Role of apoptosis and key canonical pathways in psoriasis plaque clearance in response to UVB phototherapy

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Introduction and Aims

Psoriasis is a common immune-mediated inflammatory skin and systemic disease with debilitating and life limiting effects. Currently, psoriasis is treated on a trial and error escalation basis, depending on the severity of the condition and previous response to treatment. There is increasing interest in developing a precision medicine approach, highlighting the need for predictive biomarkers. Phototherapy is an effective therapy for mild to moderate disease and may induce remission. Previous work identified the action spectrum of UVB in psoriasis (Parrish, J. Invest Dermatol 1981) and demonstrated that effective wavelengths of UVB (311nm) but not ineffective wavelengths (290nm) induced apoptosis of epidermal keratinocytes in psoriatic plaques (Weatherhead et al J. Invest Dermatol 2013) .

The aim of this study is to identify molecular signals and biomarkers within psoriatic skin which are modulated in response to 311nm UVB but not 290nm UVB which may be used to personalise patient treatment regimens by predicting patient response to therapy.

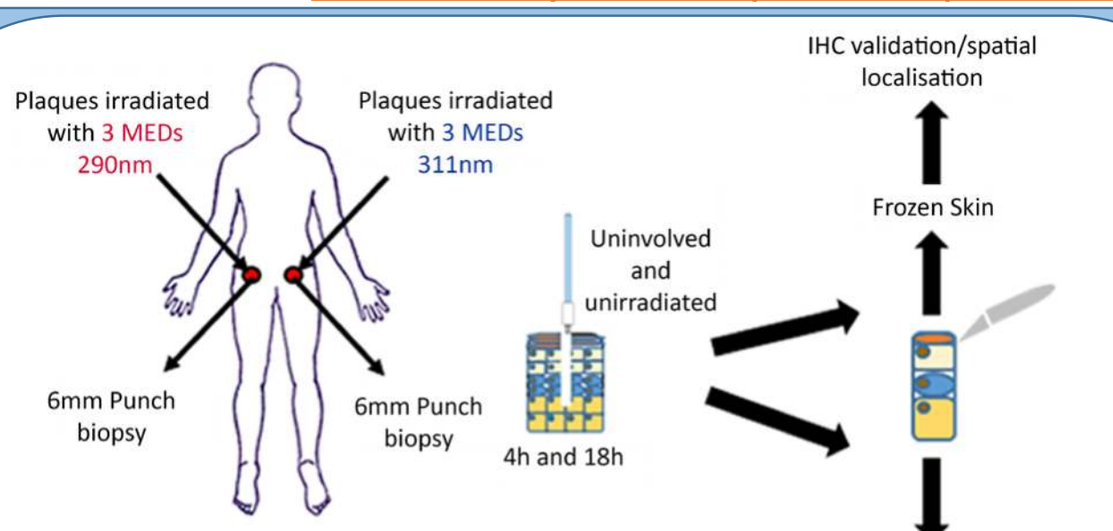


Figure 2: Diagrammatic representation of irradiation site and consequent biopsy site. Biopsies were obtained from two irradiated areas of affected skin, un-irradiated psoriasis and control non-lesional skin to ensure equi-erythemogenic doses. Samples were obtained over a period of 8 weeks and underwent testing such as IHC and mRNA sequencing.

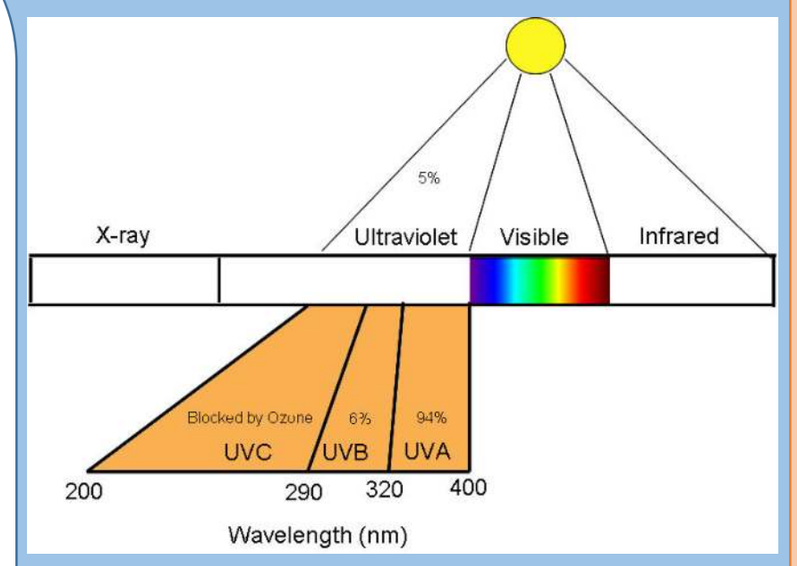


Figure 1: Diagrammatic representation of the ultraviolet spectrum. UV radiation ranges from 200nm – 400nm with only approximately 6% of UVB radiation reaching the earth. The UV proportion of the electromagnetic spectrum accounts for 5% of the suns radiative effects. A wavelength of 311nm is effective in the clearance of psoriasis, a drop to 290nm is ineffective.

