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UVA1 exposures change gene expression and circadian time-related protein CRY2 in human skin

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ABSTRACT

Background: The molecular effects involved in the cellular response to ultraviolet A1 (UVA1) exposures in human skin are incompletely understood.
Objectives: We examined the molecular mechanisms underlying the physiological effects of low-dose UVA1 exposures in human skin in vivo by observing especially the contribution of diurnal preference and circadian clock-related genes and proteins.
Methods: Healthy volunteers ($n = 21$) were exposed to a cumulative dose of 30 J/cm^2 of UVA1 (340–400 nm) or 0.42 J/cm^2 of violet light (390–440 nm, $n = 20$). Immunohistochemistry, transcriptomics, real-time quantitative PCR (RT-qPCR), gene enrichment analyses, and cellular deconvolution were performed from buttock skin samples at the start and after three days of consecutive morning exposures.
Results: UVA1 exposures significantly increased CRY2 and P53 protein staining in the IHC and yielded 16 differentially expressed genes (DEGs) involved in melanogenesis (*Pmel, Tyr, Tyrp1*), cytotoxic protection (*Aldh3a2/a1, Cdk7, Nampt, Bcl2a1, Ackr4, Rpa3, Ube2q2*) and circadian rhythm (*Csnk1e, Nampt*) in the skin compared to unexposed skin samples. RT-qPCR was performed for *Aldh3a1, Aldh3a2, Tyr, Tyrp1* and *Nampt* to strengthen the transcriptomic results. No DEGs were found when exploring the underlying adipose tissue or the violet light-exposed group. In cellular deconvolution analysis, the fraction of eosinophils and M0 macrophages was increased after UVA1 exposures, with M0 macrophages especially among morning-types.
Conclusion: Low-dose UVA1 exposures caused changes in gene expression, P53 and CRY2 protein production, and cell type fractions in the skin, but the effects did not reach the subcutaneous adipose tissue. Since the solar UVR dominates in UVA, it is essential to continue to protect the skin from harmful solar agents, regardless of the diurnal preference.

1. Introduction

The ozone layer in the stratosphere blocks all UVC and approximately 90–95% of UVB (280–315 nm). Therefore, the terrestrial UVR contains predominantly (95%) UVA (320–400 nm), of which the majority is the long wavelength UVA1 (340–400 nm) [1,2]. In addition, indoor tanning beds also contain mainly UVA wavelengths [3–5]. UVA1 reaches the reticular layer of the dermis, acting on fibroblasts, dendritic cells, and B and T lymphocytes, which is why it is used to treat, e.g., sclerotic connective tissue dermatosis, hand eczema, atopic dermatitis, and cutaneous T-cell lymphomas at high doses [6–10].

Currently, the marked role of UVA in the physiological,

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photocarcinogenic, and immunosuppressive effects is well-documented [11–14]. UVA is responsible for the generation of reactive oxygen species (ROS), the product of which induce oxidative stress and accumulate mutagenic DNA damage, leading to skin tumor progression [15–17]. Genes related to oxidative stress have been detected starting from a dose of 10 J/cm^2 of UVA1 exposure in reconstructed skin models [18]. Skin cells, however, contain DNA repair pathways to protect the integrity of the genome [19–21]. However, human skin genome studies detecting the effects of UVA1 are still limited, and they have mainly focused on skin pigmentation or photoaging [22–24].

Mammals have an approximately 24-h circadian clock, located in the suprachiasmatic nucleus of the anterior hypothalamus, which paces the peripheral clocks, e.g., in the skin cells, via nervous and hormonal signals, but external stimuli may also have direct impacts on the peripheral clock [25,26]. The genes involved in the regulation and maintenance of the circadian rhythms, e.g., Cryptochromes 1 and 2 (*Cry1, Cry2*) as well as Period 2 (*Per2)*, are called clock genes. The circadian system is regulated by a transcriptional-translational feedback loop at the cellular level, where CRY1, CRY2 and PER2 act as key components [27,28]. Diurnal preference is caused by a combination of endogenous and environmental factors such as light-dark transitions and other schedules, and reflects an individual's preferred timings (morningness/eveningness) for sleep and daily activity [29]. The role of the circadian rhythms in the skin in the context of UVR exposures has been increasingly recognized [30]. Our recent study explored the influence of UVA1 on mood between the two diurnal preferences [31]. The influence of UVR irradiation on the components of the skin circadian clock, erythema, and other inflammatory responses has previously been studied in mice and humans, but mainly with UVB wavelengths [25,32–36].

