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Review Article

Redox theory of aging

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ABSTRACT

Metazoan genomes encode exposure memory systems to enhance survival and reproductive potential by providing mechanisms for an individual to adjust during lifespan to environmental resources and challenges. These systems are inherently redox networks, arising during evolution of complex systems with O_2 as a major determinant of bioenergetics, metabolic and structural organization, defense, and reproduction. The network structure decreases flexibility from conception onward due to differentiation and cumulative responses to environment (exposome). The redox theory of aging is that aging is a decline in plasticity of genome–exposome interaction that occurs as a consequence of execution of differentiation and exposure memory systems. This includes compromised mitochondrial and bioenergetic flexibility, impaired food utilization and metabolic homeostasis, decreased barrier and defense capabilities and loss of reproductive fidelity and fecundity. This theory accounts for hallmarks of aging, including failure to maintain oxidative or xenobiotic defenses, mitochondrial integrity, proteostasis, barrier structures, DNA repair, telomeres, immune function, metabolic regulation and regenerative capacity.

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Introduction

Hundreds of philosophers and scientists have addressed the topics of longevity and aging, and many theories have been advanced. These have been recently reviewed [1], and I make no attempt to further summarize these important contributions. Rather, the present article provides a conceptual review based upon the emerging concept that redox systems function as a critical interface between the genome and the exposome [2,3]. Relying extensively upon emerging understanding of redox systems biology, acquired epigenetic memory systems, and deductive reasoning, a simple theory is derived that aging is the decline of the adaptive interface of the functional genome and exposome that occurs due to cell and tissue differentiation and cumulative exposures and responses of an organism. This theory is not limited to redox processes but has a redox-dependent character due to the over-riding importance of electron transfer in energy supply,

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defense, reproduction and molecular dynamics of protein and cell signaling.

Several years ago, I presented a redox hypothesis of oxidative stress [4] in which I concluded that oxidative stress is predominantly a process involving 2-electron, non-radical reactions rather than commonly considered 1-electron, free radical reactions. The central arguments were that (1) experimental measures showed that non-radical flux substantially exceeds free radical flux under most oxidative stress conditions, (2) radical scavenger trials in humans failed to show health benefits, and (3) normal cell functions involving sulfur switches are readily disrupted by non-radical oxidants. The redox hypothesis is thus founded upon the concept that oxidative stress includes disruption of redox circuitry [5,6] in addition to the macromolecular damage resulting from an imbalance of prooxidants and antioxidants [7].

The redox hypothesis of oxidative stress contained four postulates:

1. All biologic systems contain redox elements [e.g., redox-sensitive cysteines], which function in cell signaling, macromolecular trafficking and physiologic regulation.
2. Organization and coordination of the redox activity of these elements occurs through redox circuits dependent upon common control nodes (e.g., thioredoxin, GSH).
3. The redox-sensitive elements are spatially and kinetically insulated so that "gated" redox circuits can be activated by translocation/aggregation and/or catalytic mechanisms.
4. Oxidative stress is a disruption of the function of these redox circuits caused by specific reaction with the redox-sensitive thiol elements, altered pathways of electron transfer, or interruption of the gating mechanisms controlling the flux through these pathways.

The current article represents an extension and development of these concepts into a redox theory of aging. This redox theory is not exclusively limited to redox reactions but rather emphasizes the key role of electron transfer in supporting central energy currencies (ATP, phosphorylation, acetylation, acylation, methylation and ionic gradients across membranes) and providing the free energy to support metabolism, cell structure, biologic defense mechanisms and reproduction. Importantly, improved understanding of the integrated nature of redox control and signaling in complex, multicellular organisms [8] provide a foundation for this generalized theory.

