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Metabolic features and regulation of the healing cycle—A new model for chronic disease pathogenesis and treatment

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ABSTRACT

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. Over 60% of adults and 30% of children and teens in the United States now live with a chronic illness. Advances in mass spectrometry and metabolomics have given scientists a new lens for studying health and disease. This study defines the healing cycle in metabolic terms and reframes the pathophysiology of chronic illness as the result of metabolic signaling abnormalities that block healing and cause the normal stages of the cell danger response (CDR) to persist abnormally. Once an injury occurs, active progress through the stages of healing is driven by sequential changes in cellular bioenergetics and the disposition of oxygen and carbon skeletons used for fuel, signaling, defense, repair, and recovery. > 100 chronic illnesses can be organized into three persistent stages of the CDR. One hundred and two targetable chemosensory G-protein coupled and ionotropic receptors are presented that regulate the CDR and healing. Metabokines are signaling molecules derived from metabolism that regulate these receptors. Reframing the pathogenesis of chronic illness in this way, as a systems problem that *maintains* disease, rather than focusing on remote trigger(s) that *caused* the initial injury, permits new research to focus on novel signaling therapies to *unblock* the healing cycle, and restore health when other approaches have failed.

1. Introduction

Much of modern Western medicine is based on the principles of acute interventions for poisoning, physical injury, or infection. These principles trace to historical figures like Paracelsus (1493–1541), Ambroise Paré (1510–1590), and Louis Pasteur (1822–1895). These acute care interventions are now widely used in the modern fields of pharmacology, toxicology, urgent care, emergency medicine, and surgery. When caring for acute disruptions in health, the careful identification of the trigger, or cause of the problem, and the anatomical location of the defect, is an important part of good medical care. However, when dealing with chronic illness, treatments based on the rules of acute care medicine have proven less helpful, and can even cause harm by producing unwanted side-effects (Qato et al., 2018).

In chronic illness, the original triggering event is often remote, and may no longer be present. Emerging evidence shows that most chronic illness is caused by the biological *reaction* to an injury, and not the initial injury, or the agent of injury itself. For example, melanoma can be caused by sun exposure that occurred decades earlier, and post-traumatic stress disorder (PTSD) can occur months or years after a bullet wound has healed. If healing is incomplete between injuries, more severe disease is produced. If a new head injury is sustained before complete healing of an earlier concussion, the clinical severity of the second injury is amplified, and recovery is prolonged. This occurs even when the energy of the second impact was less than the first. Progressive dysfunction with recurrent injury after incomplete healing occurs in all organ systems, not just the brain. Chronic disease then results when cells are caught in a repeating loop of incomplete recovery and re-injury, unable to fully heal. This biology is at the root of virtually every chronic illness known, including susceptibility to sequential or recurrent infections, autoimmune diseases like rheumatoid arthritis, diabetic heart and kidney disease, asthma and chronic obstructive pulmonary disease (COPD), autism spectrum disorder (ASD), chronic fatigue syndrome (CFS), cancer, affective disorders, psychiatric illnesses, Alzheimer dementia, and many more.

Great strides have been made since the 1940s in the treatment of

Abbreviations: TOGLEs, transporters Opsins G protein-coupled receptors ligands and effectors; CDR, cell danger response; ASD, autism spectrum disorder; CFS, chronic fatigue syndrome; DAMPs, damage-associated molecular patterns; DARMs, damage-associated reactive metabolites; PTSD, post-traumatic stress disorder; M0, uncommitted; M1, pro-inflammatory; M2, anti-inflammatory mitochondrial polarization

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acute illness. This success has decreased infant mortality, lowered mortality from infections and trauma, and has improved survival after heart attacks, strokes, and cancer. However, this success has led to a sea change in medicine. Instead of spending the majority of time treating acute illness, physicians and health care workers in 2018 now spend the majority of time and effort caring for patients with chronic disease. Over $2.5 trillion is spent every year in the US to care for patients with chronic illness (Burke, 2015). While it has been tempting to treat this rising tide of chronic disease by using the principles that have proven so successful in acute care medicine, a growing literature supports the conclusion that every chronic disease is actually a whole body disease—a *systems problem*—that cannot be solved using the old paradigm. For example, autism, bipolar disorder, schizophrenia, Parkinson, and Alzheimer disease each affect the brain, but are also characterized by whole-body metabolic abnormalities that are measureable in the blood and urine (Gevi et al., 2016; Han et al., 2017; He et al., 2012; Varma et al., 2018; Yoshimi et al., 2016). Rheumatoid arthritis affects the joints, but also has metabolic abnormalities in the blood that show an activated cell danger response (CDR) (Naviaux, 2014) for several years before the onset of clinical joint disease (Surowiec et al., 2016). Coronary artery disease affects the heart, but is the result of long-standing abnormalities in metabolism called “the metabolic syndrome” (Mottillo et al., 2010).

All chronic diseases produce systems abnormalities that either block communication (signaling), or send alarm signals between cells and tissues. Cells that cannot communicate normally with neighboring or distant cells are stranded from the whole, cannot reintegrate back into normal tissue and organ function, and are functionally lost to the tissue, even when they are surrounded by a normal mosaic of differentiated cells. As this process continues, two different outcomes are produced, depending on age. If the block in cell-cell communication occurs in a child, then the normal trajectory of development can be changed, leading to alterations in brain structure and function, and changes in long-term metabolic adaptations of other organs like liver, kidney, microbiome, and immune system. If the communication block occurs in adults, then organ performance is degraded over time, more and more cells with disabled or dysfunctional signaling accumulate, and age-related deterioration of organ function, senescence, or cancer occurs.

Blocked communication and miscommunication inhibit progress through the healing cycle, and prevent normal energy-, information-, and resource-coordination with other organ systems (Wallace, 2010). This predisposes to additional damage and disease. When chronic disease is seen as a systems problem in which the healing system is blocked by key metabolites that function as signaling molecules—metabokines—new therapeutic approaches become apparent that were hidden before. What follows is a description of our best current model of the metabolic features of the healing cycle. Future research will be needed to flesh out additional details.

2. Materials and methods

2.1. Bioinformatic analysis of P2Y1R-related proteins

A TBLASTN search of the human genome was conducted using the P2Y1R protein (Uniprot P47900, ENSP00000304767) as the reference. The top 156 matching sequences were recovered. After removal of pseudogenes, partial, and duplicate sequences, the top 91 unique genes recovered ranged from 257 to 388 amino acids in length, shared a 22%–42% identity with P2Y1R, had blast scores of 70–740, and e-values of 8×10^{-10} to 2×10^{-66}. TAS2R46, a bitter taste receptor, encoded by the *T2R46* gene, was used as an outgroup for tree construction. Sequence alignments were performed using the clustal w method in MegAlign (Lasergene v15.1, DNAStar Inc., Madison, WI). Tree analysis and visualizations were performed using FigTree v1.4.3 (http://tree.bio.ed.ac.uk/software/figtree/).

2.2. Bioinformatic analysis of P2X1R-related proteins

A TBLASTN search of the human genome was conducted using the P2X1R protein (Uniprot P51575, ENSP00000225538) as the reference. The only related genes found were the other 6 known P2X receptors. A BLASTP search of related proteins recovered 46 splice variants of the 7 known ionotropic P2X receptors. The 7 top sequences were 352–399 amino acids in length, sharing 38%–52% identity with P2XR1, and had blast scores of 291–831, and e-scores of 3×10^{-91} to 5×10^{-149}.

2.3. Gene ontology

A gene ontology analysis of the 91 P2Y1R-related genes was performed using the online gene list analysis tools available on the Panther Gene Ontology website (http://www.pantherdb.org/). The top 6 pathways had gene enrichments > 3 times the expected threshold, explained 98% of the connections, and had false discovery rates from 0.02 to 2.7×10^{-65}.

3. Need for a systems biology of healing

The classical signs of inflammation that begin the process of wound healing have been known since before the time of Hippocrates (c. 460–370 BCE). Medical students today still learn the classical Latin terms for the signs of inflammation as *rubor*, *tumor*, *calor*, *dolor*, and *functio laesa* (redness, swelling, heat, pain, and loss of function). In United States, the curriculum at most medical schools does not yet include a specific course on the molecular systems biology of healing. The descriptive elements of injury and healing are taught in traditional courses like pathology, histology, and during clinical service on the surgical and burn wards. However, a dedicated systems biology course, describing our current understanding of the choreographed changes in cell metabolism, biochemistry, gene expression, cell structure, cell function, and pathophysiology that occur after injury and during healing, is missing. The rapidly growing fields of Integrative (Rakel, 2018), Functional (Baker et al., 2010), and Natural (Pizzorno and Murray, 2013) Medicine devote considerable attention to the broader, multi-dimensional study of whole-body healing as it applies to the treatment of chronic illness. However, a modern synthesis of functional and traditional medicine with state-of-the-art medical technology directed at the molecular aspects of healing has not yet been achieved.

4. Metabolomics—A new lens for chronic disease medicine

The newest “omics” technologies to be added to the systems biology toolbox are metabolomics (Jang et al., 2018) and lipidomics (Harkewicz and Dennis, 2011). Rapid advances in these emergent technologies were made possible by technological advancements in mass spectrometry that have occurred since about 2012. In 2018, we are still at least 10 years behind the technical sophistication of genomics, but a flood of new publications using metabolomics has revealed the first outlines of a missing link that connects the genes and disease. Whole-body *chemistry* appears to be this link (Fiehn, 2002).

5. Metabolites as both matter and information

Chemistry provides the link between genotype and phenotype in two ways: (1) cell metabolism is the direct result of gene-environment interactions (G × E = metabolism), and (2) chemicals (metabolites) made by and processed by the cell have a dual biology as both *matter* and *information*. Metabolites have a well-known function as *matter*; metabolites are the physical building blocks used for cell growth, structure, function, repair, and as energy and electron carriers. In ecosystem theory, this metabolic matter represents resources for system structure, function and growth, and for energy to support ecosystem connectivity and resilience to purturbation (Bernhardt and Leslie,

2013). Many metabolites also have a lesser-known function as *information*; they bind specific receptors to change behavior, regulate fetal and child development, shape the microbiome, activate neuroendocrine and immune systems, and regulate the autonomic and enteric nervous systems.

Metabolites like ATP, S-adenosylmethionine (SAMe), acetyl-CoA, NAD+, and others are used to modify DNA and histones directly to alter gene expression through epigenetics (Naviaux, 2008; Nieborak and Schneider, 2018; Wallace and Fan, 2010). Other metabolites like α-ketoglutarate, succinate, fumarate, iron, FAD, and oxygen act as essential cofactors for epigenetic modifications. These metabolites, and others like propionyl-CoA, butyryl-CoA, succinyl-CoA, myristoyl-CoA, farnesyl-diphosphate, and UDP-glucose, also alter the function of other proteins by post-translational modifications of nuclear transcription factors and enzymes throughout the cell as a function of real-time changes in metabolism. Finally, dozens of metabolites act as signaling molecules called metabokines, by binding to dedicated cell surface receptors.

6. The healing cycle

The healing process is a dynamic circle that starts with injury and ends with recovery. This process becomes less efficient as we age (Gosain and Dipietro, 2004), and reciprocally, incomplete healing results in cell senescence and accelerated aging (Valentijn et al., 2018). Reductions in mitochondrial oxidative phosphorylation and altered mitochondrial structure are fundamental features of aging (Kim et al., 2018). The changes in aging are similar to programmed changes that occur transiently during the stages of the cell danger response needed for healing (Naviaux, 2014) (Fig. 1). Although the circular nature of healing seems obvious from daily experience with cuts, scrapes, and the common cold, the extension of this notion to a unified theory to explain the pathophysiology of chronic complex disease has only recently become possible. Technological advancements in mass spectrometry and metabolomics have permitted the characterization of 4 discrete stages in the healing cycle (Fig. 1). The first of these is the health cycle, which requires wakeful activity alternating with periods of restorative sleep. The health cycle will be discussed after first reviewing the 3 stages of the cell danger response: CDR1, CDR2, and CDR3. Aspects of the CDR include the integrated stress response (ISR) (Lu et al., 2004) and the mitochondrial ISR (Khan et al., 2017; Nikkanen et al., 2016; Silva et al., 2009). While all aspects of the CDR are coordinated by nuclear-mitochondrial cross-talk, the precise controls of the transitions between the stages of the CDR are largely unknown.

The following is a current model based on evidence drawn from many experimental studies. As such, the details must be considered provisional. The 3 stages of the CDR are energetically and metabolically distinct. The smooth transition from one step to the next is choreographed by metabolic signaling and regulated by 3 sequential quality control checkpoints, CP1, CP2, and CP3 (Fig. 1). The checkpoints appear to interrogate mitochondrial and cellular function. The completion of each stage of the CDR appears to be decided largely on a cell-by-cell basis. These checkpoints are not regulated by a single, deterministic signaling molecule. Checkpoints are better considered as gates controlled by the synergistic effects of multiple permissive and inhibitory signals. The concentration of a particular signaling molecule is determined in part by the total number of cells in a tissue in each stage of the CDR. Both local and systemic signals are used. As such, the checkpoints that regulate progress through the healing cycle are probability gates. Based on real-time chemical signals and

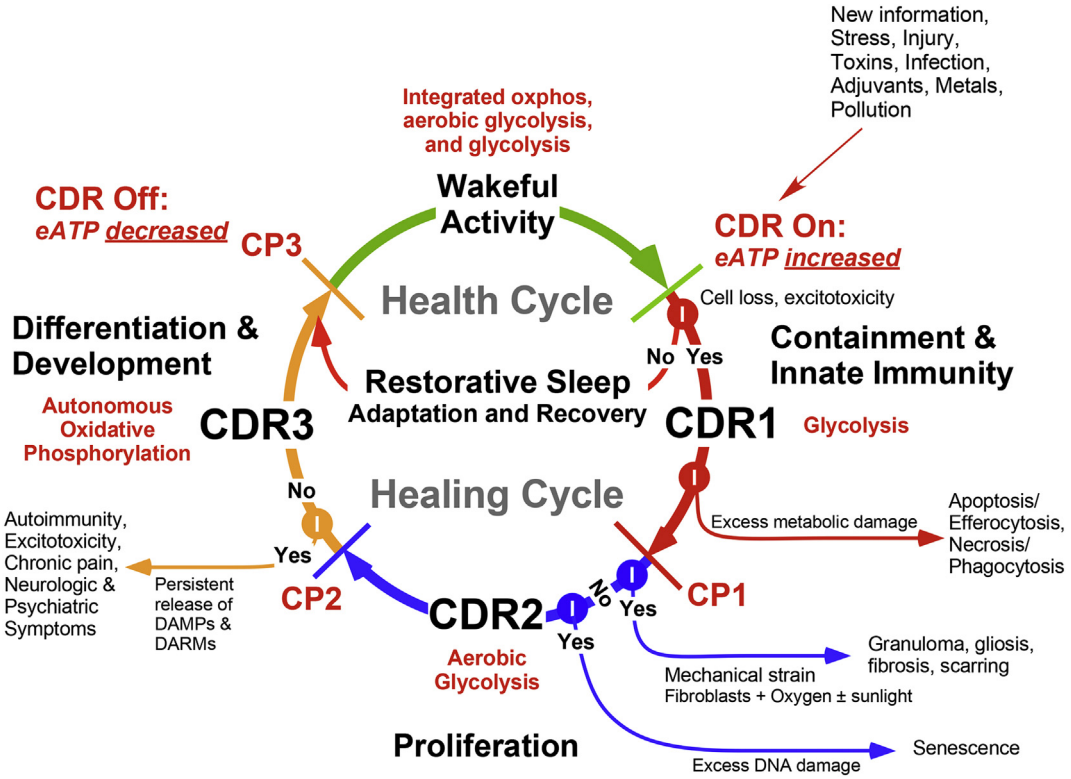

Fig. 1. A metabolic model of the health and healing cycles. Health is a dynamic process that requires regular cycling of wakeful activity and restorative sleep. The healing or damage cycle is activated when the cellular stress exceeds the capacity of restorative sleep to repair damage and restore normal cell-cell communication. CDR1 is devoted to damage control, innate immunity, inflammation, and clean up. CDR2 supports cell proliferation for biomass replacement, and blastema formation in tissues with augmented regeneration capacity. CDR3 begins when cell proliferation and migration have stopped, and recently mitotic cells can begin to differentiate and take on organ-specific functions. **Abbreviations**: eATP; extracelllular ATP; CP1–3: checkpoints 1–3; DAMPs: damage-associated molecular patterns; DARMs: damage-associated reactive metabolites.

