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# Sun exposure rapidly reduces plasmacytoid dendritic cells and inflammatory dermal dendritic cells in psoriatic skin

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## Summary

*Background* Interferon (IFN)-α-producing plasmacytoid dendritic cells (pDCs), inflammatory CD11c+CD1c− myeloid dendritic cells (mDCs) and macrophages have been found to contribute to the pathogenesis of psoriasis. Heliotherapy is a well-established treatment modality of this disease, although the details of how the effects are mediated are unknown.

*Objectives* To test the hypothesis that exposure to natural sun affects pathogenic DC subsets in lesional skin.

*Methods* Skin biopsies were obtained from lesional and nonlesional skin in 10 patients with moderate to severe psoriasis subjected to controlled sun exposure on Gran Canaria. Biopsies were obtained at baseline, day 2 and day 16 and examined by immunohistochemistry.

*Results* Sixteen days of heliotherapy had excellent clinical effect on patients with psoriasis, with significant reductions in Psoriasis Area and Severity Index (PASI) scores. In lesional skin pDC numbers and expression of MxA, a surrogate marker for IFN-α, were rapidly reduced. Inflammatory CD11c+CD1c− mDCs were significantly reduced whereas resident dermal CD11c+CD1c+ mDCs were unaffected. Expression levels of the maturation marker DC-LAMP (CD208) on mDCs were significantly reduced after sun exposure, as were the numbers of lesional dermal macrophages. A decrease of dermal DC subsets and macrophages was already observed after 1 day of sun exposure. An additional finding was that DC-SIGN (CD209) is primarily expressed on CD163+ macrophages and not DCs.

*Conclusions* The clinical improvement in psoriasis following sun exposure is associated with rapid changes in dermal DC populations and macrophages in lesional skin, preceding the clinical effect. These findings support the concept that these DC subsets are involved in the pathogenesis of psoriasis and suggest that sun-induced clinical benefit may partly be explained by its effect on dermal DCs.

Psoriasis is a chronic autoimmune skin disorder believed to be mediated by pathogenic interactions between dendritic cells (DCs), T cells and keratinocytes.[1] Several DC subsets have been shown to accumulate in psoriatic skin and as efficient antigen-presenting cells (APCs) they are thought to stimulate pathogenic T cells locally.[1,2] This concept is underscored by the fact that several new biologics with clinical effect in psoriasis specifically target molecules involved in DC–T-cell interactions.[3]

Plasmacytoid (p)DCs are present in very low numbers in normal skin[4] but recent reports have shown that pDC numbers are increased in psoriatic lesions and contribute to immune pathology, mainly through the production of interferon (IFN)-α.[5,6] Interestingly, a recent publication demonstrated that pDCs are activated through toll-like receptor (TLR) 9 via endogenous DNA coupled with the antimicrobial peptide LL37, which is upregulated in psoriasis.[7]

Under steady-state conditions human dermal myeloid APCs have been found to consist of functionally and phenotypically distinct populations of myeloid (m)DCs and macrophages.[8] 'Resident' dermal mDCs are characterized by the co-expression of CD11c and CD1c.[4] Dermal macrophages are usually CD11c− but express CD163.[8] Although the C-type lectin DC-specific integrin intercellular adhesion molecule (ICAM)-3-grabbing nonintegrin (DC-SIGN, CD209) was previously

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believed to be a marker for DCs, it has recently been reported to be expressed on macrophages in normal skin[9] as well as in other tissues.[10]

In psoriatic lesions the presence of APC populations differs markedly from normal skin. Notably, an additional mDC subset expressing CD11c but not CD1c has been identified and termed 'inflammatory DCs'.[4] These inflammatory dermal mDCs were shown to produce tumour necrosis factor (TNF)-α, inducible nitric oxide synthase (iNOS), interleukin (IL)-23, and to activate both T-helper (Th)1 and Th17 cells and could therefore potentially be central players in psoriasis pathogenesis.[11] A proportion of these, but not the CD11c+CD1c+ resident subset, also expresses the monocyte/macrophage markers CD163, DC-SIGN and CD14.[11]

In addition to pDCs and inflammatory mDCs, macrophages have also been implicated in psoriasis pathogenesis. They were shown to be a source of pathogenic TNF-α in mouse models of the disease[12,13] and there is evidence to suggest that macrophages contribute to psoriasis also in humans.[14,15]

Exposure to ultraviolet (UV) radiation induces immunosuppression and has beneficial effects on psoriasis as well as other inflammatory skin disorders.[16–18] Heliotherapy is a well-established therapeutic modality for patients with psoriasis in Scandinavian countries. We have recently shown that significant clinical improvement during 16 days of sun exposure was associated with rapid reduction in T-cell numbers in lesional skin as well as downregulation of inflammatory parameters both *in situ* and systemically.[19] Here, we further analyse the same patient material, and show that 16 days of sun exposure induces rapid reduction in IFN-α-producing pDCs, CD11c+CD1c− dermal inflammatory DCs as well as macrophages in psoriatic skin.

## Materials and methods

### Subjects

A total of 20 patients (mean/median age 47·2/48 years, range 24–65, six females and 14 males) were enrolled in the study and transported from Norway to Gran Canaria, Spain, in the month of March. The patients were evaluated by the same dermatologist for the Psoriatic Area and Severity Index (PASI)[20] before and after heliotherapy. The dermatologist was unaware of the duration of sun exposure to which the patient had been exposed at the time of examination. Before treatment all patients had mild to severe plaque psoriasis, i.e. mean/median PASI before sun exposure of 9·8/8·7, range 3·8–18·8. All patients had stopped using any psoriasis medication at least 4 weeks prior to this study. Two of the patients had skin type II and 18 had skin type III according to the Fitzpatrick classification.[21] Ten patients were randomly selected for biopsy sampling: skin samples from five patients (median age 44, range 38–56, one female; median PASI 16, range 8·4–17) were directly frozen whereas tissue from the remaining five (median age 59, range 48–61, all male; median PASI 9, range 8·1–18) were formalin-fixed.

