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NRF2 SIGNALING ANTIOXIDANTS CASCADE – A GOOD CHEMO PREVENTIVE AND THERAPEUTIC TARGET IN BREAST CANCERS: A REVIEW

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ABSTRACT Breast Cancer is a type of cancer originating in the breast tissue. It is one of the most common types of cancer in the world and is the most common cancer occurring in females worldwide. Hence, the breast cancer is the top cancer in women worldwide and is increasing particularly in developing countries such as India, where the majority of cases are diagnosed in late stages. In a press release dated 12th December 2013, The International Agency for Cancer Research (IACR) has mentioned that global cancer burden rises to 14.1 million new cases and 8.2 million deaths in 2012 with a marked increase in breast cancers49. Furthermore, IACR also mentioned that the most commonly diagnosed cancers globally are the carcinomas of lung (1.8 million), breast (1.7 million) and colon and rectum (1.4 million). Among these cancers, the incidence and mortality rates due to carcinomas of breast have increased by 20% and 14%, respectively, compared to 2008 cancer statistics. This global increase in incidence and mortality is primarily due to the shift in life style of women living in the under developed and developing countries while the efforts to increase the awareness about early detection and treatment options are failing to reach these women. Addressing these issues, Dr. Christopher Wild, the Director of IACR has mentioned that – "an urgent need in cancer control today is to develop effective and affordable approaches to the early detection, diagnosis, and treatment of breast cancer among women living in less developed countries[50]". Though it is more prevalent in women, there have been rarely reported cases of male breast cancer as well. Therefore, it is important to know whether elevated expression of NRF2 and its downstream members such as NQO1 are contributing to the development of inflammatory mediators induced tumors such as carcinomas of colon and rectum and drug resistant breast cancers.

KEYWORDS :

INTRODUCTION

Breast cancer is a slow growing tumor, which begins in milk ducts (50-75% of cases), lobules (about 10-15% of cases) or in other breast tissues [1, 2]. By the time the tumor reaches a size of a lump, it might take as long as 10 years. However, some tumors are aggressive and grow much faster [3]. Hence, early detection of breast cancers is very much essential for the better treatment and management of disease, Breast cancer is the most common cancer in women both in the developed and less developed countries. Worldwide, total number of estimated deaths due to breast cancer, in the year 2011, exceeded half a million[4]. Although breast cancer is thought to be a disease of the developed world, ~50% of breast cancer cases and ~58% of deaths occur in less developed countries [5]. Breast cancer occurs when cells in the breast tissue mutate and keep dividing, more than the normal amount. These abnormal cells form a Tumour. When these cells start showing the property of metastasis, that is, when they start invading other tissue, they are called malignant and the disease thus caused is cancer. The cells may also migrate to neighbouring tissues or other tissues far away from the primary site of origin. The symptoms of breast cancer include: Lump in breast, Change in breast shape, Fluid coming from the nipple, Dimpling of the skin, A newly inverted nipple, Red/scaly skin, Bone pain, Swollen lymph nodes, Shortness of breath &Yellow skin.

Risk Factors of Breast Cancer: There are certain factors that increase the risk of incidence of breast cancer. The risk factors include:

a) Gender: Being a female is a primary risk factor for breast cancer. Simply, the fact that a person is a female predisposes one for breast cancer.

b) Obesity: High body mass index is a risk factor for breast cancer. Overweight women seem to show a disposition toward breast cancer, possibly due to greater blood insulin levels.

c) Age: The risk increases with age. Older women usually have a greater probability of developing breast cancer. The risk increases from the age of 40 and is highest around age 70.

d) Lack of Exercise: Less amount of cardio/other forms of exercise leads to a higher risk of breast cancer.

e) Alcohol Consumption: A higher rate of regular alcohol consumption also seems to pose a risk.

f) Genetics: Women who have family history of breast cancer and those who carry BRCA1 and BRCA2 gene mutations have a higher risk of development of breast cancer.

g) Radiation/Carcinogen Exposure: Occupational hazards or carcinogen and/or exposure to radiation pose a significant risk in the development of cancer.

h) Early Menarche: Women who started menstruating before the age of 12, have a greater probability of developing breast cancer.

i) Late Menopause: Women who develop late menopause have a greater risk of breast cancer, possibly due to estrogen levels.

j) Nulliparity: Women, who have never had children, pose a greater risk of breast cancer. Having a first child after 30 may also increase breast cancer risk.

k) Lack of Breastfeeding: Women who do not breastfeed, or breastfeed for a shorter duration than required, have a greater predisposition to developing breast cancer. A longer duration of breastfeeding has a protective effect on breast cancer and women, who partake in breastfeeding longer, show a reduced risk in development of cancer.

l) Hormone Therapy: The use of hormone treatments and birth control pills pose a significant risk in the development of breast cancer.

m) Race: Certain races are more predisposed to developing breast cancer, while others are not. White women have greater probability of developing breast cancer, while Asian, Hispanic and African women show reduced risk, compared to White women. However, Asian, Hispanic and African women show more probability of developing more aggressive forms of breast cancer.

