Please cite this article in press as: Picard and Murugan, The energy resistance principle, Cell Metabolism (2025), https://doi.org/10.1016/j.cmet.2025.09.002

Cell Metabolism

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Perspective

The energy resistance principle

Martin Picard[1,2,3,4,*] and Nirosha J. Murugan[5,6]
[1]Department of Psychiatry, Division of Behavioral Medicine, Columbia University Irving Medical Center, New York, NY 10032, USA
[2]Department of Neurology, H. Houston Merritt Center for Neurological and Mitochondrial Disorders, Columbia University Irving Medical Center, New York, NY 10032, USA
[3]New York State Psychiatric Institute, New York, NY 10032, USA
[4]Robert N. Butler Columbia Aging Center, Mailman School of Public Health, New York, NY 10032, USA
[5]Department of Health Sciences, Wilfrid Laurier University, Waterloo, ON N2L3C5, Canada
[6]Allen Discovery Center, Tufts University, Medford, MA 02155, USA
*Correspondence: martin.picard@columbia.edu
https://doi.org/10.1016/j.cmet.2025.09.002

SUMMARY

Living organisms are physical-energetic systems that must obey simple principles guiding energy transformation across physical and temporal scales. The energy resistance principle (ERP) describes behavior and transformation of energy in the carbon-based circuitry of biology. We show how energy resistance (éR) is the fundamental property that enables transformation, converting into useful work the unformed energy potential of food-derived electrons fluxing toward oxygen. Although éR is required to sustain life, excess éR directly causes reductive and oxidative stress, heat, inflammation, molecular damage, and information loss—all hallmarks of disease and aging. We discuss how disease-causing stressors elevate éR and circulating growth differentiation factor 15 (GDF15) levels, whereas sleep, physical activity, and restorative interventions that promote healing minimize éR. The ERP is a testable general framework for discovering the modifiable bioenergetic forces that shape development, aging, and the dynamic health-disease continuum.

THE ENERGY RESISTANCE PRINCIPLE

Science systematically gathers knowledge about the natural world, condensing it into laws and principles.[1] Physics has identified simple, generalizable principles captured in Newton's gravity,[2] Maxwell's electromagnetism,[3] and Einstein's mass-energy equivalence $E = mc^2$, which revealed, for example, how mass is energy constrained by the constant speed of light squared ($m = E/c^2$).[4] Much of modern science and technology has developed from this and Feynman's subsequent quantum electrodynamics (QED) principle,[5] illustrating the value of principled knowledge synthesis for how energy behaves across the natural world.

Biology has similarly discovered valuable organizing principles. They include the encoding of biological information into the 4-letter genetic code[6]; the allometric scaling of body size, fractal biological structures, and metabolic rates[7,8]; electrical coordination of cellular and organismal functions[9]; how mitochondria convert chemistry into an electrochemical force to power ATP synthesis[10]; and how limits to mitochondrial energy transformation or flow capacity cause devastating human diseases.[11] However, in contrast to physics, biology has lacked a simple, principled formulation that quantitatively defines the relation between energy flow and more specific biological pathways and processes linked to health, aging, and healing—key distinguishing features of living organisms.

The energy resistance principle (ERP) is a testable framework that describes the behavior and transformation of energy in living systems. The ERP builds on Prigogine's concept of dissipative structures and efficiency as "order emerges through fluctuations"[12,13] and the notion that energy is the driving force of life and biological complexity.[14–16] The ERP draws formalism from physical laws accounting for the behavior of energy in simpler electrical and hydraulic systems, extended to biology. In essence, the ERP relates the organism's energy potential (i.e., voltage or pressure) and its capacity to support energy flow (i.e., current or flux), showing how together they quantitatively determine and regulate the system's energy resistance (*éR*) and therefore its transformation capacity.

In this manuscript, we refer to the ERP as a heuristic—an emergent generalization from the existing body of work—rather than as a fundamental or universally accepted law. In this sense, the ERP functions as a guiding framework derived from empirical observations and quantitative relationships, operationalized as a simple formula that helps generate models and testable hypotheses. Our hope is that it guides theorists and experimentalists to think energetically about the beautiful complexity of living systems.

The ERP is based on three simple assumptions (Figure 1):

(1) Life cannot exist without energy resistance. As in electrical systems where resistance is required for power dissipation (power law: $P = R \cdot I^2$; if R is zero, P also is zero), resistance is required to transform different forms of energy into work and information (Figure 2). In wet biological systems, this transformation powers the molecular operations of life. Resistance regulates energy flux to ensure that energy is transformed into useful biological work rather than being entirely dissipated as heat, as in a burning flame.

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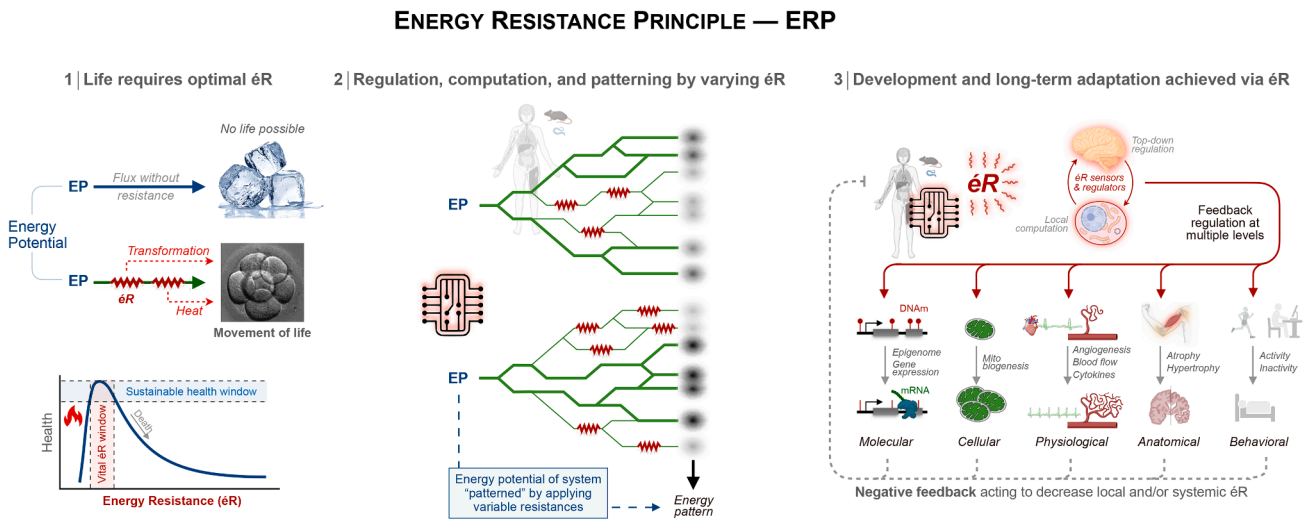

Figure 1. Assumptions of the ERP

(1) Without resistance to energy flux (e.g., in the vacuum of outer space) transformation is not possible. Energy resistance allows for transformation and dissipative energy loss, providing warmth and other required conditions for life (see Figure 2). Optimal health processes occur within a narrow window of energy resistance (*éR*) where life is maintained at a minimum energy cost and information loss, optimizing longevity. Factors that increase energy consumption beyond sustainable levels (e.g., sepsis and stress) or block electron flux in mitochondria (e.g., asphyxiation and mitochondrial defects) lead to death by excessively elevating *éR*. (2) Dynamic regulation and processing/computing of information occurs via rapid changes in *éR* within the biological network (e.g., neuronal networks, vascular networks, organellar networks, and gene networks). As in electrical systems, the reduction in resistance acts in a demand-driven manner to draw more energy flux through specific components. In addition, *éR* regulated by top-down processes (e.g., brain-mediated endocrine signaling, vasodilation or vasoconstriction of vascular bed) directs and stabilizes whole-organism *éR*. (3) Adaptive recalibrations and long-term adaptation operate by producing salutary structural and functional changes that minimize éR at different levels of complexity spanning molecular, cellular, physiological, and anatomical components, as well as whole-organism behaviors and and subjective experiences.

(2) Organisms vary resistance to direct energy flux and compute information. Energy flows down the path of least resistance, so varying resistance is the simplest way to direct energy. In microcircuits and other physical systems, varying resistance is the basis of computation and information processing. Biology harnesses the same principle. Neural, vascular, and other anatomical networks distribute and transform energy (blood, bioelectricity, and nutrients) into information by varying éR across massively distributed parallel systems.

(3) Organisms adapt and optimize fitness by achieving lasting changes in energy resistance. Resistance to energy flux (*éR*) triggers signaling outputs whose information content activates (epi)genetic regulatory pathways, which communicate and produce enduring cellular, physiological, anatomical, and behavioral changes. These changes feedback to minimize and optimize *éR* over the long term, enhancing the system's efficiency, fitness, and health.

ENERGY FLOWS THROUGH BIOLOGICAL CIRCUITRY FROM FOOD TO OXYGEN

The fundamental difference between a cadaver and the living organism is the flow of energy.[17] Breathing organisms use their mitochondria to sustain energy flux in the form of electrons (*é*) toward oxygen, the second most electronegative element of the periodic table. This process begins with ingested foods, proceeds through digestion and biochemical cascades that simplify macromolecules into metabolites, and culminates in electron flux within the mitochondrial electron transport chain,[18] where oxygen acts as the ultimate electron acceptor.[19] In biological circuits, oxygen acts like the positive (+) pole of a battery toward which the electrons arising from the negative (–) pole, foodstuff, spontaneously flow (Figure 3, inset). This is the basis for respiration in breathing creatures like humans and other animals.

At every step, the movement of electrons from one molecule to another, involving either chemical reactions with covalent bonds or electron transfer in the electron transport chain, faces biophysical constraints. Under certain conditions, electron flux may involve tunneling,[20] a quantum-scale mechanism that facilitates electron mobility and locally reduces energy barriers (electrons pass through, rather than over, energy barriers), shaped by both classical and quantum physical constraints.[21]

The mitochondrial electron transport chain is partially encoded by the mitochondrial DNA (mtDNA), the only DNA outside the nucleus. The mitochondrial system evolved to offer precisely sufficient resistance to electron flux, which powers three proton pumps (complexes I, III, and IV). These molecular pumps each carry an H^+ atom across the inner mitochondrial membrane, for each fluxing electron. By constraining electron flux, the mitochondrial electron transport chain accepts an electron from the electron donor NADH, transforming current (one form of energy) into the proton-motive force ($\Delta\mu H^+$, another form of energy).[22,23] Therefore, the energetic cascade within the organism involves the transformation of energy first from chemistry to fluxing electrons (i.e., electricity), then into the flexible electrochemical $\Delta\mu H^+$ energy gradient. All animal multicellular life is powered by this precisely resistive, transformative, and energetic process.

