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Metabolic features of the cell danger response

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ABSTRACT

The cell danger response (CDR) is the evolutionarily conserved metabolic response that protects cells and hosts from harm. It is triggered by encounters with chemical, physical, or biological threats that exceed the cellular capacity for homeostasis. The resulting metabolic mismatch between available resources and functional capacity produces a cascade of changes in cellular electron flow, oxygen consumption, redox, membrane fluidity, lipid dynamics, bioenergetics, carbon and sulfur resource allocation, protein folding and aggregation, vitamin availability, metal homeostasis, indole, pterin, 1-carbon and polyamine metabolism, and polymer formation. The first wave of danger signals consists of the release of metabolic intermediates like ATP and ADP, Krebs cycle intermediates, oxygen, and reactive oxygen species (ROS), and is sustained by purinergic signaling. After the danger has been eliminated or neutralized, a choreographed sequence of anti-inflammatory and regenerative pathways is activated to reverse the CDR and to heal. When the CDR persists abnormally, whole body metabolism and the gut microbiome are disturbed, the collective performance of multiple organ systems is impaired, behavior is changed, and chronic disease results. Metabolic memory of past stress encounters is stored in the form of altered mitochondrial and cellular macromolecule content, resulting in an increase in functional reserve capacity through a process known as mitocellular hormesis. The systemic form of the CDR, and its magnified form, the purinergic life-threat response (PLTR), are under direct control by ancient pathways in the brain that are ultimately coordinated by centers in the brainstem. Chemosensory integration of whole body metabolism occurs in the brainstem and is a prerequisite for normal brain, motor, vestibular, sensory, social, and speech development. An understanding of the CDR permits us to reframe old concepts of pathogenesis for a broad array of chronic, developmental, autoimmune, and degenerative disorders. These disorders include autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD), asthma, atopy, gluten and many other food and chemical sensitivity syndromes, emphysema, Tourette's syndrome, bipolar disorder, schizophrenia, post-traumatic stress disorder (PTSD), chronic traumatic encephalopathy (CTE), traumatic brain injury (TBI), epilepsy, suicidal ideation, organ transplant biology, diabetes, kidney, liver, and heart disease, cancer, Alzheimer and Parkinson disease, and autoimmune disorders like lupus, rheumatoid arthritis, multiple sclerosis, and primary sclerosing cholangitis.

1. Introduction

Cells have a limited number of ways they can respond to threat. An important consequence of this is that evolutionary selection preserves similar cellular responses to diverse forms of threat. The cell danger response (CDR) is an evolutionarily conserved cellular metabolic response that is activated when a cell encounters a chemical, physical, or microbial threat that could injure or kill the cell. Common microbial threats are viruses, bacteria, fungi, and parasites. Physical threats include heat, salt, or pH shock, or UV or ionizing radiation. Chemical forms of danger include heavy and trace metals like lead, mercury, cadmium, arsenic, and nickel, certain electrophilic aromatic chemicals like the plasticizer bisphenol A, the chemical flame retardants like the brominated diphenyl ethers (BDEs), and certain halogenated pesticides like chlorpyrifos and DDT. Psychological trauma, particularly during childhood, can also activate the cell danger response, produce chronic inflammation, and increase the risk of many disorders (Ehlert, 2013). Mixtures of these factors and susceptible genotypes have synergistic effects. The total load of triggers is integrated by metabolism and regulates the CDR. Mitochondria are evolved to sense all of these threats according to the induced changes in electron flow available for normal metabolism. This review will emphasize communication between mitochondria

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and the nucleus, and show how many pathways of extracellular, cell–cell communication are ultimately traceable to mitochondrial metabolism. The cell danger response is coordinated in the brain via chemosensory integration of whole body and microbiome metabolism. Abnormal persistence of the CDR ultimately leads to altered organ function and behavior, and results in chronic disease.

Small molecule nutrients and metabolites are the prime movers of the CDR. Protein, glycan, RNA, epigenetic, and genetic changes are essential, but secondary, and can only be understood with reference to the prime drivers in metabolism. Readers interested in the mitochondria-associated proteins (Arnoult et al., 2011), glycans (Angata et al., 2012), microRNAs, genetics, and epigenetics (Knight, 2013) of innate immunity and inflammation that are associated with the CDR are referred to recent reviews on those topics.

2. Historical foundations

The concept of the cell danger response described in this review has evolved from a confluence of six rivers of scholarship that have developed in relative isolation over the past 60 years. Briefly these are: 1) the recognition that inherited disorders in purine and pyrimidine metabolism produce distinct behavioral and immunologic phenotypes that are not explained by current concepts in neuropharmacology and immunology, 2) the recognition that extracellular purines and pyrimidines like ATP, ADP, UTP, and UDP bind to ubiquitous ion channels and G-protein coupled receptors (GPCRs) to control everything from neurotransmission, to cortisol production, inflammation, chronic pain signaling, and control of the autonomic nervous system, 3) the recognition that immunologic systems have evolved not to distinguish self from non-self, but rather to respond to threats that result in cellular injury, 4) the recognition from the field of virology that the most adaptive strategy is a co-evolutionary negotiation between virus and host, that the pre-exposure condition of the host determines a large fraction of the pathology of infection, and that across virtually all classes of animal cell viruses studied, considerable genetic reserves are expended to target the host mitochondrial "danger alarm system", 5) the recognition within the field of mitochondrial medicine of that extracellular nucleotides are ultimately traceable to mitochondria and that one of the most ancient functions of mitochondria is cellular defense—the detection and response to cellular danger as a fundamental component of innate immunity, and 6) the concept that humans and all other animals are ecosystems of cooperating cells, and that even the most complex ecosystems on Earth can be understood and made more resilient with attention to the relevant forcing variables of physical habitat, resource availability, complementary biodiversity, elimination of invasive species, and the recycling and removal of metabolic end products.

2.1. Biochemical genetics

Biochemical genetics is a mature medical subspecialty that dates to the publication of Sir Archibald Garrod's report of the Mendelian inheritance of alkaptonuria in 1902 (Garrod, 1902), and has been dedicated to the care of children and adults with inborn errors of metabolism since the 1960s. William Nyhan is one of the fathers of the field of biochemical genetics and a mentor to many leaders in the field today. Dr. Nyhan published the first example of an inherited defect in purine metabolism that profoundly altered behavior known as Lesch–Nyhan Disease (Lesch and Nyhan, 1964). Just a few years later he published the first example of a child with autism-like behaviors resulting from an inherited increase in purine synthesis known as phosphoribosylpyrophosphate synthase (PRPPS) super activity syndrome (Nyhan et al., 1969). Both disorders resulted in a profound increase in de novo purine biosynthesis. The complex behavioral and immunologic syndromes produced by inherited defects in purine and pyrimidine metabolism have recently been reviewed (Micheli et al., 2011; Nyhan, 2005). Although the fact that purine and pyrimidine disturbances produce these syndromes is well established, no unifying mechanistic theory exists to explain the development of these complex neuroimmuno-developmental disorders.

