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Redox–Immune Crosstalk in Autoimmune Disorders: The Underexplored Role of Antioxidants in Modulating Rheumatoid Factor Production and Activity

Kibibi Muthoni L.

Faculty of Science and Technology Kampala International University Uganda

ABSTRACT

Autoimmune disorders such as rheumatoid arthritis (RA) arise from a breakdown in immune tolerance, leading to chronic inflammation, autoantibody production, and progressive tissue destruction. Among these autoantibodies, rheumatoid factor (RF)-an immunoglobulin directed against the Fc region of IgG-serves not only as an important diagnostic biomarker but also as a mechanistic contributor to disease amplification and chronicity. Increasing evidence indicates that oxidative stress and redox imbalance are critical drivers of autoimmune activation, antigen modification, and RF production. Reactive oxygen species (ROS) generated by activated neutrophils, macrophages, and synovial fibroblasts can modulate antigen structure, enhance immunogenicity, and alter B-cell signalling dynamics, thereby creating a feed-forward loop of inflammation and autoantibody formation. However, the physiological redox system, including enzymatic and non-enzymatic antioxidants, serves as a counterbalance that can restrain excessive immune activation. Emerging research suggests that antioxidant molecules can influence B-cell tolerance, antigen processing, cytokine patterns, and Fc-receptor–mediated pathways linked to RF activity. Despite this, the therapeutic potential of antioxidants remains underinvestigated and poorly integrated into current treatment paradigms for autoimmune diseases. This review explores the redox–immune interface in autoimmune pathology, elucidates molecular mechanisms linking oxidative stress to RF production and pathogenicity, and critically evaluates the potential of antioxidant strategies in modulating these pathways. We highlight key research gaps and propose future directions for incorporating redox-based interventions into comprehensive autoimmune disease management.

Keywords: Rheumatoid factor, oxidative stress, redox signalling, antioxidants, autoimmune disorders

INTRODUCTION

Autoimmune diseases arise from inappropriate activation of the immune system, leading to chronic inflammation, progressive tissue injury, and disruption of normal physiological processes [1]. Among these conditions, rheumatoid arthritis (RA) stands as one of the most thoroughly investigated, yet its underlying molecular drivers continue to be unravelled. A central immunological hallmark of RA is the presence of rheumatoid factor (RF), an autoantibody-most frequently of the IgM isotype-that recognizes the Fc portion of IgG. Although RF has long been regarded as a diagnostic and prognostic biomarker, accumulating evidence demonstrates that it plays an active role in disease progression by facilitating immune complex formation, activating complement pathways, and promoting pro-inflammatory signalling through engagement of Fc receptors on innate immune cells [2]. Traditional models of RA pathogenesis emphasize the contributions of genetic susceptibility, environmental triggers such as cigarette smoke, and structural protein modifications that generate neoantigens. However, emerging research indicates that dysregulation of redox homeostasis is equally critical [3]. Oxidative stress, defined as an imbalance between reactive oxygen species (ROS) production and antioxidant defence mechanisms, is pronounced in autoimmune disorders. It is fuelled by mitochondrial dysfunction, cytokine-driven activation of immune effector cells, hypermetabolic synovial tissue, and persistent inflammatory signalling [4]. These redox disturbances intersect with immune pathways at multiple levels, shaping antigen presentation, modulating B- and T-cell responses, and influencing the quality and quantity of autoantibody production, including RF [5].

The convergence of oxidative stress and immune dysregulation creates a self-reinforcing cycle that enhances tissue inflammation and joint destruction. ROS not only inflict direct cellular injury but also modify proteins in

ways that increase their antigenicity, thereby facilitating autoantibody generation and broadening the immune response through epitope spreading [6]. At the same time, immune activation further elevates ROS production through enzymes such as NADPH oxidase and myeloperoxidase, sustaining a biochemical environment conducive to chronic autoimmunity [7]. This review explores the complex interactions between redox imbalance and immune signalling in autoimmune pathogenesis, with particular emphasis on the mechanisms through which oxidative stress influences RF production and activity. It also examines the emerging therapeutic potential of antioxidants as modulators of this redox-immune interface [8].

