Cellular adaptation in toxicology

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Much attention in toxicology has been given to the biotransformation of chemicals and the mechanism of action of toxicants. However, the toxicity of chemicals is also dependent upon the ability to adapt to the presence of the toxicant. One mechanism for adaptation to chemicals that has been examined in detail is the induction of the cytochrome P-450s (CYPs). However, while the induction of the CYPs will increase the biotransformation of many chemicals to less toxic products and results in adaptation, but for other chemicals the CYPs metabolize them to more toxic products and results in more toxicity. These same chemicals that induce the CYPs can also induce uptake and efflux transporters, which have the ability to also adapt cells to the presence of some chemicals, which will be addressed in this lecture. A second mechanism to be discussed is the adaptation to chemicals by the induction of metallothionein (MT). MT is a small protein that is made up of 1/3 cysteines and avidly binds metals such as zinc and cadmium. It is one of the most inducible proteins and plays in a major role in the adaptation to cadmium toxicity.

The third mechanism of adaptation to be discussed is the Nrf2-Keap1 transcription factor induction of a plethora of enzymes and transporters that protect against numerous chemicals whose mechanism of toxicity is via electrophiles and oxidative stress. These and other mechanisms of adaptation play a major role in protecting us from the toxicity of chemicals.
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