Table 1
Provisional classification of stage-specific healing cycle disorders.*

CDR1 Disorders	CDR2 Disorders	CDR3 Disorders
Innate Immune Disorders	**Proliferative Disorders**	**Differentiation Disorders**
–HPA Axis, ATP, Lipids, mtDNA	–mTOR, p21, HIF, PHDs	–DARMs, Mito Polarization
Systemic Inflammatory Response Syndromes (SIRS)	Dyslipidemia	Autism spectrum disorder
Multiple Organ Dysfunction Syndrome (MODS),	Hyperuricemia	Chronic Fatigue Syndrome
Septic shock	Diabetes	Post-traumatic stress disorder
Acute Respiratory Distress Syndrome (ARDS)	Diabetic retinopathy	Fibromyalgia, Chronic pain syndromes, Allodynia
Allergies, asthma, atopy	Hypertension	Neuropathic pain syndromes
Chronic infections (fungal, bacteria, viral, parasitic)	Heart disease	Complex regional pain syndromes
Gulf War Illness (GWI)	Peripheral vascular disease	Obsessive Compulsive Disorder
Tinea pedis, Tinea versicolor, Tinea corporis, Tinea barbae	Cerebral vascular disease	Generalized Anxiety Disorder
Histoplasmosis, Coccidiomycosis	Inflammatory bowel disease	Major depressive disorder
Aspergillosis, Chronic mucocutaneous Candidiasis,	(Crohn's, Ulcerative colitis)	Bipolar disorder
Sporotrichosis, Cryptococcosis,	Non-alcoholic steatohepatitis	Migraine headaches
Sarcoidosis, Chronic granulomatous disease,	(NASH), Cirrhosis	New daily persistent headaches
Chlamydia, Listeriosis,	Idiopathic pulmonary fibrosis	POTS, PANS, PANDAS
Toxoplasmosis, Bartonellosis,	Benign prostatic hyperplasia	Schizophrenia, acute psychosis
Syphilis, Helicobacter, Neisseria,	Keloid formation	Parkinson, Alzheimer
Vibrio cholerae, Tuberculosis,	Subacute spinal cord injury	Multiple sclerosis, Tourette's
Non-tuberculous mycobacteria infections, Leprosy, Lyme,	Dermal vasculitis,	Dystonia syndromes, Lupus Selected epilepsies, Behcet's
Typhoid, Malaria, Leishmaniasis,	Temporal arteritis,	Scleroderma, Sjögren's,
Onchocerciasis, Schistosomiasis	Kawasaki coronary arteritis	Polymyalgia rheumatica
Trypanosomiasis, Filariasis	Cancers and Leukemias	Ankylosing spondylitis
		Amyotrophic lateral sclerosis
Ecosystem disorders		Chronic traumatic encephalopathy
Coral reef fungal infections (*Aspergillus*),		Traumatic brain injury
Coral bleaching disorder (*Vibrio*),		Selected post-stroke syndromes
Shrimp black gill disease (*Hyalophysa*),		Wakeful delta wave activity (EEG)
Microsporidial gill disease in fish,		Hashimoto's thyroiditis
Colony collapse disorder in honey bees,		Psoriasis, eczema
White nose disease in bats (*Geomycosis*),		Alopecia areata, vitiligo
Chytridiomycosis in frogs and salamanders,		Autoantibodies to intrinsic factor
Potato plague (*Phytophthera*),		Rheumatoid arthritis
Sudden Oak Death (*Phytophthera*),		Osteoarthritis
Tea leaf blister,		Macular degeneration
Coffee rust,		Presbyopia, presbycusis
Cacao tree witch's broom fungus,		Diabetic neuropathy
White pine blister rust (*Cronartium*),		Diabetic nephropathy
Sudden Aspen Decline (*Cytospora*)		Irritable bowel syndrome
		Adaptive Energy Conservation and Survival States
		Dauer, diapause, torpor, estivation
		Hibernation, Persister cells
		Plant seed embryo formation
		Caloric restriction metabolism
		Longevity metabolism

* Subdivisions occur within each of the 3 main stages of the CDR.

mitochondrial function, each cell has a certain probability of entering the next stage of healing. This probability is 0%–100% based on cell-specific metabolism and the net effect of all the metabokines in the millieu around the cell. For any given cell, one step in the healing cycle cannot be entered until the previous step has been completed and mitochondrial function in that cell is ready for the next step. Restoration of normal communication between neighboring and distant cells is the last step of the healing cycle and is monitored by checkpoint 3 (Fig. 1). Some of the chronic illnesses and ecosystem disruptions that result from stage-specific interruptions in the healing cycle are listed in Table 1. Further studies will be needed to refine this provisional classification.

7. CDR1—Glycolysis, M1 mitochondria

The function of CDR1 is the activation of innate immunity, intruder and toxin detection and removal, damage control, and containment (Fig. 1). The level of inflammation produced in CDR1 is adjusted according to need. A major trigger of CDR1 appears to be a fundamental change in cellular organization or order, generalized as thermodynamic entropy (Cunliffe, 1997). Physical disruption of gap junctions that connect and coordinate cell function in tissues can activate the CDR. Other triggers include bacteria, viruses, fungi, protozoa, or exposure to biological or chemical toxins. In all cases, extracellular ATP and other metabokines are released from the cell to signal danger. This happens through stress-gated pannexin/P2X7 channels in the membrane and through an increase in vesicular export of ATP through SLC17A9, the vesicular nucleotide transporter (VNUT), and related transporters (Sakaki et al., 2013).

Mitochondria change their function rapidly under stress. Within minutes, the normal anti-inflammatory M2 form of mitochondria that is specialized to meet the metabolic needs of the differentiated cell, is polarized toward pro-inflammatory, M1 mitochondria (Naviaux, 2017) (Fig. 2). This initiates the oxidative shielding response needed for damage control and containment (Naviaux, 2012). When less oxygen is consumed by mitochondria for energy production by oxphos, more oxygen becomes available for synthesis of oxylipin signaling molecules (Gabbs et al., 2015) and reactive oxygen species (ROS) for defense. The incorporation of oxidized nucleotides produced during the oxidative shielding response that occurs during CDR1 into newly synthesized mitochondrial DNA, and the release of small fragments of this new oxy-

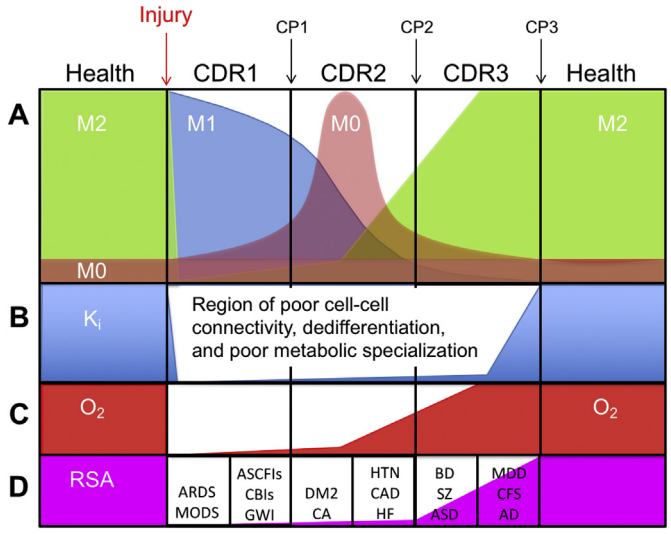

Fig. 2. Systems coordination during the healing cycle. **A.** Functional polarization of mitochondria. **B.** Connectivity (K_i): tissue and cellular responsiveness to circadian, autonomic, and neuroendocrine coordination. **C.** Tissue oxygen consumption and delivery (O_2). **D.** Ventral Vagal Complex (myelinated parasympathetic) Tone (RSA; respiratory sinus arrhythmia). Examples of chronic illnesses within subdivisions of the CDR are provisional. **Abbreviations**: M2—anti-inflammatory mitochondria specialized for oxidative phosphorylation. M1—pro-inflammatory mitochondria specialized for cellular defense in cells that use glycolysis for ATP synthesis. M0—uncommitted mitochondria adapted for rapid cellular growth and aerobic glycolysis. CP1–3: checkpoints 1–3. K_i—inter-organ, intercellular, intracellular, inter-organellar connectivity and communication. RSA: respiratory sinus arrhythmia. ARDS—acute respiratory distress syndrome. MODS—multiorgan dysfunction of sepsis. ASCFIs—Acute Staphylococcal and chronic fungal infections. CBIs—chronic bacterial infections (TB, Helicobacter, Lyme, etc). GWI—Gulf War Illness. DM2—Type 2 Diabetes. CA—cancer. HTN—hypertension. CAD—coronary artery disease. HF—heart failure. BD—Bipolar Disorder. SZ—schizophrenia. ASD—autism spectrum disorder. MDD—Major Depressive Disorder. CFS—chronic fatigue syndrome. AD—Alzheimer dementia.

mtDNA into the cytosol is required for NLRP3 inflammasome activation (Zhong et al., 2018). Release of newly synthesized double-stranded mitochondrial RNA into the cytosol also helps defend the cell during CDR1 by activating type I interferons and the antiviral response (Dhir et al., 2018).

A useful metaphor for communicating this transformation to lay audiences is as a change from powerplants to battleships. The powerplant function of M2 mitochondria is adapted for oxidative phosphorylation. The battleship function of M1 mitochondria is adapted for ROS (peroxides, superoxide, and singlet oxygen), reactive nitrogen species (RNS: nitric oxide and peroxynitrite), and reactive aliphatic hydrocarbons (RAHs: epoxides, acyl-, and amine-aldehyde) production. With M1 polarization, energy-coupled mitochondrial oxygen consumption drops, and cellular energy production switches to glycolysis and lactate production. This switch in bioenergetics is protective to cells when capillaries have been disrupted and the availability of oxygen for aerobic metabolism is compromised. Ischemic preconditioning exposes cells to a transient, sublethal stress that increases ROS and induces HIF1α and TIGAR (TP53-induced glycolysis and apoptosis regulator) for 1–3 days (Semenza, 2011; Zhou et al., 2016). This treatment causes cells to enter CDR1, decreasing mitochondrial oxidative phosphorylation and increasing glycolysis. The result is a dramatic reduction in cell death when preconditioned cells in CDR1 are exposed to potentially lethal insults within the 1–3 day window of protection. If no cells are lost, preconditioned cells return directly to CDR3 and the health cycle via the direct stress-response track that is used regularly during restorative sleep (Fig. 1).

A cell that adopts the CDR1 phenotype must functionally disconnect many lines of communication with neighboring cells. This is needed to make the metabolic and physical changes needed for cellular defense under threat. Communication with neighboring cells during this time is dramatically decreased and changed. The decrease in, and restructuring of cell-cell communication represents a kind of cellular autism that is not just beneficial, but required to initiate the healing process. However, because organs require tight cell-cell communication and coordination for optimum function, this disconnection of cells from the whole comes at a cost; normal organ function is temporarily decreased while cells pass through the steps of healing (Fig. 1). This contributes to the "*functio laesa*", loss of function, described as a canonical feature of early wound repair and inflammation. Removal of debris and damaged cells is accomplished by the combined actions of polymorphonuclear and mononuclear phagocytes recruited to the site, venous, and lymphatic drainage. This loss of function can last for weeks or months after an injury before recovery occurs. One well-studied example is the stunned myocardium that can occur after acute myocardial infarction. After injury, a segment of heart muscle can remain alive and perfused, but non-contractile for months. When recovery occurs, it is accompanied by a shift in metabolism from glycolysis (CDR1), through a blended transition phase of aerobic glycolysis (CDR2), back to oxidative phosphorylation (CDR3) (Figs. 1 and 2). This sequence is associated with an increase in mitochondrial fusion proteins and normal fatty acid oxidation (Holley et al., 2015; van der Vusse, 2011; Vogt et al., 2003), and a restoration of normal cell-cell communication needed for electromechanical coupling. CDR1 ends with passage through checkpoint 1 (CP1, Figs. 1 and 2). CP1 requires the creation of a less-oxidizing and less inflammatory extracellular environment that is conducive for shifting the thermodynamic balance from monomer to polymer synthesis needed for rebuilding RNA, DNA, proteins and membranes, and for the recruitment of previously quiescent satellite and stem cells into cell division in CDR2.

8. CDR2—Aerobic glycolysis, M0 mitochondria

The function of CDR2 is biomass replacement (Fig. 1). Every organ and tissue has an optimum number and distribution of differentiated cell types that are needed for healthy organ function. When cells are lost, they must be replaced or organ function cannot be fully restored. Once the damage associated with the initial injury, infection, or toxin exposure has been cleared or contained in CDR1, the cells that were lost need to be replaced. In CDR2, stem cells are recruited to replace the lost biomass. Stem cells are present in all tissues throughout life. When activated, they will enter the cell cycle. The mitochondria in stem cells and their immediate daughter cells exist in a youthful, metabolically uncommitted state called "M0" (Fig. 2A). M0 mitochondria help to facilitate aerobic glycolysis, also known as Warburg metabolism, which is needed for rapidly growing cells. During aerobic glycolysis, ATP is synthesized by glycolysis. However, M0 mitochondria still consume oxygen and electrons. Instead of using the potential energy gradient for synthesizing ATP by oxidative phosphorylation, M0 mitochondria dissipate the energy gradient by releasing metabolic intermediates needed for polymer synthesis and cell growth. For example, mitochondria are needed for de novo pyrimidine synthesis. The mitochondrial inner membrane protein, dihydroorotate dehydrogenase (DHODH) is required for the 4th step in de novo pyrimidine synthesis to make orotic acid. Orotic acid is needed to make UMP, which is then used to make all the Us, Cs, and Ts the cell needs for RNA and DNA synthesis, and for activated intermediates like UDP-glucose for receptor glycoprotein synthesis and glycogen synthesis, and CDP-choline for phosphatidylcholine synthesis. M0 mitochondria also supply succinyl-CoA and glycine for delta-amino levulinic acid (δ-ALA, also known as 5-ALA), porphyrin, and heme synthesis needed for cytochromes and hemoglobin. M0 mitochondria also synthesize and release citric acid, which can be used either in the cytosol or nucleus by ATP-citrate lyase

Table 2
Functional characteristics of the CDR and health cycle.

Feature	CDR1	CDR2	CDR3	Health Cycle
Cell Metabolism	Glycolysis	Aerobic glycolysis	Oxidative phosphorylation	Balanced oxphos, glycolysis, and aerobic glycolysis
Cellular Autonomy[1]	High	High	Decreasing	Low
Ventral Vagal[2] **Autonomic Tone**	Low	Low	Increasing	High, with diet and activity-related cyclic variations under circadian and seasonal control
Function	Containment, pathogen removal, toxin sequestration, Innate Immunity, clean-up	Proliferation, Biomass Restoration, Blastema Formation*	Differentiation, Cell-cell communication, Metabolic Memory, Adaptive Immunity, Detoxification	Cell-cell communication, Metabolic complementarity, Development, Learning, Fitness, Restorative sleep, Healthy Aging, Cancer suppression, neuroendocrine systems integration
Diseases	Chronic Infections, allergies, MODS, SIRS, ARDS	Diabetes, Heart disease, Cancer, Fibrosis	Pain, Autonomic, Affective, Psychiatric, Neurologic, Immune/Autoimmune, and Microbiome dysfunction, other target organ dysfunction	n/a
CDR Gene Examples	NRF2, CRF2, IDO1, NOXs, NFkB, HO1, PARs, REXO2, eIF2α, STAT1/2, MMP9, IRF1, IRF3/4, SP1, IFNα/β, IL1β, UMP-CMPK2, TNFα	mTOR, HIF1α, AhR, p53, p21, $p16^{INK4A}$, c-myc, PHDs, BRCA1/2, ATR, other DNA repair enzymes, Nanog*, Sox2*, Oct4*, Isl1*	AMPK, FOXO, PPARs, BCL2, P1, P2Y, P2X, CD38, RXRs, CD38, CD39, CD73, IL6, FXR, IFNγ, IL17, IL4, TGF, Iron-sulfur cluster proteins, Mfn1/2, Opa1, Intestinal disaccharidases	n/a

Abbreviations: MODS—multiple organ system dysfunction in sepsis; SIRS—systemic inflammatory response syndrome; ARDS—acute respiratory distress syndrome; NOXs—NADPH oxidases; PARs—protease activated receptors (F2R/PAR1, F2RL1/PAR2, F2RL2/PAR3); IRF1—interferon regulatory factor 1; PHDs—HIF1α-targeting prolyl hydroxylase domain proteins; PPARs—peroxisome proliferator activated receptors; RSA—respiratory sinus arrhythmia; HRV—heart rate variability. [1]Cell autonomy is associated with cellular disconnection, whole body stress, and activation of the HPA axis. [2]Ventral vagal tone via myelinated fibers from the *nucleus ambiguus*, measured by RSA and/or HRV. *For embryonic development and multilineage regeneration in some animals.

(ACYL) as a mobile source of acetyl-CoA. In the cytosol, the acetyl-CoA can be used to make fatty acids, triacylglycerol for energy reserves, and phospholipids for new cell membranes. In the nucleus, the acetyl-CoA is used by histone acetyl transferases (HATs) to place epigenetic marks on chromatin to regulate new gene expression and DNA repair (Sivanand et al., 2017). CDR2 is a stage in which cells with too much DNA damage exit the cell cycle and can adopt an irreversible senescence phenotype, with secretion of exosomes, inflammatory cytokines, growth factors, and proteases (He and Sharpless, 2017).

CDR2 is also the stage in which fibroblasts and myofibroblasts are recruited to help close wounds or "wall-off" an area of damage or infection with scar tissue that could not be completely cleared in CDR1 (Fig. 1). CDR2 is also when blastema formation occurs in certain aquatic organisms like the Mexican salamander (eg, *Axolotl)*, flatworms (eg, *Planaria),* and *Hydra* that display the capacity for multi-lineage tissue regeneration after injury (Heber-Katz and Messersmith, 2018). Less extensive blastema formation is seen as a feature of healing and multi-lineage regeneration in the MRL mouse, a strain of laboratory mouse with remarkable healing abilities (Heber-Katz, 2017; Naviaux et al., 2009).

Recent studies have begun to target metabolic enzymes that regulate CDR2. A class of proline hydroxylase domain proteins (PHDs) that mark HIF1α for proteasome degradation acts as a tissue oxygen sensor. Drug inhibition of a PHD increased HIF1α stability and expression in the presence of normal oxygen, permitted blastema formation, and improved epimorphic regeneration in strains of mice that cannot otherwise fully regenerate after injury (Zhang et al., 2015). During CDR2, dividing and migrating cells are unable to establish long-term metabolic cooperation between cells because their location within tissues is continuously changing. Only after cells have stopped growing and migrating can they begin to establish long-term symbiotic relationships with neighboring cells that build physiologic reserve capacity, provide resistance to re-exposure to a similar environmental danger, and benefit the whole. Once cells exit the cell cycle and establish durable cell-cell contacts through gap junctions and other structural connections, they can exit CDR2 and enter CDR3 (Figs. 1 and 2).