We aimed to study the molecular mechanisms of low-dose UVA1-induced responses by evaluating changes in skin transcriptome and in targeted responsive proteins. Additionally, we aimed to enhance the understanding of the effects of UVA1 exposure on skin clock-related genes (CRY1, CRY2 and PER2) in human skin, and the role of P53, a tumor suppressor gene that is involved in the development of several skin cancers. The skin biopsies were taken before irradiations and after the last irradiation in a series of three low-dose (10 J/cm^2) UVA1 (340–400 nm) exposures on the buttock skin in the morning hours, compared to the exposures to violet light (390–440 nm). To study UVA1 alone, we minimized the skin-burning impact of UVR by blocking out UVA2 wavelengths (320–340 nm), [1,37] whose erythrogenic effects resemble UVB. Our study will provides new insight into how low-dose UVA1 influences skin protein and gene expression, with a particular focus on the contribution of diurnal preference and key components of the transcriptional-translational feedback loop of the circadian clock in the skin.

2. Materials and methods

2.1. Study subjects

A total of 41 volunteers participated in the study. About half of the volunteers were randomized to receive either UVA1 (n = 21) or violet light (n = 20) irradiations. Fourteen women and seven men aged 30 years on average (range: 19–52 years) were treated in the UVA1 group. Seven had Fitzpatricks's skin phototype II and 14 had phototype III [38]. BMI was 23 ± 3.3 (average ± standard deviation (SD). There were 10 men and women, aged 32 years on average (range: 20–55 years) in the violet light group. Six had skin phototype II, 13 had phototype III, and one had phototype IV. BMI was 26.1 ± 4.5.

Diurnal preference was assessed with the modified Morningness-Eveningness Questionnaire (mMEQ) [39,40]. In the UVA1 group, 12 were assigned as having morningness and nine as eveningness. In the violet light group, ten participants were assigned to each category.

2.2. Exposures and biopsy collection

UVA1 (340–400 nm, dose of 10 J/cm^2/exposure) or violet light (390–440 nm, dose of 0.14 J/cm^2/exposure) (see the emission spectra, Supplementary File 2, Fig. S1) irradiations were given on buttock skin on three consecutive mornings. The total exposure dose of violet light was negligible compared to the one included in the UVA1 spectrum. The received violet light (390–440 nm) dose included in a single UVA1 exposure was 1.76 J/cm^2/exposure. Two 6-mm punch biopsies were taken from each participant (for a total of 82 biopsies). The first biopsy was taken from the skin of the non-irradiated buttock at day 1 before any irradiations (non-irradiated baseline samples), and the second biopsy was taken 10–15 min after the third irradiation at day 3 (see the study procedure in Supplementary File 2, Fig. S2). Both biopsies were split into three pieces for further examination.

2.3. Immunohistochemistry

The 4-μm-thick, paraffin-embedded skin samples were stained in a single batch with hematoxylin and eosin (H&E), CRY1, CRY2, PER2, and anti-P53 antibodies (University of Tampere, Finland). Scoring was performed by the two authors, a dermatologist (AH) and a dermatopathologist (JH), by the naked eye, and graded as negative (0), slightly positive (1), positive (2), or strongly positive (3).

2.4. RNA extraction, reverse transcription, and qPCR

Tissue samples were mechanically homogenized with an Ultra-Turrax homogenizer (IKA-Werke, Staufen, Germany). Total RNA was isolated from the epidermis/dermis samples using AllPrep Kit (Qiagen, Hilden, Germany) and from the adipose tissue samples using miRNeasy kit (Qiagen, Hilden, Germany). RNA (400 ng) was reverse transcribed from skin samples with High-Capacity RNA-to-cDNA™ Kit (Applied Biosystems/Thermo Fisher Scientific, Waltham, Massachusetts, United States) according to the manufacturer's instructions. The expression of the selected cytokines and genes was analyzed using 7500 Fast Real-Time PCR System (Applied Biosystems) with TaqMan™ Fast Advanced Master Mix for qPCR (Applied Biosystems/Thermo Fisher Scientific, Waltham, Massachusetts, United States). PCR primers and probes for cytokines and chemokines were obtained as predeveloped assay reagents from Applied Biosystems. The ribosomal 18S gene was used as the housekeeping gene in the TaqMan analyses.

2.5. RNA sequencing (RSEQ) and data analysis

The RSEQ for the samples was performed using the Drop-seq method [41] at the FuGU (University of Helsinki, Finland). Data were filtered and TMM-normalized in ExpressAnalyst (expressanalyst.ca). DEGs were identified by adjusted p-value, without a fold-change threshold. Quantitative real-time PCR was performed to verify the results of selected genes. Principal component analysis (PCA) and heatmaps were implemented in MetaboAnalyst (metaboanalyst.ca). Pathway analyses were performed using Ingenuity knowledgebase (IPA, Qiagen Inc., Hilden, Germany). The CIBERSORT analysis tool (cibersort.stanford.edu) was used for cellular deconvolution analysis. Statistical significance analyses were performed with GraphPad Prism version 10 (GraphPad Software Inc., San Diego, CA). The significance threshold was p <0.05, and the results are expressed as mean ± standard error of the mean (SEM).

