REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Effects of Intermittent Fasting on Health, Aging, and Disease

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According to Weindruch and Sohal in a 1997 article in the *Journal*, reducing food availability over a lifetime (caloric restriction) has remarkable effects on aging and the life span in animals.[1] The authors proposed that the health benefits of caloric restriction result from a passive reduction in the production of damaging oxygen free radicals. At the time, it was not generally recognized that because rodents on caloric restriction typically consume their entire daily food allotment within a few hours after its provision, they have a daily fasting period of up to 20 hours, during which ketogenesis occurs. Since then, hundreds of studies in animals and scores of clinical studies of controlled intermittent fasting regimens have been conducted in which metabolic switching from liver-derived glucose to adipose cell–derived ketones occurs daily or several days each week. Although the magnitude of the effect of intermittent fasting on life-span extension is variable (influenced by sex, diet, and genetic factors), studies in mice and nonhuman primates show consistent effects of caloric restriction on the health span (see the studies listed in Section S3 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Studies in animals and humans have shown that many of the health benefits of intermittent fasting are not simply the result of reduced free-radical production or weight loss.[2-5] Instead, intermittent fasting elicits evolutionarily conserved, adaptive cellular responses that are integrated between and within organs in a manner that improves glucose regulation, increases stress resistance, and suppresses inflammation. During fasting, cells activate pathways that enhance intrinsic defenses against oxidative and metabolic stress and those that remove or repair damaged molecules (Fig. 1).[5] During the feeding period, cells engage in tissue-specific processes of growth and plasticity. However, most people consume three meals a day plus snacks, so intermittent fasting does not occur.[2,6]

Preclinical studies consistently show the robust disease-modifying efficacy of intermittent fasting in animal models on a wide range of chronic disorders, including obesity, diabetes, cardiovascular disease, cancers, and neurodegenerative brain diseases.[3,7-10] Periodic flipping of the metabolic switch not only provides the ketones that are necessary to fuel cells during the fasting period but also elicits highly orchestrated systemic and cellular responses that carry over into the fed state to bolster mental and physical performance, as well as disease resistance.[11,12]

Here, we review studies in animals and humans that have shown how intermittent fasting affects general health indicators and slows or reverses aging and disease processes. First, we describe the most commonly studied intermittent-fasting regimens and the metabolic and cellular responses to intermittent fasting. We then present and discuss findings from preclinical studies and more recent clinical studies that tested intermittent-fasting regimens in healthy persons and in

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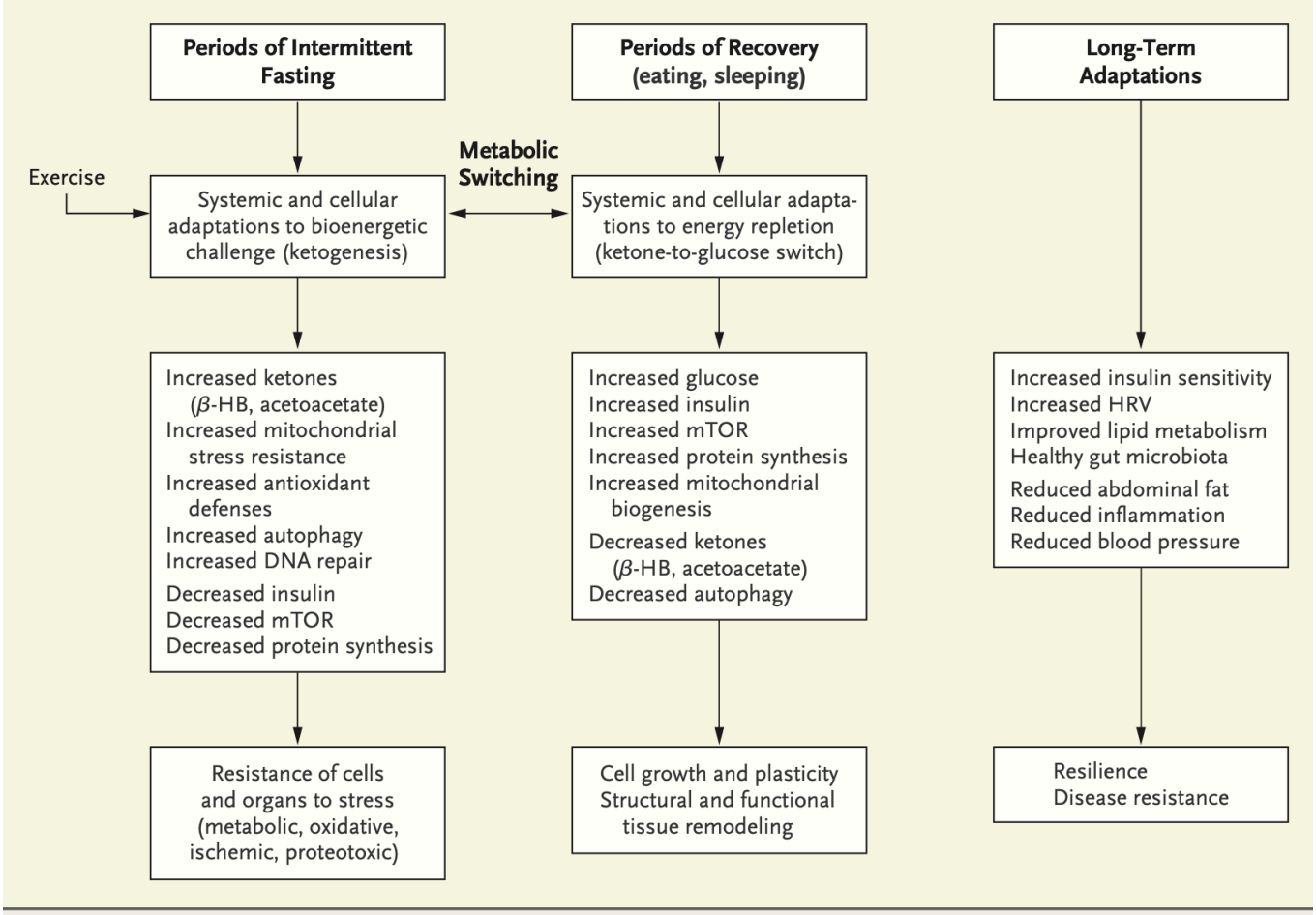


Figure 3. Cellular and Molecular Mechanisms Underlying Improved Organ Function and Resistance to Stress and Disease with Intermittent Metabolic Switching.

