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OXIDATIVE STRESS: A CONDUIT FOR DEVELOPMENT OF REDOX REGULATION MECHANISMS IN ANIMALS

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Abstract

Animal redox regulatory mechanisms emerge through oxidative stress. When ROS generation exceeds antioxidant defence mechanisms, this physiological condition occurs. ROS are natural byproducts of cellular metabolism and are required for cell signalling and homeostasis, but excessive ROS generation can damage biomolecules like lipids, proteins, and DNA. To maintain cell integrity and function under oxidative stress, animals have developed complex redox control mechanisms. A complex network of antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, scavenges ROS and prevents their injury. Vitamins C and E, glutathione, and phytochemicals also protect cells from oxidative damage. The activation of redox-sensitive signalling pathways by oxidative stress allows cells to adapt and respond appropriately. Redox signalling regulates cellular processes as proliferation, differentiation, apoptosis, and immunological responses, demonstrating the importance of oxidative stress in physiological regulation. Oxidative stress can damage cells but also help animals develop complex redox regulatory mechanisms. Understanding these pathways is essential for understanding the pathophysiology of oxidative stress-related disorders and discovering treatment targets to reduce oxidative damage and improve health and longevity.

Keywords: Antioxidant, Hydrogen Peroxide, NO, Oxidative stress, ROS, RCS

Introduction

Rise in atmospheric oxygen content shaped the pace of evolutionary changes in living creatures' physiological and metabolic systems. Many chemical systems use oxygen to produce energy, but its redox reactions generate free radicals and reactive species [1]. By oxidizing important biological components, oxygen metabolic by-products can harm an organism. Therefore, animals have created strategies to prevent or minimize reactive species from oxidative processes and defence systems to limit their damaging consequences [2]. This has created many chemical and structural antioxidant defences and redox signalling pathways that are integrated into the cellular metabolic system. The antioxidant system may not neutralise reactive species fully, especially if reactive species generation exceeds antioxidant activity [3]. This imbalance damages biomolecules oxidatively. Cell biochemical stress, or oxidative stress, is the rate of oxidative damage.

Recent animal research suggested that oxidative stress may affect life-history evolution, phenotypic development, and behavioural differences [4]. The medical field has historically concentrated on its function in human disorders. Thus, oxidative stress may have been a selective pressure that drove animal taxa to create many redox regulation mechanisms [5]. The large spectrum of antioxidant processes suggests that organisms can adapt to oxidative stress challenges over time, under different environments, and in diverse tissue types. It also suggests that different species may have adapted differently to similar oxidative stresses [6]. In the present review, authors have discussed animals' several molecular and structural RS defences.

Evolutionary adaptations to endogenous reactive species generation

In aerobic organisms, about 85–90% of cellular oxygen is consumed by the mitochondria to produce energy as ATP molecule A main side-effect of ATP production is the formation of RS. RS include a variety of molecules, mostly physiologically generated from the metabolic activity. RS can induce chemical modifications in other molecules, generating oxidative damage, but also act as second messengers in signal transduction networks [7]. RS mostly consist of reactive oxygen species (ROS) and reactive carbonyl species (RCS). Superoxide anion, the product of a one-electron reduction of oxygen, is the precursor of most ROS. Dismutation of superoxide anion (superoxide dismutase (SOD) enzymes) produces hydrogen peroxide (H_2O_2), which, in turn, may be fully reduced to water or in the presence of ferrous or cuprous ions [8], forms the highly reactive hydroxyl radical. In addition, superoxide anion may react nonenzymatically with other molecules, including nitric oxide (NO) in a reaction controlled by the rate of diffusion of both reactants[i]. The product of the reaction between superoxide anion and NO, peroxynitrite, is also a very powerful oxidant [9]. The oxidants derived from NO have been called reactive nitrogen species (RONS). On the other hand, hydrogen peroxide, although lacking radical properties, can work as a Trojan horse, diffusing away from sites of ROS production to generate the hydroxyl and other reactive radicals at other cellular locations, thereby propagating oxidative damage [10]. In addition to ROS/ RONS, the oxidation of both carbohydrates and lipids, polyunsaturated fatty acids (PUFAs) originates a new generation of RS named reactive carbonyl species, or RCS. Compared with both ROS and RONS, RCS have a much longer half-life (i.e., minutes to hours instead of microseconds to nanoseconds for most ROS/RONS) Further, the noncharged structure of carbonyls allows them to migrate with relative ease through hydrophobic membranes and hydrophilic cytosolic media, thereby extending the migration distance far from the production site [11]. Based on these features, RCS could be more destructive than ROS/RONS and may have far-reaching damaging effects on target sites within or outside membranes Diversity in antioxidant mechanisms is thought to be an expression of this high variety in RS and in their molecular consequences [12]. Although not clearly and consistently defined yet, here, we define antioxidant as “any mechanism, structure and/or substance that prevents, delays, removes or protects against oxidative nonenzymatic chemical modification (damage) to a target molecule [13]”