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 1) signaling cascade is one of the most important cell defense and survival pathways, known to protect cells and tissues from a variety of toxicants and carcinogens by increasing the expression of a number of cytoprotective genes [6, 7]. As a result, several Nrf2 activators are currently being tested as chemo preventive compounds in clinical trials. However, as Nrf2 protects normal cells, Nrf2 may also protect cancer cells from chemotherapeutic agents and facilitate cancer progression [6]. Supporting this hypothesis, several studies have shown that Nrf2 is aberrantly accumulated in many types of cancers, and its expression is associated with a poor prognosis in patients [8]. In addition, Nrf2

expression has also been demonstrated to induce drug resistance, thereby further contributing to the tumor burden [9]. Additional studies have proved even that the expression of inflammatory markers is associated with the activity of NRF2 [10, 11].

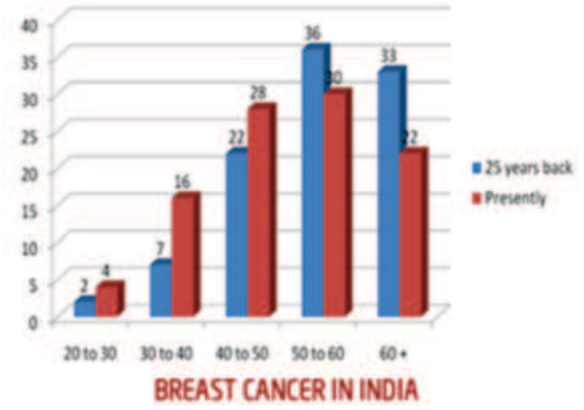
Review of Literature

The Disease: Breast cancer, which occurs when cells in the breast divide and grow without their normal control, is a slow growing tumor begins in milk ducts (50-75%), lobules (about 10-15%) or in other breast tissues. By the time it reaches to a size of a lump, it may take as long as 10 years. However, some tumors are aggressive and grow much faster [12].

Burden of Breast Cancer: Breast cancer is the second most common type of cancer in the world [12]. Even though carcinoma of breast can occur in men and women, the incidence is very rare in men [12]. Moreover, breast cancer is thought to be a disease of the developed world, however ~50% of breast cancer cases and ~58% of deaths occur in less developed countries [13]. Hence the Breast cancer is the top cancer in women worldwide and is increasing particularly in developing countries such as India, where the majority of cases are diagnosed in late stages.

More women are diagnosed with breast cancer than any other cancer. According to an estimate in United States, about 246,660 women will be diagnosed with invasive breast cancer, and 61,000 women will be diagnosed with carcinoma of breast in situ. An estimated 40,890 people (40,450 women and 440 men) are predicted to die from breast cancer in 2016. In India, the Indian Council of Medical Research (ICMR) predicted that by the end of 2016 the total number of new cancer cases is expected to be around 14.5 lakh and the figure is likely to reach nearly 17.3 lakhs by the year 2020. A significant increase in mortality rate was also expected from the cancers by ICMR. According to predictions the mortality rate due to cancers is about 7.36 lakh individuals in the year 2016 while the figure is estimated to shoot up to 8.8 lakhs by 2020 [14].

Among females, the cancer of breast with estimated 1.5 lakh stopped the list (over 10 per cent of all cancers) in the year 2016, is the number one cancer overall.



Year-wise Evaluation of Cancer Incidences in India

Year	Incidences in Male	Incidences in Female	Total Patients
2004	390803	426545	819354
2005	40000	43000	83000
2006	40000	45000	85000
2007	42000	47000	89000
2008	44000	49000	93000
2009	454842	507990	962832
2010	460428	517378	979786
2015	55000	60000	110000
2020	58000	65000	123000

Nrf2 and its target genes:

1)Nrf2: Nrf2 or **NFE2L2 Nuclear Factor (Erythroid-derived 2)-Like 2**, is a transcription factor that in humans is encoded by the *NFE2L2* gene.Nrf2 is a basic leucine zipper (bZIP) protein that regulates the expression of antioxidant proteins thereby protect against oxidative damage triggered by injury and inflammation[14]. While several drugs that stimulate the NFE2L2 pathway are being studied for the treatment of diseases that are caused by oxidative stress (such as diabetes), inhibition of Nrf2 is required where it plays a role in the tumor formation and drug resistance [15].