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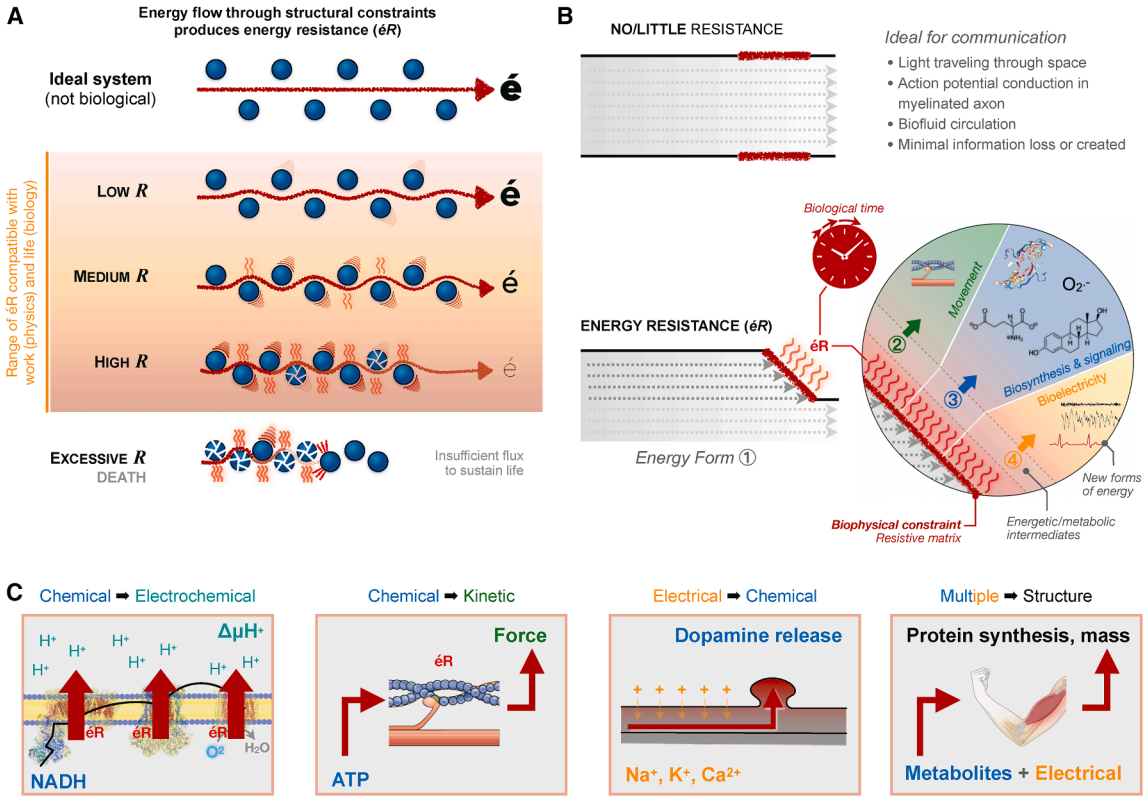

Figure 2. Energy resistance enables transformation across physical and biological systems

(A) In space or in an ideal medium, energy flows without resistance, leaving no opportunity for transformation or work to be performed (top). However, in contact with adequate biophysical constraints, such as the carbon-based matrix of biology, the path for electron flux is tortuous, from which emerges resistance that (1) dissipates energy as Brownian motion (i.e., heat) and (2) transforms raw energy into work (molecular bonds, other useful processes) that counteracts entropy (middle three rows). When energy resistance is too high, energy stalls and dissipative losses increase, damaging its substrates and failing to power the self-sustaining living system. Thus, organisms must maintain a "just right" degree of energy resistance for optimal health, efficiency, and lifespan.

(B) Example of a simple system with energy fluxing through a non-resistive matrix (top) or through a substrate offering the appropriate constraint (bottom), generating energy resistance (*éR*) that transforms, through high-energy intermediates, raw energy ① into different end products (②–④).

(C) Specific biological examples where *éR* transforms an initial form of energy into another, powering negentropic reactions and physical actions in living systems. Resistance is the basis for transformation and life. To perform meaningful work, simple physical systems harness the transformative power of resistance. Resistance emerges as an intrinsic property of the system that modulates and regulates the flow of energy through biophysical constraints. By the action of the right resistance pattern, energy in one form is thus transformed into one or more different forms. We provide some examples highlighting the fundamental expressions of this principle across non-living and living systems.

Light resistance in photosynthesis: In plants, chlorophyll constrains the flux of light, generating resistance that transforms light energy into the unlikely separation of carbon and oxygen from CO_2, into edible hydrocarbons (CHOs) and breathable oxygen (O_2).

Aerodynamic resistance and flight: For a plane in motion, the convex wing aerodynamically constrains the flow of air, generating resistance that transforms kinetic energy into lift by creating pressure differences, enabling the airplane to ascend.

Mechanical resistance: In a combustion engine, the piston constrains the pressure of explosions, generating resistance that transforms the ignited chemical energy of fuel into mechanical work and kinetic energy, propelling the car forward.

Hydrodynamic resistance: In a hydroelectric dam, the bladed electromagnet turbine rotor constrains the flow of water, generating resistance that transforms the kinetic energy of the water into electrical energy.

Reproductive resistance: In the reproductive act, the female vagina constrains the movement of the male penis, generating resistance that transforms the stored potential energy of sperm into kinetic energy to reach the oocyte. For procreation, resistance needs to be just right; too little or too much impairs function.

Psychological resistance: In the human mind, theories, problems, and unresolved questions constrain the movement of the human mind, generating resistance that transforms the unformed electrical energy of the brain or consciousness into new ideas, concepts, and technologies, advancing human knowledge. Scientific problems thus give purpose and transform the otherwise unformed potential of the human mind, making resistance an agent of mental and cultural change.

Mitochondria then use $\Delta\mu H^+$ to generate ATP,[10] to concentrate ions like Ca^{2+}, and to produce a multitude of high-energy chemical intermediates, such as guanosine triphosphate (GTP), NADPH, and GSH, that power essential cellular activities. In each cell, these chemical intermediates provide the activation energy, stored as latent potential within covalent bonds, for enzymatic reactions that enable the creation, function, and preservation of biological structures—to resist entropy.[24] Mitochondria are the auspicious site where food-derived electrons meet and re-unite with oxygen, releasing water (H_2O) and carbon dioxide (CO_2) in the process. This closes the life cycle between breathing animals and photosynthesizing plants,[17] which is ultimately sustained by solar radiation. Chloroplasts transform light into matter, trapping electrons in biochemistry. Mitochondria then dematerialize biochemistry into membrane potential and bioelectricity, a flexible energy form widely used across biology.[25]

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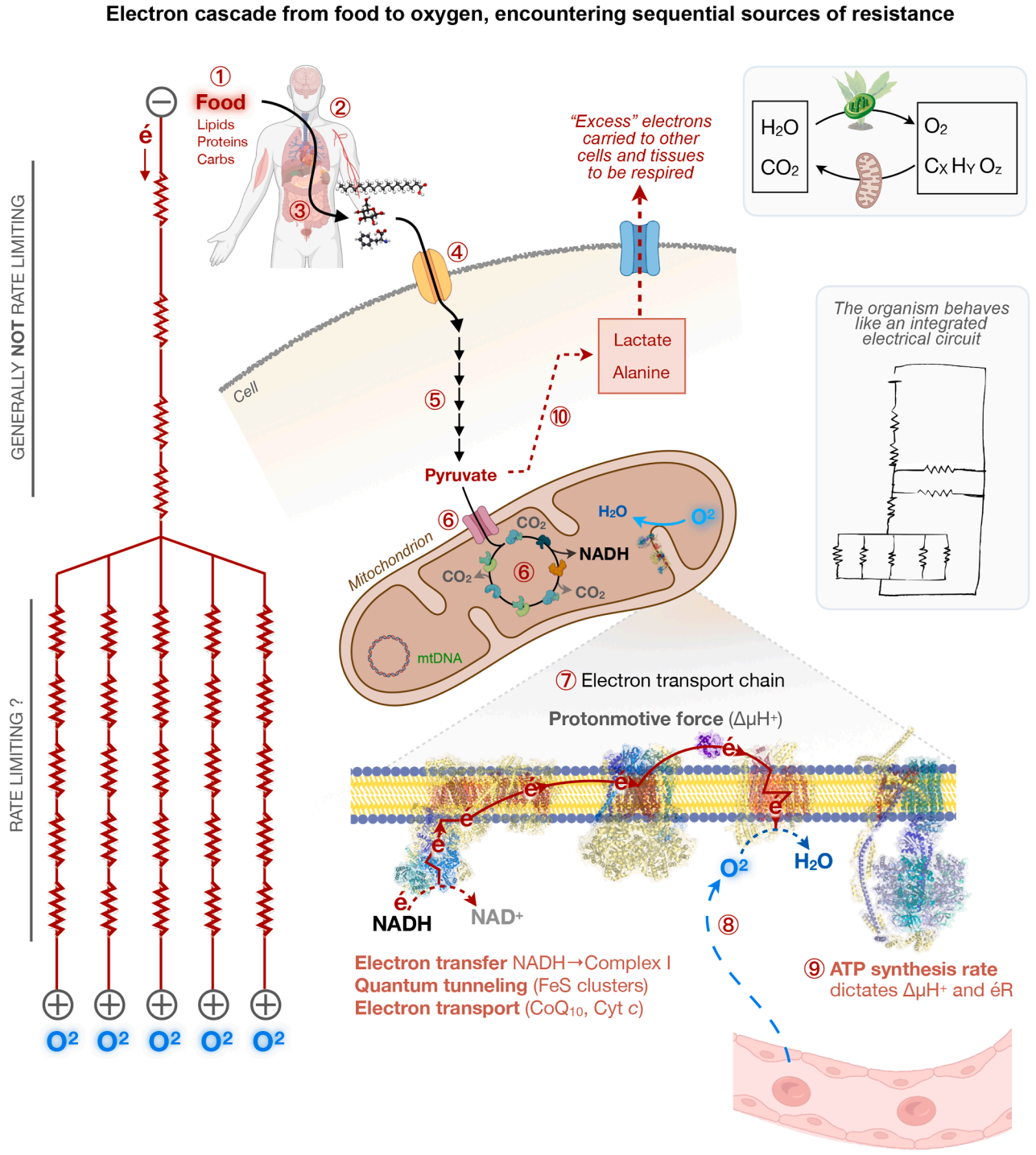

Figure 3. The energetic cascade of electrons from food to oxygen in mitochondria in the biological circuitry

Energy flux through the organism can be abstracted as a simple electrical flow diagram. The flux of electrons from ingested food to oxygen culminates in the mitochondrial electron transport chain where electrons sequestered by photosynthesis from H_2O and CO_2 onto organic molecules are electronegatively attracted by oxygen. Each "step down" transformation, or transition step, is marked by energy resistance (*éR*) that enables the transformation of energy from one form to another (e.g., chemical to electrical, electrical to proton-motive force). At the scale of the organism, physiological steps of resistance positioned in series include ① digestion (stomach) and assimilation (intestines), ② cardiac output (heart and vasculature), ③ tissue perfusion (capillary beds), ④ transport across the cell membrane (insulin-regulated and independent transport), ⑤ intracellular enzymatic cascades (e.g., glycolysis), ⑥ mitochondrial import (e.g., carnitine shuttle) and the Krebs cycle, and ⑦ electron transport chain (ETC) that generates $\Delta\mu H^+$. With ⑧ oxygen supply, this set of biophysical constraints largely determines the

(legend continued on next page)

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The ERP highlights how as bearers of the electron transport chain, also known as the "respiratory chain," mitochondria together with other metabolic networks have evolved as the ideal bioelectrical circuit where the vital pull of oxygen on electrons provides the driving force for life. As energy flows through the finely tuned resistive circuitry of biology, *éR* acts as the medium of transformation that powers all of life's operations.

