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Redox Regulation of Innate and Adaptive Immune Responses in Health and Disease

Serunjogi Ruth

Department of Clinical Pharmacy Kampala International University Uganda
Email: ruth.serunjogi@studwc.kiu.ac.ug

ABSTRACT

Redox regulation plays a critical role in the modulation of immune responses, affecting both innate and adaptive immune functions. Reactive oxygen species (ROS) and reactive nitrogen species (RNS), generated as byproducts of cellular metabolism and immune responses, are key signaling molecules in immune cell activation, differentiation, and effector function. These molecules are tightly regulated to maintain immune homeostasis, but their dysregulation can contribute to the pathogenesis of a wide array of diseases, including autoimmune disorders, cancer, and infections. This review explores the mechanisms of redox regulation in immune cells, highlighting the role of ROS/RNS in the activation of pattern recognition receptors (PRRs), antigen presentation, T cell differentiation, and the modulation of inflammation. We also examine the dual role of redox molecules in both promoting immune defense and contributing to tissue damage, with a focus on how this balance impacts health and disease. Additionally, we discuss current therapeutic strategies targeting redox pathways for the treatment of immune-related diseases and the potential for future interventions.

Keywords: Redox regulation, Immune responses, Reactive oxygen species (ROS), Autoimmune diseases, Inflammation

INTRODUCTION

The immune system is a sophisticated network of cells, tissues, and signaling molecules that work in concert to defend the body against infectious agents while maintaining tolerance to self-antigens [1]. This delicate balance is achieved through the coordinated actions of the innate and adaptive immune responses. The innate immune system provides rapid, nonspecific defense through barriers, phagocytic cells, and inflammatory mediators, while the adaptive immune system offers highly specific, long-lasting protection via antigen-specific lymphocytes and immunological memory [2]. Both arms of immunity are under strict regulatory control to prevent excessive inflammation or autoimmunity. Over the past two decades, an increasing body of evidence has revealed that redox signaling—mediated by reactive oxygen species (ROS) and reactive nitrogen species (RNS)—is a central modulator of immune function. These reactive molecules are generated as natural byproducts of aerobic metabolism, particularly through mitochondrial oxidative phosphorylation, and are further produced in response to environmental stresses such as infection, inflammation, ultraviolet radiation, and exposure to pollutants. Immune cells themselves, especially neutrophils, macrophages, and dendritic cells, actively generate ROS and RNS during pathogen clearance through mechanisms like the respiratory burst [3].

Traditionally, ROS and RNS were viewed primarily as harmful agents, implicated in oxidative damage to proteins, lipids, and nucleic acids. This perspective framed oxidative stress as a pathological condition contributing to aging and the development of chronic diseases. However, research in immunology and cell biology has transformed this view. It is now understood that ROS and RNS are not merely byproducts of metabolism or markers of cellular injury—they are integral second messengers in signal transduction pathways that govern immune cell activation,

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differentiation, and survival. Redox signaling influences a variety of critical immune processes. In innate immunity, ROS can activate pattern recognition receptor (PRR)-dependent pathways, such as Toll-like receptor (TLR) signaling, to enhance cytokine production and microbial killing. In adaptive immunity, finely tuned ROS levels are essential for T cell receptor (TCR) signaling, B cell activation, and the regulation of immune tolerance. Importantly, both insufficient and excessive ROS production can be detrimental: low ROS levels may impair host defense, while excessive or prolonged ROS generation can drive chronic inflammation, tissue damage, and autoimmune reactions [4]. Maintaining redox homeostasis in immune cells involves a complex interplay between pro-oxidant systems, such as NADPH oxidases and nitric oxide synthases, and antioxidant defenses, including enzymatic systems like superoxide dismutases (SOD), catalase, and glutathione peroxidases, as well as non-enzymatic molecules like glutathione, vitamins C and E, and polyphenols. This balance determines whether ROS and RNS serve beneficial signaling roles or contribute to pathological oxidative stress. Given the dual nature of redox molecules in immunity, dysregulation of redox balance is now recognized as a major factor in the pathogenesis of a wide range of disorders, from chronic inflammatory diseases and neurodegeneration to cancer and metabolic syndrome [5]. Understanding how ROS and RNS modulate immune responses in both health and disease is therefore of great importance. This review explores mechanistic insights into the role of oxidative stress as a central mediator of chronic inflammation, examines its impact on both innate and adaptive immune functions, and discusses emerging therapeutic strategies aimed at restoring redox balance to mitigate disease progression [6].

