Visible light and human skin pigmentation: The importance of skin phototype

Hugo Moreiras1 | Clare O'Connor2 | Mike Bell2 | Desmond J. Tobin1,3

1The Charles Institute of Dermatology, School of Medicine, University College Dublin, Dublin, Ireland
2Walgreens Boots Alliance, Nottingham, UK
3The Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland

Abstract

Melanin is synthesised within melanocytes and transferred to keratinocytes in human skin, thereby regulating skin colour and protecting skin cells against UVR-induced damage. We commonly divide human skin into six phototypes (SPT-I to -VI (Fitzpatrick scale) according to the skin's tanning response to UVR. In this pilot study, we investigated the impact of UVR (maximum 311nm), blue (peak 450nm) and green visible light (peak 530nm) on melanin production and type in healthy human skin histocultures (SPT-I, -II and -III). UVR, blue and green light stimulated a surface tanning response in SPT-II and -III, but not SPT-I. Using the Warthin-Starry stain for sensitive melanin detection, all three light treatments induced melanogenesis in SPT-II and -III skin. Surprisingly, blue and green light (but not UVR) stimulated melanin synthesis in SPT-I skin. Moreover, melanin synthesis induced by blue and green visible light in SPT-I, SPT-II, and SPT-III skin was not associated with a detectable increase in DNA damage or cell apoptosis. By contrast, both responses were detected after UVR. These data suggest that blue and green visible light can stimulate melanin production in fair-skinned individuals without, at least some of, the harmful consequences of UVR-induced pigmentation. We are currently examining the molecular basis of UVR-independent melanogenesis in fair skin.

KEYWORDS
photo-biomodulation, green light, blue light, ultra-violet radiation, melanin, skin phototypes

1 | BACKGROUND

Skin colour is regulated at both constitutive (intrinsic) and facultative (inducible) levels. Melanin synthesis in the human epidermis occurs within melanosomes of the melanocyte. When mature, these melanosomes are transferred as melanin granules to adjacent keratinocytes, where they undergo additional processing and redistribution to form supra-nuclear melanin caps. There, melanin protects the keratinocyte's genetic material from ultraviolet radiation (UVR)-induced damage. Since the early 1960s, numerous studies have investigated the role of UVR in the skin, ultimately establishing the so-called Fitzpatrick scale stratifying skin into six broad phototypes (SPT). These range from the lightest (tanning-resistant) phototype-I (SPT-I) to the darkest phototype-VI (SPT-VI). However, the impact of visible light wavelengths (400–700 nm) on human skin has not yet been classified similarly. Nonetheless, violet/indigo light (400–450 nm) and blue/cyan light (450–500 nm) have recently been reported to stimulate melanogenesis in darker skin, in particular 415 nm violet light. This is perhaps not surprising, given that violet light abuts the ultraviolet-A range (315–400 nm). While...
most of the tanning response that becomes visible on the skin surface is thought to be due to UVB (280–315 nm), little is known of how green wavelengths (500–570 nm) impact human skin biology, including pigmentation.

1.1 | Question Addressed

In this pilot study, we investigated the feasibility of more extensive study of the differential effects of UVR and visible light in short-term skin histocultures of healthy Caucasian skin including UVR tanning-resistant light SPT-I skin and UVR tanning-competent moderately pigmented SPT-II and SPT-III skin. Additionally, we explored optimal detection of melanin, both by amount and subtype, by exploiting a modified Warthin-Starkey (WTS) stain, as recently reported by our group.12

