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Review

Mitochondrial and metabolic features of salugenesis and the healing cycle

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ABSTRACT

Pathogenesis and salugenesis are the first and second stages of the two-stage problem of disease production and health recovery. Salugenesis is the automatic, evolutionarily conserved, ontogenetic sequence of molecular, cellular, organ system, and behavioral changes that is used by living systems to heal. It is a whole-body process that begins with mitochondria and the cell. The stages of salugenesis define a circle that is energy- and resource-consuming, genetically programmed, and environmentally responsive. Energy and metabolic resources are provided by mitochondrial and metabolic transformations that drive the cell danger response (CDR) and create the three phases of the healing cycle: Phase 1—Inflammation, Phase 2—Proliferation, and Phase 3—Differentiation. Each phase requires a different mitochondrial phenotype. Without different mitochondria there can be no healing. The rise and fall of extracellular ATP (eATP) signaling is a key driver of the mitochondrial and metabolic reprogramming required to progress through the healing cycle. Sphingolipid and cholesterol-enriched membrane lipid rafts act as rheostats for tuning cellular sensitivity to purinergic signaling. Abnormal persistence of any phase of the CDR inhibits the healing cycle, creates dysfunctional cellular mosaics, causes the symptoms of chronic disease, and accelerates the process of aging. New research reframes the rising tide of chronic disease around the world as a systems problem caused by the combined action of pathogenic triggers and anthropogenic factors that interfere with the mitochondrial functions needed for healing. Once chronic pain, disability, or disease is established, salugenesis-based therapies will start where pathogenesis-based therapies end.

PART 1—Dynamics

1. Introduction

Great strides in medicine have been made since World War II by focusing on the triggers and risk factors of disease. This pathogenesis-based approach has been particularly effective in developing treatments for acute illnesses caused by physical or psychological trauma, infection, vitamin deficiencies, and poisoning, and for handling the acute complications of chronic illness (Naviaux, 2019b). While effective for acute illnesses and acute complications that come and go over periods of time up to about 6 months, pathogenesis-based methods have not been successful in producing cures for chronic illnesses. In the last 70 years, not a single chronic illness is curable using current medical paradigms unless it has a cause that can be bypassed, killed, burned out, or cut out. When cures are achieved, they rely on recovery by spontaneous healing—an essential process that operates silently in the background and is still poorly understood. For example, antibiotics can cure a pneumococcal pneumonia and a stent can reopen an acutely occluded coronary artery, but active healing is required after the intervention to repair the damaged lung and heart. In most cases, pathogenesis-based drugs like insulin for diabetes and statins for dyslipidemia must be taken for life because the root cause of the chronic symptoms is not changed by treatment.

Medicine does not have a word to stand in counterpoint to *pathogenesis* to describe the scientific study of the inborn molecular mechanisms used to heal and restore health after injury. Based on a root word derived from *Salus*, the Roman goddess of personal health and welfare, the word *salugenesis* was coined to frame the process and steps that must be accomplished if an organism is to heal from any injury or stress. Pathogenesis creates the damage. Salugenesis effects the repairs. As

Abbreviations: CDR, cell danger response; M0, multipotential mitochondria; M1, pro-inflammatory mitochondria; M2, anti-inflammatory mitochondria.

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such, pathogenesis and salugenesis are non-congruent pathways that are regulated by different control networks. Genetic and environmental factors can increase or decrease the ability of biological systems to heal (Graphical abstract). Rapidly changing patterns in the incidence and prevalence of chronic disease are being caused in part by rapid shifts in the chemistry, pollution, climate, and microbial diversity in the ecosystems around us. Children are particularly hard hit by these exposures that begin even before birth (Perera and Nadeau, 2022). New research approaches are needed to explore the impact of environmental factors on the governing dynamics of the healing cycle, and to begin to address several outstanding questions (see Box 1).

2. Silos and roots of chronic disease

Each chronic disease can be studied in isolation as a silo. When the methods of systems biology are applied across several different chronic disorders, their similarities are brought into focus and a common root emerges. This shared root is the failure to heal completely (Figs. 1 and 2). Chronic illnesses today include many of the disorders for which modern medicine has developed symptomatic treatments but has been unable to cure. These include diabetes, metabolic syndromes, child neurodevelopmental disorders like autism spectrum disorder (ASD), adult neurodegenerative disorders like Alzheimer, Parkinson, and amyotrophic lateral sclerosis (ALS), allergies and autoimmune disorders, post-traumatic stress disorder (PTSD), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), post-Lyme, long-COVID, and other post-infectious multisystem chronic fatigue syndromes, major depressive disorder (MDD), bipolar disorder (BD), suicidal ideation, schizophrenia, chronic pain, addiction, heart disease, kidney disease, cancer, and many others. Each chronic illness can be reframed as the result of the abnormal persistence of a normal phase of the healing cycle (Table 1). Once the pathogenic trigger has been treated or removed, *chronic disease persists because healing is incomplete*. This new perspective has important implications for treatment. Abnormal persistence of a normal phase of healing cannot be cured using pathogenesis-based treatments. If healing can be rebooted or unblocked after it has been derailed, cures of disorders once thought incurable may one day be possible.

The classical, pathogenesis-based perspective of disease has led to many successes that have been chronicled over the past 5000 years in the *First Book of Medicine* (Fig. 2). However, this classical perspective makes a critical assumption—that once a pathogenic trigger has been removed, the living system will heal spontaneously. This assumption has been failing progressively since the beginning of the Anthropocene era in the early 1950 s (Waters et al., 2016). Since the 1980 s, the prevalence of chronic illness and years lived with disability have climbed (Atella et al., 2019; Diseases and Injuries, 2020). The co-occurrence of multiple chronic conditions has increased (Hajat and Stein, 2018), and the connections between environmental stress (Ngaruiya et al., 2022), infectious diseases, post-infection syndromes like long-COVID (Palmer et al., 2020), and common non-communicable chronic diseases (NCDs) have become clear (Coates et al., 2020). Injury triggers an exit from the health cycle, engages the healing cycle, and activates a patterned sequence of healing that occurs in three phases (Fig. 2). Viewed in this way, many chronic diseases are revealed to be avatars of the same biology. After a pathogenic trigger has been removed, chronic disease will not occur unless disruptions in the healing cycle inhibit or block recovery.

The phrase *First Book of Medicine* is used as a metaphor to describe the corpus of medical knowledge accumulated over the past 5000 years of written history. The contents of this book have focused on the study and care of *acute* injuries and infections, and chronic disorders viewed through the lens of pathogenesis. The collection of medical knowledge about the cause and treatment of complex *chronic* disorders studied through the lens of salugenesis will comprise the pages of a *Second Book of Medicine* (Fig. 2). Salugenesis-based treatments will begin where pathogenesis-based treatments end.

Box 1
Outstanding questions about healing, health, and chronic illness.

1. Is tissue defense, repair, and remodeling possible if mitochondrial fusion-fission dynamics, or mitochondrial protein, or DNA synthesis are arrested?

2. Can the cell-system phenotypes of inflammation (M1), multipotential proliferation (M0), or differentiation and memory (M2) be accomplished without changes in the mitochondria-cell system phenotypes that shift the corresponding bioenergetic programs from glycolysis, through aerobic glycolysis, to oxidative phosphorylation?

3. Can new experimental models be developed that reproducibly capture the programmatic changes in the dynamical states—the *process*—of mitochondrial and cellular transitions that are needed to heal after injury or illness?

4. Can a new class of therapeutics be developed that target the governing dynamics of the healing cycle, facilitate the transitions between phases, and increase the number of cells that successfully complete the cycle after injury?

5. Can tissue dysfunction associated with chronic illness or aging be improved by interventions that 1) recover arrested cells and stimulate them to complete their path through the healing cycle, or 2) delete senescent cells with senolytics?

6. Are the mental health and physical benefits of exercise dependent on eATP release, and its conversion to eADP, eAMP, and eAdenosine, for normal purinergic signaling?

7. What is the role of eATP signaling-associated inflammation in complex neurodevelopmental and neurodegenerative disorders like autism spectrum disorder (ASD), amyotrophic lateral sclerosis (ALS), and Alzheimer dementia?

8. What is the role of eATP signaling-associated inflammation in complex mental health phenotypes like chronic pain, post-traumatic stress disorder (PTSD), gun and domestic violence, anxiety, and depression with suicidal ideation?

9. Can new antipurinergic drugs and pannexin 1 channel inhibitors reduce the most disabling symptoms of ASD, ALS, chronic pain, PTSD, Long-COVID, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and post-Lyme syndrome?

10. Can the rising tide of chronic illness observed in the past 50 years be slowed or turned back by international efforts to curb the release of pollutants from household, agricultural, medical, veterinary, and industrial sources?

11. Can biological aging be slowed and the healthspan increased if incomplete healing and the resulting dysfunctional cellular mosaics are reduced by decreasing the number of cells lost or arrested after each turn of the healing cycle?

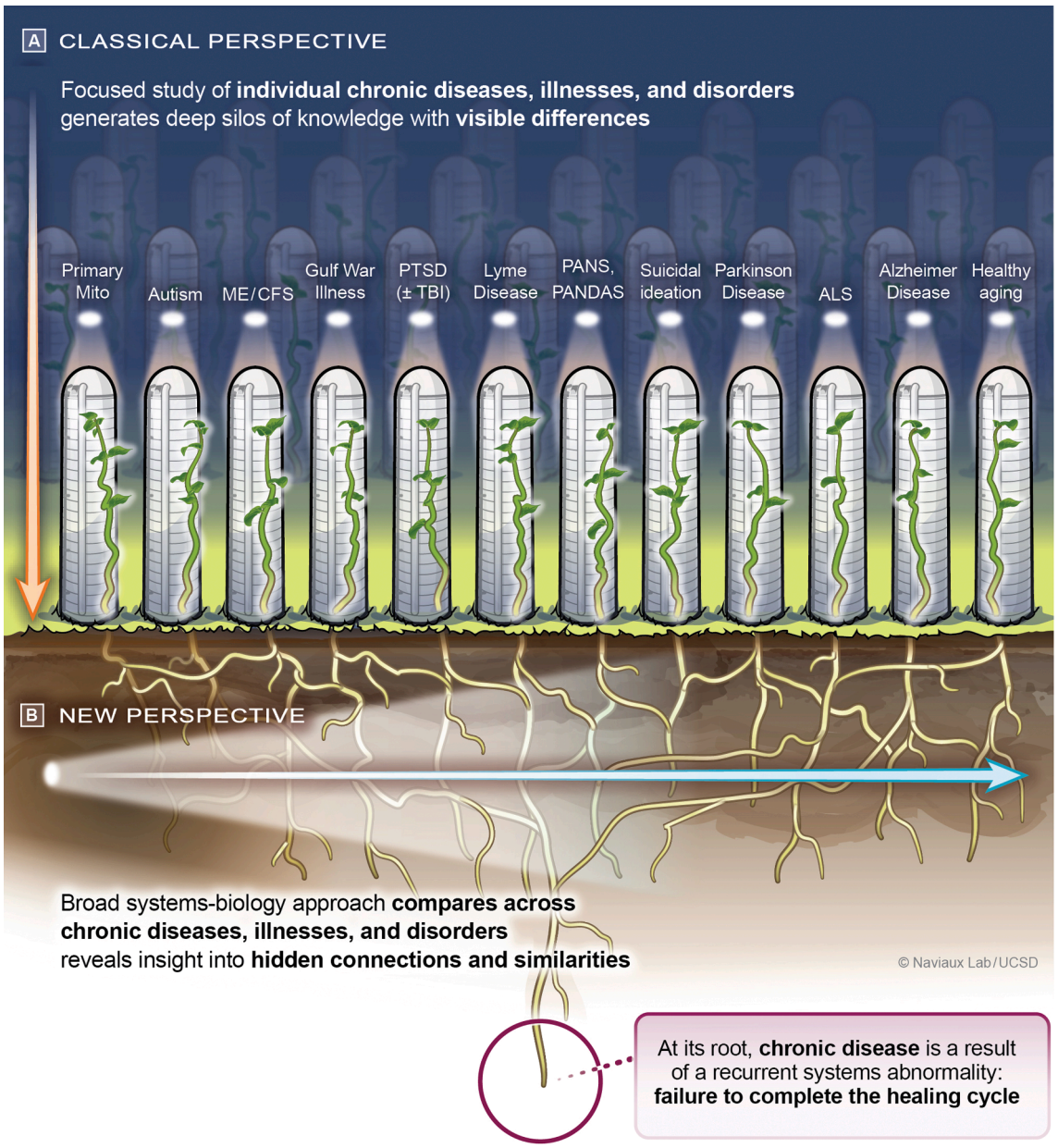

Fig. 1. Visible silos and hidden roots of chronic illness. Pathogenesis focuses on the differences between disorders. Salugenesis emphasizes the similarities. The shared root of many complex chronic disorders is incomplete healing. Incomplete healing leads to abnormalities in mitochondrial fusion-fission dynamics, dysfunctional cellular mosaics, and the symptoms of chronic disease. **Abbreviations:** Primary mito, primary mitochondrial disease; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; PTSD ± TBI, post-traumatic stress disorder ± traumatic brain injury; PANS, pediatric acute-onset neuropsychiatric syndrome; PANDAS, pediatric acute neurologic disorder associated with streptococcal infection; ALS, amyotrophic lateral sclerosis.

3. Engineering versus biological logic

The logic of engineering is used to solve problems in non-living systems. Engineering logic is inorganic, deterministic, and well-adapted to solving problems in pathogenesis. It is used so commonly in science and medicine that other ways of solving problems seem foreign by comparison. Biological logic in contrast, has evolved over millions of years to solve problems in living systems. Biological logic is organic, probabilistic, and well-adapted to solving problems caused by disturbances in salugenesis. The logic of engineering is *extrinsic* to the system in need of repair. In contrast to engineering logic, biological logic is *intrinsic*. Biological logic enables every living thing to heal from both predictable injuries like cuts, scrapes, and the common cold, and from unpredictable injuries produced by plagues and pollution that have never been encountered before.

Building a deep knowledge of the biological logic of healing has become increasingly urgent. Hans Selye pointed out over 80 years ago that living systems respond to stress in a stereotyped way, no matter whether the stress was physical, chemical, or psychological (Selye, 1998). This stereotyped response to stress has been studied on several different levels. Genetic, metabolic, microbiome, autonomic, and neuroendocrine changes are used to mediate this coordinated response of living systems to stress. Many investigators have contributed to this growing awareness (Carter et al., 2008; Cole, 2019; Kolacz et al., 2021). Others have pointed out that despite the clear societal goal of health and healthcare, virtually all of biomedical research is focused on "disease-care", and pathogenesis (Picard, 2022). In keeping with this shift away from an exclusive focus on disease biology, the hallmarks of health have recently been reviewed (Lopez-Otin and Kroemer, 2021). The systematic application of multi-omics methods has given rise to a new

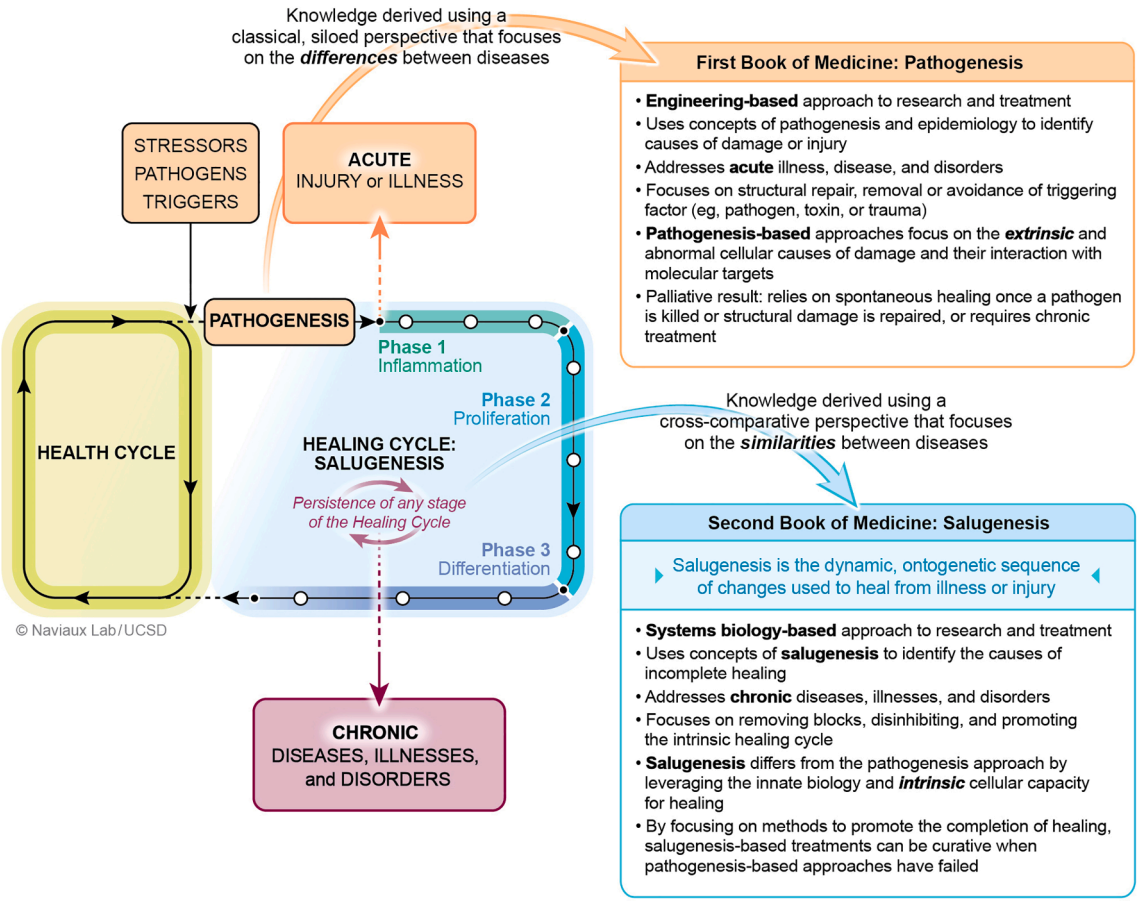

Fig. 2. Pathogenesis, salugenesis, and the evolution of the healing cycle. Pathogenesis and salugenesis are the first and second stages of the two-stage problem of disease production and health recovery. The Health Cycle is illustrated on the left. The Healing Cycle and its phases are illustrated on the right. Salugenesis starts where pathogenesis ends. Abnormal persistence of any phase of the healing cycle leads to chronic disease. The *First Book of Medicine* uses the principles of pathogenesis to develop effective treatments for acute illness. The *Second Book of Medicine* will add the principles of salugenesis to develop effective treatments for chronic illness.

field of precision medicine called phenomics that supports the emerging concept that the maintenance of health is an active process that is not yet well understood (Hood et al., 2022). The new study of salugenesis creates a systems framework for connecting each of these observations.

4. Hierarchical evolution and layered control

Biological systems are organized and regulated hierarchically. As each new system is added to older systems over evolutionary time, the newer systems are layered over, and regulate the older subsystems (Fig. 3). Like modern computer operating systems, newly evolved systems in biology must be backward compatible with older systems. This nested organization is responsible for what the 19th century neurologist John Hughlings Jackson called dissolution (Gillett and Franz, 2013). If a more recently evolved system is damaged, or the older subsystem is cut off from the newer system, the regulation by the newer system dissolves, and the function of the more ancient system is disinhibited and becomes manifest. Cuts, broken bones, obstructed arteries, and infections result in breaks and reductions in connections to the brain and heart because nerve fibers and capillaries are broken or compromised by injury. When a cell in a tissue becomes damaged or cut off from more recently evolved long-distance control systems like autonomic projections from the vagus nerve, cell-autonomous defense systems are activated, extracellular ATP (eATP) is released, and the healing cycle is initiated (Fig. 4).

To put the cell danger response (CDR) and the healing cycle into an evolutionary perspective, glycolysis used for inflammation in Phase 1 of the CDR evolved in the Archean, about 3.5 billion years ago (Fig. 3). Aerobic glycolysis and cell-autonomous oxidative phosphorylation used for proliferation in Phase 2 required the development of the first mitochondria, which occurred with the origin of the first eukaryotic cells in the Proterozoic about 1.5 BYA (Gabaldon, 2021). The ability to remotely regulate and coordinate mitochondrial ATP production in different tissues is needed for differentiation in Phase 3. Remote coordination of mitochondria and metabolism in peripheral organs was achieved with the evolution of the first enteric and central nervous systems in the Cambrian, about 0.54 BYA (Fig. 3). This layered evolutionary sequence has placed mitochondria and the hundreds of metabolic reactions they perform at the center of a mitochondrial information processing system (MIPS) used for sensing, integration, signaling, and adaptation to environmental and genetic stress (Picard and Shirihai, 2022). By shifting control from remote (long-distance), to local (short-distance) signals during times of stress, the activation of the cell danger response allows cell metabolism to be controlled by direct assessment of local, boots-on-the-ground conditions. This permits local injury to be contained and addressed without immediately changing whole-body metabolism. If the threat or damage is more extensive, then whole body metabolism can be changed in proportion to the threat to facilitate the healing cycle. If chronic, this shift to abnormal persistence of one or more phases of the healing cycle disrupts circadian and seasonal cycles, fragments sleep, derails child development, and accelerates aging (Graphical abstract).

5. The health and healing cycles

The health and healing cycles are dynamic circles that have a

Table 1
Provisional classification of chronic diseases caused by incomplete healing and persistence of the cell danger response—the pluricausal diseases.

