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Research Article

Effect of UVB Radiation on the Expression of ABC and SLC Drug Transporters in Human Dermal Fibroblasts

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Abstract

The effects of UVB radiation on the expression of drug transporters in human skin has never been studied. In this work, the effects of UVB irradiation on the expression of ATP-binding cassette (ABC) transporters and solute carrier (SLC) transporters was evaluated in normal human dermal fibroblasts (NHDF) in primary culture. NHDF were exposed to increasing doses of UVB. mRNA expression of ABC and SLC transporters was measured by quantitative real-time PCR after 24-hour incubation period following exposure to non-cytotoxic UVB dose. The results showed that cell viability decreased with increasing UVB dose. Moreover, UVB radiation (non-cytotoxic dose) induced marked increase of the expression of inflammatory markers IL-8 and TNF-alpha. Regarding drug transporters, exposure to UVB radiation induced significant downregulation of ABCC1, ABCC2, ABCG2 and SLC47A1 in human dermal fibroblasts. In summary, our findings show for the first time a significant regulation of the expression of ABC and SLC transporters in human dermal fibroblasts in response to exposure to UVB radiation. This finding is of particular interest, especially with photosensitive topical drugs substrate of drug transporters and need to be considered in pharmacokinetic evaluation of topical drugs.

Keywords: ABC transporters; SLC transporters; *In vitro*; Skin; Inflammation; Cytokines; UVB.

Introduction

Human skin is organized into two primary layers, epidermis and dermis. The epi- dermis is the outermost layer and serves as the body's point of contact with the environment. Keratinocytes are the most abundant cells in the epidermis that forms an effective physicochemical barrier. The dermis underlies the epidermis and harbors cutaneous structures including hair follicles, nerves, sebaceous glands and sweat glands.

Human skin is among the largest organs that covers the body [1] and represents the body's first line of defense. It protects the body from various environmental stressors such as infectious pathogens, chemical agents and air pollutants [2-6].

Among air pollutants with effects on the skin include the solar ultraviolet radiation (UV), polycyclic aromatic hydrocarbons, volatile organic compounds, nitrogen oxides, particulate matter, and cigarette smoke. The solar UV radiation consists of three spectral areas: UVA (320-400 nm), UVB (280-320 nm), and UVC (180-280 nm). The atmospheric ozone layer effectively blocks UVC, so that the UV radiation reaching the skin surface is a mixture of 5% UVB and 95% of UVA [7]. The depth of penetration of UV radiation into the skin and their effects are dependent on the wavelength. Longer wavelength UVA penetrates deeply into the basal layer of the epidermis and dermal fibroblasts. In contrast, UVB is largely absorbed by the epidermis, with little reaching the dermis [7-10].

Excessive exposure to solar UV radiation is one of the most impactful environmental factors affecting human skin and leads to a variety of skin diseases including cancer and inflammation [11,12]. Both UVA and UVB induce DNA damage in skin cells but with different and distinct way [13,14]. UVA induces formation of reactive oxygen species that can damage DNA via indirect photosensitizing reactions [15-17]. UVB is directly absorbed by DNA which induces the formation of DNA photolesions [14,18]. DNA modifications can lead to mutations and skin cancer initiation and progression [19-21].

Acute exposure to UV radiation induces inflammation of skin characterized by erythema and oedema. Inflammation induced by UVA and UVB irradiation results in the release of pro-inflammatory cytokines, especially interleukins (e.g., IL-1, IL-6 and IL-8), tumor necrosis factor (TNF-alpha) and interferon gamma (IFN-γ) as an acute phase response [3,4,6,22-26].

