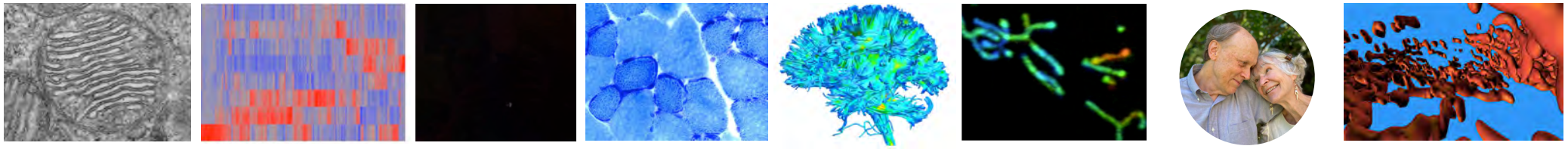
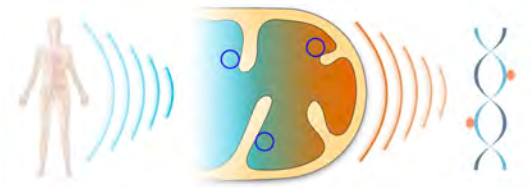


Mitochondrial science beyond function and dysfunction — a discussion



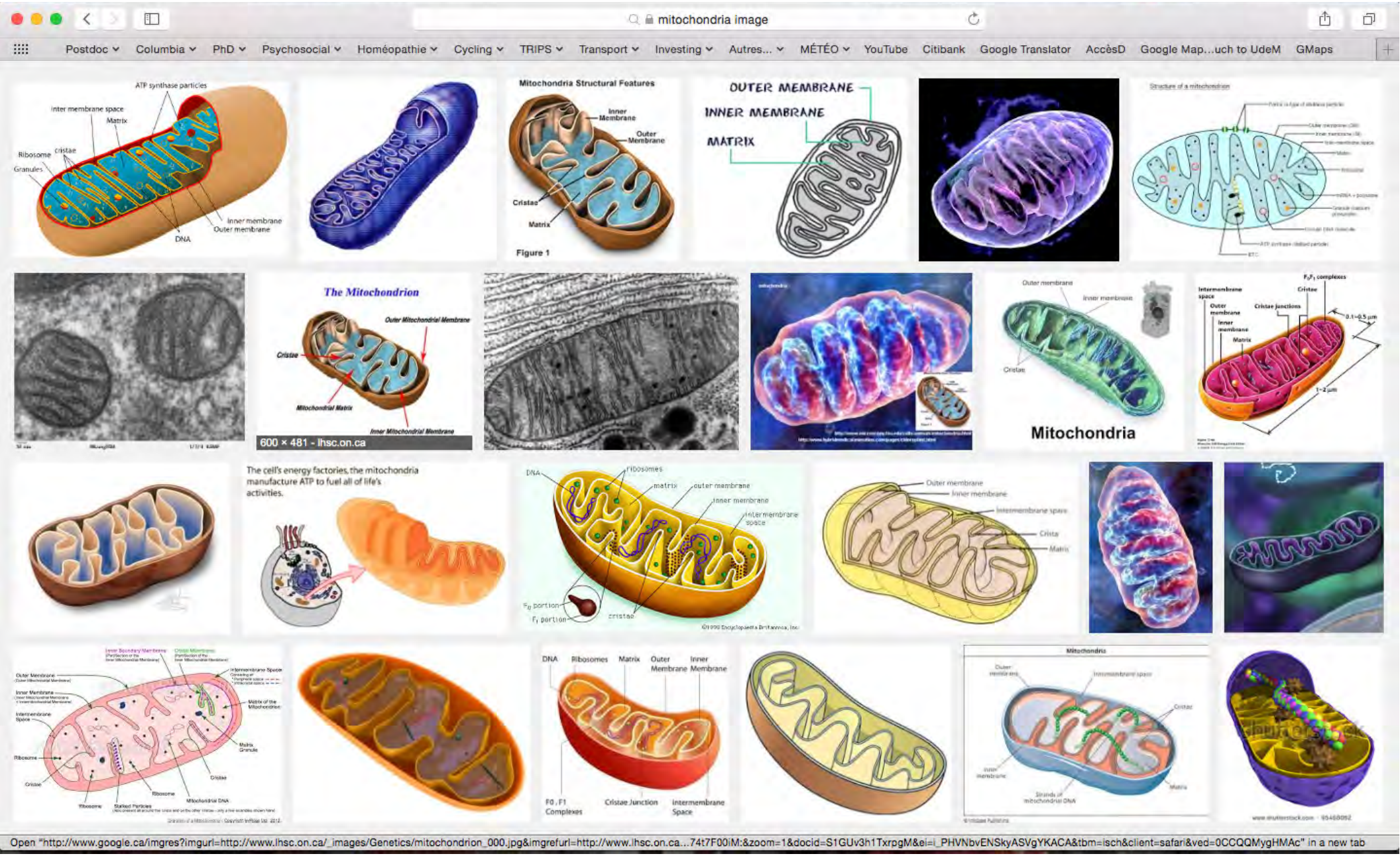
MITOtalks 2023

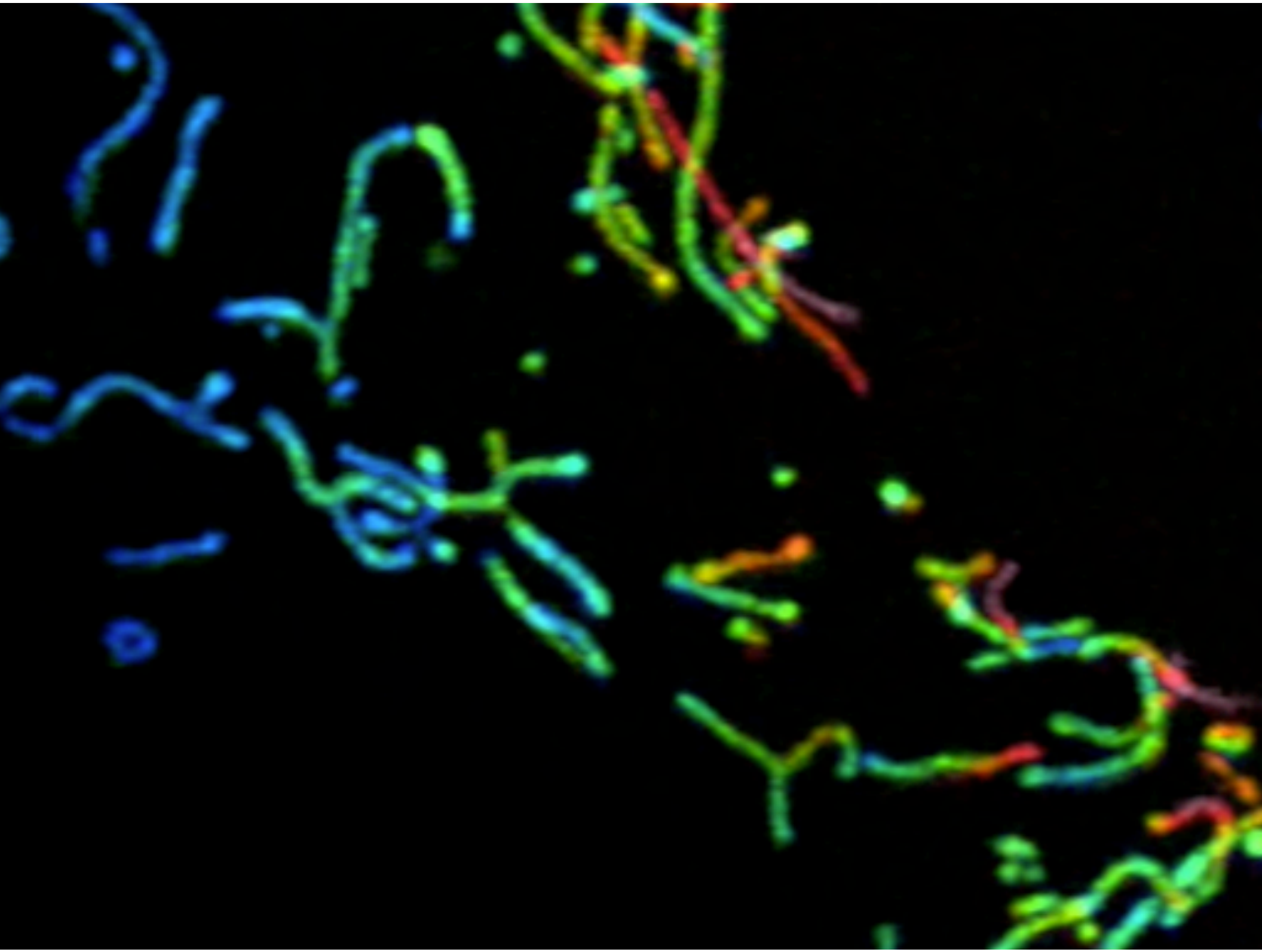
Martin Picard, Ph.D.
Department of Psychiatry, Division of Behavioral Medicine
Department of Neurology, H. Houston Merritt Center
Columbia Translational Neuroscience Initiative
New York State Psychiatric Institute (NYSPI)
Columbia Aging Center

COLUMBIA
COLUMBIA UNIVERSITY
IRVING MEDICAL CENTER

NEW YORK STATE OF OPPORTUNITY. New York State Psychiatric Institute

What do mitochondria look like?





What do mitochondria do?

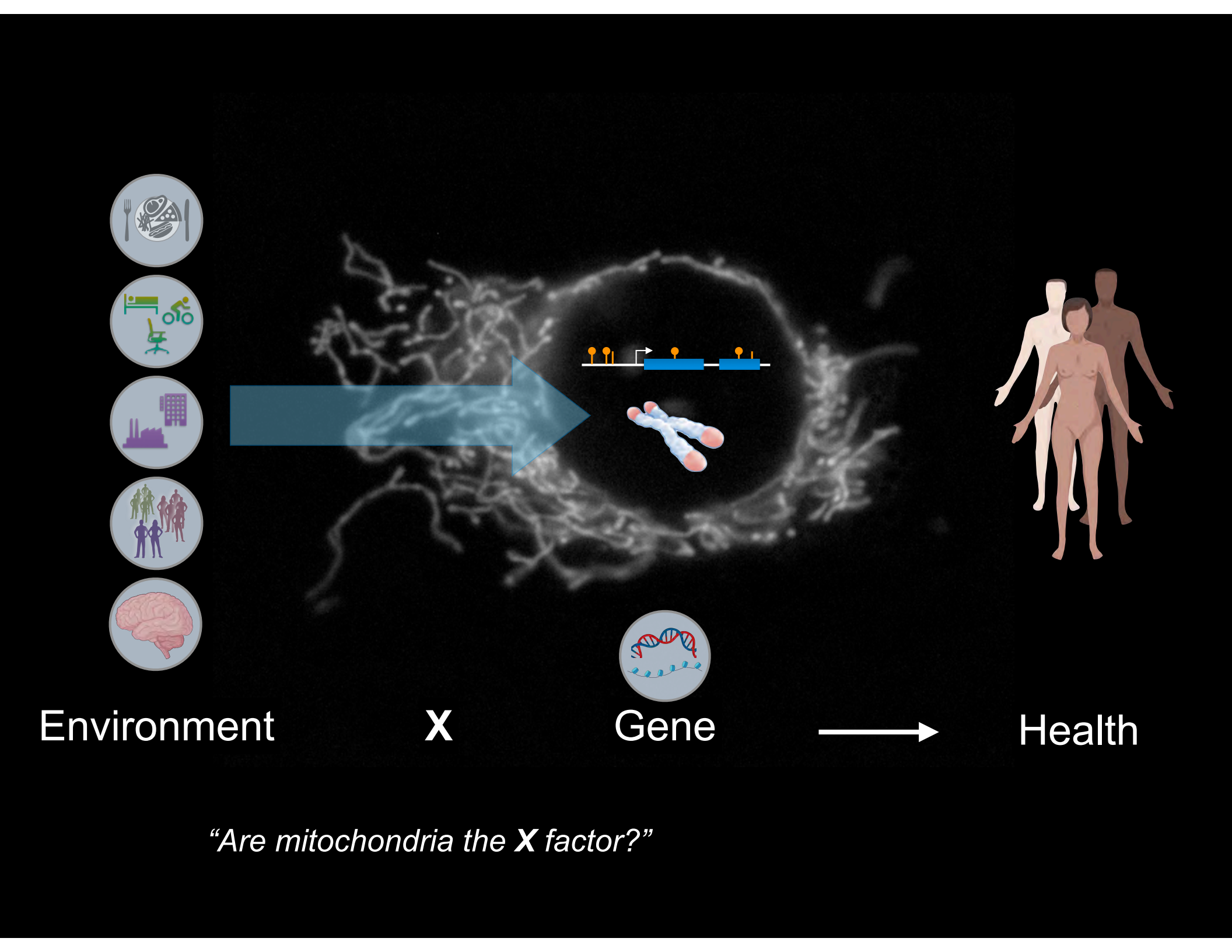
SCIENTIFIC AMERICAN®

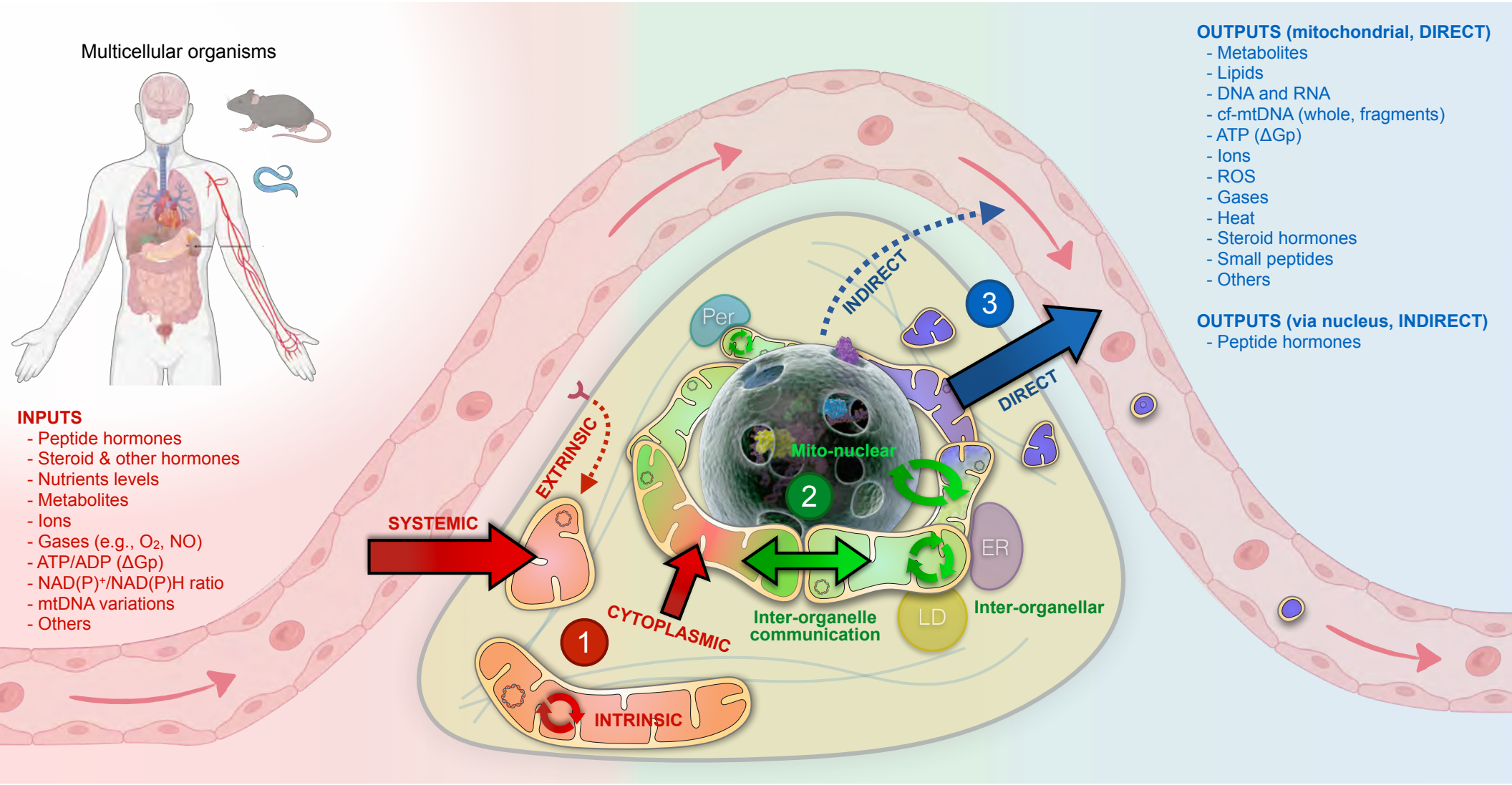
HEALTH

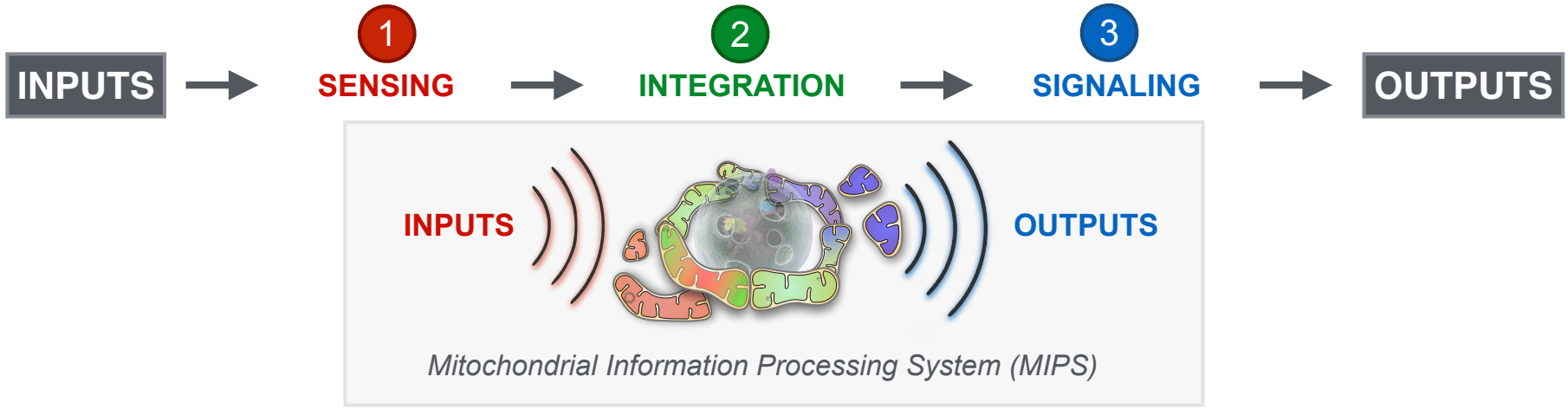
Powerhouse of the Cell

It is the mitochondrion, a small body which appears to play a central role in the oxidation of foodstuff. Its structure, as revealed by the electron microscope, mirrors its function

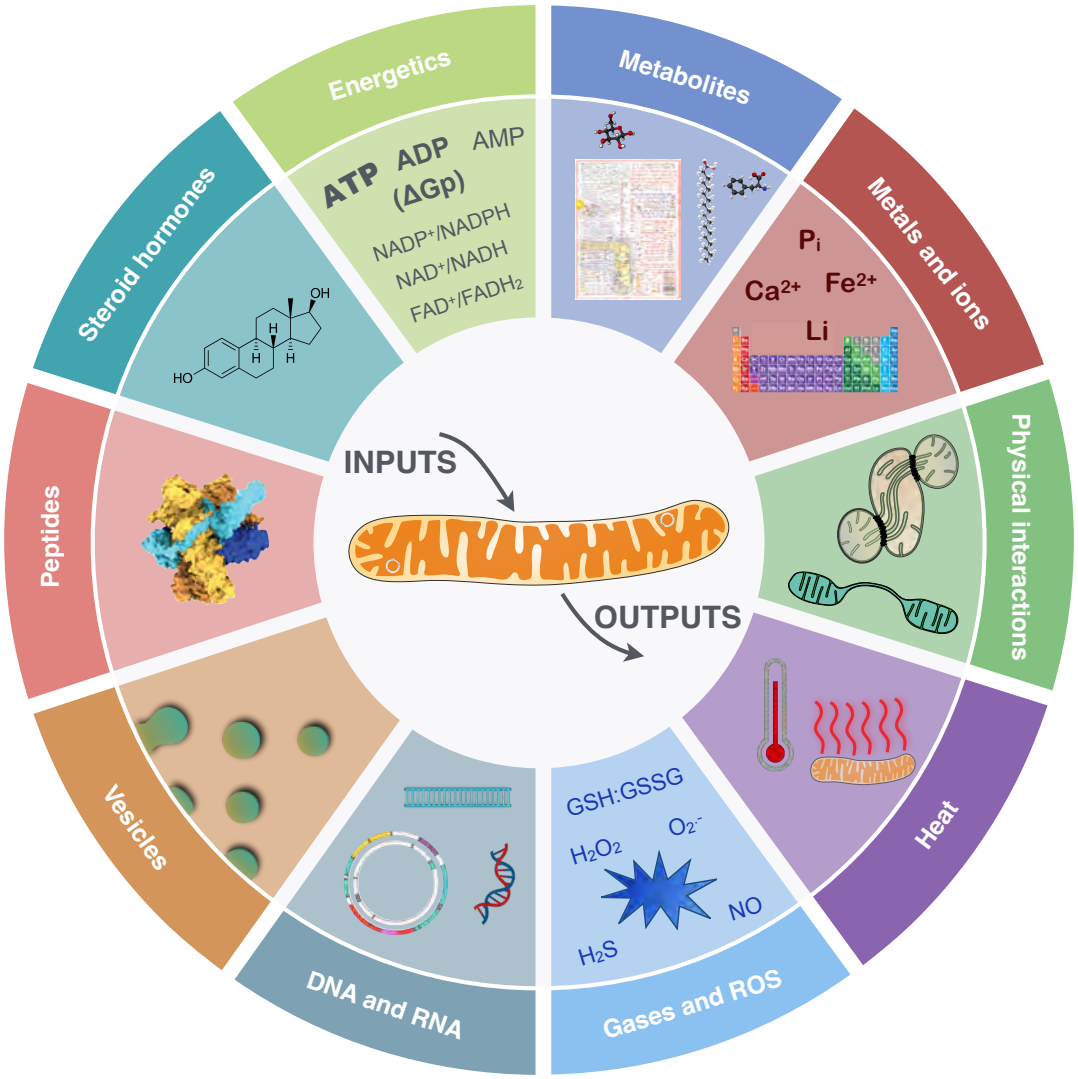
By Philip Siekevitz on July 1, 1957


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

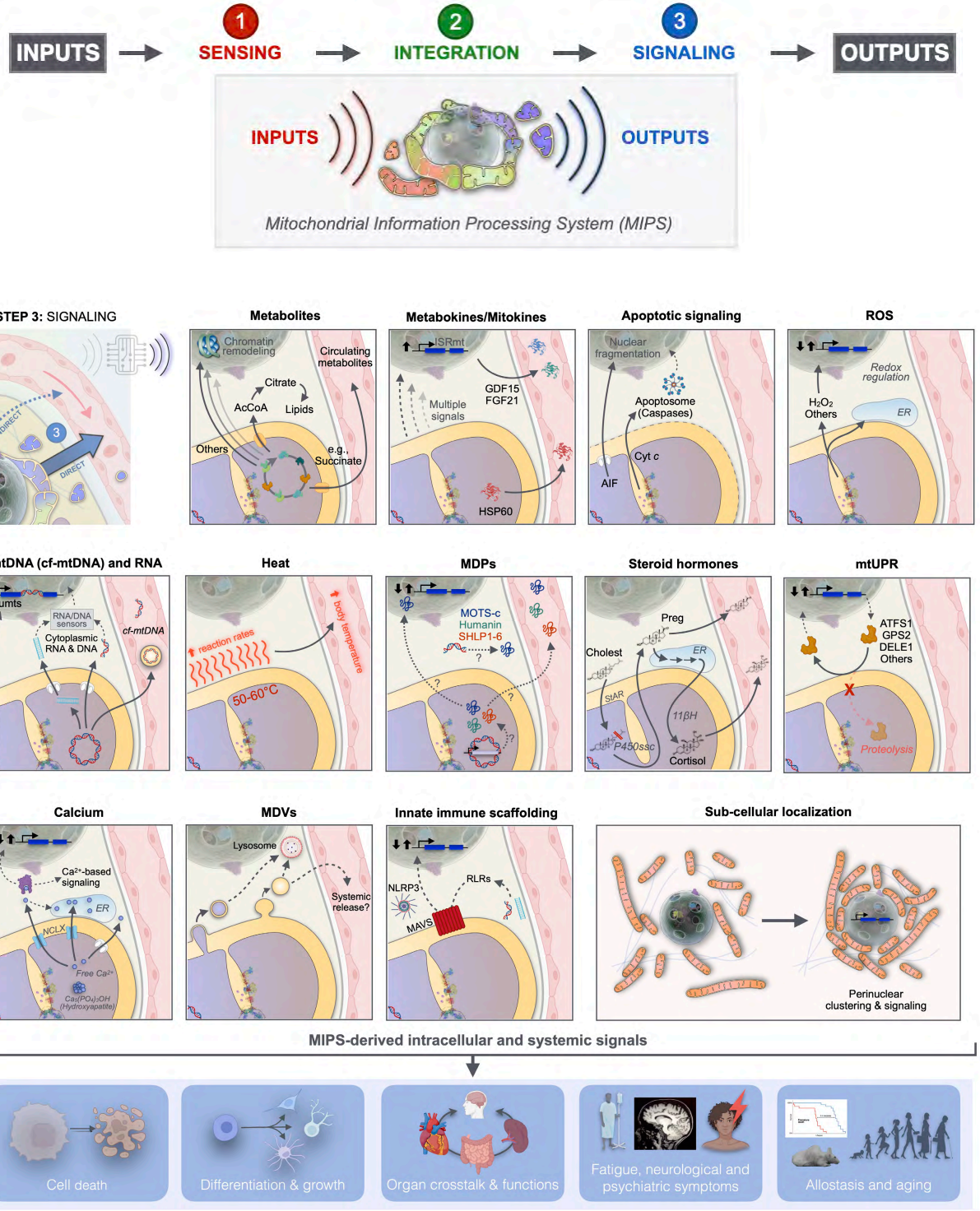

Multicellular organisms
INPUTS
- Peptide hormones
- Steroid & other hormones
- Nutrients levels
- Metabolites
- Ions
- Gases (e.g., O_2, NO)
- ATP/ADP (ΔGp)
- NAD(P)+/NAD(P)H ratio
- mtDNA variations
- Others
OUTPUTS (mitochondrial, DIRECT)
- Metabolites
- Lipids
- DNA and RNA
- cf-mtDNA (whole, fragments)
- ATP (ΔGp)
- Ions
- ROS
- Gases
- Heat
- Steroid hormones
- Small peptides
- Others
OUTPUTS (via nucleus, INDIRECT)
- Peptide hormones
EXTRINSIC
SYSTEMIC
INDIRECT
DIRECT
Per
Mito-nuclear
ER
LD
Inter-organelle communication
Inter-organellar
CYTOPLASMIC
INTRINSIC
1
2
3


