DNA DAMAGE AND REPAIR IN HUMAN CELLS INDUCED WITH (exposed to) METABOLITES CHARACTERISTIC OF TYROSINEMIA

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Hereditary Tyrosinemia (HT1) is an autosomal recessive disorder caused by a deficiency of fumarylacetoacetate hydrolase (FAH) but the mechanism by which the hepatic and renal symptoms of HT1 arise is unknown (Mitchell et al, 2000). The hypothesis is that the final metabolites of tyrosine catabolism (maleylacetoacetate and fumarylacetoacetate, and their derivatives, succinylacetone and succinylacetoacetate) are toxic, and can possibly act as alkylating agents and/or disrupt sulfhydryl metabolism. In addition, aminolevulinic acid (ALA) accumulates under pathological conditions (Douki et al, 1998). Developemnet of hepatic tumors is a characteristic of this inherited disease. Onuki et al, (2002) observed that ALA has a pro-oxidant potential and is able to promote the formation of DNA lesions such as strand-breaks and oxidized bases in vitro and in vivo. The aim of this study is to use the Comet Assay (single cell gell electrophoresis) with lymphocytes and primary hepatic cells to study the genotoxicity of the accumulating metabolites. With this we hope to contribute towards a better understanding of the underlying mechanisms responsible for the pathology of this disease.

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