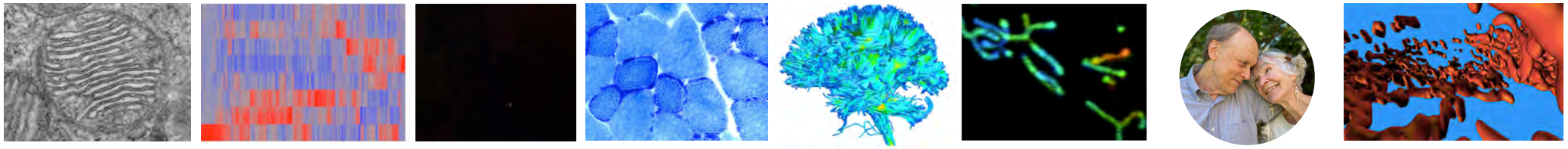
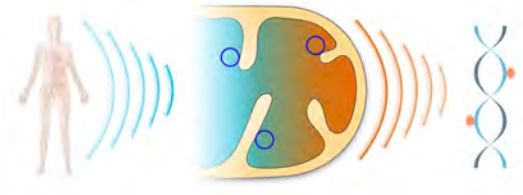


The Energetic Cost and Consequences of Living with a Mitochondrial OxPhos Defect

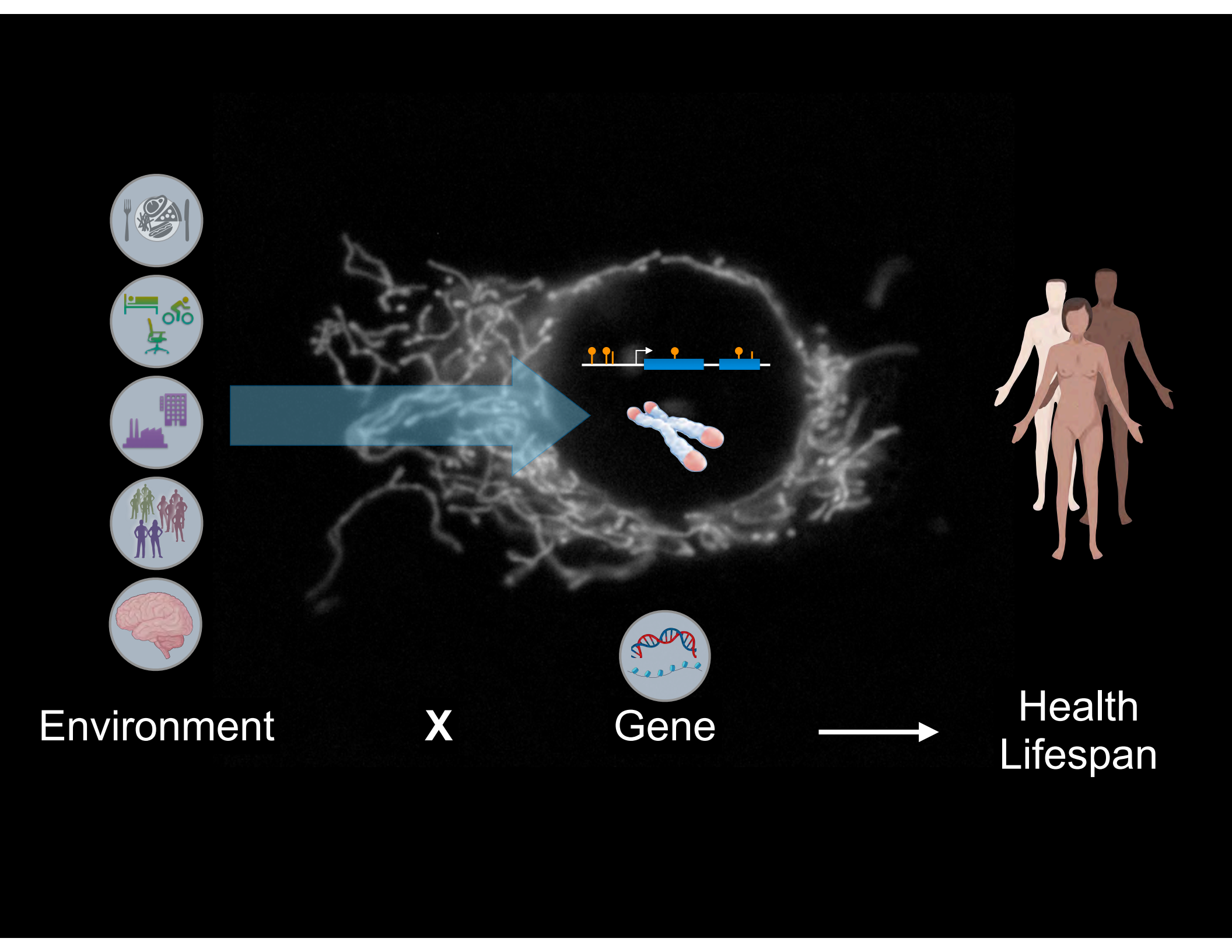


University of Utah — Sept 2023

Martin Picard, Ph.D.
Department of Psychiatry, Division of Behavioral Medicine
Department of Neurology, H. Houston Merritt 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


Environment
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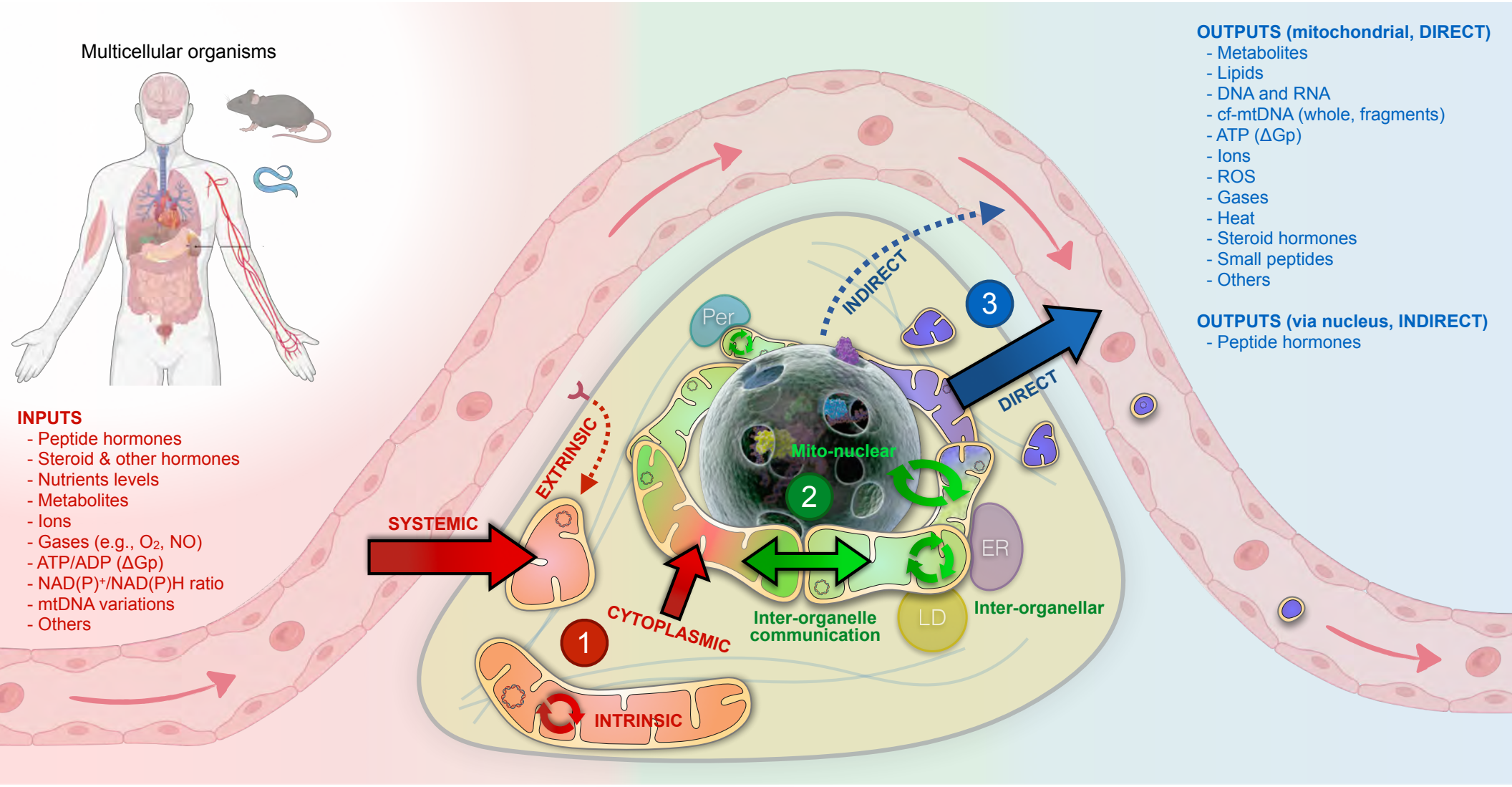
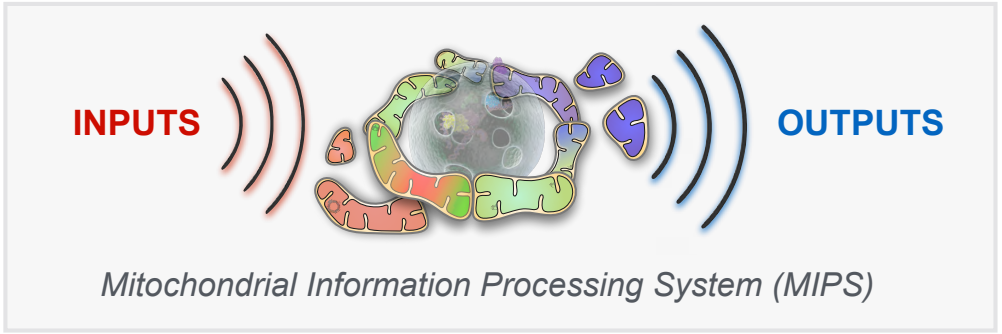
Gene
Health
Lifespan

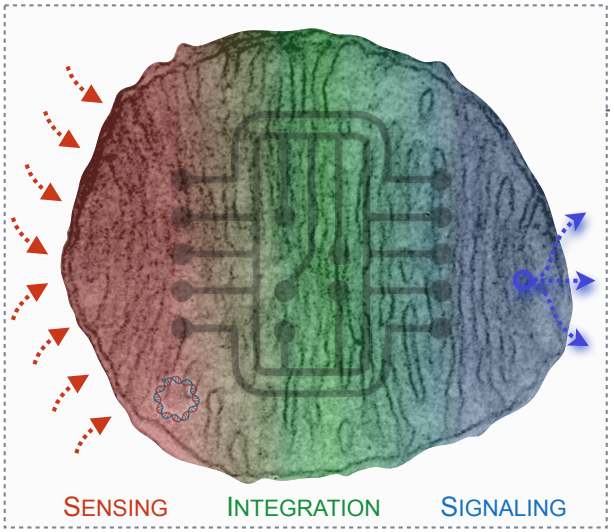




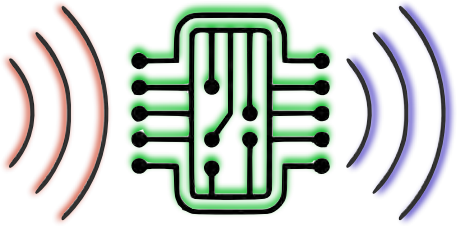
Picard and Shirihai.
Cell Metab 2022

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

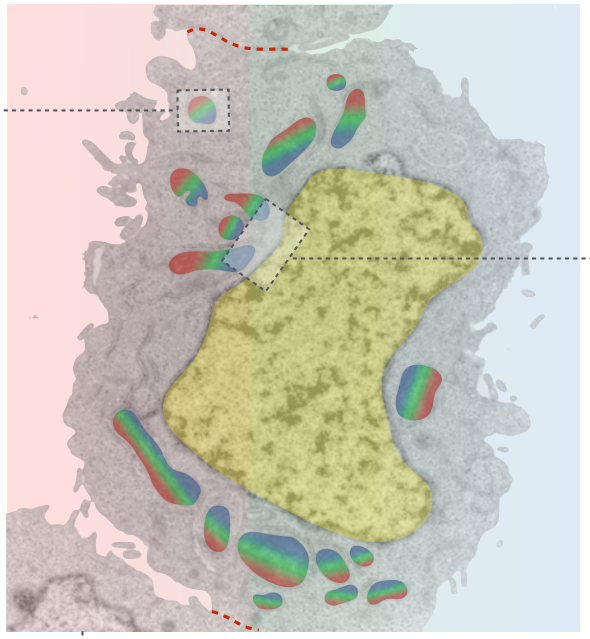
Signal transducing mitochondrion

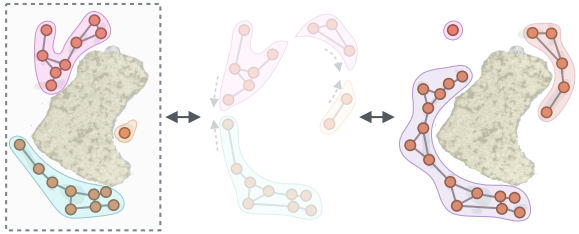


Incoming data *Outgoing data*



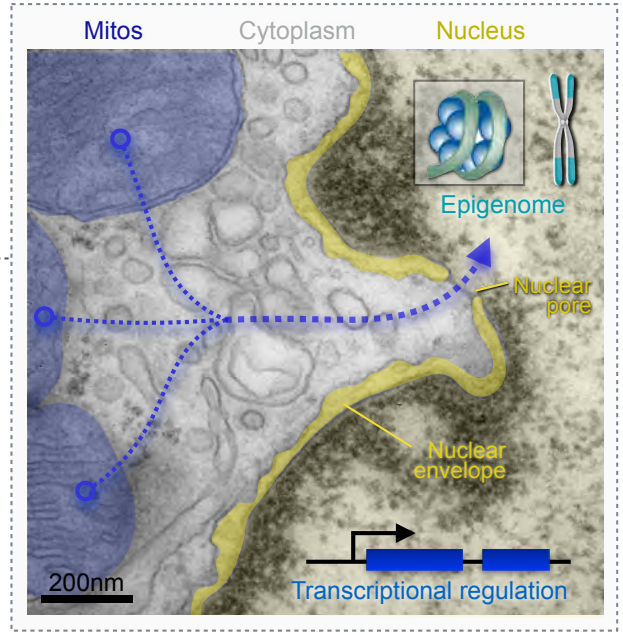
"Mitochondria are the processor of the cell"

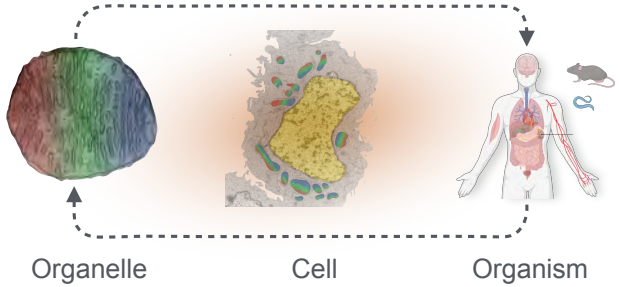


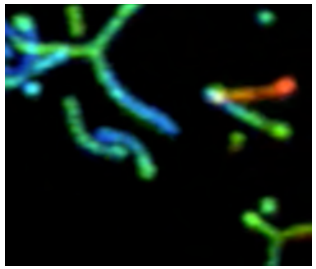


Dynamic remodeling of mito networks

Mito-nuclear unit

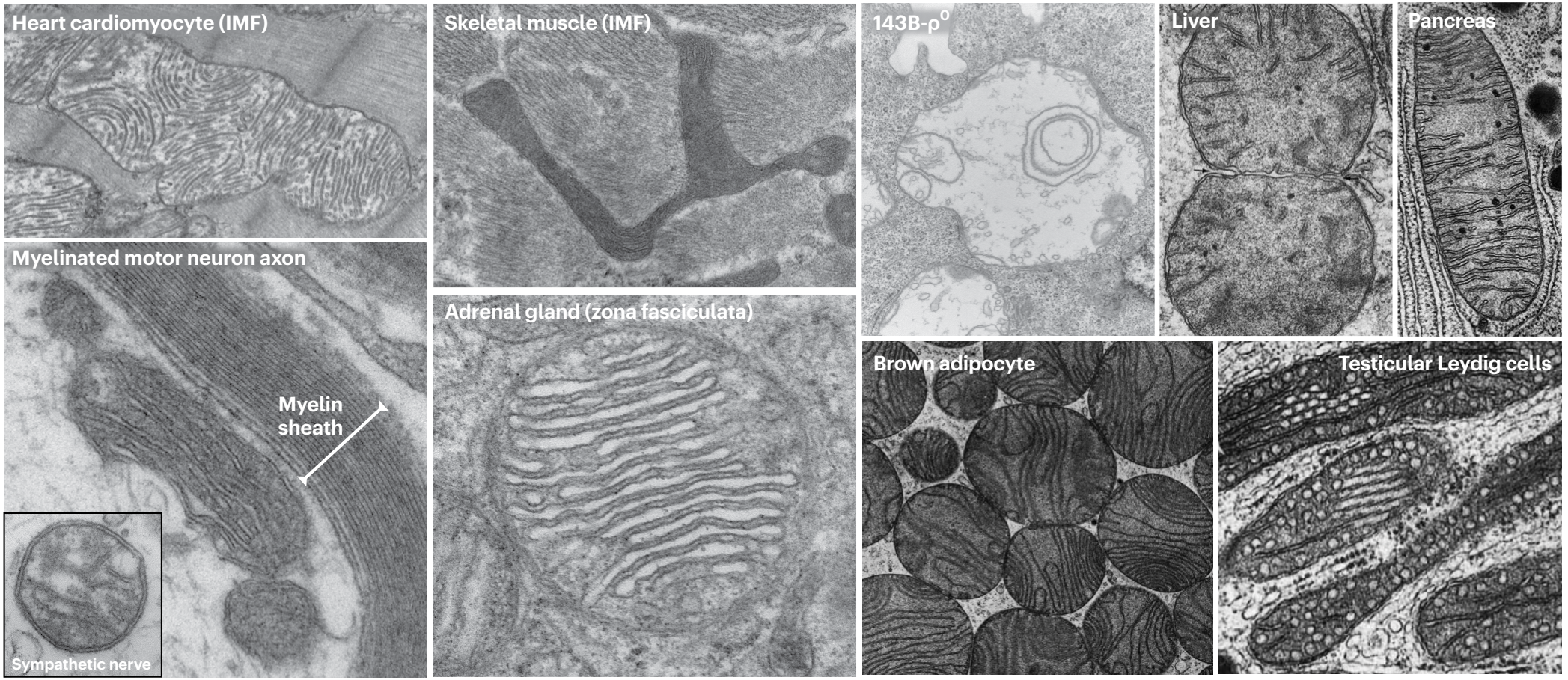


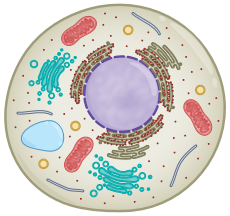




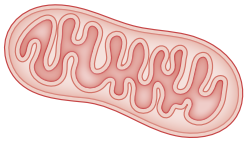
Picard and Shirihai. *Cell Metab* 2022

Different mitochondria types (mitotypes)



