

IL-1 and Allergy

Aya Nambu^{1,2} and Susumu Nakae^{1,2}

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-1 α and/or IL-1 β 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-1 α and IL-1 β can enhance IL-12-dependent IFN- γ production by Th1 cells,⁶⁻⁸ and IL-1 α 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-1 α , IL-1 β , 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-1 α and IL-1 β), one antagonist (IL-1Ra) and two receptors (IL-1R1 and IL-1R2) (Fig. 1). IL-1 α and IL-1 β are products of distinct genes and were initially synthesized as 31 kDa precursors (pro-IL-1 α and pro-IL-1 β).^{1,2,17} Processing of pro-IL-1 α and pro-IL-1 β to their mature 17 kDa forms is required for cleavage by calpain and caspase-1, respectively.^{1,2,17} In addition to mature IL-1 α and IL-1 β , pro-IL-1 α but not pro-IL-1 β , has biological activity.^{1,2,17} Despite approximately 25% identity of amino acid sequences between IL-1 α and IL-1 β , they bind to the same receptors, such as IL-1R1 and IL-1R2, with different affinities: IL-1 α has stronger binding affinity for IL-1Rs than IL-1 β .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-1 α and IL-1 β , 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-1 α and IL-1 β .^{2,17}

To elucidate the functional roles of IL-1 *in vivo*, mice deficient in IL-1 α ,¹⁸ IL-1 β ,¹⁸⁻²⁰ both IL-1 α and IL-

¹Atopy Research Center, Juntendo University and ²Frontier Research Initiative, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan.

Correspondence: Susumu Nakae, PhD, Frontier Research Initiative, The Institute of Medical Science, The University of Tokyo, 4-

6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan.

Email: snakae@ims.u-tokyo.ac.jp

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Table 1 IL-1 and IL-1R family

(A) Receptors				
systematic name	protein name	other name	form [†]	ligands
R1	IL-1RI	CD121a	M	F1, F2, F3
R2	IL-1RII	CD121b	M, S	F1, F2, F3
R3	IL-1Rap	IL-1RAcP	M, S	
R4	IL-1RL-1	ST2, T1, Ly84, Fit-1	M, S	F11
R5	IL-18RI	IL-1Rrp, IL-18R α , CD218a	M	F4, F7
R6	IL-1RL2	IL-1Rrp2	M	F5, F6, F8, F9
R7	IL-18Rap	IL-18R β , IL18RAcP, CD218b	M	
R8	IL-1RAPL1	TIGIRR-2	M	?
R9	IL-1RAPL2	TIGIRR-2	M	?
R10	Tir8	SIGIRR	M	F11

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

(B) Ligands			
systematic name	protein name	other name	receptors
F1	IL-1 α	LAF	R1/R3, R2/R3
F2	IL-1 β	LAF	R1/R3, R2/R3
F3	IL-1Ra	-	R1, R2
F4	IL-18	IGIF, IL-1 γ	R5/R7
F5	IL-1F5	IL-1Hy1, IL-1H3, FIL1 δ , IL-1L1, IL-1 δ , IL-1RP3	R6
F6	IL-1F6	FIL1 ϵ	R6/R3
F7	IL-1F7	FIL1 ζ , IL-1H4, IL-1RP1, IL-1H1	R5/R7
F8	IL-1F8	FIL1 η , IL-1H2	R6/R3
F9	IL-1F9	IL-1H1, IL-1RP2, IL-1 ϵ	R6/R3
F10	IL-1F10	IL-1Hy2, FKSG75	?
F11	IL-33	NF-HEV, DVS27	R4/R3, R10/R3

1 β ,¹⁸ IL-1Ra,^{18,21-23} IL-1R1^{24,25} 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-1 β and pro-IL-18. Caspase-1-deficient mice^{27,28} and overexpressing transgenic (Tg) mice²⁹ show reduced or increased levels of mature IL-1 β 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.³⁰ 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.³⁰ In particular, it has been thought that the development of DTH is predominantly mediated by IFN- γ -producing Th1 cells.³⁰ 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,³¹ and mice treated with anti-IFN- γ neutralizing antibodies (Abs) show reduced DTH responses to chicken RBCs and KLH.³² DTH responses during herpes simplex virus type-1 (HSV-1) infection were reduced in IFN- γ and IFN- γ R1-deficient mice,^{33,34} while DTH responses against *Mycobacterium tuberculosis* developed normally in IFN- γ -deficient mice.³⁵ Moreover, IFN- γ -deficient mice showed attenuated KLH-induced DTH^{36,37} but exacerbated OVA- and mBSA-induced DTH.^{38,39} 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 decreased in IL-4-, IL-5- and STAT6-deficient mice, but not in IL-13-deficient mice.³⁶ In terms of Th17-related molecules, IL-17- and IL-23-deficient mice, but not IL-17F-deficient mice, showed reduced mBSA-induced DTH.⁴⁰⁻⁴² DTH responses to *Mycobacterium bovis* BCG were also impaired in IL-

