IL-1 and Allergy

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ABSTRACT
IL-1 is a well-characterized proinflammatory cytokine that is involved in host defense and autoimmune diseases. IL-1 can promote activation of T cells, including Th1 cells, Th2 cells and Th17 cells, and B cells, suggesting that IL-1 may contribute to the development of various types of T-cell-mediated diseases. This report reviews and discusses the role of IL-1 in the pathogenesis of allergic diseases based on studies using IL-1-related gene-deficient mice.

KEY WORDS
Allergy, Asthma, Dermatitis, IL-1

INTRODUCTION
IL-1, which was originally variously identified as an endogenous pyrogen, a lymphocyte-activating factor, hemopoietin-1 and a osteoclast-activating factor,1,2 has been well characterized as a major proinflammatory cytokine that plays pleiotropic roles in host defense by inducing acute and chronic inflammation through activation of the innate and acquired immune systems.

As a lymphocyte-activating factor, IL-1α and/or IL-1β enhances B cell activation, leading to IgE production, etc.3,5 IL-1 was shown to be important for antigen-specific T-cell and B-cell expansion through induction of co-stimulatory molecules such as CD154 and CD134 (OX40) on the surface of T cells.3 IL-1α and IL-1β can enhance IL-12-dependent IFN-γ production by Th1 cells,6,8 and IL-1α directly stimulates transcription of the IFN-γ gene as a transcription factor.9 IL-1 may be involved in the differentiation and/or activation of Th2 cells.10,13 IL-1 is also involved in IL-6-independent Th17-cell development14 and enhances IL-23-dependent IL-17 production by Th17 cells.8 These observations suggest that IL-1 contributes to the development of T cell-mediated diseases such as allergic and autoimmune disorders by promoting activation of T cells and B cells.

IL-1 AND IL-1Rs
At least 11 members of the IL-1 family of cytokines besides IL-1α, IL-1β, IL-1 receptor antagonist (IL-1Ra) and IL-18 have been identified in humans (Table 1).15,16 Except for IL-18 and IL-33, the cluster genes of the IL-1 family cytokines are located in chromosome 2 in humans and mice.

The classical IL-1/IL-1R system is composed of three ligands, including two agonists (IL-1α and IL-1β), one antagonist (IL-1Ra) and two receptors (IL-1R1 and IL-1R2) (Fig. 1). IL-1α and IL-1β are products of distinct genes and were initially synthesized as 31 kDa precursors (pro-IL-1α and pro-IL-1β).1,2,17 Processing of pro-IL-1α and pro-IL-1β to their mature 17 kDa forms is required for cleavage by calpain and caspase-1, respectively.1,2,17 In addition to mature IL-1α and IL-1β, pro-IL-1α but not pro-IL-1β, has biological activity.1,2,17 Despite approximately 25% identity of amino acid sequences between IL-1α and IL-1β they bind to the same receptors, such as IL-1R1 and IL-1R2, with different affinities: IL-1α has stronger binding affinity for IL-1Rs than IL-1β.2 IL-1Ra also binds to IL-1Rs but does not induce signal transduction downstream of the receptor.2,17 Both IL-1R1 and IL-1R2 form a heterodimeric complex with IL-1R accessory protein (IL-1RACP). IL-1R1 is a functional receptor for IL-1α and IL-1β, while IL-1R2 is considered to be a decoy receptor due to lack of a cytoplasmic region containing essential domains for signal transduction. In addition, soluble forms of IL-1R1 and IL-1R2, which are the extracellular domains of IL-1R1 and IL-1R2, also act as inhibitors of IL-1α and IL-1β.2,17

To elucidate the functional roles of IL-1 in vivo, mice deficient in IL-1α,18 IL-1β,18,20 both IL-1α and IL-
1β, IL-1Ra, IL-1R1, IL-1RAcP were generated. There have been no reports of generation of IL-1R2-deficient mice. Caspase-1 is required for the processing of pro-IL-1β and pro-IL-18. Caspase-1-deficient mice and overexpressing transgenic (Tg) mice show reduced or increased levels of mature IL-1β and IL-18, respectively.