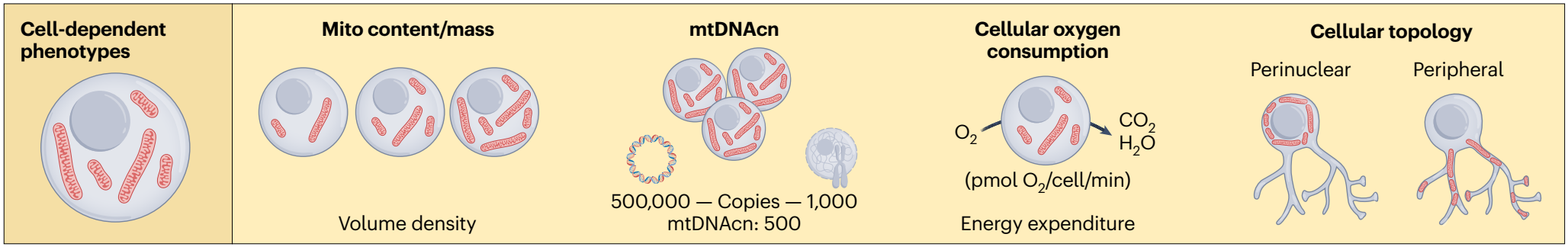


Cell types and subtypes



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
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Deletion(s)
SNPs, mutations, deletions
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Cardiolipin
Protein dynamics
Assembled protein complexes
Ultrastructure
Cristae structure
Morphology
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TIM22 complex
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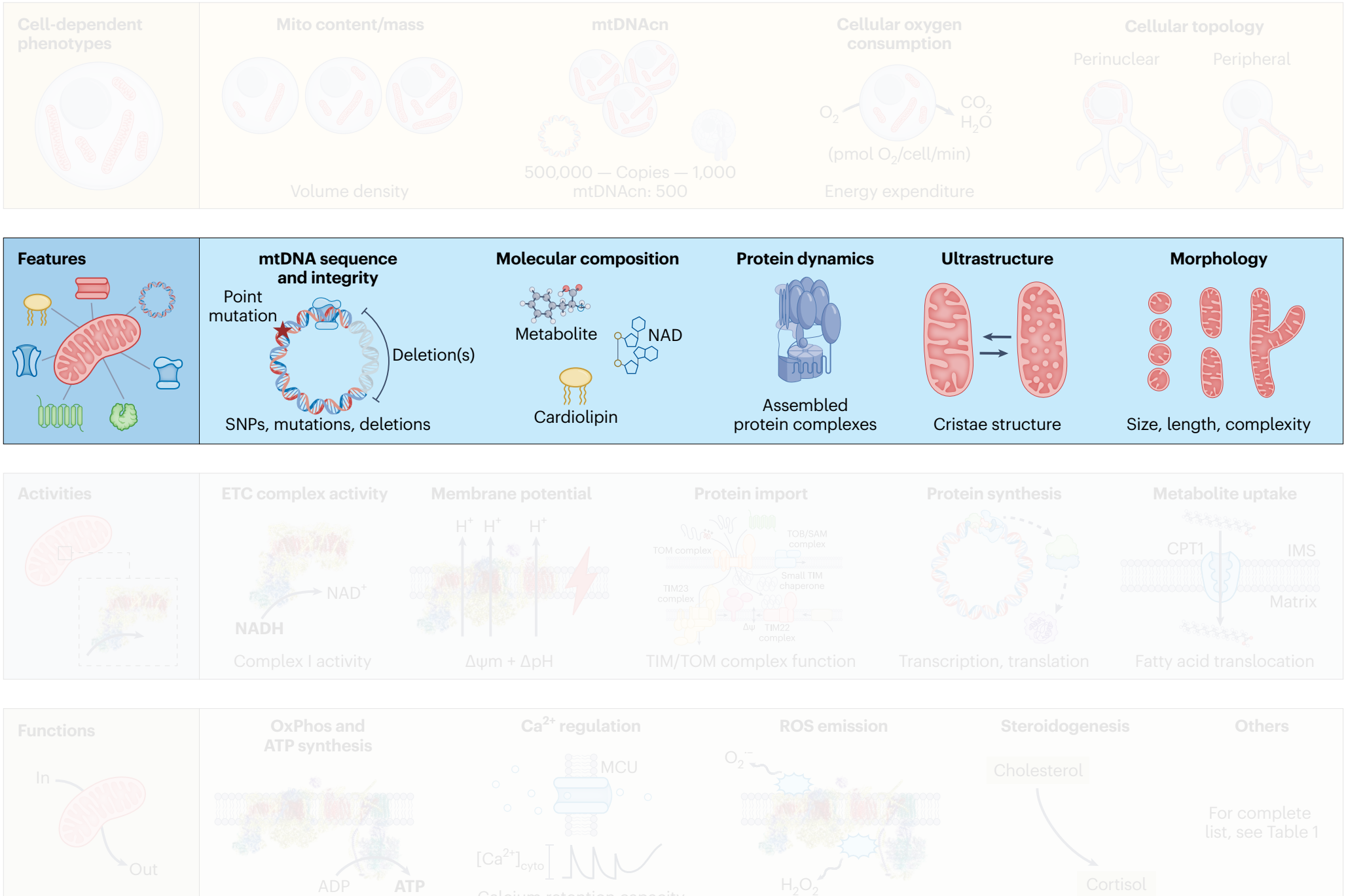
CPT1
IMS
Matrix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ROS emission
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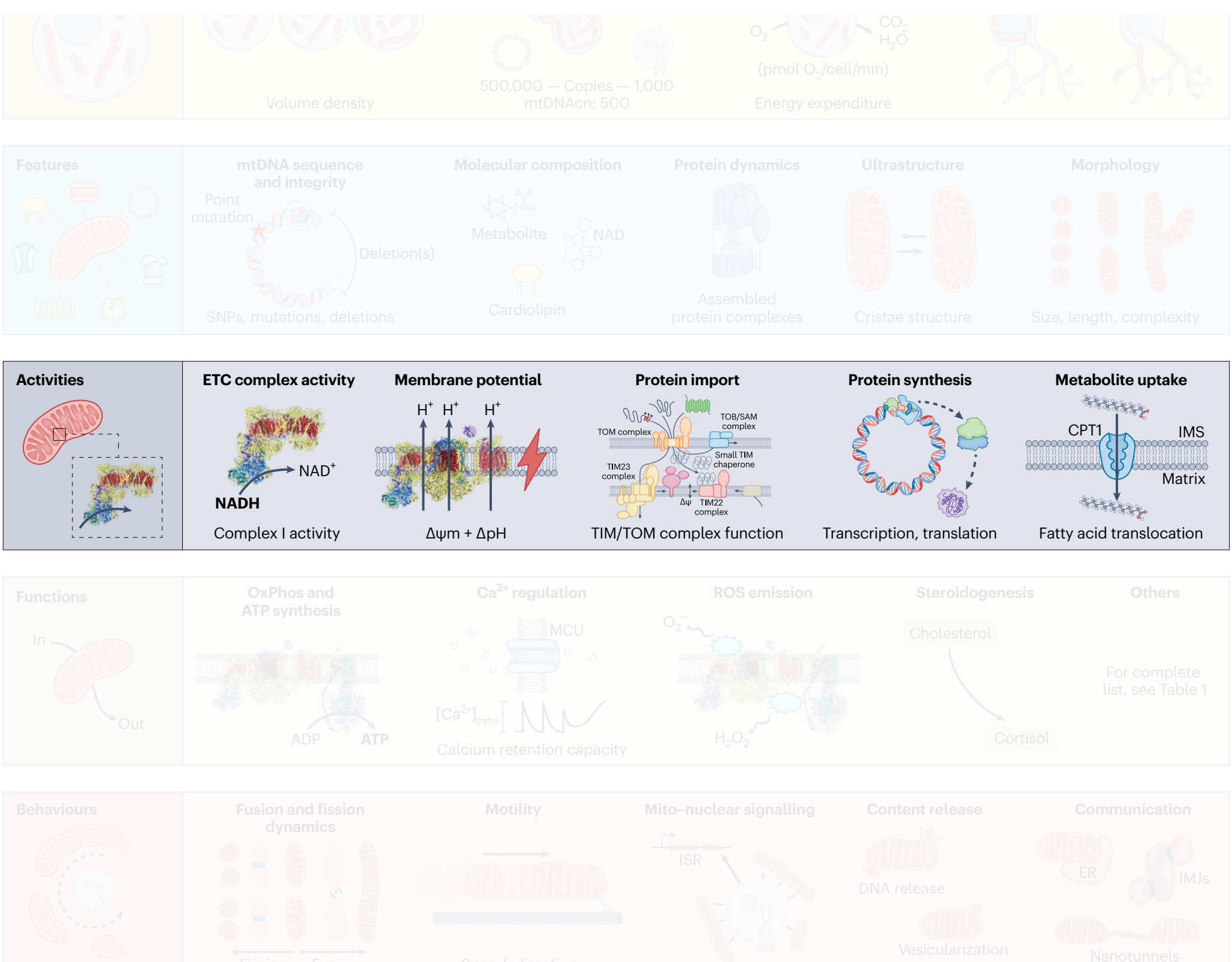
H2O2
Steroidogenesis
Cholesterol
Cortisol
Others
For complete list, see Table 1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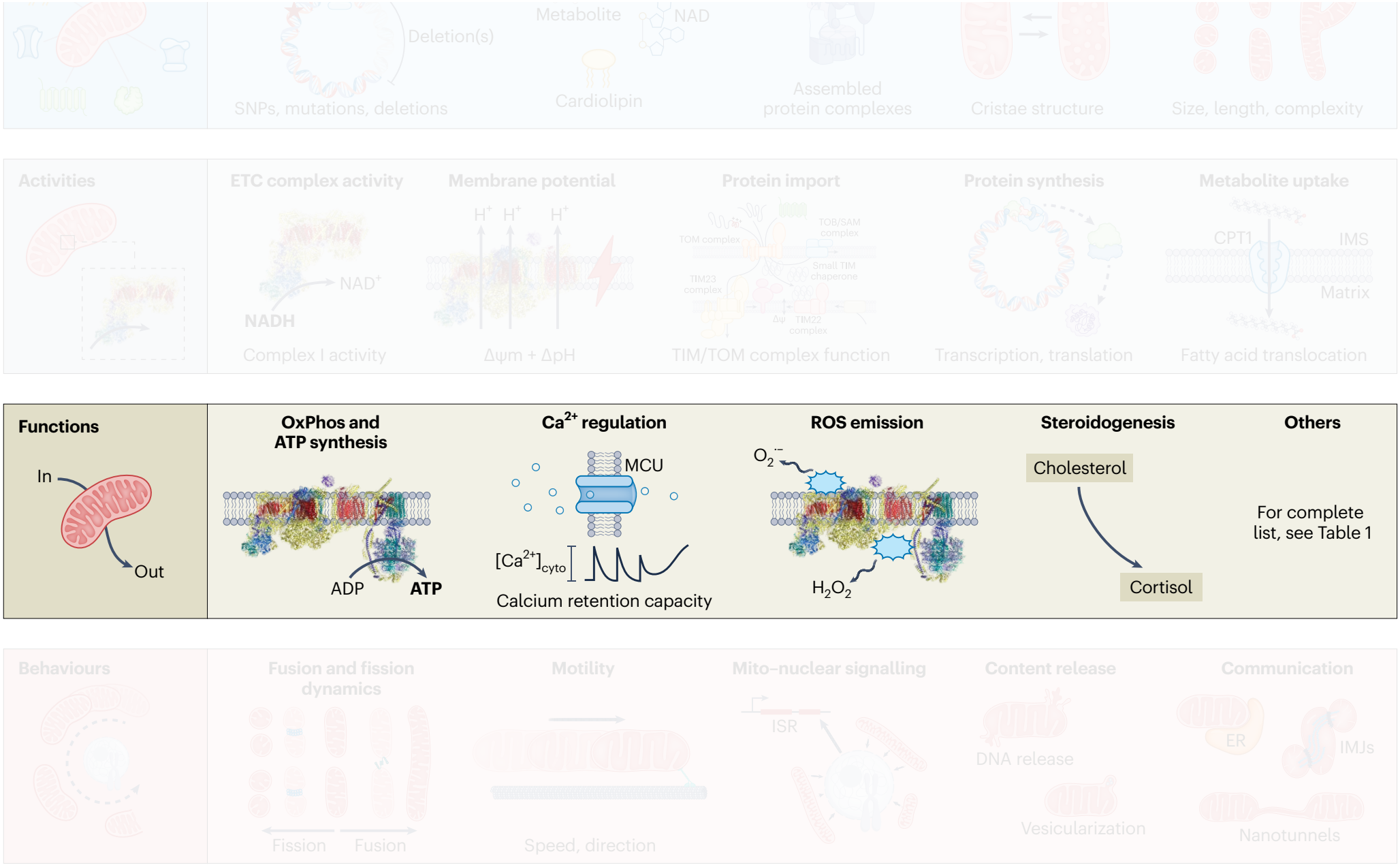
DNA release
Vesicularization
Communication
ER
IMJs
Nanotunnels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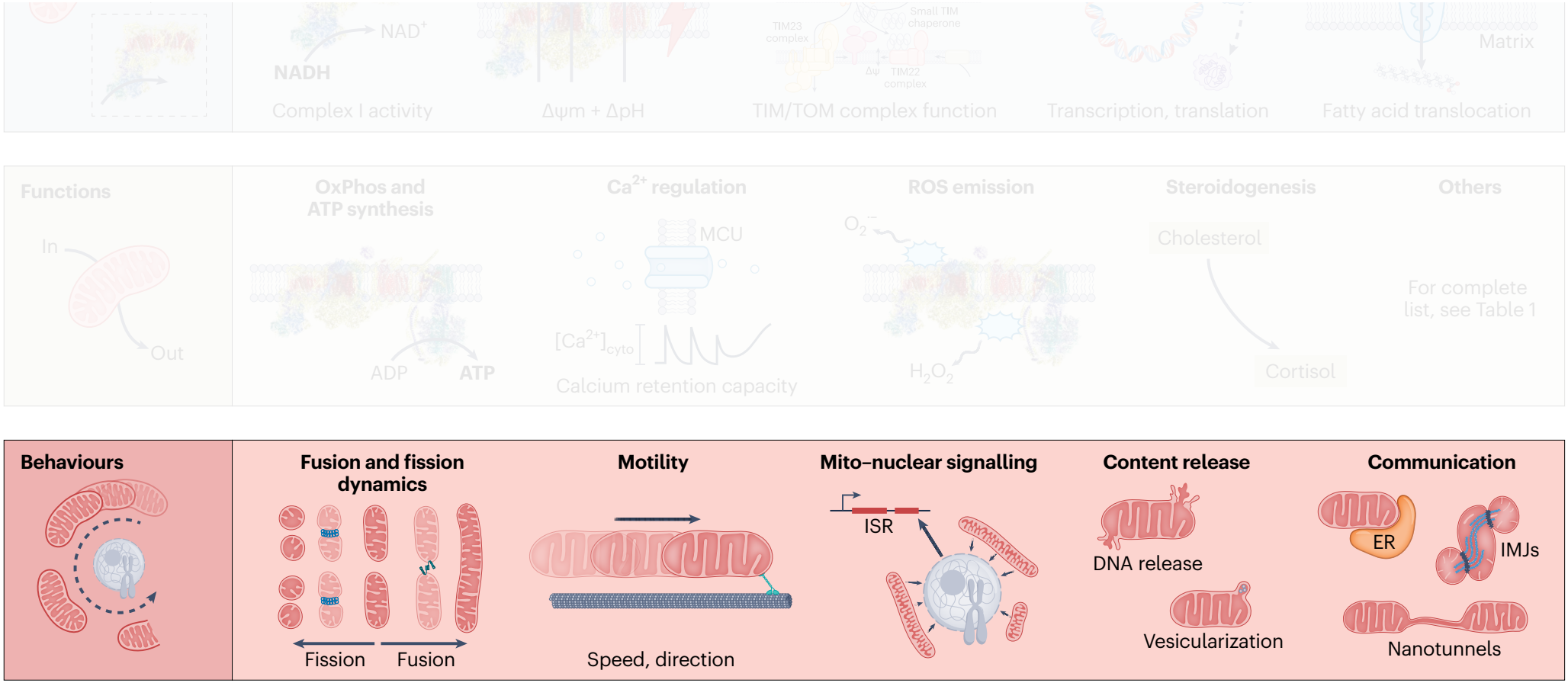
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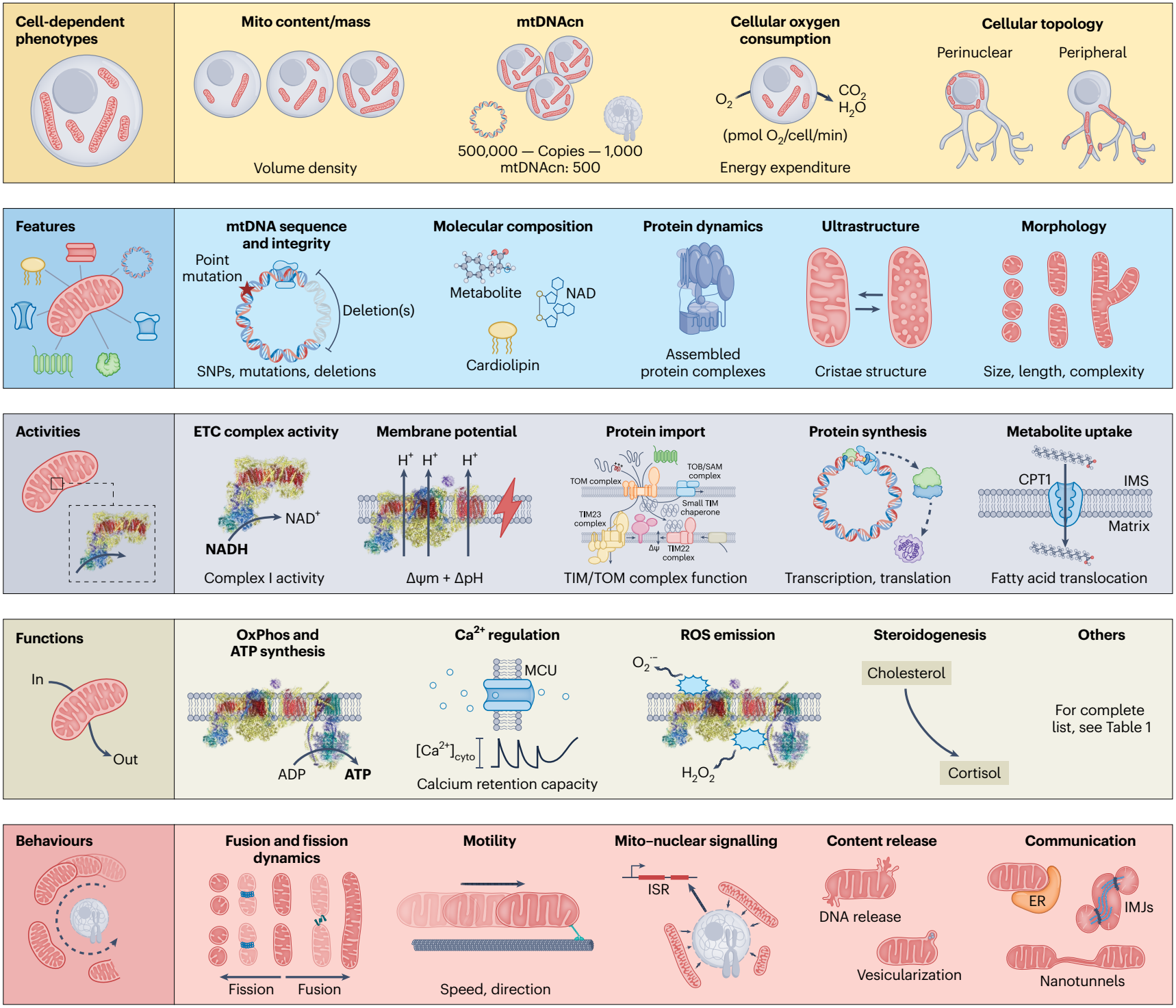
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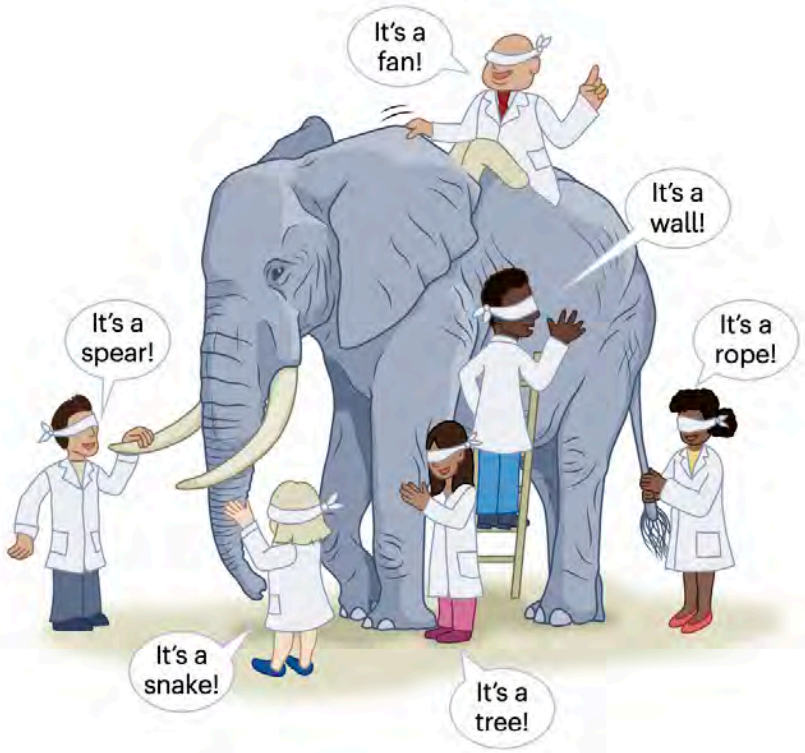
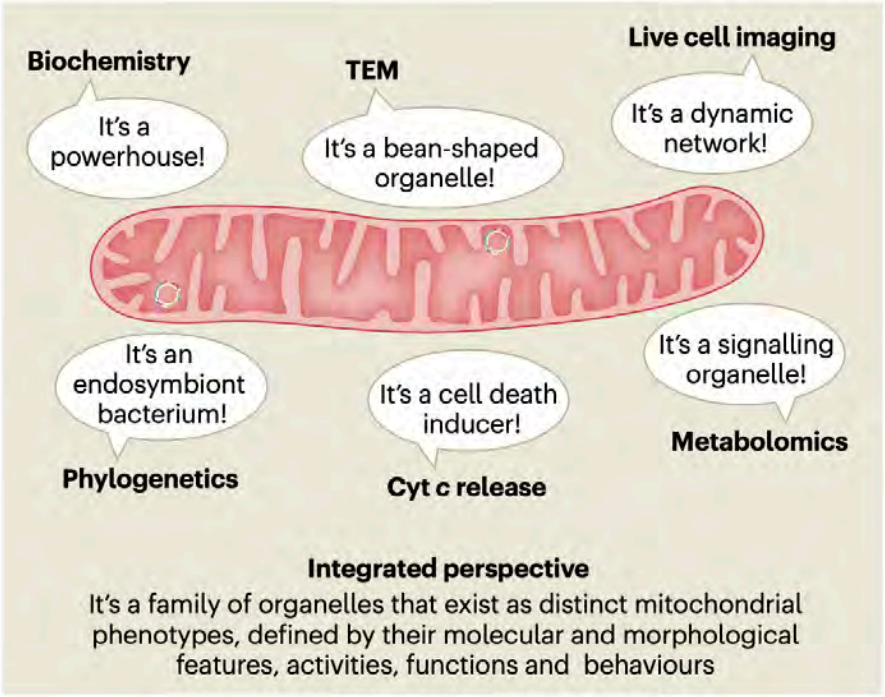
Perspective https://doi.org/10.1038/s42255-023-00783-1

Multifaceted mitochondria: moving mitochondrial science beyond function and dysfunction





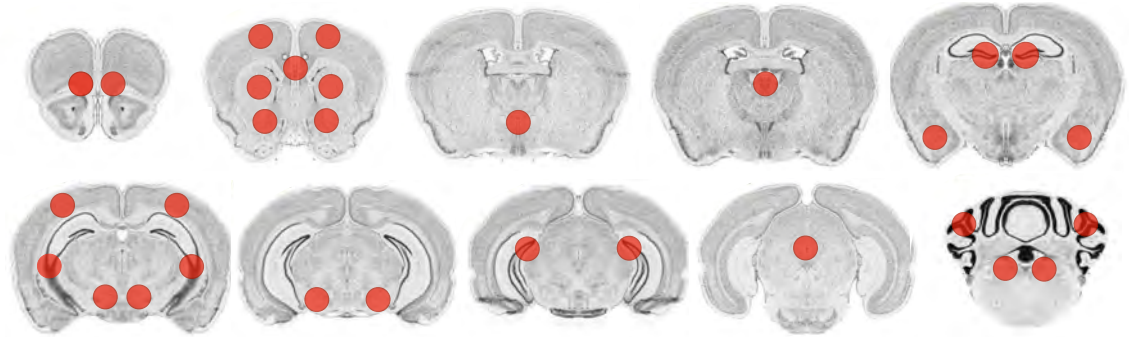
A catalogue of mitochondrial *functions*

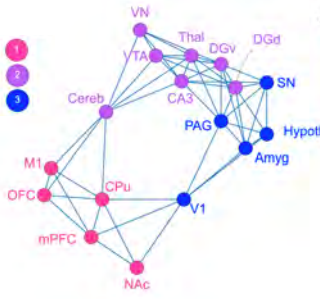
Monzel, Enriques, Picard. *Nat Metab* 2023

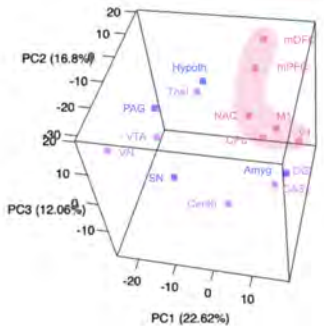
Article

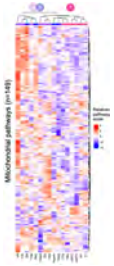
https://doi.org/10.1038/s41467-023-39941-0

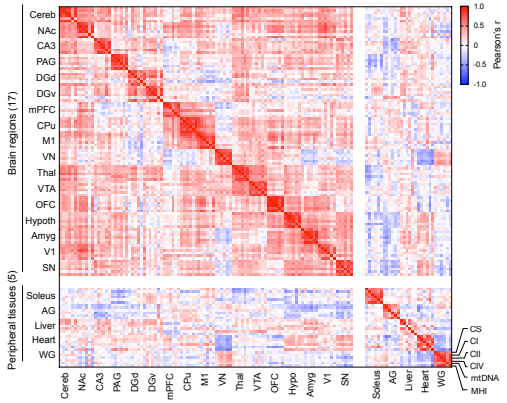
Brain mitochondrial diversity and network organization predict anxiety-like behavior in male mice

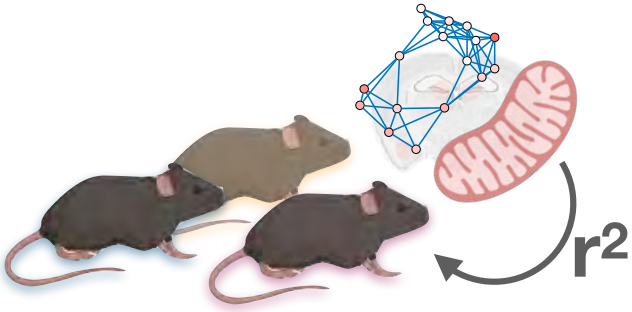












Rosenberg et al. *Nat Commun* 2023

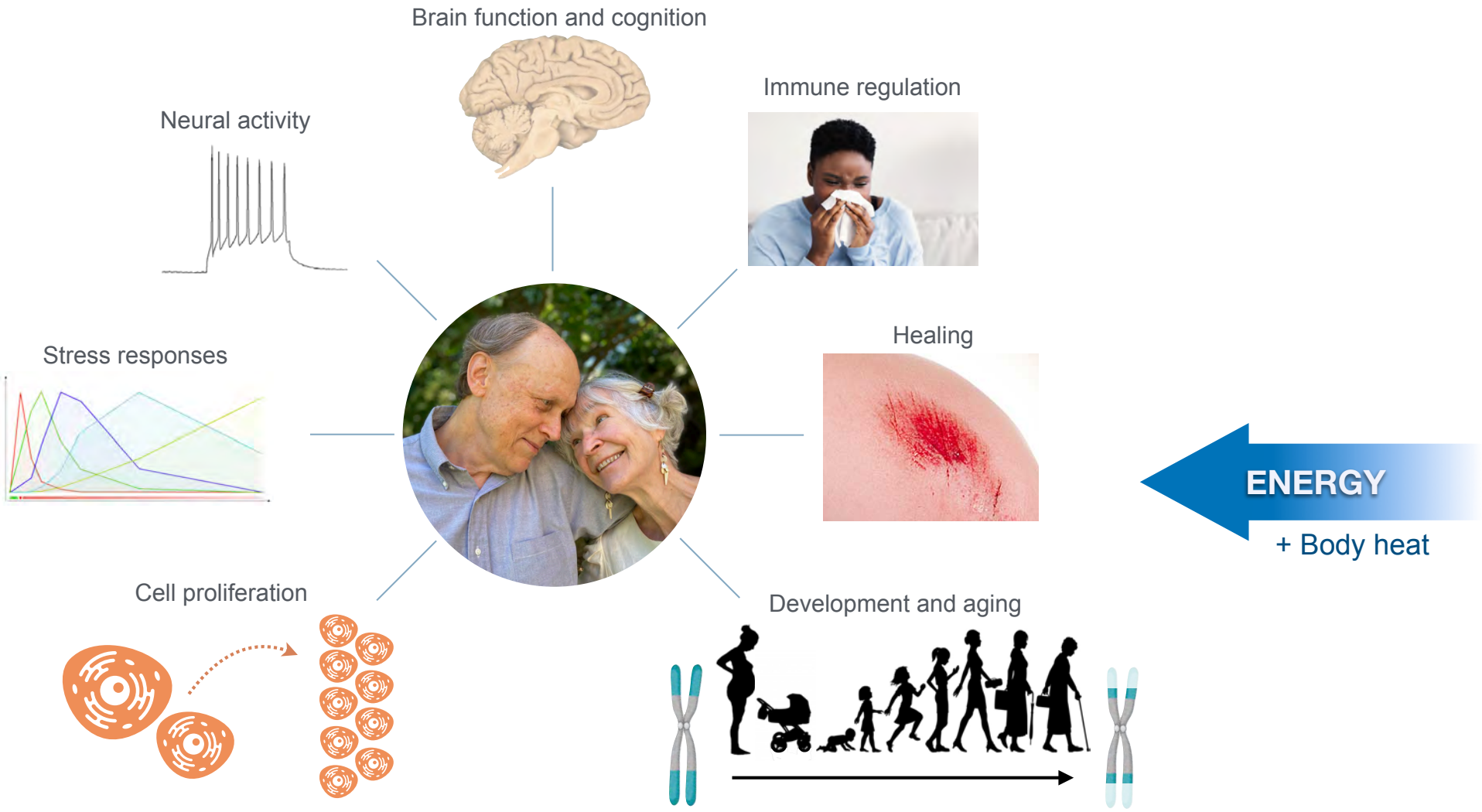
Life costs energy

How much energy does it cost to stay alive?