INPUTS
1
SENSING
2
INTEGRATION
3
SIGNALING
OUTPUTS
INPUTS
OUTPUTS
Mitochondrial Information Processing System (MIPS)

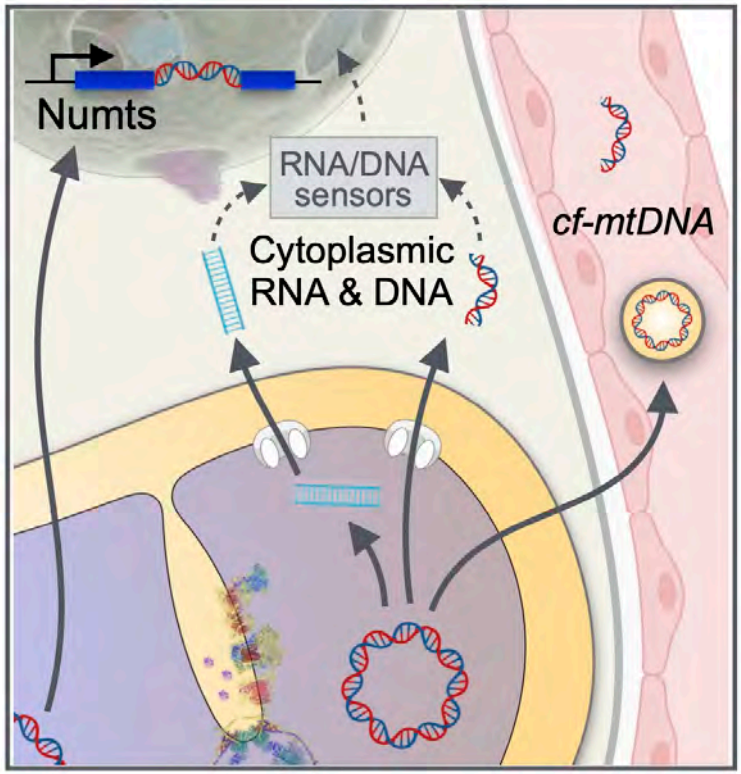
The hallmarks of mitochondrial signal transduction

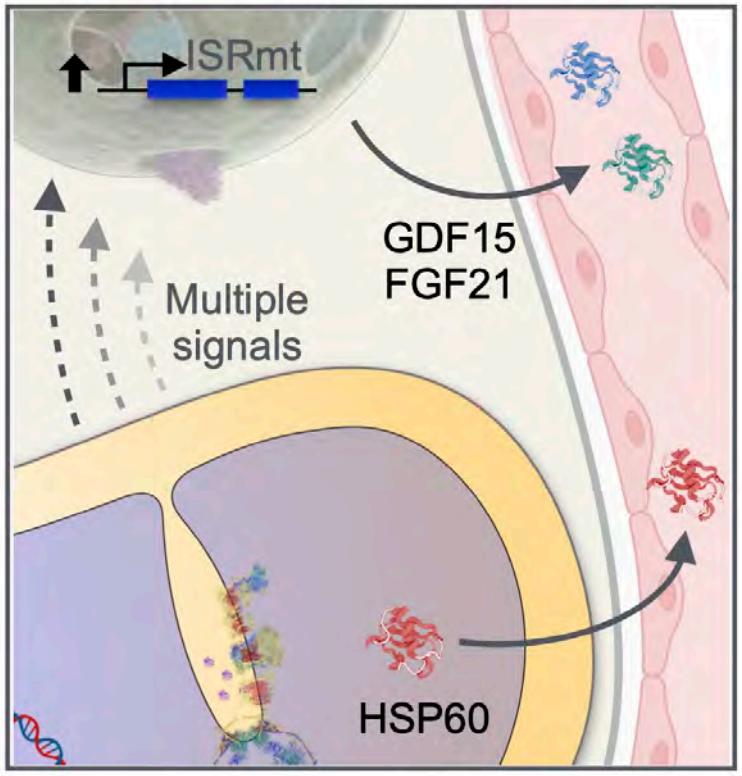


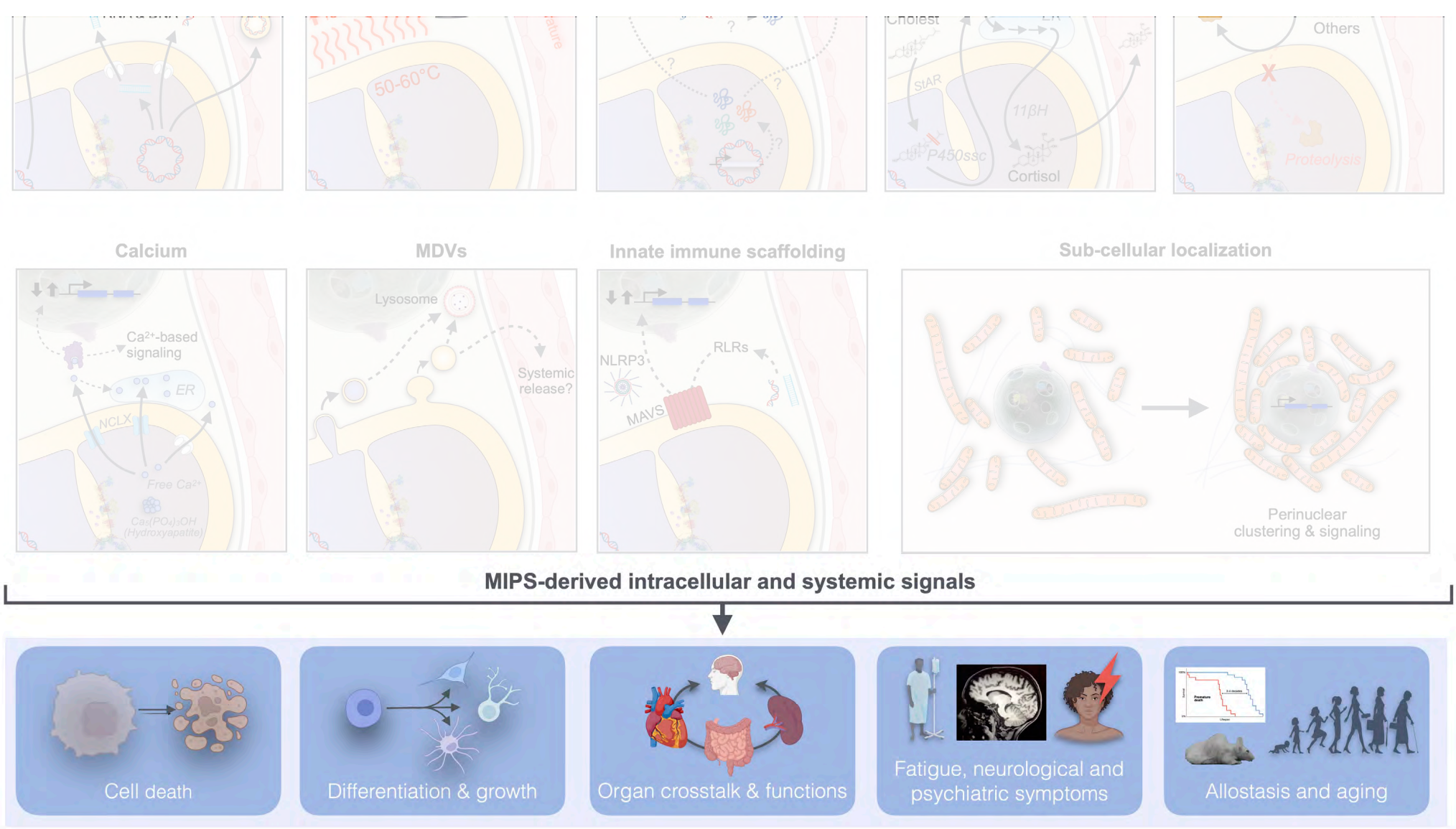
Picard and Shirihai. *Cell Metab* 2022


INPUTS
1
SENSING
2
INTEGRATION
3
SIGNALING
OUTPUTS
INPUTS
OUTPUTS
Mitochondrial Information Processing System (MIPS)
STEP 3: SIGNALING
INDIRECT
DIRECT
Metabolites
Chromatin remodeling
Circulating metabolites
Citrate
AcCoA
Lipids
Others
e.g., Succinate
Metabokines/Mitokines
ISRmt
GDF15
FGF21
Multiple signals
HSP60
Apoptotic signaling
Nuclear fragmentation
Apoptosome (Caspases)
Cyt c
AIF
ROS
Redox regulation
H_2O_2
Others
ER
mtDNA (cf-mtDNA) and RNA
Numts
RNA/DNA sensors
Cytoplasmic RNA & DNA
cf-mtDNA
Heat
reaction rates
body temperature
50-60°C
MDPs
MOTS-c
Humanin
SHLP1-6
Steroid hormones
Preg
Cholest
ER
StAR
11βH
P450ssc
Cortisol
mtUPR
ATFS1
GPS2
DELE1
Others
Proteolysis
Calcium
Ca^{2+}-based signaling
ER
NCLX
Free Ca^{2+}
$Ca_5(PO_4)_3OH$ (Hydroxyapatite)
MDVs
Lysosome
Systemic release?
Innate immune scaffolding
NLRP3
RLRs
MAVS
Sub-cellular localization
Perinuclear clustering & signaling
MIPS-derived intracellular and systemic signals
Cell death
Differentiation & growth
Organ crosstalk & functions
Fatigue, neurological and psychiatric symptoms
Allostasis and aging

mtDNA (cf-mtDNA) and RNA



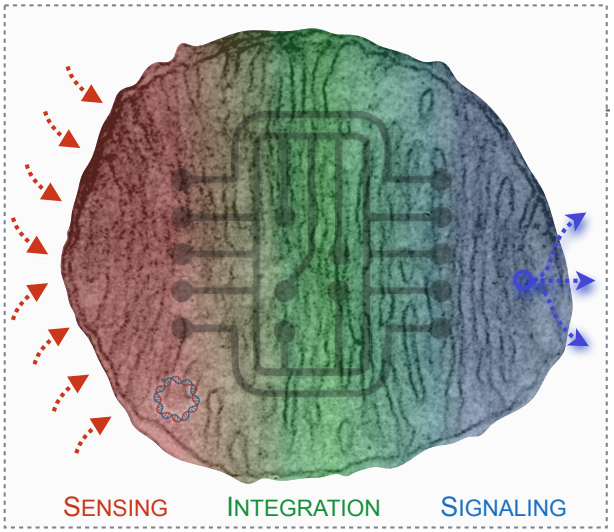

Metabokines/Mitokines
ISRmt
GDF15
FGF21
Multiple
signals
HSP60



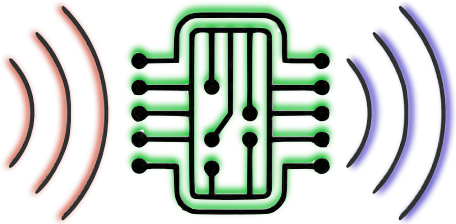
Picard and Shirihai. *Cell Metab* 2022

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

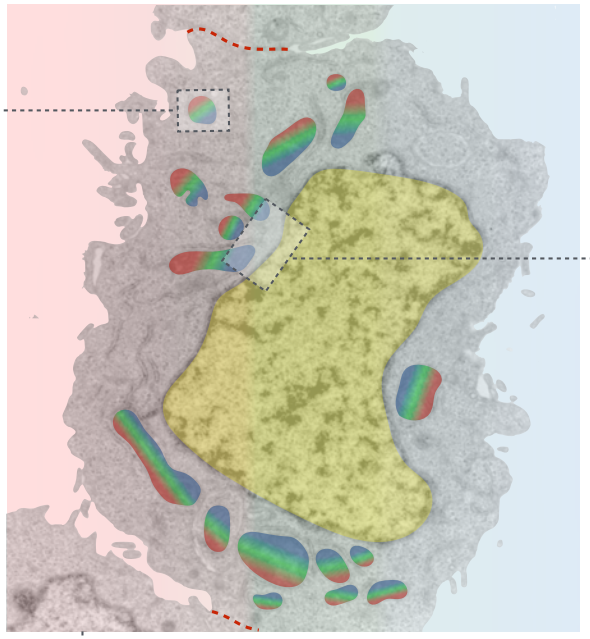
Signal transducing mitochondrion

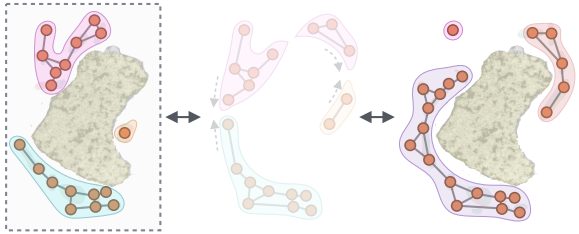


Incoming data *Outgoing data*



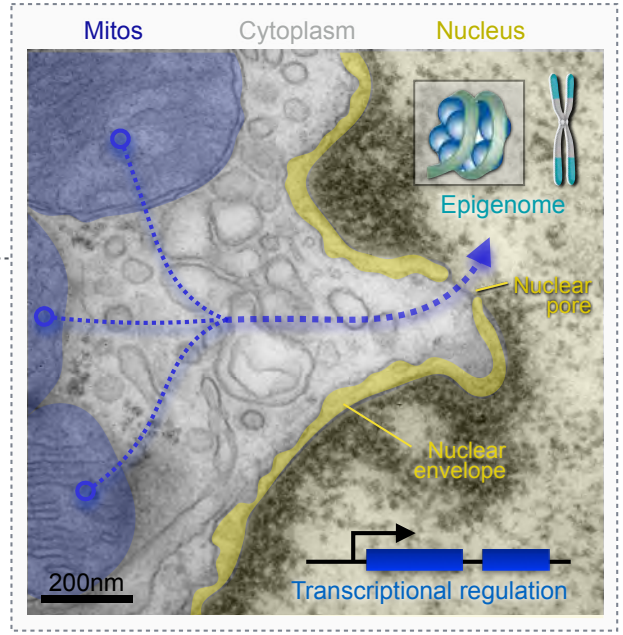
"Mitochondria are the processor of the cell"

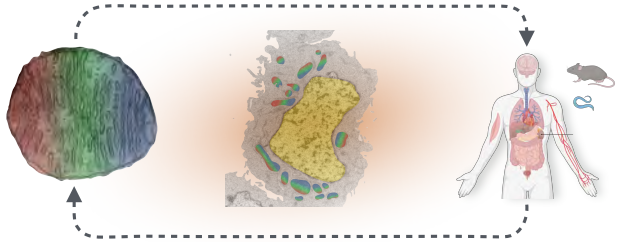


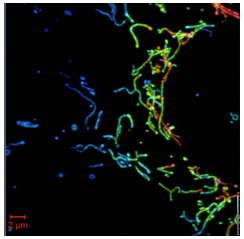


Dynamic remodeling of mito networks

Mito-nuclear unit

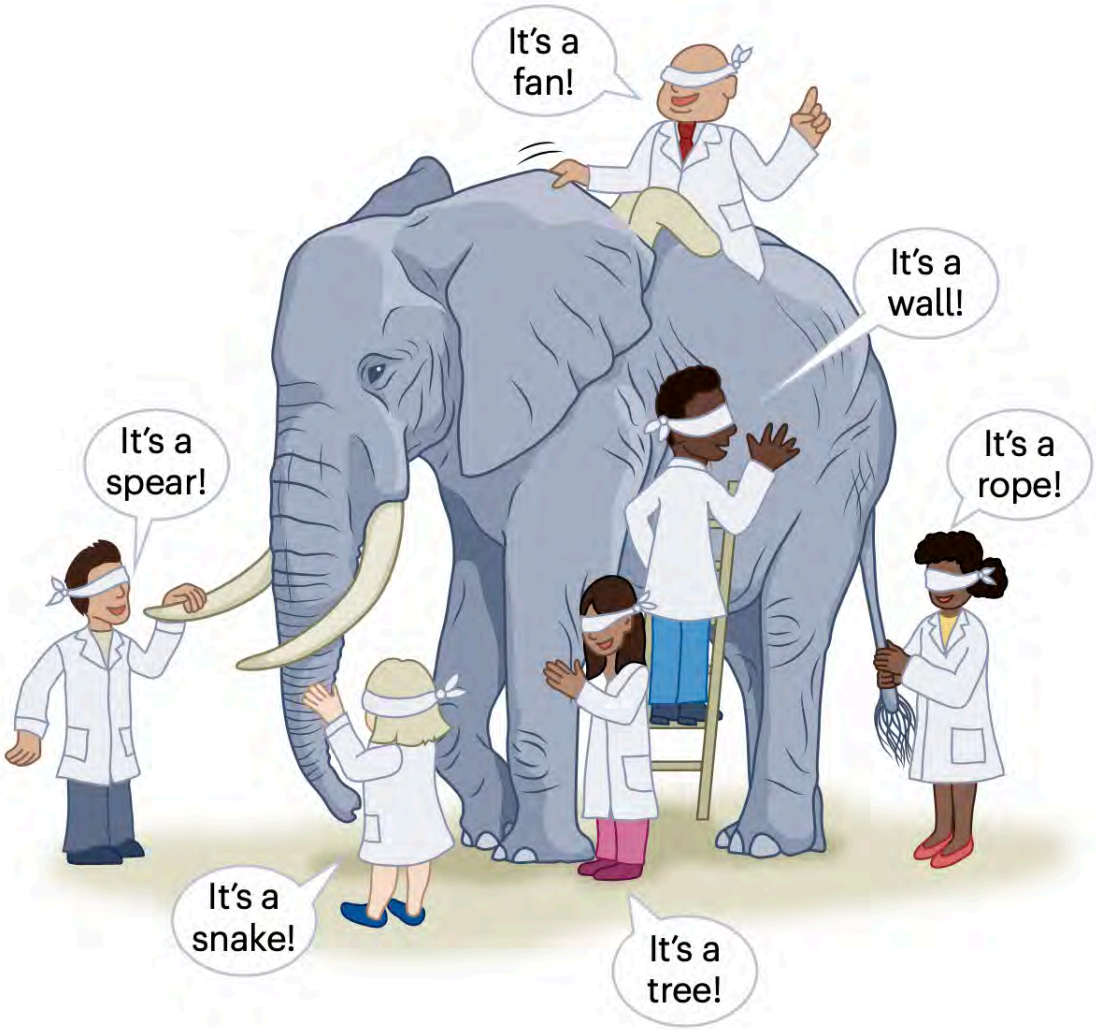




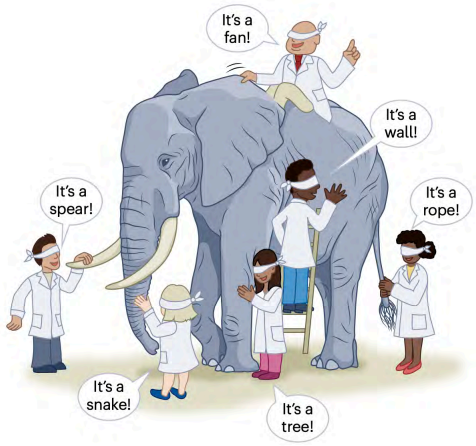


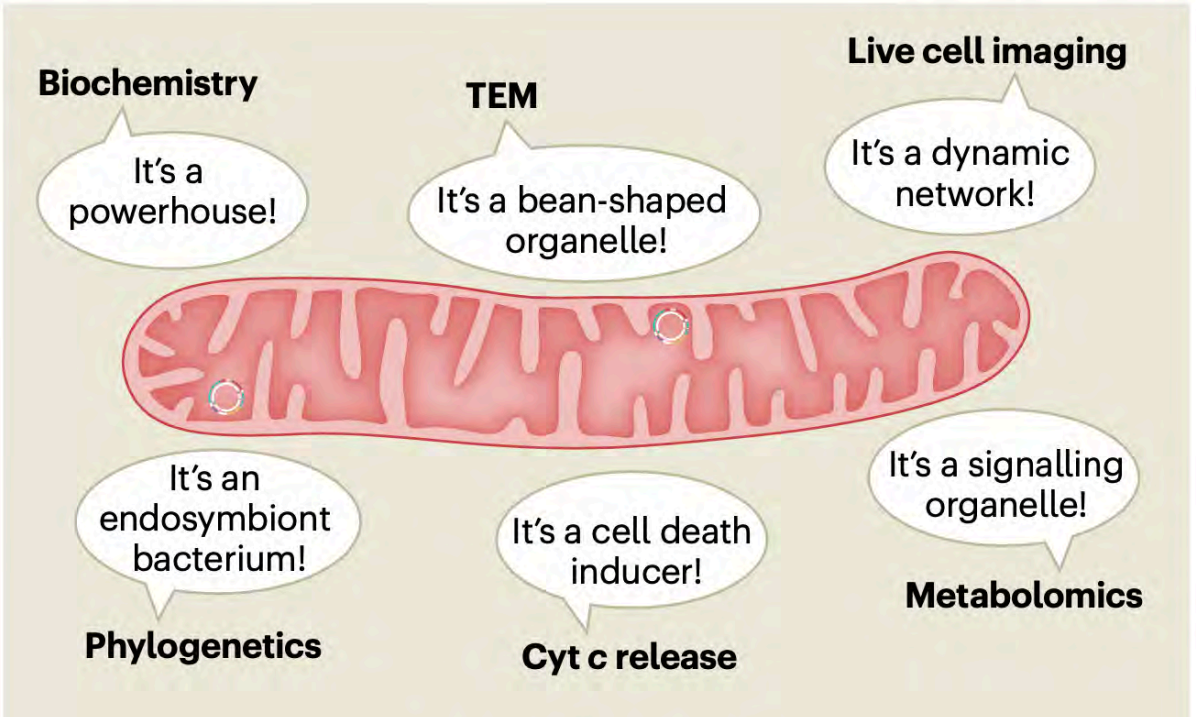
Picard and Shirihai. *Cell Metab* 2022

How do we research mitochondria?