2.2. Purinergic signaling

Purinergic signaling was pioneered by Geoffrey Burnstock in the early 1970s, when he described the first examples of non-adrenergic, non-cholinergic (NANC) signaling mediated by the stimulated release of ATP (Burnstock et al., 1972). Skepticism was high in the early days that extracellular ATP could actually be a neurotransmitter. With the cloning of 19 different purinergic receptors that are widely distributed in every neural and non-neural tissue of the body, this early skepticism has been soundly extinguished (Burnstock and Verkhratsky, 2009; Burnstock et al., 2010, 2011). Today, the role of purinergic signaling continues to expand virtually into every fundamental cell communication, stress response, autonomic, vestibular, and sensory integration pathway known (Bours et al., 2011; Burnstock, 2012; Choo et al., 2013; Halassa, 2011; Junger, 2011; Pimentel et al., 2013).

2.3. Immunologic cell danger

Polly Matzinger and Ephraim Fuchs developed the cell danger model of tolerance and immunoreactivity in the early 1990s to explain why effective adaptive immune responses are best mounted under conditions of cell danger and injury (Dreifus, 1998; Matzinger, 1994). This danger theory of immunology has produced many fruitful insights over the past 20 years ranging from contributions to tumor immunology, to graft versus host disease, allergy, asthma, and next generation adjuvants (Fuchs and Matzinger, 1996; Matzinger and Kamala, 2011; Seong and Matzinger, 2004).

2.4. Virology

Since the polio epidemics of the 1950s, we've learned that the vast majority of infections do not kill or permanently disable the host. In the case of polio, just 1 in 150 to 1 in 1800 people infected develops paralytic disease (Nathanson and Kew, 2010). More than 99% of poliovirus infections are either silent, or lead to self-limited upper respiratory tract infections ("colds"), or flu-like abdominal symptoms. Malnutrition and innate immune status are major factors that determine the probability that exposure to poliovirus will result in paralytic disease. Darwin went further. He recognized that many indigenous people were ravaged by disease that was brought by European explorers aboard ships where no disease was evident. Native people had an innate susceptibility to disease that did not affect the European explorers. He noted this phenomenon during his visit to Australia in 1836:

> *It is certainly a fact, which cannot be controverted, that most of the diseases that have raged in the islands during my residence there, have been introduced by ships; and what renders this fact remarkable is that there might be no appearance of the disease among the crew of the ship which conveyed this destructive importation* (Darwin, 1839).

The comprehensive study of viral gene structure since the 1990s has revealed that virtually every class of animal virus has incorporated into its genome the machinery to thwart, suppress, neutralize, or evade the mitochondrial "danger alarm system" (Corcoran et al., 2009; Ohta and Nishiyama, 2011; Scott, 2010). This genetic insight has cast a bright light on the role of mitochondria in antiviral signaling, and cellular defense. In this review, the role of mitochondria in the initiation and maintenance of the cell danger response is placed in context of coordinated changes in whole cell, and whole body metabolism, that together lead to changes in neurodevelopment, behavior, and to chronic disease.

2.5. Mitochondrial medicine

For many years, the treatment of inborn errors in mitochondrial oxidative phosphorylation was directed at trying to restore cellular ATP production, with limited success. At one memorable meeting in Melbourne, Australia in 1998, the distinguished yeast geneticist, biochemist, and mitochondrial biologist Dr. Anthony Linnane stood up and commented (to paraphrase), "If we are intellectually honest, we must discard old ideas and look for new paradigms to explain the cause of symptoms in a disease if we test a rationally designed therapy in patients with the disease, but it fails repeatedly." Mitochondria are located at the hub of the wheel of metabolism, contain 1500 proteins tailored to meet the needs of each different cell type, and catalyze over 500 different chemical reactions in metabolism. The connection between neurodegenerative episodes and infection in mitochondrial disease was recognized and quantified in the early 2000s (Edmonds et al., 2002). With the discovery that mitochondria represented the front lines in cellular defense and innate immunity, this connection between neurological setbacks and infection began to be understood (Seth et al., 2005; West et al., 2011). Ultimately, all the phosphorylated nucleotides of the cell are traceable to reactions in mitochondria. This makes mitochondria fundamental sources of nucleotides for purinergic signaling.

2.6. Ecology and medicine

Even the most complex ecosystem dynamics can be understood as a function of a discrete set of forcing variables that include the physical habitat, resources, complementary biodiversity, disruptive biodiversity (invasive species), and the recycling and removal of metabolic end products. Metabolism, and indeed, whole body function and development can be considered as a complex web of interconnected and interdependent pathways that change in an orderly pattern from conception to old age. Ecologists focus on the identification of drivers, forcing variables, or state variables that can alter the state of an ecosystem, preserve resilience, or drive succession. Drivers are discrete physical, chemical, or biological entities that when changed a small amount, produce large changes in the interaction and performance of the ecosystem as a whole. For example, factors like sunlight, ocean temperature, pH, CO_2, and dissolved oxygen concentration produce dramatic changes in the health of coral reef ecosystems (Riegl et al., 2009).

As we reduce the scale of analysis to the level of the cell, the details of chemistry become more important, and the time constants of response shorten from years in terrestrial ecosystems, to seconds to months in metabolism. Physical habitats are established in complementary microhabitats in each organ, like interdependent structures in the brain. Species become differentiated cell types in tissues that develop complementary and interdependent metabolisms. Within a cell, specialized proteins and enzymes are organized in complementary and interdependent compartments or microhabitats called organelles, and trophic layers in a network. These intracellular trophic layers distinguish proteins needed for the recycling of nutrients, from proteins required for the synthesis of secondary metabolites and polymers—larger structures from smaller building blocks. Resources in the cell are the chemical building blocks of proteins, fats, carbohydrates, and nucleic acids. More generally, the traffic flow patterns of resources and electrons within a cell determine its state of health, alarm, or disease.

What are the state variables in metabolism? In metabolism, pH, CO_2, and oxygen are also important state variables. However, metabolic intermediates like alpha-ketoglutarate (AKG), and cofactors and vitamins are also state variables. Deficiencies in vitamin C produce defects in collagen proline hydroxylation and neurotransmitter metabolism known as scurvy. Deficiencies in thiamine produce defects in glucose, pyruvate, and amino acid metabolism that cause Beriberi and Wernicke–Korsakoff syndrome. Other drivers or state variables in metabolism will be discovered by the systematic application of advanced mass spectrometry and metabolomics methods in each complex disease state, before and after successful treatment.

In ecology, an ecosystem can fail or become unhealthy for many reasons. The field of restoration ecology concerns itself both with identifying the governing dynamics of the complex system, and with the identification of the discrete factors that can be modified to restore health and resilience to the system (Gunderson, 2000). The same is true in medicine. An important forcing variable in the control of chronic inflammation and the cell danger response is purinergic signaling.

