Keap1-Nrf2 Signaling Pathway: Mechanisms of Regulation and Role in Protection of Cells against Toxicity Caused by Xenobiotics and Electrophiles

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Abstract—The transcription factor Nrf2 governs the expression of a considerable group of genes involved in cell protection against oxidants, electrophiles, and genotoxic compounds. The activity of Nrf2 is sensitive to xenobiotics and endogenous electrophiles. Nrf2 is negatively regulated by specific suppressor protein Keap1, which is also a receptor of electrophiles and adapter for Cul3 ubiquitin ligase. Electrophiles react with critical thiol groups of Keap1 leading to the loss of its ability to inhibit Nrf2. The Keap1-Nrf2 signaling pathway also down-regulates NF-κB transcriptional activity and attenuates cytokine-mediated induction of proinflammatory genes. Pharmacological activation of the Keap1-Nrf2 pathway can be used for treatment and prevention of many diseases. Widely known natural Keap1-Nrf2 activators include curcumin, quercetin, resveratrol, and sulforaphane. The most effective Keap1-Nrf2 activators are synthetic oleanane triterpenoids.

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