2 | EXPERIMENTAL DESIGN

To address our question, we treated skin obtained from SPT-I, SPT-II and SPT-III healthy donors with one daily dose of 6 J/cm² UVR (PL-L36W UV6 lamp; measured at peak intensity 311 nm), and 140 J/cm² blue and green light (peak intensities 450 nm and 530 nm, respectively) for a period of three days using a proprietary LED-based device with discrete wavelengths spanning the visible to near infra-red spectrum (The Philips Company, Eindhoven, NL) as we have previously described.13-15 According to Seité et al 2010, the Sun minimal erythema dose (MED) for SPT-II is between 5 and 12 J/cm² and would be greater for higher SPT.16 Since the goal of this study was to induce a tanning response and stress to different SPTs, we needed to work with a biologically effective dose (BED) that not only induces a tanning response but also a UVR-induced damage response. Del Bino and Bernerd 2013 showed that a BED of 6 J/cm² was enough to observe DNA damage, and therefore, we choose to use this dose for our experimental design.17 Regazzetti et al, 2018 showed that 90 J/cm² induce a tanning response with blue/violet light at 415 nm.10 Since we wanted to achieve a similar result using visible light at lower energy wavelengths, that is blue light at 450 nm and green light at 530 nm, we dosed at 100 J/cm² and 140 J/cm². We opted to use the latter in our experimental design, since it gave the strongest tanning response. This was followed by assessment of an observable skin surface tanning response (by brightness), histological melanin content and subtype (by WTS), DNA damage response (by cyclobutane pyrimidine dimers) and cell apoptosis (by caspase-3) at 24 hours after the last exposure. For more detailed experimental procedures, see the supplementary material.

Ethical approval and informed consent were obtained (#LS-19–71, University College Dublin) to collect SPT-I, SPT-II and SPT-III abdominal skin (moderately photo-protected) after elective surgery (Blackrock Clinic, Dublin, Ireland). In addition, highly pigmented (SPT-V and SPT-VI) healthy skin samples from African geographic ancestry donors were obtained (courtesy of Prof. Rachel Watson, University of Manchester, UK) in compliance with UK Human Tissue Authority Act (2006) regulations and Declaration of Helsinki principles. In total, a qualitative melanin assessment was made using skin from 9 healthy female adult donors (mean 41 years).

3 | RESULTS

3.1 | Effect of photo-biomodulation on pigmentation status in light and darker skin phototypes

The effect of solar radiation on human skin pigmentation has been a significant focus of research over many decades, given its key role during our human evolutionary past.7,11,15,18,19 However, these studies have been mainly restricted to examining UVR wavelengths (280–400 nm) on darker skin phototypes (SPT-III to VI), as these skin phototypes are reported to produce a robust tanning response to UVR.5,18,20 Studies have recently been extended to include visible light wavelengths, principally violet light (sometimes referred also as “blue” light), especially wavelengths (eg 415 nm) that abut UVA-I (340–400 nm), and which stimulate melanogenesis via Opsin-3 photoreceptors.5,7,11

Thus, we developed a pilot study to examine the effect of UVR (311 nm) and visible light (blue 450 nm and green 530 nm) on fair skin (SPT-I) and on darker skin (SPT-II and SPT-III). We maintained short-term (3 days) ex vivo skin histocultures obtained from each phototype and submitted these to different light stimulation treatments as described above. We first determined the skin surface-detectable tanning response of each histoculture after treatment, by acquiring images for quantification of brightness after converting images from RGB to B&W, using ImageJ.

After light stimulation of skin histocultures, we observed that UVR, blue and green light all induced a detectable drop in brightness in SPT-II and SPT-III (Figure 1E, F, I and J). By contrast, these wavelengths do not alter brightness in SPT-I (Figure 1A and B). These findings corroborate the premise postulated by Fitzpatrick5 that SPT-I never tans (always burns) after UVR exposure, while SPT-II and SPT-III can readily tan in response to UVR. However, we also observed that both blue and green visible light induced a tanning response in SPT-II and SPT-III, thereby extending our knowledge beyond what was previously shown for violet light in phototype IV.10

To complement the above macroscopic observations, we analysed alteration in melanin levels in both skin phototypes at a histological level by WTS.12,21,22 While a histologically detectable increase in melanin was present in the tanned epidermis of UVR-irradiated SPT-II and SPT-III histocultures as predicted, SPT-I epidermis responded unexpectedly to blue and green light irradiation, with an increase in WTS-detectable melanin not observed post-UVR (Figure 1C, D, G, H, K and L). Thus, while the observation in SPT-II and SPT-III correlates with the observed reduction in brightness (see above), the WTS results for SPT-I skin were unexpected in that the observed increase in histologically detectable pigment produced did...
not translate into a reduction in observable brightness (ie in a tan response) at the skin surface.

