Nrf2 as a modulator of oxidative stress

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Article Info:

Received 17 Apr 2021
Accepted 9 Sep 2021
Published 1 Dec 2021

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Abstract:

Nrf2 is active protein presents in the cytoplasm in the cells of the body. In the presence of an activators, Nrf2 can enter the nucleus which bind to Antioxidant Responses Elements (ARE) or otherwise named human ARE (hARE) which control the whole antioxidants activity in human cell. Many factors may contribute to defective or overwhelmed cellular antioxidants activities for instances aging and cellular damages. These cellular damages can be produced by free radicals or oxidative stress. In the mechanism, if Nrf2 activated in the nucleus, can caused the production of collaborative antioxidants enzymes especially: catalase, glutathione (GLT) and superoxide dismutase (SOD) as a responsible for detoxification of free radical inside the cells.

Key words: Nrf2, oxidative stress, antioxidant enzyme

Nrf2 كمعالج للإجهاد التأكسدي

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****فرع الادوية والسموم ، كلية الصيدلة ، الجامعة المستنصرية***

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الخلاصة:

Nrf2هو بروتين نشط موجود في السايتوبلازم لكل خلية في الجسم. في وجود المنشط ، سيدخل Nrf2 إلى النواة حيث يرتبط بعنصر الاستجابة لمضادات الأكسدة (ARE) أو ما يسمى بـ ARE (hARE) البشري الذي يتحكم في أنشطة مضادات الأكسدة الكاملة في الخلايا البشرية. يمكن أن تساهم العديد من العوامل في النشاط الخلوي المضاد للأكسدة المعيب أو الغامر ، مثل الشيخوخة وتلف الخلايا. ينتج هذا الضرر الخلوي عن توليد الجذور الحرة أو الإجهاد التأكسدي. عندما يتم تنشيط Nrf2 في النواة ، فإنه يتسبب في إنتاج إنزيمات تعاونية مضادة للأكسدة خاصة: الكاتلاز والجلوتاثيون (GLT) وديسموتاز الفائق (SOD) المسؤولة عن إغلاق الجذور الحرة داخل الخلية.

الكلمات المفتاحية: Nrf2 ، الإجهاد التأكسدي ، إنزيم مضاد للأكسدة.

Introduction:

Nuclear factor erythroid 2-related factor 2 (Nrf2)

A transcriptional factor is encoded by the genes in human. Other names are: nuclear factor erythroid 2-related factor 2 (Nrf2) or atomic factor erythroid-derived 2-like 2 [1]. As indicated by preliminary study Nrf2 is a basic leucine zipper (bZIP) protein that expresses cellular constituent antioxidants protein which secures against oxidative stress set off by injuries and inflammations [2]. Inflammation can be classified as either acute or chronic. Acute inflammations describe the rapid response of innate immune components to a challenge· [3]. Oxidative stress process resulted from in equilibrium between reactive oxygen production and the biological protective mechanism [4] One of the causes hormone disorders due to promote of oxidation. [5]

In vitro, Nrf2 bind to antioxidants responses element (AREs) in the nucleus elicit the transcription of ARE gene [6]. Nrf2 also caused elevation of phase II enzyme activities in vitro by increase heme oxygenase's 1[7] it's hindered the NLRP3 inflammasome [8]. Nrf2 seem to play outs a pleiotropic job in regular of metabolisms, inflammations, autophagias, proteostasis, mitochondrial physiologies, and immune response [9]. A few medications which induced the NFE2L2 path are state investigate for treatment of disease which brought nearly by oxidative stress [2, 10]).

Structural presentation

NRF2 is a basic leucine zip (bZip) transcription factors with [1], it has six highly conserve domain call NRF2-ECH homologies (Neh) domain. The Neh1 domains is a CNC-bZIP domains which permit Nrf2 to heterodimerize with small Maf protein [11]. The Neh2 domains restrict Nrf2 to its cytosolic repressors Keap1 [12]. The Neh3 domains involved in Nrf2 proteins stabilities and can induced some as a transactivation region, interact with portions of the transcriptional devices [13]. The Neh4 and Neh5 domain are transactivation domain too, yet they bind to a second proteins called cAMP Responses Elements Binding Proteins (CREB), which has histone acetyltransferase activities· [12].

The Neh6 domains may hold a degron which is associate with a redox insensitive method of degradations of Nrf2. This happens in stressed cell, which regularly alters the half-life of Nrf2 proteins comparative with unstress condition by suppressing another catabolic pathway [14].

Sulforaphane (SFN), is the mains active constituents of an isothiocyanate available in cruciferous vegetable e.g. Broccoli and cabbage. SFN has the abilities to induce Nrf2 signal pathway and inhibit NF-κB which are entangle in the antioxidant and anti-inflammatory response respectively.

Confinement and Role:

NFE2L2, NFE2, NFE2L1 and NFE2L3 gene, code leucine zipper (bZIP) transcription factor. They have conserve locations which are different from other comparable bZIP family JUN and FOS, albeit remain region are segregate from each other's [15].

At normal unstressed condition, NRF2 is confine in the cytoplasm by a number of proteins that quickly break it downs. On the other hand, under oxidative stress, NRF2 does migrate to the nucleus unbroken down, where it binds to a DNA promoter and start transcription of antioxidative genes and their protein.

Kelch like-ECH-related protein 1 (KEAP1) and Cullin 3 keep NRF2 in the cystol by, ubiquitination [16]. Where Cullin 3 caused ubiquitination of NRF2, while Keap1 is act as a substrate device accelerator protein that assist the response. NRF2 break down by

ubiquitination, is via proteasome, and its part recycled. By the way, NRF2 has a half-life of 20 minute [17]. Electrophilic (ie. oxidative stress) causes disturbance in the cysteine residue in Keap1, thus halting the Keap1-Cul3 ubiquitination processes. Un ubiquitinated NRF2, is concentrate in the cystol [18, 19] where it moves into the nucleus. NRF2 in the nucleus forms a heterodimer with either Maf protein (MAFF, MAFG, MAFK) and bind to the antioxidant responses elements (ARE) in the promoter region of many antioxidative gene, where transcriptions are started [20].

