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Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) Signaling in Oxidative Stress, Immunity, and Inflammatory Disorders

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ABSTRACT

Nuclear factor erythroid 2–related factor 2 (Nrf2) is a master transcriptional regulator that plays a central role in cellular defense mechanisms, particularly in combating oxidative stress. It exerts its effects by orchestrating the expression of a wide array of antioxidant, detoxifying, and cytoprotective genes, thereby maintaining redox homeostasis and protecting cells from oxidative damage. Beyond this classical role, growing evidence highlights the broader involvement of Nrf2 in regulating immune function and inflammatory responses. Through cross-talk with signaling pathways such as NF-κB and MAPKs, Nrf2 modulates the expression of cytokines, chemokines, and other inflammatory mediators, thereby influencing both innate and adaptive immunity. Dysregulation or impaired activation of Nrf2 has been implicated in the pathogenesis of several inflammatory and autoimmune disorders, including rheumatoid arthritis, multiple sclerosis, asthma, and chronic obstructive pulmonary disease. These findings underscore its relevance not only in oxidative stress responses but also in disease progression and immune regulation. Recent advances in pharmacology and nutraceutical research have identified small-molecule activators and natural compounds, such as polyphenols and isothiocyanates, that can enhance Nrf2 signaling. Harnessing these therapeutic strategies offers promising opportunities for controlling excessive inflammation and oxidative injury. Understanding the multifaceted roles of Nrf2 provides a foundation for novel interventions in chronic inflammatory diseases.

Keywords: Nrf2, oxidative stress, inflammation, immunity, antioxidant response

INTRODUCTION

Nuclear factor erythroid 2–related factor 2 (Nrf2) is a critical transcription factor that regulates cellular defense mechanisms against oxidative and electrophilic stress [1]. It plays a fundamental role in maintaining redox homeostasis by controlling the expression of a broad range of antioxidant, detoxification, and cytoprotective genes [2]. Under normal physiological conditions, Nrf2 is sequestered in the cytoplasm by its inhibitor Kelch-like ECH-associated protein 1 (Keap1), which promotes its ubiquitination and proteasomal degradation [3]. Upon exposure to oxidative insults, electrophiles, or other stress signals, modifications occur on key cysteine residues of Keap1, disrupting the Keap1-Nrf2 interaction [4]. This allows Nrf2 to accumulate, translocate into the nucleus, and bind to antioxidant response elements (AREs) within promoter regions of target genes. These genes encode for a variety of enzymes such as heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), glutathione S-transferases (GSTs), and others that collectively enhance cellular resilience to oxidative damage [5].

While traditionally recognized for its antioxidant functions, Nrf2 has emerged as a vital regulator of immune responses and inflammation. Oxidative stress and inflammation are intimately linked processes; reactive oxygen species (ROS) not only cause molecular damage but also act as signaling molecules that modulate immune cell activation and inflammatory gene expression [6]. Nrf2 activation counteracts excessive inflammation by suppressing redox-sensitive pro-inflammatory pathways such as nuclear factor kappa B (NF-κB) and by promoting

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anti-inflammatory phenotypes in immune cells. This multifaceted role of Nrf2 positions it as a key mediator at the interface between oxidative stress and immunity [7].

Dysregulation of Nrf2 signaling has been implicated in the pathogenesis of numerous inflammatory and autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, chronic obstructive pulmonary disease, and inflammatory bowel disease [8]. In many of these disorders, impaired Nrf2 activity leads to an imbalance favoring oxidative damage and uncontrolled inflammation, contributing to disease progression and tissue injury [9]. Therefore, therapeutic strategies aimed at enhancing Nrf2 activation hold significant promise for mitigating oxidative stress and modulating immune dysfunction in chronic inflammatory conditions [10]. This review aims to provide a comprehensive overview of Nrf2 signaling mechanisms, its role in immunity and inflammation, and its relevance to inflammatory diseases. Additionally, we discuss current and emerging therapeutic approaches targeting the Nrf2 pathway, emphasizing their potential to improve clinical outcomes in inflammatory disorders.