Using our electrical circuit analogy, the energetic cascade of life can be understood as a series of transistors, or variable resistances, connected to one another: some in series and some in parallel (Figure 3). If resistance increases in one transistor in a series circuit, it increases the resistance of the whole circuit. Whereas in electrical circuits resistance propagates instantaneously, biochemical networks exhibit natural elasticity buffering against fluctuations in resistance. Nevertheless, from first principles, we would predict that if resistance increases in mitochondria—~40,000 trillion parallel transistors—the effects on the flux of electrons/substrates would rapidly ripple upward through the biochemical circuitry to alter the flux of electron-carrying metabolites across metabolic pathways, the cell membrane (e.g., causing glucose intolerance), and other organ systems.

ORGANISMAL ENERGETICS, HEALTH, AND AGING

Two specific notions around animal energetics offer useful premises to understand the vital requirement and significance of *éR*.

Energy expenditure

Energy expenditure reflects the amount of work required to survive, resulting in the pressure or demands for energy transformation that an animal must expend or "burn" per unit of time.[24] Interestingly, energy expenditure measured via O_2 consumption and CO_2 production per unit mass scales inversely with lifespan. This means that organisms with higher mass-specific metabolic rates generally have shorter lifespans. The resulting striking mathematical regularities reveal an energy-lifespan relationship that scales across twenty orders of magnitude from mitochondria to the largest mammals on Earth.[8,26,27] Faster breathing animals also exhibit faster telomere shortening rates,[28] accumulate point mutations more quickly,[29] and have developmental clocks that tick faster.[30,31] Faster mitochondrial metabolism sets faster species-specific molecular tempo across biological processes.

In humans, people with higher energy expenditure also die earlier,[32,33] leading to the incomplete conclusion that breathing faster makes you die earlier. The so-called rate of living theory of aging has been closely examined, revealing inconsistencies and exceptions,[34] among which is the notion that temperature is a more important driver of lifespan than energy expenditure, at least in mice.[35,36] Temperature is the rate of molecular jiggling, or Brownian motion, and is a direct biophysical consequence of energy constraints and *éR*. All else being equal, increasing *éR* increases the system's temperature. Thus, the ERP predicts that entropy production rates from energy fluxing across the resistive biology of an organism should most accurately predict aging dynamics and mouse lifespan, as recently reported.[37] Therefore, energy expenditure and other related parameters reflect the demand or energy "potential" (*EP*) of the system, which is an important parameter, yet alone is insufficient to accurately account for the dynamics of health and lifespan.

Mitochondrial energy flux regulates aging biology

A second well-established energetic fact of life is that energy flux (*f*) by the main cellular energy transformer—mitochondria—is a major determinant of health and aging biology. We have learned a great deal on this topic from individuals with rare genetic mtDNA defects. mtDNA mutations alter electron transport chain components and thus increase the biophysical constraints to fluxing electrons within mitochondria. As a result, mtDNA defects reduce maximal respiration, directly increasing the resistance to energy flow across the whole physiological system.[38]

Impaired mitochondrial biology has been linked to most medical conditions and chronic illnesses[39] and become a canonical hallmark of disease and aging.[40,41] There is a common, while often untested, assumption that mitochondrial contributions to disease pathogenesis and aging are primarily driven by ATP deficiency. However, in cells, animals, and humans with impaired mitochondria, ATP is often not lower than in healthy conditions.[42] Thus, primary mitochondrial diseases caused by genetic defects in the oxidative phosphorylation (OxPhos) system may decrease electron flux capacity, but not ATP levels. Moreover, mitochondrial defects do not decrease energy expenditure as might be logically expected, but rather produce cellular and physiological recalibrations that *increase* the organism's pressure or potential to transform energy—a state termed "hypermetabolism."[43] Thus, ATP levels cannot explain how reduced energy flow capacity influences health.

Therefore, in living organisms, both the *EP* and rate of *f* are meaningful energetic parameters. However, *EP* and *f* are insufficient on their own to understand physiology and lifespan regulation. How do these basic energetic parameters interact to drive health and disease processes?

DERIVING ÉR FROM *EP* AND *F*

The solution to integrating *EP* and *f* within biology is *éR*. Simple physical systems convert or transform energy (e.g., electricity) into work through variable resistance following simple quantitative laws (Figure 4).

The simplest such law relevant here is the power law, where resistance is power divided by current squared ($R = P/I^2$). Here, we extend this law to biological systems, where electrons flux from food (anode) to oxygen (cathode), albeit at a remarkably slower rate than in electrical systems. For Ohmic physical material, resistance (*R*) is typically treated as a constant, but in biology, changing biophysical, molecular, cellular, and physiological processes dynamically alter resistance. For a cell or organism experiencing a given *EP*, we derive that *éR* is the ratio

system's respiratory capacity or energy flux capacity. ⑨ The ATP synthase dissipates $\Delta\mu H^+$ and enable electron flux when ATP is consumed. ⑩ Excessive resistance leads to electron backflow onto pyruvate, converted to lactate or alanine that can be exported to relieve excess cellular éR. Note the parallel arrangement of mitochondrial ETC transistors, which decreases the circuit's total effective resistance each time a new mitochondrion is added to the system via mitochondrial biogenesis.

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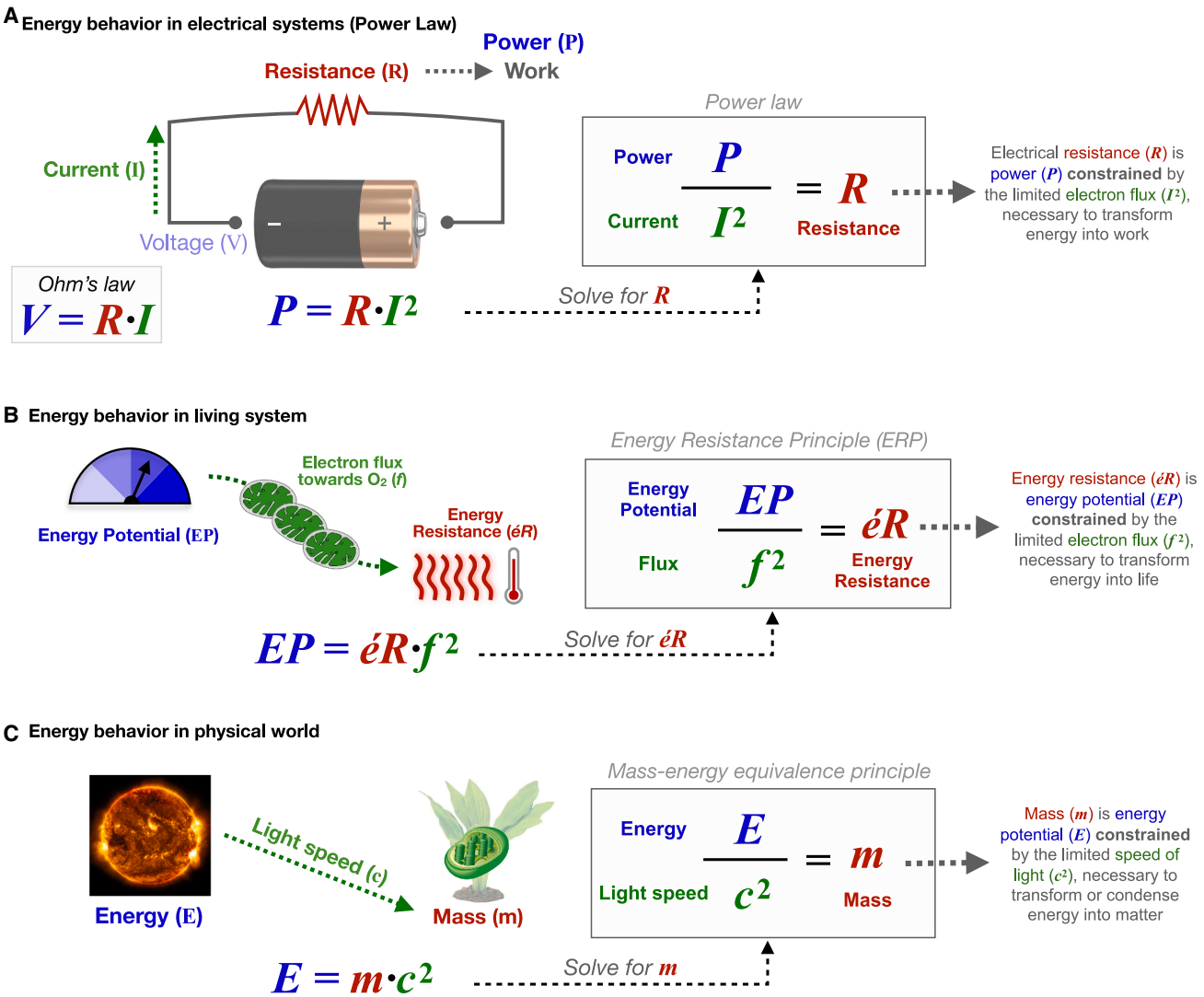

Figure 4. Simple laws dictate the behavior of energy

In electrical systems, Ohm's law relates the voltage potential (V) of a system to its resistance (R) and current (I), following $V = R \cdot I$. In turn, the power law or Joule's law states that the power (P, in Watts) of a system is equal to the voltage multiplied by current, following $P = V \cdot I$.

(A) Here, substituting V for Ohm's law, we get that $P = (R \cdot I) \cdot I$, or $P = R \cdot I^2$. This describes how electron flux in an electrical system is modulated by the biophysical constraints of its components, with resistance dissipating energy as heat. In devices like electric motors, controlled resistance converts electrical energy into useful work, despite inevitable thermal energy loss. Similarly, in biological systems, energy dissipation stabilizes flux and drives essential transformations that sustain life processes.

(B) The same principle applied to cellular and clinical data reveals how *EP* constrained by energy flux capacity (f^2) generates energy resistance (*éR*). We propose that these features scale following $EP = éR \cdot f^2$, extending the power law $P = R \cdot I^2$ to living systems. The use of f^2 reflects the nonlinear dynamics of biological energy flux, where increases in flux lead to disproportionately larger effects on energy transformation due to the complex scaling properties of biological networks. This formalized relation relates whole-body *EP* and f^2, yielding *éR*, generating warmth (heat dissipation) and transformative capacity, both of which sustain life.

(C) The power law and our ERP formulation recall the mass-energy equivalence principle ($E = mc^2$). Solving for mass ($m = E/c^2$) suggests that matter emerges from constraining energy (E) by the flux rate constant of the speed of light (c^2). Analogously, in the ERP, solving for *éR* emphasizes the intuitive notion that *éR*, and thus the potential for life, results from constraining the *EP* by the limited electron flux rate (f^2) through mitochondria and other digestive, convective, enzymatic steps along the biological circuit (see Figure 2).

Resistive circuit design: In electric circuit design, resistors limit current flux to specific portions of the system. This helps in setting the operating points of each component, determining how much flux passes through each element. In biological organisms, the meaningful components are cells, organs, and anatomical regions of the body. Their resistance to blood flow, and therefore to oxygen and nutrients, is tuned dynamically by vasoconstriction and vasodilation, tuning how much blood/energy flow passes through each biological component commensurate with energy demand. Importantly, resistances applied *in series*—similar to cascades of enzymatic reactions, or electron transfer components in the mitochondrial electron transport chain—are cumulative. They add up to their total resistance following $R_{total} = R_1 + R_2 + R_3 + R_n$. In contrast, resistances applied *in parallel*—such as the hundreds to thousands of mitochondria in each cell—behave differently. Each resistance applied in parallel decreases the circuit's total resistance following $1/R_{total} = 1/R_1 + 1/R_2 + 1/R_3 + 1/R_n$. Therefore, in relation to electron flux in biology, this means that the production of additional mitochondria through mitochondrial biogenesis decreases the system's total *éR*.