Spectral UVB (280–315 nm), UVA (315–400 nm) and CIE erythema-weighted UV irradiances were measured every hour from 9 a.m. to 5 p.m. using two broadband instruments. The method and procedures are described elsewhere.[22] Briefly, the first day all patients were exposed to sun for 1·5 h, equally divided between the front and back sides. The following days the time of sun exposure was gradually increased. The estimated mean standard erythema dose (SED) after 1 day of sun exposure was 5·1 SED and the sum of the exposure for 15 days was 166 SED. Mean estimated cumulative doses for UVB and UVA and CIE erythema-weighted UV after 15 days were 11·8 J $cm^{-2}$ [95% confidence interval (CI) 11·0–12·6], 464 J $cm^{-2}$ (95% CI 432–496) and 170 SED (95% CI 158–181), respectively. Seventy per cent of the patients reported erythema after the first day of sun exposure. On day 16 none had visible erythema.

The study was approved by the Regional Committee of Medical Ethics and all patients gave their written, informed consent.

### Skin biopsies

Four-millimetre punch biopsy specimens were obtained from lesional and nonlesional skin on the back in all 10 patients. The samples from each individual patient were obtained from the same body area on all days but at sufficient distance to avoid reactive inflammation from prior biopsy sampling. Skin samples, directly snap frozen in liquid nitrogen ($n = 5$), were obtained on day 0 (baseline), day 2 (before sun exposure the second day) and day 16, whereas formalin-fixed and paraffin-embedded samples ($n = 5$) were obtained on days 0 and 16.

### Immunohistochemistry

Frozen sections were cut at 4 μm and fixed in acetone prior to staining. Two-colour immunofluorescence staining was performed as detailed elsewhere.[19] The panel of antibodies and reagents used are given in Table S1 (see Supporting information). MxA staining was performed on formalin-fixed and paraffin-embedded specimens, because this antibody does not work on frozen sections. Details are described elsewhere.[23]

All immunostained sections were examined blindly by fluorescence microscopy (NIKON Eclipse 80i, Nikon Corporation, Tokyo, Japan) at × 400 magnification by the same investigator (I.H.). Immunostained cells were detected using fluorescent filters for red and green emission as well as filter combinations for simultaneous detection of red and green to ensure co-expression. All stained cells in the papillary dermis and in the reticular dermis, to a depth of 250 μm below the rete ridges, were counted using an ocular grid (10 × 10 lines, 250 × 250 μm). All positive cells were counted in at least one section (median 10 fields, range 6–18) from each specimen. Due to the 'dendritic' morphology of APCs only the parts considered as the main cell body were counted. Cell counts were divided on the area examined and given as total number per square millimetre. MxA staining of the epithe-

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lium was estimated on an arbitrary scale from 0 to 5 in order to perform semiquantitative comparisons.

### Statistics

The nonparametric Wilcoxon test was applied for analyses of PASI scores and epidermal thickness. The nonparametric Friedman test with Dunn's multiple comparison post-test were performed to compare cell counts obtained from five patients at three different time-points. As the cell populations investigated were carefully chosen, based on previous knowledge of the pathogenesis of psoriasis, the level of significance was accepted at the standard $P < 0{\cdot}05$.

## Results

We have previously shown that this group of patients ($n = 20$) experienced clinical improvement with significant reduction in PASI score and reduced epidermal thickening in lesional skin during the study period of 16 days.[19] Figure 1 shows changes in PASI score and epidermal thickness for the 10 patients that were biopsied. Representative haematoxylin and eosin photomicrographs before and after treatment from one patient are shown in Figure 1c.

### Plasmacytoid dendritic cells and the interferon-α-inducible protein MxA are reduced in lesional dermis after sun exposure

The density of dermal pDCs, defined as cells co-expressing the surface markers CD123 and CD45RA (Fig. 2a–e), was dramatically increased in lesional compared with nonlesional skin before sun exposure (median 80 vs. 2 cells $mm^{-2}$). After 16 days of sun exposure a significant reduction in the density of pDCs in lesional skin was observed ($P < 0{\cdot}05$; Fig. 2a,c,d). In nonlesional skin a small but significant increase ($P < 0{\cdot}05$; Fig. 2b) was observed after sun exposure.

It has been shown that production of IFN-α by pDCs contributes to the pathology of psoriasis.[5,7] We examined formalin-fixed specimens obtained at baseline and day 16 from five different patients for the expression of MxA, a well-established surrogate marker for IFN-α.[23–26] Importantly, we found that whereas MxA was undetectable in nonlesional skin both before and after sun treatment, epidermal expression of MxA was strongly upregulated in lesional epidermis with marked reduction in all patients after sun exposure (Fig. 2f–i).

Together, these findings indicated that 16 days of sun exposure significantly lowered the number of pDCs in the lesion, coinciding with evidence of reduced IFN-α production.

