Nrf2 in Chronic Obstructive Pulmonary Disease: Research Progress

Lingxi Kong, Gang Jiang*
The First Affiliated Hospital of Hunan Normal University / Hunan People's Hospital, Changsha 410005, China

Abstract: Nuclear factor erythroid 2-related factor 2 (Nrf2), a Cap'n'Collar basic leucine zipper transcription factor, regulates oxidative stress, inflammation, autophagy, metabolism, and immune responses. Chronic obstructive pulmonary disease (COPD), the most prevalent respiratory disorder in China, is marked by high morbidity and mortality, posing a substantial socioeconomic burden. This review examines Nrf2's role in COPD pathogenesis and progression through modulation of oxidative stress, ferroptosis, autophagy, and inflammatory response.

***Keywords*:** Nrf2; chronic obstructive pulmonary disease; oxidative stress; inflammatory response; autophagy

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung disorder marked by persistent and progressive airflow limitation due to airway abnormalities (bronchitis, bronchiolitis) and/or alveolar destruction (emphysema). Clinically, it manifests as dyspnea, cough, sputum production, and acute exacerbations. With its high global prevalence and mortality, COPD imposes a significant public health burden. COPD pathogenesis involves interconnected mechanisms, particularly oxidative stress, chronic inflammation, and protease-antiprotease imbalance. Nuclear factor erythroid 2-related factor 2 (Nrf2), a Cap-n-Collar transcription factor, is a master regulator of redox homeostasis. Through its seven functional Neh domains, Nrf2 governs oxidative stress responses, metabolism, and inflammation—processes central to COPD. This review examines the Nrf2-COPD axis to identify potential therapeutic strategies.

2. Overview of the Nrf2 Pathway

Nrf2 is a master transcription factor that maintains redox homeostasis by regulating cytoprotective genes, including SOD,GST,GPX and HO-1.[1]. In unstressed conditions, Nrf2 is primarily sequestered in the cytoplasm by its negative regulator, Kelch-like ECH-associated protein 1 (Keap1). Keap1, as a substrate adaptor for the CUL3-based E3 ubiquitin ligase complex, targets Nrf2 for continuous proteasomal degradation, maintaining low basal Nrf2 levels. Upon exposure to electrophiles or reactive oxygen species (ROS), critical cysteine residues in Keap1 are modified. This inhibits the ubiquitin ligase activity of the Keap1-CUL3 complex, allowing newly synthesized Nrf2 to accumulate and translocate to the nucleus. In the nucleus, Nrf2 dimerizes with small Maf proteins and binds to Antioxidant Response Elements (AREs) to activate target gene transcription. While this Keap1-Nrf2-ARE pathway serves as a critical adaptive response, its dysfunction—frequently observed in chronic diseases—leads to persistent oxidative stress and tissue damage.

3. Nrf2 in the Pathogenesis of COPD

3.1 Oxidative Stress

Oxidative stress, driven by an imbalance between ROS production and antioxidant defenses, is central to COPD pathogenesis. It originates from both exogenous sources and endogenous ROS generated by activated inflammatory cells. Cigarette smoke, a primary risk factor, delivers high concentrations of ROS that directly damage lung cells, amplify inflammation, and inactivate antiproteases.The Keap1-Nrf2 pathway is the primary cellular defense against oxidative stress. Under oxidative challenge, Nrf2 activation induces a battery of antioxidant and detoxifying enzymes. Studies in COPD patients and models have shown impaired Nrf2 activity, leading to a deficient antioxidant response and perpetuating oxidative damage[2-4]. The Nrf2/HO-1 axis, in particular, helps mitigate lung injury by reducing ROS and downregulating pro-inflammatory cytokines like TNF-α and IL-6. Agents such as irisin and astaxanthin have been shown to attenuate cigarette smoke-induced lung injury, in part, by enhancing Nrf2 pathway activity[5-6].

