Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jdermsci.2015.10.015.

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Letter to the Editor

Percutaneous exposure to high-dose hapten induces systemic immunosuppression through the inhibition of dendritic cell migration

While sensitization with the optimal dose of an antigen induces antigen-specific T-cell responses, the immune response to a supraoptimal dose of antigen is suppressed [1]. In addition, high-dose antigen exposure under certain conditions suppresses subsequent immune response to the antigen [2,3]. The mechanisms underlying high-dose antigen-induced immunosuppression appear to vary according to the administration route of the high-dose antigen: intravenous injection of high-dose hapten induces suppressor cells [2], while oral administration of high-dose hapten induces anergy or deletion of antigen-specific T cells [3].

Percutaneous sensitization of mice with an optimal dose of haptens such as dinitrofluorobenzene (DNFB), trinitrochlorobenzene (TNCB), and oxazolone induces hapten-bearing dendritic cell (DC) migration from sensitized skin into the draining lymph node (dLN), leading to the proliferation and differentiation of the hapten-specific interferon (IFN)-γ-producing $CD8^+$ effector T (Tc1) cells. Re-exposure to the relevant hapten five days after sensitization elicits allergic contact hypersensitivity (CHS) response by antigen-specific Tc1 cells [4]. A previous report has shown that topical high-dose hapten application induces dysfunction of DCs at hapten-applied sites, resulting in the impaired capacity of hapten-applied skin to support subsequent CHS induction by an optimal sensitizing dose of another hapten [5]. However, it remains unclear whether and how percutaneous exposure to high-dose antigen inhibits subsequent immune responses systemically. In this study, we investigated the systemic effect of high-dose hapten exposure on subsequent sensitization with an optimal dose of hapten.

Mice sensitized with a high dose (3%) of DNFB showed significantly attenuated CHS responses after elicitation compared to mice sensitized with an optimal dose (0.5%) of DNFB (Fig. 1A), which was consistent with a previous report [1]. In addition, CHS responses induced by an optimal dose of DNFB were significantly suppressed in mice pretreated with high-dose DNFB on the abdominal skin one day before sensitization (Fig. 1B–D). To confirm that high-dose DNFB pretreatment inhibited subsequent sensitization with the optimal dose of hapten, CHS transferred via dLN cells of sensitized mice with or without DNFB pretreatment was assessed. Mice subjected to adoptive transfer of dLN cells that had been collected from vehicle-pretreated mice five days after sensitization exhibited substantial CHS responses after elicitation. Mice subjected to adoptive transfer of dLN cells that had been