Improved understanding of redox circuitry

The logic of development of the redox theory of aging depends upon recognition that the third postulate of the redox hypothesis [4] probably applies to a relatively limited subset of redox switches that function in redox signaling [8]. Insulated pathways with gating mechanisms, as discussed in consideration of redox systems biology [9], may be relatively rare. Instead, a much larger number of redox switches exist that support redox sensing to coordinate and integrate functional networks [8,10,11]. These redox sensors exist in dynamic steady state, with Cys in multiple proteins in functional networks sharing similar redox character [10]. They have promiscuous reactivities, with multiple targets and switchable specificities. For example, most protein thiols are oxidizable by hydrogen peroxide and some are reduced by either thioredoxin or glutathione systems [12]. Furthermore, inhibition of thioredoxin reductase activity does not invariably result in thioredoxin oxidation [13], implying alternate reductant system for thioredoxin. Additionally, electron flow from thioredoxin reductase switches between targets due to the relative abundances of the targets [14]. Many thioredoxin-like proteins exist [15], but their reactivities and specificities are largely uncharacterized. These and many other observations show that protein redox systems are not highly insulated but rather part of a redox network with many possible electron pathways determined by relative abundance and reactivity of the elements.

Available evidence indicates that these redox systems are organized within interacting metabolomics and proteomics

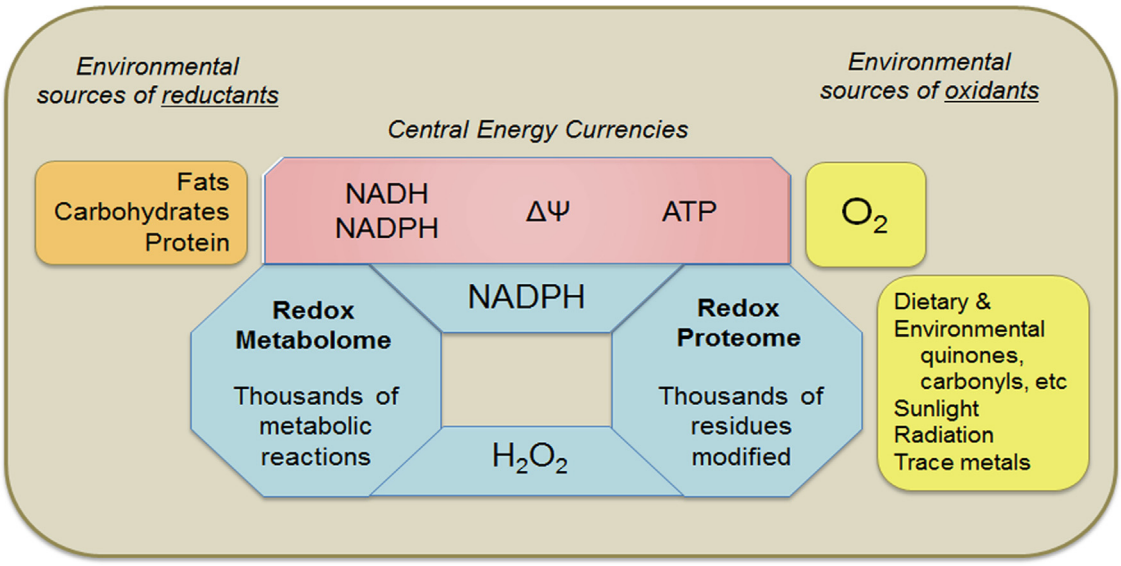

Fig 1. Redox biology of metazoans. Metazoans depend upon redox processes to support energetics, metabolic and structural organization, separation from and defense against external environment, and reproduction. The overall redox structure is a complex network including small molecules, measured by redox metabolomics, and proteins, measured by redox proteomics. Metal ions derived from the environment are a major variable not explicitly shown, but impact both the redox metabolome and redox proteome by interfering with essential metal ion functions and catalyzing non-enzymatic reactions. The enzymology of redox reactions has been studied in detail and organized by the Enzyme Commission in terms of electron donors and electron acceptors in enzyme-catalyzed reactions (see http://www.chem.qmul.ac.uk/iubmb/enzyme/EC1/). No systematic consideration of the redox metabolome is currently available. The elements of the redox proteome are mostly known, but systematic knowledge of spatial and temporal distributions is not available. Redox systems biology provides an initial framework for development, but quantitative data for abundance and kinetics are limited. Ultimately, this knowledge is needed to understand and develop strategies to improve healthy longevity.