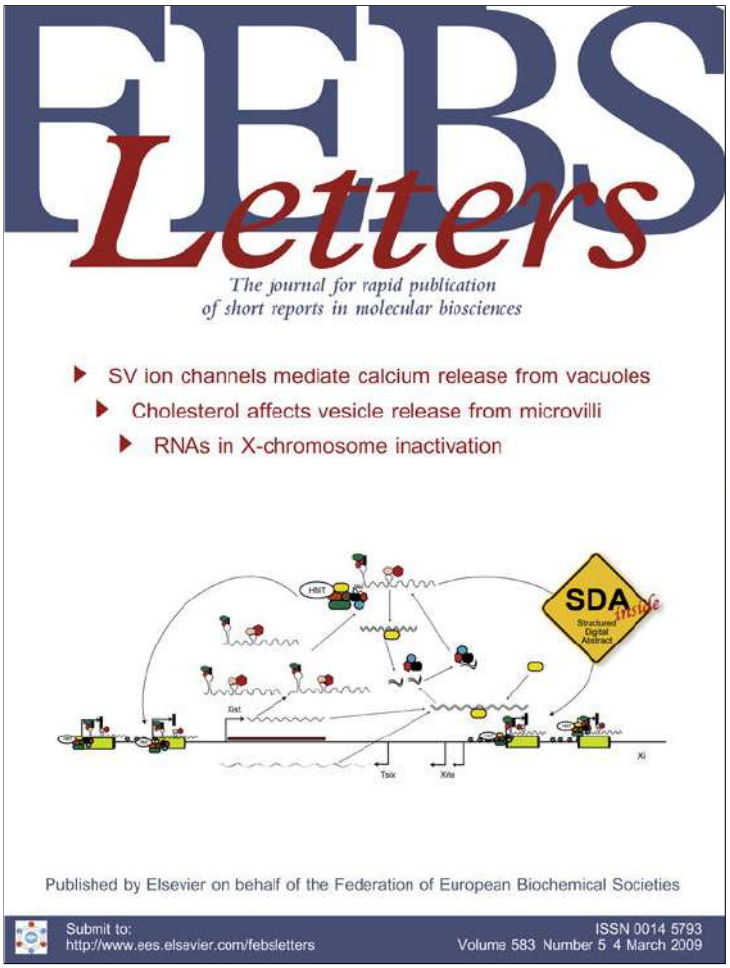

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Macrophage inhibitory cytokine MIC-1 is upregulated by short-wavelength light in cultured normal human dermal fibroblasts

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ABSTRACT

To better understand dermal response to visible light, we used DNA microarray analysis to search genes induced by blue or near-UV light in normal human dermal fibroblasts. Of about 12800 transcripts analyzed, near-UV light most prominently upregulated the transcript level of *Mic-1*, a gene encoding a TGF-β superfamily protein. Quantitative RT-PCR and immunoblot analyses revealed that mRNA and protein levels of *Mic-1* were upregulated by both short-wavelength light but not by green or red light. These results suggest that the human dermis is a site for macrophage inhibitory cytokine-1 (MIC-1) production and that visible light activates a dermal transcription cascade. Considering the role of MIC-1 in immune regulation and appetite control, photic MIC-1 regulation is of physiological importance.

1. Introduction

Sunlight that reaches the earth's surface can be divided into four categories according to effective wavelength: ultraviolet B (UVB, 280–315 nm), ultraviolet A (UVA, 315–400 nm), visible light (400–760 nm), and infrared light (760 $\times$ 10^6 nm) [1]. Of the four categories, visible light is involved in the vision and resetting of the circadian clock through photoreceptors in the retina [2]. UVB is thought to play the most important role in the biological changes to skin that are induced by sunlight, such as sunburn, skin cancers and immunosuppression [3,4]. This is mainly because DNA bases directly absorb UVB radiation, the energy of which produces severe DNA damages [4]. Both UVB and UVA radiations produce reactive oxygen species (ROS), which trigger a variety of cellular signaling pathways to promote photoageing and photocarcinogenesis [4,5]. For example, UV- and ROS-dependent activation of nuclear factor AP-1 complex reduces the synthesis of collagen in the skin, contributing to the photoageing [5]. Although the effects of visible light on the skin are less understood compared to UV radiation, their effects may also be physiologically important in terms of dermal photoreception because of their penetration to the deeper dermal layers [6]. In fact, fibroblasts synthesize essential extracellular matrix components to provide structural support when the skin absorbs visible light [7], the mechanism of which is, however, unclear to date.