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of *EP* constrained (i.e., divided) by the rate of *f*, following $éR = EP/f^2$.

While this parallels Ohm's law and the electrical power equation ($P = R \cdot I^2$), here, éR is a derived bioenergetic parameter with units analogous to resistance but emerging from dynamic biophysical constraints unique to living systems (molecular, anatomical, and systemic). We use the term energy resistance to distinguish it from purely electrical resistance and to emphasize its role as a biological transformation constraint. The terms of the ERP are defined as follows:

- *EP* is the scalar quantity representing the total drive to perform work within a system. In electricity, resistance scales according to voltage (*V*) relative to power (*P*) following $R = V^2/P$—the larger the drive (*V*) and the lower the work being done (*P*), the higher the resistance. For biology, the ERP proposes that *EP* subsumes both (1) the voltage-like accumulation of energetic substrates (e.g., glucose and lipids) and (2) the power-like physiological demand for energy transformation (e.g., physical work, in Watts or Joules). Analogous to voltage in electrical systems, EP provides the "push" for transformation, or the thermodynamic gradient for energy flux.
- *f* is the rate of electron transfer from substrates (food) to terminal electron acceptors (oxygen) in aerobic organisms. The maximal capacity, or the ceiling for *f*, is set by biophysical factors including mitochondrial content and OxPhos capacity, vascularization, cofactor availability (e.g., NAD^+), tissue oxygenation, and others. Analogous to current in electrical systems, *f* reflects the rate of energy flux. In the ERP, as in the power law (Figure 4), the squaring of flux (f^2) reflects the nonlinear dynamics of biological energy transformations, akin to Joule's law, where dissipated power scales with current squared. In biological systems, this scaling captures how modest changes in flux capacity can produce disproportionately large effects on energy transformation and éR.
- *éR* is the system's property that opposes energy flux. *éR* emerges from the system's biophysical constraints as they interact with energy flux. It regulates the conversion of *EP* into biologically usable work. By setting how easily free electrons or electrons trapped within molecules (i.e., metabolites) flux across biological structures, *éR* determines both the rate and efficiency of transformations—from ATP synthesis to signal propagation—across physical and temporal scales.

This simple formulation, $éR = EP/f^2$, leads to testable predictions. This definition of *éR* means that if flux capacity is drastically diminished, for example after the ingestion of cyanide, which inhibits mitochondrial electron flux toward oxygen, the denominator $f^2 \to 0$ and the organism's fixed cost of life or *EP* then produces infinite resistance ($éR \to \infty$). Excessive resistance is incompatible with transformation, and therefore with life. On the other hand, if the system contained excess mitochondria and a theoretically infinite capacity to flux electrons that offered no biophysical constraint ($f \to \infty$), then resistance would be zero and energy would be consumed instantaneously without performing meaningful work. The system would burst into flames. However, because increasing *éR* to non-infinite levels will also increase the system's temperature, the relationship between temperature and *éR* is nonlinear.

This principle is relatable to biology in a simple analogy. Consider a candle, in which the dense and impure carbon-based substrate of wax combined with the structure of the wick allows the candle to burn at a fixed, relatively sustainable rate. Similarly, the wet, impure carbon-based substrate of animal biology allows us to live at a fixed, relatively sustainable rate. All known living organisms operate within a fairly narrow evolutionary range of energy flux (*f*)[44] and do not carry excess mitochondria or flux capacity,[19] likely to preserve *éR* within the optimal window for life. The ERP proposes that the behavior of energy in biological systems follows similar principles as in more simple energetic systems, operationalized in the formula $éR = EP/f^2$, illustrated in Figure 5.

In essence, we propose that in biology, the transformation of chemical, thermal, electrical, and other forms of energy requires finely tuned biophysical constraints, out of which emerges resistance energy flux. We refer to this resulting property as energy resistance—*éR*.

FACTORS INFLUENCING ÉR

In mitochondria, cells, and other metabolic systems, biophysical constraints emerge from the intrinsic molecular composition and structures of biology to create *éR*, a force that transforms the energy of flowing electrons into life-sustaining energetic intermediates such as bioelectricity and ATP (Figure 2B). The structure of the formula $éR = EP/f^2$ stipulates that *éR* is determined by the ratio of energy potential and flux. Thus, two main classes of factors can increase or decrease the system's resistance (Figure 5, left).

Factors that decrease éR

éR decreases in response to either (1) decreasing demands or signals that drive *EP* or (2) increasing flux (*f*). Factors that decrease *EP* include interventions well known to increase lifespan, including calorie restriction and fasting, which decrease blood glucose and insulin levels,[37,45] as examples. Sleep and other physiologically calming states achieved through meditation or mindfulness, which are associated with lower heart rate, body temperature, and sympathetic activity, also decrease work done by the body (*EP*, imperfectly estimated in healthy systems by steady-state energy expenditure),[46,47] thereby decreasing *éR* (Figure 5, top left).

éR is also lowered by factors that increase the formula's denominator, f^2. Mitochondrial biogenesis increases the number of channels for electron flux to oxygen,[48,49] angiogenesis increases delivery of oxygen and the removal of metabolites that can slow down biochemical reactions and increase constraints,[50] and other factors that increase the oxidative or respiratory capacity of a tissue[36] are expected to coordinately decrease *éR* (Figure 5, bottom left). Supplementation with electron-carrying cofactors such as NAD^+[51] or specific diets that increase circulating ketone bodies[52,53] may also increase flux (or increase maximum flux capacity) and thereby decrease éR, possibly accounting for their health span and lifespan extension effects.

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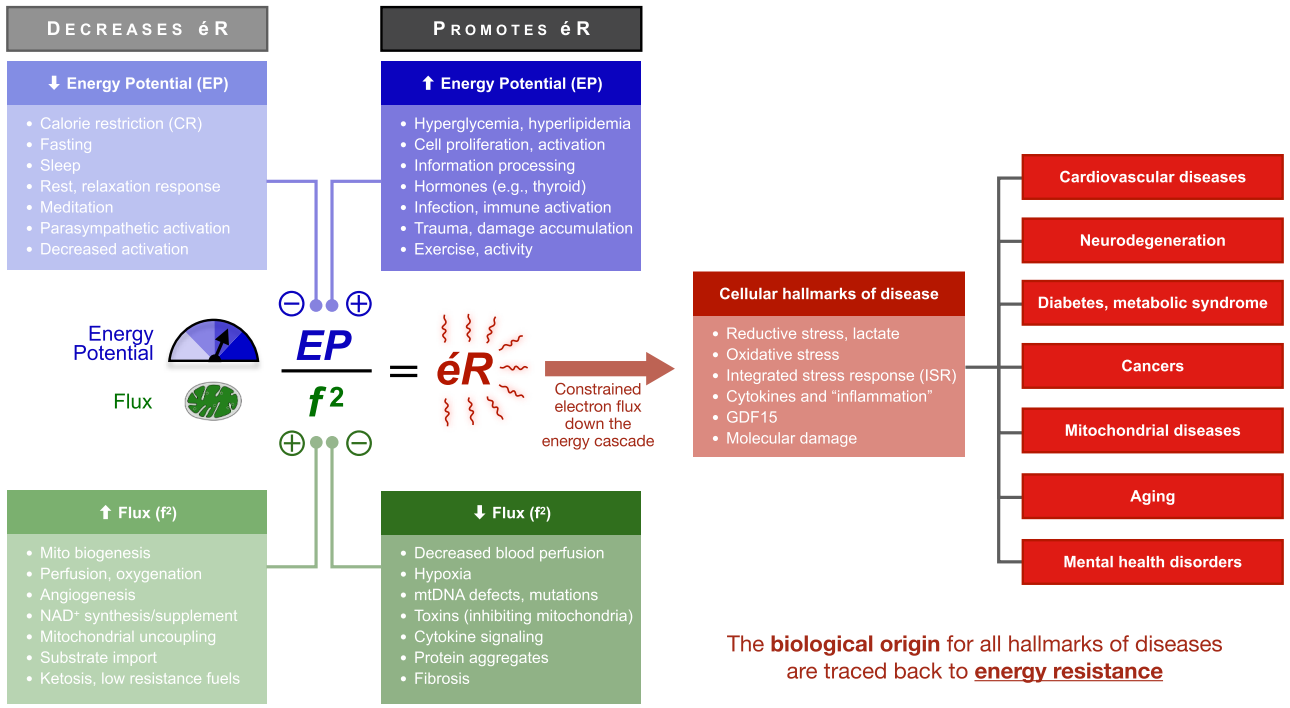

Figure 5. Health-driving or disease-promoting factors act through energy resistance to produce the hallmarks of disease

Factors influencing energy resistance (*éR*) can act on either the numerator (energy potential, *EP*) or the denominator (flux, f^2). Over time, *éR* generates the key hallmarks of human diseases either directly by impairing electron flux (reductive stress, oxidative stress, molecular damage) or indirectly by activating gene programs (pro-inflammatory states and cytokines, integrated stress response [ISR], and growth differentiation factor 15 [GDF15]). Thus, the biological origin of the hallmarks of disease can be traced back to excessive *éR*, accounting for why they frequently co-occur with co-morbidity across physical-mental disorders.

Note that given the mathematical structure of the proposed formula (following the power law), we initially propose that the term for flux, *f*, is squared. Consequently, changes in *f* are expected to produce an exponential effect on éR compared with linear changes in *EP*.

Factors that increase éR

Factors that increase *EP* include cellular and physiological processes that increase either energy demands or supply. This includes hyperglycemia, hyperlipidemia, and the elevation in other metabolites that readily seek an outlet to offload their electrons. In fact, the reason hyperglycemia and hyperlipidemia (i.e., glucolipotoxicity in diabetes) are health liabilities may, in fact, be because they increase *EP* (without a rise in energy flow), and therefore increase *éR*; similarly, in the electrical power law the energetic gradient V^2 (e.g., glucose gradient) exponentially drives *R* following $R = V^2/P$. Other factors that elevate *EP* are linked with the pathophysiology of various disorders, including cell (hyper)proliferation, which increases work performed and energy demands in excess of typical energy demands for a given tissue.[54] This occurs in cancer and in activated immune cells,[55,56] but *EP* may also increase in response to cell-cell communication, secondary to the cellular energy demands required to send, process, and receive information[57–60] (Figure 5, top right). Muscle contraction and other processes during physical activity also trigger several-fold elevations in both local and whole-body energy demand,[19] thereby linearly increasing *EP*, and therefore éR.

Factors that decrease *f* include poor vascularization and tissue hypoxia because they deplete the vital negative pole in the energetic circuit, oxygen (Figure 5, bottom right). Without oxygen's pull-on electrons, the system's flux decreases, increasing *éR*. Naturally, mtDNA mutations or environmental toxins that poison mitochondrial complex I or alter the OxPhos system (even in the absence of ATP depletion) also directly impede electron flux (e.g., Kuznetsov et al.[61]), increasing the biological constraints to energy flow from food to oxygen. Thus, among its most straightforward predictions, the ERP predicts that primary mitochondrial defects directly elevate *éR*, as confirmed below.

