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Redox-Immune Feedback Loops: Central Mechanisms Linking Autoimmunity, Metabolic Disease, and Organ Damage

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ABSTRACT

Redox–immune feedback loops represent fundamental physiological mechanisms by which cellular oxidation–reduction (redox) processes and immune signaling interact bidirectionally to regulate homeostasis and response to stress. When finely balanced, these pathways promote effective host defense and metabolic stability. However, chronic disruptions in redox signaling and immune regulation contribute to the pathogenesis of autoimmune disorders, metabolic diseases such as diabetes and obesity, and progressive organ damage. Reactive oxygen species (ROS), reactive nitrogen species (RNS), antioxidant defenses, and immune cell metabolic programs act as central nodes in these feedback loops. ROS modulate immune activation, cytokine production, and antigen presentation, while immune mediators influence redox enzyme expression and mitochondrial function. Persistent redox imbalance drives inflammatory amplification, cellular dysfunction, and tissue injury, creating self-reinforcing loops that link immune dysregulation with metabolic derangements. This review synthesizes current understanding of redox–immune interactions, highlights mechanistic insights into how these loops contribute to autoimmunity and metabolic pathology, and discusses their roles in organ damage across tissues. We also examine emerging therapeutic and biomarker strategies that target redox–immune coupling to ameliorate disease. Understanding these integrated mechanisms provides a unifying framework that connects oxidative stress, immune dysfunction, and metabolic dysregulation in chronic disease.

Keywords: redox signaling; immune regulation; reactive oxygen species; autoimmunity; metabolic disease

INTRODUCTION

The interplay between redox biology and immune function has emerged as a central theme in the pathogenesis of many chronic diseases[1]. Redox processes refer to the cellular generation and detoxification of reactive species, including superoxide, hydrogen peroxide, and nitric oxide, which influence signaling pathways, gene expression, and cellular metabolism[2]. Immune cells, particularly innate cells such as macrophages and neutrophils, actively produce reactive species as part of host defense. At the same time, redox signals influence immune activation, resolution, and tolerance[3]. The concept of redox–immune feedback loops refers to dynamic interactions whereby redox states influence immune behavior and, conversely, immune activity reshapes redox balance[4]. In acute responses, transient increases in reactive species promote pathogen clearance and signal for repair. However, when redox regulation is chronically disturbed—due to genetic predispositions, metabolic stress, or environmental factors—immune responses become dysregulated[5]. Sustained oxidative stress fosters inflammatory circuits and autoantigen exposure, while immune mediators drive further mitochondrial dysfunction and redox imbalance[6].

Metabolic disease states such as obesity and diabetes further exacerbate this cycle through nutrient excess and mitochondrial overload. These interconnected processes are increasingly recognized as central to the development of autoimmune conditions, metabolic dysfunction, and cumulative organ damage[7]. This review explores the molecular and cellular foundations of redox–immune feedback, their contributions to disease pathogenesis, and translational implications for therapy and biomarker discovery.

2. Fundamental Concepts in Redox Biology and Immune Signaling

Redox biology encompasses the generation, detoxification, and signaling functions of reactive species[8]. Mitochondria are key sources of reactive oxygen species (ROS) during oxidative phosphorylation, while specialized enzymes such as NADPH oxidases produce ROS during immune activation. Reactive nitrogen species (RNS), including nitric oxide, modulate vasodilation and immune signaling[9]. Homeostatic redox balance is maintained by antioxidant systems including superoxide dismutases, catalase, glutathione peroxidase, and thioredoxin pathways. These systems buffer reactive species and permit redox signaling without accumulation of cellular damage[10]. Redox signals influence transcription factors such as nuclear factor-kappa B (NF-κB), activator protein 1 (AP-1), and hypoxia-inducible factors (HIFs), linking oxidative cues to immune gene expression[11]. Immune cells engage metabolic programs that determine functional phenotypes. Pro-inflammatory cells often utilize glycolytic metabolism, while regulatory or anti-inflammatory subsets rely more on mitochondrial respiration and fatty acid oxidation[12]. Redox states influence these metabolic programs: oxidative stress can shift immune cells toward inflammatory phenotypes, while antioxidant environments support resolution and tolerance. ROS also modify proteins through reversible oxidation of cysteine residues, altering function of signaling molecules, kinases, and receptors involved in immune activation[13]. Similarly, redox modifications of lipids and nucleic acids contribute to the generation of neoantigens that can break self-tolerance in autoimmunity.

