IL-1α, but not IL-1β, is required for contact-allergen-specific T cell activation during the sensitization phase in contact hypersensitivity

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Abstract

Contact hypersensitivity (CHS) is a T cell-mediated cellular immune response caused by epicutaneous exposure to contact allergens. In this reaction, after the first epicutaneous allergen sensitization, Langerhans cells (LC) catch allergens and migrate from the skin to draining lymph nodes (LN) and activate naive T cells. Although IL-1 is suggested to be involved in these processes, the mechanisms have not been elucidated completely. In this report, to elucidate roles of IL-1α and IL-1β in CHS, we analyzed ear swelling in 2,4,6-trinitrochlorobenzene (TNCB)-induced CHS using gene-targeted mice. We found that ear swelling was suppressed in IL-1α-deficient (IL-1α–/–) mice but not in IL-1β–/– mice. LC migration from the skin into LN was delayed in both IL-1α–/– and IL-1β–/– mice, suggesting that this defect was not the direct cause for the reduced CHS in these mice. However, we found that the proliferative response of trinitrophenyl (TNP)-specific T cells after sensitization with TNCB was specifically reduced in IL-1α–/– mice. Furthermore, adoptive transfer of TNP-conjugated IL-1-deficient epidermal cells (EC) into wild-type mice indicated that only IL-1α, but not IL-1β, produced by antigen-presenting cells in EC could prime allergen-specific T cells. These observations indicate that IL-1α, but not IL-1β, plays a crucial role in TNCB-induced CHS by sensitizing TNP-specific T cells.

Introduction

Contact hypersensitivity (CHS) is a T cell-mediated cellular immune response caused by repeated epicutaneous exposure against contact allergens, chemically reactive haptens which are able to bind directly to soluble or cell-associated proteins. This response is divided into two phases, sensitization and elicitation phases. After the first epicutaneous allergen sensitization, Langerhans cells (LC) catch allergens and migrate from the skin to draining lymph nodes (LN) where naive T cells are thought to be primed against allergens through T cell–LC interaction (1). In the elicitation phase, allergen-specific T cells in LN are activated upon re-challenging with the same allergen and migrate from LN to the place where the allergen is challenged, resulting in local inflammation. Using MHC class I+ and MHC class II+ mice, it was shown that CD8+ T cells act as effector cells, while CD4+ T cells play a regulatory role in this reaction (2,3). It is known that LC are important as antigen-presenting cells (APC) in the sensitization phase, but they are not essential for the elicitation phase (4).

Both IL-1α and IL-1β cause inflammation and also augment immune reactions through activation of lymphocytes, although they are encoded by distinct genes and have little amino acid sequence homology (5). The expression of proinflammatory cytokine mRNAs including those of IL-1α, IL-1β and tumor necrosis factor (TNF)-α is increased in the contact-allergen-sensitized skin (6). In the epidermis, IL-1α is mainly produced...
by keratinocytes (KC) while IL-1β is mainly produced by LC (7–9). IL-1β mRNA is expressed earlier than any other proinflammatory cytokine in CHS (9,10).

It was shown that systemic administration of recombinant IL-1α (rIL-1α) or local treatment of rIL-1β causes activation and migration of LC (10–12). LC migration was impaired by systemic administration of anti-IL-1β antibody (13). Furthermore, treatment with IL-1 receptor antagonist (IL-1ra), which is a negative regulator of IL-1α and IL-1β, abolished the enhanced migration of LC (14,15) and corneal LC migration was impaired in mice deficient in the IL-1 receptor type 1 (IL-1RI) gene (16). These observations suggest that both IL-1α and IL-1β can promote LC migration that may be important in CHS. Consistent with these observations, CHS was markedly impaired in mice deficient in the IL-1 receptor type 1 (IL-1RI) gene (16). These observations suggest that both IL-1α and IL-1β can promote LC migration that may be important in CHS. Consistent with these observations, CHS was markedly reduced by the intradermal administration with anti-IL-1β mAb (10). However, it was reported that CHS was not affected by the treatment with anti-IL-1α mAb (10). On the other hand, it was shown that IL-1β was not involved in oxazolone-induced CHS using IL-1β−/− mice (17,18). Furthermore, it was shown that low-dose 2,4,6-trinitrochlorobenzene (TNCB)-induced CHS was suppressed in IL-1β−/− mice, whereas the high-dose response was not (18). Thus, these apparently controversial findings claim that the role of IL-1 in CHS still remains to be elucidated.