### IL-1 IN DTH

Delayed-type hypersensitivity (DTH) responses, which are a T-cell-mediated type IV allergy, can be experimentally elicited in rodents by immunization with exogenous antigens such as cells (sheep red blood cells [RBCs] and allogenic splenocytes), protein antigens (ovalbumin [OVA], methylated bovine serum albumin [mBSA], and key hole limpet hemocyanin [KLH]) and pathogens (Mycobacterium, Leishmania and viruses). DTH develops in two phases: a sensitization phase, in which T cells are sensitized and memory T cells are formed, and an elicitation phase, in which T cell recall responses are induced upon secondary challenge with antigens.

This second phase results in induction of inflammation, consisting of recruitment of inflammatory cells such as neutrophils, macrophages and T cells. It is thought that CD4+ T cells are effector cells, while CD8+ T cells are regulatory cells, in the induction of DTH. In particular, it has been thought that the development of DTH is predominantly mediated by IFN-γ-producing Th1 cells. Mice that have been engrafted with antigen-specific Th1 cells, but not with Th2 cells, develop DTH after antigen exposure to chicken RBCs, alloantigens or KLH, and mice treated with anti-IFN-γ neutralizing antibodies (Abs) show reduced DTH responses to chicken RBCs and KLH. DTH responses during herpes simplex virus type-1 (HSV-1) infection were reduced in IFN-γ- and IFN-γR1-deficient mice, while DTH responses against Mycobacterium tuberculosis developed normally in IFN-γ-deficient mice. Moreover, IFN-γ-deficient mice showed attenuated KLH-induced DTH, while exacerbated OVA- and mBSA-induced DTH. Thus, the contribution of IFN-γ to the induction of DTH differs depending on the sensitizing antigen. Regarding the contribution of Th2-related molecules to DTH, development of KLH-induced DTH was impaired in IL-17R-related molecules, IL-17- and IL-23-deficient mice, but not IL-17F-deficient mice, showed reduced mBSA-induced DTH, and DTH responses to Mycobacterium bovis BCG were also impaired in IL-1β.

### Table 1  IL-1 and IL-1R family

<table>
<thead>
<tr>
<th>(A) Receptors</th>
<th>systematic name</th>
<th>protein name</th>
<th>other name</th>
<th>form</th>
<th>ligands</th>
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<td>M, S</td>
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<td>R4</td>
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<td>M, S</td>
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<td>IL-1Rrp, IL-18Rα, CD218a</td>
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<td>F4, F7</td>
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<td>F5, F6, F8, F9</td>
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<td>R7</td>
<td>IL-18Rap</td>
<td>IL-18Rβ, IL18RAcP, CD218b</td>
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<tr>
<td>R8</td>
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<td>TIGIRR-2</td>
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<td>R9</td>
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<td>TIGIRR-2</td>
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<td>R10</td>
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<td>SIGIRR</td>
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<td>F11</td>
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</table>

† M, membrane-bound form; S, soluble form.

<table>
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<tr>
<th>(B) Ligands</th>
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<th>protein name</th>
<th>other name</th>
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<tr>
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<td>LAF</td>
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<td>R6</td>
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<td>IL-1F6</td>
<td>FIL1ε</td>
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<td>FIL1ζ, IL-1H4, IL-1RP1, IL-1H1</td>
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<td>IL-1F10</td>
<td>IL-1Hy2, FKSG75</td>
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<tr>
<td>F11</td>
<td>IL-33</td>
<td>NF-HEV, DVS27</td>
<td></td>
<td>R4/R3, R10/R3</td>
</tr>
</tbody>
</table>

β,18 IL-1Ra,18,21-23 IL-1R124,25 and IL-1RAcP26 were generated. There have been no reports of generation of IL-1R2-deficient mice. Caspase-1 is required for the processing of pro-IL-1β and pro-IL-18. Caspase-1-deficient mice and overexpressing transgenic (Tg) mice show reduced or increased levels of mature IL-1β and IL-18, respectively.
Role of IL-1 in Allergic Diseases

Table 2 Role of IL-1 in DTH responses

<table>
<thead>
<tr>
<th>Mice treatment with:</th>
<th>Mouse strain</th>
<th>Antigen</th>
<th>DTH</th>
<th>References</th>
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<tbody>
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<td><em>Listeria monocytogenes</em></td>
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<td>48</td>
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<tr>
<td>anti-IL-1α Ab</td>
<td>BALB/c</td>
<td>HSV-1</td>
<td>ameliorated</td>
<td>49</td>
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</table>