Periods of dietary energy restriction sufficient to cause depletion of liver glycogen stores trigger a metabolic switch toward use of fatty acids and ketones. Cells and organ systems adapt to this bioenergetic challenge by activating signaling pathways that bolster mitochondrial function, stress resistance, and antioxidant defenses while up-regulating autophagy to remove damaged molecules and recycle their components. During the period of energy restriction, cells adopt a stress-resistance mode through reduction in insulin signaling and overall protein synthesis. Exercise enhances these effects of fasting. On recovery from fasting (eating and sleeping), glucose levels increase, ketone levels plummet, and cells increase protein synthesis, undergoing growth and repair. Maintenance of an intermittent-fasting regimen, particularly when combined with regular exercise, results in many long-term adaptations that improve mental and physical performance and increase disease resistance. HRV denotes heart-rate variability.

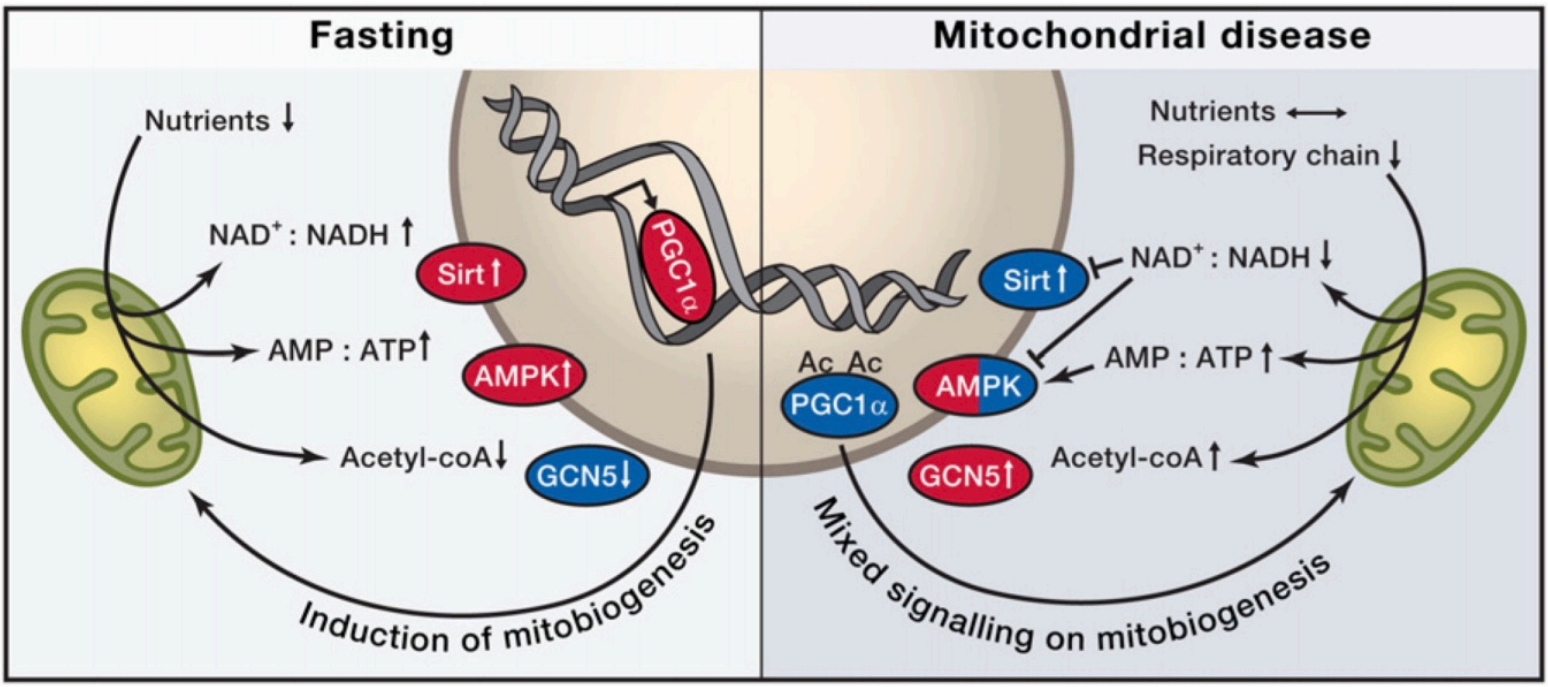


Figure 1. Nutrient Sensors in Fasting and Their Roles in Mitochondrial Disease
Both fasting and mitochondrial disease can modify NAD^+:NADH and AMP:ATP ratios through decreased nutrient availability or through reduced respiratory chain activity and have the potential to activate (red) nutrient sensors Sirtuin 1 (Sirt, an NAD^+-dependent histone deacetylase) or AMP-activated kinase (AMPK) and increase mitochondrial biogenesis by activating peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1alpha). Upon decreased utilization of acetyl-coenzyme A (acetyl-coA), GCN5 (lysine acetyltransferase 2A) is activated and acetylates PGC1alpha, to inactivate it (blue). NAD^+, nicotinamide adenine dinucleotide, oxidized form; NADH, nicotinamide adenine dinucleotide, reduced form; AMP, adenosine monophosphate; ATP, adenosine triphosphate; Ac, acetyl group.

