

Drug/Xenobiotic-Metabolizing Enzyme (XME) Expression in the EpiAirway™ In Vitro Human Airway Model: Utility for assessing Tracheal/Bronchial Biotransformation of Inhaled Pharmaceuticals and Environmental Chemicals.

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Human tracheal/bronchial epithelium contains xenobiotic metabolizing capabilities provided by a variety of phase I (oxidative) and phase II (conjugative) enzyme systems. These XMEs can play an important role in biotransformation of inhaled drugs, tobacco smoke and environmental/occupational chemicals. Biotransformation of inhaled chemicals may lead to altered drug activity or formation of toxic/mutagenic metabolites. The present work evaluated expression of XMEs in a highly differentiated in vitro model of human tracheal/bronchial epithelium that is cultured at the air-liquid interface to facilitate in vivo-like chemical exposures (EpiAirway, AIR-100). RT-PCR gene expression experiments were conducted to evaluate baseline and inducible expression of CYP isoforms in EpiAirway cultures derived from 4 individual donors. CYP1A1 (weak), CYP1B1, CYP2A6, CYP2B6 (weak), CYP2C8 (weak), CYP2C19, CYP2D6, CYP2E1 and CYP3A5 were expressed constitutively, while CYP3A4 and 3A7 were not detected. 3-Methylcholanthrene (3MC) strongly increased expression of CYP1A1 and slightly increased CYP2B6 and CYP2C8 expression. Thus CYP expression in EpiAirway showed a high concordance with CYP expression reported for in vivo human bronchial epithelium. Total GST activity in EpiAirway was also evaluated by measuring conjugation of glutathione with 1-chloro-2,4-dinitrobenzene. High baseline GST activity was not further enhanced by 3MC treatment. The results demonstrate that the EpiAirway in vitro human tracheal/bronchial epithelial model possesses numerous in vivo-like XME activities and may thus be useful for evaluating airway metabolism of drugs, tobacco smoke and environmental/occupational chemicals.

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