# The Nrf2-Keap1 System and Cancer

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Chemical carcinogenesis is tightly linked to the adaptation mechanisms equipped to our bodies against environmental stresses. Our bodies must readjust themselves to counteract insults originating from oxidative or xenobiotic stress from the environment. We found that Nrf2 is essential for the coordinated induction of cellular defense enzymes. Detailed analysis of the regulatory mechanisms governing Nrf2 activity led to the identification of a new protein, Keap1, which represses Nrf2 activity by binding to the N-terminal Neh2 domain. Electrophiles liberate Nrf2 from the repression by Keap1 and provoke the nuclear accumulation of Nrf2, suggesting that the Nrf2-Keap1 system acts as a sensor for xenobiotics and oxidative stress. The hinge and latch model proposed for the Keap1-Nrf2 system describes the regulation of nuclear accumulation of Nrf2 by a Keap1-dependent E3 ubiquitin ligase and its response to oxidative and xenobiotic stresses. We recently found cancer-related mutations of the Nrf2-Keap1 system. These mutations are concentrated in the Keap1-Nrf2 interface and act as activating mutations of Nrf2. Cancer cells acquire protection against the environment and cancer chemotherapy reagents by activating this pathway. The Keap1-Nrf2 system now opens a new avenue to the understanding of the signal transduction and regulatory processes underlying the cancer growth.