CHS develops through several distinct steps including LC migration from the skin into LN, allergen-specific T cell activation and cell infiltration into inflamed regions. It is suggested that various cytokines, chemokines, adhesion molecules and co-signal molecules are involved in these processes (19–27). Recently, we have shown that IL-1 produced by APC plays a crucial role in antigen-specific T cell priming and clonal expansion using IL-1αβ+/+ and IL-1αβ−/− mice (28). In this study we tried to elucidate roles of IL-1 in CHS using these IL-1−/− mice. We found that TNCB-induced CHS at both low and high doses was greatly reduced in IL-1α−/− and IL-1β−/− mice, but not in IL-1β+/− mice. The induction of trinitrophenyl (TNP)-specific T cells was abolished in IL-1α−/− and IL-1αβ−/− mice, whereas that in IL-1β−/− mice was normal, indicating that IL-1α produced by mature LC in LN is required to prime naive T cells against contact allergens in the sensitization phase of CHS.

CHS response
TNCB (Tokyo Kasei, Tokyo, Japan)-induced CHS was assayed as described previously (17,18). Briefly, the abdomen of mice was shaved and sensitized epicutaneously with 25 µl of low-dose (0.3%) or high-dose (3.0%) TNCB dissolved in acetone and olive oil mixture (4:1). On day 5 after sensitization, the outside of one ear (auricle) of mice was challenged with 25 µl of 1.0% TNCB and the outside of the other ear was treated with 25 µl of vehicle alone. At 24 h after the second challenge, mice were euthanized and a disk of ear tissue was removed from both ears using a 6-mm biopsy punch, then each of ear disk was weighed. The difference between TNCB-treated and vehicle-treated ear weights of each mouse is shown as the amount of swelling in TNCB-induced CHS. Ear swelling is calculated as follows: increment of ear swelling = weight of challenged ear – weight of vehicle-treated ear)/weight of vehicle-treated ear×100 (%).

Migration and maturation of LC
Mice were shaved at the dorsal and abdominal area, and painted with 50 µl of 0.5% FITC isomer I (Sigma, St Louis, MO) dissolved in acetone and dibutylphthalate mixture (1:1). At 24 h after FITC painting, inguinal, axillary and brachial LN were harvested and pooled. Single-cell suspension was prepared from collagenase-treated LN and stained with biotinylated anti-mouse CD11c mAb (HL3; PharMingen, San Diego, CA) after pre-incubation with anti-Fc receptor mAb (2.4G2; PharMingen). To assess the maturation of LC, LN cells were stained with phycoerythrin (PE)-anti-mouse CD40 (3.23; Immunotech, Marseilles, France) and PerCP-streptavidin (PharMingen). The frequency of CD11c+ FITC+ cells or expression levels of CD40 on CD11c+ FITC+ cells in LN were analyzed with a FACScan (Becton Dickinson, Mountain View, CA) using Lysys II software (Becton Dickinson). Viable cells were determined by forward and side scatter.

