Role of GSH in Chronic Illness

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Oxidative Stress and Low Glutathione in Common Ear, Nose, and Throat Conditions: A Systematic Review

- Ben Asher, Tim Guilford
- ENT conditions are associated with oxidative stress and decreased GSH, both locally in the affected tissues and systemically.

Asher BF, Guilford FT. Oxidative Stress and Low Glutathione in Common Ear, Nose, and Throat Conditions: A Systematic Review. Altern Ther Health Med. 2016;22(5):44-50. PMID: 27622960

Low GSH in common ENT conditions

- (1) rhinitis, (2) **allergic rhinitis**, (3) chronic rhinosinusitis (CRS), (4) CRS with polyps, (5) otitis media with effusion, (6) chronic otitis media (COM), (7) COM and cholesteatoma, (8) tympanic membrane sclerosis, (9) tonsillitis, (10) Meniere's disease, (11) laryngeal conditions, and (12) chronic cough.
- Pollen allergy PMID 16075057 (2 signal response)

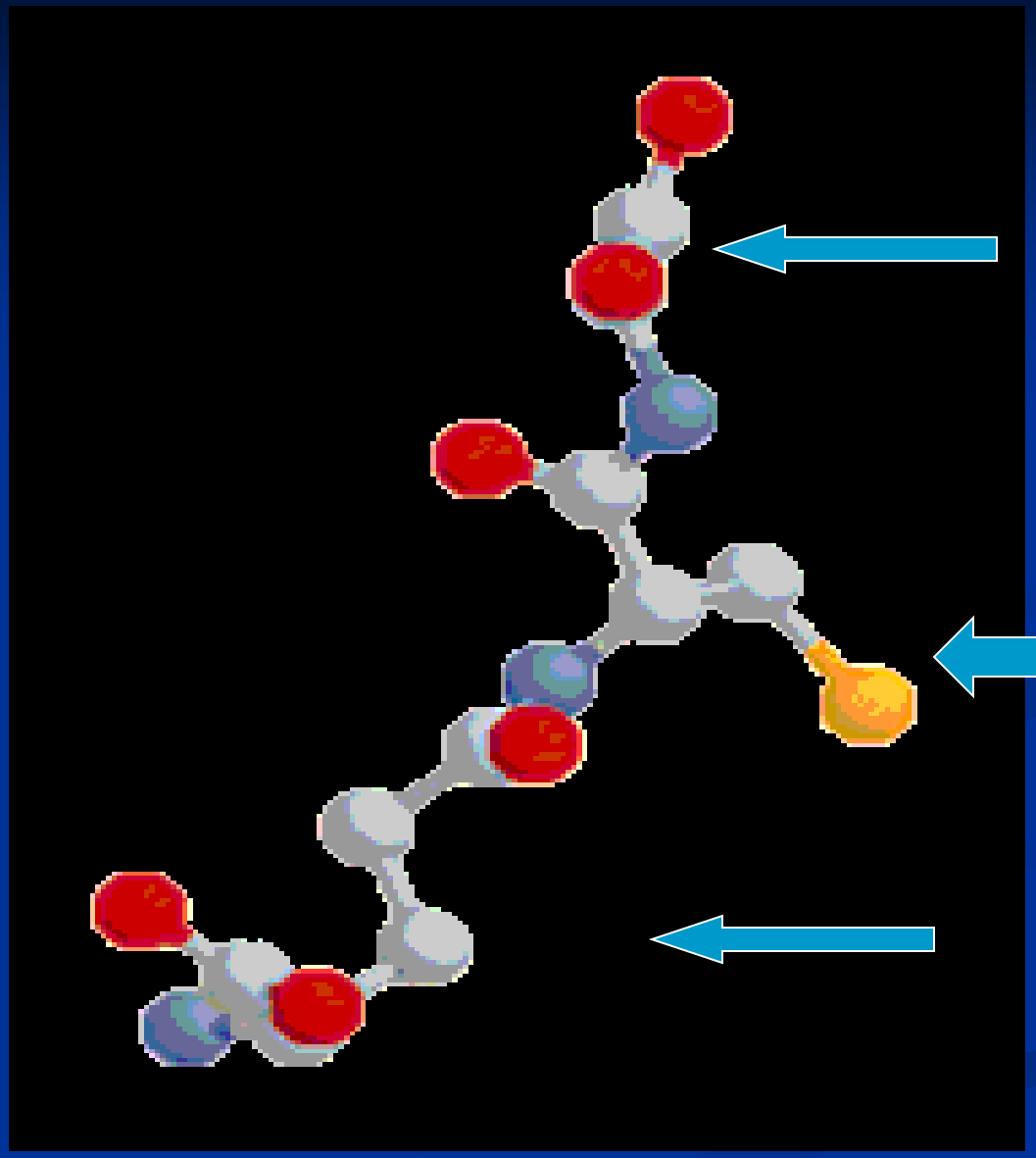
Asher BF, Guilford FT. Oxidative Stress and Low Glutathione in Common Ear, Nose, and Throat Conditions: A Systematic Review. Altern Ther Health Med. 2016;22(5):44-50. PMID: 27622960

OxStress delivered as a package with Pollen antigen -2 signals

- pollen extracts from weeds, trees, and grasses h
- Have intrinsic **NADPH oxidase** →
- Signal 1: ROS in airway epithelium within minutes, independent of the adaptive immune response.
- Signal 2: Inflammation augments specific IgE production and allergic airway inflammation induced by the major pollen antigens.

Boldogh I, Bacsi A, Choudhury BK, Dharajiya N, Alam R, Hazra TK, et al. ROS generated by pollen NADPH oxidase provide a signal that augments antigen-induced allergic airway inflammation. J Clin Invest. 2005;115(8):2169-79. PMID: 16075057

GSH



Glycine

Cysteine contains sulfur molecule

Glutamine

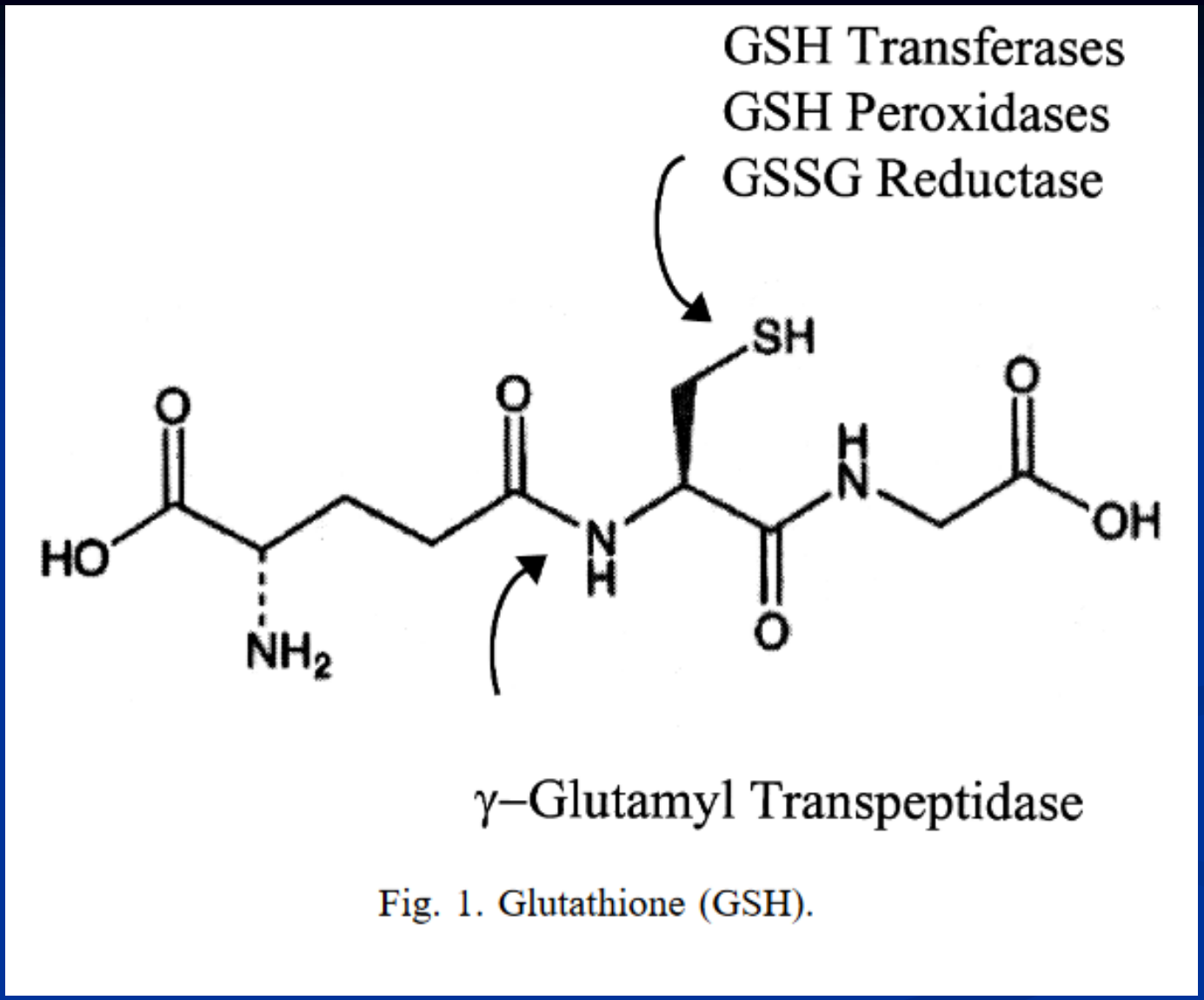
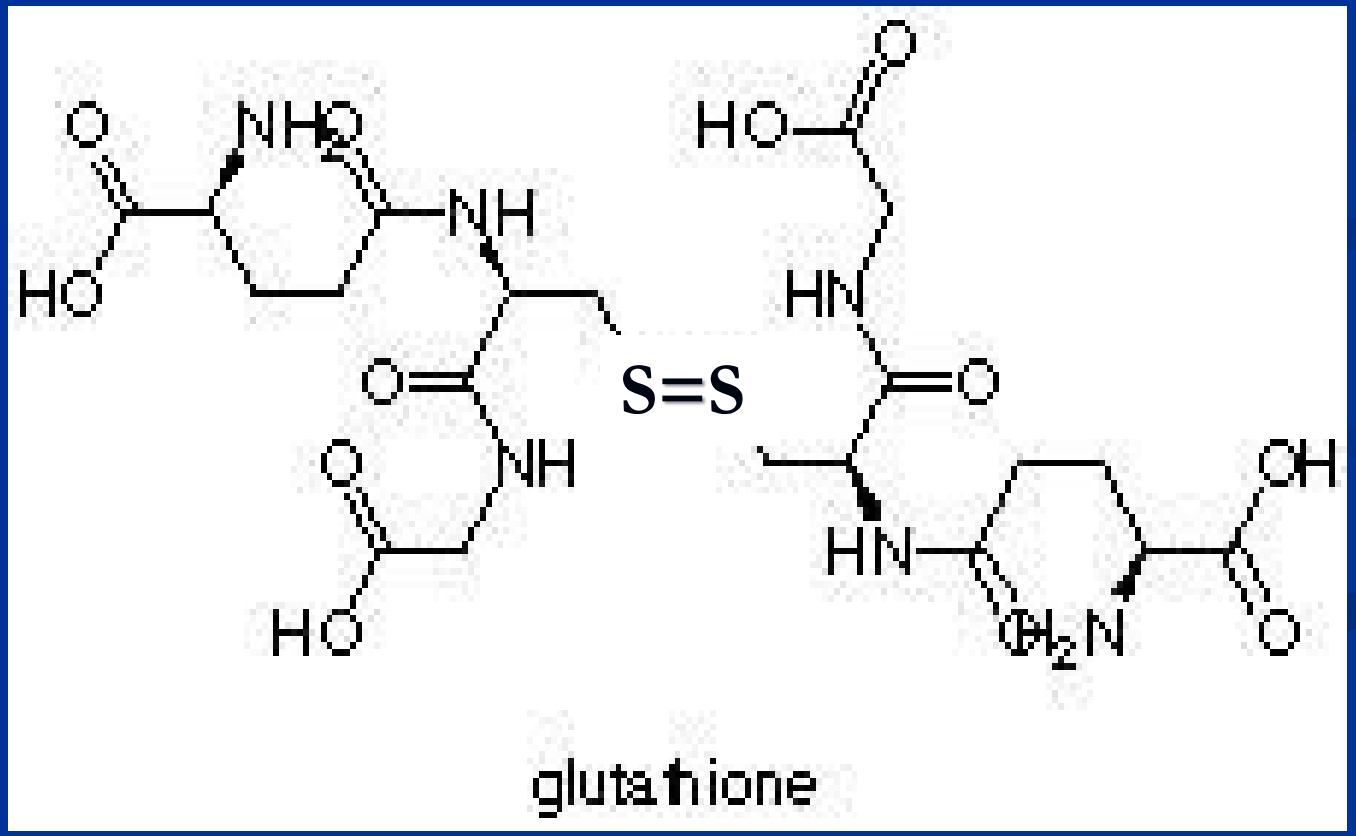


Fig. 1. Glutathione (GSH).

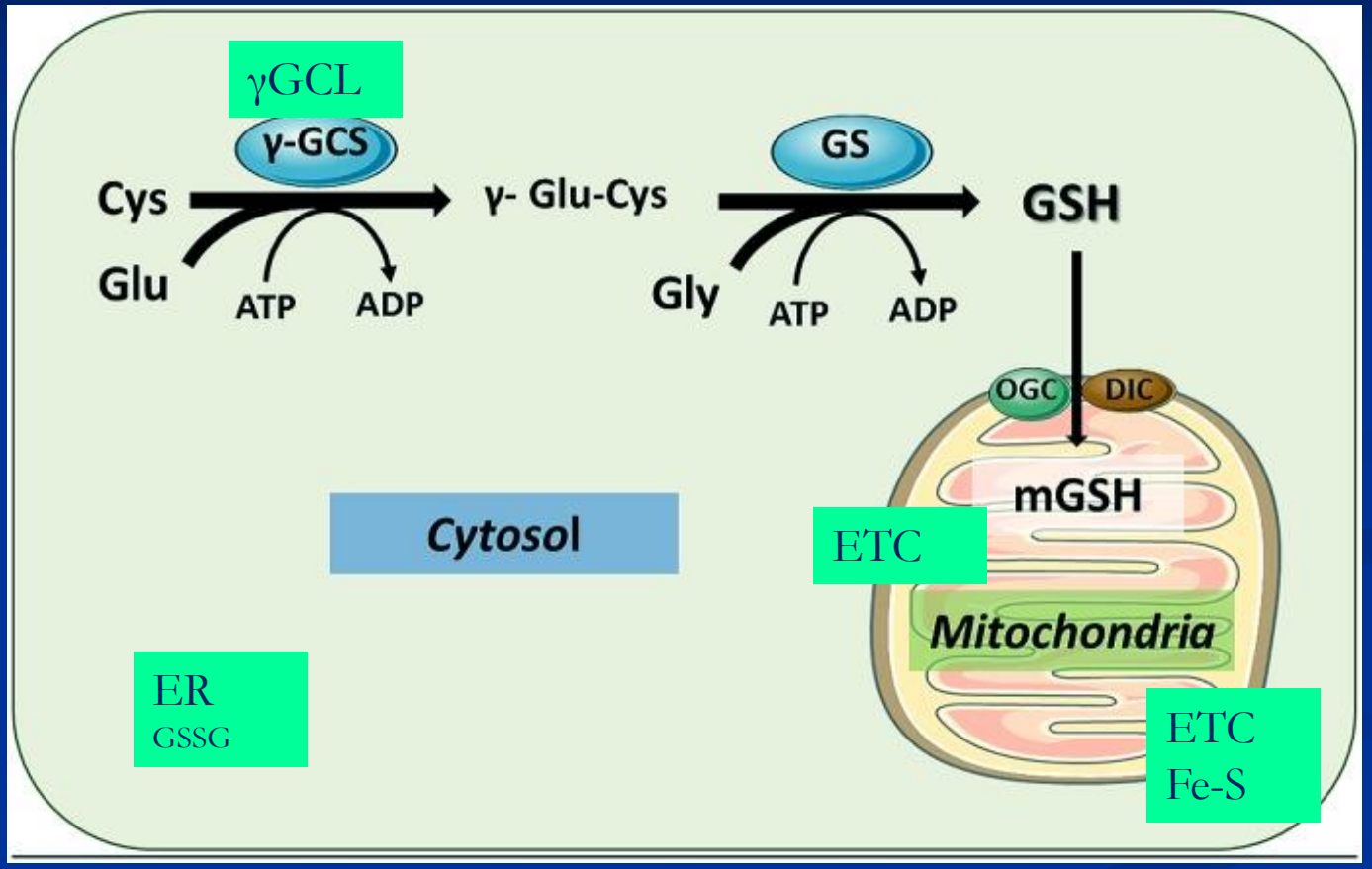
Sies H. Glutathione and its role in cellular functions. Free Radic Biol Med. 1999;27(9-10):916-21.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10569624

LEO GER

- GSH – reduced glutathione - GER
- GS=SG oxidized glutathione - LEO

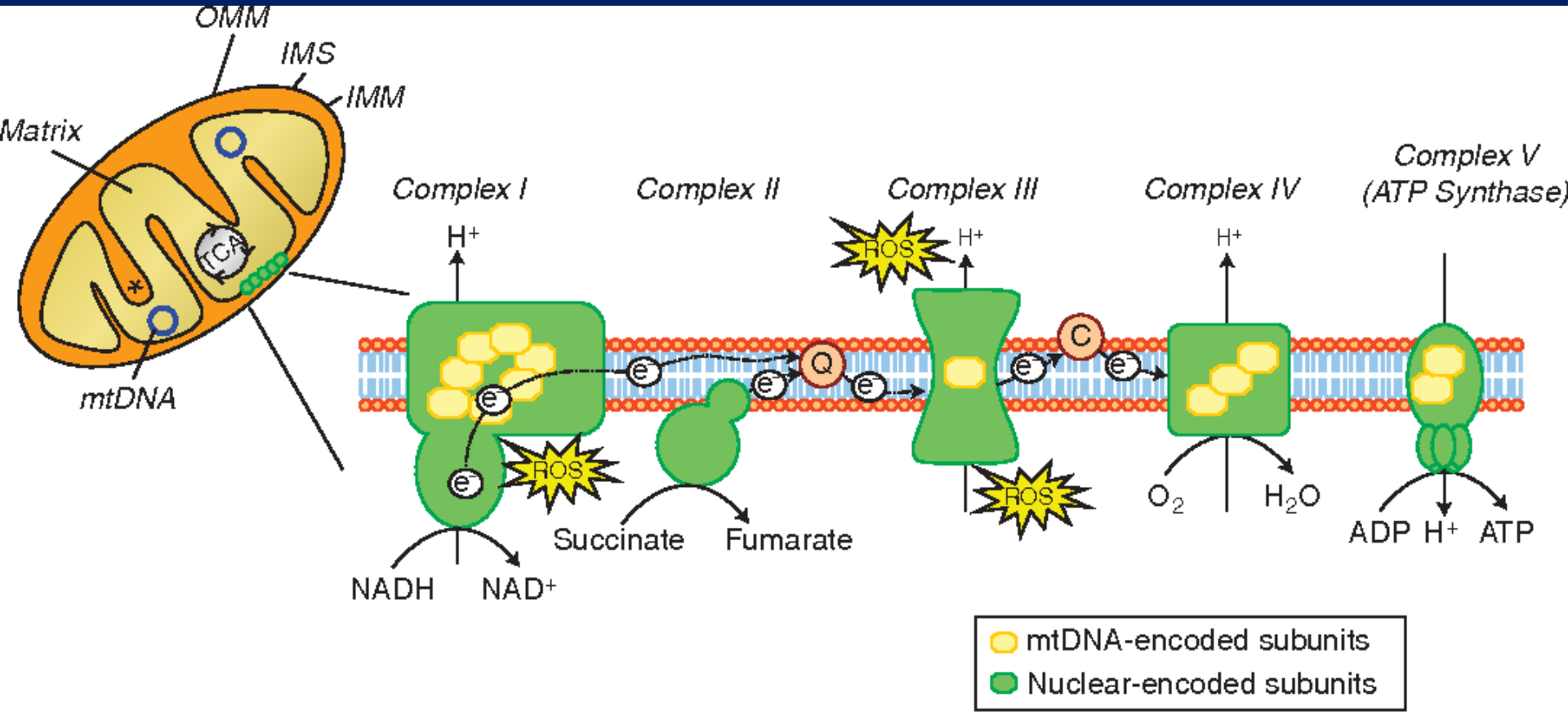


Cytosol GSH → Mt



the 2-oxoglutarate carrier (OGC) and the dicarboxylate carrier (DIC), Inner membrane tricarboxylate carrier in brain mitochondria and astrocytes