<table>
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<tr>
<th>Mice-deficient in:</th>
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<th>Antigen</th>
<th>DTH</th>
<th>References</th>
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</thead>
<tbody>
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<td>IL-1β</td>
<td>129 x B6</td>
<td>mBSA</td>
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<tr>
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<td>129 x B6</td>
<td>mBSA</td>
<td>normally developed</td>
<td>24</td>
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<tr>
<td>IL-1R1</td>
<td>C57BL/6 &amp; BALB/c</td>
<td>mBSA</td>
<td>ameliorated</td>
<td>50</td>
</tr>
<tr>
<td>IL-1α</td>
<td>C57BL/6 &amp; BALB/c</td>
<td>mBSA</td>
<td>normally developed</td>
<td>50</td>
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<tr>
<td>IL-1β</td>
<td>C57BL/6 &amp; BALB/c</td>
<td>mBSA</td>
<td>ameliorated</td>
<td>50</td>
</tr>
<tr>
<td>IL-1α/β</td>
<td>C57BL/6 &amp; BALB/c</td>
<td>mBSA</td>
<td>ameliorated</td>
<td>50</td>
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<tr>
<td>IL-1Ra</td>
<td>C57BL/6</td>
<td>mBSA</td>
<td>exacerbated</td>
<td>50</td>
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</table>

DTH, delayed-type hypersensitivity; HSV-1, herpes simplex virus type-1; mBSA, methylated bovine serum albumin.

Accumulation of IL-1α or IL-1β-producing macrophages/macrophages was observed in local inflamed skin lesions of tuberculin-induced DTH in humans and rabbits. The levels of serum IL-1Ra, but not soluble IL-1R2, were elevated in patients with tuberculosis. It was suggested that polymorphism of the IL-1Ra gene may be involved in the development of DTH and disease expression in human tuberculosis. These observations suggest that IL-1α and/or IL-1β contribute to the development of DTH to certain antigens. In support of this, administration of recombinant IL-1α (rIL-1α) resulted in augmentation of DTH responses to killed *Listeria monocytogenes* by promoting differentiation of effector T cells (Table 2). In addition, administration of anti-IL-1α Abs ameliorated DTH responses to HSV-1 in BALB/c mice (Table 2). 129 x B6-IL-1β-deficient mice normally developed mBSA-induced DTH reactions, whereas 129 x B6-IL-1R1-deficient mice failed to respond (Table 2). These observations suggest that IL-1, especially IL-1α rather than IL-1β, contributes to the development of mBSA-induced DTH. Consistent with the phenotypes seen in 129 x B6-IL-1R1-deficient mice, the development of mBSA-induced DTH was similarly reduced in IL-1R1-deficient and IL-1α/β deficient mice.
double-deficient mice on the C57BL/6 and BALB/c backgrounds (Table 2).\textsuperscript{50} In contrast to the phenotypes seen in 129 x B6-IL-1β-deficient mice,\textsuperscript{19} development of mBSA-induced DTH was significantly impaired in C57BL/6- and BALB/c-IL-1β-deficient mice as in IL-1R1- and IL-1α/β double-deficient mice, whereas it was normal in C57BL/6- and BALB/c-IL-1α-deficient mice (Table 2).\textsuperscript{50}

To generate gene-deficient mice, embryonic stem (ES) cells from the 129/Sv mouse strain are widely used, rather than those from the C57BL/6 or BALB/c mouse strains, because of the superior stability of ES cell manipulation.\textsuperscript{51-53} However, 129 mice are less well characterized than C57BL/6 and BALB/c mice and are known to show abnormal immunology\textsuperscript{54} and behavior.\textsuperscript{55} Thus, variation in the genetic background of 129 ES cell lines has sometimes resulted in complicated experimental results due to the effects of both targeted and unrelated genes.\textsuperscript{56,57} For example, the contributions of osteopontin,\textsuperscript{58,59} apolipoprotein E\textsuperscript{60} and neurokinin-1 receptor\textsuperscript{61} to the development of diseases or behaviors are known to differ among mouse strains. Thus, the different phenotypes among 129 x B6, C57BL/6 and BALB/c-IL-1β-deficient mice during mBSA-induced DTH may be due to genomic differences in the 129 mouse strains.

