"ReDox" –Our ever evolving understanding of oxidative balance, kinetics and implications in health and disease

Overview:

Four systematic review papers published in the past two years all take a different approach to describe our ever evolving and deepening understanding of the activity of Reductive-Oxidative balance (ReDox). These four papers (and many like them) have sought to update the scientific community in regard to our ever evolving understanding of this precariously balanced system. Aside from simple and outdated notions about ReDox (oxidation is bad and reduction / antioxidants are good) many factions of medical science have been striving to elucidate the actual purposes and effects of this balancing system. Even potentially deeper understanding (and more questions to answer) arises when one looks into the use of ReDox in the oncologic cell setting. Additionally some look at the effects of changes in the ReDox system on the epigenome and potentials for therapies that may inform.

Discussion:

Beyond the obvious research-fodder for the cell biology scientists, these papers and papers like them do update, expand and reinforce our current clinical understanding of the ReDox process. While it is clearly understood that neither oxidation nor reduction / antioxidant is "good or bad" it can be difficult clinically to understand where to intervene. Do we always provide antioxidants? Never provide them? Of course like all biological realities, there is not an always or never.

First, a brief review of the implications of differential kinetics as they relate to therapeutic interventions is in order. In the preventive stage of intervention often very small doses of substrate for redox are required. This in some can be appropriate diet, hydration, exercise, sunlight etc. In others it may include supplementation with low level balanced nutrient and phytochemicals. As a person has disease progression, experiences deficiency or simply ages, he or she may require either repletion or even "pharmacologic" doses of those same nutrients along with the lifestyle interventions. As the deficient person becomes replete, they often require less and less intervention. Added to this complexity is the reality that some pathology (such as cancer or infections) may demand a different balance of the ReDox state both as endogenous triggers as well as in outside interventions. Differential kinetics speaks to this broad and elegant complexity in biology and specifically the cell biology, pathology and physiology of humans.

A few brief quotes from the selected papers illustrate these concepts:

While there is a large body of research demonstrating the general effect of oxidative stress on signaling pathways, less is known about the initial and direct regulation of signaling molecules by ROS, or what we term the 'oxidative interface'."[i] "An interesting concept that has emerged more recently is that not only have cells developed efficient systems to cope with ROS/RNOS accumulation but they have also learned to profit of them under certain circumstances."[ii] "Here, we discuss how cancer-associated mutations and microenvironments can increase production of mROS, which can lead to activation of tumorigenic signaling and metabolic reprogramming. This tumorigenic signaling also increases expression of antioxidant proteins to balance the high production of ROS to maintain redox homeostasis."[iii] "This review focuses on the molecular mechanisms through which ROS directly interact with critical signaling molecules to initiate signaling in a broad variety of cellular processes, such as proliferation and survival (MAP kinases and PI3 kinase), ROS homeostasis, and antioxidant gene regulation (Ref-1 and Nrf-2). This review also deals with classification as well as mechanisms of formation of free radicals, examining their beneficial and deleterious effects on cellular activities and focusing on the potential role of antioxidants in preventing and repairing damage caused by oxidative stress."[iv]

ReDox can be considered the sum total of the balance between various fat and water soluble compartment reductive-oxidative factors and a milieu which allows the necessary oxidation when required but does not lack the reductive / antioxidant factors to restore balance. Without oxidation the cells cannot trigger repair processes, immune defenses or portions of replication. When in balance, the cell is allowed oxidant activity but the reductive / antioxidant processes are sufficient.

ReDox balance and support naturally occurring in the system:

The overall ReDox state is governed by the interplay between fat soluble (cell and mitochondrial membranes, lipid molecules such as cholesterol etc.) and water soluble (plasma, cytosol, mitochondrial) compartments. While there are a myriad of potential supports, the base of ReDox balance is tocopherols, balanced omega fats and triglyceride molecules (phosphatidyl choline, serine etc.) for lipid membranes and glutathione and ascorbate activity for the water soluble compartments.