2. Oxidative Stress as a Driver of Autoimmunity

2.1 Mechanisms of Oxidative Stress in Autoimmune Conditions

In autoimmune diseases such as RA, oxidative stress emerges from persistent excess ROS generated by multiple cellular processes[9]. Activated neutrophils, central participants in RA synovial inflammation, release large quantities of superoxide through NADPH oxidase during repeated respiratory bursts. Simultaneously, inflammatory cells undergoing metabolic reprogramming exhibit mitochondrial electron transport chain leakage, producing additional ROS[10]. Myeloperoxidase, abundantly secreted by infiltrating neutrophils, catalyses the formation of hypochlorous acid, a highly reactive oxidant that contributes to tissue damage. Endoplasmic reticulum stress, common in hyperactive synovial fibroblasts, further increases ROS output during protein misfolding responses[11]. Synovial fibroblast hypermetabolism itself sustains a chronic oxidative environment that accelerates matrix degradation and inflammatory signalling. While physiological concentrations of ROS facilitate essential processes such as microbial killing and intracellular signalling, chronically elevated levels become pathogenic[12]. Persistent ROS overload damages lipids, proteins, and nucleic acids, activates redox-sensitive transcription factors including NF-κB and AP-1, and promotes inflammatory gene expression[13]. More critically, prolonged oxidative imbalance disrupts immune tolerance by altering antigen structure, promoting autoreactive T-cell differentiation, and enhancing B-cell activation, thereby predisposing to autoantibody formation.

2.2 Oxidative Modification of Self-Antigens

A major link between oxidative stress and autoimmunity is the generation of modified self-antigens. Proteins exposed to sustained ROS undergo structural alterations such as carbonylation, nitration, citrullination, and glycation, all of which increase immunogenicity[14]. Citrullinated proteins, generated through PAD enzyme activity under inflammatory and oxidative conditions, play a defining role in RA and often appear alongside RF. Oxidized IgG becomes structurally distorted in ways that enhance its binding affinity for RF, facilitating immune complex formation and amplifying synovial inflammation[15]. Advanced glycation end-products accumulate in chronically inflamed tissues, altering antigen processing by dendritic cells and promoting the survival and differentiation of autoreactive B cells. These oxidative modifications expand the autoantigenic repertoire available to the immune system, driving epitope spreading and sustaining RF production throughout disease progression[16].

3. Redox–Immune Crosstalk in the Regulation of Rheumatoid Factor

The interplay between oxidative stress and immune activation forms one of the most influential yet underappreciated mechanisms driving rheumatoid factor production and activity[17]. RF is traditionally described as an autoantibody arising in the context of chronic immune stimulation, but emerging findings suggest that redox disturbances directly modify the environment in which B cells mature, antibodies are produced, and immune complexes are formed[18]. Oxidative stress enhances the immunogenicity of IgG molecules by promoting structural alterations that increase their recognition by RF-producing B cells. This redox-mediated modification effectively amplifies the stimulus for RF synthesis, making oxidative imbalance both a trigger and a perpetuator of autoantibody production[19].

Moreover, oxidative stress reshapes the behaviour of antigen-presenting cells, particularly dendritic cells and macrophages, which are fundamental in driving RF-associated immune responses[20]. Excess ROS promotes the maturation of dendritic cells, enhances their expression of co-stimulatory molecules, and increases production of cytokines such as IL-6 and TNF-α. These cytokines are central to B-cell activation and differentiation and create a microenvironment that favours RF-producing plasma cell expansion[21]. Simultaneously, macrophages exposed to oxidative stress shift toward a proinflammatory phenotype, secreting ROS and reactive nitrogen species that further damage surrounding proteins and generate neoepitopes. This process establishes a redox-dependent loop: oxidative stress increases antigenicity, enhanced antigenicity drives immune activation, and immune activation increases ROS production[22].