More detailed information concerning diurnal preference assessment, skin biopsy sampling, IHC, RNA extraction, sequencing, data analyses, and statistics is provided in Supplementary File 1. This study protocol was designed for a randomized controlled trial [31], where more detailed information on the study ethics, study implementation, inclusion criteria, and irradiations is also found.

3. Results

3.1. Transcriptomic changes in skin due to UVA1 exposures

We compared the gene expression profiles of the UVA1-irradiated or violet light-irradiated buttock skin (epidermis/dermis) biopsy samples with those of non-exposed samples to identify the most relevant transcriptomic changes. UVA1 irradiations yielded a total of 16 differentially expressed genes (DEGs) in the epidermis and dermis when compared to the non-irradiated baseline samples (Table 1), while violet light exposures had no effect. Two genes (*Ackr4, Ube2q2*) were downregulated, and the remaining 14 were upregulated. A heatmap of the 30 genes with the lowest adjusted *p*-values shows clustering of the genes in the UVA1-exposed skin samples compared to all non-irradiated baseline samples (Supplementary File 2, Fig. S3). A similar heatmap of the subcutaneous adipose tissue samples showed no clustering of the genes (Supplementary File 2, Fig. S4). In the analysis of these 16 DEGs, the non-irradiated baseline skin samples and the skin samples exposed to violet light were separated from the UVA1 irradiated samples in the principal component analysis (PCA; see Fig. 1A). The 16 DEGs had the most significant enrichment of the Microphthalmia-associated transcription factor-M (*Mitf-m*)-dependent transcription in the Canonical Pathways, tyrosinase-related protein 1 (*Tyrp1*) gene as an Upstream Regulator and synthesis of melanin in the Diseases and Functions analysis (Fig. 1B). Group-specific expression of *Aldh3a1*, *Aldh3a2*, *Nampt*, *Tyrp1*, *Tyr, Cry1, Cry2, Per2* and *Tp53* and quantitative real-time PCR expression for the DEGs *Aldh3a1, Aldh3a2, Nampt, Tyrp1* and *Tyr* are shown in Fig. 1C.

Table 1
The 16 DEGs after UVA1 exposures. The table shows 16 UVA1 irradiation-induced differentially expressed genes (DEGs) on day 3 (d3), their *p*-values, adjusted *p*-values, and fold changes compared to the non-irradiated baseline skin samples (BL, day 1). Two genes are downregulated (*Ackr4, Ube2q2*) and the others are upregulated.

Gene Symbol	Gene Name	*P*-value	Adj. *P*-value	Fold change
Aldh3a2	Aldehyde dehydrogenase 3 family member a2	2.2137E-10	3.9886E-6	7.3875
Aldh3a1	Aldehyde dehydrogenase 3 family member a1	9.1026E-10	8.2005E-6	7.3254
Clcl4	Chloride voltage-gated channel 4	1.2261E-8	7.364E-5	6.3872
H2az2	H2a.z variant histone 2	7.6882E-7	0.0034631	5.5551
Tyrp1	Tyrosinase related protein 1	2.0887E-6	0.0071356	5.1852
Lonfr1	Lon peptidase n-terminal domain and ring finger 1	2.3762E-6	0.0071356	5.2384
Tyr	Tyrosinase	4.118E-6	0.0094424	4.939
Stk35	Serine/threonine kinase 35	4.1924E-6	0.0094424	4.9282
Ackr4	Atypical chemokine receptor 4	6.2981E-6	0.012609	−4.7936
Nampt	Nicotinamide phosphoribosyltransferase	1.3473E-5	0.024275	4.6184
Pmel	Premelanosome protein	1.5196E-5	0.024891	4.862
Ube2q2	Ubiquitin conjugating enzyme e2 q2	1.9714E-5	0.028149	−4.5029
Cdk7	Cyclin dependent kinase 7	2.0309E-5	0.028149	4.5664
Bcl2a1	B-cell lymphoma 2-related protein a1	2.426E-5	0.031223	4.6403
Csnk1e	Casein kinase 1 epsilon	3.362E-5	0.040384	4.3652
Rpa3	Replication protein a3	4.3461E-5	0.048943	4.3752

3.2. Immunohistochemical staining of CRY1, CRY2, PER2, and P53, and expression of the corresponding genes after exposures