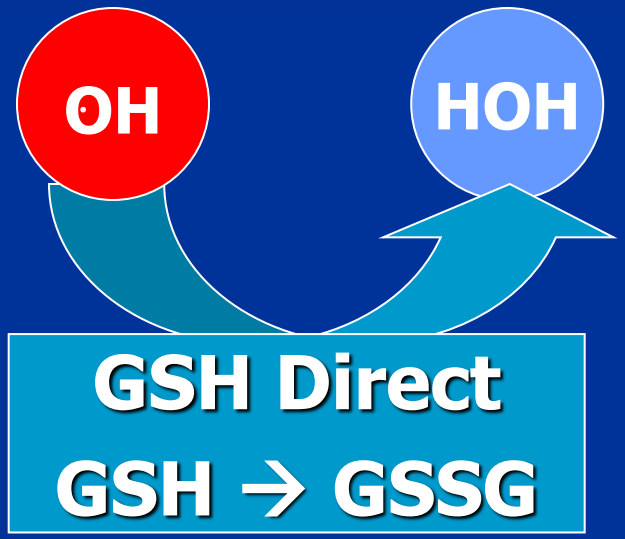
Ribas V, Garcia-Ruiz C, Fernandez-Checa JC.
Glutathione and mitochondria. Front Pharmacol. 2014;5:151. PMCID: 4079069. http://www.ncbi.nlm.nih.gov/pubmed/25024695



https://www.semanticscholar.org/paper/Mitochondrial-biology-and-Parkinson%27s-disease.-Perier-Vila/62763bc875506f702b2868ad85441c9d19ef57cc/figure/0

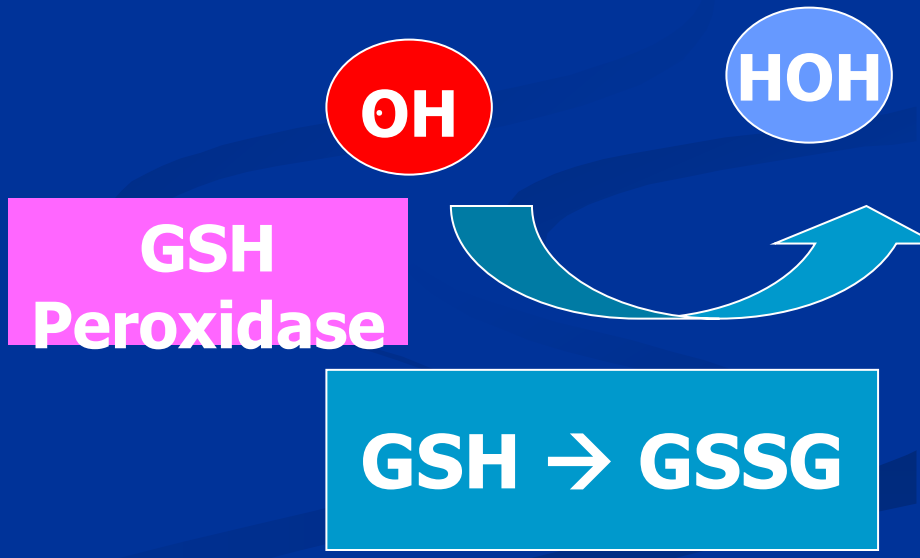
Glutathione the key player in removing free radicals in human cells

Glutathione Direct



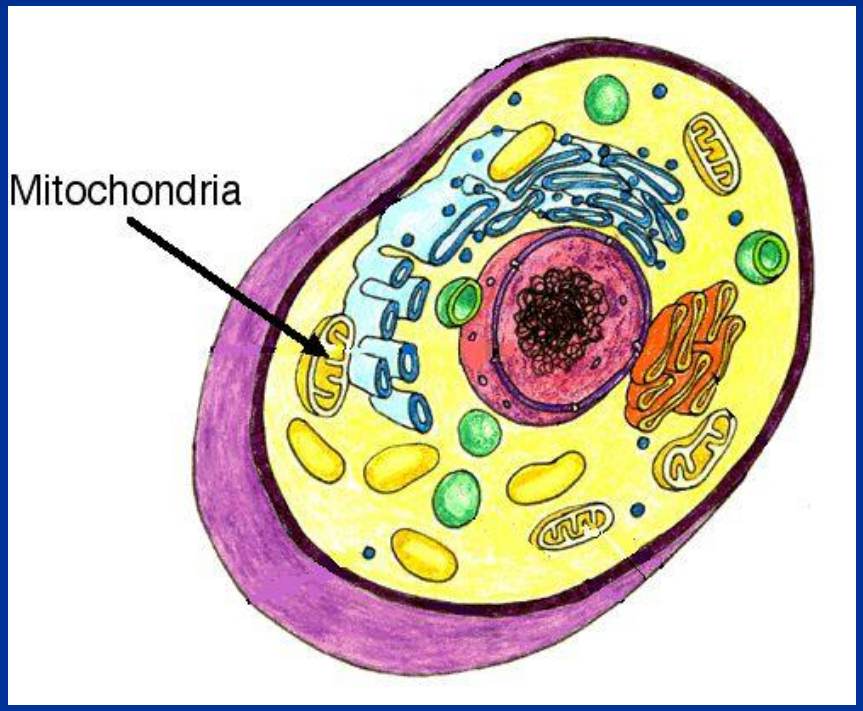
Enzyme facilitation (fast delivery)

GSH can interact directly with certain ROS (e.g., the •**OH** hydroxyl radical)



Wu D, Cederbaum AI. Alcohol, oxidative stress, and free radical damage. Alcohol Res Health. 2003;27(4):277-84.
http://pubs.niaaa.nih.gov/publications/arh27-4/277-284.pdf

Origin of Your Energy System

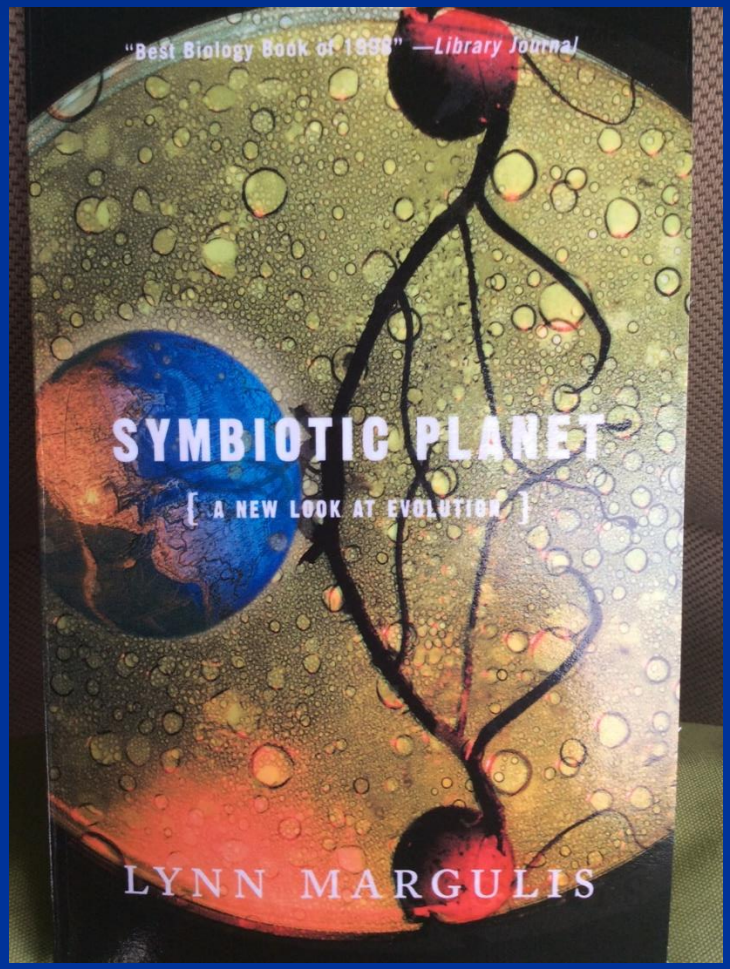


- It is believed that the mitochondria may have been independent prokaryotic cells that were absorbed into eukaryotic cells - formed a symbiotic relationship internal to the cell.

https://animalcellproject.weebly.com/mitochondria.html

Lynn Sagan Margulis

1998



1967

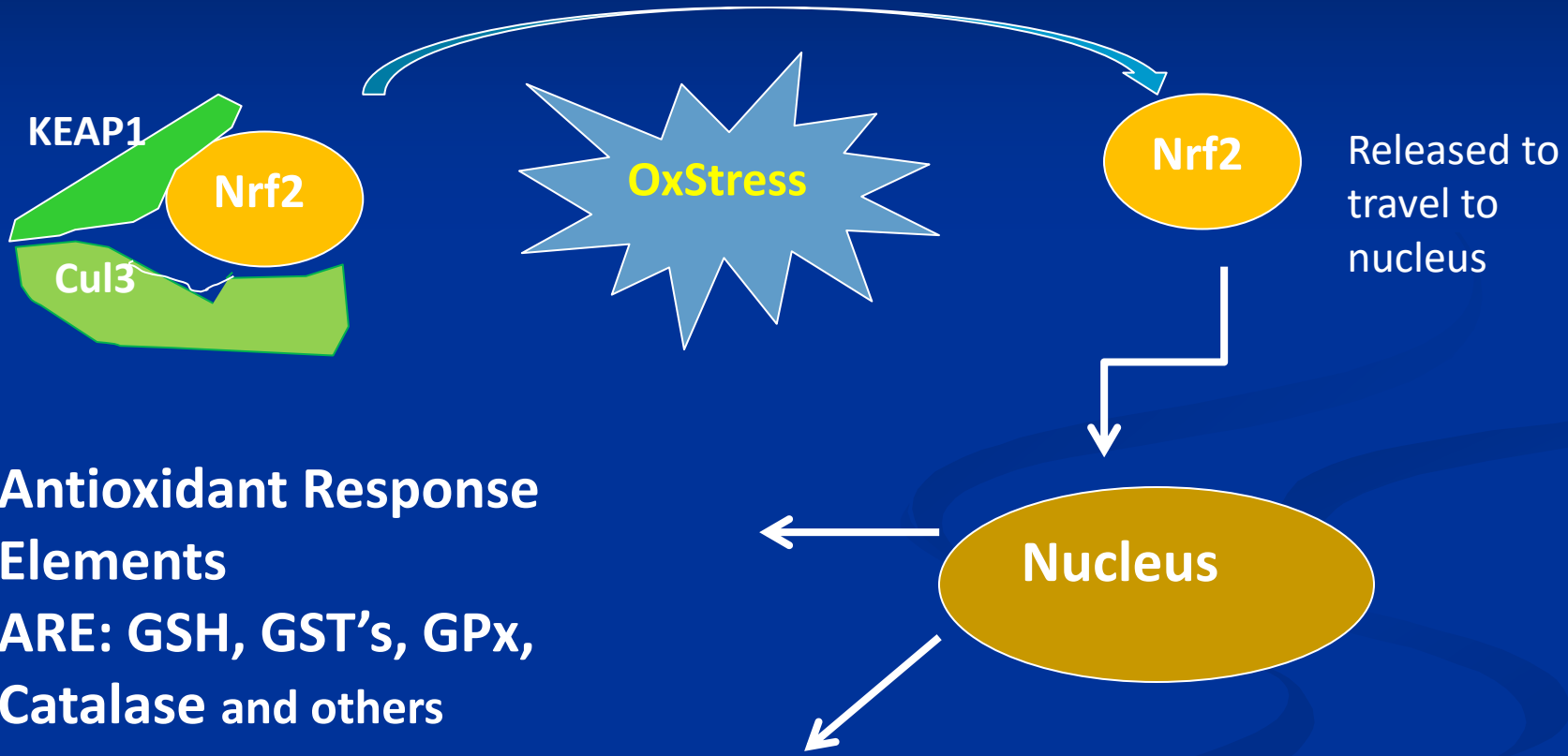
On the **origin** of mitosing cells
Sagan L.
J Theor Biol. 1967 Mar;14(3):255-74.
PMID:11541392

Origin of eukaryotic cells: Evidence and research implications for a theory of the origin and evolution of microbial, plant, and animal cells on the Precambrian earth

Yale University Press 1970.

evolution in flux

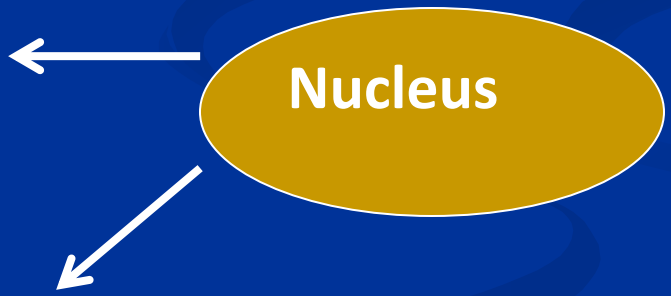
Nrf2, the Oxidant 'Thermostat' of the Cell: The 'Oxidant-stat'



Thiol redox disturbances in children with severe asthma are associated with posttranslational modification of Nrf2. Fitzpatrick AM, et al J Allergy Clin Immunol. 2011 Apr 21. PMID: 21514635

Nrf2, the Oxidant 'Thermostat' of the Cell: The 'Oxidant-stat'

Antioxidant Response Elements
ARE: GSH, GST's, GPx, Catalase and others



GSH

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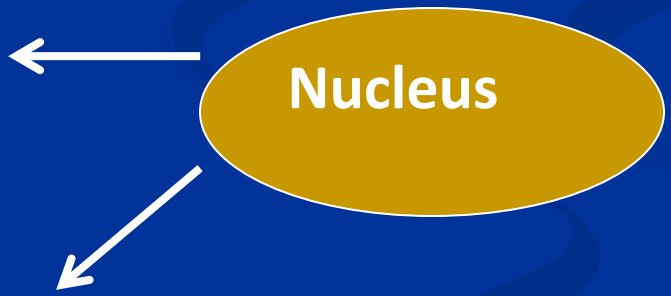

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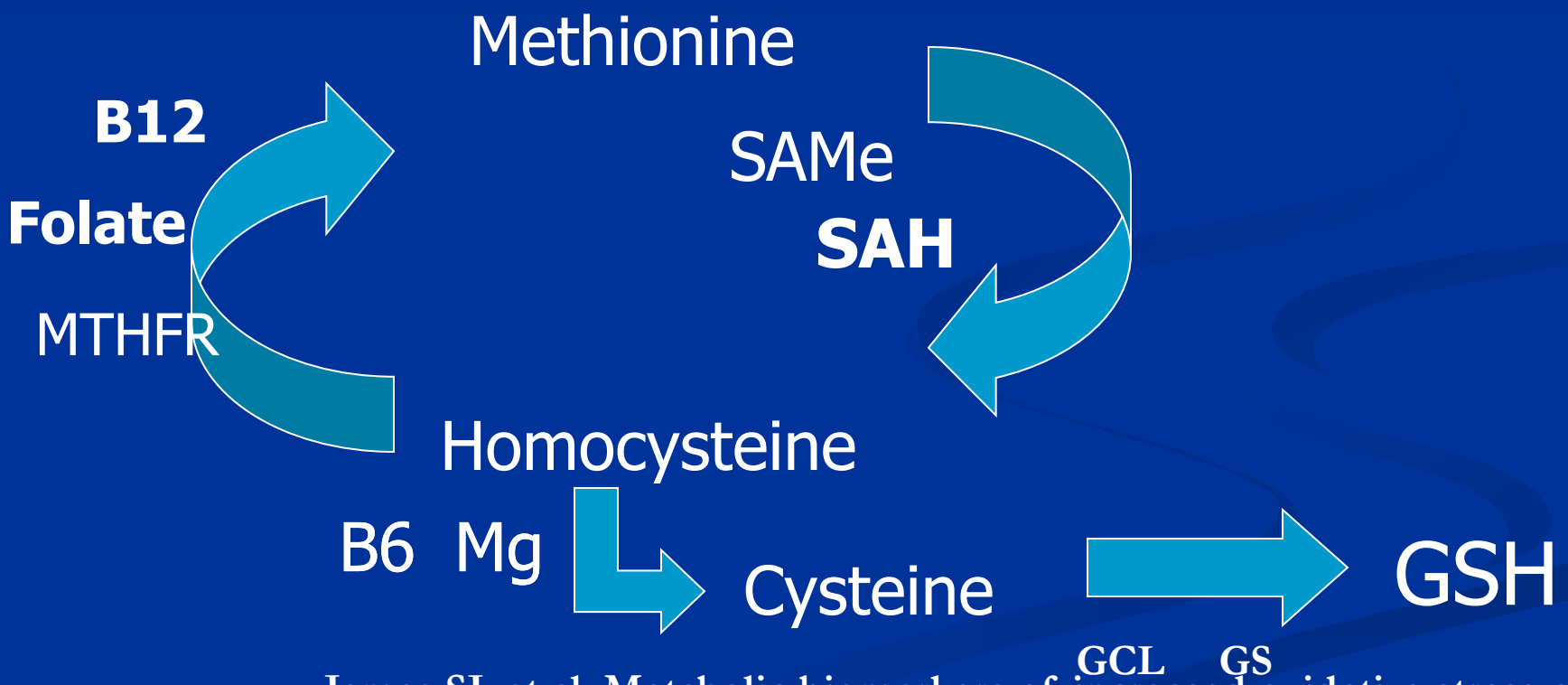
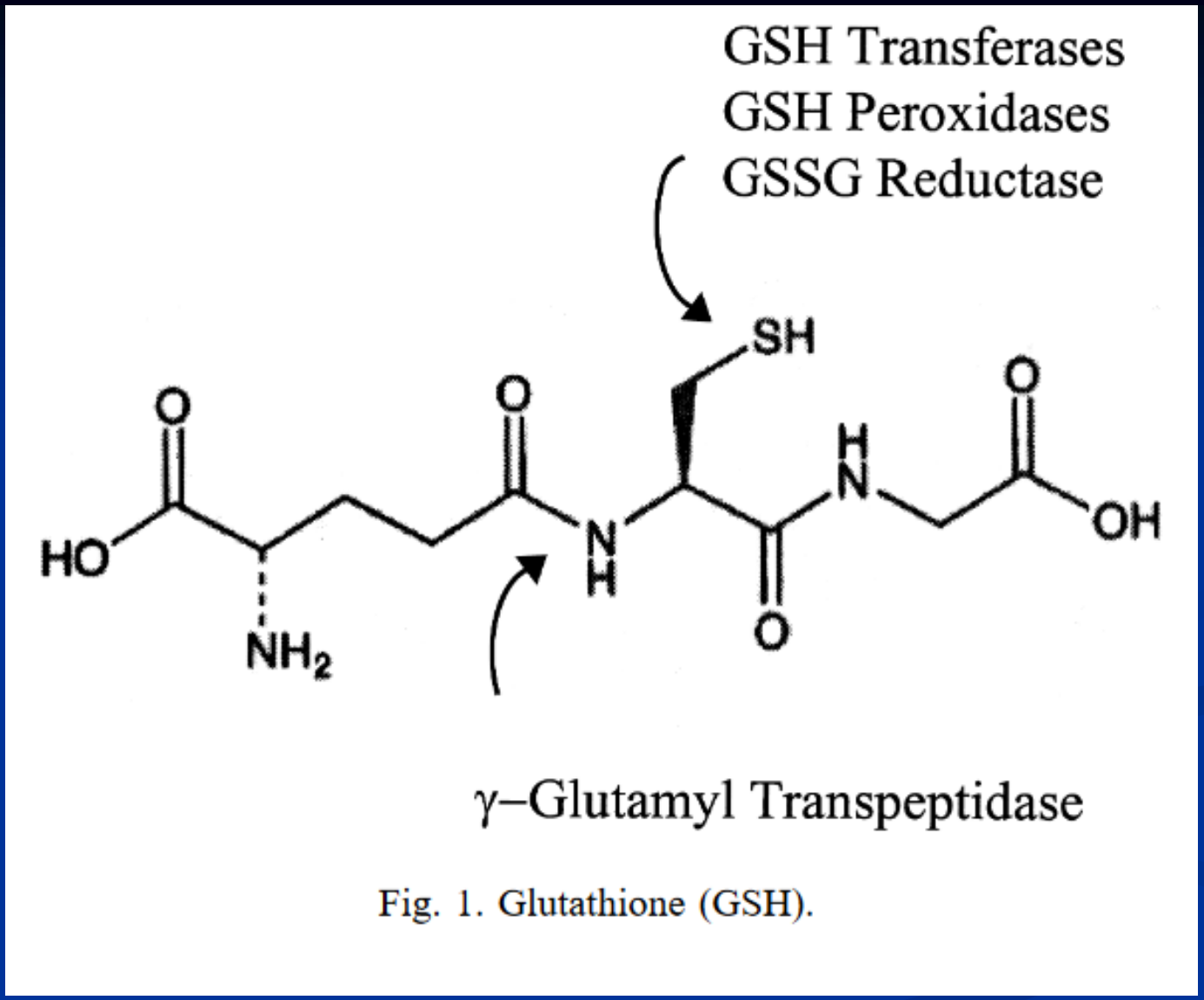
Methionine cycle
Source of Cysteine for GSH



James SJ, et al. Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. The American journal of clinical nutrition. 2004;80(6):1611-7. PubMed: 15585776.



