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Dendritic Cell Immunization Route Determines CD8$^+$ T Cell Trafficking to Inflamed Skin: Role for Tissue Microenvironment and Dendritic Cells in Establishment of T Cell-Homing Subsets

Jan C. Dudda, Jan C. Simon, and Stefan Martin

The effector/memory T cell pool branches in homing subsets selectively trafficking to organs such as gut or skin. Little is known about the critical factors in the generation of skin-homing CD8$^+$ T cells, although they are crucial effectors in skin-restricted immune responses such as contact hypersensitivity and melanoma defense. In this study, we show that intracutaneous, but not i.v. injection of bone marrow-derived dendritic cells induced skin-homing CD8$^+$ T cells with up-regulated E-selectin ligand expression and effector function in contact hypersensitivity. The skin-homing potential and E-selectin ligand expression remained stable in memory phase without further Ag contact. In contrast, i.p. injection induced T cells expressing the gut-homing integrin $\alpha_4\beta_7$. Although differential expression of these adhesion molecules was strictly associated with the immunization route, the postulated skin-homing marker CCR4 was transiently up-regulated in all conditions. Interestingly, dendritic cells from different tissues effectively induced the corresponding homing markers on T cells in vitro. Our results suggest a crucial role for the tissue microenvironment and dendritic cells in the instruction of T cells for tissue-selective homing and demonstrate that Langerhans cells are specialized to target T cells to inflamed skin.


Materials and Methods

**Mice**

C57BL/6 and transgenic P14 mice (26) expressing a TCR specific for the lymphocytic choriomeningitis virus-derived peptide GP33 (27) containing TCRV$\alpha$2/TCR V$\beta$8 were provided by the breeding facility of the Max Planck Institute for Immunobiology (Freiburg, Germany). P14.Thy-1.1 mice (28) were kindly provided by H. Pircher, Institute for Microbiology and Hygiene, University of Freiburg. All of the experimental procedures were in accordance with the Max Planck Institute and the University of Freiburg guidelines on animal welfare.
**Peptides**

The H-2D<sup>B</sup>-binding peptide GP33 from the glycoprotein of lymphocytic choriomeningitis virus has been described before (27) and was purchased from BioChip Technologies GmbH (Freiburg, Germany).

**Media and chemicals**

RP-10 consisted of RPMI 1640 supplemented with 10% heat-inactivated FCS, 2 mM L-glutamine, 25 mM HEPEs buffer, 50 µg/ml penicillin-streptomycin (all from Life Technologies, Invitrogen, Karlsruhe, Germany), and 10 µM 2-ME (Sigma-Aldrich, Deisenhofen, Germany). The 2,4,6-trinitrobenzenesulfonic acid (TNBS) was from Sigma-Aldrich, and TNCB was obtained from Department of Chemistry, University of Freiburg and from VezZet Laborsysteme GmbH (Idar-Oberstein, Germany).

**Abs and flow cytometry**

Abs and streptavidin-CyChrome were from BD Pharmingen (Heidelberg, Germany) and used as FITC, PE, or biotin conjugates at 0.1–1 µg/ml in 100 µl 2% FCS/PBS, unless indicated otherwise. PE-labeled α/β integrin Ab (clone DATK32) was used, as described elsewhere (29). Staining for ESL on cells ex vivo was done with 2 µg E-selectin/human IgG-Fc chimera (R&D Systems, Wiesbaden, Germany) in 50 µl HBSS (Life Technologies) containing 0.2% BSA (Sigma-Aldrich). Before staining, blood cells were washed with 5 mM EDTA/PBS. Cells from in vitro primings were stained with a lower chimera concentration of 0.5 µg/100 µl. Control stainings were done with naive cells or with secondary Ab only. E-selectin were stained with a lower chimera concentration of 0.5 µg/ml. E-selectin antibodies and streptavidin-CyChrome were from BD PharMingen (Heidelberg, Germany) and used as FITC, PE, or biotin conjugates at 0.1 µg/ml. E-selectin staining was done with naive cells or with secondary Ab only. E-selectin antibodies and streptavidin-CyChrome were from BD PharMingen (Heidelberg, Germany) and used as FITC, PE, or biotin conjugates at 0.1 µg/ml.

