

## Editorial

# Shining light on lupus and UV

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### Abstract

People exposed to sunlight can develop erythema, DNA damage, and photoimmunosuppression. Extended exposure of normal epidermis to sunlight will induce dysmorphic keratinocytes with pyknotic nuclei scattered throughout the spinous layer. These 'sunburn cells' are apoptotic keratinocytes and are usually cleared within 48 hours after sunburn. Patients with lupus erythematosus, however, whether it be the discoid, subacute cutaneous, systemic, or tumid form, develop new cutaneous lesions and can experience systemic worsening of their disease. Are sunlight-induced keratinocyte apoptosis and the immune response to these cells abnormal in lupus patients?

This commentary examines the question of whether sunlight-induced keratinocyte apoptosis and the immune response to these cells are abnormal in lupus patients in the context of the study by Reefman and colleagues [1], which evaluates induction and clearance of apoptotic keratinocytes in lupus skin. The response of normal keratinocytes to UV light is well documented and includes activation of signaling molecules that modify growth to allow time for DNA repair [2]. If the keratinocyte incurs irreparable damage, apoptosis ensues, generating sunburn cells in the epidermis [3]. Unlike macrophage-rich organs such as the thymus or spleen, the epidermis contains only Langerhans cells (LCs), which actually migrate out of the epidermis following UV injury. Since dermal dendritic cells and macrophages must be recruited into the epidermis to help remove the corpses, apoptotic cell clearance in the skin is a relatively slow process (days rather than minutes or hours) that occurs through shedding and influx of phagocytes. In addition, UV exposure induces local immunosuppression by stimulating transforming growth factor-beta-1 and IL-10 production by keratinocytes and macrophages [4,5], and by inducing egress of LCs to draining lymph nodes [6].

Lupus photosensitivity could be caused by an aberrant response of keratinocytes to UV injury, defective clearance of apoptotic cells or an abnormal immune response to these cells. Reefman and colleagues [7] previously reported that, 24 hours after UVB radiation, there were no differences in the numbers of epidermal apoptotic cells between lupus patients and controls, leading to the conclusion that lupus keratinocytes were not hypersensitive to UV light. However, our previous analysis of UV responses of keratinocytes *in vitro* did suggest increased sensitivity of lupus keratinocytes, as determined by translocation of lupus autoantigens to apoptotic blebs [8], and enhanced UVB induced death was also observed by others [9]. Further studies in this area are clearly needed.

There is abundant evidence in experimental animals that defective clearance of apoptotic cells predisposes to systemic lupus erythematosus (SLE; reviewed in [10]), although the evidence of an intrinsic clearance defect in lupus patients is more controversial. In the present study, the authors therefore examined the possibility that disturbed clearance of apoptotic keratinocytes contributed to lupus skin rash [1]. By quantifying the numbers of apoptotic cells at three time points up to ten days after a single dose of UVB, they observed that the numbers of apoptotic cells did not differ between patients and controls. The major positive finding was that, despite equivalent numbers of apoptotic cells, a subset of patients developed a greater inflammatory infiltrate compared to controls. The lack of uniform correlation with skin rash or photosensitivity in this subset detracts from the significance of these findings. Nevertheless, these findings could be a departure point for mechanistic studies (see below). It is also important to point out that the conclusions of several other recent studies have been inconsistent. Kuhn and colleagues [11] reported that

LC = Langerhans cell; SLE = systemic lupus erythematosus.

**Table 1****Variables in three recent studies of apoptotic cells induced by photoprovoacation**

	Reefman <i>et al.</i> [1]	Kuhn <i>et al.</i> [11]	Janssens <i>et al.</i> [12]
Patients	SLE	DLE, SCLE, TLE	DLE, SCLE, SLE
Photosensitive	6/15	All	All
Treatment	Steroids, azathioprine	No steroids	3/22 steroids
Controls	Healthy	SLE, healthy	Healthy
UV	UVB, 2MEDs	UVA or UVB, 1.5 MED	UVB, 6 MEDs
Site	Buttock	Upper back	Buttock
Frequency	Once	Three times	Once
Apoptosis detection	Sunburn cells, casp3	ISNT, TUNEL, casp3	Casp3
Time analyzed (days)	3, 10	1, 3 and up to 28	1, 2, 3

Casp3, activated caspase 3; DLE, discoid lupus erythematosus; ISNT, *in situ* nick translation; MED, minimal erythemal dose; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus; TLE, tumid lupus erythematosus; TUNEL, *in situ* nick end labeling.

apoptotic keratinocytes did accumulate to a greater extent in the epidermis of UV irradiated skin from patients compared to controls and Janssens and colleagues [12] found no differences in either the numbers of active caspase 3 positive cells nor the inflammatory infiltrate analyzed up to 72 hours after UV induced erythema in lupus patients.

The varying results and conclusions between these studies are likely explained by differences in experimental design, such as the frequency and dose of UV challenge, time of analysis, patient heterogeneity (note that the Kuhn study examined chronic lupus erythematosus rather than SLE patients) as well as by the different techniques used to quantify apoptotic cells (Table 1). Quantification of sunburn cells by an experienced dermatopathologist may be accurate but it is not objective and is not sensitive to early changes. Investigators in the studies cited above have, therefore, used either detection of cleaved caspase 3 and/or TUNEL (*in situ* nick end labeling) techniques. Each is a useful measure of cell death but has limitations. For example, activation of caspase 3 does not invariably lead to apoptosis [13] and *in situ* staining methods that rely on DNA incorporation into nicked DNA may yield false positive results in cells undergoing rapid proliferation and DNA repair (see discussion in [14]). Therefore, only when two methods that rely on different principles for detection are strongly correlated in a given sample can a reliable estimate of apoptotic cells be established.

If the authors are correct in their conclusion that clearance of apoptotic keratinocytes is normal in lupus but there is an enhanced inflammatory response (at least in a patient subset), several provocative lines of evidence connecting keratinocyte damage by UV light with the development of autoimmunity should be considered. UVB light induces multiple forms of organelle and genotoxic injury resulting in

DNA strand breaks as well as the generation of pyrimidine dimers. Single-stranded breaks are sensed by the ATR (ataxia telangiectasia and rad3 related) kinase, which orchestrates repair pathways and activation of p53. P53, in turn, leads to cell cycle arrest followed by DNA repair or apoptosis. Could abnormalities in the complex pathway of sensing and repair lead to an abnormal immune response? For example, deficiency of a p53 response gene, *Gadd45a*, that is transcriptionally upregulated in keratinocytes following UV exposure resulted in a lupus-like syndrome in mice [15].

## Conclusion

The fundamental questions regarding the origin of UV-induced rash and exacerbation of lupus remain. Is there an intrinsic keratinocyte 'malresponse' to UV that drives inflammation and do apoptotic cells have anything to do with it? Is UV induced apoptosis relevant to the recruitment of plasmacytoid DC? What roles do autoantibodies play in this process? Careful studies such as those described by Reefman and colleagues [1] will bring progress in this fertile area for discovery.

## Competing interests

The authors declare that they have no competing interests.

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