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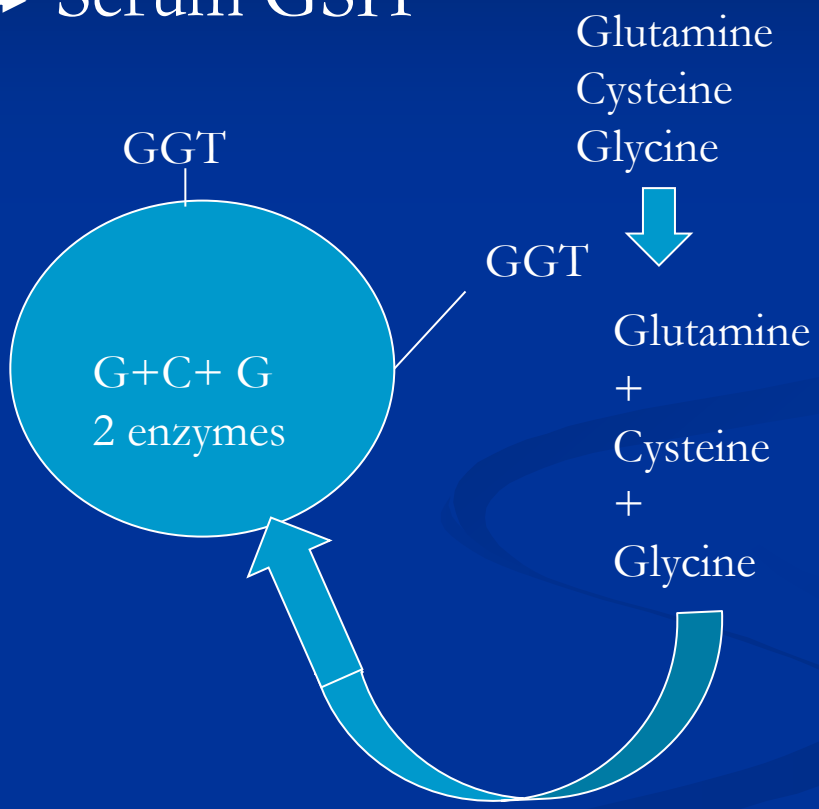
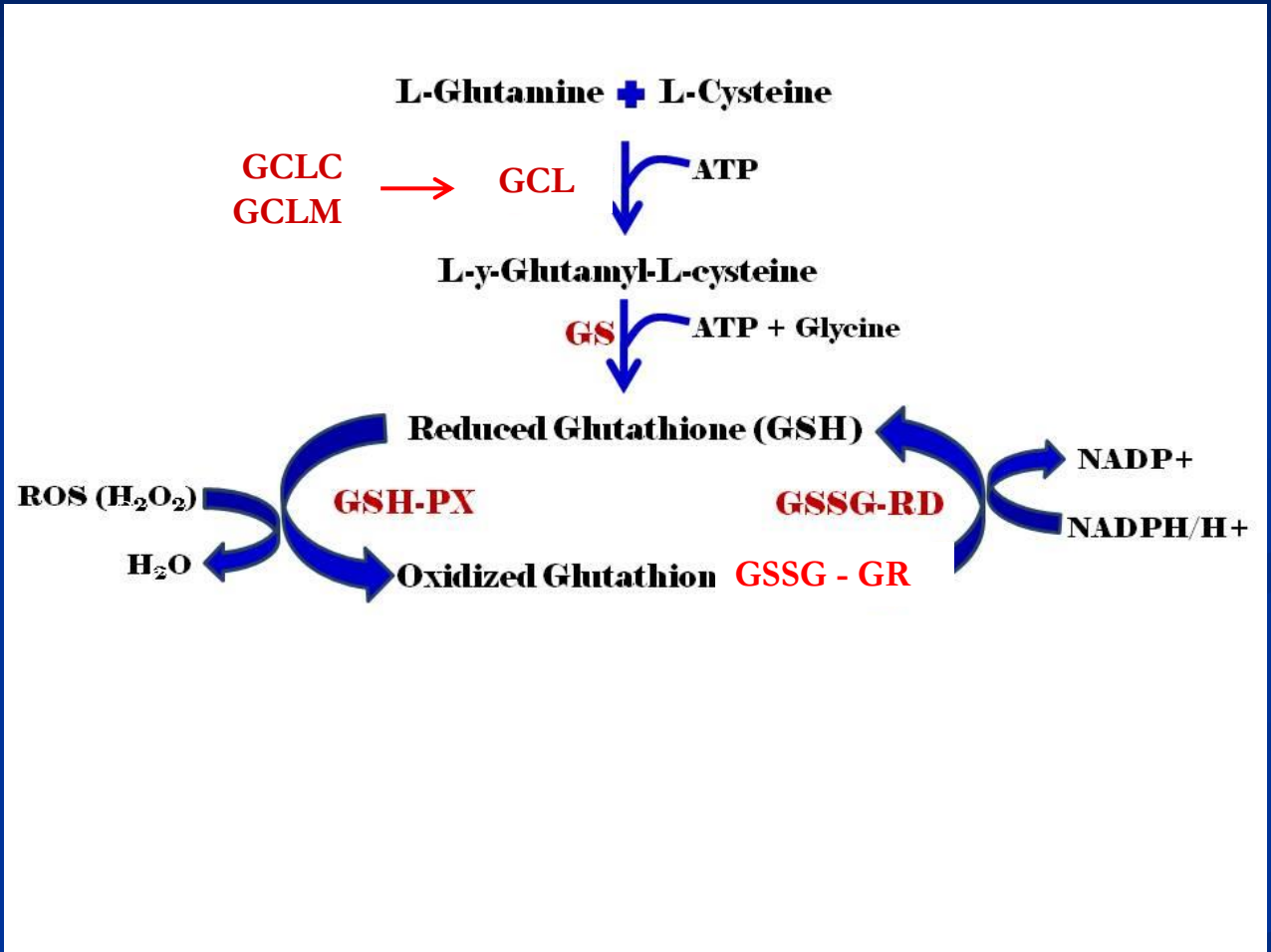
γ -GT or GGT

Liver ⟶ Serum GSH



GCLC increases GSH

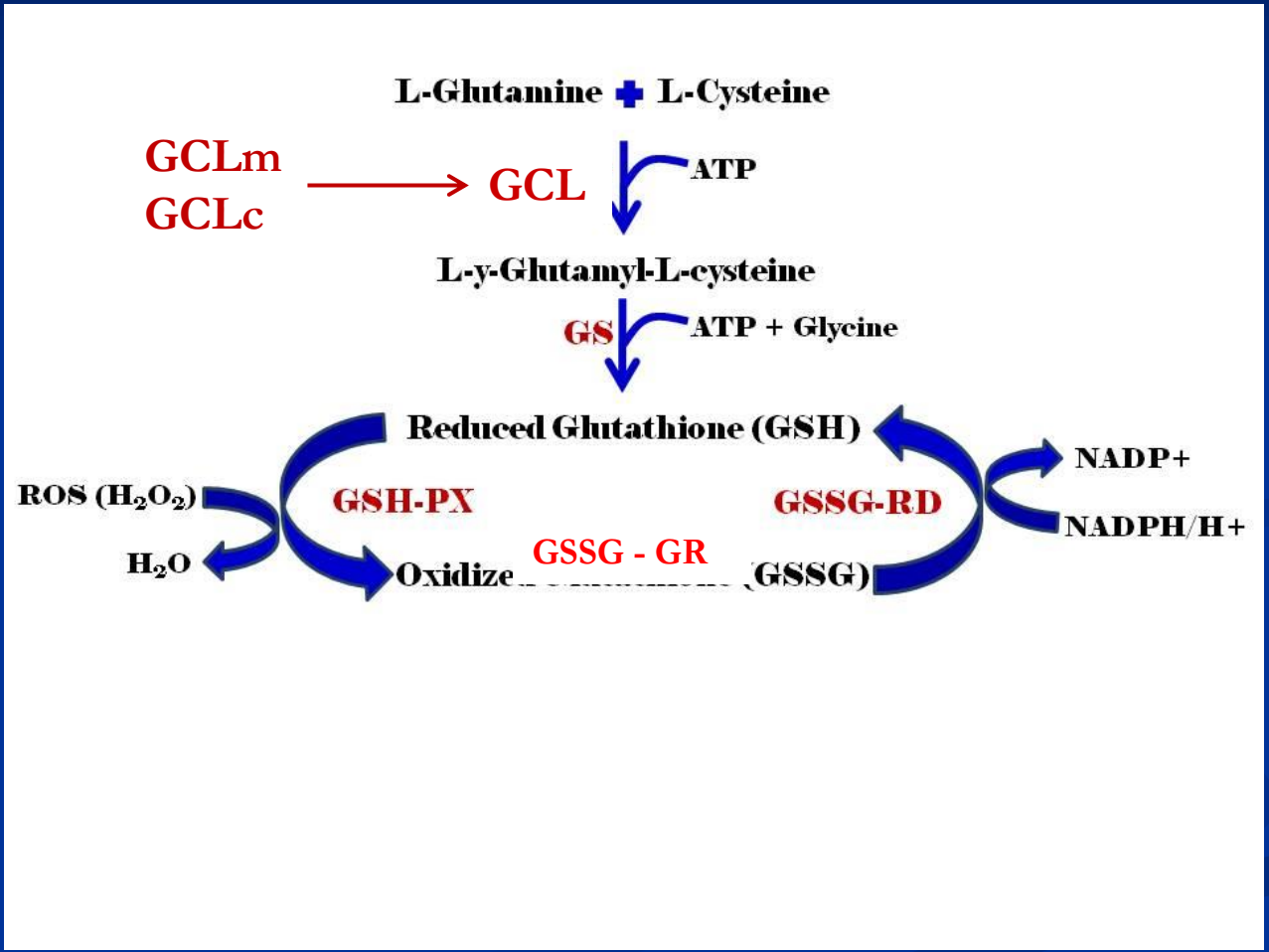


Morris D, Guerra C, Khurasany M, Guilford F, Saviola B, Huang Y, et al. Glutathione supplementation improves macrophage functions in HIV. J Interferon Cytokine Res. 2013;33(5):270-9. http://www.ncbi.nlm.nih.gov/pubmed/23409922

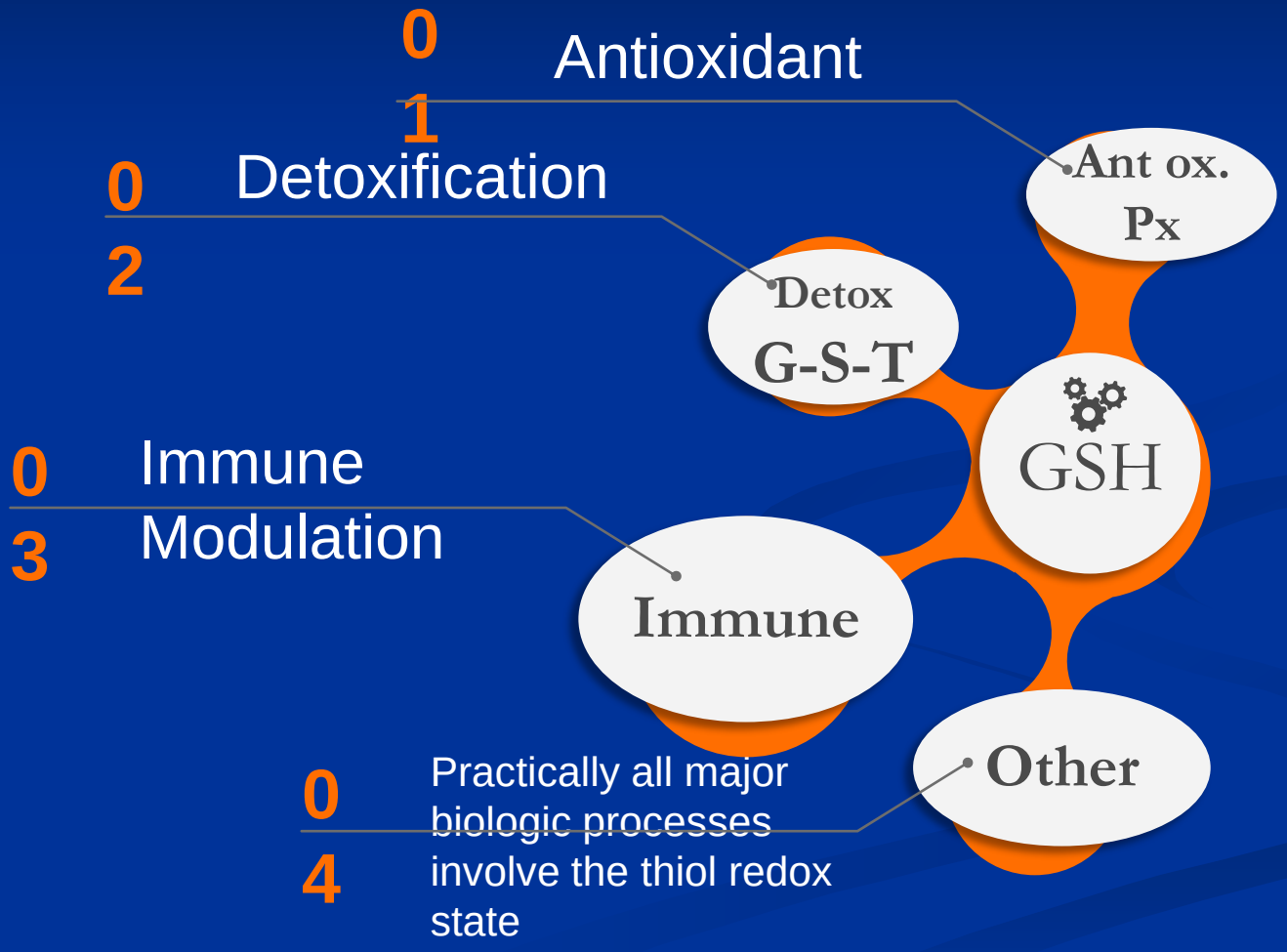
SNPs in Production occur in 20%

"relatively common genetic polymorphisms in both the catalytic (Gclc) and modifier (Gclm) subunits of GCL have been associated with increased risk for lung and cardiovascular diseases". PMID: 21967497 Oct 2011

SNP of Gclm occur in 20% of population PMCID: 3337699



1999 40,000 Pubmed references*
2019 147,612 references



* Sies, 1999 PMID 10569624

Glutathione S-transferases (GST)

- Bring GSH close to toxin for binding
- detoxify endogenous and exogenous toxic compounds directly and by binding to transport
- GSTs catalyze the conjugation of GSH—via a sulfhydryl group—to electrophilic centers on a wide variety of substrates in order to make the compounds more water-soluble.[7][8] This activity detoxifies endogenous compounds such as peroxidised lipids and enables the breakdown of xenobiotics.

https://en.wikipedia.org/wiki/Glutathione_S-transferase

l-gsh protects against Maneb+Paraquat

- A liposomal glutathione can protect cells against the deleterious effects of Maneb+Paraquat
- herbicide **paraquat**, the fungicide **maneb**
- **100X more efficient than plain GSH**
- Greater effect in protection than plain, non-liposomal glutathione (GSH).

Zeevalk GD, Bernard LP, Guilford FT. Liposomal-glutathione provides maintenance of intracellular glutathione and neuroprotection in mesencephalic neuronal cells. Neurochemical research. 2010;35(10):1575-87. PMID: 20535554.

