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Mini Review

Oxidative and Endoplasmic Reticulum Stress in Normal Cellular Physiology

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Abstract

Oxidative stress and Endoplasmic Reticulum (ER) stress are widely framed as pathological drivers; however, both represent core regulatory layers of normal cell physiology when engaged transiently and within a controlled range. Physiological Reactive Oxygen Species (ROS) are generated continuously and function as spatially restricted second messengers that tune kinase/phosphatase activity, transcriptional programs, organelle dynamics, and metabolic fluxes. In parallel, basal and inducible Unfolded Protein Response (UPR) signaling calibrates ER proteostasis, lipid handling, and calcium homeostasis, enabling cells to match secretory and metabolic demand without loss of viability. Importantly, ER proteostasis is intrinsically redox-linked because oxidative protein folding and disulfide bond formation shape luminal redox tone and can generate ROS. The reciprocal coupling of redox signaling, UPR/Integrated Stress Response (ISR) modules, and mitochondria–ER communication allows healthy cells to convert fluctuating demand (e.g., nutrient shifts, exercise-like energetic load, developmental programs) into adaptive homeostatic responses. This review synthesizes mechanistic evidence supporting oxidative and ER stress as physiological signaling systems, highlights key crosstalk nodes (PERK–ISR, IRE1 signaling, ER oxidoreductases, Nrf2-dependent redox buffering), and outlines practical considerations for interpreting "stress markers" in non-diseased models.

Keywords: ROS signaling, Redox homeostasis, Endoplasmic reticulum, Unfolded protein response, Integrated stress response, ER redox, Proteostasis, Calcium homeostasis, Mitochondria–ER crosstalk

Introduction

Cellular life proceeds under constant fluctuation rather than static equilibrium. Even in healthy tissues, oxygen tension varies across microvascular gradients, protein synthesis rates oscillate with circadian and nutrient cues, and energy demand changes rapidly in response to signaling and workload. Under these conditions, "stress responses" are not exceptional events; they are embedded control circuits that maintain functional stability. Two such circuits—oxidative (redox) signaling and ER stress signaling—are often conflated with damage. Yet modern evidence supports a more precise view: physiological ROS and adaptive ER stress/UPR activity are required for normal homeostasis, while chronic intensity or failed resolution shifts the same pathways toward dysfunction and injury [1-4]. Understanding where the adaptive regime ends and maladaptation begins is essential for interpreting experiments and for translating stress biology into preventive and therapeutic concepts.

A. Physiological ROS: from Byproduct to Compartmentalized Signal

ROS arise from multiple sources under normal conditions, including mitochondrial electron transport, NADPH oxidases, peroxisomal enzymes, and ER oxidative protein folding [2,5]. Crucially, cells do not aim to abolish ROS; they aim to shape its

amplitude, timing, and localization. Hydrogen peroxide (H_2O_2) is particularly suited for signaling because it can diffuse short distances and reversibly oxidize reactive cysteine residues on target proteins, modulating enzyme activity and protein–protein interactions [5,6]. Physiological ROS supports normal processes such as growth-factor signaling, cytoskeletal remodeling, differentiation, and adaptive metabolic regulation [6,7]. Reviews focused on mammalian systems emphasize that signaling specificity emerges from (i) microdomain generation, (ii) antioxidant buffering "gates," and (iii) proximity of ROS sources to redox-sensitive effectors [6,7]. This framework explains why identical bulk ROS measurements can reflect very different biological states depending on subcellular origin and kinetics.

B. Redox Buffering and the Logic of "Oxidative Eustress"

A modern conceptual distinction separates oxidative eustress (Regulated, Signaling-Compatible ROS) from oxidative distress (damage-promoting imbalance) [5]. Cells maintain this boundary through enzymatic and non-enzymatic antioxidant systems (e.g., superoxide dismutases, catalase, peroxidases, glutathione/thioredoxin networks) and through transcriptional programs that adjust antioxidant capacity to demand [5,8]. The Nrf2 pathway is central to this adaptation. Nrf2 controls basal and inducible expression of antioxidant and detoxification genes and thereby stabilizes redox homeostasis across physiological perturbations [8]. While much Nrf2 literature addresses disease, its mechanistic core is directly relevant to normal physiology because it explains how cells maintain a permissive redox environment for signaling without drifting into distress [8].