Monzel et al. *Nat Metab* 2023

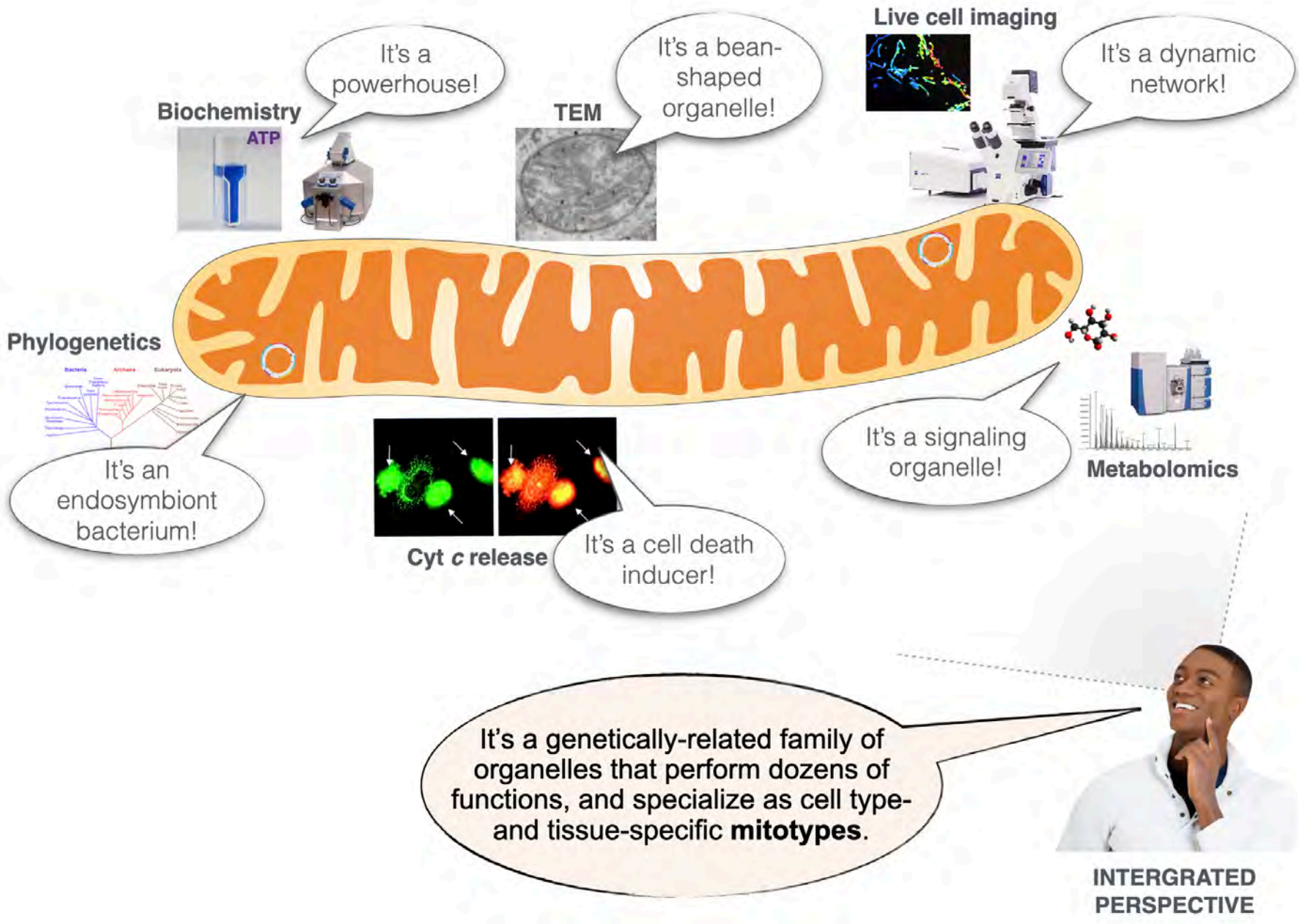




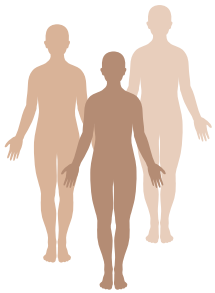
Integrated perspective

It's a family of organelles that exist as distinct mitochondrial phenotypes, defined by their molecular and morphological features, activities, functions and behaviours

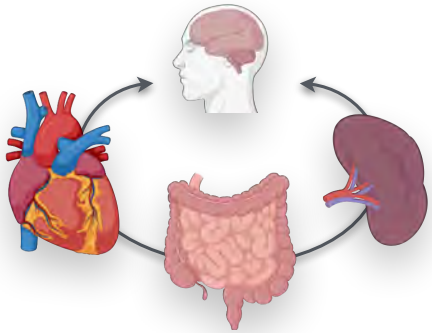
Monzel et al. *Nat Metab* 2023


Biochemistry
ATP
It's a powerhouse!
TEM
It's a bean-shaped organelle!
Live cell imaging
It's a dynamic network!
Phylogenetics
Bacteria
Archaea
Eukaryota
It's an endosymbiont bacterium!
Cyt c release
It's a cell death inducer!
It's a signaling organelle!
Metabolomics
It's a genetically-related family of organelles that perform dozens of functions, and specialize as cell type- and tissue-specific mitotypes.
INTERGRATED PERSPECTIVE

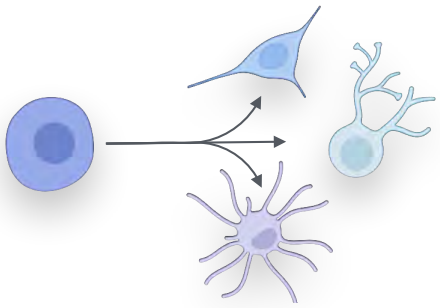
a **Domains of human health**



- Development and growth
- Physical activity
- Wound healing
- Immunity
- Cardiovascular fitness
- Locomotion
- Digestion
- Sleep
- Cognition
- Learning and memory
- Social interactions
- Others...

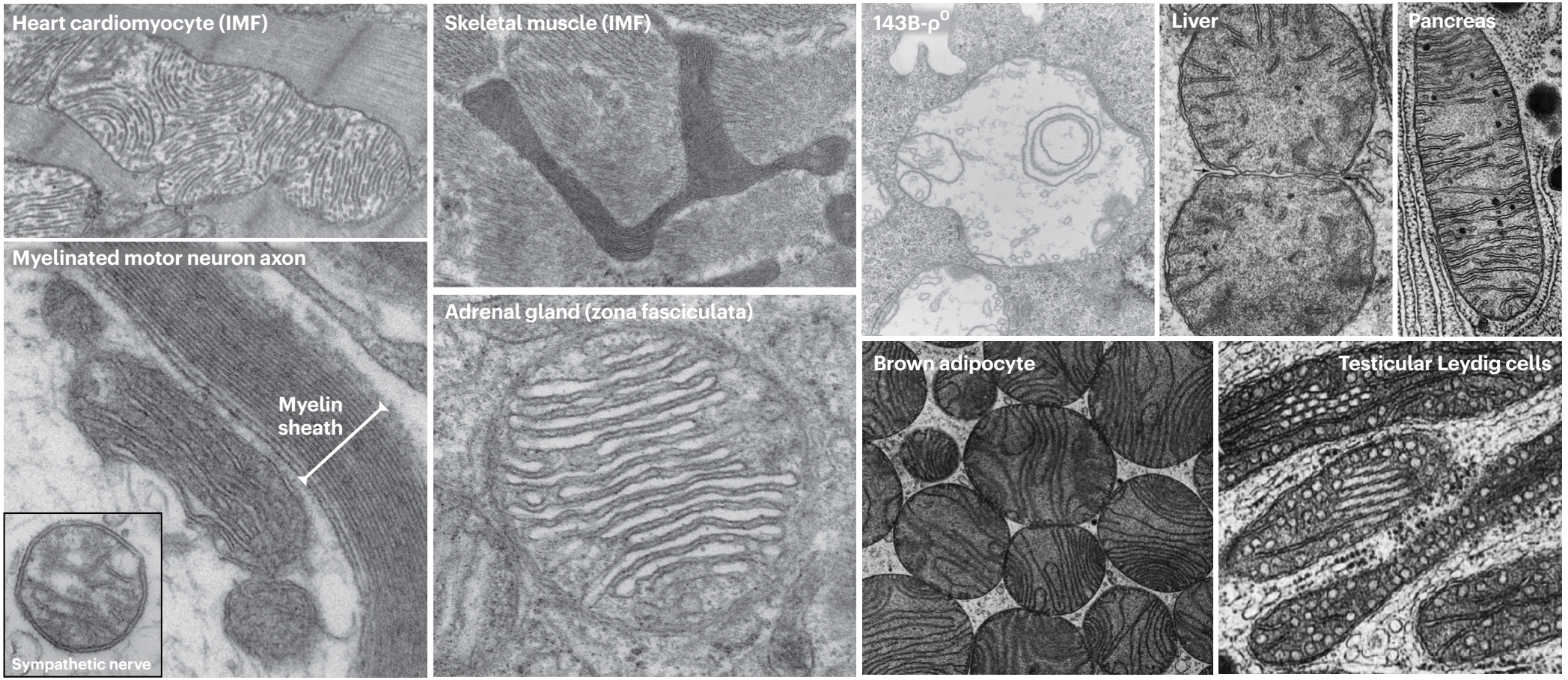


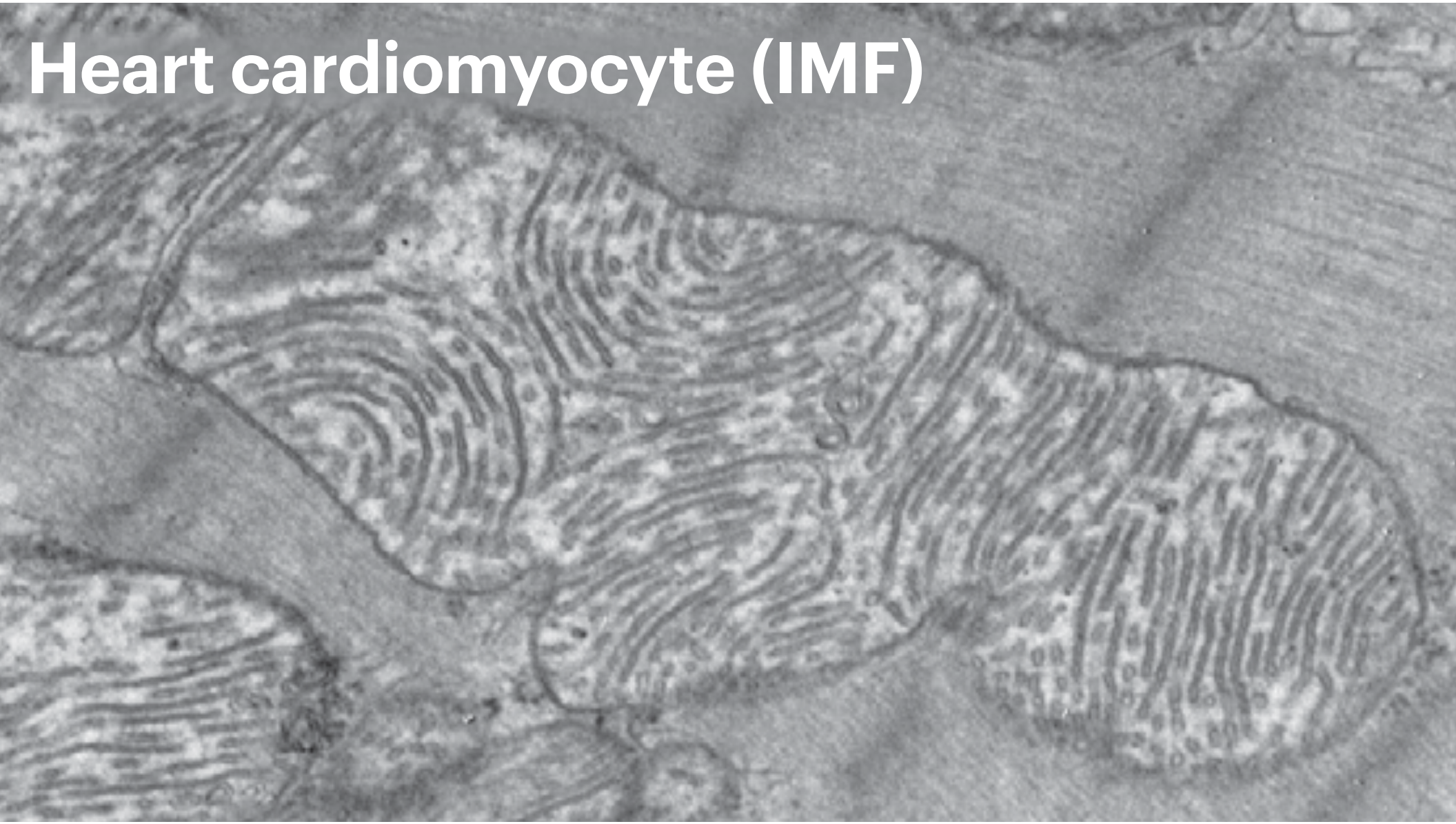
Organ systems

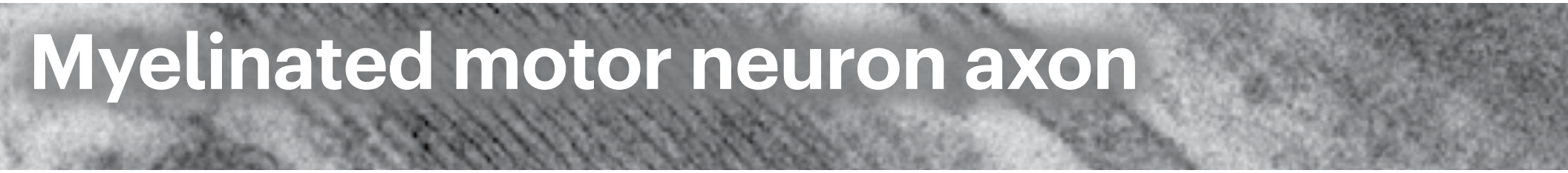


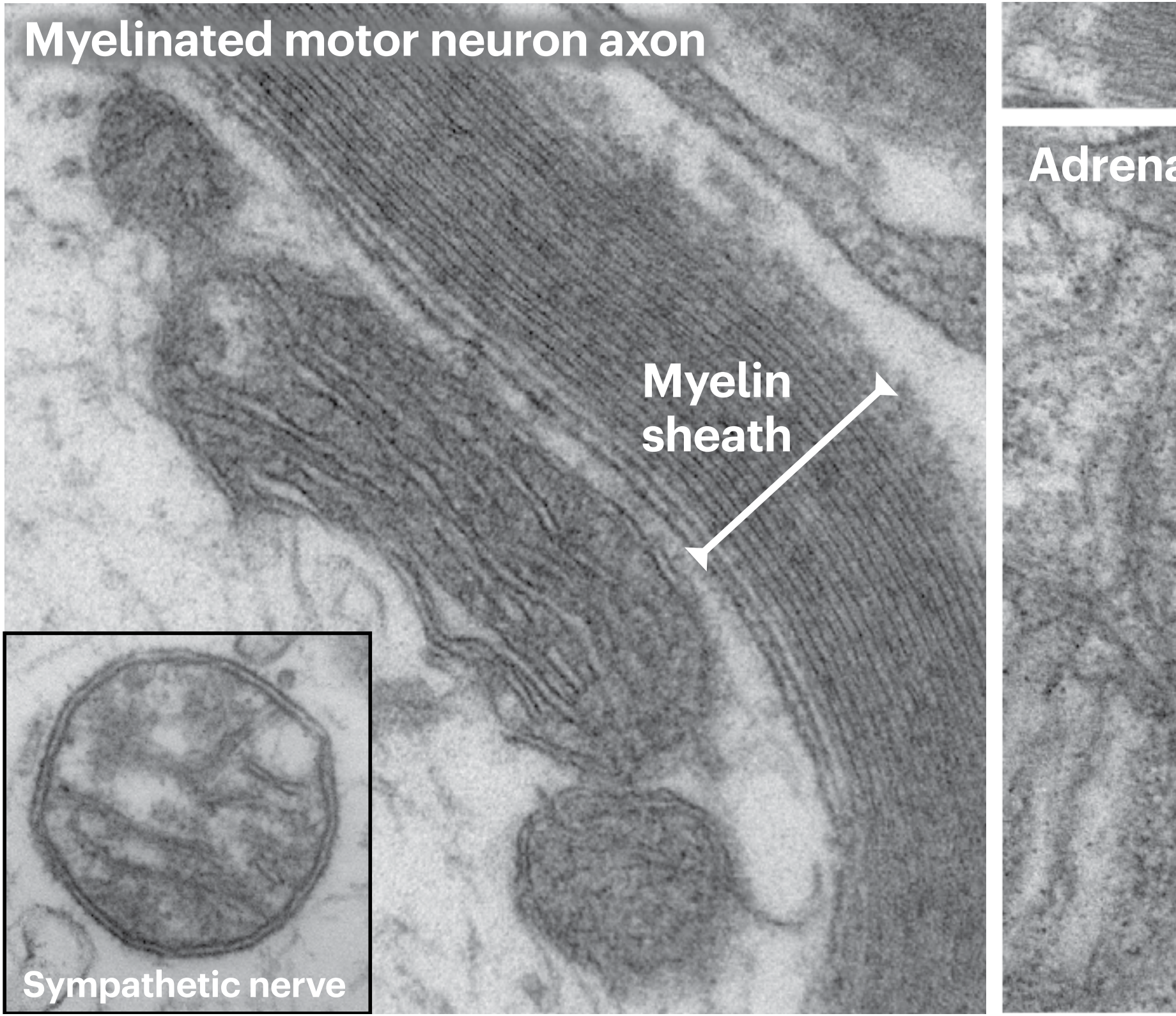
Cell types

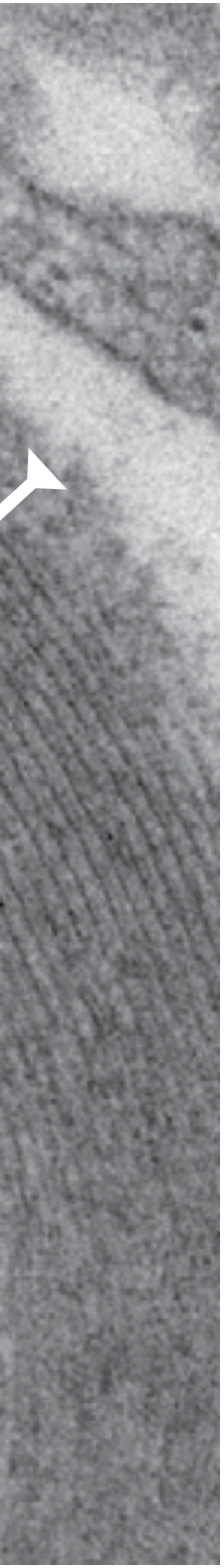
Mitotypes?

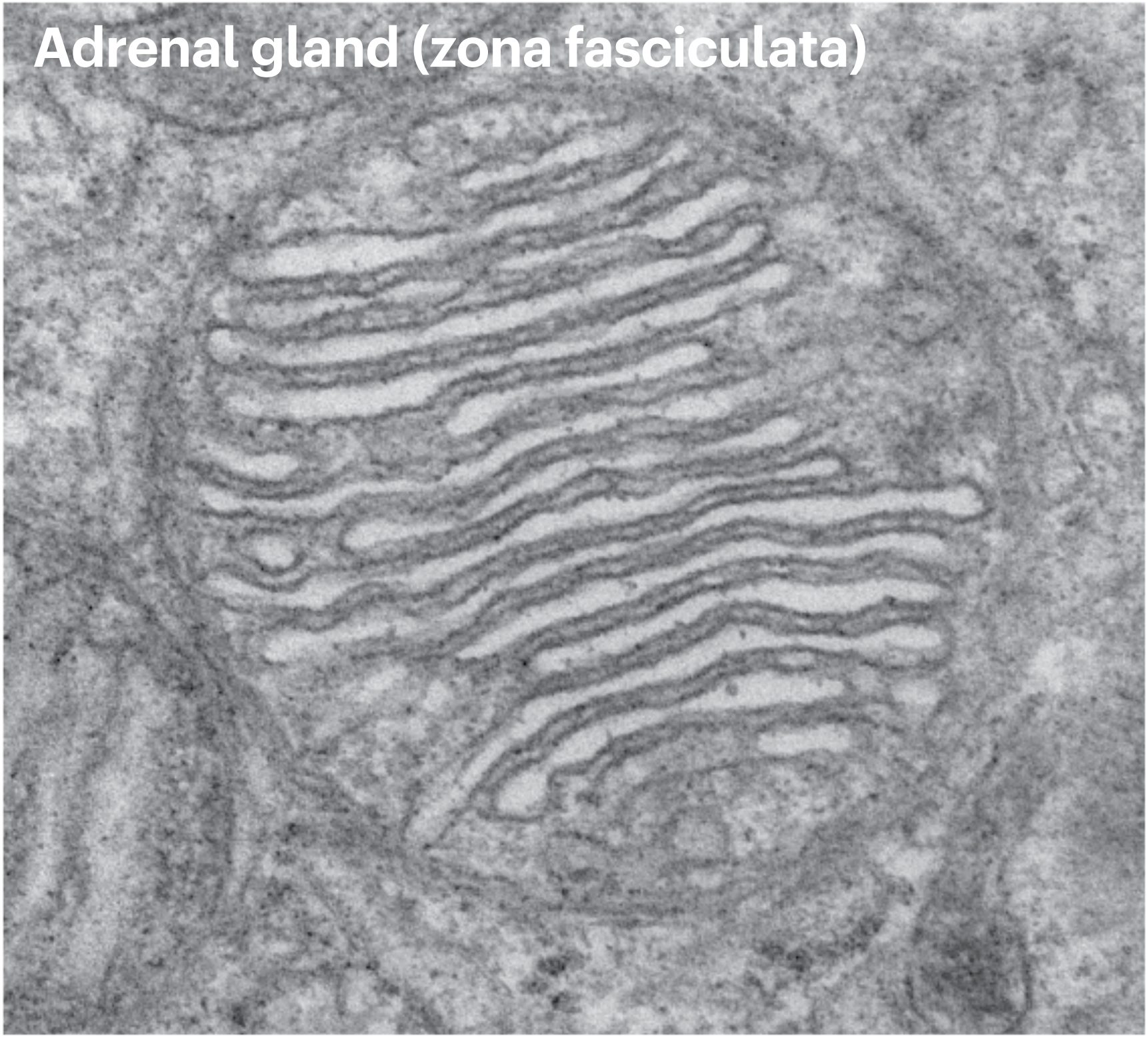

Heart cardiomyocyte (IMF)
Skeletal muscle (IMF)
143B-ρ^0
Liver
Pancreas
Myelinated motor neuron axon
Myelin sheath
Sympathetic nerve
Adrenal gland (zona fasciculata)
Brown adipocyte
Testicular Leydig cells


Heart cardiomyocyte (IMF)

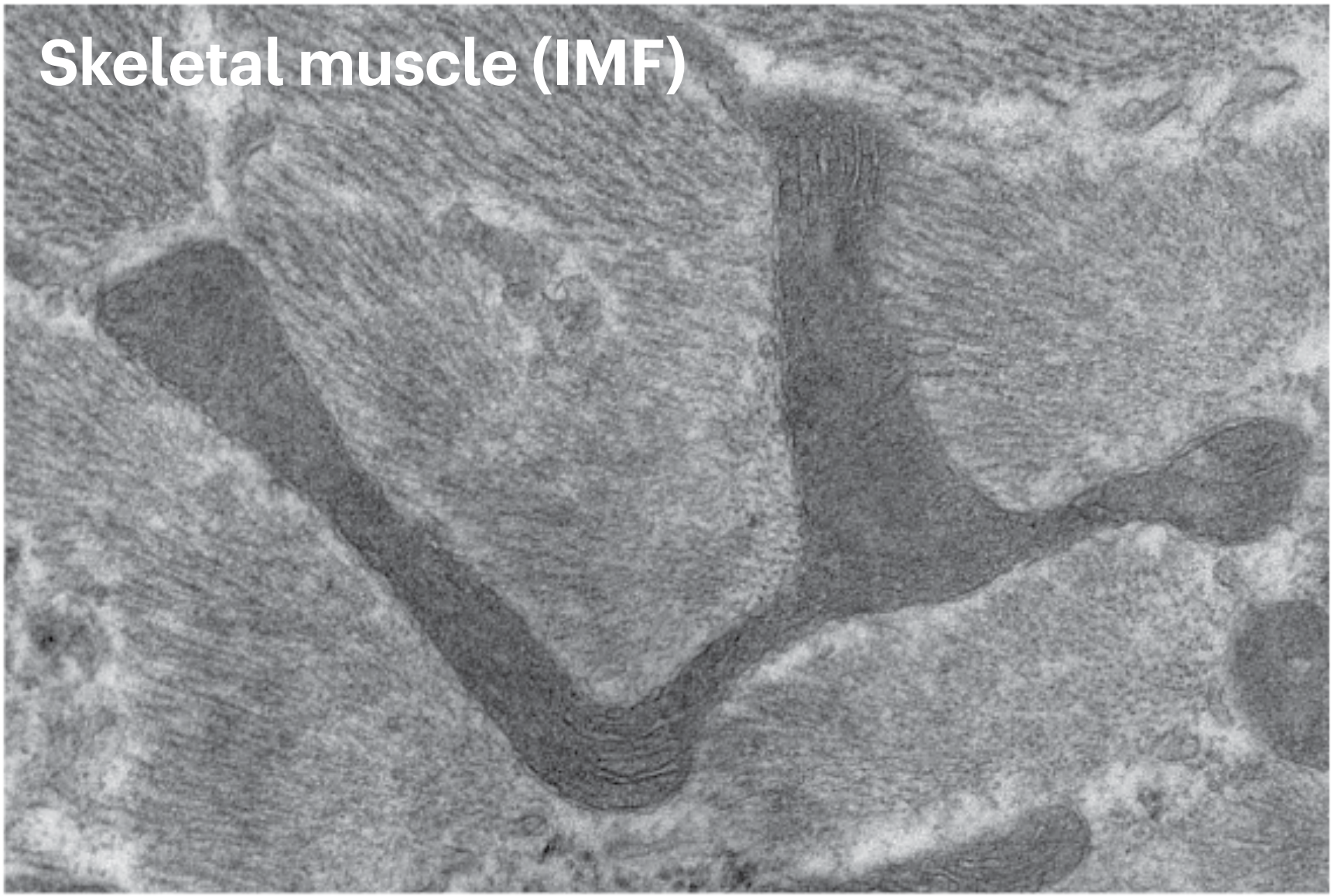

Myelinated motor neuron axon

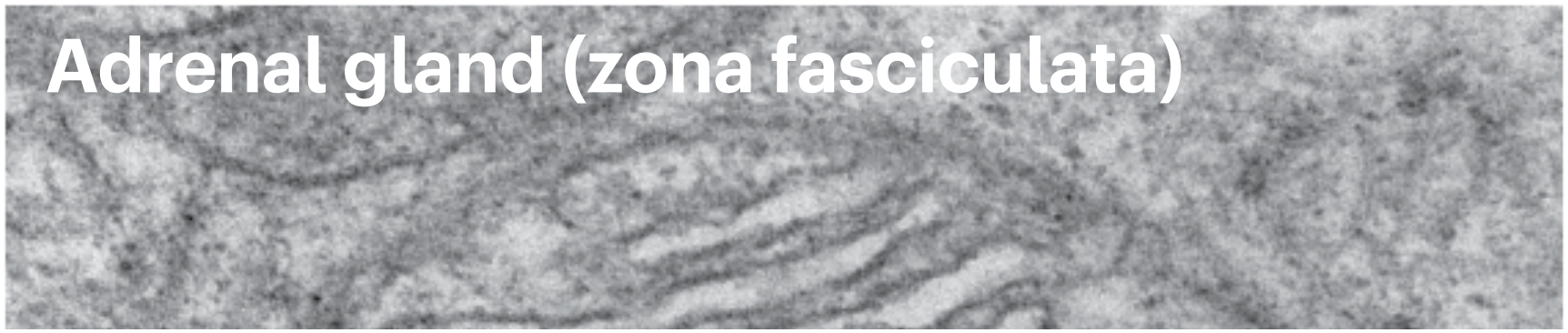

Myelinated motor neuron axon
Myelin sheath
Sympathetic nerve
Adrena

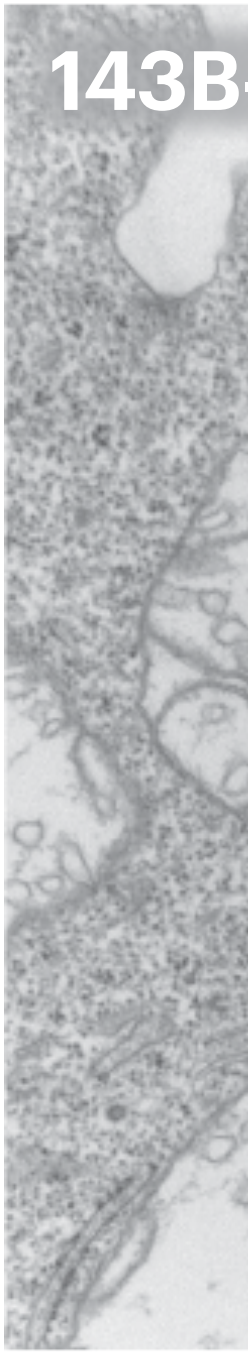



Adrenal gland (zona fasciculata)