### 3.2 Visible light wavelengths variably stimulate black versus reddish/brown pigment in light and darker skin phototypes

To further explore the basis for the above apparently paradoxical data, we further interrogated the skin samples with the WTS stain. This allowed us to distinguish two differentially stained pigment types, which included an intensely black pigment product (termed WTS-black) and a lighter reddish-brown pigment product (termed WTS-reddish/brown). To distinguish these variable WTS-staining pigment characteristics optimally for image capture, we optimised the saturation and gamma levels on microscope acquisition software to more faithfully represent what was being observed via the microscope eyepiece (Leica D2500 microscope with a DFC7000 T camera). Using ImageJ software, we applied colour thresholds to disambiguate the WTS-black or WTS-reddish/brown pigment products on the skin sections. Regions of interest (ROIs) were created to determine the mean pixel intensity per area of image. Results were presented as the percentage of total melanin pigment product per area. Using this approach, only WTS-black staining appeared to be increased by UVR or visible light in SPT-II and SPT-III histocultures (Figure 2C, D, E and F), while SPT-I skin responded to blue and green light only (ie not to UVB) with a readily detectable increase in both WTS-black and WTS-reddish/brown pigment products (Figure 2A and B). The implication of this histochemically detected response, which was not reflected in a visually detectable alteration in brightness of the skin surface, may suggest that visible light increased a mixed eumelanin/pheomelanin response in SPT-I skin that may, due to mixed optical characteristics did not translate into a perceivable drop in skin surface brightness (indicative of tanning) in SPT-I individuals.

This fascinating preliminary observation, which needs to be further investigated, including using ITA scoring, highlights the value of the modified WTS stain for detecting melanin level as well as complexity in human skin. It is perhaps noteworthy that one of the SPT-I sample donors had red hair of Celtic ancestry, which might explain the easy detection of WTS-reddish/brown pigment, due to the abundance of pheomelanin in these individuals. Nevertheless, both types of pigment (WTS-black and WTS reddish/brown) were variably detected in SPT-I samples. Although this histochemical staining method, to distinguish black eumelanin from red pheomelanin, in human skin cannot be considered fully specific and discriminatory, we were surprised to observe a distinctive colour tonal variation between the WTS readouts of the different SPTs. Although this pheomelanic SPT-I donor exhibited a striking "reddish" WTS reaction in their epidermis, unequivocal determination of melanin type will require further, including biochemical, validation. Nonetheless, it should be appreciated that while WTS-reddish staining may be overwhelmed /obscured by the more dominant WTS-black staining, this can be interpreted as a manifestation of the "casing model" of melanin granule organisation, first proposed by Agrup et al. and later supported by a study on neuromelanin granules by Bush et al., and other on iridal stroma melanosomes by Peles et al. This model was recently reappraised by Ito and Wakamatsu, which suggests that reddish pheomelanin is located within an outer black eumelanin casing.

To further validate the modified WTS stain for its potential to distinguish melanin pigment subtypes in human skin (epidermis and hair follicle), we examined a group of non-treated skin samples from SPT-I red-haired donors, SPT-I from blonde-haired donors, and SPT-II, SPT-III, SPT-V and SPT-VI health skin donors (Figure S1). Interestingly, we could detect both WTS pigment product types in all phototypes, although the intense WTS-black pigment type was far more prevalent in darker skins. In contrast, the WTS reddish/brown was much more prevalent in light skins. Moreover, the ratio of these two pigment types correlates with high-performance liquid chromatography (HPLC) quantification performed by others as discussed by Ito and Wakamatsu. These histochemical data strengthen our preliminary observations and showcases the WTS stain’s potential to study melanin subtypes in human epidermis, offering advantages versus other perhaps less-specific melanin staining techniques (eg Fontana-Masson, Haematoxylin-eosin, Von Kossa).

Our results show for the first time in fair SPT-I skin that visible light can induce melanin production, which may have a beneficial effect in protecting these individuals from the harmful effects of UVR. This finding may concur with our previously reported observation that cultured melanocytes from red-haired individuals can indeed produce significant melanin if stimulated in the absence of their keratinocyte partner. The latter study strongly suggests that the epidermal-melanin-unit (EMU) is very important in regulating a visually detectable pigmentation response in human skin. Interestingly,
the aforementioned study\textsuperscript{31} also showed that UVB-induced PGE\textsubscript{2} production in epidermal melanocytes did not correlate with their melanin content, tyrosinase expression/activity or TRP-1 or DCT expression. This observation may be important, since SPT-I individuals are more susceptible to developing skin cancer due to their lower levels of photo-stable eumelanin.

