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Supporting Information

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

Figure S1. Expression changes of photoaging-related molecules in the skin from SAMPI and SAMRI mice.

Figure S2. Age-associated changes in the TBARS levels in the skin from SAMPI and SAMRI mice.

Table S1. Changes in mRNA expression in the dorsal skin from old SAMPI mice and human photoaged skin.

Data S1. Materials and methods and supplementary results.

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Letter to the Editor

Skewed distribution of natural killer cells in psoriasis skin lesions

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Abstract: Psoriasis is a hyper-proliferative disease of the skin in which immunological mechanisms play a direct pathogenetic role. There have been limited studies of natural killer (NK) cells in psoriasis. The aim of this study was to examine the phenotype of NK cells in skin biopsies and peripheral blood mononuclear cells from patients with psoriasis and healthy controls. CD56⁺CD16⁻ and CD56⁺CD16⁺ NK cells were isolated from lesional skin, unaffected skin and PBMC of psoriasis patients, and normal skin and PBMC from healthy controls. The expression of CD57, NKG2A and NKG2C was assessed by flow cytometry. NK cells in psoriasis skin lesions were skewed in their expression of CD57, a

marker of NK cell maturity, with CD57 expression significantly reduced and NKG2A expression increased on NK cells in lesional and unaffected skin compared to controls. These data suggest that in this patient cohort, NK cells could be isolated from psoriasis lesions and exhibit an immature phenotype.

Abbreviations: IFN- γ , Interferon-gamma; NK, natural killer cell; PBMC, peripheral blood mononuclear cells.

Key words: CD57 – immunosenescence – natural killer cells – psoriasis

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Background

Psoriasis is a chronic inflammatory disease of the skin with significant morbidity (1). Whether natural killer (NK) cells are involved in the immunopathogenesis of psoriasis remains controversial, although genetic and immunological analyses support a role (2–4).

NK cells function without prior sensitization and could initiate plaque development (5,6).

NK cells express a heterogeneous repertoire of receptors that regulate their effector function (7,8). Although NK cell function (cytotoxicity and cytokine secretion) is related to their stage of

development, both immature CD56^{bright}CD16^{neg} and mature CD56^{dim}CD16⁺ NK cell subpopulations secrete IFN γ , critical in psoriasis pathogenesis (6).

Expression of CD57 identifies terminally differentiated T cells (9). CD57 is also expressed on highly mature cells within the CD56^{dim}CD16⁺ NK cell compartment and might provide a marker of 'memory' NK cells (10–12). NK cell differentiation is described as a progression from a less mature phenotype displaying high CD56 expression together with NKG2A but lacking CD16, to a more differentiated phenotype expressing CD16 and CD57 with a decreasing ability to replicate *in vitro* (10–12).

Questions addressed

We investigated the distribution of CD57⁺ NK cells in lesional skin, non-lesional skin and peripheral blood of psoriasis patients compared to controls. We also investigated the expression of the inhibitory receptor NKG2A and the activating receptor NKG2C on NK cells in the skin and blood of patients and controls.

Experimental design

Peripheral blood mononuclear cells (PBMCs) and skin biopsies were collected from 12 patients with psoriasis, and PBMCs alone were collected from 10 healthy controls.

The inclusion criteria and protocols are described in Supplemental Materials and Methods.

Results

Nine men and three women were included, median age 48 years (range, 21 to 84). Five subjects had plaque, and seven subjects had guttate psoriasis. The majority of subjects had mild disease ($n = 8$), three had moderate disease, and one had severe disease. Matched skin and PBMC samples were available from 9 of 12 psoriasis subjects. Median age of healthy controls was 45 years.

Both lesional and non-lesional skin of psoriasis patients had similar frequencies of CD56⁺CD16⁺ NK cells; however, in the blood, patients had a trend towards an increased frequency of CD56⁺CD16⁺ NK cells compared to controls (Fig. 1a). The frequency of CD57⁺ NK cells in lesional skin (<10%) was significantly lower than in non-lesional skin (approximately 40%) (Fig. 1b).

