The Glutathione System: A New Drug Target in Neuroimmune Disorders

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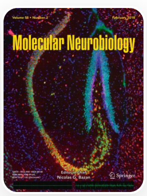

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Abstract

Glutathione (GSH) has a crucial role in cellular signaling and antioxidant defenses either by reacting directly with reactive oxygen or nitrogen species or by acting as an essential cofactor for GSH *S*-transferases and glutathione peroxidases. GSH acting in concert with its dependent enzymes, known as the glutathione system, is responsible for the detoxification of reactive oxygen and nitrogen species (ROS/RNS) and electrophiles produced by xenobiotics. Adequate levels of GSH are essential for the optimal functioning of the immune system in general and T cell activation and differentiation in particular. GSH is a ubiquitous regulator of the cell cycle per se. GSH also has crucial functions in the brain as an antioxidant, neuromodulator, neurotransmitter, and enabler of neuron survival. Depletion of GSH leads to exacerbation of damage by oxidative and nitrosative stress; hypernitrosylation; increased levels of proinflammatory mediators and inflammatory potential; dysfunctions of intracellular signaling networks, e.g., p53, nuclear factor-κB, and Janus kinases; decreased cell proliferation and DNA synthesis; inactivation of complex I of the electron transport chain; activation of cytochrome c and the apoptotic machinery; blockade of the methionine cycle; and compromised epigenetic regulation of gene expression. As such, GSH depletion has marked consequences for the homeostatic control of the immune system, oxidative and nitrosative stress (O&NS) pathways, regulation of energy production, and mitochondrial survival as well. GSH depletion and concomitant increase in O&NS and mitochondrial dysfunctions play a role in the pathophysiology of diverse neuroimmune disorders, including depression, myalgic encephalomyelitis/chronic fatigue syndrome and Parkinson's disease, suggesting that depleted GSH is an integral part of these diseases. Therapeutical interventions that aim to increase GSH concentrations in vivo include *N*-acetyl cysteine; Nrf-2 activation via hyperbaric oxygen therapy; dimethyl fumarate; phytochemicals, including curcumin, resveratrol, and cinnamon; and folate supplementation.

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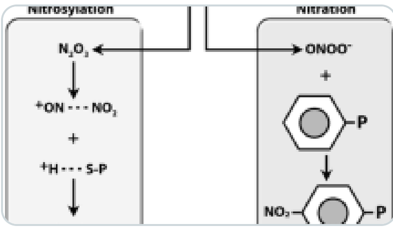

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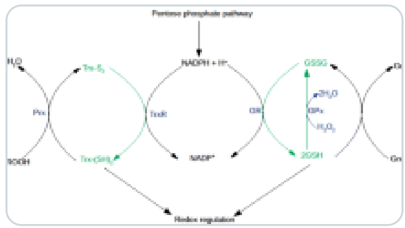

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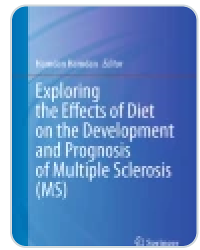

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