C57BL/6-IL-1Ra-deficient mice, which have excessive IL-1 activity, showed aggravated mBSA-induced DTH development (Table 2).\textsuperscript{50} The aggravated responses seen in C57BL/6-IL-1Ra-deficient mice were attenuated to the wild-type mouse levels, but not the IL-1α/β double-deficient mouse levels, by TNF deficiency, suggesting that TNF is at least partially involved in the induction of local inflammation downstream of IL-1.\textsuperscript{50} During mBSA-induced DTH in C57BL/6 mice, IL-1β, but not IL-1α, is required not only for induction of antigen-specific T cells in the sensitization phase, but also for induction of local inflammation in the elicitation phase, at least in part by inducing TNF.

**IL-1 IN CONTACT HYPERSENSITIVITY**

Contact hypersensitivity (CHS), which is caused by epicutaneous exposure to hapten, is a T-cell-mediated allergic disease. Classically, CHS was regarded as a form of DTH. However, since CHS develops through a distinctly different mechanism from that of DTH, CHS has recently come to be considered a different type of allergy from DTH.\textsuperscript{30,62} For example, DTH was attenuated, but CHS was exacerbated, in MHC class II-deficient mice which lack CD4+ T cells, including effector and regulatory T cells.\textsuperscript{63,64}

Induction of CHS occurs in two phases, a sensitization phase and an elicitation phase. After the first epicutaneous exposure to a hapten, Langerhans cells (LCs) capture the haptenated antigens, migrate from the skin to draining LNs and present the antigens to naïve T cells, resulting in induction of antigen-specific memory T cells. In the elicitation phase, the antigen-specific memory T cells in LNs are activated by epicutaneous challenge with the same hapten and migrate into the local challenge site, resulting in induction of inflammation.\textsuperscript{30}

CHS has been considered to be a typical allergic disease mediated by IFN-γ-producing Th1 cells and Tc1 cells.\textsuperscript{30,62} However, CHS induced by each of 2,4-dinitrofluorobenzene (DNFB), 2,4,6-trinitrochlorobenzene (TNCB), 4-ethoxymethylene-2-phenyloxazol-5-one (oxazolone) and fluorescein isothiocyanate (FITC) developed normally in IFN-γ and/or IFN-γR1-deficient mice,\textsuperscript{65-69} indicating that IFN-γ and IFN-γ producing Th1 cells and Tc1 cells are not essential for induction of CHS. On the other hand, CHS induced by DNFB and TNCB, but not oxazolone, was attenuated in IL-4-deficient mice.\textsuperscript{70-73} Moreover, CHS induced by TNCB, DNFB and FITC was also decreased in IL-17-deficient mice.\textsuperscript{60} These observations suggest that Th2 and Th17, rather than Th1, cytokines/cells are crucial for induction of CHS.

IL-1α, IL-1β and IL-1Ra are expressed in various cell types, including keratinocytes and/or Langerhans cells (LCs). Both IL-1α and/or IL-1β mRNA expression was increased in keratinocytes after epicutaneous hapten treatment.\textsuperscript{74-78} Both IL-1 and TNF downregulated expression of E-cadherin, which is an adhesion molecule that forms tight junctions between keratinocytes and LCs, in both keratinocytes and LCs,\textsuperscript{79} suggesting enhancement of the release of LCs from the epidermis and their migration into draining LNs. Indeed, administration of rIL-1α and/or rIL-1β enhanced the release/migration and activation of LCs from the skin,\textsuperscript{80-83} while treatment with rIL-1Ra inhibited those events (Table 3).\textsuperscript{84} In addition, IL-1α-, IL-1β- and IL-1R1-deficient mice showed impaired skin or corneal LC/DC release/migration after treatment with hapten/antigens such as FITC (Table 3).\textsuperscript{85-87} Since the impairment of skin LC/DC migration in IL-1α/β-double-deficient mice after sensitization with FITC was much more severe than that in IL-1α-deficient mice and IL-1β-deficient mice (Table 3),\textsuperscript{85} both IL-1α and IL-1β are important for the events induced by FITC. On the other hand, IL-1β, but not IL-1α, is known to be required for skin LC migration after sensitization with oxazolone (Table 3).\textsuperscript{83}

In spite of the importance of IL-1β for LC migration after oxazolone sensitization,\textsuperscript{83} oxazolone-induced CHS developed normally in IL-1β-deficient mice\textsuperscript{13} as well as mice treated with rIL-1Ra\textsuperscript{68} and keratinocyte-specific IL-1R2-overexpressing Tg mice (Table 4).\textsuperscript{89} When IL-1β-deficient mice were epicutaneously sensitized with a low dose, but not a high dose, of TNCB, and then intradermally challenged with trinitrobenzene sulfonate (TNBS, an aqueous analogue of TNCB) in the footpads, footpad swelling was reduced in IL-1β-deficient mice on the 129 x B6 mixed back-
Table 3  Role of IL-1 in skin DC release/migration

