

# The KEAP1-NRF2 pathway and its role in cancer

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The redox-activated transcription factor Nuclear factor E2-related factor-2 (NRF2) is the master regulator of antioxidant and cytoprotective responses upon oxidative and electrophilic stress. NRF2 functions via binding as a heterodimer with small Maf proteins to the antioxidant response element (ARE), a cis-acting sequence within the regulatory regions of a wide range of protective genes, thus affecting disease pathologies in which oxidative stress plays a role. In contrast to transient activation by NRF2 activating agents in non-malignant cells, NRF2 pathway is often constitutively activated in various cancers, particularly in non-small cell lung cancer (NSCLC), contributing to the malignant phenotype and drug resistance. Therefore both activation and inhibition of the pathway may have therapeutic potential in various age-related degenerative diseases.

Herein, the molecular mechanisms by which NRF2 is activated upon endogenous and exogenous stimuli are portrayed, emphasizing the role of NRF2 inhibiting protein KEAP1. Furthermore, dysregulation of the KEAP1-NRF2 pathway and the consequences of constitutive NRF2 activation in cancer is discussed, highlighting targetable vulnerabilities in NRF2 addicted cancers.