BIOLOGICAL EFFECTS OF ÉR

Origin and molecular signaling effects of excessive éR

Among both physical and biological systems, resistance comes with inevitable side effects. In electrical systems, excessive resistance (motor or overloaded GPU) causes overheating, leading to damage that accelerates the degradation of microcircuit components. In wet and warm cellular circuits, energy transformation also necessarily comes with energy loss as dissipative processes generating heat (thermal damage and protein unfolding),[62] reactive oxygen species (ROS, oxidative stress), biophotons (ultraweak photon emission), and other forms of energy loss limiting both mitochondrial and whole-body energy efficiency[63,64] (Figure 5, middle). These dissipative energy losses are inevitable, although modifiable, consequences of resistance.

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We understand dissipative losses to underlie the stochastic information loss[65,66] and seemingly inevitable damage accumulation[67] associated with the aging process.

Beyond increasing the entropic dissipative loss that naturally drives information loss, *éR* also produces adaptive signals. The origin of *éR*-derived signals can be traced back to electrons in mitochondria. As electrons encounter excessive constraints that limit their flux through the mitochondrial electron transport chain, electron or EP builds up, similar to the water accumulating across a dam as the flood gate is progressively closed. Electrons then build up in the electron transport chain upstream of their final desired destination, cytochrome *c* oxidase (complex IV), where electrons are efficiently and safely transferred to molecular oxygen, producing water and closing the integrated life circuit.

With excessive constraints to flux, electrons quickly backflow onto NAD^+, converting it back to NADH. The resulting increase in NADH/NAD^+ ratio is a state termed reductive stress.[68] With reductive stress, the overly reduced electron transport chain ectopically leaks electrons onto molecular oxygen, this time creating ROS. When produced in excess relative to antioxidant defenses, this leads to oxidative stress.[69] Thus, first reductive stress, and secondarily oxidative stress are the most direct molecular manifestations of impeded electron flux, or *éR* in mitochondria.

éR triggers stress responses and specific cytokines

To drive cellular and organismal adaptations, mitochondria experiencing increasing *éR* must act as signaling organelles. Accordingly, both the NADH/NAD^+ ratio and rising levels of ROS independently act on the cell as signaling molecules.[70,71] Within minutes to hours, these mitochondrial outputs trigger and stimulate cytoplasmic signal transduction cascades that converge on well-conserved stress responses gene programs related to cell fate. These in turn drive apoptotic, cell differentiation, innate immune, hypoxic, and quiescence/senescence programs.[72–74] Thus, cell fate transitions and behaviors are under the control of mitochondrial éR signals.[75,76]

Beyond the cell, mitochondrial *éR*-initiated stress responses involve cell-to-cell signaling via paracrine and endocrine secondary signals. Cells communicate their *éR* state by turning on nuclear genes, synthesizing and secreting specific combinations of small proteins called cytokines (*cyto*, meaning "cell"; *kine* meaning "to move" or "set in motion").

Cytokines are the universal language of intercellular communication. They are produced by any cell, not just immune cells.[77] Notable cytokines known to be triggered by metabolic cues related to *éR* include interleukin-6 (IL-6),[78] vascular endothelial growth factor (VEGF),[79] and growth differentiation factor 15 (GDF15, see below). Thus, the cell nucleus translates excessive *éR* into cytokines to communicate the cell's energetic status—excessive éR—to other cells. Importantly, reductive stress is a necessary and sufficient trigger for GDF15 production in different cell types.[73,80] The result is the blood "cytokine storm," traditionally referred to as inflammation. Understood through the lens of the ERP, inflammation is a systemic signal of energetic stress, or more precisely, specific cytokines are signals of excessive energy resistance.

Organisms handle reductive stress through inter-organ crosstalk

Excessive *éR* also produces metabolite signals. Backflowing electrons increasing the NADH/NAD^+ ratio inhibit the Krebs cycle, causing pyruvate to backflow onto the cytoplasmic enzyme lactate dehydrogenase A/B (LDHA/B), which converts it to lactate.[68] This reaction relieves reductive stress by regenerating NAD^+. Lactate, with two electrons in tow, is then promptly excreted from high-*éR* cells into the extracellular space and blood, acting as a pressure valve to eliminate excess electrons that mitochondria do not have the immediate capacity to flux to oxygen. In addition to lactate, accumulating pyruvate is converted to alanine, an amino acid that similarly carries excess electrons and diffuses to the bloodstream. As a result, both lactate and alanine are biomarkers of electron transport chain defects caused by mtDNA mutations—primary mitochondrial diseases.[81]

The release of so-called anaerobic metabolites such as lactate and alanine in the presence of oxygen is an apparent paradox termed aerobic glycolysis, or the Warburg effect. It reflects the metabolism of many tumors.[82] The ERP allows us to understand this state as one of high *éR*, driven, for example, by rapid cell proliferation. In cancer, the ERP predicts that increasing *éR* is necessary to sustain the biomolecular transformation and biomass production necessary to fuel rapid cell division. But in breathing animals, every electron, including the excess electrons released from highly resistive cells in the form of lactate and alanine, must eventually be respired and end up on oxygen in a mitochondrion, even if the first part of the circuit (e.g., glycolysis) was performed in a different cell or organ. Organisms are an integrated energetic circuit. Therefore, lactate oxidation is accomplished by surrounding tissues and other organs that have oxidative capacity to spare, such as the heart and brain.[83]

Thus, through this inter-organ crosstalk, the organism acts as a true cell collective and energetic circuit that respires each food-derived electron, completing the vital cascade of electrons flux from food hydrocarbons to oxygen.

FEEDBACK AND ÉR REGULATION

Understanding the molecular signals arising from *éR* helps us to resolve the mechanisms of adaptation that keep *éR* within the narrow goldilocks zone required for life. The key idea is that *éR* signals adaptations, which bring *éR* back into the most efficient state. For maximal efficiency, these adaptive changes can occur simultaneously at the level of mitochondria, cells, surrounding cells and tissues, physiology, and behavior (Figure 6A).

As one example, high-intensity endurance exercise training can "max out" the respiratory capacity of muscle mitochondria.[84] When the contracting myofibers' workload exceeds what is called the "anaerobic threshold" or "lactate threshold,"[85] the *EP* created by contraction overwhelms mitochondrial respiratory capacity, the tissue can become hypoxic, and lactate is released. During recovery, the adaptations that follow can all be understood to reduce *éR*. The first three operate by increasing flux, f^2, while the fourth one acts by reducing EP:

(1) Mitochondrial biogenesis: new mitochondria are created, thereby increasing the number of parallel channels for electrons to flow.[49]

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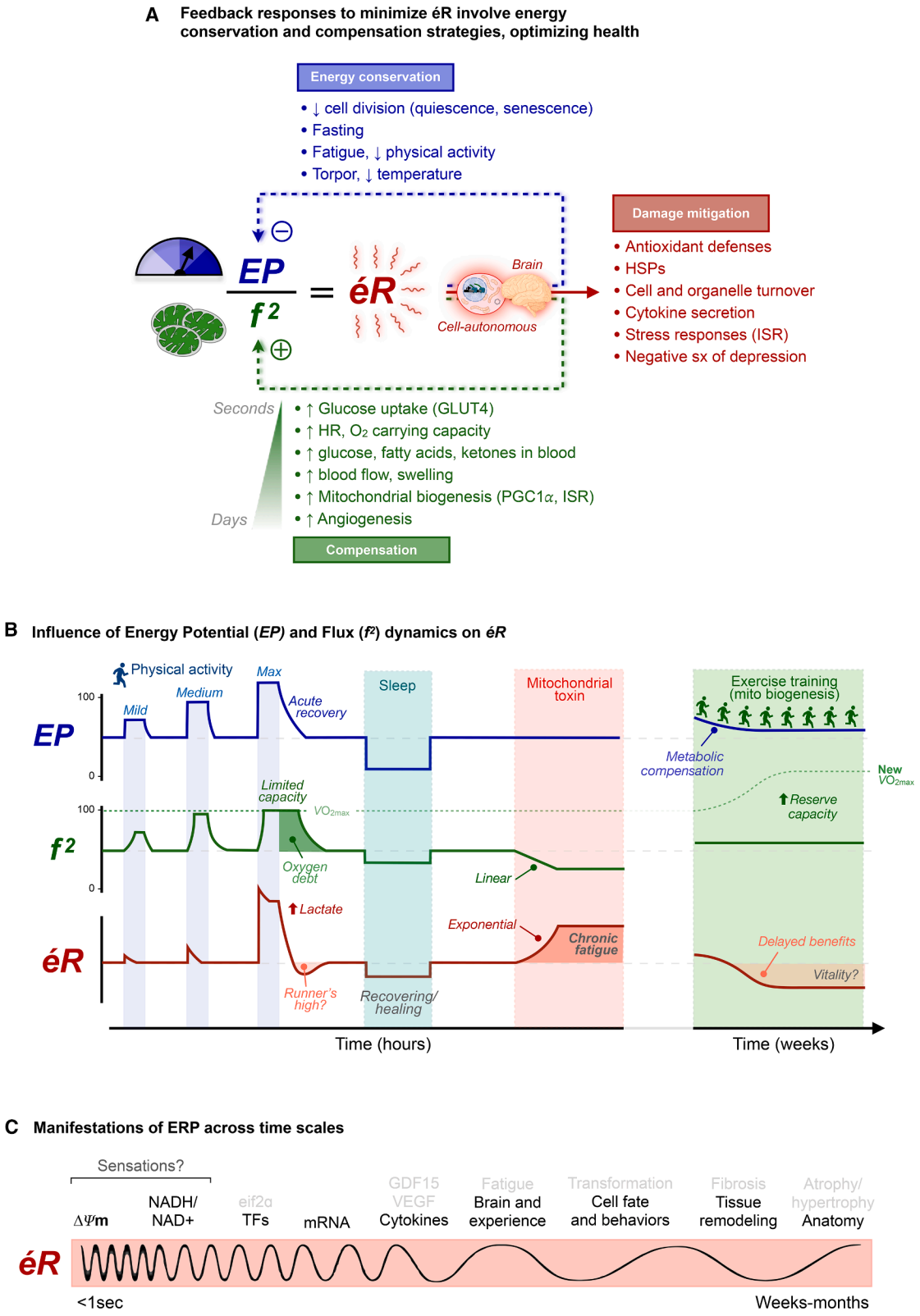

Figure 6. Dynamic changes and regulation in energy resistance in physiology and pathology

(A) Energy resistance (*éR*) triggers cell-autonomous, brain-based, and whole-organism responses that act either (1) to conserve energy and decrease energy expenditure (i.e., inhibitory, lowering the numerator; top axis) or (2) to compensate and increase flux capacity (i.e., activation, increasing the denominator; bottom axis). Excessive *éR* also triggers damage mitigation processes.