An assessment of NKG2A and NKG2C expression in skin CD56⁺CD16⁺ NK cells revealed a significant expansion of NKG2A⁺ NK cells in skin of patients (Fig. 1c). The frequency of NKG2A⁺ NK cells in PBMC was similar between patients and controls, while patients had a significantly greater frequency of circulating NKG2C⁺ NK cells compared to controls (Fig. 1d).

Co-expression of CD57, NKG2A and NKG2C on skin NK cells was different between patients and controls (Fig. S1). NK cells from the skin of patients preferentially expressed NKG2A, particularly in lesional skin. In contrast, NK cells in the skin of healthy donors contained CD57⁺ NK cells that were NKG2A⁻ and NKG2C⁻. These data suggest that NK cells in the skin of this cohort of patients are less mature.

There was a trend towards an increased frequency of CD56⁺CD16⁻ NK cells in psoriasis lesional and unaffected skin compared to control skin (Fig. 2a). CD57 expression in CD56⁺CD16⁻ NK cells was significantly reduced in lesional and non-lesional skin of patients compared to controls (Fig. 2b). A trend of greater NKG2A expression in lesional skin compared

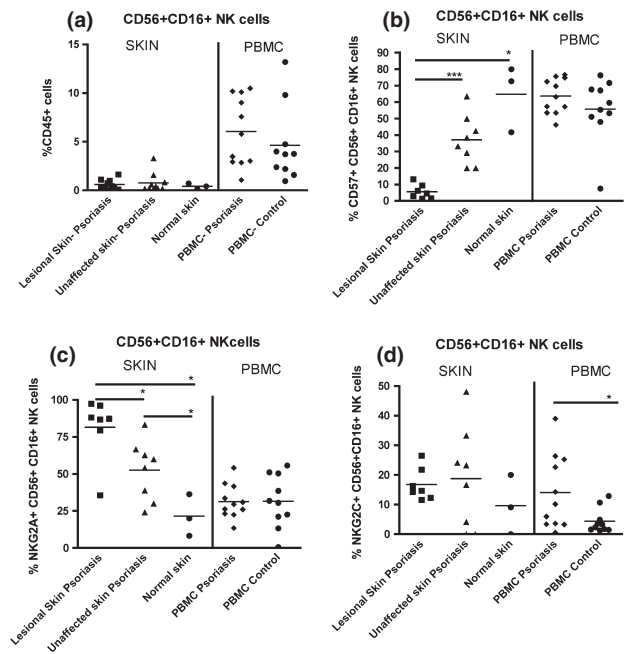


Figure 1. (a) Frequency of CD56⁺CD16⁺ NK cells in lesional skin ($n = 7$) and unaffected skin ($n = 8$) of psoriasis patients and skin from healthy controls ($n = 3$), and in the blood of psoriasis patients ($n = 11$) and healthy controls ($n = 10$). (b) CD57⁺CD56⁺CD16⁺ NK cells in skin and the blood. (c) NKG2A expression in CD56⁺CD16⁺ NK cells in skin and the blood. (d) NKG2C expression in CD56⁺CD16⁺ NK cells from skin and PBMC. * $P < 0.05$, *** $P < 0.001$.