Intracellular staining of IL-1α in peritoneal exudate cells (PEC) and mature LC
Thioglycolate (TGC)-induced PEC were prepared as described previously (29). LN cells from FITC-painted mice (at 24 h after painting) and PEC were harvested and stimulated with 5 µg/ml of LPS for 6 h, then cells were suspended in a staining buffer (HBBS containing 2% FCS and 0.1% sodium azide). After blocking with anti-FcγRIII/II receptor mAb (2.4G2; PharMingen), PEC were treated with FITC–anti-mouse Mac-1 mAb and LN cells from FITC-painted mice were treated with biotinylated anti-CD11c mAb (HL3; PharMingen). Then, cells were incubated with PerCP-streptavidin (PharMingen), followed by fixation with PBS containing 4% paraformaldehyde for 20 min. After washing with a permeabilization buffer [0.1% saponin (Sigma) in the staining buffer], cells were incubated with PE-hamster anti-mouse IL-1α mAb (ALF-161; PharMingen) or isotype-matched control mAb (PE-hamster IgG; Immunotech) in the permeabilization buffer for 30 min at 4°C. Cells were washed with the permeabilization buffer and analyzed using a FACS Calibur (Becton Dickinson) and CellQuest software (Becton Dickinson).

T cell proliferative response assay
For TNP-specific T cell proliferative response, inguinal, axillary and brachial LN were harvested and pooled 5 days after the
sensitization with 3.0% TNCB. Single-cell suspension was prepared, and T cells were purified by passing through MACS separation columns (Miltenyi Biotec, Bergisch Gladbach, Germany) to remove anti-B220 and anti-Mac-1 mAb-reactive cells. To prepare TNP-conjugated APC, the spleen was harvested from wild-type mice and single-cell suspension was prepared. After treatment with hemolysis buffer (17 mM Tris-HCl, 140 mM NaH4Cl, pH 7.2), T cells were depleted by passing through MACS columns using anti-Thy1.2, anti-CD4 and anti-CD8 magnetic beads (Miltenyi Biotec). T cell-depleted spleen cells were incubated in PBS containing 100 mM trinitrobenzene sulfonate (TNBS; Wako, Osaka, Japan) at 37°C for 5 min and irradiated with γ-rays (3500 rad). LN T cells from TNCB-sensitized mice (5×10⁶ cells/well) and TNP-conjugated APC (2×10⁵ cells/well) were cultured in 200 µl of RPMI 1640 (Sigma) containing 50 mM 2-mercaptoethanol (Gibco/BRL, Gaithersburg, MD), 50 µg/ml streptomycin (Meiji, Tokyo, Japan), 50 µg/ml penicillin (Meiji) and 10% heat-inactivated FCS (Sigma) using 96-well flat-bottom plates for 72 h. For ovalbumin (OVA)-specific primary T cell proliferative responses, inguinal, axillary and brachial LN of DO11.10 transgenic mice were incubated with anti-Thy1.2 and anti-CD8 magnetic beads (Miltenyi Biotec). T cell-depleted spleen cells were incubated in PBS containing 0.05% Tween 20, followed by the addition of alkaline phosphatase-conjugated goat anti-mouse IgG (Zymed, San Francisco, CA). Alkaline phosphatase activity was measured using Substrate Phosphatase SIGMA104 (Sigma) as the substrate. Results are expressed by the absorbancy at 415 nm.

Statistics
Student’s t-test was used for statistical evaluation of the results.

Results

CHS with high-dose TNCB
It was previously reported that CHS was markedly reduced in IL-1β−/− mice when mice were sensitized with low-dose TNCB, whereas high-dose sensitization induced comparable CHS between IL-1β−/− and wild-type mice (17). These results suggest that IL-1β-deficiency can be compensated by IL-1α at high-dose TNCB sensitization, but not at low-dose sensitization. In order to identify the differential roles of IL-1α and IL-1β, we re-examined CHS at both low and high TNCB doses using IL-1α−/−, IL-1β−/− and IL-1α−/−β−/− mice on the BALB/cA genetic background (Fig. 1A and B). In contrast to the previous report, we found that similar levels of CHS were induced in IL-1β−/− and wild-type mice with both low and high doses of TNCB. Furthermore, we found that CHS was significantly reduced in IL-1α−/− mice as well as IL-1α−/−β−/− mice at 24 h after the challenge (Fig. 1A and B). In our assay system, ear inflammation in wild-type and IL-1−/− mice calmed down to the basal levels at 48 h after the challenge (data not shown). We assessed the effect of genetic background using IL-1−/− deficient mice on the BALB/cA background, because genetic background affects CHS (31). Similar results were obtained using IL-1α−/−β−/− and IL-1β−/− mice on the BALB/cA background (data not shown). However, the effect of IL-1α deficiency was only small on the BALB/cA background compared to that on the C57BL/6J background. Since we observed more pronounced effects of the deficiency in IL-1α−/−β−/− mice compared with IL-1α−/− mice on the BALB/cA background, it was suggested that IL-1β also plays some role in a synergistic manner with IL-1α in mice of this background.