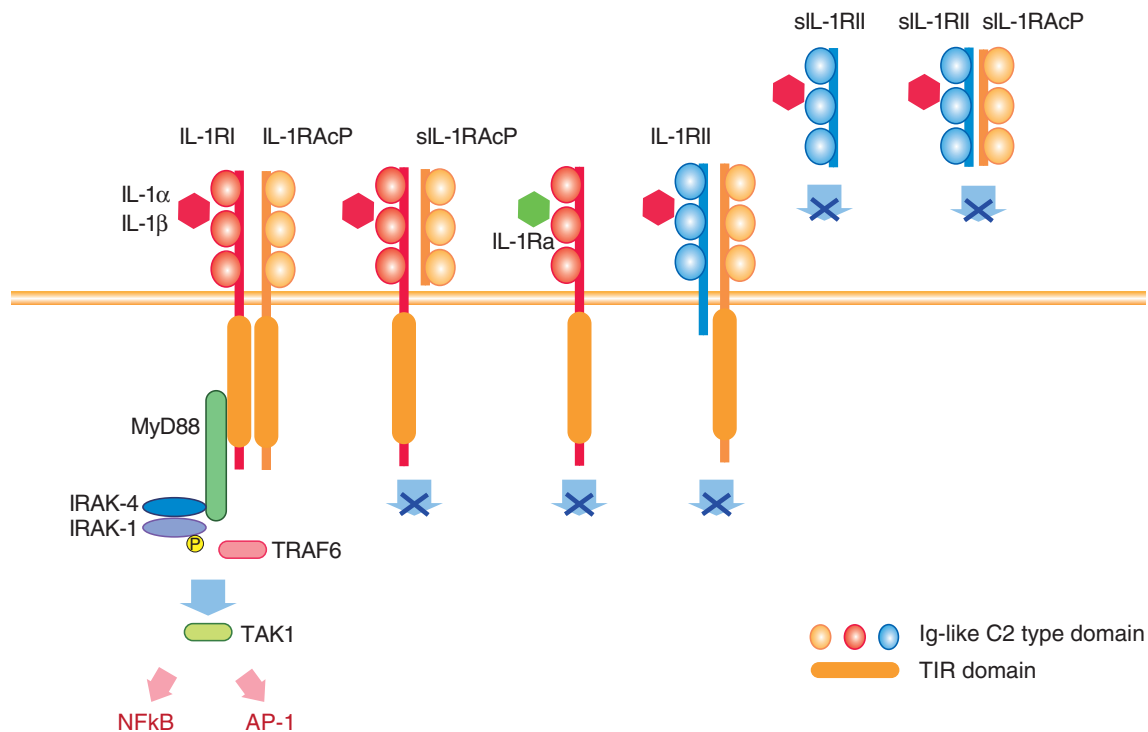


Fig. 1 IL-1 and IL-1R system.

Table 2 Role of IL-1 in DTH responses

Mice treatment with:	Mouse strain	Antigen	DTH	References
rIL-1α	C3H/He	<i>Listeria monocytogenes</i>	exacerbated	48
anti-IL-1 Ab	BALB/c	HSV-1	ameliorated	49
Mice-deficient in:	Mouse strain	Antigen	DTH	References
IL-1β	129 x B6	mBSA	normally developed	19
IL-1R1	129 x B6	mBSA	normally developed	24
IL-1R1	C57BL/6 & BALB/c	mBSA	ameliorated	50
IL-1α	C57BL/6 & BALB/c	mBSA	normally developed	50
IL-1β	C57BL/6 & BALB/c	mBSA	ameliorated	50
IL-1α/β	C57BL/6 & BALB/c	mBSA	ameliorated	50
IL-1Ra	C57BL/6	mBSA	exacerbated	50

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

17-deficient mice.⁴³

Accumulation of IL-1α- or IL-1β-producing macrophages/monocytes was observed in local inflamed skin lesions of tuberculin-induced DTH in humans⁴⁴ and rabbits.⁴⁵ The levels of serum IL-1Ra, but not soluble IL-1R2, were elevated in patients with tuberculosis.⁴⁶ It was suggested that polymorphism of the IL-1Ra gene may be involved in the development of DTH and disease expression in human tuberculosis.⁴⁷ 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).⁴⁸ In addition, administration of anti-IL-1α Abs ameliorated DTH responses to HSV-1 in BALB/c mice (Table 2).⁴⁹ 129 x B6-IL-1β-deficient mice normally developed mBSA-induced DTH reactions,¹⁹ whereas 129 x B6-IL-1R1-deficient mice failed to respond (Table 2).²⁴ 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,²⁴ the development of mBSA-induced DTH was similarly reduced in IL-1R1-deficient and IL-1α/β

double-deficient mice on the C57BL/6 and BALB/c backgrounds (Table 2).⁵⁰ In contrast to the phenotypes seen in 129 x B6-IL-1 β -deficient mice,¹⁹ development of mBSA-induced DTH was significantly impaired in C57BL/6- and BALB/c-IL-1 β -deficient mice as in IL-1R1- and IL-1 α/β double-deficient mice, whereas it was normal in C57BL/6- and BALB/c-IL-1 α -deficient mice (Table 2).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.⁵¹⁻⁵³ However, 129 mice are less well characterized than C57BL/6 and BALB/c mice and are known to show abnormal immunology⁵⁴ and behavior.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.^{56,57} For example, the contributions of osteopontin,^{58,59} apolipoprotein E⁶⁰ and neurokinin-1 receptor⁶¹ 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-1 β -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).⁵⁰ The aggravated responses seen in C57BL/6-IL-1Ra-deficient mice were attenuated to the wild-type mouse levels, but not the IL-1 α/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-1.⁵⁰ During mBSA-induced DTH in C57BL/6 mice, IL-1 β , but not IL-1 α , 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 haptens, 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.^{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.^{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.³⁰

CHS has been considered to be a typical allergic disease mediated by IFN- γ -producing Th1 cells and Tc1 cells.^{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- γ R1-deficient mice,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.⁷⁰⁻⁷³ Moreover, CHS induced by TNCB, DNFB and FITC was also decreased in IL-17-deficient mice.⁴⁰ These observations suggest that Th2 and Th17, rather than Th1, cytokines/cells are crucial for induction of CHS.

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

In spite of the importance of IL-1 β for LC migration after oxazolone sensitization,⁸³ oxazolone-induced CHS developed normally in IL-1 β -deficient mice¹⁹ as well as mice treated with rIL-1Ra⁸⁸ and keratinocyte-specific IL-1R2-overexpressing Tg mice (Table 4).⁸⁹ When IL-1 β -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-1 β -deficient mice on the 129 x B6 mixed back-

Table 3 Role of IL-1 in skin DC release/migration

Mice treatment with:	Mouse strain	Specimen	Sensitizer	LC release/migration	References
rIL-1 α	C57BL/6	epidermal sheet	N/A	no effect	81
rIL-1 β	BALB/c	epidermal sheet	N/A	enhanced	82
		draining LN	N/A	enhanced	
rIL-1 β	BALB/c	draining LN	Ox	enhanced	82
anti-IL-1 α				no effect	
anti-IL-1 β				reduced	
rIL-1 α	BALB/c	epidermal sheet	N/A	enhanced	83
rIL-1 β				enhanced	
anti-IL-1 α	BALB/c	epidermal sheet	Ox	no effect	83
anti-IL-1 β				reduced	
anti-IL-1 α	BALB/c	epidermal sheet	SLS	reduced	83
anti-IL-1 β		draining LN	(irritant)	no effect	
rIL-1Ra	C57BL/10 IL-10-deficient	draining LN	FITC	reduced	84
Mice-deficient in:	Mouse strain	Specimen	Sensitizer	LC release/migration	References
IL-1 α	C57BL/6	draining LN	FITC	reduced	85
IL-1 β				reduced	
IL-1 α/β				reduced	
IL-1 β	129 x B6	Draining LN	FITC	reduced	86

DC, dendritic cell; LC, Langerhans cell; LN, lymph node; Ox, oxazolone; SLS, Sodium lauryl sulfate.