### CD11c+CD1c− inflammatory dendritic cells are selectively reduced in lesional dermis after sun exposure

Total numbers of dermal CD11c+ DCs were increased approximately three-fold in lesional compared with nonlesional skin (Fig. 3e,g and Fig. S1, see Supporting information). In agreement with previous reports[27] we found that this increase was almost entirely due to a 20-fold increase in the putative inflammatory CD11c+CD1c− subset (Fig. 3a,c,e,g). In contrast, the 'resident' dermal CD11c+CD1c+ DC population was increased only twofold (Fig. 3b,d,e,g). After 16 days of sun exposure, the CD11c+CD1c− DC population in lesional dermis was significantly decreased ($P < 0{\cdot}01$; Fig. 3a,e,f), with marked reduction in cell numbers evident already after 1 day

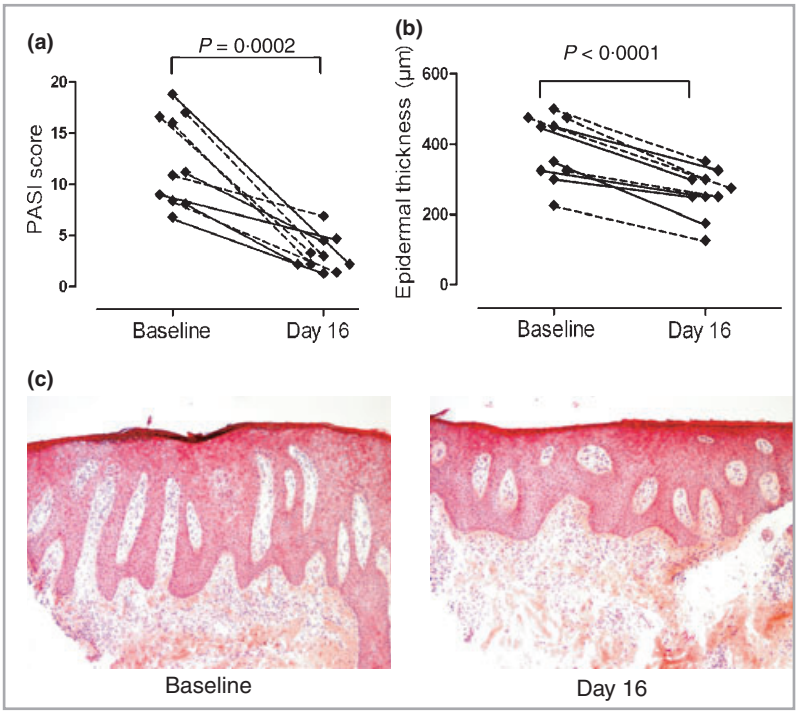


**Fig 1.** Psoriasis Area and Severity Index (PASI) scores, epidermal thickness and haematoxylin and eosin photomicrographs of lesional skin at baseline and after 16 days of sun exposure. PASI scores (a) and epidermal thickness (b) in lesional skin were significantly reduced after 16 days of sun exposure. Patients whose biopsies were frozen or formalin-fixed are indicated by broken and solid line, respectively. Panel (c) shows photomicrographs of representative sections from lesional skin from one of the patients included here. At baseline (left panel), severe pathology was seen with acanthosis, cellular infiltrates and dilated capillaries whereas at day 16 (right panel) marked reductions in these characteristics were observed. Images are at × 200 magnification.

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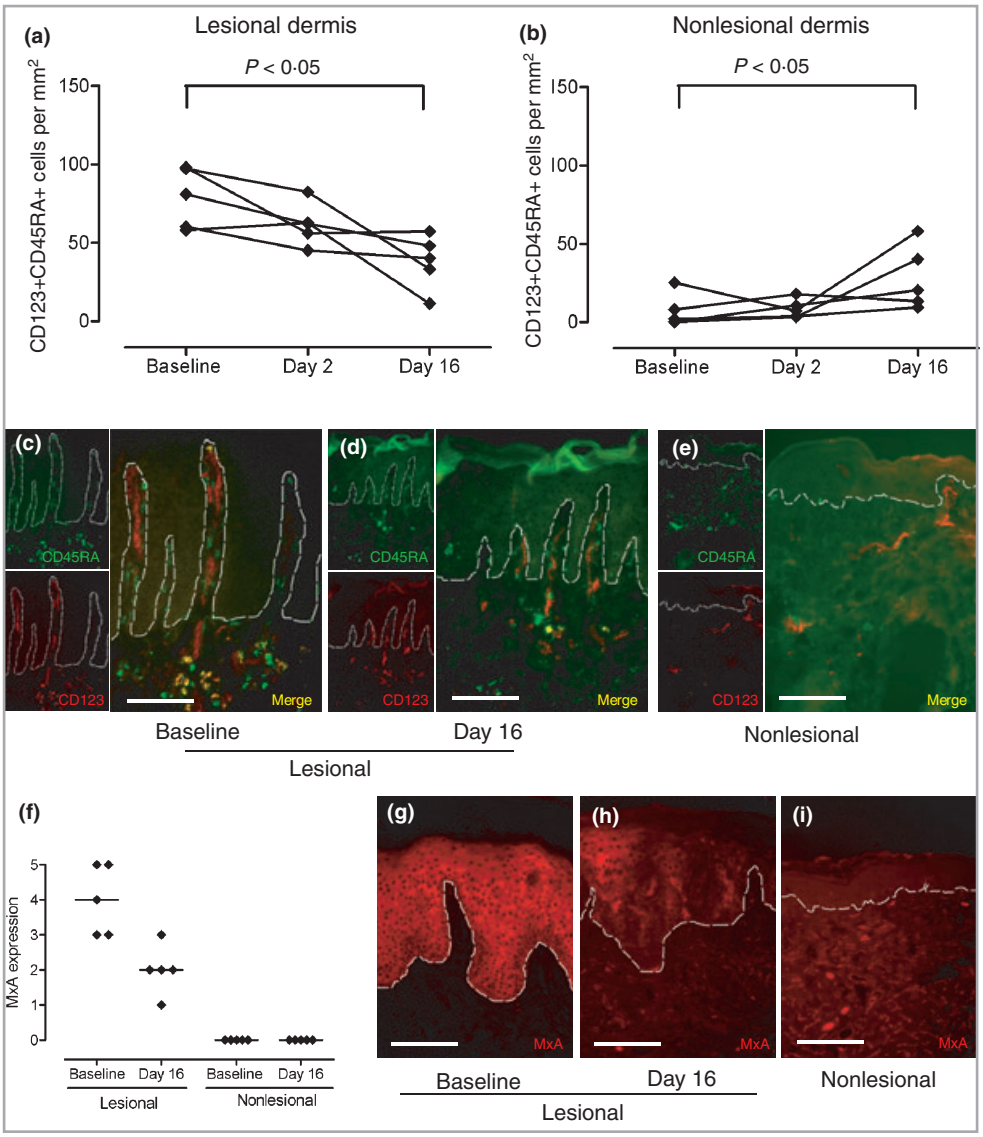