Redox Regulation in Innate Immunity

Innate immunity is the first line of defense against pathogens, and its responses are rapid and nonspecific. It involves a variety of cell types, including neutrophils, macrophages, dendritic cells, and natural killer (NK) cells [7]. These cells use PRRs, such as toll-like receptors (TLRs), to detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), triggering an inflammatory response. Upon activation, immune cells generate ROS and RNS through the NADPH oxidase complex (NOX) and inducible nitric oxide synthase (iNOS), respectively. These molecules serve multiple functions: ROS can directly kill pathogens, activate downstream signaling pathways, and regulate the expression of cytokines and chemokines that promote inflammation. The balance of ROS production is tightly controlled, as excessive or chronic ROS production can lead to tissue damage and chronic inflammation, both of which contribute to autoimmune diseases and chronic infections [8].

For instance, neutrophils, which are abundant in early immune responses, generate ROS to kill ingested pathogens through a process known as the respiratory burst. Similarly, macrophages utilize ROS and RNS to enhance antigen presentation and promote T cell priming. However, prolonged activation of these pathways can result in tissue damage, as seen in conditions such as chronic obstructive pulmonary disease (COPD) and rheumatoid arthritis (RA), where excessive ROS production drives persistent inflammation and tissue remodeling [9].

Redox Regulation in Adaptive Immunity

Adaptive immunity involves the activation of T and B lymphocytes in response to specific antigens. The redox environment plays a critical role in the differentiation, activation, and effector function of both T and B cells. One of the key processes regulated by redox signaling in adaptive immunity is T cell receptor (TCR) signaling [10]. Upon TCR engagement, a cascade of intracellular signaling events is triggered, many of which are modulated by changes in redox status. For example, ROS can regulate protein tyrosine phosphatases (such as SHP-1), which control T cell activation thresholds. Additionally, redox modulation affects the activation of kinases like Lck and ZAP70, which are crucial for T cell signaling [11].

T helper (Th) cell differentiation is also influenced by redox changes. Th1, Th2, Th17, and regulatory T cells (Tregs) each have distinct redox profiles, which contribute to their differentiation and function. For example, Th17 cells, which play a central role in autoimmune diseases, are characterized by increased ROS production, which promotes the expression of pro-inflammatory cytokines such as IL-17. Conversely, Tregs, which suppress immune responses, tend to have lower levels of ROS, which helps maintain their suppressive function [12].

In B cells, redox signaling regulates the activation of B cell receptor (BCR) signaling pathways, antibody production, and the differentiation of plasma cells. Redox regulation also impacts the formation and function of germinal centers, where affinity maturation and class switching occur. Dysregulation of redox homeostasis in B cells can contribute to autoimmune diseases such as systemic lupus erythematosus (SLE), where the immune system targets self-antigens [13].

The Dual Role of Redox Signaling: Immunity and Disease

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) serve as critical mediators of immune defense, functioning as antimicrobial agents and signaling molecules that regulate immune cell activation and function. Their production during immune responses helps to eliminate pathogens and coordinate cellular communication.

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However, the role of redox signaling is complex and context-dependent; while essential for normal immunity, dysregulation of ROS and RNS can contribute to the pathogenesis of various diseases [14].

