ARC Journal of Pharmaceutical Sciences (AJPS)
Volume 4, Issue 1, 2018, PP 17-19
ISSN No.: 2455-1538
DOI: http://dx.doi.org/10.20431/2455-1538.0401004
www.arcjournals.org

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 anextensivecollection of genes that are able to prevent the damagi8ng 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 triterpenoidsthat are derived from OAs (oleanolic acids). BM (bardoxolone methyl) is a methyl ester derivative of OA andone of the most potent Nrf2 inducers moreover, BMalso inhibits NF-κB signaling, a main proinflammatorypathway, by direct inhibition of IKKβ (inhibitorof NF-κB kinase β). Thus BM has highly antioxidative andanti-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 wayindorse expressionof ARE-driven genes[5].

Due to Nrf2's cytoprotective abilities, it has not just beenconsidered a target for treatment, but also for prevention of diseasessuch as cancer. Studies have been accompanied with dietarycompounds and synthetic substances in order to clarifywhether an Nrf2 increases protection against carcinogenicenvironmental insults. However, there is an evolving'dark side' of Nrf2, as recent data have shown a great rate ofgain-of-function mutations in the genes for Nrf2 and Keap1 inmany cancer types. Nrf2 has highly proliferative featureson various cells, proposing that it can indorse cancer.Moreover, cancer cells with Nrf2-activating mutations are moreresistant to chemotherapies, which indicates that the Nrf2/Keap1pathway has a key role in developed chemoresistance. Although

no pharmacological Nrf2 inhibitors have yet beentested in clinical trials, many promising substances have beentested in laboratory trials. For one, alkaloid trigonelline, a substancerecovered from coffee beans, reduces nuclear accumulationof Nrf2 and thereby inhibits transcription of Nrf2-driven genes. The substance brusatol, extracted from the evergreen shrub*Brucea javanica*, is an agent that increase ubiquitination of Nrf2and therefore reduces cytoplasmic Nrf2 levels[2, 6].

hepatocytesexpress high levels of Nrf2 in order to maintain homoeostasisand tissue integrity in the liver.Several liver diseases are linked to a disruption of antioxidant defense, including alcoholic and non-alcoholic liver disease, viral hepatitis, acetaminophen toxicity, and hepatocellular carcinoma. Thus 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 ofkidney disease] thus an Nrf2-inducing drugsare obvious therapeuticoptions. 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 itwas observed that the Nrf2 inducer BMdecreased 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 developmentof many degenerative diseases. In addition, an imbalance between the generation of free radicals and antioxidant defenses has been related to neuronal damage and disease progression in other neurological disorders such as stroke. Antioxidative mechanisms areconsequently a promising target for pharmacological interventions as Nrf2 is a major regulator of cellular antioxidative defense, itsup-regulation leads to induction of extensivenetwork of cytoprotectivetarget genes. In several experimental settings, Nrf2 induction did indeed improve the outcome of neurodegenerative conditions A large set of *in vivo* trials has shown that Nrf2induction modifies a diversity of conditions and protects againstdisease progression[11, 12].

In summary, this singularsubject 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.

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Citation: *G. B. Nasrin, " NRF2 as A developing Therapeutic Target", ARC Journal of Pharmaceutical Sciences (AJPS) , vol. 4, no. 1, p. 17-19, 2018. http://dx.doi.org/10.20431/2455-1538.0401004*