CDR Phase 1 Disorders— Inflammation	CDR Phase 2 Disorders— Proliferation	CDR Phase 3 Disorders— Differentiation	Hypometabolic Survival States (HSS) and Post-infection Disorders
Stereotyped sickness behavior	Dyslipidemia, hypercholesterolemia	Autism spectrum disorder (ASD)	Myalgic Encephalomyelitis
Multisystem inflammatory	Metabolic syndrome	Post-traumatic stress disorder (PTSD), suicidal ideation	Chronic Fatigue Syndrome
syndrome in children (MIS-C)	Hyperuricemia	Fibromyalgia, chronic pain	(ME/CFS)
Systemic Inflammatory Response	Insulin resistance, diabetes	syndromes, allodynia	Post-treatment Lyme disease
Syndromes (SIRS)	Diabetic retinopathy	Hyperkatifeia, opioid addiction and	syndrome (PTLDS)
Multiple Organ Dysfunction	Diabetic kidney disease	other addictive disorders	Post-coccidiomycosis
Syndrome (MODS)	Neovascularization, angiogenesis	Neuropathic pain syndromes	multisystem fatigue syndrome
Septic shock, pyroptosis	Hypertension, heart disease	Complex regional pain syndromes	Post-COVID multisystem fatigue
Acute Respiratory Distress	Peripheral vascular disease	Epilepsy	syndromes (e.g., PASC)
Syndrome (ARDS)	Cerebral vascular disease	Involuntary repetitive behaviors,	Pediatric post-chemotherapy
Autoinflammatory disorders	Inflammatory bowel disease	tics, chorea, or athetosis	frailty and multisystem fatigue
Interstitial cystitis and nephritis	(Crohn's, Ulcerative colitis)	Obsessive compulsive disorder	syndromes
Allergies, asthma, atopy	Non-alcoholic fatty liver disease	(OCD)	Post-influenza neurasthenia
Mast cell activation syndromes (MCAS), open angle glaucoma	(NAFLD)	Generalized anxiety disorder (GAD)	Post-viral myasthenia
Chronic infections: chlamydia,	Non-alcoholic steatohepatitis	Major depressive disorder (MDD)	
listeriosis, toxoplasmosis,	(NASH), Cirrhosis	Bipolar disorder, Migraines	**Hypometabolic survival states**
bartonellosis, syphilis,	Idiopathic pulmonary fibrosis	New daily persistent headaches	Caloric restriction-associated
helicobacter, Neisseria, vibrio	Benign prostatic hyperplasia	POTS, PANS, PANDAS	longevity
cholerae, tuberculosis, non-	Scarring, keloid formation	Schizophrenia, acute psychosis	Hibernation, torpor, diapause,
tuberculous mycobacterial	Subacute spinal cord injury	Parkinson, Alzheimer	dauer, estivation, brumation
infections, leprosy, Lyme,	Dermal vasculitis	Multiple sclerosis, Tourette's	The mammalian diving reflex
typhoid, malaria, leishmaniasis,	Temporal arteritis	Dystonia syndromes	Cryptobiosis, tardigrade tun
onchocerciasis, schistosomiasis	Kawasaki disease coronary arteritis	Amyotrophic lateral sclerosis (ALS)	Invertebrate dormant cysts
trypanosomiasis, filariasis, tinea	Lupus, Hashimoto's thyroiditis	Chronic traumatic encephalopathy	Plant seed embryo formation
infections, histoplasmosis,	Psoriasis, eczema	Traumatic brain injury (TBI)	Bacterial persister cells, and
coccidiomycosis, aspergillosis,	Autoantibodies to intrinsic factor	Post-stroke syndromes	spore formation
mucocutaneous candidiasis,	Rheumatoid arthritis	Wakeful delta and theta wave	Viral particle formation
sporotrichosis, cryptococcosis	Pemphigus, Bechet's	power abnormalities (EEG)	
Sarcoidosis, Chronic	Scleroderma, Sjogren's	Non-valvular atrial fibrillation	
granulomatous disease	Polymyalgia rheumatica	Osteoarthritis, macular degeneration	
Gulf War Illness (GWI)	Ankylosing spondylitis	Presbyopia, presbycusis	
Chronic inflammatory symptoms of	Osteoporosis	Accelerated aging symptoms of	
long-term spaceflight	Cancers and Leukemias	long-term spaceflight	
	Cancer chronic pain syndromes		

CDR Phase 1 Ecosystem disorders
Coral reef fungal infections (e.g., *Aspergillus*), Coral bleaching disorder (e.g., *Vibrio*), Shrimp black gill disease (*Hyalophysa*), Microsporidial gill disease in fish, Colony collapse disorder in honeybees (e.g., varroa mites, *Nosema*), White nose disease in bats (*Geomycosis*), Chytridiomycosis in frogs and salamanders, Potato plague (*Phytophthera*), Sudden Oak Death (*Phytophthera*), Tea leaf blister blight (*Exobasidium*), Coffee rust (*Hemileia*), Cacao tree witches' broom fungus (*Moniliophthora*), White pine blister rust (*Cronartium)*, Sudden Aspen Decline (*Cytospora*)

Abbreviations: CDR, cell danger response; HSS, hypometabolic survival states and disorders; POTS, postural orthostatic tachycardia syndrome; PANS, pediatric acute neuropsychiatric syndrome; PANDAS, pediatric autoimmune neuropsychiatric disorder associated with streptococcus infection.

beginning, middle, and end (Fig. 4A and B). These circles are experienced throughout life during health, illness, and recovery from common infections like the common cold, or injuries like cuts and scrapes. The same phases are used to recover from more severe injuries like myocardial infarctions, fractures, strokes, traumatic brain injuries, poisonings, surgical procedures, and from psychological traumas. The health and healing cycles are transactional—they proceed by exchanging information with other cells and the environment, and by processing this information before determining the magnitude and character of the cellular response. The healing cycle begins with the detection of stress or injury, and ends with recovery, adaptation, and hormesis. Hormesis is built from metabolic and cellular memory after stress. Mitochondrial and cellular (mitocellular) hormesis increases functional reserve capacity, improves future cellular and organismal responses to new exposures, and improves resilience (Calabrese, 2018; Fischer and Ristow, 2020).

5.1. The cardinal elements of health

The six cardinal elements of the health cycle are 1) wakeful activity, 2) nutrient intake, 3) waste and toxin removal, 4) social connection, 5) nature connection, and 6) restorative sleep (Fig. 4). Absence of, or abnormalities in, any of the cardinal elements of the health cycle can lead to pluricausal disease (Table 1). The term "pluricausal" was first used by Hans Selye to describe the clinical fact that the same chronic disorder can have a different cause in different individuals (Selye, 1973).

5.2. The phases of the cell danger response drive the healing cycle

Mitochondria are the prime sentinels and central processing units in eukaryotic cells (Picard and Shirihai, 2022). Mitochondria continuously monitor and respond to the chemistry and physical conditions within and around the cell, regulate the response to injury and infection, and drive progression through the sequential stages of healing. As such, mitochondria are the cellular canaries in the coal mine—the early warning system that determine the nature and location of the problem, and when to sound the alarm. In addition, mitochondria participate in making the early decisions about how to put out the fire. The cell danger response (CDR) is both the alarm, and the proportional response to threat. The CDR is divided into three metabolically distinct phases that make up the healing cycle (Naviaux, 2019b) (Figs. 2 and 4). Briefly, the phases of the CDR are named for a prominent function of each: Phase 1, Inflammation; Phase 2, Proliferation; and Phase 3, Differentiation. Phase 1 is pro-inflammatory and supports hemostasis, containment,

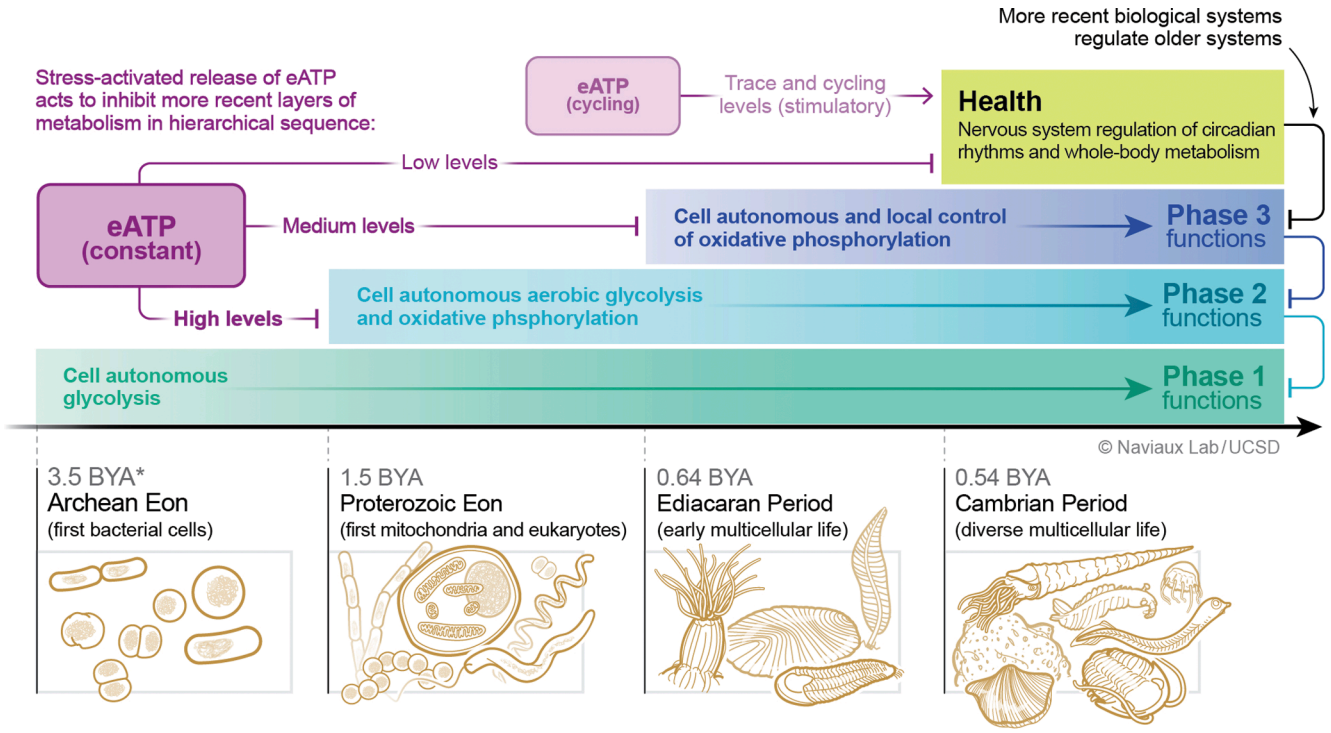

Fig. 3. Hierarchical evolution and layered control of the phases of the healing cycle. All living cells evolved over time by the addition of new layers of function over the old. The three phases of the healing cycle and multicellular cell danger response (CDR) are indicated as Phases 1, 2, and 3 in the figure. Extracellular ATP (eATP) serves as a universal regulator of each layer. After the evolution of multicellularity, single cells within tissues became responsive to long-distance coordination by neural and neuroendocrine systems. When cells in tissues become disconnected, stressed, or injured, local eATP release and other danger signals inhibit receptivity to long-distance signaling, forcing a default to local signaling and the earlier phases of the healing cycle until the damage is contained and repaired. Resilient health can only be restored after local damage is repaired, the healing cycle is completed, and brain-body coordination of mitochondrial metabolism is restored. **Abbreviations**: BYA, billion (10^9) years ago. *All dates are estimates based on the fossil record.

phagocytosis, and innate immunity. Phase 2 supports proliferation, migration, angiogenesis, adaptive immunity, stem cell recruitment, and regeneration. Phase 3 is anti-inflammatory and pro-resolving and supports differentiation, remodeling, recovery, hormesis, and long-term memory. These three, sequentially ordered phases of healing are inextricably linked to changes in mitochondrial morphology and function (Chen et al., 2018) (Table 2, Fig. 5). The sequence of metabolic progression during the healing cycle reflects the evolutionary origin of the biochemical pathways (Fig. 3). Mitochondria create the thermodynamic gradients of pH, voltage, energy, and materials between organelles, and between cells within tissues that drive the dissipative gradients (Prigogine and Nicolis, 1971) and hierarchical control systems used by life to survive and adapt to changing environmental conditions. Healing cannot be completed without the mitochondrial and metabolic reprogramming that drives the cycle forward to recovery and health (Figs. 4 and 5).

5.3. *Pleiotropy and pleiogenesis*

Systems biology is forcing a paradigm shift in the study of complex disease. In 70 years of study since the discovery of the structure of DNA in 1953, multi-omics and advanced epidemiologic studies have found that most complex diseases are pluricausal, and most causal factors are pleiotropic. However, to develop an effective treatment plan for a specific patient, the specific cause of the individual's symptoms must be diagnosed. Accurate diagnosis provides a mechanistic foundation for treatment. It also provides answers and psychological closure. An accurate diagnosis provides hope for a patient who may have been struggling with puzzling symptoms for months without knowing the cause. To achieve an accurate diagnosis, the list of *possible* causes in the population must be reduced to the *actual* risk factors relevant to the individual. The history of exposures, current symptoms, and past response to therapy becomes the basis of a differential diagnosis—a list of possible diseases that can explain the symptoms of the person seeking care. A differential diagnosis implicitly acknowledges the biological fact that *the same disease can be caused by different things in different people*. Only the single-gene forms of complex disease can be said to have a single cause in a single patient. This typically accounts for just 5-10 % of complex disorders, and no single gene accounts for more than 1-2 %. All other, non-single-gene, complex diseases are pluricausal, i.e., the same disease can be caused by different pathogenic factors. Yet, except in pandemics and other public health disasters, no single cause is responsible for more than a few percent of any given complex disease. Pluricausality—the phenomenon of multiple causes—is also known as pleiogenesis. Individualized factors like the critical windows of child developmental exposure, the order of exposure to different triggers, and recovery time elapsed between two injuries or infections, genomic vulnerability and resilience, and many other lifestyle, microbial, and chemical environmental factors combine to define the personalized landscape of risk and chain of causality that leads to complex chronic illness.

Reciprocally, the same contributing lifestyle factor, stressor, trauma, chemical exposure, infectious agent, or gene can be a risk factor for many different pluricausal disorders. Each of these causal factors is pleiotropic, i.e., they can produce several different illnesses in a population during and after an exposure. For example, tobacco, poor nutrition, excess alcohol, lack of exercise, and environmental chemical exposures are risk factors for heart disease, diabetes, cancer, and mental health disorders (Stein et al., 2019). In another example, mutations in the gene TDP43 can cause either amyotrophic lateral sclerosis (ALS) without dementia or can cause early onset frontotemporal dementia (FTD) (Kirola et al., 2022). Even well-known infectious agents are

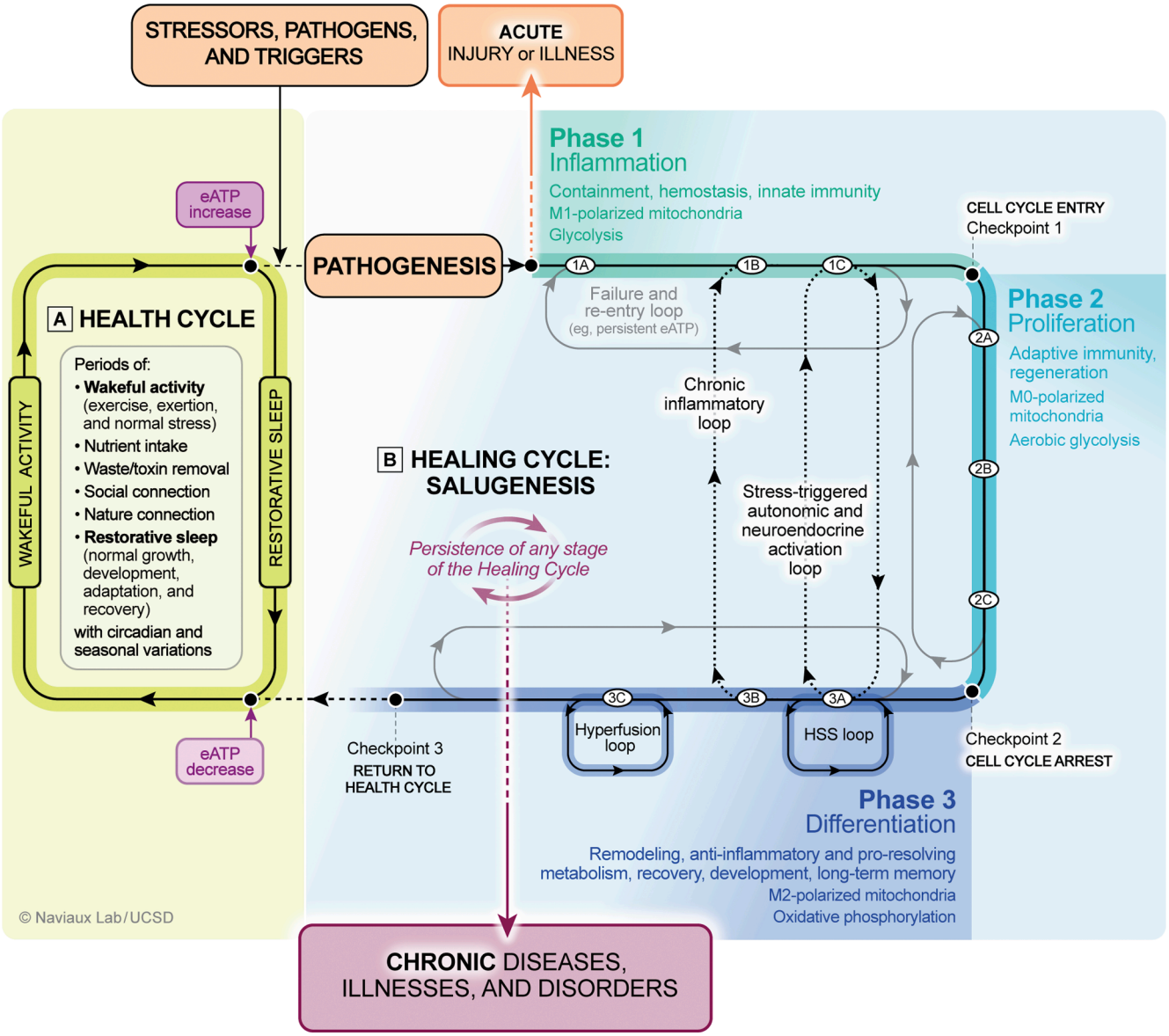

Fig. 4. Functions and metabolic features of the health and healing cycles. A. The Health Cycle. The cardinal elements of the health cycle include restorative sleep, wakeful activity, nutrient intake, waste and toxin removal, social connection, and nature connection. Regular engagement of these elements is required for resilient health. Extracellular ATP (eATP) release is triggered by normal daily activities, social interaction, learning, and exercise. eATP metabolism to adenosine is then used to initiate sleep. Distant autonomic and neuroendocrine signals from the brain directly regulate mitochondrial metabolism in peripheral tissues, enabling the programmed changes required for circadian and seasonal cycles. **B. The Healing Cycle.** Each phase of the healing cycle and cell danger response (CDR) has a beginning (A), middle (B), and end (C). Checkpoints that act as probability gates separate the phases. Abnormal persistence of any of the phases of the healing cycle causes symptoms of chronic disease. Glycolytic energy metabolism is used to initiate inflammation in CDR Phase 1. Aerobic glycolysis and Warburg metabolism are used to support cell proliferation in Phase 2. Senescence and fibrosis/gliosis are dead-end offshoots from Phase 2. Cell-autonomous oxidative phosphorylation is used to support cell and tissue differentiation in Phase 3. Health* is entered as cells and mitochondria become responsive to remote, systemic coordination signals from the brain and neuroendocrine systems, and neighboring cells specialize and develop complementary metabolic phenotypes. Hypometabolic survival states (HSS) are offshoots of Phase 3A. In the case of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), long-COVID, and related human forms of HSS's, bouts of physical and emotional stress can lead to setbacks called 'crashes' and post-exertional malaise (PEM) that result from a transient shift from Phase 3A to more glycolytic metabolism and inflammation in Phase 1C of the healing cycle caused by autonomic and neuroendocrine activation. Phase 2 can be bypassed when no cells are lost during the transient stress. Upon rest a recovery, tissue and organs can return directly from Phase 1C to the HSS loop in Phase 3A. A mitochondrial hyperfusion loop can occur in Phases 3A-C. Mitochondrial hyperfusion leads to hypersensitivity to ATP signaling, abnormalities in innate immunity, neutrophil and natural killer cell dysfunction, neurologic symptoms, latent DNA virus reactivation, endogenous retrovirus activation, misfolded protein aggregates, and a predisposition to apoptosis, ferroptosis, and other cell death pathways. Restoration of long-distance brain-body signal transduction at the end of Phase 3 of the Healing Cycle permits local eATP levels to return to normal, decreases the hypersensitivity to purinergic signaling, enables normal organ function to return, and marks the re-entry to Health Cycle.

usually pleiotropic. For example, polio virus only causes the classical paralytic disease for which it is best known in 1 out of 150, to 1 in 1800 people it infects. In the other 99 %+ of people, polio virus infection causes a self-limited gastroenteritis or cold-like upper respiratory tract symptoms (Nathanson and Kew, 2010). In another example, infection with Epstein-Barr virus (EBV) can cause mononucleosis, childhood cancer in Africa (Orem et al., 2014), or be a risk factor for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (Jason et al.,

Table 2
Mitochondria-cell system phenotypes of the healing cycle.