In autoimmune disorders, excessive or prolonged oxidative stress disrupts redox homeostasis and exacerbates tissue damage. Diseases such as multiple sclerosis, rheumatoid arthritis, and Crohn's disease exhibit heightened oxidative stress, which amplifies chronic inflammation and leads to progressive tissue injury [31]. The imbalance between pro-oxidant and antioxidant mechanisms in these conditions promotes an overactive immune response that mistakenly targets healthy cells, thereby sustaining the cycle of inflammation and damage [15]. This highlights how redox signaling is intricately involved not only in immune activation but also in immune-mediated pathology.

Conversely, in cancer, redox signaling often assumes a dual, paradoxical role. Tumor cells manipulate the oxidative environment to create an immunosuppressive tumor microenvironment that hinders effective anti-tumor immune responses [30]. Elevated levels of ROS within tumors can impair the function of cytotoxic immune cells and promote immune tolerance, allowing cancer cells to evade immune surveillance and continue unchecked growth. This redox-driven immune suppression has spurred interest in therapies that modulate oxidative stress to restore immune competence and improve cancer immunotherapy outcomes [16].

In infectious diseases, the generation of ROS and RNS is a frontline defense mechanism crucial for pathogen clearance. Immune cells produce these reactive species to kill invading microbes. However, many pathogens have evolved sophisticated mechanisms to resist or exploit oxidative stress, evading immune destruction and enhancing their virulence [17]. Understanding this dynamic interplay between redox signaling and microbial strategies remains a vibrant area of research, with implications for developing novel anti-infective therapies. Overall, the dual nature of redox signaling in immunity underscores the importance of finely tuned redox balance in health and disease, offering both challenges and opportunities for therapeutic intervention.

Therapeutic Implications

Given the pivotal role of redox regulation in controlling immune responses, therapeutic strategies that target oxidative stress pathways have gained significant interest in treating a wide array of immune-related disorders [18]. Oxidative stress, characterized by an imbalance between reactive oxygen and nitrogen species (ROS and RNS) and antioxidant defenses, contributes to the pathogenesis of chronic inflammatory and autoimmune diseases [19]. Consequently, antioxidant therapies are being developed to restore redox homeostasis and reduce persistent inflammation [20]. These therapies include the use of natural antioxidants, synthetic compounds, and enzyme modulators designed to neutralize excessive ROS/RNS or enhance endogenous antioxidant systems such as glutathione and superoxide dismutase [21].

Despite promising preclinical results, a major challenge in these therapeutic approaches is achieving selective modulation of redox signaling. This is critical because ROS and RNS also serve essential physiological functions, including pathogen clearance and regulation of immune cell signaling [22]. Over-suppression of oxidative processes may therefore impair host defense against infections or reduce immune surveillance against tumor cells [23]. To overcome this, ongoing research focuses on developing targeted delivery systems and selective inhibitors that modulate specific redox-sensitive pathways or enzymes without broadly dampening immune competence [24].

In the context of cancer immunotherapy, redox modulation offers novel opportunities to enhance treatment efficacy [25. The tumor microenvironment is often characterized by elevated oxidative stress, which can suppress effective anti-tumor immune responses [26]. By carefully altering the redox balance within tumors, researchers aim to restore immune cell function and improve the response to immune checkpoint inhibitors and adoptive cell therapies [27]. For example, pharmacological agents targeting redox enzymes such as NADPH oxidase (NOX) and inducible nitric oxide synthase (iNOS) are being investigated for their ability to reshape immune cell activity and reduce immunosuppressive factors [28]. These strategies hold promise for both autoimmune diseases and cancer, representing a growing frontier in precision immunotherapy that leverages redox biology for improved clinical outcomes [29].

CONCLUSION

Redox regulation plays a pivotal role in both innate and adaptive immune responses. While the generation of ROS and RNS is essential for pathogen defense and immune cell activation, the dysregulation of these molecules can contribute to chronic inflammation, autoimmunity, and cancer progression. Understanding the precise mechanisms of redox regulation in immune cells is critical for developing targeted therapies to treat a wide range of diseases. As research continues, the therapeutic potential of redox modulation in immune-related diseases will likely expand, offering new avenues for treatment and intervention.

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