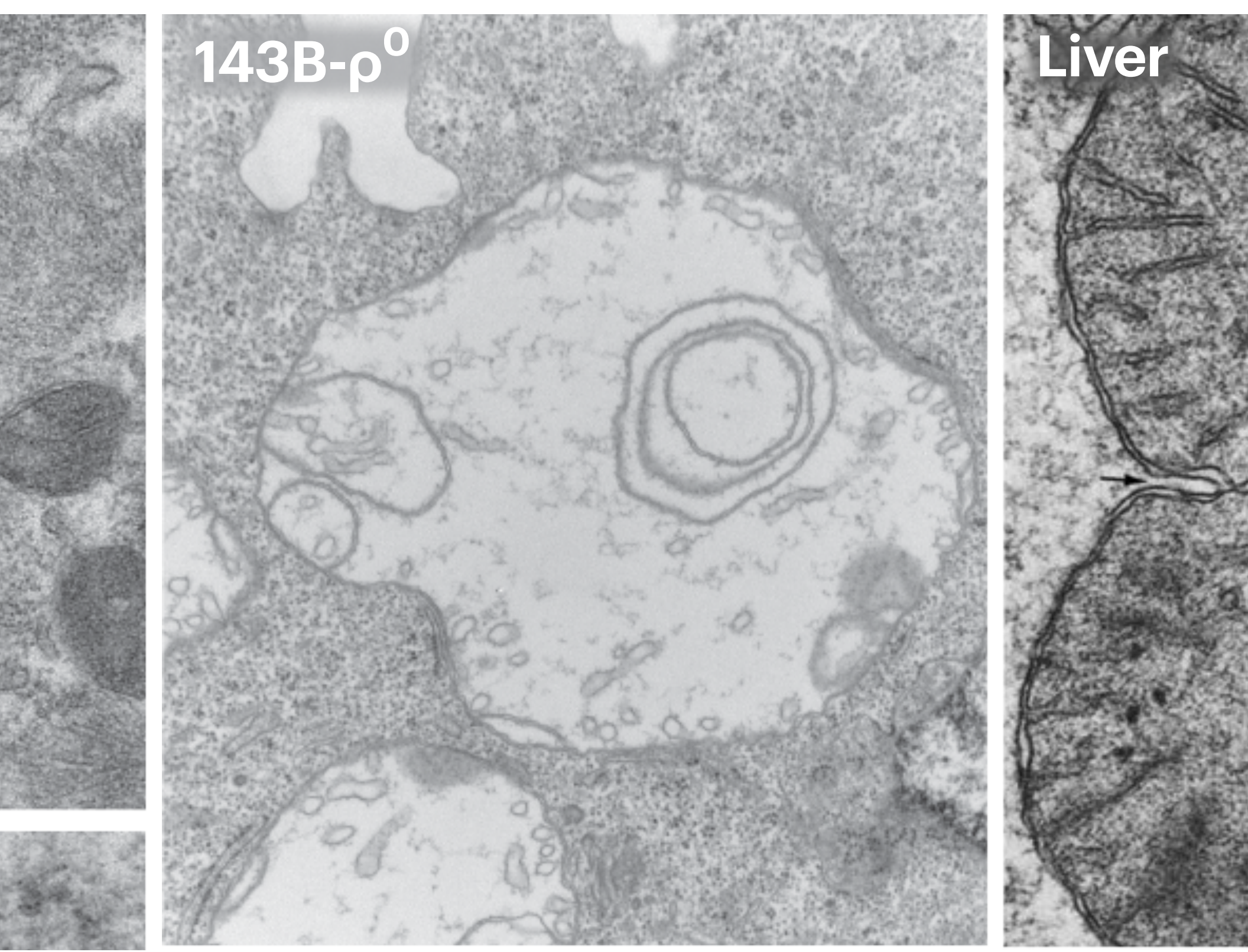

Br


Skeletal muscle (IMF)

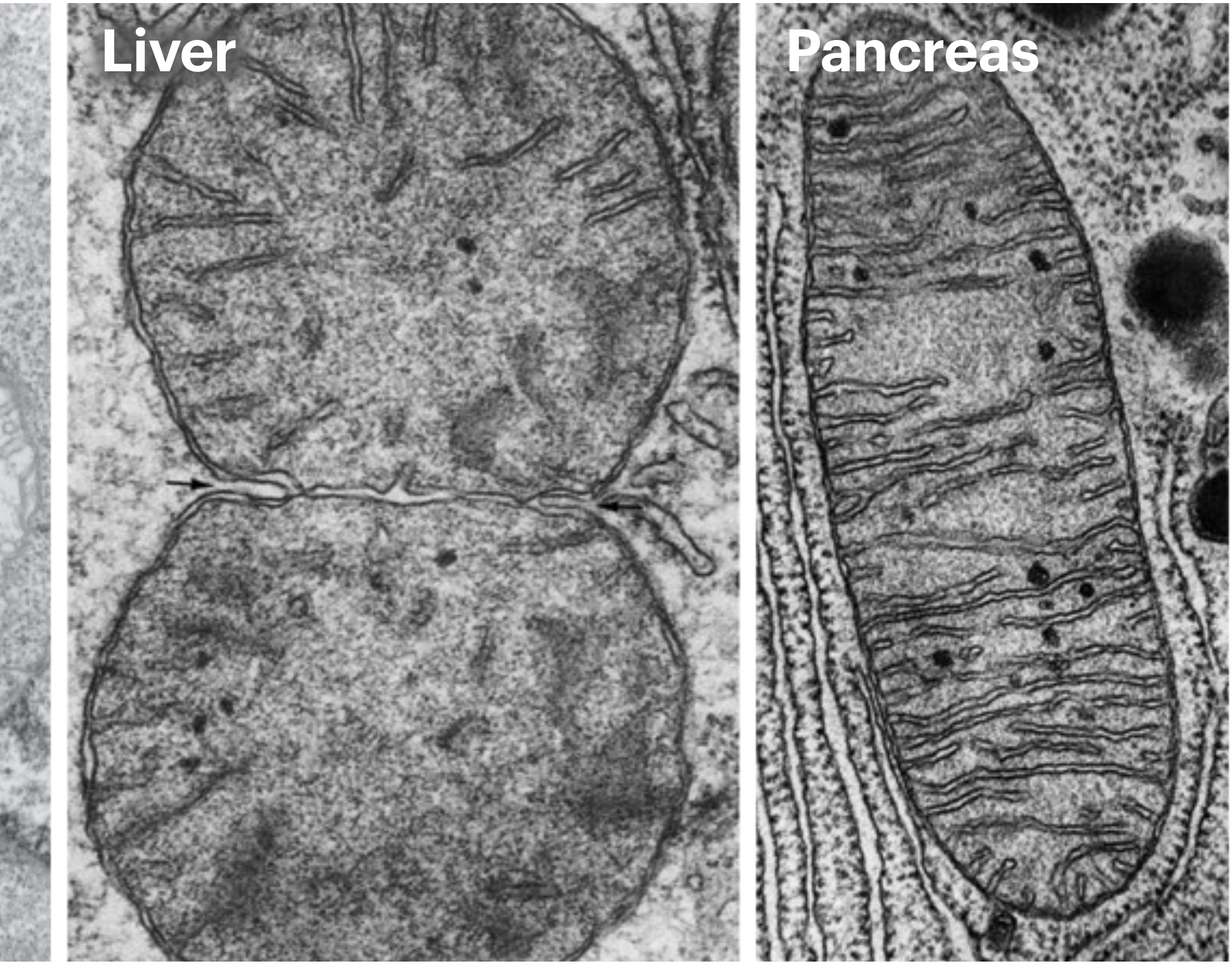

Adrenal gland (zona fasciculata)

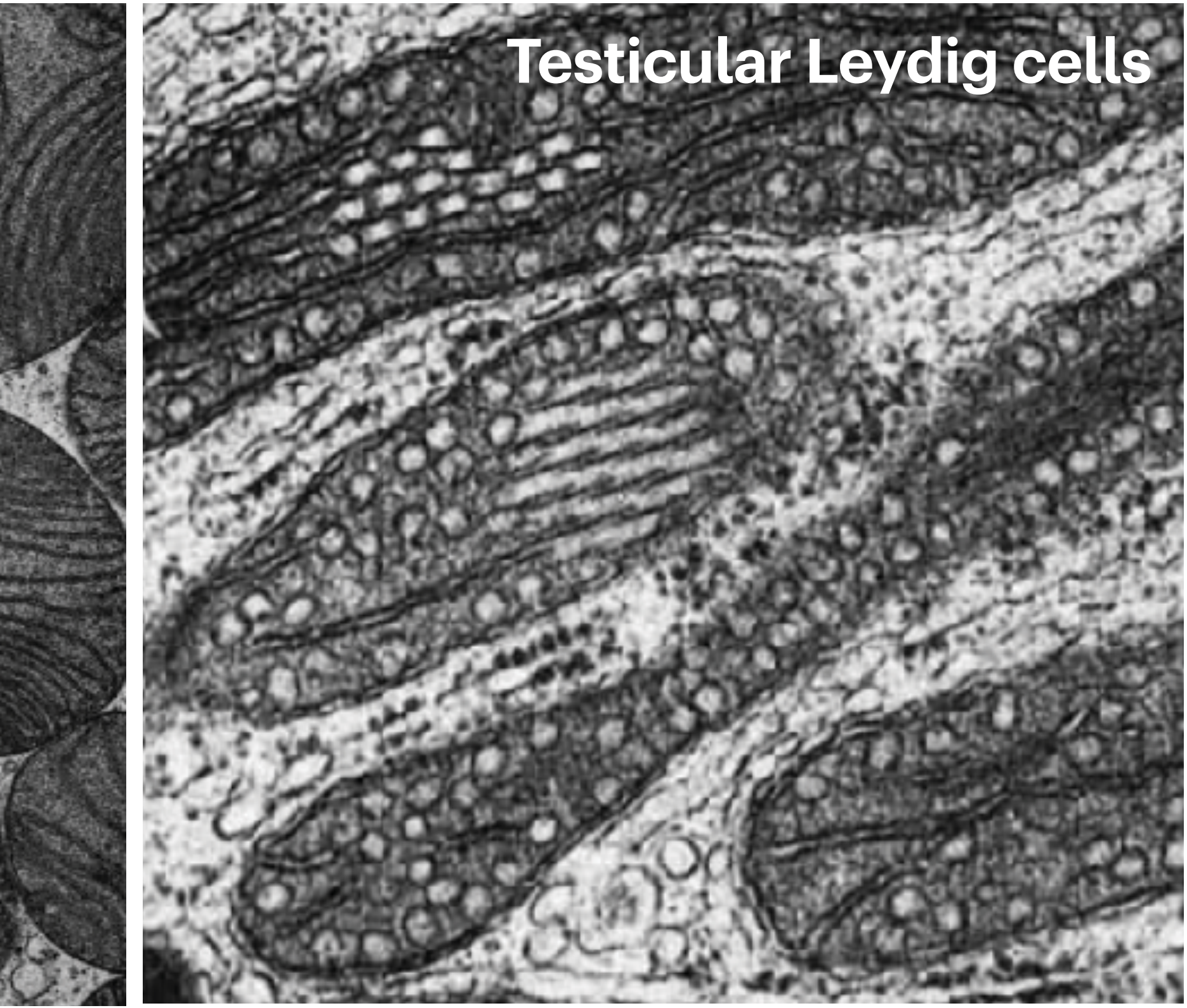

143B-

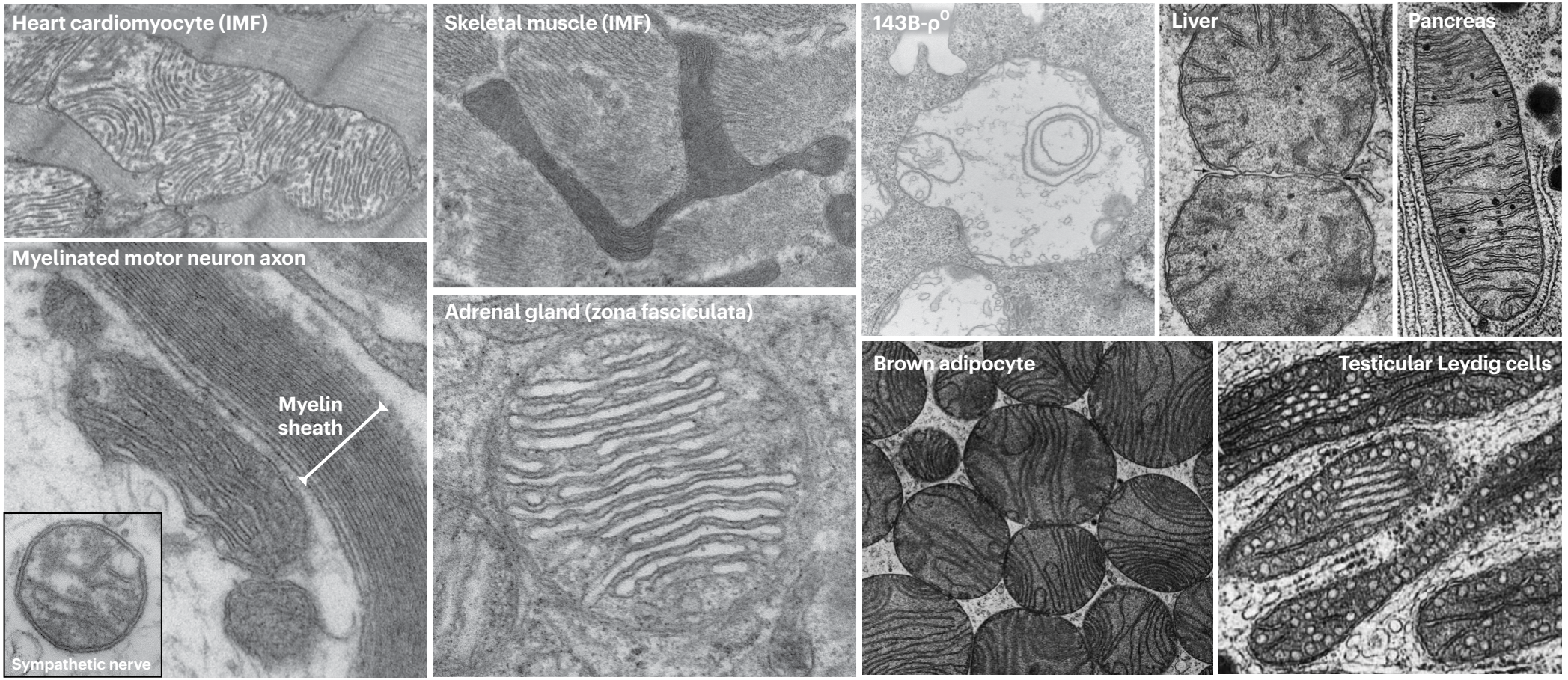

Brow


143B-ρ0
Liver


Brown adipocyte


Liver
Pancreas


Testicular Leydig cells


Heart cardiomyocyte (IMF)
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143B-ρ^0
Liver
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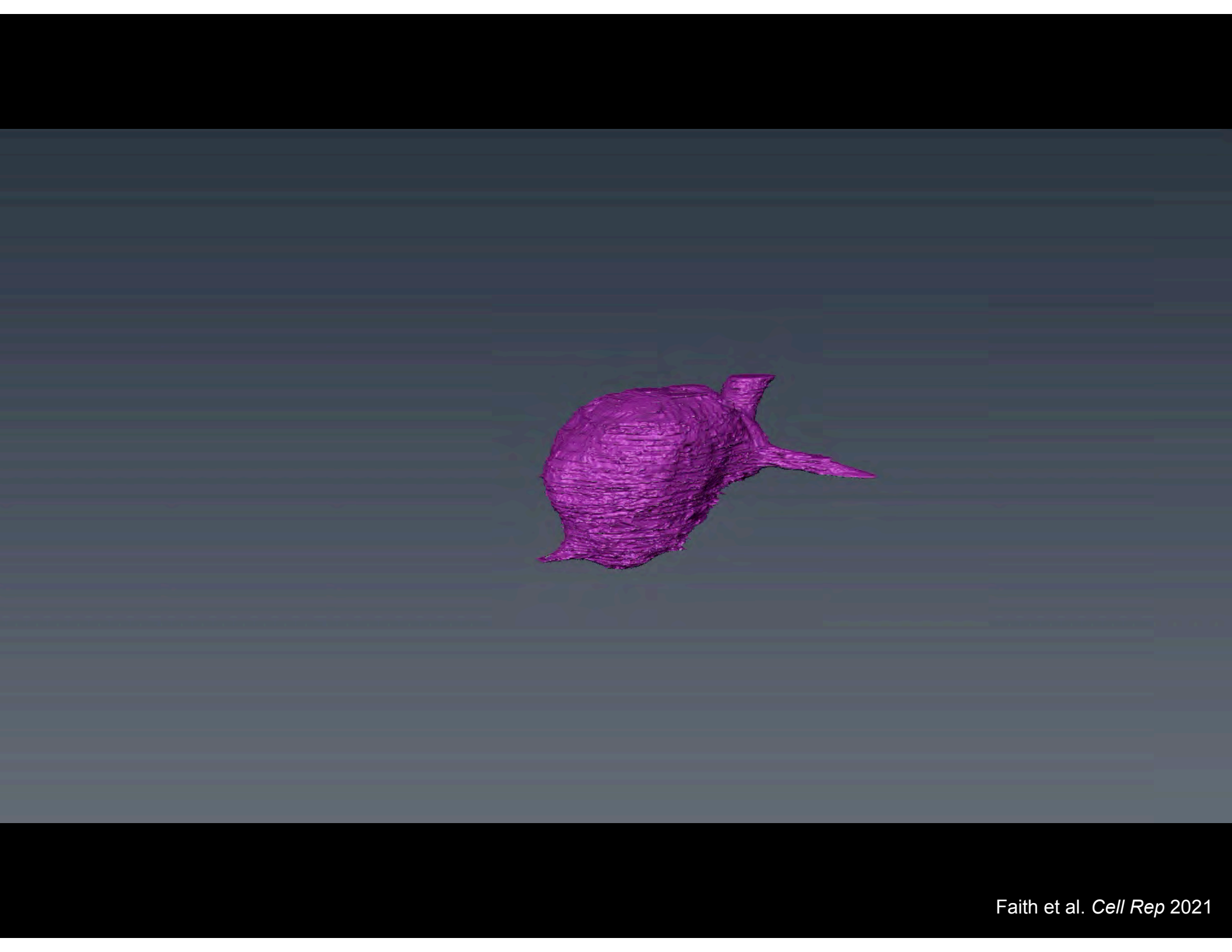
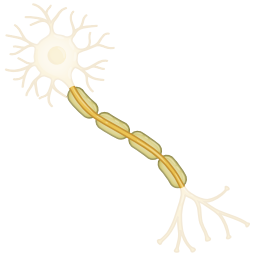
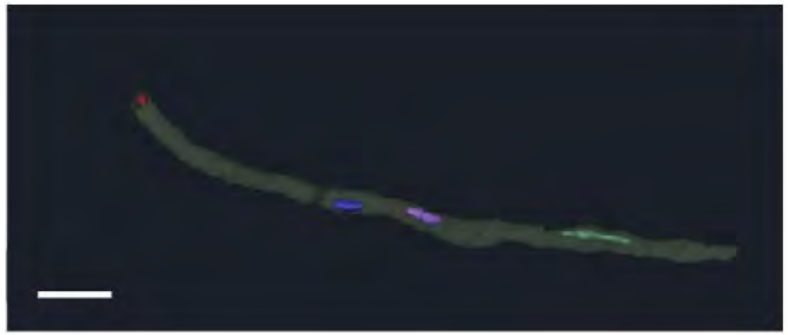


Faith et al. *Cell Rep* 2021

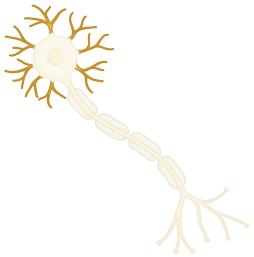
b **Mitochondrial subpopulations in mouse brain hippocampal neurons**

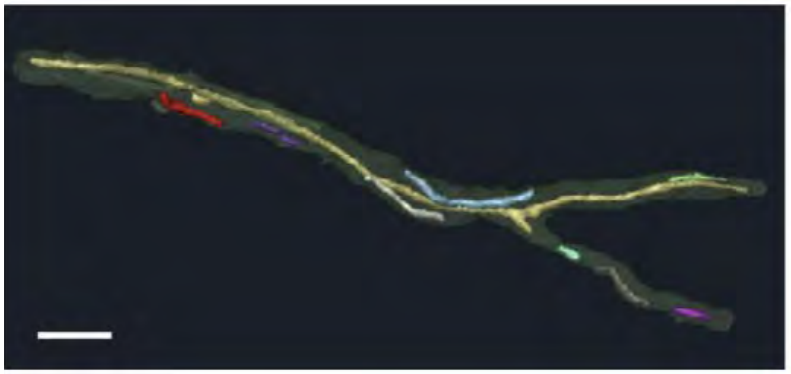
Axons



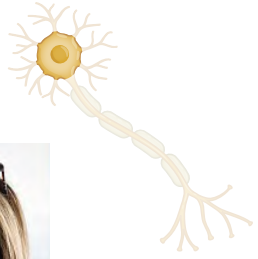


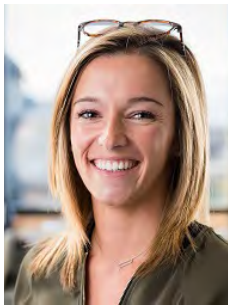
Dendrites



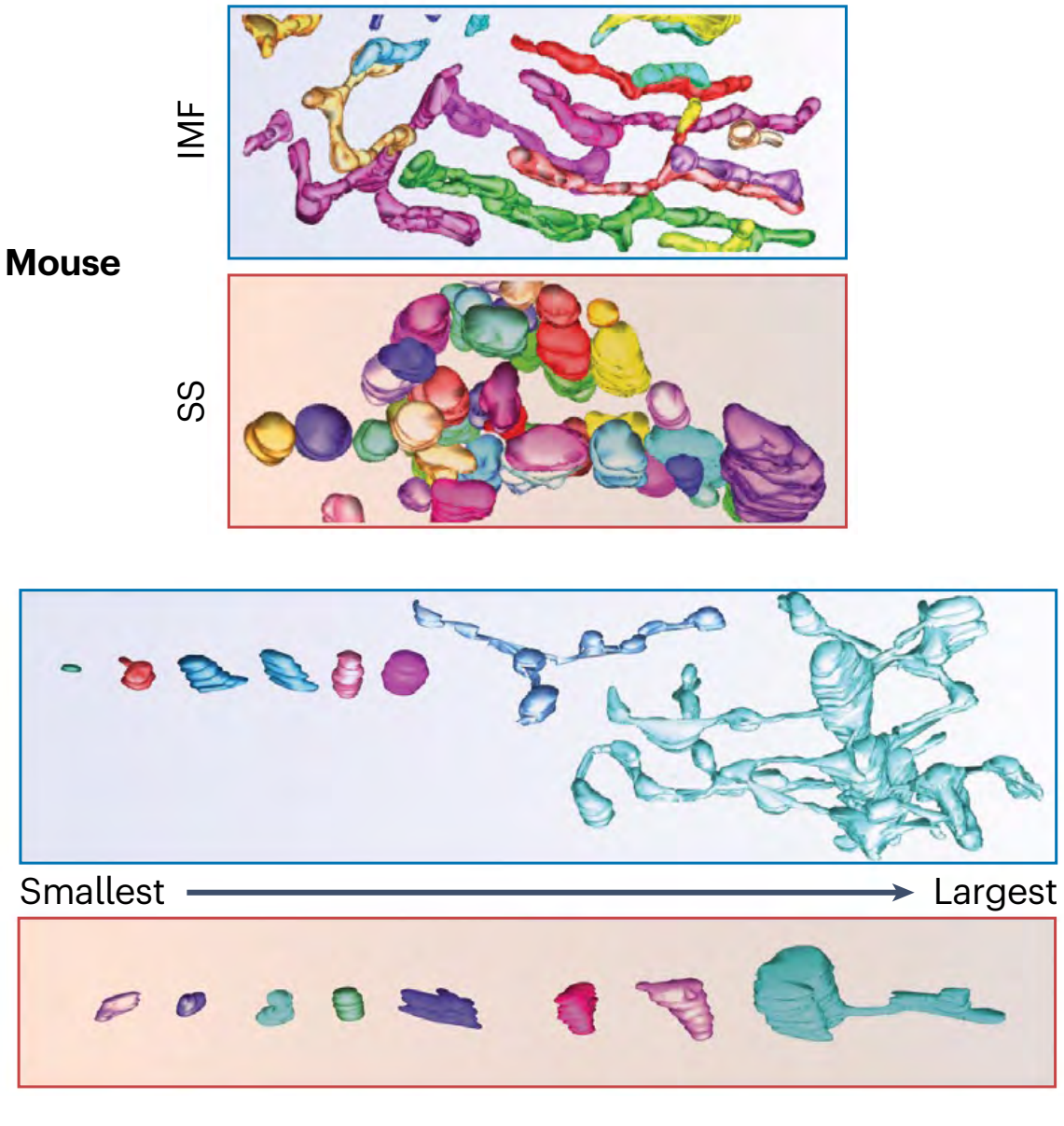


Somata



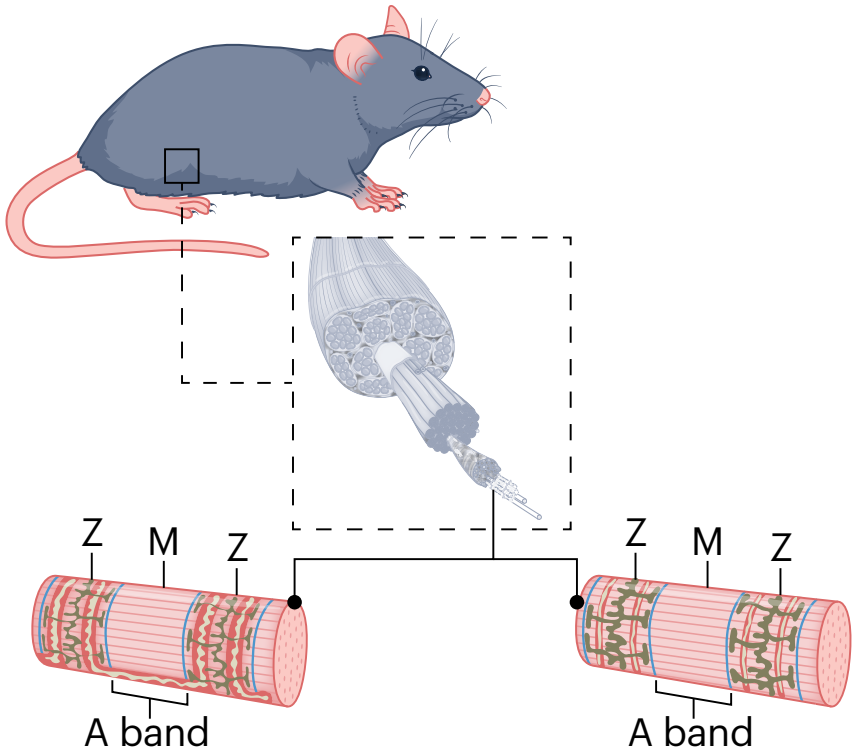


C **Mitochondrial subpopulations in mouse and human skeletal myofibre**



Vincent et al. *Cell Rep* 2019

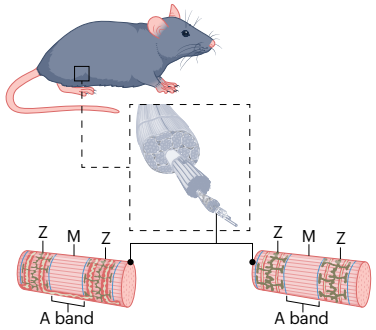
d **Skeletal muscle mitochondrial phenotypes**



