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Role of Nrf2-KEAP1 Pathway in Cancer

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ABSTRACT

The Nrf2 (nuclear factor erythroid 2 [NF-E2]-related factor 2 [Nrf2])–Keap1 (Kelch-like erythroid cell-derived protein with CNC homology [ECH]-associated protein signaling pathway is responsible for cell defense and survival pathways. Nrf2 protects cells and tissues from a variety of carcinogens by increasing the expression of the cytoprotective genes. Being the major stress regulator of the cell, NRF2 is involved in tumor formation, progression, and metastasis so, to better understand the NRF2 pathway and its roles in cancer. NRF2 displays a complex behavior in carcinogenesis. The NRF2 transcription factor is activated as a defensive mechanism during oxidative stress. During the normal condition, NRF2-dependent transcription is repressed by a negative regulator Keap1. NRF2 gets separated from Keap1-mediated repression and activates antioxidant responsive element (ARE)-dependent gene expression when cells are exposed to oxidative stress or electrophiles and maintain cellular redox homeostasis. Beyond its cancer prevention function, NRF2 has as of late been perceived as a key factor directing a variety of qualities that defend cells against the harmful impacts of environmental stress. In this review, we will discuss the NRF2 and keap1 structure, the mechanism involved in the regulation of nrf2 and keap1, the dual role of Nrf2, the role of keap1 in suppression of carcinogenesis, and the NRF2inducers and inhibitors in therapeutic implications.

1. Introduction

The transcription factor Nrf2 belongs to the Cap N Collar (CNC) family that contains a basic leucine zipper (bZIP) structure. The main function of Nrf2 is to activate the cellular antioxidant response by inducing the transcription of a wide range of genes that can overcome the destructive impacts of extraneous and intrinsic insult like xenobiotics and oxidative stress. (1)

Nrf2 has many objective qualities, for example, intracellular redox-balancing proteins like glutamate-cysteine ligase, heme oxygenase-1 (HEM-1) and glutathione peroxidases (GPX), stage II detoxifying compounds like glutathione-S-transferase (GST), quinone oxidoreductase-1 (NQO1), and multidrug opposition related proteins These downstream effectors have an essential job in cell guard instruments. Subsequently, Nrf2 addresses a vital switch for cell transformation and endurance under oxidative difficulties. (2)

Being the major stress regulator of the cell, NRF2 is involved in tumor formation, progression, and metastasis so, to better understand the NRF2 pathway and its roles in cancer. NRF2 displays a complex behavior in carcinogenesis. (3) To understand the importance of the NRF2 pathway in cancer, it is necessary to describe the negative regulator KEAP1, which interacts with NRF2 to downregulate its expression in cells and control cellular homeostasis. Under normal conditions, there is a balance between KEAP1 activity and NRF2 protein levels, which provides regulated antioxidant response, detoxification, and prevention of cancer. Notwithstanding excessive stress, overexpression of NRF2, or downregulation of KEAP1 cause a change in this equilibrium, this thus acts for carcinogenesis. Unwinding these roles would give specialists to focus on the NRF2 pathway in a more specific manner to destroy malignant growth without advancing its favorable to oncogenic works otherwise called the "negative side of NRF2" the positive role of NRF2 in controlling cancer. (4)

2.1 Structure of keap1 and nrf2 proteins

Keap1, the vital Nrf2 negative controller, has 624 amino acids that are distributed into five domains, including an N-terminal region (NTR), a broad complex, Tramtrack and Bric-à-Brac (BTB) domain, a cysteine-rich mediating region (IVR), six Kelch replays, and a C-terminal region (CTR). The BTB domain is crucial for the homodimerization of Keap1 and the binding with Cullin3 (Cul3) E3 ligase. (5),(6) The Kelch repeats are required for the binding of Keap1 with the Neh2 domain of Nrf2 as well as p62 and other E/STGE-containing

proteins IVR is located between BTB and Kelch repeats and has a nuclear export signal (NES) that regulates the cytoplasmic localization of Keap1 In addition, Keap1 is considerably rich in cysteine residues that act as detectors for electrophiles and reactive oxygen species (ROS), which is important for protecting Nrf2 from the proteasomal downgrade. (7)