9. CDR3—Cell autonomous oxphos, M2 mitochondria

The functions of CDR3 include cellular differentiation, tissue remodeling, adaptive immunity, detoxification, metabolic memory, sensory and pain modulation, and sleep architecture tuning (Fig. 1). Cells that enter CDR3 stop dividing and establish cell-cell connections with their neighbors. Newly-born cells, that were generated during cell growth from satellite or stem cells in CDR2, must undergo a process of cellular education that involves adjustments in gene expression, cell structure and metabolism, to best adapt to existing tissue conditions before they can take on the role of a fully-differentiated cell in the mature organ and tissue. Healing remains incomplete in CDR3 until newly-born cells differentiate by receiving metabolic instructions and materials from older, neighboring cells that carry the metabolic memories and programming from before the time of the tissue injury that activated the CDR.

Mitochondria in CDR3 cells repolarize from M0 to M2 organelles (Fig. 2). Most remaining M1 mitochondria also repolarize to the M2, anti-inflammatory phenotype needed for differentiated cell function and oxidative phosphorylation (oxphos). This is accomplished in part by re-establishing permanent access to oxygen and nutritional resources, while permitting free release of metabolites and waste products to neighboring capillaries and lymphatics. Oxygen, iron, and sulfur delivery are differentiating and promote mitochondrial biogenesis of iron-sulfur clusters. Iron-sulfur clusters are needed for differentiated cell functions like oxidative phosphorylation, the anti-viral response, protein translation, genome integrity maintenance, and organ-specific physiologic functions (Braymer and Lill, 2017). Outer mitochondrial membrane fusion proteins like mitofusin 1 and 2, and the inner membrane fusion protein Opa1 are also needed to achieve normal mitochondrial network morphology and fully differentiated tissue function (Cao et al., 2017; Del Dotto et al., 2017) (Table 2).

As differentiation proceeds, cells also reestablish connections with the autonomic nervous system and tissue lymphatics. All blood vessels and most tissues receive innervation from the sympathetic and parasympathetic nervous systems. Metabolite and waste product removal helps to provide remote information to and from organs like the brain, liver, intestines, and kidney. Each of these organs participates in regulating whole-body absorption, secretion, metabolism, function, and behavior according to chemical signals that are circulated in the blood. Tissue-specific detoxification restarts in CDR3 and continues through the health cycle. A major regulator of checkpoint 3 is purinergic signaling. The health cycle cannot be reentered until extracellular levels of ATP and related ligands decrease. A decrease in eATP at the completion of CDR3 is a permissive signal that facilitates new and old cells to reestablish the physical, autonomic, and neuroendocrine contact needed for health (Fig. 1, Table 2). In many instances, the completion of CDR3 results in improved baseline physiogic performance and extended reserve capacity compared to before the stress or injury. At a cellular level, this is called hormesis (Fig. 3) and lies at the heart of adaptive improvements in both baseline performance and reserve capacities in response to many forms of stress. These stresses can range from exercise to radiation or chemical toxin exposure, drug tachyphylaxis, to stimuli that result in long-term memory (Calabrese and Baldwin, 2003; Chen et al., 2013; Ristow, 2014).

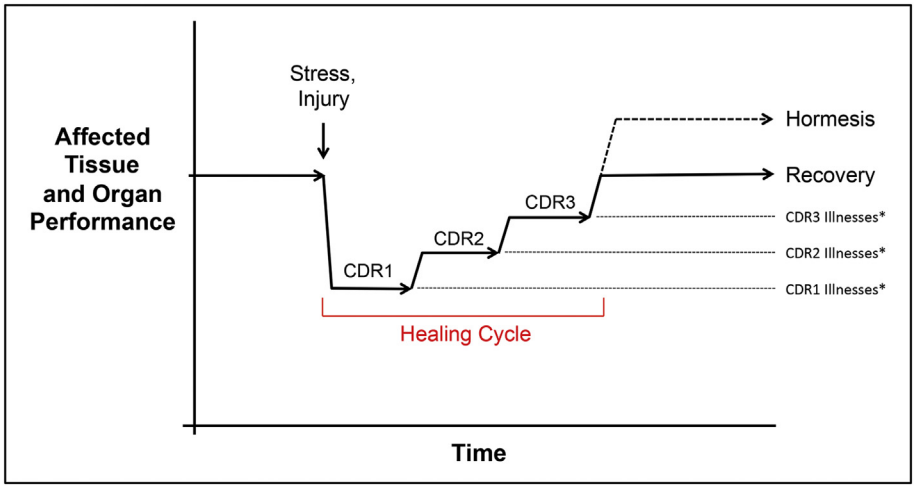

Fig. 3. Timeline of the healing cycle and hormesis. Despite a cascade of events triggered by injury, and hundreds of molecular abnormalities that can be measured in each stage of the healing cycle, the arrow of time is not reversed to heal damage and normalize abnormal functions. The metabolic stages of the healing cycle proceed sequentially forward in time. Healing follows a similar path regardless of the mechanism of injury. *Once a chronic illness occurs, there is little practical difference between the severities possible for CDR1, 2, or 3 disorders. With rare exceptions, each can produce a spectrum from mild disability to death.

10. The health cycle—Harmonized and periodized bioenergetics

The function of the health cycle is to promote wakeful activity, restorative sleep, normal child development, adaptive fitness, and healthy aging. The health cycle is characterized by the balanced, integrated, and periodized usage of all three bioenergetics programs; glycolysis, aerobic glycolysis, and oxidative phosphorylation (Fig. 1). Health requires brain integration and coordination of organ function and whole body metabolism using neuroendocrine and autonomic controls. Wakeful activity and a varied, seasonally-appropriate diet that is sourced from local ecosystems and consumed during daytime hours helped select the gene pools that humans received from their ancestors, up until about the last 200 years. Disruptions in this pattern of seasonal food availability, the increasing prevalence of night shift work, and the decline of traditionally active outdoor lifestyles, have led to new selection pressures on our inherited gene pool. Modern mass spectrometry and metabolomics have helped us achieve a more detailed understanding of the importance of dietary cycling that occurs naturally with the seasons and periodically with occasional short fasts that promote health throughout the year (Mattson et al., 2018).

Cruciferous vegetables in a healthy diet contain isothiocyanates like sulforaphane that act rapidly as chemical pro-oxidants to transiently decrease the amount of intracellular glutathione. This short-term pro-oxidant effect produces a long-term increase in antioxidant defenses by blocking KEAP1 and Cullin 3-dependent ubiquitination, and permitting the translocation of NRF2 (nuclear factor 2 erythroid related factor 2) to the nucleus. In the nucleus, NRF2 acts as a transcription factor to up-regulate over a dozen different cytoprotective proteins like glutamate-cysteine ligase (GCL) to increase glutathione synthesis, glutathione-S-transferase (GST) for xenobiotic detoxification, and heme oxygenase 1 (HO1) for local synthesis of carbon monoxide (CO) at sites of heme extravasation to attenuate M1-polarized mitochondrial pro-inflammatory effects. While oxygen inhibits the stability of HIF1α, the same conditions increase the stability and support the transcriptional activity of NRF2. Acute stress leads to a normal, NRF2 activation response. In contrast, chronic activation by stress ultimately desensitizes and decreases NRF2 activation, and permits long-term increases in inflammation-associated NFkB activation (Djordjevic et al., 2015). The normal health cycle requires the daily modulation of these cycles of increased and decreased oxygen-related redox stress associated with wakeful activity and restorative sleep (Figs. 1 and 2).

11. Exercise and healthy aging

Exercise is medicine. Wakeful activity is essential for the health cycle (Fig. 1) and healthy aging. Regular exercise appears to be the single most important habit known that mitigates the degenerative effects of aging. Moderate exercise creates a natural stimulus that facilitates restorative sleep and repair by creating balanced activation of all the stages of the healing cycle. In many important metabolic ways, exercise “reminds” the body how to heal and promotes disease-free health throughout life. Exercise is adaptogenic (Panossian, 2017). Exercise increases physiologic reserve capacity and resilience to periodic exposure to stress or acute illness. Organ reserve capacity diminishes with age (Atamna et al., 2018). Exercise combats this loss. Even just 15 min of moderate-to-vigorous exercise per day each week lowers all-cause mortality by 22%. Older adults who completed > 30 min/day for 5 days each week had a 35% decrease in mortality over 7–10 years (Hupin et al., 2015; Saint-Maurice et al., 2018).

12. Slow wave sleep and healing

Sleep is medicine. Slow wave sleep (SWS) and the associated increase in parasympathetic autonomic tone are important for healing and recovery during rapid growth in childhood (Takatani et al., 2018). Disruptions in SWS and parasympathetic tone during sleep are risk factors for many chronic illnesses (Carney et al., 2016; Rissling et al., 2016). Delta waves in an electroencephalogram (EEG) are defined as high amplitude (100–300 μV) slow waves (0.5–2 Hz). Delta waves are a normal feature of the deep stages 3 and 4 of sleep. Rapid growth and recovery after high-intensity exercise are associated with an increase SWS in children (Dworak et al., 2008; McLaughlin Crabtree and Williams, 2009). In classical mitochondrial diseases like Alpers syndrome, the need for brain repair is so great that delta waves are seen in the EEG even while awake (Naviaux et al., 1999). Wakeful delta wave activity (slow wave activity) has also proven to be a useful biomarker in studies of traumatic brain injury (Huang et al., 2016). Reciprocally, new methods are being developed to promote wakeful delta waves as therapy in patients with traumatic brain injury (Huang et al., 2017).

13. Metabokines and their receptors

13.1. Metabokines, neurotransmitters, and immune regulators

While it is clear that both exercise and sleep influence metabolism, how does the cell leverage changes in metabolism to influence progression through the healing cycle? Metabolites have long been known to act as signaling molecules in neuroscience. All the classical neurotransmitters are technically metabokines. Molecules like serotonin, melatonin, acetylcholine, glutamate, aspartate, glycine, D-serine, GABA, dopamine, norepinephrine, epinephrine, histamine, anandamide, and adenosine are all products of metabolism that act as signaling molecules by binding to cellular receptors. There are even circulating classes of memory T-cells that contain the enzyme choline acetyl transferase (ChAT) and release acetylcholine in response to vagal nerve stimulation to activate important anti-inflammatory macrophages expressing the nicotinic acetylcholine 7 alpha subunit (nAch7α) (Baez-Pagan et al., 2015; Rosas-Ballina et al., 2011). This signaling function of metabolites has not been widely incorporated into discussions of metabolic control of cellular functions and development. Metabolites act directly as informational molecules by acting as ligands for specific G-protein coupled and ionotropic receptors. Secreted metabokines alter the informational content of the extracellular millieu in many ways. One of these is through a process called *exosignalling* (Pincas et al., 2014), which can prime cells for contextually-dependent, non-linear quantitative and qualitative responses to hormones and other signaling molecules. Purinergic receptors respond to adenine and uracil nucleotides and nucleosides (Verkhratsky and Burnstock, 2014). Nineteen (19) purinergic receptors are present in the human genome (Fig. 4). Four P1 receptors are 7-transmembrane G-protein coupled receptors (GPCRs) that respond to adenosine (ADORA1, 2A, 2B, and 3). Eight GPCRs are single-exon, P2Y receptors (1, 2, 4, 6, 11, 12, 13, and 14) that respond to ATP, ADP, UTP, UDP, and UDP-glucose (Fig. 4A). Seven are multi-exon, ionotropic P2X receptors (1–7) that respond to extracellular ATP and act as ion channels for calcium and potassium (Fig. 4B).

13.2. Dendrogram and gene ontology analysis

To investigate the number of receptor systems that are related to the release of ATP and other nucleotides from stressed and damaged cells, a TBLASTN search was performed of human proteins related to the P2Y1 receptor, a prototypic purinergic receptor. The P2Y1R is a conventional, single exon, metabotropic, G-protein coupled receptor with 7 transmembrane domains. A dendrogram of the top 91 P2YR1-related proteins revealed a possibility of 6 groupings according to amino acid sequence and function in the healing cycle (Fig. 5A). These are: A) hemostasis, pH monitoring, cannabinoid, Krebs cycle, leukotriene, and purinergic signaling, B) lysophospholipid, sphingolipid, cannabinoid, and metabolite signaling, C) eicosanoid, lactate, niacin, short chain fatty acid (acetate, propionate, butyrate, and the ketone body β-hydroxybutyrate), and protease signaling, D) viral co-receptors, glucose/sucrose signaling, pro-inflammatory and anti-inflammatory peptides E)

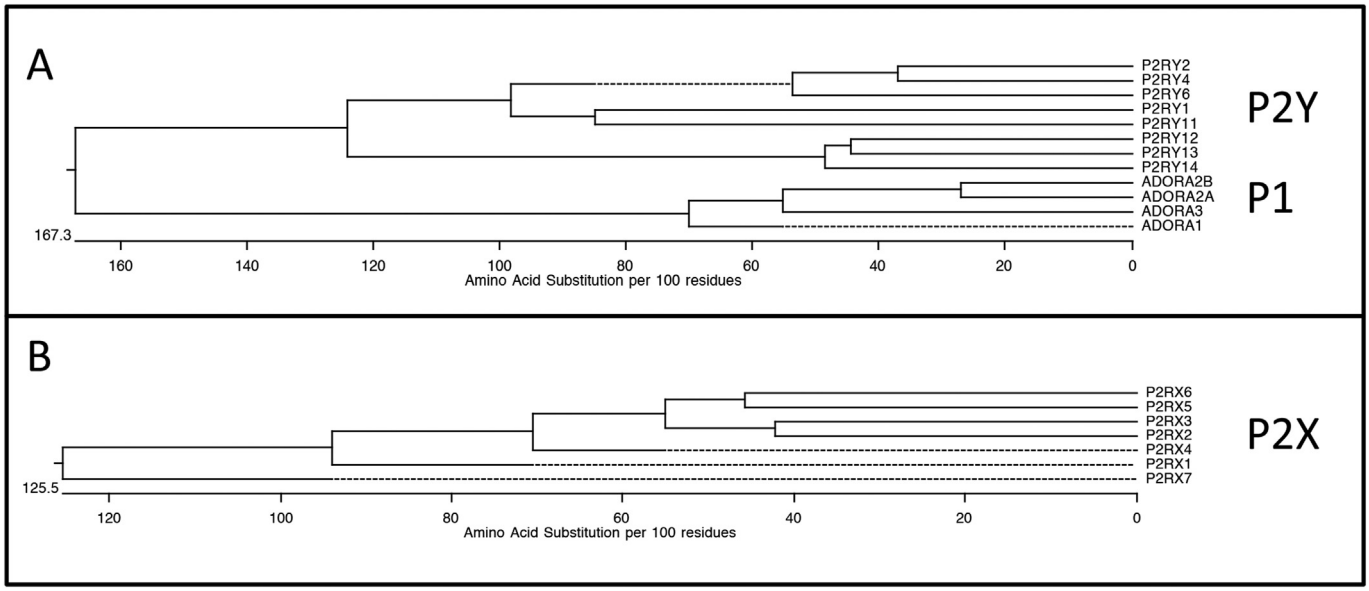

Fig. 4. Purinergic receptors. **A.** Metabotropic G-Protein Coupled Purinergic Receptors, P2Y receptors respond to ATP, ADP, UTP, UDP, UDP-glucose, and/or Ap4A (diadenosine tetraphosphate). P1 receptors respond to adenosine receptor A (ADORA1, 2A, 2B, and 3). **B.** Ionotropic Purinergic Receptors. P2X receptors respond to ATP and/or Ap4A.

neuropeptides and other peptide hormones, and F) chemokines. A gene ontology analysis of the pathways that were enriched in this set of 91 proteins showed that about 50% of the pathways were involved in calcium signaling, 20% with cell movement, and the remainder divided among molecular regulation, immune response, apoptosis, and sensory processing (Fig. 5B).

13.3. Ligand analysis

The ligands that bind to the 91 P2YR1-related proteins differ in size. Eight of the 91 related receptors in Fig. 5A use nucleotides, eg, ATP, ADP, UTP, UDP etc., as their canonical ligand. Another 35 of the receptors use other common metabolites and neurotransmitters like lactic acid, succinate, alpha-ketoglutarate, glutamate, short chain fatty acids, long chain fatty acids, eicosanoids, cannabinoids, sphingolipids, lysophospholipids, serotonin, and melatonin. A total of 43 of 91 (47%) receptors respond to metabokines less than about 400 Da in size. Twenty-four (26%) use peptides 4 to about 80 amino acids long (400–8000 Da), often released by proteolytic activation from an inactive precursor. Twenty-one (22%) respond to chemokines that are 8000 to 10,000 Da in size. Among these are receptors that are essential for innate immunity and for healing and regeneration after injury. For example, the CXCR4 binds to the chemokine CXCL12, also known as stromal derived factor 1 (SDF1), which negatively regulates multilineage regeneration (Heber-Katz, 2017). Four (4%) of the 91 GPCRs related to P2YR1 are constitutively active, or have ligands that are not yet known (Table S1).

14. The TOGLEs that regulate metabolism

Transporters, opsins, G protein-coupled receptors, and their ligands and effectors (TOGLEs) are a diverse group of proteins that share a common evolutionary origin (Saier Jr. et al., 2016; Yee et al., 2013). The single, most diverse superfamily of genes found in metagenomic surveys of ocean picoplankton (bacteria) are the bacterial rhodopsins (Venter et al., 2004). Interestingly, the opsins are related to a group of phosphate, sulfur, cystine, heavy metal, organic acid, salt, and sugar transporters that share similar structures and transmembrane topologies. Difficulties in sensing, handling, or responding to many of these molecules have been documented in complex diseases like autism spectrum disorder (ASD) (Adams et al., 2011). These transporters and opsins are related to G-protein coupled receptors (GPCRs) that constitute over 800 genes in the human genome (Gether, 2000). The functional tie that binds all the TOGLEs together is their role in monitoring the cellular environment for signs of nutrient resources, recognizing friends, signaling danger, and facilitating social and reproductive behaviors. The very receptors that now permit cells to monitor minute changes in the chemical environment are descended from ancestral genes for color vision, smell, and taste (Liman, 2012).