1. Where does the energy come from?

1. Where does the energy come from?

2. What do we spend energy on?



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

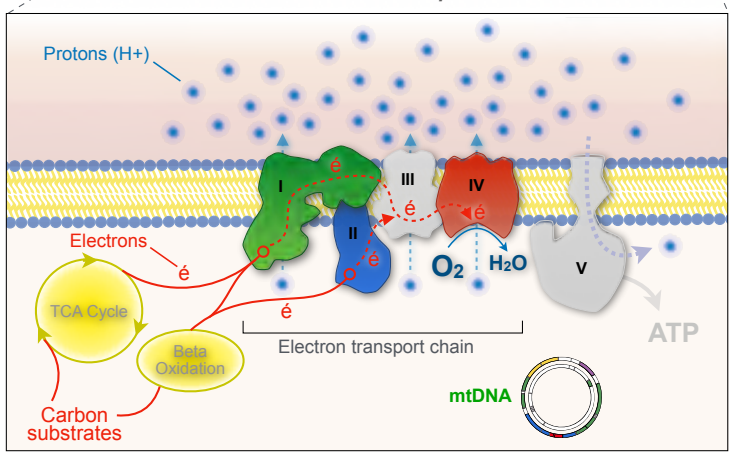
Cell proliferation

Development and aging

ENERGY
+ Body heat

PHYSIOLOGY, COGNITION, CONSCIOUSNESS
PSYCHOBIOLOGICAL ALLOSTATIC PROCESSES

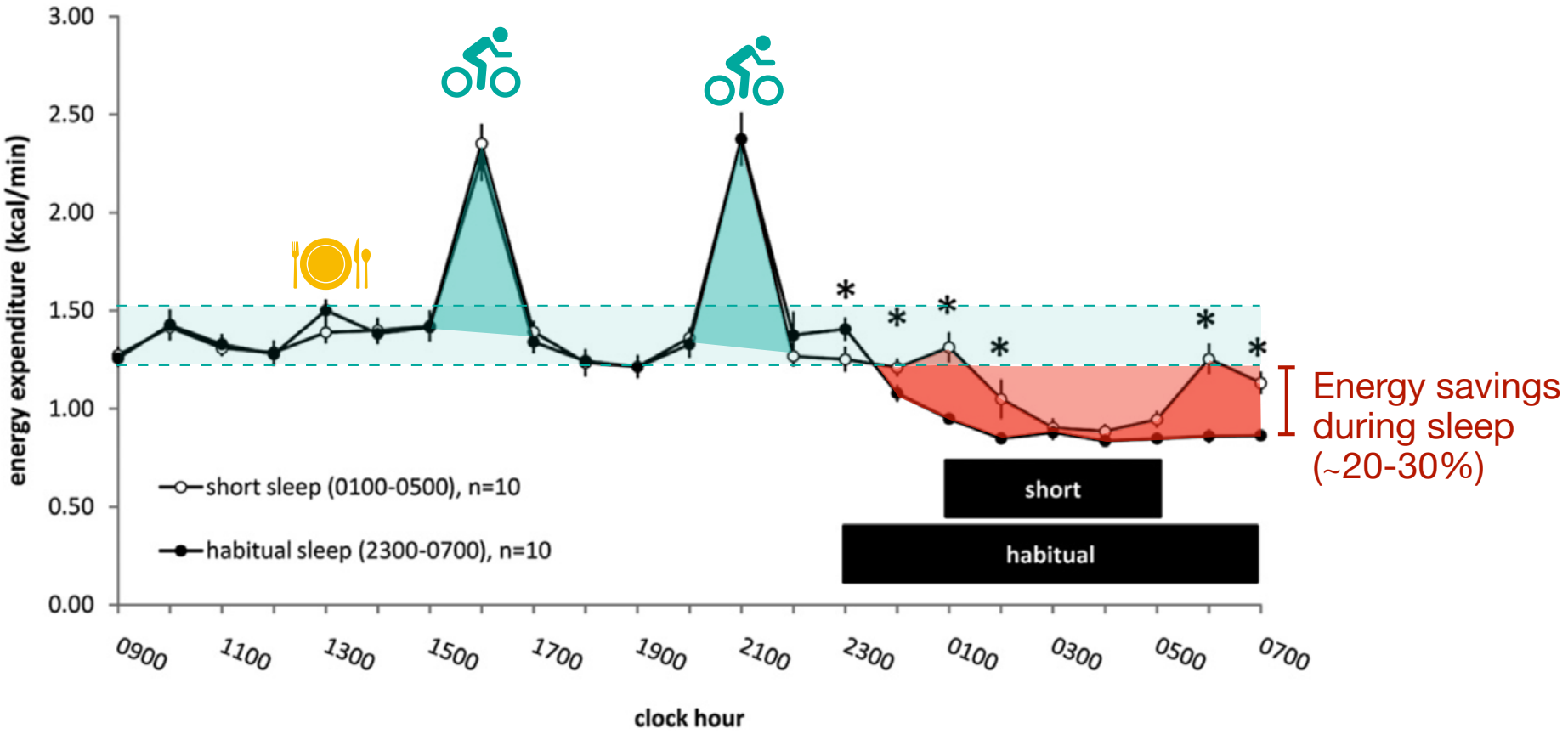
Electricity and Chemiosmosis
$\Delta\Psi m + \Delta pH$



CHEMICAL ENERGY TRANSFORMED INTO
ELECTROCHEMICAL FORCE

Biochemistry 2022

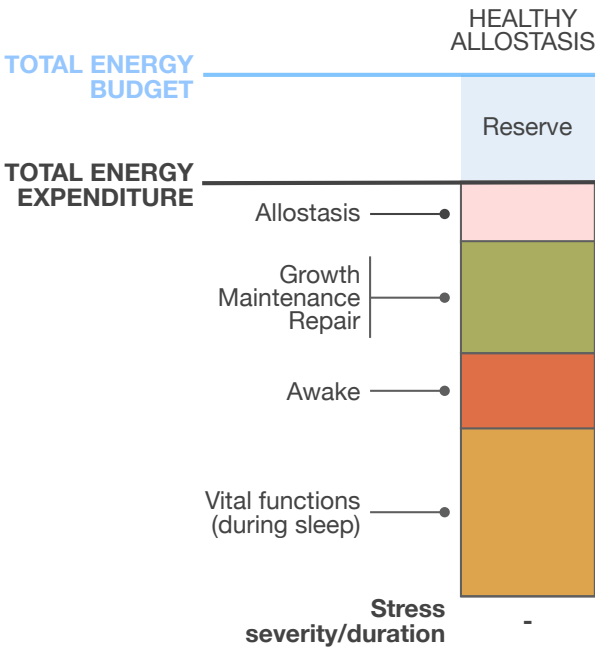
Human energy expenditure



The purpose of sleep may be to allow hypometabolism

Shechter et al. *Am J Clin Nutr* 2013

Partitioning of energetic resources in humans



Homeostasis: *corrective* actions to normalize physiological parameters

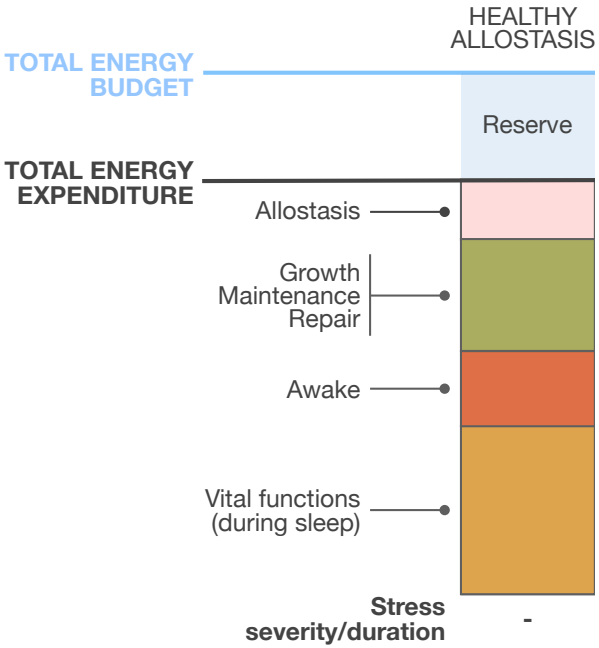
Allostasis: *anticipatory* actions mobilized to prevent deviations in physiological parameters, or optimize adaptation

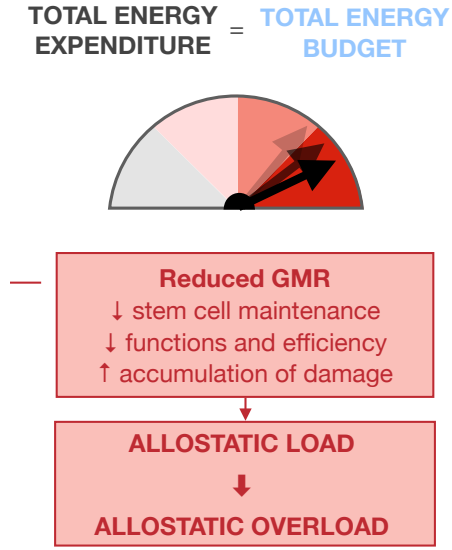
- Secretion of gastric juices and digestive enzymes at the sight/smell of food
- Cortisol and catecholamine secretion from perceived (mental) stress

Allostasis costs energy

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

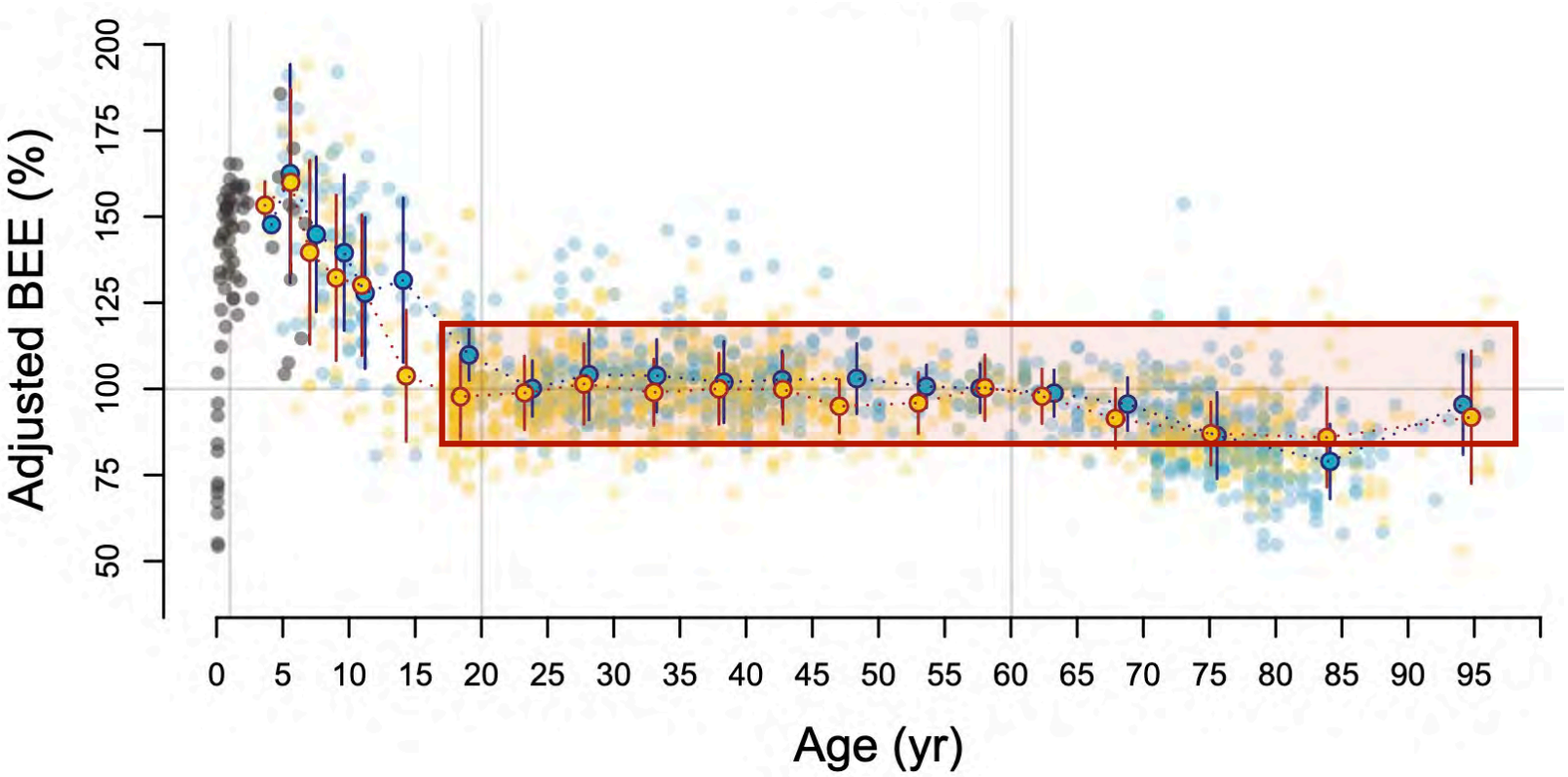
Partitioning of energetic resources in humans





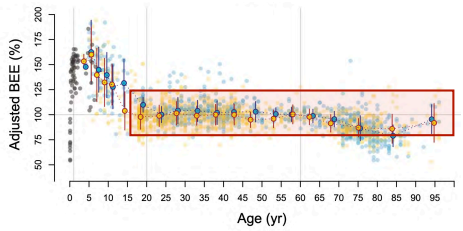
Bobba-Alves et al. The energetic cost of allostasis and allostatic load. *Psychoneuroendocrinol* 2022

How much energy do we spend to stay alive?

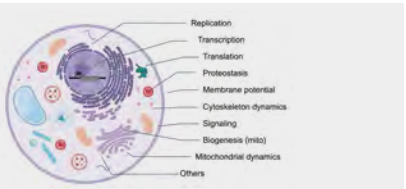


Pontzer et al. *Science* 2021

ENERGY EXPENDITURE and OxPhos defects



Intracellular



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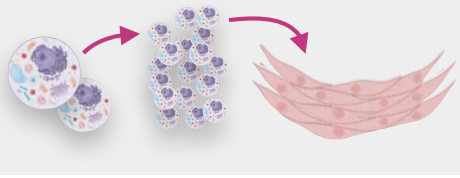
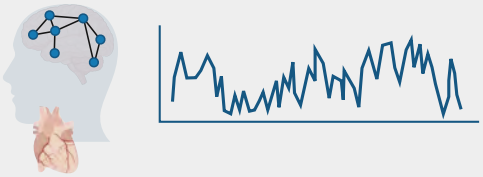
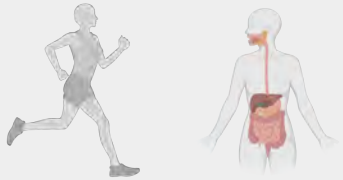
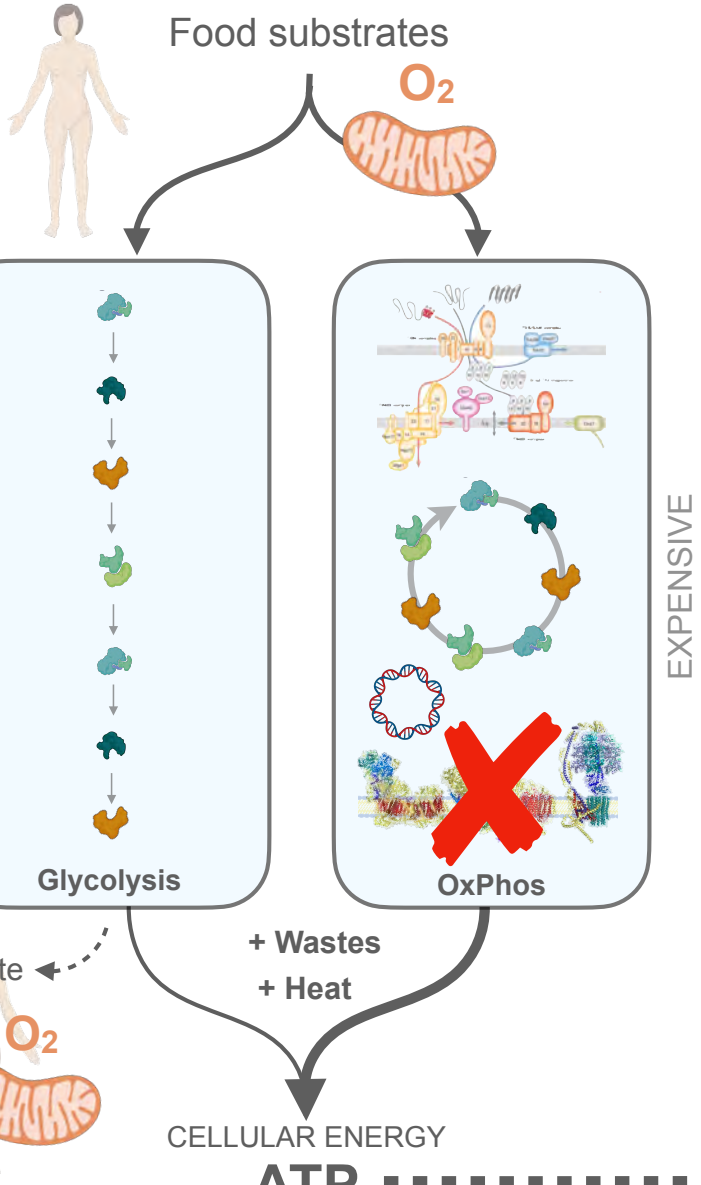


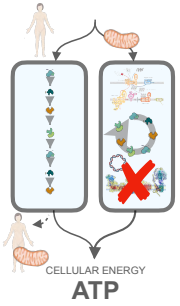
Physiology



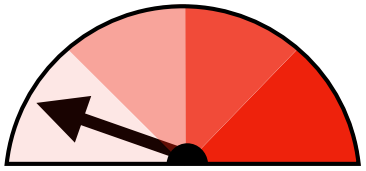
Behaviors



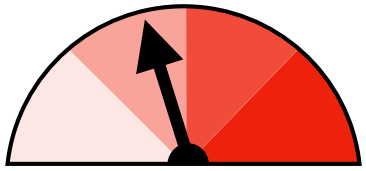




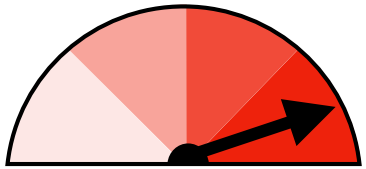
How does cellular energy expenditure / consumption change with OxPhos defects?



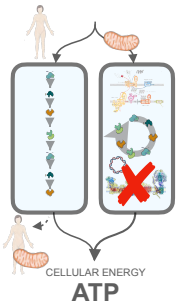
HYPOmetabolism



NORMOmetabolism



HYPERmetabolism



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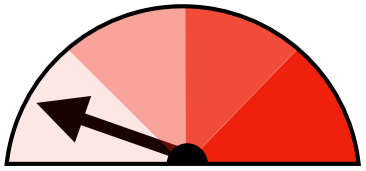
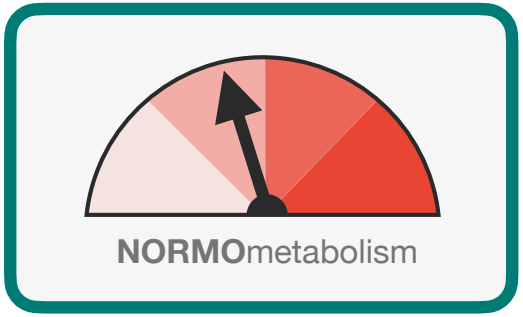
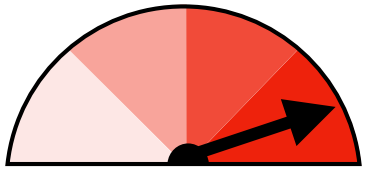
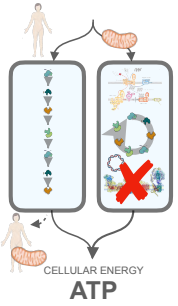


HYPOmetabolism

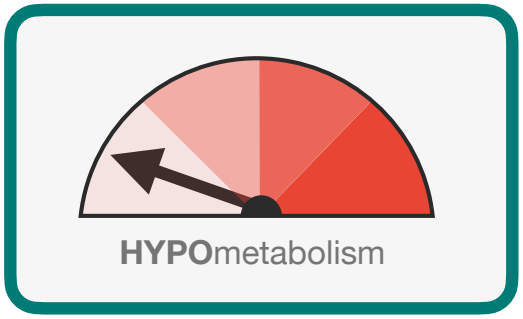


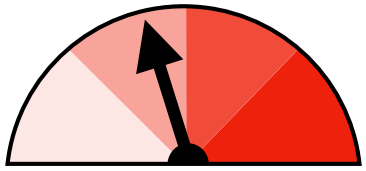


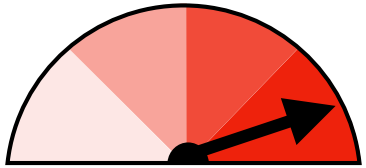
HYPERmetabolism

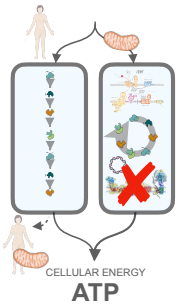


How does cellular energy expenditure / consumption change with OxPhos defects?

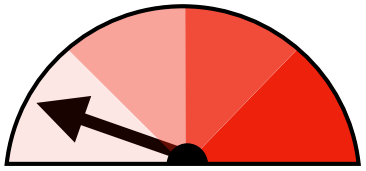




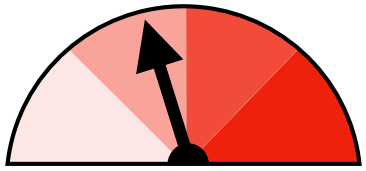




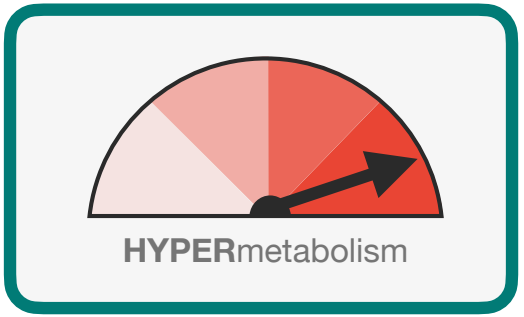
How does cellular energy expenditure / consumption change with OxPhos defects?



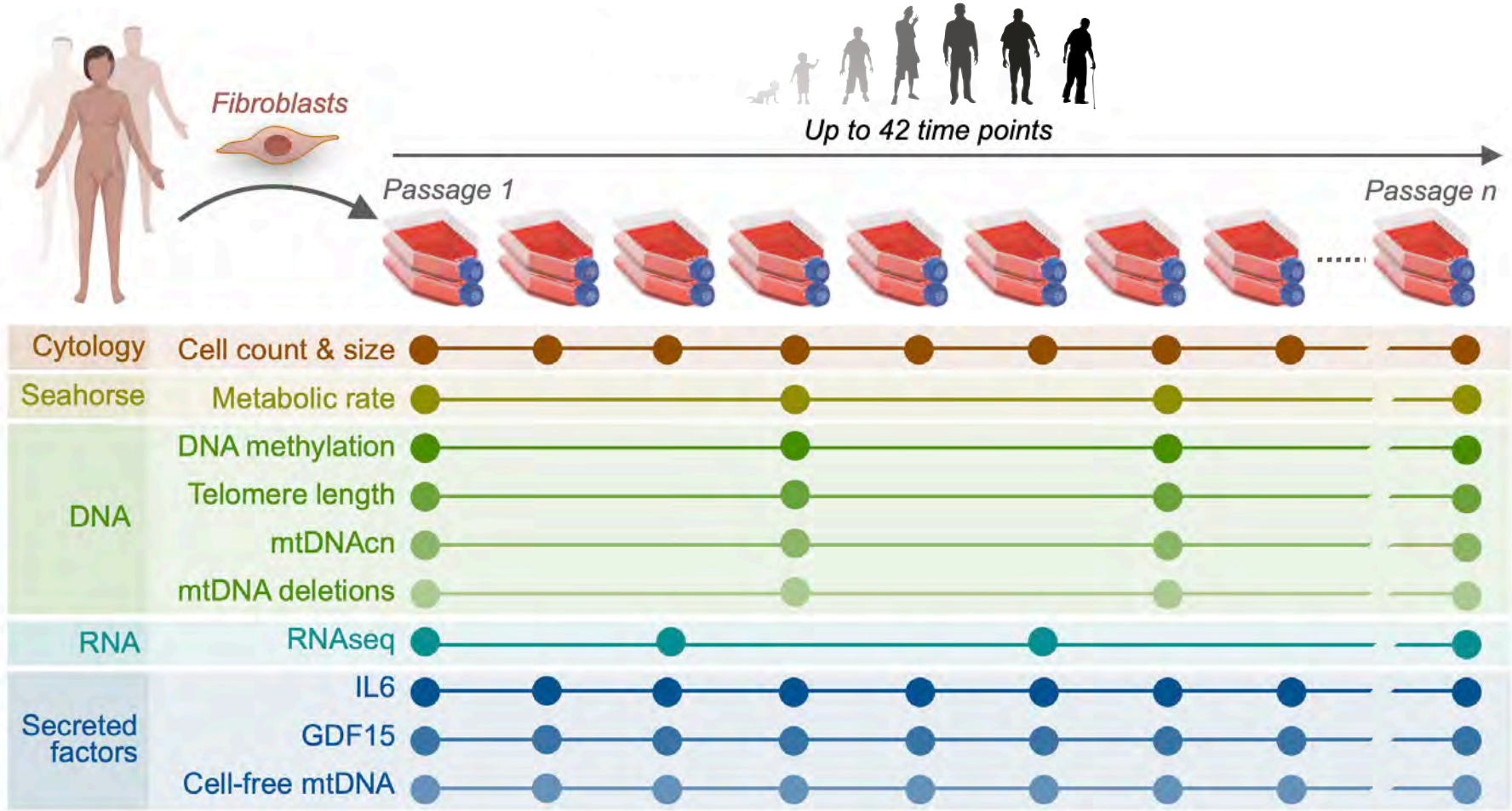
HYPOmetabolism

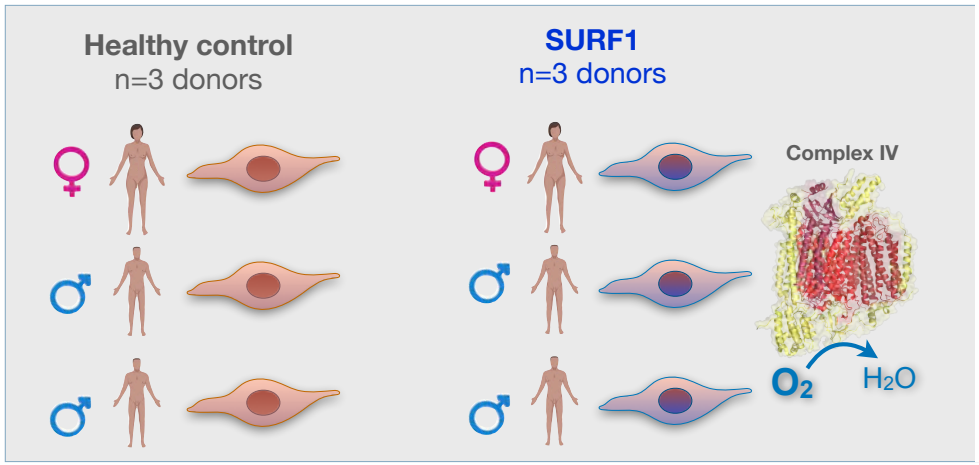


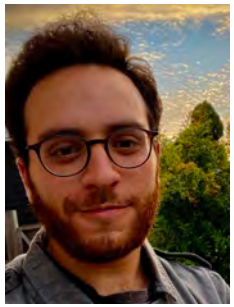
NORMOmetabolism



HYPERmetabolism







Gabriel Sturm

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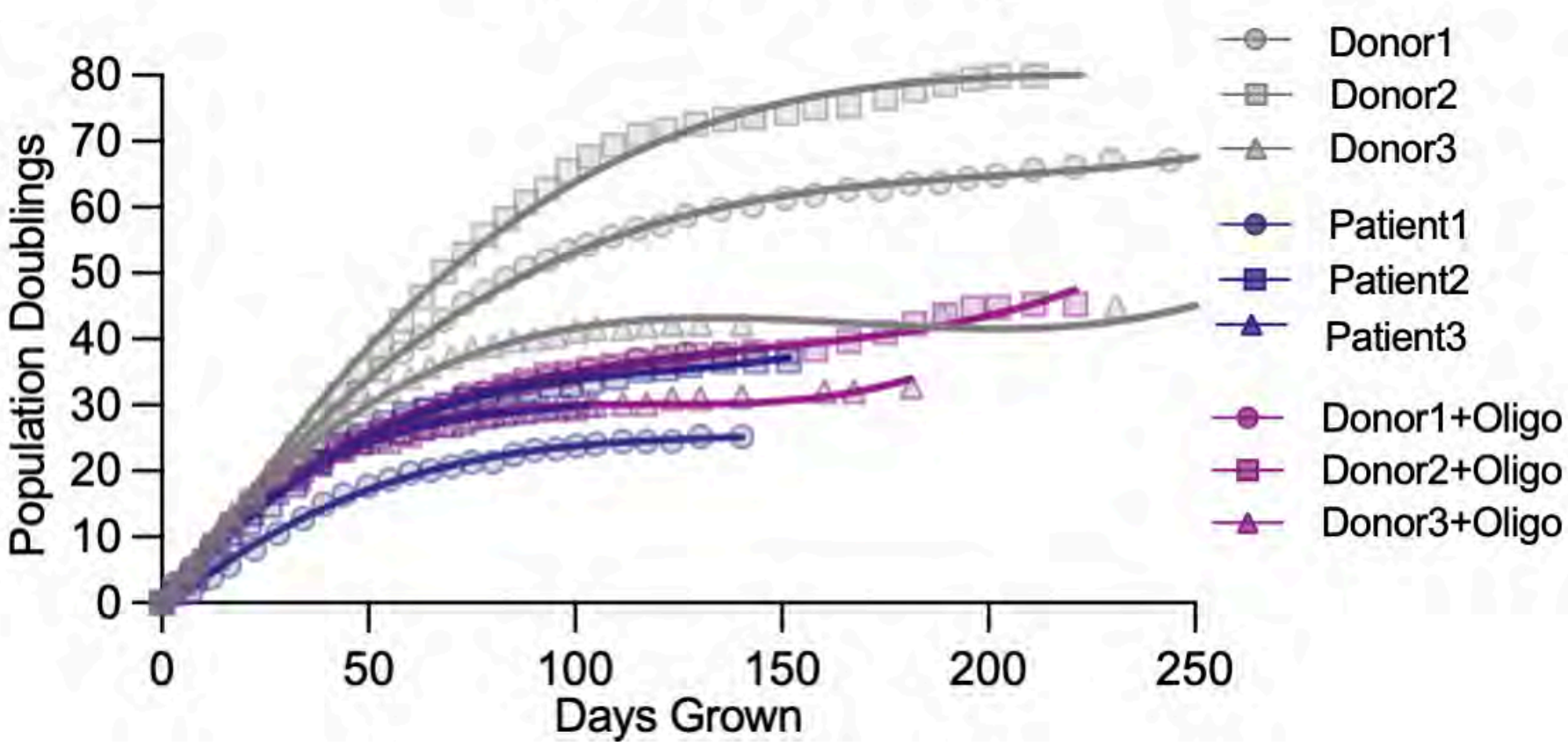
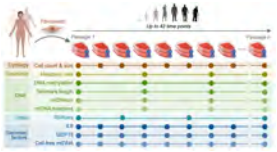
OxPhos defects **reduce** cell division rate by 32-48%

