

GLUTATHIONE (GSH) DEFICIENCY AND THE PATHOGENESIS OF MULTIPLE SCLEROSIS

Recent findings in tissue from multiple sclerosis victims corroborate the mechanisms documented in a growing body of research based evidence as to the steps leading to disease expression. “Observed depletion of GSH, elevation of ceramide level and apoptosis in banked human brains from patients with neuroinflammatory diseases (e.g. x-adrenoleukodystrophy and multiple sclerosis) suggest that the intracellular level of GSH may play a crucial role in the regulation of cytokine-induced generation of ceramide leading to apoptosis of brain cells in these diseases.”¹

Cytokine, tumor necrosis factor-alpha (TNF- α) or interleukin-1 beta (IL-1 β)-mediated activation of sphingomyelinases (SMases), leads to degradation of sphingomyelin to ceramide, a sphingolipid 1,2, and the universal lipid second messenger. This potentiated a 2-fold increase in H₂O₂ generation, leading to lipid peroxidation and loss of activity of respiratory chain complex IV in the GSH depleted state compared to GSH-replete mitochondria ³. “Mitochondria are a target of ceramide produced in the signaling of TNF.³” Pretreatment of cells so as to increase intracellular GSH inhibited the TNF- α -induced sphingomyelin hydrolysis and ceramide generation as well as cell death ⁴.

The literature implicates excessive or inappropriate generation of nitric oxide (NO) in Parkinson’s Disease, Alzheimer’s Disease, multiple sclerosis, stroke and amyotrophic lateral sclerosis ⁵. “Human astrocytes released abundant NO upon stimulation with the pro-inflammatory cytokine (IL)-1 β , which was potentiated by interferon (IFN)-gamma and TNF- α . IL-1 receptor antagonist protein markedly attenuated astrocyte NO production.⁶” “It is now well documented that NO and its toxic metabolite, peroxynitrite (ONOO⁻) can inhibit components of the mitochondrial respiratory chain...⁵” “...neurons, in contrast to astrocytes, appear particularly vulnerable to the action of these molecules.⁵” “...the susceptibility of different brain cells to NO and ONOO⁻ exposure may be dependent on factors such as the intracellular GSH concentration...⁵” “Evidence is now available to support this scenario for neurological disorders, such as multiple sclerosis.⁵”

Variable vulnerability to oxidative stress has been well documented in various neurological cell types. “Astrocytes maintain high intracellular concentrations of certain antioxidants, making these cells resistant to oxidative stress relative to oligodendrocytes and neurons.⁷” In fact, astrocytes appear to play a central role in the antioxidant defense of the brain.⁷ One of the major antioxidants used by astrocytes is GSH and, “...astroglial cells prefer cystine from [instead of] cysteine for GSH synthesis...⁸”

Other conditions give insight into the effect of GSH on SMases and ceramide. “Cell culture studies of hypoxic PC12 cell death...suggest that GSH protects cells from hypoxic injury by direct inhibition of neutral SMases activity and ceramide formation...⁹” This protection appears to be lost in MS patients as GSH is decreased in plaques¹⁰, and was absent in the CSF in MS.¹¹ Protective mechanisms involving GSH appear to occur in MS, “...blood GSH was increased (p<0.01) [in MS] during exacerbation and remission as well. This rise in this thiol is likely to be a compensatory mechanism defending the cells from further oxidant injuries.¹²”

The relationship between cytokines and GSH has been demonstrated in cell cultures of TNF-resistant (TNFr) and TNF-sensitive (TNFs) cell lines. "The basic level of GSH was significantly higher in the TNFr cells than in TNFs cells. Treatment with 20 micromM ceramide decreased cellular GSH in TNFs cells by 50% in contrast to an insignificant decrease in the TNFr cells.¹³"

Also, the effect of intracellular GSH on neutrophil and lymphoid apoptosis give further insight into the crucial regulator role played by this important thiol. "Because apoptosis is a critical mechanism regulating PMN survival in vivo, manipulation of PMN intracellular thiols may represent a novel therapeutic target for the regulation of cellular function.¹⁴" "Thiol compounds, such as L-cysteine and GSH, play crucial roles in the regulation of lymphocyte proliferation.¹⁵" "These data suggest that the inability to neutralize oxidative stress results in the apoptosis of lymphoid cells under L-cystine- and GSH-depleted conditions. The protective effects of rADF may be explained by...enhancing the L-cystine internalization and elevating the intracellular GSH content.¹⁵"

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