Glycolytic (**type II**) vs. Oxidative (**type I**)

Myofibre mitochondrial phenotypes

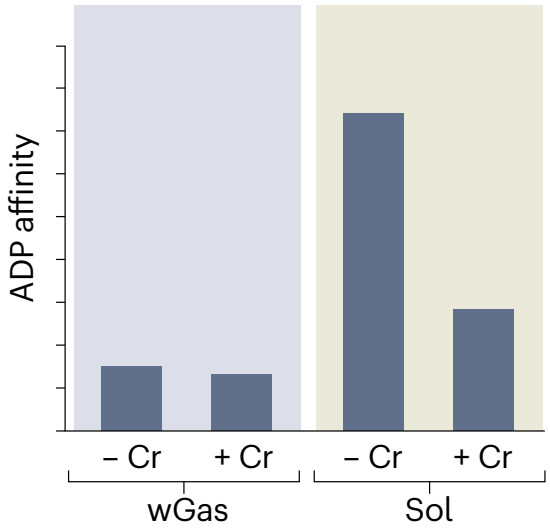
d **Skeletal muscle mitochondrial phenotypes**



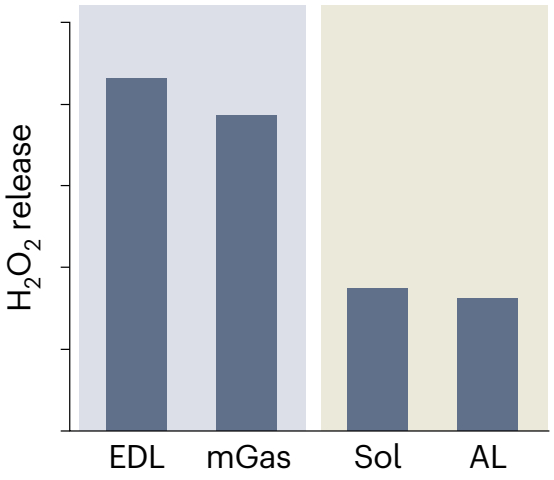
Glycolytic (**type II**) vs. Oxidative (**type I**)

Myofibre mitochondrial phenotypes

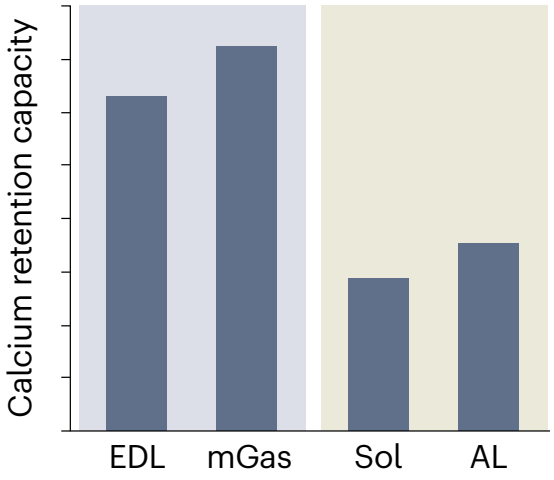
e **Respiration**

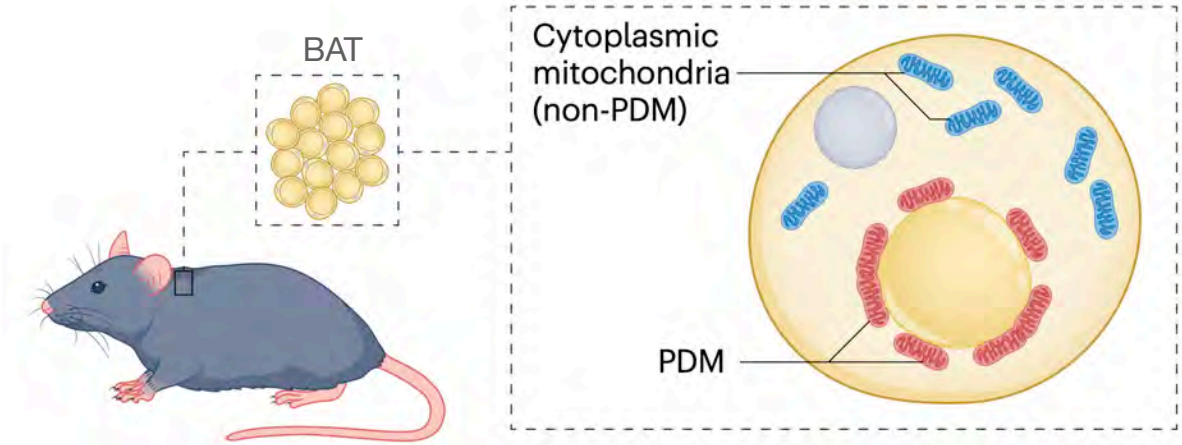


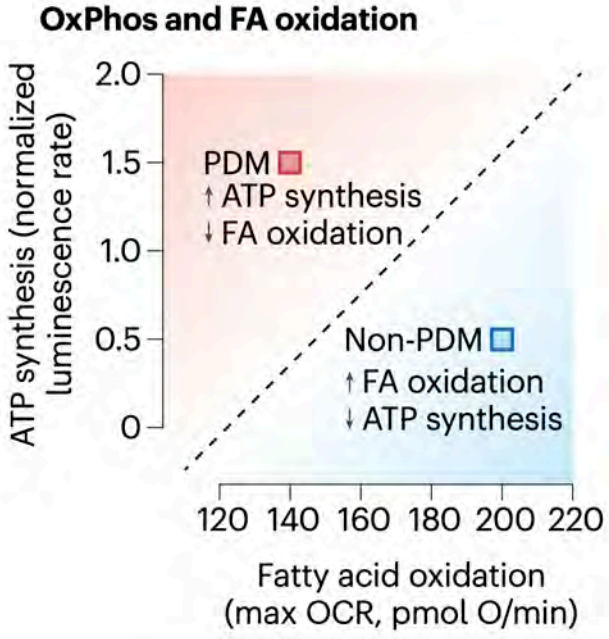
f **ROS emission**

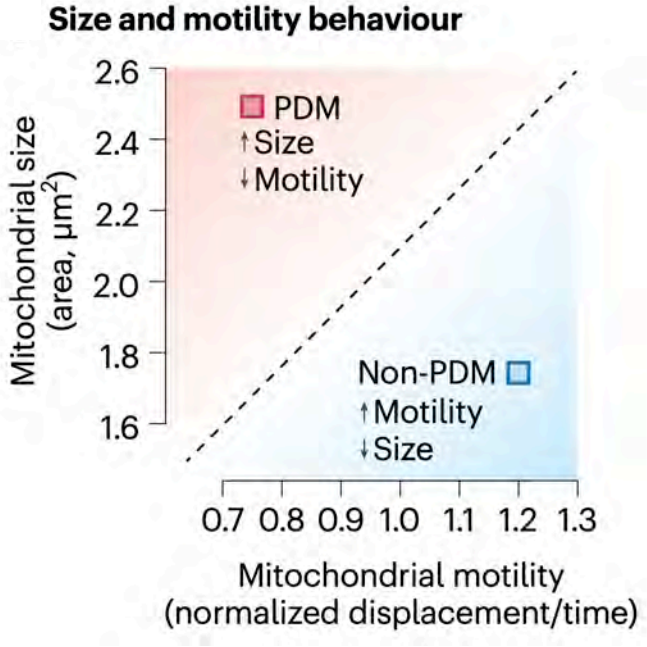


g **Calcium uptake**



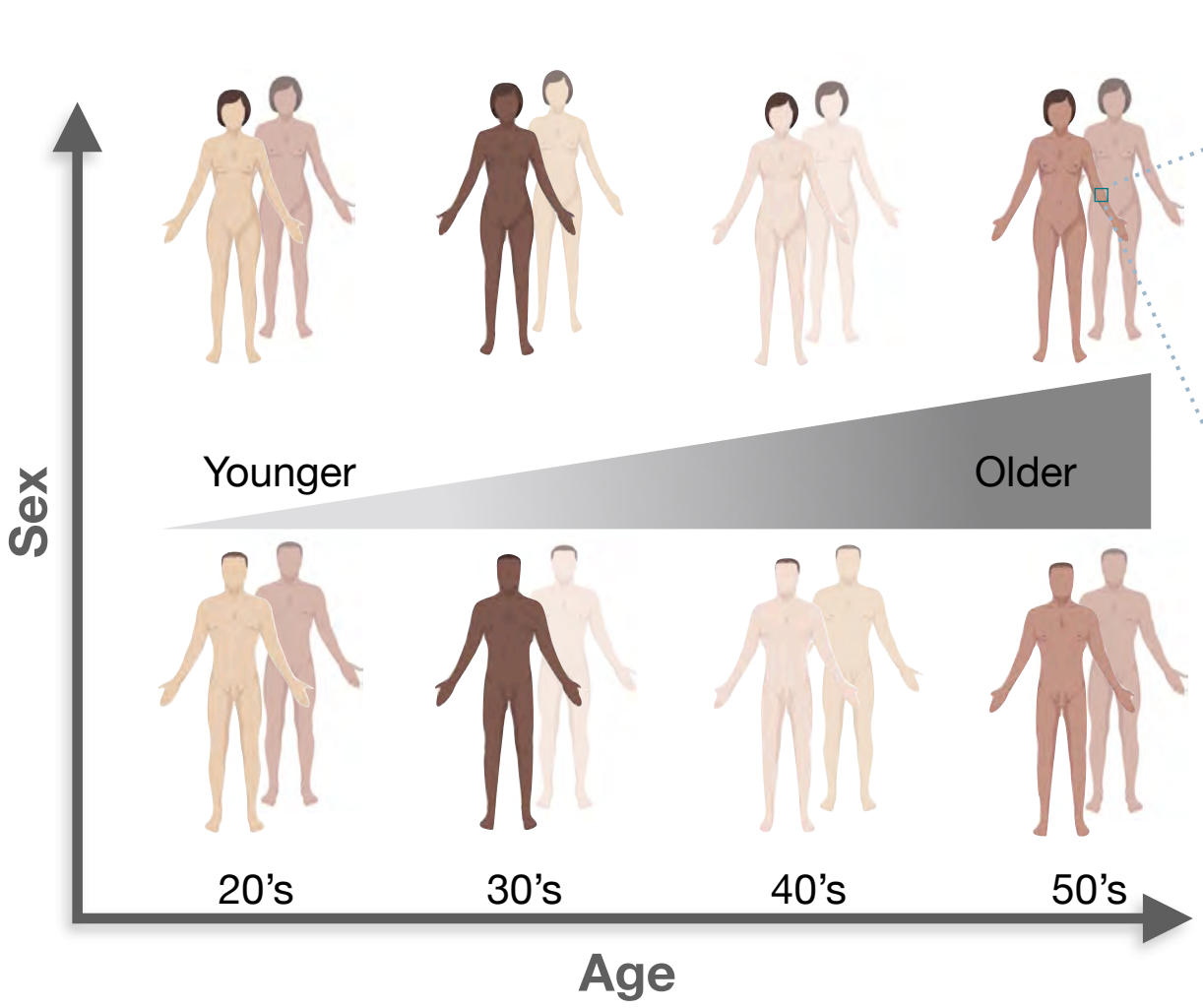


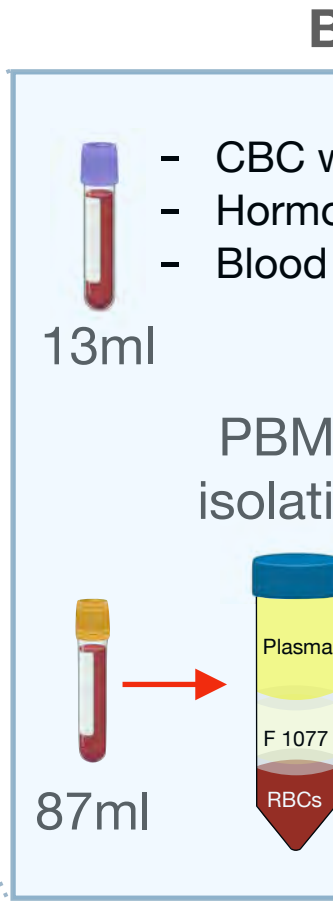




Monzel, Enriquez & Picard, Nat metab. 2023
(Adapted from Benador et al. Cell Metab. 2018)

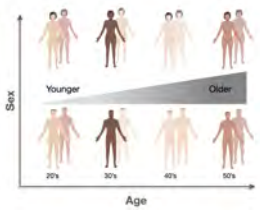
Study design (PART 1)



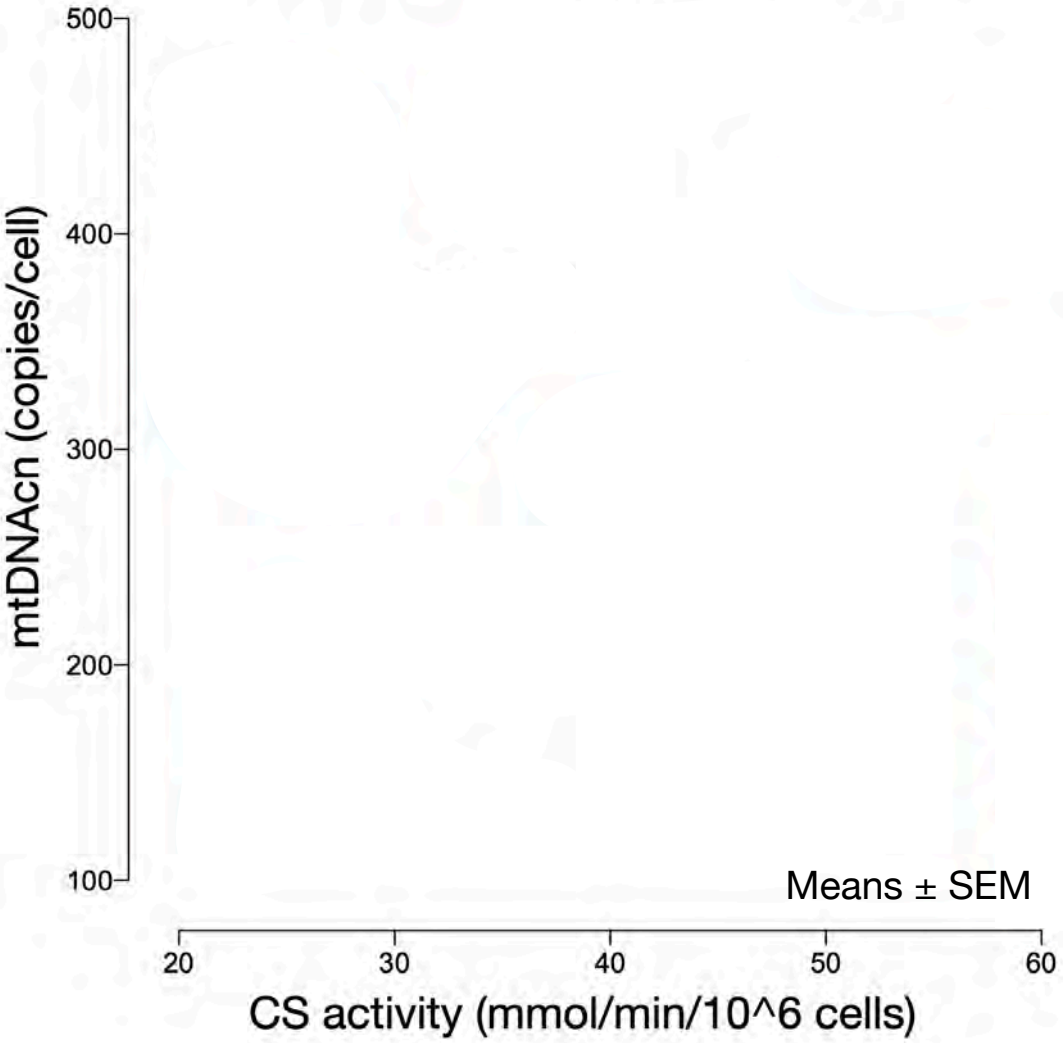


n=21 (11 Women, 10 Men)
(2 African American, 7 Asian, 12 Caucasian)

Rausser et al. *Elife* 2021



Mitochondrial phenotypes (mitotypes)



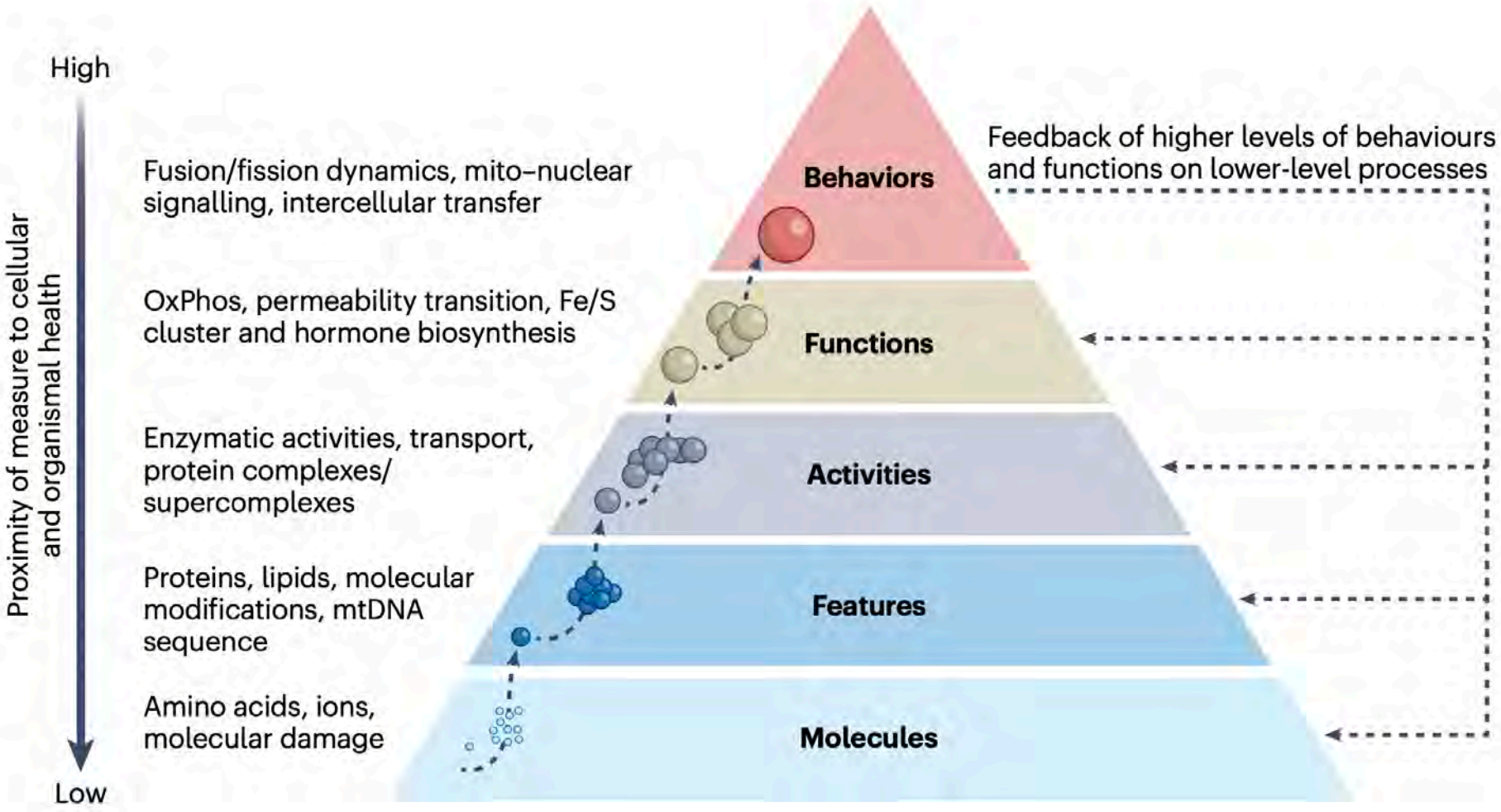
Rausser et al. *Elife* 2021

Morphological diversity

Topological diversity

Functional diversity

Hierarchy of mitochondrial biology



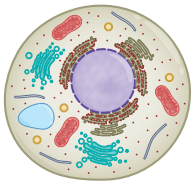
Monzel et al. *Nat Metab* 2023

Organism

Features	**Body characteristics** Height, body mass index, hydration level, muscle mass, biological sex
Activities	**Organ-level processes** Skeletal muscle contraction, insulin secretion, cardiac output, peristalsis
Functions	**Physiological processes** Glycemic control, blood pressure, digestion, wound healing, circadian rhythms, sleep
Behaviours	**Goal-directed complex set of functions** Social behaviours, reproduction, thinking and feeling, walking and running, ageing
Context-dependent phenotypes	**Physiological states driven by social and environmental demands** Homeostasis, allostasis and allostatic load

Analogous levels of biology

Organism



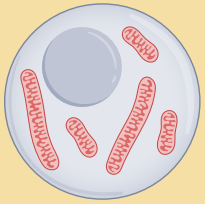
Cell types and subtypes

Features	**Body characteristics** Height, body mass index, hydration level, muscle mass, biological sex	**Molecular components that define cell types and subtypes** Cell surface receptors, gene expression patterns, DNAm epigenetic marks
Activities	**Organ-level processes** Skeletal muscle contraction, insulin secretion, cardiac output, peristalsis	**Sub-cellular processes** Transcription, translation, autophagy, receptor-mediated signal transduction
Functions	**Physiological processes** Glycemic control, blood pressure, digestion, wound healing, circadian rhythms, sleep	**Integrated cellular processes** Specific cytokines release, phagocytotic activity, cell migration, contraction
Behaviours	**Goal-directed complex set of functions** Social behaviours, reproduction, thinking and feeling, walking and running, ageing	**Goal-directed processes involving the cell as a whole** Differentiation, extravasation, developmental apoptosis
Context-dependent phenotypes	**Physiological states driven by social and environmental demands** Homeostasis, allostasis and allostatic load	**Cellular characteristics relevant only at the organ level** Hyperplasia, inflammation, elasticity