Protection against oxidative damage is pivotal for organism function. A major consequence of oxidative damage is the loss of function and structural integrity of modified biomolecules, which have a wide range of downstream functional consequences [14], such as induction of cellular

dysfunctions and tissue damage. Alterations of biochemical and physiological pathways can have a number of detrimental consequences for an individual's health, potentially decreasing its Darwinian fitness perspectives [15]. Given that environmental conditions (e.g., weather, food quantity and quality[ii], predation risk, and competition) across a range of habitat types, as well as phases of the life-cycle (e.g., reproduction and hibernation) may be associated with oxidative stress threats, individuals are continually under pressure [16].

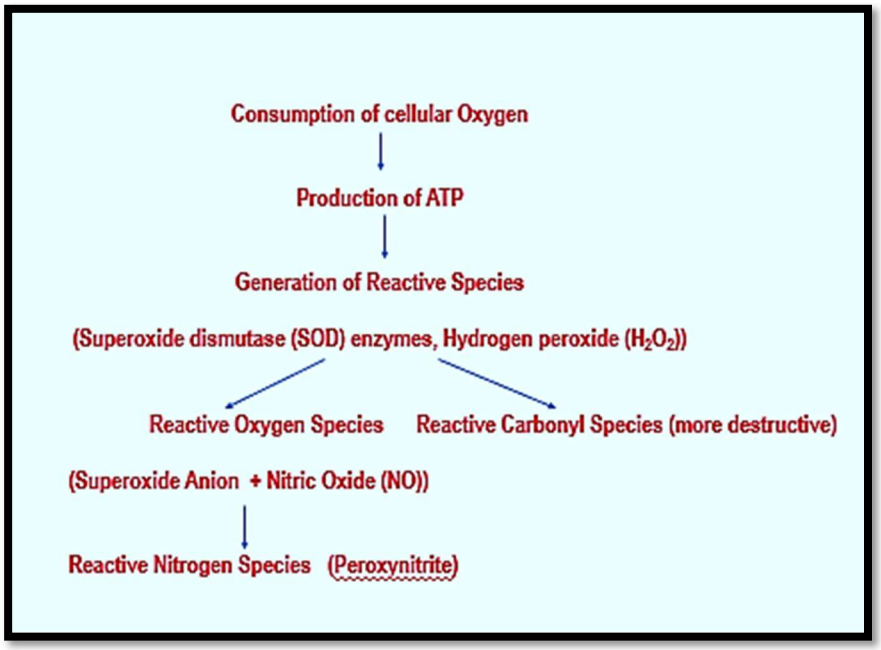

Figure 1: Generation of Reactive Species

In this scenario, animals have evolved several antioxidant defenses to control and mitigate the action of RS. Individuals may, therefore, be exposed to relevant physiological costs, mainly expressed in terms of oxidative damage and consumption of energy needed to keep the antioxidant defenses upregulated and to activate repair systems [17]. It is possible that the need to regulate the redox system exposes individuals to a number of trade-offs and, therefore, oxidative stress could have represented a relevant modulator of life-history strategies [18]. Animals show, however, large variation in antioxidant defenses, and it is, therefore, pivotal to review them to figure out the association among oxidative stress, life-history strategies, and response of natural populations to environmental stressors [19].