In this study, we searched and identified those genes in cultured NB1RGB human dermal fibroblasts that are inducible by visible light of shorter wavelengths such as near-UV (405 nm) and blue (471 nm) light. Macrophage inhibitory cytokine-1 (MIC-1) exhibited the most prominent upregulation of the subset of genes induced by both types of short-wavelength light suggesting that *Mic-1* induction may play a role in light-dependent physiology in humans.

2. Materials and methods

2.1. Cell culture

NB1RGB human normal neonatal dermal fibroblasts (NB1 cells) were obtained from the RIKEN CELL BANK (Cell No. RCB0222) (Ibaraki, Japan). The cells were maintained in Dulbecco's modified Eagle medium supplemented with non-essential amino acids

Abbreviations: LED, light-emitting diode; MIC-1, macrophage inhibitory cytokine-1; NSAID, non-steroidal anti-inflammatory drug

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(Invitrogen, CA) and 10% (v/v) fetal bovine serum (DMEM/FBS) at 37 °C under 5% CO_2 conditions. At least 24 h before light irradiation, the NB1 cell culture medium (5×10^5 cells in a 60-mm in diameter culture plate) was replaced with phenol-red-free DMEM/FBS and kept in the dark for 24 h. The culture medium was replaced with serum-free DMEM 12 h before light irradiation in quantitative PCR analyses (some samples in Fig. 2 and all samples in Figs. 3 and 5) and immunoblot analysis (Fig. 4). The cells were then transferred to light-irradiation apparatus in the CO_2 incubator (see below). Unexposed control cells were also processed in a similar manner, with only the light treatment omitted.