Table 4 Role of IL-1 in CHS responses

Mice treatment with:	Mouse strain	Hapten	CHS	References
rIL-1Ra	CD1	Ox	normally developed	88
rIL-1Ra	BALB/c	DNFB	attenuated	90
anti-IL-1 α	BALB/c	TNCB	normally developed	80
anti-IL-1 β			attenuated	
Mice-deficient in:	Mouse strain	Hapten	CHS	References
IL-1 β	129 x B6	Ox	normally developed	19
IL-1 β	129 x B6	TNCB (high dose)	normally developed [†]	20
		TNCB (low dose)	attenuated [†]	
IL-1 α	C57BL/6 & BALB/c	TNCB	attenuated	85
IL-1 β		(low & high dose)	normally developed	
IL-1 α/β			attenuated	
Transgenic mouse	Mouse strain	Hapten	CHS	References
IL-1R2 Tg	FVB/N	Ox	normally developed	89

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-1 β 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-1 β in the induction of CHS was unclear.²⁰

Administration of anti-IL-1 β mAb or rIL-1Ra, but not anti-IL-1 α mAb, to BALB/c mice attenuated CHS induced by TNCB or DNFB (Table 4).^{80,90} On the

contrary, development of TNCB-induced CHS was similarly impaired in C57BL/6-IL-1 α -deficient mice and -IL-1 α/β double-deficient mice, but developed normally in C57BL/6-IL-1 β -deficient mice (Table 4).⁸⁵ Likewise, BALB/c-IL-1 α -, but not BALB/c-IL-1 β -, deficient mice showed reduced CHS induced by TNCB (Table 4). However, in contrast to the phenotypes of C57BL/6-IL-1 α -deficient mice and -IL-1 α/β double-deficient mice, the impaired CHS induced by TNCB in BALB/c-IL-1 α/β double-deficient mice was much

more severe than that in BALB/c-IL-1 α -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-1 α -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-1 β -injected skin, but not PBS- or IL-1 α -injected skin, of mice.⁸⁰ It is thought that the main source of IL-1 α is keratinocytes, rather than LCs, while that of IL-1 β is LCs, rather than keratinocytes.^{74,92-94} These observations suggest that IL-1 β , which is produced by LCs and enhances antigen-presentation by LCs, may be more important than IL-1 α for hapten-specific T cell activation in the sensitization phase of CHS. However, IL-1 β is not essential for the process: hapten-specific T cells developed normally in IL-1 β -deficient mice after epicutaneous sensitization with TNCB.⁸⁵ On the other hand, IL-1 α , which is produced by the MHC class II^{hi} 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-1 α , rather than IL-1 β , is important for induction of hapten-specific T cells, especially IL-17-producing Th17 cells, in the sensitization phase of CHS.^{68,85} 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-1 α , 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-1 β mRNA/protein expression was upregulated in the skin of AD patients, but not healthy subjects.^{100,101} Intradermal injection of rIL-1 α induced mononuclear cell and neutrophil accumulation in the skin of normal human volunteers.¹⁰² In addition, keratinocyte-specific IL-4-overexpressing Tg mice, which spontaneously develop skin inflammation resembling human AD, showed increased IL-1 β 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-1 α 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-1 α / β double-deficiency resulted in attenuated skin inflammation in both IL-18 and caspase-1 Tg mice, suggesting that IL-1 α and/or IL-1 β 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-1 α , IL-1 β and IL-1Ra genes/promoter in patients with allergic asthma may be associated with susceptibility to the disease.¹¹⁶⁻¹¹⁹ Serum IL-1 β is increased in atopic asthmatics in comparison with non-atopic asthmatics and patients with chronic obstructive pulmonary disease (COPD).¹²⁰ In addition, IL-1 β and/or IL-1Ra expression was increased in the bronchial epithelium and macrophages of patients with asthma.¹²¹ Inhalation of rIL-1 α or rIL-1 β resulted in enhanced vascular permeability of the trachea¹²² and airway neutrophilia.¹²³ IL-1 β inhibited acetylcholine-induced bronchoconstriction,¹²⁴ but enhanced bradykinin-induced bronchoconstriction.¹²⁵ Treatment with rIL-1Ra reduced airway hyperresponsiveness and eosinophilia in guinea pigs during Ascaris 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-1 α / 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.¹³¹ 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 mice¹²⁹ and -IL-1 α / β double-deficient mice,⁵ and exacerbated in BALB/c-IL-1Ra-deficient mice.⁵ Both IL-1 α and IL-1 β are required for OVA-specific T cell expansion, OVA-specific IgE production and induction of eosinophilic airway inflammation.⁵

As described above, administration of rIL-1 resulted in local inflammation associated with neutrophils,^{102,123} 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-1 β in lungs of mice and/or rats resulted in spontaneous pulmonary inflammation accompanied by neutrophil and macrophage recruitment, mucous cell metaplasia and airway fibrosis.^{132,133} On the other hand, IL-1 α -mediated airway neutrophilia was reduced in lung-specific IL-1Ra-overexpressing Tg mice.¹²³ 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.¹³⁴ Airway inflammation induced in rats by chemicals such as toluene diisocyanate (TDI), hexamethylene isocyanate or DNFB is characterized by infiltration of neutrophils into the airways and is considered to be a rodent model resembling human occupational asthma.⁶⁹ Mice deficient in IL-1R1 and treated with anti-IL-1 α and/or anti-IL-1 β Ab showed reduced airway inflammation induced by TDI.¹³⁵ 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.^{40,136} Induction of Th17 cell-mediated airway neutrophilia was attenuated in IL-1R1-deficient mice on the OTII background after OVA inhalation.¹³⁶ 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,¹³⁷ 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.^{138,139}

A genome-wide association study suggested that polymorphism in the IL-1 α , IL-1 β and IL-1Ra genes of patients with allergic rhinitis is associated with susceptibility to the disease.¹⁴⁰ IL-1 α and IL-1 β , which are produced by nasal epithelial cells,¹⁴¹ were in-

creased in nasal lavage fluids from patients with allergic rhinitis after allergen challenge.^{142,143} Development of allergic rhinitis induced by TDI was reduced in guinea pigs treated with rIL-1Ra.¹⁴⁴

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,¹⁴⁵ and treatment of mice with rIL-1Ra resulted in reduced inflammation during allergen-induced conjunctivitis.¹⁴⁶

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-1 α and IL-1 β , 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.