2.2 Molecular Mechanisms Underlying NRF2 Activation

Nuclear factor erythroid-derived 2-like gene (NRF2) is a transcription factor that controls the environmental stress response by changing gene expression profiles. NRF2 regulates a subset of target genes that generally descramble cytoprotective enzymes/proteins critical to the antioxidative response and detoxication. (8)NRF2 is triggered when cells are exposed to oxidative stresses or toxic chemicals (electrophiles). This activation of NRF2 is fine-tuned by Kelch-like ECH-associated protein (KEAP11), an adaptor for Cullin 3 (Cul3)-based ubiquitin E3 ligase KEAP1 ties NRF2 and advances the ubiquitination of NRF2. Under consistent state conditions, ubiquitinated NRF2 is quickly debased by the 26S proteasome. The transcription factor Nrf2 contains seven highly conserved Nrf2-ECH homologies (Neh) domains, Neh1-Neh7, Among these domains, Neh1 has a cap 'n' collar (CNC) basic-region leucine zipper (bZIP) domain, which is critical for binding to DNA and forming heterodimers with small MAF (sMAF) proteins, additionally, Neh1 contains a nuclear localization signal (NLS) that enables the nuclear translocation of Nrf2 . The Neh2 domain is located In the N-terminal region the Neh2 domain is located and contains lysine residues. Neh2 is especially chargeable for the binding with Keap1 homodimers yet because of the subsequent ubiquitination and proteasomal degradation of Nrf2 additionally, Neh6, rich in serine residues, is negative regulatory domain responsible for Nrf2 ubiquitination and degradation by restricting to β-transducin repeat-containing protein (β-TrCP. On the other hand, the Neh3 domain enriches the Nrf2 protein with stability. The Neh3, Neh4, and Neh5 are transactivation domains that interact with other coactivators Neh7 which is necessary for the binding of Nrf2 to retinoid X receptor α (RXRα), resulting in the inhibition of the Nrf2-ARE signaling pathway. (9),(10),(11)

3. The dual role of nrf2 in cancer

3.1 Tumor suppressor functions of Nrf2: ‘the positive side of Nrf2’

A few investigations utilizing Nrf2 knockout mice (Nrf2−/−) show that Nrf2 ensures against compound cancer-causing agent incited tumor arrangement in the stomach, bladder, and skin.

The mechanism by which Nrf2 ensures against compound incited carcinogenesis might be expected to a limited extent to its capacity to lessen the number of reactive oxygen species (ROS) and DNA damage in cells. (12)

Additional proof supporting the defensive job of Nrf2 comes from concentrates with mice holding onto a single nucleotide polymorphism (SNP) in the promoter area of the mouse Nrf2 gene. Mice with this SNP have diminished articulation of Nrf2 and are more helpless to harmed cells. The human NRF2 quality likewise harbors a SNP in its advertiser area. Individuals with this SNP have fundamentally lower NRF2 courier RNA (mRNA) levels and an increased risk of cancer. (13)

Tumor suppressor functions of Nrf2: 'the negative side of Nrf2'

activation of Nrf2 protects against a spread of toxicants and diseases, the prolonged activation of Nrf2 has been shown to favor the progression of several kinds of cancers Nrf2 is constitutively elevated in lung, breast, head, and neck, ovarian, and endometrial carcinomas. The prognosis of patients with tumors expressing high levels of Nrf2 in the clinic is poor partly due to Nrf2's ability to enhance cancer cell proliferation and promote chemoresistance and radioresistance. (13),(14)

3.2 Tumor suppression role of Keap1

To understand the direct role of KEAP1 in tumor development generated Keap1-knockout mice (Keap1-/-) these animals developed hyperkeratosis of the esophagus and forestomach and showed postnatal lethality within thefirst3weeksKeap1-deficient mice demonstrated upregulation of detoxifying enzymes, including GST and NQO1, and better NRF2 signaling before death. KEAP1 was also reported to target NRF2/S100P pathway in non-small cell lung cancer (NSCLC) cells, acting as a tumor suppressor. Consequently, it was proposed that KEAP1 can be utilized as a biomarker to screen cancer progression. (15)

3.3 Carcinogenic role of Nrf2

The elevated levels of Nrf2 in malignancy cells have been displayed to advance cancer cell proliferation. They performed microarray examination to distinguish Nrf2 target qualities engaged with malignant growth cell expansion and recognized a few qualities associated with the pentose phosphate pathway, including glucose-6-phosphate dehydrogenase (G6PD), phosphogluconate dehydrogenase (PGD), transketolase (TKT), phosphoribosyl

pyrophosphate amidotransferase (PPAT), methylenetetrahydrofolate dehydrogenase 2 (MTHFD2), and isocitrate dehydrogenase 1 (IDH1), were additionally recognized as record focuses of Nrf2. Nrf2 straightforwardly initiated G6PD, PGD, TKT, TALDO1, ME1, and IDH1 by restricting to their particular AREs. These proteins support glucose motion and produce purines, which are the structure squares of DNA and RNA and are significant for speeding up multiplication in malignant growth cells. (16)

Nrf2 may likewise advance malignancy cell multiplication and tumorigenesis by keeping up with the redox balance and creating cancer antioxidants in tumor cells. Ongoing examinations have uncovered that glutathione is basic for cell expansion additionally tracked down that, in A549 cells, the cell levels of glutamine are raised and that a considerable measure of the glutamine was utilized for the age of glutathione. Hence, the upgrade of glutathione union is another significant impact of Nrf2 in speeding up cancer cell proliferation. (17)

3.4 Carcinogenic Role of KEAP1

Rather than defensive consequences for malignancy movement, considers have likewise exhibited the cancer-causing job of KEAP1 transformations in different tumors like gallbladder, prostate, liver, colorectal, lung, bosom, and prostate diseases Some changes found in the N-terminal and BTB spaces of KEAP1 forestalled ubiquitination of NRF2 through the disturbance of KEAP1-CUL3 development, and different changes in the Kelch areas restrained the association of KEAP1-NRF2 and caused adjustment of NRF2.[19]Additionally, changes in KEAP1 were likewise distinguished in liver and gallbladder, which caused overexpression of cell reinforcement and stage II detoxification chemicals that have a role in cancer chemo-opposition. (18)