No.	Trait	Mitochondria-Cell System Phenotypes*		
		M1 Pro-inflammatory	**M0 Proliferative**	**M2 Anti-inflammatory**
1	Phase of greatest use in the healing cycle	Inflammation— CDR Phase 1	Proliferation— CDR Phase 2	Differentiation— CDR Phase 3
2	Form of cellular energy metabolism	Glycolysis	Aerobic glycolysis	Oxidative phosphorylation
3	Approximate evolutionary origin	3.5 BYA (Archean)	1.5 BYA (Proterozoic)	0.54 BYA (Cambrian)
4	Predominant mitochondrial morphology	Fragmented	Intermediate	Filamentous
5	Predominant cell cycle stages	G0, G1	G1, S, G2, M	G0, G2
6	Mitochondrial matrix Ca^{2+}, increased electron density in electron micrographs	Low	High	Intermediate to Low
7	Extracellular ATP (eATP) release	High	Intermediate	Low
8	Extracellular release of UTP	High	Intermediate to High	Low
9	P/O coupling of oxidative phosphorylation (oligomycin-sensitive respiration)	Low	Intermediate	High
10	Cellular oxygen consumption rate	Low	Intermediate to High	High
11	Fumarate reduction to succinate (Spinelli et al., 2021)	Medium	High	Low
12	Mitochondrial heat production (Chretien et al., 2018)	High → fever	Intermediate to High	Low
13	Intracellular dissolved oxygen concentration	High	Low	Low
14	Cellular redox imbalance (NADH/NAD +)	High	Intermediate	Low
15	Purinergic chemotropic recruitment and transactivation of neutrophils, NK cells, macrophages, and microglia	High	High	Low
16	Lactate release from cells	High	Intermediate	Low
17	Arginase 1 (Arg-1) expression	Low	Intermediate	High
18	Inducible nitric oxide synthase (iNOS) expression	High	Intermediate	Low
19	Tissue ammonia (NH_3) concentration	Intermediate	High	Low
20	Pyruvate dehydrogenase (PDH) activity	Low	Low	High
21	Extramitochondrial ROS (H_2O_2, $O_2^{\cdot-}$), RNS ($^{\cdot}NO$, $ONOO^-$), CO, and H_2S	High	Intermediate	Low
22	ROS-stimulated ultraweak photon emission (UPE)	High	Intermediate	Low
23	Homocysteine, sulfite (SO_3^{2-}), and cysteine-S-Sulfate production	High	Intermediate	Low
24	Mitochondrial hydrogen peroxide (H_2O_2)	Low	Intermediate to High	Low
25	Mitochondrial inner membrane potential ($\Delta\Psi_{mit}$)	Low to Hyperpolarized	Hyperpolarized	Intermediate
26	Mitochondrial inner membrane surface area (cristae)	Low	Intermediate	High
27	Metabolic synapses and organellar-mitochondria associated membrane contacts (MAMs)	Low	Intermediate	High
28	NLRP3 inflammasome assembly	High	Low to Intermediate	Low
29	Extracellular release of oxidized mitochondrial DNA	High	Intermediate	Low
30	Mitochondrial DNA copy number	Low	Intermediate	High
31	Cell replicative potential, proliferation	Intermediate	High (Warburg metabolism)	Low
32	Multilineage cell regenerative potential	Low	High	Low
33	Use during epimorphic regeneration	High after injury, then low	High early, Low late	Low early, High late
34	Cell differentiation potential	Intermediate	Low	High
35	Cell cancer potential	Intermediate	High	Low
36	Inflammatory and chronic pain potential	High	Intermediate	Low
37	Cell susceptibility to killing by apoptosis	Intermediate	Low	High
38	Inducible organellar quality control	Low	Intermediate	High
39	FCCP uncoupled oxygen consumption above baseline (spare respiratory capacity)	Low	Intermediate	High
40	Pentose phosphate pathway (PPP)	Intermediate—NADPH for NOX	High—NADPH for biosynthesis and cell growth	Intermediate— NADPH for redox and synthesis
41	Use of fatty acid oxidation (FAO)	For ROS and NLRP3 activation	Fatty acid synthesis for growth > FAO	For oxphos
42	Use of glucose	Glycolysis and lactate release	Glycolysis and PPP	PPP and pyruvate for oxphos
43	Use of glutamine	Low	High: citrate for ATP, citrate lyase and acetyl-CoA	High: oxphos via alpha-ketoglutarate and OAA

*Hundreds of different mitochondria-cell system phenotypes exist that define the function of each differentiated cell type. The M1, M0, and M2 phenotypes are core configurations needed for healing after any injury in any tissue. **References**: (Chen et al., 2018; Liu and Ho, 2019; Motori et al., 2013; Naviaux, 2019a; Picard et al., 2013). **Abbreviations:** ROS—reactive oxygen species, RNS—reactive nitrogen species, FCCP—trifluoromethoxy carbonyl cyanide phenylhydrazone, CO—carbon monoxide, NLRP3—NLR family pyrin domain containing protein 3, NOX—NADPH oxidases, OAA—oxaloacetic acid.

2017), depression (Vindegaard et al., 2021), and multiple sclerosis (Xu et al., 2021).

Other pleiotropic hazards are common but are often not recognized until extreme cases of exposure or large epidemiologic studies are published. A common but invisible household hazard comes from natural gas stoves. Gas stoves are operated by 70 % of households in California and leak fugitive non-methane hazardous air pollutants (HAPs) like benzene, toluene, and xylenes. A surprising 75 % of these emissions occur while the stoves and gas water heaters are off (Lebel et al., 2022). Hazardous volatile organic chemicals (HVOCs) are leaked at levels sufficient to degrade indoor air quality and contribute to an increased risk of several complex chronic disorders. Some risks are known only from animal studies but are suspected in humans. These range from infertility and developmental defects from gestational and early childhood exposures, to heart disease and cancer (EPA, 2023).

5.4. Host resilience and contextual pathogenesis

The importance of physiologic context in determining the outcome of any interaction with an environmental factor was originally

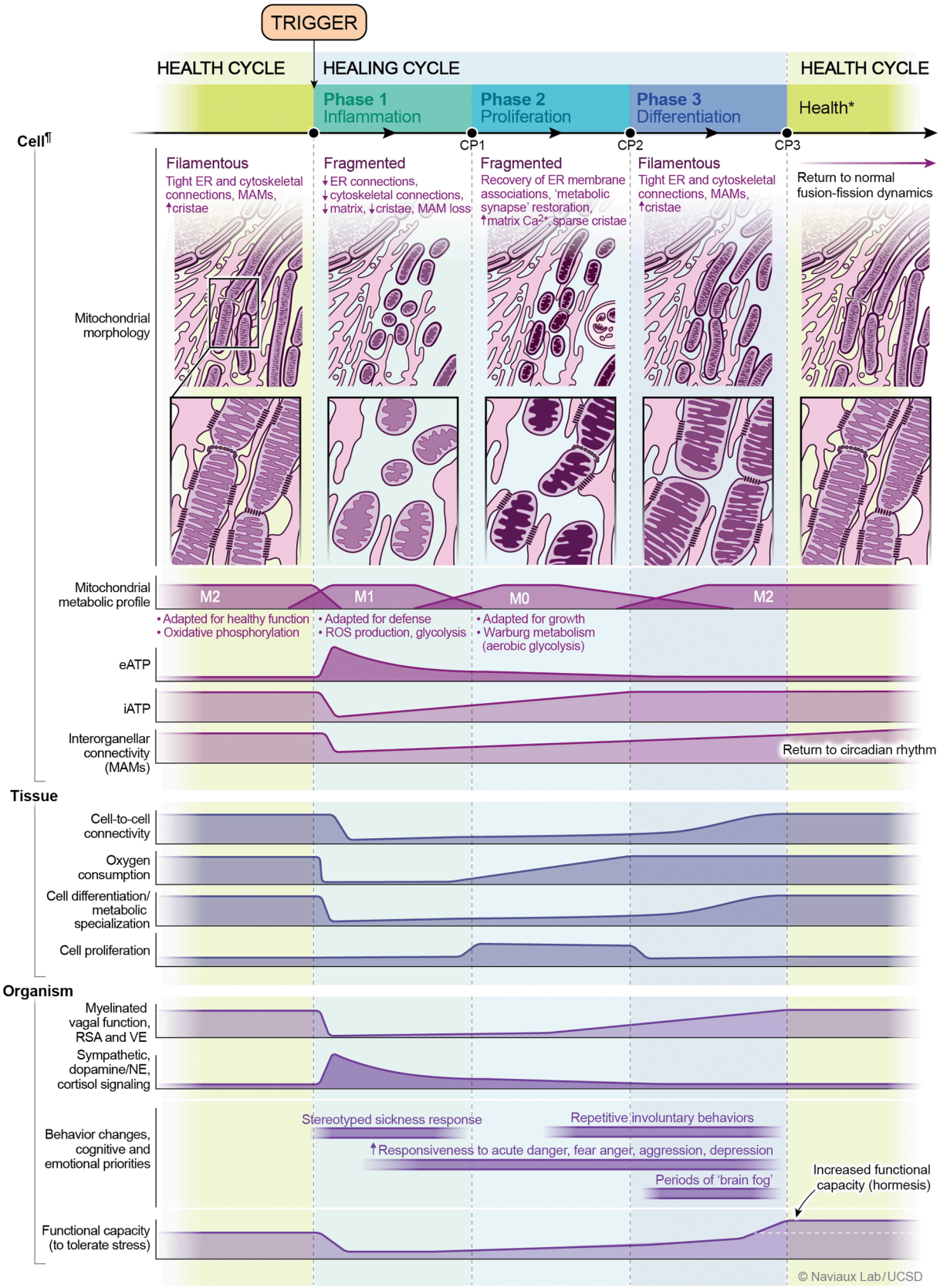

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Fig. 5. Multisystem integration of the CDR. Coordination of the mitochondrial, cellular, tissue, and organism level changes during the cell danger response, health, and healing cycles. The structural and functional changes associated with the cell danger response are tightly regulated in time, and at all spatial scales from mitochondria, to cells, tissues, and the whole organism. The phases of salugenesis are driven by mitochondrial phenotypic transitions. M1 mitochondria are dominant in Phase 1. M0 are dominant in Phase 2, and M2 are the dominant form in Phase 3. Health* is a fragile state of health that occurs immediately after healing from injury or infection. Repeated triggers or re-injury during this phase can lead to chronic disease. In the absence of repeated triggers or re-injury, strength and functional capacity are restored after additional convalescence, recovery, and regular engagement of the cardinal elements of the health cycle. Additional gains and increased reserve capacity associated with hormesis lead to resilient health. [†]Every tissue starts and ends as a mosaic of cells that encompasses a spectrum of mitochondrial networks from filamentous M2-polarized, to fragmented M1- and M0-polarized mitochondria-cell systems. The proportion of organelles in each form determines the net functional state of the cell and enables metabolic specialization between cells. **Definition:** Health* is a meta-stable state of health the occurs immediately after healing from injury or infection. This is a fragile stage of early health recovery that is vulnerable to re-injury, secondary infection, or exposure to new triggers. **Abbreviations:** CDR, cell danger response; CP, check point; MAMs, mitochondria-associated membranes, and metabolic synapses; eATP, extracellular ATP; iATP, intracellular ATP; RSA, respiratory sinus arrhythmia, VE, vagal efficiency.

encapsulated in the concept of the *milieu intérieur*—the internal milieu of the body and the cell—by the French physiologist Claude Bernard (1813–1878) (Holmes, 1986). Later, Elie Metchnikoff (1845–1916), known best for his discovery of importance of neutrophils and macrophages in phagocytosis, inflammation, and innate immunity, noticed that in a cholera epidemic sweeping through France in 1892, some people exposed to the same doses of the causal bacterium got sick, while others remained healthy. He hypothesized that natural bacteria present in the intestinal tract created a *milieu intérieur* or *terrain* (the biological *terroir*, soil quality, or gastrointestinal habitat) that was either resistant or susceptible to infection by pathogens. Experimenting on himself, he drank a known amount of the *Vibrio cholerae* pathogen and did not get sick, while another volunteer who drank the same culture got very sick (Vikhanski, 2016).

A conclusion from these examples of pluricausal illness and pleiotropic causal factors is that the *terrain,* or context in which the gene, microbial infection, trauma, or toxin exposure occurs, is a major determinant of the outcome. And for children especially, the *timing* of the exposure during critical developmental windows in child development is an important part of the context. The new paradigm of linked health and healing cycles, provides a way of combining pathogenesis-based and salugenesis-based problem solving to yield novel insights into the causes, prevention, and treatment of pluricausal chronic illness (Fig. 4).

5.5. Perfect storms and precision medicine

When health care for a complex chronic disease is individualized and a careful medical history is taken, a perfect storm of pathogenic triggers is found in most patients. The tools of precision medicine reveal that hundreds of different molecular abnormalities are present in each patient (Castelli et al., 2022). However, metabolomics studies show that only about 25 % of the detected abnormalities are diagnostic and specific for a particular disease, while 75 % of the abnormalities are personalized and non-specific (Naviaux et al., 2016). The personalized abnormalities are a fingerprint of the perfect storm, reflecting the unique path of causal factors—the personalized chain of causality—that was experienced by the patient. While the risk of chronic illness in a population can be calculated in the form of a probability—a percentage per year, or a number per 100,000 people that will be affected—individual risk is changeable and notoriously difficult to predict. Each year, an individual moves through a series of invisible fitness landscapes by their choices that can tip their personal risk for illness up or down. Each choice creates a new cascading network of virtual future timelines and collapses many others. Viewed in this way, the occurrence of a pluricausal disease in a particular person, at a particular time, can be imagined as a stochastic singularity in time and space that crystallizes out of an imaginary sea of convergent risks. This sea of risk is determined by the environment—the family, community, ecosystem, and chemosphere in which each person lives. This perspective helps to understand how the health of the ecosystem, and all the microbes, plants, and animals living in it, materially affects the health of each person breathing the same air, drinking the same water, eating the same food, and sheltering from the same weather.

5.6. Penultimate and ultimate causes

Once a person develops an illness, their personal probability of disease jumps discontinuously from a calculatable *a priori* or Bayesian risk between 0 and 1, to a 100 % certainty. Once this happens, the opportunity for disease prevention is lost and the goal of medical care shifts from prevention to treatment. In most cases, the penultimate cause of illness is found to be a personalized perfect storm of causal factors. No one gene or one environmental factor causes all cases of a complex chronic disease. This happens because biological populations are heterogeneous, and individuals are unique. Every population contains individuals who are more sensitive, and others who are more resistant to any risk factor or stress.

While the penultimate cause of disease in a single patient reflects a personalized path of causality, an ultimate cause of most chronic illness in a population can be identified when the search is reframed, and the process of pathogenesis is separated from the process of salugenesis. The ultimate cause of chronic illness that is both necessary and sufficient in all affected individuals is the *biological response* to threat that persists abnormally. This conserved biological response to threat is the healing cycle (Fig. 4). When the cell danger response remains chronically activated, the healing cycle persists abnormally.

5.7. Early life stress and chronic disease

Chronic activation of the cell danger response changes the developmental trajectory of a child and can result in life-long vulnerabilities and disabilities. For example, social deprivation during infancy is a form of early life stress (ELS), also called an adverse childhood experience (ACE), that can cause permanent brain damage, and lead to increased heart disease, diabetes, and other chronic illnesses in adults (Miller and Lacey, 2022). The devastating effects of ACEs have been observed In children who were orphaned by sociopolitical upheaval or military conflict in Romania and other parts of eastern Europe in the 1980s and 90s (Bos et al., 2011). Early psychosocial deprivation leads to a chronic state of immune activation that can be measured in the blood as increased interleukin-6 (IL-6) (Tang et al., 2020). Nature connectivity is also required as a source of healthy microbes needed to establish a normal microbiome for tuning tolerance, innate and adaptive immunity (Haahtela, 2009). Worsening environmental pollution is a chemical ACE. For example, complex public health trends like the increase in precocious puberty in girls since the 1980s has been linked to ACEs and early exposure to endocrine disrupting chemicals (Lee et al., 2019).

5.8. Preventing, diagnosing, and treating pluricausal disease

Prevention of chronic illness is two-pronged, requiring attention to both environmental and personal risks. First, the risk to the general population can be reduced at the level of public health by the federal and community management of pathogenic and anti-salugenic factors in the environment like pollution, sociopolitical disruption, poverty, food and

housing insecurity, and the loss of biodiversity (Romanelli et al., 2015). Second, metabolomics, genomics, exposomics, and other tools of precision medicine, can be used to identify personal risk factors and monitor the biological response to preventive care. Once a person develops a chronic illness, a shift from prevention to treatment must be made. Treatment outcomes are improved when individualized medical care is 4-pronged. First, disease-specific abnormalities shared by unrelated patients with the same illness must be identified and treated. Second, the personalized, non-specific factors that lead to symptoms must be identified and treated. Third, anti-salugenic factors that inhibit the healing cycle, including dysfunctional metabolic memory caused by hypersensitivity to eATP signaling (sections 10 and 11), must be identified, removed, or treated. Fourth, assessment and re-engagement of the cardinal elements of the health cycle (Fig. 4) must be gradually reintroduced to build resilient health.

5.9. *Dynamical properties of the health and healing cycles*

Bistable and multi-stable dynamical systems are common in biology and biochemistry (Akhtar et al., 2022; Gupta et al., 2007; Kashi et al., 2019). Persistent activity of the cell danger response shifts the control of metabolism from long-distance, coordinating signals from brain, autonomic, and neuroendocrine systems, to local signals from affected cells during times of stress. Coordinating brain signals during the health cycle are pulsatile. Pulsatility of health signals is critical. Fitness is a physiologic adaptation to environmental conditions and endocrine signaling that requires a period of unstressed, post-signal rest and recovery to build. At the cellular level, pulsatility is the natural outcome of oscillations in mitochondrial metabolism (Merrins et al., 2022), the rise and fall of intracellular calcium (Ca^{2+}), and associated oscillations in intracellular ATP, potassium efflux through ATP-inhibited K^+ channels, and membrane potential (Fletcher et al., 2022). In contrast, local cell danger signals are tonic. In the language of dynamics, this difference creates distinct phase spaces for the health and healing cycles. CDR persistence in injured tissue has the effect of collapsing healthy bistable and multistable systems to a simpler dynamical state associated with disease and disease risk. The new dynamical system that underlies disease and the risk of disease, can be measured in time scales from milliseconds, to circadian, seasonal, and annual cycles relevant to child development. The simplified system dynamics result from decreased coherence between stressed or injured subsystems, e.g., between cells, tissues, and organs. This is caused by a local signal jamming effect produced by tonic cell danger and inflammatory signals, making injured tissues resistant to, or unable to respond to long-distance, coordinating signals from the brain and endocrine systems. Although non-specific, this common and perhaps universal feature of risk for complex disease creates a public health opportunity. Like newborn screening for phenylketonuria (PKU) and other treatable genetic disorders (Brosco and Paul, 2013), if children and adults who are at risk of a disease can be identified before the first symptoms occur, prevention becomes possible.

The change in system dynamics that is diagnostic of disease and disease risk can be visualized by attractor reconstructions and recurrence plots (Marwan et al., 2007). Recent methods in non-linear time-series analysis have been used to distinguish cause from effect variables in complex systems at local and global scales (Ye et al., 2015). In medical applications, these methods use the rise and fall of metabolites and metals measured in teeth or hair over time during child development, or use the periodicities of fine motor coordination, electroencephalograms (EEGs), blood oxygen level dependent (BOLD) signals from functional magnetic resonance imaging (fMRI) scans (Curtin et al., 2022), or heart rate variability. When a person gets stuck in a phase of the healing cycle, it is energetically analogous to being stuck in a local energy well in the curvature of phase space, unable to progress to the next phase of the CDR. Progression through each phase of the CDR is needed to heal and return to health. The shift from multi-stability or bistability to a simplified or unimodal dynamical state has been used recently to create remarkably accurate fingerprints for several complex chronic disorders. These include amyotrophic lateral sclerosis (ALS) (Curtin et al., 2020), autism spectrum disorder (Austin et al., 2022), and Parkinson disease (Afonso et al., 2019).

6. Pluricausal disease and cellular mosaics

If healing cannot be completed within a few months of time, the biological cost of the persistent CDR cannot be sustained. Energy, material, and mental health resources become depleted. The resulting Pyrrhic war leads to chronic symptoms of pain, disability, and pluricausal disease (Table 1) (Selye, 1973). As described above, the specific illness in a particular person is determined by a personalized set of penultimate causes. These include personalized genetic vulnerabilities, developmental exposures, nutritional factors, infections, and traumas. However, the ultimate cause for each complex illness in a population is the same. Pluricausal diseases are the result of the body's *reaction* to chronic stress or threat signaling. Acute and chronic stress are different and lead to different biological responses. Under the salugenesis paradigm, pluricausal disorders can be seen as the result of chronic persistence of one or more stages of the healing cycle (Table 1, Figs. 4 and 5). In this way, all chronic illness can be classified according to the stage or stages of the CDR that are blocked or incomplete. Blocks in completing, exiting, and/or extinguishing Phase 1 of the healing cycle lead to chronic inflammatory disorders. Blocks in Phase 2 lead to chronic proliferative disorders. Blocks in Phase 3 lead to neurodevelopmental, affective, neuropsychiatric, neurodegenerative, and many other disorders of complementary cell specialization. And conserved detours, short-circuits, and one-way offramps can lead to a large but finite number of complex chronic disorders (Fig. 4, and Table 1).

6.1. *Asynchronous healing and cellular mosaics*

Two or more phases of the healing cycle can co-exist. For example, coronary artery disease results from the combination of local vascular inflammation (Phase 1), proliferation (Phase 2), and altered differentiation (Phase 3). This occurs because the healing cycle is asynchronous at the cellular level, and because healing is transactional—neighboring cells in every tissue communicate by exchanging metabolites and signaling molecules. For example, cells in the four different layers of a blood vessel—the endothelium, tunica intima, tunica media, and tunica externa—cooperate in the response to stress. During stress, endothelial cells enter the pro-inflammatory Phase 1 and send signals to the underlying layers. Acutely, nitric oxide production can cause vasodilation to increase oxygen and phagocyte delivery to stressed tissues to help make repairs. However, subacutely, growth factors from the intima cause smooth muscle cells in the intima and media to enter the proliferative Phase 2, leading to arterial narrowing. In the short term, narrowing reduces the delivery of bacteria or virus, or inflammatory material to the zone served by the narrowed blood vessel. However, when this process continues beyond the acute threat, chronic disease results. The intimal and subintimal layers release chemotactic factors and are invaded by circulating mononuclear blood cells. After invasion into the arterial wall, monocytes and macrophages respond to local signals that trigger an alternate fate of differentiation in Phase 3 that causes them to synthesize and accumulate cholesterol and other lipids and to become foam cells. When all three phases of the healing cycle fail to resolve, atherosclerosis results (Gui et al., 2022).

