INTRODUCTION

Human exposure to environmental toxins has been associated with etiology of many diseases including inflammation, cancer, cardiovascular and neurodegenerative disorders, sepsis, repulsion damage and diabetes. To counteract the detrimental effect of environmental insults, mammalian cells have evolved a hierarchy of sophisticated sensing and signaling mechanisms to turn on or off endogenous antioxidant responses accordingly. One of the major cellular sensors activated during oxidative stress is the nuclear factor E2-related factor 2 (Nrf2), a transcription factor that regulates expression of cytoprotective genes involved in cholesterol/lipid biosynthesis.

The Nrf2 transcription factor leads to transcriptional activation of phase 2, phase 3 and antioxidant enzymes, as well as other defensive proteins, via the nuclear factor erythroid 2 (NF-E2) -related factor 2 (Nrf2)/antioxidant response element (ARE) signaling pathway.

DISCUSSION

Epidemiological studies indicate that cancer susceptibility is influenced significantly by diet. This probably involves either dietary consumption of carcinogens that exceed the detoxification defences of the host, or consumption of diets that contain insufficient amounts of anticarcinogens, otherwise called cancer chemopreventive agents. The underlying molecular mechanisms by which diet influences the development of cancer are poorly understood. In this study, we have highlighted recent advances in understanding how cancer chemopreventive agents transcriptionally activate the expression of genes encoding phase 2, phase 3 and antioxidant enzymes as well as other defensive proteins. Various models have been proposed to explain how the Nrf2 protein is stabilized during the induction of ARE-containing genes. In one model, Nrf2 is phosphorylated by PKC, MAPK, P38K or PERK in response to inducing agents, thereby enabling the 2 beta-protein to either associate with Keap1 or dissociate from Keap1 (Fig.3). In another model, Keap1 is modified directly by the chemopreventive agents at cytosolic Nrf2 cytoplasmic-nuclear shuttling of Nrf2, Keap1, and the complex is omitted.

Figure 3. Proposed pathway for the induction of cytoprotective genes by chemopreventive agents. Keap1 controls postinduction repression of the Nrf2-mediated antioxidant response by escorting nuclear export of Nrf2. (Adapted from Sun Z, Zhang S, Chan JY, Zhang DD. Keap1 controls postinduction repression of the Nrf2-mediated antioxidant response by escorting nuclear export of Nrf2. Mol Cell Biol. 2007 Sep;27(18):6334-49."

Figure 4. Proposed pathways for the induction of cytoprotective genes by chemopreventive agents. Keap1 controls postinduction repression of the Nrf2-mediated antioxidant response by escorting nuclear export of Nrf2. (Adapted from Sun Z, Zhang S, Chan JY, Zhang DD. Keap1 controls postinduction repression of the Nrf2-mediated antioxidant response by escorting nuclear export of Nrf2. Mol Cell Biol. 2007 Sep;27(18):6334-49.)

References

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