(legend continued on next page)

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(2) Cell and tissue level angiogenesis: myofibrils experiencing excessive *éR* secrete cytokines such as VEGF, which stimulates the growth of new capillary blood vessels to increase oxygen and nutrient supply to the newly formed mitochondria.[50]
(3) Physiological delivery: energy substrates are mobilized via the sympathetic nervous system (norepinephrine) and the hypothalamic-pituitary-adrenal axis (cortisol), increasing circulating blood glucose and lipid concentrations to support energy flow in the system.[86]
(4) Behavioral adaptations: maximal exercise in untrained individuals is aversive and elicits brain-derived ratings on the perceived exertion scale,[87] dampening one's motivation to pursue effort, thereby reducing EP, and preventing excessive and potentially damaging elevations in *éR*. The multiscale adaptations to *éR* are illustrated in Figure 1 (right).

As predicted by the ERP, all *éR*-driven adaptive features to exercise are recapitulated by primary mitochondrial defects that increase biophysical constraints within the electron transport chain, decrease f^2, and thus elevate *éR*. People with genetic mitochondrial diseases exhibit:

(1) Excess mitochondrial biogenesis mimicking endurance training.[88,89]
(2) Increased VEGF and angiogenesis around cells with defective mitochondria.[90]
(3) Elevated catecholamines associated with excess blood glucose and lipids.[43,91]
(4) Constant feelings of fatigue and aversion to exercise or other efforts (e.g., climbing stairs).[92]

Thus, increased constraints to electron flux in mitochondria is sufficient to stimulate multi-level adaptations that recapitulate exercise-induced adaptations, pointing to a central role of mitochondrial *éR* in driving both short- and long-term human physiology and health.

TEMPORAL DYNAMICS IN ÉR REGULATION

EP can vary within minutes by 10–20 times at the whole-organism level and by over two orders of magnitude in muscle cells from rest to maximal contraction.[19,93] Under healthy conditions, the increase in work performed is rapidly followed by a rise in energy flow in a demand-driven manner (e.g., ADP stimulates electron flux and respiration[94]). However, the maximal capacity for electron flux is relatively fixed on the scale of hours to days, largely determined by the integrated biophysical constraints of the existing energy delivery hardware or infrastructure: ventilatory, cardiocirculatory, cellular, cytoplasmic, and mitochondrial components.[19] As proposed in our initial formula, *éR* scales linearly with *EP* but exponentially with f^2, a relation that predicts that organisms can accommodate relatively large fluctuations in *EP* on the scale of seconds to hours via relatively small changes in flux. In addition, over the long term, relatively minor adjustments in flux—for example, by making more mitochondria or growing more blood vessels—can effectively relieve biophysical constraints and afford sustained lowering of éR (Figure 6A).

Because building and sustaining the biological hardware required to rapidly flux and transform energy is energetically costly,[95,96] this dual regulatory strategy appears as an optimal solution to maximize the system's flexibility or resilience, while remaining efficient. The ERP shows how the relation and scaling of *EP* and f^2 derived from the power law allows biological systems to accommodate rapid changes in *EP* (required to face acute challenges) while minimizing the energetic costs of adaptation (Figure 6B).

One energy-inspired way to interpret cellular and physiological adaptations is to view them as transformative processes. When the system never encounters resistance, there is little transformation possible and therefore little potential to build and sustain tissue mass. This logic accounts for the high *éR* in cancer mentioned above (high *éR*→high transformation→rapid growth possible).[82] This concept also accounts for the use-it-or-lose-it principle: without effort, muscles atrophy, but with resistance training, muscles grow bigger and stronger. The same applies to endurance exercise and mitochondria. Use them, feel the resistance (i.e., the discomfort of being out of breath), and the organism adapts by making more mitochondria and vasculature to decrease *éR*. Alternatively, never be out of breath, and you shall eliminate the unnecessary mitochondria that are costing energy to sustain.[95,96] A possible corollary for understanding subcellular control of mitochondrial mass is that cells tune the number of mitochondria they have not by tracking actual mitochondrial mass but by monitoring *éR*.

Adaptations likely cannot proceed *during* periods of high éR and must instead be mobilized after, during recovery when éR returns to lower levels. This explains why the onset of skeletal muscle mitochondrial biogenesis does not take place during exercise (when éR is maximal) but in the recovery phase when éR returns to normal levels.[49] The ERP also allows us to understand why a week-long fasting/starvation period triggers gene expression and biochemical adaptations that actively suppress mitochondrial carbohydrate influx and respiratory capacity[97]: as the *EP* of the starved organism diminishes, mitochondrial flux (f^2) must also decrease to balance the energetic state of the organism and stabilize overall éR. Therefore, mitochondria restrict electron import.

Milder fluctuations in metabolic states across sleep and wake cycles may similarly provide broader fluctuations of elevated and

(B) Depiction of dynamic energetic processes illustrating how (1) physical activity acutely increases energy potential (*EP*), eliciting a rapid increase in flux (f^2), whereas max flux capacity remains unchanged (quasi-constant on short timescales). Mild and moderate physical activity produce minimal increases in *éR* that trigger adaptive, health-promoting changes. Exercise intensities above maximal flux capacity (anaerobic threshold) trigger large rises in *éR*. (2) Sleep decreases *EP* but, similar to exercise, does not alter f^2, producing a sustained reduction in *éR* associated with recovery, consolidation, growth, and repair. (3) Exposure to a toxin (or going to high altitude with low O_2) that linearly inhibits mitochondrial respiration produces an exponential rise in *éR*, likely experienced as exhaustion. (4) Exercise training over weeks has a minimal effect on *EP* (energy compensation) but gradually increases f^2, exponentially reducing *éR*. We postulate that the effects of aerobic fitness and the feeling arise from the reduction in *éR*.
(C) Changes in *éR* manifest across levels of biological complexity over wide timescales.
HR, heart rate; sx, symptoms; TFs, transcription factors; VO2max, maximal oxygen consumption rate; $\Delta\psi m$, mitochondrial membrane potential.

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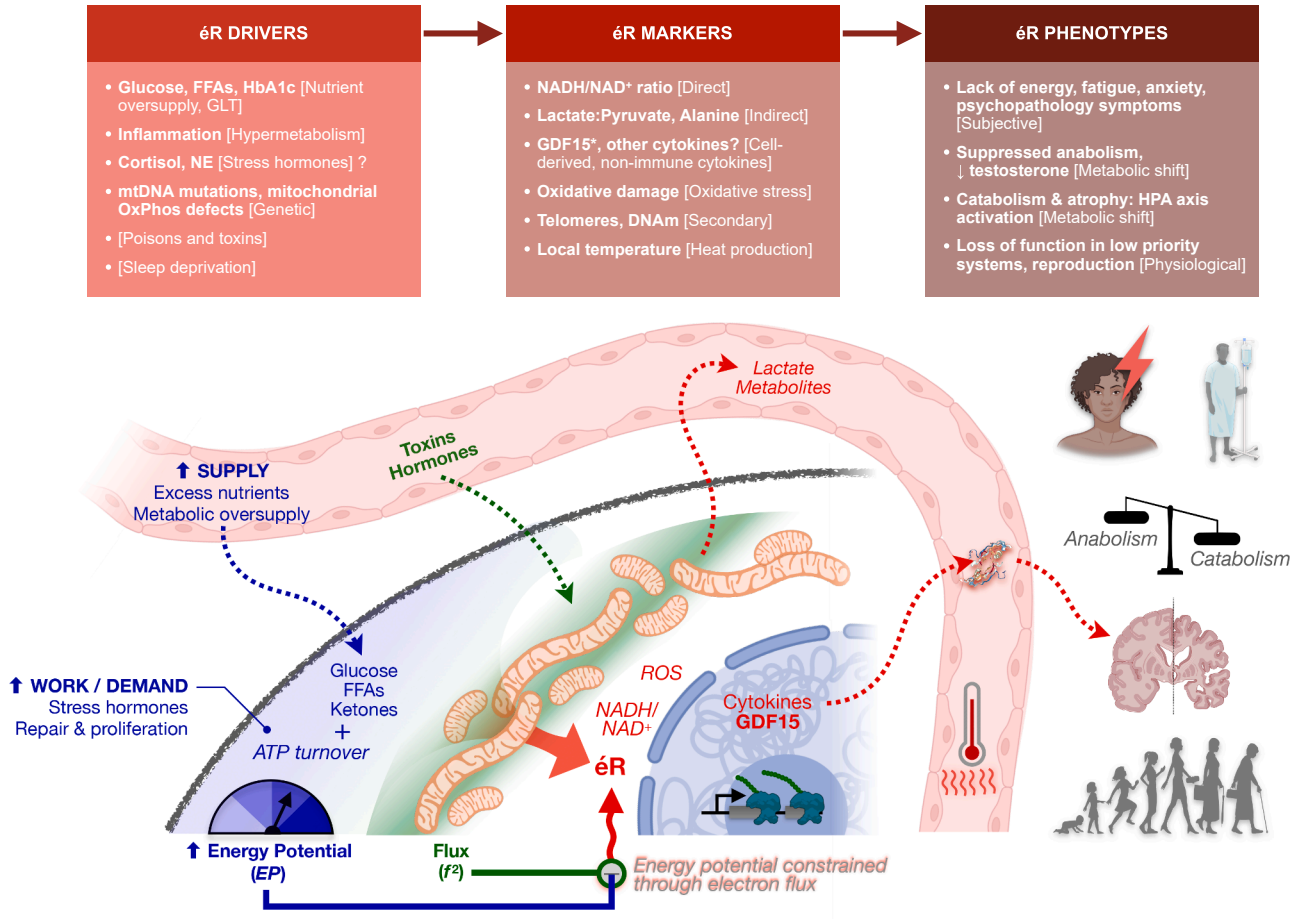

Figure 7. Testable predictions and operationalization of key terms in the ERP model

Measurable factors that contribute to elevate energy potential (*EP*) or that decrease flux (f^2) are *éR* drivers. Factors that become elevated directly or indirectly with high *éR* are *éR* markers. Signs and symptoms that result from acute or chronically elevated *éR* are *éR* phenotypes. FFAs, free fatty acids; GDF15, growth differentiation factor 15; HbA1c, glycated hemoglobin; HPA, hypothalamic-pituitary-adrenal; GLT, glucolipotoxicity; NE, norepinephrine; OxPhos, oxidative phosphorylation.

reduced éR in specific organs,[98] respectively, allowing for the stimulation (catabolic) and adaptation (anabolic) cycles that permeate biology and health.[47] Figure 6C outlines the timescales across which *éR* manifests to produce molecular, cellular, physiological, behavioral, and anatomical recalibrations.

MEASURING ÉR AND ITS ASSOCIATION WITH DISEASE AND BEHAVIOR

One way to examine the ERP in relation to human health is to define éR drivers, markers, and phenotypes/consequences (Figure 7).