Different organs can also exist in different phases of the health and healing cycles at the same time. There are about 6.9×10^{13} cells in a 70 kg adult. Forty-three percent (43 %) of these (about 3.0×10^{13}) are human cells that weigh about 69.8 kg. The other 57 % (about 3.9×10^{13}) is comprised of microbial cells that weigh just 0.2 kg (Sender et al., 2016). Despite its smaller mass, the human microbiome contains a repository of gene sequences and metabolic diversity that exceeds the genetic and metabolic capacity of the host by 150 times (Zhu et al.,

2010). Once the CDR is triggered, affected lymph nodes, skeletal muscle, joints, liver, lungs, kidneys, bones, eyes, ears, gut, and/or the brain are reprogrammed to begin the healing cycle. Although billions of cells (1 g equals 0.1 to 5 $\times$ 10^9 cells depending on their size (Del Monte, 2009)) and more can start the process after injury, not all these cells complete the full circle of the healing cycle. Some cells die and others become arrested in the intermediate phases of the healing cycle. The proportion of cells lost or left behind in Phase 1, 2, or 3 of the healing cycle determines the risk of a given chronic disease listed in Table 1. Individual outcomes depend on personalized weak links in the genome, past exposures, physiologic reserve capacity, and resilience. Over a lifetime, the aggregate effects of incomplete healing lead to cellular mosaics and organ functional declines associated with aging (Naviaux, 2019a). The effect of accumulating dysfunctional cellular mosaics has been quantified. By injecting increasing numbers of senescent cells that expressed a characteristic senescence associated secretory phenotype (SASP), Xu, et al. showed that as few as 1 senescent cell in a tissue mosaic of 350 other cells will objectively diminish the function of that tissue (Xu et al., 2018). While studied best in the liver (Gebhardt, 1992) and brain (Magistretti and Allaman, 2015), metabolic complementarity, cell specialization, and tissue mosaicism are universal features of healthy organs and tissues. Asynchronous disruption of specialized cell function is necessary during the healing cycle but comes at the cost of a temporary decrease in optimum organ performance.

6.2. Ecoalleles and structural changes

DNA polymorphisms in genes used for the cell danger response can display fitness advantages or disadvantages when exposed to certain environmental conditions. These environment-responsive gene variants are called ecoalleles. Some gene variations can weaken the ability of cells to complete all the phases of the healing cycle. Other factors like microbial ecology and exposure to microbial pathogens, toxins, or environmental chemicals, also impact the ability to complete the full circle of the healing cycle. In addition to germline variations, somatic mutations, copy number variations, mitochondrial DNA (mtDNA) deletions, changes in mtDNA copy number, and epigenetic changes lead to somatic cell heterogeneity and tissue mosaicism. When vulnerable cells in the tissue are delayed or stuck in a phase of the CDR after injury, dysfunctional cellular mosaics diminish organ functional capacity. In the subacute time after an initial injury or illness, non-specific and pluricausal *functional changes* can lead to symptoms like fatigue, autonomic and neuroendocrine disturbances, chronic pain, cognitive impairment with episodes of brain fog, and non-restorative sleep. These are a symptom complex that is seen in disorders like myalgic encephalomyopathy/chronic fatigue syndrome (ME/CFS) (Bateman et al., 2021). In principle, these functional changes are readily reversible with the right treatment. Later, *structural changes* like vascular plaques and calcification, osteoporosis, scarring, tissue fibrosis, gliosis, weakened connective tissue in joints and vertebrae, or cell losses in the pancreas, liver, kidney, heart, or brain, or the emergence of cancer or autoimmunity can make a full recovery more difficult. Mitochondria supply the energy and metabolic building blocks needed to reprogram metabolism, drive progress, and complete the health and healing cycles.

7. Adaptive changes in mitochondrial function

For years, the mitochondrial phenotype of organelles isolated from healthy tissue from animals in the prime of life was used as the gold standard for "normal" mitochondrial function. This static view of optimum function, detached from the real-time physiologic context of the cell and the biological age and sex of the organism, has delayed progress in the understanding of the stages of healing, aging, and chronic disease. It is a biochemical fact that isolated mitochondria in a test tube do not function the same as mitochondria within cells that are responding to extracellular hormones and signals from the nervous system. This problem of defining optimum mitochondrial function detached from physiologic context has persisted for over 70 years since the first protocols for isolating and measuring high-quality mitochondria were developed in the 1940s and 50s (Chance and Williams, 1955; Hogeboom et al., 1947). It is now understood that mitochondria are reprogrammed when the living system in which they reside is threatened or injured. Reprogramming triggers the healing cycle and enables recovery. What is "abnormal" in healthy tissue, is "normal" for a cell that must defend itself from microbial attack, and vice versa.

7.1. Pathological loops and detours from active healing

Detours from the main path of the healing cycle can lead to pathological states and to the symptoms of chronic illness (Fig. 4). Fibrosis, gliosis, and scarring occur when cells divide in a region of unresolved inflammation and/or mechanical stress (Heindryckx and Li, 2018). The key role of eATP signaling in controlling this inflammation and the associated reactive gliosis and pathological epigenetic changes has recently been shown experimentally. Early antipurinergic therapy after injury has been shown to prevent pathological chromatin remodeling, inhibit inflammation, and rescue damage in spinal cord neurons, microglia, and astrocytes (De Luca et al., 2022). When nuclear DNA damage accumulates, cells exit the cell cycle and can become senescent (He and Sharpless, 2017) or lost by non-apoptotic cell death pathways (Prokhorova et al., 2020). Persistent release of mitochondrial DNA, peptides, cardiolipin, and other mitochondrial products into the cytoplasm or extracellular space creates cell danger signals known as damage associated molecular patterns (DAMPs) and contributes to chronic inflammation (Deus et al., 2022). Both senescence and fibrosis are one-way off-ramps from Phase 2 of the healing cycle. Senescence can also occur as a one-way offshoot in non-dividing cells like neurons in Phase 3 when the DNA damage response persists (Wong and Chow, 2022).

When cell losses during Phase 1 are negligible, cell-cycle re-entry into Phase 2 is unnecessary since tissue biomass is replete, and cells can proceed directly to Phase 3. However, hypersensitivity to environmental stimuli can lead to crashes and post-exertional malaise (PEM) in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) that short-circuit cells from a hypometabolic survival state (HSS) near Phase 3A back to more glycolytic metabolism in Phase 1C (Fig. 4). A chronic inflammatory loop connects with Phase 1B and Phase 3B. This loop is caused in part by accumulation of cholesterol in the inner membrane of mitochondria and is active in coronary artery disease and many other chronic inflammatory disorders (Niyonzima et al., 2021) (Fig. 4).

The hyperfusion loop at Phase 3C is characterized by pleomorphic mitochondria, with hyperfused organelles and mitophagy dysfunction. The stress-induced mitochondrial hyperfusion (SIMH) response can be triggered by double-strand RNA-activated protein kinase R-like endoplasmic reticulum (ER) kinase (PERK)-dependent phosphorylation and inhibition of eIF2α (Lebeau et al., 2018) and ubiquitination of Miro1 (Lopez-Domenech et al., 2021). In the short term, SIMH protects cellular ATP production by preserving oxidative phosphorylation. However, in the long term, SIMH comes at the cost of decreased mitochondrial quality control by mitophagy, and sustained cellular hypersensitivity to environmental triggers (Patergnani et al., 2022). Chronic mitochondrial hyperfusion leads to proteostasis, protein aggregation and the unfolded protein response (UPR) (Almeida et al., 2022), hypersensitivity to apoptosis (Das and Chakrabarti, 2020), autoimmunity, endogenous retrovirus (ERV) reactivations, L1 and other retrotransposon mobilizations (Baeken et al., 2020), latent Epstein Barr virus (EBV), herpes simplex virus 1 and 2 (HSV1/2) virus, and human herpes virus 6 (HHV6) reactivation (Schreiner et al., 2020), glutamate excitotoxicity, chronic pain syndromes, neurodevelopmental and neurodegenerative disorders, and behavioral, cognitive, affective, and psychiatric symptoms. Protein aggregates accumulate because of the resulting redox changes (Dupuy et al., 2023), and insufficient intracellular ATP production to keep pace

with the need for protein folding and refolding by ATP-dependent chaperones (Fauvet et al., 2021). Persistent CDR stress results in proteostatic aggregates of β-amyloid (leading to neuritic plaques), hyperphosphorylated tau (leading to neurofibrillary tangles), α-synuclein (leading to Lewy bodies), creatine kinase paracrystalline arrays (leading to intramitochondrial "parking lot" arrays), huntingtin aggregates, and repeat associated non-AUG (RAN) translation products (Nguyen et al., 2019).

Aggregation of the abundant glycolytic protein glyceraldehyde-3-phosphate dehydrogenase (GAPDH) has been proposed as a ROS and nitric oxide (NO) sensor. Coaggregation of oxidized GAPDH oligomers with β-amyloid, tau, or α-synuclein, with and without extracellular matrix glycosaminoglycans (GAGs), alters glycolytic carbon flux and provides thermodynamic stabilization for self-assembly of several structurally and functionally distinct forms of these proteins (Avila et al., 2017). Proteostasis and protein aggregation that occur during the hyperfusion loop of a persistent Phase 3 in the healing cycle (Fig. 4), activate alternative functions of these classical proteins that are best known for their accumulation in neurodegenerative disease. GAPDH-facilitated protein aggregation is a mechanism for triggering autophagy and cellular quality control in the context of oxidative stress (Lee et al., 2021b) that is produced by cell danger signals of many different kinds. Subsequent removal of the irreversibly damaged cells creates space in healing tissues and permits replacement of lost cells with newly born cells produced by stem cell activation, division, and differentiation.

7.2. Mitochondrial phenotypic reprogramming for defense and healing

Inflammation and oxidation are manifestations of the same underlying biological response to environmental stress (Naviaux, 2012, 2014). Both are oxidative and occur automatically in Phase 1 of the healing cycle, also called CDR1. Oxidation is used to contain the injury or infection. Phase 1 starts with a regulated decrease in mitochondrial and tissue oxygen consumption. When diatomic oxygen (O_2) is not consumed and converted to water (H_2O) in mitochondria for bioenergetics, the excess oxygen delivered by capillaries to the cell is redirected for reactive oxygen species (ROS) production. Peroxisomal ROS production also occurs during Phase 1 of the healing cycle. Together, peroxisomes and mitochondria constitute a key signaling platform in the innate immune response and anti-viral immunity (Mohanty and McBride, 2013). Associated with the inhibition of mitochondrial oxidative phosphorylation is a cataplerotic release of molecules like fumarate and *cis*-aconitate from the Krebs cycle, and hyperpolarization of the mitochondrial membrane. Membrane hyperpolarization stimulates mitochondrial ROS production. Fumarate accumulation results in covalent binding to free thiols of cysteine residues in mitochondrial proteins. This process is called succinylation and triggers the formation of BAX/BAK pores in the membrane, and mitochondria-derived vesicles, leading to the release of mitochondrial RNA (mtRNA) and DNA (mtDNA) into the cytoplasm and extracellular space. Cytoplasmic mtRNA activates the RIG1-MDA5/MAVS pathway. Cytoplasmic mtDNA activates the cGAS-STING pathway. Both contribute to activating type I interferons (IFNα's and IFNβ's), antiviral immunity, and amplify the inflammatory response (Hooftman et al., 2023; Zecchini et al., 2023) needed in Phase 1 of the healing cycle.

7.3. Itaconate

The 6-carbon *cis*-aconitate is decarboxylated by *cis*-aconitate decarboxylase (CAD) to form itaconic acid. CAD is encoded by the immune response gene-1 (*Irg1*, also known as *Acod1*). Like the 4-carbon fumarate, the 5-carbon itaconate is a dicarboxylic acid and contains a reactive carbon–carbon double bond. However, in contrast to fumarate, itaconate has direct antimicrobial properties (Zhang et al., 2022) and net anti-inflammatory actions. The double bond in itaconate reacts with free thiols in KEAP1 and glycolytic proteins, leading to cysteine alkylation, NRF2 induction (Mills et al., 2018), and to the redirection of 3-carbon intermediates from glycolysis to fatty acid synthesis and lipid storage. Metabolic reprogramming and redirection of 3-carbon subunits from glycolysis to lipid storage is a common feature of several stress survival mechanisms like hibernation and dauer (Hellerer et al., 2007). The stored lipid is used later for energy to power Phases 2 and 3 of the healing cycle once environmental conditions improve.

The orderly progression through the three phases of the healing cycle is guided by changes in the environmental conditions that surround each cell. Mitochondria sense, integrate, and respond to local conditions by altering their energy and matter processing characteristics. Nuclear-mitochondrial crosstalk shifts the dynamic state of the mitochondrial network to create M1-, M0-, and M2-polarized mitochondria-cell systems (Table 2, Figs. 4 and 5).

8. The M2, M1, and M0 mitochondria-cell system phenotypes

Hundreds of different mitochondria-cell system phenotypes exist that define the function of each differentiated cell type. The M1, M0, and M2 phenotypes are core configurations needed for healing after any injury in any tissue (Table 2). The naming of the functionally polarized forms of mitochondria used during the healing cycle was designed to correspond to the functionally polarized macrophages (Liu and Ho, 2019) and microglia (Orihuela et al., 2016). Macrophages and microglia achieve pro-inflammatory (M1), proliferative multipotential (M0), and anti-inflammatory (M2) phenotypes by using the functionally polarized mitochondria they contain (Chen et al., 2018). Over 40 biochemical and structural traits have been shown to distinguish the mitochondria used to enter and exit the phases of the cell danger response (Table 2). M1-polarized mitochondria in Phase 1 of the healing cycle are fragmented, consume less oxygen, disconnect from many mitochondria-associated membranes (MAMs), and help adapt the cell for glycolytic metabolism (Fig. 5). Healing after completing Phase 1 requires an orderly exit from oxidative conditions and return to a chemically reducing environment. This starts when mitochondria are reprogrammed from inflammatory M1 to multipotential M0 metabolism, which marks the transition from Phase 1 to Phase 2 of the healing cycle.

M0-polarized mitochondria facilitate aerobic glycolysis and polymer synthesis for cell growth and division in Phase 2 of the healing cycle (Fig. 4). Cell division is needed to replace cells lost during inflammation in Phase 1. Stem cells are activated and $p21^{CIP1/WAF}$ is inhibited (Arthur and Heber-Katz, 2011) to facilitate tissue regeneration in Phase 2 of the healing cycle. M0 mitochondria support Warburg metabolism, consume more oxygen, convert it to water, and maintain higher levels of glycolytic intermediates needed for anabolic cell growth (Lunt and Vander Heiden, 2011). M0-polarized mitochondria remain mostly fragmented, but the matrix becomes more electron dense because of calcium uptake that facilitates aerobic glycolysis. Matrix accumulation of calcium occurs in many but not all mitochondria in proliferating cells after exiting inflammatory conditions in Phase 1 (Fig. 5). The anti-inflammatory M2 transition occurs upon exiting the cell cycle that is active during Phase 2 and entering Phase 3 (Figs. 4 and 5). Substages in the healing cycle permit cells to bypass cell cycle entry. At the completion of Phase 1B and 1C, cells can skip Phase 2 and transition directly to Phase 3 by polarizing mitochondria to the M2, anti-inflammatory and pro-resolving phenotype (Figs. 4 and 5). As M2-polarized mitochondria in Phase 3 start to elongate by fusion, more MAMs are reestablished, the infoldings of the inner membrane increase in surface area to form more complex cristae, and oxidative phosphorylation becomes the dominant source of energy for the cell.

8.1. Mitotypes

The multilayered, hierarchical coordination of molecular, mitochondrial, cellular, tissue, autonomic, neuroendocrine, and behavioral features of the phases of the healing cycle and CDR are illustrated in

Fig. 5. It should be noted that the organization of mitochondrial functions into 3 fundamental mitotypes needed for healing is part of mitochondrial diversity. Several different mitochondrial phenotypes are known. For example, 16 functionally distinct mitotypes can be identified in 9 different white blood cell types (Rausser et al., 2021). This study showed that mitochondrial function is not only specialized for the function of each cell type, but also differs according to sex and age, and between basal and stimulated conditions. The systematic reprogramming of mitochondrial function is needed to complete each phase of the healing cycle. Without mitochondrial reprogramming, healing fails.

9. Decoupling cells for defense, recoupling for recovery

All tissues are cellular mosaics, comprised of metabolically complementary cell types. The composition and connectivity of cells in the mosaics, and the organization of mitochondria within each cell, is regulated over time and throughout the healing cycle (Fig. 5). Changes in the topology—the structural organization—of mitochondrial and

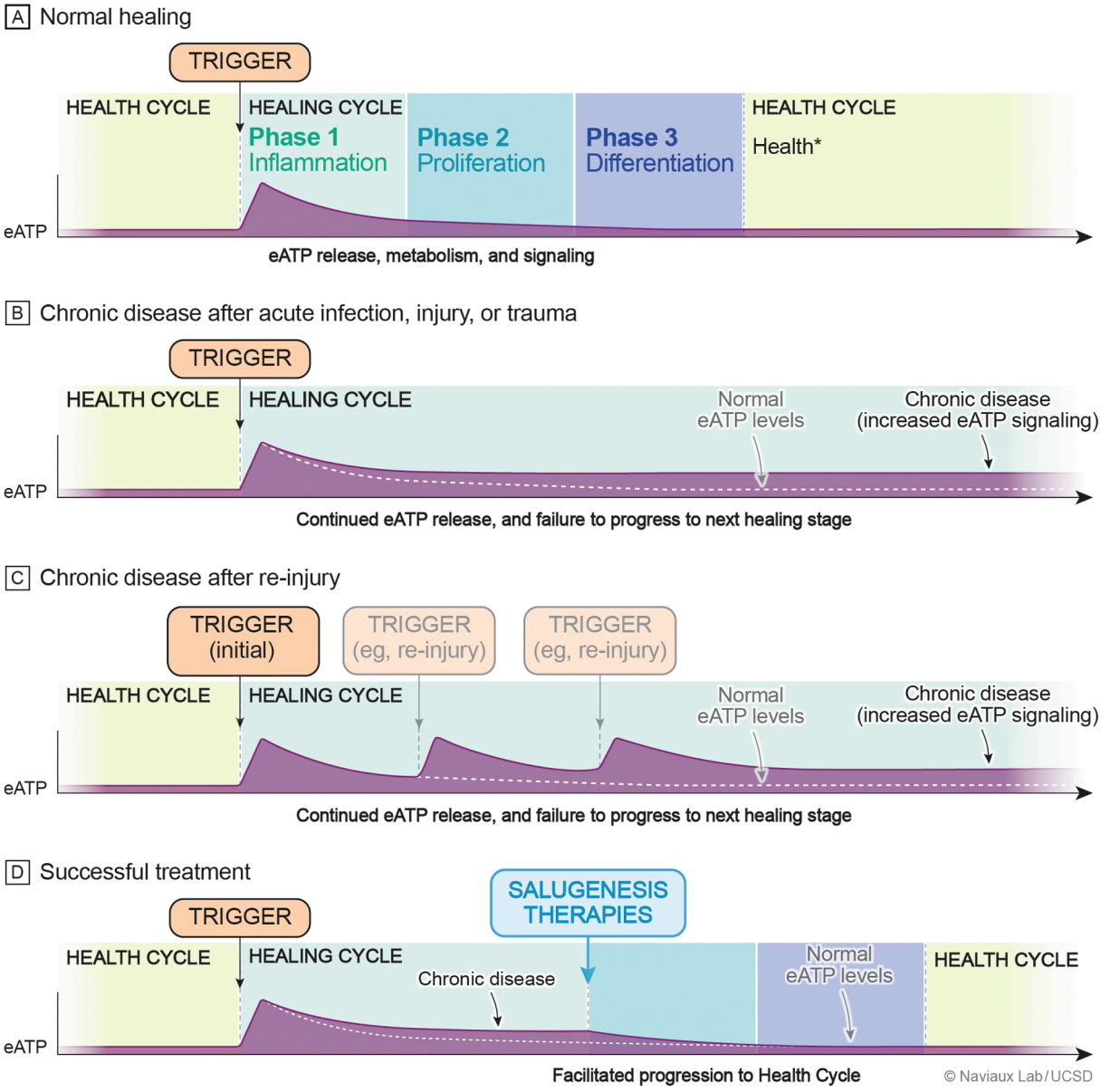


Fig. 6. Patterns of extracellular ATP (eATP) signaling in health and chronic disease. A. Normal healing. All pathogens and stressors trigger the efflux of ATP from cells to initiate the healing cycle. Extracellular ATP (eATP) levels decrease as healing progresses. **B. Chronic disease after acute infection, injury, or trauma.** Persistent and recurrent eATP signaling inhibit metabolic reprogramming needed to complete the healing cycle. **C. Chronic disease after re-injury.** Re-injury leads to pulses of eATP release that trigger inflammation, inhibit progress, and reactivate glycolytic metabolism, **D. Successful treatment.** Interventions that facilitate healing and recovery decrease eATP release and decrease the hypersensitivity to eATP signaling so mitochondrial structure and function are restored, and the metabolic reprogramming needed to complete the healing cycle can proceed. [1]eATP is the extracellular ATP concentration in the unstirred water layer (UWL) around every cell. This layer creates a shell, about 50–100 nm thick, that includes what has been called the purinergic halo. The UWL is the diffusion-limited zone in which hormones, cytokines, and other ligands bind to their cell surface receptors. eATP concentrations in this zone vary between about 1–10 μM. The concentration of ATP in plasma varies between 20 and 2000 nM, about 1–100 times lower than in the pericellular UWL. The concentration of eATP in the UWL is controlled by autocrine and paracrine release of ATP from neighboring cells, free plasma levels, and by cell surface phosphatases and nucleotidases like ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), CD39, and CD73. In comparison, intracellular ATP (iATP) concentrations are 2–20 mM, 1000–5000 times higher than eATP in the UWL.

cellular networks lead to changes in the signaling output of each network (Picard and Shirihai, 2022). The highest levels of organ performance and functional reserve capacity are achieved when differentiated and metabolically complementary cells in the tissue are well-coupled through tight junctions and gap junctions. Further connectivity is achieved by remote sensing and signaling (RSS) via metabokines, their receptors, and membrane solute channels (Nigam, 2018), and by the brain via neural connections and neuroendocrine signals. Connectivity and complementarity allow cells to exchange coordinating electrochemical, paracrine, and endocrine signals, and metabolic resources. Physical injury and stresses of many kinds disrupt cellular connectivity. Injured cells that become isolated and metabolically uncoupled from their neighbors survive by shifting away from dependence on neighboring cells for supplies. Decoupled cells dedifferentiate toward a metabolism that is more cell-autonomous and self-reliant. This shift produces large changes in the intracellular compartmentalization of resources. By changing the organellar and intercellular concentrations of energy (ATP) and matter (amino acids, carbohydrates, lipids, etc.), the metabolism of injured cells is reprogrammed. Metabolic reprogramming is used to shift cells from the housekeeping functions of the health cycle (the left of Figs. 2 and 4) and toward the danger and threat-response functions needed for the healing cycle (the right of Figs. 2 and 4).