<table>
<thead>
<tr>
<th>Mice treatment with:</th>
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<th>Specimen</th>
<th>Sensitizer</th>
<th>LC release/migration</th>
<th>References</th>
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<td>rIL-1α</td>
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<td>enhanced</td>
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<tr>
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<td>epidermal sheet</td>
<td>Ox</td>
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Mice-deficient in:

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<th>Mice-deficient in:</th>
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<th>Specimen</th>
<th>Sensitizer</th>
<th>LC release/migration</th>
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<td>FITC</td>
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<td>IL-1β</td>
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<td>IL-1α/β</td>
<td>129 x B6</td>
<td>Draining LN</td>
<td>FITC</td>
<td>reduced</td>
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DC, dendritic cell; LC, Langerhans cell; LN, lymph node; Ox, oxazolone; SLS, Sodium lauryl sulfate.

Table 4  Role of IL-1 in CHS responses

<table>
<thead>
<tr>
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<th>Hapten</th>
<th>CHS</th>
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<td>TNCB</td>
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Mice-deficient in:

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<th>Hapten</th>
<th>CHS</th>
<th>References</th>
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<tr>
<td>IL-1β</td>
<td>129 x B6</td>
<td>TNCB (high dose)</td>
<td>normally developed</td>
<td>20</td>
</tr>
<tr>
<td>IL-1β</td>
<td>129 x B6</td>
<td>TNCB (low dose)</td>
<td>attenuated</td>
<td></td>
</tr>
<tr>
<td>IL-1α</td>
<td>C57BL/6 &amp; BALB/c</td>
<td>TNCB</td>
<td>attenuated</td>
<td>85</td>
</tr>
<tr>
<td>IL-1β</td>
<td>(low &amp; high dose)</td>
<td>TNCB</td>
<td>attenuated</td>
<td></td>
</tr>
<tr>
<td>Transgenic mouse</td>
<td>FVB/N</td>
<td>Ox</td>
<td>normally developed</td>
<td>89</td>
</tr>
</tbody>
</table>

CHS, contact hypersensitivity; Ox, oxazolone.

† Mice were epicutaneously sensitized with TNCB on the skin, then intradermally challenged with TNBS in footpads.

Thus, the phenotypes were seemed to be mixed results in epidermal CHS and dermal DTH.

ground (Table 4).20 That reduced footpad swelling seemed to be mediated by the effects of IL-1β on the sensitization phase of CHS and the elicitation phase of DTH. Since, as noted above, the molecular mechanisms for development of CHS and DTH are entirely different, the precise role of IL-1β in the induction of CHS was unclear.20

Administration of anti-IL-1β mAb or rIL-1Ra, but not anti-IL-1α mAb, to BALB/c mice attenuated CHS induced by TNCB or DNB (Table 4). On the contrary, development of TNCB-induced CHS was similarly impaired in C57BL/6-IL-1α-deficient mice and -IL-1α/β double-deficient mice, but developed normally in C57BL/6-IL-1β-deficient mice (Table 4). Likewise, BALB/c-IL-1α-, but not BALB/c-IL-1β-, deficient mice showed reduced CHS induced by TNCB (Table 4). However, in contrast to the phenotypes of C57BL/6-IL-1α-deficient mice and -IL-1α/β double-deficient mice, the impaired CHS induced by TNCB in BALB/c-IL-1α/β double-deficient mice was much
more severe than that in BALB/c-IL-1α-deficient mice.85 Although the reason for the discrepancy between the study using mice treated with anti-IL-1 mAb and IL-1-deficient mice is unknown, the differences between C57BL/6 and BALB/c-IL-1α-deficient mice may be explained by their genetic backgrounds. In support of this, chronic CHS induced by repeated challenge with DNFB was reduced in IL-4-deficient mice on the BALB/c, but not C57BL/6, background.91

