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The pharmacogenetics of chemical carcinogenesis

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The human body is endowed with a large number of xenobiotic chemical metabolizing enzymes, a significant proportion of which are polymorphic and thus render one individual at greater or lesser risk than another of chemically-induced disease. All examples of genetic polymorphism of chemical metabolizing enzymes have been reviewed in relation to their potential to activate and detoxicate procarcinogens and promutagens. Many examples are cited whereby phenotype can act as a carcinogenic risk factor. With the availability of a large amount of DNA sequence data for chemical metabolizing enzymes there has emerged a number of polymerase chain reaction (PCR) strategies aimed at discerning one metabolic phenotype or another. This is seen as a very positive and *democratic* scientific development, widening the franchise for studies of disease risk. Nevertheless, it is argued that, at these early stages with many laboratory-based scientists scarcely familiar with epidemiological study design, a cautious approach should obtain when interpreting single studies.

Introduction

Metabolism is an essential part of the chemical carcinogenic process. Rarely does metabolism leave the biological profile of a chemical unaltered. By its very nature, metabolism of xenobiotic chemicals may alter the gross lipophilicity of a molecule or more subtly may introduce or unmask electronegative moieties within the molecule. In the case of the conjugation reactions, the addition of glucuronic acid or glutathione may even double the relative molecular mass of the substrate. Since quite conservative molecular modifications of agonists are usually required to yield receptor antagonists, not surprisingly the intervention of the body's metabolic armamentarium can abolish or augment a chemical's mutagenic or carcinogenic potential. This principle is clearly illuminated by the experiences of short-term mutagenicity testing, whereby addition to *Salmonella typhimurium*-based assays of cytochrome P450-containing preparations (typically Arochlor-induced rat liver S9 fraction) converts the great majority of 'direct-acting non-mutagens' into 'indirect-acting mutagens' (Ashby & Tennant, 1991). Since a large number of these chemicals are also carcinogens, similar metabolic activation processes must also occur *in vivo*.

As far as human carcinogenesis is concerned, the target epithelia for chemical carcinogens do not contain an Arochlor-induced spectrum of P450 isozymes, rather 20 or so differentially expressed P450s (Gonzalez, 1992), together with a wide array of other oxidative, reductive, hydrolytic and conjugating enzymes. The best guess at this present time of the number of xenobiotic metabolizing discrete gene products is certainly in excess of 100. Perusal of the literature reveals that a significant proportion of xenobiotic metabolizing enzymes are polymorphic. The existence therefore of multiple alleles at loci encoding chemical metabolizing enzymes offers the possibility of the expression of host susceptibility and resistance phenotypes that might go some way to explain the differential susceptibility of individuals to the mutagenic and carcinogenic effects of environmental chemicals.

The purpose of this Review is to delineate the structural and functional polymorphisms of chemical metabolism, to summarize the evidence for the

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