The pro-inflammatory cytokines are known to impact the expression and activity of drug transporters [27,28]. Drug transporters are membrane transporters belonging to both the ATP-binding cassette (ABC) and solute carrier (SLC) families [29-37]. Drug transporters have broad specificity and are involved in both uptake (influx) and secretion (efflux) of their substrates, thereby affecting their cellular disposition. Published reports from different laboratories including ours have shown that human skin contains a range of influx and efflux transporters capable of drug transport, although expression of some of them ismore limited than in other organs [29-39]. Using reverse transcription polymerase chain reaction (RT-PCR) we have shown expression of ABCB1, ABCC1, ABCC2 and ABCG2 in ex vivo human skin and in 3D-reconstructed human epidermis models, with ABCB1 and ABCG2 being barely expressed and ABCC1 being with the highest expression level. Functional analysis has shown that MDR1 and MRP1 expressed in the skin facilitate drug transdermal delivery. The ABC transporter-mediated mechanism of absorptive transport represents a critical component of the effectiveness of the topical products [38,40]. In a sub-sequent RT-PCR analysis for the SLC gene family, we have shown expression of SLCO3A1, SLCO2B1, SLC47A2, SLCO4A1 and SLC47A1 in *ex vivo* human skin model, with SLC47A1 being highly expressed [36].

Drug transporters are critically important for the absorption, distribution, metabolism, and excretion of many drugs and endogenous compounds. Therefore, alteration of transporters activity can have profound effects on drug pharmacokinetics which impact drug efficacy and toxicity. Inflammation-induced changes in the expression and function of membrane transporters have been documented in various models of acute inflammation *in vitro* and *in vivo* and reviewed in [28,41]. Most often, studies use IL-6, IFN, IL-1β, TNF-α, and lipopolysaccharides (LPS) as inducers of inflammation in *in vitro* models. Although there has been significant progress in our understanding of the expression of inflammatory markers in response to UV radiation, little is known about the effects of inflammation induced by UV radiation on the expression of drug transporters in human skin.

The purpose of this study was to investigate the effect of UVB irradiation on the modulation of the expression of ABC and SLC transporters in human dermal fibroblasts in primary culture.

We first measured constitutive expression of ABC and SLC transporters in primary culture of Normal Human Dermal Fibroblasts (NHDF). We then measured the effects of UVB irradiation on the expression of inflammatory markers IL-8 and TNF-alpha to ensure the efficacy of UV radiation in NHDF and the changes of expression of ABC and SLC transporters induced by UVB radiation.

In this study, we show for the first time that UVB irradiation induced significant downregulation of the expression of ABC transporters and SLC47A1 in human dermal fibroblasts.

Results

Viability Assay

Figure 1 shows the results of cell viability after exposure of normal human dermal fibroblasts to increasing doses of UVB. Results are expressed as relative cell viability compared to control. In human dermal fibroblasts, exposure to 40 mJ/cm² UVB had no significant effect on cell viability ($p > 0.05$). On the contrary, exposure of human dermal fibroblasts to UVB doses higher than 40 mJ/cm² induced significant dose-dependent decrease of cell viability ($p < 0.01$). Consequently, the dose of 40 mJ/cm² has been chosen in the subsequent experiments [42-44].

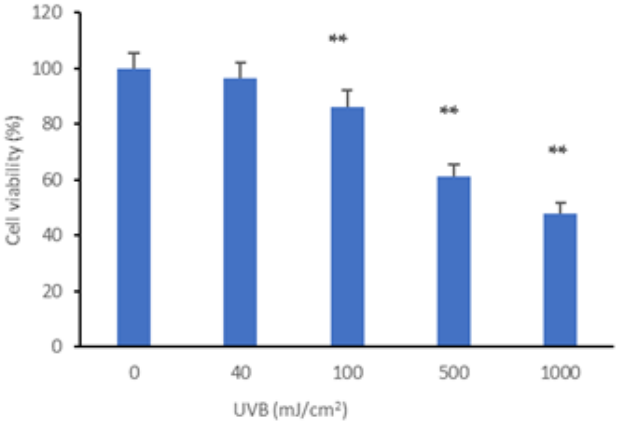

Figure 1: Effect of UVB exposure on cell viability in normal human dermal fibroblasts in primary culture. Normal human dermal fibroblasts were exposed to increasing doses of UVB and cultured for 24 hours. Unexposed cells were used as control. Cell viability was measured using MTT assay. Data are expressed as % relative to control cells and represent mean and standard deviation of 11 replicates. ** $p < 0.01$.

