Synopsis of Original Research Paper

Analysis of genetic polymorphisms and expression of drug transporter genes in human skin and their effects on transdermal absorption

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Membrane transporters have broad specificity and facilitate the uptake and efflux of their substrates across plasma membranes. Two major superfamilies, the ATP-Binding Cassette (ABC) and Solute Carrier (SLC) families, strongly influence the absorption, distribution, and excretion of drugs. Although the skin penetration of xenobiotics was previously attributed to passive diffusion, increasing evidence indicates that transporters have a function in the biochemical barrier of skin epithelial cells beneath the stratum corneum. The identification of drug transporters expressed in human skin and inter-individual differences in gene expression are important for understanding the role of drug transporters in human skin. Twenty-two ABC and 15 SLC transporters were expressed at detectable levels in human skin, and ABCC3, SLC22A3, SLCO3A1, SLC16A7, ABCA2, ABCC1, and SLCO2B1 were strongly expressed in skin. The expression of ABCC3 (MRP3) and SLC22A3 (OCT3) mRNAs showed large inter-individual variabilities. None of the SNPs tested (−1767G>A, −1328G>A, −1213C>G, −897delC, −260T>A, and −211C>T) in the promoter region of the ABCC3 gene showed a significant change in ABCC3 mRNA levels. ABCC3 expression levels negatively correlated with the methylation status of the CpG island (CGI) located approximately 10 kbp upstream of ABCC3 (Rs: −0.323, $P < 0.05$). As a result of systematic screening in the 5'-flanking region of SLC22A3, fourteen SNPs were identified; of these variants, 4 were novel. Of the 14 SNPs the variant, −1603G>A suppressed transcriptional activity in reporter assays and was associated with lower expression levels of SLC22A3 in skin samples obtained from Caucasian female origin. In humans, the concentration of squalene in samples taken from the back at baseline was significantly lower in homozygotes for −1603A/A than in homozygotes for −1603G/G. These results suggest that the genetic mutation contributes to the variation in the expression and activity of the drug transporter in human skin.