

# **REGULATION OF NRF2 BY A KEAP1-DEPENDENT E3 UBIQUITIN LIGASE**

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## **ABSTRACT**

Oxidative damage to biological macromolecules has been implicated in diverse pathophysiological processes, including cancer, neurodegeneration, aging and cardiovascular disease. The Nrf2 transcription factor regulates expression of ROS (reactive oxygen species)-scavenging enzymes and enables mammalian cells to counteract oxidative stress and maintain redox homeostasis. The Keap1 protein functions as a substrate adaptor for a Cul3-RING dependent E3 ubiquitin ligase complex and targets Nrf2 for proteasome-mediated degradation under homeostatic conditions. The Keap1-Cul3-RING ubiquitin ligase is inactivated following exposure of cells to oxidative stress or electrophilic chemicals, resulting in accumulation of Nrf2 and activation of Nrf2-dependent cytoprotective gene expression. The Keap1-Cul3-RING ubiquitin ligase complex is modulated at multiple levels. Neddylation of Cul3 on Lys 712 and CAND1-dependent cyclical assembly and disassembly of the Keap1-Cul3-RING ubiquitin ligase are required for optimal activity of the ligase. A number of critical amino acid residues located within the substrate-binding pocket of Kelch  $\beta$ -propeller domain of Keap1 make key contacts with the conserved (D/N)xE(T/S)GE motifs in the substrate protein. A distinct subpopulation of the Keap1-Nrf2 complex is anchored at mitochondria by PGAM5 and may thereby facilitate communication between the nuclear anti-oxidant genes that are regulated by Nrf2 and ROS produced by mitochondria.