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Metabolism and membrane transporters influence the genomic damage induced by pyrrolizidine alkaloids in a co-culture model system

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Pyrrolizidine alkaloids (PAs) are natural phytotoxins distributed extensively in thousands of plants species. PAs require metabolic activation in the liver to instigate toxicity. Humans are exposed with PAs via cross-contamination in food products, spices and herbal medicines. PA induced hepatic sinusoidal obstruction syndrome (HSOS) is mainly characterized as hepatic sinusoidal endothelial cell (HSECs) damage which later leads to hepatotoxicity and carcinogenicity. However, the mechanism is not yet fully known because HSECs in the liver lack metabolic enzymes.

To mimic the in vivo situation to some extend in vitro, we co-cultured HepG2 liver cells with metabolically inactive fluorescence labelled HeLa cells (HeLa H2B-GFP) and analyzed micronucleus formation in the HeLa cells after treatment with PAs. The genomic damage induced by the PAs europine, riddelline and lasiocarpine was investigated and increased micronucleus formation was observed in HeLa H2B-GFP cells after treatment of the co-culture with PAs. The CYP450 inhibitor ketoconazole, and the outwards membrane transporter inhibitors verapamil (MDR1 inhibitor) and benzbromarone (MRP2 inhibitor) reduced the micronucleus formation. Mitotic disturbances as a possible mechanism of micronucleus formation were also observed in HeLa cells after treatment of the co-culture.

Thus, within the applied co-culture model system, PAs were activated by HepG2 liver cells and the metabolites were taken up by HeLa cells in which they induced genomic damage.

Keywords:
Include; pyrrolizidine alkaloids; micronuclei; HepG2 cells; HeLa H2B-GFP cells.