We investigated changes in immunohistochemical protein staining scores for the circadian clock-related CRY1, CRY2, PER2, and tumor suppressor protein P53(Fig. 2) and the expression of the corresponding genes (Fig. 1C) after exposures. There were no significant changes at the gene expression level after the irradiations (Fig. 1C). No significant changes were detected in CRY1 protein staining in the skin samples after three UVA1 or violet light exposures, whereas the increase in CRY2 protein staining intensity scores was significant ($p = 0.0093$) after UVA1 exposures in the skin samples (Fig. 2 A-B). The protein expression of PER2 remained stable regardless of the exposure (Fig. 2C). P53 protein expression increased significantly after UVA1 exposures ($p < 0.001$); however, only slightly positive (score 1) staining was observed, but no positive or strongly positive (scores ≥ 2) staining was detected (Fig. 2D). Representative IHC images of the rest of the detected sample groups for the 4 proteins are found in Supplementary File 2 in Fig. S5. Only one sunburn cell (H&E) was detected in a sample after UVA1 exposures, and no sunburn cells were observed in the violet light-exposed group samples.

3.3. Contribution of diurnal preference in DEGs after UVA1 exposures

We studied how the gene expression of the 16 DEGs varied between groups with different diurnal preferences (Fig. 3A). *Aldh3a1* expression was significantly increased after UVA1 exposures among individuals displaying morningness ($p < 0.001$). *Bcl2a1* gene expression increased among individuals displaying eveningness ($p < 0.01$). *Aldh3a2* (morningness, $p < 0.005$; eveningness, $p < 0.01$) and *Clc4* ($p < 0.01$) expression increased significantly after UVA1 exposures regardless of diurnal preference. Quantitative real-time PCR expression of *Aldh3a1* (morningness, $p < 0.005$; eveningness, $p < 0.05$) and *Bcl2a1* (morningness, $p < 0.05$; eveningness, $p < 0.01$) was significantly increased after UVA1 exposures, while no significant changes were detected for *Aldh3a2* or *Clc4* by qPCR (Fig. 3B).

3.4. The fractions of macrophages and eosinophils increased in the cellular deconvolution analysis after UVA1 exposures

The cellular deconvolution method, which is based on the cell-specific gene signatures, was used to detect changes in the cell content of the irradiated skin. We used the validated cell signature gene set *Lm22* identifying 22 immune cell types in the skin [42]. The baseline M0 macrophage values of the violet light and UVA1 groups were different; however, the difference was not statistically significant ($p = 0.2324$). After the UVA1 exposures, the fraction of M0 macrophages was significantly increased in all participants, and especially among those found to display morningness (Fig. 4A, $p < 0.005$ and $p < 0.05$). The fraction of M0 macrophages was preferentially slightly decreased after the violet light exposures. Eosinophils showed a small accumulation after the UVA1 exposures for all participants (Fig. 4B, $p < 0.05$), but there were no significant differences between the groups by diurnal preference.

4. Discussion

Our study characterized the early molecular UVA1-induced responses in the skin before visible erythema or pigmentation and explored whether these responses are related to changes in circadian clock components. We exposed the buttock skin of participants to 10 J/cm^2 UVA1 irradiations, which equals to 45 min exposure time to sunlight on a summer day in Helsinki latitudes (author LY personal measurements), on three consecutive mornings. Skin biopsy samples were taken after the last irradiation for further IHC, gene expression, and cellular deconvolution analysis, and associations with diurnal preference were studied. The violet light group was practically used as an