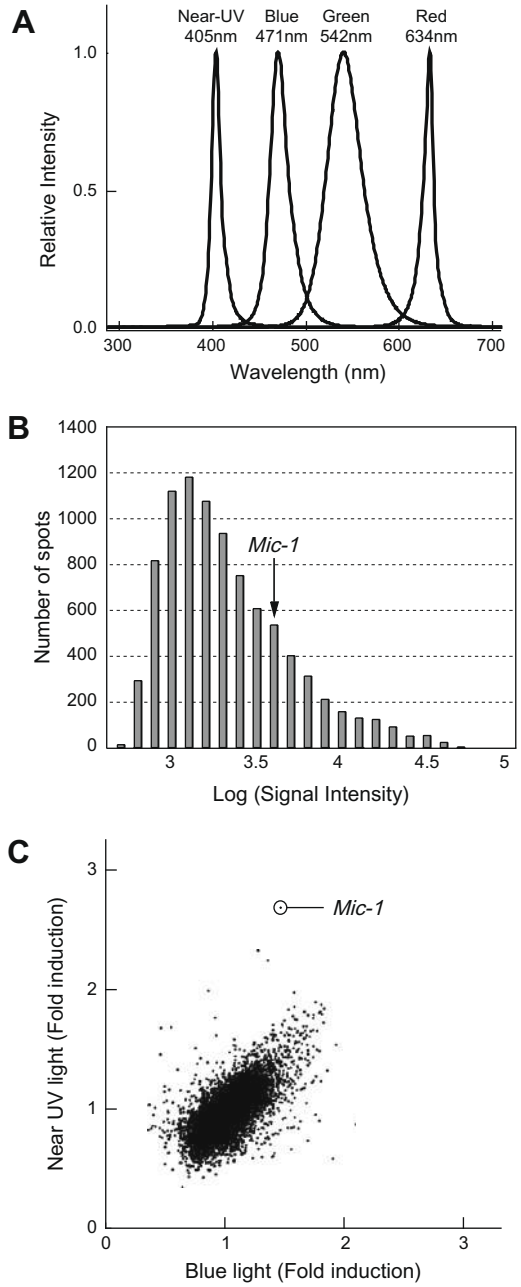

Fig. 1. Identification of *Mic*-1 as a near-UV- and blue light-induced gene by DNA microarray. (A) Spectra of light sources. Emission maxima are shown above the spectra. Emission spectra were measured using a photonic multichannel spectral analyzer, PMA-11 (Hamamatsu Photonics). (B) Histogram of relative signal intensities of gene expression in NB1 cells maintained in the dark. Averaged signal intensities of 12 844 spots that were validated in all three independent blue and near-UV experiments (total of six arrays) are shown. (C) Averaged fold induction of genes exposed to 3-h blue and near-UV light irradiation was plotted (horizontal axis vs. vertical axis).

2.2. LED and light irradiation

Each light-irradiation apparatus (200 mm × 300 mm) was constructed using 660 red (λ_{max} = 634 nm, $\lambda_{1/2}$ = 8 nm, SLI560UT3F, Rohm, Kyoto, Japan) or 414 green (λ_{max} = 542 nm, $\lambda_{1/2}$ = 43 nm, E1L53-3G0A2-02-5, Toyoda Gosei, Aichi, Japan) or 368 blue (λ_{max} = 471 nm, $\lambda_{1/2}$ = 23 nm, NSPB500S Nichia, Tokushima, Japan) or 368 near-UV (λ_{max} = 405 nm, $\lambda_{1/2}$ = 11 nm, SDL-5N3CUV-A, Sander Electronic, Berlin, Germany) light-emitting diodes (LEDs, Fig. 1A). The LEDs were driven by direct current using a power supply (LX035-1B, Takasago, Kanagawa, Japan). In a CO_2 incubator, cells were irradiated through the bottom of the polystyrene culture plate (BD Falcon, 353002) that does not absorb or emit light in a wavelength range of 380–900 nm. Light intensity was set to 60 μmol/m^2/s on the inner surface of the plate just before each irradiation. This intensity corresponded to 1.5 mW/cm^2 and 1.8 mW/cm^2 for near-UV and blue light, respectively, and the total doses (16.2 J/cm^2, blue; and 19.4 J/cm^2, near-UV) for the 3-h irradiations were lower than the median minimal erythema dose (MED) at 360 nm (32 J/cm^2, [8]). The irradiation apparatus was placed on top of an acrylic box, in which chilled water was circulated to remove heat from LEDs. The temperature of the culture medium was monitored and maintained at 37 ± 0.3 °C during the time of light exposure.

2.3. Microarray hybridization and data analysis

Total RNA was isolated using RNeasy reagent (Qiagen, CA) and treated with DNase I according to the manufacturer's instructions. We employed AceGene Human Oligo Chip 30K A–C microarray slides (HitachiSoft, Tokyo, Japan), each containing about 10 000 oligo probes. Labeling, hybridization, and detection steps were performed by DNA Chip Research Inc. (Kanagawa, Japan). Three independent series of experiments including cell culture, hybridization, and detection were performed for each blue and near-UV light irradiation experiment.

2.4. Real-time quantitative PCR

Total RNA was isolated as described above and reverse transcription was performed by using Superscript II reverse transcriptase (Invitrogen). Quantitative PCR was carried out using the GeneAmp 5700 Sequence Detection System (Applied Biosystems, CA) and QuantiTect SYBR Green PCR Kit (Qiagen) according to the manufacturer's instructions. Oligonucleotide primers for real-time PCR (Table 1) were designed using the Primer Express program (Ver. 1, Applied Biosystems). After reverse transcription for 30 min at 50 °C and polymerase activation for 15 min at 98 °C, PCR amplification was performed followed by 40 cycles consisting of 15 s at 95 °C, 15 s at 55 °C and 1 min at 72 °C. Relative levels of mRNA expression were calculated by the ΔΔCt method according to the manufacturer's instructions (Applied Biosystems).

