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Review Article

NRF2-Mediated Supersulfide Bridging for Mitochondrial Function

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Abstract

In eukaryotic cells, mitochondria serve as the energy power-house. Through proper electron transport chain to get ATP, and mitochondrial membrane potential (MMP) are the common manifestation of mitochondrial functions. Mitochondria are also regarded as the redox reaction cellular organelle. NRF2-KEAP1 system acts as the major redox homeostatic system in the biological environment. In some studies, it was observed that impaired NRF2-KEAP1 system reduces mitochondrial function but the underlying mechanism was not well studied. Alam., *et al.* (2023), in their recent study proved that NRF2 regulates the supersulfide species generation by increasing the availability of cysteine and its further metabolism directly modulates the mitochondrial function, which has been focused here.

***Keywords**: Supersulfide Species; NRF2; KEAP1; Mitochondrial Membrane Potential; SQOR; CARS2*

Introduction

Mitochondria works as a powerhouse of the eukaryotic cells, which is an established fact and oxidation-reduction reaction is key issue in this context. There are various pathways or mechanisms to modulate the mitochondrial functions. Malfunction of mitochondria is the causative fact of many aging associated diseases [1]. A recent study by Alam., *et al*. [2] showed a new pathway for the modulation of mitochondrial function with the involvement of NRF2-mediated supersulfide metabolism. Before this study, there were some studies stated that NRF2 may play regulatory role in mitochondrial function, but the mechanism underlying this event was quite in veil. A previous study stated that increased NRF2 activity or activation of NRF2 downstream target genes increased the mitochondrial membrane potential (MMP) [3], and another study also suggested that activated NRF2 facilitates fatty acid oxidation in the mitochondria [4]. In both of the cases and some other relevant studies though suggested the relation of NRF2 activity-based mitochondrial function or MMP, but the scientific world was not aware about the key mechanism, which was explored by the Alam., *et al*. [2]. As dysfunctional mitochondria is responsible for many aging associated diseases, so that understanding in depth about the regulators or key mechanisms of redox-related mitochondrial function will pave the way to explore new drugs for the treatment of these disorders.

NRF2-KEAP1 system

Master gene regulator, NRF2 (nuclear factor-erythroid 2-related factor 2) is a transcription factor that upon activation, translocates into the nucleus and by binding to the antioxidant response elements, activates cytoprotective genes like *SLC7A11* (encoding the cysteine transporter xCT), NQO1, GCLC, GCLM, TXNRD1 and so on that are related to antioxidant function [5,6]. KEAP1 (Kelch-like ECH-

associated protein 1) is a negative regulator of NRF2 that under normal physiological/homeostatic condition constitutively directs NRF2 ubiquitination and proteasomal degradation. In the presence of electrophilic stress and oxidative stimuli, KEAP1 unable to degrade NRF2 followed by its stability, it translocates into nucleus [7,8]. NRF2-mediated interference of the accumulation of oxidative damage in tissues also showed antiaging effects and recent studies have also supported this notion [9].

Supersulfide species

Supersulfide species is an emerging concept that describes sulfur species having catenated sulfur moieties such as hydropersulfides (RSSH), polysulfides (RSSnR, n > 1), hydropolysulfides (RSSnH, n > 1) and inorganic persulfides and polysulfides [10,11]. They are found in the cells at the submillimolar to millimolar level and remain attached to the cysteine amino acid side chains of some proteins [12]. The very specific feature of this species is that it is a class redox molecule species with unique antioxidant and nucleophilic properties [12]. Besides, it is also known that supersulfides can be self-renewed [13]. Concerning with mitochondrial function, it has been reported that supersulfide species act as electron acceptor produced by mitochondrial electron transport chain (ETC) and also helps to maintain the mitochondrial membrane potential (MMP) [10]. In addition, several biological roles of supersulfide species have been reported such as radical scavenger, antioxidants, anti-inflammatory, anti-ferroptotic, antiviral, enzyme activity, protein folding, hypoxic response and so on [8,14].

NRF2 role in supersulfide species metabolism and mitochondrial activity control

In biological system, synthesis of supersulfide molecules are enzyme catalyzed system and it is thought that the key enzymes in this line are cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-marcaptopyruvate sulfurtransferase (3-MST) but study in a triple negative CBS, CSE, 3-MST mice confirmed a compensatory supersulfide synthesis pathway [15]. One such mechanism involves cysteinyl-tRNA synthetase (CARS), which is canonically responsible for cysteinyl-tRNA synthesis [10]. Further research suggested that its two isoforms, cytosolic CARS1 and mitochondrial CARS2 are involved in the synthesis of cysteine persulfide (CsySSH) in the presence of the substrate L-cysteine and it was also proved that mitochondrial isoform, CARS2, is responsible for the maintenance of mitochondrial membrane potential (MMP) [10].

