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The Central Role of Oxidative Stress in Chronic Inflammation: Pathways and Treatment Targets

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ABSTRACT

Oxidative stress, characterized by an imbalance between reactive oxygen and nitrogen species (ROS/RNS) and antioxidant defenses, is a central mediator of chronic inflammation. This review explores the mechanistic pathways linking oxidative stress to sustained inflammatory responses and highlights therapeutic strategies targeting these pathways. We examine how ROS/RNS influence key inflammatory signaling cascades, including NF-κB, MAPK, and NLRP3 inflammasome activation, leading to the perpetuation of inflammation in various chronic diseases. Additionally, we discuss the role of redox-sensitive transcription factors such as Nrf2 in modulating antioxidant responses and their therapeutic potential. The review also addresses the challenges and opportunities in developing antioxidant-based therapies, considering the dual role of oxidative species in both promoting and resolving inflammation. By integrating current research, we provide insights into the complex interplay between oxidative stress and chronic inflammation, offering a foundation for future therapeutic interventions.

Keywords: Oxidative Stress, Chronic Inflammation, NF-κB, Nrf2, Therapeutic Targets

INTRODUCTION

Oxidative stress is a biochemical condition characterized by an imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and the capacity of the body's antioxidant defense mechanisms to neutralize these reactive molecules [1]. Under physiological conditions, ROS and RNS serve essential roles as signaling molecules involved in the regulation of cellular processes such as proliferation, differentiation, and immune defense [2]. However, when the generation of these reactive species exceeds the antioxidant capacity, oxidative stress ensues, leading to molecular damage to lipids, proteins, and DNA. This damage contributes significantly to cellular dysfunction and the development of various pathologies [3]. Chronic inflammation is a prolonged and dysregulated immune response that contributes to the pathogenesis of many non-communicable diseases, including cardiovascular diseases, neurodegenerative disorders like Alzheimer's disease, diabetes mellitus, chronic kidney disease, and several types of cancer [4]. A growing body of evidence has established oxidative stress as a central mediator in sustaining this inflammatory state. ROS and RNS not only cause direct cellular injury but also act as key signaling molecules that activate various inflammatory pathways. These pathways induce the production of pro-inflammatory cytokines, chemokines, and adhesion molecules, which perpetuate immune cell recruitment and activation at sites of injury or infection [5].One of the primary mechanisms linking oxidative stress and inflammation is the activation of redox-sensitive transcription factors such as nuclear factor kappa B (NF-κB) and activator protein-1 (AP-1) [6]. These transcription factors regulate the expression of numerous genes involved in

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immune responses and inflammation. Additionally, oxidative stress can activate inflammasomes, such as the NLRP3 complex, which are multiprotein intracellular complexes that regulate the maturation and secretion of pro-inflammatory cytokines like interleukin-1β [7]. Moreover, mitochondria, a major source of intracellular ROS, play a critical role in amplifying oxidative stress and inflammatory signaling when dysfunctional [8]. Given the central role of oxidative stress in driving chronic inflammation, therapeutic strategies targeting this axis hold considerable promise. However, the dual nature of ROS and RNS-as both essential signaling molecules and agents of damage-poses challenges in designing effective interventions [9]. A deeper understanding of the molecular mechanisms by which oxidative stress modulates inflammation is essential to identify novel therapeutic targets and develop precise treatments that can restore redox balance without impairing necessary immune functions [10]. This review aims to provide a comprehensive overview of the mechanistic insights into oxidative stress-mediated chronic inflammation and discuss emerging therapeutic approaches targeting these pathways.

Mechanisms Linking Oxidative Stress to Chronic Inflammation

Oxidative stress contributes to chronic inflammation through several interconnected molecular and cellular mechanisms [11]. At the core of these processes is the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which function as signaling molecules but can also cause tissue damage when present in excess [12]. One key mechanism involves the activation of inflammatory signaling pathways, notably the nuclear factor kappa B (NF-κB) pathway. ROS can activate NF-κB by inducing the degradation of its inhibitory protein IκB, allowing NF-κB to translocate into the nucleus and promote the transcription of pro-inflammatory cytokines, chemokines, and adhesion molecules [13]. This cascade amplifies immune cell recruitment and sustains inflammation in affected tissues.

In addition to NF-κB, the mitogen-activated protein kinase (MAPK) pathway is sensitive to redox changes and contributes to inflammatory gene expression. MAPKs regulate a variety of cellular responses, including cytokine production, cell survival, and apoptosis, which are often dysregulated in chronic inflammation [14]. Another important mechanism is the activation of the NLRP3 inflammasome, a multiprotein complex that senses cellular stress signals, including those generated by oxidative stress. Activation of the NLRP3 inflammasome leads to the cleavage and secretion of pro-inflammatory cytokines interleukin-1β (IL-1β) and interleukin-18 (IL-18), which further drive inflammation [15].

Mitochondrial dysfunction is another critical contributor to oxidative stress-induced inflammation. Mitochondria are a major source of ROS, and when damaged, they release damage-associated molecular patterns (DAMPs) such as mitochondrial DNA into the cytoplasm, which can activate pattern recognition receptors (PRRs) on immune cells, further promoting inflammatory signaling [16]. The interplay between oxidative stress, mitochondrial dysfunction, and immune activation creates a vicious cycle that perpetuates chronic inflammation [17]. Collectively, these mechanisms highlight the central role of redox imbalance in promoting and maintaining inflammatory states. Understanding these pathways offers important opportunities for therapeutic intervention aimed at disrupting this cycle and restoring tissue homeostasis.