2.5. Immunoblotting

Total cellular proteins were separated with SDS–PAGE and transferred to polyvinylidene difluoride membranes (Millipore, MS). The blots were blocked using 1% (w/v) skim milk in TBS (pH 7.4) for 1 h at 37 °C and then incubated at 4 °C overnight with anti-MIC1 (GDF-15) polyclonal antibody (1:500) (07–217, Upstate, VA) in blocking solution. After incubation with alkaline phosphatase-linked anti-rabbit IgG antibody (1:5000) (Cell Signaling, MA), positive signals were visualized using the chemiluminescent CDP-Star substrate (New England Biolabs, MA).

2.6. Statistics

All values are expressed as the mean ± S.E. The significance of the differences between groups was determined using the Student's *t*-test or one-way analysis of variance following the Tukey–Kramer test using statistical analysis software (StatView for Windows version 5.0, SAS Institute, NC).

3. Results

3.1. Identification of light-responsive genes using cDNA microarray analysis

Oligonucleotide microarray analysis was employed to obtain the gene expression profiles of human dermal fibroblasts that were irradiated for 3 h with blue or near-UV light. Under these conditions, there were no significant effects of light irradiation on cell growth (data not shown). Out of approximately 30 000 spots (probe sets) on the AceGene Human Oligo Chip 30K A–C slides, a total of 12 844 spots survived the filtering process in all three independent sets of each experiment with blue and near-UV irradiation (Fig. 1B, Supplementary data). In the expression profile for the transcripts of control cells kept in the dark (Fig. 1B), signal intensities spread over two logarithmic units (>100-fold), confirming efficient detection and a wide range of coverage of the expressed genes. The fold induction of signal intensity relative to that of

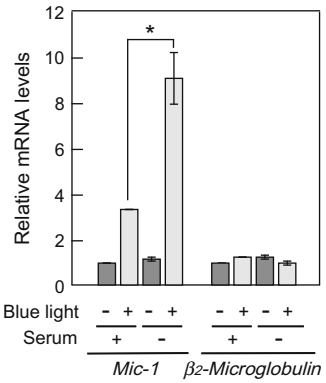

Fig. 2. Effect of serum starvation on *Mic-1* mRNA upregulation. Culture medium of NB1 cells was replaced with normal (serum-containing) or serum-free medium and kept in the dark for 12 h. Cells either irradiated with blue light for 3 h (Blue light +) or kept in the dark (Blue light −) were harvested, and relative mRNA abundance of *macrophage inhibitory factor-1* (*Mic-1*) and β_2-*microglobulin* genes was examined using real-time PCR. The mean values for the samples incubated in the dark in the presence of 10% serum were set to 1. $^{*}P < 0.05$.

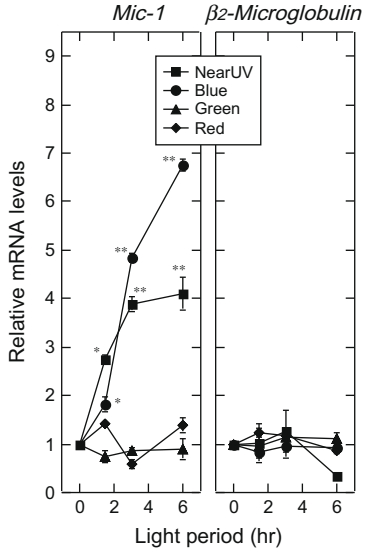

Fig. 3. Temporal and spectral change in mRNA abundance during light irradiation. NB1 cells were irradiated with near-UV, blue, green, or red light, and relative mRNA abundance of *Mic-1*, β_2-*microglobulin*, and *TATA-binding protein* (*Tbp*) genes at 0, 1.5, 3, and 6 h after irradiation was examined using real-time PCR. Relative mRNA levels of *Mic-1* (left) and β_2-*microglobulin* (right) to that of *Tbp* were plotted. $^{*}P < 0.05$; $^{**}P < 0.001$ vs. time = 0.

