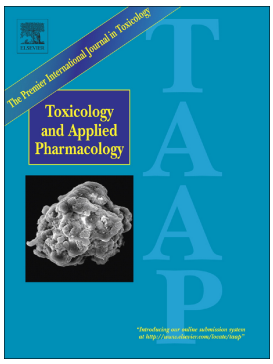

Nrf1 is paved as a new strategic avenue to prevent and treat cancer, neurodegenerative and other diseases

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Nrf1 is paved as a new strategic avenue to prevent and treat cancer, neurodegenerative and other diseases

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HIGHLIGHTS:

- **Nrf1 is a new strategic target for chemoprevention of cancer and other diseases**
- **Inhibitors of Nrf1 to unbalance proteostasis facilitate treatment of malignancies**
- **Nrf1 activators to rescue redox proteostasis favor therapy of proteotoxic diseases**

Abstract: Transcription factor Nrf1 acts as an unique vital player in maintaining cellular homeostasis and organ integrity during normal development and growth throughout the life process. Loss-of-function of Nrf1 results in severe oxidative stress, genomic instability, embryonic lethality, developmental disorders, and adult diseases such as non-alcoholic steatohepatitis, hepatocellular carcinoma, diabetes and neurogenerative diseases. Thereby, Nrf1 is critically implicated in a variety of important physio-pathological processes by governing robust target genes in order to reinforce antioxidant, detoxification and cytoprotective responses to cellular stress. Notably, there also exists a proteasomal 'bounce-back' response mediated by Nrf1, insofar as to enhance the drug resistance to proteasomal inhibitors in clinical treatment of neuroblastoma, multiple myeloma and triple-negative breast cancers. Recently, several drugs or chemicals are found or re-found in new ways to block the proteasomal compensatory process through inhibiting the multistep processing of Nrf1. Conversely, activation of Nrf1 induced by some drugs or chemicals leads to cytoprotection from cell apoptosis and promotes cell viability. This is the start of constructive and meaningful studies, approaching to explore the mechanism(s) by which Nrf1 is activated to protect neurons and other cells from malignant and degenerative diseases. Overall, Nrf1 has appealed attentions as a new attractive therapeutic strategy for human diseases including cancers.

Short title: Nrf1 is a new therapeutic strategic target

Keywords: Nrf1, drug, cancer, neurodegenerative, proteasome, chemoprevention, therapy

1. Introduction

It is clear that development of cancer and other diseases is always accompanied by an imbalance of cellular redox, lipid and protein homeostasis, and even in a state of sever metabolic stasis (Zhang and Xiang, 2016). If