éR drivers

As summarized in Figure 5, direct *éR* drivers are factors that elevate systemic *EP*, including elevated concentrations of oxidizable glucose and lipids in the bloodstream, energy expenditure, and stress hormones such as norepinephrine and cortisol, and factors that reduce f^2, such as poisons and toxins or physical inactivity that reduces mitochondrial content. Specific cytokines acting on target cells can either increase[99] or decrease[100] mitochondrial OxPhos capacity (max capacity for f^2), regulate blood flow,[101] and have widespread activating or repressing effects on cellular activities (*EP*), thus modulating cellular or tissue éR. Genetically encoded tools also exist to directly elevate[102] or decrease[80,103] the NADH/NAD$^+$ ratio (and NADPH) in cells and organisms, acting on the system's f^2 to shape *éR* and GDF15 levels.[73]

éR markers

The best available *éR* marker in humans is the secreted cytokine GDF15, a member of the transforming growth factor β (TGF-β) family.[104] GDF15 increases when mitochondrial *éR* is elevated in cells,[43,73] mice,[105–107] and humans[68,81,108] with mtDNA defects that increase the biophysical constraints for electrons to reach oxygen. Mitochondria-deficient cells and animals experience high *éR* and an elevated NADH:NAD$^+$ ratio reflecting reductive stress.[68] This activates the nuclear integrated stress response (ISR)[43,72,73,109] and stimulates the production and release of cytokines signaling excessive energy resistance, particularly GDF15. The cytokine fibroblast growth factor 21 (FGF21), but interestingly not other traditional cytokines (ILs

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and interferons), has also been reported to be elevated in animals and people with mtDNA defects.[68,107,110] In ERP terms, mtDNA-mutant organisms have reduced capacity for flux, f^2. Thus, for a given *EP*—which is either the same, or may in fact be elevated in mitochondrial disorders[42]—reduced f^2 should exponentially elevate *éR* (following $éR = EP/f^2$). This state is detectable as elevated circulating GDF15,[107,110] an éR marker validated across cellular, preclinical, and clinical studies.

éR phenotypes

The best mapped *éR* phenotypes are produced by the brain.[111] *GDF15* is expressed in all organs and tissues in the body except the brain.[108] In turn, the receptor for GDF15, GFRAL, is expressed only in a subset of neurons in the brainstem region.[104] This expression pattern is a robust example of a canonical body-to-brain metaboception signaling axis conveying somatic energetic distress to the brain. In parallel with other metaboceptive cues, the brain appears to respond to the *éR* signal GDF15 by triggering phenotypes that decrease the system's *EP*.[111] This includes visceral malaise,[112] nausea and fasting,[113] social isolation,[114] and depression.[115] Thus, physiological and behavioral phenotypes of excessive *éR* offer opportunities to examine how subcellular *éR* relates to human health.

To facilitate empirical testing of the ERP in various contexts and systems, we provide an ERP measurement toolkit. Summarized in Figure 8, this toolkit provides established and tentative approaches to selectively increase or decrease *EP* and f^2 in mitochondria, cells or tissues, and whole organisms. We also highlight an initial set of strategies to monitor *éR* at each level.

ERP AND HUMAN HEALTH

Several attempts have been made to define health both biologically and functionally, recognizing that health is more than the absence of disease.[116,117] Aiming to define health from first principles, we recently proposed that health is a field-like state emerging from the dynamic interplay of energy, communication, and structure within the organism, giving rise to robustness/resilience, plasticity, performance, and sustainability.[118] Extending this definition to the ERP, we propose that health is the ability to sustain life at an optimal level of *éR*. This then predicts that deviations in *éR*, quantified from either *éR* drivers or *éR* markers, should predict and/or track with changes in health status. On the other hand, healing may be defined as the dynamic process of achieving functional or structural adaptations that optimize *éR* dynamics. These proposed operationalizations provide a basis to develop heretofore missing quantitative metrics and to eventually track human health and healing processes over time.

This is supported by UK Biobank results in >52,000 individuals where the top circulating protein associated with prevalent and incident diabetes, cardiovascular, psychiatric, and other disorders is the *éR* marker GDF15.[119] Data S1 summarizes UK Biobank results[119] validating initial ERP predictions: (1) metabolic oversupply, immune profiles, and tissue damage markers expected to increase *EP* are linked to elevated *éR*; (2) *éR* is associated with metabolite profiles of reductive stress including lactate and alanine; and (3) elevated GDF15 is linked to *éR* phenotypes—experiences, behaviors, and physiology—including fatigue, pain, sedentarism, neuroticism, and suppression of growth/anabolic axes.

Considering non-pathological examples where *éR* is partitioned across the mammalian body, we suggest that pregnancy is an example where the ERP integrates heretofore disconnected processes. For reasons that remain unclear, the placenta expresses exceptionally high GDF15 levels (Figure 9). Based on evidence reviewed above, this may reflect how placental biology operates at high *éR*. This contention accounts for (1) why maternal blood GDF15 reaches levels >100-fold higher than in the non-pregnant state, driven by systemic GDF15 placental secretion[113,120]; (2) why the high *éR* of the placenta may be required to counterbalance or "insulate" the proliferative and low *éR* proliferative state of the fetus (as in an electrical circuit, low-energy-resistance components operate as energy sinks and must be counterbalanced by resistive elements), balancing each other to protect the mother[121,122]; and (3) why the placenta ages faster than other human tissues,[123,124] a predicted necessary consequence of the dissipative losses and pro-aging effects in tissues chronically operating at high-*éR* values.

LIMITATIONS AND FUTURE OUTLOOK

The ERP provides a predictive framework that can be applied to understand the behavior of energy in living systems; however, its full explanatory potential will remain untapped unless several outstanding limitations can be addressed. While we have provided initial definitions for key states and processes subsumed under three terms (*EP*, f^2, and *éR*), these should be reflexively informed by empirical data. Because falsifiable hypotheses can be generated with the ERP, experimentation will either confirm its validity in different contexts or provide guidance for its successive iterations. One general prediction is that *éR* is the vital parameter and that cells and organisms directly respond to changes in *éR*, rather than to *EP* or flux (f^2) parameters.

The existence of biophysical structures or processes that display features of energy capacitors would further develop the framework. In particular, the nature of resistance in biological circuits should be further characterized. Can any energy-transducing molecular structure act as a resistor? If so, what are the necessary and sufficient elements of a biological resistor? Further, it will be necessary to determine which factors, material or otherwise, contribute to the efficiency of the interaction between energy flux and particular biophysical constraints. When cells and tissues vary their resistance to energy flux, for example, with insulin resistance, is the effect on work and/or heat dissipation additive, multiplicative, or uniquely tied to a particular configuration? Despite the many parallel lines of evidence in support of the ERP discussed above, foundational experiments are needed to evaluate its validity.

One of the many benefits of paradigm shifts in our understanding of human health is the ability to reveal hidden connections between diseases and disorders that were previously unrecognized, until viewed through a new lens. The ERP may offer such a lens bringing into focus causal links between comorbidities, potentially revealing a common underlying etiology to diverse syndromes. Just as germ theory identified the pathogenic microorganism as the common factor in consumption (tuberculosis, caused by *M. tuberculosis*), lockjaw (trismus, tetanus caused by *C. tetani*), and Saint Vitus dance (Sydenham's chorea, caused by autoimmune response to *S. pyogenes*), new

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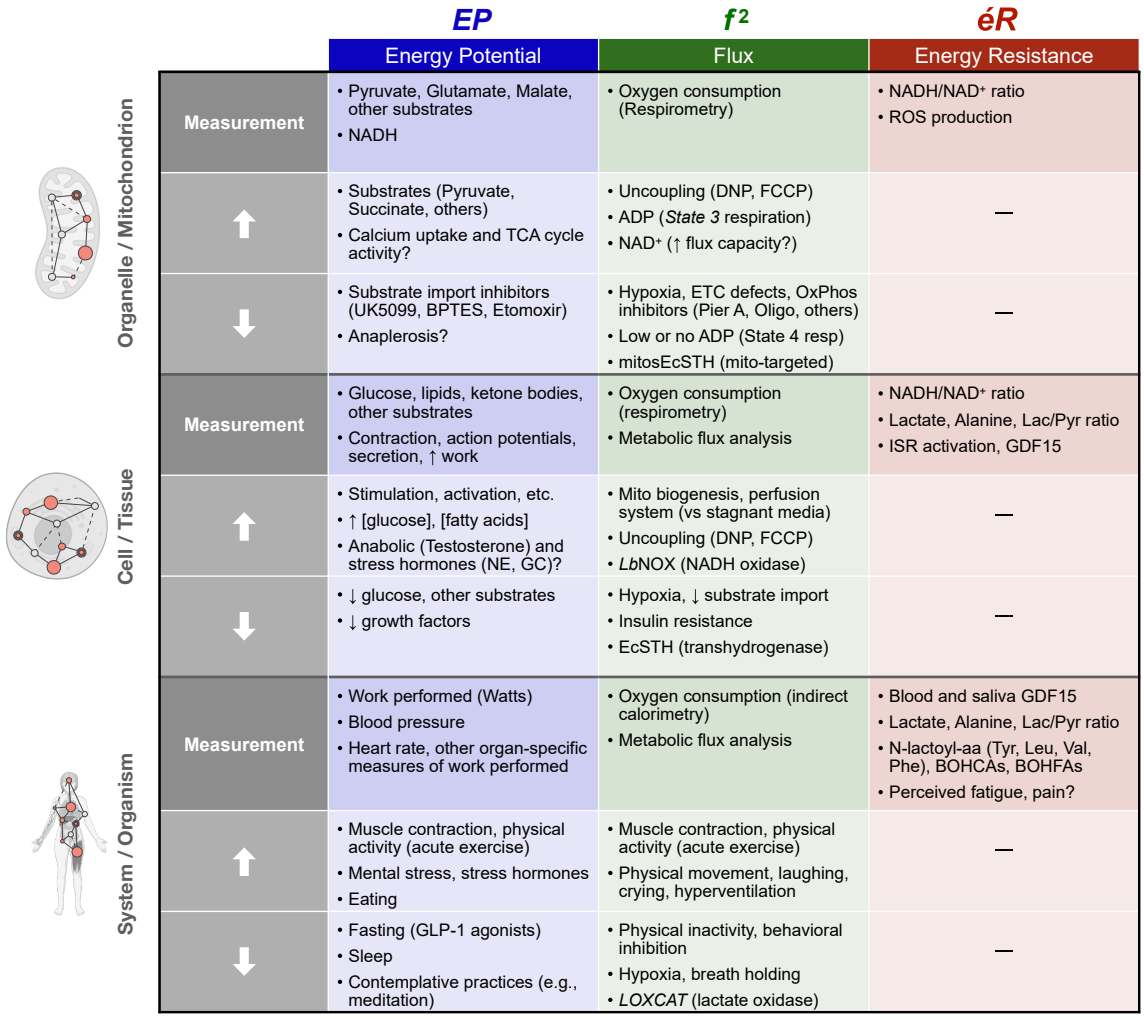

Figure 8. ERP measurement toolkit

Upward and downward arrows indicate strategies to acutely increase or decrease *EP* or f^2; applied chronically, some treatments can produce compensatory responses with the opposite effect. Energy resistance (*éR*) is the product of *EP* flowing through constrained flux, f^2, so we emphasize experimental approaches to manipulating *EP* and f^2 and to measuring all three variables at the organellar, cellular, and systemic level.