As cells progress through the healing cycle, recovery is marked by recoupling of cells in the mosaic and the restoration of cyclical coordination by the brain and enteric nervous systems via neural and neuroendocrine connections, and the restoration of metabolic complementarity between neighboring cells. Full recovery after illness or injury requires completion of the organelle-to-organism-to-organelle signal transduction circle. This signaling circle of the healing cycle begins with local signals of danger from mitochondria and the cellular release of eATP, and ends with safety signals from the long-distance signaling network that connects all levels of the mind-brain-body system in resilient health (Figs. 4-6, 8 and 9).

PART 2—Chemistry

10. Graded release of extracellular ATP

The graded release of ATP from cells in proportion to the degree of environmental stress is a universal feature of life (Burnstock and Verkhratsky, 2009; Verkhratsky and Burnstock, 2014). Extracellular ATP (eATP) is released in free form through redox-gated, voltage-gated, and/or mechanical stress-gated effects on pannexin 1 channels (Wang and Dahl, 2018), and connexin channels (Taruno, 2018). eATP is also released in vesicular form through export mechanisms regulated by proteins like SLC17A9 (Sakaki et al., 2013) and caveolae (Yamamoto et al., 2018). Released eATP has several functions. Higher levels of eATP serve as a damage associated molecular pattern (DAMP), can be converted to uric acid, trigger potassium efflux through P2X7 channels (Xu et al., 2020), and activate NLRP3 inflammasomes (Pittman and Kubes, 2013).

10.1. Pleiotropic effects of eATP

eATP is a potent regulator of whole-body bioenergetics, behavior, and metabolism. A total of 789 of the 1158 mitochondrial proteins indexed in MitoCarta 3.0 (Rath et al., 2021) are enzymes or transporters with catalytic functions. At least 433 of the 789 enzymes (55 %) were found to be regulated by nucleotides like ATP (Naviaux, 2019a). When tested *in vivo,* systemic injection of eATP is profoundly hypometabolic. eATP injection lowered the basal metabolic rate (BMR) by 74 %, and core body temperature by 6-8C in mice. BMR is measured as a function of the rate of oxygen consumption ($\dot{V}\,O_2$) and carbon dioxide production ($\dot{V}\,CO_2$) (Singer, 2016). Since 95 % of oxygen consumption occurs within mitochondria, BMR is a regulated function of mitochondria. Whole body oxygen consumption was found to be tightly correlated with body temperature. Heat is generated in mitochondria by regulating the thermodynamic coupling efficiency between ATP synthesis and oxygen consumption. Under basal conditions, enough chemical free energy is released as heat to raise the average matrix temperature of mitochondria to 50C, permitting the maintenance of a core body temperature of 37C (Chretien et al., 2018). Further uncoupling, or an increase in ATP-consuming futile cycles (Brownstein et al., 2022), will raise body temperature. These heat-generating reactions are used during infection to produce fevers. Reciprocally, decreased mitochondrial mass or electron flow, decreased $\dot{V}\,O_2$, decreased futile cycles, or increased coupling, in will lower body temperature. Both $\dot{V}\,O_2$ and body temperature returned to normal withing 60 min after injection of eATP in mouse models. One of the behavioral effects of systemic ATP injection was a decrease in motor activity that lasted for about 90 min and contributed to additional energy sparing. In addition to the effects on BMR, temperature, and behavior, systemic ATP injection remodeled the metabolome, changed over 200 metabolites from 37 biochemical pathways, and triggered CXCL1, IL-6, IL-10, and corticosterone release within 30 min (Zolkipli-Cunningham et al., 2021).

10.2. Neurotransmission and calcium signaling

ATP has been found to be a neuromodulator and co-neurotransmitter at every synapse in which it has been studied, acting as a ligand for both ionotropic P2X and metabotropic P2Y receptors (Burnstock, 2020). Further metabolism of released eATP creates adenosine, which binds P1 receptors (e.g., ADORA1, 2A, 2B, and 3) and completes the ATP signaling cycle. NAD^+ is also released from stressed cells, binds to P2X and P2Y receptors, and acts as a DAMP (Kuzmin et al., 2016). Released NAD^+ and $NADP^+$ are metabolized by membrane associated CD38 to cyclic ADP ribose (cADPR), and nicotinic acid adenine dinucleotide phosphate (NAADP), respectively. cADPR is the endogenous ligand of the ryanodine receptor. NAADP is the endogenous ligand of the acidic endosome- and lysosome-associated two pore channels (TPCs). Both cADPR and NAADP play key roles in amplifying the cell danger response by releasing intracellular calcium stores for cell activation (Hao et al., 2016). Highly nuanced, cell-type specificity is achieved by assembly of P2Y and P1 receptors into heterooligomers (Guo et al., 2021). In combination with CD39, also known as the ectonucleoside triphosphate diphosphohydrolase-1 (ENTPD1), and ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) (Linden et al., 2019), P2Y and P2X receptors control the calcium waves that regulate the activation of microglia and inflammation in the brain (Chun et al., 2022) (Fig. 6). ATP signaling also potentiates pain and heat sensory perception through interactions with transient receptor potential vanilloid (TRPV) receptors through P2Y1 receptors and protein kinase C (PKC) activation (Tominaga et al., 2001).

10.3. Exercise benefits, injuries, and recovery

ATP release and signaling also happen with everyday activities. Normal amounts of daily stress and recovery are two points in the same circle separated by wakefulness and sleep (Fig. 4A). Some danger or physiologic stress is an intrinsic risk of any wakeful activity and leads to proportional eATP release. Safety is signaled by ATP conversion to adenosine, which sets the stage for restorative sleep (Chennaoui et al., 2017) and completes one turn of the circadian health cycle (Fig. 4). Recently, ATP release has been found to be an early initiator of the kinetic cascade that leads to the adaptive benefits in mental health and fitness after acute endurance exercise (Li et al., 2022b). eATP release also occurs after resistance training and mediates the chronic blood pressure lowering and anti-inflammatory effects of exercise (Lammers

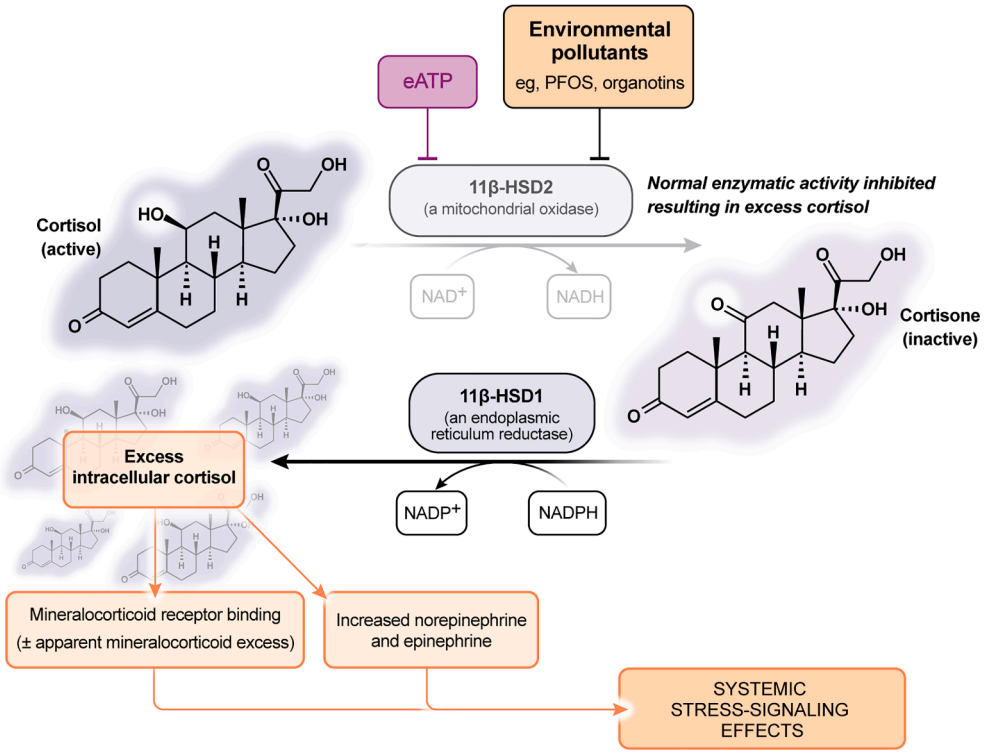


Fig. 7. ATP signaling, pollution, and intracellular cortisol excess. ATP and environmental pollutants like perfluorooctanesulfonate (PFOS), and organotins are potent inhibitors of the NAD + dependent, mitochondrial enzyme 11-β-hydroxysteroid dehydrogenase 2 (11β-HSD2). Inhibition of 11β-HSD2 prevents the normal oxidation and inactivation of cortisol and can lead to intracellular cortisol excess that promotes systemic stress signaling and inhibits resolution of the healing cycle. Basal activity of the NADPH-dependent reductase, 11β-HSD1 in the endoplasmic reticulum, converts inactive cortisone to active cortisol.

et al., 2020). The rise and fall of eATP release are regulated during acute and chronic illness as principal drivers of the stages of the healing cycle. Reinjury before complete healing after an acute injury can lead to episodic exposures to elevated eATP that inhibit healing, delay recovery, and contribute to chronic illness (Fig. 6).

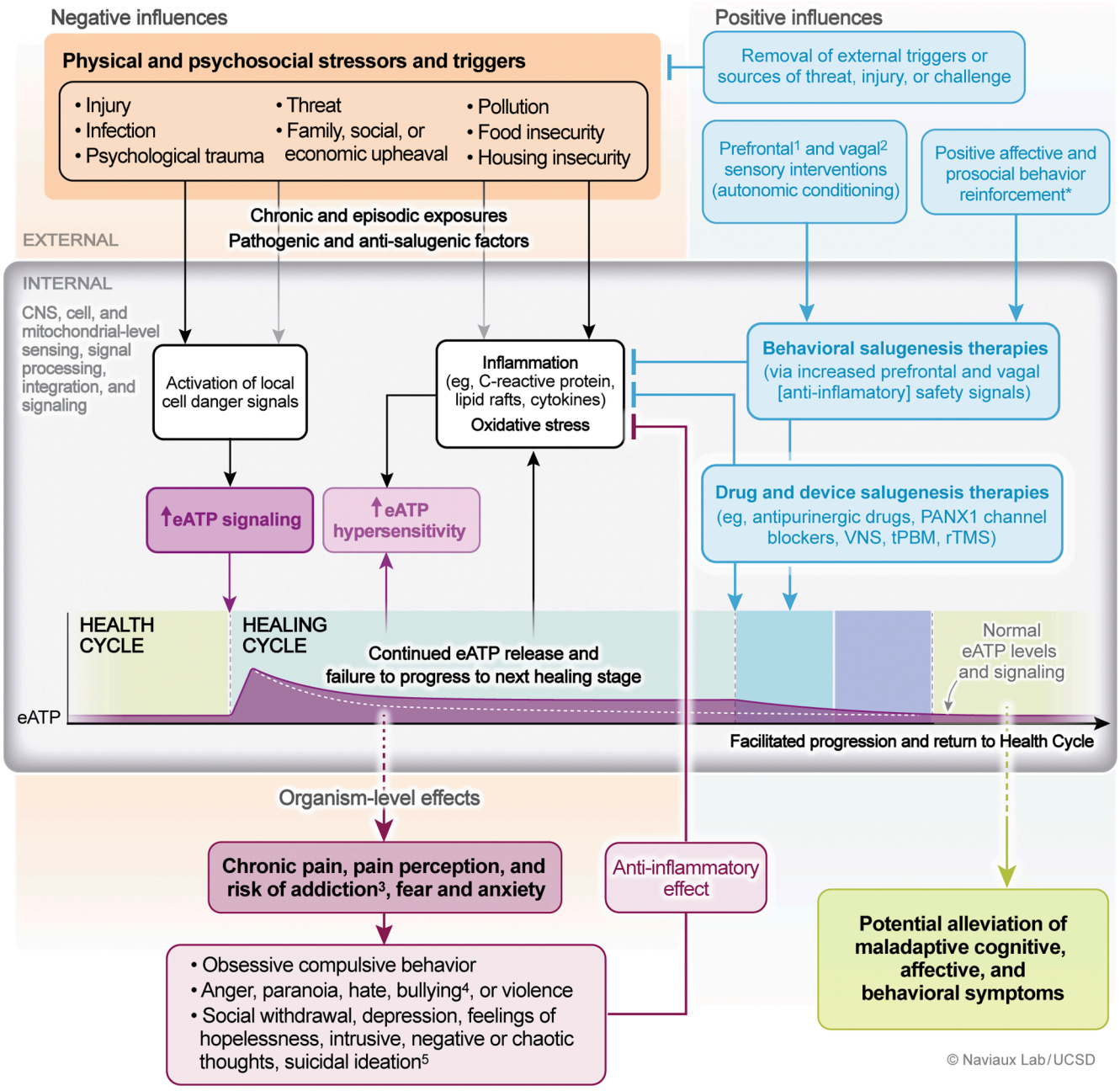
10.4. Healing cycle GPCRs

Twelve purinergic receptors, 8 P2Y and 4 P1 (ADORA) receptors, are G-protein coupled receptors (GPCRs) that co-evolved with nearly 80 other metabolite signaling (metabokine), chemokine, and peptide receptors. The members of this subfamily of GPCRs are functionally related. Each plays a role in the phases of the healing cycle (Fig. 4) (Naviaux, 2019b). Members include receptors for blood pressure regulation through angiotensin receptors (AGTRs), pain regulation through the bradykinin B receptors (BDKRBs), platelet activating factor receptors (PTAFR) and a protease-activated thrombin receptor (PAR1) used for hemostasis, two viral coreceptors (GPR15 and 25), formyl-peptide receptors to detect danger signaled by the release of formyl-methionine-initiated mitochondrial peptides (FPR1-3), short-chain fatty acids and ketone body signaling through the free fatty acid receptors (FFAR2 and 3), pH and sphingolipid sensing (GPR65 and 68), lactic acid sensing (HCAR1), mitochondrial Krebs cycle signaling via the alpha-ketoglutarate (OXGR1) and succinate (SUCNR1) receptors, innate immunity and priming of adaptive immunity using the complement 5a (C5a) receptor, inflammatory eicosanoid (GPR31 and OXER1) and oxysterol signaling (GPR183), leukotriene signaling (LTB4R, CYSLTRs, and GPR17), chemokine signaling to regulate inflammatory and immune cell chemotaxis (CCR1-9, and CXCR1-6), somatostatin signaling to inhibit hormone secretion for long-distance signaling (SSTR1-5), anti-inflammatory signaling by nicotinic acid (niacin) and hydroxyfumarate (enol-oxaloacetate) (HCAR2, GPR109A), estrogen anti-inflammatory signaling through the membrane-associated receptor GPER1, anti-inflammatory endocannabinoid and resolvin signaling (GPR18, 32, and 55), and many more. Each is coordinately regulated after injury to facilitate progression through the three phases of the healing cycle (Fig. 4B).

11. Lipid raft rheostats and the regulation of eATP signaling

The sensitivity of many cell membrane receptors to circulating metabokines like ATP, peptides, hormones, and cytokines is regulated by cholesterol and sphingolipid-enriched microdomains called membrane lipid rafts that surround the receptors. These membrane lipid rafts act like a rheostat to tune the cellular response of many different receptor-ligand signaling systems (Roy and Patra, 2022). Some of these include purinergic signaling systems (Ando et al., 2010; Lam et al., 2009), eATP processing by ectonucleotidases (Papanikolaou et al., 2005), redox signaling by NADPH oxidases (Jin et al., 2011), cancer-related tyrosine kinase signaling (Young et al., 2003), and neurotransmitters (Hayashi, 2022). Mobilization of intracellular calcium (Ca^{2+}), regulated by both cell membrane lipid raft associated receptor signaling and similar lipid raft microdomains in ER-mitochondria associated membranes (MAMs), appears to be a final common pathway for cell activation or death (Manganelli et al., 2021). By dynamically regulating the composition and leaflet polarization of cholesterol and sphingolipids, long-term metabolic memories of past danger and safety signals can be integrated and retained over time in tissue-specific ways that allow adapted responses to future threats. In the brain, the regulation of membrane lipid rafts determines the long-term setpoint for neuroinflammation (Taoro-Gonzalez et al., 2022).

Inside the cell, accumulation of cholesterol in the mitochondrial inner membrane leads to membrane stiffening by increasing the packing density of polyunsaturated fatty acyl side chains (Chakraborty et al., 2020) in cardiolipin, impairs cristae and supercomplex formation, and decreases ATP synthesis by oxidative phosphorylation (Solsona-Vilarrasa et al., 2019). Cholesterol accumulation in mitochondria leads to persistent innate immune activation by complement 5a (C5a) and IL-1β signaling and reversal of ATP synthesis to ATP consumption for mitochondrial ROS production (Niyonzima et al., 2021). Reciprocally, depletion of cholesterol and/or ceramides from mitochondria associated membranes (MAMs) increased phosphatidylserine transfer from the ER



*These include self-compassion, self-care, hope, joy, laughter, love, forgiveness, faith, generosity, trust, compassion, gratitude, belonging, wonder, and awe.[6]

Fig. 8. Counter-regulatory signaling systems and negative behaviors in chronic disease—A hypothetical framework incorporating the pathogenesis and salugenesis paradigms. Complex negative and maladaptive behavioral responses to adversity can be paradoxically reinforced by an anti-inflammatory effect they produce at the cellular level. The salugenesis model proposes that the organism-level behavioral effects can be mitigated by a combination of behavioral and medical treatments that signal safety and interrupt the reinforcement circuit by decreasing the maladaptive hypersensitivity to eATP-related purinergic signaling. **Abbreviations**: CNS, central nervous system; eATP, extracellular adenosine triphosphate; PANX1, pannexin 1; VNS, vagal nerve stimulation; tPBM, transcranial photobiomodulation; rTMS, repetitive transcranial magnetic stimulation; CRP, c-reactive protein. **References:** [1](Brosschot et al., 2018), [2](Porges, 2022a), [3](Koob et al., 2020), [4](Copeland et al., 2014), [5](Pan et al., in review, 2023), [6](Vaillant, 2013).

to mitochondria, improved the functional connectivity, and caused sigma 1 receptors (S1Rs, also called SIGMAR1) and IP3 receptors used for stress responses and calcium signaling, respectively, to relocate from MAMs to free ER membranes (Fujimoto et al., 2012). These cholesterol- and ceramide-mediated functional changes in mitochondria create a dysfunctional metabolic memory that can last for weeks to years, derail the healing cycle, and trigger the chronic inflammatory loops between Phase 3 and Phase 1 (Fig. 4).