15. Hormone target resistance and axis suppression by the CDR

End organ resistance to hormone signaling is an intrinsic part of the CDR. Once a tissue suffers injury, a shift to dependence on local chemical cues and paracrine signaling is essential. Remote decision-making by endocrine glands cannot provide “boots on the ground”, real-time instructions to injured cells when bidirectional lines of communication are disrupted. A shift from fully integrated and periodized metabolism to cell-autonomous metabolism is an obligate feature of CDR stages 1 and 2 (Figs. 1 and 2, Table 2). *Re*-establishment of hormone sensitivity begins during CDR3, and is required for re-entry into the health cycle (Fig. 1, Table 2). All known mechanisms of hormone resistance have been cataloged. Hormone release, target cell hormone metabolism (Incollingo Rodriguez et al., 2015), and intracellular hormone signaling can each be attenuated by the CDR. End organ resistance during the CDR can affect all the major endocrine systems. Thyroid, adrenal cortical glucocorticoid and mineralocorticoid, and renin-angiotensin system attenuation states are common in patients with chronic fatigue syndrome (CFS). The most common forms of stimulus-response dysregulation lead to complex endocrine syndromes that do not fit classical medical definitions of deficiency or failure because residual hormone production can usually be shown by physiologic stimulation, but is suppressed. These complex disorders have sometimes been called thyroid or adrenal exhaustion syndromes. On the other side of the intracellular energy spectrum, insulin resistance associated with caloric excess and inactivity can lead to type 2 diabetes mellitus (DM2). In all these end-organ resistance states, the treatments that have been most effective are metabolic, diet, and lifestyle interventions that restore normal bidirectional function of the endocrine system. In contrast, chronic treatment with the hormone in question typically leads to

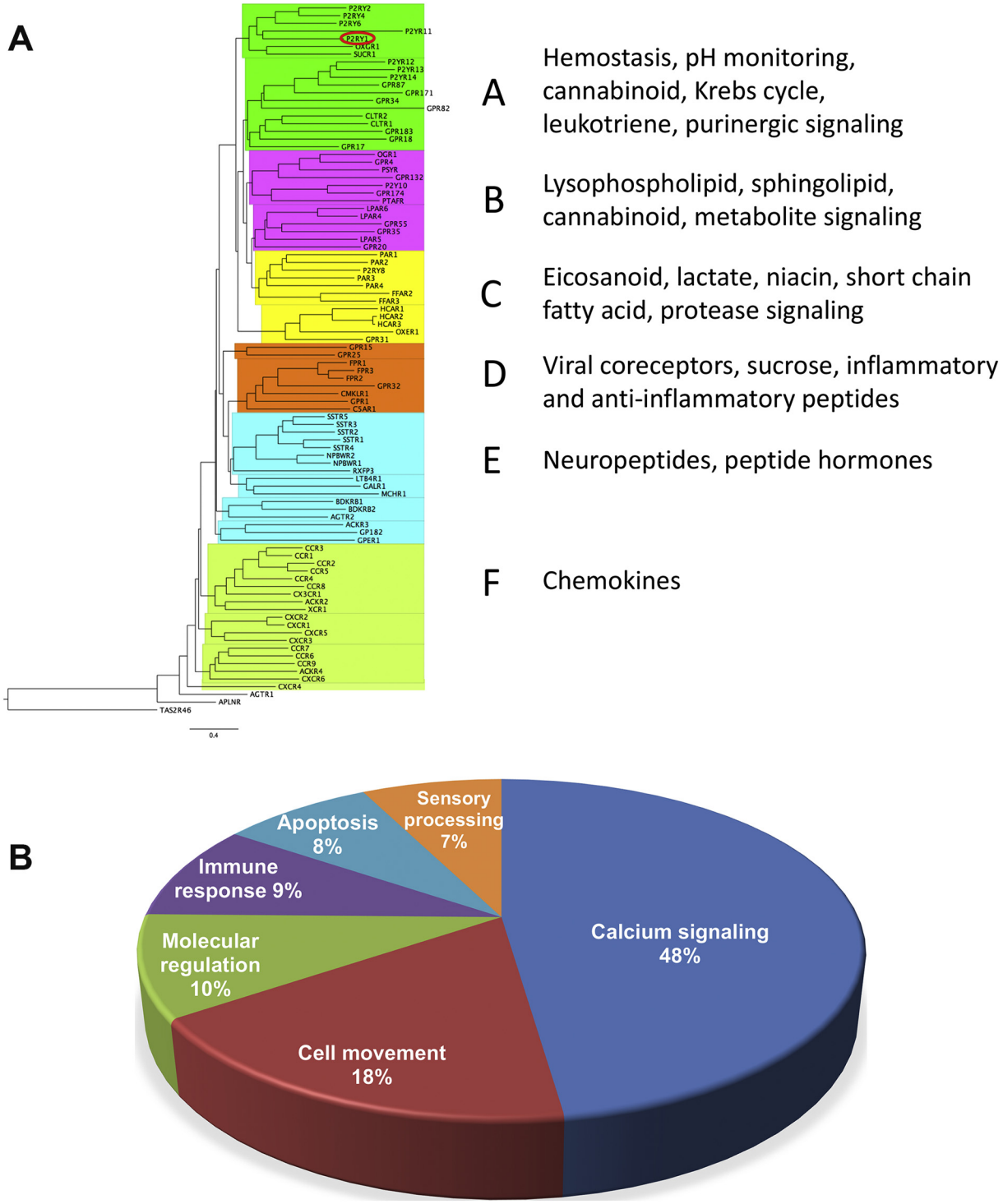

Fig. 5. P2Y1R-related GPCR genes in the human genome. **A.** Dendrogram analysis. P2RY1 is circled to indicate the reference protein used in the TBLASTN search that recovered the 91 proteins analyzed. Colored functional groupings were loosely associated with sequence similarity. **B.** Gene ontology pathway enrichment analysis. (N = 91 P2Y1R-related genes; PANTHER analysis).

iatrogenic side-effects, and dependence on the exogenous hormone. Knowledge of the cell autonomy requirement of the CDR helps reframe the causal mechanisms behind these previously unconnected syndromes (Figs. 1–3, and Table 2).

16. Vagal target resistance and axis suppression by the CDR

The activity of the parasympathetic nervous system measured along a gradient of environmental safety is U-shaped. The ventral vagus complex (VVC) is comprised of myelinated fibers from the *nucleus ambiguus* to the vagus nerve. The VVC is most active under conditions of social attachment, caloric security, and physical safety. At the other extreme is the dorsal vagal complex (DVC). The DVC is also called the dorsal motor nucleus of the 10th cranial nerve (DMNX). The DMNX sends unmyelinated fibers to the vagus nerve. The DMNX is most active acutely under life-threatening conditions, and periodically in synchrony with the VVC during predictable changes in physiology associated with feeding, sleep, and reproduction. Since the majority of wakeful activity

occurs between these two extremes of absolute safety and absolute danger, a large part of life is spent at the bottom of the "U", poised between the neurophysiologic and neuroendocrine commitment to one or the other. A shift to the left on the U-curve is in the direction of health and fitness (Lucas et al., 2018). A shift to the right leads to chronic illness, disability, and death. When the CDR is chronically activated, the coordination between the two limbs of the vagus is disrupted. This results in disinhibiting the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA), which dominate during illness (Fig. 2, Table 2).

Disruption of cellular communication, and the associated increase in cell-autonomous and paracrine signaling by metabokines during the CDR is tightly associated with either a disruption in normal parasympathetic tone from the VVC, or end-organ resistance to cholinergic signals. This is typically quantified by measurements of respiratory sinus arrhythmia (RSA) and heart rate variability (HRV) (Porges, 2007). Substages of the CDR occur during the transition between a fully active ventral vagus complex in health, its rapid inhibition by CDR1, and its gradual return in CDR3. The return of oxygen utilization by healing tissues during CDR2 and CDR3 is associated with increases in RSA and HRV (Fig. 2, Panel D). Increased RSA and HRV are also known to be associated with endurance exercise and aerobic health (De Meersman, 1992, 1993).

When the normal cyclic variations in vagal outflow are disrupted during the CDR, a number of autonomic abnormalities occur. These include postural orthostatic tachycardia syndrome (POTS), and autoimmune disorders like pediatric autoimmune neuropsychiatric syndrome (PANS), and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). All three of these disorders have autoimmune components that appear tied to a decrease or absence of normal anti-inflammatory signaling by the vagus. Vagal efferents mobilize T-cells from gut associated lymphoid tissue (GALT) in the GI tract. The T-cells then induce the anti-inflammatory M2 macrophage phenotype through nicotinic acetylcholine 7 alpha (nAch7α) receptors (Baez-Pagan et al., 2015). Vagal efferents also inhibit cysteinyl leukotriene release by mast cells via nicotinic cholinergic signaling (Mishra et al., 2010). Cysteinyl leukotrienes C4, D4, and E4 are also called the slow reacting substances of anaphylaxis, and bind to receptors closely related to P2Y receptors (CTLR1 and 2 in Fig. 5A). Additional support for the important role played by cholinergic signaling from the vagus comes from the use of nicotinic cholinergic antagonists for neuromuscular blockade (NMBA) during anesthesia. Drugs like suxamethonium and atracurium are used for NMBA, and block nicotinic cholinergic signaling everywhere receptors exist, not just at the neuromuscular junction. These drugs are associated with a risk for anesthesia-induced allergic and non-allergic immediate type hypersensitivity reactions, especially in patients with known allergies and mast cell hypersensitivity (Laroche et al., 2017). Even POTS has recently been shown to be associated with autoantibodies to the angiotensin II receptor (Yu et al., 2018).

17. Tissue mosaics and cellular dyssynchrony in healing

Healing is necessarily heterogeneous and dyssynchronous at the cellular level. This occurs for three reasons: 1) all differentiated tissues and organs are mosaics of metabolically specialized cells with differing gene expression profiles that permit the metabolic complementarity needed for optimum organ performance, 2) physical injury, poisoning, infection, or stress do not affect all cells equally within a tissue, and 3) once a tissue is injured, cells that have not yet completed the healing cycle have not yet reintegrated back into the tissue mosaic, creating chinks or weaknesses in tissue defenses from the old injuries that makes a tissue more vulnerable to new injuries. This process gradually decreases organ function and cellular functional reserve capacity as we age.

Severe threats or injuries cause cells to disconnect from neighboring cells. The initial stages of healing require cell-autonomous actions. If a an entire organ or tissue is threatened, millions of cells will activate the cell danger response (CDR) program in an effort to survive, at the expense of their normal differentiated cell functions. If injury, or the threat of injury, is severe enough, signals are sent from the brain to alter organismal behavior to limit the chances of worsening injury, or the chance of spreading contagion to family or community members. The brain coordinates this stereotyped sickness behavior during activation of the CDR (Dantzer and Kelley, 2007; Naviaux, 2014). The rate at which cells are able to progress through the healing cycle differs according to the local severity of the danger and the ability of the host to mount protective defenses. Metabolic memory of past exposures primes the cellular response to future exposures, even when the original trigger or stress is no longer present.

18. Genes, drugs, and devices that regulate stages of the CDR

To date, the only drug that has been tried explicitly as a treatment for a blocked CDR to promote healing is suramin (Naviaux et al., 2014; Naviaux et al., 2015; Naviaux et al., 2017; Naviaux et al., 2013). A recent study of a device for pulse-based transcranial electrical stimulation to stimulate restorative, wake-time delta wave activity and to improve the quality of sleep has shown promise in the treatment of traumatic brain injury (TBI) (Huang et al., 2017). Brain delta waves are associated with a shift in metabolism that facilitates brain and body repair, recovery, and healing. Once the healing cycle (Figs. 1 and 2) is understood in greater detail, many other drugs and treatments may emerge that are designed to provide novel approaches to treating CDR-associated chronic diseases (Table 1). While increased ATP release from cells is a part of each of the 3 stages of the CDR (Fig. 1), other metabolites and genes play more selective roles. By studying the metabolites, genes, and cell types involved in each stage, more selective therapies can be developed. For example, the NRF2 and hypothalamic-pituitary-adrenal (HPA) axis appear to be involved early in CDR1 and do not require the physical loss of cells as a decision point indicated by the "I" for "information" in Fig. 1.

Organisms have the capacity to mount a similar metabolomic response to stress, regardless of whether the triggering event is neuropsychiatric (Picard et al., 2015), or physical cell damage (Nishi et al., 2013). In both cases, mitochondria are the pivotal organelle (Picard et al., 2017). In both cases extracellular ATP is released by stressed cells as a first alarm for entering CDR1 and the healing cycle (Fig. 1) and intracellular calcium handling is regulated (Schmunk et al., 2017). When glucocorticoids are directly released by ATP stimulation of the adrenal cortex by stressed or damaged cells, hypothalamic corticotrophin releasing factor (CRF) and pituitary ACTH are decreased by feedback inhibition. On the other hand, childhood or adult neuropsychological stress can lead to direct stimulation of CRF. In addition to CRF receptors in the brain, peripheral CRF receptors exist in the GI tract and other organs (Buckinx et al., 2011). Peripheral metabolic responses to stress appear to be regulated in part by urocortin acting on peripheral CRF2 receptors in the kidneys and GI tract (Lovejoy et al., 2014). Drugs and supplements directed at NRF2 or CRF2 signaling may have broad-reaching effects since they will affect the entry and completion of the earliest stage of the cell danger response (Fig. 1, Table 2).

HIF1α (hypoxia induced factor 1α), mTOR (mammalian target of rapamycin), and the arylhydrocarbon receptor (AhR) are important for CDR2-associated cell proliferation (Figs. 1 and 2, Table 2). Because CDR2 involves cell growth and proliferation, the risk for side-effects and iatrogenic complications of CDR2-modulating therapies is high. The drug 1,4-DPCA has been used to target proline hydroxylase domain (PHD) proteins. By inhibiting PHDs, HIF1α is stabilized even under normal oxygen levels. This creates a metabolic state of pseudohypoxia and facilitates tissue regeneration after injury (Zhang et al., 2015).

mTOR and its partners are needed to help coordinate anabolic cell growth. Phosphatidic acid that is newly synthesized from fatty acids

Table 3
Stress-response systems regulated by the mitochondrial CDR.

No.	Stress response system	References
1	Apoptosis and anti-apoptosis	(Portt et al., 2011)
2	NRF2 activation	(Esteras et al., 2016; Naviaux, 2012)
3	Sirtuins and epigenetics	(Lin et al., 2018)
4	Scar formation	(Kuehl and Lagares, 2018)
5	Autophagy	(Boya et al., 2018)
6	Mitophagy	(Zimmermann and Reichert, 2017)
7	Exosomes and secretion	(Claude-Taupin et al., 2017; Saeed-Zidane et al., 2017)
8	Lipid raft formation	(Sorice et al., 2012)
9	Efferocytosis	(Wang et al., 2017)
10	Endoplasmic reticulum (ER) stress	(Carreras-Sureda et al., 2018)
11	Proteostasis and the unfolded protein response	(Murao and Nishitoh, 2017)
12	Transglutaminase activation	(Nurminskaya and Belkin, 2012)
13	DNA damage and repair	(Prates Mori and de Souza-Pinto, 2017)
14	Sensory processing	(Kann, 2016)
15	Allodynia, fibromyalgia, chronic pain	(Gerdle et al., 2013)
16	Hypothalamic-Pituitary-Adrenal (HPA) axis	(Lapp et al., 2018)
17	Liver xenobiotic detoxification	(Jeske et al., 2017)
18	Renal tubular secretion and reabsorption	(Kim et al., 2012)
19	Autonomic nervous system dynamics	(Ford et al., 2015)
20	Innate immunity, inflammation, allergies, autoimmunity	(Hoffmann and Griffiths, 2018; Mills et al., 2017)
21	Energy, glucose, and lipid metabolism	(Anupama et al., 2018)
22	Hypertension and cardiovascular stress responses	(Lahera et al., 2017)

and glycerol-3-phosphate, binds mTOR, alters metabolism, and stimulates growth (Menon et al., 2017). Rapamycin and other mTOR inhibitors have antiproliferative and immunomodulatory effects and have been used to treat a mouse model of a mitochondrial disease called Leigh syndrome (Johnson et al., 2015), but side-effects like delayed wound healing, stomatitis, hypercholesterolemia, and susceptibility to viral infections, may complicate broad extension to CDR-related chronic diseases in humans.

The AhR connects many pathways in CDR2. These include effects on redox signaling and HIF1α, circadian rhythm regulation through BMAL, and immune function via T_{reg} cells (Gutierrez-Vazquez and Quintana, 2018). Indoles from food and the microbiome, and kynurenine from the inflammatory arm of tryptophan metabolism, are natural ligands for the AhR. These effectors act through AhR to facilitate anti-inflammatory T cell and macrophage responses to prevent runaway inflammation during CDR2.

The differentiated functions of cells begin to appear again as cells leave the cell cycle of CDR2 and enter CDR3 (Figs. 1 and 2). Cells become integrated intro the extracellular matrix and 3-dimensional structure of tissues once they have stopped growing in CDR3. Genes important for CDR3 function include AMPK (AMP-activated protein kinase), PPARs (peroxisome proliferator activated receptors α, β/δ, γ), RXRs (retinoid × receptors), BCL2, iron-sulfur cluster proteins, FXR (farnesoid × receptor; also called the BAR: bile acid receptor), and mitochondrial fusion proteins (Table 2). The literature on each of these genes and gene families is extensive. Each plays a role in facilitating mitochondrial polarization from M0 and M1 in CDR2 to M2 organelles adapted for oxidative phosphorylation and the beginnings of metabolic complementarity and differentiated cell function in CDR3 (Fig. 2).

