The Role of Glutathione in Cell Defense, with References to Clinical Deficiencies and Treatment

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Glutathione Precursors: Amino Acids

- L-Glutamate
- L-Cysteine
  - the rate-limiting substrate
  - cystine (cysteine=cysteine) is an ideal form of cysteine for glutathione synthesis
- Glycine
Glutathione: L-glutamylcysteinylglycine

- DNA synthesis and repair
- Protein synthesis
- Prostaglandin synthesis
- Amino acid transport
- Metabolism of toxins and carcinogens
- Immune system enhancement
- Prevention of oxidative cell damage
- Enzyme activation
Immunonutrition in the Critically Ill: a Systematic Review of Clinical Outcomes (12 studies with 1,557 subjects, 1,482 of whom were analyzed)

“Objective: To perform a meta-analysis addressing whether enteral nutrition with immune-enhancing feeds benefit critically ill patients after trauma, sepsis, or major surgery.”

“Main outcome measures were mortality, infection, ventilator days, intensive care unit stay, hospital stay, diarrhea days, calorie intake and nitrogen intake.”

Immunonutrition in the Critically Ill: a Systematic Review of Clinical Outcomes (Summary)

◆ BENEFITS:
  ◆ Infection: a significant reduction in the relative risk of acquiring infection.
  ◆ Ventilator Days: a significant reduction overall.
  ◆ Hospital Length of Stay: the reduction in hospital LOS was significant.

◆ SAFETY:
  ◆ No increase in side effects of feeding was reported in patients receiving immunonutrition.
Effect of Immune Enhancement on Length of Therapeutic Intervention in Severe Abdominal Trauma
Effect of Immune Enhancement on Total Hospitalization Cost in Severe Abdominal Trauma
Effect of Immune Enhancement on Total Hospital Days in Severe Abdominal Trauma
“Glutathione Levels in Antigen-presenting Cells Modulate Th1 Versus Th2 Response Patterns.” (Title of Article)

“...the Th1 pattern is characterized by interleukin 12 (IL-12) and interferon γ (IFN-γ) production and the up-regulation cell-mediated, e.g., delayed hypersensitivity, (DTH) responses.”

“The Th2 response pattern is characterized by IL-4 and IL-10 production and up-regulation of a variety of antibody responses.”

“Antigen-presenting cells (APC) -- macrophages, dendritic cells, and B cells -- are central to the development of either Th1 or Th2 immunity because antigen presentation and recognition are required to initiate responses.”

“...GSH depletion inhibits Th1-associated cytokine production and/or favors Th2-associated responses.”

“Defective Antigen Processing Correlates with a Low Level of Intracellular Glutathione”

Therefore, low intracellular glutathione levels in antigen-presenting cells correlate with defective processing of antigen with disulfide bonds, indicating that this thiol may be a critical factor in regulating productive antigen processing.


Most antigens are proteins with disulfide bonds. GSH reduces disulfide bonds. Low GSH prevents disulfide bond reduction.

1. $RSSR' + GSH \rightleftharpoons RSH + GSSR'$
2. $GSSR' + GSH \rightleftharpoons GSSG + R'SH$
“Lymphocyte Proliferation in Glutathione-depleted Lymphocytes: Direct Relationship Between Glutathione Availability and the Proliferative Response”

- “Lymphocyte proliferation in response to mitogenic lectins is directly dependent upon glutathione (GSH) availability.”
- “…the restoration of lymphocyte proliferation by exogenous GSH is more closely linked to effects on intracellular rather than extracellular GSH.”
- “These studies confirm the importance of intracellular GSH in lymphocyte proliferation.”
Pathogenesis of Glutathione Deficiency in the Immune Response: Summary

- Glutathione levels in antigen-presenting cells modulate Th1 versus Th2 response patterns.
- Antigen presentation and recognition are required to initiate immune responses.
- Key events that determine whether IFN-$\gamma$ is produced occur almost immediately.
- IFN-$\gamma$ production predominates when GSH levels are high.
- GSH depletion may play a key role in exacerbating HIV and other infectious diseases in which Th2 predominance is an important aspect of the disease pathology.
“Glutathione Deficiency is Associated with Impaired Survival in HIV Disease.” (Title of Article from Stanford)

“The crucial connection revealed here between GSH deficiency and survival in HIV disease was foreshadowed by several studies.”

Survival in all HIV+: $\text{GSB} \geq 0.91 = 90\%, \text{ GS}B < 0.91 = 32\%$.

Survival in CD4 < 200: $\text{GSB} \geq 1.05 = 87\%, \text{ GS}B < 1.05 = 17\%$.

“Type 1 and Type 2 Cytokines in HIV Infection -- a Possible Role in Apoptosis and Disease Progression.” (Title of Article)

“...a strong type 1/weak type 2 cytokine production profile was observed in HIV-seropositive patients with delayed or absent disease progression, whereas progression of HIV infection was characterized by a weak type 1/strong type 2 cytokine production profile.”