Effect of UVB irradiation on the expression of inflammatory markers in normal human dermal fibroblasts

Figure 2 shows that exposure of normal human dermal fibroblasts to 40 mJ/cm^2 UVB increased IL-8 and TNF-alpha mRNA expression by 19-fold and 5-fold, respectively. Thus, the results validate the treatment conditions.

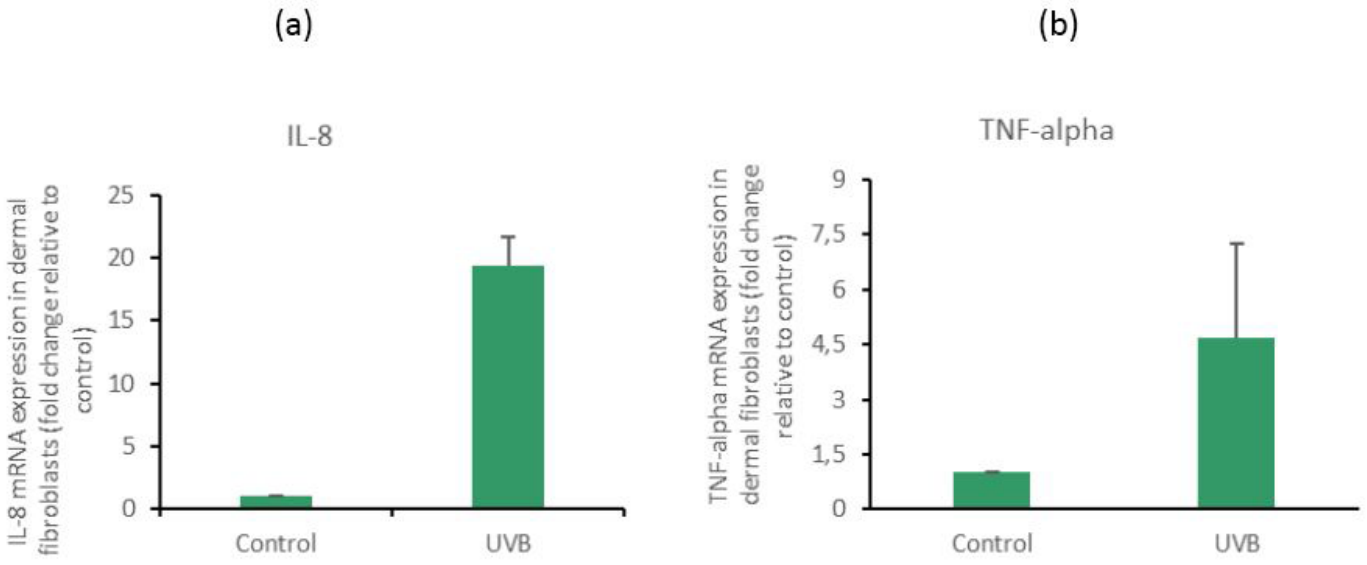

Figure 2: Effect of UVB exposure on the expression of inflammatory markers in normal human dermal fibroblasts. Normal human dermal fibroblasts were exposed to 40 mJ/cm² UVB and cultured for 24 hours. Unexposed cells were used as control. mRNA expression of CXCL-8 or IL-8 (a) and TNF- alpha (b) was measured by quantitative real-time PCR. Data are expressed as $2^{-\Delta\Delta}$Ct and represent mean and standard deviation of 3 experiments.

Constitutive Expression of ABC and SLC Transporters in Normal Human Dermal Fibroblasts

Constitutive expression of four ABC transporters (ABCB1, ABCC1, ABCC2, ABCG2) and five SLC transporters (SLCO3A1, SLCO4A1, SLCO2B1, SLC47A1, SLC47A2) was measured in normal human dermal fibroblasts.

Figure 3 shows that expression levels of ABCB1 and ABCC2 were very low, or even non detected in dermal fibroblasts. However, ABCG2 was well expressed followed by ABCC1 with the highest expression level.