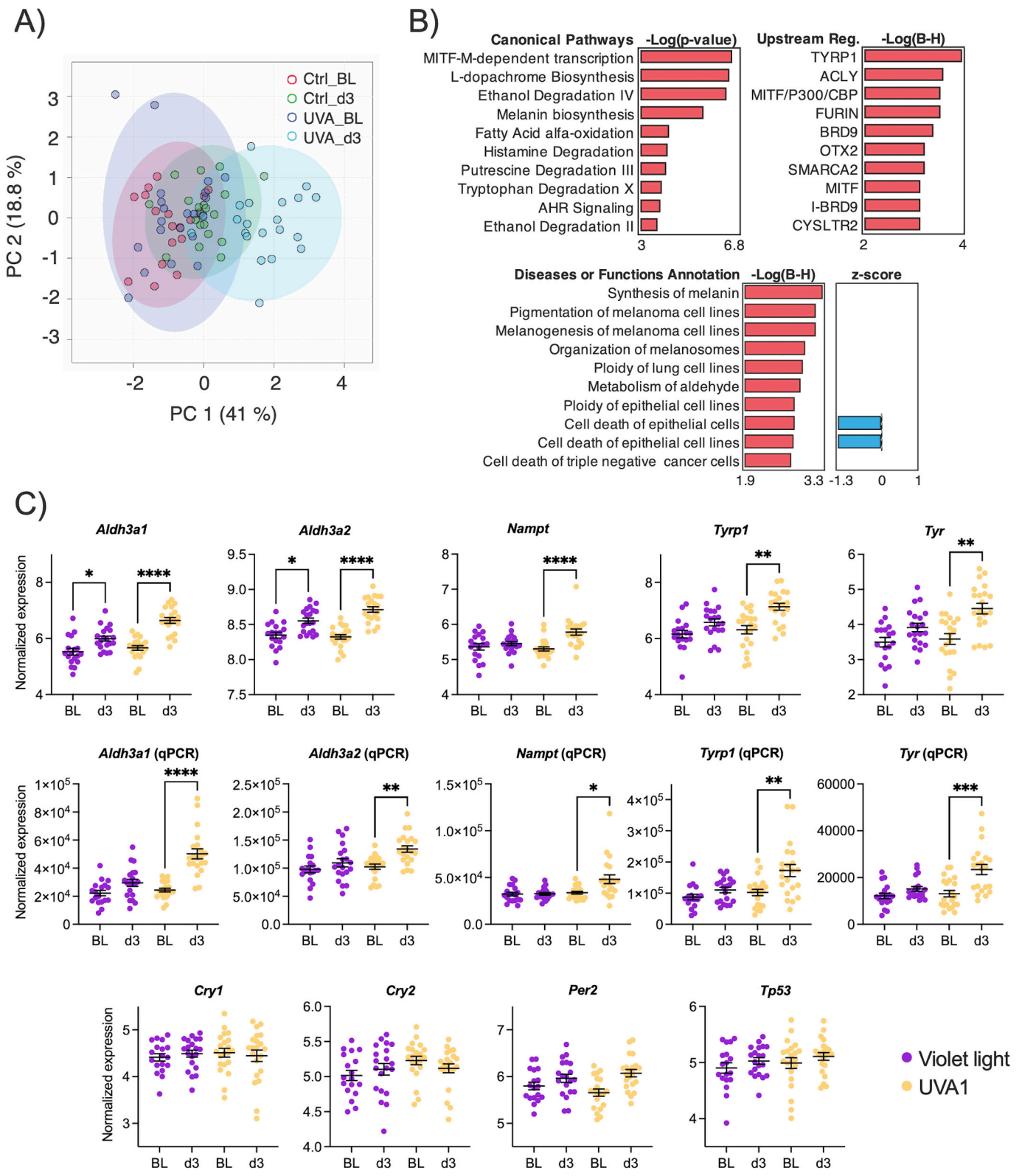

Fig. 1. PCA, enrichment pathways and example genes after UVA1 exposures in skin samples. A) The 16 DEGs differentiate the groups in the principal component analysis (PCA); non-irradiated (UVA_BL) and violet light (Ctrl)groups are shown as distinguished from the UVA1 exposure group (UVA_d3). B) The function of the UVA1-regulated DEGs was enriched in Canonical pathways, Upstream Regulator and Diseases and Functions Annotation in IPA analysis. The ten most significant pathways and a negative logarithm of the Benjamini-Hochberg-corrected *p*-value (−Log(B—H)) and Fisher's Exact test *p*-value (−Log(*p*-value)) are shown. The activation *z*-scores are used to predict the inhibition state of the pathway. C) Individual gene expression of *Aldh3a1, Aldh3a2, Nampt, Tyrp1, Tyr, Tp53, Per2, Cry1* and *Cry2* and quantitative real-time PCR (qPCR) expression for the DEGs *Aldh3a1, Aldh3a2, Nampt, Tyrp1* and *Tyr*. *P*-values by Kruskal-Wallis with Dunn's multiple comparisons test indicate significance as * < 0.05, ** < 0.01, *** < 0.005 and **** <0.001. BL: baseline, day 1, non-irradiated samples; d3: day 3, 10–15 min after the three consecutive morning irradiations.

