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The expression of ABCC4 and ABCG2 xenobiotic transporters during keratinocyte proliferation/differentiation and in psoriasis

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Xenobiotic transporters are members of the ATP binding cassette (ABC) superfamily of proteins, responsible for the energy dependent transport of a broad range of chemically and structurally different compounds thus provide chemoresistance for various tumors. However, they also play a very important role in maintaining the chemical barrier function of organs such as brain, liver and gut (see for review Leslie et al. 2004). The human epidermis is one of the largest physical and biochemical barrier of the body. There have been only a few studies conducted regarding xenobiotic transporter expression in normal human keratinocytes and in human skin (Baron et al. 2001; Kielar et al. 2003).

We aimed to study the expression of eight xenobiotic transporters: ABCB1, ABCC1-6 and ABCG2 in in vitro models of keratinocyte differentiation. Terminal differentiation of normal human keratinocytes was promoted by increasing Ca^{2+} concentration. Validation of the differentiation model was achieved by the detection of proliferation markers Ki67 and integrin alpha 5 and differentiation markers keratin 1 and involucrin. The chemical-free synchronization of the immortalized keratinocyte cell line, HaCaT was used as another model (Pivarcsi et al. 2001), in which contact inhibiton and serum starving forces the cells into a highly differentiated quiescent state. Releasing HaCaT keratinocytes from cell quiescence by passaging and serum re-addition initiate redifferentiation and the cells start to proliferate synchronously.

Among the transporter genes tested ABCC4 and ABCG2 showed a proliferation associated expression in both *in vitro* models. ABCC4 and ABCG2 were highly expressed in undifferentiated, proliferating keratinocytes and their mRNA levels decreased in parallel with differentiation. ABCC4 and ABCG2 transporter protein levels also showed a decrease in differentiating keratinocytes, as revealed by Western blot and immunocytochemistry. Similarly, induction of ABCC4 and ABCG2 mRNAs and proteins were observed in synchronized HaCaT keratinocytes after release from cell quiescence, which further supported that ABCC4 and ABCG2 transporters have a possible function in proliferating keratinocytes.

ABCC4 protein was overexpressed in the basal layers of psoriatic lesional epidermis, supporting our *in vitro* results, while in keratinocytes of normal and non-involved skin it was expressed at very low levels. ABCC4 transporter may contribute to the pathogenesis of psoriasis since antiapoptotic/proliferation related cyclic nucleotides and important inflammatory mediators are ABCC4 substrates. ABCG2 transporter was expressed in normal and psoriatic non-involved epidermis and its expression was restricted to basal layer keratinocytes. Increased levels of ABCG2 protein was detected in psoriatic lesions, however its highest level of expression was observed in keratinocytes in the abnormally differentiating granular layer. It is known that human epidermis is a constitutively hypoxic tissue, which is more pronounced in psoriatic lesions. Hypoxia induces the generation of harmful porphyrins that are substrates of ABCG2, thus ABCG2 may protect keratinocytes from the accumulation of these compounds. The upregulation of ABCC4 and ABCG2 xenobiotic transporters in psoriatic lesions could significantly modulate drug distribution and effectiveness in the skin.

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