Cellular structural defence against oxidative damage

Cellular protection against oxidative damage includes RS elimination and repair/turnover systems. Recent evidence, however, support the notion of another line of defense based on the inherent susceptibility of macromolecules to oxidative damage [20]. This susceptibility, defined as the ease with which macromolecules suffer an oxidative injury, is intrinsically linked to the specific

structure or chemical composition of carbohydrates, lipids, nucleic acids, and proteins. Available evidence on the differential susceptibility to oxidative damage of biomolecules shows that in living systems [21]: It was proposed that glucose emerged as the most important carrier of energy from cell to cell in animal species[iii], because it is the slowest and stable reacting carbohydrate and, consequently, poorly susceptible to oxidation [22]. The lower cellular concentration of highly reactive glycolytic intermediates was, in fact, interpreted as an adaptation to suffer less oxidative stress [23]. This intracellular condition is particularly critical for birds, given their high blood glucose levels.

Shreds of evidence

Available evidence demonstrates that birds possess lower glucose cellular permeability and sensitivity to insulin signaling, mechanisms that probably lead to lower intracellular concentration of glycolytic intermediates [24]. So, it is proposed that the high blood glucose level showed by birds in comparison with mammals should be interpreted as a nonreactive and stable functional compartment ready to use exclusively in physiological conditions that require a high energetic demand, thus maintaining cellular integrity against molecular damage [25].

Highly unsaturated fatty acids (more than 2 double bonds) are on average the least abundant fatty acids in cell membranes and are less abundant in species that live longer [26]. Unsaturated fatty acids are the macromolecules most susceptible to oxidative damage in cells, and this sensitivity increases as a function of the number of double bonds they contain [27]. This means that saturated and monounsaturated fatty acyl chains are essentially resistant to oxidation, whereas polyunsaturated are easily damaged [28].

Another antioxidant adaptive structural system evolved to prevent the oxidation of polyunsaturated fatty acids is linked to the plasmalogens. Substantial evidence accumulated in the last decade indicates that plasmalogens, a class of ethanolamine (and choline) phospholipids, could represent a major lipid-soluble antioxidant component based on the ability of the plasmalogens to scavenge several RS [29]. The structural peculiarity of plasmalogens lies in the enol ether double bond present within the hydrocarbon chain linked to the C-1 atom of the glycerol backbone of phospholipids [30].

Guanine is the least abundant nucleotide in mitochondrial DNA, with the lowest oxidation potential, and is thus generally most easily oxidized. Methionine is the amino acid that on average has the smallest percentage presence in cellular proteins and most susceptible to oxidation by free radicals [31]. Consequently, the lower the protein Met content, the higher should be the protein resistance to oxidative damage. In accordance with this, the amino acid compositional analysis of cellular proteins from different tissues (e.g., skeletal muscle, heart, and brain) in birds and mammals revealed that Met is present in the smallest percentage in cellular proteins [32]. Selection has, therefore, possibly disfavoured the usage of Met in animal tissues, given its higher proneness to be oxidized compared with other amino acids [33]. Although available evidence suggests that

aerobic life has evolved by reducing the relative abundance of those structural components that are highly susceptible to oxidative damage there still exists great variation among species in body composition, whose causes and meaning are still not well understood, despite that it seems to be a relevant determinant of life span [34].

The link between body composition and susceptibility to oxidative stress can be ecologically and evolutionary relevant. For example, an environmental factor that can contribute to explain some body composition variation is the diet quality [35]. Diet not only is a source of molecular antioxidants, but it is also a source of nutrients, such as fatty acids and amino acids [36], which can expose the organism to different oxidative stress threats because of their different molecular susceptibility to be oxidized. Animals can, however, actively make their cell composition through an active regulation of metabolism of nutrients [37]. For example, the lower proportion of n-3 to n-6 polyunsaturated fatty acids in marine bird cardiac membranes compared with their diet suggests a highly selective nature of fatty acid incorporation into membrane lipids [38]. Such discrimination of dietary fats is especially important because n-3 polyunsaturated fatty acids are less resistant to oxidative damage than their n-6 counterparts [39]. Such regulation abilities of cell membrane composition may also be important when the female is depositing nutrients into the egg or milk [40]. Females could influence the future susceptibility to oxidative stress of their offspring not only through the investment of antioxidants, but also through other nutrients that do not have any antioxidant propertie [41].