3. Mechanisms of Redox–Immune Feedback Loops

Redox–immune feedback arises through multiple intersecting mechanisms:

3.1 ROS as Immune Modulators

Reactive species produced by immune cells during pathogen challenge contribute to microbial killing[14]. However, ROS act beyond microbicidal functions; they modulate cytokine expression, inflammasome activation, and antigen presentation[15]. For example, moderate ROS levels enhance NF-κB activation and pro-inflammatory cytokine transcription, whereas excessive ROS can trigger cell death pathways such as apoptosis or pyroptosis.

3.2 Immune Regulation of Redox Enzymes

Cytokines and immune signals influence the expression of redox enzymes[16]. Interferons and tumor necrosis factor-α (TNF-α) upregulate inducible nitric oxide synthase and NADPH oxidase pathways in macrophages, while anti-inflammatory signals like interleukin-10 enhance antioxidant defenses[17]. These adjustments influence cellular susceptibility to oxidative damage and immune responsiveness.

3.3 Metabolic Integration

Immune cell metabolism is tightly coupled to redox balance. Glycolysis and mitochondrial respiration generate distinct redox signatures that favor specific immune phenotypes[18]. Shifts in nutrient availability or metabolic stress can therefore reciprocally influence redox and immune outputs[19]. For instance, succinate accumulation in activated macrophages stabilizes HIF-1α and boosts inflammatory cytokine production.

3.4 Redox-Driven Neoantigens and Autoimmunity

Persistent oxidative damage to proteins and DNA can generate modified self-molecules recognized as foreign by adaptive immunity[20]. Oxidized lipids and citrullinated proteins are implicated in autoimmune diseases such as rheumatoid arthritis. These neoantigens perpetuate immune activation and feed back to further oxidative stress[21]. These interconnected mechanisms establish loops in which redox signals influence immune activity, and immune mediators reshape redox balance, creating potential for both protective responses and pathological amplification.

4. Redox–Immune Feedback in Autoimmune Diseases

Autoimmune disorders arise when immune tolerance to self-antigens breaks down. Redox–immune interactions contribute to this process through several pathways:

4.1 Oxidative Stress and Antigen Modification

Oxidative modifications generate altered self-epitopes that can be more immunogenic than their native counterparts[22]. For example, oxidative fragmentation of DNA and proteins in tissues such as joints or pancreas

yields neoantigens recognized by autoreactive T cells. These modified molecules also activate innate immune receptors, fueling inflammatory circuits.

4.2 Dysregulated Immune Redox Programs

In autoimmune diseases, immune cells often display intrinsic redox imbalances[23]. Elevated ROS in T cells can enhance effector functions and reduce regulatory T cell stability. Similarly, macrophages in autoimmune tissues express high levels of NADPH oxidase and produce sustained ROS that amplify local inflammation.

4.3 Environmental and Genetic Interactions

Environmental factors like smoking and pollution increase systemic oxidative stress, which may interact with genetic predispositions to lower thresholds for autoimmunity[24]. For instance, polymorphisms in antioxidant enzyme genes correlate with disease severity in multiple autoimmune conditions. Collectively, these redox–immune feedback processes not only initiate but also sustain chronic inflammation and tissue destruction characteristic of autoimmunity[25].

5. Redox–Immune Coupling in Metabolic Disease

Metabolic disorders, including obesity and type 2 diabetes, are characterized by chronic low-grade inflammation and oxidative stress[26]. Adipose tissue expansion and nutrient excess trigger redox–immune loops that link metabolism with immune dysregulation.

