Clinical Pharmacology and Translational Medicine

Applis Publishers

CommentaryArticle ISSN: 2572-7656

NRF2: A Potential Therapeutic Agent in Cancer

Patricia Muñoz S* and Paula Castillo

Department of Molecular & Clinical Pharmacology, ICBM, Faculty of Medicine, University of Chile, Santiago, Chile.

Abstract: Cancer entails an imbalance between cellular renewal and death, which consequently leads to uncontrolled cell proliferation. Oxidative stress has been established as one of the key factors that trigger cancer. Eukaryotic cells have efficient intracellular cytoprotection systems. In this regard, the Keap 1-NRF2 signaling pathway is one of the most important mechanisms involved in cell defense and survival in response to xenobiotics and oxidative stress. New evidence suggests that NRF2 may have a dual role in cancer. In one hand, it may protect normal cells against carcinogenesis; whereas in cancer cells it induces the expression of genes involved in survival and proliferation which ultimately lead to chemo-resistance. The induction of NRF2 results in an accelerated detoxification of carcinogenic molecules from the environment. One of the major concerns regarding NRF2 activators which are currently used in pharmacological therapy is cytotoxicity due to off-target effects. In light of current evidence indicating that the constitutive activation of NRF2 could promote cancer progression and also aid in the development of resistance against anti-carcinogenic drugs; it appears logical that the pharmacological inhibition of NRF2 may constitute and adequate alternative for cancer treatment. Thus, further investigation will be needed to clearly establish the specificity and mechanism of action of these and other possible inhibitors of NRF2, before they can be proposed in therapies for cancer patients.

Keywords: *Cancer; NRF-2; Keap I; Oxidative stress.*

Abbreviations: *ROS: Reactive oxygen species; Keap 1: (Kelch like ECH associated protein; NRF2: Nuclear factor erythroid 2 [NF-E2] – related factor 2; ARE: Antioxidant response element.*

Cancer and NRF2

Cancer is a disease that affects 14.1 million people each year, constituting a main cause of death worldwide [1]. In simple terms, cancer is the imbalance between cellular renewal and death, consequently leading to uncontrolled cell proliferation. Oxidative stress has been established as one of the key factors that trigger cancer, where extrinsic and intrinsic factors contribute to the imbalance between production and elimination of reactive oxygen species (ROS). The constant exposure to harmful chemicals from the environment, drugs, heavy metals, radiation as well as toxic metabolites and pro-inflammatory cytokines, also contributes to increasing the oxidative stress.

Free radicals are compounds that have an unpaired number of electrons which allow them to induce oxidative stress by damaging other molecules such as proteins, lipids or DNA, and consequently lead to loss of function and cell cytotoxicity. To avoid these deleterious effects, eukaryotic cells have efficient intracellular cytoprotection systems. The Keap 1- NRF2 signaling pathway (Kelch like ECH associated protein - Nuclear factor erythroid 2 [NF-E2] related factor 2, respectively) is one of the most important mechanisms involved in cell defense and survival against xenobiotics and oxidative stress [2]. This pathway is activated in response to endogenous and exogenous stress. In normal conditions, the expression of NRF2 is very low, due to its binding to Keap I, an adaptor protein for Cullin 3 (Cul3), that latter being a ligase capable of ubiquitinating NRF2, in turn labeling it forproteosomal degradation [3]. Under oxidative stress, oxidative modifications in Keap I reduces its binding to NRF2, altering its ubiquitination and allowing NRF2 to be translocated into the nucleus. This scenario could be induced by using electrophilic compounds such as tert-butyl hydroquinone (tBHQ), which is able to interact with cysteine residues in Keap I [4]. TBHQ has been shown to not interfere in KeapI and NRF2 interaction, acting instead by inactivating Keap I and consequently, allowing the intracellular accumulation and stabilization of NRF2 [5].