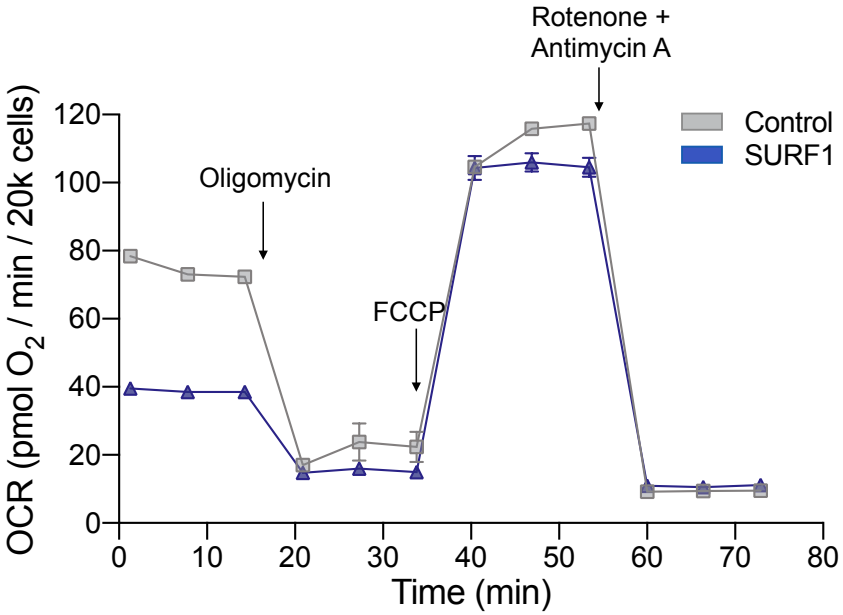


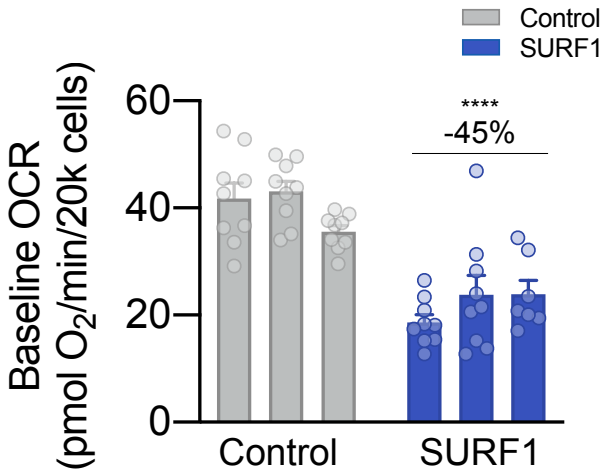
Slower division = less protein synthesis, less DNA replication, less telomerase activity, less mitochondrial biogenesis, … **ENERGY SAVINGS?**

Bioenergetic recalibrations to OxPhos defects

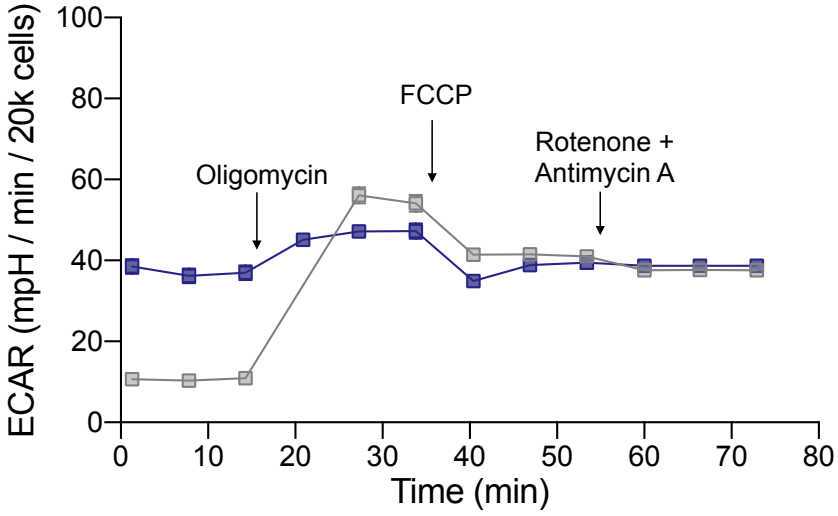


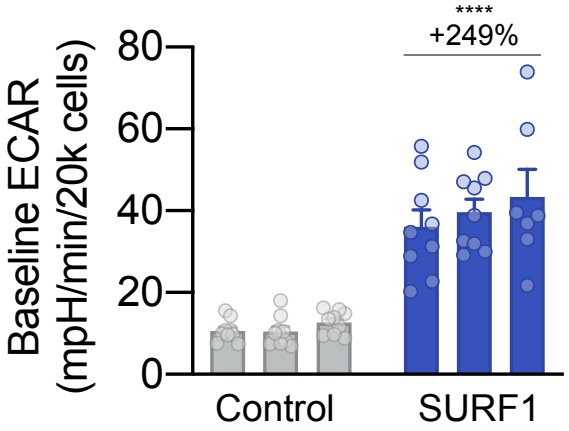
OxPhos





Glycolysis





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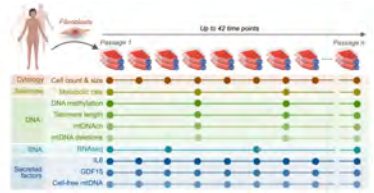
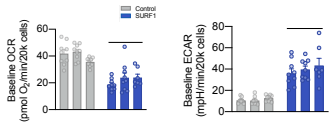
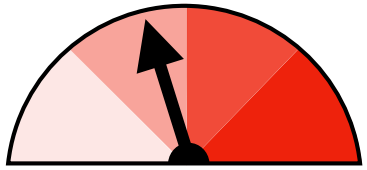
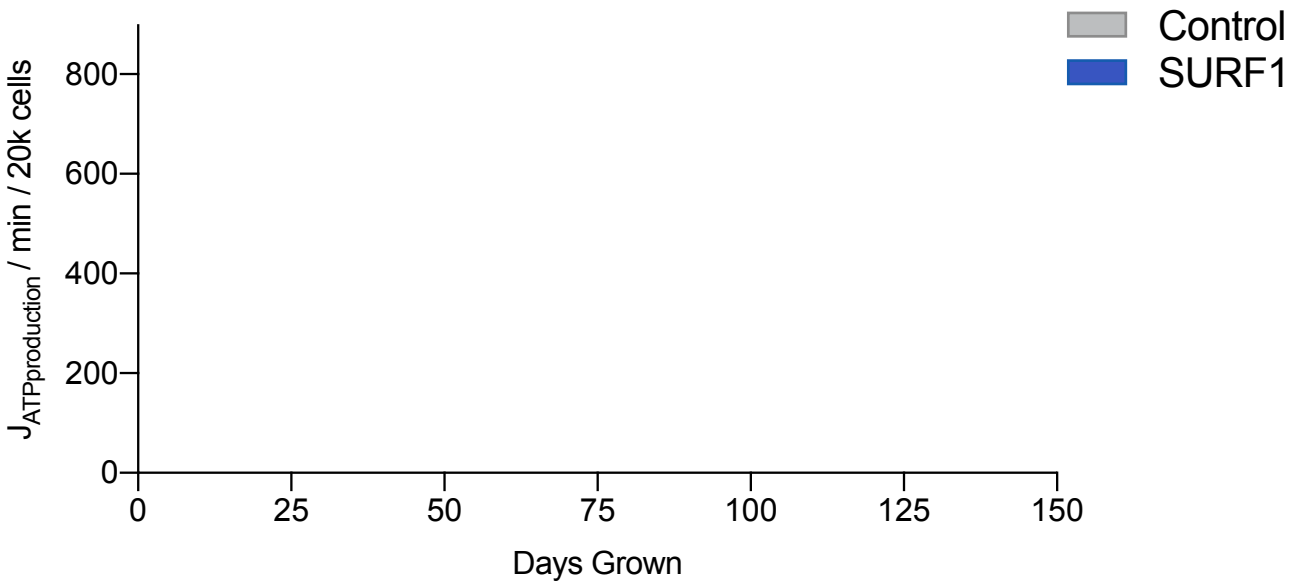
Lifespan trajectories of energy expenditure





Total energy consumption





Method from Mookerjee et al. *JBC* 2017

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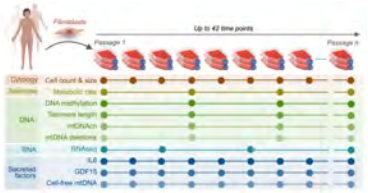
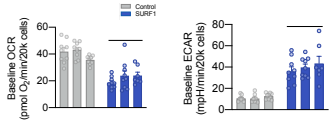
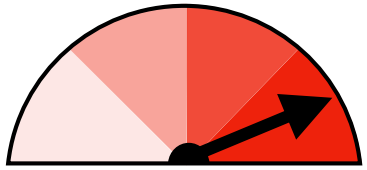
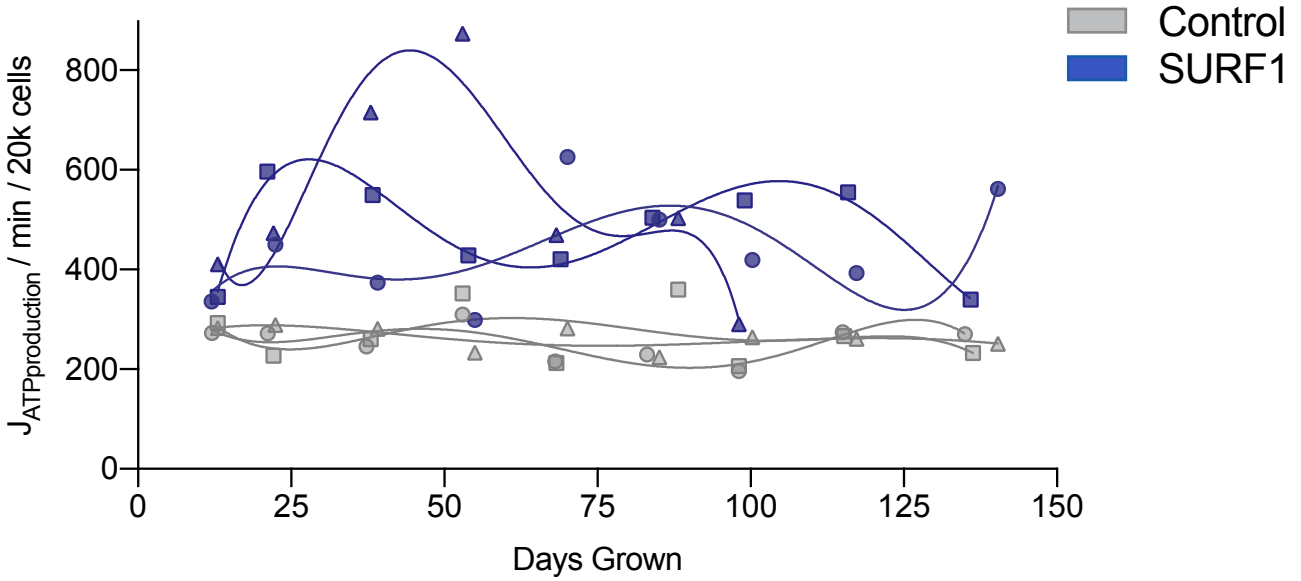
Lifespan trajectories of energy expenditure





Total energy consumption





Method from Mookerjee et al. *JBC* 2017

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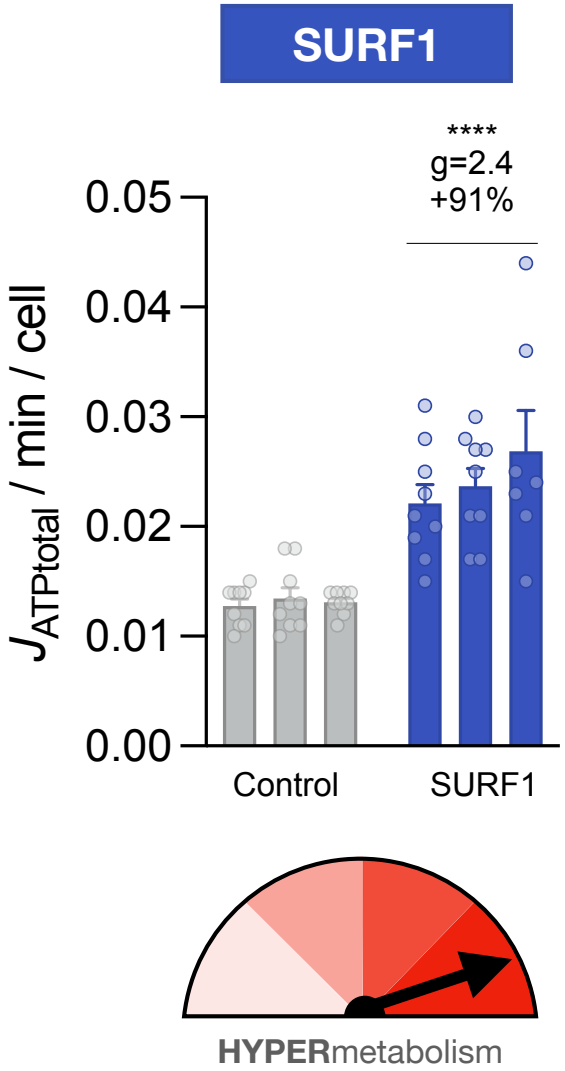
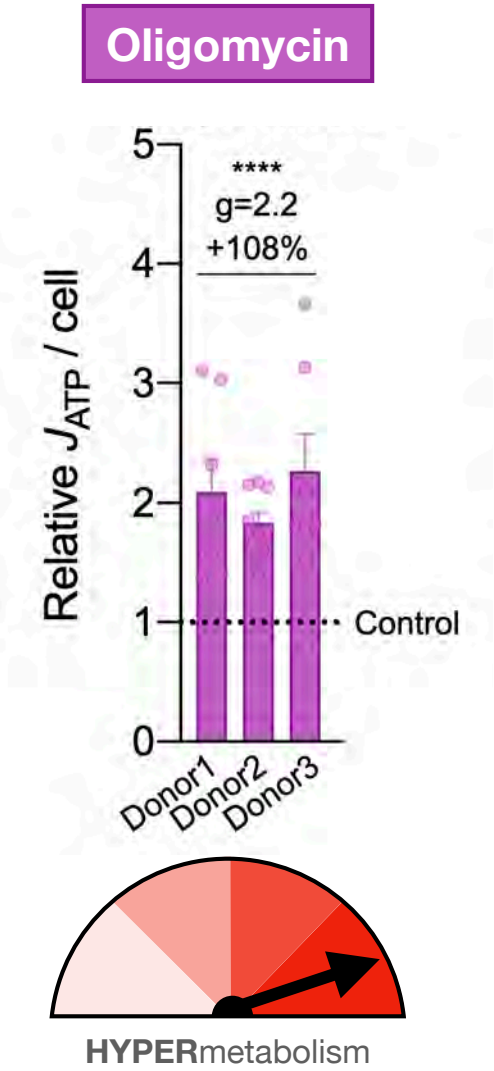
OxPhos-deficient cells are **hypermetabolic**





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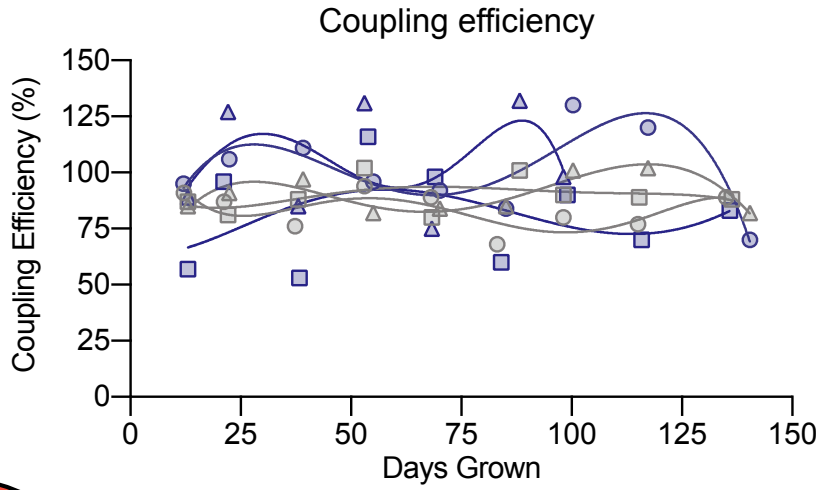
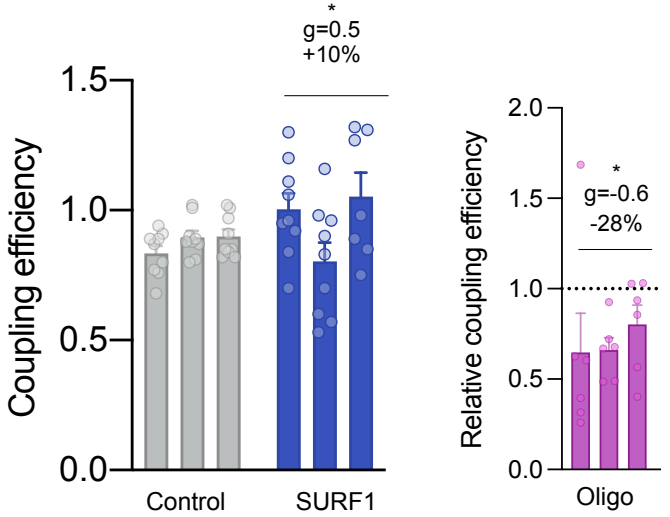
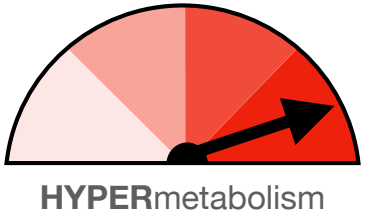
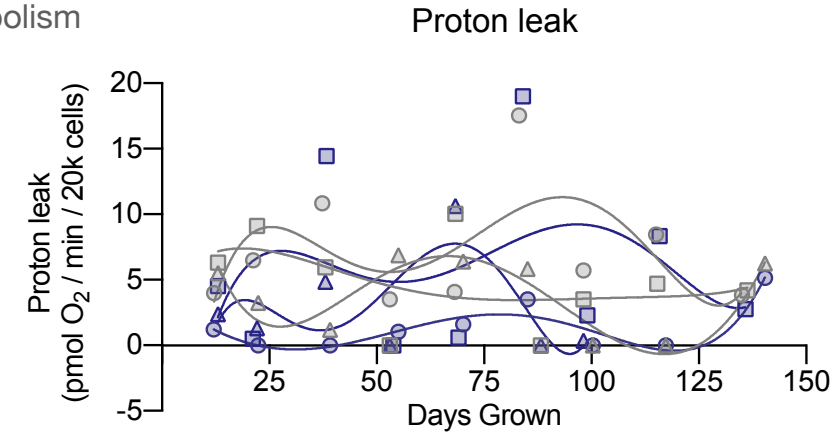
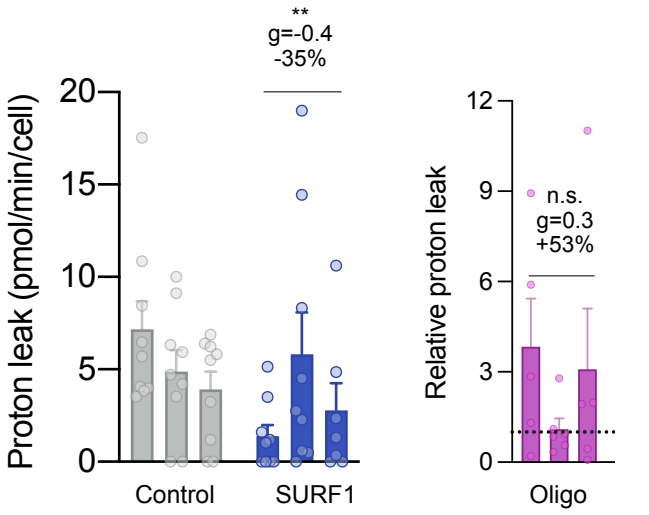
Hypermetabolism is not driven by OxPhos uncoupling











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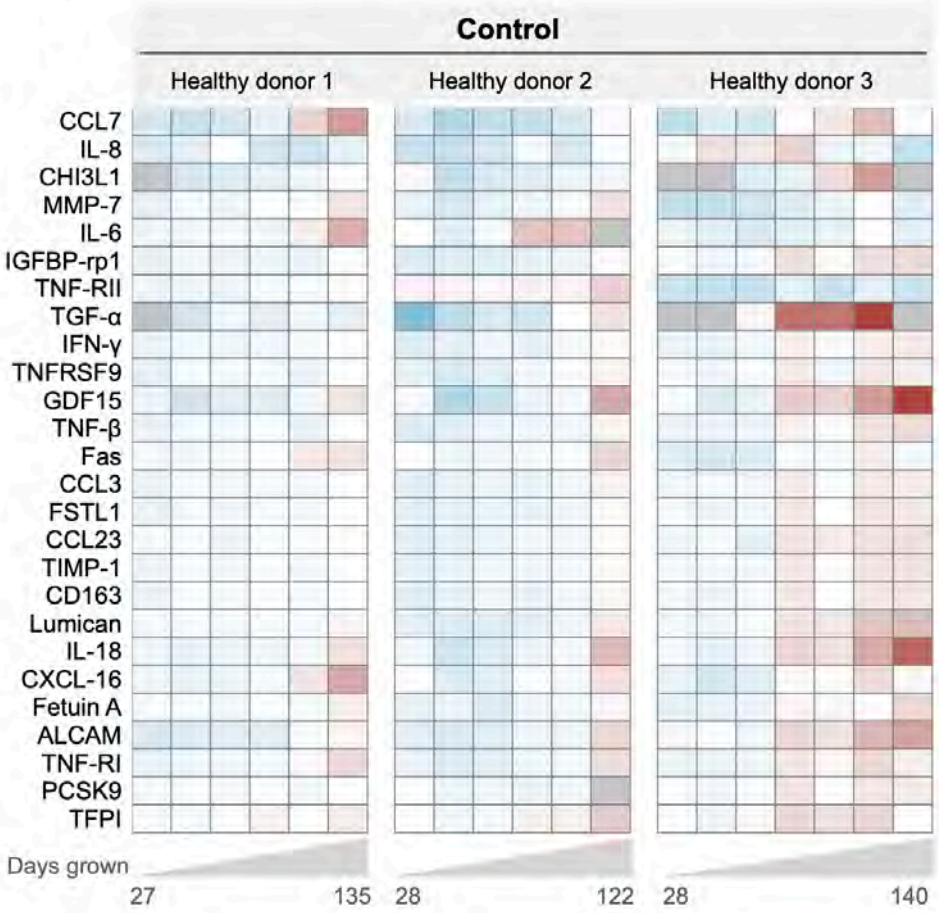
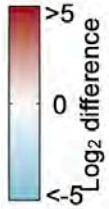
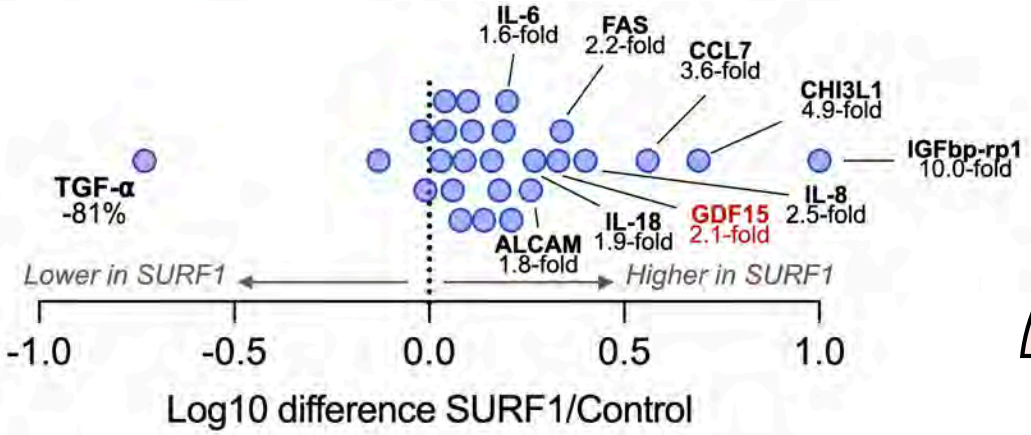
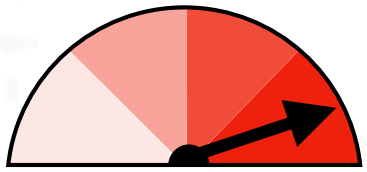
OxPhos defects increase cytokine release