**Generation of BM-DC**

Bone marrow cells were cultured at 7 × 10<sup>6</sup> cells/ml in the presence of 40 ng/ml GM-CSF (supernatant from producer line X63-Ag8 (30)) and 10 ng/ml IL-4 (Promocell, Heidelberg, Germany) in 10 ml medium in 10-cm petri dishes (Greiner, Nütingen, Germany). On day 3, 10 ml of fresh medium containing 40 ng/ml GM-CSF was added. On days 3 and 7, 10 ml of medium was replaced with fresh GM-CSF medium. DC were used on days 7–9 after centrifugation over a 14.5% metrizamide/RP-10 gradient to a purity of 95%. Langerhans cells (LC) were isolated from earsheets. Ears were split in dorsal and ventral sheets using forceps. Sheets were incubated for 35 min at 37°C in 40% (v/v) ventral, cartilage-containing halibut in 1% trypsin/PBS solution at 37°C, and the epidermal layer was separated from the dermis by scraping off with forceps. After extensive up-and-down pipetting, cells were isolated by passing through a cell strainer (70 µm), followed by metrizamide gradient centrifugation.

DC were incubated with GP33 peptide (1 µg/ml) for 45 min at 37°C and washed three times. A total of 5 × 10<sup>6</sup> DC and 4 × 10<sup>4</sup> P14 spleen cells/well was cocultured in 96-well plates (Corning Life Sciences, Wiesbaden, Germany) in 200 µl of RP-10. In some experiments, magnetic bead (Miltenyi Biotec) negatively isolated CD8<sup>+</sup> T cells were used and similar results were obtained.

**Isolation of DC and in vitro priming**

DC were isolated from peripheral and mesenteric lymph nodes (LN) by CD11c<sup>+</sup> AutoMACS bead separation (Miltenyi Biotec, Cologne, Germany) or 15% metrizamide/RP-10 gradient centrifugation to a purity of ~80–95%. Langerhans cells (LC) were isolated from earsheets. Ears were split in dorsal and ventral sheets using forceps. Sheets were incubated for 35 min at 37°C, cartilage-containing halibut in 1% trypsin/PBS solution at 37°C, and the epidermal layer was separated from the dermis by scraping off with forceps. After extensive up-and-down pipetting, cells were isolated by passing through a cell strainer (70 µm), followed by metrizamide gradient centrifugation.

DC were incubated with GP33 peptide (1 µg/ml) for 45 min at 37°C and washed three times. A total of 5 × 10<sup>6</sup> DC and 4 × 10<sup>4</sup> P14 spleen cells/well was cocultured in 96-well plates (Corning Life Sciences, Wiesbaden, Germany) in 200 µl of RP-10. In some experiments, magnetic bead (Miltenyi Biotec) negatively isolated CD8<sup>+</sup> T cells were used and similar results were obtained.

**Proliferation assay**

On day 4 of in vitro priming, 20 µl medium containing 1 µCi of [<sup>3</sup>H]thymidine was added to cultures, and incorporation was measured after 18 h with a TopCount plate reader (PerkinElmer Life Sciences).

**Results**

**Sensitization for CHS by i.c., but not i.v. DC immunization**

DC-TNP were injected i.c. or i.v. into C57BL/6 mice, and elicitation of CHS was performed 5 days later by ear challenge with TNCB. A strong ear-swelling response after 24 h was detected only with DC i.c., but not DC i.v. (Fig. 1A). Ear swelling after i.v. injection was similar to that of mice after injection of unmodified control DC.

We have previously shown that cytotoxic CD8<sup>+</sup> T cells (Tc1) cells are the crucial effector cells in TNP-induced CHS (22, 23), and cytotoxicity is believed to be mandatory for CHS responses (31). To test whether the lack of ear swelling after i.v. immunization was due to defective generation of CTLs, draining LN cells from DC i.c. and spleen cells from DC i.v. sensitized mice were restimulated in vitro with TNP-modified splenocytes and then used in a cytotoxicity assay. Comparable TNP-specific cytotoxic activity was measured, indicating that also i.v. injection of DC efficiently generates CTLs (Fig. 1B). We then addressed the question as to why these cells did not induce skin inflammation.

**CHS effector CD8<sup>+</sup> T cells express ESL and CCR4**

We hypothesized that DC i.v. in contrast to DC i.c. immunization may fail to induce skin-homing CD8<sup>+</sup> T cells. Therefore, we first analyzed the expression of the postulated skin-homing markers ESL and CCR4 on CD8<sup>+</sup> T cells from skin-draining LN in TNP-induced CHS. Three days after elicitation, T cells from auricular LN were compared with LN cells of unsensitized control mice. In fact, a subpopulation of CD8<sup>+</sup> T cells in the CHS LN coexpressed ESL and CCR4 (Fig. 2), suggesting these cells were CHS effector cells.
DC immunization route determines homing marker expression