3. The cell danger response

When ATP synthesis, nucleotide metabolism, and associated purinergic signaling are disturbed, a coordinated set of cellular responses is triggered that evolved to help the cell defend itself from microbial attack or physical harm. Elements of this cell danger response (CDR) have been given many names that reflect the level and tools of analysis used to study it. The CDR includes the endoplasmic reticulum (ER) stress response (Liu et al., 2008), the unfolded protein response (Lee and Glimcher, 2009), the mitochondrial unfolded protein response (Haynes et al., 2013), the heat shock protein response (Kim et al., 2006), the integrated cell stress response (Silva et al., 2009), the oxidative stress response (Lushchak, 2010), the oxidative shielding response (Naviaux, 2012), innate immunity (West et al., 2011), and inflammation (Zhou et al., 2011). These can be understood as a unified, and functionally coordinated response by considering the CDR in its most fundamental and most ancient role; to improve cell and host survival after viral attack. The acute CDR produces at least 8 functional changes: 1) it shifts cellular metabolism from net polymer synthesis to monomer synthesis to prevent the hijacking and assembly of cellular resources by intracellular pathogens, 2) it stiffens the membranes of the cell and circumscribes an area of damage to limit pathogen egress, 3) releases antiviral and antimicrobial chemicals into the pericellular environment, 4) increases autophagy and mitochondrial fission to remove intracellular pathogens, 5) changes DNA methylation and histone modification to alter gene expression, 6) mobilizes endogenous retroviruses and other mobile genetic elements like the long interspersed nuclear elements (LINEs) to produce genetic variations, 7) warns neighboring cells and distant effector cells of the danger, and 8) alters the behavior of the host to prevent the spread of infection to kin and sleep patterns to facilitate healing (Fig. 1).

3.1. Ancient and modern triggers of the CDR

In the Precambrian seas, the only cells that could transmit their DNA to the next generation were cells that had successfully survived infection by viruses and other microbial pathogens, and exposure to a wide array of chemical and physical forces that were fixtures of the young biosphere. Early cells synthesized ATP and other nucleotides for a diverse array of metabolic functions in addition to RNA and DNA synthesis. The concentration of ATP inside of single cells is typically about 1–5 mM—nearly one million times more than in the extracellular environment (<5–10 nM). When a cell was injured or lysed by a virus, ATP and other nucleotides and metabolites were released into the surrounding area, creating a bright chemical "flare" warning other cells of the danger and the presence of a pathogen.

Before a cell is broken or lysed, mitochondria in an infected eukaryotic cell sense the presence of an intruding microbe by detecting the diversion of electrons (as NADH and NADPH) and carbon to viral biogenesis centers for polymer synthesis to make viral RNA, protein, and DNA from building blocks in the host cell. This "electron steal" is sensed as a voltage drop, or decrease in electron flow available within the cell for oxidative phosphorylation in mitochondria. The metabolic consequences are nearly instantaneous. Mitochondria rapidly decrease their oxygen consumption, which is coupled to electron flow. The dissolved oxygen concentration in the cell begins to rise because mitochondria

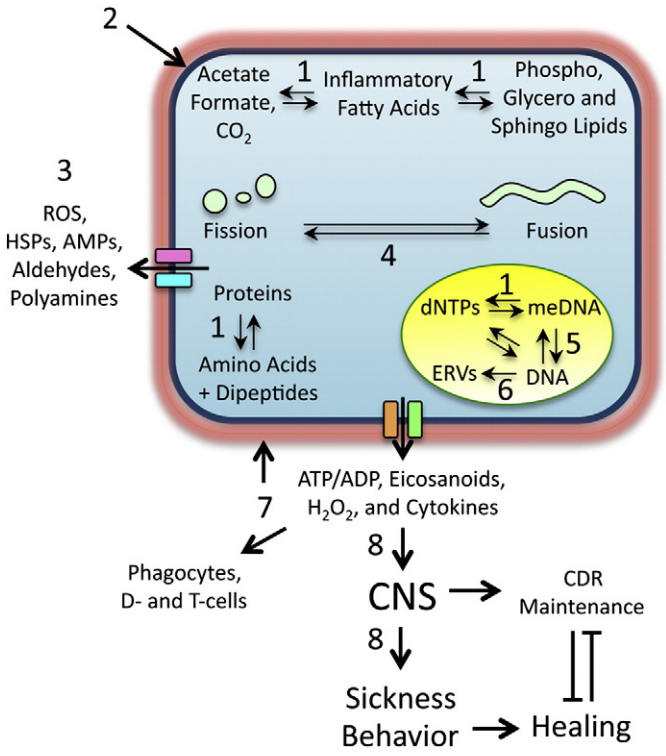


Fig. 1. Functions of the acute cell danger response. The acute CDR includes 8 functional changes in cell structure, physiology, metabolism, and gene expression. These are: 1) shift cellular metabolism from polymer to monomer synthesis to prevent the hijacking and assembly of cellular resources by intracellular pathogens, 2) stiffen the cell membranes to limit superinfection and pathogen egress, 3) release antiviral and antimicrobial chemicals into the pericellular environment, 4) increase autophagy, mitochondrial fission, and mitophagy to facilitate removal of intracellular pathogens and biogenesis centers, 5) change DNA methylation and histone modification to alter gene expression, 6) mobilize endogenous retroviruses and LINEs to produce genetic variations, 7) warn neighboring cells and distant effector cells of the danger with extracellular nucleotides, H_2O_2, eicosanoids, metabolites, and cytokines, and 8) alter the behavior of the host to prevent the spread of infection to kin, and sleep patterns to facilitate healing. *Abbreviations*: HSPs: heat shock proteins; AMPs: antimicrobial peptides; D-cells: Dendritic Cells; ERVs: endogenous retroviruses; LINEs: long interspersed nuclear elements; meDNA: methylated DNA; dNTPs: deoxynucleoside triphosphates; CNS: central nervous system.

are the oxygen sink in every eukaryotic cell. This makes the cellular redox chemistry more oxidizing (Naviaux, 2012). Highly oxidizing environments strongly inhibit the assembly of monomeric building blocks into polymers, and rapidly decrease the efficiency of RNA, protein, and DNA synthesis by the infecting virus. Oxidizing conditions also result in the oxidation of sulfur in methionine, and thiols like cysteine, homocysteine, and glutathione, and the disassembly of iron–sulfur clusters in many enzyme systems, and decrease the availability of the thiol of coenzyme A that is essential for intermediary metabolism.

