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Review Article

Oncogenic functions of the transcription factor Nrf2

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ABSTRACT

Nuclear factor E2-related factor 2 (Nrf2) is a transcription factor that controls the expression of a large pool of antioxidant and cytoprotective genes regulating the cellular response to oxidative and electrophilic stress. Nrf2 is negatively regulated by Kelch-like ECH-associated protein 1 (Keap1) and, upon stimulation by an oxidative or electrophilic insult, is rapidly activated by protein stabilization. Owing to its cytoprotective functions, Nrf2 has been traditionally studied in the field of chemoprevention; however, there is accumulated evidence that Keap1/Nrf2 mutations or unbalanced regulation that leads to overexpression or hyperactivation of Nrf2 may participate in tumorigenesis and be involved in chemoresistance of a wide number of solid cancers and leukemias. In addition to protecting cells from reactive oxygen species, Nrf2 seems to play a direct role in cell growth control and is related to apoptosis-regulating pathways. Moreover, Nrf2 activity is connected with oncogenic kinase pathways, structural proteins, hormonal regulation, other transcription factors, and epigenetic enzymes involved in the pathogenesis of various types of tumors. The aim of this review is to compile and summarize existing knowledge of the oncogenic functions of Nrf2 to provide a solid basis for its potential use as a molecular marker and pharmacological target in cancer.

Contents

Abbreviations: b-ZIP, leucine-zipper protein; ARE, antioxidant response element; PT, primary tumor; LOH, loss of heterogeneity; NSCLC, non-small-cell lung carcinoma; EOC, epithelial ovarian carcinoma; ESCC, esophagus squamous cell carcinoma; SCC, squamous cell carcinoma; STC, stomach carcinoma; HCC, hepatocellular carcinoma; COL, colorectal carcinoma; AML, acute myeloid leukemia; CML, chronic myelogenous leukemia; ER, estrogen receptor; MGMT, methylguanine DNA-methyltransferase; ERK, extracellular-regulated MAP kinase; PI3K, phosphatidylinositol-4, 5-bisphosphate 3-kinase; MEK, MAP kinase-ERK kinase; JNK, c-Jun N-terminal kinase; PKC, protein kinase C; GSK-3β, glycogen synthase kinase 3β; LC3α, kinase light chain 3α; MDR, multidrug resistance; CHOP, C/EBP homologous protein; SAHA, suberoylanilide hydroxamic acid; mTOR, mammalian target of rapamycin.

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Introduction

Nrf2, or nuclear factor E2-related factor 2, is a transcription factor belonging to the cap′n'collar family of leucine-zipper (b-ZIP) proteins [1], which regulates cell response to oxidative and electrophilic insults.

Under homeostatic conditions, Nrf2 is generally localized in the cytoplasm, where it is sequestered by its inhibitor, Keap1, or Kelch-like ECH-associated protein 1 (Fig. 1A). Keap1 interacts with the Nrf2 N-terminal domain Neh2 [2,3] through two binding sites located on its Kelch-like domains and facilitates the association of Cul3, a Cullin-3-based E3 ubiquitin ligase [4–6]. Cul3 then mediates the ubiquitination and subsequent degradation of Nrf2 by 26 S proteasome [7,8]. Thus, under basal conditions, Nrf2 undergoes a rapid physiological turnover triggered by Keap1.

Under oxidative or electrophilic stress conditions (Fig. 1B), however, Keap1 acts as a molecular sensor and undergoes chemical modifications in a series of reactive cysteine residues (reviewed in [9,10]), allowing the release of Nrf2 [11,12], which escapes from degradation and translocates to the nucleus. Therefore, protein stabilization is the main mechanism for the activation of the Nrf2 response [13,14].

Once in the nucleus, Nrf2 heterodimerizes with proteins from a family of b-ZIP oncogenes called small Maf (musculoaponeurotic fibrosarcoma) proteins [15] and binds antioxidant response elements (AREs) localized in the promoter region of its target genes. Nrf2 target genes are mainly antioxidant and phase II enzymes such as heme oxygenase-1 (HO-1) [16], NAD(P)H–quinone oxidoreductase 1 (NQO1) [15,17], glutathione *S*-transferases (GSTs) [18], γ-glutamylcysteinyl synthetase [19], glutathione peroxidases [20], thioredoxin reductase 1 (TrxR1) [21,22], peroxiredoxin 1 [23], aldehyde oxygenase [24], and other genes regulating the response to oxidative stress [25]. Nrf2 also activates the transcription of some genes of the multidrug resistance (MDR) family such as MRP1 [26], MRP2 [27,28], MRP3, and MRP4 [28]. Overall, Nrf2 regulates the expression, both basal and inducible [29], of enzymes and other proteins involved in cell protection from physical/chemical insults, detoxification, and restoration of homeostasis. For this reason, Nrf2 is considered a cytoprotective transcription factor.