Analogous levels of biology

	Organism	Cell types and subtypes	Mitochondrial phenotypes
Features	**Body characteristics** Height, body mass index, hydration level, muscle mass, biological sex	**Molecular components that define cell types and subtypes** Cell surface receptors, gene expression patterns, DNAm epigenetic marks	**Static, molecular characteristics that define mitochondrial phenotypes** RNA, proteins, OxPhos subunits, mtDNA integrity, morphology, lipid composition
Activities	**Organ-level processes** Skeletal muscle contraction, insulin secretion, cardiac output, peristalsis	**Sub-cellular processes** Transcription, translation, autophagy, receptor-mediated signal transduction	**Processes of individual molecular components** ETC enzyme kinetics, other enzymes, Fe buffering, DNA repair
Functions	**Physiological processes** Glycemic control, blood pressure, digestion, wound healing, circadian rhythms, sleep	**Integrated cellular processes** Specific cytokines release, phagocytotic activity, cell migration, contraction	**Integrated processes of mitochondria requiring multiple individual activities** OxPhos, Fe/S cluster synthesis, ROS production, steroidogenesis, anaplerosis
Behaviours	**Goal-directed complex set of functions** Social behaviours, reproduction, thinking and feeling, walking and running, ageing	**Goal-directed processes involving the cell as a whole** Differentiation, extravasation, developmental apoptosis	**Goal-directed complex processes involving the mitochondrion as a whole** Fusion, fission, motility, inter-organellar signalling
Context-dependent phenotypes	**Physiological states driven by social and environmental demands** Homeostasis, allostasis and allostatic load	**Cellular characteristics relevant only at the organ level** Hyperplasia, inflammation, elasticity	**Mitochondrial characteristics relevant in the context of the host cell** Mitochondrial content, mtDNAcn, cellular O_2 consumption

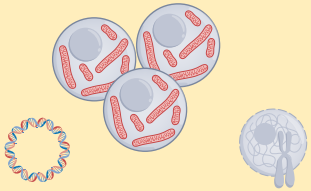
Cell-dependent phenotypes



Mito content/mass

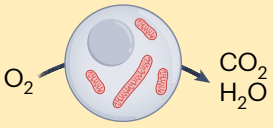
Volume density

mtDNAcn



500,000 — Copies — 1,000
mtDNAcn: 500

Cellular oxygen consumption

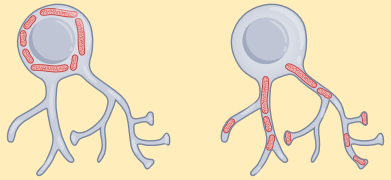


(pmol O_2/cell/min)

Energy expenditure

Cellular topology

Perinuclear Peripheral



Features

mtDNA sequence and integrity

SNPs, mutations, deletions

Molecular composition

Protein dynamics

Assembled protein complexes

Ultrastructure

Cristae structure

Morphology

Size, length, complexity

Activities

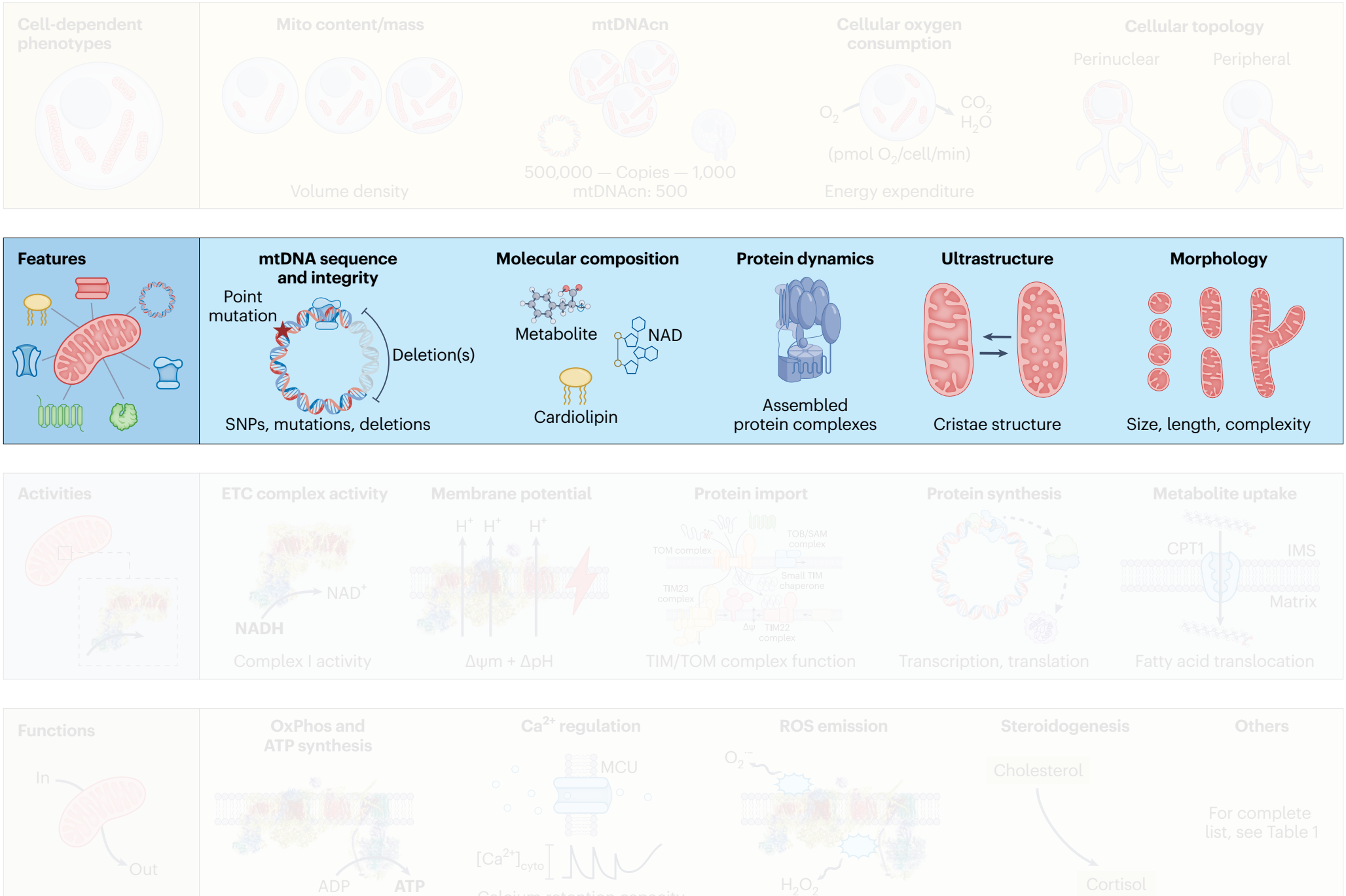
ETC complex activity

Membrane potential

Protein import

Protein synthesis

Metabolite uptake


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
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Protein dynamics
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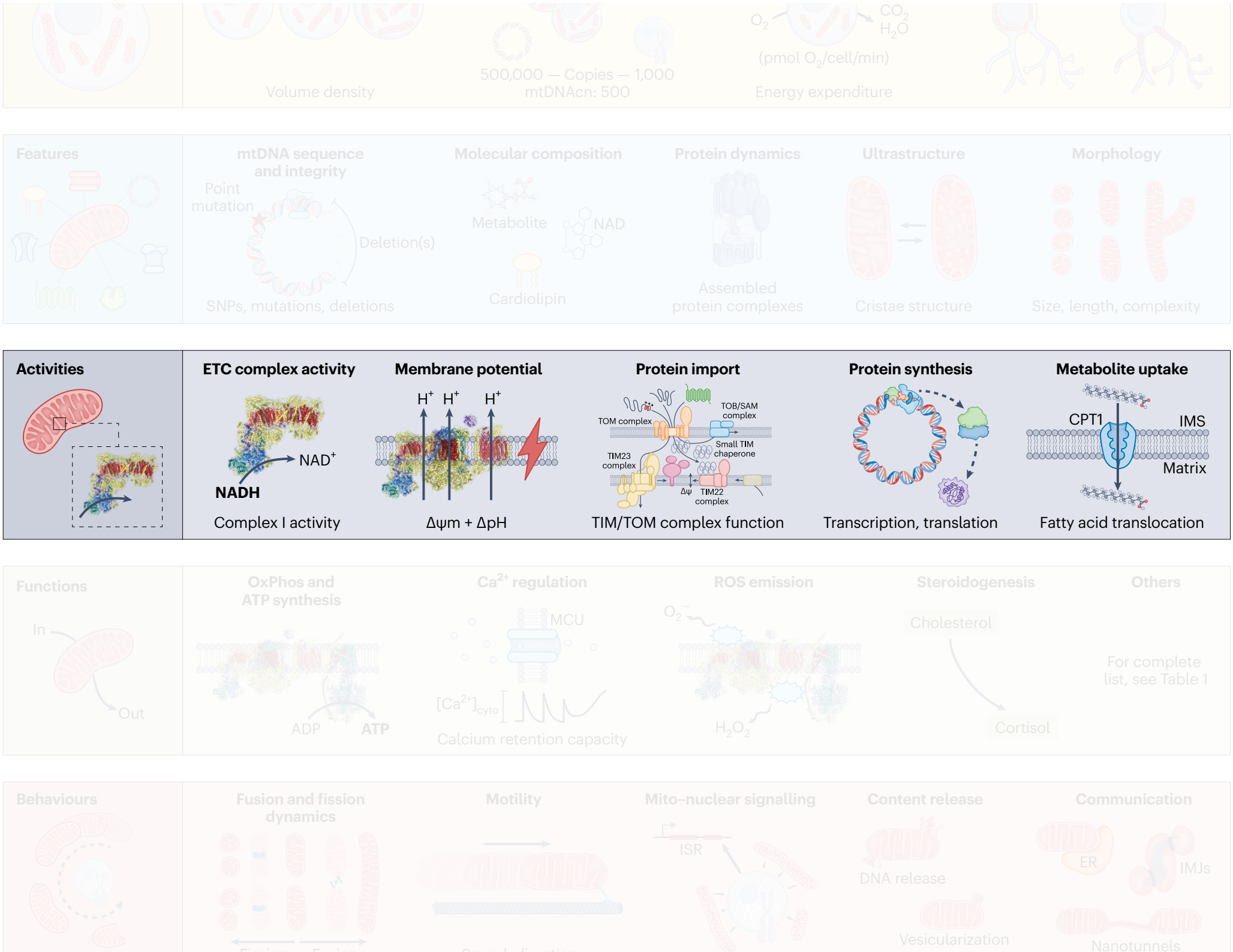
Ultrastructure
Cristae structure
Morphology
Size, length, complexity
Activities
ETC complex activity
NAD+
NADH
Complex I activity
Membrane potential
H+ H+ H+
Δψm + ΔpH
Protein import
TOM complex
TOB/SAM complex
Small TIM chaperone
TIM23 complex
Δψ
TIM22 complex
TIM/TOM complex function
Protein synthesis
Transcription, translation
Metabolite uptake
CPT1
IMS
Matrix
Fatty acid translocation
Functions
In
Out
OxPhos and ATP synthesis
ADP
ATP
Ca2+ regulation
MCU
[Ca2+]cyto
ROS emission
O2•−
H2O2
Steroidogenesis
Cholesterol
Cortisol
Others
For complete list, see Table 1


Volume density
500,000 — Copies — 1,000
mtDNAcn: 500
O_2
CO_2
H_2O
(pmol O_2/cell/min)
Energy expenditure
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MCU
$[Ca^{2+}]_{cyto}$
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Others
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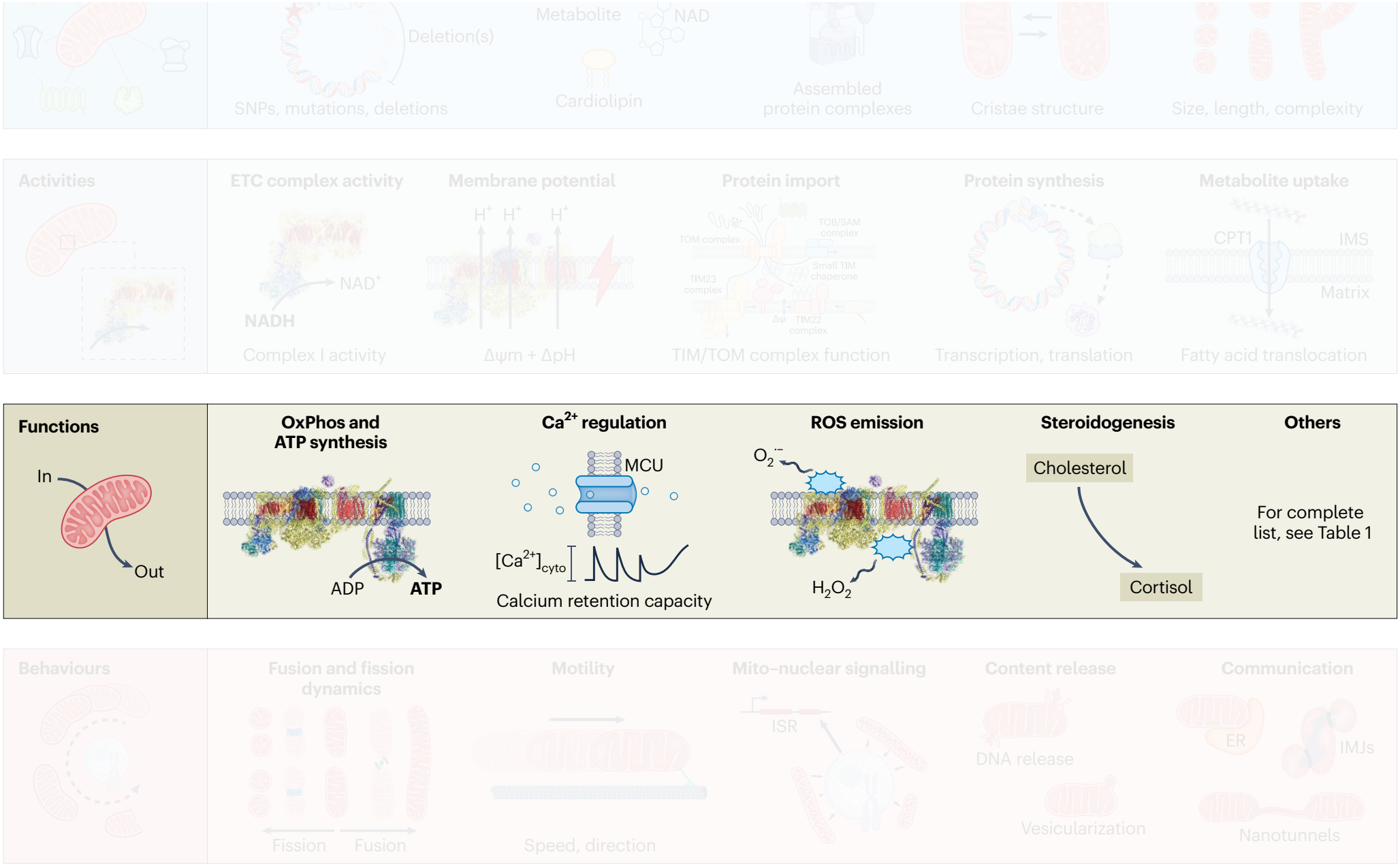
Behaviours
Fusion and fission dynamics
Fission
Fusion
Motility
Speed, direction
Mito–nuclear signalling
ISR
Content release
DNA release
Vesicularization
Communication
ER
IMJs
Nanotunnels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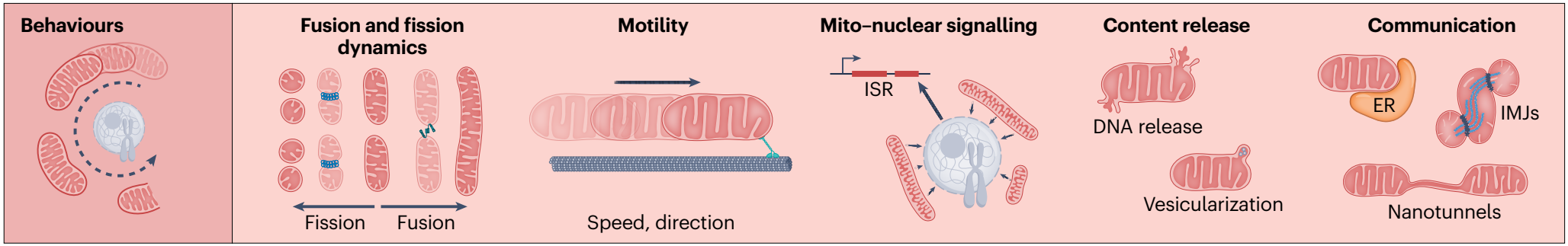
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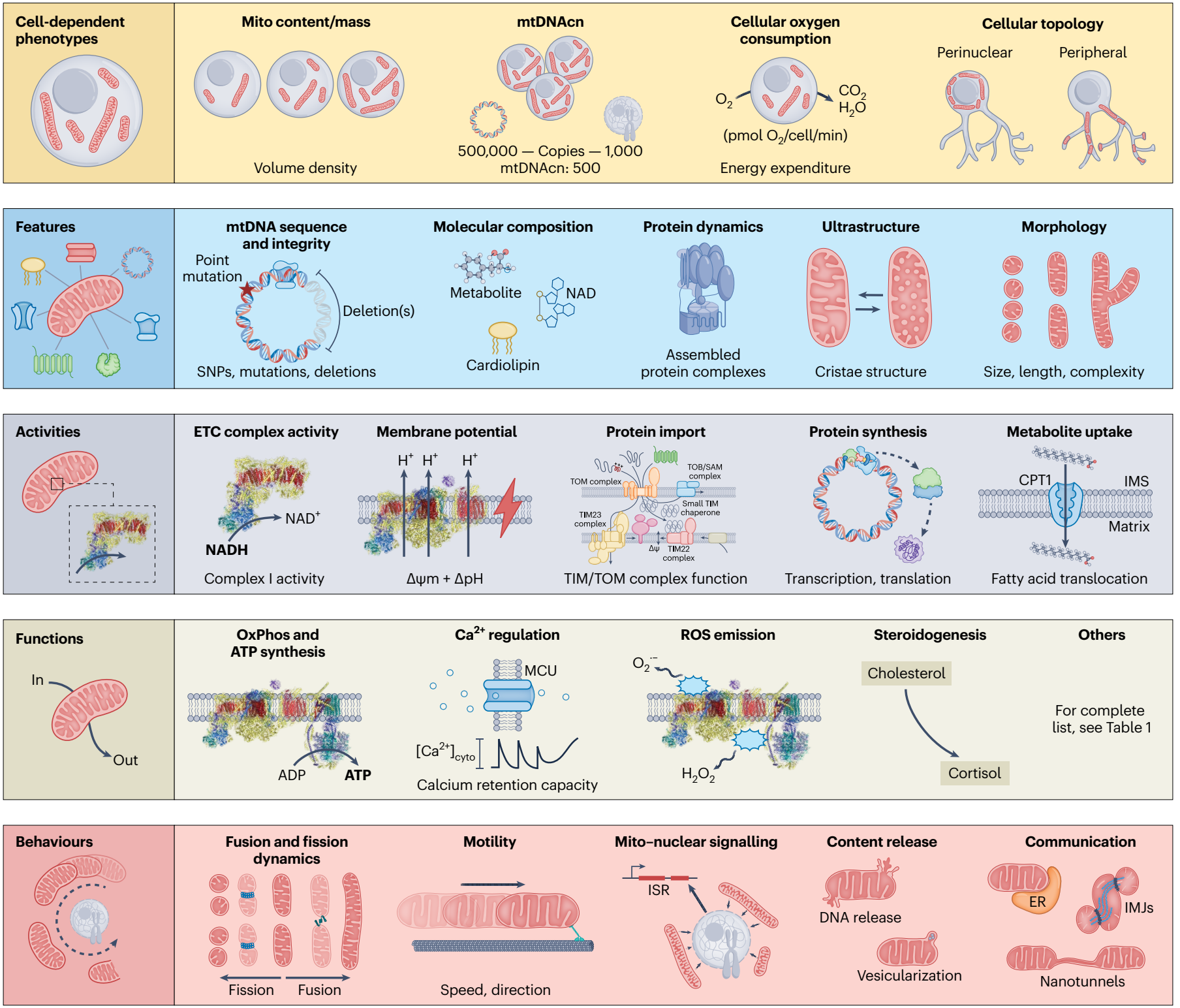
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https://doi.org/10.1038/s42255-023-00783-1

Table 1 | Mitochondrial functions and behaviours

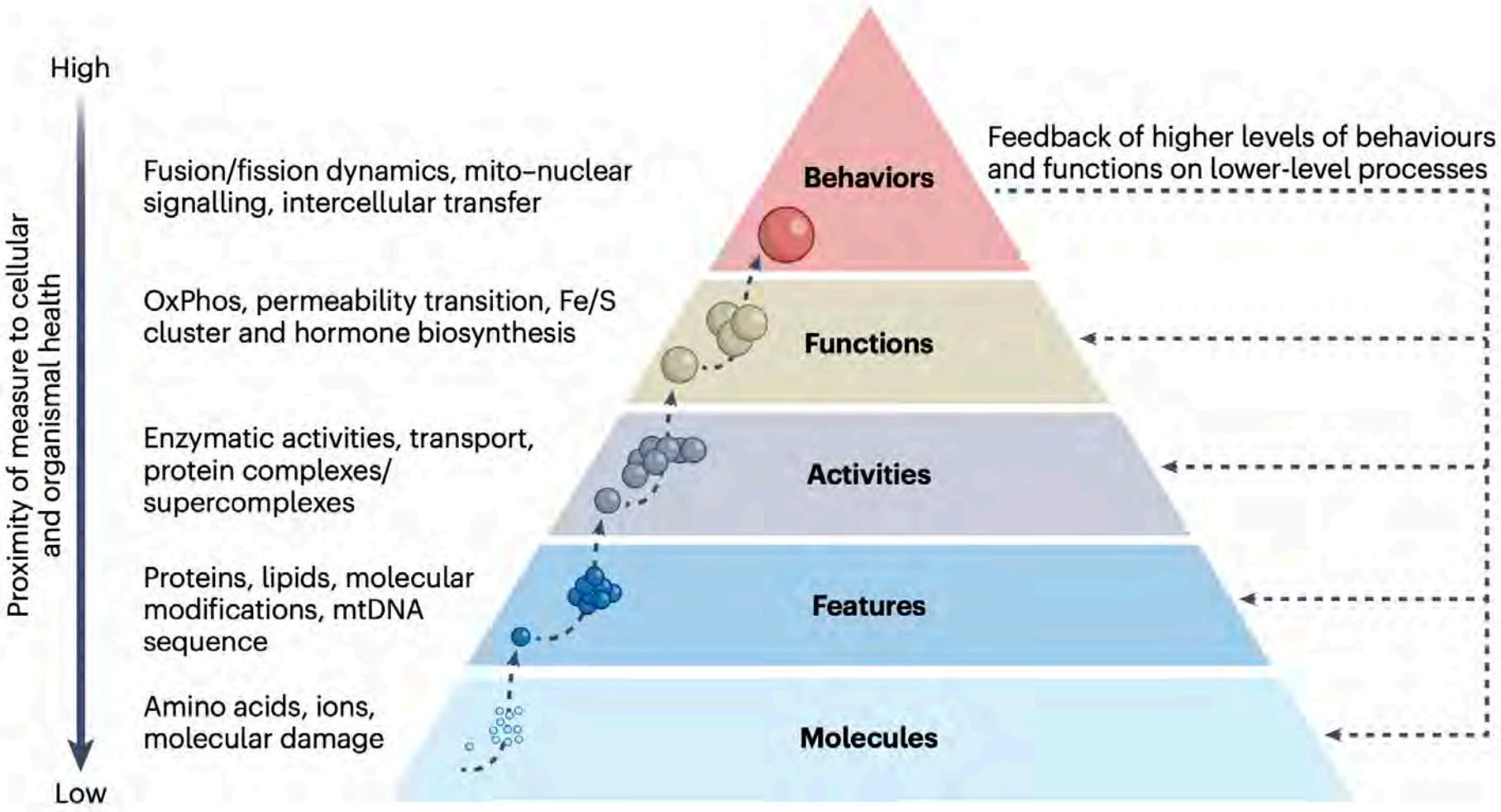
	Description	Reviewed in ref(s).	Methods described in ref(s).
Functions			
[a]**Membrane potential generation**	Formation of the electrochemical gradient (ΔΨm+ΔpH) across the IMM, usually by the electron pumping capacity of the respiratory complexes I, III and IV, but also by other processes including through ATP hydrolysis by the F_oF_1 ATP synthase (complex V).	104	105,106
Amino acid metabolism	Lysine metabolism (lysine-α-ketoglutarate reductase, encoded by *AASS*). Electrogenic malate–aspartate shuttle system, which is important for balancing pyridine dinucleotide redox states across subcellular compartments. Branched-chain keto and amino acids. Choline and derivatives as structural precursors for lipoproteins, membrane lipids and the neurotransmitter acetylcholine. Betaine as osmoregulator and an intermediate in the cytosolic transulfuration pathway.	107–111	112–119
Ascorbate metabolism	L-ascorbate (vitamin C) biosynthesis in many plants and animals, but not in primates, which serves as osmoregulator and antioxidant. Mitochondria may recycle oxidized (dehydro)ascorbic acid.	120	121,122
Bicarbonate metabolism	Production of bicarbonate (HCO_3^-) by mitochondrial carbonic anhydrase V (encoded by *CA5A*), used as a cofactor for anaplerotic reactions (for example, ureagenesis and gluconeogenesis) and acid–base balance. The TCA cycle is an important contributor to cellular/extracellular acidification due to CO_2 production.	123	–
Calcium uptake and extrusion	Uptake of cytoplasmic Ca^{2+} via the mitochondrial calcium uniporter in a ΔΨm-dependent manner; extrusion by the sodium/calcium exchanger NCLX (encoded by *SLC8B1*).	124–126	127,128
Hydrogen sulfide detoxification	Mitochondrial sulfide quinone oxidoreductase (encoded by *SQOR*) oxidizes hydrogen sulfide to glutathione persulfide by reducing CoQ.	129–132	133
Heat production	Heat generation is stimulated by uncoupling ΔΨm+ΔpH from ATP synthesis (thereby increasing electron flux and respiration) by UCP1 (encoded by *UCP1*), the ADP/ATP carrier (*AAC*, also *ANT1*), or by creatine-dependent substrate cycling and other futile cycles.	134–137	138
Intermediate metabolism	Enzymatic interconversion of metabolic intermediates to enable the synthesis of specific macromolecules, including five major anaplerotic ones. This includes the conversion of pyruvate into oxaloacetate by pyruvate carboxylase (encoded by *PC*), a critical step for de novo glucose synthesis (gluconeogenesis); citrate export to the cytoplasm where it is used for lipid synthesis or converted to acetyl-CoA for acetylation reactions; synthesis of itaconate, a derivative of *cis*-aconitate; succinate, α-ketoglutarate and others that participate in a variety of signalling	25,139,140	141,142