3 CARBURANTI: immediato, intermedio, tardivo

GLUCOSIO ACIDI GRASSI CHETONI

1 MOTORE CHE: si riproduce, si ripara, si distrugge

MITOCONDRIO

3 POSSIBILI REGOLAZIONI CELLULARI: apoptosi, proliferazione, differenziamento

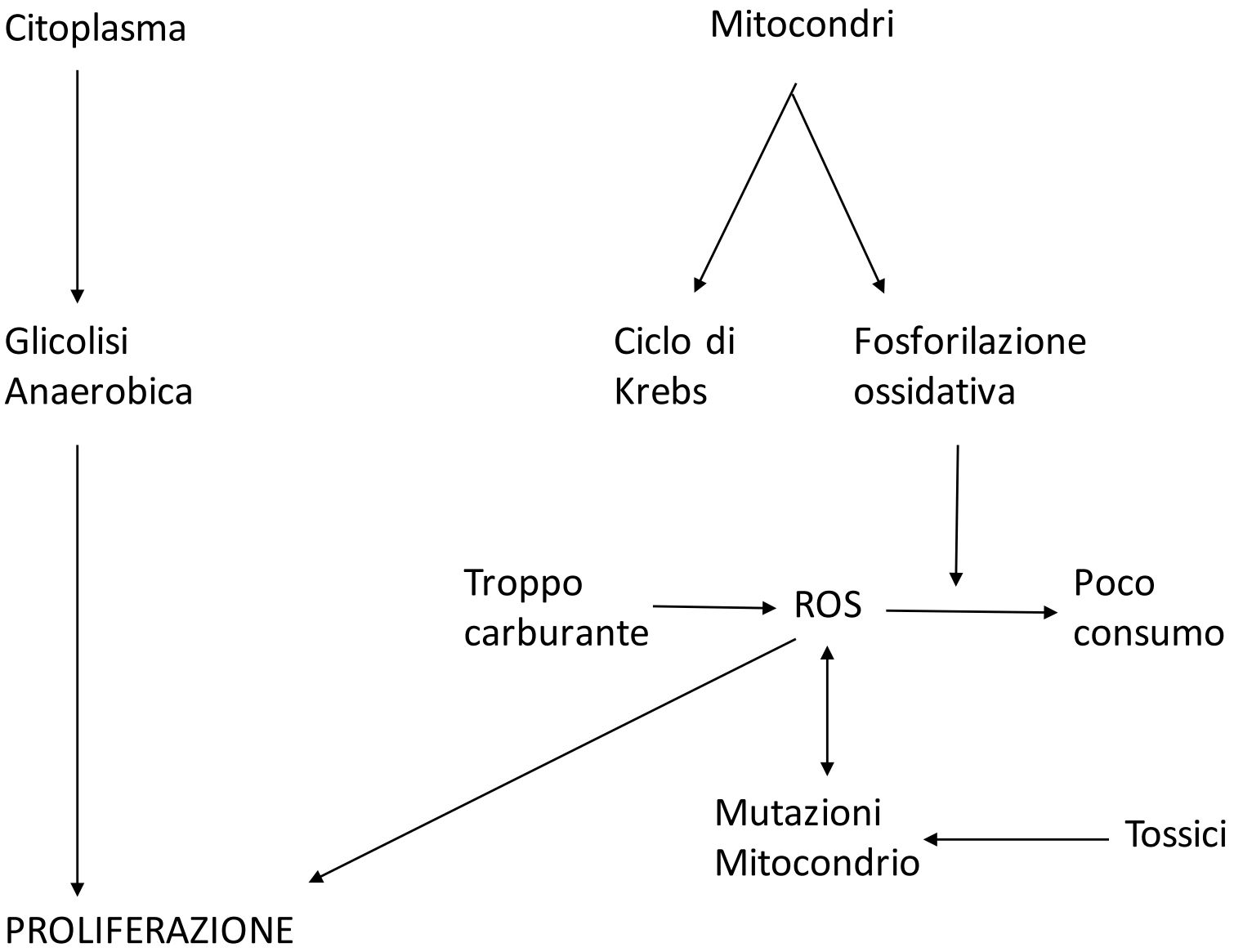
EPIGENOMA

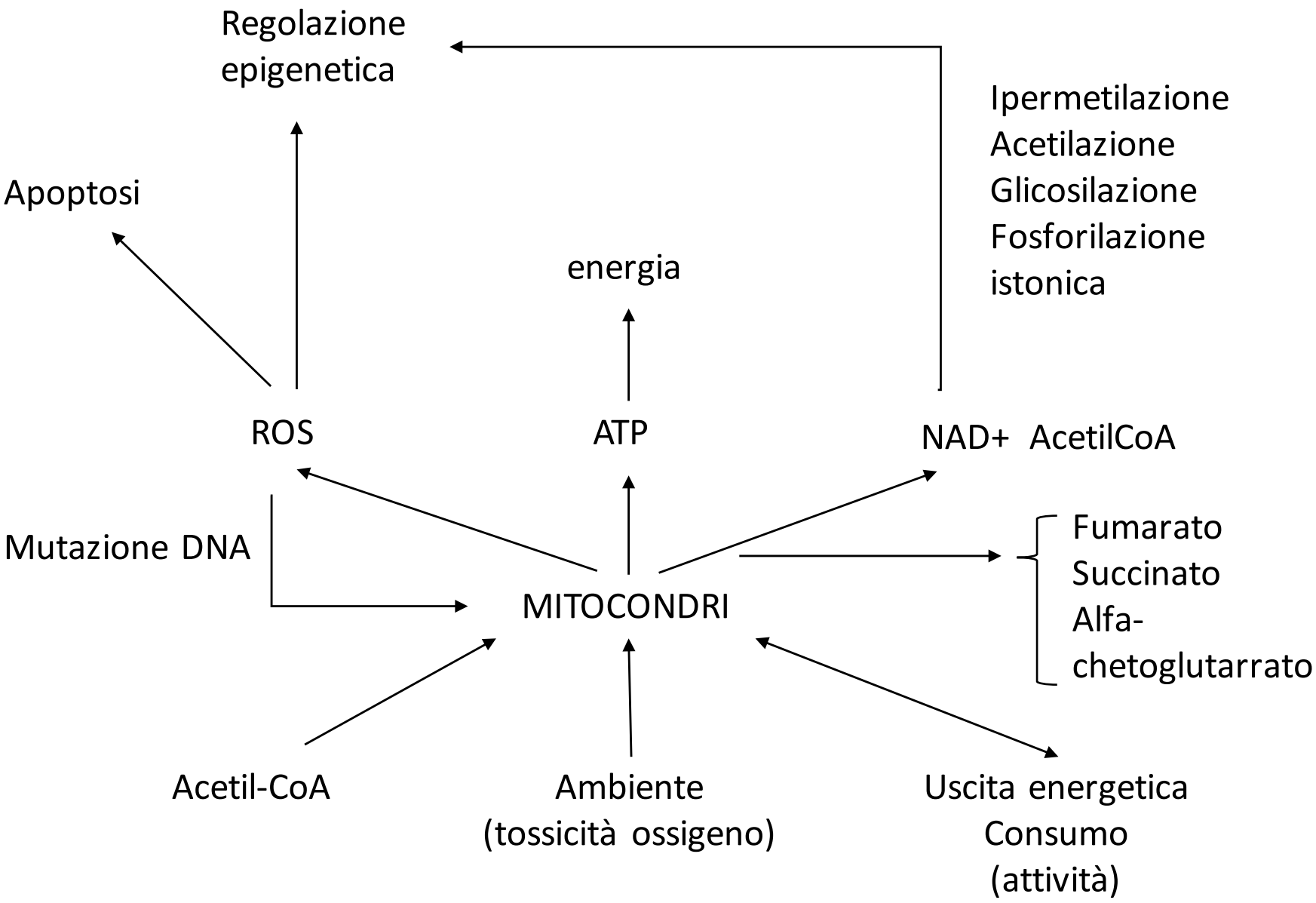
MOLTEPLICI INTERFERENZE:

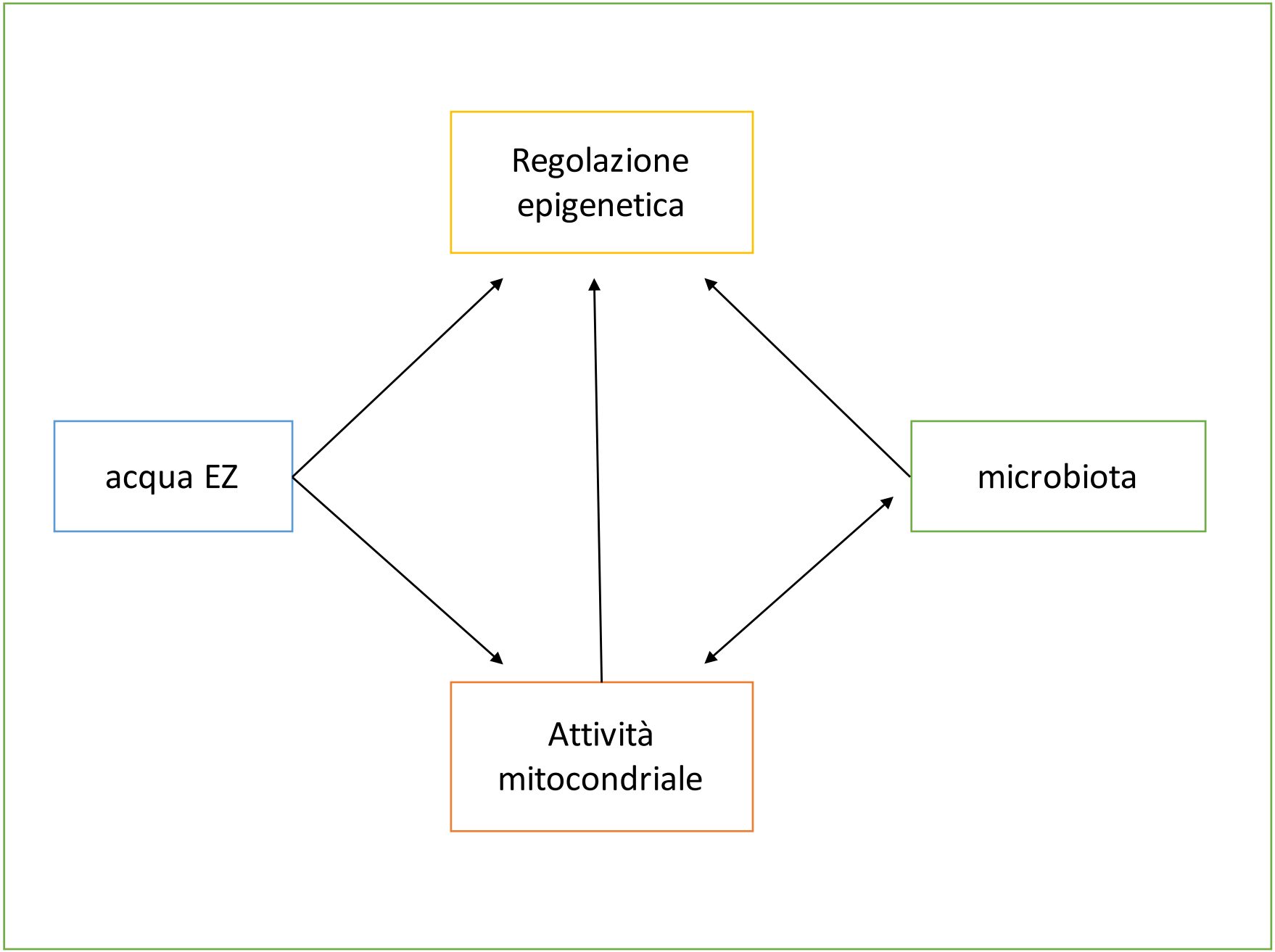
dieta, attività fisica, tossici, microbiota, ormoni