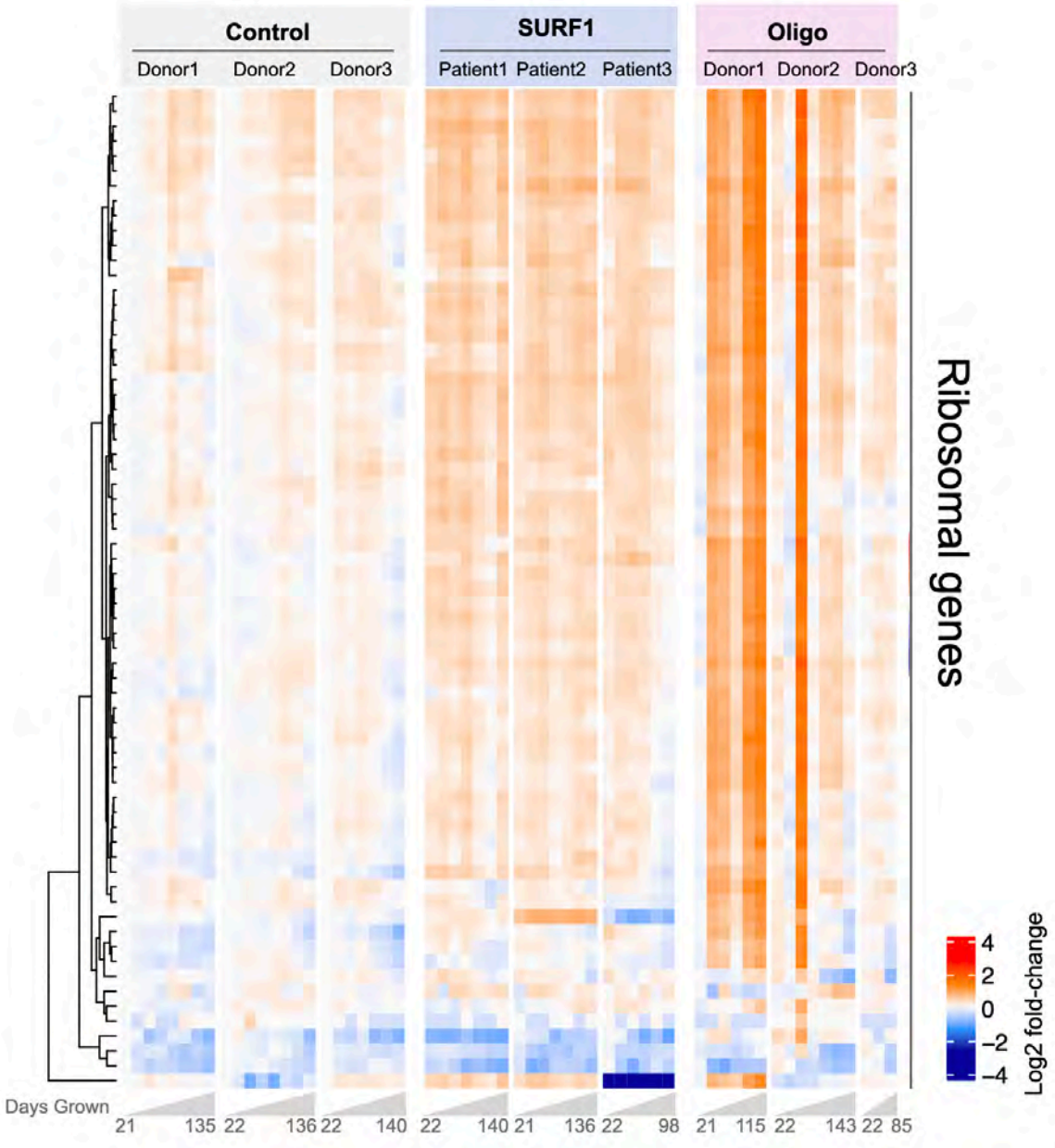
Maximum cytokine levels across the lifespan

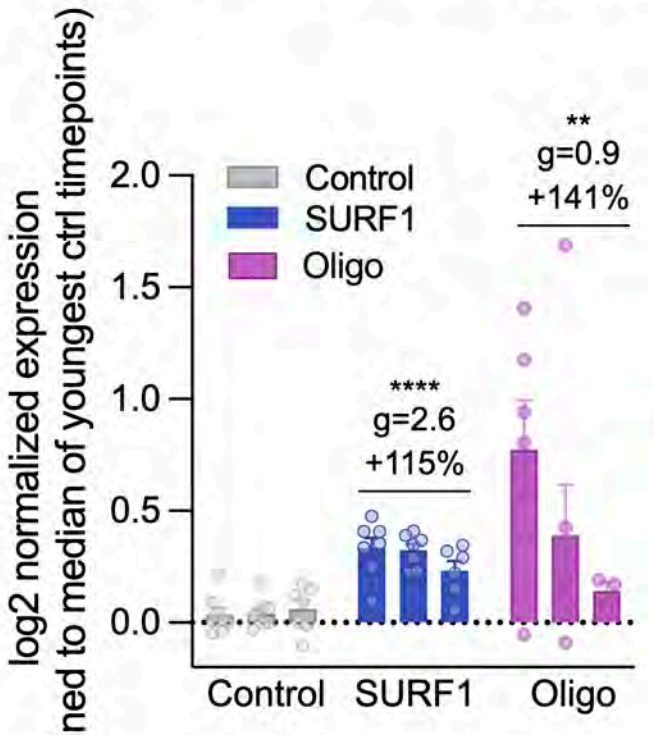


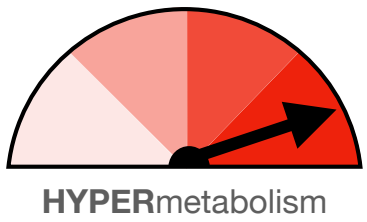


HYPERmetabolism

OxPhos defects upregulate the translation machinery







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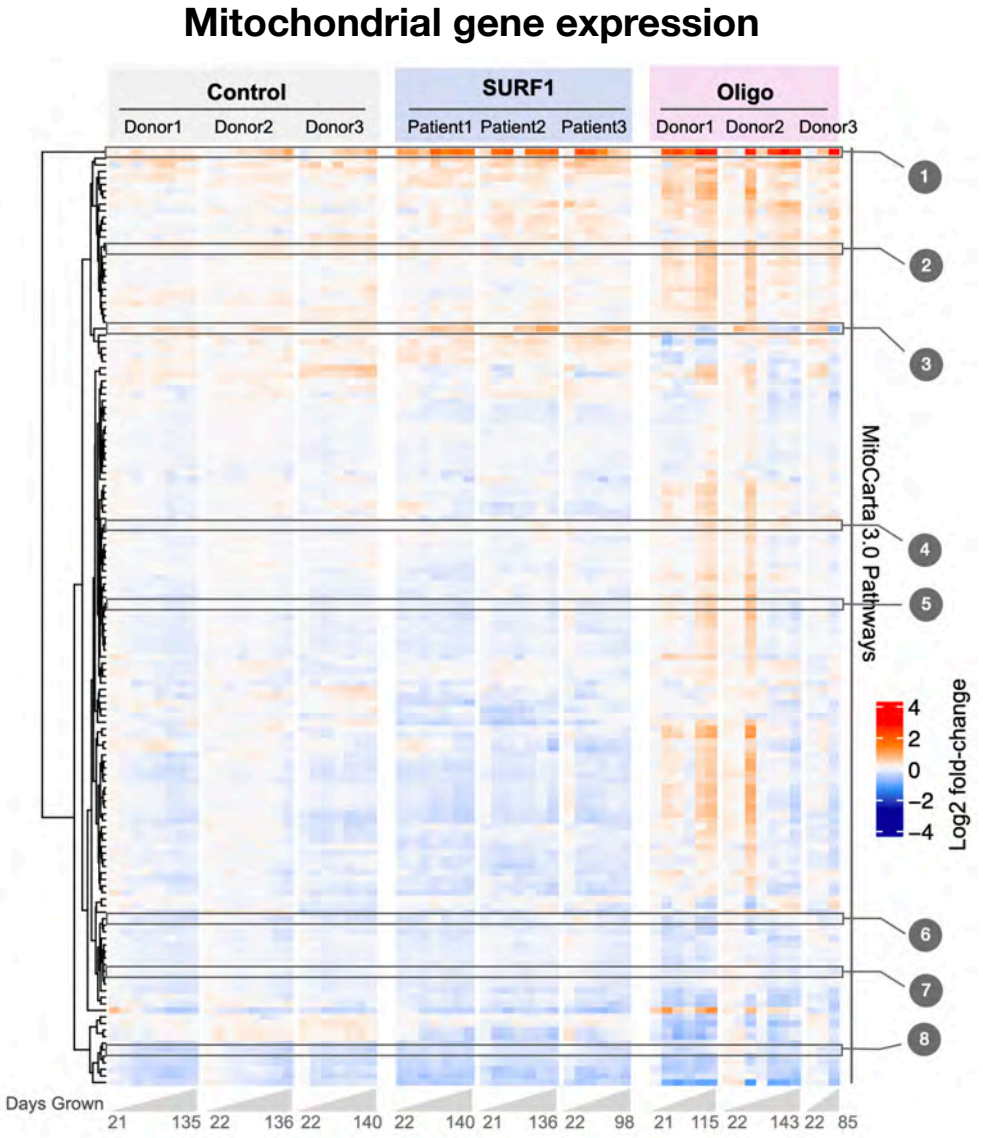
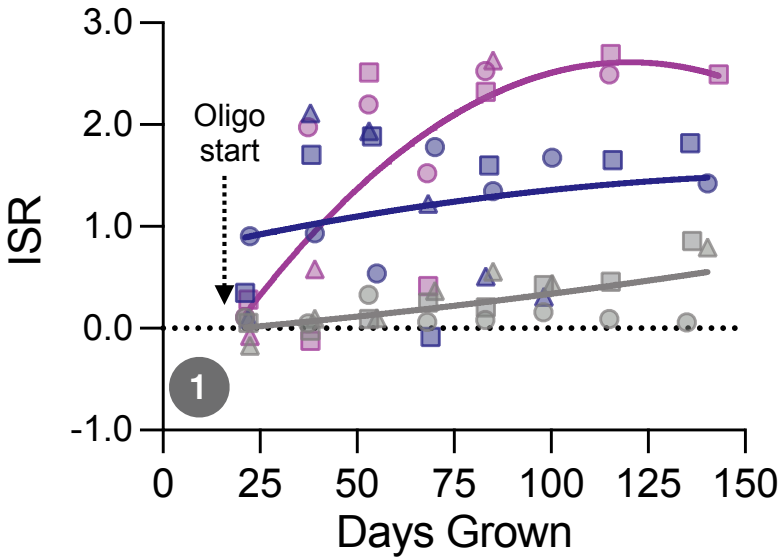
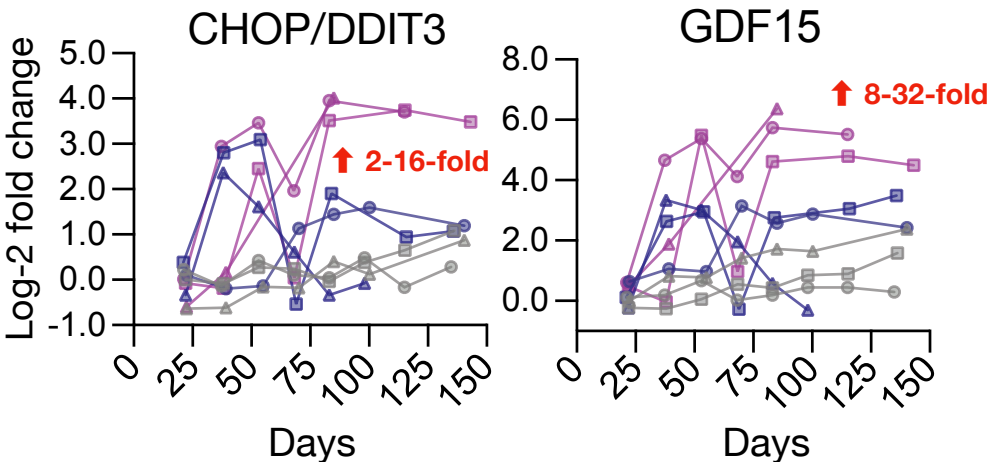
Buttgereit et al. *Biochem J* 1995

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







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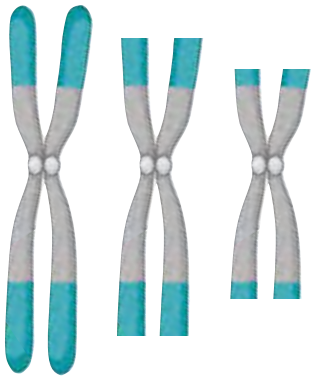
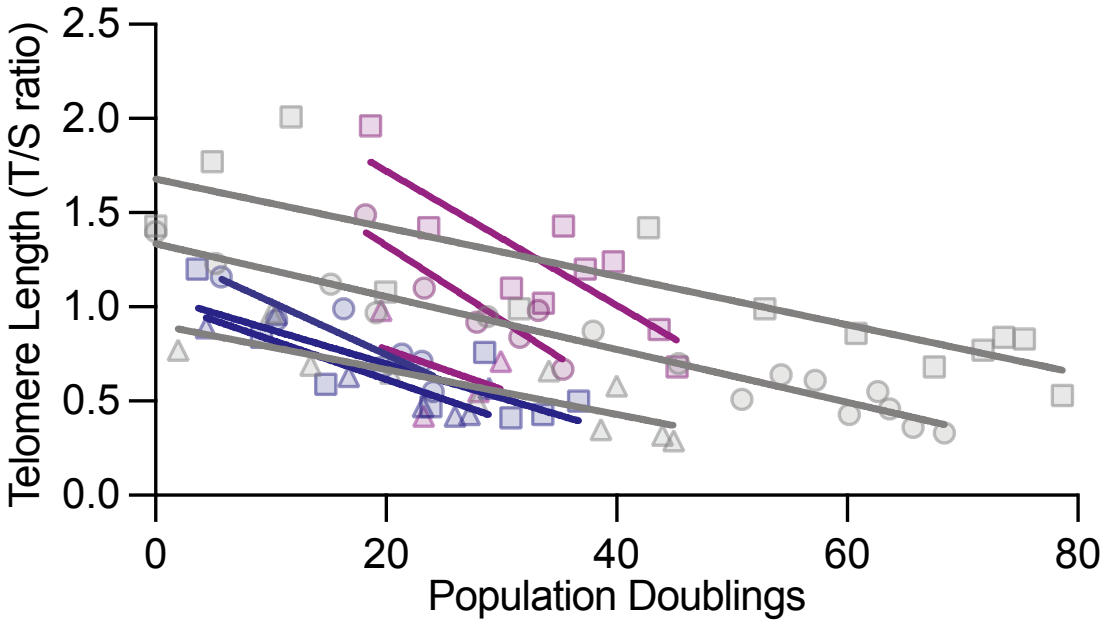
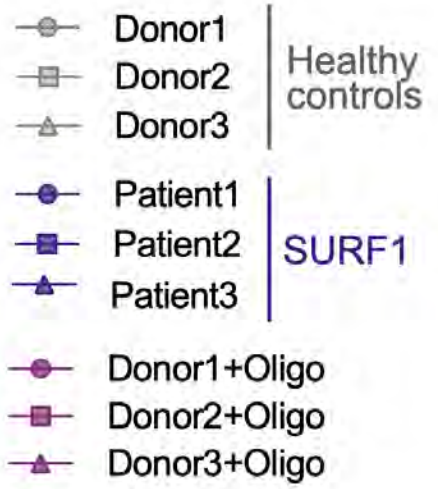
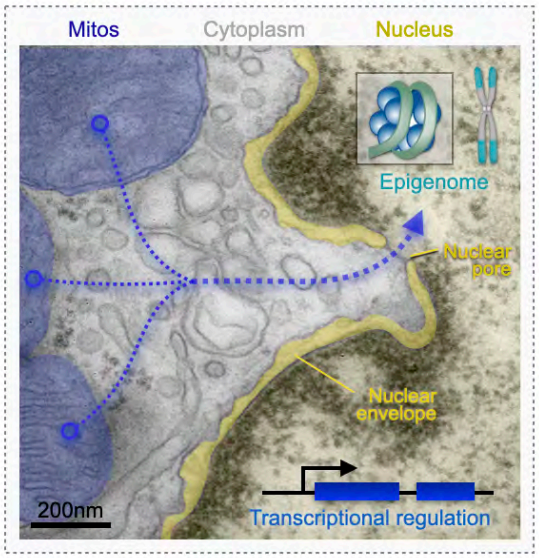
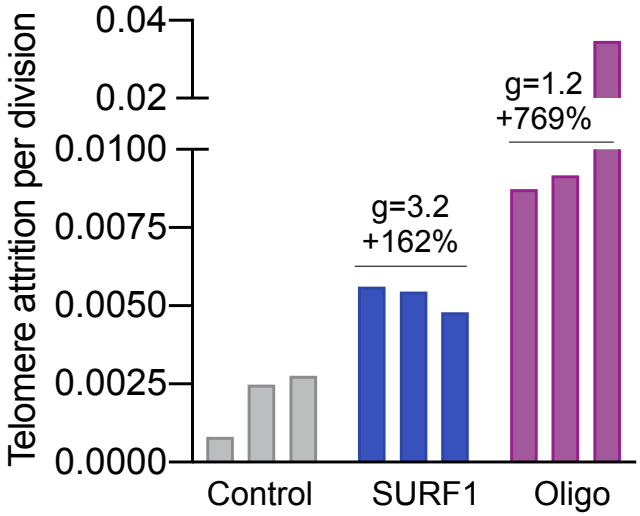
OxPhos defects accelerate telomere shortening rate