NRF2, in addition to regulating the cytoprotective genes and anti-inflammatory genes, also modulates supersulfide species metabolizing genes such as CBS, CSE are the direct target downstream genes. Since the maintenance of mitochondrial MMP requires cysteine as a substrate, so that, its substantial supply would be a key factor for mitochondrial supersulfide synthesis. Cysteine is generated through the reduction of cystine and this is known that cystine is incorporated into cell through xCT, encoded by SLC7A11 that is the direct downstream target gene of NRF2, anti-porter and then converted to cysteine, the substrate for supersulfide molecules. Cysteine persulfide in mitochondria goes through further metabolism by forming sulfide and finally accept electrons from electron transport chain (ETC) by the activity of sulfur oxidation enzyme, sulfur quinone oxidoreductase (SQOR) [16]. Since SQOR transfers electrons from sulfide to ubiquinone of the ETC, it supports the smooth ETC activity by bringing back the electrons to ETC. From Alam., *et al*. [2], a novel breakthrough came in front underlying the molecular mechanism by focusing on SQOR-mediated supersulfur metabolism that modulates the mitochondrial MMP and the process has been largely dependent on NRF2 activity. It was observed that activated NRF2 can increase the mitochondrial membrane potential, increased oxygen consumption and ATP production as well. Cystine uptake through xCT is increased through NRF2-mediated *SLC7A11* activation that increased the availability of cysteine, which was further metabolized to CysSSH and was involved in ETC as electron provider to ubiquinone by SQOR to keep on functional of the mitochondria to produce ATP. Their unpublished understanding also conveyed a new message that SQOR is the direct binding target of NRF2, which means that SQOR is the downstream target gene of NRF2 and as such, NRF2 directly involved in supersufide-based regulation of mitochondrial membrane potential, oxygen consumption, and ATP generation [2].

Conclusion

Supersulfide species biology is now an emerging research area having versatile biological role and maintenance of mitochondrial function is one of the key areas that could be of great applicable area of this new era for the development of personalized medicine. Direct involvement of NRF2-mediated supersulfur metabolism and redox balance will also pave the way to unveil several ways to treat many aging associated diseases where malfunction of mitochondria is observed.

Bibliography

1. Uruno A., *et al*. "Nrf2 suppresses oxidative stress and inflammation in app knock-in Alzheimer's disease model mice". *Molecular and Cellular Biology* 40.6 (2020): e00467-19.
2. Alam MM., *et al*. "Contribution of NRF2 to sulfur metabolism and mitochondrial activity". *Redox Biology* 60 (2023): 102624.
3. Holmstro¨m KM., *et al*. "Nrf2 impacts cellular bioenergetics by controlling substrate availability for mitochondrial respiration". *Biology Open* 2.8 (2013): 761-770.
4. Ludtmann MH., *et al*. "Nrf2 affects the efficiency of mitochondrial fatty acid oxidation". *Biochemical Journal* 457.3 (2014): 415-424.
5. Alam MM. "Essence of antioxidants in aging science: NRF2 a true fact". *CPQ Medicine* 5.5 (2019): 1-5.
6. Alam MM., *et al*. "Glucocorticoid receptor signaling represses the antioxidant response by inhibiting histone acetylation mediated by the transcriptional activator NRF2". *Journal of Biological Chemistry* 292.18 (2017): 7519-7530.
7. Yamamoto M., *et al*. "The KEAP1-NRF2 system: A thiol-based sensor-effector apparatus for maintaining redox homeostasis". *Physiological Reviews* 98.3 (2018): 1169-1203.
8. Motohashi H., *et al*. "Sulfur-utilizing cytoprotection and energy metabolism". *Current Opinion in Physiology* 9 (2019): 1-8.
9. Wati SM., *et al*. "NRF2 pathway activation by KEAP1 inhibition attenuates the manifestation of aging phenotypes in salivary glands". *Redox Biology* 36 (2020): 101603.
10. Akaike T., *et al*. "Cysteinyl-tRNA synthetase governs cysteine polysulfidation and mitochondrial bioenergetics". *Nature Communications* 8.1 (2017): 1177.
11. Kasamatsu S., *et al*. "Supersulfide catalysis for nitric oxide and aldehyde metabolism". *Science Advances* 9.33 (2023): eadg8631.
12. Ida T., *et al*. "Reactive cysteine persulfides and S-polythiolation regulate oxidative stress and redox signaling". *Proceedings of the National Academy of Sciences of the United States of America* 111.21 (2014): 7606-7611.
13. Alam MM. "Does the self-regenerated persulfide fuel tumor progression through bypassing ferroptosis?". *EC Pharmacology and Toxicology* 11.4 (2023): 3-4.
14. Alam MM. "Enzyme catalysis modulation through polysulfidation". *Annals of Reviews and Research* 11.4 (2024): 555816.
15. Abidin QHZ., *et al*. "Synthesis of sulfides and persulfides is not impeded by disruption of three canonical enzymes in sulfur metabolism". *Antioxidants* 12.4 (2023): 868.
16. Filipovic MR., *et al*. "Chemical biology of H_2S signaling through persulfidation". *Chemical Reviews* 118.3 (2018): 1253-1337.

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