On the other hand, expression profile of SLC transporters show that SLC47A2 was not expressed in dermal fibroblast. SLCO2B1 and SLCO4A1 were well expressed in dermal fibroblasts followed by SLCO3A1 and SLC47A1 with the highest expression levels.

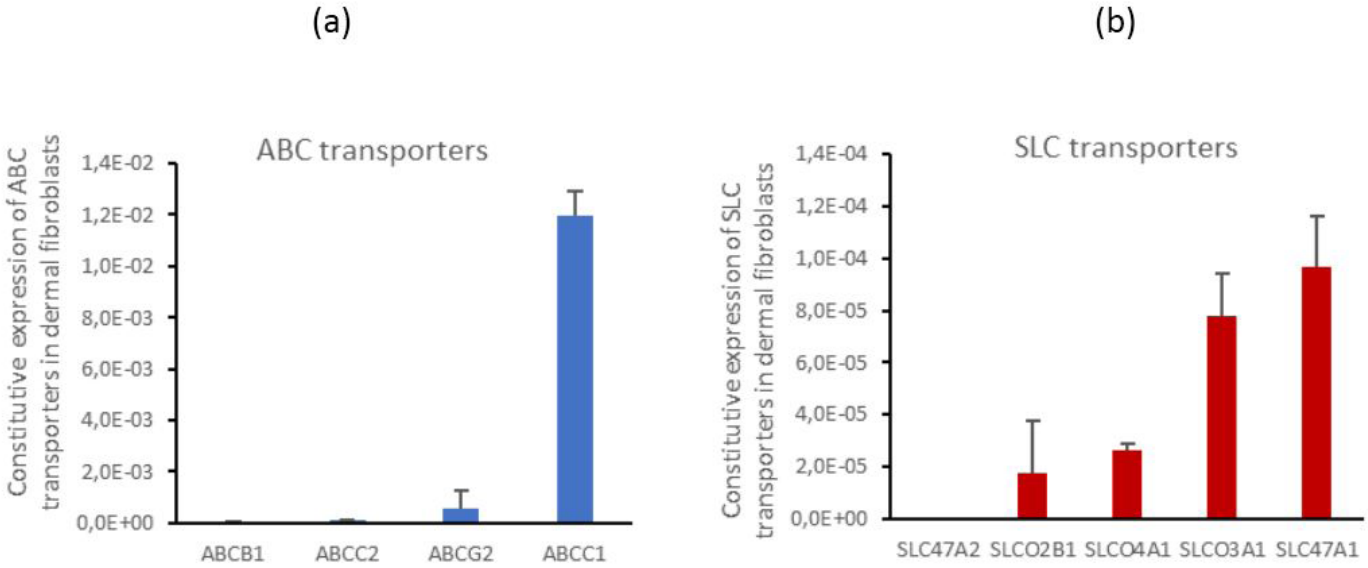

Figure 3: Constitutive expression of ABC and SLC transporters in normal human dermal fibroblasts. mRNA expression of ABC transporters (a) and SLC transporters (b) was measured in control untreated normal human dermal fibroblasts in primary culture. mRNA expression of each transporter was measured by quantitative realtime PCR and expressed as $2^{-\Delta}$Ct. Data represent mean and standard deviation of 3 experiments.

Effect of UVB irradiation on the expression of ABC and SLC transporters in normal human dermal fibroblasts in primary culture

ABC transporters

Effects of UVB irradiation on the expression of ABCB1 have not been measured due to low expression level of ABCB1 in normal human dermal fibroblasts. UVB irradiation (40 mJ/cm²) induced significant decrease ($p < 0.01$) of the expression of ABCC1, ABCC2 and ABCG2 in normal human dermal fibroblast as shown in Figure 4.

