

## Genetic and Metabolic Effects of Chemical Carcinogens: A Complex Interplay

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Exposure to chemicals, whether naturally occurring or industrially produced, is a constant and inescapable fact of life. While the vast majority of these chemical compounds are beneficial or completely harmless, a number of them are known to alter cellular genetics and metabolic activity leading to cancer development. Examples of such chemicals with an established causative relationship with human cancer include aflatoxins (found in food) and tobacco products [1].

Chemical-induced genetic and metabolic alterations are attributable to their deleterious effect on DNA repair, gene expression, activation of proto-oncogenes, and inhibition of tumor suppressor genes. Also, proteins and lipids that are normally responsible for maintenance of metabolic homeostasis, may be impaired by chemical carcinogens. These changes can result from the direct interaction of the chemicals with DNA, leading to double-strand DNA breakage, hindered repair of random DNA mutation or/and accumulation of bulky DNA adducts. Alternatively, a chemical carcinogen may deregulate the complex network of signaling pathways that is otherwise responsible for normal physiologic responses. These effects result in abnormal cellular DNA damage response and oxidative stress response [2].

Impaired cellular DNA damage is mediated primarily by two distinct kinase dependent pathways, namely the Ataxia Telangiectasia Mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR). Also, deregulation of the p53 or Mitogen Activated Kinase (MAPK) p38/MAPK-Activated Protein Kinase 2 (MK2) pathways can result in abnormal response to DNA damage. Oxidative stress, caused by Reactive Oxygen Species (ROS) such as hydrogen peroxide, superoxide and hydroxyl radicals can directly or indirectly cause DNA damage, affect free nucleotides, and denature proteins and lipids, eventually inducing mutagenesis and carcinogenesis [3]. ROS can be propagated by exposure to exogenous oxidative chemicals or by endogenous mitochondrial production during stress response. Chemical carcinogens can also activate NF- $\kappa$ B (nuclear transcriptional factor) inflammation associated pathways, stimulating the anti-apoptotic tumor promoting factors (i.e. STAT3) and pro-apoptotic tumor suppressor genes (i.e. p53, ARF) [4,5].

Damage can also be imparted by chemical carcinogens onto proteins and lipids, leading to genetic or epigenetic alterations. Many cancer-causing chemicals in humans must be metabolized by the cytochrome p450 system in order to become chemically/biologically active. Once activated, these metabolites are able to interact with cellular macromolecules to induce misfolding/unfolding of proteins and disruption of regulatory complexes such as the pro-apoptotic and heat shock response pathways.

It must be noted that the specific effect of chemical carcinogens on genetic integrity and metabolic pathways is largely dependent upon and modulated by a variety of factors. These include host susceptibility (age, race, gender, polymorphisms of carcinogen metabolism genes, etc.), dose and duration of chemical exposure, metabolic pathway, biotransformation, and interaction with myriad other environmental factors [6]. Thus, chemical carcinogenicity must be regarded as an end-product of a complex and multifactorial process involving the chemical, the host and other environmental factors.

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