19. Dangers of tonic, single-stage, CDR interventions

Many drugs have mitochondrial toxicity (Will and Dykens, 2018). These drugs can benefit some people, but lead to catastrophic side effects in others. Predicting the mitochondrial risk has proven difficult. The reason for this may lie in the fact that different drugs target mitochondrial functions in different stages of the healing cycle. Visualization of the healing cycle permits a conceptual understanding of how these drugs and certain genetic polymorphisms called ecoalleles (Naviaux, 2017), can have a beneficial effect on one class of aging-related disorders, while having a detrimental effect on others. For example, mitochondrial DNA variants that increase the risk of Parkinson disease (a CDR3-associated disease) also decrease the risk of prostate cancer (a CDR2-associated disease). This amphitropic effect of CDR-selective factors is seen in both genes and drugs. It is likely that chronic treatments directed at any one of the checkpoints governing the healing cycle, will increase the risk of disease caused by unbalanced accumulation of cells in another stage of the CDR. For example, certain treatments of cancer (a CDR2 disease) will increase the risk of Alzheimer dementia (a CDR3 disease) (Driver, 2014). Or a treatment for cardiovascular disease and hypertension (CDR2 disorders) will increase the risk of autoimmune disorders (CDR3). Evidence for this includes data on statin-associated polymyalgia rheumatica (de Jong et al., 2012), and drug-associated Lupus. Likewise, it is theoretically possible, although not yet demonstrated, that chronic preventive therapy for dementia (CDR3), will increase the risk of certain cancers (CDR2) by decreasing excitotoxicity and the removal of mutant cells by immune surveillance. Chronic treatments for pain and inflammation syndromes associated with CDR1 disease may increase the risk of diabetes and cardiovascular disease (CDR2-assoicated disorders), and/or autoimmune disease (CDR3-associated disorders) (Chang and Gershwin, 2011). Subdivisions within each of the CDR stages are likely to exist. For example, the fact that statin treatment for cardiovascular disease increases the risk of diabetes (Chrysant, 2017) suggests that these two disorders belong to functionally separate subdivisions within CDR2 (Table 1, Fig. 2). Further resolution of subdivisions within each stage of the CDR, and corrections of any errors in this first version of the model will require future research. However, without an understanding of the pathophysiology of the healing cycle (Figs. 1 and 2), there is no unified framework for predicting the complex side-effects of old and new treatments for chronic disease.

20. Evolutionary origins

It is no accident that the stages of healing recapitulate the chemical evolution of animal cells. The Precambrian Earth had an atmosphere that was largely devoid of oxygen. When capillaries, lymphatics, or glymphatics in the brain (Plog and Nedergaard, 2018) are torn by injury or decreased by disease, oxygen delivery and waste removal are impaired. An alternative method of energy production must occur if cells experiencing hypoxia are to survive. Under conditions of impaired oxygen delivery, oxidative phosphorylation is handicapped and glycolysis becomes a more reliable source of energy. Once the damage is contained, aerobic glycolysis provides a way of removing excess oxygen, which is genotoxic, to protect against DNA damage, while permitting rapid cell growth needed for biomass replacement. This patterned sequence of metabolic transitions needed for orderly wound repair, tissue regeneration, and differentiation has been studied recently in a classic model of healing and regeneration in flatworms (*Planaria)* (Osuma et al., 2018).

21. Allostasis and the mitochondrial nexus

Allostasis is a concept that was introduced in the late 1980s by Sterling and Eyer (Sterling and Eyer, 1988). The authors gave credit to Professor Charles Kahn at the University of Pennsylvania for suggesting the term. Allostasis literally means “stability through change”. Brain control of metabolism was a fundamental principle described in this paper. Allostasis embodied the idea that all body functions need to be adjusted dynamically according to continuously changing environmental conditions to achieve maximum fitness for long-term survival

and reproduction. While the concept of "homeostasis" taught in medical schools today describes the idea that every measureable parameter in the body has an "optimum set-point" that is continuously defended based on local signals, allostasis points out that all physiologic parameters vary within large dynamic limits according to recent, current, and anticipated future environmental conditions based on brain coordination of the needed physiologic adjustments.

The range of variation for any given parameter is very large in the young, but the capacity to achieve the same dynamic highs and lows decreases with age. This decline is associated with an age-related decrease in the physiologic reserve capacity of every organ system. In an example given by the authors, when blood pressure was measured continuously for 24 h in a young man, values of 110/70 were maintained for several hours during the day. It dropped to 90/55 for an hour when he fell asleep during a lecture. Preparing for work in the morning produced a value of 140/80 for 2 h, while dropping to 70/40 for 6 h at night during sleep, and to 50/30 for 1 h during deep sleep (Sterling and Eyer, 1988). The point of allostasis is that each of these blood pressures is "normal" for the conditions during which they occurred. Over time, if higher blood pressure is maintained, the smooth muscle lining of blood vessels becomes thickened and even higher blood pressures are required to maintain the same resting blood flow. Sterling and Eyer point out that under conditions of unpredictable environmental stress, the brain becomes "addicted" to systems and signaling molecules (hormones, neurotransmitters, cytokines, and metabokines) needed to produce rapid arousal states, and the anticipatory stress responses become the norm. This complicates treatment. Some therapies can result in "withdrawal" symptoms, making a return to a healthy ground state difficult to maintain without a persistent change in diet and lifestyle.

McEwen and Stellar introduced the concept of allostatic load (AL) in the early 1990s (McEwen and Stellar, 1993). Under this concept, when homeostasis fails in the face of multiple types of environmental stress, many different types of disease can result. Recent multivariate analysis of 23 measurable parameters, reporting on 7 physiologic systems that regulate the stress response concluded that AL was a valid construct for operationalizing the components of variance contributed by many different stressors (Wiley et al., 2016). Interestingly, all the metabolic, inflammatory, neuroendocrine, and gene expression changes that occur in response to stress are regulated by mitochondria (Picard et al., 2015). McEwen and coworkers have recently incorporated the idea of mitochondria as the nexus for regulating the biomarkers of AL and chronic disease (Picard et al., 2017). Mitochondria help coordinate the large majority of stress response systems that become activated by allostatic load (Table 3).

Under the healing cycle model for chronic disease, allostatic load initiates the CDR and the healing cycle. In most cases of persistent chronic illness lasting for > 3–6 months, mitochondria are not dysfunctional. They are just stuck in a developmental stage that was intended to be temporary, unable to complete the healing cycle. The healing cycle requires a *programmed change* in mitochondrial function—a shift from M2, to M1, to M0 organelles, and back to M2 (Figs. 1 and 2). When the programmed change becomes fixed and is unable to cycle normally, chronic illness results (Table 1). Over time, sustained changes in mitochondrial function can lead to structural changes in tissues and organs that can make full recovery more difficult.

22. The dauer failsafe response in humans—ME/CFS

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is an energy conservation program—a suite of metabolic and gene expression changes—that permits persistence under harsh environmental conditions at the expense of reduced functional capacity, chronic suffering, and disability (Naviaux et al., 2016). A formal animal model for ME/CFS has not yet been developed. However, several energy conservation states are known that are activated by harsh environmental conditions. One of these is called dauer, the German word for persistence, or to endure. When dauer is triggered by harsh conditions, the life expectancy of a classical genetic model system, the 1 mm long worm *Caenorhabditis elegans,* is extended from 2 to 3 weeks to up to 4 months. Animals that fail to enter dauer under harsh conditions die at an increased rate. In this sense, the metabolic program activated by dauer is a failsafe mechanism that increases the chances of survival in a harsh and unpredictable environment.

Interestingly, the genes involved in inhibiting and promoting dauer have been a rich resource for the study of longevity (Uno and Nishida, 2016). Many DAF (dauer associated factor) genes are also regulated by caloric restriction, a common environmental stress known to increase life expectancy in mammals and many other animals. Despite the fact that dauer worms live longer than unstressed animals, it is not a fully functional life. Mitochondria polarize toward a hardened M1 configuration that is adapted for inducible reactive oxygen species (ROS) production, metabolic energy production shifts toward increased usage of glycolysis, which allows dauer animals to survive in reduced oxygen environments (Hand et al., 2011). Some fatty acid oxidation is still conducted by the newly-polarized mitochondria to permit stored fat reserves to be used for energy, while peroxisomes use very long chain fatty acids to synthesize a glycolipid pheromone (a daumone) needed to induce and maintain the dauer state (Joo et al., 2009). Behavioral responses become "brittle", such that small stimuli produce large responses in otherwise docile animals. Dauer animals are also more resistant to cold-stress (Hu et al., 2015), ultraviolet (UV) light (Murakami and Johnson, 1996), and salt stress. Significant changes in circadian rhythm regulation (Driver et al., 2013), innate immunity (Holt, 2006), behavior (Lee et al., 2017), and sensory processing (Chen and Chalfie, 2014) also accompany the dauer phenotype. Overall, the dauer state and other hypometabolic states permit survival under harsh conditions, but at a high price of much-altered and much-restricted normal function.

The good news is that the dauer state in the worm model is completely reversible. If dauer is a good model for ME/CFS, then there is hope that by studying the molecular controls of the dauer phenotype, new treatments might be discovered rationally to help stimulate the exit from the dauer-like state and begin the process of recovery. The following is a summary of a plausible sequence of pathogenesis for ME/CFS. All stressed cells leak ATP through stress-gated pannexin/P2X7 and other channels. Extracellular ATP (eATP) signals danger and CDR1 is initiated (Fig. 1). If the acute cell danger response and healing cycle fail to eliminate the stress and stop the ATP leak by successful completion of CDR3, then an energy conservation program is activated. Normal cell activation pathways utilize lipid rafts and sphingolipid microdomains on the cell membrane to facilitate metabokine- and cytokine-receptor binding and signaling by receptor subunit dimerization. Sphingolipids are downregulated in most cases of ME/CFS (Naviaux et al., 2016) and may facilitate an energy conservation state.

The dauer-like energy conservation program in mammals may also involve a ligand-receptor desensitization process, decreasing the ability of cells to release intracellular calcium when needed. Calcium stimulates mitochondrial oxidative phosphorylation. When stimulated by ATP and related nucleotides, IP3-gated calcium release is decreased (Schmunk et al., 2017), and mitochondrial and whole cell reserve capacity is reduced. Other mechanisms for downregulating mitochondrial energy production can contribute to this energy conservation state. A multifactorial reduction in mitochondrial pyruvate dehydrogenase complex activity in ME/CFS has been described (Fluge et al., 2016). Upregulation of ectonucleotidases like CD39 and CD73 can increase the conversion of ATP and ADP to AMP and adenosine. Both AMP and adenosine bind adenosine receptors (Fig. 4A) and produce a reversible hypometabolic state in mice that is protective against many environmental stresses, including lethal irradiation (Ghosh et al., 2017). Continued leakage of ATP to the extracellular space for CDR signaling also creates a source for the hypometabolic signaling molecules AMP and adenosine, while depleting intracellular reserves of ATP. Although not

yet tested in a clinical trial in patients with ME/CFS, the ATP and UTP leak might be stopped by blocking the efflux of nucleotides through the pannexin/P2X7 channel with an antipurinergic drug, thereby unblocking the healing cycle (Fig. 1) and permitting recovery to begin. This is similar to a strategy recently tested in a clinical trial in autism spectrum disorder (Naviaux et al., 2017) and illustrated in a whiteboard animation available at: https://www.youtube.com/watch?v=zIdUufy8Lks.

23. Reversibility of chronic illness

If a chronic illness occurs because of a change in function associated with blocks in the CDR, and not a change in structure or loss of cells, that illness is theoretically reversible, ie, curable. When the healing cycle is unblocked, a full recovery is possible. Because the path leading to healing and recovery is different from, and not the reverse of the path that led originally to the disease (Fig. 3), the term "reversibility" is technically incorrect. This point is expanded in Section 29 below. Even when there is some cell loss, scarring, calcification, or other structural change, some healing is still possible by tissue remodeling, but a full recovery becomes more difficult to achieve. Autism spectrum disorder (ASD) can be classified as a CDR3 disorder (Table 1), characterized by both functional and brain structural changes that can vary significantly in severity. In a mouse model of autism, when treatment was delayed until the human biological age-equivalent of 30 years old, the core functional abnormalities in behavior and metabolism in ASD could still be completely corrected with antipurinergic therapy (APT) with suramin, but the gait abnormalities associated with the structural loss of cerebellar Purkinje cells were not reversed (Naviaux et al., 2014).

In the case of cancer, cardiovascular disease, and other proliferative disorders associated with CDR2 diseases (Table 1), metabolic, innate immune, and adaptive immunity can reduce the burden of abnormal cells by removing them. Successful reactivation of CDR1 in the surrounding normal cells, followed by entry into CDR2 for biomass replacement and CDR3 to facilitate tissue remodeling, may result in functional cures for the major symptoms of some CDR2 disorders, even if some limitations remain because of imperfect biomass replacement and tissue remodeling. In the case of CDR3 diseases like autism, treatments directed at unblocking the healing cycle and rebooting metabolism may lead to remarkable clinical improvements (Naviaux et al., 2017).

24. The tempo of physiologic change

The tempo of chronic disease is slower than many people might think. Like a new exercise program, and shifts in metabolism after making an abrupt change in diet, new metabolism and physiology take at least 3 weeks in young adults to settle in to the "new normal". The temporal parallel between disease, diet, and exercise is no accident. The ability to shift metabolism according to seasonal changes and new patterns of food availability within a few weeks of migration to a new location was key to the survival of our ancestors. This timing is built into our genes. It takes 3–4 days before new patterns of gene expression begin to consolidate, and about 3 weeks for new physiologic patterns to "reset" to a new normal after a change in diet, exercise, and other environmental conditions. It takes more time to fully commit to the change. Ultimately, it takes a season of about 3 months or more to fully commit to new foods, physical activities, and environmental exposures (sun, monsoons, droughts, hard freezes, etc) of the season. Three months is also the average minimum time needed to demonstrate synaptic remodeling with exercise or meditation (Thomas and Baker, 2013). A similar tempo might be needed to "reboot" and reset metabolism to a new normal after starting a new treatment for a chronic disease.

25. Metabolic addiction

Once the CDR is unblocked and the healing cycle rebooted, the simplest form of the CDR model predicts that recovery will follow naturally, and health will persist because the genes inherited from our ancestors will defend health in preference to disease and disability. Clinical experience suggests this is not always true. Many patients tend to drift back to the old disease state unless they continue to take measures to actively prevent relapse. This phenomenon may be metabolically similar to addiction. Addiction is a physiologic condition characterized by a baseline physiologic arousal or anxiety state that is temporarily quenched or relieved by a particular behavior or drug. A large body of research has shown that the predisposition to addiction is conditioned by genetics, epigenetics, environmental chemicals, and life stress (Yuan et al., 2016). The most successful alcohol and drug rehabilitation programs teach that recovery is a lifelong process. An addict is never "cured". They are taught to identify themselves as a "recovering alcoholic" or "recovering gambling addict" for life to strengthen resilience and decrease the risk of relapse.

The concept of metabolic addiction suggests that the increased risk of relapse after recovery from chronic illness is the result of a physiologic dependence on the endogenous chemical state produced by a particular stage of the CDR. For example, once a person has suffered from an episode of major depressive disorder (MDD) and recovered, the risk of recurrence is 3–6 times greater than the background population risk (Hoertel et al., 2017). This latent risk suggests that predisposing genetic and/or metabolic factors persist that facilitate a drift back to chronic illness, even after predisposing environmental risks are removed. New studies using metabolomics methods will be needed to test this hypothesis directly.

26. The brain controls metabolism and exit from the CDR

The last step in the healing cycle, CDR3, is ended when the brain re-establishes bidirectional neuroendocrine and autonomic communication with each organ system. Only after the brain re-integrates metabolism over the periodized course of wakeful activity and restorative sleep can the health cycle be re-established. The vagus nerve plays and important role in communicating information from tissues to the CNS. Vagal mechanoreceptors and chemoreceptors monitor organ physiology (Powley et al., 2011). Eighty percent of vagus nerve fibers are made up of sensory fibers returning information from all organ systems to the brain. Among the chemoreceptors are vanilloid (TPRV1) and the purinergic P2X3 receptors responding to noxious stimuli, and extracellular ATP, respectively (Hermes et al., 2016). Vagal afferents terminate in excitatory glutamatergic synapses in the *nucleus tractus solitarius* (NTS). From the NTS, extracranial sensory information is transduced and distributed widely throughout the brain. NTS fibers project back to the ventral vagal complex of the *nucleus ambiguus* and the dorsal vagal complex of the dorsal motor nucleus of the 10th cranial nerve (DMNX) as feedback to the vagus. Feedback to the *nucleus ambiguus* modulates signals conducted along myelinated motor fibers to the vagus nerve for rapid changes in cardiorespiratory and vasomotor function, swallowing, speech, and hearing that occur with stress and well-being (Porges, 2011). The NTS also projects to the locus coeruleus in the reticular activating system to regulate behavioral responses to stress and panic, and to the amygdala in the limbic system, and the paraventricular nuclei of the hypothalamus to regulate physiologic and neuroendocrine responses to stress.

Brain neuroendocrine and autonomic systems function as bidirectional circuits. When CDR stages 1 and 2, or the first parts of CDR3 are active in the periphery, this information is carried to the brain along three channels; endocrine feedback, autonomic afferents, and chemosensory neurons. When this information is received, the brain initiates sickness behavior and sends pro-inflammatory, pro-stress, pro-arousal endocrine and autonomic efferent signals to the periphery. Sleep

structure is also altered to facilitate recovery and promote survival. The default state in both the brain and peripheral tissues is CDR activation. In the absence of additional information, danger and threat are assumed. Healing is an active process that requires positive reinforcement with non-danger, safety and security signals from the brain. Brain inflammation can last for a lifetime after physical injury (Johnson et al., 2013) or early life stress (ELS) and psychological trauma (Cameron et al., 2017). In addition, peripheral pain syndromes and organ inflammation are common after brain or spinal cord injury (Irvine et al., 2018) or brain death (Esmaeilzadeh et al., 2017; Jafari et al., 2018). Unresolved CDR activation by adverse childhood experiences (ACEs) and socioeconomic factors may also play a role in many other adult illnesses like heart disease, cancer, and stroke (Cassel, 1976; Hughes et al., 2017). Once the CNS efferent and local tissue CDR signals are effective, metabokines in the blood return to normal, cell danger signals diminish, and non-danger, pro-resolving, and pro-healing signals predominate.