### 3.3 Variable induction of DNA damage and apoptosis by UVR and visible light wavelengths in light versus darker phototype epidermis

We next assessed how both SPT-I, SPT-II and SPT-III skin responds to UVR and visible light irradiation at the cellular level, by assessing
**FIGURE 2** Visible light differentially induces pigmentation according to the skin phototype. Warthin-starry (WTS) stain analysis to distinguish different melanin pigment subtypes in skin phototype (SPT) I, II and III after light stimulation. A, Representative pictures of SPT-I samples submitted to the modified WTS melanin stain after treatment with UVR or visible light (blue or green), scale bar = 50 µm. B, Graphic representation of the quantification of 60 images per condition of both sample duplicates. C, Representative pictures of SPT-II samples submitted to the modified WTS melanin stain after treatment with UVR or Visible light (blue or green), scale bar = 50 µm. D, Graphic representation of the quantification of 60 images per condition of both sample duplicates. E, Representative pictures of SPT-III samples submitted to the modified WTS melanin stain after treatment with UVR or Visible light (blue or green), scale bar = 50 µm. F, Graphic representation of the quantification of 60 images per condition of both sample duplicates. Arrows represent WTS-black pigment and arrowheads represent WTS reddish/brown. Statistical analysis was performed using Prism software (GraphPad Software Inc.). Two-way ANOVA test was used to analyse the p value of the differences. p values were considered statistically significant when <0.01 (**) or <0.001 (***)
the DNA damage or cell death (apoptosis) response. The level of cyclobutane pyrimidine dimers (CPDs) formation was used as a marker of UVR-induced DNA damage, \(^{20,32}\) while levels of cleaved caspase-3 were used to assess cell death by apoptosis.

Both CPD and caspase-3 levels were found to increase after UVR irradiation in both SPT-I, SPT-II and SPT-III compared with the non-treated controls (Figure 3A, B, E, F, I and J). Levels of CPDs formation and caspase-3 expression were higher in SPT-I than in SPT-II and SPT-III samples after UVR stimulation, which likely reflects the lack of a robust eumelanin protective response to UVR in light skin. By contrast, we found no detectable induction of CPDs formation and caspase-3 expression in either SPT-I, SPT-II or SPT-III when...
irradiated with either blue or green visible light (Figure 3C, D, G, H, K and L). This observation suggests that while all the doses of visible light used in this study, particularly blue and green wavelengths, can induce melanin synthesis in both fair and darker skin individuals, this occurs without the UVR-associated deleterious effect of DNA damage and cell death, as assessed by CPD level and cell apoptosis, respectively.

4 | CONCLUSIONS AND PERSPECTIVE

This study raises important questions about the role of visible light (approx. 50% of solar light detected by skin) in the homeostasis or photo-biomodulation in lighter skin individuals. The role of opsins, already identified to be expressed in human skin and hair follicle cells (Table 1), and their related signalling pathways are likely to be of significant interest for both clinical and cosmetic applications. As shown by Regazzetti et al, SPT-III and SPT-IV respond to blue light through OPN3. Interestingly, this opsin was shown to sense both blue and green light (Table 1) and it will be interesting to address in future studies if the response we detect in this pilot work is due to an activation of OPN3 or OPN2, the latter which is reported to sense only green light.

These preliminary data, which need to be confirmed in larger studies, tempt us to suggest a potential role for green visible light, and only green light.

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CONFLICT OF INTERESTS

MB and CO’C are employees of Walgreen-Boots-Alliance (UK).

AUTHORS’ CONTRIBUTIONS

DJT, MB and CO’C: Conceptualisation. HM and DJT: Methodology. HM and DJT: Validation. HM: Formal analysis, investigation, data curation and visualisation. MB and CO’C: Resources. HM and DJT: Writing—original draft preparation. HM, DJT, MB and CO’C: Writing—review and editing. DJT: Supervision, project administration and funding acquisition. All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Hugo Moreiras https://orcid.org/0000-0003-0984-7921
Desmond J. Tobin https://orcid.org/0000-0003-4566-9392

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

Supplementary Material
Figure S1

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