Nrf2 Target Genes: Activation of Nrf2 results in the induction of many cyto-protective proteins. These include:

NAD (P) H Quinone Oxidoreductase 1 (Nqo1): It is a prototypical Nrf2 target gene that catalyzes the reduction and detoxification of highly reactive quinones that can cause redox cycling and oxidative stress.

Glutamate Cysteine Ligase - Catalytic (GCLC) and Glutamate Cysteine Ligase - Modifier (GCLM) subunits form a heterodimer during the synthesis of glutathione (GSH), one of the most powerful endogenous antioxidant.

Heme Oxygenase-1 (HMOX1, HO-1):It is an enzyme that catalyzes the breakdown of heme into the antioxidant biliverdin, the anti-inflammatory agent carbon monoxide, and iron. HO-1 is an Nrf2 target gene that has been shown to protect from a variety of pathologies, including sepsis, hypertension, atherosclerosis, acute lung injury, kidney injury, and pain. In a recent study, however, induction of HO-1 has been shown to exacerbate early brain injury after intra-cerebral hemorrhage.

Glutathione S-Transferase (GST) family includes cytosolic, mitochondrial, and microsomal enzymes that catalyze the conjugation of GSH with endogenous and xenobioticelectrophiles. After detoxification by glutathione (GSH) conjugation catalyzed by GSTs, the body can eliminate potentially harmful and toxic compounds. GSTs are induced by Nrf2 activation and represent an important route of detoxification.

The UDP-glucuronosyltransferase (UGT) family catalyzes the conjugation of a glucuronic acid moiety to a variety of endogenous and exogenous substances, making them more water-soluble and readily excreted.

The important substances for glucuronidation include bilirubin and acetaminophen, Nrf2 has been shown to induce UGT1A1 and UGT1A6.

Multidrug Resistance-associated Proteins (MRP) are important membrane transporters that efflux various compounds from various organs and into bile or plasma, with subsequent excretion in the feces or urine, respectively. MRPs have been shown to be up regulated by Nrf2 and alteration in their expression can dramatically alter the pharmacokinetics and toxicity of compounds.

Interactions: NRF2 has been shown to interact with C-Jun, Cyclic AMP (Adenosine 3',5' Mono Phosphate) Response Element Binding Protein (CREBP),Eukaryotic Translation Initiation Factor 2 Alpha Kinase-3 (EIF2AK3),Kelch-like ECH-associated protein 1 (KEAP1), and Ubiquitin-C (UBC) proteins.

Functions of Nrf2: Nrf2 is a sensor of cellular stress. In normal conditions it resides in the cytoplasm in association with a cluster of proteins that degrade Nrf2 pretty quickly. However, when cells are exposed to stress inducing conditions, Nrf2 gets translocated to the nucleus where it binds to a DNA promoter and initiates transcription of genes involved in destroying stress inducing agents or help cell to express defense proteins. Mechanistically, Nrf2 is kept in the cytoplasm by Kelch like-ECH-associated protein 1 (KEAP1) and Cullin-3 proteins, which degrade Nrf2 by ubiquitination. Cullin-3 ubiquitinates Nrf2, while Keap1 is a substrate adaptor protein that facilitates the reaction. Once Nrf2 is ubiquitinated, it is transported to the proteasome, where it is degraded and its components recycled. Under normal conditions Nrf2 has a half-life of only 20 minutes. Oxidative stress or electrophilic stress disrupts critical cysteine residues in Keap1, thereby disrupting the Keap1-Cul3 ubiquitination system. When Nrf2 is not ubiquitinated, it builds up in the cytoplasm

and translocates into the nucleus, where it combines (forms a heterodimer) with a small Maf protein and binds to the **Antioxidant Response Element(ARE)** in the upstream promoter region of many genes coding for antioxidant enzymes and drug export proteins [16,17].

2) KEAP1: Kelch-like ECH-Associated Protein 1 is a protein that in humans is encoded by the Keap1 gene [18]. Keap1 is an attractive drug target as it is the key regulator of Nrf2.Several pharmaceutical companies have developed compounds that can modulate the expression of Keap1, which in turn help in controlling the levels of Nrf2. For example, Reata Pharmaceuticals has developed a series of synthetic oleane tri terpenoid compounds, known as antioxidant inflammation modulators (AIMs) to block Keap1-dependent Nrf2 ubiquitination. The lead compound in this series, bardoxolone methyl (also known as CDDO-Me or RTA 402), has been tested in late-stage clinical trials for the treatment of chronic kidney disease (CKD) in patients with type 2 diabetes mellitus and showed an ability to improve markers of renal function in these patients [19,20].