12. ATP signaling and the microbiome

The health and healing cycles regulate the function of the cells that make up the intestinal lining. The intestinal lining, in turn, regulates the habitat of the microbial ecosystem of the gut. As with terrestrial or coral reef ecosystems, structures like the glycocalyx, crypts, villi, subepithelial domes (SEDs), and mucous layer thickness determine the physical habitat used by microbes to shelter, feed, and reproduce. The cells lining the gut also act as a barrier that determines the balance of nutrients

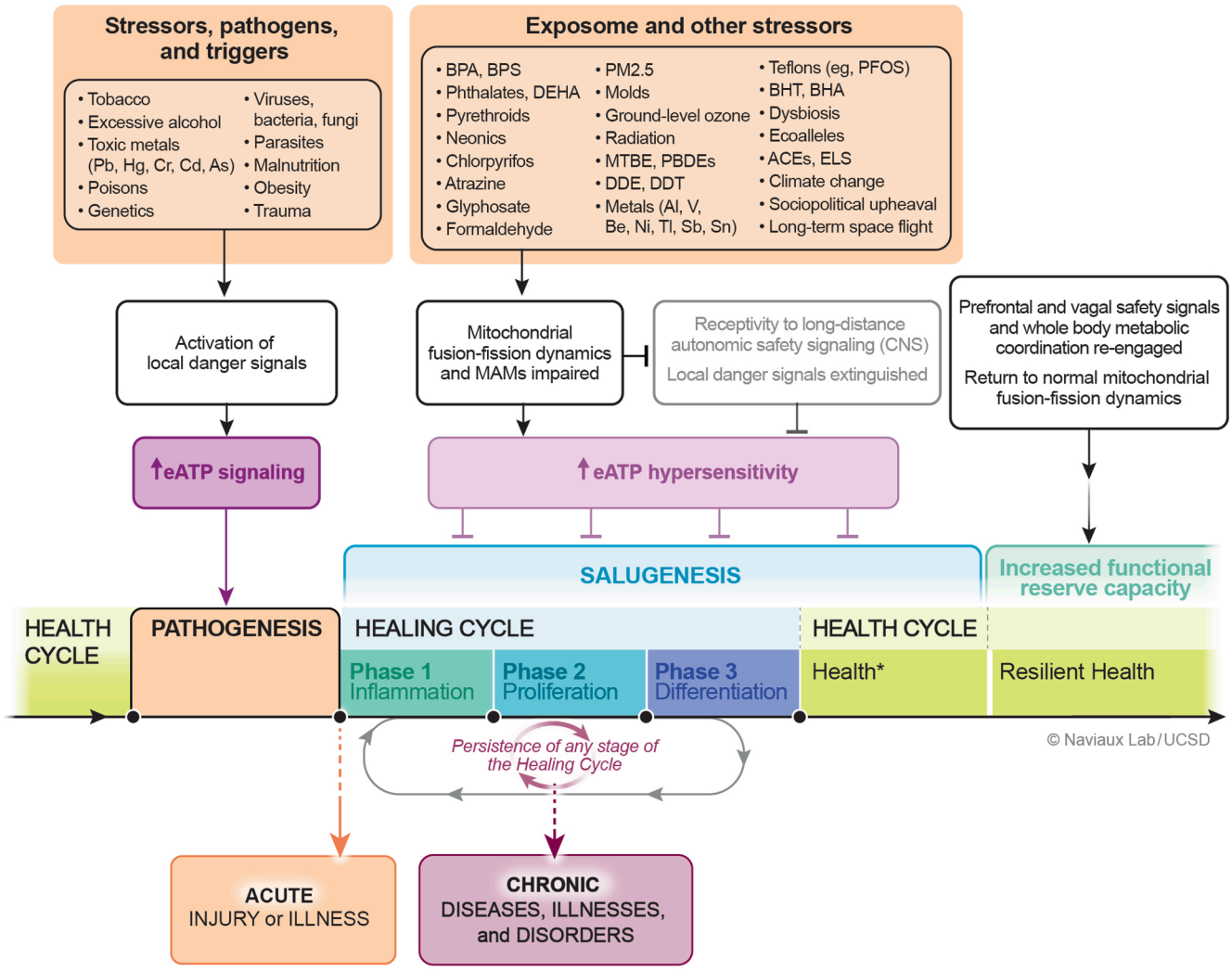


Fig. 9. Integrating the systems biology of chronic disease. Once an injury has occurred and the cause removed or treated, the rate and efficiency of healing are determined by the completion of the healing cycle. Many environmental factors, including anthropogenic chemicals in the air, water, and food chain, slow and inhibit the healing cycle by changing mitochondrial fusion-fission dynamics. The absence of parasympathetic autonomic safety signals leads to hypersensitivity to local purinergic (ATP-related) danger signaling and slows healing. Increased functional reserve capacity helps to build resilient health. **Definition**: Health* is a meta-stable state of health that occurs immediately after healing from injury or infection. This is a fragile state of early health recovery that is vulnerable to re-injury, secondary infection, or exposure to new triggers. **Abbreviations:** ACEs, adverse childhood experiences; ELS, early life stress; BPA, bisphenol A; BPS, bisphenol S; BDEs, brominated diphenyl ethers; Neonics, neonicotinoid pesticides; DEHA, bis(2-ethylhexyl) adipate; BHT, butylated hydroxytoluene; BHA, butylated hydroxyanisole; Teflons, include perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA); PCBs, polychlorinated biphenyls; MTBE, methyl *tert*-butyl ether; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethylene; EMF, electromagnetic fields; PM2.5, 2.5-μm sized airborne particulate matter.

absorbed, and the growth factors, antimicrobial peptides, mucin, secretory immunoglobulin A (SIgA), and inflammatory cytokines that are released. Safety and alarm signals from the gut epithelial cells regulate the amount of serotonin made by underlying enterochromaffin cells (Liu et al., 2021a), and modulate the uptake of secondary bile acids in the terminal ileum for farnesoid X receptor (FXR) (MahmoudianDehkordi et al., 2022), and G-protein bile acid receptor 1 (GPBAR1) signaling in the liver (Fiorucci et al., 2021). The balance of nutrients and inhibitors released by host cells lining the gut ensures that the microbiome reflects the host's state of health, safety, or alarm.

12.1. eATP as an interkingdom signaling molecule

Communication between the gut and microbiome is bidirectional. The organisms of the microbiome release key metabolites like ATP during glycolysis and rapid population growth (Hironaka et al., 2013). The receptors for microbial eATP are the purinergic P2X, P2Y, and P1 receptors described above. Under basal conditions, the thousands of bacterial species in the healthy microbiome are well adapted for host conditions and normal amounts of eATP are released. Adequate eATP released from a healthy microbiome is critical for tuning immunity and maintaining normal amounts of T-cell-independent secretory immunoglobulin A (SIgA). Low-affinity, glycan-dependent and T-cell independent SIgA is used to coat and retain beneficial bacteria that provide metabolic services for the host and to stimulate healthy intestinal mucus production (Nakajima et al., 2018). eATP also maintains the release of normal anti-microbial peptides like angiogenin 4, lysozyme, and defensin-α (Perruzza et al., 2017). On the other hand, eATP inhibits high-affinity T-cell dependent SIgA production via P2X7 receptors on follicular T helper cells (Tfh) (Perruzza et al., 2022). Because eATP is used for communication between prokaryotes and eukaryotes, it has been called an interkingdom signaling molecule (Spari and Beldi, 2020). Interestingly, ATP-related purinergic signaling has recently been shown to play a key role in inflammatory bowel diseases (IBDs) like ulcerative colitis and Crohn's disease. The P2X1 receptor is elevated in patients with IBD. When a P2X1 antagonist NF449 was given to a mouse model of

IBD, not only was inflammation improved, but the response to anti-TNFα immunoglobulin therapy was also improved (Wang et al., 2021).

12.2. Short chain fatty acids as interkingdom signaling molecules

The healthy microbiome produces short chain fatty acids (SCFAs) like formate (C1), acetate (C2), propionate (C3), butyrate (C4), and valerate (C5) from complex polysaccharides in fermentable dietary fiber (Morrison and Preston, 2016). The relative affinity of the free fatty acid receptor 2 (FFAR2, previously known as GPR43) is C2 = C3 > C4 > C5 = C1. Ranking of the affinity of SCFAs for FFAR3 (previously known as GPR41) is C3 = C4 = C5 > C2 > C1 (He et al., 2020b). Butyrate also signals via the GPR109A receptor. GPR109A is also known as the hydroxycarboxylic acid receptor 2 (HCAR2) and is the receptor for niacin. Short chain fatty acids are natural inhibitors of histone deacetylases (HDACs). HDACs and the NAD + dependent sirtuins remove acetyl groups from histones, compact DNA in nucleosomes, and silence gene expression. SFCAs from a healthy microbiome inhibit HDACs, increase net histone acetylation, open chromatin, and stimulate cell specific gene transcription. Both butyrate and propionate are protective in several inflammatory models, reducing NF-κB activation, TNF-α secretion, and nitric oxide (NO) synthesis after lipopolysaccharide (LPS) stimulation (He et al., 2020b).

12.3. Liver integration of gut eATP and SCFA signaling

The vascular architecture of the gut ensures that all blood from the intestines must first pass through the liver for screening, and nutrient and signal processing before it is passed along to the brain and other organs to complete the food-microbiome-gut-liver-brain signaling system. Short chain fatty acids from dietary fiber not only benefit the gut epithelium directly by FFAR signaling but protect the liver against inflammation by a FFAR2- and FFAR3-independent mechanism called the SCFA-PPARγ-UCP2-eATP axis (Yamaguchi et al., 2021). Butyrate activates the peroxisomal proliferator activator receptor γ (PPARγ) in the liver. PPARγ then activates transcription of uncoupling protein 2 (UCP2). UCP2 uncouples mitochondrial oxidative phosphorylation and decreases hepatic ATP. Decreased hepatic ATP pools decreased P2Y2-dependent neutrophil infiltration (Ayata et al., 2012), decreased hepatocyte sensitivity to pro-apoptotic triggers, and increased resistance to hepatic inflammation. The importance of SCFAs and the final common pathway of purinergic signaling in liver inflammation is underscored by the observation that the antipurinergic drug suramin protects against Fas-induced acute fulminant hepatitis in mouse models (Eichhorst et al., 2004).

13. ATP signaling and mast cell activation

Mast cells contain over 50 different signaling molecules and mediators (Theoharides et al., 2019). Some mediators like histamine, dopamine, and serotonin are prestored in granules and released upon stimulation. Other mediators like nitric oxide, IL1β, IL8, IL17, TNFα, tryptase, matrix metalloprotease 9 (MMP9), and TGFβ, are synthesized and released. Still other are expressed on the cell surface and can also be released like the receptor activator of nuclear factor kappa B ligand (RANKL) (Ng et al., 2022). Mast cell activation produces a spectrum of biological actions that range from acute reactions like IgE-mediated anaphylaxis, to more chronic symptoms like irritable bowel syndrome with episodic constipation, abdominal pain, and diarrhea, muscle and bone pain, osteoporosis, migraine headaches, episodic nasal congestion, hypotension, tachycardia, chronic fatigue, and brain fog. Because symptoms can arise from excess mast cell production of any of its mediators, the term mast cell mediator disorder (MCMD) has been proposed to encompass the disorders formerly called mast cell activation syndromes (MCAS) (Theoharides et al., 2019). Mast cells evolved to respond to local danger signals like extracellular ATP (eATP) (Gao and Jacobson, 2017). Recent studies have shown that IgE-associated mast cell activation requires eATP release through pannexin 1 channels. ATP-associated purinergic signaling via P2X and P2Y receptors then activates intracellular calcium signaling needed for mast cell granule release. Mast cell degranulation is inhibited by treatment with the purinergic signaling antagonist suramin (Harcha et al., 2019). These results suggest that purinergic signaling may be a novel target for treatment of mast cell mediator disorders.

14. ATP signaling and the excitation-inhibition imbalance paradigm in autism spectrum disorder

Rubenstein and Merzenich proposed the model of excitation-inhibition imbalance in autism spectrum disorder (ASD) in 2003 (Rubenstein and Merzenich, 2003). An increased ratio of excitatory to inhibitory signaling was proposed as a fundamental cause of the core symptoms of ASD. After a review of the genetic causes of autism, they proposed that in most cases, the imbalance was the result of both genetic and environmental factors. Increased excitation-inhibition (E-I) balance can be conceptualized with the example of excess excitatory glutamatergic signaling and/or deficient inhibitory GABAergic signaling. This framework has recently been expanded and integrated with the growing knowledge of neural circuits, genetics, and metabolism (Sohal and Rubenstein, 2019). Extracellular ATP, glutamate, and intracellular calcium are coupled—when one effector is altered, the other two respond. ATP-stimulated purinergic signaling potentiates excitatory glutamate signaling in stressed neurons (Ferreira-Neto et al., 2021). ATP-related metabolites like ADP and adenosine engage additional purinergic P2X, P2Y, and P1 (adenosine) receptors. ATP and ADP lead to excitatory purinergic signaling. However, the ATP metabolites AMP, adenosine, and the purine base xanthine, are bipotential signaling molecules. Adenosine is inhibitory and calming when signaling via the adenosine A1 receptor (ADORA1). Adenosine is activating when signaling via the A2A receptor (Pasquini et al., 2022). Xanthine release from stressed cells undergoing mitochondrial fission binds the adenosine A1 receptor, regulates T-cell immunity and triggers anxiety-associated behaviors (Fan et al., 2019). During development, GABAergic synapses are stabilized by adenosine receptor A2A (ADORA2A) signaling (Gomez-Castro et al., 2021). Excitatory circuits are used to trigger the cell danger response and anxiety signaling, while inhibitory circuits are used for calming and safety signaling. Future studies and clinical trials will be required to test the practical benefit, safety, and efficacy of therapies directed at inhibiting excitatory ATP-signaling in ASD by using antipurinergic drugs like suramin (Naviaux et al., 2017) and others to restore the E-I and danger/safety signaling balance and improve symptoms.

15. ATP signaling, MIPS, and metabolic network regulation

The mitochondrial information processing system (MIPS) ensures that diverse chemical and physical signals are sensed and integrated by mitochondria (Picard and Shirihai, 2022). Effectors like ATP lead a double life as both a metabolite and a signaling molecule. Other metabolic effectors that lead a double life include reactive oxygen species (ROS) like peroxide (H_2O_2) and superoxide ($O_2^{\cdot-}$), nitric oxide (NO), hydrogen sulfide (H_2S), and endogenously produced carbon monoxide (CO). Once triggered by stress, injury, or infection, the release of mitochondrial DNA (mtDNA) and RNA (mtRNA), mitochondrially-derived peptides like MOTS-c and humanin (Miller et al., 2022), intracellular calcium, stress-related mitokines like FGF21 and GDF15 (Keipert and Ost, 2021), innate immune scaffolding proteins like the mitochondrial antiviral sensor (MAVS) and stimulator of interferon genes (STING) (Bahat et al., 2021), steroid hormone metabolism (Bassi et al., 2021), and mitochondrially-derived vesicles and exosomes (Lazo et al., 2021) each participate in amplifying and propagating the cell danger signal initiated by eATP and signaling through P2Y, P2X, and P1 receptors.

While eATP is just one of many signals ultimately used by the cell to signal stress, it is kinetically the first to be triggered by either ROS or threats of any kind. As such, eATP is located at the epicenter of the multilayered cascade of signaling events that regulate and drive the transitions between mitochondrial phenotypes and the dynamical states of metabolism needed to heal.

16. ATP signaling, pollution, and intracellular cortisol excess

Extracellular ATP (eATP) and purinergic signaling are potent inhibitory regulators of the mitochondrial enzyme 11-beta-hydroxysteroid dehydrogenase type 2 (11β-HSD2) (Kadereit et al., 2005). This enzyme uses mitochondrial NAD + to inactivate cortisol by oxidation to cortisone. A number of anthropogenic environmental chemicals like organotin compounds used in pesticides, paints, and as wood and metal preservatives on ships and in buildings, teflons like perfluorooctanesulfonate (PFOS), and fungicides like thiram, are potent inhibitors of 11β-HSD2 (Zhou et al., 2017) (Fig. 7). In the case of PFOS, just 50 pM (5×10^{-11} mol/L) is enough to inhibit 50 % of the activity of 11β-HSD2. PFOS and other perfluoroalkyl substances (PFAS) are called forever chemicals because they bioaccumulate in many species, are now found in the blood of 97 % of infants and adults in the United States (Lewis et al., 2015), and have biological half-lives of 3–5 years in the blood (Li et al., 2018). These chemicals in the human exposome cause intracellular cortisol excess, potentiate whole-body stress signaling, and delay or block progress through the healing cycle. Because cortisol can bind to the mineralocorticoid receptor, enzymatic inhibition of 11β-HSD2, DNA mutations, or epigenetic downregulation can also lead to essential hypertension and apparent mineralocorticoid excess in some patients despite low levels of renin and aldosterone (White et al., 1997).

Elevated intracellular cortisol stimulates phenylethanolamine N-methyl transferase (PNMT), which leads directly to more epinephrine synthesis by methylation of norepinephrine and more storage in granules for later release (Wurtman, 2002). Exposure to stress levels of cortisol in young birds has been shown to produce long-term defects in mitochondrial oxidative phosphorylation and impair reproductive fitness as adults (Crino et al., 2022). The predicted result of childhood exposure to environmental pollutants like PFOS is systemic intracellular cortisol excess, increased norepinephrine and epinephrine synthesis, increased sympathetic tone, and prolonged autonomic imbalance of excitation and inhibition. After preconditioning in childhood by environmental toxicant exposures and other adverse childhood experiences (ACEs), excitatory sympathetic fight or flight and its associated non-social behaviors, cell danger metabolic signaling, and inflammation is excessive, and inhibitory parasympathetic tone associated with rest and recovery and pro-social behaviors, and CNS safety signaling is deficient. eATP and several common environmental pollutants act synergistically to impair the healing cycle and add to the dysfunctional mosaic of cells in the tissues affected (Figs. 5-7, and 9).

17. Diverse biochemical pathways are used to create the cell danger response

The careful regulation of the cellular fates for each of the major atoms extracted from the chemosphere and utilized by living systems in the biosphere is critical for survival. This means that the regulation of oxygen (O), carbon (C), nitrogen (N), sulfur (S), phosphorus (P), sodium (Na), potassium (K), calcium (Ca), chloride (Cl), magnesium (Mg), iron (Fe), and 30 other trace elements in regulated proportion, is critical for survival. The stoichiometry of these elements, classically a 106:16:1 ratio of carbon to nitrogen to phosphorus (C:N:P), was first studied by Alfred Redfield in ocean plankton and thought to be a fixed biological property of life (Redfield, 1934). Today it is known that short-term changes elemental ratios in cells are determined by the chemical balance between oxidation and reduction, which is determined in large part by the dissolved oxygen concentration in the surrounding water. At ocean scales, the oxygen content of water is decreased by things like agricultural runoff and fertilizer. These pollutants create dead zones caused by hypoxia (Diaz and Rosenberg, 2008). Hypoxia triggers a cellular stress response that changes metabolism and changes the C:N:P ratio in cells (Quan and Falkowski, 2009). Hypoxia can be caused by decreased oxygen delivery, increased oxygen consumption, or both. Because mitochondria operate as the biochemical sinks for oxygen consumption, small changes in oxygen consumption by mitochondria lead to rapid changes in the dissolved oxygen content in the cytoplasm of cells. When mitochondrial oxygen consumption decreases and the delivery of oxygen to the cell by surrounding capillaries is unchanged, the dissolved oxygen concentration in the cytoplasm rises like water in a bowl. When mitochondria use less oxygen for basal energy metabolism, the remaining excess of cytoplasmic oxygen is used for ROS production and oxidative shielding to protect the cell from many different kinds of physical, chemical, and microbial danger (Naviaux, 2012).

In a model of acute cell danger signaling, systemic injection of extracellular ATP was found to reprogram over 30 different biochemical pathways, and caused changes in body temperature, basal metabolic rate, and behavior in mice. The top 15 pathways that were changed by ATP-associated purinergic signaling included phospholipids, sphingolipids, microbiome, purines, methylation and 1-carbon metabolism, fatty acid oxidation, eicosanoids, glycolysis, bile acids, pyrimidines, the Krebs cycle, transsulfuration and glutathione, polyamines, and the urea cycle. ATP injection also unmasked a latent metabolic memory response in a mouse model of autism. ADP, AMP, cAMP, and adenosine injection produced similar but non-identical effects. In contrast, systemic injection of GTP, cGMP, UTP, TTP, or CTP had no significant effect. Males were found to be more sensitive to the behavioral effects of eATP. Females were more sensitive to the metabolic effects (Zolkipli-Cunningham et al., 2021).

18. Multichannel, continuous monitoring of the CDR and healing

The phases of the healing cycle have a chemical and mitochondrial basis. This fact makes the stages of the cell danger response amenable to biochemical and tissue microstructural monitoring. Biomarkers and potential surrogates for toxicant exposure, infection, and progression through the phases of the CDR are listed in Table 3. Many of these biomarkers might one day be monitored continuously using multichannel transdermal spectroscopic or percutaneous microneedle devices (Tehrani et al., 2022) like the smart phone devices now used for continuous glucose monitoring in diabetes (Lee et al., 2021a). Continuous monitoring devices collect time-series data, and create the opportunity to discover new dynamical properties, time constants, cycles, and periodicities that cannot be measured in a snapshot of blood chemistry. Application of continuous, multi-channel, transdermal CDR-monitoring devices, breath and blood analysis, may one day permit new research into the sensitivity and specificity of dozens of small molecules and biophotonic parameters (Liu et al., 2021b) for monitoring toxin exposure, and even for tracking the efficacy of new treatments to facilitate healing in many different intensive care, inpatient, outpatient, and occupational settings.

PART 3—Integration

19. Pónos, stress, ROS, and the cell danger response

Pónos is the word used by Hippocrates to describe the energy- and resource-consuming struggle or toil against the visible and invisible forces that cause disease. In modern terms, pónos is the work required to cope with forces that oppose health (Dubos, 1987). Some authors translate pónos as “pain”, but the original word Pónos (Πόνος) was more nuanced and referred to an ancient elemental god, the personification of

Table 3
Biomarkers and potential surrogates for monitoring the cell danger response and healing cycle.

