Small Molecule Compounds and the Nrf2 Signaling Pathway

The Nrf2 signaling pathway represents a very promising pharmacological target to control common pathologic mechanisms of many diseases. Smolecule explains.

SAN ANTONIO, TEXAS, UNITED STATES, February 8, 2021 /EINPresswire.com/ -- Nrf2 (NF-E2-related factor 2), a member of the Cap'n'collar (CNC) transcription factor family, consists of 605 amino acids and is divided into seven highly conserved functional domains, known as Neh1-Neh7. The N-terminal domain influences the stability and ubiquitination of Nrf2 by its negative regulator Keap1, while the Neh5 domain is responsible for the cytoplasmic localization of Nrf2. The Neh1 domain has a cap 'n' collar basic-region leucine zipper (bZIP) domain, which regulates DNA-binding, and a nuclear localization signal (NLS) that is responsible for the nuclear translocation of Nrf2. Nrf2 has seven highly conserved functional domains, called Nrf2-ECH homology (Neh1 to Neh7).

The Nrf2 signaling pathway contributes to the maintenance of cellular and tissue homeostasis and protects cells against oxidative stress. Nrf2 is ubiquitously and constitutively expressed by cells, thus ensuring their prompt protective response to oxidative, inflammatory, and metabolic stresses. The main control of Nrf2 stability is exerted by the E3 ligase adapter Kelch-like ECH-associated protein 1 (KEAP1). Under oxidative stress or upon exposure to Nrf2 activators, Nrf2 dissociates from Keap1 binding due to the thiol modification of Keap1 cysteine residues which ultimately prevents Nrf2 ubiquitination and proteasomal degradation. Then Nrf2 translocates into the nucleus, heterodimerizes with small Maf proteins, and transactivates an ARE battery of genes. An alternative mechanism for proteasomal degradation of Nrf2 is mediated by the glycogen synthase kinase 3 (GSK-3) and the E3 ligase adapter β-TrCP. GSK-3α and β are serine/threonine protein kinases involved in several signaling pathways such as receptor tyrosine kinase, WNT, and Hedgehog that influence cell division, survival, and development.

Deregulation of Nrf2 and/or Keap1 due to mutation and stimulated upstream oncogenes is related to nuclear accumulation and activation of Nrf2 to protect cells from apoptosis and induce proliferation, metastasis, and chemoresistance. Nrf2 modulation appears to be significant in the personalization of cancer therapy, anti-inflammation treatment, and implications in fighting vascular diseases.

Some Nrf2 inhibitors have been stated for the treatment of Nrf2-addicted cancers. One of them is brusatol, which is a natural quassinoid. It was found that brusatol stimulates poly-ubiquitination of Nrf2, which decreases the Nrf2 protein level. The inhibitory effect of brusatol to Nrf2 is revealed to not be dependent of its repressor Keap1. Brusatol was found beneficial for the inhibition of Nrf2 signaling. Luteolin was found as an inhibitor of antioxidant response element-driven gene expression. Using non-small-cell lung cancer cell lines (A549 cells), which have active Nrf2, luteolin provoked an intense decrease in Nrf2 at both the mRNA and the protein levels. Moreover, luteolin considerably sensitized A549 cells to the neoplastic drugs oxaliplatin, bleomycin, and doxorubicin. The effective protection activity of Nrf2 has been stated generally during tumor initiation. However, it is now well recognized that Nrf2 shows a dual effect in carcinogenesis. A growing number of research showed the oncogenic properties of Nrf2 in lung cancer, esophagus, and skin and renal cell cancer.

However, some would consider the implication of the role of Nrf2 in cancer is still controversial. Several studies described that Nrf2 knockout mice are more susceptible to chemically induced carcinogenesis, pointing Nrf2 as a potential tumor suppressor that limits carcinogenesis. On the other hand, Nrf2 is overexpressed in many types of tumors, and it has been related to poor disease prognosis because it confers a survival and growth advantage to cancer cells, along with resistance to chemo- and radiotherapy. Altogether, these results suggest a protective role of Nrf2 in the first steps of cancer, but in advanced stages, Nrf2 overexpression helps cancer cells to adapt to the tumorigenic demands. It is reasonable to assume that Nrf2 inhibitors should sensitize tumor cells to anticancer therapies.

Several compounds of natural origin have been reported to inhibit Nrf2, including brusatol which is mentioned earlier. The flavonoids luteolin and wogonin were reported to inhibit Nrf2 and sensitize cells to anticancer drugs by increasing the instability to its transcript. However, later studies also indicated that these compounds may elicit Nrf2 activation. Other natural compounds such the mycotoxin ochratoxin A and the coffee alkaloid trigonelline prevent the nuclear translocation of Nrf2. In leukemic cells, malabaricone-A, a plant-derived prooxidant, effectively inhibits Nrf2 transcriptional activity as reflected by a reduction in HO-1 protein levels and leads to ROS accumulation and subsequent cell apoptosis.

Isoniazid is an antitubercular drug that is also found can effectively inhibit the mRNA expression of Nrf2-driven genes in mouse preadipocyte 3T3-L1 cells. It was later reported that INH decreased Nrf2 nuclear protein levels and induced apoptosis in human hepatic carcinoma Hep3B cells through attenuating Nrf2 nuclear translocation and reducing of ERK1

phosphorylation. Ethionamide is a compound with a similar chemical structure to Isoniazid. It was found that treatment of THP-1 cells with ethionamide decreased mRNA expression of many Nrf2-dependent genes and enhanced sensitivity to ATO-induced cytotoxicity. However, the specific mechanism by which ethionamide inhibits Nrf2 is not known yet. Of interest, many known antitubercular agents, such as ethambutol dihydrochloride, ethionamide, rifampicin, and sparfloxacin have inhibitory effects on Nrf2 activity.

Compared to the diverse array of Nrf2 activators, the number of inhibitors is quite small. The so-called “Nrf2 activators” should be more precisely termed “KEAP1 inhibitors” as their molecular target is in fact KEAP1. Most pharmacological Nrf2 activators are electrophilic molecules that covalently modify cysteine residues present in the thiol-rich KEAP1 protein by oxidation or alkylation. The most successful Nrf2 activator to date is the fumaric acid ester dimethyl fumarate (DMF) that has been approved in 2013 by FDA for relapsing-remitting multiple sclerosis (MS). The DMF-induced activation of Nrf2 in the central nervous system was described in the MS mice model of experimental allergic encephalomyelitis. Other compounds include Oltipraz (4-methyl-5(pyrazinyl-2)-1-2-dithiole-3-thione), and Ursodiol (ursodeoxycholic acid).

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