Lipid oxidation	Beta-oxidation of long-chain, medium-chain and short-chain fatty acids into acetyl-CoA.	145	146
Lipid synthesis	Synthesis of cardiolipin and phosphatidylethanolamine from ER precursors in the IMM.	147–150	–
mtDNA maintenance and expression	mtDNA replication, transcription, protein synthesis and assembly of the OxPhos system.	151,152	153,154
Na^+import/export	Sodium (Na^+) uptake and release against cytoplasmic Ca^{2+} by the sodium/calcium exchanger protein NCLX (encoded by *SLC8B1*) or by Na^+/H^+ antiporter (molecular identity pending).	124,155	156
Neurotransmitter synthesis and degradation	Synthesis of the cofactor BH4 (tetrahydrobiopterin), used by hydrolase enzymes to synthesize catecholamines and neurotransmitters (serotonin, melatonin, norepinephrine and epinephrine) and nitric oxide. Mitochondria with OMM-anchored monoamine oxidases (encoded by *MAOA* and *MAOB*, donate electrons and contribute to electron flow in the ETC) also degrade catecholamines. Mitochondria also participate in GABA metabolism.	9,157	158,159
One-carbon metabolism and pyrimidine synthesis	The one-carbon metabolism connects the synthesis of nucleotides (purine and pyrimidine), amino acids (methionine, serine and glycine), *S*-adenosyl-methionine and folate. Ubiquinone-mediated oxidation of dihydroorotate to orotate by dihydroorotate dehydrogenase (encoded by *DHODH*) is a key step in pyrimidine synthesis.	160–163	164
OxPhos	Transduction of $\Delta\Psi m + \Delta pH$ generated by the electron transport chain (ETC, also 'respiratory chain') into ATP synthesis by the F_oF_1 ATP synthase (complex V), abbreviated as OxPhos.	165	166
Oxygen sensing	The electron transport and free-radical generation by ETC complexes I and III is modulated by the partial pressure of oxygen, which can limit respiration at very low partial pressures of O_2.	167–170	–
Permeability transition	Opening of the high-conductance permeability transition pore (PTP), which dissipates membrane potential and promotes the release of intracristae and matrix-located components into the cytoplasm.	171,172	173–175
Protein import	Import, processing and folding of nuclear-encoded polypeptides from the cytoplasm by the translocator of the inner membrane (TIM) and outer membrane (TOM) complexes and associated proteins.	176	–
Redox homeostasis	Re-oxidation of enzymes and/or their redox cofactors (involved in anabolic and catabolic reactions) by the electron acceptors CoQ and cytochrome c (encoded by *CYTC*) within the mitochondrial respiratory chain, and production of NADPH by *NNT*.	177,178	–
Respiration	Electrons stored in reducing equivalents NADH and $FADH_2$, or derived from diverse redox reactions are sequentially delivered to respiratory complex I and CoQ, or cytochrome c, respectively, to promote the reduction of molecular oxygen at cytochrome c oxidase (complex IV).	179,180	181
ROS production	Production and release of ROS (H_2O_2, $O_2^{\bullet-}$, others) mainly at respiratory chain complexes I and III.	182,183	184
Steroidogenesis	Production of pregnanolone from cholesterol imported via IMM steroidogenic	33,34,185,186	187

	cytochrome c oxidase (complex IV).		
ROS production	Production and release of ROS (H_2O_2, $O_2^{\bullet-}$, others) mainly at respiratory chain complexes I and III.	182,183	184
Steroidogenesis	Production of pregnanolone from cholesterol imported via IMM steroidogenic acute regulatory protein (encoded by *STAR*) followed by enzymatic transformation by P450ssc (encoded by *CYP11A1*) in the matrix. Intermediate or terminal steps for some steroids occur in the ER. Cytochrome P450 family members participate also in xenobiotic metabolism as well as bile acid and vitamin D biosynthesis.	33,34,185,186	187
Behaviours			
Antiviral signalling	Assembly of the mitochondrial antiviral signal (encoded by *MAVS*) adaptor protein on the OMM to potentiate downstream signalling, and activation of nuclear interferon pathways in the nucleus by mtDNA release.	39,188	–
Apoptotic signalling	Release of cytochrome c (encoded by *CYCS*), apoptosis-inducing factor (encoded by *AIF*), and other proteins that trigger different forms of cell death by acting on cytoplasmic and nuclear effectors.	189,190	–
Cristae remodelling	Dynamic remodelling of IMM cristae junctions, cristae shape and distribution via the combined action of optic atrophy 1 (encoded by *OPA1*) and mitochondrial contact site and cristae organizing system (MICOS) proteins.	103,191	95
DNA signalling	mtDNA extrusion in the cytoplasm, particularly in the form of oxidized mtDNA fragments via proteinaceous pores forming across the IMM and OMM, which trigger inflammasome activation.	189,190,192,193	175
Epigenetic remodelling	Transduction of mitochondrial states into changes in epigenome via several functions including metabolic intermediates, DNA release, ROS production and others.	30,194	–
Inter-organelle communication	Exchange of information between mitochondria and other organelles, particular the ER, where mitofusin 2 (encoded by *MFN2*) plays a key role in tethering organelles.	195,196	197,198
Mitochondrial dynamics	Mitochondrial fusion and fission through OMM-anchored and IMM-anchored GTPase proteins capable of merging or constricting mitochondrial membranes to enact fragmentation of larger organelles into smaller ones.	191,199–201	202
Mito–mito communication	Exchange of information between mitochondria by soluble signals (for example, ROS-induced ROS release, RIRR), by complete membrane fusion, or by physical extensions of thin protein-carrying OMM and IMM membrane protrusions (that is, nanotunnels) and trans-mitochondrial cristae alignment between energized mitochondria.	203–206	207–209
Motility	Movement of energized mitochondria across the cytoplasm via the combined action of motor and adaptor proteins interacting with cytoskeletal elements.	6,210	211
Vesicle formation	Release of MDVs destined to different cellular fates by the action of motor and accessory proteins acting on the OMM and IMM.	212	213,214

[a]Generation of mitochondrial membrane potential is the 'mother' of many other functions and behaviours, providing the driving force for the movement of ions, solutes and proteins across the IMM, the driving force for key enzymes and processes, including the phosphorylation of ADP into ATP (OxPhos). Mitochondrial features (that is, molecular components) and activities (individual enzyme and non-enzymatic activities) are too numerous to be comprehensively listed, so only functions and behaviours are included. CoQ, coenzyme Q.

Hierarchy of mitochondrial needs



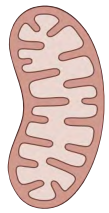
Monzel et al. *Nat Metab* 2023

Should we avoid the terms?

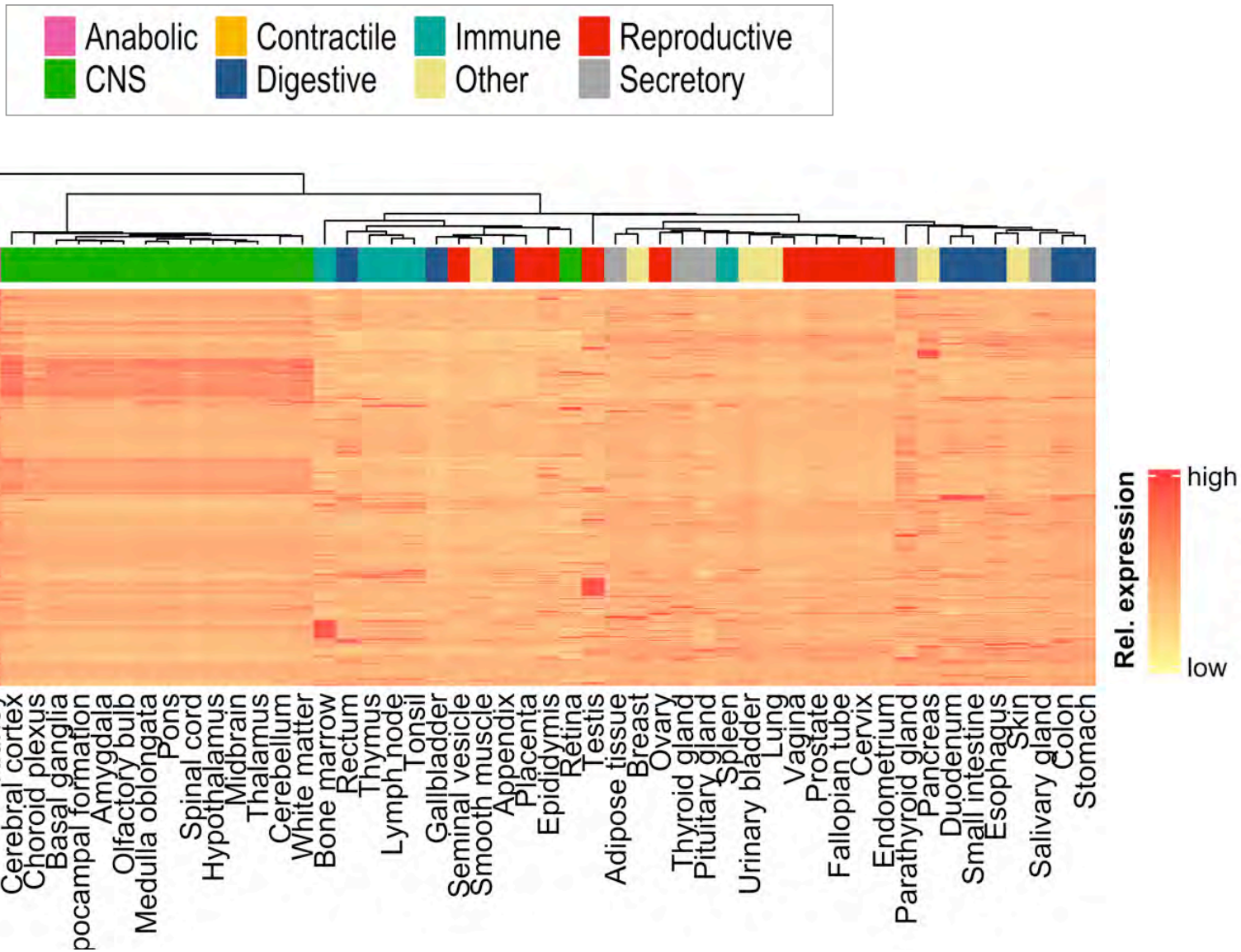
“mitochondrial function” **&** “mitochondrial dysfunction”

Mitotypes across human tissues

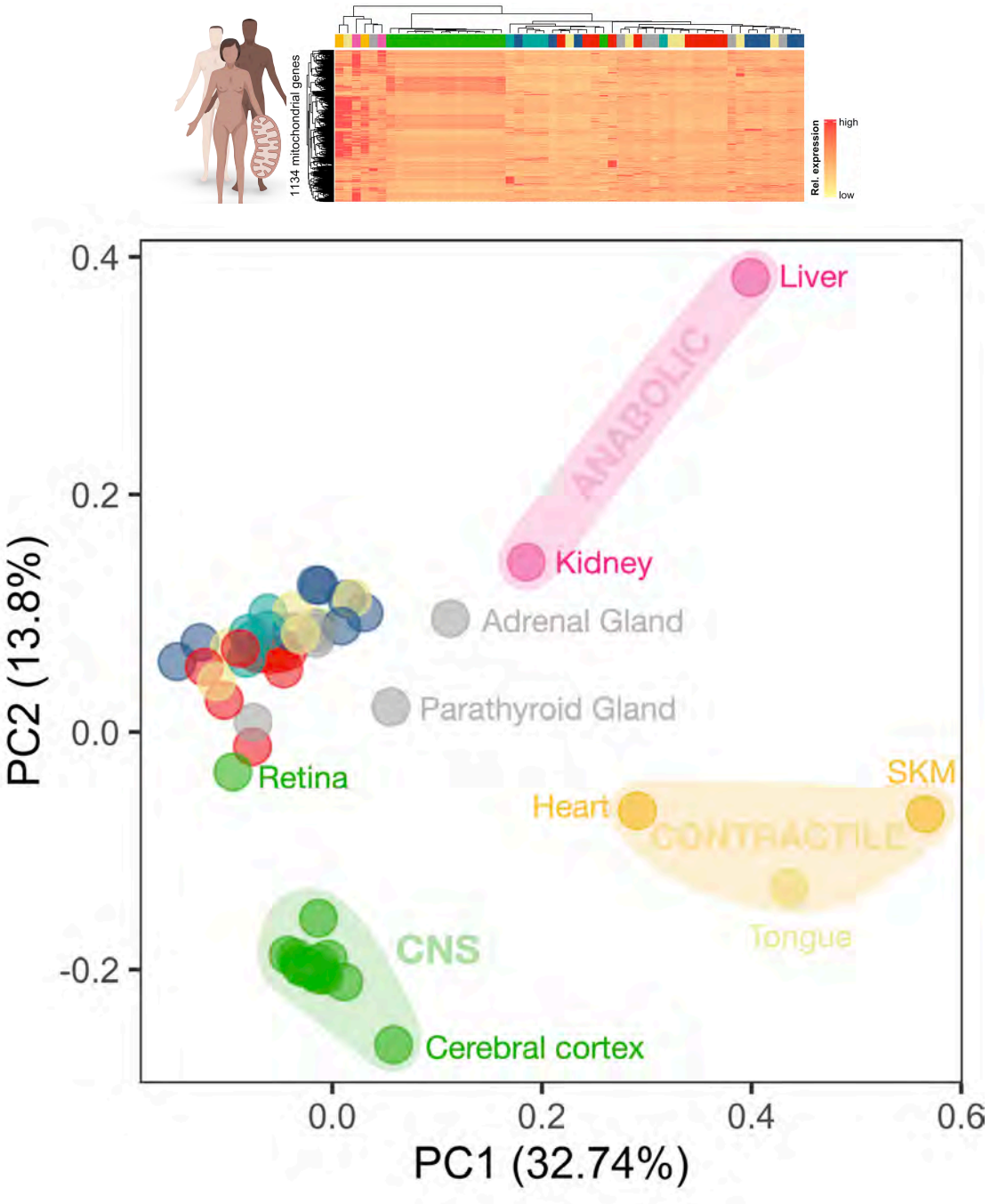
50 tissues



Anna Monzel

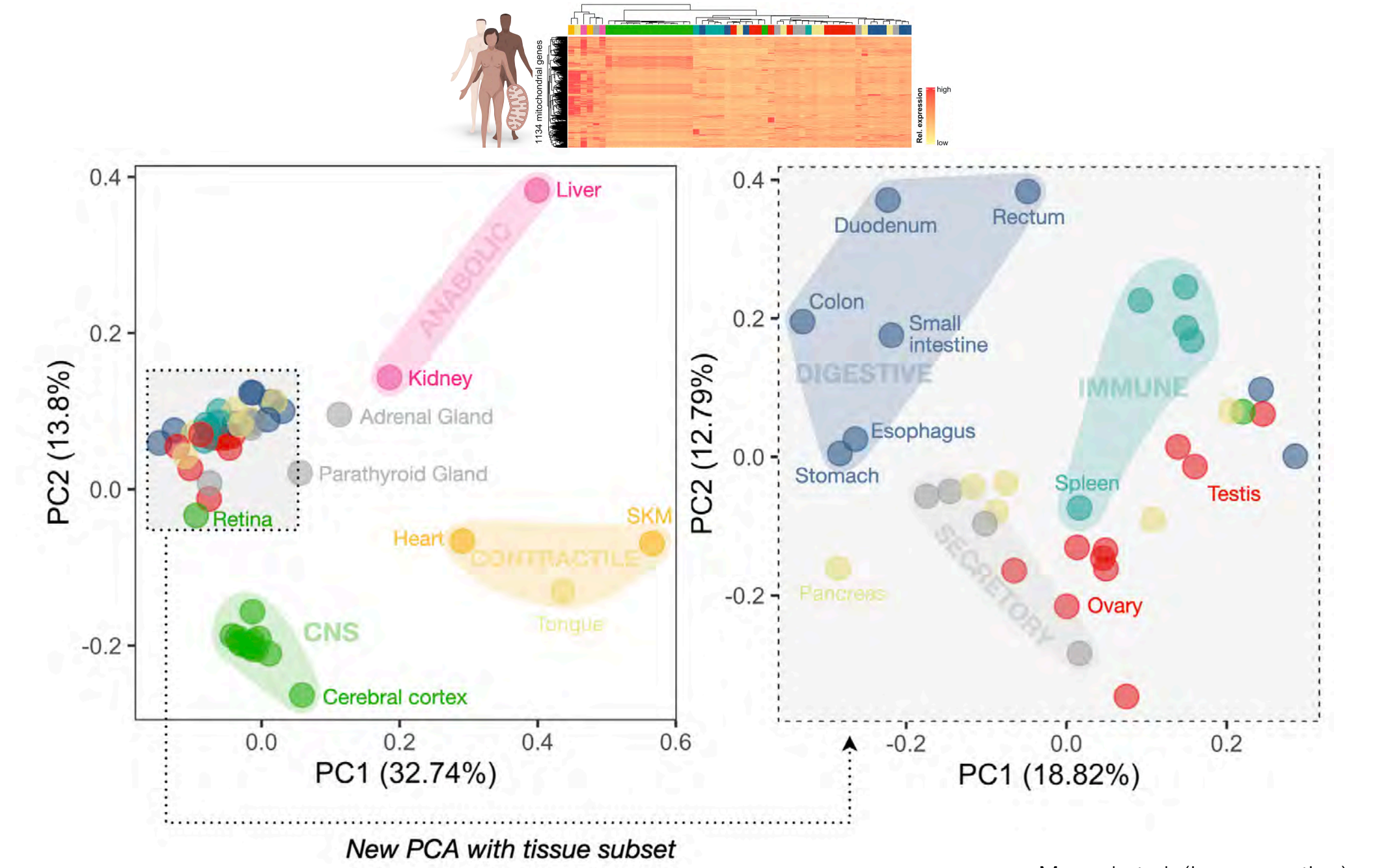


There are different mitochondria types — Mitotypes



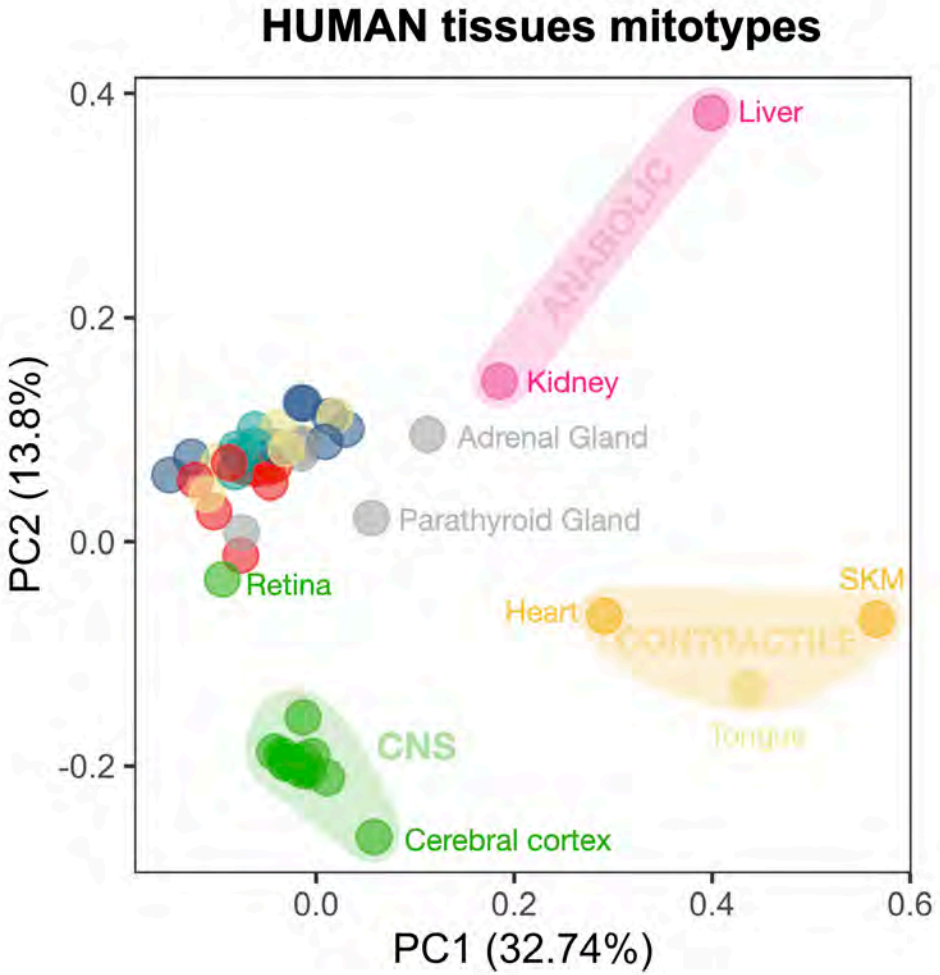
Mitochondrial genes alone

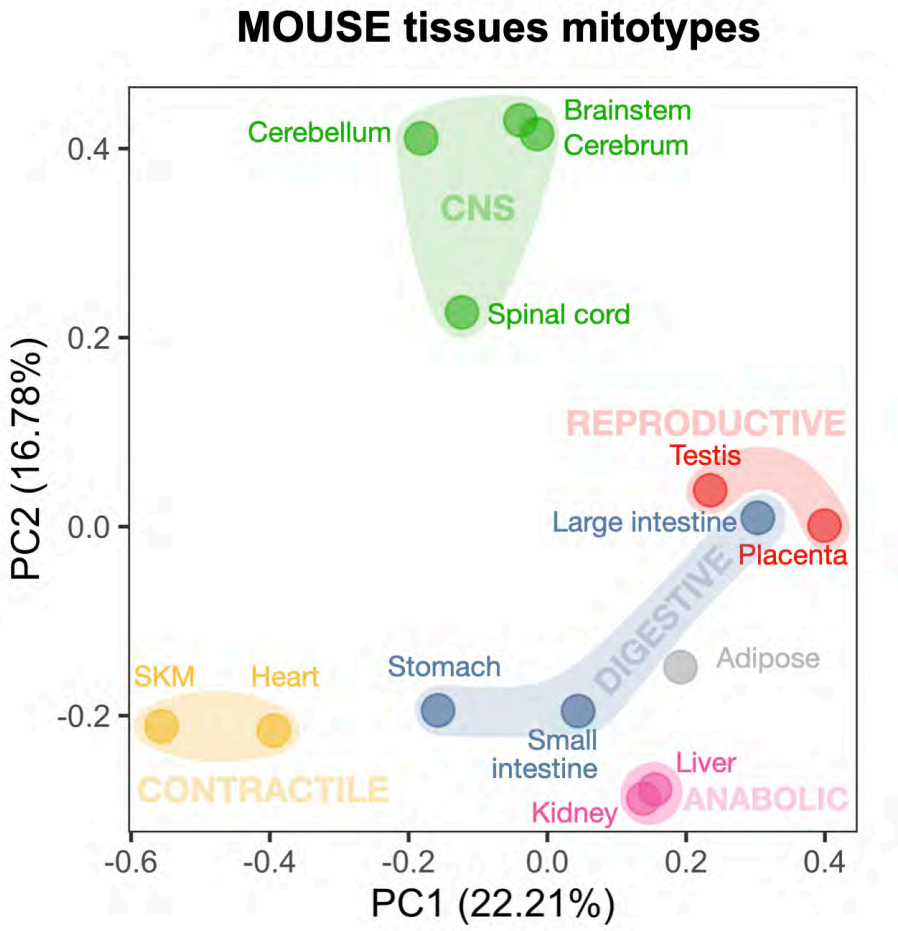
There are different mitochondria types — Mitotypes



Monzel et al. (in preparation)

Conserved mitotype signatures in human and mouse tissues



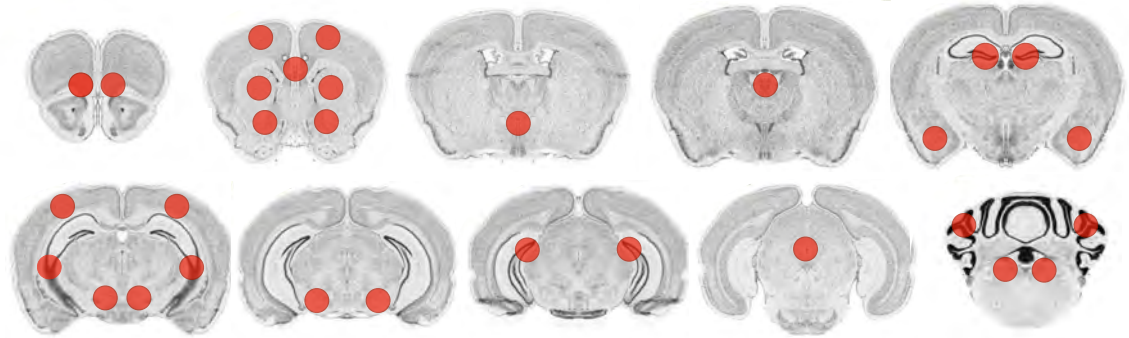


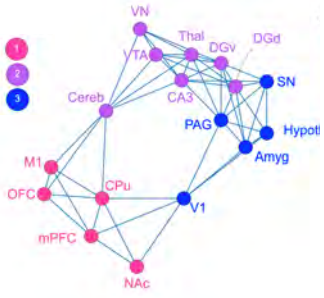
Monzel et al. (in preparation)