5.1 Adipose-Derived ROS and Cytokines

Metabolically stressed adipocytes produce increased ROS due to mitochondrial overload and impaired antioxidant capacity[27]. These reactive species enhance secretion of pro-inflammatory adipokines such as TNF-α and interleukin-6, which recruit immune cells into adipose tissue. Infiltrating macrophages further generate ROS, establishing a feed-forward inflammatory loop.

5.2 Insulin Resistance and Immune Activation

Oxidative stress impairs insulin signaling in muscle and liver tissues by activating stress kinases and inducing serine phosphorylation of insulin receptors[28]. Concurrently, immune cells in metabolic organs adopt pro-inflammatory phenotypes that secrete cytokines exacerbating insulin resistance. These processes feed back to increase nutrient overflow and mitochondrial stress.

5.3 Metabolite Signaling

Metabolites such as free fatty acids and ceramides act as damage-associated molecular patterns (DAMPs) that activate innate immune receptors like toll-like receptors[29]. This metabolic–immune engagement intensifies ROS production and reinforces systemic inflammation. Through these mechanisms, redox–immune feedback loops link metabolic stress with chronic inflammation, contributing to the pathogenesis and complications of metabolic disease[30].

6. Organ Damage as an Outcome of Persistent Redox–Immune Dysregulation

When redox–immune feedback loops remain chronically activated, they lead to cumulative organ injury[31]. Persistent oxidative stress and inflammation compromise cellular integrity, promote fibrotic remodeling, and impair organ function.

6.1 Cardiovascular Damage

Endothelial cells exposed to oxidative stress lose nitric oxide bioavailability, leading to vascular dysfunction[32]. Immune-mediated inflammation accelerates atherosclerotic plaque formation, with macrophage ROS production contributing to plaque instability.

6.2 Renal Injury

Kidney tissues exposed to high ROS levels from hemodynamic stress and immune cell infiltration undergo glomerulosclerosis and tubulointerstitial fibrosis[33]. Cytokine-mediated induction of pro-oxidant enzymes in renal cells ensures perpetuation of injury.

6.3 Neuroinflammation

Microglia, the resident macrophages of the central nervous system, generate ROS and cytokines in response to stress, contributing to neurodegenerative processes[34]. Redox–immune feedback amplifies protein aggregation and neuronal damage. Across tissues, sustained loops of oxidative stress and immune activation drive progressive damage, underscoring the need to understand and disrupt these cycles.

7. Therapeutic and Biomarker Perspectives

Targeting redox–immune feedback offers promising avenues for intervention. Therapies may focus on antioxidant enhancement, modulation of immune metabolism, or inhibition of specific signaling pathways that link oxidative stress with inflammation[35].

7.1 Modulating Redox Balance

Pharmacologic antioxidants such as N-acetylcysteine and agents that upregulate endogenous antioxidant responses (e.g., Nrf2 activators) aim to buffer excessive ROS and restore homeostasis[36].

7.2 Immune Metabolic Targets

Drugs that alter immune cell metabolism, such as inhibitors of glycolysis in pro-inflammatory cells or activators of fatty acid oxidation in regulatory cells, can shift immune phenotypes toward resolution[37].

7.3 Biomarker Discovery

Circulating indicators of redox state (e.g., oxidized lipids, glutathione ratios) and immune activation (e.g., cytokine panels, immune metabolic profiles) hold potential as biomarkers to monitor disease activity and therapeutic responses[38]. By aligning interventions with the mechanisms of redox–immune feedback, it may be possible to mitigate chronic inflammation and organ damage in diverse diseases.

CONCLUSION

Redox–immune feedback loops comprise a central mechanistic nexus that integrates oxidative biology with immune regulation and metabolism. When balanced, these interactions support host defense and metabolic resilience. When chronically perturbed, they drive autoimmune activation, metabolic dysfunction, and progressive organ damage. Unraveling the complexity of these loops not only deepens understanding of disease pathogenesis across systems but also reveals opportunities for novel therapeutic and biomarker strategies. Continued research into the molecular mediators of redox–immune coupling holds promise for transforming the management of chronic inflammatory and metabolic diseases.

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