3) Hypoxia-inducible factor 1-alpha (H1F1α): It is a subunit of a hetero dimeric transcription factor hypoxia-inducible factor 1 (HIF-1) that is encoded by the *HIF1A* gene [21, 22]. HIF1α is amaster transcriptional regulator of cellular and developmental response to hypoxic conditions.Deregulation of *HIF1A* by either hypoxia or genetic alternations has been implicated in cancer biology, as well as in various diseases associated with vascularization and angiogenesis, energy metabolism, cell survival, and tumor invasion [23]. For example, HIF1α is overexpressed in many human cancers, which include cancers of the colon, breast, pancreas and kidney. Clinically, elevated HIF1αserves as a predictive and prognostic marker for resistance to radiation treatment, chemotherapy, and increased mortality.For instance, HIF1α expression regulates breast tumor progression, as elevated HIF1a levels were detected in early ductal carcinoma "in situ", a pre-invasive stage in breast cancer development.

4) Glutathione *S*-transferases (GSTs): Known as **ligandins** (named so, as GSTs bind toxins and act as transport proteins), GST family comprises of eukaryotic and prokaryotic phase II metabolic isozymes that catalyze the conjugation of reduced form of glutathione (GSH) to xenobiotic substrates for detoxification [24, 25]. The GST family consists of three enzyme forms: the cytosolic, mitochondrial, and microsomal also known as MAPEG-proteins. GSTs catalyze the conjugation of GSH via a sulphydryl group to electrophilic centers on a wide variety of substrates in order to make the compounds more water-soluble. This activity detoxifies endogenous compounds such as peroxidised lipids and enables the breakdown of xenobiotics [26].

In addition to itsability to conjugate xenobiotics to GSH, GSTs can also bind non substrate ligands. For instance, GST isozymes have been shown to inhibit the function of MAPK pathway. Cytosolic GSTP1-1, the most common GST expressed outside the liver, is predominant in heart, lung, and brain tissues. Based on its over expression in a majority of human tumor cell lines and prevalence in chemotherapeutic-resistant tumors, GSTP1-1 has been proven to play a key role in the development of cancer and drug resistance.Moreover, GSTP can selectively inhibit C-jun phosphorylation by JNK, preventing cells from undergoing apoptosis [27].

GCLC: Glutamate-cysteine ligase also known as gamma-glutamylcysteine synthetase, it is the first rate limiting enzyme in glutathione synthesis. The enzyme consists of two subunits, a heavy catalytic subunit and a light regulatory subunit. Deficiency leads to hemolytic anemia [28].

5) Heme Oxygenase 1 (HMOX1 or HO1): Heme oxygenase mediates the first step of heme catabolism, ie. Cleavage of heme to form biliverdin. Carbonmonoxide and ferrous iron.The biliverdin is subsequently converted to bilirubin by biliverdin reductase. Heme oxygenase activity is induced by its substrate heme and by various nonheme substances. Heme oxygenase occurs as 2 isozymes, an inducible heme oxygenase-1 and a constitutive heme oxygenase-2 [29].In addition to its primary role in heme catabolism, HO-1 exhibits anti-oxidative and anti-inflammatory functions via the actions of biliverdin and CO, respectively. Biologically, HMOX1 helps in maintaining the iron homeostasis and protecting against cellular stress. Whereas HO-1 deficiency in normal cells enhances DNA damage and carcinogenesis, HO-1 over expression in cancer cells promotes proliferation and survival. Moreover, HO-1 induces angiogenesis through modulating expression of angiogenic factors. Mechanistically, HO-1 is susceptible to proteolytic cleavage and translocates to nucleus to facilitate tumor growth and invasion independent of its enzymatic activity. Further, HO-1 also impacts cancer progression through modulating tumor microenvironment [30,31].

6) NQO1 or NAD(P)H dehydrogenase [quinone] 1: NQO1 is an enzyme that in humans is encoded by the *NQO1* gene.This FAD-binding protein forms homodimers and performs two-electron reduction of quinones to hydroquinones [32]. Catalytically, NQO1 removes quinones from biological systems by complete oxidation of the substrate without the formation of semiquinones and reactive oxygen radicals that are otherwise deleterious to cells. In addition, the ubiquitin-independent p53 degradation pathway is regulated by NQO1, as NQO1 stabilizes p53 thereby protecting it from degradation [33]. Mechanistically, in the presence of NADH, NQO1 non-catalytically interacts with P53 thereby by protect it from 20S proteasomal degradation pathway. Individuals with decreased NQO1 expression/activity have reduced p53 stability, which may lead to oncogenic transformation of cells as well as drug resistance. Recent studies have identified mutations in NQO1.For example C609T mutant version of NQO1 has been reported in the carcinomas of breast, colon and rectum and prostate [34].