Metabokines like purines, pyrimidines, amino acids, bioamines, fatty acids, eicosanoids, sphingolipids, phosphatidic acids, lysophospholipids, and many others, in addition to critical blood chemistry information like sodium and osmolality are independently monitored by chemosensory neurons in the 8 circumventricular organs (CVOs) of the brain (Siso et al., 2010). These chemosensory neurons lack a blood brain barrier and provide continuous sensory information that is independent of endocrine feedback and autonomic afferents. One of the well-known CVOs is the *area postrema* (AP) located at the floor of the 4th ventricle that contains the chemoreceptor trigger zone and regulates nausea and vomiting. The AP sends fibers that project to the *nucleus tractus solitarius* (NTS) to modulate the response to vagal sensory information (Hay and Bishop, 1991). Once blood chemistry starts returning to normal, chemosensory neurons of the CVO system communicate this information to neuroendocrine and autonomic systems to gradually shift efferent information back to anti-inflammatory, anxiolytic, pro-resolving, and pro-social signals. This shift in outflowing information from the brain marks the last stages of CDR3 and is required for re-entry into the health cycle of wakeful activity and restorative sleep (Fig. 1, Table 2).

27. Deterministic health and stochastic disease

While it is not possible to predict when and how an injury will happen, the chance that injuries and infections will happen is a certainty for all life on Earth. Without a way to heal after these injuries, any species would go extinct. The genetic program that facilitates recovery from any injury has been highly selected and tuned over evolutionary time. We now know that the healing cycle activates discrete sets of genes in a predictable sequence after injury. While injury is random, recovery and health are deterministic. Recovery is the programed result of the healing cycle (Fig. 1). Recovery occurs in the large majority of cases when the healing cycle is activated. Yet, why is it that some individuals get sick from common exposures, and cannot complete the healing cycle? For example, Epstein-Barr virus (EBV) is a risk factor for ME/CFS. In the US, 82% of people have been exposed to EBV by the time they are 19 years old (Dowd et al., 2013). If EBV is "the" cause, why do fewer than 1% of the US population have ME/CFS? Clinicians have documented dozens of other risk factors that can contribute to the chances of developing ME/CFS. An interesting point about chronic disease is that every non-infectious, chronic illness is caused by a perfect storm of several factors, not by one factor. The chances that this perfect storm of factors for a particular disease will occur for any one patient in a population of millions is small. But once disease strikes, the small initial probability rises to 100% certainty for that person. Therefore, as the environmental factors like pollution and food chain contamination start to increase, more people are exposed to risk, and more individuals will develop chronic illness. Reducing the environmental factors that contribute to risk will reduce the incidence of chronic illness.

So is chronic illness deterministic or stochastic? Scientists are most comfortable with deterministic, linear chains of logic. If cause "A" leads to disease "B" in 100% of people exposed and disease "B" never occurs without an exposure to cause "A", then there is little room for debate. Cause "A" is necessary and sufficient to produce disease "B". The problem is that literally none of the top 10, non-infectious chronic illnesses in the world has a single cause that produces the disease in every person exposed. Heart disease, diabetes, stroke, dementia, cancer, arthritis, autism, ADHD, depression, and schizophrenia all have dozens of risk factors, but no single "cause". By reducing the exposure to the risk factors, a nation can prevent a large percentage of all chronic illness in its citizens. Chronic illness is best modeled as a stochastic process, with an incidence that is modifiable by increasing or decreasing risk factors. This means that in large populations like the 325 million people in the United States, the management of even small chemical risk factors by a proactive government can produce dramatic changes in the incidence of chronic illness and its ripple effects in society. For example, if a hypothetical chemical were ubiquitous and synergized with the background mix of factors to increase the risk of mental illness leading to gun violence in just 0.001% of the population, removal of that chemical from the environment would result in 3250 (0.001% × 325 million) fewer cases of mental illness and gun violence each year.

28. A new pharmacology

In the past, student physicians and pharmacologists have been taught that drugs work by mechanisms that are the same in health and disease. While this was true for drugs designed to treat acute illneses, the treatment of chronic disease forces a revision of the old teaching. The health cycle and the healing cycle represent different biological states that have different bioenergetics, and different governing dynamics (Fig. 1, Table 2). *Biology* and *pathobiology* are qualitatively distinct states of function. Both are normal. However, the functional state associated with *pathobiology* (the healing cycle) is only normal when it occurs transiently. Pathological persistence of the stages of the healing cycle lead to chronic illness and the inability to heal. Drugs that will work best for treating chronic illness will target receptors like those illustrated in Fig. 5A that play key roles in the healing cycle, but remain virtually unused, or are used differently in health.

Personalized pharmacogenomics will help refine the new pharmacology as it has the old (Caudle et al., 2016), once the best targets in the healing cycle have been identified. A goal of the new pharmacology will be to discover new treatments for chronic illness that have targets that are active in disease, but are dormant in health, and therefore have little or no effect in healthy children and adults. Like Paul Ehrlich's magic bullet (Tan and Grimes, 2010), the new drugs will have fewer side effects because once the disease is cured and the patient has recovered, the target of the drug will have disappeared, and the bullet can pass without causing harm. The need for chronic drug use is then eliminated. While the simile is evocative, it is important to remember that "magic" bullets are not really magic. They just work by scientific mechanisms that have not yet been discovered, or are not yet well understood.

29. Failures of failure analysis

A fundamental difference between living and inanimate systems is that living systems can heal and inanimate systems cannot. When a machine or other manmade object of technology fails, the analysis of the mechanism of failure has proven to be a logical and effective way to discover a fix for the problem. For example, once the defect in the optics of the Hubble Space Telescope was precisely characterized, a solution was engineered to compensate for the defect, thereby fixing the problem. This same engineering logic is often applied successfully to "fix" acute illnesses in living systems. In contrast to acute illnesses, many

chronic disorders are self-sustaining alternative performance or failure states that limit the potential for independence in a child and reduce the quality of life in children and adults for years.

New tools in systems biology like genomics, RNAseq, proteomics, and metabolomics have created the ability to minutely characterize the way a system has failed in any one of the complex disorders listed in Table 1. The same tools can be applied to individuals with any given chronic disease as part of a precision medicine effort to phenotype that patient at the molecular level. The results of this precision medicine analysis have shown that chronic illnesses are characterized by hundreds of molecular differences from healthy control states. Historically, the pharmaceutical industry has systematically analyzed the molecular paths that lead to a recognizable disease state and have cataloged the defects present once that disease state becomes persistent. This information was then used to identify drugable targets. This approach to treat chronic disease in living systems has failed to produce cures because it is more like engineering than biology. Living systems engage the same evolutionarily conserved path to cellular recovery after injury—the same healing cycle with minor modifications—regardless of the mechanism of injury (Fig. 1). Biological healing in a living system does not involve the precise identification and point-for-point correction of each of the hundreds of defects present in chronic illness. Living systems do not turn back the arrow of time to retrace the path that led to the injury and illness. They move forward along a new path in order to heal (Fig. 3), eliminating hundreds of abnormalities in step with progress through each stage of the CDR. Each step in healing represents a concerted regime change in metabolism and gene expression, like the rapid succession of cellular ecosystems that return the system back to optimum integrated performance. For these reasons, treating a unique target for each individual disease may not be necessary. The path that permits a patient to exit any given disease state, i.e., to recover from chronic illness, may be the same for hundreds of diseases. A new generation of drugs and devices designed to unblock the healing cycle may turn out to be able to treat many diseases. Only time, and good clinical trials, will tell if this hypothesis is true.

30. Conclusions

30.1. Beginning a 2nd book of medicine

Much of western medical teaching in the US in 2018 is based on principles that were developed historically to treat acute illnesses from poisoning, physical injury, and infections. These principles have been incorporated into the books and literature used to train modern physicians and health care workers. Philosophically, this corpus of knowledge can be thought of as “the 1st book of medicine”. When treatments developed to treat acute causes and specific organ system dysfunction are applied to chronic illness, they produce marginal improvements, almost never cure a chronic disease, and must be given for life. This is good from the point of view of a drug company that manufactures a drug, but not for patients, and not for a nation whose economic health is tied to the health of its citizens.

Healing is a biologically active, energy-requiring process that is intrinsic to all life. Healing chronic illness cannot occur without engaging, unblocking, and actively supporting this universal system. “The 2nd book of medicine” will focus on the prevention of chronic illness and the care and recovery of patients with chronic disease. This book will introduce the concept that many treatments for chronic illness will be directed at the processes that block the healing cycle. These new treatments may only need to be given for a short period of time to cure or improve a chronic illness. This might be functionally similar to applying a cast to promote the healing of a broken leg. Treatment only needs to be given for a period of time needed for tissues to complete the healing cycle. When the cast is removed, the limb is weak, but after a period of time needed for reconditioning, the muscles have recovered, and the bone that was once broken is actually stronger at the point of injury than it was before. New drug treatments for chronic disorders like autism or PTSD, may only need to be given for a few months at a time, until the healing cycle can be completed, or the process of recovery, building strength, fitness, and resilience can be started and become self-sustaining again. Individuals may need occasional “tune-ups” to maintain recovery over the years, since genetic predispositions, environmental conditions, and metabolic memories of past exposures may cause health to drift back to the previous disease pattern, but the majority of time might be spent without the need for chronic treatment, or the limitations caused by chronic illness.

30.2. Potential economic impact

Eighty-six percent (86%) of the $3.3 trillion spent annually on medical costs in the US is spent to care for chronic conditions (CDC.gov, 2017). The cost of health care is predicted to rise to $5.5 trillion by 2025 because of chronic disease. This will require nearly 20% of the GDP of the US, estimated to be about $27 trillion (CMS.gov, 2017), if the trend of relentlessly growing chronic disease is not reversed. Today, 30% of children under 12 years have a chronic disease, and another 20% will develop a serious mental illness in their teens (HHS, 2018). Sixty percent of adult US citizens 18–64 years have a chronic disease, 90% of people over age 65 have at least one chronic illness, and 81% over 65 have 2 or more chronic conditions (CDC.gov, 2017). Shifting healthcare insurance policies from multi-payer to single-payer or back will have little effect on this cost. The fact that more Americans are getting sick, and not small variations in insurance policies, is driving the lion's share of rising costs. If just 10% of people now suffering with chronic illness could be cured by new methods directed at the healing cycle, more than $250 billion (10% × $2.5 trillion) would be saved annually. The savings in a single year would be more than the annual budgets of the National Institutes of Health (NIH; $37 billion), Environmental Protection Agency (EPA; $8.7 billion), Food and Drug Administration (FDA; $5.1 billion), and the US Department of Agriculture (USDA; $151 billion) combined.

31. Summary

Interruptions in the molecular stages of the healing cycle may be at the root of many complex, chronic illnesses. Three stages of the cell danger response (CDR1, 2, and 3) comprise the healing cycle. These stages are triggered by stress or injury and controlled by changes in mitochondrial function and metabolism (Figs. 1 and 2, Table 2). Many metabolites are metabokines that bind to dedicated receptors and signal when a cell is ready to enter the next stage of healing (Figs. 4 and 5). Purinergic signaling from the release and metabolism of extracellular nucleotides plays an important role in all stages of the healing cycle (Fig. 1). Programmed changes in the differentiation state of mitochondria, known as M0, M1, and M2-polarized organelles, and corresponding changes in cellular redox and the repurposing of cellular energy for cell defense and healing, also play fundamental roles (Fig. 2, Table 3) (Naviaux, 2017). When a stage of the healing cycle cannot be completed, dysfunctional cells accumulate that contain developmentally inappropriate forms of mitochondria, organ function is compromised, and chronic illness results (Fig. 3). Over 100 chronic illnesses can be classified according to the stage of the CDR that is blocked (Table 1). Unblocking therapies directed at stimulating the completion of the healing cycle by regulating metabokine signaling hold promise as a new approach to treatment. A small clinical trial of the antipurinergic drug suramin in autism spectrum disorder (ASD) has shown promise for this approach (Naviaux, 2017; Naviaux et al., 2017). Metabolic addiction to the chemistry produced by different stages of the CDR can occur. When this happens, it can create a life-long risk of relapse or slow return to chronic illness if diet and lifestyle interventions are not maintained.

Prevention and treatment of chronic illness require distinctly

different, but complementary approaches. New cases of chronic illness can be *prevented* by reducing the environmental risks that trigger the damage cycle of the CDR, and by promoting exercise, nutritional and life-style changes that promote resilience and maintain the health cycle (Fig. 1). However, once illness has occurred in a given patient, the opportunity for prevention is lost, and a perfect storm of multiple triggers can usually be identified. Many triggers are remote and no longer present. Once any remaining triggers have been identified and removed, and any symptoms or primed sensitivities caused by the metabolic memory of those triggers have been treated, a new approach to *treatment* is required to improve the chances of completing the healing cycle and achieving a full recovery. By shifting the focus away from the *initial causes*, to the metabolic factors and signaling pathways that *maintain* chronic illness by blocking progress through the healing cycle, new research will be stimulated and novel treatments will follow.

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Conflicts of interest

RKN is a scientific advisory board member for the Autism Research Institute and the Open Medicine Foundation, and has submitted a patent application for the use of antipurinergic therapy in autism and related disorders.

References

Adams, J.B., Audhya, T., McDonough-Means, S., Rubin, R.A., Quig, D., Geis, E., Gehn, E., Loresto, M., Mitchell, J., Atwood, S., Barnhouse, S., Lee, W., 2011. Nutritional and metabolic status of children with autism vs. neurotypical children, and the association with autism severity. Nutr. Metabol. 8, 34.

Anupama, N., Sindhu, G., Raghu, K.G., 2018. Significance of mitochondria on cardiometabolic syndromes. Fundam. Clin. Pharmacol. 32 (4), 346–356.

Atamna, H., Tenore, A., Lui, F., Dhahbi, J.M., 2018. Organ reserve, excess metabolic capacity, and aging. Biogerontology 19, 171–184.

Baez-Pagan, C.A., Delgado-Velez, M., Lasalde-Dominicci, J.A., 2015. Activation of the macrophage alpha7 nicotinic acetylcholine receptor and control of inflammation. J. Neuroimmune Pharmacol. Official J. Soc. NeuroImmune Pharmacol. 10, 468–476.

Baker, S., Bennett, P., Bland, J., Galland, L., Hedaya, R., Houston, M., Hyman, M., Lombard, J., Roundtree, R., Vasquez, A., 2010. Textbook of Functional Medicine. The Institute for Functional Medicine, Gig Harbor, WA.

Bernhardt, J.R., Leslie, H.M., 2013. Resilience to climate change in coastal marine ecosystems. Annu. Rev. Mar. Sci. 5, 371–392.

Boya, P., Codogno, P., Rodriguez-Muela, N., 2018. Autophagy in stem cells: repair, remodelling and metabolic reprogramming. Development 145.

Braymer, J.J., Lill, R., 2017. Iron-sulfur cluster biogenesis and trafficking in mitochondria. J. Biol. Chem. 292, 12754–12763.

Buckinx, R., Adriaensen, D., Nassauw, L.V., Timmermans, J.P., 2011. Corticotrophin-releasing factor, related peptides, and receptors in the normal and inflamed gastrointestinal tract. Front. Neurosci. 5, 54.

Burke, J., 2015. In: Thorpe, K. (Ed.), Partnership to Fight Chronic Disease. Emory University, Atlanta, GA. https://www.fightchronicdisease.org/latest-news/130-million-americans-chronic-disease-cost-more-25-trillion-annually.

Calabrese, E.J., Baldwin, L.A., 2003. Hormesis: the dose-response revolution. Annu. Rev. Pharmacol. Toxicol. 43, 175–197.

Cameron, J.L., Eagleson, K.L., Fox, N.A., Hensch, T.K., Levitt, P., 2017. Social origins of developmental risk for mental and physical illness. J. Neurosci. 37, 10783–10791.

Cao, Y.L., Meng, S., Chen, Y., Feng, J.X., Gu, D.D., Yu, B., Li, Y.J., Yang, J.Y., Liao, S., Chan, D.C., Gao, S., 2017. MFN1 structures reveal nucleotide-triggered dimerization critical for mitochondrial fusion. Nature 542, 372–376.

Carney, R.M., Freedland, K.E., Steinmeyer, B.C., Rubin, E.H., Stein, P.K., Rich, M.W., 2016. Nighttime heart rate predicts response to depression treatment in patients with coronary heart disease. J. Affect. Disord. 200, 165–171.

Carreras-Sureda, A., Pihan, P., Hetz, C., 2018. Calcium signaling at the endoplasmic reticulum: fine-tuning stress responses. Cell Calcium 70, 24–31.

Cassel, J., 1976. The contribution of the social environment to host resistance: the Fourth Wade Hampton Frost Lecture. Am. J. Epidemiol. 104, 107–123.

Caudle, K.E., Gammal, R.S., Whirl-Carrillo, M., Hoffman, J.M., Relling, M.V., Klein, T.E., 2016. Evidence and resources to implement pharmacogenetic knowledge for precision medicine. Am. J. Health Syst. Pharm. 73, 1977–1985.

Cdc.Gov, 2017. Chronic Disease Overview. National Center for Chronic Disease Prevention and Health Promotion. Atlanta, GA. https://www.cdc.gov/chronicdisease/overview/index.htm#ref17.

Chang, C., Gershwin, M.E., 2011. Drug-induced lupus erythematosus: incidence, management and prevention. Drug Saf. 34, 357–374.

Chen, X., Chalfie, M., 2014. Modulation of C. elegans touch sensitivity is integrated at multiple levels. J. Neurosci. 34, 6522–6536.

Chen, J., Tan, Z., Zeng, L., Zhang, X., He, Y., Gao, W., Wu, X., Li, Y., Bu, B., Wang, W., Duan, S., 2013. Heterosynaptic long-term depression mediated by ATP released from astrocytes. Glia 61, 178–191.

Chrysant, S.G., 2017. New onset diabetes mellitus induced by statins: current evidence. Postgrad. Med. 129, 430–435.

