NRF2 as a Developing Therapeutic Target

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EDITORIAL

The transcription factor nuclear factor erythroid 2 (NF-E2)-related factor 2 (Nrf2) belongs to the Cap ‘N’ Collar (CNC) family that contains a conserved basic leucine zipper (bZIP) structure. The key function of Nrf2 is to activate the cellular antioxidant response by inducing the transcription of an extensive collection of genes that are able to prevent the damaging effects of exogenous and endogenous insults, such as xenobiotic and oxidative stress. Nrf2 controls the cellular oxidant level and oxidant signaling by controlling the expression of three groups of ARE-dependent genes: drug metabolizing enzymes/transporters, antioxidant enzymes/proteins, and oxidant signaling proteins. Nrf2 participates in the regulation of oxidant-stimulated programmatic functions, including autophagy, inflammasome assembly, ER stress/UPR, mitochondrial biogenesis, and stem cell regulation[1].

Nrf2 broadly protects against toxicity and chronic diseases in normal cells or through pharmacological interference. So, Nrf2 has customarily been considered as the cell’s main defense mechanism and a master regulator of cell survival. As Nrf2 regulates the expression of a large series of cytoprotective genes, it plays a critical role in the prevention of degenerative disease in multiple organs. Activation of the Nrf2 response has been shown to protect against neurodegenerative diseases, aging, diabetes, photo-oxidative stress, cardiovascular disease, inflammation, pulmonary fibrosis, acute pulmonary injury and cancer. Therefore, it has been the emphasis of research as a pharmacological target that could be used for deterrence and treatment of various chronic diseases[2].

Due to Nrf2’s critical role in antioxidative protection, Nrf2-targeting molecules have been studied extremely in recent years. This has been enhanced by the development of modern methods which let a greatly responsive and efficient screening of chemicals that are likely to activate Nrf2. One of the most assuring agents is a group of triterpenoids that are derived from OAs (oleanolic acids). BM (bardoxolone methyl) is a methyl ester derivative of OA and one of the most potent Nrf2 inducers moreover, BM also inhibits NF-κB signaling, a main proinflammatory pathway, by direct inhibition of IKKβ (inhibitor of NF-κB kinase β). Thus BM has highly antioxidative and anti-inflammatory properties, which make it a very attractive[3, 4].

Another very remarkable substance is DMF (dimethyl fumarate), which activates Nrf2 through unknown mechanism. In basic research, isothiocyanates such as SFN (sulforaphane) are very extensively used to induce Nrf2 activity in both in vivo and in vitro studies. SFN is an indirect antioxidant which interrupts the Nrf2–Keap1 interaction and in the way endorse expression of ARE-driven genes[5].

Due to Nrf2’s cytoprotective abilities, it has not just been considered a target for treatment, but also for prevention of diseases such as cancer. Studies have been accompanied with dietary compounds and synthetic substances in order to clarify whether an Nrf2 increases protection against carcinogenic environmental insults. However, there is an evolving ‘dark side’ of Nrf2, as recent data have shown a great rate of gain-of-function mutations in the genes for Nrf2 and Keap1 in many cancer types. Nrf2 has highly proliferative features on various cells, proposing that it can indorse cancer. Moreover, cancer cells with Nrf2-activating mutations are more resistant to chemotherapies, which indicates that the Nrf2/Keap1 pathway has a key role in developed chemoresistance. Although
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no pharmacological Nrf2 inhibitors have yet been tested in clinical trials, many promising substances have been tested in laboratory trials. For one, alkaloid trigonelline, a substance recovered from coffee beans, reduces nuclear accumulation of Nrf2 and thereby inhibits transcription of Nrf2-driven genes. The substance brusatol, extracted from the evergreen shrub Brueca javanica, is an agent that increase ubiquitination of Nrf2 and therefore reduces cytoplasmic Nrf2 levels[2, 6].

Nrf2 inducers and its target antioxidative enzymes can results in an amelioration of disease activity[7, 8].

Numerous kidney injury models in Nrf2-KO (knockout) mice have disclosed a greater susceptibility for renal damage than in WT (wild-type) mice. kidney diseases such as focal segmental glomerulosclerosis or renal fibrosis are also promoted by an impaired Nrf2 activation, leading to disease progression. so lack of Nrf2 activity seems to be crucial for progression of kidney disease] thus an Nrf2-inducing drugs are obvious therapeutic options. For example, BM is a very potent Nrf2 inducer that has beneficial effects on CKD progression or even renal regeneration[9].

As the lung is continuously exposed to oxidants from cigarette smoke, air pollutants or infections, effective antioxidative signaling is critical for its integrity. The most usual pulmonary condition is COPD, which is characterized by chronic inflammation and subsequent remodeling of small airways, resulting in pulmonary emphysema. It has been shown that Nrf2-deficient mice exposed to cigarette smoke have a much higher susceptibility to COPD and emphysema compared with WT Nrf2 mice. Pharmacological Nrf2 induction reduced the rate of right heart failure in mice with PAH. Besides it was observed that the Nrf2 inducer BM decreased endothelin secretion and ETA expression. Endothelin is a main target of therapy in pulmonary hypertension, as it causes vasoconstriction of pulmonary vessels[2, 10].

Oxidative stress and damage are hallmarks for the development of many degenerative diseases. In addition, an imbalance between the generation of free radicals and antioxidative defenses has been related to neuronal damage and disease progression in other neurological disorders such as stroke. Antioxidative mechanisms are consequently a promising target for pharmacological interventions as Nrf2 is a major regulator of cellular antioxidative defense, its up-regulation leads to induction of extensive network of cytoprotective target genes. In several experimental settings, Nrf2 induction did improve the outcome of neurodegenerative conditions. A large set of in vivo trials has shown that Nrf2 induction modifies a diversity of conditions and protects against disease progression[11, 12].

In summary, this singular subject highlights recent progresses in mechanisms, physiological roles, and cytoprotective effects of NRF2 in a range of studies. currently, the benefits and risks of modulating NRF2 pathway activity in patients are not fully understood, and it is known that NRF2 and KEAP1 may cross-talk with other signaling pathways. So many other comprehensive investigations need to explore the nrf2-ARE pathway role in various types of disease.

REFERENCES


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