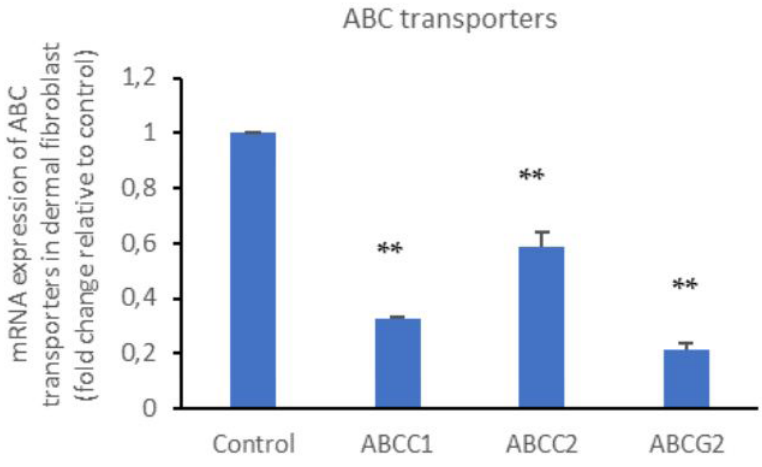

Figure 4: Effect of UVB irradiation on the expression of ABC transporters in normal human dermal fibroblasts in primary culture. Normal human dermal fibroblasts were exposed to 40 mJ/cm² UVB and cultured for 24 hours. Unexposed cells were used as control.

mRNA expression of ABCC1, ABCC2 and ABCG2 was measured by quantitative real-time PCR. mRNA expression was normalized with GAPDH mRNA for each experimental condition. Data are expressed as $2^{-\Delta\Delta}$Ct and represent mean and standard deviation of 3 experiments. Statistically significant differences in mRNA expression over control were determined by ANOVA.

$^{**}p < 0.01$.

SLC Transporters

We only focused on SLCO4A1 and SLC47A1 representative of low and high expression levels in dermal fibroblasts, respectively. Figure 5 shows that exposure of normal human dermal fibroblasts to 40 mJ/cm^2 UVB had no significant effect on the expression of SLCO4A1 while it significantly decreased ($p < 0.05$) the expression of SLC47A1 by 50%.

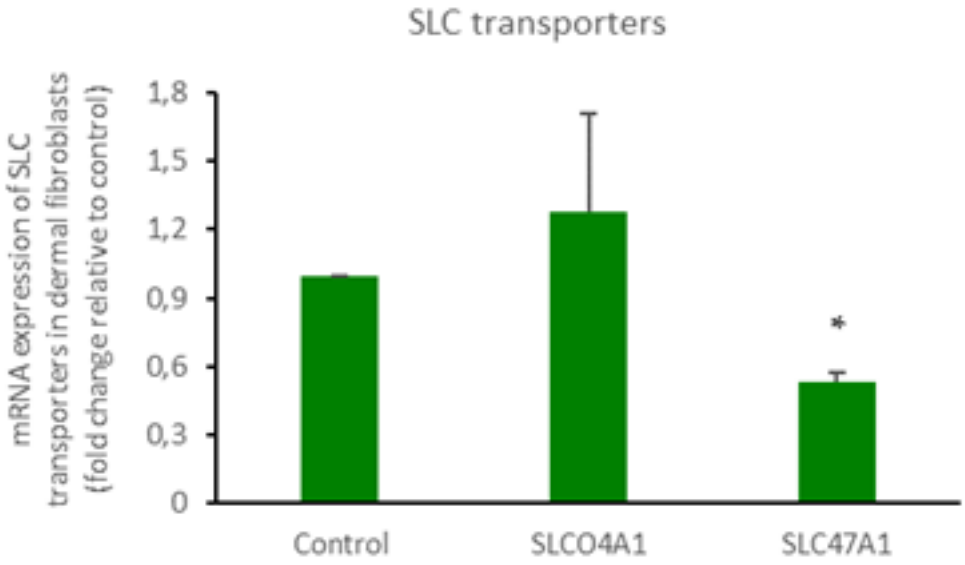

Figure 5: Effect of UVB exposure on the expression of SLC transporters in normal human dermal fibroblasts. Normal hun dermal fibroblasts were exposed to 40 mJ/cm^2 UVB and cultured for 24 hours. Unexposed cells were used as control. mRNA expression of SLCO4A1 and SLC47A1 was measured by quantitative real-time PCR. mRNA expression was normalized with GAPDH mRNA for each experimental condition. Data are expressed as $2^{-\Delta\Delta}$Ct and represent mean and standard deviation of 3 experiments. Statistically significant differences in mRNA expression over control were determined by ANOVA. $^{*}p < 0.05$.