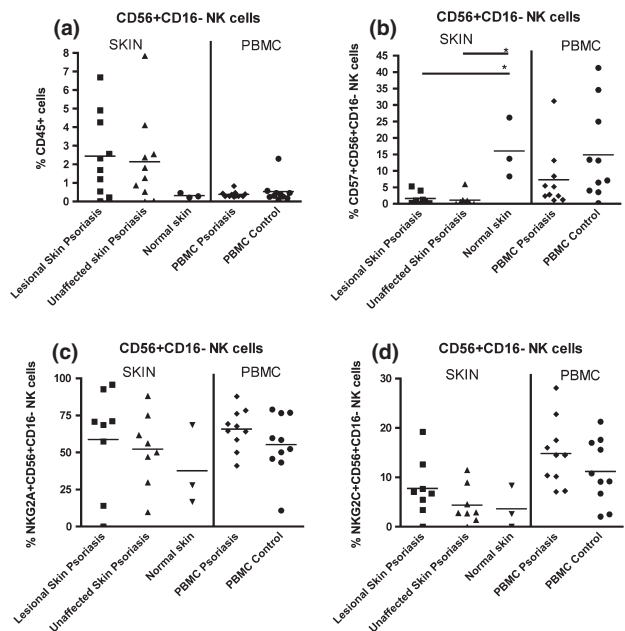


Figure 2. (a) Frequency of CD56⁺CD16⁻ NK cells in lesional skin and unaffected skin of psoriasis patients and skin from healthy controls and in the blood of psoriasis patients and healthy controls. (b) CD57⁺CD56⁺CD16⁻ NK cells in skin and the blood. (c) NKG2A expression in CD56⁺CD16⁻ NK cells in skin and the blood. (d) NKG2C expression in CD56⁺CD16⁻ NK cells from skin and PBMC. * $P < 0.05$.

to unaffected skin and control skin was observed (Fig. 2c), with lack of difference for NKG2C expression in the skin or blood of patients versus controls (Fig. 2d).

Comparison between plaque and guttate psoriasis for all measured parameters demonstrated no difference, although numbers for each group were small (Figs S2 and S3).

Conclusions

In this study, we found variations in NK cell distribution in blood and tissue of psoriasis patients compared to healthy controls.

We observed a substantially lower percentage of CD57⁺CD56⁺CD16⁺ NK cells in lesional skin compared to control skin. CD57⁻CD56⁺CD16⁺ NK cells correspond to activated cells with a higher turnover and degranulation ability (13). They are highly responsive to IL-2 stimulation, which could determine their preferential migration to the skin (14). CD57⁻CD56⁺CD16⁺ NK cells produce higher amounts of IFN γ following cytokine stimulation compared to CD57⁺CD56⁺CD16⁺ NK cells and could contribute to the inflammatory environment (11,13).

We observed a significant difference in the proportion of NKG2A⁺ cells in lesional skin. NKG2A is inducible by IL-12, which is likely to be highly expressed in lesions. The acquisition of functional capacities by NK cells, specifically IFN γ production, is correlated with NKG2A expression in CD56⁺CD16⁺ NK cells (15).

The difference observed in the proportion of circulating NKG2C⁺ NK cells could be due to differences in CMV serostatus, as NK cells expressing NKG2C are preferentially expanded in CMV seropositive individuals (12).

Together, these data suggest that NK cells from this group of psoriasis patients harbour a less differentiated phenotype. Future

studies are needed to determine the functional significance of these less differentiated NK cells in psoriasis lesions, as this study included only a small number of patients with heterogenous characteristics.

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Author contribution

MB, EH, VY performed experiments. MB, EH, JM, EK, DN designed study. DC provided samples. MB, EH, JM analysed data. MB, PK, JM, LL, EK, WL and DN wrote paper. WL, PU, KL, TM involved patient recruitment/critical revision of manuscript.

Conflict of interests

No conflicts of interest to disclose.

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Supporting Information

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

Figure S1. Co-expression of CD57, NKG2A, and NKG2C on CD56⁺CD16⁺ NK cells in lesional and unaf-

ected skin of psoriasis patients and normal skin of healthy controls. Both pie charts and bar graphs are shown. Comparisons are made between psoriasis groups (lesional and unaffected skin) in relation to the control group (normal skin). Significant differences ($P < 0.05$) are represented by a (+). A significant difference between groups was noted in CD57 and NKG2A expression alone and in NKG2A and NKG2C co-expression. $+P < 0.05$.

Figure S2. Lack of difference between plaque and guttate psoriasis for the expression of markers on CD56⁺ CD16⁺ NK cells. (a) CD57. (b) NKG2A. (c) NKG2C.

Figure S3. Lack of difference between plaque and guttate psoriasis for the expression of markers on CD56⁺ CD16⁻ NK cells: (a) CD57. (b) NKG2A. (c) NKG2C.