**Fig 2.** Plasmacytoid dendritic cell (pDC) numbers and interferon (IFN)-α expression in lesional skin were reduced by sun exposure. The number of pDCs, defined as cells expressing both CD123 (red images) and CD45RA (green images), was markedly increased in lesional compared with nonlesional dermis (a,b) and was significantly reduced in lesional dermis after 16 days of sun exposure (a,c,d). In contrast, a significant increase in pDCs was seen in nonlesional skin after sun exposure. Note that the anti-CD123 antibody (red) stains endothelial cells (c–e). In nonlesional skin, expression of MxA, a surrogate marker for IFN-α expression, was markedly upregulated in lesional skin whereas it was undetectable in nonlesional skin (f,g,i). After 16 days of sun exposure, MxA expression was markedly reduced in lesional skin (f,h). The increase in pDC numbers after sun exposure in nonlesional skin was not paralleled by an increase in MxA staining (b,f). All images are at × 200 magnification. Bars = 25 μm.

of sun exposure (at day 2), whereas the number of dermal CD11c+CD1c+ DCs was unchanged (Fig. 3b).

Additional co-staining experiments showed that a large proportion of CD11c+ DCs co-expressed monocyte/macrophage markers CD163, CD14 and DC-SIGN in lesional dermis (Fig. 4a–c), whereas in nonlesional dermis these double-positive cells were very rare (Fig. 4e–g). Co-staining with CD163 and DC-SIGN showed near complete overlap and confirmed that the latter is primarily a macrophage marker (Fig. 4d,h). In contrast, CD1c+ DCs did not co-express CD163 or DC-SIGN, either in lesional (Fig. 5a,b) or in nonlesional dermis (Fig. 5c,d), although a small number of CD1c+ cells did co-express CD14 (not shown). Together, these findings demonstrated that the majority of inflammatory CD11c+CD1c− DCs co-expressed several monocyte/macrophage markers, whereas the resident CD11c+CD1c+ DC population did not.

The percentage of CD11c+ DCs expressing the maturation marker DC-LAMP was increased twofold in lesional compared with nonlesional skin (Fig. 6a–e). DC-LAMP+ cells were mainly located in dermal cellular aggregates, in which most, but not all co-expressed CD1c (Fig. 6f). The percentage of CD11c+ DCs co-expressing DC-LAMP was significantly

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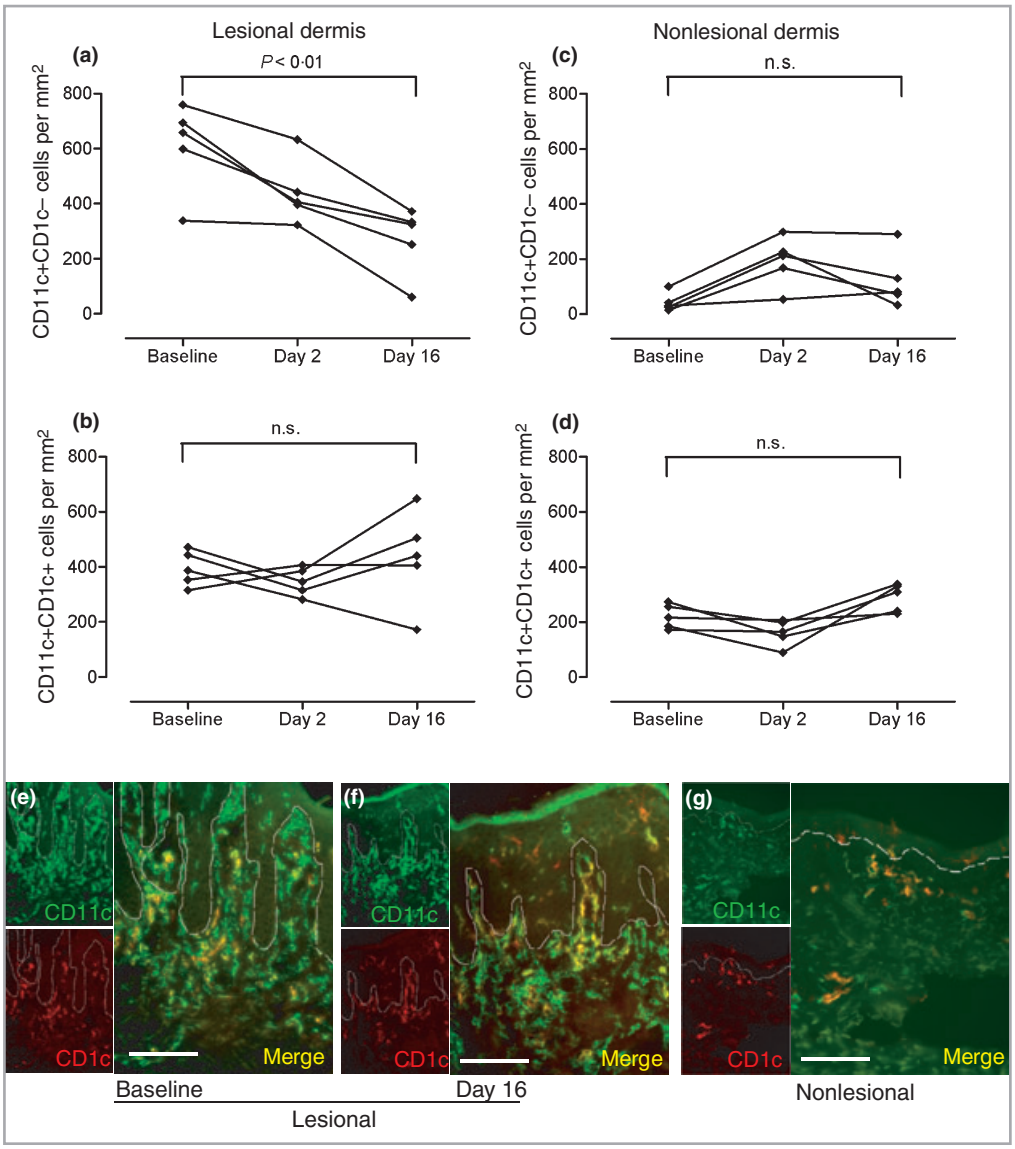