Effects of IL-1-deficiency on LC migration and maturation
To elucidate roles of IL-1 in CHS, we first examined the migration ability of LC from the skin into draining LN. After

Adapted transfer of TNP-conjugated splenocytes and induction of CHS
TNP-conjugated EC from wild-type or IL-1-deficient mice were suspended in PBS and injected into wild-type mice s.c. (2×10⁶ cells/mouse). At 7 days after injection, the outside of one ear of mice was challenged with 25 µl of 1.0% TNCB and the outside of the other ear was applied with 25 µl of vehicle alone. At 24 h after the challenge, ear swelling was measured as described above.

Measurement of antibody titers
Mice were sensitized and challenged with TNCB as described above. Four days after the challenge, the sera were collected. TNP-specific Ig levels in the sera were measured by sandwich ELISA. To TNP-specific antibodies, TNP-BSA in PBS (10 µg/ml) was coated on Falcon 3912 Micro Test III flexible assay plates (Becton Dickinson, Oxnard, CA) at 37°C overnight. After washing with TBS, serial diluted serum samples were applied and incubated at room temperature for 1 h. After incubation for 1 h the well was washed with TBS + 0.05% Tween 20, followed by the addition of alkaline phosphatase-conjugated goat anti-mouse IgG (Zymed, San Francisco, CA). Alkaline phosphatase activity was measured using Substrate Phosphatase SIGMA104 (Sigma) as the substrate. Results are expressed by the absorbancy at 415 nm.

Preparation of epidermal sheets (EC)
Mice were shaved at the dorsal and abdominal areas, and the hair completely removed with a hair-remover cream at 2 days before experiments. The shaved skin were harvested and the hypodermal tissue removed. The skin was incubated with 0.15% trypsin (Gibco) and 50 U/ml of dispase (Godoeshi, Tokyo, Japan) in PBS for 1 h at 37°C and epidermal sheets were prepared. A single-cell suspension from epidermal sheets was prepared and CD11c+ LC were isolated with the MACS system by positive selection using biotinylated anti-CD11c and streptavidin–magnetic beads (Miltenyi Biotec). DO11.10 CD4+ T cells (5×10⁵ cells/well) were cultured with TGC-induced PEC or CD11c+ skin LC (5×10⁵ cells/well) in the absence or presence of the OVA peptide (0.1 µM) with or without rIL-1α (100 pg/ml) for 72 h. After 72 h, cells were labeled with [3H]thymidine (0.25 µCi/ml; Amersham, Little Chalfont, UK), then harvested using a Micro 96 cell harvester (Skatron, Lier, Norway) and [3H] radioactivity was measured using Micro Beta System (Pharmacia Biotech, Piscataway, NJ).

Roles of IL-1 in contact hypersensitivity
Fig. 1. TNCB-induced CHS in wild-type, IL-1α−/−, IL-1β−/− and IL-1α/β+ mice. Increment of ear swelling in TNCB-induced CHS. (A) Low-dose (0.3%) TNCB-induced CHS in wild-type (n = 7), IL-1α−/− (n = 8), IL-1β−/− (n = 7) and IL-1αβ−/− (n = 6) mice. (B) High-dose (3.0%) TNCB-induced CHS in wild-type (n = 8), IL-1α−/− (n = 10), IL-1β−/− (n = 14) and IL-1αβ−/− (n = 6) mice. Each circle represents an individual mouse and an average ± SD are shown. *P < 0.01 and #P < 0.001.