4. Oxidative Stress and Cytokine Networks in Autoimmune Progression

Cytokine networks represent another major interface where redox imbalance shapes autoimmune pathology[23]. Many key cytokines involved in RA pathogenesis are themselves regulated by redox-sensitive transcription factors. For example, excessive ROS levels activate NF-κB, a master regulator of inflammatory gene expression,

leading to heightened production of TNF-α, IL-1β, IL-6, and GM-CSF[24]. These cytokines do more than perpetuate inflammation; they also directly influence autoantibody formation by modulating T-cell help, B-cell survival, and germinal-center reactions. As a result, redox stress becomes a powerful determinant of both cytokine amplification and RF-related immune responses[25]. The relationship is bidirectional. Cytokines further intensify oxidative stress by stimulating NADPH oxidase activity in neutrophils and macrophages and by increasing mitochondrial metabolic rate in synovial fibroblasts. IL-17, a cytokine frequently elevated in RA, is particularly associated with heightened ROS production and neutrophil recruitment. The resulting oxidative environment contributes to joint erosion, pannus formation, and sustained autoantigen generation[26]. Additionally, cytokine-driven oxidative burst mechanisms contribute to the citrullination and carbonylation of synovial proteins, which not only drive anti-citrullinated protein antibody (ACPA) production but also potentiate RF formation through enhanced immune complex deposition[27].

The interaction between cytokines and ROS also influences T-cell polarization. High levels of ROS promote differentiation toward Th17 cells while inhibiting regulatory T-cell function, thereby skewing the immune response toward autoimmunity[28]. This cytokine-redox axis reinforces chronic inflammation and fosters conditions conducive to persistent RF production. Thus, oxidative stress not only initiates cytokine release but is continually amplified by it, forming a tightly interwoven feedback system that sustains autoantibody-mediated tissue damage.

5. Future Directions

Advancing understanding of redox–immune interactions in rheumatoid arthritis requires a more targeted and mechanistic research agenda that bridges immunology, redox biology, and clinical therapeutics[29]. Although observational studies consistently reveal elevated oxidative stress in RF-positive patients, controlled clinical trials specifically evaluating antioxidant therapy in this subgroup remain scarce. Future investigations must determine whether redox-modulating interventions can reduce RF titres, alter immune complex dynamics, or attenuate synovial inflammation when used alongside standard DMARD therapy[30]. Such studies should incorporate stratified patient cohorts, as individuals with high oxidative stress may respond differently than those with predominantly cytokine-driven disease. A second major priority is the development of sensitive and clinically applicable biomarkers capable of assessing redox status in real time[31]. Current measures, such as serum malondialdehyde or total antioxidant capacity, lack specificity and do not reliably correlate with immune activity. More refined biomarkers including redox-sensitive transcriptional signatures, circulating oxidized IgG, and ROS-linked protein modifications may enable more precise monitoring of oxidative burden and therapeutic response[32]. These tools would also facilitate personalized antioxidant strategies tailored to the biochemical profile of each patient. Another promising avenue lies in the therapeutic manipulation of endogenous antioxidant pathways. Pharmacologic activators of Nrf2, a master regulator of cellular antioxidant defense, have shown potential in reducing oxidative injury and modulating inflammation in preclinical autoimmune models[33]. Integrating such agents with existing RA treatments could provide dual benefits: reducing oxidative antigen modification while dampening the immune pathways that sustain RF production.

There is also growing interest in designing redox-sensitive immunomodulatory drugs that directly target B-cell activation and plasma cell survival[34]. Molecules capable of altering intracellular redox thresholds may selectively suppress autoreactive clones without broadly compromising immune function. Complementing these pharmacologic approaches, nutritional strategies that enhance endogenous antioxidant systems including polyphenol-rich diets, micronutrient optimization, and metabolic interventions represent an accessible and potentially powerful adjunct to standard care[35]. Collectively, these future directions reflect the evolving recognition that redox regulation is integral to autoantibody biology. Deeper exploration of these mechanisms may unveil novel therapeutic opportunities capable of transforming the management of RF-mediated autoimmune disease.

CONCLUSION

Redox–immune crosstalk represents a fundamental yet underexplored axis in autoimmune disease pathogenesis. Oxidative stress promotes the formation of neoantigens, enhances antigen presentation, and dysregulates B-cell responses, collectively contributing to sustained RF production and activity. While antioxidants have the theoretical potential to modulate these pathways and suppress RF-mediated inflammation, current research remains limited. Emerging data support a meaningful role for antioxidant systems in restoring immunological balance and mitigating autoantibody-driven tissue damage. Future investigations should prioritize mechanistic studies and targeted clinical trials to determine the therapeutic value of antioxidant strategies in RF-associated autoimmune disorders. A deeper appreciation of redox biology may ultimately inform novel treatment modalities that address both the immunological and metabolic underpinnings of autoimmune disease.

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