Markers of Oxidation

- Lipid peroxidation of polyunsaturated fatty acids
- OxLDL – oxidized LDL
- HNE - 4-hydroxy-2-nonenal diffusible & mediates cell signaling PMID 16075057
- MDA- Malondialdehydes
- DNA Oxidation - 8oxodG (8-OHDG)
  - 7,8-dihydroxy-8-oxo-2'-deoxyguanosine

Frijhoff J, Winyard PG, Zarkovic N, Davies SS, Stocker R, Cheng D, et al. Clinical Relevance of Biomarkers of Oxidative Stress. Antioxid Redox Signal. 2015;23(14):1144-70. https://www.ncbi.nlm.nih.gov/pubmed/26415143

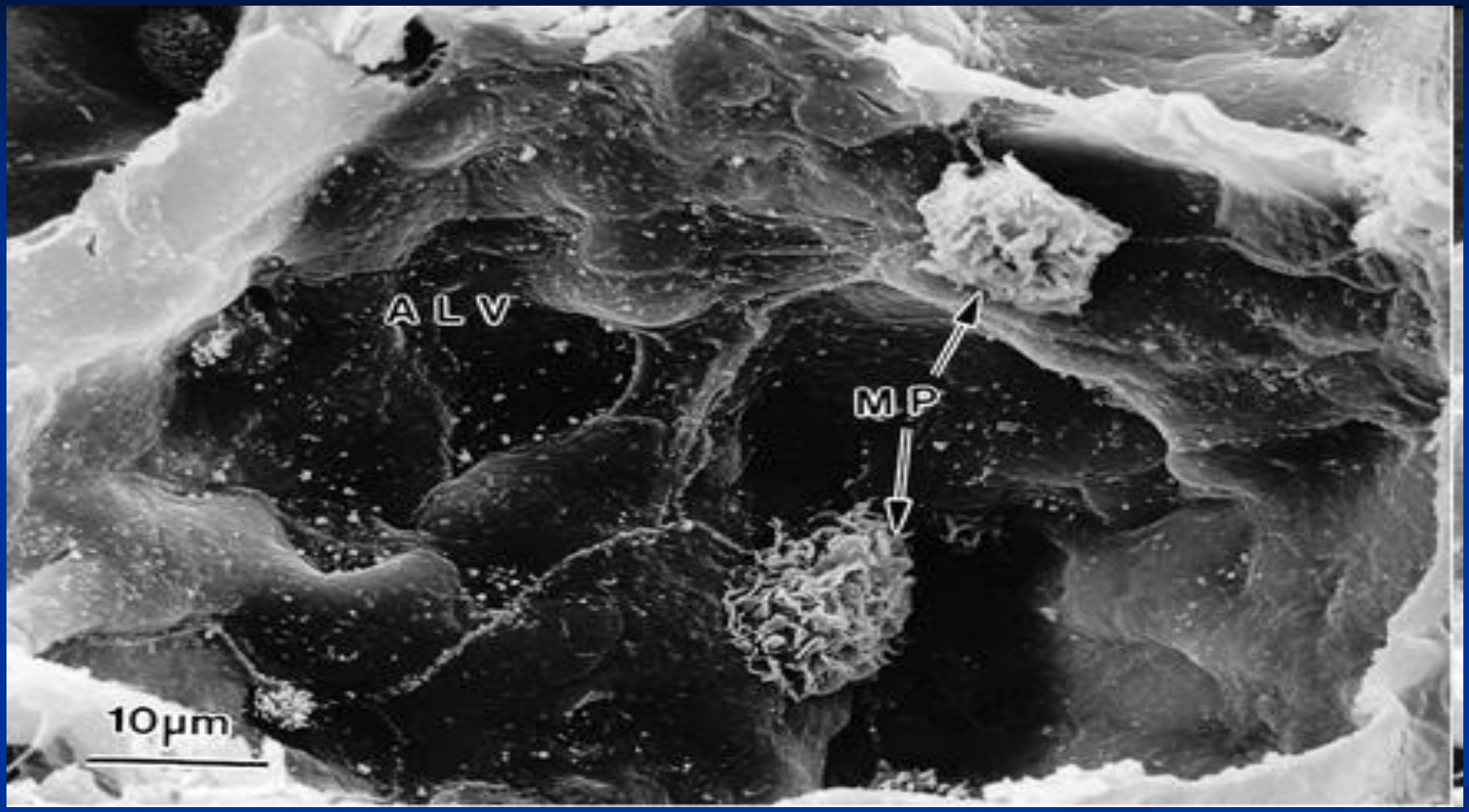
GSH Decreased by

- Genetics
- Toxins
  - Metals
  - Chemical to mold related mycotoxins

  Viruses

  RSV reactive oxygen species and by inhibiting at the same time expression of antioxidant enzymes, via degradation of the transcription factor NF-E2-related factor 2 (NRF2) PMID 29107745

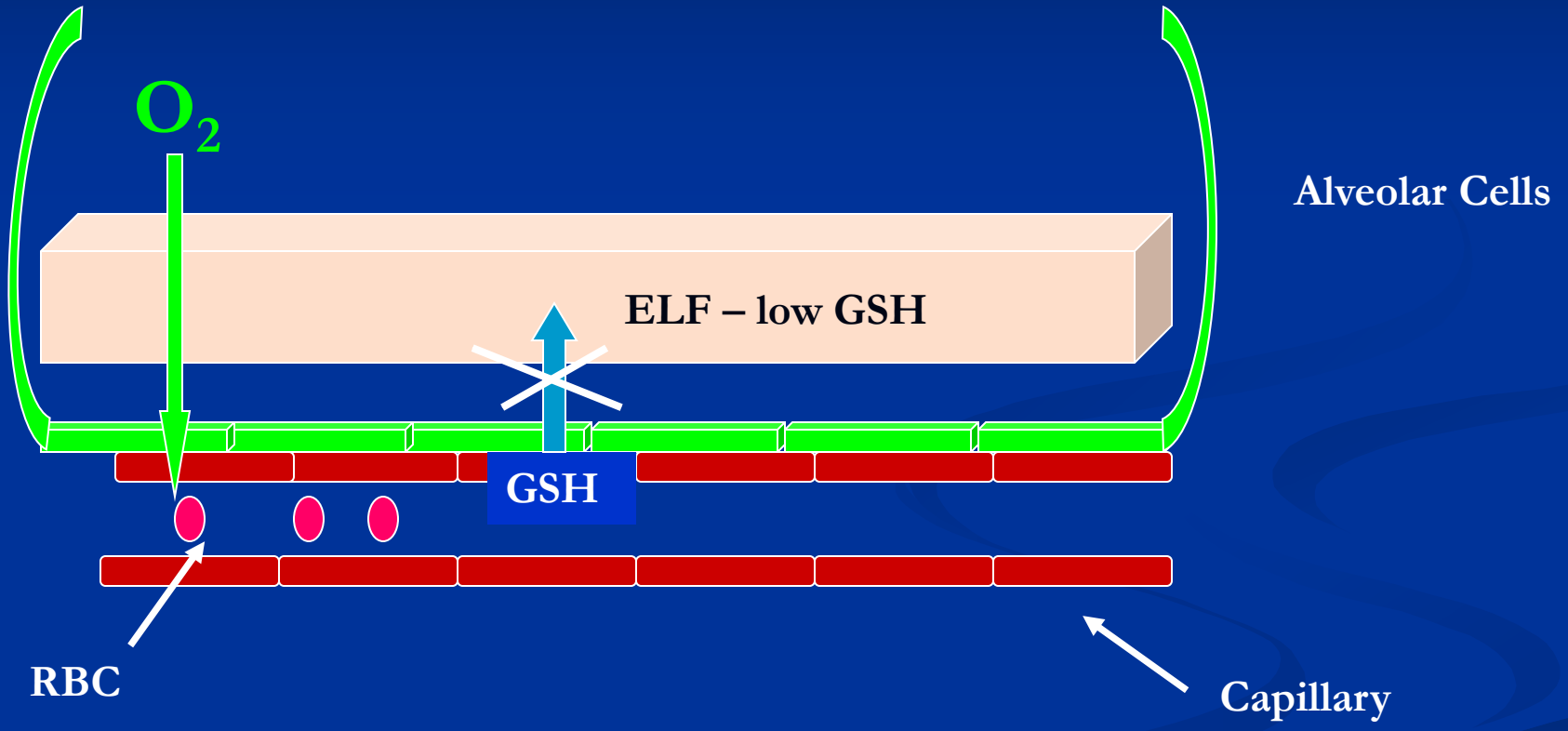
Alveolar macrophages



Scanning EM of rat Alveolus. Alveolar macrophages make up approximately 95% of the leukocytes in the airspaces of human lungs, and 100% of the leukocytes in the lungs of pathogen-free mice.

Innate immunity in the lungs. Martin TR, Frevert CW. Proc Am Thorac Soc. 2005;2(5):403-11. Review. PMID: 16322590

Cystic Fibrosis Transmembrane Receptor (CFTR) is missing in CF



Cantin AM, North SL, Hubbard RC, Crystal RG. Normal alveolar epithelial lining fluid contains high levels of glutathione. J Appl Physiol. 1987;63(1):152-7. Cited in PubMed; 3040659

GCL modifier gene SNPs and CF

- CF is a genetic disease of CFTR
- Significant associations were found between SNPs in GCL modifier genes (GCLC and GCLM) and severity of disease

Polymorphisms in the **glutathione** pathway modulate **cystic** fibrosis **severity**: a cross-sectional study. Marson FA, et al. BMC Med Genet 2014. PMID 24593045 Free PMC article.

SNPs in Production occur in 20%

"relatively common genetic polymorphisms in both the catalytic (Gclc) and modifier (Gclm) subunits of GCL have been associated with increased risk for lung and cardiovascular diseases". PMID: 21967497 Oct 2011

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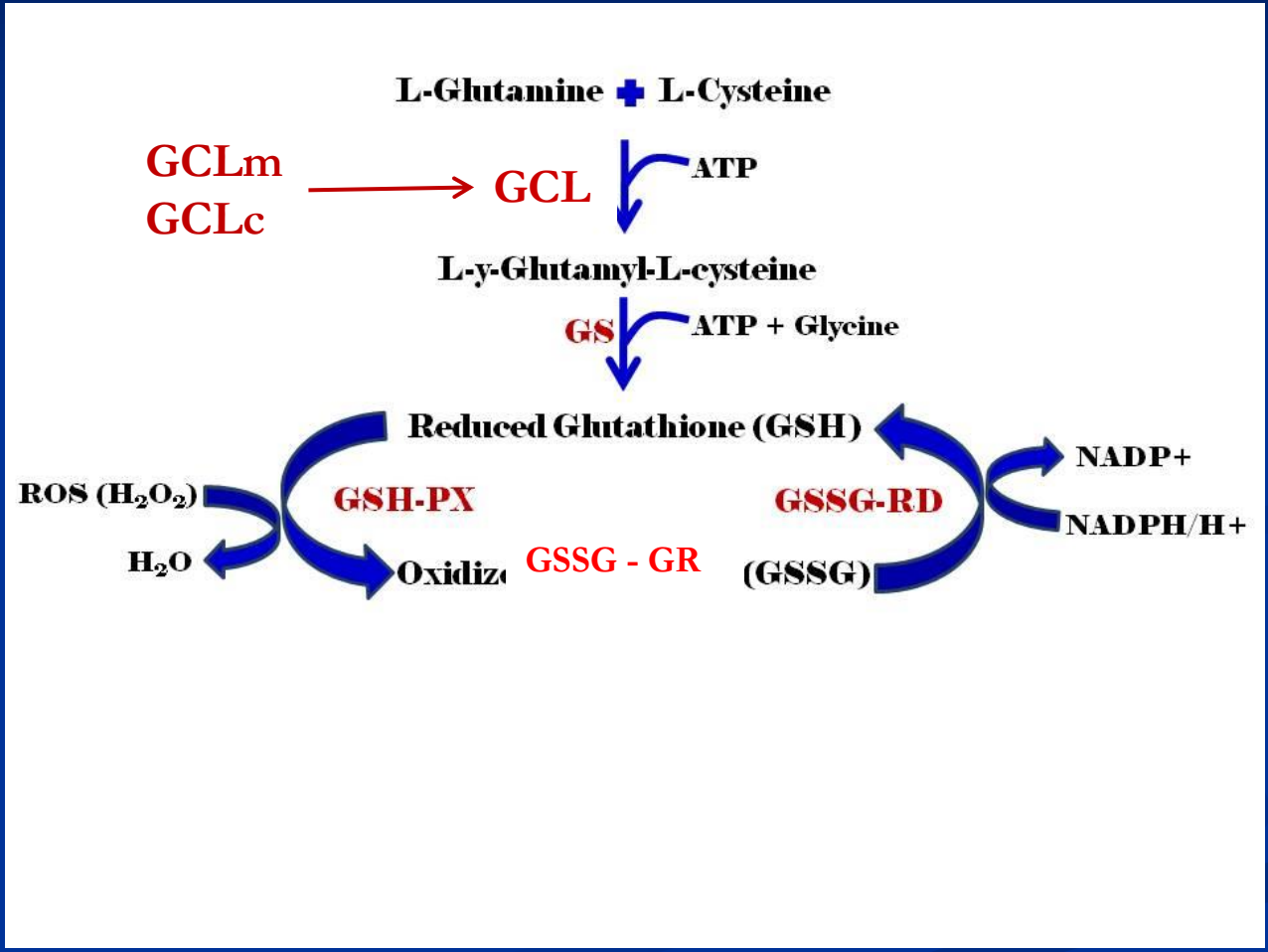
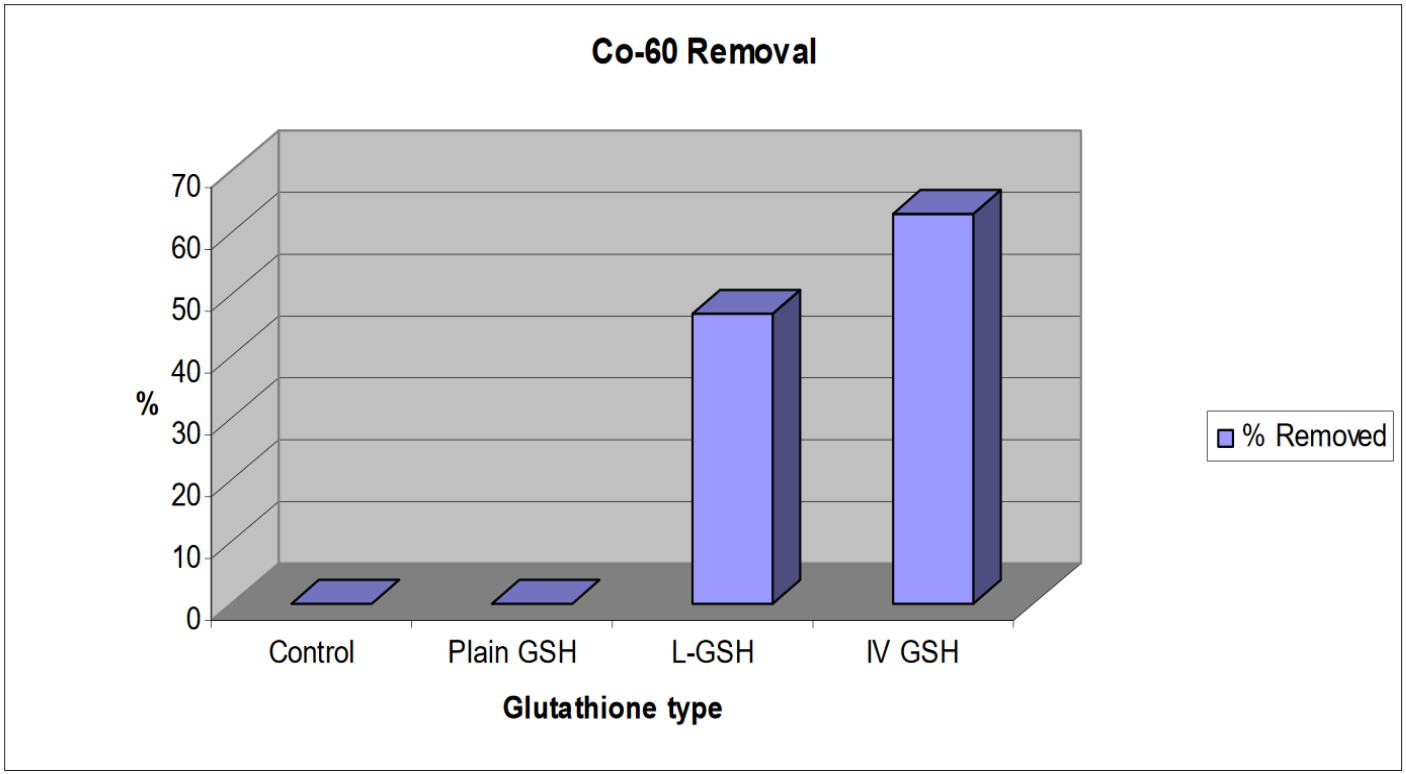


Pb and Hg found in almost all adults

- PCBs, lead, and mercury are present in nearly all U.S. adults. Lead Found in 99.6% of Adults
- Whole-blood total mercury, present in 92.5%
- MeHg has been recognized as one of the most hazardous environmental pollutants.
- poisoning of cysteine-containing proteins

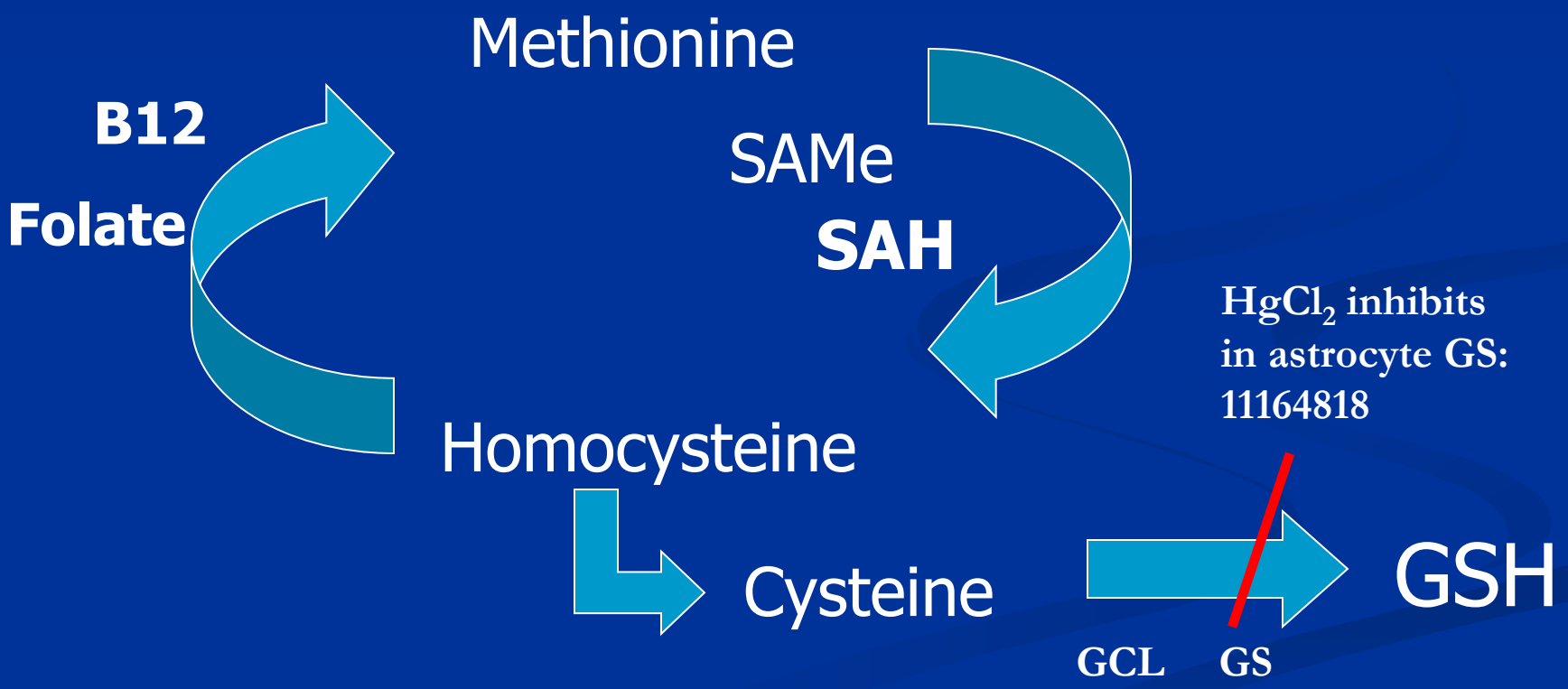
Polychlorinated biphenyls, lead, and mercury are associated with liver disease in American adults: NHANES 2003-2004.
Cave M, et al,Environ Health Perspect. 2010 Dec;118(12):1735-42.
PMID: 21126940

ReadiSorb GSH Function in removal of Co-60 from rat liver



Levitskaia TG, et al. Aminothiol receptors for decorporation of intravenously administered (60)Co in the rat. Health physics. 2010;98(1):53-60. PubMed; 19959951.