Claude-Taupin, A., Jia, J., Mudd, M., Deretic, V., 2017. Autophagy's secret life: secretion instead of degradation. Essays Biochem. 61, 637–647.

CMS.gov, 2017. 2016–2025 Projections of national health expenditures data released. In: M.M, C.f. (Ed.), Services, Baltimore, MD. https://www.cms.gov/Newsroom/MediaReleaseDatabase/Press-releases/2017-Press-releases-items/2017-02-15-2.html.

Cunliffe, J., 1997. Morphostasis: an evolving perspective. Med. Hypotheses 49, 449–459.

Dantzer, R., Kelley, K.W., 2007. Twenty years of research on cytokine-induced sickness behavior. Brain Behav. Immun. 21, 153–160.

de Jong, H.J., Saldi, S.R., Klungel, O.H., Vandebriel, R.J., Souverein, P.C., Meyboom, R.H., Passier, J.L., van Loveren, H., Cohen Tervaert, J.W., 2012. Statin-associated polymyalgia rheumatica. An analysis using WHO global individual case safety database: a case/non-case approach. PloS one 7, e41289.

De Meersman, R.E., 1992. Respiratory sinus arrhythmia alteration following training in endurance athletes. Eur. J. Appl. Physiol. Occup. Physiol. 64, 434–436.

De Meersman, R.E., 1993. Heart rate variability and aerobic fitness. Am. Heart J. 125, 726–731.

Del Dotto, V., Mishra, P., Vidoni, S., Fogazza, M., Maresca, A., Caporali, L., McCaffery, J.M., Cappelletti, M., Baruffini, E., Lenaers, G., Chan, D., Rugolo, M., Carelli, V., Zanna, C., 2017. OPA1 isoforms in the hierarchical organization of mitochondrial functions. Cell Rep. 19, 2557–2571.

Dhir, A., Dhir, S., Borowski, L.S., Jimenez, L., Teitell, M., Rötig, A., Crow, Y.J., Rice, G.I., Duffy, D., Tamby, C., Nojima, T., Munnich, A., Schiff, M., Ribeiro De Almeida, C., Rehwinkel, J., Dziembowski, A., Szczesny, R.J., Proudfoot, N.J., 2018. Mitochondrial double-stranded RNA triggers antiviral signalling in humans. Nature (Epub ahead of print).

Djordjevic, J., Djordjevic, A., Adzic, M., Mitic, M., Lukic, I., Radojcic, M.B., 2015. Alterations in the Nrf2-Keap1 signaling pathway and its downstream target genes in rat brain under stress. Brain Res. 1602, 20–31.

Dowd, J.B., Palermo, T., Brite, J., McDade, T.W., Aiello, A., 2013. Seroprevalence of Epstein-Barr virus infection in U.S. children ages 6–19, 2003–2010. PLoS One 8, e64921.

Driver, J.A., 2014. Inverse association between cancer and neurodegenerative disease: review of the epidemiologic and biological evidence. Biogerontology 15, 547–557.

Driver, R.J., Lamb, A.L., Wyner, A.J., Raizen, D.M., 2013. DAF-16/FOXO regulates homeostasis of essential sleep-like behavior during larval transitions in C. elegans. Curr. Biol. 23, 501–506.

Dworak, M., Wiater, A., Alfer, D., Stephan, E., Hollmann, W., Struder, H.K., 2008. Increased slow wave sleep and reduced stage 2 sleep in children depending on exercise intensity. Sleep Med. 9, 266–272.

Esmaeilzadeh, M., Sadeghi, M., Galmbacher, R., Daniel, V., Knapp, J., Heissler, H.E., Krauss, J.K., Mehrabi, A., 2017. Time-course of plasma inflammatory mediators in a rat model of brain death. Transpl. Immunol. 43–44, 21–26.

Esteras, N., Dinkova-Kostova, A.T., Abramov, A.Y., 2016. Nrf2 activation in the treatment of neurodegenerative diseases: a focus on its role in mitochondrial bioenergetics and function. Biol. Chem. 397, 383–400.

Fiehn, O., 2002. Metabolomics–the link between genotypes and phenotypes. Plant Mol. Biol. 48, 155–171.

Fluge, O., Mella, O., Bruland, O., Risa, K., Dyrstad, S.E., Alme, K., Rekeland, I.G., Sapkota,

D., Rosland, G.V., Fossa, A., Ktoridou-Valen, I., Lunde, S., Sorland, K., Lien, K., Herder, I., Thurmer, H., Gotaas, M.E., Baranowska, K.A., Bohnen, L.M., Schafer, C., McCann, A., Sommerfelt, K., Helgeland, L., Ueland, P.M., Dahl, O., Tronstad, K.J., 2016. Metabolic profiling indicates impaired pyruvate dehydrogenase function in myalgic encephalopathy/chronic fatigue syndrome. JCI Insight 1, e89376.

Ford, A.P., Undem, B.J., Birder, L.A., Grundy, D., Pijacka, W., Paton, J.F., 2015. P2X3 receptors and sensitization of autonomic reflexes. Auton. Neurosci. 191, 16–24.

Gabbs, M., Leng, S., Devassy, J.G., Monirujjaman, M., Aukema, H.M., 2015. Advances in our understanding of oxylipins derived from dietary PUFAs. Adv. Nutr. 6, 513–540.

Gerdle, B., Forsgren, M.F., Bengtsson, A., Leinhard, O.D., Soren, B., Karlsson, A., Brandejsky, V., Lund, E., Lundberg, P., 2013. Decreased muscle concentrations of ATP and PCR in the quadriceps muscle of fibromyalgia patients–a 31P-MRS study. Eur. J. Pain 17, 1205–1215.

Gether, U., 2000. Uncovering molecular mechanisms involved in activation of G protein-coupled receptors. Endocr. Rev. 21, 90–113.

Gevi, F., Zolla, L., Gabriele, S., Persico, A.M., 2016. Urinary metabolomics of young Italian autistic children supports abnormal tryptophan and purine metabolism. Mol. Autism 7, 47.

Ghosh, S., Indracanti, N., Joshi, J., Ray, J., Indraganti, P.K., 2017. Pharmacologically induced reversible hypometabolic state mitigates radiation induced lethality in mice. Sci. Rep. 7, 14900.

Gosain, A., Dipietro, L.A., 2004. Aging and wound healing. World J. Surg. 28, 321–326.

Gutierrez-Vazquez, C., Quintana, F.J., 2018. Regulation of the immune response by the aryl hydrocarbon receptor. Immunity 48, 19–33.

Han, W., Sapkota, S., Camicioli, R., Dixon, R.A., Li, L., 2017. Profiling novel metabolic biomarkers for Parkinson's disease using in-depth metabolomic analysis. Mov. Disord. 32, 1720–1728.

Hand, S.C., Menze, M.A., Borcar, A., Patil, Y., Covi, J.A., Reynolds, J.A., Toner, M., 2011. Metabolic restructuring during energy-limited states: insights from Artemia franciscana embryos and other animals. J. Insect Physiol. 57, 584–594.

Harkewicz, R., Dennis, E.A., 2011. Applications of mass spectrometry to lipids and membranes. Annu. Rev. Biochem. 80, 301–325.

Hay, M., Bishop, V.S., 1991. Interactions of area postrema and solitary tract in the nucleus tractus solitarius. Am. J. Phys. 260, H1466–H1473.

He, S., Sharpless, N.E., 2017. Senescence in health and disease. Cell 169, 1000–1011.

He, Y., Yu, Z., Giegling, I., Xie, L., Hartmann, A.M., Prehn, C., Adamski, J., Kahn, R., Li, Y., Illig, T., Wang-Sattler, R., Rujescu, D., 2012. Schizophrenia shows a unique metabolomics signature in plasma. Transl. Psychiatry 2, e149.

Heber-Katz, E., 2017. Oxygen, metabolism, and regeneration: lessons from mice. Trends Mol. Med. 23, 1024–1036.

Heber-Katz, E., Messersmith, P., 2018. Drug delivery and epimorphic salamander-type mouse regeneration: a full parts and labor plan. Adv. Drug Deliv. Rev. 129, 254–261.

Hermes, S.M., Andresen, M.C., Aicher, S.A., 2016. Localization of TRPV1 and P2X3 in unmyelinated and myelinated vagal afferents in the rat. J. Chem. Neuroanat. 72, 1–7.

HHS, U.S., 2018. United States Adolescent Mental Health Facts.

Hoertel, N., Blanco, C., Oquendo, M.A., Wall, M.M., Olfson, M., Falissard, B., Franco, S., Peyre, H., Lemogne, C., Limosin, F., 2017. A comprehensive model of predictors of persistence and recurrence in adults with major depression: results from a national 3-year prospective study. J. Psychiatr. Res. 95, 19–27.

Hoffmann, M.H., Griffiths, H.R., 2018. The dual role of ROS in autoimmune and inflammatory diseases: evidence from preclinical models. Free Radic. Biol. Med (Epub ahead of print).

Holley, C.T., Long, E.K., Butterick, T.A., Duffy, C.M., Lindsey, M.E., Stone, L.H., McFalls, E.O., Kelly, R.F., 2015. Mitochondrial fusion proteins in revascularized hibernating hearts. J. Surg. Res. 195, 29–36.

Holt, S.J., 2006. Staying alive in adversity: transcriptome dynamics in the stress-resistant dauer larva. Funct. Integr. Genomics 6, 285–299.

Hu, J.P., Xu, X.Y., Huang, L.Y., Wang, L.S., Fang, N.Y., 2015. Freeze-thaw Caenorhabditis elegans freeze-thaw stress response is regulated by the insulin/IGF-1 receptor daf-2. BMC Genet. 16, 139.

Huang, M., Risling, M., Baker, D.G., 2016. The role of biomarkers and MEG-based imaging markers in the diagnosis of post-traumatic stress disorder and blast-induced mild traumatic brain injury. Psychoneuroendocrinology 63, 398–409.

Huang, M.X., Swan, A.R., Quinto, A.A., Matthews, S., Harrington, D.L., Nichols, S., Bruder, B.J., Snook, C.C., Huang, C.W., Baker, D.G., Lee, R.R., 2017. A pilot treatment study for mild traumatic brain injury: neuroimaging changes detected by MEG after low-intensity pulse-based transcranial electrical stimulation. Brain Inj. 31, 1951–1963.

Hughes, K., Bellis, M.A., Hardcastle, K.A., Sethi, D., Butchart, A., Mikton, C., Jones, L., Dunne, M.P., 2017. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. Lancet Public Health 2, e356–e366.

Hupin, D., Roche, F., Gremeaux, V., Chatard, J.C., Oriol, M., Gaspoz, J.M., Barthelemy, J.C., Edouard, P., 2015. Even a low-dose of moderate-to-vigorous physical activity reduces mortality by 22% in adults aged > /=60 years: a systematic review and meta-analysis. Br. J. Sports Med. 49, 1262–1267.

Incollingo Rodriguez, A.C., Epel, E.S., White, M.L., Standen, E.C., Seckl, J.R., Tomiyama, A.J., 2015. Hypothalamic-pituitary-adrenal axis dysregulation and cortisol activity in obesity: a systematic review. Psychoneuroendocrinology 62, 301–318.

Irvine, K.A., Sahbaie, P., Liang, D.Y., Clark, D., 2018. TBI disrupts pain signaling in the brainstem and spinal cord. J. Neurotrauma 35 (13), 1495–1509.

Jafari, R., Aflatoonian, R., Falak, R., Pourmand, G., Dehghani, S., Mortazavi, M., Adelipour, A., Rezaei, A., Tajik, N., 2018. Down-regulation of inflammatory signaling pathways despite up-regulation of Toll-like receptors; the effects of corticosteroid therapy in brain-dead kidney donors, a double-blind, randomized, controlled trial. Mol. Immunol. 94, 36–44.

Jang, C., Chen, L., Rabinowitz, J.D., 2018. Metabolomics and isotope tracing. Cell 173, 822–837.

Jeske, J., Bitter, A., Thasler, W.E., Weiss, T.S., Schwab, M., Burk, O., 2017. Ligand-dependent and -independent regulation of human hepatic sphingomyelin phosphodiesterase acid-like 3A expression by pregnane X receptor and crosstalk with liver X receptor. Biochem. Pharmacol. 136, 122–135.

Johnson, V.E., Stewart, J.E., Begbie, F.D., Trojanowski, J.Q., Smith, D.H., Stewart, W., 2013. Inflammation and white matter degeneration persist for years after a single traumatic brain injury. Brain J. Neurol. 136, 28–42.

Johnson, S.C., Yanos, M.E., Bitto, A., Castanza, A., Gagnidze, A., Gonzalez, B., Gupta, K., Hui, J., Jarvie, C., Johnson, B.M., Letexier, N., McCanta, L., Sangesland, M., Tamis, O., Uhde, L., Van Den Ende, A., Rabinovitch, P.S., Suh, Y., Kaeberlein, M., 2015. Dose-dependent effects of mTOR inhibition on weight and mitochondrial disease in mice. Front. Genet. 6, 247.

Joo, H.J., Yim, Y.H., Jeong, P.Y., Jin, Y.X., Lee, J.E., Kim, H., Jeong, S.K., Chitwood, D.J., Paik, Y.K., 2009. Caenorhabditis elegans utilizes dauer pheromone biosynthesis to dispose of toxic peroxisomal fatty acids for cellular homoeostasis. Biochem. J. 422, 61–71.

Kann, O., 2016. The interneuron energy hypothesis: implications for brain disease. Neurobiol. Dis. 90, 75–85.

Khan, N.A., Nikkanen, J., Yatsuga, S., Jackson, C., Wang, L., Pradhan, S., Kivela, R., Pessia, A., Velagapudi, V., Suomalainen, A., 2017. mTORC1 regulates mitochondrial integrated stress response and mitochondrial myopathy progression. Cell Metab. 26 (419–428), e415.

Kim, S.M., Kim, Y.G., Jeong, K.H., Lee, S.H., Lee, T.W., Ihm, C.G., Moon, J.Y., 2012. Angiotensin II-induced mitochondrial Nox4 is a major endogenous source of oxidative stress in kidney tubular cells. PLoS One 7, e39739.

Kim, Y., Zheng, X., Ansari, Z., Bunnell, M.C., Herdy, J.R., Traxler, L., Lee, H., Paquola, A.C.M., Blithikioti, C., Ku, M., Schlachetzki, J.C.M., Winkler, J., Edenhofer, F., Glass, C.K., Paucar, A.A., Jaeger, B.N., Pham, S., Boyer, L., Campbell, B.C., Hunter, T., Mertens, J., Gage, F.H., 2018. Mitochondrial aging defects emerge in directly reprogrammed human neurons due to their metabolic profile. Cell Rep. 23, 2550–2558.

Kuehl, T., Lagares, D., 2018. BH3 mimetics as anti-fibrotic therapy: unleashing the mitochondrial pathway of apoptosis in myofibroblasts. Matrix Biol. 68-69, 94–105.

Lahera, V., de Las Heras, N., Lopez-Farre, A., Manucha, W., Ferder, L., 2017. Role of mitochondrial dysfunction in hypertension and obesity. Curr. Hypertens. Rep. 19, 11.

Lapp, H.E., Ahmed, S., Moore, C.L., Hunter, R.G., 2018. Toxic stress history and hypothalamic-pituitary-adrenal axis function in a social stress task: genetic and epigenetic factors. Neurotoxicol. Teratol (Epub ahead of print).

Laroche, D., Leturgie, P., Mariotte, D., Ollivier, Y., Hanouz, J.L., Le Mauff, B., Parienti, J.J., 2017. In vivo cysteinyl leukotriene release in allergic and nonallergic immediate hypersensitivity reactions during anesthesia. Anesthesiology 126, 834–841.

Lee, D., Lee, H., Kim, N., Lim, D.S., Lee, J., 2017. Regulation of a hitchhiking behavior by neuronal insulin and TGF-beta signaling in the nematode Caenorhabditis elegans. Biochem. Biophys. Res. Commun. 484, 323–330.

Liman, E.R., 2012. Changing senses: chemosensory signaling and primate evolution. Adv. Exp. Med. Biol. 739, 206–217.

Lin, S., Xing, H., Zang, T., Ruan, X., Wo, L., He, M., 2018. Sirtuins in mitochondrial stress: indispensable helpers behind the scenes. Ageing Res. Rev. 44, 22–32.

Lovejoy, D.A., Chang, B.S., Lovejoy, N.R., del Castillo, J., 2014. Molecular evolution of GPCRs: CRH/CRH receptors. J. Mol. Endocrinol. 52, T43–T60.

Lu, P.D., Harding, H.P., Ron, D., 2004. Translation reinitiation at alternative open reading frames regulates gene expression in an integrated stress response. J. Cell Biol. 167, 27–33.

Lucas, A.R., Klepin, H.D., Porges, S.W., Rejeski, W.J., 2018. Mindfulness-based movement: a polyvagal perspective. Integr. Cancer Ther. 17, 5–15.

Mattson, M.P., Moehl, K., Ghena, N., Schmaedick, M., Cheng, A., 2018. Intermittent metabolic switching, neuroplasticity and brain health. Nat. Rev. Neurosci. 19, 63–80.

McEwen, B.S., Stellar, E., 1993. Stress and the individual. Mechanisms leading to disease. Arch. intern. Med. 153, 2093–2101.

McLaughlin Crabtree, V., Williams, N.A., 2009. Normal sleep in children and adolescents. Child Adolesc. Psychiatr. Clin. N. Am. 18, 799–811.

Menon, D., Salloum, D., Bernfeld, E., Gorodetsky, E., Akselrod, A., Frias, M.A., Sudderth, J., Chen, P.H., DeBerardinis, R., Foster, D.A., 2017. Lipid sensing by mTOR complexes via de novo synthesis of phosphatidic acid. J. Biol. Chem. 292, 6303–6311.

Mills, E.L., Kelly, B., O'Neill, L.A.J., 2017. Mitochondria are the powerhouses of immunity. Nat. Immunol. 18, 488–498.