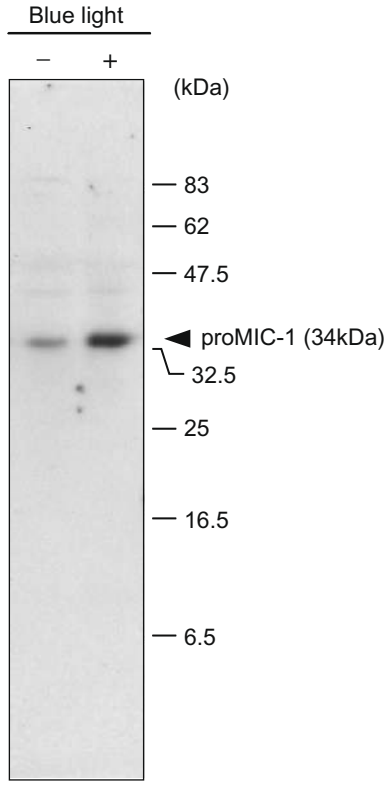

Fig. 4. Immunoblot analysis of protein expression of proMIC-1 in NB1 cells irradiated with blue light for 6 h. Cells either irradiated with blue light for 6 h or kept under dark conditions were harvested, and protein levels of proMIC-1 (34 kDa) were examined using immunoblot.

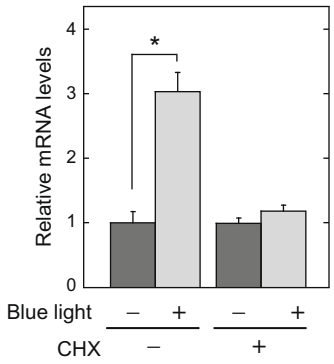

Fig. 5. Effect of cycloheximide on blue light-dependent *Mic-1* mRNA expression. Cycloheximide solution (36 μM final concentration, CHX +) or water (solvent, CHX −) was added to culture medium 30 min before exposure to blue-light irradiation. Cells were collected 6 h after blue-light irradiation (Blue light +) or incubation in the dark (Blue light −), and the relative mRNA levels of *Mic-1* to β_2-*microglobulin* were determined using real-time PCR analysis. The mean values for the dark samples were set to 1. $^{*}P < 0.05$.

Table 1
Oligonucleotide primers used for quantitative RT-PCR.

Gene	Accession No.	Strand	Sequence
Macrophage inhibitory cytokine-1 (Mic-1)	NM_004864	Sense	5′-CCCAT GGTGC TCATT CAAAA G-3′
		Antisense	5′-GCTCA TATGC AGTGG CAGTC TT-3′
TATA-binding protein (Tbp)	NM_003194	Sense	5′-CCTAA AGACC ATTGC ACTTC GTG-3′
		Antisense	5′-ATCCT CATGA TTACC GCAGC A-3′
β_2-*Microglobulin*	NM_004048	Sense	5′-AGCGT ACTCC AAAGA TTCAG GTT-3′
		Antisense	5′-TACAT GTCTC GATCC CACTT AACTA T-3′

the dark-kept sample revealed that a small subset of genes were significantly upregulated by short-wavelength light stimuli (Fig. 1C). Of the top twenty genes, listed in order of the geometric means of induction ratios (blue/dark and near-UV/dark ratios) (Table 2), only *Mic-1* showed higher than two-fold increases in averaged signal ratios with blue and near-UV light exposure (Fig. 1C, Table 2). It is important to note that *Mic-1* was expressed at a high level even in the non-irradiated control NB1 cells (Fig. 1B).

3.2. Analyses of light-dependent Mic-1 upregulation

To confirm light-dependent upregulation of *Mic-1* transcript, we performed quantitative RT-PCR analysis. Blue-light irradiation for 3 h significantly upregulated *Mic-1* mRNA levels in comparison with mRNA levels of β_2-*microglobulin*, which was used as a putative light-unresponsive control gene (Fig. 2). We further found that light-dependent *Mic-1* upregulation was enhanced by the removal of fetal bovine serum from the culture medium (Fig. 2). This result suggested the presence of unidentified factor(s) in the fetal bovine serum that has inhibitory effect on light-dependent *Mic-1* upregulation, so we investigated the temporal profiles and wavelength dependency in the absence of serum (Fig. 3). When all values were normalized by the internal mRNA levels of *TATA-binding protein* (*Tbp*), another light-unresponsive control gene, the mRNA levels of *Mic-1* dramatically increased with blue- or near-UV-light irradiation, even shortly (1.5 h) after the onset of irradiation (Fig. 3). On the other hand, exposure to green or red light for as long as 6 h had only a marginal effect on *Mic-1* mRNA level (Fig. 3). The transcript levels of the control gene β_2-*microgrobulin* were almost unchanged after exposure to any spectra of light, confirming the wavelength-dependent, specific induction of *Mic-1* gene.