Mercury block GSH Formation



GSH may play a role in the etiology of autism 2019

- Concern about mercury has led more than one group to focus on
- Glutathione's importance in facilitating detoxification of xenobiotic agents and antioxidant cellular activity suggests that it may play a role in the etiology of autism.

Faber S, Fahrenholz T, Wolle MM, Kern JC, 2nd, Pamuku M, Miller L, et al. Chronic exposure to xenobiotic pollution leads to significantly higher total glutathione and lower reduced to oxidized glutathione ratio in red blood cells of children with autism. Free Radic Biol Med. 2019;134:666-77. PMID: 30763613

Influenza Vaccination ↑'s oxLDL

- OxLDL a marker of oxidation
- ↑ LDL oxidation after a mild systemic inflammation induced by influenza vaccination
- Healthy males age 17-30
- LDL oxidation may persist for at least 2 weeks

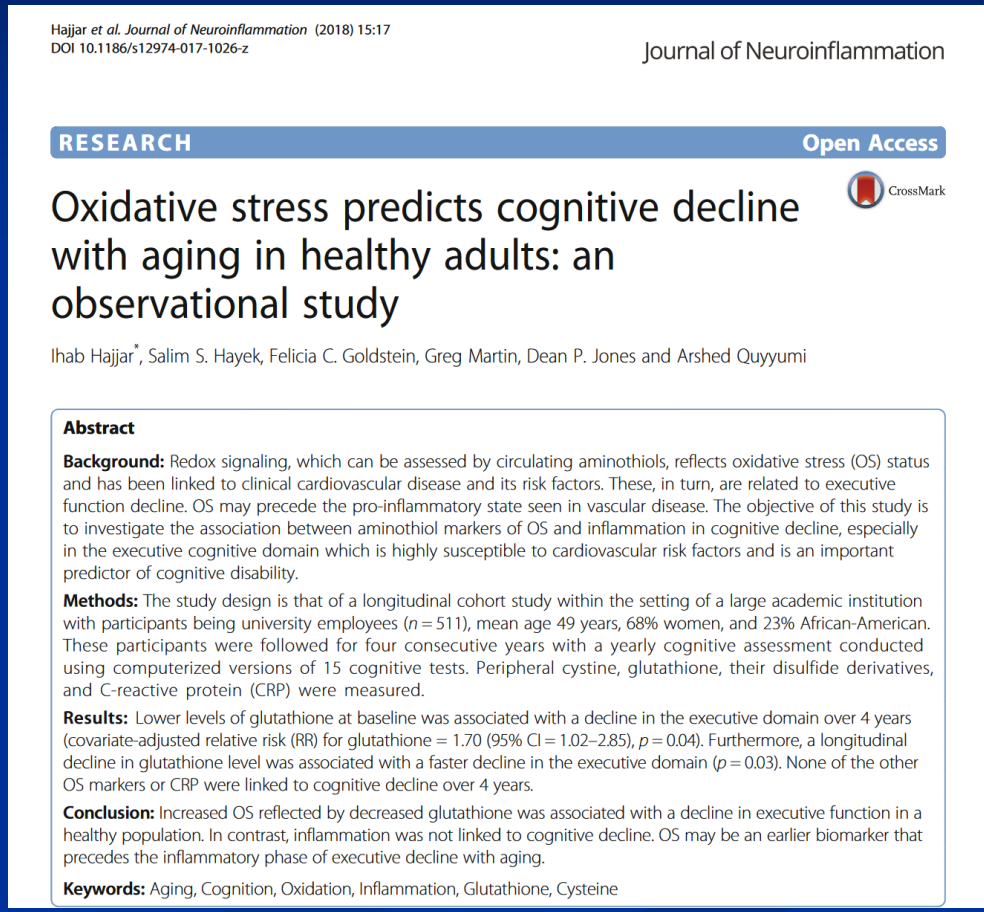
Liuba P, Aburawi EH, Pesonen E, Andersson S, Truedsson L, Yla-Herttuala S, et al. Residual adverse changes in arterial endothelial function and LDL oxidation after a mild systemic inflammation induced by influenza vaccination. Ann Med. 2007;39(5):392-9. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17701480

Factors that may accumulate when GSH was low.

- While low glutathione may be related to autism, to allow normal restoration of GSH, we need to consider the Aldehydes &Xenobiotics – chemical, metal
- Biologics – viral, bacterial, fungi and **parasite**
- Leading to inflammation in brain
- Microbiome alterations PMID: **30747427**
- Loss of neuron development and coordination

Serum GSH and Cognitive function

- OS reflected by a low or a progressive decrease in [serum] GSH levels is associated with a decline in executive function with aging.
- In otherwise healthy aging adults



Hajjar *et al. Journal of Neuroinflammation* (2018) 15:17
DOI 10.1186/s12974-017-1026-z

Journal of Neuroinflammation

RESEARCH Open Access

Oxidative stress predicts cognitive decline with aging in healthy adults: an observational study

Ihab Hajjar*, Salim S. Hayek, Felicia C. Goldstein, Greg Martin, Dean P. Jones and Arshed Quyyumi

Abstract

Background: Redox signaling, which can be assessed by circulating aminothiols, reflects oxidative stress (OS) status and has been linked to clinical cardiovascular disease and its risk factors. These, in turn, are related to executive function decline. OS may precede the pro-inflammatory state seen in vascular disease. The objective of this study is to investigate the association between aminothiol markers of OS and inflammation in cognitive decline, especially in the executive cognitive domain which is highly susceptible to cardiovascular risk factors and is an important predictor of cognitive disability.

Methods: The study design is that of a longitudinal cohort study within the setting of a large academic institution with participants being university employees ($n = 511$), mean age 49 years, 68% women, and 23% African-American. These participants were followed for four consecutive years with a yearly cognitive assessment conducted using computerized versions of 15 cognitive tests. Peripheral cystine, glutathione, their disulfide derivatives, and C-reactive protein (CRP) were measured.

Results: Lower levels of glutathione at baseline was associated with a decline in the executive domain over 4 years (covariate-adjusted relative risk (RR) for glutathione = 1.70 (95% CI = 1.02–2.85), $p = 0.04$). Furthermore, a longitudinal decline in glutathione level was associated with a faster decline in the executive domain ($p = 0.03$). None of the other OS markers or CRP were linked to cognitive decline over 4 years.

Conclusion: Increased OS reflected by decreased glutathione was associated with a decline in executive function in a healthy population. In contrast, inflammation was not linked to cognitive decline. OS may be an earlier biomarker that precedes the inflammatory phase of executive decline with aging.

Keywords: Aging, Cognition, Oxidation, Inflammation, Glutathione, Cysteine

Oxidative stress predicts **cognitive** decline with aging in healthy adults: an observational study
Ihab **Hajjar**, Salim S. Hayek, Felicia C. Goldstein, Greg Martin, Dean P. **Jones**, Arshed Quyyumi
J Neuroinflammation. 2018; 15: 17. PMCID: PMC5771063

Need for GSH in MCI & AD

- An editorial review highlights the need for GSH supplementation for the cognitive enhancement in MCI and AD.

BBA Clin. 2016 May 29;6:38-44.
Analysis of glutathione levels in the brain tissue samples from HIV-1-positive individuals and subject with Alzheimer's disease and its implication in the pathophysiology of the disease process.
Saing T[1], Lagman M[1], Castrillon J[2], Gutierrez E[2], Guilford FT[3], Venketaraman V[2].

Cognitive Improvement with Glutathione Supplement in Alzheimer's Disease: A Way Forward.
Mandal PK, Shukla D, Tripathi M, Ersland L.
J Alzheimers Dis. 2019;68(2):531-535. doi: 10.3233/JAD-181054.
PMID:30776003

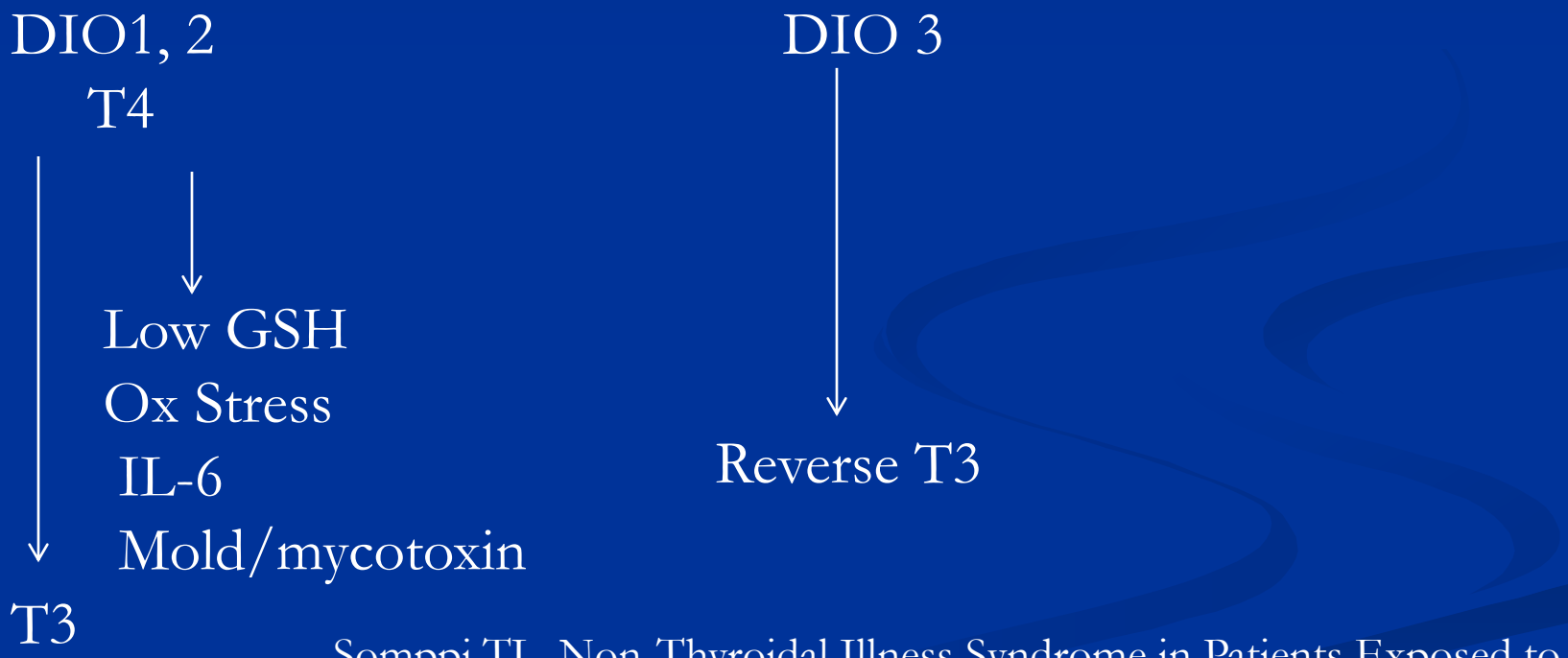
AD subjects show significantly increased rT(3)

- Despite normal circulating thyroid hormone levels, AD subjects showed significantly increased rT(3) levels and an increased rT(3) to T(4) ratio in the face of unchanged CSF total T(4) and transthyretin levels.
- abnormal intracerebral thyroid hormone metabolism and possibly the occurrence of brain hypothyroidism, either as a secondary consequence of the ongoing process or as a cofactor in the progression of the disease.
- 2017 article on Thyroid and AD does not report on rT3 PMID 28818092

Increased Cerebrospinal Fluid Levels of 3,3',5'-triiodothyronine in Patients With Alzheimer's Disease S Sampaolo et al. J Clin Endocrinol Metab 90 (1), 198-202. Jan 2005. PMID 15483087.

Low GSH → NTIS

- Normal Thyroid illness syndrome



Somppi TL. Non-Thyroidal Illness Syndrome in Patients Exposed to Indoor Air Dampness Microbiota Treated Successfully with Triiodothyronine. Front Immunol. 2017;8:919. PMCID: 5545575. http://www.ncbi.nlm.nih.gov/pubmed/28824644

Toxins **2014**, *6*, 608-623; doi:10.3390/toxins6020608

OPEN ACCESS

toxins

ISSN 2072-6651

www.mdpi.com/journal/toxins

Deficient Glutathione in the Pathophysiology of Mycotoxin-related Illness

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[2] Environmental Medicine, 304 W, Los Olivos Street, Santa Barbara, CA 93105, USA; E-Mail: janettehopemd@yahoo.com

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Received: 30 October 2013; in revised form: 21 January 2014 / Accepted: 23 January 2014 / Published: 10 February 2014

Abstract: Evidence for the role of oxidative stress in the pathophysiology of mycotoxin-related illness is increasing. The glutathione antioxidant and detoxification systems play a major role in the antioxidant function of cells. Exposure to mycotoxins in humans requires the production of glutathione on an "as needed" basis. Research suggests that mycotoxins can decrease the formation of glutathione due to decreased gene expression of the enzymes needed to form glutathione. Mycotoxin-related compromise of glutathione production can result in an excess of oxidative stress that leads to tissue damage and systemic illness. The review discusses the mechanisms by which mycotoxin-related deficiency of glutathione may lead to both acute and chronic illnesses.

Health conditions with↓ GSH

Autism PMID: 22129897

Predicts **mortality** Coronary art disease PMC5771063

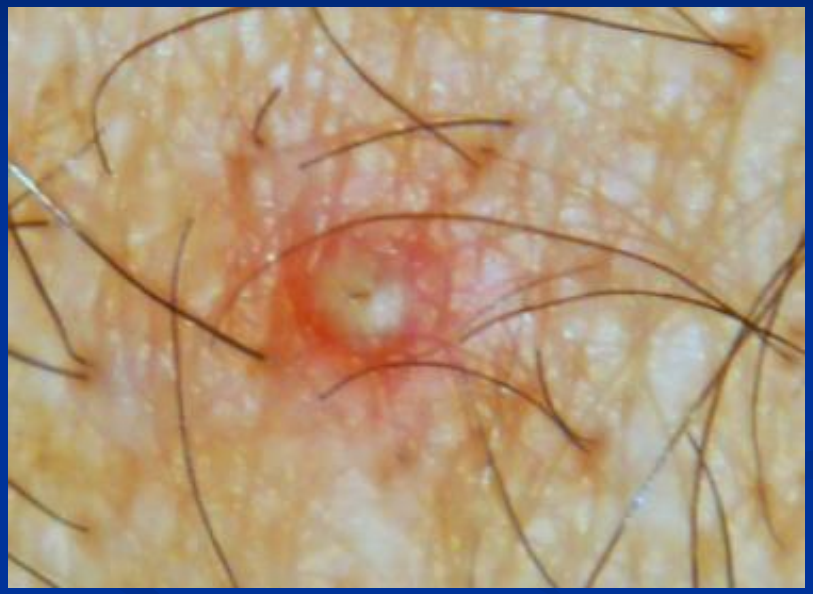
Cognitive function ↓ in healthy PMC5771063

NASH PMID:28585211

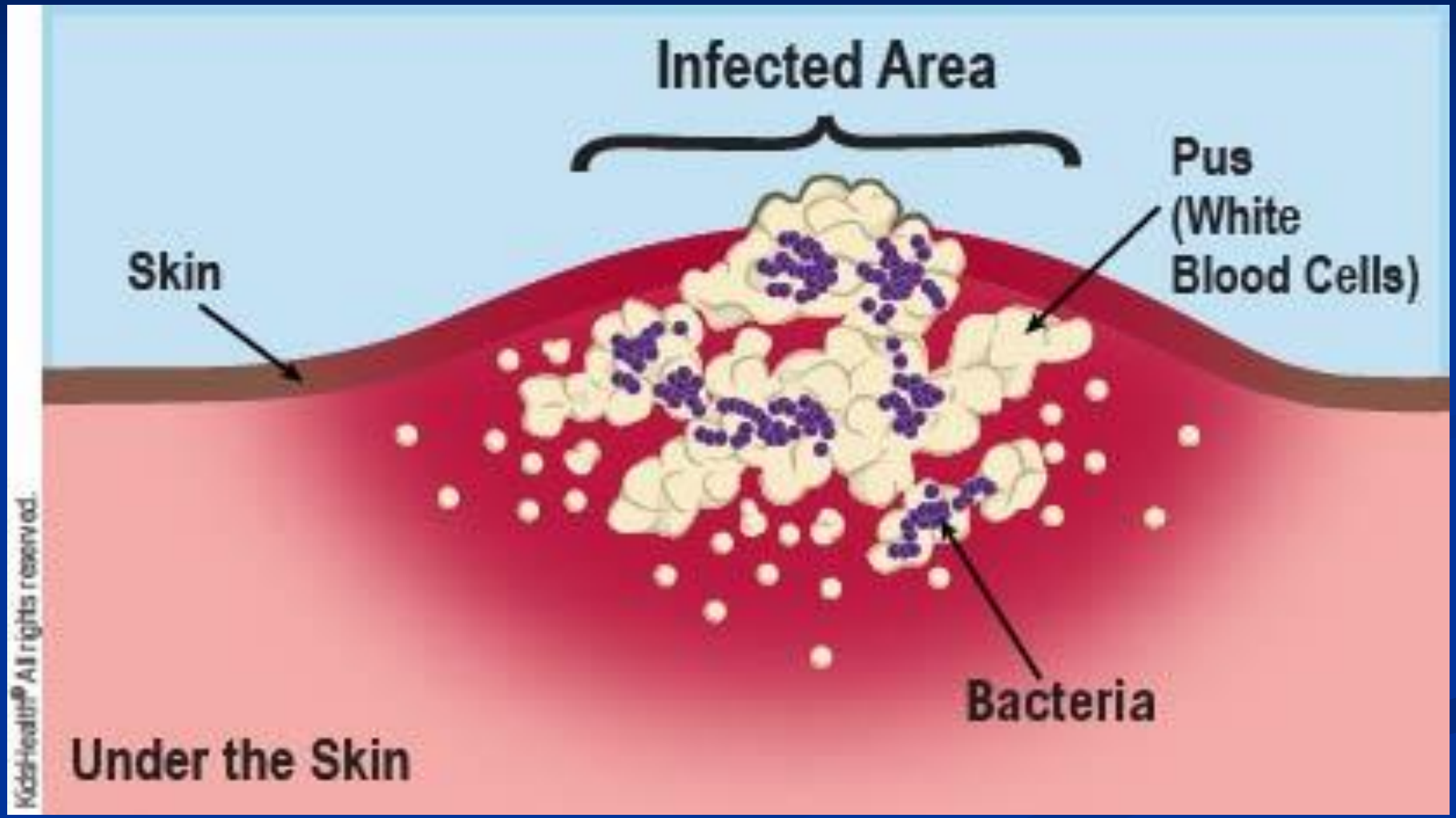
- HIV - Other viruses ↓ GCLC PMID 26133750
- AD ↓ GCLC PMID 27335804
- DM ↓ GCLC PMID 25790445
- Cystic Fibrosis PMID: 24593045
- Mycotoxin ↓ GCLC PMID: 24517907
- Autoimmune SLE ↓ GCL PMID 2494462
  - SLE low serum GSH in meta-analysis of 1120 SLE patients and 1024 healthy controls 2019 PMID: 31475863

Folliculitis

- **Calor, dolor, rubor, and tumor:**
- Heat, Pain, Redness, and Swelling.
  The four classical signs of inflammation



Folliculitis/Purulent accumulation



https://kidshealth.org/en/teens/abscess.html

HDL mediated cholesterol efflux aids MΦ survival

- HDL also has been shown to reduce **macrophage apoptosis in response to oxidized LDL** PMID: 20431058