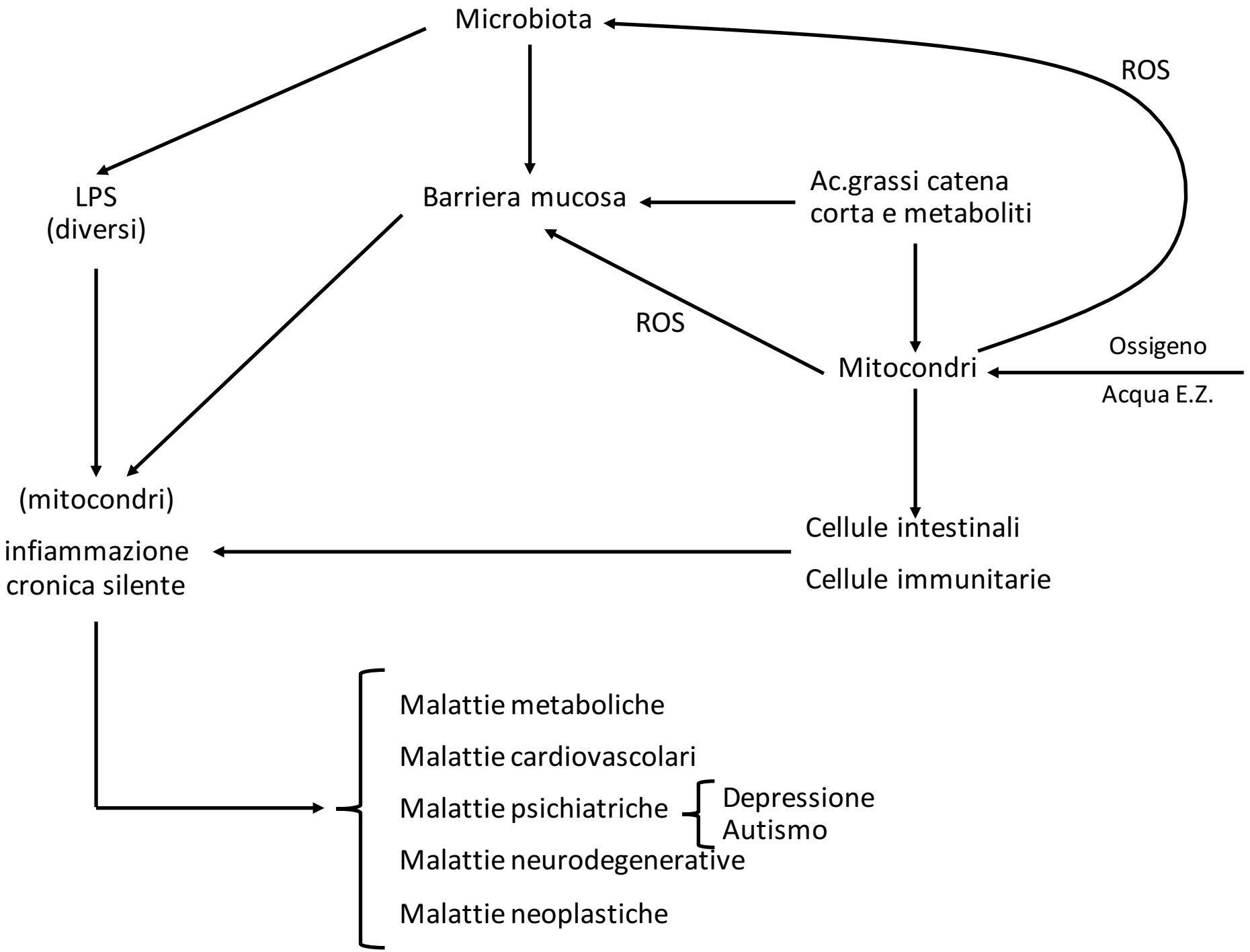
1 PROBLEMA CENTRALE:

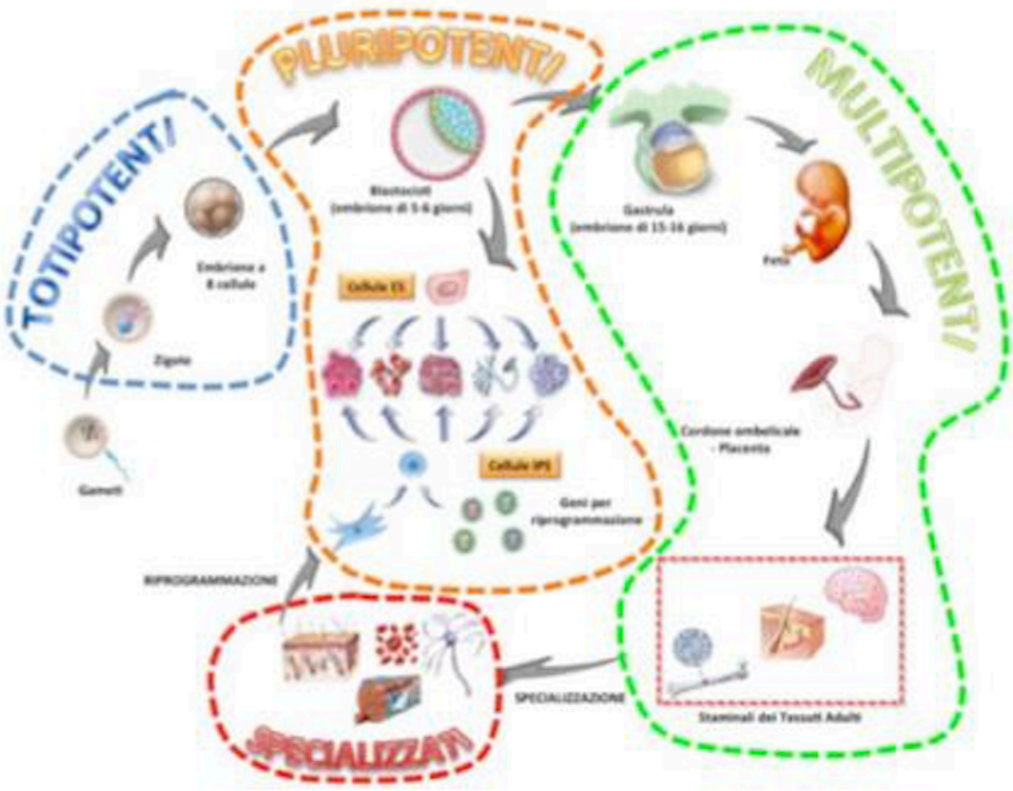
FLOGOSI SILENTE

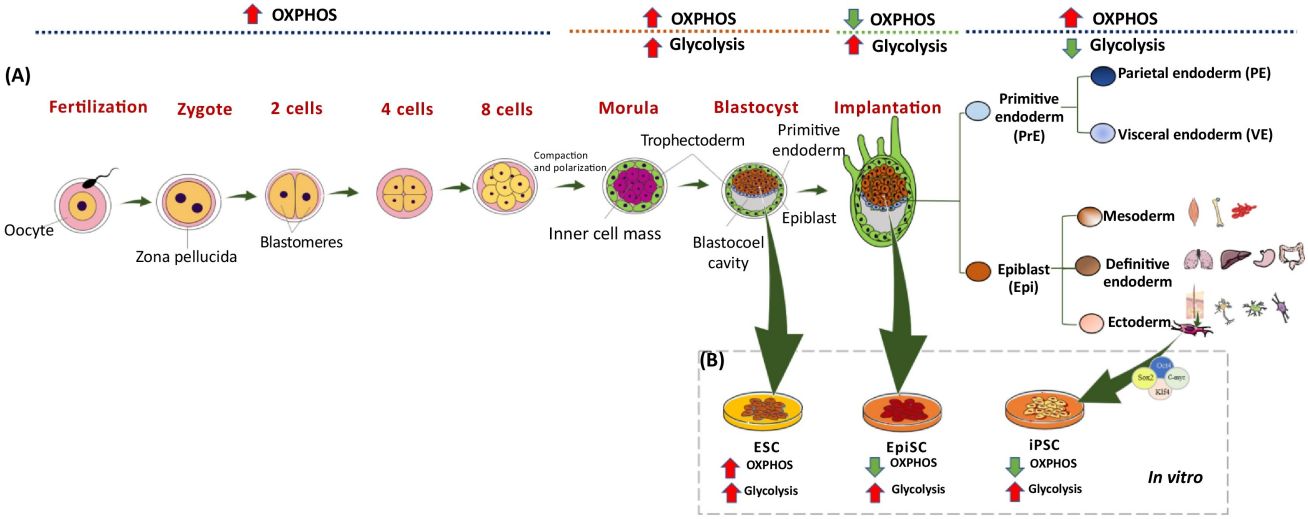

Citoplasma
Mitocondri
Glicolisi
Anaerobica
Ciclo di
Krebs
Fosforilazione
ossidativa
Troppo
carburante
ROS
Poco
consumo
Mutazioni
Mitocondrio
Tossici
PROLIFERAZIONE


Regolazione epigenetica
Ipermetilazione
Acetilazione
Glicosilazione
Fosforilazione istonica
Apoptosi
energia
ROS
ATP
NAD+ AcetilCoA
Mutazione DNA
Fumarato
Succinato
Alfa-chetoglutarrato
MITOCONDRI
Acetil-CoA
Ambiente (tossicità ossigeno)
Uscita energetica
Consumo (attività)