To analyze a traceable Ag-specific CD8$^+$ T cell population, we adoptively transferred the TCR transgenic P14 Thy-1.1$^+$ T cells (26, 28) into recipient Thy-1.2$^+$ C57BL/6 mice and immunized twice with peptide-pulsed DC i.c., i.v., or i.p. This protocol results in similar expansion rates and kinetics of T cells that peak between day 6 and 8 in blood (data not shown). Up-regulation of the skin-homing marker ESL and the gut-homing integrin $\alpha_\text{E}\beta_7$ on CD8$^+$ P14 T cells was strictly correlated with the DC immunization route. ESL was up-regulated on blood T cells on day 6 after transfer only after DC i.c. (Fig. 3A), whereas $\alpha_\text{E}\beta_7$ was up-regulated only after i.p. injection of DC. P14 T cells were found in mesenteric LN (data not shown) on day 3 after transfer and DC immunization i.p., indicating that T cell priming had occurred at this site.

These data suggest that skin-homing T cells were generated during priming in skin-draining peripheral LN, whereas gut-homing T cells were induced in mesenteric LN draining the gastrointestinal tract and peritoneum. In contrast, i.v. immunization did not efficiently induce these adhesion molecules.

Interestingly, CCR4 was strongly up-regulated on a major subpopulation of blood T cells at the peak of expansion (day 6) in-dependently of the immunization route (Fig. 3A). Monitoring of CCR4 expression from day 5 to 9 revealed a fast down-regulation between day 6 and 8 (Fig. 3B). The expression was transient and activation dependent and was most elevated on freshly activated T cells. In contrast, memory cells lacked CCR4 (data not shown). These data suggest that CCR4 is not an exclusive skin-homing marker and that it may be more important for skin homing of effector rather than memory T cells.

We also injected peptide-loaded, heat-killed DC in some experiments to exclude the possibility of cross-presentation of Ag from dead BM-DC by skin-resident DC. No significant expansion and skin homing of T cells were observed (data not shown).

Stable ESL expression on memory T cells

It has been reported that up-regulation of ESL on T cells in vitro can be simply activation dependent (12). However, we found that i.v. and i.c. injection of DC led to differential expression of ESL in vivo on effector T cells on day 7 (Fig. 3A) and on memory T cells on day 20 after transfer (Fig. 4), respectively. We observed similar expansion kinetics and memory T cell counts in blood (Fig. 5, C and D), indicating a comparable and maximal activation of T cells. These results show that the expression of ESL following T cell priming by DC in vivo is stable and tissue specific, but not simply activation dependent.
Intracutaneous DC immunization induces skin-homing T cells

The skin-homing potential of CD8<sup>+</sup> T cells after DC i.c. vs DC i.v. immunization was compared using the contact sensitizer TNCB as an inflammatory stimulus (28) to attract T cells into skin. At the peak of expansion on day 7, TNCB was painted on ears. Blood levels of P14 T cells were measured 24 h later (Fig. 5, A and B, upper panels). Ear skin sheets were prepared and incubated overnight. The emigrated T cells were quantified by flow cytometry (Fig. 5, A and B, lower panels). Cumulative data for cell counts from three experiments are shown in Fig. 5, B and D. In i.c. immunized mice, we found that 10–30% of emigrated cells were P14 T cells, whereas in ear sheets from control mice (transfer without DC immunization) no TCR transgenic P14 T cells, and in i.v. immunized mice 0.1–5% were detected. Interestingly, we could also detect cohoming of endogenous nontransgenic CD8<sup>+</sup> T cells, which exerted GP33-specific cytotoxicity (data not shown). This demonstrates that the induction of skin-homing T cells following i.c. DC priming is not restricted to the TCR transgenic P14 system, but seems to be of general relevance. The total number of emigrated cells was ~0.5–2 × 10<sup>5</sup> per ear. At the peak of expansion at ~day 7, P14 T cells represented up to 55% of total CD8<sup>+</sup> T cells. Three days later, a dramatic contraction of the effector T cell pool was observed, with levels below 15% (data not shown), followed by an ongoing decline over the next weeks. Three weeks after P14 transfer and DC injection, Thy-1.1<sup>+</sup> memory T cells were quantified in blood by flow cytometry to test the stability of the skin-homing phenotype. We observed similar levels with both immunization protocols (Fig. 5D, upper panels). However, in our skin-homing test, hardly any CD8<sup>+</sup> memory T cells entered the site of inflammation after i.v. immunization. In contrast, in i.c. immunized mice, up to 7% of total live emigrated cells were P14 T cells (Fig. 5, C and D, lower panels).