Arachidonic acid makes up 8%–19% (wt/wt) of the phospholipid fatty acids in Morus bassanus, Catharacta skua, Pelecanus erythrorhynchos, and Phalacrocorax auratus egg yolks [42]. The gannet and skua, which eat marine fish with low arachidonic acid content, have a more difficult time explaining their yolk fatty acid profile than the pelican and cormorant, which eat freshwater fish with high arachidonic acid content [43]. These findings suggest that females may actively control fatty acid deposition in the egg and that pelicans and cormorants may have invested more arachidonic acid in the egg than its bioavailability to reduce oxidative stress in embryo tissues [44]. Recent reptile and bird research suggest that blood oxidant balance may be inherited. However, the data were collected to assess heritability using additive genetic effects and maternal/paternal effects (i.e., indirect genetic or environmental effects on the offspring's phenotype caused by the mother or father). It is difficult to determine how much variance in offspring oxidative balance was related to female food allocation tactics or heredity [45]. This appears to be a promising field of research for understanding transgenerational effects, long-term consequences of early life environments on adult phenotype, and passive and active nutrition transfer from female to offspring [46]. Thus, natural selection, possibly through directional selection, reduced the relative abundance of structural components that are highly susceptible to oxidative damage, giving macromolecules a lower susceptibility to oxidative stress and a higher structural stability [47].

Oxidative balance controls

It can be grouped in “internal” and “external”[iv].

Internal mechanisms

In animal cells, the major sites of physiological ROS generation are the complex I and III of the mitochondrial electron transport chain, which contain several redox centres (flavins, iron-sulfur clust and ubi-semiquinone) capable of transferring one electron to oxygen to form superoxide anion [48]. It is, therefore, proposed that important internal mechanisms are those inherently linked with the structure and function of the mitochondrial free radical generators that include modulation of the absolute content of the mitochondrial electron transport chain (very complexes I and III, reduction state of complex I, modulation of the free radical production by uncoupling proteins, potential post-translational modifications [49].

A first internal mechanism operates through the decrease in the concentration of the respiratory complexes responsible for ROS generation. For example, birds have a lower content of complex I than mammals, as well as a lower degree of ROS production [50]. Therefore, regulation of the expression of the mitochondrial complexes (and especially complex I) could be part of an adaptive mechanism to adjust ROS production [51].

A second internal mechanism that controls free radical generation is the regulation of the degree of electronic reduction of these generators: the higher their degree of reduction [52], the higher will be their rate of ROS production. It is known that the rate of mitochondrial ROS generation strongly increases with a sigmoidal kinetics when the ratio between the reduced (NADH), an oxidized (NAD) form of nicotinamide adenine nucleotide, is increased, because this dramatically increases the degree of reduction of the complex I ROS generator [53].

A third internal mechanism is characterized by regulation of uncoupling proteins (UCPs). During oxidation of substrates, the complexes of the mitochondrial electron transport chain reduce oxygen to water and pump protons into the intermembrane space [54], forming a proton-motive force (p). However, some electrons in the reduced complexes also react with oxygen to produce superoxide [55]. Superoxide can peroxidize membrane phospholipids, forming hydroxynonenal, which induces proton transport through the UCPs and the adenine nucleotide translocase. The mild uncoupling caused by proton transport slightly stimulates electron transport, causing the complexes to become more oxidized and lowering the local concentration of oxygen; both of these effects decrease superoxide production [56]. Thus, the induction of proton leak by hydroxynonenal limits mitochondrial ROS production as a feedback response to the overproduction of superoxide by the respiratory chain. So, a possible antioxidant physiological function for UCPs has been proposed. In this model, UCPs respond to the overproduction of matrix superoxide by catalyzing mild uncoupling, [57] which lowers protonmotive force and decreases superoxide production by the electron transport chain (Fig. 1). This negative feedback loop protects cells from RS-induced damage and might represent the ancestral function of all UCPs. Finally, post-translational modifications (i.e., chemical modifications of a protein after its translation), such as acetylation,

S-nitrosation, and glutathionylation, are another important mechanism regulating RS production [58].

Finally, recent studies seem to indicate that acetylation can be used as post-translational modification able to regulate the activity of the mitochondrial electron transport chain complexes by modifying specific subunits [59]. In the light of these mechanisms, mitochondrial activity and structure could be under strong selection. For example, mitochondria, being the energy makers of organisms, could expose the individual to energetic constraints because any damage could reduce their efficiency in ATP synthesis [60]. The daily metabolizable energy intake of an animal is potentially limited by either the available feeding time, food availability [61], or its capacity to process energy. Oxidative mitochondrial damage could, therefore, increase the energy demands of the individual, particularly during demanding phases of the year, such as reproduction or migration. Moreover, organisms can actively respond to environmental stressors [62], not only through upregulation or downregulation of specific mitochondrial proteins but also through changes in mitochondria density, as shown in compensatory responses to changes in physical activity in birds or to cold acclimation in marine invertebrates or fish [63]

