SL3  Molecular basis of Keap1-Nrf2 system function

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Our bodies must counteract insults originating from the environment. Toxic chemicals (electrophiles) and reactive oxygen species (ROS) activate expression of detoxifying and antioxidant genes through antioxidant responsive element (ARE). Transcription factor Nrf2 is essential for the coordinated induction of cellular defense enzymes through ARE. This notion is best demonstrated in animal models, showing that Nrf2-null mice are sensitive to a wide variety of electrophiles and ROS. Keap1 is identified as a negative regulator of Nrf2. Electrophiles liberate Nrf2 from the repression by Keap1 and provoke nuclear accumulation of Nrf2. Keap1 possesses multiple reactive cysteine residues that covalently bind with electrophiles, indicating that Keap1 acts as a sensor for xenobiotic stresses and we refer this system to as the Cysteine Code. Mouse and zebrafish models demonstrate that multiple sensor functions reside within Keap1. The hinge and latch model proposed for the Keap1-Nrf2 system describes the regulation of nuclear accumulation of Nrf2 by a Cul3-Keap1 E3 ubiquitin ligase-dependent mechanism. We have verified this model through structure biology, mouse/zebrafish genetics and human cancer analyses. In human cancers, missense mutations have been identified in KEAP1 and NRF2 genes. These mutations disrupt the KEAP1-NRF2 complex and result in constitutive activation of NRF2. Elevated expression of NRF2 target genes confers advantages on cancer cells. Transgenic mouse models provide evidence that mutated form of Keap1 analogous to cancer genotypes lose the ability to repress Nrf2 in vivo. Thus, the Keap1-Nrf2 system opens a new avenue to the understanding of the signal transduction and regulatory processes underlying the stress response and cancer progression.

SL4  Fifty years after the discovery of cytochrome P450: what do we really know about the positive and negative roles in toxicology & health issues?

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The discovery of cytochrome P450 (P450) was reported in 1962 by R. Sato and T. Omura (J. Biol. Chem. 237, 1375-1376). Since then, this enzyme system has come to be recognized as having a critical role in toxicology. P450s are involved in ~ 3/4 of human enzymatic transformations of drugs and ~ 2/3 of the bioactivation of carcinogens. Bioactivation, induction, and inhibition are important aspects of P450 in toxicology, especially with drugs and drug candidates. Notable examples of P450 involvement in drug toxicity include terfenadine and acetaminophen. The toxicity of the notorious teratogen thalidomide has been revisited in the context of P450 bioactivation. Knowledge of human P450 enzymes has figured prominently in current efforts in molecular epidemiology, pharmacogenomics, chemoprevention, and risk assessment. Current issues related to P450 are predictions of drug toxicity based upon in silico modeling and the role of covalent protein binding. A general need exists to produce more innovative methods of screening for drug toxicity, with the hope of replicating the success seen in predicting metabolism and pharmacokinetics to the areas of pre-clinical toxicity and especially adverse events in humans. In summary, the understanding of P450s has been a remarkable success story in understanding the metabolism and its consequences with drugs, steroids, and carcinogens.