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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.

**Keywords:** Inflammation; Innate immunity; Mitochondria; Oxidative shielding; Oxidative stress; Purinergic signaling.

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