Target genes

Numerous cytoprotective proteins are activated by NRF2. These may include but not restrict to the following:

o NAD(P)H quinone oxidoreductase 1 (Nqo1) is a prototypical NRF2 target gene that catalyzed the reduction and detoxification of increased unstable quinone which may produce redox cycling and oxidative stress [21].

o Glutamate-cysteine ligase catalytic sub-unit (GCLC) and glutamate-cysteine ligase regulatory sub-unit (GCLM) form a heterodimer, that is the rate-limiting step in the production of glutathione (GSH), an extreme impressive endogenous antioxidant. each Gclc and Gclm are typical NRF2 target gene, that set up NRF2 as a regulator of glutathione, the principal antioxidants in the bodies [22].

o Sulfiredoxin 1 (SRXN1) and Thioredoxin reductase 1 (TXNRD1) assist the decrements and recall of peroxiredoxins, protein crucial in the detoxification of extreme reactive peroxide, include hydrogen peroxide and peroxynitrite [23, 24].

o Heme oxygenase-1 (HMOX1, HO-1) one of the enzymes that catalyze the destructions of heme in to the antioxidants biliverdin, the anti-inflammatory carbon monoxide, and iron. HO-1 is a NRF2 target gene which appear to protect from various disease, include sepsis, hypertension, atherosclerosis, acute lung injuries, kidney injuries, and pains [25]. However, induction of HO-1 has been appeared to exaggerate early brain injuries after intracerebral hemorrhage [26].

o the glutathione S-transferase (GST) family include cytosolic, mitochondrial, and microsomal enzyme which catalyzed the conjugated of GSH with endogenous and xenobiotic electrophiles. After detoxifications by glutathione (GSH) conjugation catalyze by GSTs, the body may dispose deleterious and toxic compound. GSTs are prompt by NRF2 activations and direct different detoxification pathway [27].

o the UDP-glucuronosyltransferase (UGT) family catalyzed the formations of a glucuronic acid moieties to an assortment of endogenous and exogenous substance, making them water soluble and renal removable. Evidential substrate for glucuronidation include bilirubin and acetaminophen. NRF2 has been appear to activate UGT1A1 and UGT1A6 (28).

o Multidrug resistance associate protein (Mrps) are big membrane carrier that efflux assortment of compound from diver organ in to bile or plasma, with subsequent eliminations in the feces or urine, respective. Mrps are upregulate by NRF2 and hence a profound modification in pharmacokinetic and toxicokinetic of a compound may ensue [29, 30].

o Kelch like ECH-associated protein 1 is a necessary target of NFE2L2. In mouse Keap1 (INrf2) gene, Lee and colleagues [31] observe in mouse Keap1 (INrf2) gene, which AREs situate on a negative strand may tie Nrf2 activations to Keap1transcriptions. At NRF2 occupancy in human lymphocyte, Chorley and colleagues established a roughly 700 bp locus inside the KEAP1 promoter region is

reliably high level advance, yet at the whole genome scale [32]. These basic discovery screws portray a mutually influence pattern between NRF2 and KEAP1. NRF2 driven KEAP1 expression describe in human cancer setting in particular human cell cancer involve another viewpoint in understand NRF2 signaling regulations [33].

Tissue distribution

In a descend order: kidney, muscle, lung, heart, liver, and brain are site where NRF2 is ubiquitous expresses at higher concentration [1].

Clinical relevance

Tecfidera marketed by Biogen Idec that a dimethyl fumarate, was appoved by the Food and Drug Administrations in March 2013 after Phase III clinical trial that showed that the drugs reduced the rate of relapse and distend durations to progressions disablement in multiple sclerosis patient [2]. Performance by its application of therapeutic validity was not determine

Dimethyl fumarate (and its metabolite, monomethyl fumarate) induced the NRF2 path and is characterize as a nicotinic acid receptors agonist in vitro. The label of the above products incorporates cautions notice regarding the danger of anaphylaxis and angioedema, progressive multifocal leukoencephalopathy (PML), lymphopenia, and liver damages; in addition, untoward effect includes flush and gastrointestinal event, diarrhoea, nausea, and upper abdominal pains [34].

Oltipraz a dithiolethiones an organosulfur compound that is best studied inducers of NRF2 [35]. It represses cancer development in rat organ, includ the bladder, blood, colon, kidney, liver, lung, pancreas, stomach, trachea, skin, and mammary tissue [36]. Unfortunate clinical preliminary regarding Oltipraz has shown many drawbacks causing substantial adverse effect, include neurotoxicity and gastrointestinal toxicities. Oltipraz can further produce superoxide anion and additional toxicity [37].

Respective pathology

Genetic activations of NRF2 can set the process of de novo malignant tumor [38]. Like the process of atherosclerosis by bringing plasma cholesterol level and cholesterol constituent in the liver [39]. It suggests that the later influence can overshadow the potential advantage of antioxidant provide by NRF2 activations [40].

Conclusion:

In summary, its seem that Nrf2 has currently the ability to modulate several diverse pharmacological and physiological effect like aging, cancers, oxidative stress and inflammatory response. However, many questions await further explanations if Nrf2 is a protective or deleterious role? Further studies must explain the role of Nrf2 in pancreatic and other type of cancers.

Acknowledgment

We would like to thank Mustansiriyah University for their valuable assistance in completing this review.

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