3.2 Ferroptosis

Ferroptosis is an iron-dependent form of regulated cell death driven by lethal accumulation of phospholipid hydroperoxides. It is distinct from apoptosis and can be inhibited by iron chelators and specific antioxidants[7]. Ferroptosis is driven by iron overload, glutathione depletion, GPX4 inactivation, and subsequent lipid peroxidation. Emerging

evidence implicates this pathway in COPD pathogenesis. Cigarette smoke exposure leads to iron accumulation, increased lipid peroxidation, and decreased GPX4 activity in the lungs[8]. Furthermore, PM2.5 exposure can trigger ferroptosis by elevating ROS and iron while depleting GSH[9].Nrf2 activation suppresses ferroptosis by upregulating genes involved in iron metabolism, glutathione synthesis, and lipid peroxidation defense. For example, dihydroquercetin protects lung epithelial cells from cigarette smoke-induced ferroptosis via Nrf2 activation[10].

3.3 Autophagy

Autophagy is a lysosomal degradation pathway that maintains cellular homeostasis by clearing damaged proteins and organelles. While basal autophagy is protective, its dysregulation—either impairment or excessive activation, can contribute to disease.In COPD, autophagy is dysregulated. Impaired autophagy may fail to remove damaged mitochondria and protein aggregates, while excessive autophagy can lead to epithelial cell death and cilia loss, promoting emphysema[11].A reciprocal regulatory relationship exists between Nrf2 and autophagy. The selective autophagy receptor p62 can bind and degrade Keap1, leading to Nrf2 activation. Conversely, Nrf2 can transcriptionally upregulate p62, forming a positive feedback loop[12]. Nrf2 activation has been shown to suppress cigarette smoke extract (CSE)-induced excessive autophagy and to promote chaperone-mediated autophagy, thereby protecting lung epithelial cells[13]. Furthermore, Nrf2 activators can enhance healthy mitophagy, improving mitochondrial function[14]. In contrast, pollutants like PM2.5 can disrupt the NOX4-Nrf2 balance,causing ROS overproduction and pathogenic mitophagy[15].

3.4 Inflammatory Response

Chronic inflammation is a hallmark of COPD, driven by macrophages, neutrophils, and other immune cells. Alveolar macrophages, upon cigarette smoke exposure, often polarize toward a pro-inflammatory M1 phenotype and release cytokines such as IL-6, IL-8, and TNF-α, amplifying the inflammatory cascade. Nrf2 exerts potent anti-inflammatory effects, in part by inhibiting NF-κB activation through stabilization of its inhibitor, IκBα. Furthermore, by reducing intracellular ROS levels, Nrf2 activation can suppress the ROS-sensitive NLRP3 inflammasome, a complex that drives the maturation and release of IL-1β and IL-18 [16].Therefore, boosting Nrf2 signaling represents a strategy to dampen the persistent inflammation characteristic of COPD.

4. Summary

Nrf2 contributes to COPD pathogenesis through regulation of oxidative stress, ferroptosis, and autophagy. Its downregulation correlates with disease severity and progression, making it a promising therapeutic target. However, COPD is a systemic disorder, and Nrf2's role in mediating local versus systemic oxidative stress responses remains complex. Further studies are required to elucidate its precise mechanisms.

References

[1] Audousset C, McGovern T, Martin J G. Role of Nrf2 in Disease: Novel Molecular Mechanisms and Therapeutic Approaches - Pulmonary Disease/Asthma [J]. Front Physiol, 2021, 12: 727806.

[2] Ying M, Yang Y, Huo Q, Sun J, Hong X, Yang F, Fang Y, Lu L, Mao T, Xiao P, Tao G. Nrf-2/HO-1 activation protects against oxidative stress and inflammation induced by metal welding fume UFPs in 16HBE cells. Sci Rep. 2024 Oct 14;14(1):24057. doi: 10.1038/s41598-024-74599-8. PMID: 39402078; PMCID: PMC11473639.

[3] Zhang C, Kong X, Ma D. miR-141-3p inhibits vascular smooth muscle cell proliferation and migration via regulating Keap1/Nrf2/HO-1 pathway. IUBMB Life. 2020 Oct;72(10):2167-2179. doi: 10.1002/iub.2374. Epub 2020 Sep 8. PMID: 32897647.

[4] Yamamoto M, Kensler TW, Motohashi H. The KEAP1-NRF2 System: a Thiol-Based Sensor-Effector Apparatus for Maintaining Redox Homeostasis. Physiol Rev. 2018 Jul 1;98(3):1169-1203. doi: 10.1152/physrev.00023.2017. PMID: 29717933; PMCID: PMC9762786.