Anti-CD3 mAb-mediated T cell proliferation was enhanced in the presence of LCs obtained from IL-1β-injected skin, but not PBS- or IL-1α-injected skin, of mice.86 It is thought that the main source of IL-1α is keratinocytes, rather than LCs, while that of IL-1β is LCs, rather than keratinocytes.74,92,94 These observations suggest that IL-1β, which is produced by LCs and enhances antigen-presentation by LCs, may be more important than IL-1α for hapten-specific T cell activation in the sensitization phase of CHS. However, IL-1β is not essential for the process: hapten-specific T cells developed normally in IL-1β-deficient mice after epicutaneous sensitization with TNCB.85 On the other hand, IL-1α, which is produced by the MHC class II⁺ CD11c⁺ DC population including LCs and dermal DCs migrated from the skin to draining LNs, is crucial for hapten-specific T-cell development.85 Therefore, IL-1α, rather than IL-1β, is important for induction of hapten-specific T cells, especially IL-17-producing Th17 cells, in the sensitization phase of CHS.88,85 In addition, in the elicitation phase of CHS, IL-1 is required for induction of TNF in local lesions. Then the IL-1-induced TNF induces local inflammation by inducing expression of CXCL10 independently of IFN-γ,68 resulting in infiltration of Th17 cells which express CXCR3 (the receptor of CXCL10) as well as Th1 cells.8 Therefore, IL-1, especially IL-1α, is crucial for induction and activation of hapten-specific Th17 cells in the sensitization phase, and for induction of Th17 cell-mediated local inflammation in the elicitation phase of CHS.

IL-1 IN ATOPIC DERMATITIS

Some studies found that the levels of IL-1 and caspase-1 mRNA produced by monocytes from patients with atopic dermatitis (AD) were lower than those from healthy subjects,95-98 while others found the reverse.99 After epicutaneous application of ragweed or house dust mite antigens, IL-1β mRNA protein expression was upregulated in the skin of AD patients, but not healthy subjects.100,101 Intradermal injection of rIL-1α induced mononuclear cell and neutrophil accumulation in the skin of normal volunteers.102 In addition, keratinocyte-specific IL-4-overexpressing Tg mice, which spontaneously develop skin inflammation resembling human AD, showed increased IL-1β mRNA expression in local inflamed lesions.103,104 These observations suggest that IL-1 may be involved in the development of AD. In support of this, mice overexpressing IL-1α and IL-1R1 under the K14 promoter spontaneously developed AD-like skin inflammation.105,106 Moreover, keratinocyte-specific IL-18- and caspase-1-overexpressing Tg mice also spontaneously developed AD-like dermatitis independently of IgE and STAT-6.29,107 IL-1α/β double-deficiency resulted in attenuated skin inflammation in both IL-18 and caspase-1 Tg mice, suggesting that IL-1α and/or IL-1β is involved in the development of IgE-independent dermatitis.107

IL-1 IN ASTHMA

Alveolar macrophages produce IL-1 in response to stimuli such as silica and LPS,108,109 and IL-1 induces proinflammatory mediators such as TNF, IL-6 or IL-8 and adhesion molecules in airway smooth muscle cells, epithelial cells and endothelial cells. In addition, IL-1 can augment IgE-mediated mast cell activation, such as Th2 cytokine secretion,110-115 suggesting involvement of IL-1 in the development of IgE-mediated allergic diseases such as allergic asthma. Polymorphism in the IL-1α, IL-1β and IL-1Ra genes/promoter in patients with allergic asthma may be associated with susceptibility to the disease.116-119 Serum IL-1β is increased in atopic asthmatics in comparison with non-atopic asthmatics and patients with chronic obstructive pulmonary disease (COPD).120 In addition, IL-1β and/or IL-1Ra expression was increased in the bronchial epithelium and macrophages of patients with asthma.121 Inhalation of rIL-1α or rIL-1β resulted in enhanced vascular permeability of the trachea122 and airway neutrophilia.123 IL-1β inhibited acetylcholine-induced bronchoconstriction,124 but enhanced bradykinin-induced bronchoconstriction.125 Treatment with rIL-1Ra reduced airway hyperresponsiveness and eosinophilia in guinea pigs during A. carinii antigen-induced airway inflammation.126