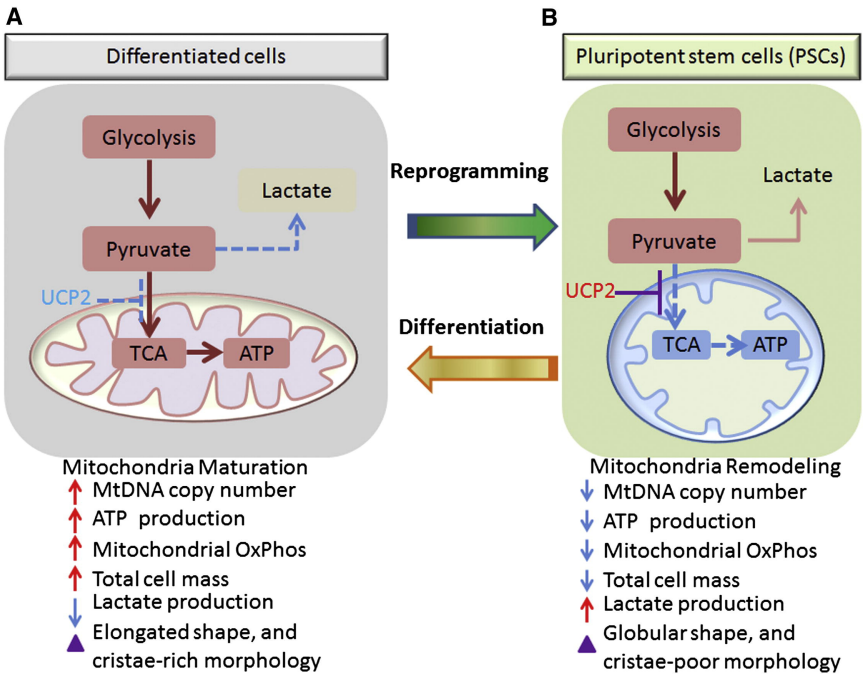

Regolazione epigenetica
acqua EZ
microbiota
Attività mitocondriale

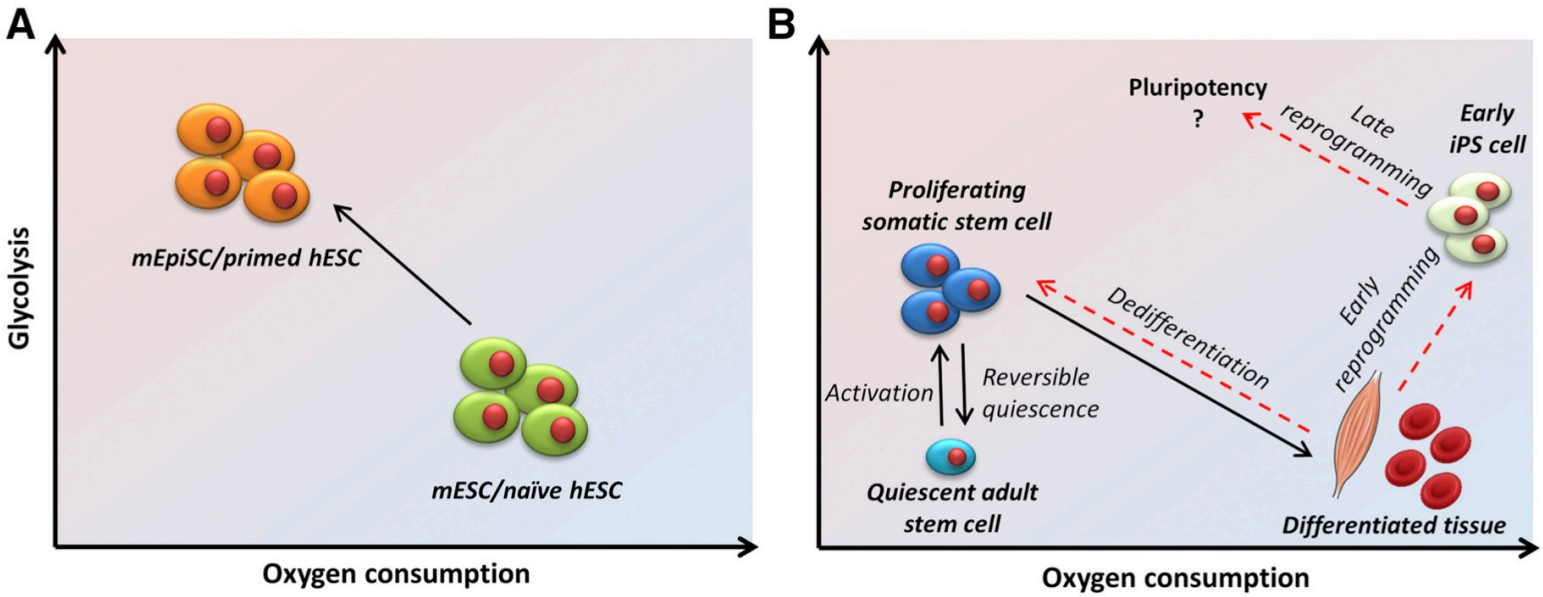

Microbiota
ROS
LPS
(diversi)
Barriera mucosa
Ac.grassi catena
corta e metaboliti
ROS
Ossigeno
Mitocondri
Acqua E.Z.
(mitocondri)
Cellule intestinali
infiammazione
cronica silente
Cellule immunitarie
Malattie metaboliche
Malattie cardiovascolari
Malattie psichiatriche
Depressione
Autismo
Malattie neurodegenerative
Malattie neoplastiche

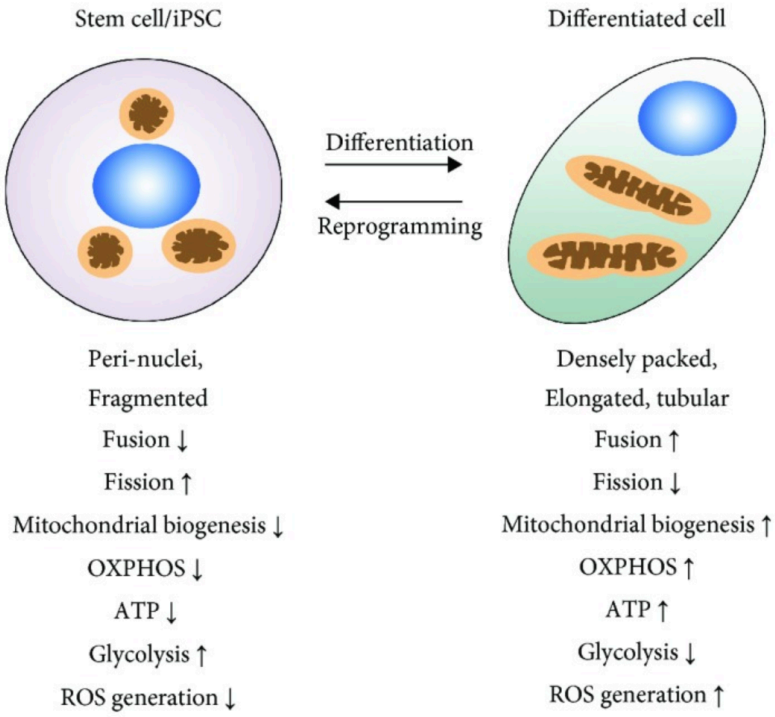

TOTIPOTENTI
PLURIPOTENTI
MULTIPOTENTI
SPECIALIZZATI
Embrione a 8 cellule
Zigote
Gameti
Blastocisti (embrione di 5-6 giorni)
Cellule ES
Cellule iPS
Geni per riprogrammazione
RIPROGRAMMAZIONE
Gastrula (embrione di 15-16 giorni)
Feto
Cordone ombelicale - Placenta
SPECIALIZZAZIONE
Staminali dei Tessuti Adulti