No.	Measurement	CDR Phase 1—Inflammation	CDR Phase 2—Proliferation	CDR Phase 3—Differentiation	Health with Circadian Cycling
1	eATP	Highest	High	Low	Lowest-Circadian
2	eAdenosine	Highest	High	Low	Lowest-Circadian
3	eUTP	Highest	High	Low	Lowest
4	eUDP-glucose	Highest	High	Low	Lowest
5	eUridine	Highest	High	Low	Lowest
6	Lactate	Highest	High	Low	Lowest
7	Alanine	Highest	High	Low	Lowest
8	Propionic acid	Highest	High	Low	Lowest
9	Glucose	Medium	Higher	Medium	Lower
10	Bicarbonate (HCO_3^-)	Lowest	Low	Increasing to Normal	Narrow Circadian
11	pCO_2 (and calculated dissolved CO_2)	High	Medium	Decreasing to Normal	Circadian
12	Extracellular K^+	High	Medium	Decreasing to Normal	Narrow Circadian
13	Urea (needed for osmolality calculations)	High	Low	Lower	Lowest
14	Peptide oncotic pressure (mOsm)	Increasing late	Decreasing early	Low	Lowest
15	Osmolar gap (Measured mOsm – Calculated mOsm)	High late	Low	Low	Lowest
16	Interstitial pressure (for TBI and compartment syndromes)	Increasing late to greater than 20 mm Hg	Decreasing early	<15 mm Hg	−10 to + 15 mm Hg Circadian & Positional
17	pO_2 (and calculated dissolved O_2 in μM)	High	Low	Medium	Circadian
18	pH	Lowest	Low	7.2–7.6	7.4 ± 0.1
19	Ammonia ($NH_3 + NH_4^+$)	High	Higher	Low	Lowest
20	Glutamine	High	Higher	Low	Lowest
21	Nitric oxide ($NO^·$)	High	Low	Lower	Lowest
22	Nitrite (NO_2^-)	High	Low	Lower	Lowest
23	Asymmetric dimethylarginine ($C_8H_{18}N_4O_2$)	High	Low	Lower	Lowest
24	Hydrogen peroxide (H_2O_2)	High	High	Lower	Circadian
25	Histamine, N-methylhistamine, imidazoleacetic acid	High	Medium	Low	Lowest
26	Carbon monoxide (CO) from free Hgb-Heme oxygenase 1 (HO1) activity	High	Medium	Low	Lowest
27	Methanol (CH_3OH)	High	Medium	Low	Lowest
28	Formaldehyde (CH_2O)	High	Low	Lower	Lowest
29	Formate (CH_2O_2)	Medium	High	Lower	Circadian
30	Hydrogen sulfide (H_2S)	High	Low	Lower	Lowest
31	Sulfite (SO_3^{2-})	High	Low	Lower	Lowest
32	Dimethylsulfide (DMS, C_2H_6S)	High	Low	Lower	Lowest
33	Beta-hydroxybutyrate ($C_4H_8O_3$, ketone body)	Low	Low	Variable with fasting and carbohydrate intake	Variable with fasting and carbohydrate intake
34	Acetoacetate ($C_4H_6O_3$, ketone body)	Low	Low	Variable with fasting and carbohydrate intake	Variable with fasting and carbohydrate intake
35	Alpha-ketoglutarate ($C_5H_6O_5$)	High	Higher	Lower	Lowest
36	Isoprene (C_5H_8) in breath	High	Low	Lower	Lowest
37	Tissue A-V pO_2 Difference (O_2 extraction)	Lowest	Medium	High	Highest
38	Tissue A-V pCO2 Difference (CO_2 production)	High	Medium	Lower	Lowest
39	Cytochrome *c* oxidase (CCO) oxidation state by near-infrared (NIR) spectroscopy	Reduced	Oxidized	Oxidized	Circadian
40	Mitochondrial network fragmentation	High	Medium	Low	Circadian
41	Formylated mitochondrial peptide release	High	Medium	Low	Undetectable
42	Circular mitochondrial DNA and nuclear RNA (circRNA) release (Zaiou, 2020)	High	Medium	Low	Undetectable
43	Mitochondrial network hyper-fusion	Low	Low	Higher (highest in CDR3 persistence states)	Circadian
44	Cell organization (autocorrelation) between cells and tissue layers by stratified light scattering (Pouli et al., 2016)	Low (uncorrelated)	Medium	High	Highest (organized, autocorrelated)
45	Ultra-weak photon emission (450–900 nm; stimulated and spontaneous biophotons)	High	High	Lower	Circadian

toil and struggle against hardship. The cell danger response (CDR) and salugenesis unpack the molecular mechanisms that underlie pónos. Because the CDR is an energy- and resource-consuming process that is costly to life, it can be considered the biophysical definition of "stress". Pónos, stress, and the CDR are equivalent terms for the work of salugenesis and the healing cycle viewed from different perspectives. The energy used for the biophysical work of the CDR can be expressed quantitatively in calories or joules. Genetic and environmental factors that challenge homeostasis and change the circadian and seasonal energy cycles and metabolic cycles of the cell change the *milieu intérieur* of the cell. These factors are "stressors" or ponogens.

19.1. Purinergic regulation of ROS and redox biology

All stressors trigger a mismatch between four factors: 1) the rate of fuel *supply* (electrons and protons), and atomic *building blocks* (carbon, oxygen, nitrogen, sulfur, phosphorus, etc.), 2) the rate of energy *demand* (cellular ATP turnover), 3) the rate of cellular metabolic waste and toxin removal (set by vascular and cell membrane permeability factors), and 4) the maximum work *capacity* (set jointly by the rate of oxygen delivery and the mitochondrial capacity to convert dissolved O_2 to H_2O and ATP). Any mismatch in these factors results in an increase in intracellular reactive oxygen species (ROS), which inhibits mitochondrial network fusion and the ability to fully metabolize eATP to adenosine. Purinergic signaling through P2X, P2Y, and P1 receptors exerts powerful control over redox biology. While eATP and eADP promote the

production of ROS and reactive nitrogen species (RNS), their metabolic end products eAMP and extracellular adenosine (eAdo) downregulate ROS and RNS production (Savio et al., 2021). Sequential metabolic transformations of ATP to adenosine are used to extinguish cell danger signals and to prepare for the return of safety and housekeeping functions. Because of this pivotal importance for the regulation of danger and safety signals, eATP and adenosine have been called the primordial signaling molecules (Rho and Boison, 2022). Persistence of any phase of the CDR leads to incomplete healing and symptoms of chronic disease, pain, and disability. The restoration of the natural periodicities—the circadian and seasonal rhythms—of the health cycle (Fig. 4A) helps to actively extinguish the metabolic memories caused by CDR persistence associated with chronic illness (Fig. 4B).

20. Chronic pain and vagal safety signaling

Pain and safety signaling co-evolved as cross-inhibitory systems. On the one hand, social interactions and pro-social behaviors reinforce safety signaling and the health cycle (Fig. 4A and 8). On the other hand, pain inhibits cell and tissue receptivity to remote autonomic safety signals, which prevents the gene expression changes needed to alter metabolism and progress through the healing cycle (Fig. 4B). Both the pro-inflammatory signals that cause CDR persistence, and the pro-resolving, anti-inflammatory signals that promote completion of the CDR are conducted to the perceived site of pain via descending cholinergic vagal and C-fiber efferents and by systemic metabolic cues (Kawada et al., 2020). After integration of these stimuli at the level of the affected tissue, locally-contextualized sensory information is sent back to the brain via vagal and spinal afferent axons, completing the stimulus-organ status assessment-response (S-O-R) circuit (Porges, 2022b). This organ system view is analogous to the mitochondrial information processing system (MIPS) that is comprised of three pillars: sensing, integration, and signaling (Picard and Shirihai, 2022). Seventy to 80 % of the fibers of the vagus nerve (8,000 of 11,000 fibers at the level of the subdiaphragmatic vagus in the rat) are ascending afferent fibers that carry sensory information from every organ in the body back to the brain via the nodose ganglion and nucleus tractus solitarius (Berthoud and Neuhuber, 2000), with polysynaptic projections to the paraventricular nucleus of the hypothalamus (Fawley et al., 2021). Both the ventral vagal complex (VVC) of the nucleus ambiguus, and the dorsal vagal complex (DVC) in the brainstem use afferent ATP signaling from the periphery (Blanke et al., 2019) and from brain microglia and satellite glial cells (Hanani, 2015) to monitor and respond to threats of all kinds. This information is then used to guide the reprogramming of metabolism and mitochondrial function. The facts that the vagus nerve is the largest nerve in the body and that a large part of its function is dedicated to sensing and responding to danger have led to it being called the “great wandering protector” (Andrews and Lawes, 1992).

20.1. Autonomic regulation of safety signals, anxiety, and chronic pain

The integration of evolution, neuroanatomy, anti-inflammatory, and safety signals regulated by the components of the vagal system forms the basis of polyvagal theory (Porges, 2022b). Polyvagal theory creates a framework for understanding of the evolution and regulation of evolutionarily recent VVC and ancient DVC circuits in the control of safety and danger signaling, and pro-social behaviors. If long-distance safety signals are not re-established after the initial damage from infection or injury are repaired, the tissue defaults to chronic defense at the cellular level. Mouse models show that anxiety-related behaviors are not determined by the brain alone. Stress-associated behaviors require the interaction of the sensory system, T cells, mitochondrial and metabolic reprogramming, and brain purinergic signaling (Fan et al., 2019). The vagus nerve is critical for determining the balance between local tissue danger signals and long-distance safety signals from the brain. Vagal safety signaling stimulates T cells in the spleen and lymph nodes to release acetylcholine and activate nicotinic acetylcholine receptor 7 alpha (nAchR7α)-containing receptors expressed on macrophages, and dendritic cells. Vagal safety signals reprogram the immune system to create the anti-inflammatory, pro-resolving functions (Wu et al., 2021) needed for progression through the resolving stages of the healing cycle (Figs. 4, 5, 8 and 9). Neuropsychiatric symptoms like generalized anxiety, obsessive thoughts, hypervigilance, and fear after trauma or injury, and many other symptoms appear to trace to defects in this recently discovered cholinergic anti-inflammatory pathway (CAP) associated with vagal safety signaling (Kelly et al., 2022). A similar conclusion flows from the GUTS model (generalized unsafety theory of stress model) of Brosschot and Thayer (Brosschot et al., 2018). Whole body stress responses are default and must be inhibited by consistent CNS safety signals initiated by the prefrontal cortex and transduced to the body system by the brainstem and autonomic nervous system.

20.2. Paradoxical effects of chronic pain and its behavioral comorbidities

When pain, or a threat to physical safety, social status, shelter- or food-insecurity, or poverty persists chronically, it can be transformed to psychological symptoms and behaviors (Iob et al., 2022). Chronic pain, fear, or anxiety can lead to repetitive negative thoughts that can be chaotic and intrusive and feed back to exacerbate inflammatory signaling (Fig. 8). The cognitive consequences of chronic cell danger signaling can progress to obsessive behaviors, or to anger, paranoia, hate, bullying or gun violence on the one hand, or to social withdrawal, depression, hopelessness, and suicidal ideation on the other. This phenomenon has been studied as the “comorbidities” of chronic pain (Jordan and Okifuji, 2011). However, an additional interpretation is plausible under the salugenesis paradigm. Could bullying and violence against others on the one hand, and depression with suicidal thoughts on the other hand, be common but unconscious behavioral responses that evolved to counter-regulate the chronic cell danger response? If true, then these pathological behaviors, cognitive, and affective abnormalities serve a specific physiologic function—they act to decrease the specialized form of inflammation caused by eATP release. By staunching the loss of ATP from cells, these behaviors might act to counter-regulate many of the downstream inflammatory effects of eATP like cholesterol and sphingolipid accumulation in mitochondria and membrane lipid rafts, reactive oxygen and nitrogen species (ROS and RNS), C-reactive protein (CRP), and inflammatory cytokines like IL-1β and IL-6. In support of this hypothesis, bullying behavior has been shown to oppose oxidative stress and decrease inflammatory markers like C-reactive protein, while being bullied has the opposite effect and increases these markers (Copeland et al., 2014). If these arguments are true, then antipurinergic therapy my help to rebalance one of the metabolic factors that can contribute to complex psychobiological phenotypes like bullying, hate, violence, depression and suicidal thoughts.

Studies have shown that chronic fear, anxiety, or pain creates suffering that is transduced at the cellular level to inflammatory signals (Shenhar-Tsarfaty et al., 2015). The stress-associated changes in the metabolic network activate patterned changes in gene expression called the conserved transcriptional response to adversity (CTRA) (Cole, 2019). Cell-based inflammatory signals in the periphery regulate centralized behavior by creating inflammation in the amygdala (Hu et al., 2022). Even the memory of fear from past traumas is inflammatory and leads to post-traumatic stress disorders (PTSD) (Young et al., 2018). Fear, anxiety, and the perception of chronic pain are prime drivers of perseverative thoughts and behaviors, repetitively searching for a solution to relieve the suffering. The salugenesis model posits that the chronic inflammation at the root of these symptoms is caused by chronic hypersensitivity to eATP signaling. Unless resolved at the cellular level, pathological thoughts and behaviors emerge and appear to be reinforced by their anti-inflammatory effect (Copeland et al., 2014) (Fig. 8). If the model shown in Fig. 8 is correct, then solutions to treat symptoms like chronic pain directly with opioid analgesics, chronic

inflammation with glucocorticoids, oxidative changes with antioxidants, or chronic anxiety with benzodiazepines, will have only a temporizing effect. These interventions do not correct the fundamental cause of the pathology that lies at the root of chronic symptoms. Although helpful to relieve acute symptoms, these interventions show only moderate benefit when used chronically (Bradlow et al., 2022; Cassanego et al., 2022), and can cause undesirable side effects that range from osteoporosis and vertebral fractures (Oray et al., 2016), to reductive stress (Sharma et al., 2021), insulin resistance (Smith et al., 2021), addiction, and hyperkatifeia (Koob et al., 2020). An alternative focus of research is needed if the proximate cause of these complex symptoms is to be discovered.

20.3. Retrograde signaling and mitonuclear crosstalk

Changes in mitochondrial function alter the messaging from mitochondria to the nucleus. This is called retrograde signaling, which occurs in two forms: 1) short-path retrograde signals move from mitochondria to the nucleus, taking a path within the cell, and 2) long-path retrograde signaling involves changes in eATP and metabolites released from the cell that then bind in an autocrine and paracrine fashion to receptors on the cell surface. The activation of cell surface receptors then signals to the nucleus, completing the long-path circuit. Mitochondrial functional changes also trigger changes in anterograde signaling from the nucleus (English et al., 2020), drive epigenetic changes (Wallace and Fan, 2010), and tune gene expression. Metabolic memories and persistent hypersensitivity to eATP signaling can lead to chronic anxiety, cognitive changes, and behavioral habits that become the seeds of mental health consequences of past traumas. Later, after years of persistent symptoms and functional abnormalities, structural changes within the cell lead to structural changes outside the cell. Misrepairs like vascular plaques and calcification, tissue scarring, fibrosis, and gliosis, endocrine, muscle, bone, or brain cell loss and atrophy, or the emergence of cancer or autoimmunity, then make a full recovery more difficult. In the case of cancer and autoimmunity, the emergence of these disorders is a stochastic event that occurs at a singularity in place and time, after long persistence of incomplete healing, and results in the clonal outgrowth of pathological cells in which senescence has failed. By actively inhibiting the mitochondrial functions and the morphological transformations required for progression through the healing cycle, the persistence of local eATP danger signals inhibit the cellular receptivity—technically the cellular capacity to respond—to long-distance, anti-inflammatory, pro-resolving, safety, and pro-social signals sent by vagal, neuroendocrine, neuropeptide systems like oxytocin and vasopressin, and endocrine systems like insulin. Insulin resistance, and target organ resistance to other growth factors and hormones are common consequences of CDR persistence.

20.4. Purinosis and its comorbidities

Acute inflammation is known by its signs: *tumor* (swelling), *dolor* (pain), *rubor* (redness), *calor* (heat), and *functio laesa* (dysfunction). Emerging evidence suggests that the symptoms of inflammation and pain are downstream effects of the most fundamental threat to the life of a cell—the loss of the store of energy that drives the engines of life, the loss of intracellular pools of ATP (iATP), and subsequent eATP-related purinergic signaling (Inoue, 2022). Loss of iATP from a cell is like the loss of blood in an animal. If the loss cannot be stopped, the cell and the animal perish. The life-or-death stakes have led to the evolution of powerful gene sets and countermeasures to stop these archetypal threats to life. Hemorrhage is the term used to describe life-threatening blood loss. There is not yet a term to describe the life-threatening ATP loss from the cell. The term *purinosis* is proposed to describe the loss of iATP pools (ATP chemical pressure) in the cell, stress- and redox-gated ATP efflux, and the associated increase in purinergic and metabokine signaling to neighboring cells by eATP, related nucleotides, and metabolites.

The salugenesis model posits that purinosis is the proximate cause of acute inflammation, chronic pain, and their behavioral comorbidities. One cause of purinosis is a non-physiologic drop in, or inhibition of, mitochondrial oxygen consumption. This is associated with an increase in ROS and RNS. In the absence of a decreased blood supply, decreased mitochondrial oxygen, hydrogen, and electron consumption lead to a decrease in mitochondrial water (H_2O) production by cytochrome *c* oxidase, and to an increase the dissolved oxygen content of the cell. Oxygen is lipophilic and the excess diatomic oxygen (O_2) is absorbed into organellar and cellular membranes, driving the production of superoxide (O_2^-), hydrogen peroxide (H_2O_2), nitric oxide ($NO^\cdot$), peroxynitrite (ONOO–), and reactive aldehydes for purposes of oxidative shielding and defense against microbial attack and many other kinds of threat.

By placing mitochondrial oxygen consumption at the hub of all the cell threat detection systems, even biophysical threats like hypertension that inhibit mitochondrial oxygen consumption will trigger an increase in dissolved oxygen and a cascade of downstream effects (Ryanto et al., 2023). Once a threat is detected, expression of inflammatory proteins like the mitochondrial cholesterol transporter known as the 18 kDa translocator protein (TSPO, formerly known as PBR, the peripheral benzodiazepine receptor) is increased (El Chemali et al., 2022). Cellular cholesterol is biophysically concentrated in oxygen-enriched phospholipid membranes. This permits mitochondrial and cell membranes to buffer the excess oxygen by absorbing it from the cytoplasm (Al-Samir et al., 2021). Sphingolipids are recruited to the cholesterol-enriched membrane lipid rafts and sensitize cells to purinergic and cytokine signaling. Further membrane oxygen accumulation leads to carbonylation and cross-linking of membrane proteins, lipid peroxidation, membrane stiffening, and changes in cell membrane potential that activate voltage-gated calcium influx (Klug et al., 2023), membrane lipid glutathione peroxidases, lipoxygenases, and phospholipase A_2 (PLA_2) (Hermann et al., 2014). Time-resolved fluorescence anisotropy experiments show that changes in membrane fluidity occur very rapidly, within 0.15 ms of a change in the partial pressure of oxygen (pO_2) or temperature (Dumas et al., 1997). Excess oxygen dissolved in the cytosolic and nuclear compartments is converted to H_2O_2 by the polyamine oxidase, spermine oxidase (SMOX) (Diaz et al., 2022), which simultaneously produces highly reactive aldehydes like 3-aminopropanal and acrolein (Murray Stewart et al., 2018). If counter-regulatory mechanisms are unable to repair the damage, the cell is removed by ferroptosis (Xie et al., 2022), apoptosis, or by other active cell death pathways. This makes good sense from an evolutionary perspective. The most damaged cells are likely to contain the largest pools of invading viruses, bacteria, fungi, or parasites, or contain the highest exposure to uncaged metals and to toxins that could endanger neighboring cells. By removing the most damaged cells and sounding the alarm, neighboring cells are protected. One of the earliest signs of the abnormal rise in dissolved oxygen concentration is the opening of redox-gated PANX1 channels in the cell membrane to release ATP and signal danger (Retamal, 2014). Supporting the key importance of ATP release in chronic pain and neuroinflammation is the finding that PANX1 channel inhibitors are potent inhibitors of both (Bravo et al., 2014; Seo et al., 2021).

Purinosis is distinct from the concept of hyperpurinergia. Hyperpurinergia can result from one or more of four processes: 1) cell damage or stress-related release of increased amounts of ATP from the cell resulting in decreased intracellular pools (purinosis *sensu stricto*), 2) excess production and subsequent release of purines from the cell as caused by certain genetic disorders of purine salvage, e.g., Lesch-Nyhan syndrome, and synthesis, e.g., phosphoribosyl pyrophosphate (PRPP) synthase superactivity, 3) increased levels of eATP associated with increased receptor activation and signaling, and 4) hypersensitivity to normal, decreased, or pulsed levels of eATP leading to amplified or brittle responses to purinergic signaling. The use of the word purinosis permits mechanistic studies of inflammation to be redirected and

refocused on the proximate cause of the myriad downstream effects of inflammation. If the feedback circuits illustrated in Fig. 8 are correct, then at least three intervention points can be identified that will relieve chronic pain and result in improvements in its comorbidities. These interventions include: 1) removal of any remaining external triggers and sources of injury, 2) behavioral salugenesis therapies, and 3) drug and device salugenesis therapies. As with many salugenesis-directed therapies, these three interventions are expected to be synergistic.

20.5. Salugenesis induction, consolidation, and maintenance therapy

The stages of the therapeutic approach to salugenesis can be divided into induction, consolidation, and maintenance phases. Antipurinergic drugs like suramin, pannexin 1 (PANX1) channel blockers, and other salugenesis therapies are part of induction therapy to reboot healing. They are not meant to be taken for life. These interventions are meant to be bridges. During the induction phase, interventions are meant to act like a cast for a broken leg—they are intended to support the healing process and protect injured tissues from further damage. Once the healing cycle is completed and reentry into the health cycle occurs, then antipurinergic therapy can be discontinued. Slightly before or during the stage of lowering antipurinergic intervention, methods to restore prefrontal and vagal safety signals and autonomic balance by engaging positive affective and pro-social emotions can be gradually reintroduced to build resilient health. The cardinal elements of health must be gradually restored. These interventions can be thought of as the consolidation phase. Intermittent tune-ups with antipurinergic therapies may be needed over time during the maintenance phase. This happens because of drift back to old metabolic patterns. However, the intent of comprehensive salugenesis therapy is for the return of vibrant health to be self-sustaining. The maintenance phase will require sustainable changes in lifestyle, exercise, sleep, nutrition, and a healthy balance of activities to reinforce positive emotions (Vaillant, 2013), inhibit the default "unsafety" response (Brosschot et al., 2018), and prosocial experiences to restore autonomic balance (Porges, 2022b) (Figs. 4 and 8).

21. Supertraits, healing, and longevity

The health and healing cycles are evolutionary supertraits that undergo selection like physical traits like fins and wings. Selection occurs by both predictable and unpredictable environmental factors in the context of life history exposures during each generation. The phenotype of successful healing relies upon the synergistic interaction of at least 7 elements or subsystems that must co-evolve as a supertrait. These subsystems include 1) purinergic (ATP-related) and ROS signaling, 2) mitochondrial metabolism and quality control by mitophagy, 3) the autonomic polyvagal parasympathetic (Porges, 2001) and sympathetic nervous systems, 4) the neuroendocrine and hypothalamic pituitary axis (HPA) systems, 5) cytokines, innate and adaptive immune systems, 6) the microbiome and enteric nervous system, and 7) the gene expression network known as the conserved transcriptional response to adversity (CTRA) (Cole, 2019). Primary disturbance of any one of the elements of the healing cycle will produce adaptive changes in the other 6 elements. None can be changed without changing the others. Not surprisingly, the functional elements of the healing cycle overlap with genetic subsystems that regulate longevity (Farre et al., 2021). Longevity is tightly calibrated to match changes in whole-body mitochondrial function. For example, mitochondrial bioenergetic function measured as the basal metabolic rate (BMR) in calories and calculated from the basal rate of oxygen consumption ($\dot{V}\ O_2$) is a predictor of longevity and mortality. Hypermetabolism is costly. Even a 10 % increase in BMR above age-matched healthy control levels leads to increased mortality (Ruggiero et al., 2008). Reciprocally, many different hypometabolic states have evolved like hibernation and dauer, to provide protection during times of life-threatening environmental stress or illness (Gorr, 2017).