The ability of mitochondria to monitor electron flow and sulfur oxidation makes them ideally suited as generalized cell "danger alarms". Their rapid metabolism makes mitochondria the "canaries in the coal mine" for the cell. Any trace or heavy metal that acts as an electrophile or sulfurophile in the cell will trigger a mitochondrial response that is similar to that of a viral infection, because metal electrophiles and replicating pathogens both divert and consume electrons. Likewise, a large number of molecules have been synthesized since the 1850s as dyes, pesticides, drugs, and industrial chemicals. Many are polyaromatic and halogenated. These modern chemicals with conjugated ring systems, multiple double bonds, and delocalized π orbital electron clouds are highly electrophilic and will produce an electron steal within the cell that can also activate the CDR. The CDR is a generic, but highly evolved response that often complicates more specific molecular effects that occur when a synthetic molecule binds to a receptor, or competes with and disrupts normal metabolic or hormone signaling. Mixtures of chemical and biological threats can have synergistic effects, and the total load of danger triggers can influence the magnitude and form of the CDR. When danger is detected, mitochondria alter cellular metabolism to help shield the cell from further injury. This is accomplished by stiffening cell membranes, activating the production of reactive oxygen species (ROS), and producing changes in many different pathways in intermediary metabolism that have the effect of limiting pathogen replication and limiting the spread of danger (Naviaux, 2012). These pathways are immature in newborns and growing children (Wood et al., 2010), leading to effects that are not limited to inflammation and innate immunity in peripheral tissues, but can also alter neurodevelopment (Landrigan et al., 2012) and increase the risk of other chronic childhood diseases.

3.2. Summer and winter metabolism

Large trends in the seasonal variation of metabolism can be placed in context by considering the evolutionary forces that have acted on our ancestors. Seasonal changes in calorie availability were the rule. Summer was a time of plenty, when the environment provided abundant calories, which were harvested with physical exercise. This was a natural time for cell growth, during which building blocks were polymerized to produce new cells and increase biomass. Physical exercise ensured that the added biomass was functionally efficient. The master fuel sensor in the cell during summer is mTOR (mammalian target of rapamycin) (Yang and Ming, 2012). mTOR facilitates protein synthesis and growth using new materials taken in from the environment. mTOR inhibits the internal recycling of used or damaged cellular resources by autophagy. The pathways supported by mTOR are Janus faced. In cells capable of dividing, mTOR promotes rapid growth with net polymer synthesis, without inflammation. Used or damaged proteins, lipids, glycans, RNA, and DNA are diluted by new synthesis from fresh building blocks obtained from rich summer ecosystems. In differentiated cells that cannot dispose of excess calories without hypertrophy, mTOR excess results in the accumulation of old and damaged macromolecules like oxidized or aggregated proteins, and produces chronic inflammation—oxidizing conditions that act as a thermodynamic break on the inexorable accumulation of intracellular polymers like lipids, proteins, glycogen, and nucleic acids from their monomer building blocks.

Winter was a time of caloric restriction and a time when resources stored in the summer and fall had to be used with great efficiency if survival was to be assured. The master fuel sensor in the winter is AMPK (AMP activated protein kinase) (Salminen and Kaarniranta, 2012). AMPK optimizes energy efficiency and stimulates the recycling of cellular materials in autophagy. This cycle occurs to a lesser extent each night and during fasting. The pathways activated by AMPK support regeneration and are anti-inflammatory because they work to break down damaged proteins, lipids, glycans, RNA, and DNA. AMPK facilitates the resynthesis of these macromolecules from newly synthesized monomers and refreshed building blocks. Monomer synthesis and polymer synthesis are balanced for winter maintenance. Historically, before the 1980s, most human nutrition research was focused on disorders of deficiency. After the 1980s, much of human nutrition research has been redirected to disorders of caloric excess. Indeed many of the genes that have been found to guard against age-related diseases like diabetes, cancer, and heart disease are found to be "winter genes" coordinated by AMPK, while the "summer genes" coordinated by mTOR lead to chronic disease and inflammation when combined with caloric excess and physical inactivity. Technological progress and industrial scale farming practices have been a double-edge sword for the health of populations around the world. Many developed nations now experience an "endless summer" of calorie availability, decreased physical exercise, and an absence of the historical norm of winter caloric restriction. This has led to

modern epidemics of obesity in both adults and children, and to a growing tide of chronic disease traceable to cellular inflammation.

4. Metabolic features of the CDR

The following section is designed to be read with close reference to Fig. 2. Panels A and B illustrate 21 branch points in metabolism that are normally tipped in the direction of "healthy development", reducing conditions, polymer synthesis and renewal (upward in the figure). However, when a cell is infected by a virus or other microbial pathogen, metabolism is shifted to innate immunity, inflammation, oxidizing conditions, and monomer synthesis to oppose the efforts of the pathogen to parasitize resources and replicate itself by assembling polymers. The shift in metabolism during this cell danger response (CDR) is indicated in the downward direction in the Figure. When these changes occur in the context of cell division and the distribution of accumulated biomass to daughter cells during growth, then inflammation is avoided unless accompanied by significant cell damage. Problems arise when these conditions are activated in post-mitotic tissues that have a limited capacity for growth. The list of metabolic branch points in Fig. 2AB is not intended to be comprehensive, and not all metabolic fates of the branch-point metabolites are discussed. The reader is referred to topical reviews of each of the branch point metabolites of interest for more comprehensive discussion.

4.1. Mitochondria

Mitochondria fragment under conditions of the CDR leading to ineffective control and propagation of intracellular calcium transients (Eisner et al., 2010). When cells are injured and mitochondrial proteins are released to the extracellular space, formyl-methionine initiated mitochondrial proteins can stimulate inflammation via the formyl-peptide receptor (Rabiet et al., 2005). Extracellular mitochondrial DNA activates innate immunity via the TLR9 receptor (West et al., 2011), and is specifically released during infection by eosinophils as an antimicrobial net (Yousefi et al., 2008).

4.2. Oxygen

When mitochondrial oxygen consumption decrease, dissolve cytoplasmic oxygen rises and activates reactive oxygen species (ROS) production by many enzyme systems including NOX4 (Hecker et al., 2009). Increased dissolved oxygen, superoxide and hydrogen peroxide activate many proteins including the central inflammatory regulator NFkB (Lluis et al., 2007) and the multifunctional transglutaminase 2 (Caccamo et al., 2012). Although ROS are sometimes considered intrinsically inflammatory, it is interesting to note that one of the most destructive genetic forms of chronic inflammatory disease is one that cannot produce ROS in response to infection. Chronic granulomatous disease (CGD) is caused by the genetic deficiency of subunits of phagocyte NADPH oxidase 2 (NOX2) that makes the child unable to produce significant amounts of superoxide, hydrogen peroxide, and hypochlorous acid for antibacterial and antifungal defense (Kuijpers and Lutter, 2012). In another example, ROS are protective, and now recognized as important inhibitors of inflammation in autoimmune disorders like rheumatoid arthritis, multiple sclerosis, thyroiditis, and type 1 diabetes (Hultqvist et al., 2009).

4.3. ATP

Purinergic signaling nucleotides like ATP, ADP, UTP, and UDP are released in increased amounts from cells under stress and activate inflammation (Xia et al., 2012). Cells need not be broken or lysed to increase the release of ATP, other nucleotides, and metabolites. ATP and sodium urate crystals are activators of NLRP3 inflammasome assembly (Riteau et al., 2012). Purinergic signaling via ATP directly stimulates cortisol synthesis and release from the adrenal cortex, independent of ACTH stimulation (Kawamura et al., 1991).

