Role of the Nrf2-ARE signaling pathway in prostate tumorigenesis


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Introduction

Prostate cancer, one of the most frequent cancers in males in Western industrialized countries, is characterized by increased intracellular oxidative stress (1). Chronic oxidative stress and its associated pathological conditions including inflammation and metabolic disorders have been postulated to drive somatic mutations and neoplastic transformation, thus playing an important role in the development and progression of prostate cancer. Recent evidence has shown that oxidative stress, which is able to maintain redox homeostasis, may be able to mediate various cellular responses, including the regulation of gene expression through the Nrf2-ARE signaling pathway. Nrf2 (nuclear factor, erythroid-derived 2-like 2) is a basic leucine zipper transcription factor that mediates the cellular response to oxidative stress and toxicants (2). Upon activation, Nrf2 translocates from the cytoplasm to the nucleus where it binds to the antioxidant response element (ARE) and initiates the transcription of detoxification and antioxidant genes. In this review, we will discuss the role of Nrf2 in the development and progression of prostate cancer, with a focus on its potential therapeutic implications.

Prostate cancer is one of the most common malignancies in men, with an estimated incidence of 174,800 new cases in the United States in 2020 (3). It is the second leading cause of cancer death in men, after lung cancer (4). Chronic oxidative stress and inflammation have been implicated in the development and progression of prostate cancer. Recent studies have demonstrated that Nrf2, a transcription factor that plays a crucial role in the cellular response to oxidative stress, is frequently upregulated in prostate cancer tissues (5-7). Nrf2 activation leads to the induction of various antioxidant enzymes and detoxification pathways, which may help to protect cells from the damaging effects of reactive oxygen species (ROS). However, the dysregulation of Nrf2 has also been associated with cancer progression, as evidenced by the finding that Nrf2 expression is upregulated in many prostate cancer cell lines and xenograft models (8).

The Nrf2-ARE signaling pathway is a complex mechanism that involves multiple signaling cascades and transcription factors. It is activated in response to various oxidants and electrophiles, which lead to the binding of Nrf2 to the ARE located in the promoter region of target genes. This binding results in the recruitment of the Cul3-Rbx1 core ubiquitin machinery, leading to degradation of Nrf2. For clarity, the ARE. The Nrf2-Keap1 complex is then transported out of the nucleus by the cellular redox homeostasis, Keap1 travels into the nucleus to remove Nrf2 from the nucleus. Once in the cytoplasm, the Nrf2-Keap1 complex associates with the Cul3-Rbx1 core ubiquitin machinery, resulting in degradation of Nrf2 and termination of the Nrf2/ARE signaling pathway (see Fig. 2) (5). Interestingly, recent studies also suggest that overexpression of an importin α protein, KPNA6 not only promotes nuclear import of Keap1 but also accelerates the clearance of Nrf2 protein from the nucleus during post-induction phase, therefore, promoting retention of Nrf2 protein to sublocal levels (8). It seems that Keap1 may interact with KPNA6 via a mechanism other the classical nuclear localization signals (see Fig. 2) (9).

In this study, we provided compelling evidence that the expression of Nrf2 is epigenetically suppressed by its promoter methylation associated with Methyl-CpG-binding Domain 2 (MBD2) and histone modifications in the prostate cancer tissues of TRAMP mice. In addition, we reported that both loss of Nrf2 and subsequent induction of the E-cadherin transcriptional repressor Slug can also enhance cellular plasticity and motility in prostate tumor cells, in part by using TGF-β/MAD5 malignant signaling.

Discussions

Previous studies from several laboratories indicate that Nrf2 plays an essential role in the development of various cancers. (9,10) Nrf2 regulates the expression of a distinct set of antioxidant genes that efficiently protect mammalian cells from various forms of stress, and consequently, reduce the propensity of tissues and organisms to develop disease or malignancy. (11) Upon recovery of cellular redox homeostasis, Keap1 travels into the nucleus to dissociate Nrf2 from the ARE. Subsequently, the Nrf2-Keap1 complex is exported out of the nucleus by the nuclear export sequence (NES) in Keap1. Once in the cytoplasm, the Nrf2-Keap1 complex associates with the Cul3-Rbx1 core ubiquitin machinery, leading to degradation of Nrf2 and termination of the Nrf2/ARE signaling pathway (see Fig. 2) (5).

Figure 1. Proposed pathway for the induction of cytoprotective genes by enzyme inducers. Inducers promote the release of Nrf2 from a cytosolic inhibitor Keap1 by altering the structure of the nuclear localization signal of Keap1. Protein kinase C (PKC) phosphorylates Nrf2 which can alter the binding of Nrf2 to Keap1. Other signal transduction pathways such as the MAPK cascade and phosphatidylinositol 3-kinase (PI3K) also affect the activation process of Nrf2. Nrf2 then accumulates in the nucleus and transactivates known ARE-containing genes as well as Nrf2 itself. The gene families regulated by the Nrf2 pathway include phase 2 enzyme inducers, and their modifying enzymes, and the 26S proteasome subunits. Inducers may also be required for detoxification, although specific mechanisms are not yet clear. The induction of cytoprotective genes may facilitate the detoxification of carcinogens, enhance the reducing potential against electrophiles and free radicals, and elevate cellular capacity for repair/removal of oxidatively damaged proteins.

References