External mechanisms

The characteristics of the environment (e.g., local oxygen concentration and membrane phospholipid composition [64], where complexes are embedded) surrounding the mitochondrial electron transport chain complexes can be mentioned as external factors able to modify the free radical generation and, consequently, they can be considered as potential antioxidant mechanisms [65]

The first mechanism operates through the regulation of the mitochondrial partial pressure of O_2. Normally, animal cells are exposed to quite low oxygen concentrations, likely to minimize oxygen toxicity, which is interpreted as an antioxidant defence. When the level of oxygen decreases dramatically and the animal enters a prolonged state of hypoxia, hypoxia-inducible transcription factors (HIFs), especially HIF-1 [66], promote expression of genes encoding proteins that help cells to respond to a hypoxic or anoxic status. There exists, however, high variation in how species can tolerate hypoxia. For example, low oxygen flux fauna (e.g., marine organisms) can tolerate prolonged hypoxia without any detrimental consequence for the organism. Also, in high oxygen flux fauna, we can observe special adaptations to hypoxia, such as those described in seals [67]. Seals cope with regular exposure to diving hypoxia by storing oxygen in blood and skeletal muscles (both very rich in hemoglobin and myoglobin, respectively) and by limiting the distribution of blood-borne oxygen to all but the most hypoxia-vulnerable tissues (brain, heart), through cardiovascular adjustments [68].

A second mechanism is dependent on the cardiolipin content of mitochondria. Cardiolipin, a phospholipid located almost exclusively within the inner mitochondrial membrane, is particularly rich in unsaturated fatty acids, but with a low degree of unsaturation [69]. This

phospholipid plays an important role in mitochondrial bioenergetics by influencing the activity of key mitochondrial inner membrane proteins [70], including several anion carriers and electron transport complexes I, III, and IV. Mitochondrial cardiolipin molecules are potential targets of ROS attack because of their content of unsaturated fatty acids and because of their location in the inner mitochondrial membrane near the site of ROS production. In this regard [71], it has been recently demonstrated that mitochondria-mediated ROS generation affects the activity of complex I, as well as complexes III and IV, via peroxidation of cardiolipin following ROS-mediated damage to its fatty acid constituent [72]

Table 1: Enzymatic and nonenzymatic antioxidants

Enzymatic Antioxidant	Protective action through	Non-Enzymatic antioxidant	Protective action through
Superoxide dismutase (SOD)	Dismutation of superoxide by SOD generates the less reactive H_2O_2	**Glutathione**	Thiol group of its cysteine residue
Glutathione peroxidase	Work coordinately to eliminate the hydrogen peroxide	**Thioredoxin**	Redox-active disulfide/dithiol, Scavenging ROS
Catalase	Catalase decomposes H_2O_2 at high rates	**Vitamins (C, E), Polyphenols and Carotenoids**	Scavenging ROS

Repairing and detoxifying antioxidant systems

Phospholipase A2 is a key enzyme for removing acyl chains from phospholipids, while acyltransferase and transacylase enzymes are responsible for the re-acylation of phospholipids [v]. There is, however, a decrease in the unsaturated fatty acid content of cellular triacylglycerols. This mechanism could have evolved because it is less energetically demanding than activation of repair systems, hence possibly less constraining for life-history decisions [73]. As mentioned above, RCS are compounds produced under oxidative stress conditions. These compounds are detoxified in multiple ways, including conjugation to GSH, oxidation by aldehyde dehydrogenases, or reduction by aldo-ketoreductases [74]. Once GSH is depleted, cells exhibit an intracellular change in redox status and propagate an oxidative stress response following their production. Reaction of RCS with GSH can proceed in one of two ways: by nonenzymatic conjugation or through GSH transferase-mediated conjugation to form Michael adducts. Glutathione-S-transferases (GSTs) belong to a supergene family of multifunctional enzymes [75] , which are particularly involved in the detoxification of highly reactive intermediate aldehydes. Interestingly, protection against oxidative stress is the major driver of positive selection in mammalian GSTs, explaining the overall

expansion pattern of this enzyme's family. Finally, detoxifying mechanisms to protect tissues from RCS damage also include the cytosolic GSH-dependent glyoxalases [76] thiol- and histidine-containing dipeptides—presumably acting as trapping agents—and ascorbic acid.