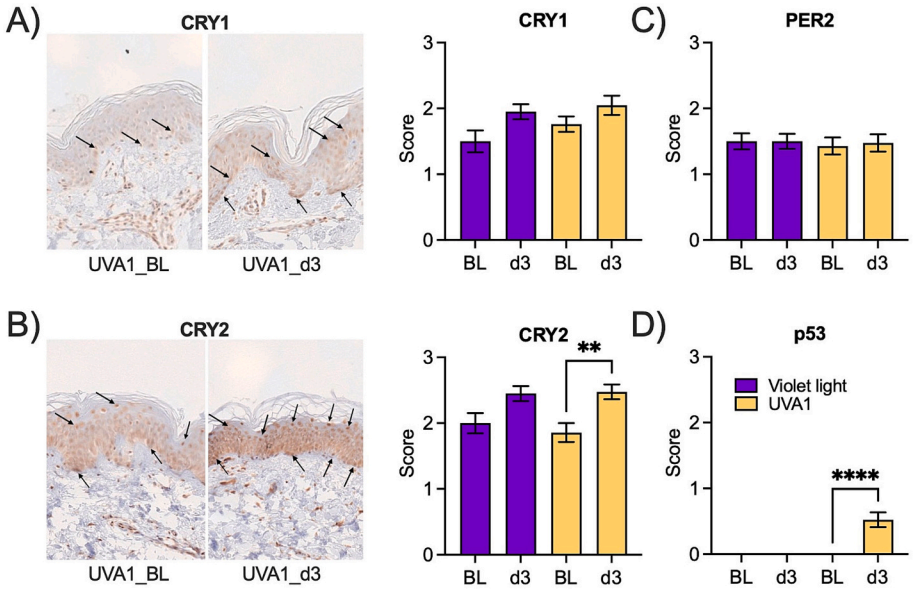

Fig. 2. CRY1, CRY2, PER2, and P53 protein expression in the skin samples after UVA1 exposures. Representative IHC images (CRY1 and CRY2) and scoring of IHC-stained skin before and after UVA1 exposures. A) CRY1, where the staining intensity score in the non-irradiated image is 1 at baseline and 2 after the three exposures, B) CRY2, where the staining intensity score in the non-irradiated image is 2 at baseline and 3 after the three exposures, C) PER2, and D) P53. Kruskal-Wallis with Dunn's multiple comparisons test was used and is referred to by $p = 0.0093$ (**) and $p < 0.0001$ (****). BL: baseline, day 1, non-irradiated samples; d3: day 3, 10–15 min after the three consecutive morning irradiations. Staining intensity is graded as negative (0), slightly positive (1), positive (2) or strongly positive (3).

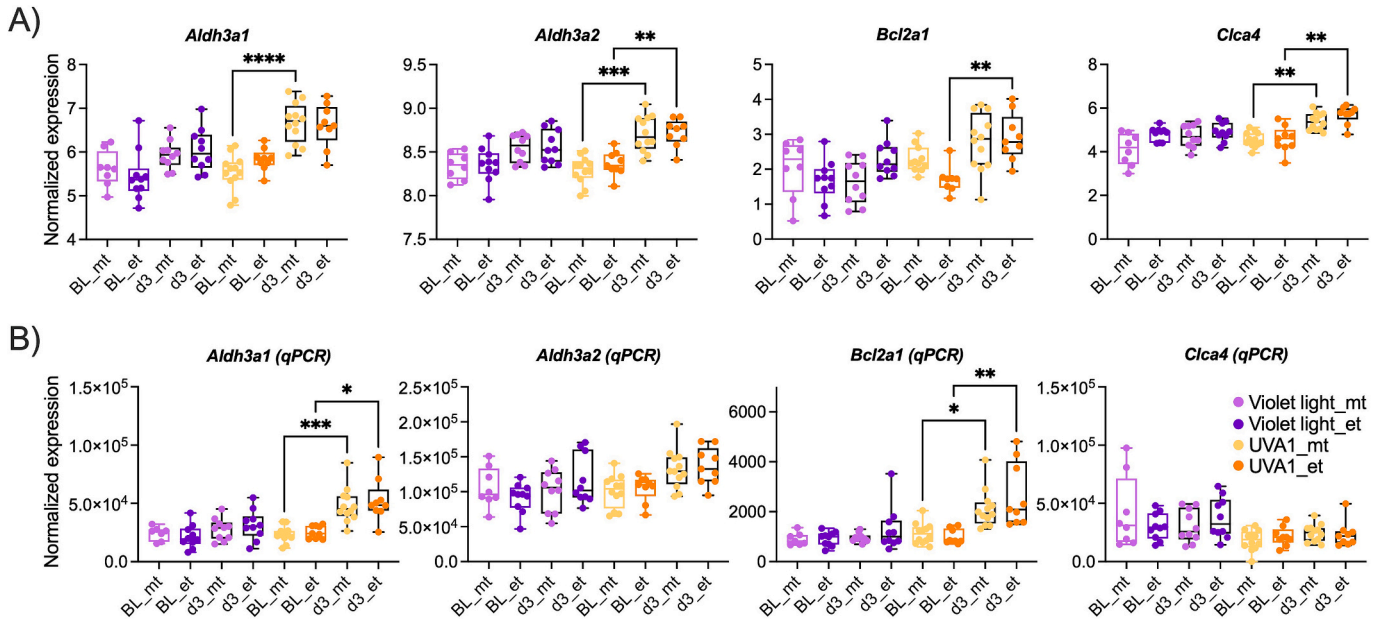

Fig. 3. Contribution of diurnal preference in response to UVA1 exposures. A) Out of the 16 DEGs, UVA1 activates *Aldh3a1 Aldh3a2, Bcl2a1* and *Clca4* genes based on the study subject's diurnal preference. B) Quantitative real-time PCR (qPCR) expression for *Aldh3a1* and *Bcl2a1* were significantly increased regardless of the diurnal preference after UVA1 exposures. *P*-values by Kruskal-Wallis test with Dunn's multiple comparisons test indicate significance as *<0.05, ** < 0.01, *** < 0.005 and **** < 0.001. BL: baseline, day 1, non-irradiated samples; d3: day 3, 10–15 min after the three consecutive morning irradiations. M: morningness, E: eveningness.

active placebo; this group showed that the timing of the biopsy (d1 vs d3) had no impact on the results, allowing conclusions to be attributed to UVA1 exposure.