Discussion

The objective of the study was to evaluate the effects of UVB irradiation on the expression of drug transporters in normal human dermal fibroblasts in primary culture. We first analyzed the constitutive expression of ABC and SLC transporters in dermal fibroblasts. We mainly focused on drug transporters involved in drug-drug interactions. The results showed that ABCC1 (MRP1) had the highest expression level whereas ABCB1 (MDR1 Pg-p) and ABCG2 (BCRP) were barely expressed, even not detected in dermal fibroblasts. These results are in accordance with our previous results in ex vivo skin in organ-culture model [32,28] showing the high expression level of ABCC1. On the other hand, expression profile of SLC transporters in fibroblasts showed that SLC47A1 had the highest expression level while SLC47A2 was barely expressed. In our previous work on *ex vivo* human skin in organ-culture model, we have shown that SLC47A1 was the most expressed transporter followed by SLCO4A1 [36]. *Ex vivo* human skin model contains both keratinocytes and fibroblasts. Therefore, results in *ex vivo* skin reflected the sum of expression level in both keratinocytes and fibroblasts and can in part explain the different expression profile in dermal fibroblasts in the current work.

UVB irradiation (40 mJ/cm^2) induced marked increase of both IL-8 and TNF-alpha mRNA expression in dermal fibroblasts. These results are in agreement with published report showing skin inflammation and increased production of cytokines following exposure to UV radiation [42,43].

We then analyzed the effects of UVB radiation on the expression of ABC and SLC transporters. We showed that UVB radiation significantly downregulated the expression of ABCC1, ABCC2 and ABCG2 in human dermal fibroblasts. ABC transporters are involved in dermal absorption of topical drugs; therefore, downregulation of the expression of drug transporters may have an important impact on the dermal absorption of topical products and on the safety and efficacy profile after acute exposure to sunlight. Moreover, photosensitive drugs applied to the skin are susceptible to photo degradation after exposure to UV irradiation [44-46]. The effects of radiation could be amplified incase the photosensitive drugs are substrate of ABC transporters. Further functional investigations are needed to confirm this hypothesis.

Moreover, UVB radiation significantly downregulated the expression of SLC47A1 in dermal fibroblasts. This result confirms our previous work showing significant down regulation of SLC47A1 expression in *ex vivo* human skin in organ-culture after exposure to solar simulator [36]. The biological significance of this result is to date not understood and further proteomic and functional analyses are needed to confirm this finding.

The next question to be considered is whether another treatment with a known inflammatory agent, i.e., lipopolysaccharide, may have the same effect on the expression of drug transporters, or whether the effect shown in this work is specific to UVB radiation. Also, this question can shed light on the potential link between cytokine production and drug transporter expression.

In summary, our findings show for the first time a significant regulation of the expression of ABC and SLC transporters in human dermal fibroblasts in response to UVB radiation. Further investigations still needed to identify the potential impact of sun exposure on the pharmacokinetic of topical drugs.

Materials and Methods

Primary Culture of Normal Human Dermal Fibroblasts

Pre-plated Normal Human Dermal Fibroblasts (NHDF) were obtained from Sterlab (Vallauris, France). Isolated from the foreskin, dermal fibroblasts were cultured in DMEM according to the supplier's recommendations. Upon arrival, cells were allowed to equilibrate in cell incubator set at 37˚C, 5% CO_2 and saturated humidity for 24 hours. After the cells had equilibrated, the culture medium was removed, and fresh medium was placed in all the wells. The cells were then remained in cell incubator until they were at 80% confluent.