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REFERENCES

1. Dinarello CA. Interleukin-1 and interleukin-1 antagonism. *Blood* 1991;**77**:1627-52.
2. Dinarello CA. Biologic basis for interleukin-1 in disease. *Blood* 1996;**87**:2095-147.
3. Nakae S, Asano M, Horai R, Sakaguchi N, Iwakura Y. IL-1 enhances T cell-dependent antibody production through induction of CD40 ligand and OX40 on T cells. *J Immunol* 2001;**167**:90-7.
4. Nakae S, Asano M, Horai R, Iwakura Y. Interleukin-1b, but not interleukin-1a, is required for T-cell-dependent antibody production. *Immunology* 2001;**104**:402-9.
5. Nakae S, Komiyama Y, Yokoyama H *et al.* IL-1 is required for allergen-specific Th2 cell activation and the development of airway hypersensitivity response. *Int Immunol* 2003;**15**:483-90.
6. Shibuya K, Robinson D, Zonin F *et al.* IL-1a and TNF-a are required for IL-12-induced development of Th1 cells producing high levels of IFN-g in BALB/c but not C57BL/6 mice. *J Immunol* 1998;**160**:1708-16.
7. Von Stebut E, Ehrchen JM, Belkaid Y *et al.* Interleukin-1a promotes Th1 differentiation and inhibits disease progression in Leishmania major-susceptible BALB/c mice. *J Exp Med* 2003;**198**:191-9.
8. Nakae S, Iwakura Y, Suto H, Galli SJ. Phenotypic differences between Th1 and Th17 cells and negative regulation of Th1 cell differentiation by IL-17. *J Leukoc Biol*

- 2007;**81**:1258-68.
9. Werman A, Werman-Venkert R, White R *et al.* The precursor form of IL-1a is an intracrine proinflammatory activator of transcription. *Proc Natl Acad Sci U S A* 2004;**101**: 2434-9.
 10. Kurt-Jones EA, Hamberg S, Ohara J, Paul WE, Abbas AK. Heterogeneity of helper/inducer T lymphocytes. I. Lymphokine production and lymphokine responsiveness. *J Exp Med* 1987;**166**:1774-87.
 11. Manetti R, Barak V, Piccinni MP *et al.* Interleukin-1 favours the in vitro development of type 2 T helper (Th2) human T-cell clones. *Res Immunol* 1994;**145**:93-100.
 12. Huber M, Beuscher HU, Rohwer P, Kurrle R, Rollinghoff M, Lohoff M. Costimulation via TCR and IL-1 receptor reveals a novel IL-1a-mediated autocrine pathway of Th2 cell proliferation. *J Immunol* 1998;**160**:4242-7.
 13. Ben-Sasson SZ, Hu-Li J, Quiel J *et al.* IL-1 acts directly on CD4 T cells to enhance their antigen-driven expansion and differentiation. *Proc Natl Acad Sci U S A* 2009;**106**: 7119-24.
 14. Iwakura Y, Nakae S, Saijo S, Ishigame H. The roles of IL-17A in inflammatory immune responses and host defense against pathogens. *Immunol Rev* 2008;**226**:57-79.
 15. O'Neill LA. The interleukin-1 receptor/Toll-like receptor superfamily: 10 years of progress. *Immunol Rev* 2008;**226**:10-8.
 16. Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol* 2009;**27**: 519-50.
 17. Arend WP, Palmer G, Gabay C. IL-1, IL-18, and IL-33 families of cytokines. *Immunol Rev* 2008;**223**:20-38.
 18. Horai R, Asano M, Sudo K *et al.* Production of mice deficient in genes for interleukin (IL)-1a, IL-1b, IL-1a/b, and IL-1 receptor antagonist shows that IL-1b is crucial in turpentine-induced fever development and glucocorticoid secretion. *J Exp Med* 1998;**187**:1463-75.
 19. Zheng H, Fletcher D, Kozak W *et al.* Resistance to fever induction and impaired acute-phase response in interleukin-1b-deficient mice. *Immunity* 1995;**3**:9-19.
 20. Shornick LP, De Togni P, Mariathasan S *et al.* Mice deficient in IL-1b manifest impaired contact hypersensitivity to trinitrochlorobenzene. *J Exp Med* 1996;**183**:1427-36.
 21. Hirsch E, Irikura VM, Paul SM, Hirsh D. Functions of interleukin 1 receptor antagonist in gene knockout and overproducing mice. *Proc Natl Acad Sci U S A* 1996;**93**: 11008-13.
 22. Nicklin MJ, Hughes DE, Barton JL, Ure JM, Duff GW. Arterial inflammation in mice lacking the interleukin 1 receptor antagonist gene. *J Exp Med* 2000;**191**:303-12.
 23. Iizasa H, Yoneyama H, Mukaida N *et al.* Exacerbation of granuloma formation in IL-1 receptor antagonist-deficient mice with impaired dendritic cell maturation associated with Th2 cytokine production. *J Immunol* 2005;**174**:3273-80.