Mishra, N.C., Rir-sima-ah, J., Boyd, R.T., Singh, S.P., Gundavarapu, S., Langley, R.J., Razani-Boroujerdi, S., Sopori, M.L., 2010. Nicotine inhibits Fc epsilon RI-induced cysteinyl leukotrienes and cytokine production without affecting mast cell degranulation through alpha 7/alpha 9/alpha 10-nicotinic receptors. J. Immunol. 185, 588–596.

Mottillo, S., Filion, K.B., Genest, J., Joseph, L., Pilote, L., Poirier, P., Rinfret, S., Schiffrin, E.L., Eisenberg, M.J., 2010. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J. Am. Coll. Cardiol. 56, 1113–1132.

Murakami, S., Johnson, T.E., 1996. A genetic pathway conferring life extension and resistance to UV stress in Caenorhabditis elegans. Genetics 143, 1207–1218.

Murao, N., Nishitoh, H., 2017. Role of the unfolded protein response in the development of central nervous system. J. Biochem. 162, 155–162.

Naviaux, R.K., 2008. Mitochondrial control of epigenetics. Cancer Biol. Ther. 7, 1191–1193.

Naviaux, R.K., 2012. Oxidative shielding or oxidative stress? J. Pharmacol. Exp. Ther. 342, 608–618.

Naviaux, R.K., 2014. Metabolic features of the cell danger response. Mitochondrion 16, 7–17.

Naviaux, R.K., 2017. Antipurinergic therapy for autism-an in-depth review. Mitochondrion.

Naviaux, R.K., Nyhan, W.L., Barshop, B.A., Poulton, J., Markusic, D., Karpinski, N.C., Haas, R.H., 1999. Mitochondrial DNA polymerase gamma deficiency and mtDNA depletion in a child with Alpers' syndrome. Ann. Neurol. 45, 54–58.
Naviaux, R.K., Le, T.P., Bedelbaeva, K., Leferovich, J., Gourevitch, D., Sachadyn, P., Zhang, X.M., Clark, L., Heber-Katz, E., 2009. Retained features of embryonic metabolism in the adult MRL mouse. Mol. Genet. Metab. 96, 133–144.
Naviaux, R.K., Zolkipli-Cunningham, Z., Nakayama, T., Naviaux, J.C., Le, T., Wang, L., Schuchbauer, M., Rogac, M., Li, Q., Dugan, L.L., Powell, S., 2013. Antipurinergic therapy corrects the autism-like features in the poly(IC) mouse model. PLoS One 8, e57380.
Naviaux, J.C., Schuchbauer, M.A., Li, K., Wang, L., Risbrough, V.B., Powell, S.B., Naviaux, R.K., 2014. Reversal of autism-like behaviors and metabolism in adult mice with single-dose antipurinergic therapy. Transl. Psychiatry 4, e400.
Naviaux, J.C., Wang, L., Li, K., Bright, A.T., Alaynick, W.A., Williams, K.R., Powell, S.B., Naviaux, R.K., 2015. Antipurinergic therapy corrects the autism-like features in the Fragile X (Fmr1 knockout) mouse model. Mol. Autism 6, 1.
Naviaux, R.K., Naviaux, J.C., Li, K., Bright, A.T., Alaynick, W.A., Wang, L., Baxter, A., Nathan, N., Anderson, W., Gordon, E., 2016. Metabolic features of chronic fatigue syndrome. Proc. Natl. Acad. Sci. U. S. A. 113, E5472–E5480.
Naviaux, R.K., Curtis, B., Li, K., Naviaux, J.C., Bright, A.T., Reiner, G.E., Westerfield, M., Goh, S., Alaynick, W.A., Wang, L., Capparelli, E.V., Adams, C., Sun, J., Jain, S., He, F., Arellano, D.A., Mash, L.E., Chukoskie, L., Lincoln, A., Townsend, J., 2017. Low-dose suramin in autism spectrum disorder: a small, phase I/II, randomized clinical trial. Ann. Clin. Transl. Neurol. 4, 491–505.
Nieborak, A., Schneider, R., 2018. Metabolic intermediates – Cellular messengers talking to chromatin modifiers. Mol. Metab (Epub ahead of print).
Nikkanen, J., Forsstrom, S., Euro, L., Paetau, I., Kohnz, R.A., Wang, L., Chilov, D., Viinamaki, J., Roivainen, A., Marjamaki, P., Liljenback, H., Ahola, S., Buzkova, J., Terzioglu, M., Khan, N.A., Pirnes-Karhu, S., Paetau, A., Lonnqvist, T., Sajantila, A., Isohanni, P., Tyynismaa, H., Nomura, D.K., Battersby, B.J., Velagapudi, V., Carroll, C.J., Suomalainen, A., 2016. Mitochondrial DNA replication defects disturb cellular dNTP pools and remodel one-carbon metabolism. Cell Metab. 23, 635–648.
Nishi, H., Arai, H., Momiyama, T., 2013. NCI-H295R, a human adrenal cortex-derived cell line, expresses purinergic receptors linked to Ca(2)(+)-mobilization/influx and cortisol secretion. PLoS One 8, e71022.
Nurminskaya, M.V., Belkin, A.M., 2012. Cellular functions of tissue transglutaminase. Int. Rev. Cell Mol. Biol. 294, 1–97.
Osuma, E.A., Riggs, D.W., Gibb, A.A., Hill, B.G., 2018. High throughput measurement of metabolism in planarians reveals activation of glycolysis during regeneration. Regeneration (Wiley) 5, 78–86.
Panossian, A., 2017. Understanding adaptogenic activity: specificity of the pharmacological action of adaptogens and other phytochemicals. Ann. N. Y. Acad. Sci. 1401, 49–64.
Picard, M., McManus, M.J., Gray, J.D., Nasca, C., Moffat, C., Kopinski, P.K., Seifert, E.L., McEwen, B.S., Wallace, D.C., 2015. Mitochondrial functions modulate neuroendocrine, metabolic, inflammatory, and transcriptional responses to acute psychological stress. Proc. Natl. Acad. Sci. U. S. A. 112, E6614–E6623.
Picard, M., Juster, R.P., Sloan, R.P., McEwen, B.S., 2017. Mitochondrial nexus to allostatic load biomarkers. Psychosom. Med. 79, 114–117.
Pincas, H., Choi, S.G., Wang, Q., Jia, J., Turgeon, J.L., Sealfon, S.C., 2014. Outside the box signaling: secreted factors modulate GnRH receptor-mediated gonadotropin regulation. Mol. Cell. Endocrinol. 385, 56–61.
Pizzorno, J.E., Murray, M.T., 2013. Textbook of Natural Medicine, 4th Edition, 4th ed. Elsevier Health Sciences.
Plog, B.A., Nedergaard, M., 2018. The glymphatic system in central nervous system health and disease: past, present, and future. Annu. Rev. Pathol. 13, 379–394.
Porges, S.W., 2007. The polyvagal perspective. Biol. Psychol. 74, 116–143.
Porges, S.W., 2011. The Polyvagal Theory: Neurophysiological Foundations of Emotions, Attachment, Communication, and Self-Regulation. W. W. Norton & Company, New York, NY.
Portt, L., Norman, G., Clapp, C., Greenwood, M., Greenwood, M.T., 2011. Anti-apoptosis and cell survival: a review. Biochim. Biophys. Acta 1813, 238–259.
Powley, T.L., Spaulding, R.A., Haglof, S.A., 2011. Vagal afferent innervation of the proximal gastrointestinal tract mucosa: chemoreceptor and mechanoreceptor architecture. J. Comp. Neurol. 519, 644–660.
Prates Mori, M., de Souza-Pinto, N.C., 2017. Role of mitochondrial dysfunction in the pathophysiology of DNA repair disorders. Cell Biol. Int. 42 (6), 643–650.
Qato, D.M., Ozenberger, K., Olfson, M., 2018. Prevalence of prescription medications with depression as a potential adverse effect among adults in the United States. JAMA J. Am. Med. Assoc. 319, 2289–2298.
Rakel, D., 2018. Integrative Medicine, 4th edition. Elsevier, Philadelphia, PA.
Rissling, M.B., Dennis, P.A., Watkins, L.L., Calhoun, P.S., Dennis, M.F., Beckham, J.C., Hayano, J., Ulmer, C.S., 2016. Circadian contrasts in heart rate variability associated with posttraumatic stress disorder symptoms in a young adult cohort. J. Trauma. Stress. 29, 415–421.
Ristow, M., 2014. Unraveling the truth about antioxidants: mitohormesis explains ROS-induced health benefits. Nat. Med. 20, 709–711.
Rosas-Ballina, M., Olofsson, P.S., Ochani, M., Valdes-Ferrer, S.I., Levine, Y.A., Reardon, C., Tusche, M.W., Pavlov, V.A., Andersson, U., Chavan, S., Mak, T.W., Tracey, K.J., 2011. Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. Science 334, 98–101.
Saeed-Zidane, M., Linden, L., Salilew-Wondim, D., Held, E., Neuhoff, C., Tholen, E., Hoelker, M., Schellander, K., Tesfaye, D., 2017. Cellular and exosome mediated molecular defense mechanism in bovine granulosa cells exposed to oxidative stress. PLoS One 12, e0187569.
Saier Jr., M.H., Reddy, V.S., Tsu, B.V., Ahmed, M.S., Li, C., Moreno-Hagelsieb, G., 2016. The transporter classification database (TCDB): recent advances. Nucleic Acids Res. 44, D372–D379.
Saint-Maurice, P.F., Troiano, R.P., Matthews, C.E., Kraus, W.E., 2018. Moderate-to-vigorous physical activity and all-cause mortality: do bouts matter? J. Am. Heart Assoc. 7.
Sakaki, H., Tsukimoto, M., Harada, H., Moriyama, Y., Kojima, S., 2013. Autocrine regulation of macrophage activation via exocytosis of ATP and activation of P2Y11 receptor. PLoS One 8, e59778.
Schmunk, G., Nguyen, R.L., Ferguson, D.L., Kumar, K., Parker, I., Gargus, J.J., 2017. High-throughput screen detects calcium signaling dysfunction in typical sporadic autism spectrum disorder. Sci. Rep. 7, 40740.
Semenza, G.L., 2011. Hypoxia-inducible factor 1: regulator of mitochondrial metabolism and mediator of ischemic preconditioning. Biochim. Biophys. Acta 1813, 1263–1268.
Silva, J.M., Wong, A., Carelli, V., Cortopassi, G.A., 2009. Inhibition of mitochondrial function induces an integrated stress response in oligodendroglia. Neurobiol. Dis. 34, 357–365.
Siso, S., Jeffrey, M., Gonzalez, L., 2010. Sensory circumventricular organs in health and disease. Acta Neuropathol. 120, 689–705.
Sivanand, S., Rhoades, S., Jiang, Q., Lee, J.V., Benci, J., Zhang, J., Yuan, S., Viney, I., Zhao, S., Carrer, A., Bennett, M.J., Minn, A.J., Weljie, A.M., Greenberg, R.A., Wellen, K.E., 2017. Nuclear acetyl-CoA production by ACLY promotes homologous recombination. Mol. Cell 67 (252–265), e256.
Sorice, M., Garofalo, T., Misasi, R., Manganelli, V., Vona, R., Malorni, W., 2012. Ganglioside GD3 as a raft component in cell death regulation. Anti Cancer Agents Med. Chem. 12, 376–382.
Sterling, P., Eyer, J., 1988. Allostasis: a new paradigm to explain arousal pathology. In: Fisher, S., Reason, J. (Eds.), Handbook of Life Stress, Cognition, and Health. John Wiley & Sons, Inc., New York, NY, pp. 629–649.
Surowiec, I., Arlestig, L., Rantapaa-Dahlqvist, S., Trygg, J., 2016. Metabolite and lipid profiling of biobank plasma samples collected prior to onset of rheumatoid arthritis. PLoS One 11, e0164196.
Takatani, T., Takahashi, Y., Yoshida, R., Imai, R., Uchiike, T., Yamazaki, M., Shima, M., Nishikubo, T., Ikada, Y., Fujimoto, S., 2018. Relationship between frequency spectrum of heart rate variability and autonomic nervous activities during sleep in newborns. Brain and Development 40, 165–171.
Tan, S.Y., Grimes, S., 2010. Paul Ehrlich (1854–1915): man with the magic bullet. Singap. Med. J. 51, 842–843.
Thomas, C., Baker, C.I., 2013. Teaching an adult brain new tricks: a critical review of evidence for training-dependent structural plasticity in humans. NeuroImage 73, 225–236.
Uno, M., Nishida, E., 2016. Lifespan-regulating genes in *C. elegans*. NPJ. Aging Mech. Dis. 2, 16010.
Valentijn, F.A., Falke, L.L., Nguyen, T.Q., Goldschmeding, R., 2018. Cellular senescence in the aging and diseased kidney. J Cell Commun Signal 12, 69–82.
van der Vusse, G.J., 2011. The fascinating and elusive life of cardiac fatty acids. Cardiovasc. Res. 92, 363–364.
Varma, V.R., Oommen, A.M., Varma, S., Casanova, R., An, Y., Andrews, R.M., O'Brien, R., Pletnikova, O., Troncoso, J.C., Toledo, J., Baillie, R., Arnold, M., Kastenmueller, G., Nho, K., Doraiswamy, P.M., Saykin, A.J., Kaddurah-Daouk, R., Legido-Quigley, C., Thambisetty, M., 2018. Brain and blood metabolite signatures of pathology and progression in Alzheimer disease: a targeted metabolomics study. PLoS Med. 15, e1002482.
Venter, J.C., Remington, K., Heidelberg, J.F., Halpern, A.L., Rusch, D., Eisen, J.A., Wu, D., Paulsen, I., Nelson, K.E., Nelson, W., Fouts, D.E., Levy, S., Knap, A.H., Lomas, M.W., Nealson, K., White, O., Peterson, J., Hoffman, J., Parsons, R., Baden-Tillson, H., Pfannkoch, C., Rogers, Y.H., Smith, H.O., 2004. Environmental genome shotgun sequencing of the Sargasso Sea. Science 304, 66–74.
Verkhratsky, A., Burnstock, G., 2014. Biology of purinergic signalling: its ancient evolutionary roots, its omnipresence and its multiple functional significance. BioEssays News Rev. Mol. Cellular Dev. Biol. 36, 697–705.
Vogt, A.M., Elsasser, A., Nef, H., Bode, C., Kubler, W., Schaper, J., 2003. Increased glycolysis as protective adaptation of energy depleted, degenerating human hibernating myocardium. Mol. Cell. Biochem. 242, 101–107.
Wallace, D.C., 2010. Colloquium paper: bioenergetics, the origins of complexity, and the ascent of man. Proc. Natl. Acad. Sci. U. S. A. 107 (Suppl. 2), 8947–8953.
Wallace, D.C., Fan, W., 2010. Energetics, epigenetics, mitochondrial genetics. Mitochondrion 10, 12–31.
Wang, Y., Subramanian, M., Yurdagul Jr., A., Barbosa-Lorenzi, V.C., Cai, B., de Juan-Sanz, J., Ryan, T.A., Nomura, M., Maxfield, F.R., Tabas, I., 2017. Mitochondrial fission promotes the continued clearance of apoptotic cells by macrophages. Cell 171 (331–345), e322.
Wiley, J.F., Gruenewald, T.L., Karlamangla, A.S., Seeman, T.E., 2016. Modeling multisystem physiological dysregulation. Psychosom. Med. 78, 290–301.
Will, Y., Dykens, J.A., 2018. Mitochondrial Dysfunction Caused by Drugs and Environmental Toxicants. John Wiley & Sons, Inc., Hoboken, NJ, USA.
Yee, D.C., Shlykov, M.A., Vastermark, A., Reddy, V.S., Arora, S., Sun, E.I., Saier Jr., M.H., 2013. The transporter-opsin-G protein-coupled receptor (TOG) superfamily. FEBS J. 280, 5780–5800.
Yoshimi, N., Futamura, T., Kakumoto, K., Salehi, A.M., Sellgren, C.M., Holmen-Larsson, J., Jakobsson, J., Palsson, E., Landen, M., Hashimoto, K., 2016. Blood metabolomics analysis identifies abnormalities in the citric acid cycle, urea cycle, and amino acid metabolism in bipolar disorder. BBA Clin. 5, 151–158.
Yu, X., Li, H., Murphy, T.A., Nuss, Z., Liles, J., Liles, C., Aston, C.E., Raj, S.R., Fedorowski, A., Kem, D.C., 2018. Angiotensin II type 1 receptor autoantibodies in postural tachycardia syndrome. J. Am. Heart Assoc. 7.
Yuan, T.F., Li, A., Sun, X., Ouyang, H., Campos, C., Rocha, N.B.F., Arias-Carrion, O.,

Machado, S., Hou, G., So, K.F., 2016. Transgenerational inheritance of paternal neurobehavioral phenotypes: stress, addiction, ageing and metabolism. Mol. Neurobiol. 53, 6367–6376.
Zhang, Y., Strehin, I., Bedelbaeva, K., Gourevitch, D., Clark, L., Leferovich, J., Messersmith, P.B., Heber-Katz, E., 2015. Drug-induced regeneration in adult mice. Sci. Transl. Med. 7, 290ra292.
Zhong, Z., Liang, S., Sanchez-Lopez, E., He, F., Shalapour, S., Lin, X.-J., Wong, J., Ding, S., Seki, E., Schnabl, B., Hevener, A.L., Greenberg, H.B., Kisseleva, T., Karin, M., 2018. New mitochondrial DNA synthesis enables NLRP3 inflammasome activation. Nature (Epub ahead of print).
Zhou, J.H., Zhang, T.T., Song, D.D., Xia, Y.F., Qin, Z.H., Sheng, R., 2016. TIGAR contributes to ischemic tolerance induced by cerebral preconditioning through scavenging of reactive oxygen species and inhibition of apoptosis. Sci. Rep. 6, 27096.
Zimmermann, M., Reichert, A.S., 2017. How to get rid of mitochondria: crosstalk and regulation of multiple mitophagy pathways. Biol. Chem. 399, 29–45.