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Keratinocytes derived from late-onset psoriasis skin do not impair Langerhans cell migration

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To the editor

Chronic plaque psoriasis (CPP) is associated with over-expression of interleukin (IL)-17 and systemic antibody therapies targeting this cytokine are highly efficacious¹. Psoriasis presents as either early- or late-onset disease (before or after 40 years of age, respectively). Langerhans cells (LC) are the dendritic cells of the epidermis that regulate cutaneous immune responses². In the uninvolved skin of early-onset CPP there is impaired LC migration after exposure to a contact allergen, tumour necrosis factor- α (TNF- α) or IL-1 β *in vivo*³. However, in late-onset psoriasis there is impaired migration in response to TNF- α , but normal responses to IL-1 β ⁴. We have recently shown that in early-onset psoriasis, LC migration is impaired as a result of IL-17A causing changes in the psoriasis

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keratinocyte secretome⁵. Here we sought to examine whether keratinocytes isolated from uninvolved late-onset psoriasis skin also impair LC migration.

Volunteers were aged 18-65 years and either healthy with no history of skin disease or had psoriasis that first presented at age 40 or later; all provided 6 mm skin punch biopsies. The study was approved by the NRES Committee Northwest (13/NW/0867) and was conducted according to the Declaration of Helsinki and all subjects provided written, informed consent. To investigate LC migration *ex vivo* we utilised an epidermal explant model, described previously⁶. Firstly we wished to determine levels of LC migration in this model in late-onset psoriasis. Briefly, two skin biopsies were taken and one epidermal sheet was fixed immediately (T0) and the other cultured for 24 h (T24). We compared LC frequency in the T0 and T24 epidermal sheets and calculated LC migration in the T24 compared with the T0 epidermal sheet for the same volunteer. There was a significant reduction in LC frequency in the late-onset psoriasis T24 epidermal sheets (Figure 1a). When comparing the percentage migration data for late-onset volunteers to historical healthy data there was no significant difference between groups (Figure 1b). To examine the effect of late-onset psoriasis keratinocytes on LC migration we generated conditioned media from healthy and late-onset psoriasis keratinocytes according to a method described previously⁵. We used this conditioned media in the healthy epidermal explant model to determine the effect on LC migration. In the EpiLife media control there was a significant reduction in LC frequency in the T24 cultured epidermal sheet (Figure 1c). Likewise, when epidermal sheets were cultured with healthy keratinocyte conditioned media there was significant loss of LC from the epidermis (Figure 1d). The same was true for epidermal sheets cultured in late-onset psoriasis keratinocyte conditioned media (Figure 1e). When comparing percentage LC migration between the three groups there was no significant difference in migration levels (Figure 1f).

Our data show that, in an *ex vivo* explant model LC migration in late-onset psoriasis uninvolved skin was normal, further confirming that LC function can be used to distinguish between the two ages of onset of psoriasis. As *in vivo* TNF- α doesn't stimulate LC mobilisation in late-onset psoriasis skin, it is likely that it may play a lesser role in this sub-type of the disease. We have previously shown, in a mouse model, that TNF- α is not always required for LC migration⁷. There are known changes in IL1 β in late-onset psoriasis⁸, and therefore it is possible that IL-1 β may play a more dominant role than in early-onset. Unlike early-onset, late-onset psoriasis keratinocytes don't secrete a factor that inhibits healthy LC migration. These findings confirm our previous observations that early and late-onset psoriasis can be distinguished based on epidermal LC function⁴. Our previous findings have shown that over-expression of IL-17A can inhibit LC migration probably due to an alteration of the keratinocyte secretome^{5,6}. As conditioned medium generated from late-onset keratinocytes is unable to impair LC migration, it is likely that late-onset psoriasis may not have the same IL-17 pathology, at least in the uninvolved skin. Further studies should examine whether late-onset psoriasis is associated with over-expression of IL-17 as this could have consequences for treatment, in particular the use of anti-IL-17 therapies. Taken together, our results show that late-onset psoriasis keratinocytes have a phenotype that is distinguishable to that of early-onset disease which in turn produces significant differences in LC mobilisation. This may have relevance both to the pathology of psoriasis as LC are important in regulating the skin immune response and in the manner that these two subsets of the disease are managed.

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Figure Legends

Figure 1 No impaired Langerhans cell migration in a late-onset psoriasis explants model

Two 6 mm punch skin biopsies were taken from the uninvolved skin of patients with late-onset (presenting age 40 or over) chronic plaque psoriasis. Epidermal sheets were isolated and one was fixed immediately (T0). The other was cultured by floating on RPMI media for 24 h before fixing (T24). The LC frequency in epidermal sheets was determined, each line represents one volunteer (a). The significance of differences was analysed by paired t test, ***p<0.001. (b) The percentage LC migration was calculated as a reduction in the T24 cultured epidermal sheet compared with the T0 sheet for the same volunteer. Historical healthy data is shown as a comparison. The significance of differences between groups was analysed by t test but was not significant.

Conditioned media was generated from healthy (H) and uninvolved late-onset psoriasis (LOP) keratinocytes (KC), n = 3. Healthy volunteers provided 3-4 six mm skin biopsies. Epidermal sheets were isolated and one was fixed immediately (T0) and the other was cultured in either EpiLife keratinocyte media control, conditioned media from healthy or late-onset psoriasis keratinocytes for

24 h before fixing. The LC frequency was determined for each epidermal sheet and shown for (c) EpiLife, (d) healthy keratinocyte conditioned media and (e) late-onset psoriasis keratinocyte conditioned media compared with the T0 sample, each line represents data from one healthy individual (n=6-8). The significance of differences between T0 and T24 was analysed by paired t test $**p<0.01$, $***p<0.001$. (f) The percentage LC migration data calculated as the percentage loss in the T24 epidermal sheet compared with the T0 epidermal sheet from the same sample. The significance of differences was analysed by one-way ANOVA followed by Tukey post test but differences were not significant.