 24. Labow M, Shuster D, Zetterstrom M *et al.* Absence of IL-1 signaling and reduced inflammatory response in IL-1 type I receptor-deficient mice. *J Immunol* 1997;**159**:2452-61.
 25. Glaccum MB, Stocking KL, Charrier K *et al.* Phenotypic and functional characterization of mice that lack the type I receptor for IL-1. *J Immunol* 1997;**159**:3364-71.
 26. Cullinan EB, Kwee L, Nunes P *et al.* IL-1 receptor accessory protein is an essential component of the IL-1 receptor. *J Immunol* 1998;**161**:5614-20.
 27. Li P, Allen H, Banerjee S *et al.* Mice deficient in IL-1b-converting enzyme are defective in production of mature IL-1b and resistant to endotoxic shock. *Cell* 1995;**80**:401-11.
 28. Kuida K, Lippke JA, Ku G *et al.* Altered cytokine export and apoptosis in mice deficient in interleukin-1 beta converting enzyme. *Science* 1995;**267**:2000-3.
 29. Yamanaka K, Tanaka M, Tsutsui H *et al.* Skin-specific caspase-1-transgenic mice show cutaneous apoptosis and pre-endotoxin shock condition with a high serum level of IL-18. *J Immunol* 2000;**165**:997-1003.
 30. Grabbe S, Schwarz T. Immunoregulatory mechanisms involved in elicitation of allergic contact hypersensitivity. *Immunol Today* 1998;**19**:37-44.
 31. Cher DJ, Mosmann TR. Two types of murine helper T cell clone. II. Delayed-type hypersensitivity is mediated by TH1 clones. *J Immunol* 1987;**138**:3688-94.
 32. Fong TA, Mosmann TR. The role of IFN-g in delayed-type hypersensitivity mediated by Th1 clones. *J Immunol* 1989;**143**:2887-93.
 33. Bouley DM, Kanangat S, Wire W, Rouse BT. Characterization of herpes simplex virus type-1 infection and herpetic stromal keratitis development in IFN-gamma knockout mice. *J Immunol* 1995;**155**:3964-71.
 34. Molesworth-Kenyon SJ, Oakes JE, Lausch RN. A novel role for neutrophils as a source of T cell-recruiting chemokines IP-10 and Mig during the DTH response to HSV-1 antigen. *J Leukoc Biol* 2005;**77**:552-9.
 35. Cooper AM, Dalton DK, Stewart TA, Griffin JP, Russell DG, Orme IM. Disseminated tuberculosis in interferon g gene-disrupted mice. *J Exp Med* 1993;**178**:2243-7.
 36. Akahira-Azuma M, Szczepanik M, Tsuji RF *et al.* Early delayed-type hypersensitivity eosinophil infiltrates depend on T helper 2 cytokines and interferon-g via CXCR3 chemokines. *Immunology* 2004;**111**:306-17.
 37. Gao D, Kasten-Jolly J, Lawrence DA. The paradoxical effects of lead in interferon-g knockout BALB/c mice. *Toxicol Sci* 2006;**89**:444-53.
 38. Feuerer M, Eulenburg K, Loddenkemper C, Hamann A, Huehn J. Self-limitation of Th1-mediated inflammation by IFN-g. *J Immunol* 2006;**176**:2857-63.
 39. Irmeler IM, Gajda M, Brauer R. Exacerbation of antigen-induced arthritis in IFN-g-deficient mice as a result of unrestricted IL-17 response. *J Immunol* 2007;**179**:6228-36.
 40. Nakae S, Komiyama Y, Nambu A *et al.* Antigen-specific T cell sensitization is impaired in IL-17-deficient mice, causing suppression of allergic cellular and humoral responses. *Immunity* 2002;**17**:375-87.
 41. Ghilardi N, Kljavin N, Chen Q, Lucas S, Gurney AL, De Sauvage FJ. Compromised humoral and delayed-type hypersensitivity responses in IL-23-deficient mice. *J Immunol* 2004;**172**:2827-33.
 42. Ishigame H, Kakuta S, Nagai T *et al.* Differential roles of interleukin-17A and -17F in host defense against mucocutaneous bacterial infection and allergic responses. *Immunity* 2009;**30**:108-19.
 43. Umemura M, Yahagi A, Hamada S *et al.* IL-17-mediated regulation of innate and acquired immune response against pulmonary Mycobacterium bovis bacille Calmette-Guerin infection. *J Immunol* 2007;**178**:3786-96.
 44. Chu CQ, Field M, Andrew E, Haskard D, Feldmann M, Maini RN. Detection of cytokines at the site of tuberculin-induced delayed-type hypersensitivity in man. *Clin Exp Immunol* 1992;**90**:522-9.
 45. Sugisaki K, Dannenberg AM Jr, Abe Y *et al.* Nonspecific and immune-specific up-regulation of cytokines in rabbit dermal tuberculous (BCG) lesions. *J Leukoc Biol* 1998;**63**: 440-50.
 46. Juffermans NP, Verbon A, van Deventer SJ, van Deute-