Once the lipid membrane substrates (omega fats and triglycerides mentioned above) are in place and balanced the overall ReDox state can be maintained by ascorbate, glutathione and the tocopherols. The general balance of reductive / antioxidant status in the water soluble compartments is maintained by the cycling of ascorbate (ASC) and glutathione (GSH) with each being a reductant for the other at various times. ASC is cycled between ASC and dehydroascorbate (DHA) while GSH is cycled between its reduced

state (GSH) and its oxidized state (GSSG). DHA is reduced to ASC by GSH and GSSG is reduced to GSH by ASC. At the cell, lipid and mitochondrial membranes the tocopherols (TOCO) are the main ReDox molecule being cycled between reduced TOCO and oxidized TOCO by both GSH and ASC.

Nutrient and supplemental intake required to keep the ReDox system balanced:

Omega oils, arachadonate (or precursors) and triglycerides (such as phosphatidylcholine) and its relatives should be targeted first in the diet. Then supplemental additions can be added using the variable dose strategy outlined below.

Ascorbate and tocopherols are straight forward in their dietary and supplemental use and administration, and support the recycling of other ReDox agents.

Glutathione can be administered parenterally or as an oral liposome as well as supported by lipoic acid, l-glutamine and N-acetyl-cysteine as precursors. Additionally the cycling and support of glutathione requires specific nutrients, without which glutathione activity decreases. These include magnesium, selenium, zinc, and vitamins B-2, B-3 and B-5 [1-7].

Due to deficiency, disease and state of repletion, the above may be required at various doses. Assuming that the patient is being advised to consume the cleanest, balanced and nutrient rich diet as baseline therapy, then supplementation to address the above deficits can be considered which will vary in dose over time depending on need. A model using intake and supplement dosing equivalent to need includes lower supplemental dosing when in a healthy and preventive state, progressively elevated doses for a time in repletion or disease states and lower maintenance doses when balance is restored. Thoughtful assessment of the complete patient picture coupled with appropriate dietary advice and supplementation varied over time has the best potential for long term ReDox balance and control and thus the best maintenance of this important and sensitive system.

References:

Primary Papers Reviewed:

[i] Ray PD, Huang BW, and Tsuji Y. Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. Cell Signal. 2012 May ; 24(5): 981–990. doi:10.1016/j.cellsig.2012.01.008.

[ii] Olsen LF, Issinger OG, Guerra B. The Yin and Yang of redox regulation. Redox Rep. 2013;18(6):245-52. doi: 10.1179/1351000213Y.0000000059. PMID 24112960.

[iii] Sullivan LB, and Navdeep S Chandel NS. Mitochondrial reactive oxygen species and cancer. Cancer & Metabolism 2014, 2:17 http://www.cancerandmetabolism.com/content/2/1/17

[iv] Gupta RK, et.al. Oxidative Stress and Antioxidants in Disease and Cancer: A Review. Asian Pac J Cancer Prev. 2014, 15 (11), 4405-4409

Additional References Cited:

1. Johnston CS, Meyer CG, Srilakshmi JC. Vitamin C elevates red blood cell glutathione in healthy adults. Am J Clin Nutr. 1993 Jul;58(1):103-105.

2. Barbagallo M, et.al. Effects of Glutathione on Red Blood Cell Intracellular Magnesium Relation to Glucose Metabolism. Hypertension. 1999;34:76-82.

3. Eroglu A. The Effect of Intravenous Alanyl-Glutamine Supplementation on Plasma Glutathione Levels in Intensive Care Unit Trauma Patients Receiving Enteral Nutrition: The Results of a Randomized Controlled Trial. Anesth Analg 2009;109:502–5

4. Slyshenkov VS, Dymkowska D, Wojtczak L. Pantothenic acid and pantothenol increase biosynthesis of glutathione by boosting cell energetics. FEBS Lett. 2004 Jul 2;569(1-3):169-72. PMID: 15225628

5. Wojtczak L, Slyshenkov VS. Protection by pantothenic acid against apoptosis and cell damage by oxygen free radicals--the role of glutathione. BioFactors Volume 17, Issue 1-4, pages 61–73, 2003. PMID: 12897429

6. Mills BJ, et.al. Effect of Zinc Deficiency on Blood Glutathione Levels. J. Nutr. Ill: 1098-1102, 1981.

7. Omata Y, Salvador GA, Supasai S, Keenan AH, Oteiza PI. Decreased zinc availability affects glutathione metabolism in neuronal cells and in the developing brain. Toxicol Sci. 2013 May;133(1):90-100. doi: 10.1093/toxsci/kft022. Epub 2013 Feb 1. PMID: 23377617