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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.

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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.

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