- kom H, Speelman P, van der Poll T. Tumor necrosis factor and interleukin-1 inhibitors as markers of disease activity of tuberculosis. *Am J Respir Crit Care Med* 1998; **157**:1328-31.
47. Wilkinson RJ, Patel P, Llewelyn M *et al*. Influence of polymorphism in the genes for the interleukin (IL)-1 receptor antagonist and IL-1b on tuberculosis. *J Exp Med* 1999; **189**:1863-74.
48. Igarashi K, Mitsuyama M, Muramori K, Tsukada H, Nomoto K. Interleukin-1-induced promotion of T-cell differentiation in mice immunized with killed *Listeria monocytogenes*. *Infect Immun* 1990; **58**:3973-9.
49. Tumpey TM, Fenton R, Molesworth-Kenyon S, Oakes JE, Lausch RN. Role for macrophage inflammatory protein 2 (MIP-2), MIP-1a, and interleukin-1a in the delayed-type hypersensitivity response to viral antigen. *J Virol* 2002; **76**: 8050-7.
50. Nambu A, Nakae S, Iwakura Y. IL-1b, but not IL-1a, is required for antigen-specific T cell activation and the induction of local inflammation in the delayed-type hypersensitivity responses. *Int Immunol* 2006; **18**:701-12.
51. Brook FA, Gardner RL. The origin and efficient derivation of embryonic stem cells in the mouse. *Proc Natl Acad Sci U S A* 1997; **94**:5709-12.
52. Auerbach W, Dunmore JH, Fairchild-Huntress V *et al*. Establishment and chimera analysis of 129/SvEv- and C57BL/6-derived mouse embryonic stem cell lines. *Biotechniques* 2000; **29**:1024-8, 1030, 1032.
53. Ware CB, Siverts LA, Nelson AM, Morton JF, Ladiges WC. Utility of a C57BL/6 ES line versus 129 ES lines for targeted mutations in mice. *Transgenic Res* 2003; **12**:743-6.
54. McVicar DW, Winkler-Pickett R, Taylor LS *et al*. Aberrant DAP12 signaling in the 129 strain of mice: implications for the analysis of gene-targeted mice. *J Immunol* 2002; **169**: 1721-8.
55. Crawley JN, Belknap JK, Collins A *et al*. Behavioral phenotypes of inbred mouse strains: implications and recommendations for molecular studies. *Psychopharmacology (Berl)* 1997; **132**:107-24.
56. Linder CC. The influence of genetic background on spontaneous and genetically engineered mouse models of complex diseases. *Lab Anim (NY)* 2001; **30**:34-9.
57. Carlucci F, Cortes-Hernandez J, Fossati-Jimack L *et al*. Genetic dissection of spontaneous autoimmunity driven by 129-derived chromosome 1 Loci when expressed on C57BL/6 mice. *J Immunol* 2007; **178**:2352-60.
58. Chabas D, Baranzini SE, Mitchell D *et al*. The influence of the proinflammatory cytokine, osteopontin, on autoimmune demyelinating disease. *Science* 2001; **294**:1731-5.
59. Blom T, Franzen A, Heinegard D, Holmdahl R. Comment on "The influence of the proinflammatory cytokine, osteopontin, on autoimmune demyelinating disease". *Science* 2003; **299**:1845; author reply 1845.
60. Maeda N, Johnson L, Kim S, Hagaman J, Friedman M, Reddick R. Anatomical differences and atherosclerosis in apolipoprotein E-deficient mice with 129/SvEv and C57BL/6 genetic backgrounds. *Atherosclerosis* 2007; **195**: 75-82.
61. McCutcheon JE, Fisher AS, Guzdar E, Wood SA, Lightman SL, Hunt SP. Genetic background influences the behavioural and molecular consequences of neurokinin-1 receptor knockout. *Eur J Neurosci* 2008; **27**:683-90.
62. Kimber I, Dearman RJ. Allergic contact dermatitis: the cellular effectors. *Contact Dermatitis* 2002; **46**:1-5.
63. Bour H, Peyron E, Gaucherand M *et al*. Major histocompatibility complex class I-restricted CD8+ T cells and class II-restricted CD4+ T cells, respectively, mediate and regulate contact sensitivity to dinitrofluorobenzene. *Eur J Immunol* 1995; **25**:3006-10.
64. Boulloc A, Cavani A, Katz SI. Contact hypersensitivity in MHC class II-deficient mice depends on CD8 T lymphocytes primed by immunostimulating Langerhans cells. *J Invest Dermatol* 1998; **111**:44-9.
65. Saulnier M, Huang S, Aguet M, Ryffel B. Role of interferon-g in contact hypersensitivity assessed in interferon-g receptor-deficient mice. *Toxicology* 1995; **102**: 301-12.
66. Reeve VE, Bosnic M, Nishimura N. Interferon-g is involved in photoimmunoprotection by UVA (320-400 nm) radiation in mice. *J Invest Dermatol* 1999; **112**:945-50.
67. Dhabhar FS, Satoskar AR, Bluethmann H, David JR, McEwen BS. Stress-induced enhancement of skin immune function: A role for g interferon. *Proc Natl Acad Sci U S A* 2000; **97**:2846-51.
68. Nakae S, Komiyama Y, Narumi S *et al*. IL-1-induced tumor necrosis factor-a elicits inflammatory cell infiltration in the skin by inducing IFN-g-inducible protein 10 in the elicitation phase of the contact hypersensitivity response. *Int Immunol* 2003; **15**:251-60.
69. Oboki K, Ohno T, Saito H, Nakae S. Th17 and allergy. *Allergol Int* 2008; **57**:121-34.
70. Berg DJ, Leach MW, Kuhn R *et al*. Interleukin 10 but not interleukin 4 is a natural suppressant of cutaneous inflammatory responses. *J Exp Med* 1995; **182**:99-108.
71. Traidl C, Jugert F, Krieg T, Merk H, Hunzelmann N. Inhibition of allergic contact dermatitis to DNCB but not to oxazolone in interleukin-4-deficient mice. *J Invest Dermatol* 1999; **112**:476-82.
72. Dieli F, Sireci G, Scire E, Salerno A, Bellavia A. Impaired contact hypersensitivity to trinitrochlorobenzene in interleukin-4-deficient mice. *Immunology* 1999; **98**:71-9.
73. Weigmann B, Schwing J, Huber H *et al*. Diminished contact hypersensitivity response in IL-4 deficient mice at a late phase of the elicitation reaction. *Scand J Immunol* 1997; **45**:308-14.
74. Enk AH, Katz SI. Early molecular events in the induction phase of contact sensitivity. *Proc Natl Acad Sci U S A* 1992; **89**:1398-402.
75. Bigler CF, Norris DA, Weston WL, Arend WP. Interleukin-1 receptor antagonist production by human keratinocytes. *J Invest Dermatol* 1992; **98**:38-44.
76. Rambukkana A, Pistoer FH, Bos JD, Kapsenberg ML, Das PK. Effects of contact allergens on human Langerhans cells in skin organ culture: migration, modulation of cell surface molecules, and early expression of interleukin-1b protein. *Lab Invest* 1996; **74**:422-36.
77. La E, Fischer SM. Transcriptional regulation of intracellular IL-1 receptor antagonist gene by IL-1a in primary mouse keratinocytes. *J Immunol* 2001; **166**:6149-55.
78. Kermani F, Flint MS, Hotchkiss SA. Induction and localization of cutaneous interleukin-1b mRNA during contact sensitization. *Toxicol Appl Pharmacol* 2000; **169**:231-7.
79. Jakob T, Udey MC. Regulation of E-cadherin-mediated adhesion in Langerhans cell-like dendritic cells by inflammatory mediators that mobilize Langerhans cells in vivo. *J Immunol* 1998; **160**:4067-73.
80. Enk AH, Angeloni VL, Udey MC, Katz SI. An essential role for Langerhans cell-derived IL-1b in the initiation of primary immune responses in skin. *J Immunol* 1993; **150**: 3698-704.
81. Roake JA, Rao AS, Morris PJ, Larsen CP, Hankins DF, Austyn JM. Dendritic cell loss from nonlymphoid tissues