Once in the nucleus, NRF2 can bind to Antioxidant Response Elements (ARE) which are regulatory regions upstream of specific genes and induce their expression. Such genes correspond to detoxification enzymes like NAD(P)H:quinoneoxidoreductase 1 (NQO1) and Glutathione-S-Transferase (GST); as well as antioxidant enzymes like Hemeoxygenase 1 (HMOX-1). In addition, NRF2 regulate proteosomal proteins and chaperones, suggesting that this transcription factor may have an important role in removal and repair of damaged proteins [2-6]. Overall, the main function of NRF2 is to activate the antioxidant intracellular response through induction of the expression of many genes which are involved in the defense against extrinsic/intrinsic factors, xenobiotics, or oxidative stress. This defense mechanism plays a major role in cell survival, and it had been established that its activation protects against several diseases (i.e, neurodegenerative, diabetes, photo- oxidative stress, cardiovascular disease, inflammation, pulmonary fibrosis, acute pulmonary injury, and cancer) [7].

As aforementioned, oxidative stress plays a key role in carcinogenesis including its initiation and progression, by inducing an

*Address for Correspondence: Patricia Muñoz S, Ph.D, Department of Molecular & Clinical Pharmacology, ICBM, Faculty of Medicine, University of Chile, Santiago, Chile, Tel: +56 229786637; E-Mail: bioquimica.pams@gmail.com

Received: July 31, 2017; **Accepted:** August 22, 2017; **Published:** August 23, 2017

increase in cellular metabolism as well as mitochondrial activity, both of which are required for cell proliferation and tumor growth [8, 9]. In relation to this, new evidence suggests that NRF2 may have a dual role in cancer. In one hand, it may protect normal cells against carcinogenesis; while in cancer cells, it induces the expression of genes involved in survival and proliferation which ultimately lead to chemo-resistance [9]. Several genes induced by NRF2, including NQ01 and GST, are overexpressed in cancer cells, suggesting they may be helping to decrease the amount of ROS and hence arrest DNA damage.

Chemotherapy-resistant cancer cells express high levels of GSH as well as other metabolic enzymes, and drug efflux pumps whose gene expression are regulated by NRF2. Thus, the hyperactivity of the Keap I-NRF2 signaling pathway leads to an unpromising diagnosis in patients [8].

The expression of NRF2 is induced during the development of drug resistance, suggesting that NRF2 may contribute to intrinsic and acquired chemoresistance [7]. Currently, resistance had been reported for several chemotherapeutic drugs such as etoposide, carboplatin, cisplatin, 5-fluorouracil, and doxorubicin [10-11].

Mutations in Keap I y NRF2 has been reported in about 0.9% of all cancer cases examined in COSMIC 2016 (COSMIC: http://cancer.sanger.ac.uk/cosmic). Interestingly, NRF2 mutants are unable to bind Keap I, leading to a constitutive activation of the pathway, even in absence of oxidative stress. Similarly, mutations in Keap I also affect its binding capacity to NRF2 [5]. This evidence presents NRF2 as an attractive therapeutic target against cancer; and currently, two strategies had been developed: the inhibition and induction of NRF2. The induction of Nrf2 reportedly results in an accelerated detoxification of carcinogenic molecules from the environment as well as an increased protection of the body against chemical carcinogenesis. Molecules that interfere with the binding KEAPI-NRF2 are called "NRF2 activators", and most of them act by binding the DC domain in KeapI which is specific for NRF2 [5]. Some of these molecules have a natural origin and are obtained from plants, such as: sulforaphane (SF), curcumin, epigallocatechin-3-gallate, resveratrol, cafestrol, kahweol, cinnamonyl-based compounds, zerumbone, garlic oganosulfur compounds, lycopene, and carnosol [7, 8, 9-12]. These compounds exert their effects through the activation of phase II detoxification enzymes, antioxidants, and transporters which protect the cell from carcinogenic elements. One of the major concerns regarding NRF2 activators which are currently used in pharmacological therapy is their cytotoxicity due to off-target effects; especially because these compounds may interact with cysteine residues in proteins involved in multiple intracellular signaling pathways that cross-talk with Keap 1-NRF2 [13].