UVA1 exposures increased the expression of 14 DEGs in the skin that mostly play a role in melanin biosynthesis, cytotoxic protection, and circadian rhythm regulation. *Mitf-m*-dependent transcription, upstream regulator *Tyrp1* and synthesis of melanin pathways are related to melanocytes and melanogenesis [43,44]. UVA1 is known to cause both short-term immediate [45] and persistent pigment darkening of the skin after doses of >10 J/cm^2 [46,47]. A previous human study showed pigment-related DEGs (*Tyr, Tyrp1*) after repeated irradiation with UVA/UVB combination, whereas UVA alone had no significant effect [24], departing from our findings. Nicotinamide phosphoribosyl transferase (*Nampt*) contributes to peripheral molecular clocks in a tissue-specific manner through *Nampt*-dependent NAD$^+$ synthesis [48,49] and protects the skin against the mild-dose UVA/B-induced stress [50]. In addition, casein kinase 1 epsilon (*Csnk1e*) is a core circadian clock gene needed for phosphorylation of the *Cry-Per* complex [51,52]. Previously

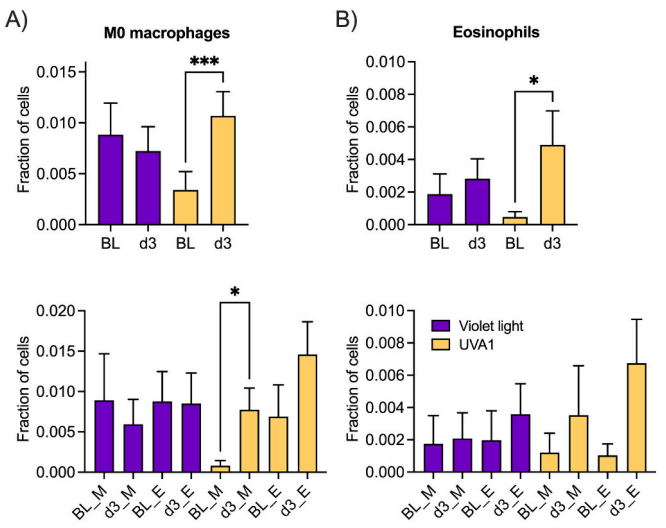

Fig. 4. Cellular deconvolution. Cellular deconvolution in the cell signature gene set of *Lm22* shows differences in the ratios of A) M0 macrophages both in the study subjects as a whole and in groups based on diurnal preference and B) eosinophils in all study subjects, based on the Wilcoxon signed-rank test between BL and d3 timepoints (n = 18–21 per timepoint). Significance is indicated by p-values <0.05 (*) and p < 0.005 (***). BL: baseline, day 1, non-irradiated samples; d3: day 3, 10–15 min after the three consecutive morning irradiations. M: morningness, E: eveningness.

published studies have been conducted either in keratinocytes in vitro [18] or using high-energetic UVB [36,53,54], possibly explaining the larger numbers of DEGs reported. Our results highlight that repeated exposure to low-dose UVA1 can enhance melanin biosynthesis and alter the expression of circadian-associated genes.

Production of CRY2 and P53, were increased in the skin after repeated UVA1 exposures, although no changes in gene expression were observed at the studied time points. The effects of UVR on *Cry2* gene are rapid but changes in CRY2 protein levels take much longer and may depend on various signaling pathways, e.g., DNA damage response or P53-mediated degradation, so their timelines do not necessarily match [32]. *Cry1* and *Cry2* are transcriptional repressors in the core transcription-translation feedback loop together with *Per2*, and they are essential for the maintenance of circadian rhythmicity in the body [28,55–57]. Their production and expression have been studied previously in humans after UVB exposure [33,34], but not in the context of UVA1. In our in vivo set-up, UVA1 exposure enhances the production of CRY2 and P53, which together may slow or attenuate circadian clock rhythmicity, thereby affecting cell division, DNA repair, and metabolism, which together could be beneficial by more efficiently blocking the effects of UVR on the skin. In our study, *Tp53* regulation was not significantly changed. This may be because *Tp53* regulation is a complex system that occurs mainly trough protein stability (MDM2), activity (post-translational modifications such as phosphorylation and acetylation) and protein localization [58]. Therefore, while accurate, this result may not fully represent *Tp53* regulation in a broader biological context.