Owing to its role in protecting the cell from cytotoxicity associated with reactive oxygen species (ROS) and electrophilic stressors, Nrf2 is especially important in chemoprevention of diseases. The role of Nrf2 in this field has been widely studied and a great number of Nrf2 inductors, mainly natural compounds present in vegetables, have been described (reviewed in [30,31]). Moreover, there are currently several active clinical trials for activators of the Nrf2 pathway with potential utility in chemoprevention of various pathologies that are generally characterized by the production of intracellular ROS and eventual cell death [32]. Among those pathologies, the role of Nrf2 has been deeply studied in cancer, in which the response of cells to physical (radiation) and chemical (pollution, toxins, drugs) insults is especially important. Consequently, the number of citations relating Nrf2 and cancer has exponentially increased in the past decade [33].

As a cytoprotective gene, Nrf2 has been traditionally considered to be a tumor suppressor. For instance, Nrf2-deficient mice seem to be more sensitive to carcinogenesis [34,35] and Nrf2 loss has been related to enhanced metastasis [36,37]. Accordingly, there are multiple reports describing the beneficial effects of Nrf2 signaling in cancer chemoprevention (reviewed in [30]). However, in the past few years, mounting evidence that the activation of the Nrf2 pathway might not be beneficial in all cancer types and stages has started to arise. In fact, there are many reports that support the idea that Nrf2 activation in malignant cells could be detrimental for the evolution of the disease as well as for the outcomes of the treatment, and findings of several mutations and aberrant signaling of the Nrf2 pathway in cancer reveal a new role for this factor beyond its functions in chemoprevention. Thus, the beneficial effects of the activation of Nrf2 signaling in cancer have become a controversial issue (reviewed in [38]).

From either perspective, it seems to be clear that Nrf2 is an interesting pharmacological target for the prevention or treatment of malignant diseases. There is therefore an increasing need to define the limits between Nrf2's positive and negative effects in cancer and establish the basis for rational Nrf2-targeted therapies. In this article, we attempt to address this issue, focusing on Nrf2 as a potential oncogene and reviewing the most recent advances in this field to help provide a solid basis for the use of Nrf2 as a molecular marker and pharmacological target in cancer.

Nrf2 as a proto-oncogene

Nrf2 signaling in physiological conditions acts as a switch that is turned on by the presence of stressors in the cellular microenvironment and that is rapidly deactivated when the insult is withdrawn and homeostasis is restored. However, under pathological conditions, the tight regulation of Nrf2 by rapid protein turnover is highly susceptible to being altered. This could result in the loss of responsiveness to cell stressors and subsequent vulnerability of the cell to various insults. For instance, $Nrf2^{-/-}$ mouse models have shown a high sensitivity to chemical and physical insults [39–41].

On the other hand, Nrf2 regulation could be unbalanced toward the loss of the inducible nature of Nrf2 signaling and the acquisition of a constitutively active phenotype. Constitutive signaling toward the expression of cytoprotective enzymes would confer cells a survival advantage under adverse conditions. This advantage would become a serious drawback in the context of cancer pathogenesis and treatment. Therefore, constitutive activation or augmented signaling of the Nrf2 pathway might be decisive for cell fate during tumorigenesis and affect the response to chemotherapy. Under these conditions, Nrf2 can be defined as a proto-oncogene [42].

Nrf2 in tumorigenesis

The participation of Nrf2 in cancer pathogenesis is a controversial topic, provided a number of reports that still assign Nrf2 a role in cancer chemoprevention from genotoxic agents [43–45] or inflammation [46]. However, some reports have shown that drugs that activate Nrf2 can promote cell growth [47–49] and an increasing number of works point to a potential role for Nrf2 and its transcriptional target genes in tumorigenesis.

Nrf2-induced antioxidant enzymes in cancer

Many Nrf2 target genes have been profusely described to play a role in cell growth and tumorigenesis.

HO-1 is one of the best-known Nrf2 targets [16] and its involvement in cell growth and cancer development has been widely documented. HO-1 is overexpressed in a variety of solid tumors [50–52] and has been reported to play a role in metastasis