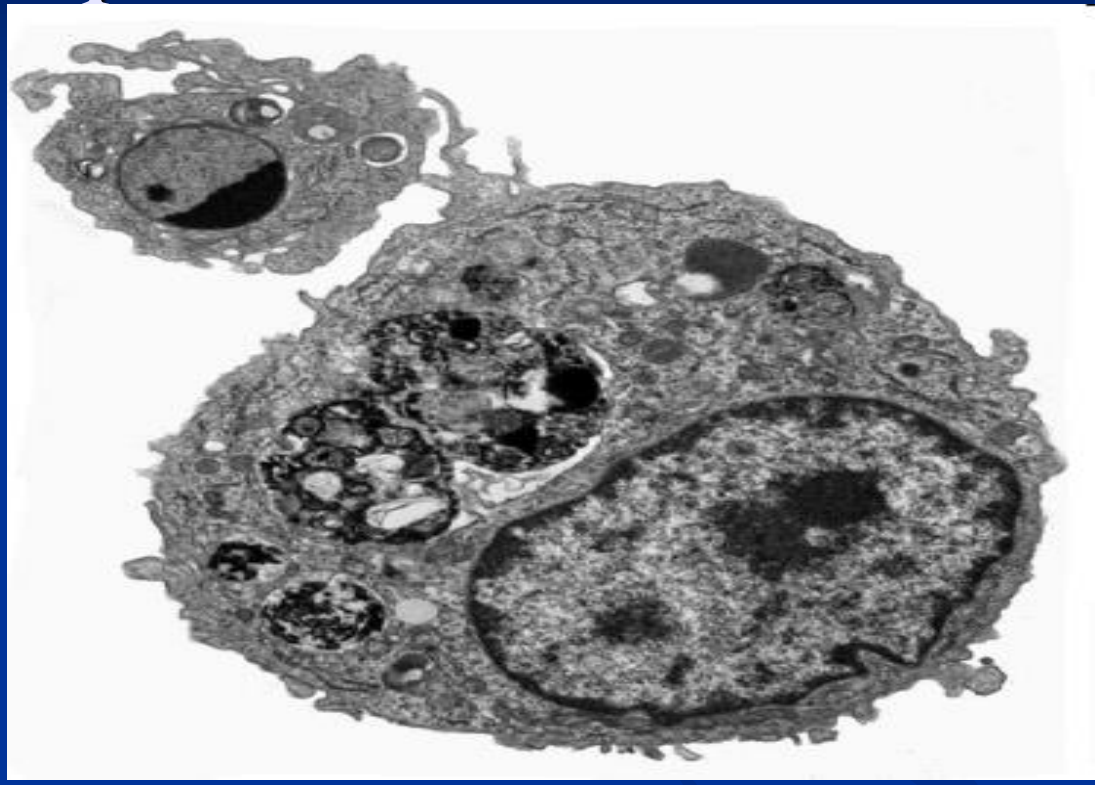
ABCA1 and ABCG1 protect against oxidative stress-induced macrophage apoptosis during efferocytosis.
Yvan-Charvet L, et al, Tall AR. Circ Res. 2010 Jun 25;106(12):1861-9. PMID:20431058

A major function of MΦ is to engulf apoptotic cells (ACs)

- ACs deliver to the phagocytes large amounts of membrane cholesterol, which can be cytotoxic
- macrophages that have ingested apoptotic cells (ACs) successfully employ three survival mechanisms
- cholesterol esterification (unesterified Chol more toxic) **massive cholesterol efflux,**
- and cell-survival signaling - NF-κB).

J Leukoc Biol. 2007 Nov;82(5):1040-50. PMID:17576822

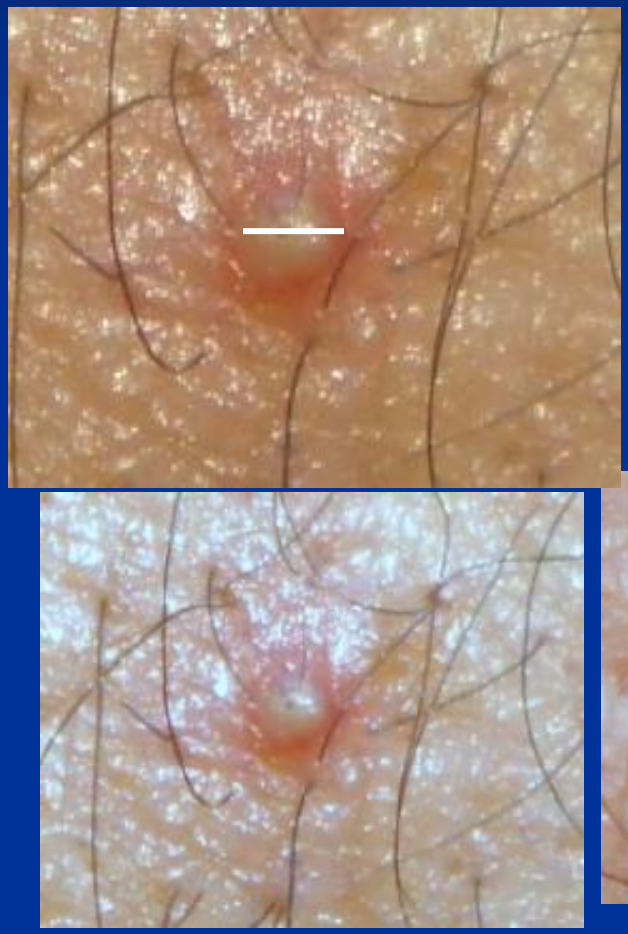
macrophage ingesting apoptotic neutrophils dampens inflammation



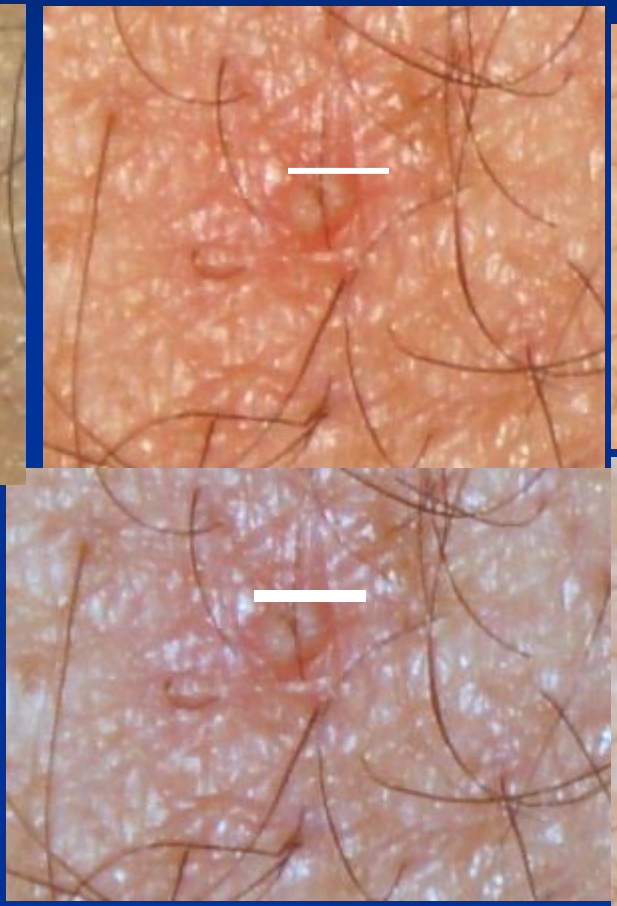
Landes Bioscience

Macrophage engulfment of apoptotic neutrophils are temporally correlated with the resolution of acute inflammation.
Lung inflammation following a single exposure to swine barn air.
Gamage LN, Charavaryamath C, Swift TL, Singh B.J Occup Med Toxicol. 2007 Dec 18;2:18. PMID: 18088427

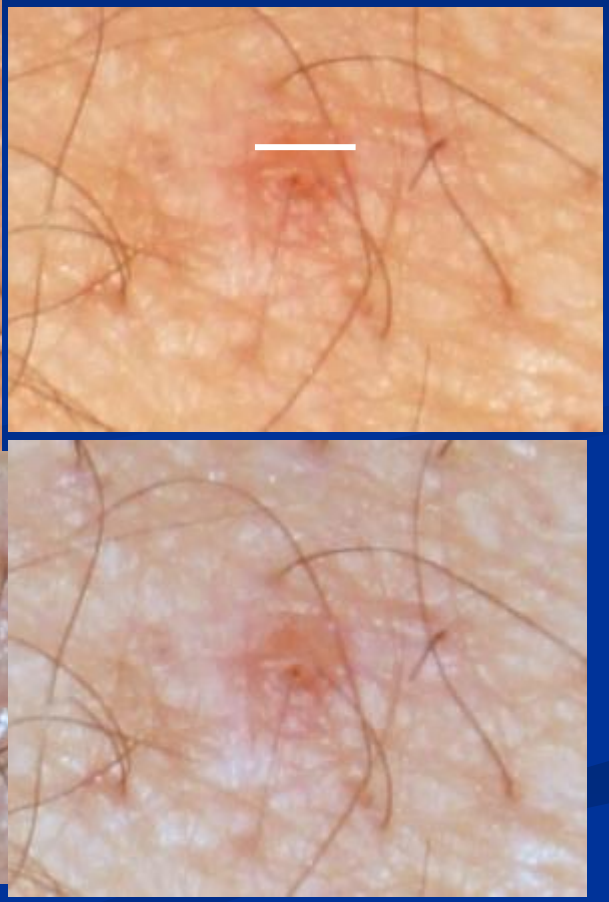
Resolution of Follicular Exudate



3.5 Hrs

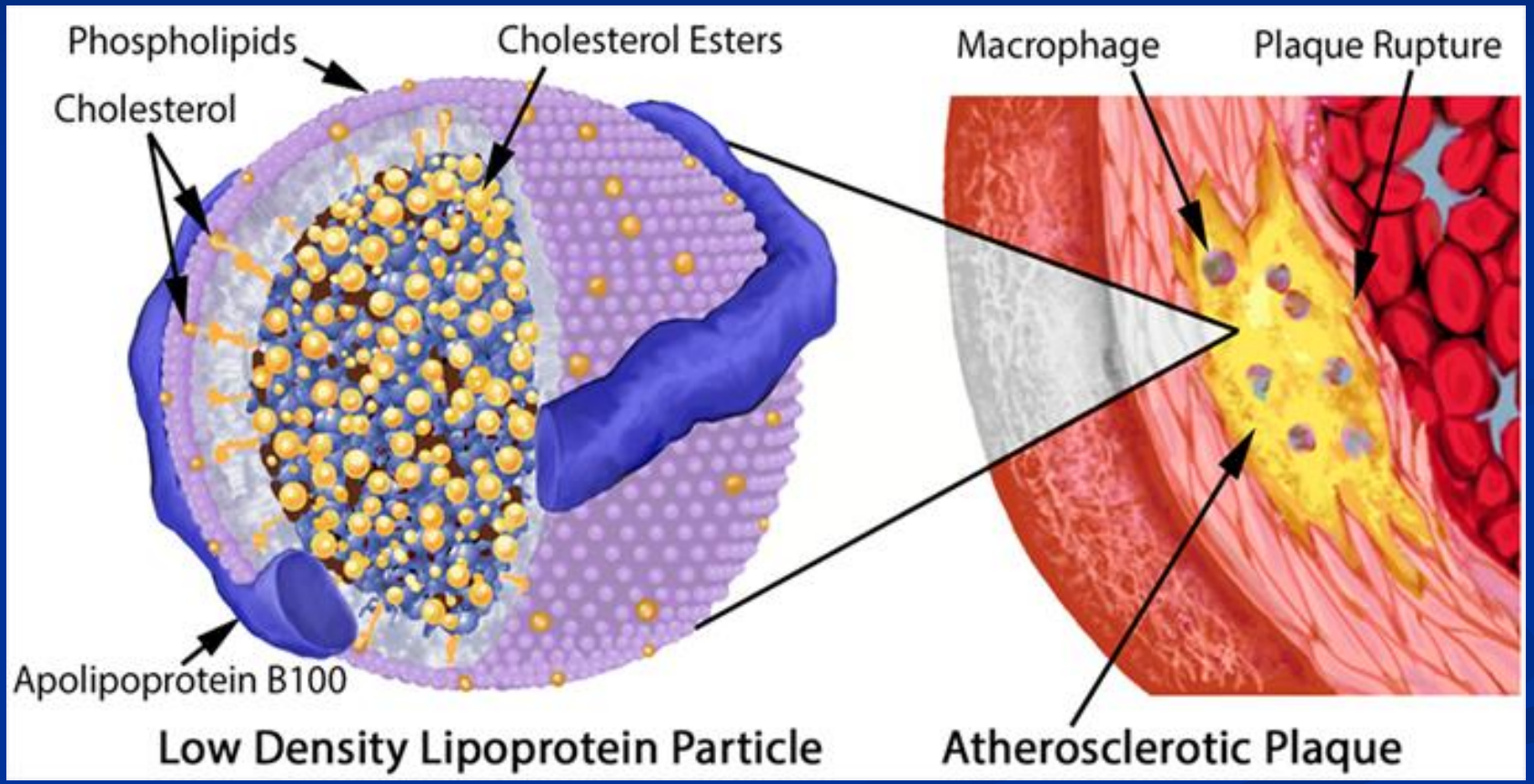


24 Hrs



36 Hrs

Another collection of dead cells and cholesterol - atherosclerosis



https://html.scirp.org/file/1-1910650x2.png

ELSEVIER

Atherosclerosis 195 (2007) e61–e68

ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

Anti-oxidant and anti-atherogenic properties of liposomal glutathione: Studies in vitro, and in the atherosclerotic apolipoprotein E-deficient mice

Rosenblat Mira [a], Volkova Nina [a], Coleman Raymond [b], Aviram Michael [a,*]

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Available online 22 June 2007

Abstract **HDL-induced Macrophage Cholesterol Efflux increase 78%**

Liposomal glutathione, but not the control liposomes (with no glutathione), dose-dependently inhibited copper ion-induced low density lipoprotein (LDL) and HDL oxidation. As peroxidase activity was found to be present in both LDL and HDL, it has contributed to the anti-oxidative effects of liposomal glutathione. In-vitro, no significant effect of liposomal glutathione on J774 A.1 macrophage cell-line oxidative stress and on cellular cholesterol metabolism was observed. In contrast, in the atherosclerotic apolipoprotein E-deficient (E^0) mice, consumption of liposomal glutathione (12.5 or 50 mg/kg/day, for 2 months), but not control liposomes, resulted in a significant reduction in the serum susceptibility to AAPH-induced oxidation by 33%. Liposomal glutathione (50 mg/kg/day) consumption also resulted in an increment (by 12%) in the mice peritoneal macrophages (MPM) glutathione content, paralleled by a significant reduction in total cellular lipid peroxides content (by 40%), compared to placebo-treated mice MPM. MPM paraoxonase 2 activity was significantly increased by 27% and by 121%, after liposomal glutathione consumption (12.5 or 50 mg/kg/day, respectively). Analyses of cellular cholesterol fluxes revealed that, liposomal glutathione (12.5 mg/kg/day) consumption, decreased the extent of oxidized-LDL (Ox-LDL) uptake by 17% and the cellular cholesterol biosynthesis rate, by 34%, and stimulated HDL-induced macrophage cholesterol efflux, by 19%. Most important, a significant reduction in macrophage cholesterol mass (by 24%), and in the atherosclerotic lesion area (by 30%) was noted.

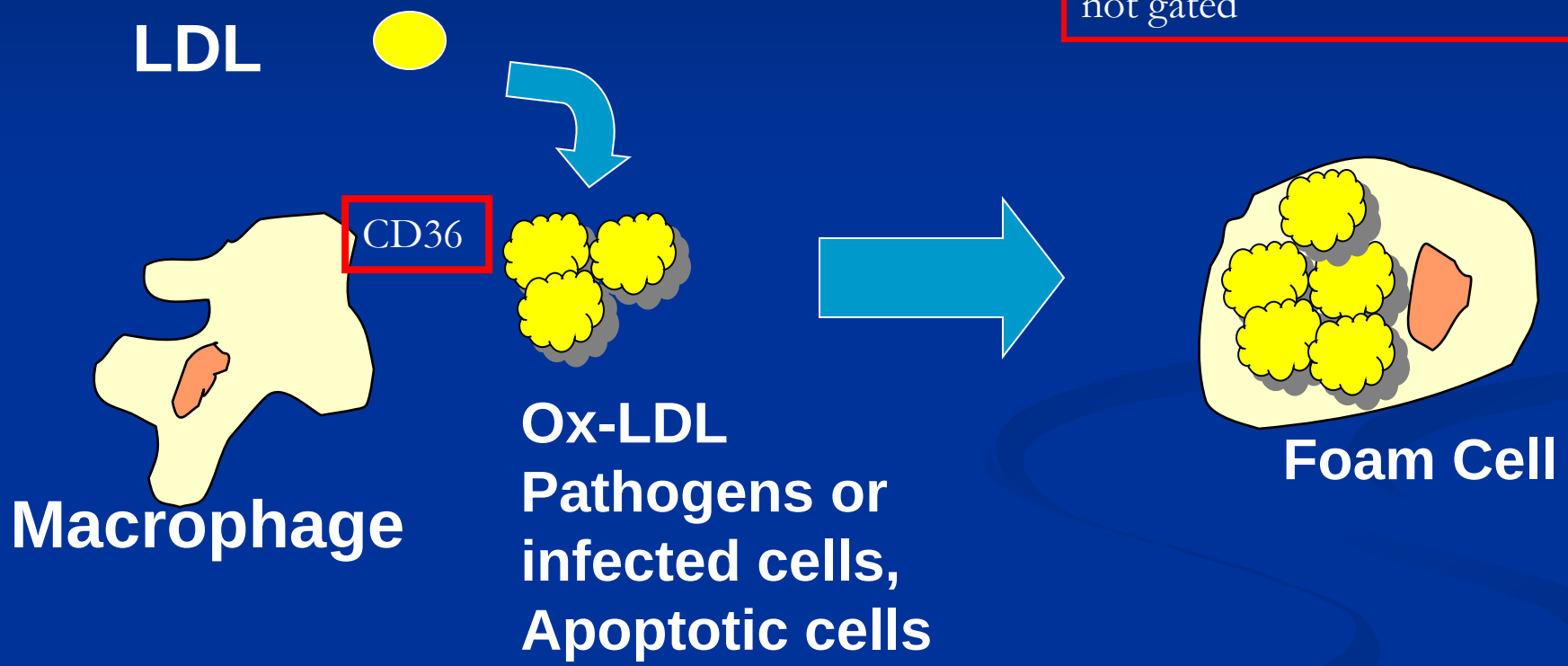
We thus conclude that liposomal glutathione possesses anti-oxidative and anti-atherogenic properties towards lipoproteins and macrophages, leading to attenuation of atherosclerosis development.