Objective Of The Study

Review of Nrf2 regulation in the expression of several genes involved in regulating antioxidant response in the transformation of cancer cell to normal cell by targeting Nrf2, helps in the prevention and treatment of Breast Cancers.

Limitations

1. Study Population not applicable as it is a review of literature study
2. Informed consent Form Not required as it is a literature study.

CONCLUSION

Since Nrf2 regulate the expression of several genes involved in regulating antioxidant response of a cell and play a prominent function in the transformation of normal cell in to a cancer cell, targeting Nrf2 helps in the prevention and treatment of cancers. Moreover, several recent studies reported over expression of Nrf2 or mutational inactivation of its inhibitor Keap1 in cancers. Further, accumulating evidences point that Nrf2 inhibitors alone and/or in combination with other chemotherapeutic agents help to overcome drug resistance in cancers [35, 36].In addition, targeted inhibition of Nrf2 sensitizes cancer cells to radiation treatment. Therefore, Nrf2 is an important target to consider for pharmacological agents development to treat cancers. Hence, in this study we propose to measure the expression and activity of Nrf2 and its target genes NQO1, GST, HIF1α and HO1, and its inhibitor Keap1 in cell lines representing carcinomas of breast viz., MCF7, MDA-MB-231 and T47D [37, 38]. Results of this study helps to identify a suitable cell line for screening Nrf2 inhibitors.

DISCUSSION

Breast cancer, which occurs when cells in the breast divide and grow without their normal control, is a slow growing tumor begins in milk ducts (50-75%),lobules (about 10-15%)or in other breast tissues. By the time it reaches to a size of a lump, it may take as long as 10 years. However, some tumors are aggressive and grow much faster [39].Oxidative stress is a major factor linked to various chronic diseases including cancer, atherosclerosis, ageing, diabetes, inflammatory disorders, and neurodegenerative diseases [40, 41]. By definition, oxidative stress is an imbalance in a cellular redox homeostasis, and is characterized by an excessive amount of reactive oxygen species (ROS) which, unless detoxified, cause damage to cellular components [42]. ROS are oxygen-containing molecules, which are reactive such as free-radicals. ROS can react with many molecules around the cell thereby disrupt their function [43, 44]. Nrf2 regulate the expression of several genes involved in regulating antioxidant response of a cell and play a prominent function in the transformation of normal cell in to a cancer cell, targeting Nrf2 helps in the prevention and treatment of cancers. Moreover, several recent studies reported over expression of Nrf2 or mutational inactivation of its inhibitor Keap1 in cancers. Further, accumulating evidences point that Nrf2 inhibitors alone and/or in combination with other chemotherapeutic agents help to overcome drug resistance in cancers [45, 46].In addition, targeted inhibition of Nrf2 sensitizes cancer cells to radiation treatment.

Nrf2 is a Key Regulator of Oxidative Stress in Cancer Cells: There are many mechanisms by which cells protect themselves from ROS-

induced damage [47]. Nuclear factor erythroid 2 related factor 2 (Nrf2) is a key regulator of oxidative stress. Nrf2 is regulated by Keap1, which targets it for the degradation [48]. Disruption of the Nrf2/Keap1 interaction results in the activation of Nrf2. Functionally active Nrf2 protects cells against oxidative stress by inducing cytoprotective proteins such as heme oxygenase-1 (HO-1), NAD(P)H:Quinone Oxidoreductase 1 (NQO1), Ferritin, glutathione synthesis enzymes, glutathione S-transferase (GST), superoxide dismutase (SOD), catalase and multidrug-associated resistance proteins [36-38]. Many of the enzymes induced by Nrf2 are phase II and III detoxification enzymes, which convert toxins into less harmful metabolites and facilitate their export from the cell [37, 38]. While this anti-oxidant potential of Nrf2 is a useful function for the survival of normal cells under oxidative stress conditions and is much desired for treating diseases such as diabetes, cancer prevention and cardiovascular disease, it is a very detrimental function in case of cancers. In cancers, the activated Nrf2 is hijacked to induce chemo- and radio- resistance, and form much more aggressive metastatic tumor types [48]. Therefore, targeted inhibition of Nrf2 or its target genes is required for treating advanced cancers. However, it is not fully known which among various Nrf2 target genes to inhibit.

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