Fig. 2. Effects of IL-1-deficiency on LC migration and maturation. Wild-type mice and IL-1-deficient mice were epicutaneously sensitized with 0.5% FITC. After FITC painting, draining LN were harvested and analyzed for FITC and CD40 expression by flow cytometry. (A) Content of FITC+ cells among CD11c+ cells at 24 h after FITC painting. (B) Kinetics of CD11c+ FITC+ LC migration. (C) Expression of CD40 on CD11c+ FITC+ cells. One set of representative data from six independent experiments is shown.

...sensitization with 0.5% FITC, CD11c+ FITC+ cell counts in draining LN were measured by flow cytometry analysis (Fig. 2A). The content of CD11c+ FITC+ cells in LN from both IL-1α−/−, IL-1β−/− and IL-1αβ−/− mice was significantly reduced compared with wild-type mice after FITC treatment. The migration in IL-1αβ−/− mice was most severely affected at 24 h after the treatment. However, the FITC+ LC content in LN of both IL-1α−/− and IL-1β−/− mice became similar to that of wild-type mice at 36 h after FITC treatment (Fig. 2B).

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...effect of IL-1 deficiency on the induction of antigen-specific T cells

We have recently reported that IL-1 produced by APC plays an important role in antigen-specific T cell priming (28). Thus, we examined the role of IL-1 in the induction of antigen-specific T cells by sensitizing with high-dose TNCB. LN T cells from IL-1-deficient mice sensitized with TNCB were cultured with TNP-conjugated and T cell-depleted wild-type splenocytes (Fig. 3). Proliferative responses of IL-1α−/− T cells as well as IL-1αβ−/− T cells were markedly impaired, while those of IL-1β−/− T cells were comparable with those of wild-type T cells. Previously, we showed that T cell development and intrinsic T cell function is normal in IL-1-deficient mice (28). Thus, the reduced proliferative responses of IL-1α−/− and IL-1αβ−/− T cells suggest that LN T cells from these IL-1-deficient mice were not sensitized sufficiently in vivo, because APC were derived from wild-type mice.

...expression of LC migrating into draining LN

Although LC are known as APC in the sensitization phase of CHS, in immature skin, LC do not produce IL-1α (32,33). It is not known whether or not mature LC which migrate from the skin into draining LN produce IL-1α. We carried out flow cytometric analysis of the LN cells from FITC-painted wild-type mice after stimulation with LPS for 12 h. As shown in Fig. 4(A and B), both CD11c+ FITC+ LN cells and CD11b+ PEC produced IL-1α. Cells from IL-1α−/− mice (Fig. 4A and B) and non-stimulated TGC-induced CD11b+ PEC (data not shown) did not produce IL-1α. Agonistic anti-CD40 mAb-treated CD11c+FITC+ cells also produced IL-1α (data not shown).

...CD4+ T cells from DO11.10 transgenic mice were cultured with CD11c+ cells from the skin or CD11b+ PEC in...
Roles of IL-1 in contact hypersensitivity

Fig. 3. Proliferation of TNCB-sensitized LN T cells after in vitro re-stimulation. On day 5 after sensitization with 3.0% TNCB, LN were harvested and T cells were purified through MACS columns. These T cells and irradiated TNP-conjugated APC or non-treated APC from wild-type splenocytes were cultured for 72 h, and then the proliferative response was assessed by the incorporation of [3H]thymidine. The data were reproducible in three independent experiments.

Fig. 4. IL-1α expression in LC migrating into draining LN. Intracellular IL-1α in LPS-stimulated CD11b/Mac-1+ PEC (A) and in CD11c+ FITC+ LC from LN (B) was stained with PE-anti-mouse IL-1α mAb (solid lines) and with isotype-matched control IgG (shaded), and analyzed by flow cytometry. DO11.10 CD4+ T cells were cultured with either CD11c+ skin LC or TGC-induced PEC from wild-type mice in the presence of the OVA peptide with or without rIL-1α for 72 h and then the proliferative response was assessed by the incorporation of [3H]thymidine (C). WT, wild-type mice; KO, IL-1α/β−/− mice.