Keywords: Liposomal glutathione; Oxidative stress; Macrophages; Atherosclerosis

78% Pg e65

Oxidized LDL cholesterol

CD36 binds and transports not gated



Macrophage scavenger receptors and foam cell formation. J Leukoc Biol. 1999 Nov;66(5):740-6. PMID: 10577503 & PMID: 24621857

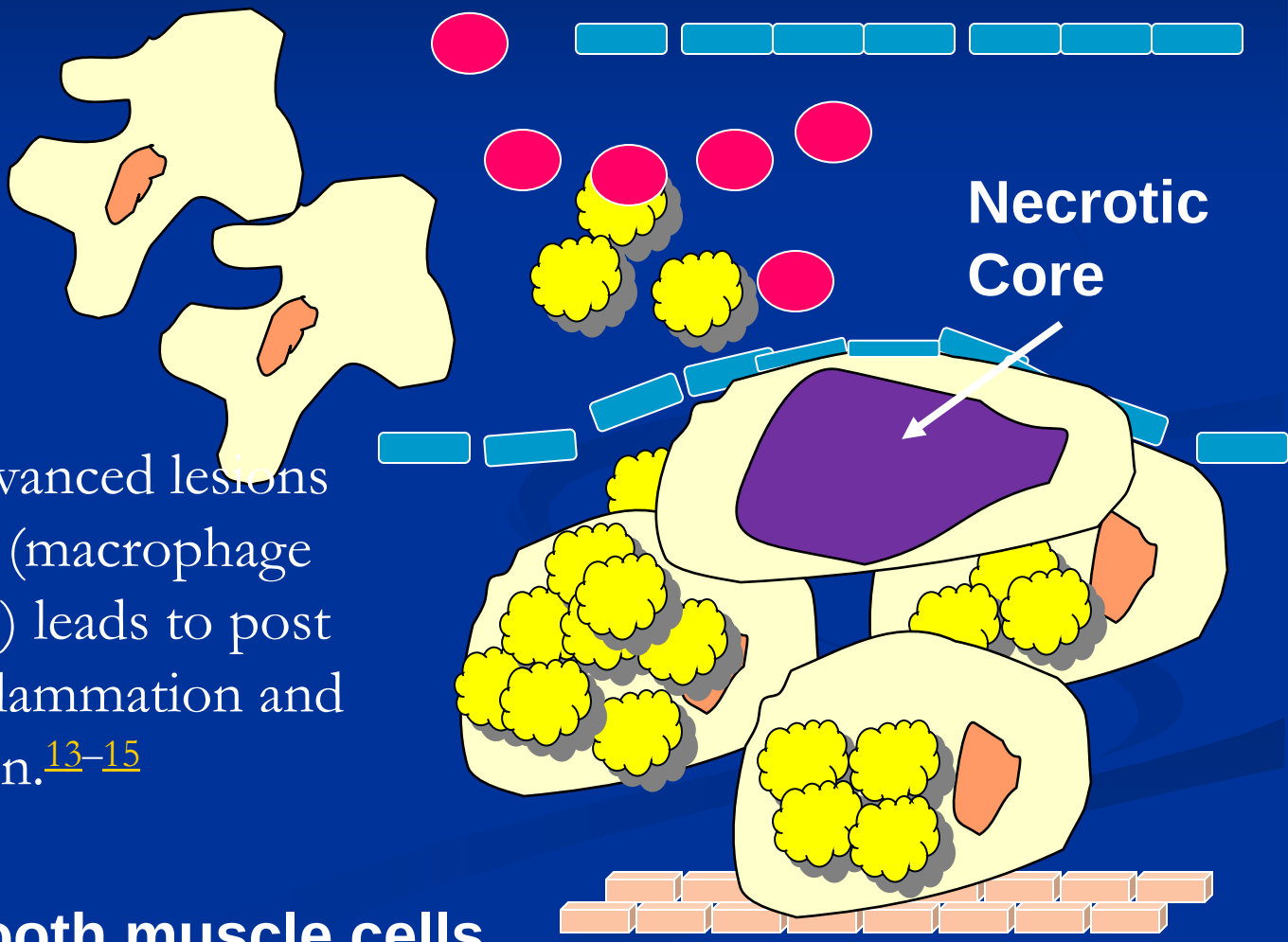
MΦ & GSH key in atherosclerosis

- Macrophages are now recognized as key players in the pathogenesis of atherosclerosis, contributing to all stages of the disease process
- ↑ GSH advantageous

Shirai T, Hilhorst M, Harrison DG, Goronzy JJ, Weyand CM. Macrophages in vascular inflammation--From atherosclerosis to vasculitis. Autoimmunity. 2015;48(3):139-51. PMCID: PMC4606880. https://www.ncbi.nlm.nih.gov/pubmed/25811915

Shirai T, Hilhorst M, Harrison DG, Goronzy JJ, Weyand CM. Macrophages in vascular inflammation--From atherosclerosis to vasculitis. Autoimmunity. 2015;48(3):139-51. PMCID: PMC4606880. https://www.ncbi.nlm.nih.gov/pubmed/25811915

Rupture → Sudden Obstruction



it is thought that in advanced lesions impaired efferocytosis (macrophage ingestion of dead cells) leads to post apoptotic necrosis, inflammation and necrotic core formation.[13–15]

PMID: 20431058

Decrease of GCLM assoc with MI

- Nakamura S, Kugiyama K, Sugiyama S, Miyamoto S, Koide S, Fukushima H, et al.
- Polymorphism in the 5'-flanking region of human glutamate-cysteine ligase modifier subunit gene is associated with myocardial infarction. Circulation. 2002;105(25):2968-73. http://circ.ahajournals.org/cgi/content/full/105/25/2968

Serum GSH/CysSS predicts Mortality in Coronary Artery Disease

- Novel Biomarker of Oxidative Stress Is Associated With Risk of Death in Patients With Coronary Artery Disease. Circulation. 2016;133(4):361-9. PMCID: 4722941.
- Patel RS, et al Jones DP.
- http://www.ncbi.nlm.nih.gov/pubmed/26673559

JOURNAL OF INTERFERON & CYTOKINE RESEARCH
Volume 00, Number 00, 2013

DOI: 10.1089/jir.2012.0103

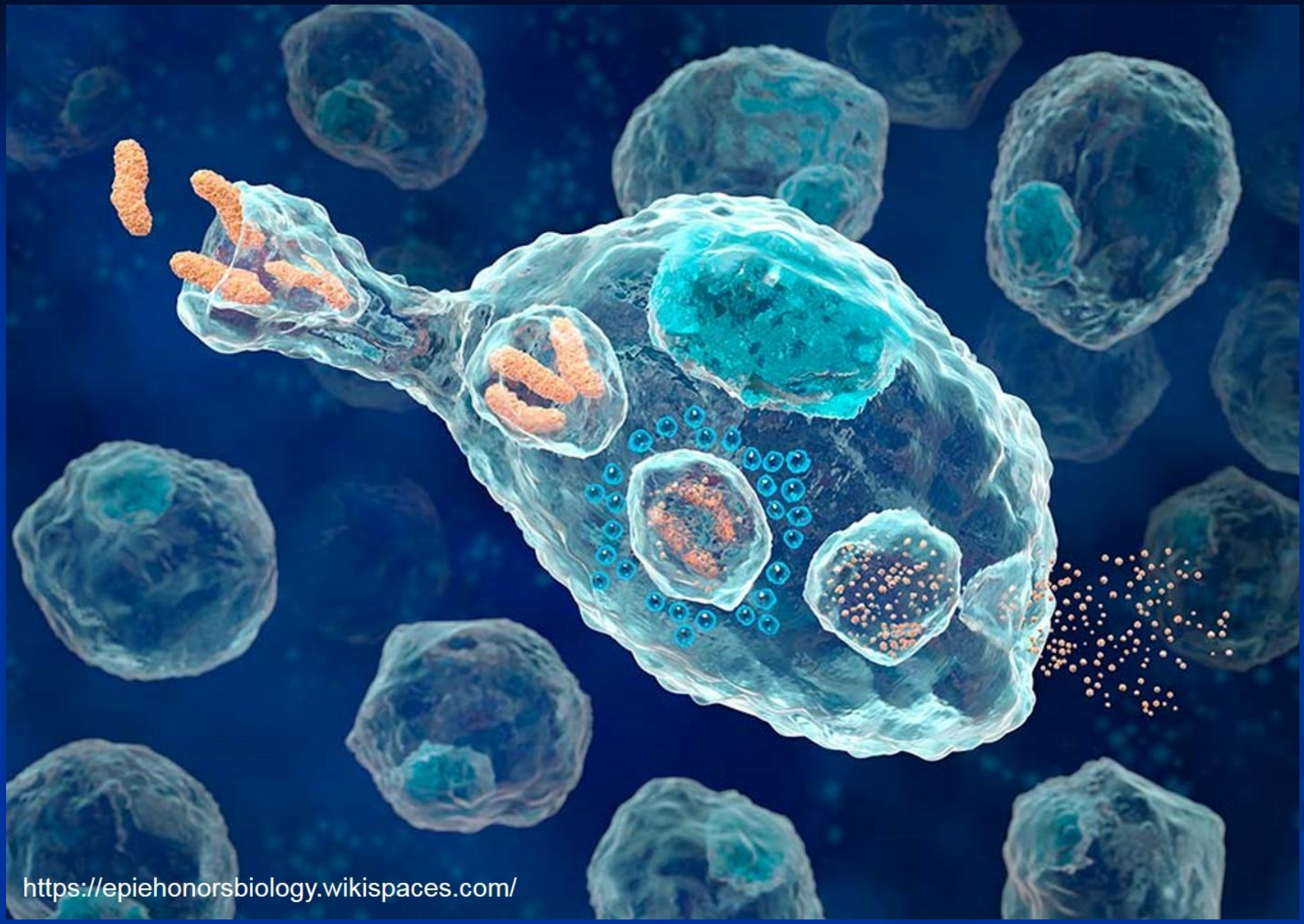
FULL MANUSCRIPT

Glutathione Supplementation Improves Macrophage Functions in HIV

Devin Morris,[1] Carlos Guerra,[2] Melissa Khurasany,[3] Frederick Guilford,[4] Beatrice Saviola,[2] Ying Huang,[5] and Vishwanath Venketaraman[1,2]

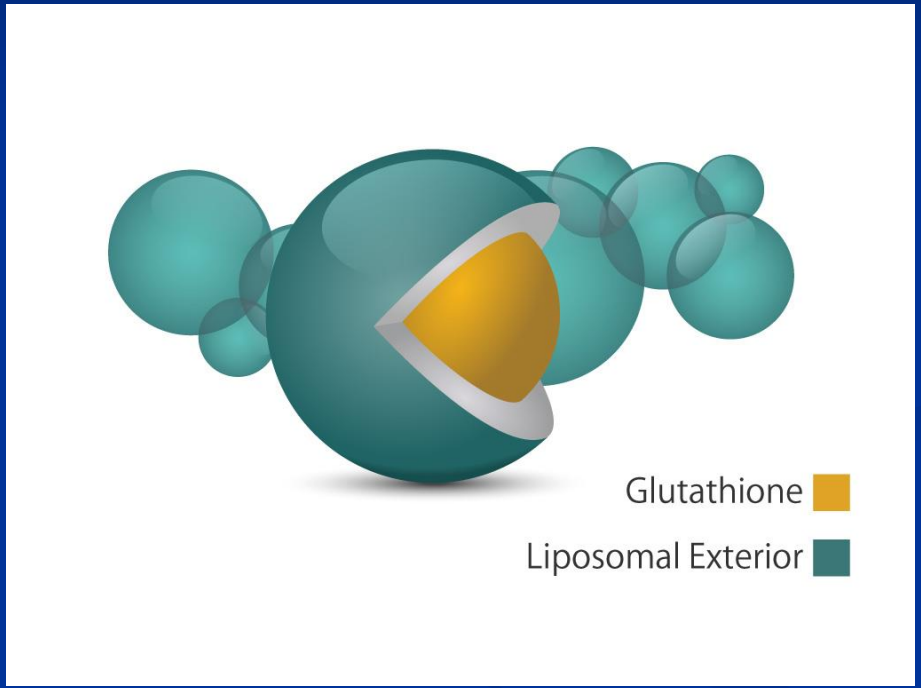
In this study, we determined the effects of glutathione (GSH)-enhancing agents in restoring the levels of GSH in isolated macrophages from individuals with HIV infection thereby resulting in improved control of *Mycobacterium tuberculosis*. Our results indicate that treatment with N-acetyl cysteine or a liposomal formulation of glutathione (*l*GSH) resulted in replenishment of reduced also known as free GSH (*r*GSH), and correlated with a decrease in the intracellular growth of *M. tuberculosis*. Finally, we observed differences in the amount of the catalytic subunit of glutamine-cysteine ligase (GCLC), glutathione synthase, and glutathione reductase present in macrophages derived from healthy and HIV-infected individuals. These changes correlated with changes in free radicals as well as *r*GSH levels. Our results indicate that HIV infection leads to increased production of free radicals and decreased production of GCLC resulting in depletion of *r*GSH and this may lead, in part, to the loss of innate immune function observed in HIV patients. These findings represent a novel mechanism for control of *M. tuberculosis* infection, and a possible supplement to current HIV treatments.

https://www.ncbi.nlm.nih.gov/pubmed/23409922


https://epiehonorsbiology.wikispaces.com/

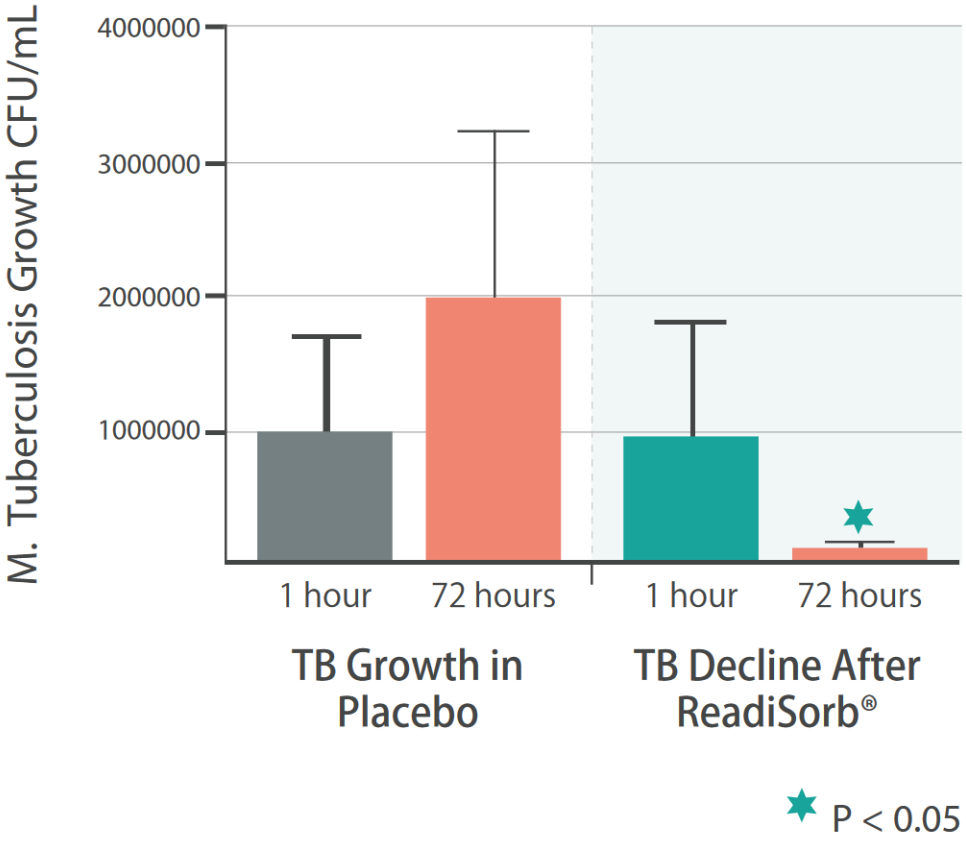
lGSH is more efficient than NAC by a factor of 1,000

- L-GSH is more efficient by a factor of 1,000 than NAC in replenishing the macrophage GSH to a level that could control the intracellular replication of M. tuberculosis.



Morris D, Guerra C, Khurasany M, Guilford F, Saviola B, Huang Y, et al. Glutathione supplementation improves macrophage functions in HIV. J Interferon Cytokine Res. 2013;33(5):270-9. http://www.ncbi.nlm.nih.gov/pubmed/23409922

Restriction of TB growth when RLG is taken by individuals



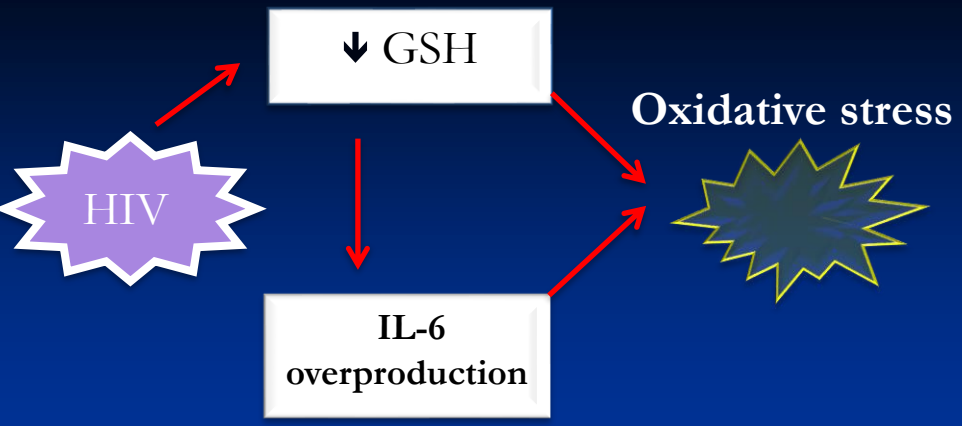
Ly J, Lagman M, Saing T, Singh MK, Tudela EV, Morris D, et al. Liposomal Glutathione Supplementation Restores TH1 Cytokine Response to Mycobacterium tuberculosis Infection in HIV-Infected Individuals. J Interferon Cytokine Res. 2015;35(11):875-87. PMID: 26133750

JOURNAL OF INTERFERON & CYTOKINE RESEARCH
Volume 35, Number 11, 2015
DOI: 10.1089/jir.2014.0210

Liposomal Glutathione Supplementation Restores T_H1 Cytokine Response to *Mycobacterium tuberculosis* Infection in HIV-Infected Individuals

Judy Ly,[1,2] Minette Lagman,[1,2] Tommy Saing,[1,*] Manpreet Kaur Singh,[1,2,*] Enrique Vera Tudela,[1,2,*]
Devin Morris,[2] Jessica Anderson,[2] John Daliva,[2] Cesar Ochoa,[3] Nishita Patel,[3]
Daniel Pearce,[4] and Vishwanath Venketaraman[1,2]

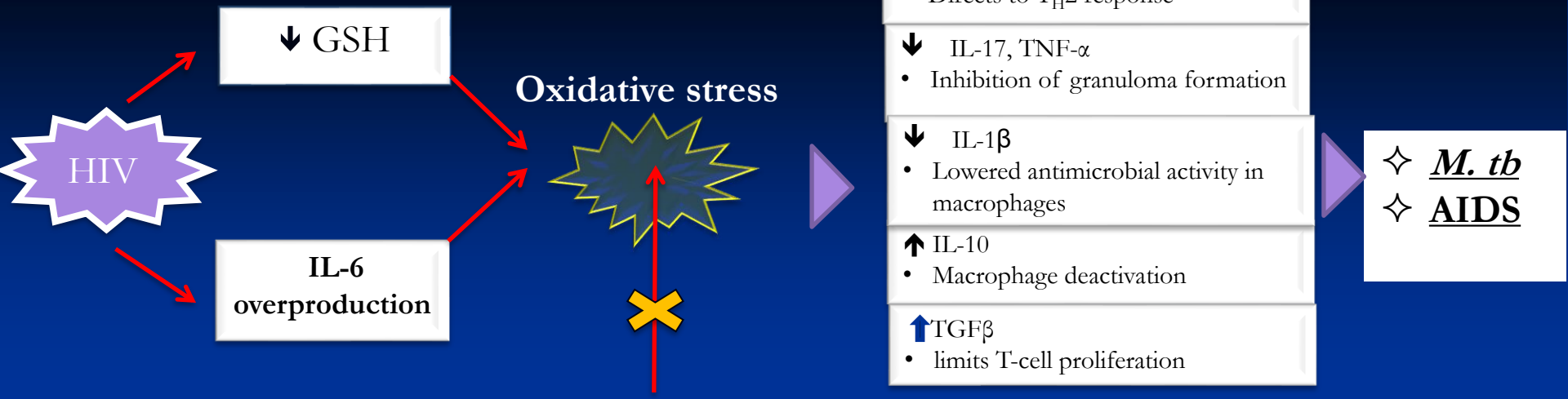
Cytokines are signaling biomolecules that serve as key regulators of our immune system. $CD4^+$ T-cells can be grouped into 2 major categories based on their cytokine profile: T-helper 1 (T_H1) subset and T-helper 2 (T_H2) subset. Protective immunity against HIV infection requires T_H1-directed CD4 T-cell responses, mediated by cytokines, such as interleukin-1β (IL-1β), IL-12, interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α). Cytokines released by the T_H1 subset of CD4 T-cells are considered important for mediating effective immune responses against intracellular pathogens such as *Mycobacterium tuberculosis (M. tb)*. Oxidative stress and redox imbalance that occur during HIV infection often lead to inappropriate immune responses. Glutathione (GSH) is an antioxidant present in nearly all cells and is recognized for its function in maintaining redox homeostasis. Our laboratory previously reported that individuals with HIV infection have lower levels of GSH. In this study, we report a link between lower levels of GSH and dysregulation of T_H1- and T_H2-associated cytokines in the plasma samples of HIV-positive subjects. Furthermore, we demonstrate that supplementing individuals with HIV infection for 13 weeks with liposomal GSH (lGSH) resulted in a significant increase in the levels of T_H1 cytokines, IL-1β, IL-12, IFN-γ, and TNF-α. lGSH supplementation in individuals with HIV infection also resulted in a substantial decrease in the levels of free radicals and immunosuppressive cytokines, IL-10 and TGF-β, relative to those in a placebo-controlled cohort. Finally, we determined the effects of lGSH supplementation in improving the functions of immune cells to control *M. tb* infection by conducting *in vitro* assays using peripheral blood mononuclear cells collected from HIV-positive individuals at post-GSH supplementation. Our studies establish a correlation between low levels of GSH and increased susceptibility to *M. tb* infection through T_H2-directed response, which may be relieved with lGSH supplementation enhancing the T_H1 response.