2. Molecular Mechanisms of Nrf2 Activation and Regulation

Nrf2 activation is tightly controlled through its interaction with the cytoplasmic protein Kelch-like ECH-associated protein 1 (Keap1), which functions as a sensor of oxidative and electrophilic stress [11]. Under basal, non-stressed conditions, Keap1 binds to Nrf2 and promotes its ubiquitination via the Cullin 3 (Cul3)-based E3 ligase complex, targeting Nrf2 for proteasomal degradation [12]. This regulatory mechanism maintains low intracellular levels of Nrf2, preventing unwarranted activation of its target genes [13]. When cells experience oxidative stress or electrophilic insults, critical cysteine residues on Keap1 undergo covalent modifications, inducing conformational changes that impair its ability to ubiquitinate Nrf2 [14]. As a result, newly synthesized Nrf2 evades degradation, accumulates in the cytoplasm, and translocates into the nucleus. In the nucleus, Nrf2 forms heterodimers with small Maf proteins and binds to antioxidant response elements (AREs) in the promoter regions of a diverse set of genes involved in antioxidant defense, phase II detoxification, and cellular repair [15]. These genes include those encoding heme oxygenase-1 (HO-1), NAD(P)H:quinone oxidoreductase 1 (NQO1), glutathione S-transferases (GSTs), and enzymes involved in glutathione biosynthesis. Activation of this gene network enhances the cell's capacity to neutralize reactive oxygen and nitrogen species and detoxify harmful compounds [16].

Post-translational modifications further modulate Nrf2 activity. Phosphorylation by kinases such as protein kinase C (PKC), extracellular signal-regulated kinase (ERK), and AMP-activated protein kinase (AMPK) can enhance Nrf2 stability and promote its nuclear translocation [17]. Additionally, epigenetic factors, including histone modifications and microRNAs, influence Nrf2 gene expression and activity. Negative feedback mechanisms also exist; for example, the protein Bach1 competes with Nrf2 for binding to AREs, suppressing transcription of antioxidant genes [18]. Together, these regulatory layers ensure precise control of Nrf2 activity, allowing cells to respond dynamically to changing redox conditions while avoiding excessive or prolonged activation that might disrupt cellular homeostasis.

3. Nrf2 in Immunity and Inflammation

Nrf2 plays a crucial role in regulating both innate and adaptive immune responses, primarily through its capacity to modulate oxidative stress and inflammatory signaling pathways [19]. Reactive oxygen species generated during immune activation serve as essential signaling molecules but can also propagate tissue damage and amplify inflammation if not adequately controlled [20]. By inducing the expression of antioxidant and cytoprotective genes, Nrf2 limits the accumulation of harmful reactive species, thereby reducing oxidative damage to immune and non-immune cells [21]. One of the major anti-inflammatory effects of Nrf2 involves its negative regulation of the nuclear factor kappa B (NF-κB) pathway, a central driver of inflammation. Activation of Nrf2 suppresses NF-κB-mediated transcription of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) [22]. This crosstalk modulates immune cell activation and cytokine release, thereby attenuating excessive inflammatory responses [23]. Moreover, Nrf2 influences the phenotype and function of various immune cells. In macrophages, Nrf2 activation promotes an anti-inflammatory M2 phenotype, which is involved in tissue repair and resolution of inflammation [24]. In dendritic cells, Nrf2 reduces the expression of co-stimulatory molecules and limits antigen presentation, thereby modulating adaptive immunity. Nrf2 also supports the maintenance and function of regulatory T cells (Tregs), which are essential for immune tolerance and prevention of autoimmunity [25]. Through these multifaceted actions, Nrf2 maintains immune homeostasis and prevents chronic inflammatory states [26]. Dysregulation of Nrf2 can shift the balance towards heightened inflammation and tissue injury, highlighting its importance in immune regulation [27].

4. Dysregulation of Nrf2 in Inflammatory Disorders

Altered Nrf2 signaling has been implicated in the pathogenesis of a wide range of inflammatory and autoimmune diseases. In many chronic inflammatory conditions, insufficient Nrf2 activity leads to an inability to counteract oxidative stress and unchecked activation of pro-inflammatory pathways, contributing to disease progression and tissue damage [28].