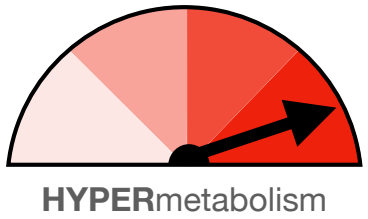






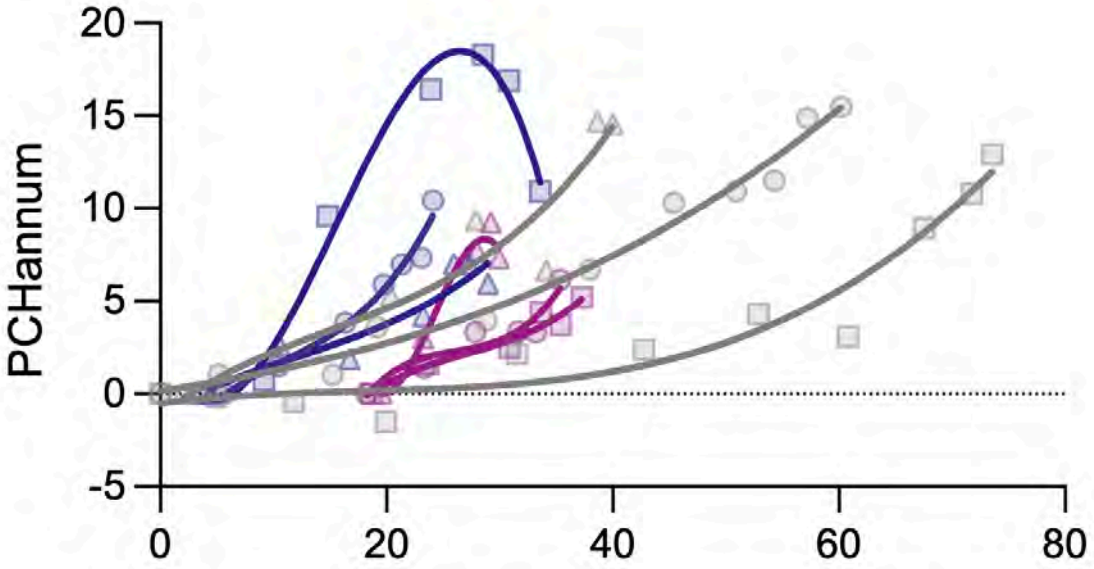


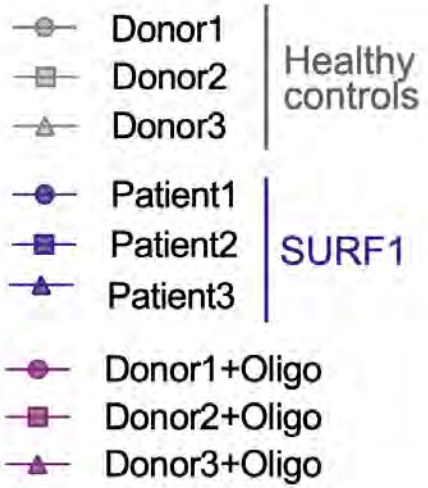


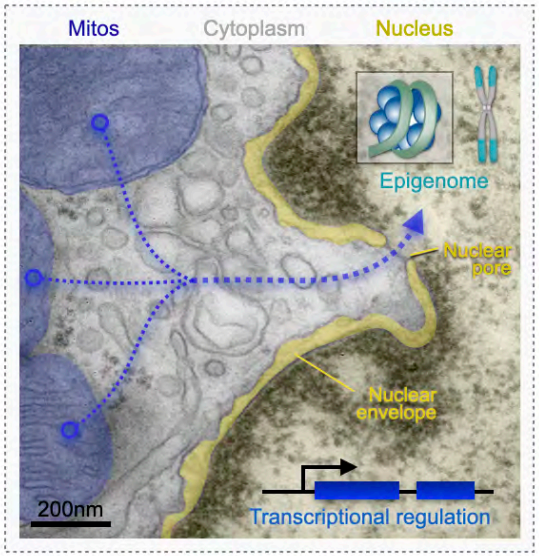


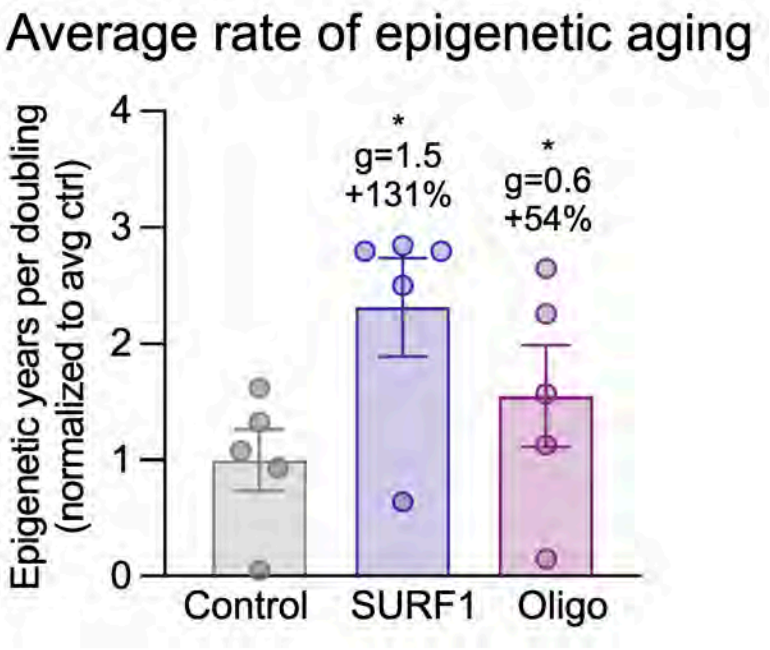
Jue Lin, Elissa Epel
Gabriel Sturm

OxPhos defects accelerate epigenetic aging DNA methylation clocks



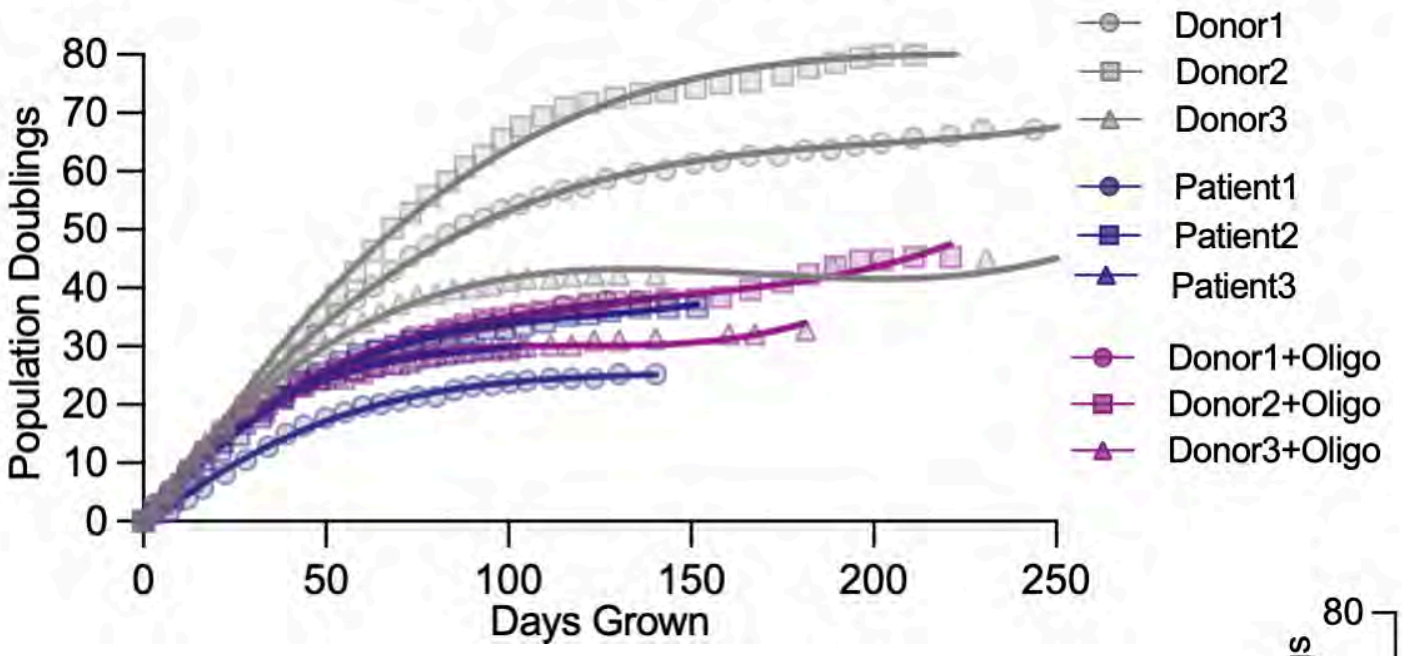


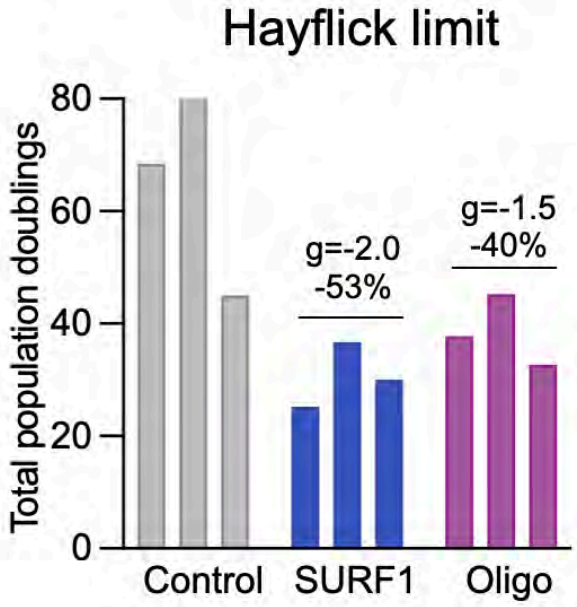




Steve Horvath, Morgan Levine.
Albert Higgins-Chen
Gabriel Sturm

Hypermetabolic cells have a reduced Hayflick limit





Gabriel Sturm

scientific data

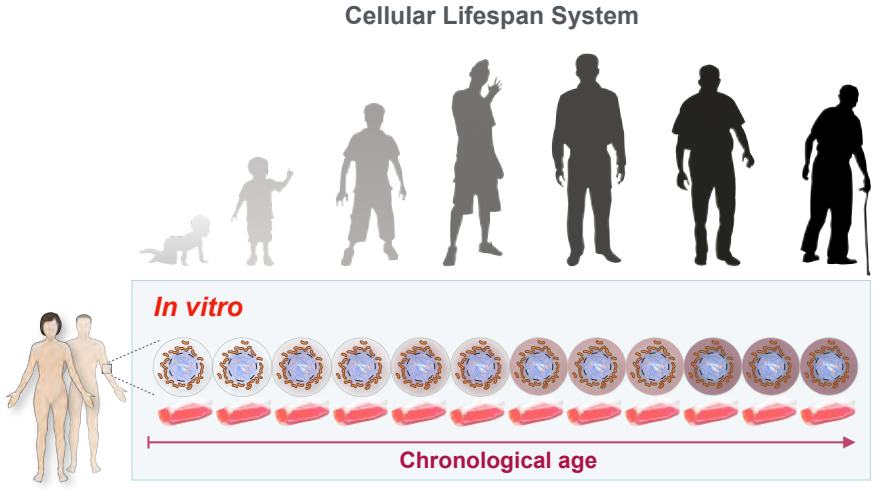
OPEN

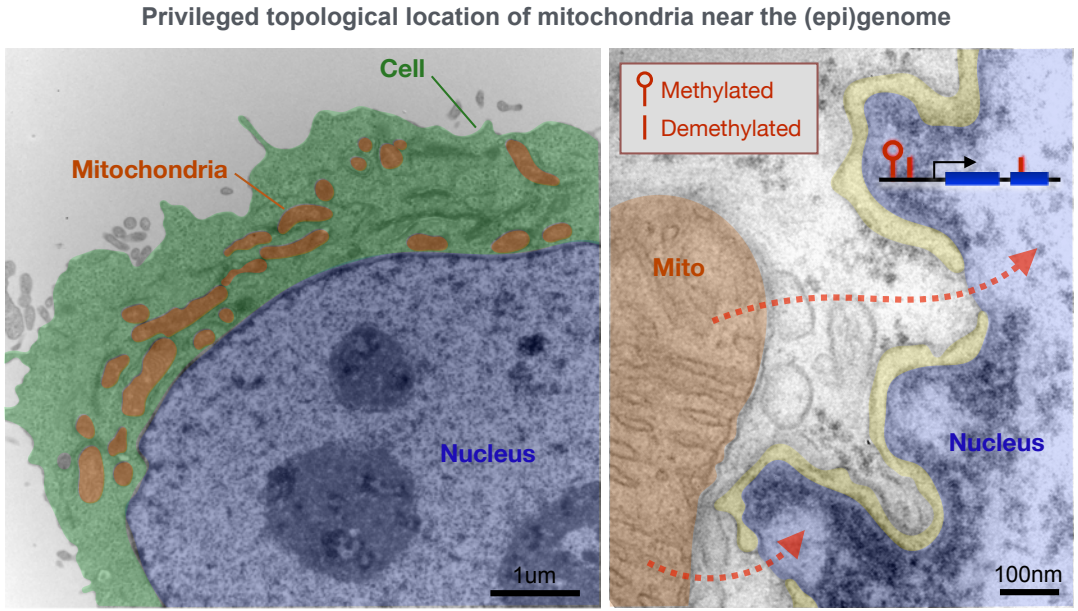
DATA DESCRIPTOR

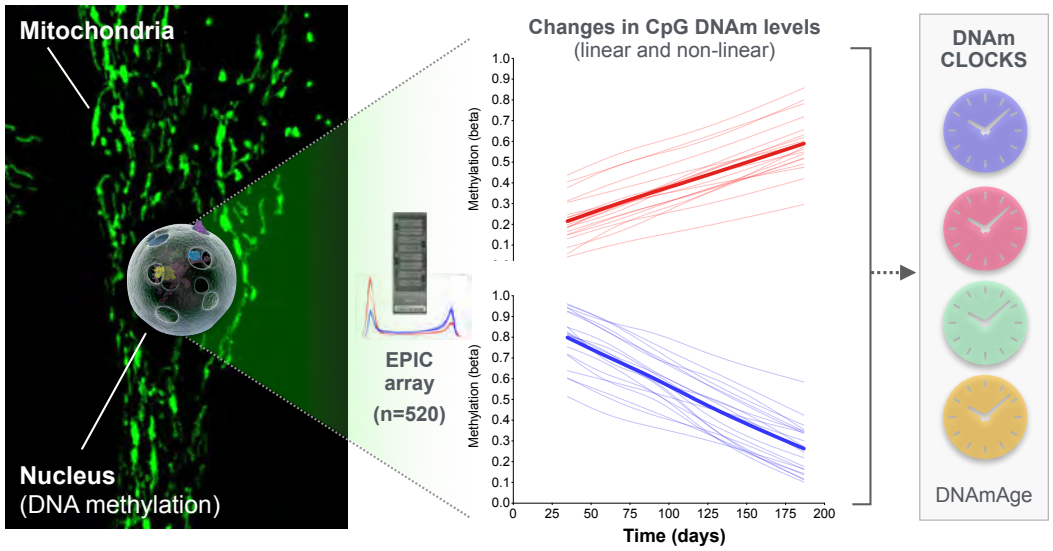
A multi-omics longitudinal aging dataset in primary human fibroblasts with mitochondrial perturbations

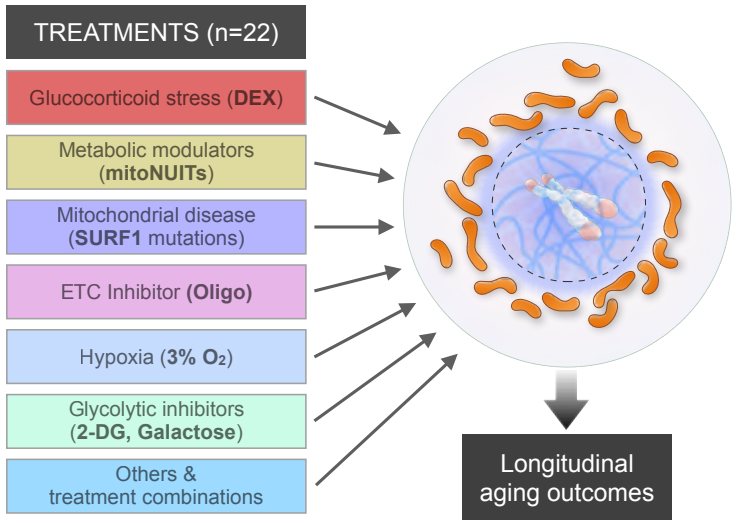
Gabriel Sturm[1,2], Anna S. Monzel[1], Kalpita R. Karan[1], Jeremy Michelson[1], Sarah A. Ware[3], Andres Cardenas[4], Jue Lin[2], Céline Bris[5,6], Balaji Santhanam[7], Michael P. Murphy[8], Morgan E. Levine[9,10], Steve Horvath[10,11], Daniel W. Belsky[12], Shuang Wang[13], Vincent Procaccio[5,6],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

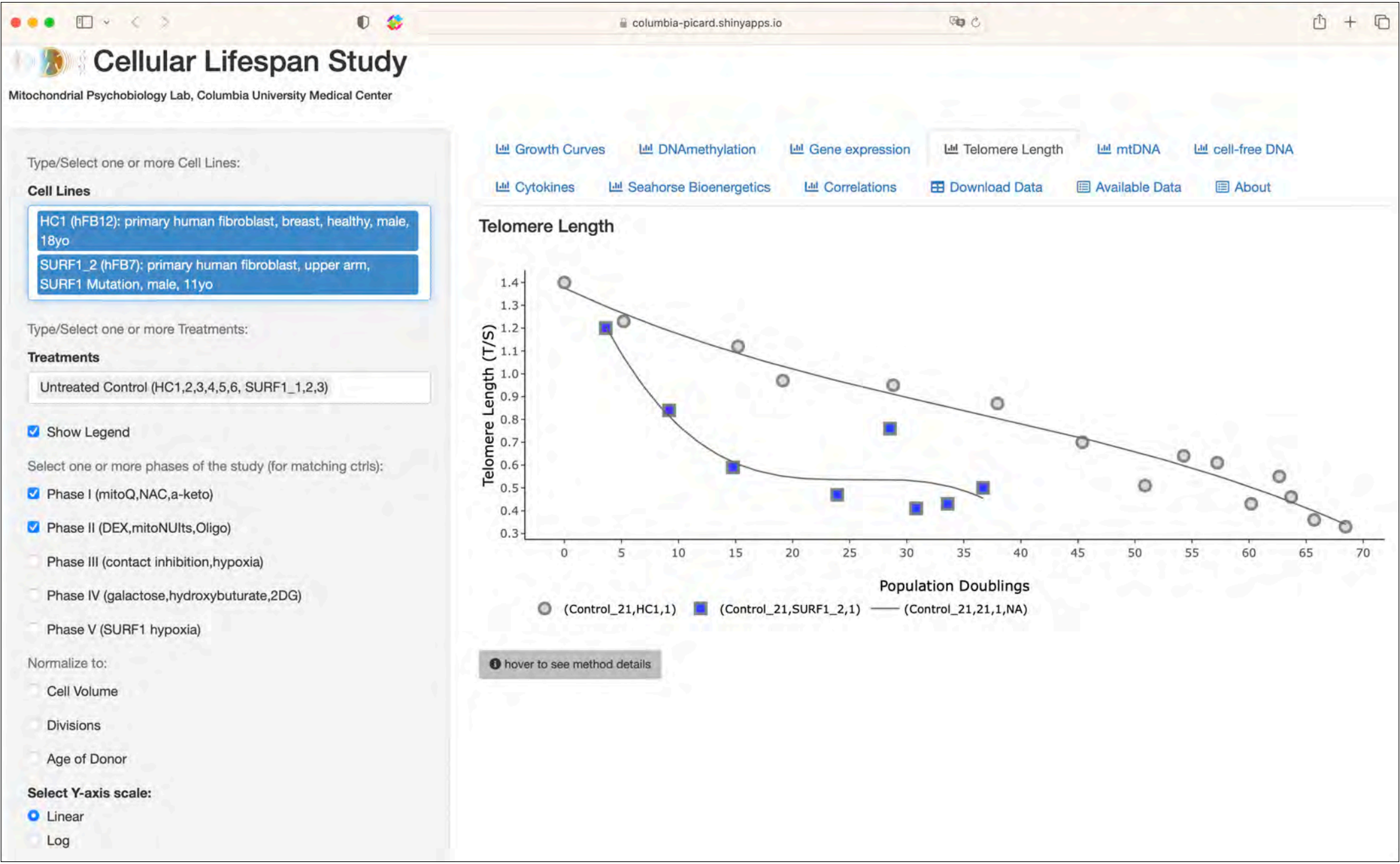








Sturm et al. *Sci Data* 2022



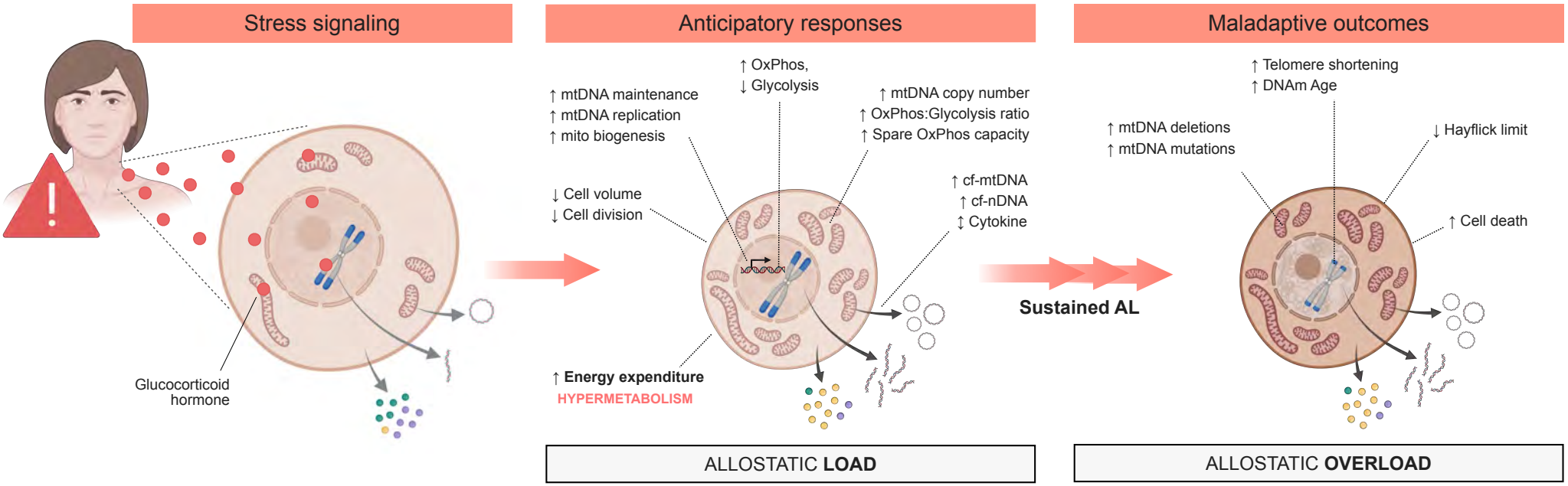
https://columbia-picard.shinyapps.io/shinyapp-Lifespan_Study/

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

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



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

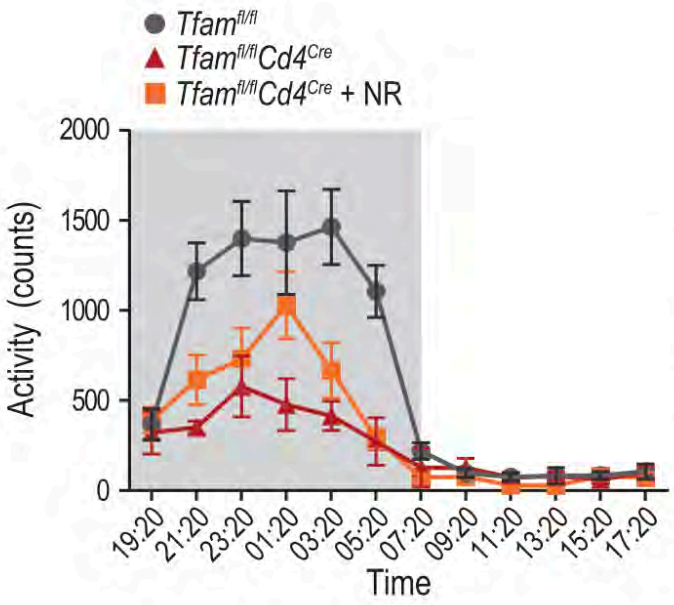
Bobba-Alves et al. *PNEC* 2023

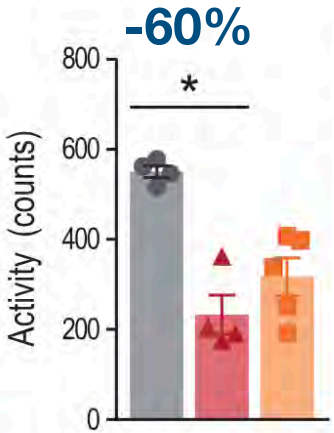
IMMUNOMETABOLISM

T cells with dysfunctional mitochondria induce multimorbidity and premature senescence

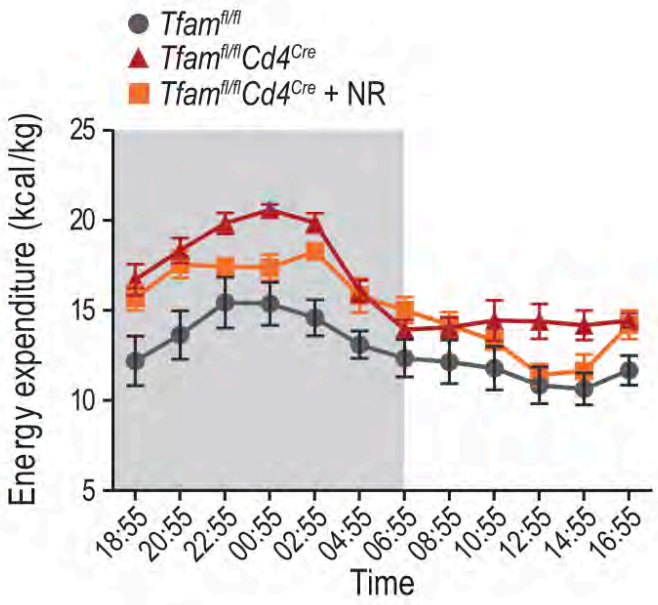
T cell-specific **Tfam KO**

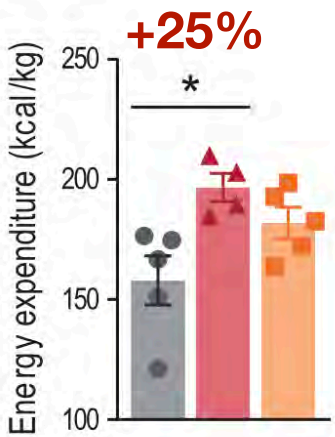
LOWER physical activity





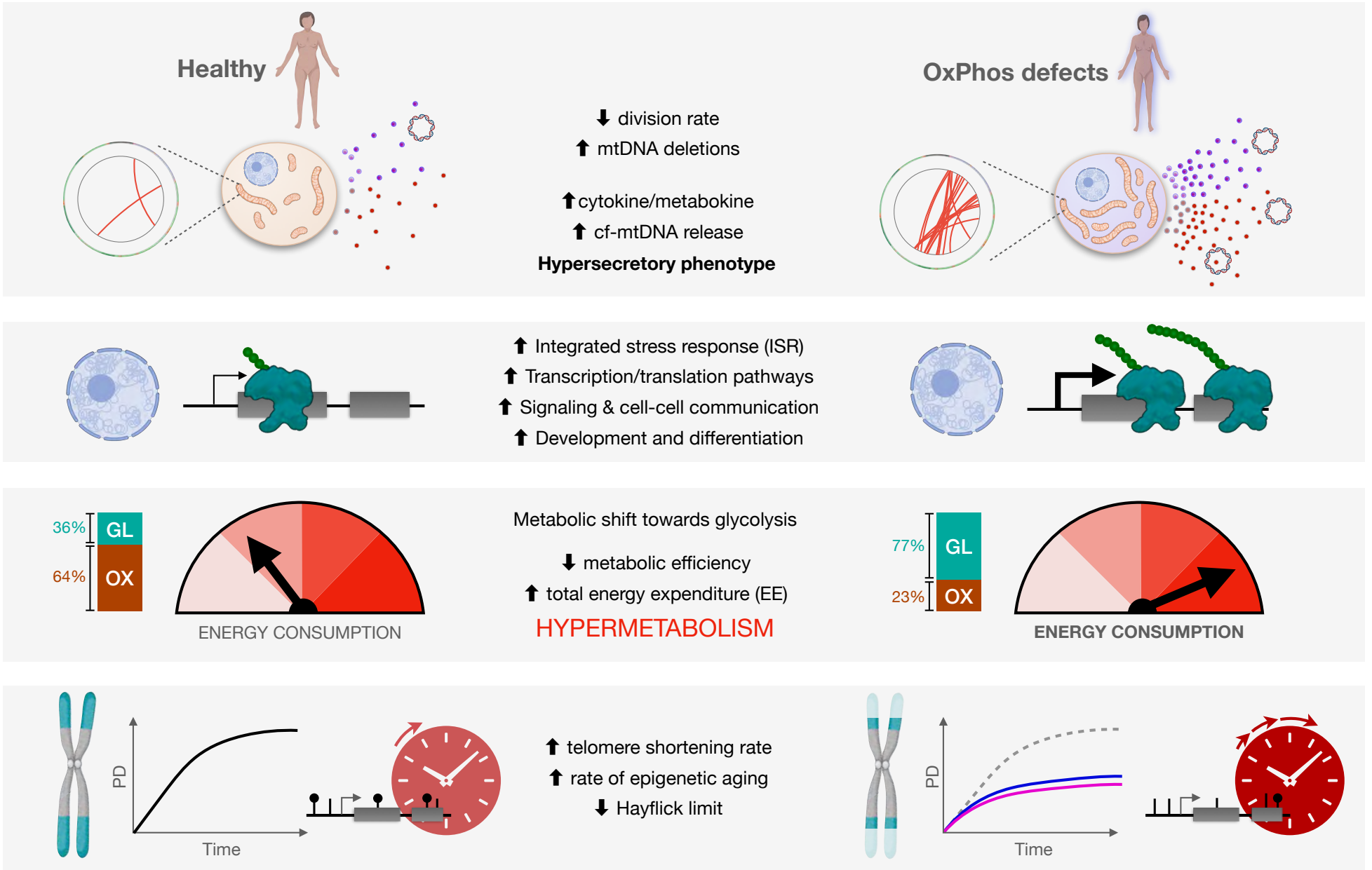
HIGHER metabolic rate





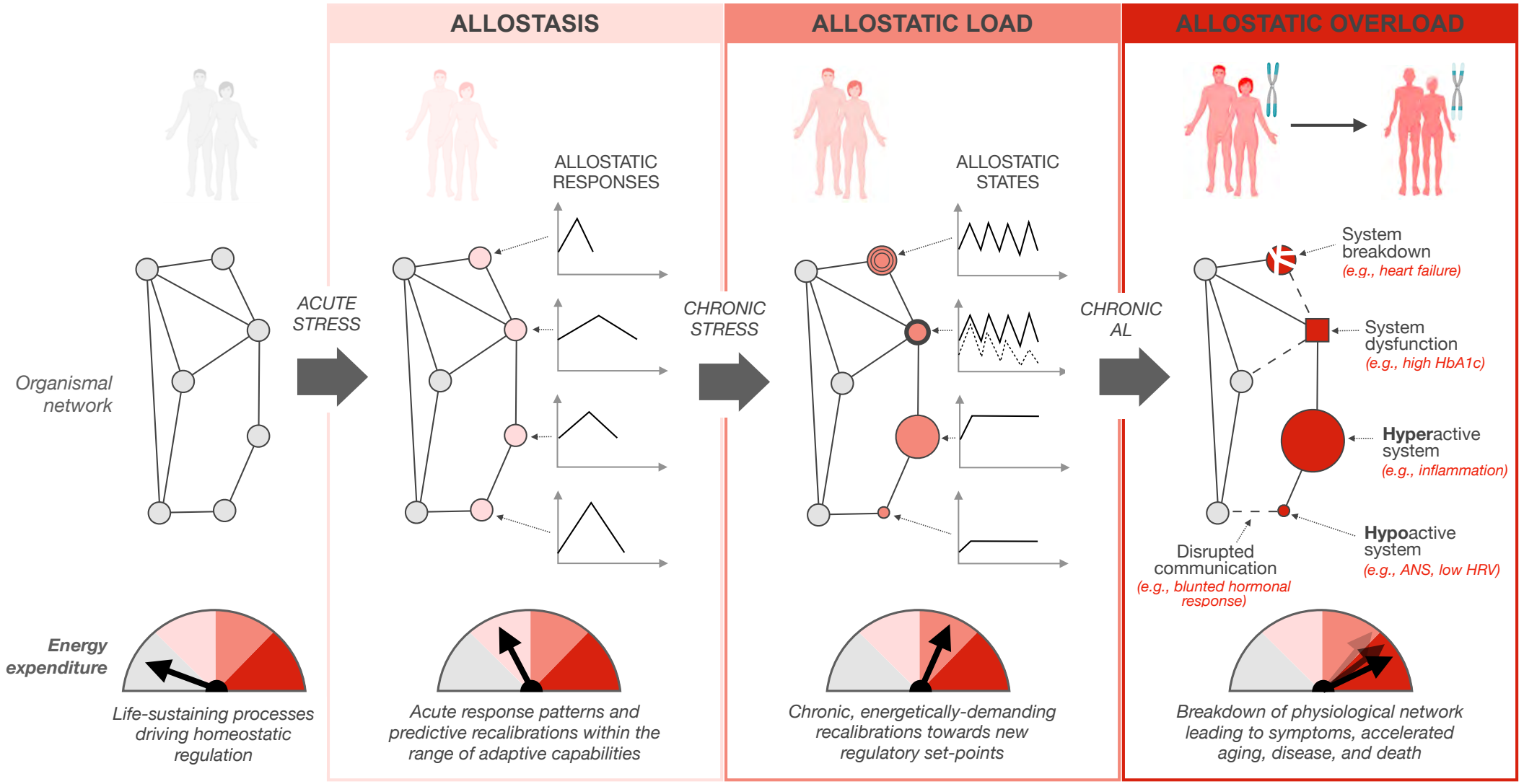
T cell-specific TFAM deficiency causes **HYPERMETABOLISM**