BOHCAs, β-hydroxy acylcarnitines[68]; BOHFAs, β-hydroxy fatty acids[68]; BPTES, Bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl)ethyl sulfide; Cort, cortisol or glucocorticoids; DNP, 2,4-dinitrophenol; etomoxir, carnitine palmitoyltransferase 1a (CPT1a) inhibitor (mitochondrial fatty acid uptake inhibitor); *EcSTH*, soluble transhydrogenase from *Escherichia coli*[102]; FCCP, carbonyl cyanide-p-trifluoromethoxyphenylhydrazone (proton uncoupler); GDF15, growth differentiation factor 15; GLP-1, glucagon-like peptide 1; Lac/Pyr ratio, lactate-to-pyruvate ratio; *LbNOX*, water-forming NADH oxidase from *Lactobacillus brevis*[103]; *LOXCAT*, bacterial lactate oxidase (LOX) and catalase (CAT) fusion protein[80]; mitoEcSTH, soluble transhydrogenase from *Escherichia coli* targeted to mitochondria[102]; NAD^+, oxidized nicotinamide adenine dinucleotide (reducing equivalent); NADH, reduced form of nicotinamide adenine dinucleotide (containing an electron to donate); N-lactoyl-aa (Tyr, Leu, Val, Phe), N-lactoyl-amino acids (tyrosine, leucine/isoleucine, valine, phenylalanine)[68]; NE, norepinephrine; Oligo, oligomycin A (ATP synthase inhibitor); Pier A, piericidin A (complex I inhibitor); TCA, tricarboxylic acid cycle (or Krebs cycle); UK5099, pyruvate carrier inhibitor.

perspectives on energy flux may similarly reveal hidden connections positioning excessive *éR* (or insufficient *éR*) as the Rosetta stone that underlies common, co-morbid clinical conditions.[125–127]

Such insights could motivate new approaches to diagnose and treat disease states using bioenergetic principles, in conjunction with molecular and pharmacological approaches.

Mechanistic insights into interventions and human experiences

Beyond a formal energetic perspective on disease states, the ERP may provide a fertile ground to critically examine the touted effects and healing potential of interventions and therapies that are widely used worldwide yet remain mechanistically elusive. These include transcranial magnetic stimulation[128]; meditation, breathwork, and other contemplative practices[47,129]; the use of psychedelic substances[130]; cryotherapy[131]; acupuncture[132]; and photobiomodulation,[133] among others. Rather than acting molecularly—like conventional pharmacotherapy—could these approaches operate by modulating *éR* directly? The ERP provides a quantitative framework to begin testing this possibility.

Similarly, the ERP offers an energy-informed testing ground to understand the mechanisms underlying the broad-ranging health effects of exercise,[134] sleep,[135] nutritional states including

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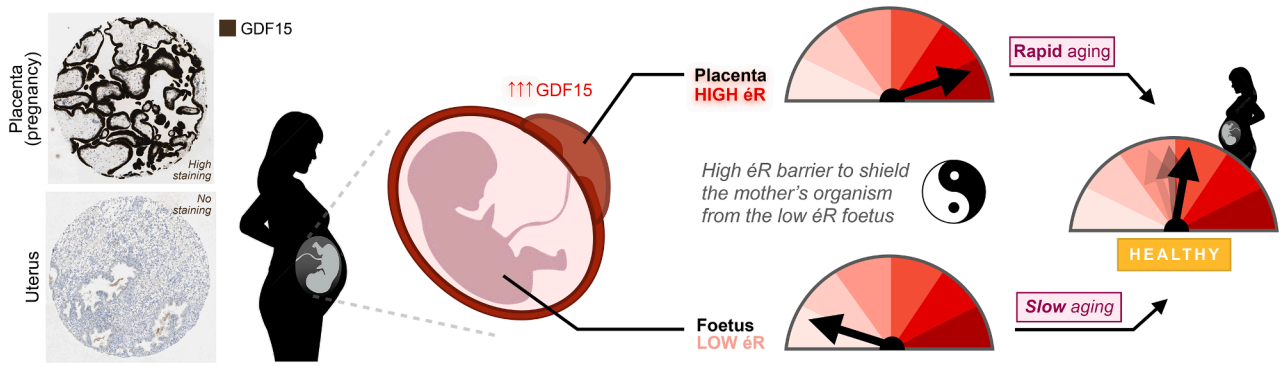

Figure 9. Possible distribution of energy resistance in the context of pregnancy

Left: the placenta syncytiotrophoblasts express unusually high levels of GDF15 protein—the highest reported of all human tissues in the Fantom RNA-seq dataset (immunohistochemistry, antibody HPA011191, https://www.proteinatlas.org/). According to the ERP, GDF15 is a marker of elevated energy resistance (*éR*), implying that the placenta operates at remarkably high *éR*, accounting for the >2 orders of magnitude increase in maternal blood GDF15 during pregnancy. On the other hand, the ERP predicts that the stemness and proliferative state during embryogenesis require an abnormally low *éR* environment. Right: from an energetic circuit perspective, excessively low *éR* is unsustainable at the whole-organism level since the low *éR* state of the fetus would operate as a sink (energy flows down the path of least resistance), uncontrollably drawing in organismal energy resources. The ERP suggests that the female body establishes a rapidly aging, signaling (through GDF15) high-*éR* barrier, balancing out the low *éR* state of its embryonic content in a Yin-Yang fashion, normalizing *éR* at the whole-organism level.

ketosis,[136–138] and social (dis)connection and loneliness associated with elevated GDF15[114] as possible *éR* regulators. If a causal connection between behavioral, nutritional, and psychosocial exposures and *éR* was substantiated, this could yield additional clarity into their underlying psychobiological processes that confer resilience or modify the rate of aging.[139,140] In the context of embodied cognition where experiences can arise through somatic biological processes,[25,141] could sudden increases in *éR* be felt directly, for example, as the pain during an ischemic myocardial infarction (causing a sudden rise in *éR*) or the burning sensation in skeletal muscle during strenuous exercise (increasing *EP* above flux capacity, thus acutely elevating *éR*)?

Should the ERP extend to the transformation of biochemical energy into mental energy (i.e., brain-body processes underlying cognitive processes), then the spectrum of human experiences including chronic pain and mental health disorders—which frequently exist without discernible structural or somatic alterations—could emerge as manifestations of excessive or insufficient *éR* involving mitochondria.[142,143] Initial evidence relating GDF15 to fatigue and psychosocial factors,[119,144] as well as brain reductive stress (elevated NADH/NAD^+) in schizophrenia and bipolar disorder,[145] supports this contention, calling for more research grounded into a quantitative energetic framework like the ERP.

Technical considerations

As our goal here was to focus on the transformation of energy within biological systems, we centered our perspective on this specific aspect, leaving related processes such as energy distribution and diffusion as promising avenues for future discussions. The relationship between *éR* and temperature likely plays a significant role in shaping energy diffusion rates within biological systems, potentially generating feedback effects that remain to be fully characterized. These effects may depend on factors such as the topology and density of resistors within the system, calling for localized measures of energy density across subcellular compartments, cells, and organs. Given the inordinate number of boundary conditions present within cells, from membranes to microtubules, developing *in silico* models with tunable complexity could provide a powerful tool for evaluating these dynamics on a larger scale.

Furthermore, while our focus remained on aerobic systems and mitochondria, there is ample opportunity for future work to investigate analogous mechanisms governing the role of resistance to energy flow as an engine of transformation in anaerobic organisms, including methanogens, archaea, and bacteria. Exploring how extreme environments such as high-pressure, low-temperature, and high-salinity conditions found on the ocean floor affect these parameters could also yield valuable insights into the behavior of energy in biology more generally.

The ERP extends beyond humans to other life forms. Organisms with broader thermal ranges may offer natural experiments in *éR* modulation, representing opportunities to link temperature, metabolism, and lifespan.[35,36,146,147] Within organisms, temperature gradients also could reflect meaningful *éR* distributions. For example, the brain's higher temperature[148] and limited regenerative capacity may signal elevated baseline *éR*, whereas the liver's cooler profile[149] could reflect lower *éR* and align with its greater regenerative capacity. In relation to diseases, elevated systemic or regional temperatures often accompany pathological processes, consistent with ERP predictions that higher *éR* contributes to disease. This includes neurodegeneration and dementia, which are linked to both elevated brain temperature[150] and blood GDF15.[151] Mitochondrial heat generation (some evidence suggests they operate at ~50°C[152,153]) and diurnal temperature variation[148] could suggest that rhythmic shifts in *éR* (not a fixed, optimal *éR*) are necessary to sustain health. This need for shifting between periods of higher and lower *éR* could be the basis of the universal requirement for sleep across breathing organisms.[154]

When evaluating energy dynamics in living systems across diverse environments, it is crucial to consider how timescales influence patterns of energy transformation. The ERP may offer a valuable framework for understanding the conditions under

which life emerges and health is sustained by defining the constraints necessary for energy flow and transformation under different environmental or psychobiological conditions. For example, different phases of human development and lifespan may feature different *éR* dynamics: it possibly exhibits the highest fluctuations in childhood[155] and during stressful life transitions,[75] becoming chronically elevated in the aging body where GDF15 increases exponentially.[140,156]

By shaping the balance between *EP* and *éR*, the ERP could help identify the physical parameters that pattern the organization of matter into life-sustaining systems. Applied to humans, this includes the emergence of the mind and conscious experiences that necessarily arise from the patterned flow of energy through the resistive and otherwise inert matrix of our biology.

CONCLUSIONS

The ERP extends the general energetic principle of the power law to biology, explaining how biological systems live, transform, and age because they offer fine-tuned resistance to energy flow. Living systems flux energy as electrons through their imperfect, carbon-based biological circuitry, constraining the available *EP* through a limited oxidative capacity to flux (f^2) energy, generating *éR*. Our initial proposal that the relation between these terms follows $EP = éR \cdot f^2$ (Figure 4) calls for empirical validation. While this formula serves as a foundational scaffold, a more complete equation will need to incorporate variables such as capacitance, elasticity, energy conversion efficiency, and system-scale constraints. We envision that the pressure testing the validity of specific ERP formulations will evolve iteratively alongside experimental and translational work in diverse models, and across the lifespan.

The ERP makes three core assumptions: (1) life cannot exist without *éR*, (2) organisms vary resistance to direct energy flux and compute information, and (3) organisms adapt and optimize fitness by producing lasting changes in *éR*. Integrating existing evidence under this simple energetic framework supports these assumptions and leads to several questions, some of which are discussed above, many of which remain to be tested.

The ERP explains why energy expenditure or mitochondrial oxidative capacity alone are insufficient to fully account for health dynamics and longevity: because one can compensate for a change in the other. Positioning *éR* as the vital parameter that is monitored and regulated sheds light on the quantitative interdependency of energy expenditure and mitochondrial biology and other domains relevant to health and healing.

Energy is the largely missing dimension of biomedicine. The ERP offers a general, testable framework to bridge physics and biology and to understand the role of energy across various domains of life, including human health, disease, and the experiences that define the human condition.

ACKNOWLEDGMENTS

We are grateful to Judyann McNamara for foundational discussions that inspired the ERP. We thank Janell Smith, Jack Devine, Cynthia Liu, David Shire, Evan Shaulson, Christopher Kempes, Alan Cohen, Eugene Mosharov, Michael Levin, Caroline Trumpff, Vanessa Giardino, Mattia Bonzanni, Martin Grube, Carlo Ventura, Joseph McCard, Iain George Johnston, and members of the Mitochondrial Psychobiology Group and the Murugan Lab for helpful discussions and input. We gratefully acknowledge support from NIH grants R01MH119336, R01MH122706, R01AG066828, RF1AG076821, R01AG086764, and R01MH137190; the Wharton Fund; and Baszucki Group to M.P. and the National Sciences and Engineering Research Council of Canada Discovery grant RGPIN-2021-03783 to N.J.M.

AUTHOR CONTRIBUTIONS

M.P. and N.J.M. wrote the manuscript. M.P. prepared the figures.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.cmet.2025.09.002.

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