Adoptive transfer of TNP-conjugated EC

As shown above, IL-1, especially IL-1α, may play an important role not only in LC migration but also in contact-allergen-specific T cell activation. To examine roles of IL-1 produced by LC in T cell activation, we performed adoptive transfer of TNP-conjugated wild-type or IL-1-deficient EC, which contain ~2% LC, into wild-type mice which were not sensitized with contact allergens. When TNP-conjugated IL-1α/β−/− EC as well as IL-1α/β−/− EC were transferred into wild-type mice, their ear swelling after treatment with 1.0% TNCB was markedly reduced compared with those transferred with TNP-conjugated wild-type EC (Fig. 5). On the other hand, when transferred with TNP-conjugated IL-1β−/− EC, ear swelling was similar to that of wild-type mice (Fig. 5). These results suggest that IL-1α, but not IL-1β, produced by APC in EC, most likely to be LC, is required for TNP-specific T cell activation.

Distinctive roles of IL-1α and IL-1β in allergen-specific antibody production

To examine the possibility that IL-1 is involved in CHS through contact-allergen-specific antibody production, TNCB-specific antibody production was measured in those IL-1-deficient mice. TNCB-specific antibody production was measured in those IL-1-deficient mice. As shown in Fig. 6, serum TNP-specific IgG levels in IL-1β−/− mice as well as in IL-1α/β−/− mice were lower than those in wild-type mice, while those in IL-1α−/− mice were comparable. These results are consistent with our previous report (38) showing that IL-1β, but not IL-1α, is mainly involved in the antibody production. Thus, it was shown that molecular species of IL-1 differ between CHS and antibody production, suggesting different mechanisms are involved in those reactions.

Discussion

Previously, IL-1β rather than IL-1α was thought of as a mediator of CHS, because CHS was suppressed by the administration of anti-IL-1β mAb, but not by anti-IL-1α mAb (10). Furthermore, low-dose TNCB-induced CHS was suppressed in IL-1β−/− mice, although high-dose TNCB-induced CHS and oxazolone-induced CHS were normal in these mice (17,18). Here, we demonstrated that TNCB-induced CHS was markedly impaired in IL-1α−/− mice as well as in IL-1α/β−/−
indicating that IL-1α mice, while that in IL-1β mice is involved in contact-allergen-specific antibody production. Recently, we have also shown that antibody production against sheep red blood cells is severely impaired in IL-1β mice, in agreement with the present observation (38). Thus, it is shown that IL-1α and IL-1β play distinct roles in CHS; IL-1α is mainly involved in contact-allergen-specific T cell priming, while IL-1β is involved in contact-allergen-specific antibody production. In this context, it was reported that, in germinal centers of human tonsils, IL-1β, but not IL-1α, is strongly expressed in follicular dendritic cells which play important roles in affinity maturation and isotype switching of Ig through interaction with B cells (34). Since Ig class switching depends on CD40-CD40 ligand interaction, IL-1β may be required for the B cell—follicular dendritic cell interaction. Consistent with this notion, we have recently reported that IL-1 is required for the induction of CD40 ligand on naive T cells (28). On the other hand, it is known that T cell priming through T cell–LC interactions occurs in the T-cell zones in LN. We showed that IL-1α plays a major role in this process. Thus, the functional specificity background was similar to that of IL-1αβ−/− mice, whereas that of IL-1αβ+ mice of the BALB/cA background was milder compared with that of IL-1αβ−/− mice (data not shown). Thus, the action of each IL-1 molecular species may be different in 129×B6 background mice, which were used in the previous reports (17,18), from that in the C57BL/6J background mice, which we used in this study.