Skin-homing T cells elicit peptide-dependent skin inflammation

The functional relevance of these differences in skin-homing capacity was tested by establishing a peptide-dependent CHS protocol. TNCB was painted on ears of mice 8 days after P14 T cell transfer and i.c. or i.v. DC immunization. TNCB was painted on ears of mice 8 days after P14 T cell transfer and i.c. or i.v. DC immunization, followed by epicutaneous application of the antigenic peptide GP33 to attract T cells into
skin. Strong ear swelling after 24 h was detected if the mice had been immunized by peptide-loaded DC i.c., but not after i.v. immunization (Fig. 6). Control mice were painted with TNCB and GP33 and then injected i.c. with peptide-free control DC.

**Tissue-derived DC induce differential homing marker expression**

To address the role of the APC in instructing CD8<sup>+</sup> T cells for tissue-selective homing, we performed in vitro priming experiments of P14 T cells with DC isolated from different tissues or with BM-DC. Despite similar T cell activation, as detected by proliferation assay on day 4 (Fig. 7), we observed differential expression of homing markers on day 6 (Fig. 8). Only small differences in T cell proliferation were detected when graded numbers of the different DC populations were used in the assays (data not shown). Most interestingly, LC were usually slightly less efficient in these T cell stimulation assays (data not shown), but were always the most efficient inducers of ESL. This underscores their potent intrinsic capacity to induce this homing marker. Peripheral skin-draining LN-DC (pDC) induced ESL less efficiently. ESL on T cells primed with mesenteric, gastrointestinal tract-draining LN-DC (mDC) were present, but much lower compared with LC-primed T cells, whereas BM-DC did not efficiently up-regulate ESL.

**FIGURE 6.** Skin-homing P14 T cells elicit a peptide-dependent ear-swelling response. On day 8 after adoptive P14 transfer and DC immunization i.v or i.c., TNCB and peptide GP33 were painted on ear skin. Mean increase in ear thickness after 24 h is shown. Data from three mice ± SD. Control mice (Ctrl.) received DC without GP33. Representative results from one of three experiments are shown.

**FIGURE 7.** Similar T cell activation by DC from different tissues. Proliferation of P14 cells was measured by [3H]thymidine incorporation on day 4 after in vitro priming with peptide GP33-loaded BM-DC or DC isolated from mesenteric (mDC) or peripheral LN (pDC) or skin (LC). Data represent mean values from triplicate measurements ± SD. Representative results from one of two experiments.

CCR4 was most elevated in priming experiments with pDC and LC, but to a lesser extent also present on P14 T cells primed by BM-DC and mDC. As suggested by the in vivo results (Fig. 3A), CCR4 expression does not seem to have a strong tissue-specific correlation. Expression of the gut-homing integrin α<sub>4</sub>β<sub>7</sub> on P14 T cells was most elevated in in vitro priming cultures with mDC (Fig. 8) or with DC from Peyer’s patches (data not shown), whereas T cells in cultures with LC and pDC were negative. Interestingly, BM-DC also significantly up-regulated α<sub>4</sub>β<sub>7</sub> expression in vitro. These results suggest that mDC promote a gut-homing T cell phenotype, whereas DC derived from other tissues fail to do so (Fig. 8).

**Discussion**

Our results reveal the induction of three different CD8<sup>+</sup> T cell-homing subsets in dependence of the DC injection route: DC given i.c. primed T cells that up-regulated ESL and efficiently homed to inflamed skin, while, in contrast, DC injected i.v. failed to do so. Most importantly, only these skin-homing T cells efficiently elicited a skin-specific immune response, i.e., CHS to epicutaneously applied hapten or peptide. Furthermore, DC given i.p. induced a gut-homing T cell phenotype by up-regulation of integrin α<sub>4</sub>β<sub>7</sub>.

**FIGURE 8.** Differential in vitro induction of homing markers with DC from different tissues. P14 T cells were analyzed for expression of ESL, CCR4, and α<sub>4</sub>β<sub>7</sub>, on day 6 of in vitro culture after priming with GP33-loaded BM-DC, mDC, pDC, or LC, as described in Fig. 7. As control (filled gray), T cells from LC-priming cultures were stained with FITC-conjugated anti-human IgG only (control for ESL staining) or isotype control Abs. Data are gated on CD8<sup>+</sup> cells with activated phenotype in forward/side scatter. Representative results from one of three to eight experiments.
but not ESL. It has to be considered that i.c. injected DC activate T cells in skin-draining LN, i.v. mostly in the spleen, whereas i.p. injected DC meet T cells most probably in mesenteric/peritoneal LN (24, 32, 33).