Allergic airway inflammation induced by ovalbumin in rodents is extensively used as a rodent model of human atopic asthma.127 However, the responses are differentially induced by the experimental protocols and mouse backgrounds.127,128 In mice sensitized with OVA emulsified in aluminum hydroxide (alum), airway inflammation developed independently of mast cells, B cells and IgE.69 On the other hand, these cells and IgE are required for the development of airway inflammation in mice sensitized with OVA in the absence of alum.69 Airway inflammation induced by OVA sensitization with alum (the mast cell and IgE-independent responses) developed normally in BALB/c-IL-1R1-deficient mice129 and IL-1α/β double-deficient mice,5 but was impaired in 129 x B6-IL-1R1-deficient mice.130 The different phenotypes between the BALB/c and 129 x B6 strain-IL-1R1-deficient mice may be due to the different genetic backgrounds of the mice, as described above. Indeed, the BALB/c mouse strain is much more sensi-
tive to OVA-induced airway hypersensitivity than the C57BL/6 and 129 mouse strains. On the other hand, airway hypersensitivity induced by OVA-alone sensitization without alum (the mast cell- and IgE-dependent responses) was attenuated in BALB/c-IL-1R1-deficient mice and -IL-1α/β double-deficient mice, and exacerbated in BALB/c-IL-1Ra-deficient mice. Both IL-1α and IL-1β are required for OVA-specific T cell expansion, OVA-specific IgE production and induction of eosinophilic airway inflammation.

As described above, administration of rIL-1 resulted in local inflammation associated with neutrophils, suggesting that IL-1 contributes to induction of neutrophil, rather than eosinophil, associated airway inflammation, such as non-Th2 type asthma and/or COPD. Indeed, excessive expression of IL-1β in lungs of mice and/or rats resulted in spontaneous pulmonary inflammation accompanied by neutrophil and macrophage recruitment, mucous cell metaplasia and airway fibrosis. On the other hand, IL-1α-mediated airway neutrophilia was reduced in lung-specific IL-1Ra-overexpressing Tg mice. Ozone exposure induces airway neutrophilia and structural damage, such as to epithelial cells, in the lungs, and administration of rIL-1Ra attenuated the development of ozone-mediated airway inflammation. Airway inflammation induced in rats by chemicals such as toluene diisocyanate (TDI), hezemethylene isocyanate or DNFB is characterized by infiltration of neutrophils into the airways and is considered to be a rodent model resembling human occupational asthma. Mice deficient in IL-1R1 and treated with anti-IL-1α and/or anti-IL-1β Ab showed reduced airway inflammation induced by TDI. In addition, DO11.10 and OTII mice, which express OVA-specific T cell receptors, developed Th17 cell-mediated airway neutrophilia after intranasal OVA treatment without prior OVA sensitization. Induction of Th17 cell-mediated airway neutrophilia was attenuated in IL-1R1-deficient mice on the OTII background after OVA inhalation. These observations suggest that IL-1 may be important for the development of non-Th2 type asthma and/or COPD.

IL-1 IN FOOD ALLERGY, ALLERGIC RHINITIS AND CONJUNCTIVITIS

Since IL-1 can enhance mast cell cytokine secretion, as described above, and histamine release, IL-1 may be involved in induction of food allergy. Administration of rIL-1Ra to guinea pigs resulted in reduced IgE production and anaphylaxis induced by cow’s milk. A genome-wide association study suggested that polymorphism in the IL-1α, IL-1β and IL-1Ra genes of patients with allergic rhinitis is associated with susceptibility to the disease. IL-1α and IL-1β, which are produced by nasal epithelial cells, were increased in nasal lavage fluids from patients with allergic rhinitis after allergen challenge. Development of allergic rhinitis induced by TDI was reduced in guinea pigs treated with rIL-1Ra.

IL-1 can enhance production of vascular endothelial growth factor (VEGF), which is involved in angiogenesis by enhancing the growth of vascular endothelial cells, by human conjunctival fibroblasts, and treatment of mice with rIL-1Ra resulted in reduced inflammation during allergen-induced conjunctivitis.

These observations suggest a contribution of IL-1 to the pathogenesis of food allergy, allergic rhinitis and conjunctivitis, but the precise role(s) of IL-1 in the development of these allergic diseases has not yet been investigated using IL-1-related gene-deficient mice.

CONCLUSIONS

Although IL-1 is a well-characterized proinflammatory cytokine in infections and autoimmune diseases, the precise roles of IL-1α and IL-1β, i.e., redundant or distinct roles, in the pathogenesis of certain allergic disorders are not fully understood. The use of IL-1-related gene-deficient mice has great potential for increasing our understanding of the molecular mechanisms of IL-1 in disease processes.

ACKNOWLEDGEMENTS

This work was supported by the Program for Improvement of Research Environment for Young Researchers, The Special Coordination Funds for Promoting Science and Technology, the MEXT, Japan (S.N.).

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