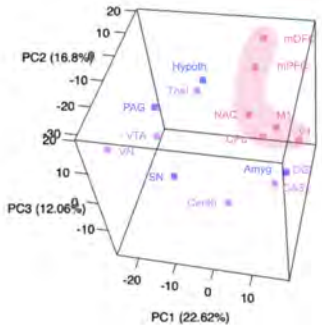
Anna Monzel

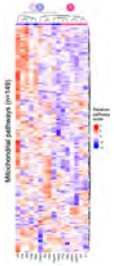
Article https://doi.org/10.1038/s41467-023-39941-0

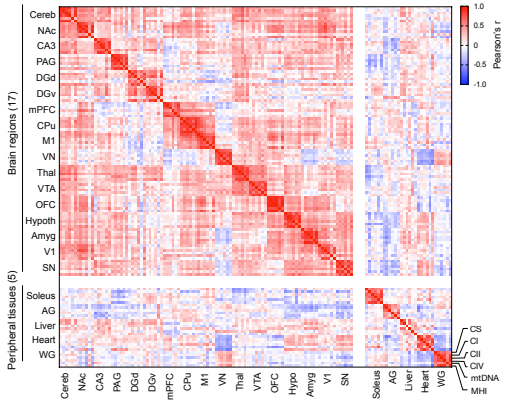
Brain mitochondrial diversity and network organization predict anxiety-like behavior in male mice

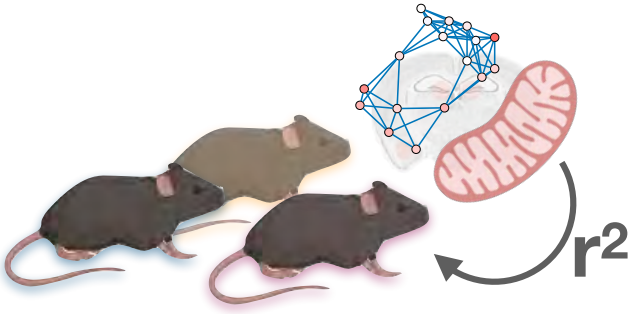






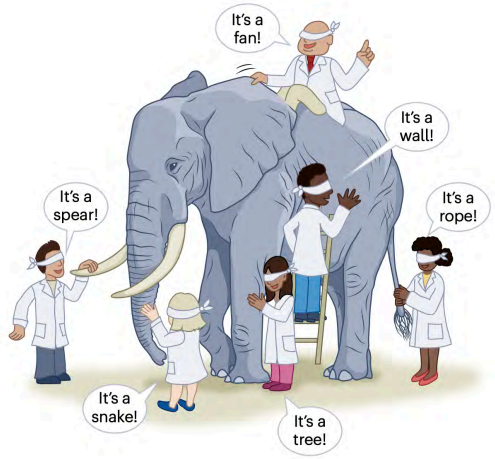


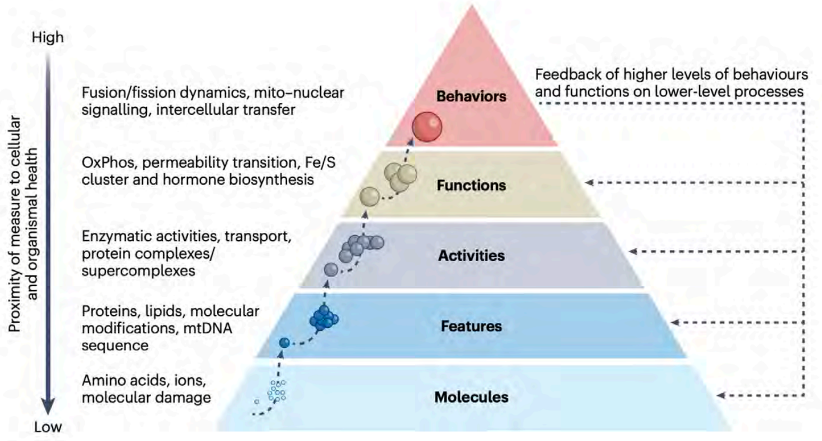


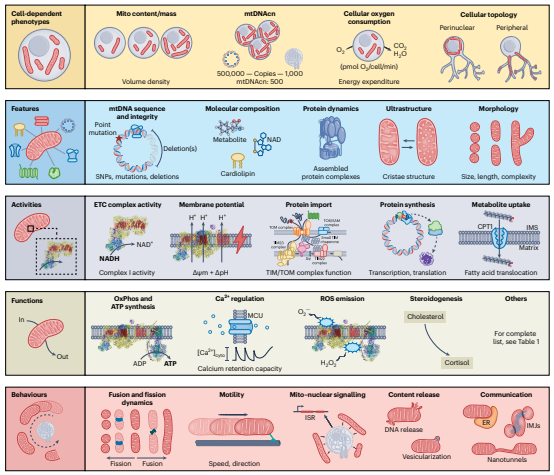


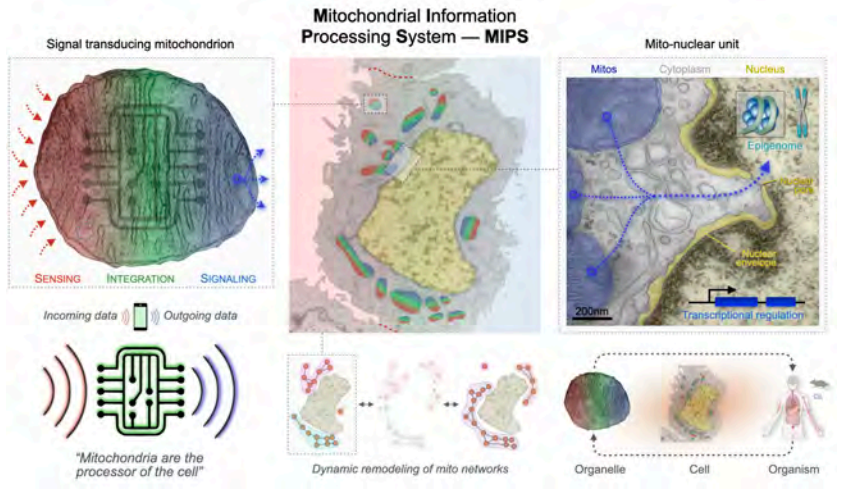
Rosenberg et al. *Nat Commun* 2023

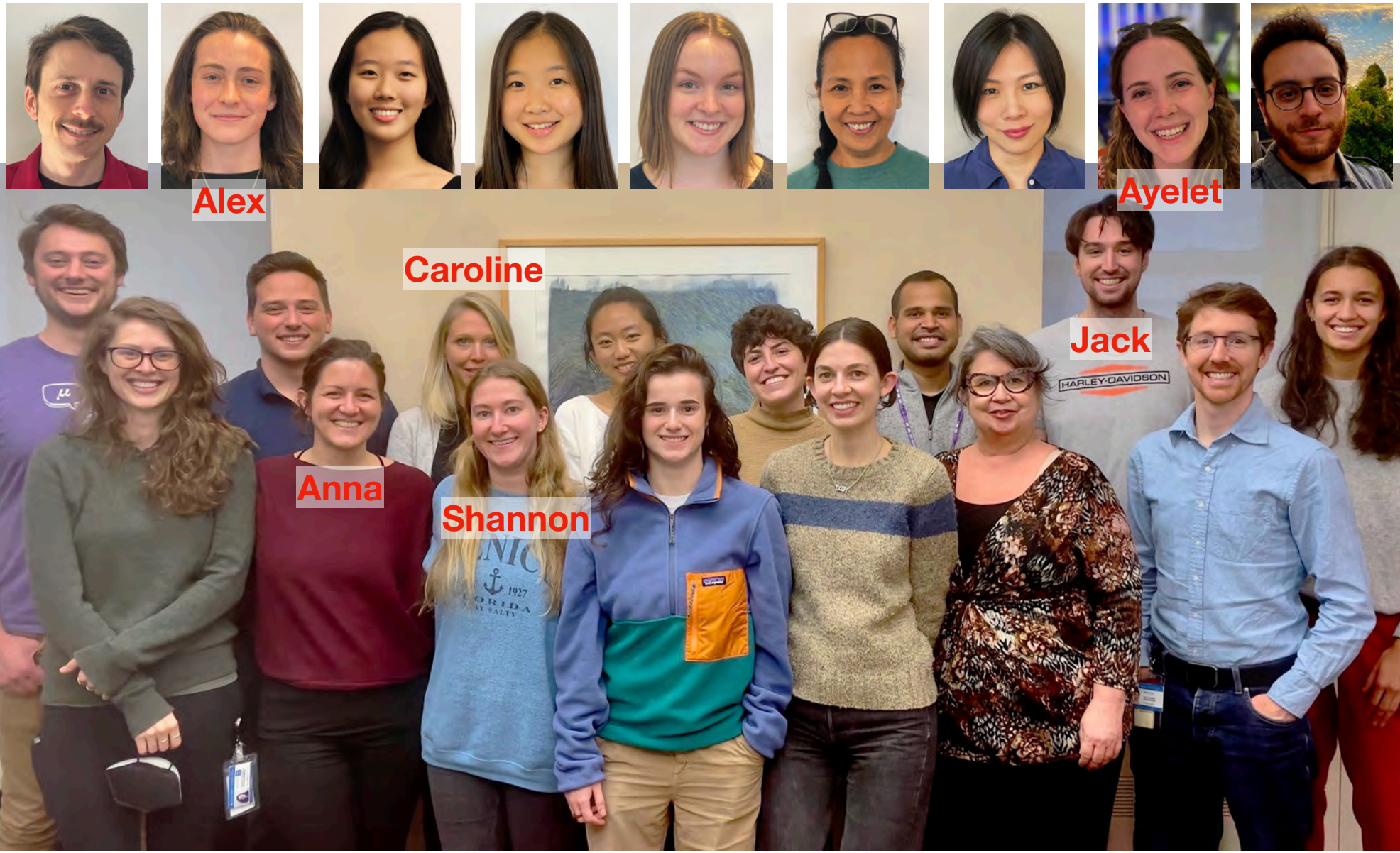
Mitochondria are diverse, multifunctional organelles that transduce information







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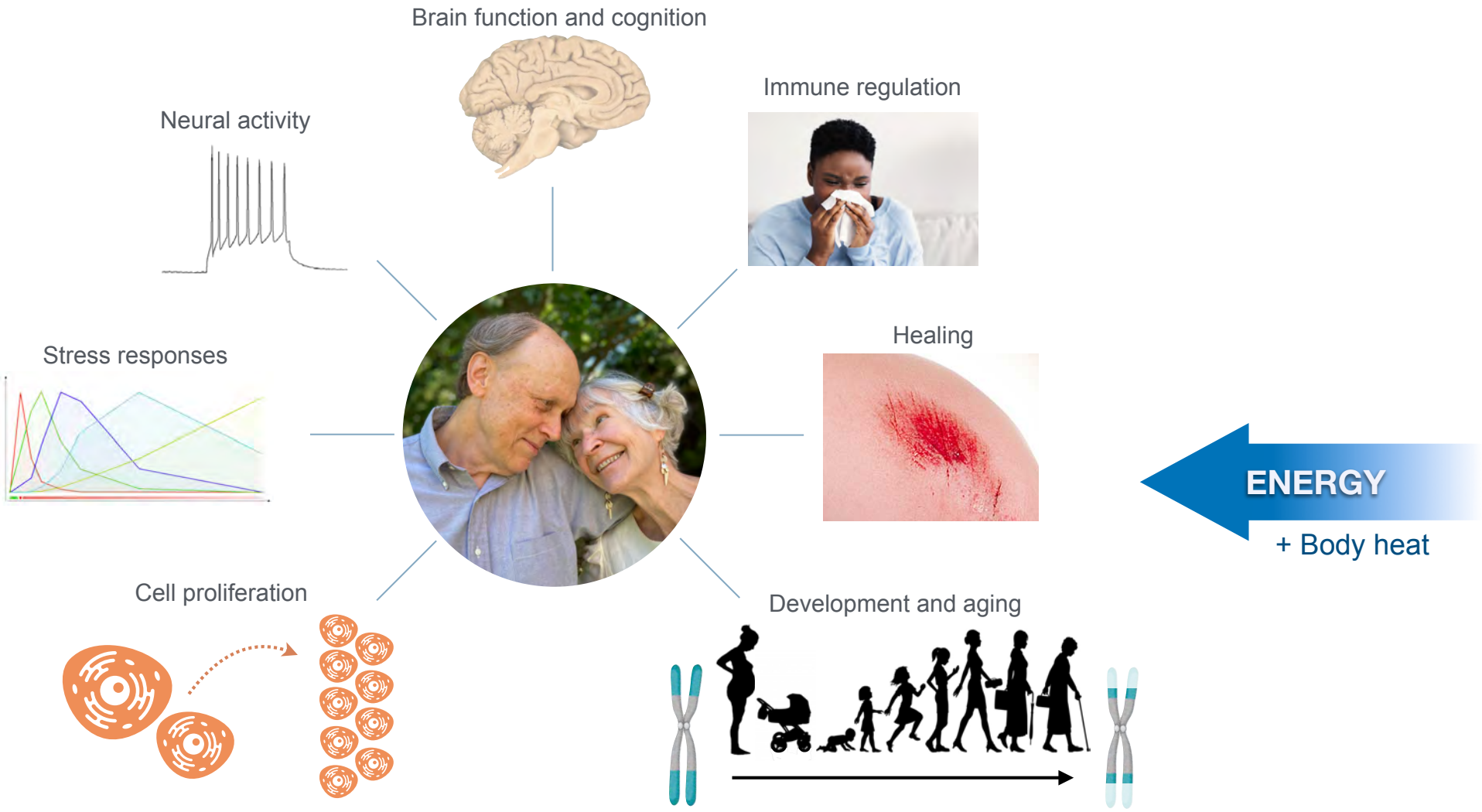
BASZUCKI BRAIN RESEARCH FUND

The Nathaniel Wharton Fund

NIH National Institute of Mental Health

NIH National Institute of General Medical Sciences

NIH National Institute on Aging


Brain function and cognition
Neural activity
Immune regulation
Stress responses
Healing
ENERGY
+ Body heat
Cell proliferation
Development and aging
PHYSIOLOGY, COGNITION, CONSCIOUSNESS
PSYCHOBIOLOGICAL PROCESSES & ALLOSTASIS

Nuclear fusion
Quantum electrodynamics

Photons and heat

Oils and fats, proteins, carbohydrates

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

ENERGY STORED AS CHEMISTRY

Food

O_2

EATING and BREATHING

CO_2 H_2O

'Waste' products

Brain function and cognition

Neural activity

Immune regulation

Stress responses

Healing

Cell proliferation

Development and aging

ENERGY
+ Body heat

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

Protons (H+)

Electrons

TCA Cycle

Beta Oxidation

Carbon substrates

Electron transport chain

O_2 H_2O

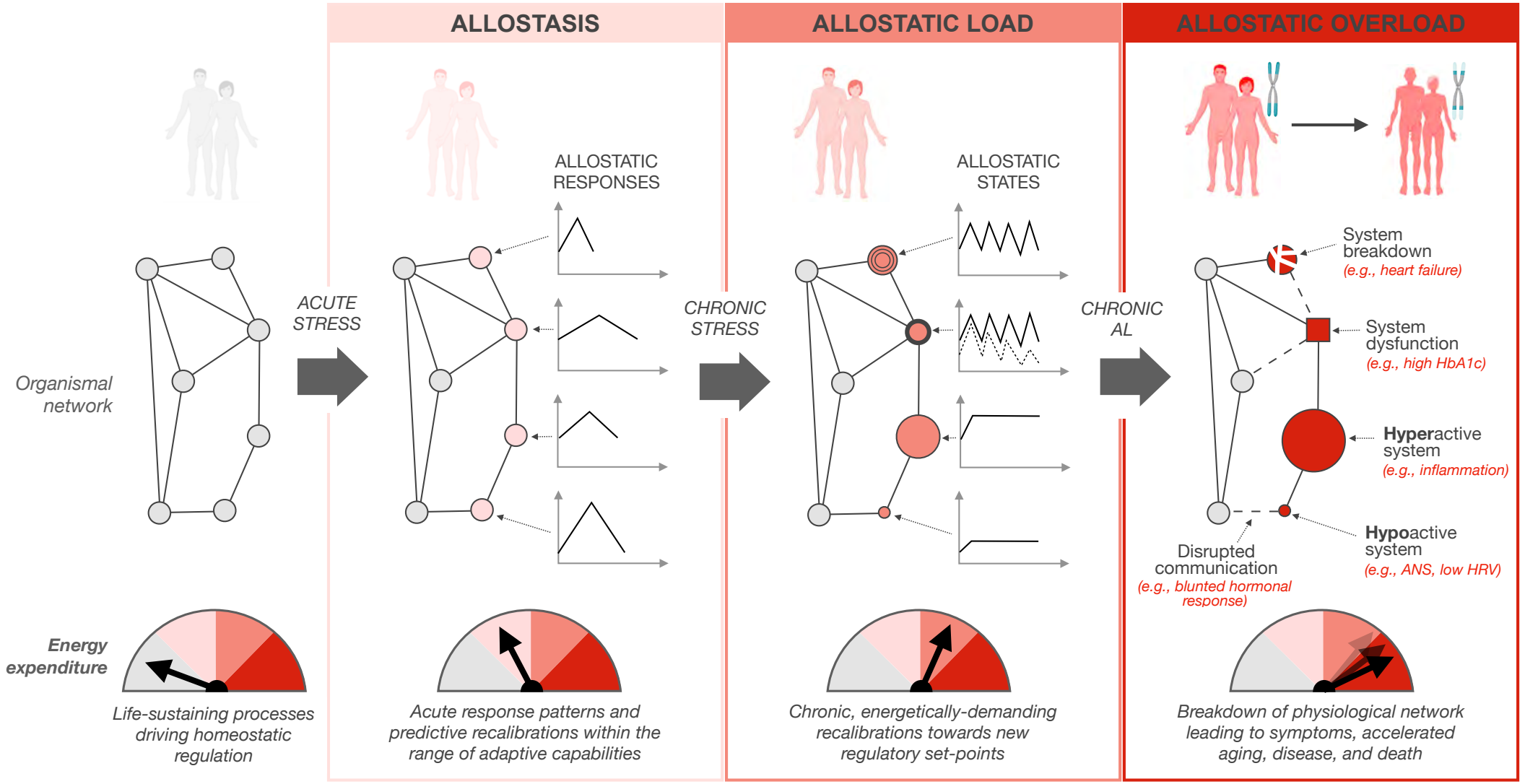
ATP

mtDNA

PHYSIOLOGY, COGNITION, CONSCIOUSNESS
PSYCHOBIOLOGICAL PROCESSES & ALLOSTASIS

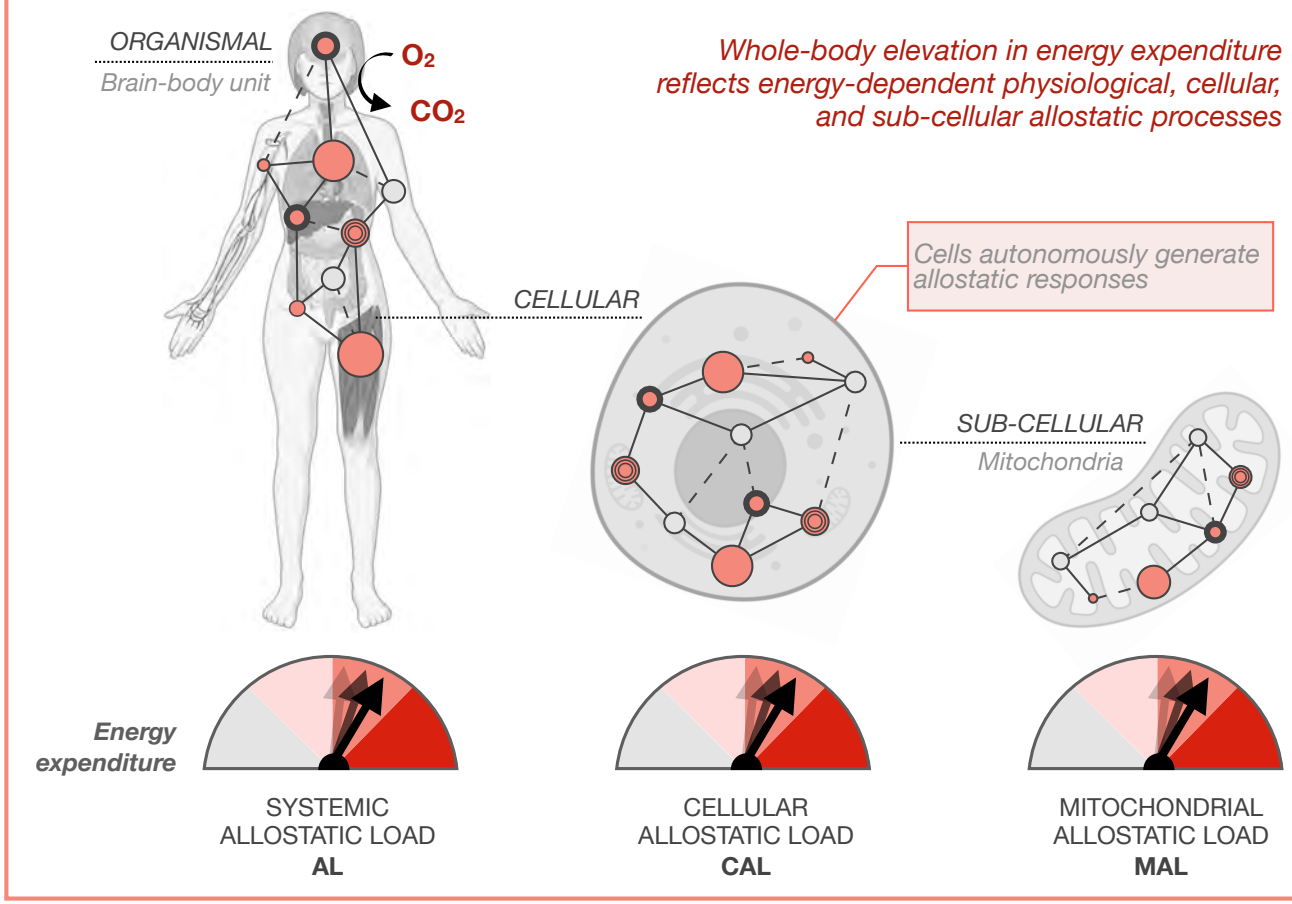
CHEMICAL ENERGY TRANSFORMED INTO
ELECTROCHEMICAL FORCE

Biochemistry 2022

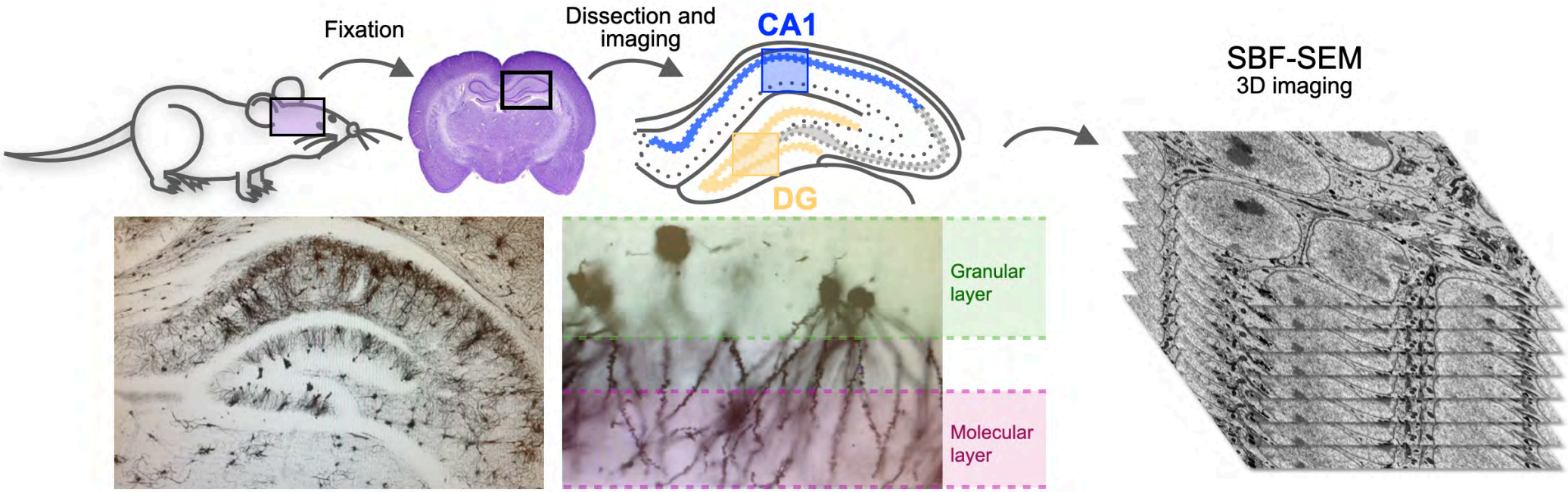


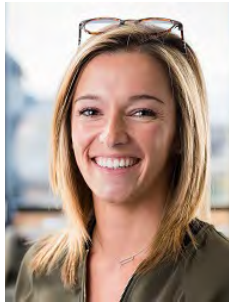
Bobba-Alves, Juster, Picard. *Psychoneuroendocrinol* 2022

ALLOSTATIC LOAD ACROSS LEVELS OF BIOLOGICAL COMPLEXITY



Whole-body elevation in energy expenditure reflects energy-dependent physiological, cellular, and sub-cellular allostatic processes





Julie Faitg

Amy Vincent

Faitg et al. *Cell Rep* 2021

Faith et al. *Cell Rep* 2021