- ↓ IL-12, IL-2, IFNγ
  - Directs to T_H2 response
- ↓ IL-17, TNF-α
  - Inhibition of granuloma formation
- ↓ IL-1β
  - Lowered antimicrobial activity in macrophages
- ↑ IL-10
  - Macrophage deactivation
- ↑ TGFβ
  - limits T-cell proliferation

✧ ***M. tb***
✧ **AIDS**

Ly J, Lagman M, Saing T, Singh MK, Tudela EV, Morris D, et al. Liposomal Glutathione Supplementation Restores TH1 Cytokine Response to Mycobacterium tuberculosis Infection in HIV-Infected Individuals. J Interferon Cytokine Res. 2015;35(11):875-87. PMID: 26133750



Liposomal Glutathione

- ↓IL-6
  - Decreased ROS production
- ↑ IL-12, IL-2, IFNγ
  - Directs to T_H1 response
- ↑ IL-17, TNF-α
  - Granuloma formation
- ↑ IL-1 β
  - Antimicrobial activity in macrophages
- ↓ IL-10
  - Macrophage activation
- ↓TGFβ
  - T-cell proliferation

✧ Control of *M. tb* infection.
✧ Control of AIDS progression.

Ly 2015 PMID: 26133750

HIV

↓ GSH

IL-6 overproduction

Oxidative stress

↓ IL-12, IL-2, IFNγ
- Directs to T_H2 response

↓ IL-17, TNF-α
- Inhibition of granuloma formation

↓ IL-1β
- Lowered antimicrobial activity in macrophages

↑ IL-10
- Macrophage deactivation

↑TGFβ
- limits T-cell proliferation

✧ ***M. tb***
✧ **AIDS**

Liposomal Glutathione

↓IL-6
- Decreased ROS production

↑ IL-12, IL-2, IFNγ
- Directs to T_H1 response

↑ IL-17, TNF-α
- Granuloma formation

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- Antimicrobial activity in macrophages

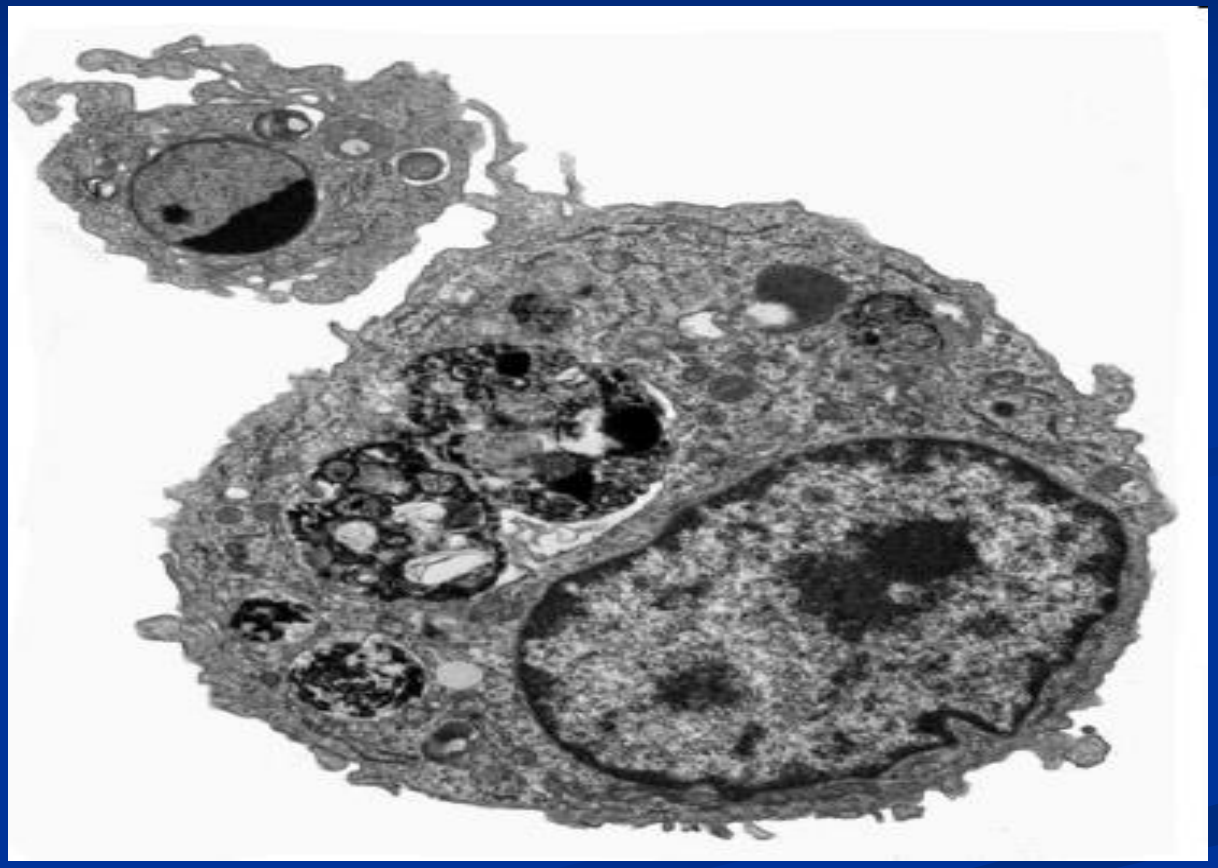
↓ IL-10
- Macrophage activation

↓TGFβ
- T-cell proliferation

✧ Control of *M. tb* infection.
✧ Control of AIDS progression.

Ly 2015 PMID: 26133750

Macrophage engulfment of apoptotic neutrophils correlates with the resolution of acute inflammation.



Landes Bioscience

Macrophage engulfment of apoptotic neutrophils are temporally correlated with the resolution of acute inflammation.
Lung inflammation following a single exposure to swine barn air.
Gamage LN, Charavaryamath C, Swift TL, Singh B.J Occup Med Toxicol. 2007 Dec 18;2:18. PMID: 18088427

Cancer and Oxidation Stress

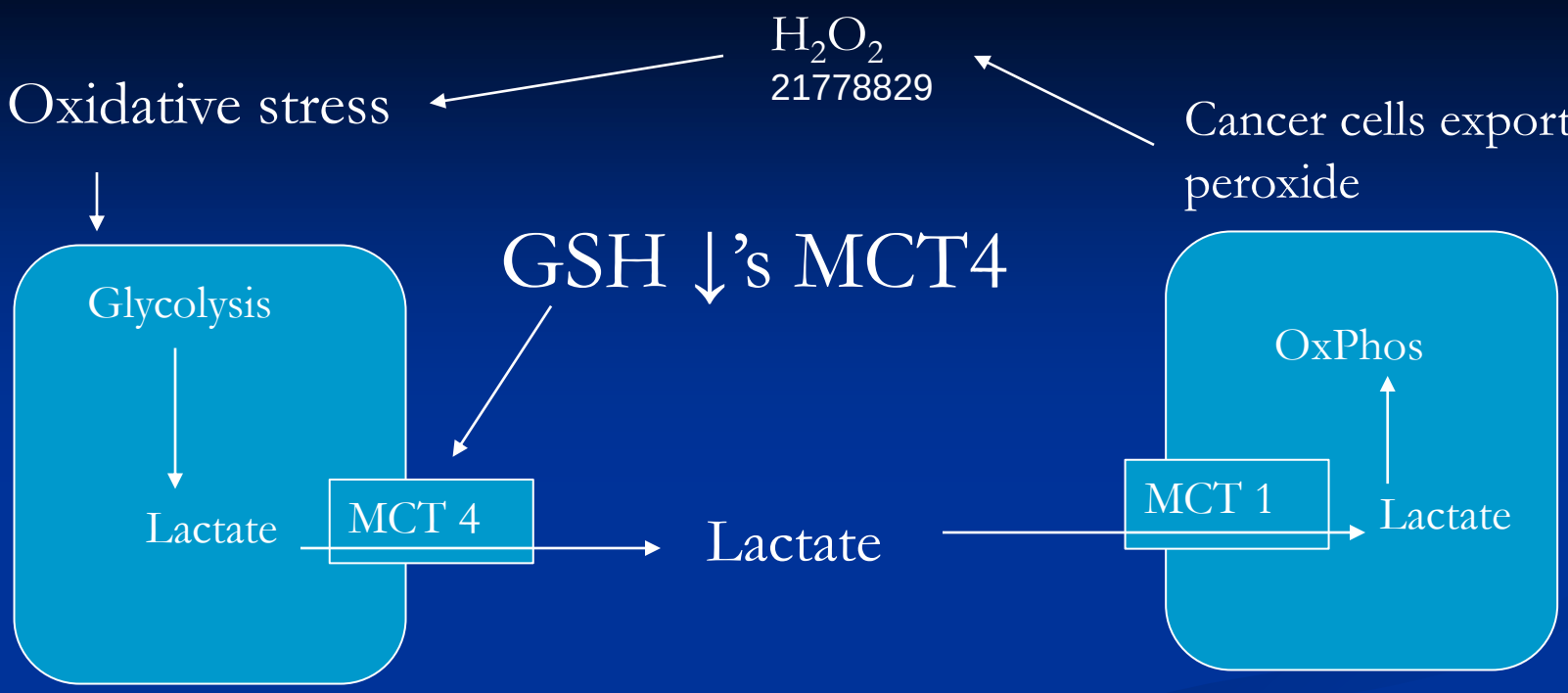
- The finding of evidence of lipid peroxidation (4HNE in tissue) in the mammary epithelium of girls as young as 14, living in our high breast cancer risk-posing environment, with all its functional implications, is reminiscent of the finding of atherosclerotic plaques at autopsy in young US soldiers killed in the Korean war.[95] It was this finding that led to the realization of the need to learn about the early, silent stages in the evolution of cardiovascular disease, and the need for early intervention if its progression to its potentially deadly ultimate manifestations were to be prevented. Hershey, PA USA

Weisz J, Shearer DA, Murata E, Patrick SD, Han B, Berg A, et al. Identification of mammary epithelial cells subject to chronic oxidative stress in mammary epithelium of young women and teenagers living in USA: implication for breast carcinogenesis. Cancer Biol Ther. 2012;13(2):101-13. PMCID: 3336067. http://www.ncbi.nlm.nih.gov/pubmed/22231390

ROS &RNS promote cancer

- Common agreement that reactive oxygen and nitrogen species are involved in the development and progression of several human cancers like breast, prostate, colorectal, gynecological, cervical, eye, skin, leukemia, gastric.

Kruk J, Aboul-Enein HY. Reactive Oxygen and Nitrogen Species in Carcinogenesis: Implications of Oxidative Stress on the Progression and Development of Several Cancer Types. Mini Rev Med Chem. 2017;17(11):904-19. https://www.ncbi.nlm.nih.gov/pubmed/28245782



Cancer-associated fibroblasts (CAF) and nonproliferative carcinoma cells display a glycolytic metabolism,

proliferative carcinoma cells rely on mitochondrial oxidative metabolism fueled by the catabolites provided by the adjacent CAFs

Pilot study demonstrating metabolic and anti-proliferative effects of in vivo anti-oxidant supplementation with N-Acetylcysteine in Breast Cancer.
Monti D, Sotgia F, et al, Lisanti MP, Martinez-Outschoorn U.
Semin Oncol. 2017 Jun;44(3):226-232. PMID: 29248134

LRG supports allows TNF-α defense in neutrophils

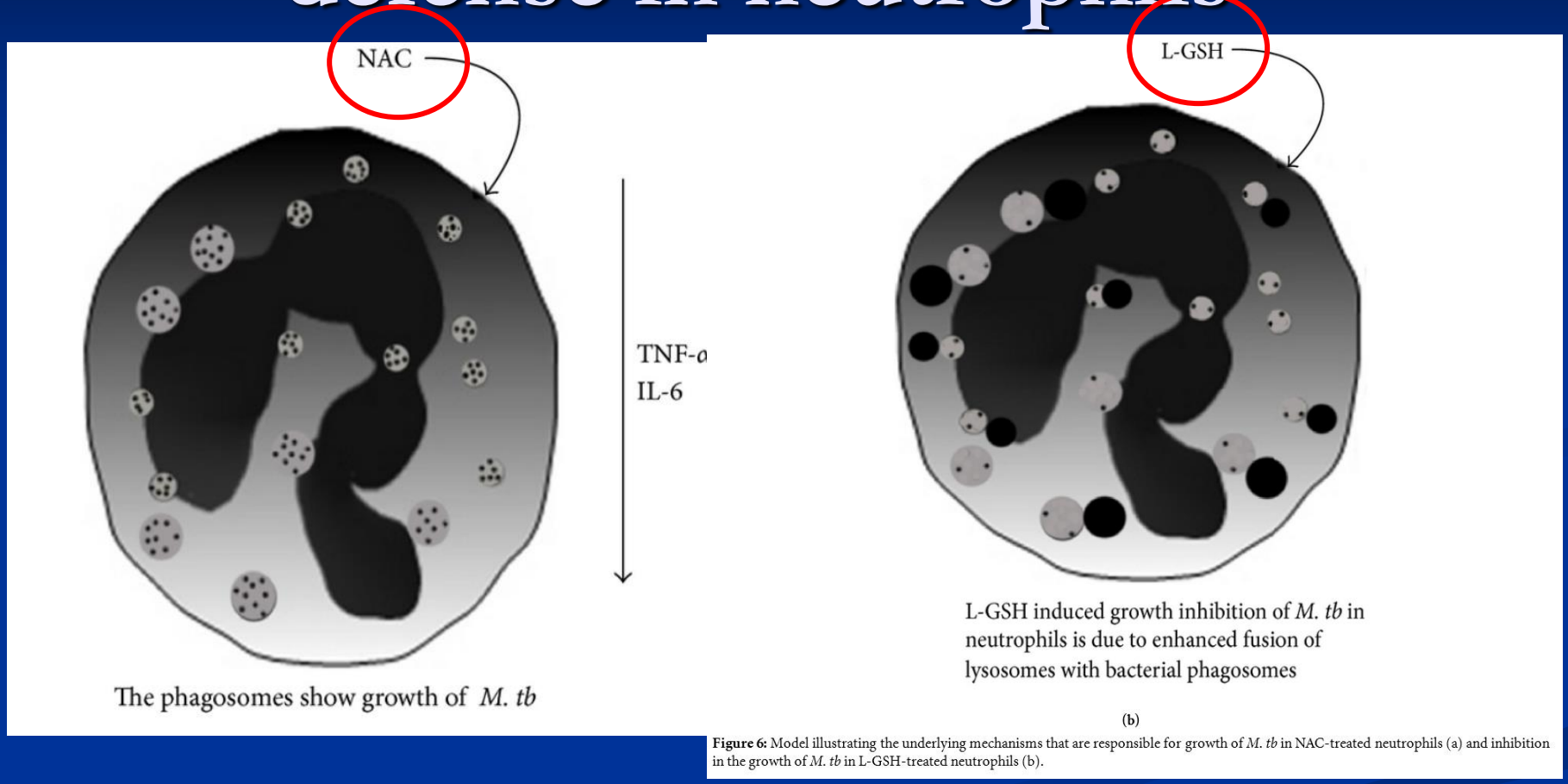


Figure 6: Model illustrating the underlying mechanisms that are responsible for growth of *M. tb* in NAC-treated neutrophils (a) and inhibition in the growth of *M. tb* in L-GSH-treated neutrophils (b).

Morris D, Nguyen T, Kim J, Kassissa C, Khurasany M, Luong J, et al. An Elucidation of Neutrophil Functions against Mycobacterium tuberculosis Infection. Clinical and Developmental Immunology. 2013;Volume 2013 (2013):11. http://www.hindawi.com/journals/cdi/2013/959650/

REVIEW ARTICLE

Antiparasitic and Antifungal Medications for Targeting Cancer Cells Literature Review and Case Studies

Frederick T. Guilford, MD; Simon Yu, MD

Altern Ther Health Med 25 (4), 26-31 Jul 2019

ABSTRACT

Context • Chronic inflammation is a new catch phrase for the explanation of all chronic degenerative diseases, from asthma, arthritis, heart disease, auto-immune disease, and irritable bowel disease to cancer. Occult infections from oncovirus, bacterial, and fungal infections as well as from lesser known parasitic infections are driving forces in the cellular evolution and degeneration of cancer cells. An approach using currently available medications that target both fungal and parasitic metabolism appears to interfere with the metabolic synergy that is associated with tumor growth and aggressiveness.

Objective • The review examined whether antiparasitic and antifungal medications that interfere with the metabolism of cancers, can be useful in cancer therapy by treating cancer as an infectious disease and as a metabolic parasite.

Design • The research team searched the National Center for Biotechnology Information (NCBI) PubMed database databases, using different keyword combinations, including repurposed drug, antifungal, antiparasitic, cancer, parasite, anti-cancer repurposed.

Setting • Prevention and Healing, St Louis, Mo, USA.

Results • The literature search identified a number of studies, including *in vitro*, *in vivo* and clinical, which support the use of antifungal and antiparasitic medication in the treatment of cancer. In the clinical area, the authors observed benefit from the use of antifungal and antiparasitic medication in the treatment of a variety of cancer cases.

Conclusions • Due to the complexity of the behavior and biology of cells, scientists' primary focus should be on detection and elimination of sources of inflammation. Antiparasitic medications, and also antiviral, antibiotic, and antifungal medications should be thought of as underrecognized, underappreciated, and forgotten medications that can be part of cancer therapy. The information offered in this review suggests scientists should think of cancer not only as a metabolic disease but also as a metabolic parasite and should consider using antiparasitic medications under a new understanding of the role of inflammation, infection, and mitochondrial dysfunction in the development of cancer cells. (*Altern Ther Health Med.* [E-pub ahead of print.])