**Fig 3.** CD11c+CD1c− dendritic cell (DC) populations in lesional dermis are rapidly and selectively reduced on sun exposure. The putative inflammatory CD11c+CD1c− DCs were increased 20-fold at baseline in lesional dermis (a) compared with nonlesional dermis (c). This cell population was significantly reduced at day 16 of sun exposure with marked reductions evident already at day 2 (a,e,f). CD11c+CD1c+ DCs, i.e. putative homeostatic DCs, were increased only twofold in lesional dermis and were unchanged after sun exposure (b,e,f). In nonlesional dermis only very few CD11c+CD1c− cells were found at baseline (c,g). No significant changes in CD11c+CD1c− or CD1c+ DCs were seen in nonlesional dermis after sun exposure (c,d). Images are at × 200 magnification. Bars = 25 μm.

reduced in both lesional and nonlesional dermis ($P < 0{\cdot}05$ for both) after sun exposure (Fig. 6a–d).

Together, our findings demonstrated that sun treatment led to a significant and selective reduction of putative inflammatory mDCs as well as a decrease in mature DCs, indicating that a situation more closely resembling homeostatic conditions was established.

### Dermal macrophages are reduced after sun exposure

Differential expression of CD11c and CD163 has been shown to distinguish DCs from macrophages under steady-state conditions.[8] Accordingly, we found that the majority of CD163+ cells in nonlesional skin were negative for CD11c (Figs 4e, 7d), but expressed DC-SIGN (Fig. 4d); and a substantial proportion also expressed CD14. In lesional skin a large proportion of putative inflammatory DCs co-expressed several macrophage markers as described above. We therefore defined dermal macrophages as CD11c−CD163+ cells. This population was increased approximately twofold in lesional skin but returned to non-lesional levels after sun treatment ($P < 0{\cdot}05$; Fig. 7a). Also the numbers of CD11c−DC-SIGN+ cells were significantly reduced in lesional dermis after sun exposure ($P < 0{\cdot}05$;

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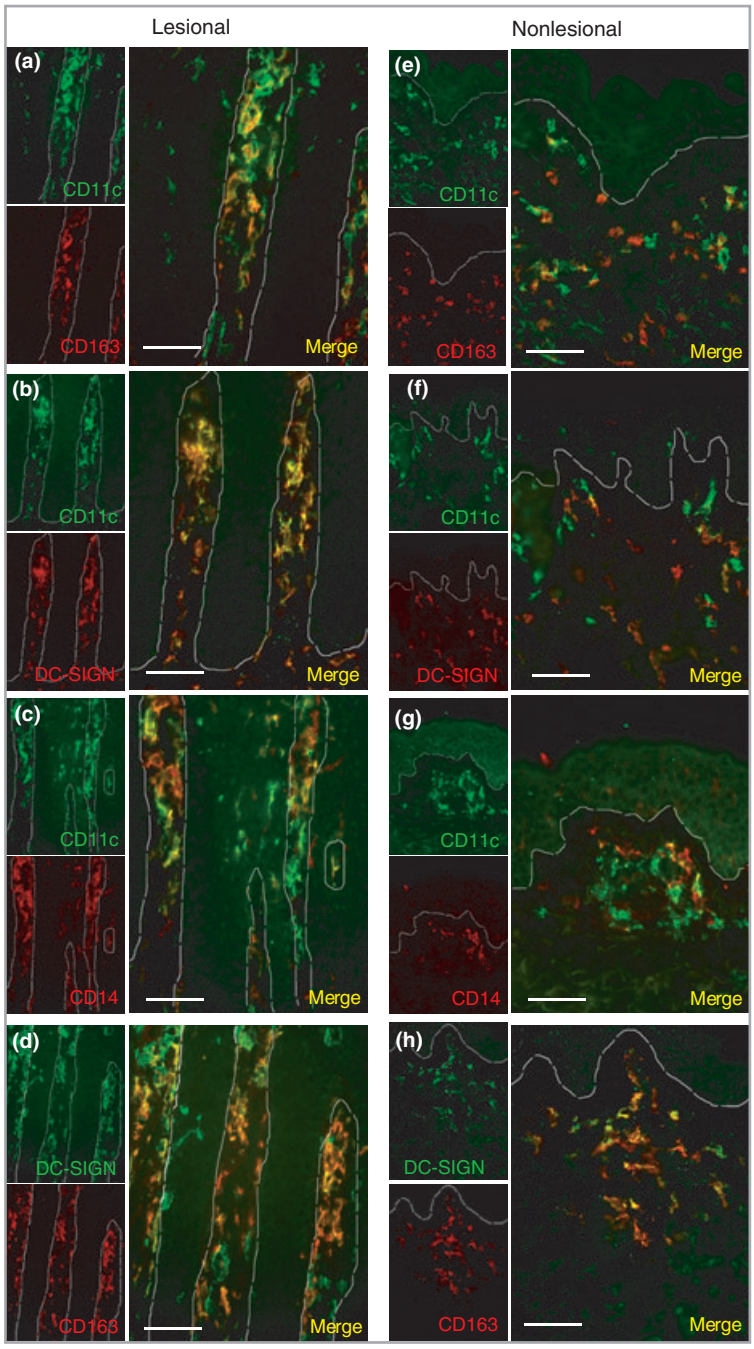