22. Allostasis and the mitochondrial nexus

The work of Martin Picard and Doug Wallace (Picard et al., 2015), Picard and Bruce McEwen (Picard et al., 2017), Wiley and Seeman (Wiley et al., 2016), Jos Brosschot (Brosschot et al., 2018), and Steven Cole (Cole, 2019; Uchida et al., 2018; Xiao et al., 2018), has helped to weave together two long threads of independent inquiry regarding stress biology and complex neuropsychiatric disorders. These authors showed that physical and psychologic stressors activate similar cellular responses that can be traced to changes in mitochondrial function and ancient pathways that evolved to defend cells from intracellular and extracellular pathogens. Mental health and neurodegenerative disorders share many of the same risk factors as common non-communicable chronic diseases (NCDs) like heart disease, diabetes, and cancer (Stein et al., 2019). Allostasis refers to the anticipatory regulation of adaptive responses prior to re-exposure to stress as a mechanism for dampening the magnitude of physiologic excursions from the mean. The concept of allostasis helps to explain how many complex disorders share the same risk factors (Sterling, 2012). The point of convergence between allostasis and the physiologic response to stress has been called the mitochondrial nexus (Picard et al., 2018).

The concept of the cell danger response was developed to place the mitochondrial nexus in temporal context. The reprogramming of mitochondria and metabolism during the CDR and healing is carefully choreographed and responsive to local cellular conditions. Experiments have shown that mitochondria reside at the epicenter of a multi-layered kinetic cascade of metabolic, cellular, and behavioral ripple effects that are initiated by environmental change (Figs. 4, 5, 7, and 9). Metabolic studies have shown that specific molecular stages could be identified that were developmentally controlled, entered, exited, and extinguished in a predictable sequence during the process of healing and regeneration (Naviaux et al., 2009). When metabolomics was used to study the similarities across several different complex disorders a common theme emerged. Metabolic abnormalities caused by abnormal persistence of normal pathways used in different stages of the cell danger response during the healing cycle were a shared feature of each disorder. The scientific study of the molecular features and governing dynamics of the healing cycle is the study of salugenesis.

23. Salugenesis and salutogenesis

Salugenesis and salutogenesis have different meanings. In 1979, the word salutogenesis was coined by the American-Israeli medical sociologist, Aaron Antonovsky (1923–1994) (Antonovsky, 1979, 1987, 1993) to describe the lifestyle choices and coping skills that were associated with the production and preservation of health despite sociologic, economic, or environmental hardships. In contrast, salugenesis was coined in 2019[1] to describe the factors needed for healing. Salugenesis concerns itself with the regulation and molecular, metabolic, cellular, organ system, obligate (involuntary) and facultative behavioral features of the healing cycle (Figs. 2-5). Salutogenesis and salugenesis are complementary. Salutogenesis emphasizes a top-down perspective. Salugenesis emphasizes a bottom-up perspective. Both salugenesis and salutogenesis refer to the integrative, order-restoring processes required for resilience, regeneration, and the restoration of health. These processes oppose the disintegrative, order-disrupting processes of pathogenesis. Salugenesis uses cellular energy to reverse the arrow of entropy, from disease production to health recovery. In contrast to pathology—the formal study of the mechanisms of disease—salutology, or perhaps salogy, pronounced "sal' ogy"—might be coined as a

[1] First used in public lectures on 3/23/19 for the MINDD Foundation in Sydney, Australia: https://www.youtube.com/watch?v=QG5eNvRfH7M, and 4/11/19 at the National Institutes of Health in Bethesda, Maryland: https://www.youtube.com/watch?v=OcrxK-PAe_I.

corresponding word for the formal study of the mechanisms of healing. Although salugenesis and salutogenesis differ by referring to molecular and lifestyle scale events, respectively, their conceptual origin is the same; the healing cycle starts when pathogenesis ends (Figs. 2 and 4).

24. Building functional reserve capacity and resilient health

After the steps of salugenesis are complete, the initial state of recovered health is fragile. This is referred to as health* (pronounced 'health star') in Figs. 5, 6, and 9. During this early phase of recovery, the organ or tissue that was damaged is hypersensitive to re-injury and to environmental triggers that cause eATP release and restart the healing cycle. This occurs in part because the accumulation of cholesterol and sphingolipids in lipid rafts around purinergic and other cell membrane receptors, has not yet been redistributed, making cells sensitive to re-injury during convalescence. Resilient health is rebuilt gradually during this time by reinforcing long-distance, vagal and neuroendocrine safety signals, preventing re-injury, and inhibiting local cellular danger signals. Over time, lipid membranes are remodeled, mitochondrial and cellular specialization is restored, and full and robust healing is achieved (Fig. 9). Regular reengagement of the cardinal elements of the health cycle (Fig. 4A) is required to restore and build resilient health. Wakeful activity, nutrient intake, waste and toxin removal, social engagement, nature engagement, and restorative sleep each contribute to the building of functional reserve capacity and resilient health over the weeks and months after injury or illness.

25. The changing chemosphere and exposome

The rising tide of environmental chemicals in our air, water, and food chain has altered the human exposome from conception through old age (Vermeulen et al., 2020). This has recently been measured in marine plankton, which were examined as possible canaries in the coal mine for measuring the impact of manmade chemicals on ecosystem health and human health (Li et al., 2022a). 100 % of the plankton samples collected from the North Pacific Ocean from 2002 to 2020, contained manmade pollutants. These included low but measurable amounts of endocrine disrupting chemicals like phthalates and teflons (e.g., perfluorononanoic acid), pesticides like chlorpyrifos, cancer causing chemicals like pyrene, and antibiotics like amoxicillin. Today, 1 in 6 people die from pollution-related illnesses around the world (Fuller et al., 2022). Mixtures of endocrine disrupting chemicals are now accumulating that contribute to the rising rates of cardiometabolic disease (Lucas et al., 2022) and the obesity pandemic (Catalan et al., 2022). The biological effects of these anthropogenic mixtures cannot be predicted by conventional scientific studies of the effects of a purified chemical in isolation (Caporale et al., 2022). Pharmaceuticals used by physicians and veterinarians to treat chronic illness, and by farmers to increase yields, now contaminate over half of all the lakes and waterways around the world (Wilkinson et al., 2022).

Many chemicals have been used for years without adequate testing. Some of these, like titanium dioxide nanoparticles in food, pharmaceuticals, and personal care products (Rolo et al., 2022), and pesticides like chlorpyrifos (Wolejko et al., 2022) and glyphosate (Peillex and Pelletier, 2020), crept quietly into broad usage before their deleterious biological effects were widely recognized and federal authorities banned them. Many manmade pollutants now contaminate drinking water supplies in cities making it difficult for citizens to avoid exposure (Jiang et al., 2019). Many of these chemicals are known to have effects on mitochondrial structure and function (Will and Dykens, 2018), trigger the cell danger response, and lead to eATP release, inflammation, endocrine disruption, and chronic disease (Figs. 7 and 9). However, because of complex interactions with diet, exercise, and age, and synergistic effects with co-occurring chemicals below the usual single-chemical, no observable adverse effect level (NOAEL), benchmark doses (BMDs), and points of departure (PODs), used by federal and state environmental protection agencies, isolated chemicals within the complex exposome often cannot be proven to be the singular agent of harm, i.e., "the" cause, in humans (Lee and Jacobs, 2019). The total toxic load of chemicals in the environment has damaging synergistic effects on mitochondria, the healing cycle and health, even when no single chemical is present at harmful levels (Kim et al., 2022).

Health and disease are complex synthetic phenotypes that are produced by the interaction of many genes, chemicals, lifestyle, and environmental factors. These interactions require the development of new methods of systems analysis for study. The application of conventional experimental methods designed to isolate single variables is insufficient. Without new methods to address mixture effects, the fact that chronic disease can be caused in vulnerable populations by interacting chemicals present at doses below the safety threshold for any single chemical, can be used to cast doubt by companies that benefit financially from unregulated production (Oreskes and Conway, 2011). Because many different kinds of environmental and genetic stresses are translated by cells into the release of extracellular ATP (Figs. 6, 8, and 9) (Burnstock and Knight, 2017; Erlinge, 2004), new methods for measuring the activation and inhibition of eATP release and the downstream consequences of purinergic signaling may one day provide generic solutions to the challenge of chemical mixture effects.

The number and amount of anthropogenic chemicals released into the environment each year has increased to a point that will be very hard to reverse without concerted and coordinated effort by governments around the world. In the US, over 3,000 chemicals are made and released into the environment at amounts over 1 million pounds each year (Landrigan and Landrigan, 2018). The associated rise in incomplete healing after injury, infection, malnutrition, or sociopolitical upheaval is a global problem. Aquatic ecosystems (Hader et al., 2020), forests (Percy and Ferretti, 2004), wildlife (Acevedo-Whitehouse and Duffus, 2009), and human populations (Naviaux, 2020) are each being affected. Remote sensing methods can now monitor changes in the physical and biotic risk factors for chronic disease on global scales over many years (Jia et al., 2019; Sogno et al., 2020) but local actions are needed.

26. Implications for ME/CFS and long-COVID

Conceptualizing myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and related multisystem chronic fatigue syndromes like long-COVID as hypometabolic survival states (HSS, Table 1) has important implications for treatment. A highly evolved hypometabolic state like hibernation, brumation, estivation, torpor, diapause, or dauer (Gorr, 2017) may be at the root of ME/CFS (Naviaux et al., 2016) and long-COVID. If this is true, then a deeper understanding of the mitochondrial information processing system (MIPS) (Picard and Shirihai, 2022) that is controlled in part by ATP signaling, may lead to treatments that might not be discovered by applying conventional damage and dysfunction paradigms.

Evidence is emerging that patients with long-COVID, also known as post-acute sequelae of SARS-CoV-2 infection (PASC), do not have a generalized defect in mitochondria. Instead of a generalized defect, long-COVID is associated with entry into a specifically altered state of mitochondria function. The evidence for this comes from metabolomics. PASC patients display a chronic pattern of impaired mitochondrial fatty acid oxidation marked by an increase in plasma acyl-carnitines and free fatty acids, along with decreased lactate, pyruvate, malate, and citrate, and a generalized decrease amino acids like methionine, alanine, leucine, isoleucine, tryptophan, asparagine, and taurine (Guntur and D'Alessandro, 2022). This metabolic pattern indicates a specific shift in mitochondrial function to a new hypometabolic state. In contrast, acute mitochondrial oxphos dysfunction brought on by exercising to exhaustion, is marked by an overlapping but distinct pattern of increased lactate, pyruvate, malate, citrate, and amino acids like leucine, isoleucine, tyrosine, tryptophan, and asparagine, but a similar pattern of impaired mitochondrial fatty acid oxidation marked be increased

medium- and long-chain acyl-carnitines (San-Millan et al., 2020). The pattern of increased lactate, pyruvate, malate and citrate, in combination with an increase in short- and long-chain acylcarnitines has also been reported in patients with the classic mitochondrial disease called MELAS (mitochondrial encephalomyopathy with lactic acidemia and stroke-like episodes) associated with reductive stress (Sharma et al., 2021).

Further support for the concept of specific states of altered mitochondrial function triggered by life-threatening stress comes from a study of 795 patients with severe COVID infection requiring mechanical ventilation. Remarkably, COVID patients took nearly 30 days to regain consciousness and follow commands after coming off the ventilator. This time was increased by 16 days if the patient also suffered an episode of hypoxia. Yet, when most patients regained consciousness, cognitive recovery was good. The authors proposed that by reducing brain neural activity during extreme stress, a physiologic state was entered that was ultimately protective (Waldrop et al., 2022).

While it is a well-known axiom in medicine that no treatment works well for every patient, if the common denominator in ME/CFS, long-COVID, and some of the pluricausal diseases listed in Table 1, is proven to be blocks to the healing cycle caused by hypersensitivity to ATP signaling (Fig. 9), expanded research and testing of ATP signaling modifiers like pannexin channel blockers (Mousseau et al., 2018), antipurinergic signaling therapies (Vultaggio-Poma et al., 2022), and other salugenesis-directed interventions may one day lead to new ways of thinking about the origin and treatment of complex chronic illness.

27. Summary and conclusions

Pathogenesis and salugenesis are the first and second stages of the two-stage problem of disease production and health recovery. Salugenesis regulates the choreography of the molecular, cellular, inflammatory, immunologic, autonomic, neuroendocrine, and behavioral steps needed to heal. The study of pathogenesis asks the question, "What are the causes of disease?" The study of salugenesis asks the question, "What are the causes of healing?" Salugenesis is a whole-body process that begins with mitochondria and the cell. In the past 5000 years of written medical history, there was little incentive to develop a detailed mechanistic understanding of the molecular stages of the healing cycle because earlier physicians had learned that treatment of the acute injury was sufficient to achieve recovery. In most cases, healing occurred spontaneously once the cause of the original injury had been removed and the risk to life had passed. Today, incomplete healing has become common.

Without healing, multicellular life on Earth would not exist. Without healing, one injury predisposes to another, leading to disability, chronic disease, accelerated aging, and death (Naviaux, 2019b). Salugenesis is a new area of study that encompasses the genetics and biology of the healing cycle. Salugenesis provides a new framework for understanding the unitary biological response to heterogeneous forms of environmental stress that was first described by Hans Selye over 80 years ago (Selye, 1998). Pathogenesis-based treatments and salugenesis-based treatments target different aspects of chronic disease. Pathogenesis-based treatments are inherently disease-specific. In contrast, salugenesis-based treatments are inherently non-specific because they target the process of incomplete healing that is a shared root of many different chronic illnesses. By targeting the root cause of what Selye called pluricausal disease, non-specific but pluri-beneficial new treatments might be discovered. The development of a new class of medications and non-drug interventions designed to reboot, unblock, disinhibit, support, and promote the natural biology of the healing cycle may one day facilitate recovery from chronic disorders that are currently incurable.

27.1. Salugenesis research

To discover and test new treatments, new experimental models of salugenesis must be developed. Experimental models of salugenesis must address its fundamental dynamics. While acute illness is a temporary *state*, health and chronic illness are two separate and mutually extinguishing *processes*—two linked but separate dynamical systems (Graphical abstract, and Figs. 4 and 9). Salugenesis models will be like ecosystem restoration and succession models (Yackinous, 2015). Salugenesis models will embrace the biological fact that healing is a moving target, with phases that are driven by mitochondrial phenotypic transitions. There will be a temptation to apply pathogenesis-based problem solving and to think that the right therapy will depend on the stage or stages of healing cycle that are impaired. However, this is pathogenesis-based thinking retains the limitations of the old paradigm. Molecular lock-and-key and target-and-silver-bullet models that target a single pathogenic molecule may provide some symptomatic relief but fail to promote research efforts that step back and look for ways to regulate the governing dynamics of the *process* of healing. Salugenesis-based solutions will focus on developing new methods to facilitate the transitions between the stages healing. Interacting networks, drivers, forcing variables, limiters, and modifiers must be sought that regulate the sequential progression of dynamical states of physiology needed to heal.

27.2. Salugenesis therapies

Salugenesis therapies will act synergistically with behavioral, non-drug, and device therapies, and are less likely to cause toxicity (Fig. 8). The improved safety of salugenesis therapies occurs because the goal is not to force a change in one dysfunctional molecule. The goal of salugenesis research is to fix the reason why normal molecules, proteins, organelles, and cells become dysfunctional in chronic disease. The solution comes down to the environmental context. What is a normal function of cells under conditions of microbial infection or trauma, becomes abnormal when it persists after the stress is gone. The goal of salugenesis research will be to discover ways to shift the whole-body system from the phase space of the healing cycle, back to the phase space of the health cycle.

Many of the systems targeted by salugenesis therapies will be found to regulate the connectivity of the metabolic network—the correlations between hundreds of metabolites that are in turn regulated by the mitochondrial information processing system (MIPS). The correlation state of the metabolic network determines the capacity and balance of resources directed for damage repair, growth, or specialized cell functions. By regulating the root signaling systems used to coordinate the transitions between the stages of the cell danger response, cellular energy and resources can be redirected, and the symptoms of chronic illness extinguished as the energy- and resource-consuming process of healing and recovery is completed. Similarly, medical devices, prosocial and behavioral interventions, diet, and lifestyle changes that reinforce the dynamics of the health cycle, will help to build more resilient health, and prevent future disease.

27.3. Mitochondrial dynamics versus damage

Mitochondria are social organelles that form dynamic networks that change in structure according to environmental conditions (Picard and Sandi, 2021). Mitochondria are the prime sensors, integrators, early warning system, and the early response system for environmental chemical and physical threats in and around the cell (Naviaux, 2020). Programmed changes in mitochondrial function are required to create the energy gradients and the biochemical materials needed to drive and complete the three stages of the healing cycle (Graphical abstract). When incomplete healing occurs, biopsy of the affected tissue will reveal mitochondrial dysfunction. However, this apparent dysfunction is more about mitochondrial dynamics than damage. Changes in mitochondrial

dynamics have direct effects on organellar quality control and function via mitochondria-associated membranes (MAMs) (Johri and Chandra, 2021). Organellar neighbors become disconnected and dysfunctional. These changes are transient, normal, and necessary to heal after any acute illness or injury.

In contrast to acute illness, most cases of chronic disease are not caused by an active threat. Instead, most symptoms of chronic disease result from incomplete healing and recovery after a threat or injury has passed. In some cases, chronic symptoms are caused by the inability to actively extinguish the metabolic program (metabolic memories) triggered by a past life-threatening exposure. In other cases, incomplete healing is caused by persistent local tissue danger signals, periodic reinjury, reinfection, reexposure to, or hypersensitivity to threats like certain environmental chemicals that trigger changes in mitochondrial structure and function (Fig. 9). Therefore, the earliest symptoms of chronic illness are often the result of changes in mitochondrial dynamics associated with healing (Fig. 5, and Graphical abstract), and not the result of physical damage. Initially, these symptoms are reversible. Long-term metabolic memories are first encoded by physical changes in the organization and number of organelles and cytoskeleton within the cell. Like beads on an abacus, the shape and placement of organelles within the cell create a structural memory of past exposures, adjusting the flow of metabolites and changing mitochondrial function (Cheikhi et al., 2019). For example, by changing the shape of mitochondria, their capacity for ATP production by fatty acid oxidation can be dialed up or down (Ngo et al., 2023), and their capacity for oxidative phosphorylation can be regulated (Baker et al., 2019).

27.4. The rising tide of chronic disease

Although epidemiologic studies of common, chronic, non-communicable disease (NCDs) in children are rare prior to the 21st century, the best estimates suggest that 5–15 %[2] of children born in the 1980s lived with a chronic illness (Van Cleave et al., 2010). Today, 54 % of children in the US live with at least one chronic illness (Bethell et al., 2011). Adverse childhood experiences (ACEs) (Sonu et al., 2019), lack of exercise, malnutrition, and childhood disease, each contribute to the risk of later chronic disease as adults (Rumrich et al., 2020). As adults, social isolation, socioeconomic and political adversity, food and housing insecurity, sleep disturbances, increasingly sedentary lifestyles, and greater separation from healthy ecosystems, forests, and soils, each add to the fragility of health. Sixty percent of adults under the age of 65, and 90 % of adults over the age of 65 live with at least one chronic disease (Buttorff et al., 2017). To take Alzheimer dementia as just one example, if preventive measures are not discovered, the number of people developing dementia is estimated to increase by 300 % by 2050 (Prince et al., 2015). It is not just the absolute numbers of children and adults with chronic illness that are growing. The fraction of people affected is increasing. Despite advances in medicine, we are becoming sicker. As of this writing in 2023, the prevalence of pluricausal diseases listed in Table 1 continues to rise.

27.5. Economics

The health care costs associated with the rising tide of chronic disease are staggering. Even before the COVID pandemic of 2020–2023, the annual health care cost of chronic illness in the US was $3.4 trillion, which was 90 % of the total health care budget in 2019 (Martin et al., 2021). In 2022, the cost was $4.1 trillion (CDC and NCCDPHP, 2022). This was up from $2.8 trillion in 2017 and is predicted to reach $5.5 trillion by 2025. If the current trends continue, the cost of caring for chronic illness in the US will reach 20 % of the US gross domestic product within the next five years (Martin et al., 2021). Growing concern for the epidemic of chronic disease in the US prompted the creation of a National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) (CDC, 2021). The tens of millions of COVID survivors left with chronic fatigue syndrome and other disabilities from long-COVID (Xie et al., 2021) makes the mission of the NCCDPHP even more urgent. Without cures, the 10–30 % of post-COVID survivors with long-term disabilities (Yoo et al., 2022) will be unable to recover their pre-COVID quality of life for years, the economic recovery will be slowed, and care for the disabled survivors will add crippling weight to federal and global health care budgets.

The US devotes much of the $52 billion annual budget of the National Institutes of Health (NIH, 2022) to pathogenesis and risk research. If a portion of this budget can be set aside for salugenesis research, the results would help create a new book of medicine.

28. Dedication

This work is dedicated to Christine Shimizu (1996–1998) who had a mitochondrial disease called Leigh syndrome. Her memory has rallied a community and inspired over 25 years of cutting-edge research into mitochondrial disease, autism, and dozens of other complex medical disorders.

Declaration of Competing Interest

The author is a scientific advisory board member of the Open Medicine Foundation (OMF), The Autism Community in Action (TACA), Autism Research Institute (ARI), Yuva Biosciences, Kuzani, and Paxmedica.

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[2] 5 % chronic illness in children was the number taught in US medical schools in 1982.

response (ISR), and Keshav Singh's work on mitochondrial control of epigenetics (Smiraglia et al., 2008), the mitocheckpoint (Minocherhomji et al., 2012), and the generation of genetic diversity by the transfer of mitochondrial DNA fragments to the nucleus (Singh et al., 2017).

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