Due to all the evidence indicating that the constitutive activation of NRF2 could promote cancer progression and also aid in the development of resistance against anti-carcinogenic drugs; it appears that the pharmacological inhibition of NRF2 may be a better alternative for cancer treatment, especially in cases with exhibit high levels of NRF2. Plant extracts like brusatol are able to inhibit the NRF2 pathway. Alternatively, small molecules that also act as inhibitors are: ascorbic acid, luteolin, ochratoxin A, and trigonelline [14]. Interestingly, some of these compounds have been reported as inhibitors of NRF2 in some studies, yet they act like activators in others. Thus, further investigation will be needed to clearly establish the specificity and mode of action of these and other possible inhibitors of NRF2, before they can be proposed in therapies for Cancer patients.

References

1. World Cancer Report. World Health Organization. 2014. pp. Chapter1.1. [Crossref]
2. Pandey P, Singh AK, Singh M, Tewari M, Shukla HS and Gambhir IS. The see- saw of Keap1-Nrf2 pathway in cancer. Crit Rev Oncol Hematol. 2017; 116:89-98. [Crossref]
3. Jaiswal A.K. Nrf2 signaling in coordinated activation of antioxidant gene expression. Free Radic Biol Med. 2004; 36:1199-1207. [Crossref]
4. Kobayashi A, Kang M I, Okawa H, Ohtsuji M, Zenke Y, Chiba T, et al. Oxidative stress sensor Keap1 functions as an adaptor for Cul3-based E3 ligase to regulate proteasomal degradation of Nrf2. Mol Cell Biol. 2004; 24:7130-7139. [Crossref]
5. Taguchi K and Yamamoto M . The KEAP1–NRF2 System in Cancer. Front Oncol. 2017; 7:85. [Crossref]
6. Kobayashi A, Kang MI, Watai Y, Tong KI, Shibata T, Uchida K, et al. Oxidative and electrophilic stresses activate Nrf2 through inhibition of ubiq-uitination activity of Keap1. Mol Cell Biol. 2006; 26:221-229. [Crossref]
7. Jaramillo MC and Zhang DD. The emergingroleof theNrf2- Keap1 signaling pathway in cancer. Genes Dev. 2013; 27:2179-2191. [Crossref]
8. Leinonen HM, Kansanen E, Polonen P, Heinaniemi M and Levonen AL. Role of the Keap1-Nrf2 pathway in cancer. Adv Cancer Res. 2014; 122:281-320. [Crossref]
9. Leinonen HM, Kansanen E, Pölönen P, Heinäniemi M and Levonen AL. Dysregulation of the Keap1-Nrf2 pathway in cancer. Bio chem Soc Trans. 2015; 43:645-649. [Crossref]
10. Ohta T, Iijima K, Miyamoto M, Nakahara I, Tanaka H, Ohtsuji M, et al. Loss of Keap1 function activates Nrf2 and provides advantages for lung cancer cell growth. Cancer Res. 2008; 68:1303-1309. [Crossref]
11. Shibata T, Kokubu A, Gotoh M, Ojima H, Ohta T, Yamamoto M, et al. Genetic alteration of Keap1 confers constitutive Nrf2 activation and resistance to chemotherapy in gallbladder cancer. Gastroenterology. 2008; 135:1358-1368. [Crossref]
12. Jeong WS, Jun M and Kong AN. Nrf2: A potential molecular target for cancer chemoprevention by natural compounds. Antioxid Redox Signal. 2006; 8:99-106. [Crossref]
13. Wakabayashi N, Slocum SL, Skoko JJ, Shin S and Kensler TW. When NRF2 talks, who's listening? Antioxid Redox Signal. 2010; 13:1649-1663. [Crossref]
14. Magesh S, Chen Y and Hu L. Small molecule modulators of Keap1–Nrf2–ARE pathway as potential preventive and therapeutic agents. Med Res Rev. 2012; 32:687-726. [Crossref]