Antioxidants and Animal Maximum Life Span

Long-lived animal species maintain themselves by decreasing RS production and possessing macromolecules less susceptible to oxidative degradation. Longer animal lifespans reduce oxidative stress-prone structural component composition [77]. The percentage of adenine (A), cytosine (C), guanine (G), and thymine (T) in mtDNA may affect its damage susceptibility. Short-lived animals had higher A and T abundances and lower C abundances than long-lived species, but G is nearly uniformly low in all species [78], according to a study of 94 animal species' mtDNA sequences. This may indicate substantial directional selection of G abundance. Mechanisms suggest that the asymmetric replication of the mtDNA molecule increases G to A transition mutations on the light strand, depriving it of G nucleotides [79]. Additional findings showed that this nucleotide pattern impacts a key DNA sequence feature, the free energy (related to the binding energy between the two DNA strands). More negative free energy reduces the likelihood that thermal fluctuations will spontaneously split the two strands, making mtDNA more structurally stable and damage-resistant [80]. Comparative findings demonstrate a high correlation between mtDNA free energy and maximal life span, supporting these mechanisms. This shows that long-lived species' mitochondrial mutation rate has dropped due to natural selection. Finally, a recent phylogenomic study that identified the genetic targets of natural selection for increased life span in mammals found that genes involved in DNA replication/repair or antioxidation have played no detectable role in the evolution of longevity in mammals [81], reinforcing the relevance of the mitochondrial fr connection. Thus, short-lived mammals have more methionyl residues in their mtDNA-encoded proteins.

High-life span animals show reduced membrane fatty acid desaturation due to PUFA redistribution without changes in total (%) PUFA content, average chain length, or phospholipid distribution. The first double bond increases membrane fluidity acutely [82], while the second double bond decreases it due to "kinks" in the fatty acid molecule. The third and subsequent double bonds cause further fluidity variations [83]. Thus, long-lived animals' sensitivity to lipid peroxidation is greatly reduced by replacing fatty acids with four or six double bonds with those with two or three. The optimised feature is the cellular membrane. All published studies on mitochondrial free radical generation and maximum life span have found that long-lived animal species produce less mitochondrial RS than short-lived species, regardless of their mass-adjusted O2 consumption. Due to reduced mitochondrial free radical generation of long-lived species [84], endogenous cellular antioxidant mechanisms adjust. Longevity is associated with reduced tissue levels of antioxidant enzymes and low-molecular-weight endogenous antioxidants. In particular, the interaction between environmental quality and species life cycle phase (e.g., reproduction, moult, migration, hibernation) may affect antioxidant needs and oxidative challenges [85]. Future studies should examine environmental quality as a modulator of oxidative stress's impacts on life-history

strategies and fitness. In conclusion [86], natural selection reduces structural components that are sensitive to oxidative damage, making macromolecules more stable [87].

Conclusions

Researchers believe RS exposure reduces the frequency of structural components susceptible to oxidative breakdown. Consequently, aerobic organisms have several structural and molecular antioxidant defences. Energy costs from antioxidant responses including enzyme activity and repair and the wide variety of defences can alter lifelong trade-offs. To achieve these compromises, self-maintenance, reproduction, antioxidant, and immunological responses may need careful regulation. Integrating antioxidant processes into ecological-evolutionary models helps explain generational impacts. Integration can help or hinder progeny adaptation to current and future environments. This is crucial when unanticipated environmental changes induce a gap between development and adulthood. This is feasible because several nutrients and antioxidant molecules change mitochondrial activity, body composition, and ROS resistance. An unbalanced mother's oxidant levels may harm her offspring. The effects of oxidative stress on life-history trait trade-offs, phenotypic development, and natural population responses to environmental changes are unclear due to the complexity and variety of redox physiology mechanisms. It's vital not to apply processes from one species to another, especially when the taxa are not evolutionarily related and the redox system's activities are unknown. We conclude that oxidative damage, antioxidant status, and gene expression measures must be interpreted biologically. A more extensive mechanical explanation is sometimes preferred. Thus, more research is needed to determine if redox state trait variants are inherited, impacted by natural selection, and functional.

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