Glutathione Deficiency is Associated with Impaired Survival in HIV Disease.

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Antiretroviral therapies will not successfully eradicate HIV and HIV-seropositive patients will not be ultimately cured unless therapies aimed at restoring the immune system are associated with the antiretroviral drugs currently employed.
“We describe a case of a patient who had obstructive lung disease responsive to corticosteroids, and low whole blood GSH levels.”

“After 1 month of supplementation with a whey-based oral supplement designed to provide GSH precursors, whole blood GSH levels and pulmonary function increased significantly and dramatically.”

Benefits of Glutathione Enhancement in Disease or Stress: Pulmonary Disease

- Relationship to Immunocal® intake:
  - Time 6 on Immunocal® 1 month.
  - Time 7 off Immunocal®.
  - Time 8 back on Immunocal®.
  - Immunocal® significantly and dramatically increased pulmonary function.
Method of Intracellular GSH Enhancement: Undenatured Whey Protein Concentration

- Contains highly concentrated amounts of cystine (cysteine = cysteine) because of a new Pasteurization technique which preserves the disulfide bond between the two cysteines.
- The naturally occurring constituent heat labile proteins found in “Mother’s Milk” that imparts immune enhancement.
- Dose: 10 - 40 grams per day for adults and ½ gram/Kg for infants and young children up to 40 Kg.
- High dose to reverse cachexia: up to 120 grams has been reported (anecdotal) to increase total body weight 15% in two weeks in a near death AIDS patient with cachexia.
Cystine: the Preferred Substrate for Optimal Glutathione Synthesis and Immune Enhancement

- Hepatic Nitrogen Metabolism: Cysteine from muscle catabolism arrives in the liver in the form of cystine. Enteral feeding of cystine takes advantage of this well-developed metabolic pathway that is also utilized when digesting breast milk which has well documented and indisputable immune enhancing properties.

- Antigen Presenting Cells: Prefer cystine for GSH synthesis which is required to initiate the immune response then feed lymphocytes cysteine as an immunoregulatory signal.

- Astrocytes: Prefer cystine for GSH synthesis and feed cysteine to neurons to protect against neurodegenerative diseases.
Proton Donation is the Basis for Preservation of the Amino Acid Pool (Positive Nitrogen Balance)  
Proton Donation: the Sulfur of Glutathione can give up a Proton (H⁺)

$$\text{GSH} + \text{GSH} \rightarrow \text{GSSG} + 2\text{H}^+$$
“Role of Cysteine and Glutathione in HIV Infection and Other Diseases Associated with Muscle Wasting and Immunological Dysfunction.” (Title of Article)

“Evidence suggests that 1) the cystine level is regulated primarily by the normal postabsorptive skeletal muscle protein catabolism, 2) the cystine level itself is a physiological regulator of nitrogen balance and body cell mass...”

AIDS, sepsis, major injury, trauma, cancer, chronic fatigue syndrome, Crohn’s disease, ulcerative colitis, and athletic over-training are associated with:

- low cystine,
- low glutamine,
- elevated glutamate,
- increased urea production, and
- reduced natural killer (NK) cell activity.
This diagram demonstrates the relationship between cystine and nitrogen balance to be as follows:

- ↑ Cystine.
- ↑ Protons (H⁺).
- ↓ Bicarbonate (HCO₃⁻).
- ↓ Carbamoylphosphate.
- Ammonium ion (NH₄⁺) is saved.

This results in positive nitrogen balance with maintenance or increase in weight.
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- ↓ Cystine.
- ↓ Protons (H⁺).
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- ↑ Carbamoylphosphate.
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This results in negative nitrogen balance with decrease in weight and possible cachexia.
Glutathione Precursor Transport: Cystine is Preferred form of Cysteine for GSH Synthesis

- Cystine (cysteine=cysteine) is the preferred form of cysteine for macrophages and astrocytes.
  - “These results demonstrate that astroglial cells prefer cystine...” Kranich, O., Glia, 1998, Jan.;22(1): 11-8.
Glutathione Depleting Agents

- Smoking.
- Alcohol.
- Caffeine.
- Acetaminophen.
- Drugs.
- Vigorous exercise.
- $\times$, $\gamma$- and UV radiation
- Xenobiotics.
Enterocyte nutrient transport is one way: from the gut to the cell to the capillary.

Enterocytes cannot transport nutrients from the blood vessel.

Enterocytes starve as the rest of the body is fed by way of the vasculature.

Enterocytes pull away from each other as a consequence of gut atrophy.
Total Parenteral Nutrition: the Road to Enteral Atrophy, Leaky Gut Syndrome and Pneumonitis

- Bacteria slip between the atrophying enterocytes.
- Bacteria enter lymph nodes and then gain access to thoracic duct.
- The thoracic duct empties into the blood flowing toward the right heart and into the pulmonary circulation.
- Atrophic gut cannot generate sufficient amounts of secretory IgA.
- The lungs are also compromised and pneumonitis frequently occurs due to constant seeding and lack of IgA.