Xenobiotic metabolizing capabilities of the EpiDerm in vitro human skin equivalent: Utility for assessing dermal biotransformation of pharmaceuticals and environmental chemicals.

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The EpiDerm in vitro human skin equivalent has shown utility as an alternative to animal tests for assessment of skin corrosivity, irritation, and photoxicity. Efforts are now underway to expand the use of the model for skin genotoxicity screening. Human skin 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 topically exposed chemicals, leading to formation of mutagenic metabolites. The present work evaluated expression of XMEs in EPI-200. Affymetrix gene expression microarrays were utilized to compare XME gene expression in EpiDerm to that of excised human skin. Numerous XMEs including cytochrome P450s (CYPs), epoxide hydrolases, flavin-containing monooxygenases, N-acetyltransferases, glutathione peroxidases, glutathione S-transferases (GST) and UDP glycosyltransferases were detected, with a high concordance between specific XMEs expressed in the ex vivo skin and the EpiDerm model. Additional RT-PCR gene expression experiments were conducted to evaluate baseline and inducible expression of CYP isoforms in EpiDerm cultures. 3-Methylcholanthrene (3MC) and ß-naphthoflavone (ßNF) strongly increased expression of CYP1A1 and CYP1B1, and slightly enhanced expression of CYP2C19, CYP2D6, CYP3A4 and CYP3A5. Enhanced metabolism of the CYP1A1 and CYP1B1 substrate ethoxyresorufin confirmed increased activity following treatment with 3MC or ßNF. Total GST activity in EpiDerm was also evaluated by measuring conjugation of glutathione with 1-chloro-2,4-dinitrobenzene. High baseline GST activity was not further enhanced by 3MC or ßNF treatment. The results demonstrate that the EpiDerm in vitro human skin equivalent possesses numerous in vivo-like XME activities and may thus be useful for evaluating dermal metabolism of drugs, cosmetics and environmental chemicals.

http://www.mattek.com/pages/products/epiderm