

## **Drug Metabolizing Enzyme Activity in Human In Vitro Dermal ( EpiDerm™ ) and Airway ( EpiAirway™ ) Epithelial Models.**

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Human dermal and airway epithelia contain xenobiotic metabolizing enzymes (XME) including a variety of phase I (oxidative) and phase II (conjugative) activities. These XMEs play an important role in biotransformation of drugs and environmental/occupational chemicals. Biotransformation of chemicals may lead to altered drug activity or formation of toxic/mutagenic metabolites. The present work evaluated expression of XMEs in highly differentiated in vitro models of human dermal (EpiDerm) and airway(EpiAirway) epithelia that are cultured at the air-liquid interface to facilitate in vivo-like chemical exposures. RT-PCR experiments were conducted to evaluate baseline and inducible expression of CYP isoforms in the epithelial cultures. EpiAirway cultures constitutively expressed CYP 1A1 (weak), CYP 1B1, CYP2A6, CYP2B6 (weak), CYP2C8 (weak), CYP2C19, CYP2D6, CYP2E1 and CYP3A5, while CYP3A4 and 3A7 were not detected. 3-Methylcholanthrene (SMC) strongly increased expression of CYP1A1 and slightly increased CYP2B6 and CYP2C8 expression in EpiAirway. In EpiDerm, CYP1B1, CYP2C19, CYP2D6, CYP3A4 (weak) and CYP3A5 were constitutively expressed. 3-Methylcholanthrene (SMC) strongly increased expression of CYP1A1 and CYP 1B1 in EpiDerm. Enhanced metabolism of the CYP1A1 and CYP1B1 substrate ethoxyresorufin confirmed increased activity following treatment with SMC. Thus CYP expression in EpiAirway and EpiDerm showed a high concordance with CYP expression reported for in vivo human airway and dermal epithelia. Total GST activity in the epithelial models was also evaluated by measuring conjugation of glutathione with 1-chloro-2,4-dinitrobenzene and UDP-Glucuronyltransferase activity was determined by 4-methylumbelliferone conjugation. High baseline GST and UDP-glucuronyltransferase activity in both models was not further enhanced by SMC treatment. The results demonstrate that the EpiDerm and EpiAirway in vitro human epithelial models possess in vivo-like XME activities and may thus be useful for evaluating epithelial metabolism of drugs and environmental/occupational chemicals.

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