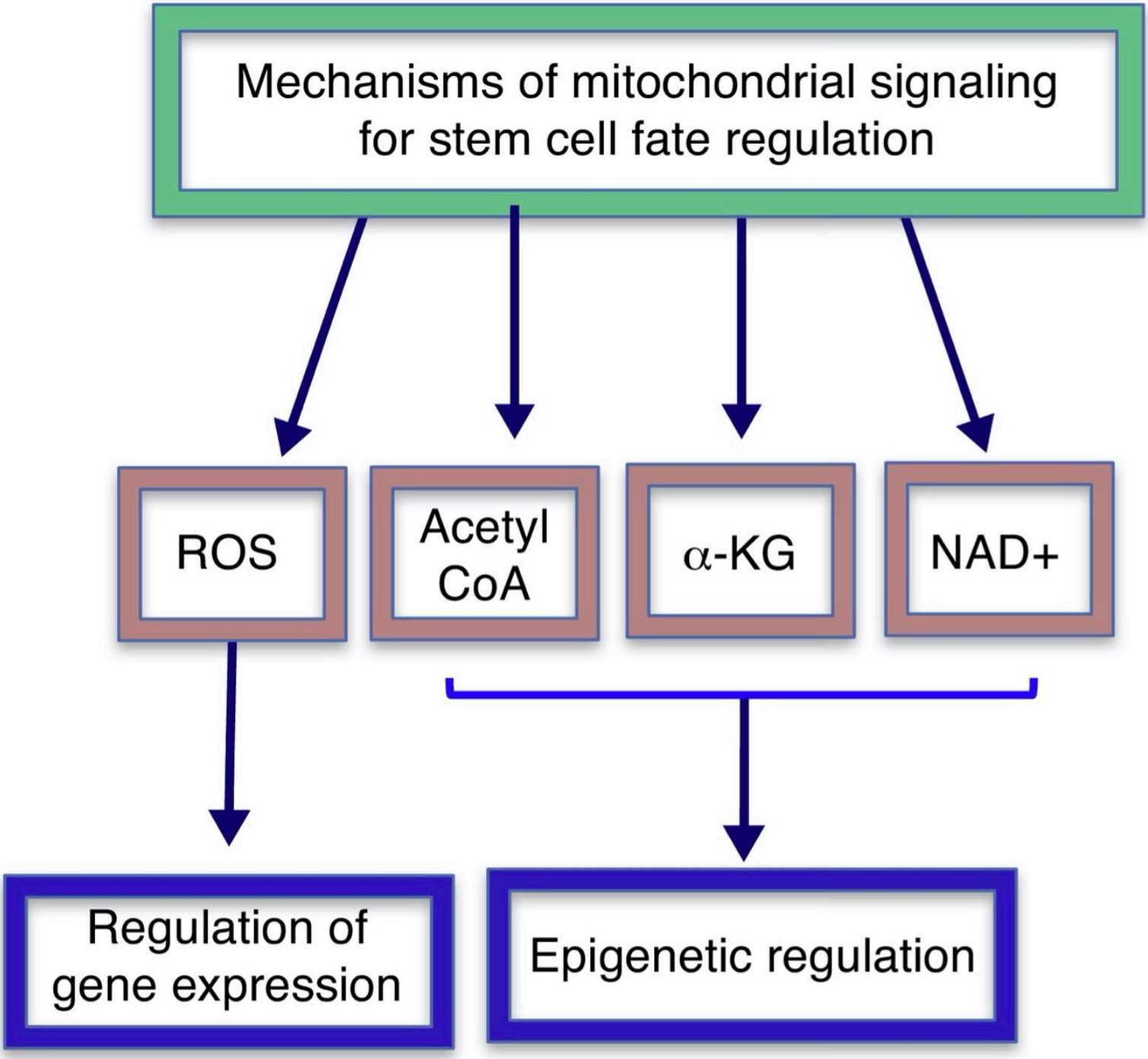
Trends in Cell Biology


A
Differentiated cells
Glycolysis
Lactate
Pyruvate
UCP2
TCA
ATP
Mitochondria Maturation
MtDNA copy number
ATP production
Mitochondrial OxPhos
Total cell mass
Lactate production
Elongated shape, and
cristae-rich morphology
Reprogramming
Differentiation
B
Pluripotent stem cells (PSCs)
Glycolysis
Lactate
Pyruvate
UCP2
TCA
ATP
Mitochondria Remodeling
MtDNA copy number
ATP production
Mitochondrial OxPhos
Total cell mass
Lactate production
Globular shape, and
cristae-poor morphology


A
Glycolysis
mEpiSC/primed hESC
mESC/naïve hESC
Oxygen consumption
B
Pluripotency
?
Late
reprogramming
Early
iPS cell
Proliferating
somatic stem cell
Dedifferentiation
Early
reprogramming
Activation
Reversible
quiescence
Quiescent adult
stem cell
Differentiated tissue
Oxygen consumption



A simplified common scheme of mitochondrial dynamics in stem cells and differentiated cells. In most types of stem cells and reprogrammed iPSCs, mitochondria are usually localized in the nuclear periphery and characterized by sphere, fragmented, and punctate morphologies with fewer cristae (immature morphology). Correspondingly, mito-fission is high whereas mitochondrial biogenesis is low, which maintains low mitochondrial mass. Stem cells generally rely on glycolysis as the major energy source and have low levels of ATP, OXPHOS, and ROS levels. In differentiated cells, mitochondria change to more enlarged and elongated tubular morphology. Correspondingly, mito-fusion and biogenesis increase with the accumulation of mitochondria. Comparably, differentiated cells have higher ATP, ROS, and OXPHOS levels.


Mechanisms of mitochondrial signaling for stem cell fate regulation
ROS
Acetyl CoA
α-KG
NAD+
Regulation of gene expression
Epigenetic regulation