We next examined the protein level of MIC-1. Secreted form of MIC-1 is disulfide-linked dimer of the mature MIC-1 peptide that is produced by proteolytic cleavage of the cellular precursor propeptide proMIC-1 [9]. Under reducing conditions, Flag-tagged mature MIC-1 and Flag-tagged proMIC-1 expressed in 293-EBNA cells were reported to migrate as 15 kDa and 40 kDa proteins, respectively [9]. Non-tagged proMIC-1 was detected as 35 kDa protein in the lysate of sulindac sulfide-treated HCT-116 cells [10]. In immunoblot analysis of NB1 cell lysates using an anti-proMIC-1 polyclonal antibody, we detected a single band migrating as 34 kDa protein (Fig. 4), which is likely to correspond to proMIC-1. We did not detect a band for mature MIC-1 in the NB1 cell lysates, and this is consistent with the previous report that mature MIC-1 (secreted form) is detected in the culture medium of *Mic-1*-overexpressing 293-EBNA cells but not in the cell lysate [9]. In NB1 cells, proMIC-1 protein level was stimulated by blue-light irradiation for 6 h (Fig. 4), most likely reflecting the photic induction of *Mic-1* transcript.

During our examination of whether light-dependent upregulation of *Mic-1* represented an immediate-early response, we found that blue light-dependent induction was completely inhibited by the pretreatment of NB1 cells with a translation inhibitor cycloheximide (Fig. 5). Thus, *Mic-1* induction required a novel synthesis of transcription factors to activate its transcription.

4. Discussion

In this investigation, we identified a small subset of genes whose transcripts were upregulated in normal skin fibroblasts by short-wavelength light. The upregulated genes encode a variety of proteins such as transcription factors, DNA damage-related genes, and proteins related to the stress response (Table 2). In this study, we focused our attention on *Mic-1* because it showed the most prominent upregulation with exposure to specific wavelengths of light.

Mic-1 gene was originally identified in macrophage as an upregulated gene that can be activated in association with cytokines such as IL-1β, IL-2, and TNF-α [9]. The product of this gene, MIC-1 or also called NAG-1 (non-steroidal anti-inflammatory drug

Table 2
Blue and near-UV light-induced genes (top 20 genes).

	Gene	Blue (fold induction)	Near-UV (fold induction)	Averaged induction	Accession No.	Description
1	*Mic-1*	1.47	2.79	2.02	NM_004864	Macrophage inhibitory cytokine-1 (also called *nag-1, gdf-15, plab*)
2	*flj10597*	1.80	1.95	1.87	NM_018150	Ring finger protein 220, RNF220
3	*dj620e11*	1.82	1.91	1.86	AL449762	Novel helicase c-terminal domain and snf2 n-terminal domains containing protein, similar to kiaa0308
4	*man1a1*	1.80	1.86	1.83	NM_005907	Mannosidase, alpha, class 1a, member 1
5	*aldh3*	1.78	1.86	1.83	NM_000691	Aldehyde dehydrogenase 3
6	*flj23829*	1.81	1.79	1.80	AK074409	RAB GTPase activating protein 1-like
7	*loc93017*	1.57	2.05	1.79	XM_048772	Similar to coilin; coilin p80
8	*mrps10*	1.73	1.83	1.78	NM_018141	Mitochondrial ribosomal protein s10
9	*ddit3*	1.35	2.33	1.77	NM_004083	DNA-damage-inducible transcript 3
10	*rnf39*	1.68	1.86	1.77	NM_025236	Ring finger protein 39, RNF39
11	*pfkm*	1.66	1.89	1.77	U24183	Phosphofructokinase, muscle
12	*hspa1a*	1.27	2.42	1.75	NM005345	Heat shock 70kd protein 1a
13	*s100a4*	1.92	1.70	1.75	NM_002961	s100 calcium-binding protein a4
14	*klf8*	1.76	1.72	1.74	NM_007250	Kruppel-like factor 8
15	*slamf7*	1.73	1.73	1.73	NM_021181	SLAM family member 7
16	*slc3a2*	1.67	1.76	1.72	NM_002394	Solute carrier family 3, member 2
17	*pga5*	1.71	1.72	1.71	AW869654	Pepsinogen A5
18	*loc400174*	1.64	1.76	1.70	XR_016147	Similar to single stranded DNA binding protein 3
19	*zfp692*	1.52	1.90	1.70	AK000538	Zinc finger protein 692, ZNF692
20	*caa75359.1*	1.59	1.82	1.70	Y15083	Translational inhibitor protein p14.5-related sequence