4. Disrupted protein-protein interaction of Keap1–Nrf2

loss-of-function mutations in the KEAP1 gene were identified in human adenocarcinoma cell lines These mutations within the Gly to Cys in the Kelch domain of Keap1, which reduces the affinity of Nrf2 binding. Mutations have also been observed in many other cancer types including breast cancer gallbladder cancer, liver cancer, ovarian cancer, clear renal cell carcinoma, and lung papillary carcinomas, and the greater part of them are situated inside the Kelch space of KEAP1 However, changes in different areas of KEAP1 have additionally been discovered Importantly, a heteroallelic transformation in KEAP1 is adequate to expand Nrf2 movement, as transformed Keap1 capacities during the predominant negative style.

Notwithstanding point changes, shortened mRNA records of Keap1 have been seen in prostate disease cells. These differentially grafted records are nonfunctional and in this way unfit to smother Nrf2 movement (20) In the Nrf2 quality (NFE2L2), acquire of-work changes are successive. These changes have been accounted for in a few diseases, including lung, head and neck, and esophageal carcinomas. These changes are found only inside the ETGE and DLG themes of Nrf2 coming about in diminished Keap1 restricting fondness and restraint of the Nrf2 corruption. Substantial transformations of the CUL3 quality have been recognized in squamous cell cellular breakdown in the lungs and papillary renal cell carcinoma. Cul3 is that the sub-atomic platform restricting Keap1, Rbx1, and E2 ligase inside the ubiquitin ligase complex. Nonetheless, transformations in CUL3 are probably going to impact additionally numerous other pathways, as Cul3 ties to various other BTB-containing proteins. (20),(21)

Like changes in KEAP1, transformations in NRF2 allegedly constitutively enact stage II medication processing chemicals in human diseases. Investigations of the cell lines got from the diseases uncovered that these changes happen in the DLG and ETGE themes of the KEAP1-restricting space of the NRF2 quality. The disappointment of the changed NRF2 to tie to KEAP1 might get away from NRF2 from the ubiquitination, recommending to give protection from chemoprevention. (21)

5. Nrf2 inducers and inhibitors in the treatment

NRF2 is an appealing molecule as a healing goal in most cancers. There are major techniques used to goal NRF2 via way of means of healing drug treatment: one is NRF2 inhibition, and the opposite is NRF2 induction. NRF2 inducers had been proven to boost up the cleansing of cancer-causing agents (regularly electrophiles) from the surroundings and defend the frame from chemical carcinogenesis (22) Of note, the NRF2 inducer dimethyl fumarate has been permitted via way of means of the FDA for more than one sclerosis treatment, and bardoxolone methyl (CDDO-Me or RTA 402) is now in segment II scientific trials for pulmonary high blood pressure and persistent kidney diseases. Some phytochemicals, consisting of sulforaphane from broccoli sprouts, curcumin from turmeric, or carnosic acid from rosemary, additionally spark off NRF2. These chemical substances had been used as nutritional supplements. Two techniques for most cancers remedy targeted on NRF2. (23) Chemoprevention in opposition to cancer-causing agents via way of means of NRF2 inducers in regular cells. Anticancer remedy in opposition to NRF2-addicted most cancers cells via

way of means of NRF2 inhibitors. As defined inside the preceding section, the chemical substances defined above act to regulate KEAP1 cysteine residues. Therefore, issues stay concerning glutathione depletion or redox facet effects. An opportunity method for the improvement of NRF2 inducers is using chemical substances that disrupt the KEAP1–NRF2 interface, particularly chemical substances that focus on a pocket that is living withinside the backside of the KEAP1 DC domain. In this regard, it ought to be cited that there are numerous cancers in numerous tissues that display intrinsically excessive NRF2 activity. We talk to those cancers as NRF2-addicted cancers, as NRF2 gives cytoprotection to those most cancers cells via way of means of activating detoxifying and anti-oxidative enzymes and via metabolic reprogramming. For those cancers, NRF2 inhibitors may also display healing effects. (24),(23)

6. Conclusions

The Nrf2 have both a positive role and a negative role in the regulation of the carcinogenesis pathway the nrf2 inducers and inhibitors are used in reducing the carcinogenesis.

list of abbreviations

NRF2- nuclear factor erythroid 2- related factor

ARE - Adenosine receptor

KEAP1- kelch like-ECH-associated protein

MAF - macrophage activating factor.

ROS - reactive oxygen species

SNP - single nucleotide polymorphism

G6P- glucose-6-phosphate dehydrogenase

PGD - phosphogluconate dehydrogenase

TKt- transketolase

PPAT- phosphoribosyl pyrophosphate amidotransferase

MTHFD2- methylenetetrahydrofolate dehydrogenase 2

IDH1- isocitrate dehydrogenase 1

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