LC migration was suppressed both in IL-1α+ and IL-1β+ mice. However, ear swelling was only suppressed in IL-1α+ mice, indicating that the delayed LC migration may not completely explain the suppression of CHS in IL-1α+ mice. On the other hand, we found that allergen-specific T cell priming was reduced in IL-1α+ mice, but not in IL-1β+ mice (Figs 2 and 4C). Furthermore, we showed that ear swelling upon treatment with TNCB was significantly reduced in mice previously transferred with TNP-conjugated EC from IL-1α−/− or IL-1αβ−/− mice compared with the mice transferred with those cells from wild-type mice or IL-1β+ mice. These observations suggest that IL-1α produced by APC plays a crucial role in the initiation of a primary immune response by activating allergen-specific T cells. In this context, we showed that IL-1α was produced by mature CD11c+ FITC+ LC in LN, although so far it was only believed that IL-1α was produced in skin KC, but not in immature skin LC (6–8). Taken together, these observations suggest that IL-1α produced by mature LC in LN migrating from the skin plays an important role in allergen-specific T cell priming.

We demonstrated that IL-1α+ but not IL-1β−/− produced by APC was responsible for the proliferative responses of antigen-specific T cells. This observation suggests that IL-1α is required for the development of antigen-specific memory T cells. Although we tried to demonstrate that the proportion of memory T cells (CD44+ or CD45RB− cells) in LN T cells was decreased in TNCB-sensitized IL-1α−/− mice compared to the wild-type mice, we could not detect the difference (data not shown). Probably, the proportion of TNP-specific memory T cells was too small to detect in the total T cell population. At this moment, we cannot exclude the possibility completely that TNP-specific T cells of IL-1α−/− mice became anergic because of insufficient activation.

This shows a clear contrast with the essential role of IL-1β in contact-allergen-specific antibody production. We think that probably the difference in the experimental conditions and genetic background of the mice may have affected the results (31). With regard to this, we found that suppression of ear swelling in IL-1α−/− mice of the C57BL/6J background was similar to that of IL-1αβ−/− mice, whereas that of IL-1αβ+ mice of the BALB/cA background was milder compared with that of IL-1αβ−/− mice (data not shown). Thus, the action of each IL-1 molecular species may be different in 129×B6 background mice, which were used in the previous reports (17,18), from that in the C57BL/6J background mice, which we used in this study.
of IL-1α and IL-1β seems to depend on the difference of the producing cells and the sites of production.

It was reported that CHS was suppressed in FcγR−/− mice (36), suggesting antibodies were involved in this reaction. This observation apparently contradicts our data that hapten-specific antibody levels were not correlated with the development of CHS. However, since athymic mice displayed a similar neutrophil response in oxazolone-induced contact dermatitis (36) and MHC II−/− mice in which CD4+ cells are absent displayed elevated CHS (3), it seems unlikely that hapten-specific antibody is involved in this reaction. Similar dissociation between CHS and allergen-specific antibody production was observed in CD80/CD86−/−, CD154−/− and OX40 ligand−/− mice (24,27,35). However, it is not well resolved how FcγR is involved in CHS. With regard to this, Zhang and Tinkle have shown that production of inflammatory cytokines, such as TNF-α and IL-1β, was reduced in FcγR−/− mice (36). Since these cytokines are induced in the skin during the first allergen sensitization in mice due to the irritant effects of the chemicals, it is considered that allergen-specific Ig is not involved in this reaction. Therefore, FcγR may be involved in the activation of the cutaneous innate immune system that is important for the inflammatory cell infiltration and cytokine response (36). It is possible that this defect of proinflammatory cytokine production is responsible for the diminished CHS in FcγR−/− mice.

In conclusion, we have shown that IL-1α, but not IL-1β, produced by mature LC migrating into LN is essential for contact-allergen-specific T cell activation during the sensitization phase of CHS. Thus, IL-1α and IL-1β play clearly distinct roles in the immune system, probably depending on the localization of the producing cells and responding cells in a lymphoid organ. We are now trying to further elucidate these complex regulatory mechanisms of the immune system involving IL-1α and IL-1β. These studies may provide important cues for the control of CHS.

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Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>APC</td>
<td>antigen-presenting cell</td>
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<td>CHS</td>
<td>contact hypersensitivity</td>
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<td>EC</td>
<td>epidermal cell</td>
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<td>IL-1ra</td>
<td>IL-1 receptor antagonist</td>
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References