[5] Kubo H, Asai K, Kojima K, et al. Exercise Ameliorates Emphysema Of Cigarette Smoke-Induced COPD In Mice Through The Exercise-Irisin-Nrf2 Axis [J]. Int J Chron Obstruct Pulmon Dis, 2019, 14: 2507-16.

[6] Kubo H, Asai K, Kojima K, Sugitani A, Kyomoto Y, Okamoto A, Yamada K, Ijiri N, Watanabe T, Hirata K, Kawaguchi T. Astaxanthin Suppresses Cigarette Smoke-Induced Emphysema through Nrf2 Activation in Mice. Mar Drugs. 2019 Nov 28;17(12):673. doi: 10.3390/md17120673IF: 4.9 Q1 . PMID: 31795292; PMCID: PMC6950584.

[7] Yang WS, Stockwell BR. Synthetic lethal screening identifies compounds activating iron-dependent, nonapoptotic cell death in oncogenic-RAS-harboring cancer cells. Chem Biol. 2008 Mar;15(3):234-45. doi: 10.1016/j.chembiol.2008.02.010. PMID: 18355723; PMCID: PMC2683762.

[8] Lin W, Wang C, Liu G, Bi C, Wang X, Zhou Q, Jin H. SLC7A11/xCT in cancer: biological functions and therapeutic implications. Am J Cancer Res. 2020 Oct 1;10(10):3106-3126. PMID: 33163260; PMCID: PMC7642655.
[9] Wang Y, Tang M. PM2.5 induces ferroptosis in human endothelial cells through iron overload and redox imbalance. Environ Pollut. 2019 Nov;254(Pt A):112937. doi: 10.1016/j.envpol.2019.07.105. Epub 2019 Jul 30. Erratum in: Environ Pollut. 2021 May 1;276:113640. doi: 10.1016/j.envpol.2019.113640. PMID: 31401526.
[10] Liu X, Ma Y, Luo L, Zong D, Li H, Zeng Z, Cui Y, Meng W, Chen Y. Dihydroquercetin suppresses cigarette smoke induced ferroptosis in the pathogenesis of chronic obstructive pulmonary disease by activating Nrf2-mediated pathway. Phytomedicine. 2022 Feb;96:153894. doi: 10.1016/j.phymed.2021.153894 Q1 . Epub 2021 Dec 14. PMID: 34942457.
[11] Liu Y, Levine B. Autosis and autophagic cell death: the dark side of autophagy. Cell Death Differ. 2015;22(3):367-376. doi:10.1038/cdd.2014.143
[12] Nakatogawa H. Two ubiquitin-like conjugation systems that mediate membrane formation during autophagy. Essays Biochem. 2013;55:39-50. doi:10.1042/bse0550039IF: 5.6 Q1
[13] Hosaka Y, Araya J, Fujita Y, et al. Chaperone-Mediated Autophagy Suppresses Apoptosis via Regulation of the Unfolded Protein Response during Chronic Obstructive Pulmonary Disease Pathogenesis [J]. J Immunol, 2020, 205(5): 1256-67.
[14] Li M-y, Qin Y-q, Tian Y-g, et al. Effective-component compatibility of Bufei Yishen formula III ameliorated COPD by improving airway epithelial cell senescence by promoting mitophagy via the NRF2/PINK1 pathway [J]. BMC Pulmonary Medicine, 2022, 22(1).
[15] Fan X, Dong T, Yan K, et al. PM2.5 increases susceptibility to acute exacerbation of COPD via NOX4/Nrf2 redox imbalance-mediated mitophagy [J]. Redox Biol, 2023, 59: 102587.
[16] Sun Y, Liu Y, Guan X, et al. Atorvastatin inhibits renal inflammatory response induced by calcium oxalate crystals via inhibiting the activation of TLR4/NF-κB and NLRP3 inflammasome. IUBMB Life. 2020;72(5):1065-1074. doi:10.1002/iub.2250.

Author Bio

Lingxi Kong (1999.08-), female, Han ethnicity, Changsha City, Hunan Province, master's student, research direction: Respiratory Medicine.