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Rheumatoid arthritis (RA) is a prototypical autoimmune disorder where reduced Nrf2 expression correlates with increased oxidative stress in synovial tissues and exacerbated joint inflammation [29]. Studies demonstrate that diminished Nrf2 activity allows persistent activation of NF-κB and elevated levels of pro-inflammatory cytokines, which promote synovial hyperplasia and cartilage destruction. Experimental models of RA confirm that genetic deletion of Nrf2 worsens disease severity, whereas pharmacological activation of Nrf2 mitigates inflammation and joint damage [30].

In neuroinflammatory diseases such as multiple sclerosis (MS), impaired Nrf2 signaling contributes to increased oxidative damage and demyelination [31]. The central nervous system is particularly vulnerable to oxidative stress, and reduced Nrf2 function compromises the protective antioxidant response, exacerbating neurodegeneration [32]. Clinical trials of Nrf2 activators in MS have shown promising results in slowing disease progression [33].

Chronic obstructive pulmonary disease (COPD) is another condition associated with defective Nrf2 signaling. Exposure to cigarette smoke and environmental pollutants leads to oxidative stress and inflammation in lung tissues. In COPD patients, decreased Nrf2 expression is linked to heightened oxidative injury, impaired lung function, and sustained inflammation [34]. Overall, the dysregulation of Nrf2 compromises the balance between oxidants and antioxidants, fostering a pro-inflammatory environment that drives chronic disease pathology. Restoring Nrf2 function represents a potential therapeutic strategy to ameliorate inflammation and oxidative damage in these disorders [35].

5. Therapeutic Targeting of Nrf2

Given the central role of Nrf2 in regulating oxidative stress and inflammation, pharmacological modulation of this pathway has emerged as a promising therapeutic approach for a variety of inflammatory and degenerative diseases. Several natural and synthetic compounds have been identified as Nrf2 activators and are under investigation for their protective effects [36].

Natural phytochemicals such as sulforaphane, found in cruciferous vegetables, curcumin from turmeric, and resveratrol from grapes have demonstrated the ability to activate Nrf2 by modifying Keap1 cysteine residues and enhancing antioxidant gene expression. These compounds have shown anti-inflammatory and cytoprotective effects in preclinical models and some clinical trials, although their bioavailability and potency can be limiting factors [37].

Synthetic Nrf2 activators, including bardoxolone methyl and dimethyl fumarate, have been developed with improved pharmacokinetic properties. Dimethyl fumarate is approved for the treatment of multiple sclerosis and works partly by activating Nrf2, which contributes to its anti-inflammatory and neuroprotective effects. Bardoxolone methyl is being evaluated for chronic kidney disease and other conditions, although safety concerns have slowed its clinical development [38].

Despite these advances, challenges remain in targeting Nrf2 therapeutically. Prolonged or excessive Nrf2 activation may interfere with normal cellular signaling and has been linked to tumorigenesis in some contexts, underscoring the need for careful dose optimization. Additionally, patient heterogeneity in Nrf2 pathway function necessitates precision medicine approaches to identify those most likely to benefit from Nrf2-targeted therapies [39].

Future strategies may include combination therapies that pair Nrf2 activators with other anti-inflammatory agents or antioxidants, as well as novel drug delivery systems that enhance specificity and efficacy. Continued research will be essential to fully harness the therapeutic potential of Nrf2 modulation in inflammatory diseases.

CONCLUSION

Nrf2 is a pivotal transcription factor that governs the cellular antioxidant defense system and plays a crucial role in regulating immune responses and inflammation. Its ability to maintain redox balance and suppress pro-inflammatory signaling pathways makes it an essential mediator in preventing and controlling chronic inflammatory and autoimmune diseases. Dysregulation of Nrf2 contributes to the pathogenesis of multiple disorders characterized by oxidative stress and excessive inflammation. Therapeutic activation of Nrf2 holds great promise for managing these conditions. However, further research is needed to optimize safe and effective Nrf2-targeted treatments and fully realize their clinical potential.

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