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THE USE OF ISOLATED LUNG CELLS IN *IN VITRO* PULMONARY TOXICOLOGY: STUDIES OF DNA DAMAGE, APOPTOSIS AND ALTERATION OF GENE EXPRESSION

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SUMMARY

Isolated lung cells constitute a valuable system for studying mechanisms involved in chemically induced toxicity in the lung. Different lung cells isolated from various species may be studied. Bronchiolar Clara and alveolar type 2 cells produce important lung-specific proteins, hold a major role in the metabolism of xenobiotics and serve as progenitor cells for other lung cell types. They are possible target cells in lung carcinogenesis. Alveolar macrophages play an important role in lung defence and in inflammatory responses. In the present study we have characterised chemically induced DNA damage, apoptosis, changes in cell cycle progression, transformation and alterations in gene expression in these specific lung cells isolated from rat, rabbit and human. Major differences between the cell types and the various species in the induction of DNA damage by chemicals were found, as measured by the ^{32}P-postlabelling and alkaline filter elution techniques. Benzo(a)pyrene and hydrogen fluoride were found to induce apoptosis in the isolated cells as measured by microscopical analysis and flow cytometry. The function of various important tissue- or cell type specific proteins (CYP 2B1, Clara cell protein) and/or cellular signal transduction pathways constitute important targets that may be affected by exposure to toxic compounds. Using immunological and molecular techniques the differential expression of specific proteins/RNAs and their activity can be studied. Among other proteins, c/ebp is involved in the regulation of transcription at the end of signal pathways. The protein is differentially expressed in rat lung cells and thus could be suitable for studying differential toxic effects in various lung cells. In humans, bronchoalveolar lavage (BAL) fluid from human volunteers can be readily obtained and examined after exposure to different chemical compounds. An increase in the percentage of CD3-positive cells (T-lymphocytes) was found after exposure to hydrogen fluoride. The number of certain cell types and cytokines may be used to estimate the degree of inflammatory reaction. In conclusion, the use of *in vitro* data including the use of specific, primary human lung cell types may contribute considerably to the quality of risk assessment, together with *in vivo* data from animals and man.

Key words: lung cells, toxicity end points, *in vitro* pulmonary toxicology

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