Methods

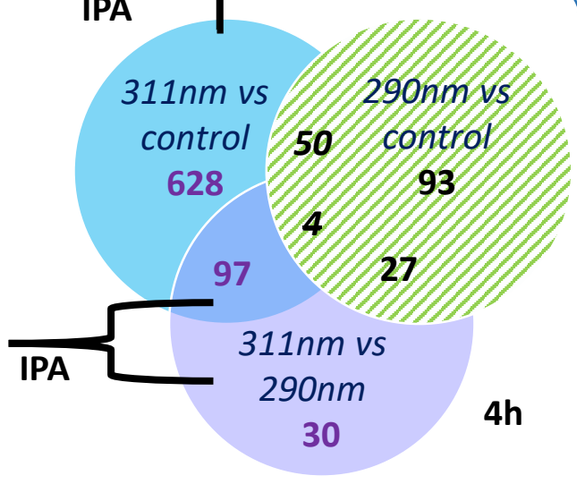
Bioinformatic analysis was performed on microarray data derived from skin biopsies (n=48) obtained at 4h and 18h following a single irradiation with 311nm or 290nm of psoriatic skin. Differentially expressed genes (DEGs) associated with 311nm but not 290nm were analysed for their upstream regulators and associated canonical pathways.
Validation, localisation patterns and quantification of biomarkers was determined using confocal and Volocity.

Results 1:

Diseases/ Functions
Necrosis
Morbidity or mortality
Organismal death
Cell death of tumour cell lines
Apoptosis
Apoptosis of tumour cell lines

IPA

Disease/Functions
Apoptosis of T lymphocytes
Repair of cells
Infiltration of T lymphocytes
Apoptosis of B lymphocytes
Apoptosis of epithelial cells
Apoptosis of leucocytes



Diseases/Functions
Apoptosis of lymphatic system cells
Antimicrobial response
Apoptosis of leucocytes
Apoptosis of hematopoietic progenitor cells
Lung cancer
Apoptosis of blood cells

IPA

Disease/Functions
Apoptosis of carcinoma cell lines
Cell death of carcinoma cell lines
Organismal death
Morbidity or mortality
S phase of tumour cell lines
Apoptosis of tumour cell lines
Differentiation of mesenchymal cells