**Fig 4.** CD11c+ dendritic cells (DCs) in lesional skin co-express monocyte/macrophage markers. Immunohistochemical staining shows the infiltration of CD11c+ cells (green images) co-expressing the monocyte/macrophage markers CD163 (a), DC-SIGN (b) and CD14 (c) (all red images). In nonlesional dermis only occasional CD11c+ DCs co-expressed CD163 (e), DC-SIGN (f) or CD14 (g). DC-SIGN was primarily expressed on CD163+ cells in both lesional (d) and nonlesional skin (h). Images are at × 400 magnification. Bars = 50 μm.

Fig. 7b), whereas no significant change in CD11c−CD14+ cell numbers was observed (Fig. 7c).

## Discussion

It is well documented that UV therapy has beneficial effects in various immune-mediated skin disorders. This effect is believed to be mediated by UV-induced immunosuppression.[16,18] We have demonstrated here that distinct populations of putative pathogenic dermal DCs were dramatically reduced in psoriatic lesions after 16 days of controlled sun exposure. In contrast, we recently found that the densities of lesional epidermal Langerhans cells (LCs) were only marginally affected, examining the same tissue material.[19]

Others have shown that inflammatory CD11c+CD1c− DCs accumulate in psoriatic lesions and drive the inflammatory process by producing IL-23, iNOS and TNF-α.[11,28] As expected we also found that CD11c+CD1c− DCs were dramatically increased (20-fold) in lesional skin, and importantly, the number of these cells was significantly decreased after 16 days of sun exposure. Moreover, this decrease concurred with reduced mRNA expression for IL-23.[19] Already after 2 days we observed reduced

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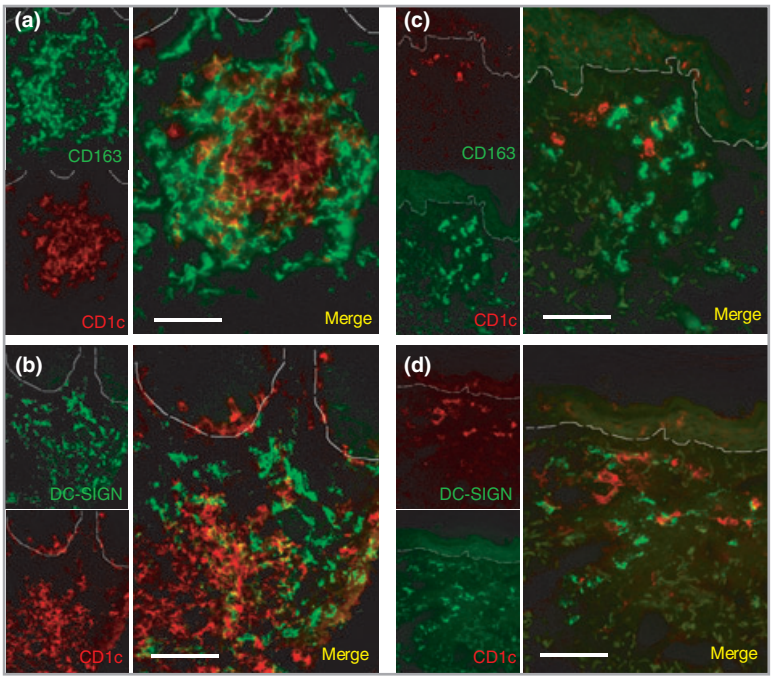


**Fig 5.** CD1c+ dendritic cells (DCs) did not express CD163 or DC-SIGN. CD1c+ DCs (red images) accumulate in dermal cellular aggregates in lesional dermis (a,b). No CD1c+ DCs co-expressed CD163 or DC-SIGN at baseline in lesional dermis (a,b) or nonlesional (c,d). Images are at × 400 magnification. Bars = 50 μm.