4.4. Cysteine and sulfur

Sulfur metabolism is shifted such that glutathione is consumed in glutathionylation regulatory (McLain et al., 2013) and liver phase II detoxification reactions (Zamek-Gliszczynski et al., 2006), and cysteine is diverted to H_2S, taurine, and sulfate excretion (Stipanuk and Ueki, 2011). As an important compensation, the increased plasma oxidation state of the CDR favors cysteine oxidation to cystine (CySSCy), which is used to transport needed cysteine across the blood–brain barrier to the brain (Bridges et al., 2012; Lewerenz et al., 2013), and into macrophages for glutathione synthesis (Kobayashi et al., 2012).

4.5. Vitamin D

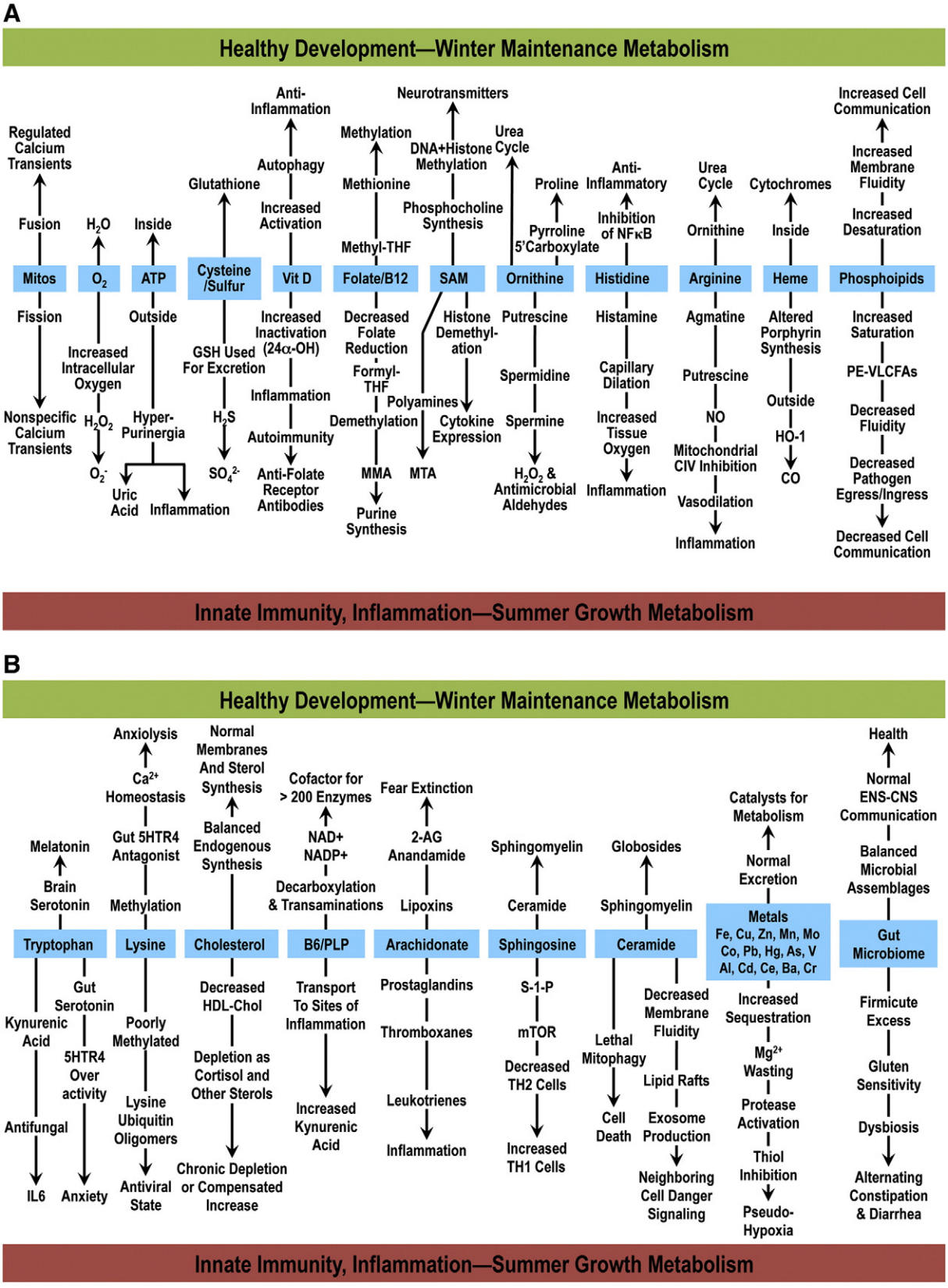
In the face of normal body stores of calcium and phosphorus, vitamin D metabolism is altered significantly by the CDR. A mitochondrial P450 enzyme, the 1α hydroxylase, in the kidney is required to activate 25-Hydroxyvitamin D to hormonally active, 1,25-Dihydroxyvitamin D. Another mitochondrial enzyme, the 24α-hydroxylase, is used to inactivate vitamin D. The 24α-hydroxylase is increased by cell danger threats like endotoxin (Shanmugasundaram and Selvaraj, 2012). This decreases the concentration of active vitamin D and contributes to the CDR by increasing inflammation, but also increases the risk of developing of autoantibodies that may include anti-thyroid antibodies (Kivity et al., 2011), and may contribute to the development of other autoantibodies like anti-folate receptor antibodies.

4.6. Folate and B12 metabolism

The metabolism of folic acid and vitamin B12 is tightly interconnected with mitochondrial function, sulfur metabolism, glycine, serine, nucleotide synthesis, and DNA and histone methylation (Naviaux, 2008). Out of over 2700 enzymes encoded by the human genome (Romero et al., 2005) only two require B12, but no fewer than 15 proteins are dedicated to the absorption, transport, and metabolism of B12 (Nielsen et al., 2012). One of the two enzymes is methylmalonyl CoA mutase. It is located in mitochondria and uses the adenosyl form of B12, adenosylcobalamin to convert methylmalonyl-CoA to succinyl-CoA for import into the Krebs cycle. The other B12-dependent enzyme, methionine synthase (MS), is located in the cytosol and uses the methyl form of B12, methylcobalamin, to synthesize methionine from homocysteine. Methionine can be used to initiate protein synthesis, or as a precursor for S-adenosyl methionine (SAM) synthesis. Ultimately the flux through alternative pathways of folate, glutathione, and methionine metabolism is determined by cellular redox poise. Under oxidizing conditions of the CDR, SAM is directed preferentially to polyamine synthesis to assist with ROS and antiviral and antimicrobial polyamine aldehyde synthesis and release (Bachrach, 2007). This lowers the SAM/SAH ratio, while simultaneously decreasing net availability of SAM for DNA methylation reactions. Gene- and cell type-specific demethylation of histones is stimulated by oxidizing conditions of the CDR by the Jumonji histone demethylases, increasing expression of pro-inflammatory cytokines like TNFα (Kruidenier et al., 2012). In addition, the oxidizing conditions of the CDR increase the ratio of formyl-tetrahydrofolate to methyl-tetrahydrofolate (fTHF/mTHF) and the ratio of methylene-THF to mTHF. This favors the de novo synthesis of nucleotides like IMP and dTMP that require 1-carbon donation from fTHR and methylene-THF, respectively. The resulting increase in IMP synthesis can be used to make purine nucleotides like ATP for purinergic signaling. The oxidizing conditions of the CDR ensure that the resulting nucleotides will be used preferentially as monomers for metabolic and signaling purposes, since assembly into polymers of RNA and DNA is chemically unfavorable.