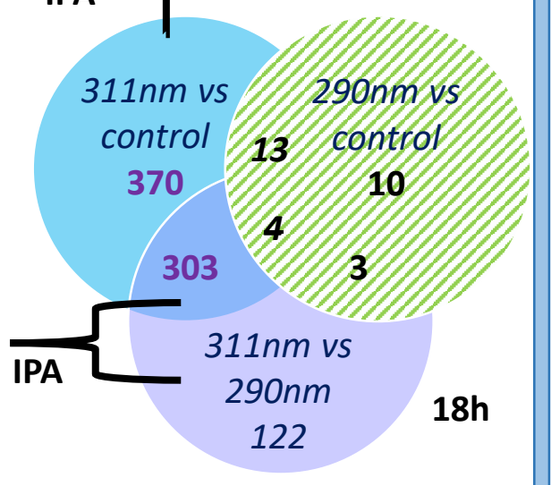
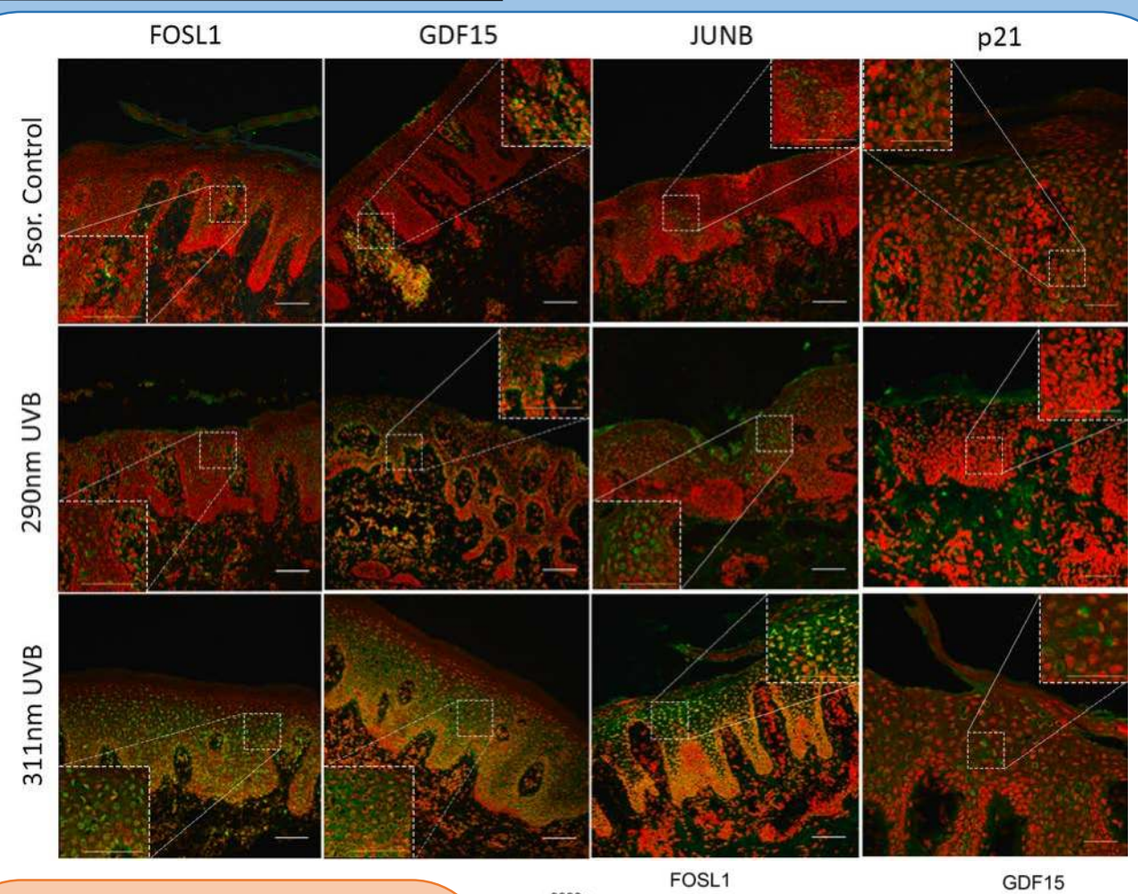


Figure 3: Venn diagrams showing the top disease and functions ranked according to activation Z scores following irradiation with 311nm but not 290nm UVB at 4h and 18h. Microarray data shows that a high proportion of upstream pathways are associated with cell death, necrosis or apoptosis. 311nm UVB is linked to cell death in a variety of cell types.

Results 2:



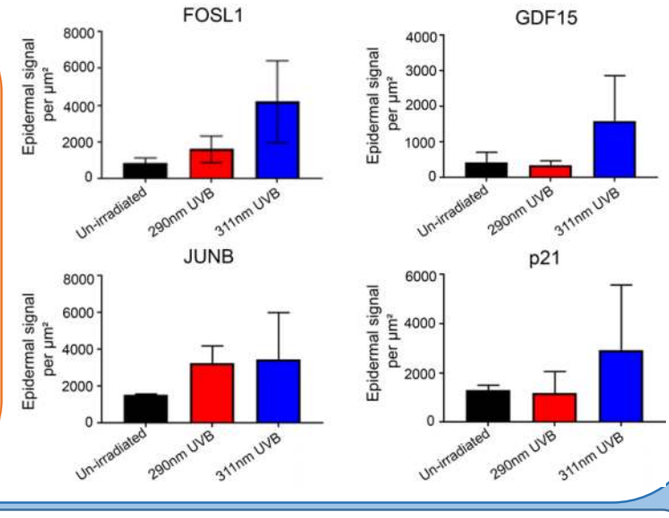


Figure 4: 311nm NB-UVB upregulates expression of nuclear FOSL1, GDF15, JUNB and p21 in human epidermis compared to 290nm and un-irradiated control. Confocal and Volocity analysis demonstrated increased signal within psoriatic epidermis for all biomarkers.

Conclusions

- Apoptosis and necrosis identified as key cellular mechanisms induced by effective (311nm) UVB but not by ineffective (290nm) UVB in lesional psoriatic skin.
- Key genes upregulated by 311nm compared to 290nm and implicated in apoptosis validated at protein level.
- These data support a key role for apoptosis and necrosis in epidermal remodelling and plaque clearance in response to UVB.

Parrish, J.A. and K.F. Jaenicke, *Action Spectrum for Phototherapy of Psoriasis.* Journal of Investigative Dermatology, 1981. **76**(5): p. 359-362.
Weatherhead, S.C., et al., *Keratinocyte Apoptosis in Epidermal Remodeling and Clearance of Psoriasis Induced by UV Radiation.* Journal of Investigative Dermatology, 2011. **131**(9): p. 1916-1926