Desdin-Mico et al. *Science* 2020



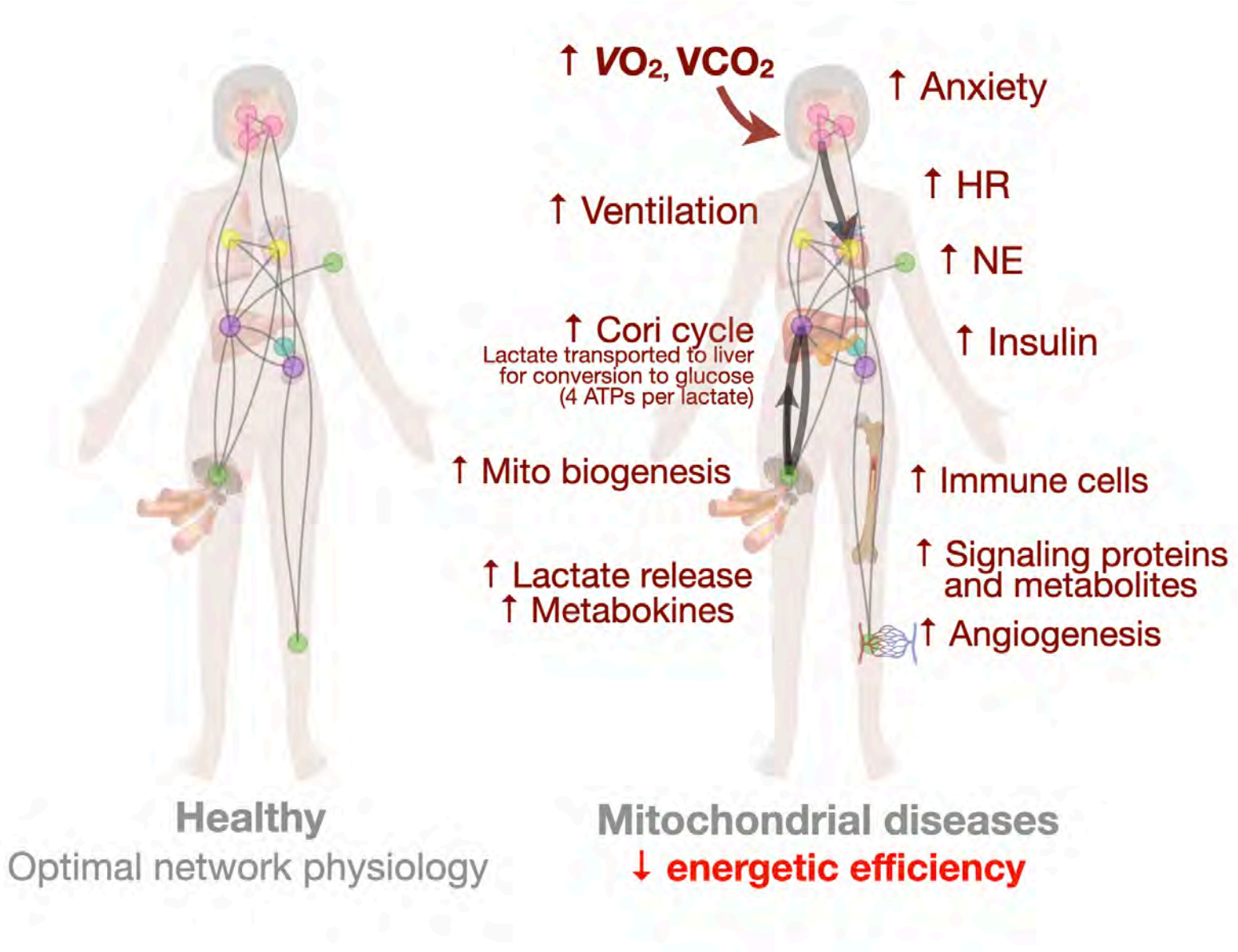
Sturm et al. *Commun Biol (2023)*

Energetic Model of Allostatic Load (EMAL)



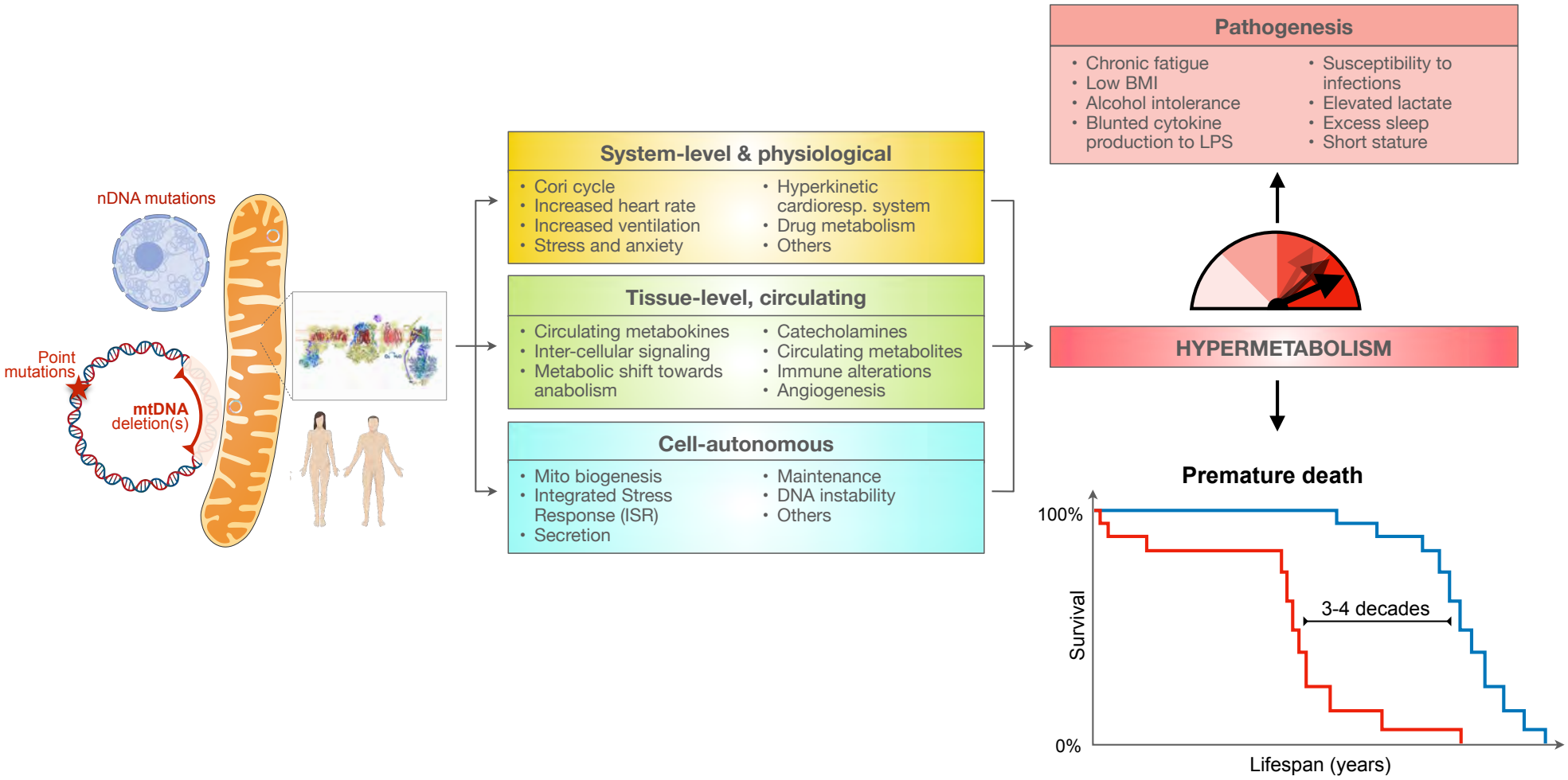
Bobba-Alves et al. *Psychoneuroendocrinol* 2022

Physiological mechanisms of hypermetabolism?



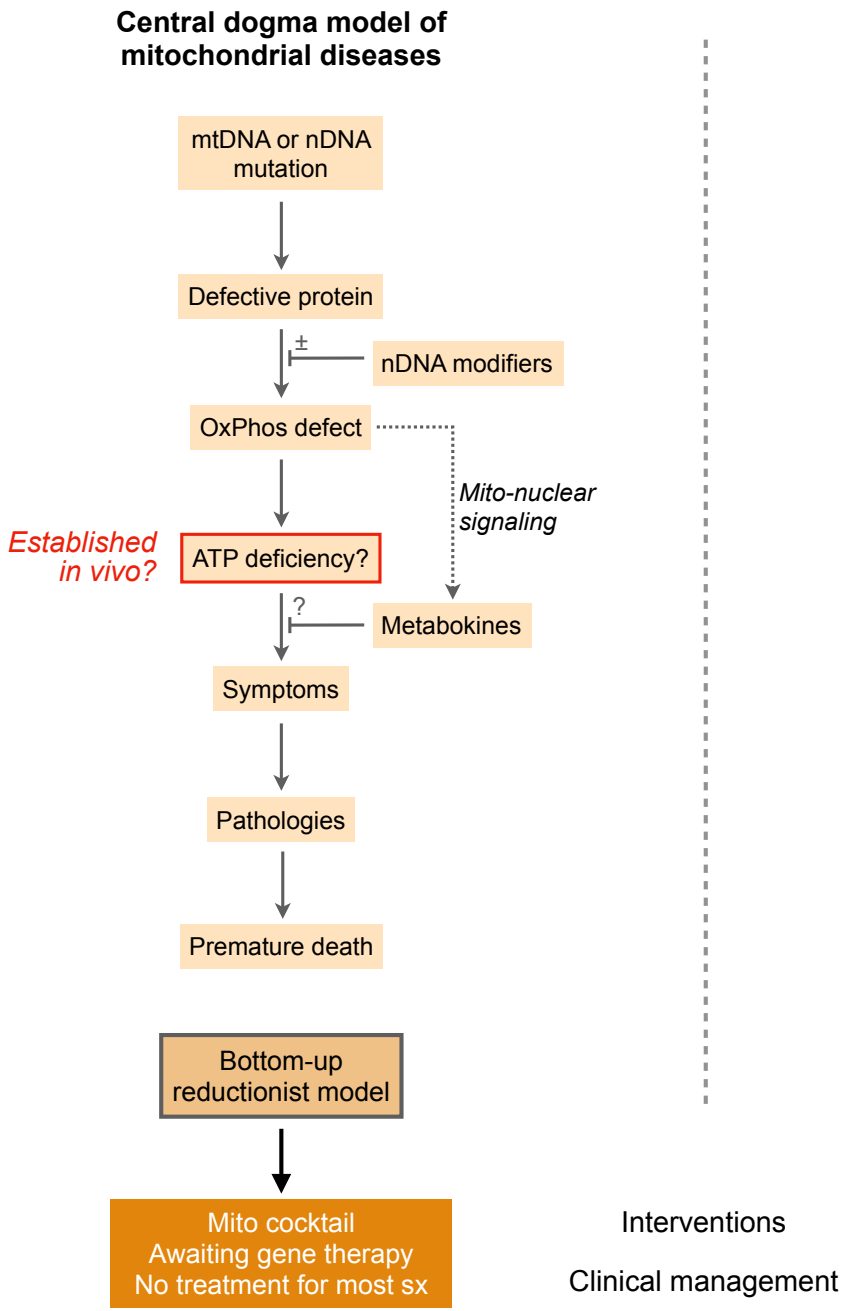
Sercel et al. (BioRxiv)

Potential sources of hypermetabolism

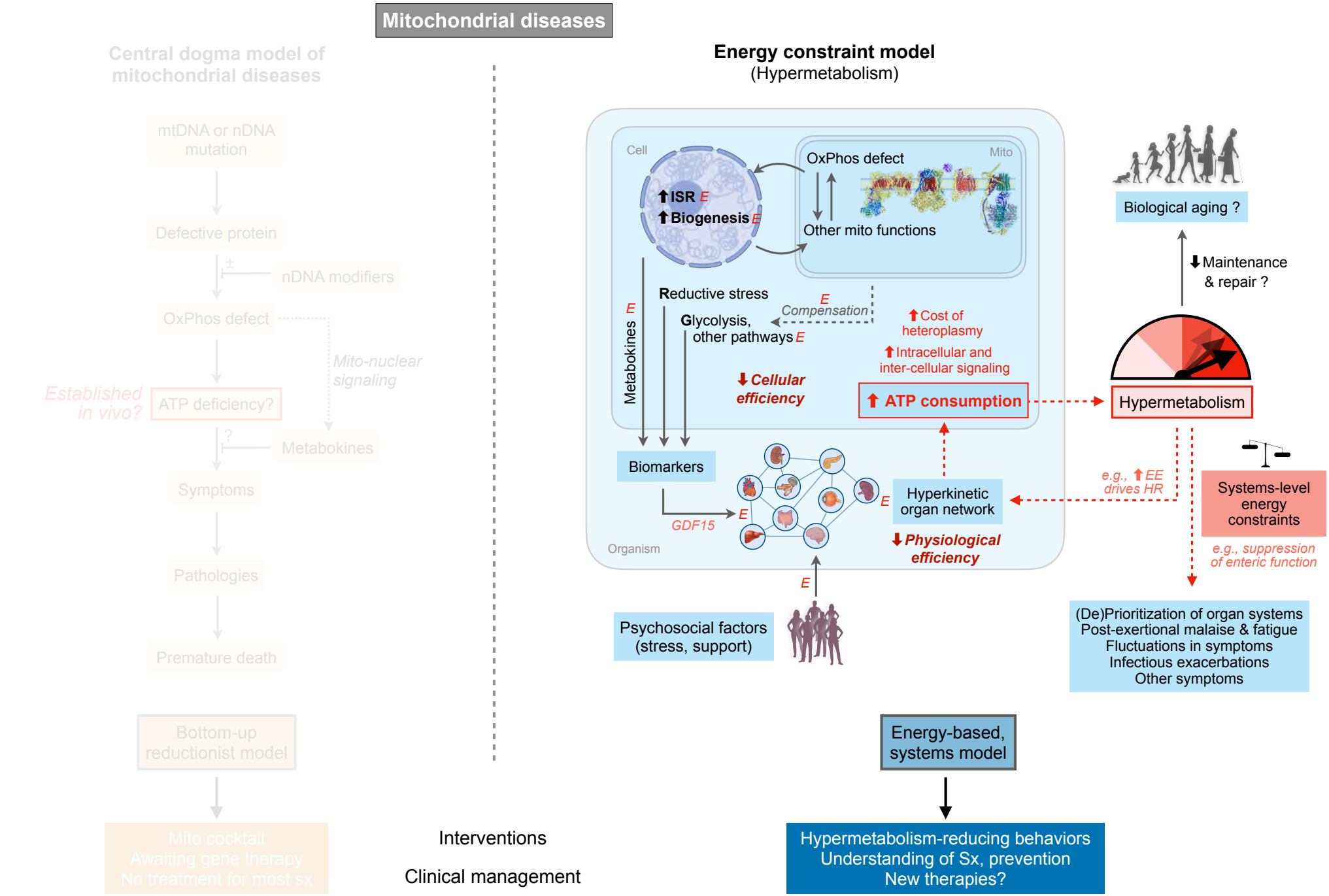


Sercel et al. (BioRxiv)

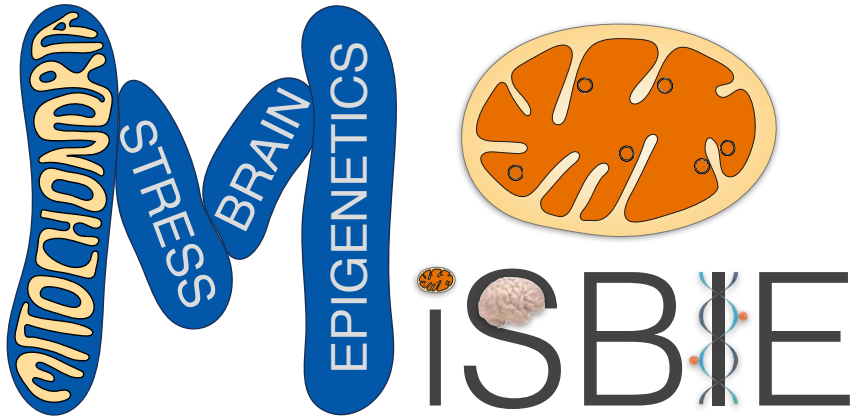
Is ATP deficiency the cause of disease in OxPhos defects?



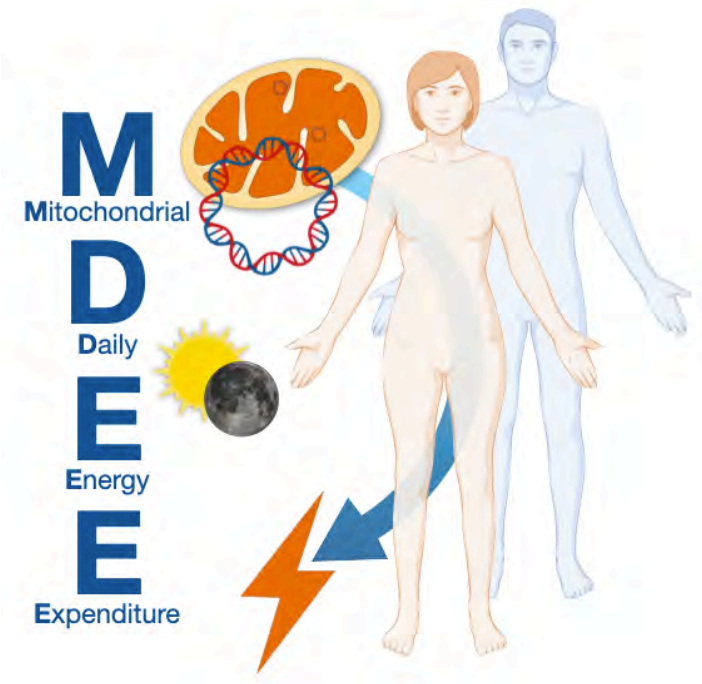
Sercel et al. (under review)



Sercel et al. (under review)

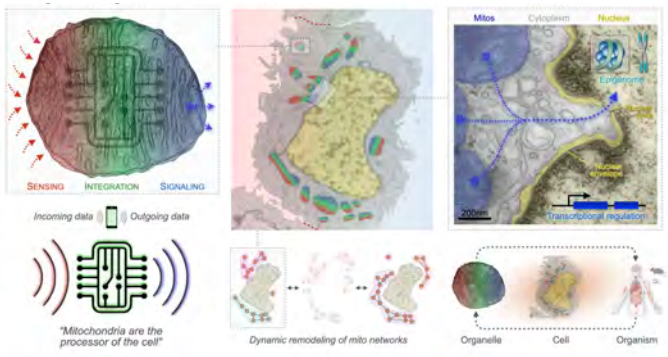


Mitochondrial **S**tress, **B**rain **I**maging, and **E**pigenetics — **MiSBIE**

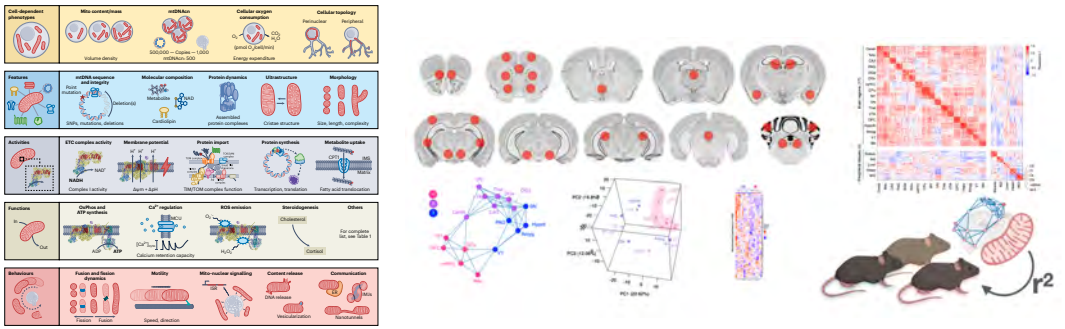


Mitochondrial **D**aily **E**nergy **E**xpenditure — **MDEE**

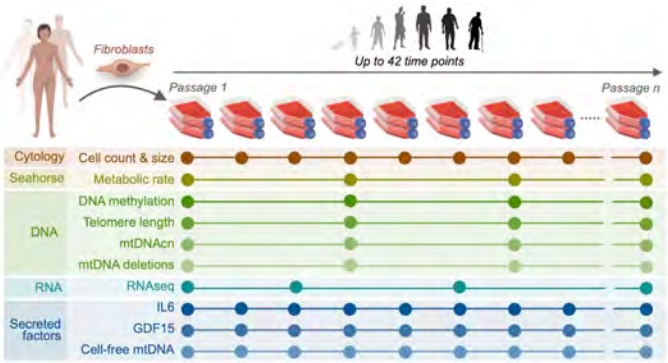
Mito Signal Transduction



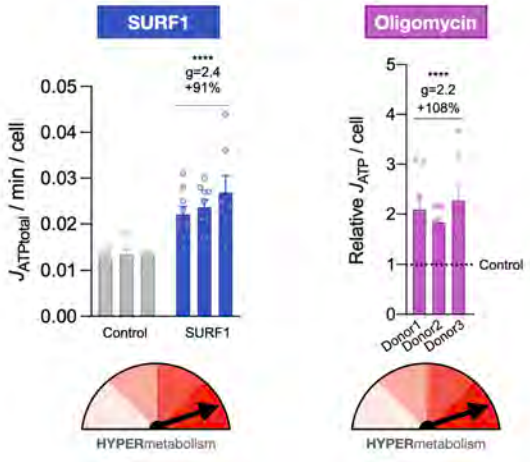
Mito Diversity & Behavior



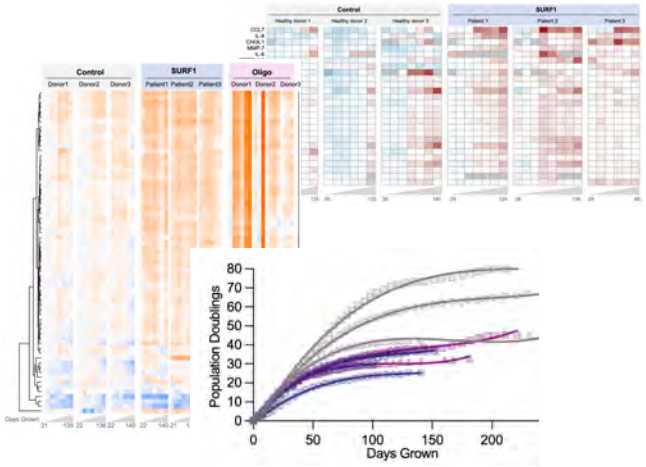
Multi-Omics Cellular Lifespan System (WebApp)



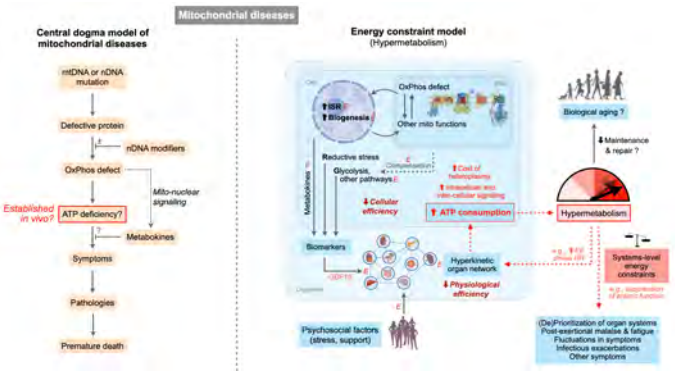
Hypermetabolism



Energy tradeoffs



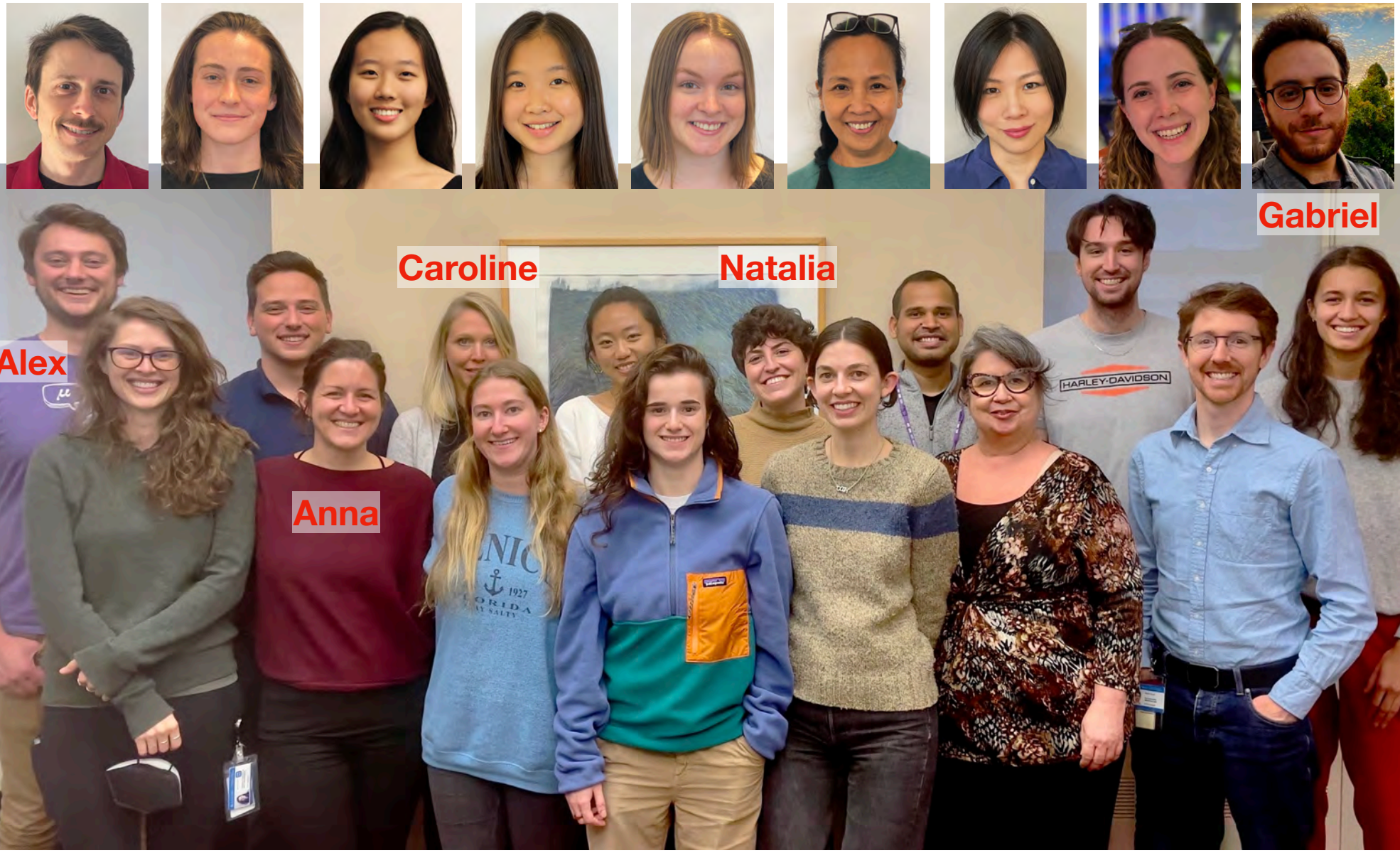
Mechanisms and clinical significance



Mitochondrial PsychoBiology Lab

Linking molecular processes within mitochondria with the human experience

OUR RESEARCH



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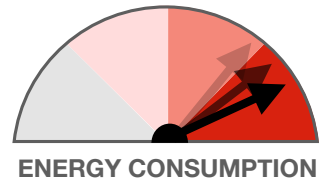
BASZUCKI BRAIN RESEARCH FUND
The Nathaniel Wharton Fund
NIH National Institute of Mental Health
NIH National Institute of General Medical Sciences
NIH National Institute on Aging

OUTSTANDING QUESTIONS

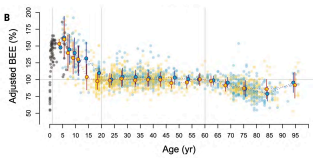


1. Are mito disease patients consistently hypermetabolic?
2. What costs more energy in OxPhos-deficient **cells**?
3. What costs more energy in OxPhos-deficient **bodies & brains**?
4. Does this play a causal role in **accelerating decline** and organ failure?
5. Does this contribute to **immune alterations** in mitochondrial diseases?
6. Can this explain clinical symptoms and observations?

