

Reactive Metabolites in Toxicology: A Focus on Protein Adducts

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The observation that proteins can be adducted by reactive metabolites began with the investigations of James and Elizabeth Miller during the late 1940's. Their seminal work demonstrated that supposedly inert chemicals often undergo metabolic transformation to metabolites capable of covalently modifying protein. Understanding of protein adducts has grown considerably and their involvement in xenobiotic toxicity is now recognized. Of a practical nature, protein adducts have been exploited as biomarkers of exposure to genotoxic chemicals such as ethylene oxide. Idiosyncratic drug toxicity is particularly important to the pharmaceutical industry today and is often explained, in part, by the hapten hypothesis that entails protein modification by reactive metabolites eliciting an adverse immune response. Both phase I and II enzymes can bioactivate xenobiotics and the resulting reactive metabolites, most often electrophilic species, target accessible "soft" nucleophilic residues on proteins. This talk will provide an overview of the nature and role of protein modifications in causing toxicity and what can be learned about the mechanisms involved.