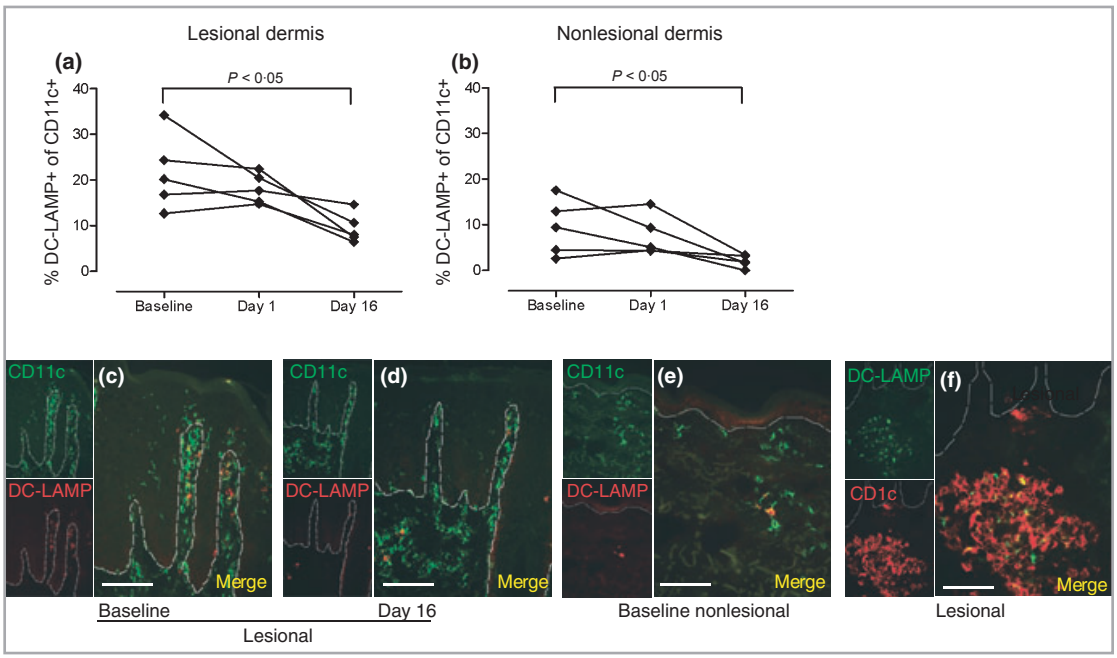


**Fig 6.** Expression of dendritic cell (DC) maturation marker DC-LAMP (CD208) was reduced in both lesional and nonlesional dermis after sun exposure. The percentage of dermal CD11c+ cells (green images) that co-expressed the maturation marker DC-LAMP (red images) was increased approximately twofold in lesional skin (a,c) compared with nonlesional skin (b,e) at baseline. After 16 days of sun exposure significant reductions in this percentage were seen in both lesional (a,c,d) and nonlesional dermis (b). DC-LAMP+ cells (f, green image) accumulated in dermal cellular aggregates, with CD1c+ cells (f, red image) and most, but not all DC-LAMP+ cells were CD1c+ (f). Images (c–e) are at × 200 magnification, bars = 25 μm. Image (f) is at × 400 magnification. Bars = 50 μm.

numbers of CD11c+CD1c− DCs, which preceded the clinical improvement. The density of 'resident' dermal CD11c+CD1c+ DCs was unaffected by sun exposure, but the expression of the maturation marker DC-LAMP, primarily found on the CD11c+CD1c+ population, was significantly reduced. This implies that local activation of T cells in the dermis will be less effective. Our results therefore suggest that sun treatment has several effects on DC subsets: selective reduction of the number

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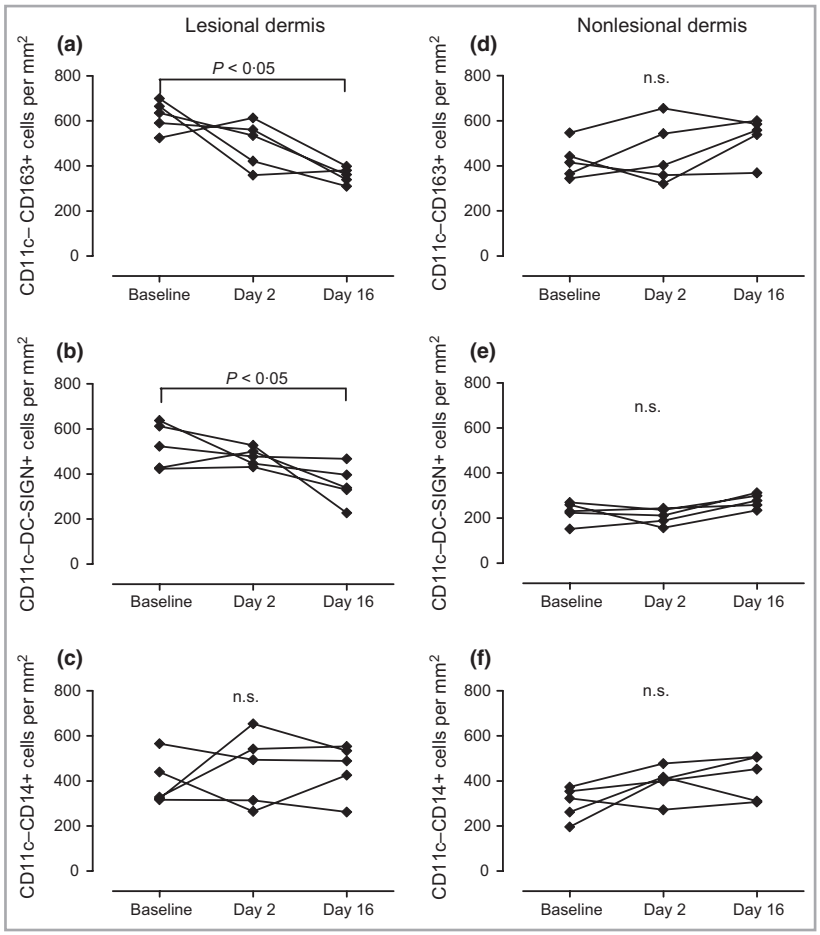


**Fig 7.** The numbers of CD11c−CD163+ and CD11c−DC-SIGN+ macrophages were significantly reduced in lesional dermis after sun exposure. In lesional dermis single positive (i.e. CD11c−) CD163+ (a) and DC-SIGN+ macrophages (b) were increased approximately twofold compared with nonlesional dermis (d,e) and significantly reduced after sun exposure. Single positive CD14+ cells (c) were also increased twofold in lesional dermis compared with nonlesional (f) with no significant change on sun exposure. No significant changes in any of these cell subsets were observed in nonlesional dermis (d–f).

of inflammatory mDCs and inhibition of maturation of resident mDCs, both mechanisms contributing to the reestablishment of homeostasis.