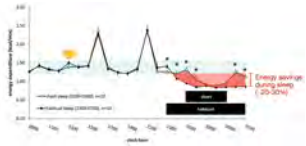
Potential clinical implications for mitochondrial diseases

Hypermetabolism could explain why …

- Many mitochondrial diseases present and are more **severe in childhood** (Pearson syndrome)
  EE is highest in childhood, added costs to OxPhos defect-induced hypermetabolism



- Patients experience **fatigue**, **sleep** more, and **nap** frequently
  Sleep decreases basal EE (hypometabolism), countermeasure to hypermetabolism?



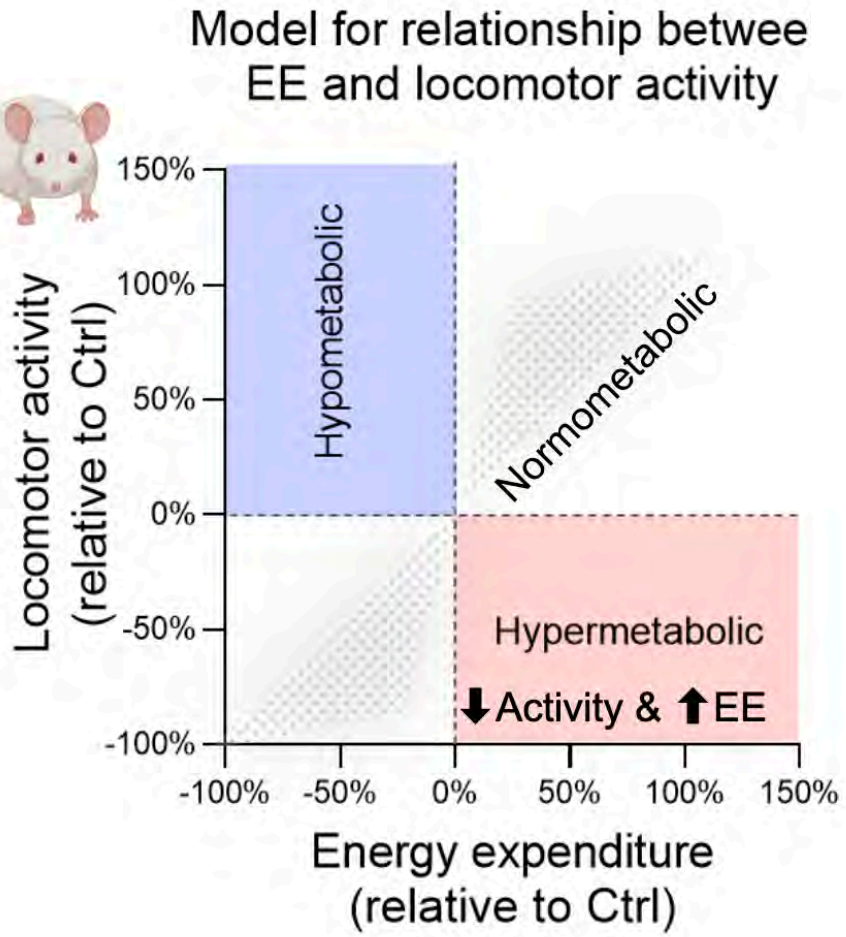
- In some patients **alcohol** triggers fatigue and decompensation (alcohol intolerance)
  Alcohol consumption increases basal EE (+16%), exacerbating hypermetabolism

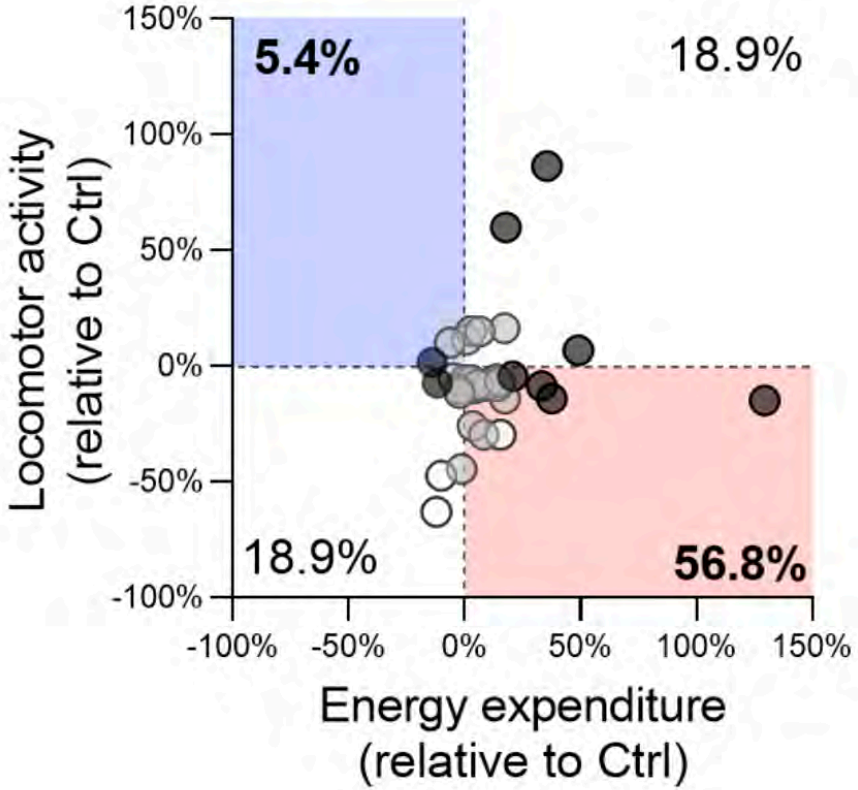
- **Infectious conditions** can trigger clinical exacerbations, symptoms onset, death
  Immune activation costs energy(!), increasing basal EE, exacerbating hypermetabolism

- The **brain is particularly vulnerable** to OxPhos defects, leading to neurological symptoms
  Brain resting EE is one of the highest (20-24% of whole body EE), tradeoff with other organs

- **Psychological stress** may trigger or exaggerate some symptoms of mitochondrial diseases
  Activation of stress response costs energy, increases EE by 9-67%, exacerbating hypermetabolism

OxPhos defects cause **hypermetabolism** in mouse models?

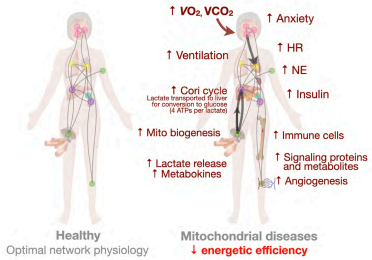


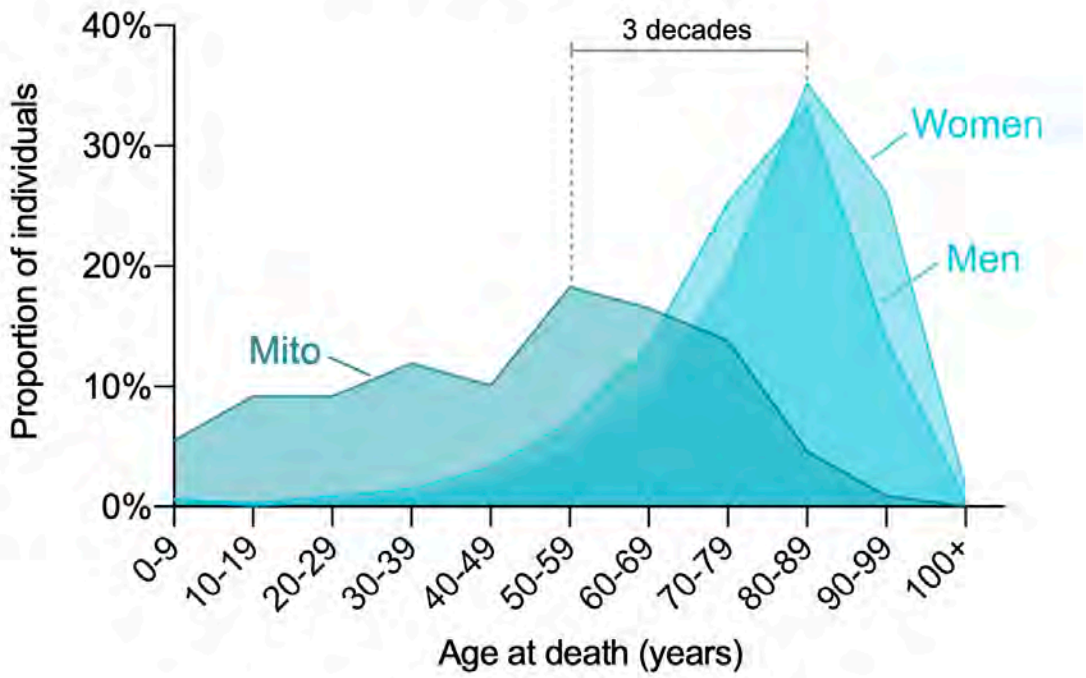


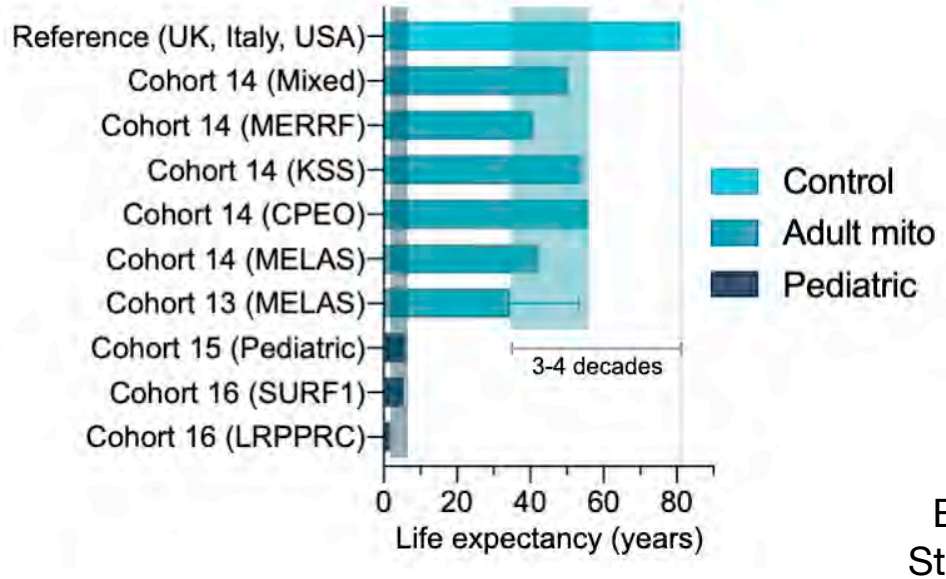
OxPhos deficient mice are **less active**, yet expend the **same or more energy** per hour to sustain life

Sercel et al. (BioRxiv)

OxPhos defects shorten lifespan by ~3-4 decades in adults





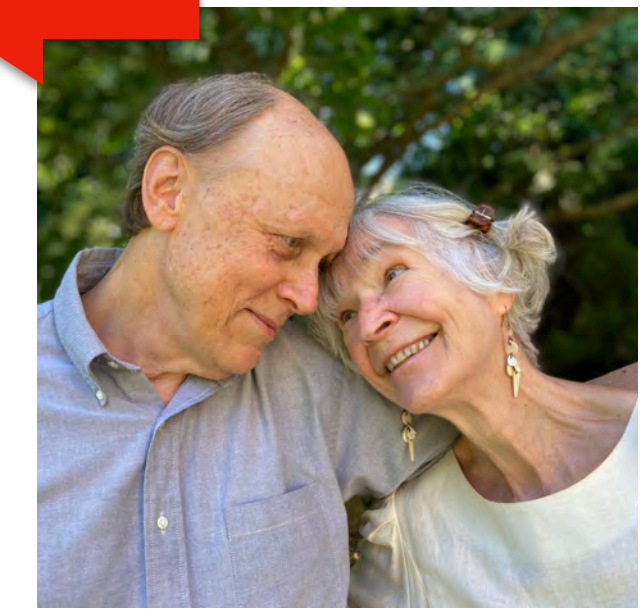


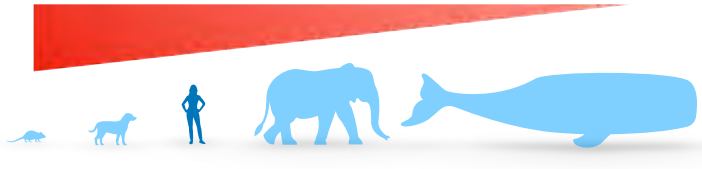
Bobby McFarland (Newcastle)
Sturm et al. *Commun Biol* 2023

Imperfection

Energy flow ➡ entropy production ➡ decay and finite lifespan

HYPERMETABOLISM





Seconds

Years / Decades

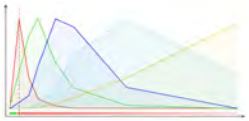
Centuries

Energy efficiency is highly evolutionary favorable

ENERGY

Resilient

Fight or flight

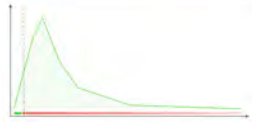


High fertility

ENERGY

Vulnerable

Low resources



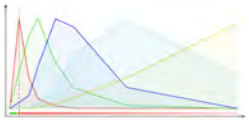
Low fertility

Energy efficiency is highly evolutionary favorable

ENERGY

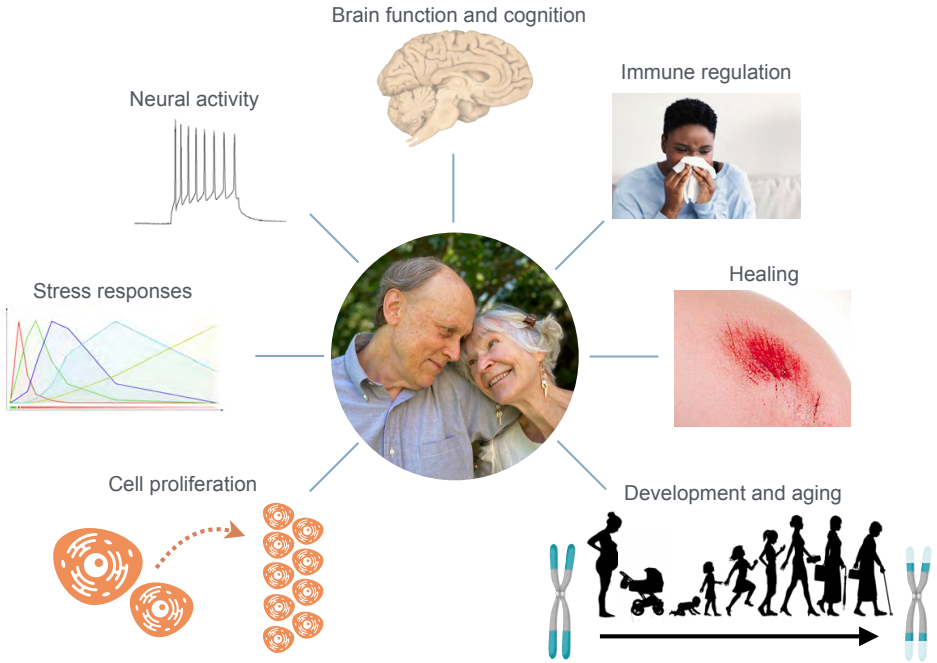
Resilient

Fight or flight



High fertility

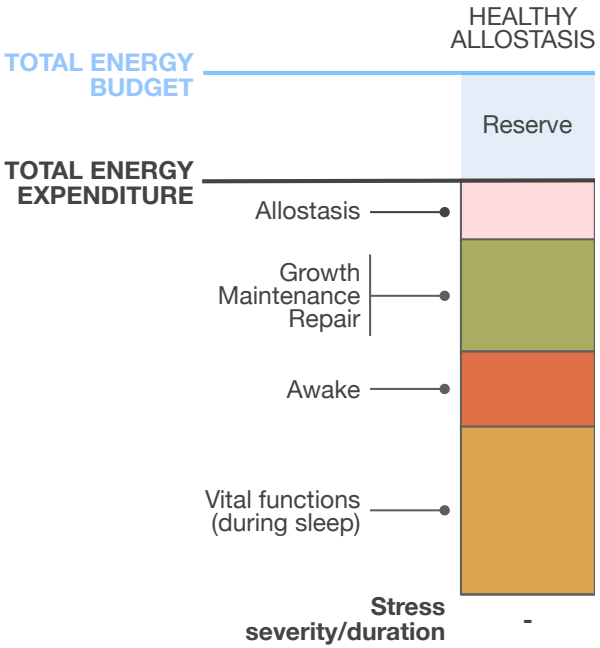
ENERGY



PHYSIOLOGY, COGNITION, PSYCHOBIOLOGICAL PROCESSES & ALLOSTASIS

Picard. *Biochemistry* 2022

Partitioning of energetic resources in humans



Allostasis costs energy

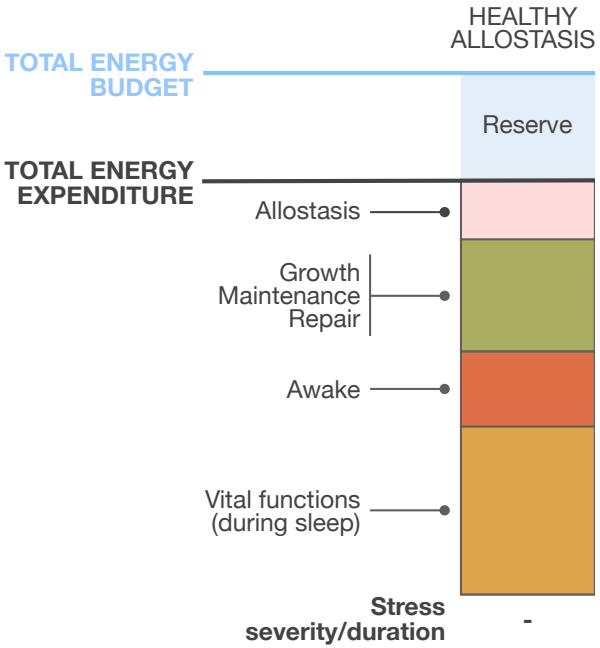
Homeostasis: *corrective* actions to normalize physiological parameters

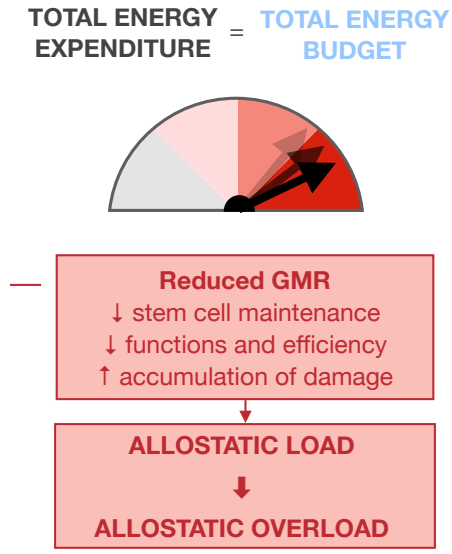
Allostasis: *anticipatory* actions mobilized to prevent deviations in physiological parameters, or optimize adaptation

- Secretion of gastric juices and digestive enzymes at the sight/smell of food
- Cortisol and catecholamine secretion from perceived (mental) stress

Bobba-Alves, Juster, Picard. The energetic cost of allostasis and allostatic load. *Psychoneuroendocrinol* 2022

Partitioning of energetic resources in humans

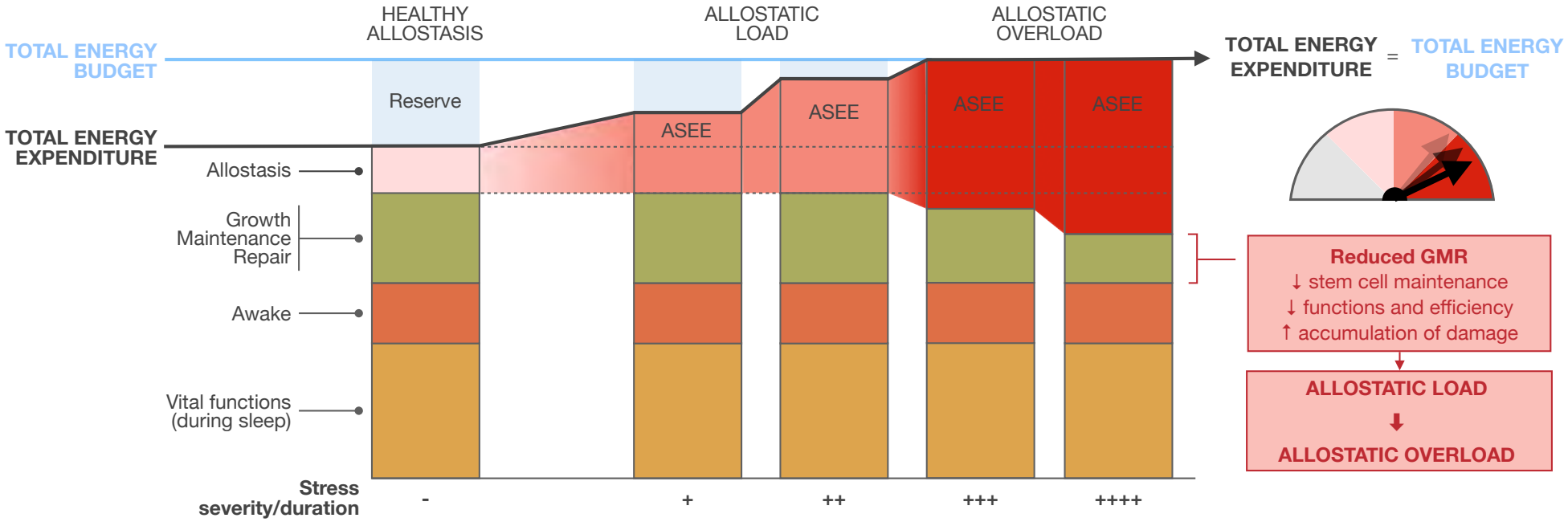




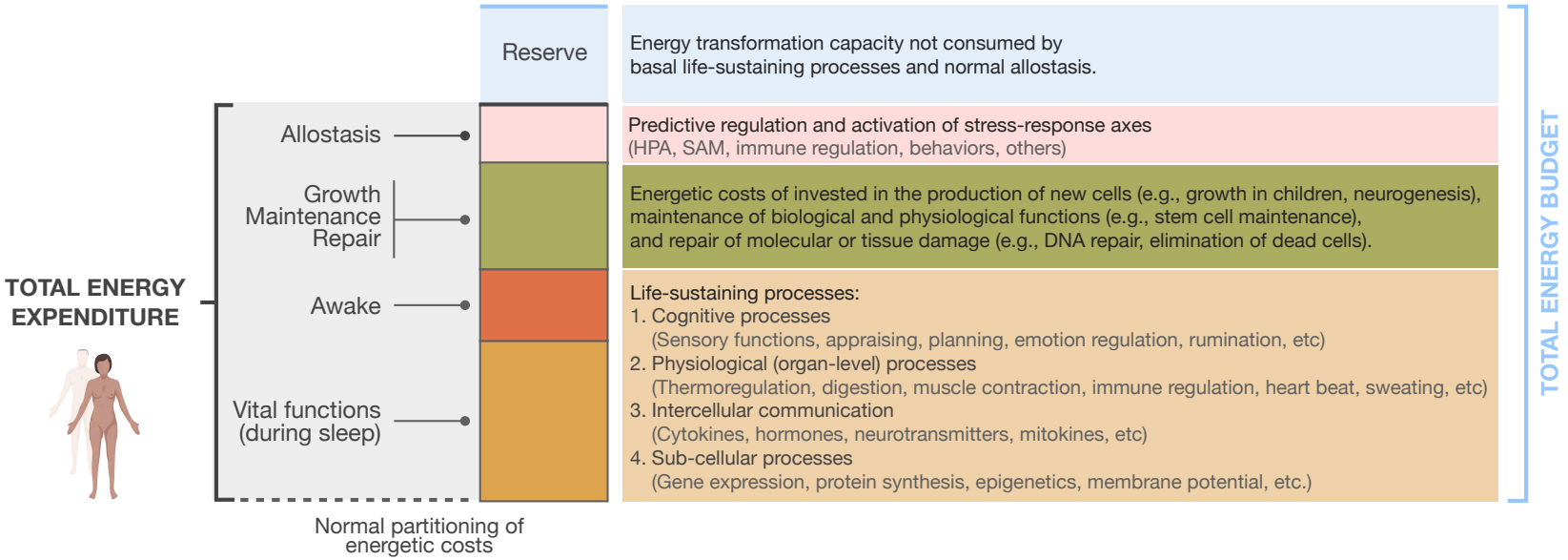
Arising questions for mitochondrial diseases:

- **Failure to thrive** caused by physiological energy tradeoffs?
- Is **hyperglycemia** a physiological strategy to avoid energy tradeoffs?
- Do **infections** trigger decompensation because they force tradeoffs among systems?
- Is **hypothyroidism** a strategy to avoid hypermetabolism and energy tradeoffs?
- Others

Bobba-Alves, Juster, Picard. The energetic cost of allostasis and allostatic load. *Psychoneuroendocrinol* 2022



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


TOTAL ENERGY EXPENDITURE
Reserve
Allostasis
Growth
Maintenance
Repair
Awake
Vital functions
(during sleep)
Normal partitioning of energetic costs
Energy transformation capacity not consumed by basal life-sustaining processes and normal allostasis.
Predictive regulation and activation of stress-response axes
(HPA, SAM, immune regulation, behaviors, others)
Energetic costs of invested in the production of new cells (e.g., growth in children, neurogenesis), maintenance of biological and physiological functions (e.g., stem cell maintenance), and repair of molecular or tissue damage (e.g., DNA repair, elimination of dead cells).
Life-sustaining processes:
1. Cognitive processes
(Sensory functions, appraising, planning, emotion regulation, rumination, etc)
2. Physiological (organ-level) processes
(Thermoregulation, digestion, muscle contraction, immune regulation, heart beat, sweating, etc)
3. Intercellular communication
(Cytokines, hormones, neurotransmitters, mitokines, etc)
4. Sub-cellular processes
(Gene expression, protein synthesis, epigenetics, membrane potential, etc.)
TOTAL ENERGY BUDGET