Nrf2 and Keap1 Regulation of Antioxidant and Phase II Enzyme Genes

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Antioxidant responsive element (ARE) mediates the transcriptional activation of the genes encoding phase II drug metabolizing enzymes and antioxidative stress genes. The ARE consensus sequence shows high similarity to NF-E2 binding sequence, a *cis*-acting erythroid gene regulatory element. Based on the observation, we carried out targeted disruption of the *nrf2* gene in mouse and examined the inducible expression by BHA of several detoxifying enzyme genes.The induction of phase II drug metabolizing enzyme genes by BHA or other electrophonic agents was significantly affected in the *nrf2* gene knockout mouse. Nrf2 also regulates the expression of anti-oxidative stress enzyme genes in the mouse, indicating that Nrf2 is essential for the coordinate induction of phase II detoxifying enzymes and antioxidant enzymes. Detailed analysis of the regulatory mechanisms of Nrf2 activity have led us to the identification of a new protein, Keap1, that suppresses Nrf2 activity by specific binding to its evolutionarily-conserved N-terminal Neh2 regulatory domain. Nrf2 was liberated from Keap1 by electrophonic agents/phase II inducers, suggesting that the Nrf2-Keap1 system acts as a sensor for the xenobiotics and oxidative stresses. We also executed targeted disruption of mouse *Keap1* gene. Keap1-deficient mouse shows constitutive overexpression of Nrf2-target genes. These data demonstrates that the Nrf2-Keap1 system contributes to the expression of cytoprotective enzyme genes