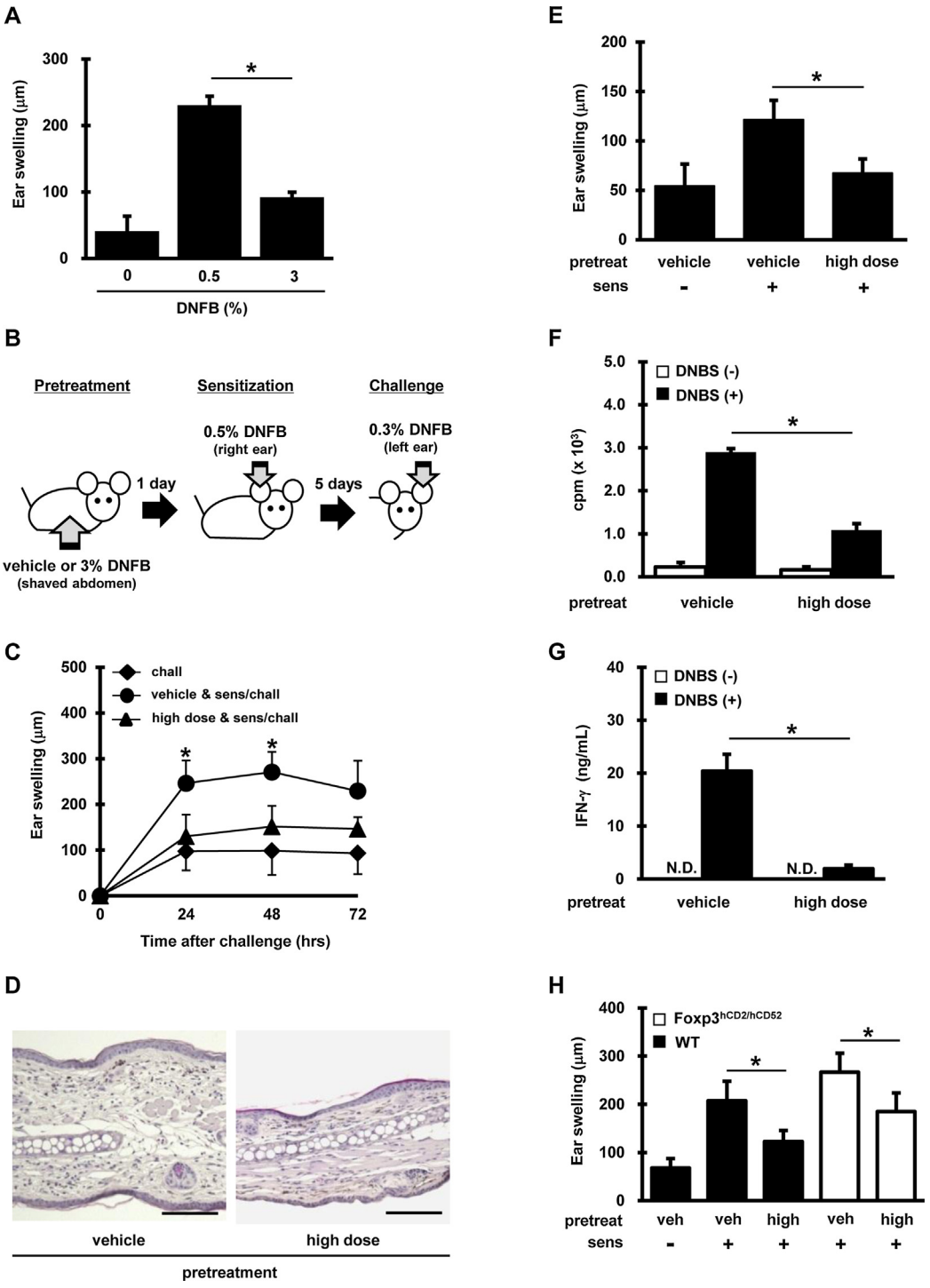

Fig. 1. Topical high-dose DNFB application systemically inhibited subsequent sensitization with an optimal dose of hapten.
(A) CHS was induced with DNFB as previously described [6] with some modifications. C57BL/6 (B6) mice were sensitized with 25 μl of the indicated concentration (v/v) of DNFB onto shaved abdomen and challenged with 20 μl of 0.3% DNFB on each ear 5 days post-sensitization. Ear swelling was measured 24 h after challenge. (B–D) High-dose DNFB pretreatment and CHS induction. (B) Schematic illustration of experimental protocol. B6 mice were sensitized with 20 μl of 0.5% DNFB on right ear one day after pretreatment with 25 μl of vehicle or 3% DNFB onto shaved abdomen, followed by a challenge on left ear as described in A. (C) Ear swelling at 24, 48, and 72 h post-challenge. (D) Hematoxylin and eosin staining of ear sections 24 h post-challenge (scale bar; 100 μm). (E) B6 mice were pretreated and sensitized as described in B. Five days after sensitization, cervical LN cells were removed and adoptively transferred into naïve recipient mice (from two donors to one recipient). Immediately after the cell transfer, the ears were challenged with 0.5% DNFB, and ear swelling was measured 24 h later. (F and G) 2.5×10^5 $CD8^+$ T cells isolated from draining LNs of mice pretreated and sensitized as described in B were stimulated with DNBS (100 μg/mL) in the presence of 5.0×10^5 mitomycin C-treated splenocytes for three days. (F) Cell proliferation was assessed by [^{3}H] thymidine incorporation during the last 24 h. G, The amount of IFN-γ in the culture supernatant was measured by ELISA. N.D., not detected. (H) Effect of $Foxp3^+$ regulatory T-cell depletion on high-dose DNFB-induced suppression of CHS. For selective depletion of $Foxp3^+$ regulatory T cells, $Foxp3^{hCD2/hCD52}$ mice (kindly provided by Dr. Hori), which express human CD2/CD52 fusion protein specifically on cell surfaces of $Foxp3^+$ cells [8], were injected intravenously with anti-human CD2 antibody (clone 35.1). Wild-type (WT) and $Foxp3^{hCD2/hCD52}$ mice were pretreated with vehicle (veh) or 3% DNFB (high), sensitized, and challenged as in B. All mice were injected with anti-human CD2 antibody (0.1 mg/mouse) one day before challenge. Ear swelling was measured 24 h after challenge. Data are shown as the mean ± SD values. Statistical analyses were performed by Student's *t* test. At least four mice per group. $^*p < 0.05$.