The expression of aldehyde dehydrogenase *Aldh3a1-Aldh3a2* enzymes was markedly upregulated after UVA1 exposures, and further in morning-type individuals, whereas *Bcl2* was upregulated in evening-type individuals and *Clca4* in all volunteers tested. However, after performing RT-qPCR the expression levels were significantly increased only for *Aldh3a1* and *Bcl2a1,* regardless of the diurnal preference. ALDHs are critical in the detoxification of aldehydes, e.g., *Aldh3a1* and *Aldh3a2* are involved in UVR-induced lipid peroxidation [59–62] and associated damage e.g., in ocular tissues [63–65]. BCL2 proteins are known to regulate cell apoptosis, are often dysregulated in cancer, and are linked to malignancies like melanoma [66], the progression of which UVA is a known risk factor for [67,68]. In addition, *Clc4* is implicated as a tumor suppressor gene in various cancers [69]. Our findings suggest that *Aldh3a1* plays a role in the cellular defense against oxidative stress in the human skin epithelium, especially in morning-type individuals, whereas *Blc2a1* may regulate cell apoptosis to a greater extent among evening-type individuals.

The fractions of M0 macrophages and eosinophils were increased in all individuals in cellular deconvolution analysis after UVA1 exposures regardless of their fractions before irradiations. M0 macrophages are resting or naive macrophages which monitor the skin microenvironment for pathogens, damage, and abnormal cells and maintain skin homeostasis, whereas eosinophils are usually present in low numbers and can be quickly recruited when skin defense is needed. M0 macrophages and eosinophils can influence each other, e.g., after UV damage, by recruiting and activating each other and other cells, thereby inducing inflammation [70]. Peters et al. examined in vitro whether UVA1 alters bloodstream monocytes, which migrate to tissues and then differentiate into macrophages. They found that low-dose UVA1 radiation interfered with both pro- and anti-inflammatory capacities, while it did not affect the viability and migratory properties of the monocytes [71]. The influence of UVA on macrophages was studied using normal human skin-mimicking 3D models, where transcriptomic results revealed a mixed M1 and M2 phenotype [72]. Our study findings suggest that UVA1 may recruit cells from the immune compartments, which could lead to an inflammatory response if prolonged. However, the changes in the proportions of the M0 macrophages and eosinophils were biologically quite small (<1%), and the increase may also be explained by a relative decrease in other cell types.

The limitation of our study is the small sample size, which may have affected the statistical power; however, this was due to the invasive nature of the human study procedure. The non-irradiated UVA1 group gene expression differed significantly from the violet light group, mostly due to unknown inter-individual variation, and this may have influenced the outcome as well. On the other hand, the human study setting is a strength of this work, and it provides a new insight into the effects of UVA1 on transcriptomic changes and protein expression in vivo. We strengthened our results by performing RT-qPCR for the selected genes. The biopsies were collected at the same time in the morning and in the wintertime However, the biopsies were collected on day 1 and day 3, thus, the non-irradiated samples should ideally have been collected at the same time point on day 3 as the irradiated samples. In addition, the semiquantitative and subjective nature of IHC, scored by the naked eye, must be noted as a limitation. Finally, our findings should be interpreted in the appropriate context. To elucidate the dose-response relationship, more studies are needed with a single dose or multiple doses of UVA1 of higher intensity, as well as with exposures on darker skin phototypes (IV–VI). It must be noted that our results are a combination of cumulative dose effect and immediate responses to low-dose UVA1 in the skin. The influence of the time of day, the required dose for a given UVA1 irradiation, and the effect on the cutaneous circadian clock (e.g., other circadian clock-related proteins) require further investigation.

In conclusion, our results show that low-dose UVA1 exposures play a role in melanin biosynthesis and the activation of cytoprotective mechanism of the skin against UVR. UVA1 appears to impact P53 protein production, as well as expression of the circadian clock-related protein and genes in the skin, and the skin's protective mechanisms against UVR and the circadian clock appear to interact. Although the effects of UVA1 did not reach the subcutaneous adipose tissue, UVA1 may influence resting M0 macrophages and eosinophils in the upper layers of the skin, and the effects of these changes require further investigation in future studies.

CRediT authorship contribution statement

Annina Haapasalo: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data

curation, Conceptualization. **Olivia Liong:** Writing – review & editing, Writing – original draft, Validation, Resources, Investigation. **Juha Jernman:** Writing – review & editing, Validation, Resources, Investigation, Formal analysis. **Lasse Ylianttila:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Data curation. **Erna Snellman:** Writing – review & editing, Validation, Resources, Project administration, Formal analysis, Data curation, Conceptualization. **Rafael Pasternack:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Timo Partonen:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Piia Karisola:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jphotobiol.2026.113387.

Data availability

The data that has been used is confidential.

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