- after systemic administration of lipopolysaccharide, tumor necrosis factor, and interleukin 1. *J Exp Med* 1995; **181**:2237-47.
82. Cumberbatch M, Dearman RJ, Kimber I. Langerhans cells require signals from both tumour necrosis factor- α and interleukin-1b for migration. *Immunology* 1997; **92**: 388-95.
 83. Cumberbatch M, Dearman RJ, Groves RW, Antonopoulos C, Kimber I. Differential regulation of epidermal langerhans cell migration by interleukins (IL)-1a and IL-1b during irritant- and allergen-induced cutaneous immune responses. *Toxicol Appl Pharmacol* 2002; **182**:126-35.
 84. Wang B, Zhuang L, Fujisawa H *et al.* Enhanced epidermal Langerhans cell migration in IL-10 knockout mice. *J Immunol* 1999; **162**:277-83.
 85. Nakae S, Naruse-Nakajima C, Sudo K, Horai R, Asano M, Iwakura Y. IL-1a, but not IL-1b, is required for contact-allergen-specific T cell activation during the sensitization phase in contact hypersensitivity. *Int Immunol* 2001; **13**: 1471-8.
 86. Shornick LP, Bisarya AK, Chaplin DD. IL-1b is essential for langerhans cell activation and antigen delivery to the lymph nodes during contact sensitization: evidence for a dermal source of IL-1b. *Cell Immunol* 2001; **211**:105-12.
 87. Dekaris I, Zhu SN, Dana MR. TNF- α regulates corneal Langerhans cell migration. *J Immunol* 1999; **162**:4235-9.
 88. Faherty DA, Claudy V, Plocinski JM *et al.* Failure of IL-1 receptor antagonist and monoclonal anti-IL-1 receptor antibody to inhibit antigen-specific immune responses in vivo. *J Immunol* 1992; **148**:766-71.
 89. Rauschmayr T, Groves RW, Kupper TS. Keratinocyte expression of the type 2 interleukin 1 receptor mediates local and specific inhibition of interleukin 1-mediated inflammation. *Proc Natl Acad Sci U S A* 1997; **94**:5814-9.
 90. Kondo S, Pastore S, Fujisawa H *et al.* Interleukin-1 receptor antagonist suppresses contact hypersensitivity. *J Invest Dermatol* 1995; **105**:334-8.
 91. Nagai H, Ueda Y, Ochi T *et al.* Different role of IL-4 in the onset of hapten-induced contact hypersensitivity in BALB/c and C57BL/6 mice. *Br J Pharmacol* 2000; **129**: 299-306.
 92. Kupper TS, Ballard DW, Chua AO *et al.* Human keratinocytes contain mRNA indistinguishable from monocyte interleukin 1a and b mRNA. Keratinocyte epidermal cell-derived thymocyte-activating factor is identical to interleukin 1. *J Exp Med* 1986; **164**:2095-100.
 93. Heufler C, Topar G, Koch F *et al.* Cytokine gene expression in murine epidermal cell suspensions: interleukin 1b and macrophage inflammatory protein 1a are selectively expressed in Langerhans cells but are differentially regulated in culture. *J Exp Med* 1992; **176**:1221-6.
 94. Enk AH, Katz SI. Early events in the induction phase of contact sensitivity. *J Invest Dermatol* 1992; **99**:39S-41.
 95. Rasanen L, Lehto M, Reunala T, Jansen C, Leinikki P. Decreased monocyte production of interleukin-1 and impaired lymphocyte proliferation in atopic dermatitis. *Arch Dermatol Res* 1987; **279**:215-8.
 96. Kapp A, Kimbaurer R, Luger TA, Schopf E. Altered production of immuno-modulating cytokines in patients with atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1989; **144**:97-9.
 97. Jakob T, Neuber K, Ring J. Decreased monocyte interleukin-1b production in atopic eczema. *Br J Dermatol* 1995; **132**:384-90.
 98. Higashi N, Gesser B, Kawana S, Thestrup-Pedersen K. Expression of IL-18 mRNA and secretion of IL-18 are reduced in monocytes from patients with atopic dermatitis. *J Allergy Clin Immunol* 2001; **108**:607-14.
 99. Thestrup-Pedersen K, Larsen CS, Kristensen M, Zachariae C. Interleukin-1 release from peripheral blood monocytes and soluble interleukin-2 and CD8 receptors in serum from patients with atopic dermatitis. *Acta Derm Venereol* 1990; **70**:395-9.
 100. Bochner BS, Charlesworth EN, Lichtenstein LM *et al.* Interleukin-1 is released at sites of human cutaneous allergic reactions. *J Allergy Clin Immunol* 1990; **86**:830-9.
 101. Junghans V, Gutgesell C, Jung T, Neumann C. Epidermal cytokines IL-1b, TNF- α , and IL-12 in patients with atopic dermatitis: response to application of house dust mite antigens. *J Invest Dermatol* 1998; **111**:1184-8.
 102. Dowd PM, Camp RD, Greaves MW. Human recombinant interleukin-1a is proinflammatory in normal human skin. *Skin Pharmacol* 1988; **1**:30-7.
 103. Chan LS, Robinson N, Xu L. Expression of interleukin-4 in the epidermis of transgenic mice results in a pruritic inflammatory skin disease: an experimental animal model to study atopic dermatitis. *J Invest Dermatol* 2001; **117**: 977-83.
 104. Chen L, Overbergh L, Mathieu C, Chan LS. The development of atopic dermatitis is independent of Immunoglobulin E up-regulation in the K14-IL-4 SKH1 transgenic mouse model. *Clin Exp Allergy* 2008; **38**:1367-80.
 105. Groves RW, Mizutani H, Kieffer JD, Kupper TS. Inflammatory skin disease in transgenic mice that express high levels of interleukin 1 alpha in basal epidermis. *Proc Natl Acad Sci U S A* 1995; **92**:11874-8.
 106. Groves RW, Rauschmayr T, Nakamura K, Sarkar S, Williams IR, Kupper TS. Inflammatory and hyperproliferative skin disease in mice that express elevated levels of the IL-1 receptor (type I) on epidermal keratinocytes. Evidence that IL-1-inducible secondary cytokines produced by keratinocytes in vivo can cause skin disease. *J Clin Invest* 1996; **98**:336-44.
 107. Konishi H, Tsutsui H, Murakami T *et al.* IL-18 contributes to the spontaneous development of atopic dermatitis-like inflammatory skin lesion independently of IgE/stat6 under specific pathogen-free conditions. *Proc Natl Acad Sci U S A* 2002; **99**:11340-5.
 108. Oghiso Y, Kubota Y. Enhanced interleukin 1 production by alveolar macrophages and increase in Ia-positive lung cells in silica-exposed rats. *Microbiol Immunol* 1986; **30**: 1189-98.
 109. Becker S, Devlin RB, Haskill JS. Differential production of tumor necrosis factor, macrophage colony stimulating factor, and interleukin 1 by human alveolar macrophages. *J Leukoc Biol* 1989; **45**:353-61.
 110. Stassen M, Arnold M, Hultner L *et al.* Murine bone marrow-derived mast cells as potent producers of IL-9: costimulatory function of IL-10 and kit ligand in the presence of IL-1. *J Immunol* 2000; **164**:5549-55.
 111. Hultner L, Kolsch S, Stassen M *et al.* In activated mast cells, IL-1 up-regulates the production of several Th2-related cytokines including IL-9. *J Immunol* 2000; **164**: 5556-63.
 112. Kandere-Grzybowska K, Letourneau R, Kempuraj D *et al.* IL-1 induces vesicular secretion of IL-6 without degranulation from human mast cells. *J Immunol* 2003; **171**:4830-6.
 113. Lee SA, Fitzgerald SM, Huang SK *et al.* Molecular regulation of interleukin-13 and monocyte chemoattractant protein-1 expression in human mast cells by interleukin-1 beta. *Am J Respir Cell Mol Biol* 2004; **31**:283-91.
 114. Ho LH, Ohno T, Oboki K *et al.* IL-33 induces IL-13 pro-

