information about the study, please contact the clinical coordinator (see contact information on the back).

Sponsors

NIH National Institutes of Health

Irving Institute for clinical and translational research

Contact Information

Questions about the study? Interested to participate?

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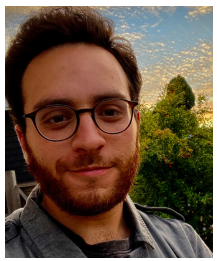
Gabriel Sturm

MITOCHONDRIA STRESS BRAIN EPIGENETICS MiSBIE

NIH National Institute of Mental Health

IRVING INSTITUTE FOR clinical and translational research

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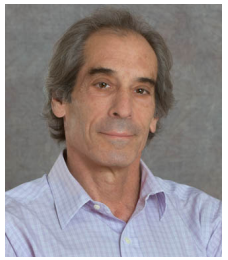

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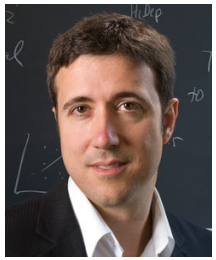

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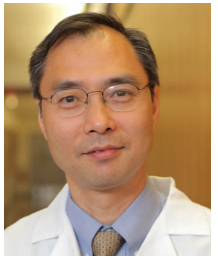

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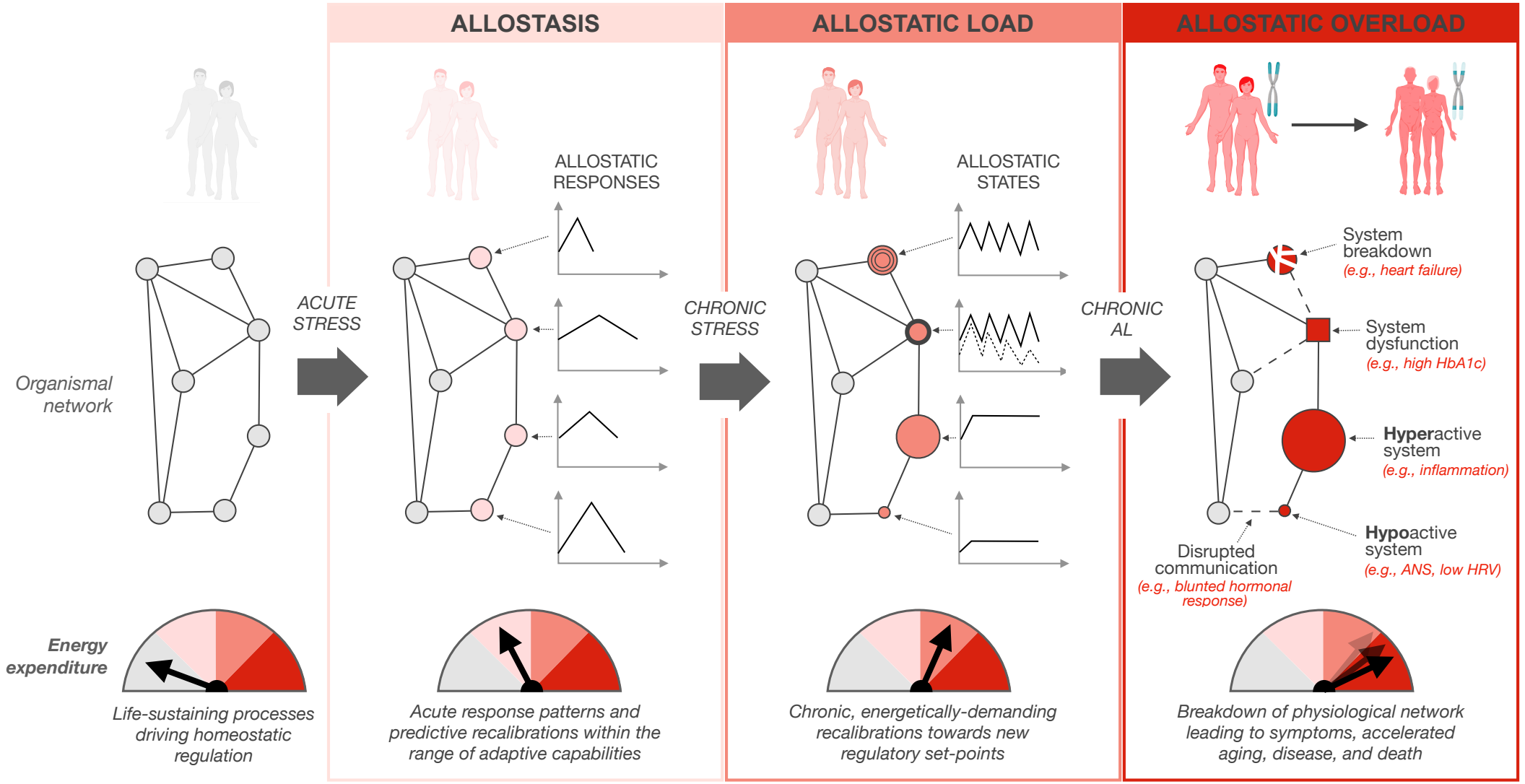

Bobba-Alves, Juster, Picard. *Psychoneuroendocrinol* 2022