4.7. SAM

S-adenosyl methionine (SAM) is used as a universal methyl donor for DNA, histone, and neurotransmitter methylation reactions. After decarboxylation by SAM decarboxylase, dcSAM is used as an essential aminopropyl donor for polyamine and methylthioadenosine (MTA) synthesis (Fontecave et al., 2004). When the CDR is activated, a larger portion of SAM is diverted to the synthesis of polyamines like



spermidine and spermine, which can be used to synthesize hydrogen peroxide and potent antimicrobial aldehydes like 3-aminopropanal, and 3-acetoaminopropanal (Cervelli et al., 2012). SAM can be usurped by invading pathogens as a methyl donor for the maturation of pathogen mRNAs. S-adenosylhomocysteine (SAH) is a potent feedback inhibitor of SAM-mediated methylation reactions. By decreasing the SAM/SAH ratio, the CDR further consolidates an intracellular environment that is unfavorable for pathogen replication. Adenosine and several purine nucleosides and nucleotides help to maintain a low SAM/SAH ratio by inhibiting SAH hydrolase (SAHH), a key enzyme known to be the target of several synthetic antiviral drugs (De Clercq, 2009).

4.8. Ornithine

Ornithine is a non-proteogenic amino acid synthesized from arginine by arginase I in the liver, and arginase II in many other tissues. When the CDR is activated, ornithine is decarboxylated by the B6-dependent enzyme ornithine decarboxylase (ODC) to putrescine, the polyamine used for all higher molecular weight polyamines like spermidine and spermine. Sustained activation of ODC contributes to increased inflammation and the development of autoantibodies in animal models of lupus erythematosis (Hsu et al., 1994).

4.9. Histidine

Acute activation of the CDR stimulates the B6-dependent enzyme histidine decarboxylase to yield histamine. Histamine is a potent vasodilator that facilitates the delivery of increased oxygen and immune effector cells to sites of inflammation. Histamine is also critical for mast cell and eosinophil function in allergy and the anti-parasite limb of innate immunity (Fulkerson and Rothenberg, 2013).

4.10. Arginine

Arginine has several fates in metabolism. It is a substrate for the tetrahydrobiopterin-dependent nitric oxide synthase. The resulting nitric oxide (NO) gas is a potent and reversible inhibitor of mitochondrial cytochrome c oxidase, also known as complex IV (Forstermann and Sessa, 2012). Arginine can also be decarboxylated to synthesize agmatine, a natural anti-depressant neurotransmitter (Bernstein et al., 2012). Under conditions of the CDR, agmatine is hydrolyzed to produce urea and the antiviral polyamine, putrescine (Bernstein et al., 2012).

4.11. Heme

Heme is abundant in erythrocyte hemoglobin, but is also present as an important prosthetic group in the mitochondrial cytochromes of respiratory chain complexes II, III, and IV (Kim et al., 2012). In a sequence of events that activates the CDR, red cell and mitochondrial heme centers are released from damaged cells. In the extracellular space, heme is metabolized by heme oxygenase I (HO-1) to produce carbon monoxide (CO), releasing iron and biliverdin. Like NO, CO is a potent inhibitor of mitochondrial complex IV. In non-erythroid cells, heme is a feedback inhibitor of porphyrin biosynthesis (Ajioka et al., 2006).

4.12. Phospholipids

The membranes of all eukaryotic cells are composed largely of phospholipids. Most of these are phosphoglycerolipids that are comprised of a glycerol backbone, two fatty acid side chains, and a phosphate-containing polar head group. The fluidity of the cell membrane is a biophysical consequence of thermal packing of the fatty acid side chains. In general, the shorter and more polyunsaturated (more cis double bonds) the side chain, the more fluid the membrane. Reciprocally, the longer the carbon side chain, and the more saturated, the stiffer the membranes become. In the plasma, phosphoethanolamine-containing saturated very long chain fatty acids (PE-VLCFAs) are more abundant (Pastural et al., 2009). Under conditions of cell danger, both Jumonji demethylases (Liu et al., 2012) and heme oxygenase I (Nie et al., 2013) upregulate lipoxygenase expression. The double bonds of fatty acids in the membrane are targets for peroxidation by lipoxygenases. Under conditions of the CDR, the cell membrane is stiffened by progressive replacement of shorter polyunsaturated lipids with longer, more saturated lipids. The activation of phospholipase D2 leads to coupling of G-protein activation (Mahankali et al., 2011) and release of the potent signaling lipids as phosphatidic acid (Peng and Frohman, 2012). Since a large number of purinergic and other innate immune signaling receptors are G-protein coupled receptors, the early translocation of PLD2 to the membrane has the effect of priming purinergic signaling in the early steps of the CDR.

4.13. Tryptophan

The many metabolic fates of tryptophan make it an important molecule in both the early and late stages of the CDR. Tryptophan can be metabolized either to serotonin and melatonin via the hydroxylation (tryptophan hydroxylase) pathway, or to kynurenic acid, quinolinic acid, niacin, and the pyridine nucleotides (NAD+, NADP+) via the dioxygenase (indoleamine 2,3-dioxygenase, IDO) pathway. About 90% of the total body stores of serotonin are synthesized in gut enterochromaffin cells, and transported in platelets in the form of dense, δ-granules, which also contain ADP, ATP, histamine and calcium. Gut microbial metabolism of tryptophan results in the synthesis of a large family of indoles, several of which can also be metabolized to kynurenine. Kynurenic acid acts as an endogenous ligand for the aryl hydrocarbon receptor and synergistic inducer of IL6 (DiNatale et al., 2010), stimulates the innate immune functions like the anti-fungal activity of neutrophils, and stimulates TH2 cells, while attenuating adaptive immunity by the stimulation of TH1-inhibitory, regulatory T cells (T_{reg}) (Mandi and Vecsei, 2012).