Our finding that the same BM-DC differentially induce homing markers in vivo points out an important role for the specific tissue microenvironment that may directly provide trafficking information to T cells. This is supported by recent studies demonstrating a role for the local microenvironment in the differential regulation of T cell migration and effector functions (34, 35). Campbell and Butcher (34) demonstrated the rapid up-regulation of skin- vs gut-homing markers on CD4+ T cells in the corresponding LN after systemic peptide injection. Our findings suggest that this is also true for CD8+ T cells after in vivo priming by DC injection via different routes, and that the skin-homing potential remains stable in the memory phase without Ag contact at the effector site.

As we know about the multiple functions of DC to shape the immune response, we now also propose a role for the priming DC in the instruction of T cells for tissue-specific homing. Due to its functional plasticity (36), the injected semimature BM-DC may, after acquisition of characteristics of a tissue-specific DC, confer trafficking information to T cells. Thus, LC as specialized skin-resident DC are most effective in up-regulating ESL on T cells in vitro, compared with DC from other tissues, whereas, in turn, mDC induced the gut-homing integrin α4β7. Similarly, recent data (29) revealed that mDC, but not pDC, induce α4β7 on T cells activated in vitro by anti-CD3 Ab. In similar experiments, Mora et al. (37) found that CD8+ P14 T cells primed in vitro with Peyer’s patch DC expressed α4β7 and CCR9. Upon in vivo transfer, these T cells preferentially homed to small intestine. The important role for CCR9 in gut-specific homing of CD8+ T cells was also demonstrated by others (8, 38). We have now extended these findings by demonstrating an Ag-specific in vivo induction of α4β7 on CD8+ P14 T cells after DC i.p., but not i.v. or i.c. injection. These data show that DC can up-regulate this homing marker without Ag-specific contact, and also raise the possibility that in our DC injection experiments, endogenous DC may influence the generation of T cell-homing subsets in trans.

Interestingly, we observed much higher levels of ESL on T cells in vitro than in vivo, and also priming with BM-DC and mDC induced ESL to some extent. This up-regulation in vitro is most likely influenced by the absence of negative regulatory factors such as IL-4 and an accumulation of inflammatory cytokines such as IL-12, which has been shown to be a potent inducer of ESL (12, 39). However, levels induced by LC were 10- to 100-fold higher despite similar T cell proliferation. These results suggest a tissue-selective instruction of T cells directly by the priming DC, and for the first time provide evidence that LC possess the intrinsic ability to induce a skin-homing phenotype on CD8+ T cells.

The specialization for skin vs gut homing observed in this study is restricted to the differential expression of the adhesion molecules ESL and integrin α4β7, but not CCR4 on CD8+ T cells. Recently, differential expression of ESL/cutaneous lymphocyte Ag on human T cells specific for skin tropic HSV-2, but not the nonskin-tropic herpes viruses, has been reported (40). These data underline the crucial role of ESL in a skin-selective specialization of CD8+ T cells.

A tissue-specific chemokine pattern has been reported to match a specialized chemokine receptor expression of effector T cells trafficking to skin vs small intestine (1–3). However, in our experiments, CCR4 was up-regulated independently of the DC immunization route. We therefore suggest that CCR4 is an important, but not an exclusive marker of skin-homing CD8+ T cells. CCR4-deficient T cells have been shown to retain their skin-homing capacity (19). Furthermore, an involvement of this chemokine receptor in T cell homing to the lung has recently been reported (41–45). The observed down-regulation of CCR4 in the late effector phase and its absence on memory T cells as judged by flow cytometry (data not shown) may point to a more important role in orchestrating the early immune response as a receptor for DC-derived CCL22 (46) rather than in skin homing of memory CD8+ T cells. However, it is also possible that CCR4 is reinduced on memory CD8+ T cells, e.g., when they enter inflamed skin. Alternatively, CCR4-negative memory cells may use other chemokine receptors such as CCR6 (47) and CCR10 (1, 18, 19, 48, 49) for this purpose.

In summary, we have shown that the T cell-homing phenotype is influenced by the tissue microenvironment and also by the tissue-specific Ag-presenting DC. Future work should identify the nature of the factors that define the influence of the tissue microenvironment and of the inductive signals that target T cells to different peripheral tissues. Finally, these results point out a crucial role for the application route of in vitro generated DC in immunotherapies. In this context, the recent observation that tumor surveillance by effector/memory CD8+ T cells is governed by the DC immunization route is of interest (50). Interference with T cell trafficking will lead to the development of more specific immunotherapies for organ-restricted autoimmune, cancer, and allergies as encouraged by several recent in vivo studies in mice (18, 19, 51, 52) and humans (53, 54).

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