C. ER Proteostasis as a Physiological Stress Sensor

The ER supports synthesis, folding, and maturation of secreted and membrane proteins. Even in healthy cells, a fraction of nascent chains misfolds, requiring continuous quality control. When folding demand transiently exceeds folding capacity-during differentiation, hormonal stimulation, immune activation, or metabolic transitions-cells activate UPR signaling to restore balance [3,4]. UPR signaling is initiated by IRE1, PERK, and ATF6. In adaptive modes, the UPR reduces translational load, expands chaperone capacity, and promotes ER-Associated degradation (ERAD), restoring proteostasis without triggering apoptosis [3,4]. Importantly, recent physiological perspectives emphasize that UPR components can exhibit baseline activity consistent with a homeostatic "set-point" role rather than a purely emergency function [4]. A 2024 synthesis explicitly frames UPR activity as part of physiological regulation across tissues, emphasizing resolution and plasticity rather than pathology [4].

D. ER Redox Chemistry: Oxidative Folding Links ER Stress to ROS

Oxidative protein folding in the ER involves formation and isomerization of disulfide bonds, largely mediated by Protein Disulfide Isomerases (PDIs) and ER oxidoreductases (e.g., ERO1). These reactions inherently couple proteostasis to redox flux and can generate ROS as electrons are transferred to oxygen [2,9,10]. Thus, increased secretory demand can raise local oxidative pressure within the ER lumen, and ER redox tone becomes a functional parameter of protein quality control rather than a mere damage signal. Recent reviews highlight the ER "redoxome" as a dynamic network controlling disulfide kinetics, luminal redox state, and signaling outputs beyond folding itself [10]. Complementary work connects ER oxidoreductase activity (including ERO1–PDI interactions) to redox balance and stress sensitivity, reinforcing the idea that "ER stress" and "oxidative stress" are often two faces of a single adaptive system [9,11].

E. Bidirectional Crosstalk Between Oxidative Stress and UPR

Oxidative signaling can modulate UPR sensors and ER calcium handling, while UPR activation can reprogram redox buffering, metabolism, and mitochondrial function—forming a tightly coupled loop [2,3,11]. A 2023 review focused on ER–oxidative stress interactions summarize how ER function, ROS, and UPR signaling influence each other, including feedback loops that determine whether cells return to homeostasis or transition toward maladaptive programs [2]. At the systems level, the PERK arm of the UPR intersects with the Integrated Stress Response (ISR), a broader translational control network that responds to diverse physiological perturbations (nutrient limitation, proteostasis strain, redox shifts) by regulating eIF2α phosphorylation and selective translation [12,13]. These connections help explain why modest ER stress or redox shifts can sometimes enhance resilience (a hormetic effect), whereas prolonged activation can impair function.

F. Mitochondria–ER Communication as an Adaptive Hub

Mitochondria and ER communicate via contact sites that coordinate calcium transfer, lipid exchange, and bioenergetic alignment. Because mitochondria are major ROS sources and the ER is a major folding/calcium organelle, mitochondria–ER crosstalk provides an anatomical basis for integrating redox tone with proteostasis and energetic demand [2,3]. Reviews of redox regulation emphasize that redox signaling affects genome stability, repair pathways, and broader cellular integrity—again underscoring that redox is a pervasive regulatory layer, not merely a damage marker [14].

G. Practical Implications for Experimental Physiology

i. Avoid Equating "Stress Markers" with Pathology: Markers such as BiP/GRP78, XBP1 splicing, ATF4 induction, or modest increases in ROS-sensitive dyes can represent adaptive engagement rather than injury, especially when accompanied by preserved viability and restored proteostasis [3,4].

ii. Time-Course Matters More than Single Timepoints: Physiological stress signaling is often pulsatile. Distinguishing

adaptive from maladaptive states requires kinetics: rapid induction plus resolution differs fundamentally from sustained activation [2-4].

iii. Compartmentalization is Essential: Bulk ROS measures can miss microdomain specificity. Interpreting "oxidative stress" without source localization (mitochondrial vs NADPH oxidase vs ER folding) risks overgeneralization [5-7,11].

Conclusion

Oxidative and ER stress are not inherently pathological; they are physiological control systems that preserve homeostasis under fluctuating demand. Physiological ROS orchestrate signaling and metabolic adaptation, while UPR/ISR modules maintain proteostasis, lipid balance, and calcium homeostasis. Because oxidative protein folding intrinsically couples ER function to redox flux, ER stress and oxidative stress frequently co-emerge as integrated signals. The key determinant of outcome is not activation per se, but magnitude, duration, compartmentalization, and resolution. Positioning these pathways within normal physiology improves experimental interpretation and clarifies how resilience is maintained—and how maladaptation may arise when adaptive limits are exceeded.

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Conflict of Interest

None.

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