Modulation of Redox-Sensitive Transcription Factors

Redox-sensitive transcription factors play crucial roles in regulating the balance between oxidative stress and inflammation [18]. Among these, nuclear factor kappa B (NF-κB) and nuclear factor erythroid 2-related factor 2 (Nrf2) are the most extensively studied and serve as master regulators of inflammatory and antioxidant responses, respectively [19].

NF-κB is a family of transcription factors that regulate genes involved in immune responses, inflammation, cell proliferation, and survival. Under basal conditions, NF-κB remains inactive in the cytoplasm bound to inhibitory proteins called IκBs [20]. Oxidative stress induces phosphorylation and degradation of IκBs, allowing NF-κB to translocate to the nucleus and initiate the transcription of numerous pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) [21]. This redox-sensitive regulation of NF-κB enables ROS and RNS to modulate inflammatory responses directly.

In contrast, Nrf2 serves as a protective transcription factor that orchestrates the cellular antioxidant defense system. Under normal conditions, Nrf2 is sequestered in the cytoplasm by Kelch-like ECH-associated protein 1 (Keap1), which targets it for proteasomal degradation. Oxidative stress modifies cysteine residues on Keap1, leading to Nrf2 stabilization and its translocation into the nucleus [22]. Once inside the nucleus, Nrf2 binds to antioxidant response

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elements (AREs) in the promoter regions of genes encoding detoxifying and antioxidant enzymes, including glutathione S-transferase, heme oxygenase-1, and superoxide dismutase [23]. Activation of Nrf2 thus enhances cellular capacity to neutralize ROS/RNS and mitigate oxidative damage.

The interplay between NF-κB and Nrf2 pathways is complex and often antagonistic [24]. While NF-κB promotes inflammation, Nrf2 activation tends to suppress it by reducing oxidative stress and limiting the inflammatory stimulus [25]. Dysregulation of this balance contributes to chronic inflammatory diseases, making these transcription factors promising targets for therapeutic intervention aimed at restoring redox homeostasis and resolving inflammation [26].

Mitochondrial Dysfunction and Cellular Damage

Mitochondria are vital organelles responsible for energy production and cellular metabolism, but they also play a significant role in generating reactive oxygen species (ROS) during oxidative phosphorylation [27]. Under physiological conditions, mitochondrial ROS serve as signaling molecules; however, mitochondrial dysfunction leads to excessive ROS production, which can damage mitochondrial components and propagate oxidative stress [28].

When mitochondria become dysfunctional, they release damage-associated molecular patterns (DAMPs), such as mitochondrial DNA (mtDNA), cardiolipin, and mitochondrial transcription factor A (TFAM), into the cytosol [29]. These DAMPs activate innate immune receptors, including Toll-like receptors (TLRs) and the NLRP3 inflammasome, triggering inflammatory responses. This release not only signals cellular distress but also promotes the recruitment and activation of immune cells, sustaining chronic inflammation [30].

Furthermore, mitochondrial dysfunction impairs ATP production, resulting in an energy deficit that compromises cell survival and repair mechanisms [31]. The accumulation of damaged mitochondria can also initiate apoptotic or necrotic cell death pathways, releasing intracellular contents that exacerbate inflammation [32].

The interplay between mitochondrial damage and oxidative stress forms a self-amplifying cycle: mitochondrial ROS cause further mitochondrial damage, which leads to increased ROS release and inflammation [33]. This vicious cycle is implicated in the pathogenesis of many chronic inflammatory diseases, including neurodegenerative disorders, metabolic syndrome, and cardiovascular disease [34,35].

Targeting mitochondrial dysfunction to reduce ROS generation, improve mitochondrial quality control through mitophagy, and block DAMP release represents a promising therapeutic avenue [36]. Pharmacological agents that support mitochondrial function or scavenge mitochondrial ROS are currently under investigation for their potential to break this cycle and ameliorate chronic inflammation [37].

CONCLUSION

Oxidative stress is a fundamental driver in both the initiation and maintenance of chronic inflammation, acting through multiple interconnected molecular pathways that disrupt cellular homeostasis and promote sustained immune activation. The intricate interplay between reactive oxygen and nitrogen species, redox-sensitive signaling cascades, and mitochondrial dysfunction creates a vicious cycle that perpetuates tissue damage and inflammatory responses. Understanding these mechanistic links has significantly advanced our knowledge of how chronic inflammatory diseases develop and progress. Importantly, this insight opens new avenues for the design of targeted therapeutic interventions aimed at restoring redox balance, modulating inflammatory signaling, and protecting mitochondrial function. While challenges remain-such as the dual roles of reactive species in physiological and pathological processes-ongoing research continues to refine strategies that can selectively mitigate harmful oxidative stress without compromising essential immune functions. Future studies and clinical trials will be crucial to translating these findings into safe and effective treatments that improve outcomes for patients suffering from chronic inflammatory disorders.

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