Exposure to UVB Radiation

Before irradiation, cells were washed with phosphate-buffered saline (PBS) and then irradiated through a thin film of PBS. NHDF were irradiated with 40 mJ/cm^2 UVB. UV exposure was performed using Bio-Link UV irradiation system (Vilber-Lourmat, France). BLX-312 was used for exposure to UVB (wavelength 312 nm). After irradiation, cells were provided with fresh medium and maintained in culture for 24 hours.

Measurement of Cell Viability

Normal human dermal fibroblasts were seeded in 96-well plate and exposed to increasing doses of UVB. Cell viability was measured after 24-hour treatment period using Promega CellTiter 96® Non-Radioactive Cell Proliferation Assay (MTT assay) according to instructions provided by the manufacturer. Absorbance was measured at 570 nm using GloMax® Explorer plate reader (Promega France). Each measurement was done on eleven replicates.

Isolation of total RNA

Total RNA was isolated using ReliaPrep™ RNA Tissue miniprep System (Promega France) according to the instructions provided by the manufacturer. RNA concentrations were quantified using QuantiFluor® RNA System (Promega France) according to the instructions provided by the manufacturer.

Reverse Transcription and Quantitative Real-Time PCR

Total RNA (150-500 ng) was converted into cDNA using High Capacity RNA to cDNA Master Mix kit according to the instructions provided by the manufacturer (Applied Biosystems, Foster City, CA, USA).

Real time PCR was performed on an ABI 7500 Real-Time PCR System (Applied Biosystems). Validated PCR primers and TaqMan MGB-FAM labelled probes (TaqMan® Assay on Demand; Applied Biosystems) were used in the study. The references of the sequences used are indicated in Table 1.

PCR amplifications were performed in a total volume of 25 µL using TaqMan® Universal PCR Master Mix No Amperase® UNG according to the manufacturer's instructions (Applied Biosystems). Thermal cycling parameters were as follows: Polymerase activation (10 min, 95˚C) followed by 40 cycles' denaturation (15 s, 95˚C) and combined annealing/extension (1 min, 60˚C). Target and reference gene sequences were amplified independently in separate reactions and each PCR reaction was performed in triplicate. The PCR fluorescence data were analyzed with 7500 software (version 2.0.6, Applied Biosystems). The results were expressed as threshold cycle (Ct), which is inversely proportional to the copy number of a given gene in the sample.

Table 1: Assay-on-demand used in gene expression experiments.

TaqMan® Assay on Demand	
Gene/Protein	**Reference**
GAPDH / GAPDH	Hs99999905_m1
CXCL8 / IL-8	Hs00174103_m1
TNF-alpha / TNF-alpha	Hs00174128_m1
ABCB1 / MDR1	Hs01067802_m1
ABCC1 / MRP1	Hs01561502_m1
ABCC2 / MRP2	Hs00166123_m1
ABCG2 / BCRP	Hs01053790_m1
SLCO2B1 / OATPB	Hs01030343_m1
SLCO3A1 / OATPD	Hs00939778_m1
SLCO4A1 / OATPE	Hs00983988_m1
SLC47A1 / MATE1	Hs00217320_m1
SLC47A2 / MATE2	Hs00945650_m1

The quantification approach used is termed the comparative Ct method [47]. The increase of the expression of a target gene was expressed as fold change and calculated as $2^{-\Delta\Delta}$Ct. On the other hand, the constitutive expression of a given gene was expressed as $2^{-\Delta}$Ct.

Statistical Analysis

All experiments were performed at least three times, except where indicated. Data are expressed as mean ± Standard Deviation (SD). Statistical analysis was performed using a two-way analysis of variance without replication (ANOVA) test using Excel's Data Analysis ToolPack. A p value of less than 0.05 was considered as statistically significant.

Author Contributions

Conceptualization, Manon Barthe and Hanan Osman-Ponchet; Methodology, Manon Barthe; Supervision, Hanan Osman-Ponchet; Writing-original draft, Manon Barthe and Hanan Osman-Ponchet; Writing-review & editing, Jean-Paul Thénot.

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