Recent reports have suggested that accumulating IFN-α-producing pDCs also play a pivotal role in psoriasis. IFN-α has diverse downstream effects, among which are activation of mDCs.[29] The recent report of pDCs triggered by endogenous DNA coupled with LL37[7] puts this cell population at the centre stage of psoriasis pathogenesis. Our finding that both pDC densities and MxA expression levels were reduced in response to sun exposure underscores this concept. To our knowledge, the effect of UV exposure on pDCs has not been examined previously.

Macrophages as producers of TNF-α may also contribute to psoriasis in humans.[14,15] Although single positive CD11c−CD163+ and CD11c−DC-SIGN+ macrophages were increased only twofold in lesional dermis compared with nonlesional skin, these cells were significantly reduced in lesional skin on sun exposure, suggesting that reduction of these cells may also have contributed to clinical improvement.

The psoriatic lesion was dominated by CD11c+CD1c− DCs, many of them co-expressing the monocyte/macrophage markers CD14, CD163 and DC-SIGN. Recent reports have demonstrated that circulating monocytes are an important source for DCs in peripheral tissues under inflammatory conditions.[30] Our phenotypic characterization of inflammatory DCs in psoriatic skin is compatible with this concept. Monocytes, macrophages and DCs all show high degrees of plasticity and their phenotype and function depend on the local microenvironment.[30] Therefore, further studies are needed to define the origin and differentiation pathways of dermal APC populations both under steady-state and during inflammation.

The current view of psoriasis immunopathogenesis suggests an intimate crosstalk between stressed keratinocytes, activated pDCs and mDCs, and pathogenic T cells.[1] Here we show that sun exposure rapidly decreased the number of both inflammatory mDCs and pDCs in the dermis. Whether this was caused by increased exit, increased apoptosis/cell death, or decreased recruitment, or a combination of these mechanisms, could not be determined in this study. However, previous work has suggested that UV increases the migration of both LCs and mDCs into the draining lymph nodes.[31,32] Moreover, it was recently shown that psoralen with UVA treatment significantly increased apoptosis in monocyte-derived DCs *in vitro*.[33] Recruitment of circulating leucocytes in an inflammatory setting depends on local production of chemokines and cytokines. In psoriatic lesions proinflammatory cytokines and chemokines are to a large extent produced by pathogenic T cells, keratinocytes and DCs. We have recently shown, in the same biopsy material, that the density of T cells displayed a similar rapid decrease in response to sun exposure.[19] There are also reports showing that UV impairs the capacity of APCs to present anti-

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gens for T cells[16] and abrogates the capacity of DCs to induce Th1 immune responses.[33] Moreover, UV increases the production of the anti-inflammatory cytokine IL-10 in keratinocytes[34] and macrophages,[35] and by increasing the number of regulatory T cells in lesional skin.[16,18,36,37] In agreement with this, we found a relative increase in the number of FOXP3+ T cells and mRNA for IL-10 after treatment in our biopsy material.[19] These findings suggest that the rapid sunlight-induced reduction of dermal DC subsets observed here is mediated partly by a direct effect on the DCs and partly by an indirect effect through its action on other cell types, firstly T cells, keratinocytes and macrophages.

Sunlight contains both UVB and UVA and high cumulative doses were measured for both wavelengths in this study as described in detail elsewhere.[22] However, several studies have shown that UVB, especially narrowband UVB, is much more efficient than UVA in the treatment of psoriasis.[38,39] It is therefore reasonable to assume that the sun-induced effect observed in this study firstly is mediated by UVB. This is consistent with a recent report demonstrating that narrowband UVB radiation decreased the number of inflammatory DCs and their products in psoriasis plaque.[40]

In conclusion, it appears that sun exposure induces an immunosuppressive microenvironment by its action on several cell types in the skin, which together break the vicious circle of chronic inflammation and restore homeostasis. The demonstration that rapid reduction of pathogenic DC subsets and macrophages in psoriatic lesional dermis preceded clinical improvement suggests that UV-induced immunosuppression is mediated, at least in part, through an effect on dermal APCs and their products.

### What's already known about this topic?

- In psoriatic skin, plasmacytoid dendritic cells (pDCs) accumulate and contribute to pathogenesis through the production of interferon (IFN)-α.
- A subset of 'inflammatory' CD11c+CD1c− myeloid (m)DCs producing tumour necrosis factor-α, inducible nitric oxide synthase and interleukin-23 is dramatically increased and macrophages have also been suggested to contribute to this disease.
- In contrast, CD11c+CD1c+ mDCs, the major dermal DC subset under steady-state conditions, is not increased in psoriasis. Exposure to sunlight induces clinical improvement in psoriasis, but the mechanisms are not fully understood.

### What does this study add?

- We show that clinical improvement in patients with psoriasis after 16 days of sun exposure is associated with rapid reduction in the numbers of pDCs and levels of IFN-α.
- CD11c+CD1c− DCs were rapidly and selectively reduced whereas the number of CD11c+CD1c+ DCs remained unchanged.
- Macrophages were also significantly reduced after sun exposure.
- This suggests that sun-induced clinical improvement is mediated via effects on these antigen-presenting cell populations.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Fig S1.** The total number of CD11c+ DCs was unchanged in lesional dermis after sun exposure. The total number of CD11c+ cells was markedly increased in lesional (a) compared with nonlesional dermis (b). In lesional dermis, numbers were reduced in all individuals but the change was nonsignificant (a). In nonlesional dermis a small but significant increase in total CD11c+ numbers was seen at day 16 of sun exposure (b).

**Table S1.** List of primary and secondary antibodies and reagents with manufacturers used in this paper.

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