[NSAID]-activated gene-1, [10]), GDF-15 (growth differentiation factor-15, [11]), PLAB (placental BMP, [12]), PTGFB [13] or PDF [14], is a member of the TGF-β superfamily. MIC-1 is produced by macrophage and can inhibit its own production of TNF-α, and therefore it is thought to be an autocrine regulator of macrophage activation [9]. MIC-1 has been characterized in terms of (i) its high expression in the placenta [12] and (ii) its induction by NSAIDs in colon cancer cells [10,15–17]. Based on the present findings, the dermal fibroblast may be a new site for MIC-1 production, with implications that MIC-1 may inhibit macrophages in the dermis in a light-dependent manner. Because macrophages are capable of presenting antigens to the other immune cells, it is interesting to speculate that visible light may suppress or modify the immune response, not just UV radiation which is widely known to cause immunosuppression in the skin [3]. By application of NSAIDs [10,15] or catechins [16] or an anticancer drug doxorubicin [17], MIC-1 is highly induced in HCT-116 colon cancer cells, in which the transcription of *Mic-1* is activated through p53-dependent [16,17] and p53-independent [16] pathways. Considering that the *Mic-1* induction in HCT-116 cells is associated with growth inhibition and apoptosis [15,16], analyses of the photic induction of *Mic-1* in NB1 cells might help us to not only compare *Mic-1* transcription mechanisms between cancer and non-cancer cells but also understand a molecular link from sunlight reception to skin cancer prevention or promotion.

Mic-1 expression was induced by blue and near-UV light but not by green or red light (Fig. 3), suggesting that shorter wavelength light-sensitive photoreceptors are involved in the MIC-1 induction mechanism. In vertebrate genomes, a number of opsin family genes have been identified, and some of these opsins with blue-light sensitivity might operate in the dermal fibroblasts. FAD-based cryptochromes are also candidates for blue-light photoreceptors in the skin, as seen in plants [18] and *Drosophila* [19]. Another possible photoreceptive molecule is a blue light-sensitive, flavin-containing oxidase [20] that produces ROS in a light-dependent manner. In fact, it is reported that ROS are produced by extracellular matrix proteins in the skin with light exposure [21]. Investigation of the photoreceptive molecule(s) responsible for *Mic-1* upregulation is an important issue to be addressed in future study.

Recently, Johnen et al. [22] reported that MIC-1 plays a key role in prostate cancer-associated anorexia and weight loss. Mice with subcutaneous injection of MIC-1 show hypophagia and reduced body weight [22], suggesting its involvement in human appetite control in the non-cancer state. In this context, the light-dependent MIC-1 protein expression in normal human fibroblasts raises the possibility of systemic effects of the light signal, from which we can speculate as to whether MIC-1 can transmit photic information to other organs such as the brain to decrease appetite in a light-dependent manner. Future investigation of MIC-1 expression in the human skin and/or plasma during bright light irradiation may provide clues to the physiological importance of MIC-1 production in dermal cells.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.febslet.2009.02.006.

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