4.14. Lysine

The antiviral CDR is strongly regulated by the post-translational state of lysines on histones and immune effector proteins like the double strand RNA binding protein known as RIG1 (retinoic acid inducible gene 1), and the mitochondrial antiviral sensor (MAVS) (Jiang et al., 2012). Lysine ubiquitination facilitates oligomerization of RIG1, which is required for efficient binding to MAVS and interferon induction. SAM-mediated lysine methylation stabilizes proteins, inhibits ubiquitination, and works to oppose increased proteasome-mediated protein turnover that is part of the CDR. Dietary lysine is an antagonist of the gut

Fig. 2. Metabolic features of the cell danger response. A. Twelve branch-point metabolites from mitochondria to phospholipids. Each of the metabolites and effectors indicated can be metabolized in two or more alternative pathways. The pathways indicated in the upward direction in the figure are characteristic of healthy development. They are also active during conditions of caloric restriction, such as those that occurred historically during the winter, during which the maintenance and preservation of limiting resources and energy is essential. The metabolic pathways indicated in the bottom half of the Figure are active during periods of unrestricted nutrient and resource availability, as is characteristic of the abundance of summer. When cell division can occur, healthy growth without inflammation results. However, when cell division cannot occur readily, as is the case in many differentiated tissues like the brain, and physical exercise is limited, innate immune disease and chronic inflammation result. B. Nine branch-point metabolites and effectors from tryptophan to the gut microbiome. The reactions illustrated in the bottom half of the Figure are characteristic of the CDR. The list of CDR metabolites and their metabolic fates illustrated in panels A and B is not intended to be complete. Other metabolites, effectors, and metabolic fates also exist and are coordinately regulated with those indicated, and tailored by metabolic memory to help defend the cell during danger. When the CDR persists pathologically, chronic disease results.

serotonin receptor 4 (5HTR4), is anxiolytic (Smriga and Torii, 2003), and opposes the CDR.

4.15. Cholesterol

Unesterified cholesterol increases the shear-stress resistance and activation of neutrophils (Zhang et al., 2011). Low cholesterol inhibits calcium activation and oxidative burst in neutrophils (Kannan et al., 2007). High cholesterol also makes neuronal cells more resistant to the cytotoxic effects of amyloid beta peptides (AβP) (Arispe and Doh, 2002). The plasma membrane of many eukaryotic cells consists of nearly 50 mol% unesterified cholesterol, which acts as an intramembrane space filler, with a small polar head group (a single hydroxyl), to help solubilize phospholipids. Cholesterol accumulates with GM1 ganglioside in microdomains called caveolae that continuously sample the pericellular environment. When the cell is activated, GM1 and cholesterol concentrate to form lipid rafts, which cause many proteins to patch and concentrate into the rafts for more efficient anti-microbial defense. CDR proteins like the formyl peptide receptor and NADPH oxidase (NOX) are assembled in lipid rafts for efficient ROS production (Jin and Zhou, 2009).

4.16. Vitamin B6

Low plasma levels of the active metabolite of vitamin B6, pyridoxal 5′-phosphate (PLP) are a common feature of inflammation and the CDR (Paul et al., 2013). PLP is a cofactor in 4 reactions in the dioxygenase (IDO) pathway of tryptophan metabolism, after the formation of kynurenine, leading to the synthesis of quinolinic acid and NAD+ and NADP+. PLP is also required by the enzyme S1P lyase for inactivating the lymphocyte chemoattractant sphingosine-1-phosphate (S1P). Low systemic levels of PLP have the effect of increasing the kynurenine/tryptophan ratio, and increase S1P in inflamed tissues, thereby sustaining an active CDR.

4.17. Arachidonate

Cells that are especially rich in mitochondria, like brain, nerve, and epithelial cells, are also rich in plasmalogen lipids, which contain arachidonic acid in the sn-2 position. This is the preferred substrate for phospholipase A2 (PLA2) isoforms for the release of arachidonate for prostaglandin, leukotriene, and other inflammatory lipid synthesis (Ong et al., 2010) during an active CDR.

4.18. Sphingosine

Several intracellular pathogens have evolved mechanisms to either inhibit the synthesis and translocation of sphingosine 1-phosphate (S1P) (Thompson et al., 2005), or stimulate its degradation in mitochondria (Degtyar et al., 2009). S1P is a phosphorylated sphingolipid that contains a single fatty acid linked to a phosphoserine head group. Intracellular S1P traffics to phagosomes where it facilitates calcium-dependent acidification during autophagy and the elimination of intracellular parasites and modulates histone acetylation in the nucleus (Lucki and Sewer, 2012). Extracellular S1P binds to 5 G-protein linked receptors, acts to inhibit apoptosis, prevents lymphocyte egress from sites of production as well as sites of inflammation (Takabe et al., 2008), and is essential for normal development of hearing and vestibular function (MacLennan et al., 2006). S1P opposes the immunomodulatory effects of kynurenine by inhibiting T_{regs}, stimulating TH1, and activating mTOR (Liu et al., 2010).

4.19. Ceramide

Ceramide is the precursor to GM1 ganglioside, sphingosine, and S1P. Ceramide both requires mitochondria for synthesis (Novgorodov and Gudz, 2011), and targets mitochondria under conditions that lead to cell death (Sentelle et al., 2012). The cell death or cell survival result of the CDR depends in part on the balance between S1P and ceramide.

4.20. Metals

Normal metabolism depends critically on the presence of a large number of metals like Mg^{2+}, Ca^{2+}, Fe^{2+}, Cu^{+}, Zn^{2+}, Mn^{2+}, Mo^{4+}, Se^{2+}, and Co^{2+} that interact with nucleotides and other metabolites, and with proteins to stabilize structure and create organometallic reaction centers. Many other metals like Pb, Hg, As, V, Ni, Al, Cd, Ce, and Cr are toxic. Under reducing redox conditions of cell health, these toxic metals are not accumulated because excretion normally exceeds exposure. When the CDR is activated, the oxidizing intracellular conditions favor sequestration, toxic amounts of trace and heavy metals can be accumulated, and are not easily mobilized. Many toxic metals act not only as electrophiles because of their positive charge, but are also sulfurophiles—they readily form sulfides with free thiols of cysteine, and glutathione. This makes free thiols unavailable for normal metabolic reactions and can create a condition known as pseudohypoxia in which intrapeptide cysteine residues of redox-sensing proteins remain uncrosslinked, disulfide bonds cannot form normally, and the three dimensional structure of the reduced form of the protein is favored under normal oxygen concentrations that would otherwise stabilize disulfide bonding. In addition to these effects, the more specific neurotoxic effects of metals like lead and mercury are well known (Ibrahim et al., 2006). When functional vitamin D is decreased by a chronically active CDR, subclinical renal wasting of magnesium can occur (Sutton and Domrongkitchaiporn, 1993).

4.21. Gut microbiome

Healthy metabolism acts as a survival engine that computes the optimum chemical solution for fitness based on the developmental history, current environmental conditions, and the genetic resources available to the individual. When we sample blood or urine, we are actually sampling the collective metabolism of the host-microbiome system. This collective metabolism also controls the epigenetic modification of DNA in somatic cells that creates long-term changes in gene expression (Naviaux, 2008). The human metabotype consists of a dynamically regulated core vocabulary of about 400–1200 chemical words that cells use to communicate. These are small molecule metabolites with a mass less than 2000 Da in size. The stoichiometric proportions of these metabolites are a reflection of our state of health at the time of sampling. The adult human body consists of about 10^{14} human cells and 10^{15} bacterial cells that act as a living shield to help protect us from opportunistic pathogens and keep us healthy. About 99% of our microbiome is in our gut. The biomass of our microbiome is about 1.5 kg, or about 2% of our body weight. Collectively, the bacteria, archaea, rare fungi, protists, and invertebrate metazoans that constitute the 3000 to 30,000 species in our gut microbiome contain a genetic complexity of about 4.5×10^{11} Gb—about 150 fold more genetic information than in the human haploid genome. This is evidence that the metabolic diversity in the gut microbiome far exceeds that of the human host.

The composition and function of the microbiome are best considered as an ecosystem that is continuously shaped by the developmental history, diet, health, and activity of the host. As with any ecosystem, the health and species composition of the microbiome are determined by a discrete set of forcing variables that include the physical habitat, resources, complementary biodiversity, disruptive biodiversity (invasive species), and the recycling and removal of metabolic end products. When the host is sick, the microbiome is also sick. The chronic activation of the CDR alters both the physical habitat of the distal bowel and the availability of resources in the form of dietary nutrients. For example, in children with autism spectrum disorders (ASD), the expression of

intestinal disaccharidases is decreased so that the microbiota of the distal bowel receives a larger number of simple disaccharides like sucrose, lactose, and maltose (Williams et al., 2011). In addition, the increase in oxidizing conditions associated with the CDR in cells lining the intestine leads to changes in the uptake, intracellular processing, and folding of the proline and glutamine-rich, processed gliadin 33-mer peptide (Oguma et al., 2007), and to an increase in gluten sensitivity (Jacobs, 2007). These and other factors combine to alter the permeability and species composition in the gut. Among children with ASD, this commonly leads to dysbiosis and alternating bouts of constipation and diarrhea. It also leads to changes in behavior that are a result of communication abnormalities between the enteric nervous system (ENS) that monitors the health and function of the microbiome, and the central nervous system (CNS). Restoring a sick microbiome is not as simple as adding back missing or underrepresented species. Both the physical habitat of the gut and the nutrient resources delivered must be durably changed in order to produce a durable change in the complex microbial ecosystem.

5. Resolution of the CDR

Once the danger has been eliminated or neutralized, two things happen naturally. First, a choreographed sequence of anti-inflammatory and regenerative pathways is activated that helps replace lost cells and restore normal organ function (Heber-Katz and Stocum, 2013). Next, a metabolic memory of the exposure that led to the CDR is stored in a way similar to the way the brain stores memories, in the form of durable changes in mitochondrial biomass, and cellular protein, lipid and other macromolecule content, cell structure, and gene expression via somatic epigenetic modifications (Naviaux, 2008). This metabolic memory is also called mitocellular hormesis (Naviaux, 2012). Under conditions that are determined by a mixture of host genotype, and the character, developmental timing, magnitude, and frequency of exposure, a dysfunctional form of the CDR can persist that leads to chronic disease. Because the CDR is initially adaptive and coordinated by the close interplay of mitochondria and the cell, but becomes maladaptive once the environmental danger is gone, this can be referred to as "anachroadaptive mitocellular dysfunction".

6. Disease implications and summary

When the CDR fails to resolve, chronic disease results. Beginning in the first trimester, the brainstem is responsible for the chemosensory integration of whole body metabolism with neurodevelopment. After birth, the trajectory of normal development can be altered if the CDR and its attendant metabolic changes persist. Some of the diseases that result from a pathological persistence of the CDR include: autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD), food allergies, asthma, atopy, emphysema, Tourette's syndrome, bipolar disorder, schizophrenia, post-traumatic stress disorder (PTSD), traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), suicidal ideation, ischemic brain injury, spinal cord injury, diabetes, kidney, liver, and heart disease, cancer, Alzheimer and Parkinson disease, and autoimmune disorders like lupus, rheumatoid arthritis, multiple sclerosis, and primary sclerosing cholangitis. Pathological persistence of the CDR can occur after the inciting agent has gone. This can be the result of hormesis and metabolic memory, somatic epigenetic changes (Blumberg et al., 2013), or both. Purinergic signaling appears to play an important role in sustaining the multifaceted metabolic features of the CDR. This observation led to the successful correction of all 16 of 16 multi-system, autism-like features in a classic animal model of ASD using antipurinergic therapy (APT) (Naviaux et al., 2013).

The chronic CDR disorders listed above produce abnormalities in a broad range of target tissues and cell types. The genotype and health of the host, and the developmental timing and the nature of the exposure determine the risk of developing a particular disease. In many cases, it appears that mixtures of cell danger exposures are required. When the abnormalities appear later in childhood or young adult life, and have not persisted long enough to produce structural abnormalities, there is a chance that many disorders currently thought to be static, irreversible, and poorly responsive to treatment, or even degenerative, might actually be dynamic functional states that respond well to anti-CDR treatments. Many of the disorders named above have already shown response to APT in animal models (Table 1). An important caveat to APT is that if the physical, chemical, or biological trigger of the CDR has not been eliminated or neutralized, treatments designed to inhibit a persistent CDR may have mixed effects. For example, if the CDR is a response to perinatal exposure to PBDE flame retardants (Blumberg et al., 2013), but the PBDEs have not been removed from living space of an affected child, then a persistent CDR can be adaptive and not anachroadaptive. APT under these conditions may cause net harm.

Table 1
Disorders corrected or improved by antipurinergic therapy.

Disease	Species	Antipurinergic drug	Reference
Autism	Mice	Suramin	Naviaux et al. (2013)
Spinal cord injury	Rats	Brilliant Blue G	Peng et al. (2009)
Traumatic brain injury	Rats and Mice	MRS2179	Choo et al. (2013)
Ischemic brain injury	Rats	Suramin	Kharlamov et al. (2002)
Glutamate excitotoxicity	Rats	Suramin	Bezvenyuk et al. (2000)
Epilepsy	Mice	A438079	Engel et al. (2012)
Rheumatoid arthritis	Rats	Suramin	Sahu et al. (2012))
Chronic pain	Rats	P2X3-15h	Cantin et al. (2012)
Multiple sclerosis	Mice	Suramin	Novales-Li (1996)
Lupus erythematosis	Mice	Suramin	Ballok and Sakic (2008)
Restenosis after angioplasty	Rabbits	Suramin	Gray et al. (1999)
Duchenne cardiomyopathy	Mice	Suramin	de Oliveira Moreira et al. (2013)
Heart failure	Rats	Apyrase	Marina et al. (2013)
Alcoholic liver disease/cirrhosis	Rats	Suramin	He et al. (2013))
Asthma	Guinea Pigs	Suramin	Oguma et al. (2007)
Emphysema	Mice	Suramin	Cicko et al. (2010)
Diabetic kidney disease	Rats	Suramin	Korrapati et al. (2012)

Each of the metabolic features of the CDR illustrated in Figs. 1 and 2AB can be addressed individually with specific treatments, or more globally with a combination of supplements, dietary and activity changes, or with adaptogen therapies (Panossian and Wikman, 2009). However, since the CDR appears to be a functional response that is coordinated by purinergic signaling, a new chapter in complex disease therapeutics can be imagined in which the pharmacology of purinergic antagonists is expanded, natural products are sought, and new anti-inflammatory drugs are developed that selectively target one or more of the 19 known classes of purinergic receptors.

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Conflict of interest

None.

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