- duction by mouse mast cells independently of IgE-FcεRI signals. *J Leukoc Biol* 2007;**82**:1481-90.
115. Iikura M, Suto H, Kajiwara N *et al*. IL-33 can promote survival, adhesion and cytokine production in human mast cells. *Lab Invest* 2007;**87**:971-8.
116. Karjalainen J, Hulkkonen J, Pessi T *et al*. The IL1A genotype associates with atopy in nonasthmatic adults. *J Allergy Clin Immunol* 2002;**110**:429-34.
117. Karjalainen J, Nieminen MM, Aromaa A, Klaukka T, Hurme M. The IL-1b genotype carries asthma susceptibility only in men. *J Allergy Clin Immunol* 2002;**109**:514-6.
118. Adjers K, Pessi T, Karjalainen J, Huhtala H, Hurme M. Epistatic effect of IL1A and IL4RA genes on the risk of atopy. *J Allergy Clin Immunol* 2004;**113**:445-7.
119. Zeyrek D, Demir E, Alpman A, Ozkinay F, Gulen F, Tanac R. Association of interleukin-1b and interleukin-1 receptor antagonist gene polymorphisms in Turkish children with atopic asthma. *Allergy Asthma Proc* 2008;**29**:468-74.
120. Mahajan B, Vijayan VK, Agarwal MK, Bansal SK. Serum interleukin-1b as a marker for differentiation of asthma and chronic obstructive pulmonary disease. *Biomarkers* 2008;**13**:713-27.
121. Sousa AR, Lane SJ, Nakhosteen JA, Lee TH, Poston RN. Expression of interleukin-1b (IL-1b) and interleukin-1 receptor antagonist (IL-1ra) on asthmatic bronchial epithelium. *Am J Respir Crit Care Med* 1996;**154**:1061-6.
122. Reynolds AM, Holmes MD, Scicchitano R. Interleukin-1b and tumour necrosis factor-α increase microvascular leakage in the guinea pig trachea. *Respirology* 2002;**7**:23-8.
123. Wilmott RW, Kitzmiller JA, Fiedler MA, Stark JM. Generation of a transgenic mouse with lung-specific overexpression of the human interleukin-1 receptor antagonist protein. *Am J Respir Cell Mol Biol* 1998;**18**:429-34.
124. Tamaoki J, Yamawaki I, Takeyama K, Chiyotani A, Yamauchi F, Konno K. Interleukin-1b inhibits airway smooth muscle contraction via epithelium-dependent mechanism. *Am J Respir Crit Care Med* 1994;**149**:134-7.
125. Tsukagoshi H, Sun J, Kwon O, Barnes PJ, Chung KF. Role of neutral endopeptidase in bronchial hyperresponsiveness to bradykinin induced by IL-1b. *J Appl Physiol* 1995;**78**:921-7.
126. Okada S, Inoue H, Yamauchi K *et al*. Potential role of interleukin-1 in allergen-induced late asthmatic reactions in guinea pigs: suppressive effect of interleukin-1 receptor antagonist on late asthmatic reaction. *J Allergy Clin Immunol* 1995;**95**:1236-45.
127. Lloyd CM, Gonzalo JA, Coyle AJ, Gutierrez-Ramos JC. Mouse models of allergic airway disease. *Adv Immunol* 2001;**77**:263-95.
128. Moffatt JD. What targets have knockouts revealed in asthma? *Pharmacol Ther* 2005;**107**:343-57.
129. Schmitz N, Kurrer M, Kopf M. The IL-1 receptor 1 is critical for Th2 cell type airway immune responses in a mild but not in a more severe asthma model. *Eur J Immunol* 2003;**33**:991-1000.
130. Broide DH, Campbell K, Gifford T, Sriramarao P. Inhibition of eosinophilic inflammation in allergen-challenged, IL-1 receptor type 1-deficient mice is associated with reduced eosinophil rolling and adhesion on vascular endothelium. *Blood* 2000;**95**:263-9.
131. Zosky GR, Larcombe AN, White OJ *et al*. Airway hyperresponsiveness is associated with activated CD4⁺ T cells in the airways. *Am J Physiol Lung Cell Mol Physiol* 2009;**297**:L373-9.
132. Kolb M, Margetts PJ, Anthony DC, Pitossi F, Gauldie J. Transient expression of IL-1b induces acute lung injury and chronic repair leading to pulmonary fibrosis. *J Clin Invest* 2001;**107**:1529-36.
133. Lappalainen U, Whitsett JA, Wert SE, Tichelaar JW, Bry K. Interleukin-1b causes pulmonary inflammation, emphysema, and airway remodeling in the adult murine lung. *Am J Respir Cell Mol Biol* 2005;**32**:311-8.
134. Park JW, Taube C, Swasey C *et al*. Interleukin-1 receptor antagonist attenuates airway hyperresponsiveness following exposure to ozone. *Am J Respir Cell Mol Biol* 2004;**30**:830-6.
135. Johnson VJ, Yucesoy B, Luster MI. Prevention of IL-1 signaling attenuates airway hyperresponsiveness and inflammation in a murine model of toluene diisocyanate-induced asthma. *J Allergy Clin Immunol* 2005;**116**:851-8.
136. Nakae S, Suto H, Berry GJ, Galli SJ. Mast cell-derived TNF can promote Th17 cell-dependent neutrophil recruitment in ovalbumin-challenged OTII mice. *Blood* 2007;**109**:3640-8.
137. Subramanian N, Bray MA. Interleukin 1 releases histamine from human basophils and mast cells in vitro. *J Immunol* 1987;**138**:271-5.
138. Theodorou V, Fioramonti J, Bueno L. Recombinant interleukin-1 receptor antagonist protein prevents sensitization and intestinal anaphylaxis in guinea pigs. *Life Sci* 1993;**53**:733-8.
139. Theodorou V, Fioramonti J, Junien JL, Bueno L. Anaphylactic colonic hypersecretion in cow's milk sensitized guinea-pigs depends upon release of interleukin-1, prostaglandins and mast cell degranulation. *Aliment Pharmacol Ther* 1994;**8**:301-7.
140. Joki-Erkila VP, Karjalainen J, Hulkkonen J *et al*. Allergic rhinitis and polymorphisms of the interleukin 1 gene complex. *Ann Allergy Asthma Immunol* 2003;**91**:275-9.
141. Kenney JS, Baker C, Welch MR, Altman LC. Synthesis of interleukin-1a, interleukin-6, and interleukin-8 by cultured human nasal epithelial cells. *J Allergy Clin Immunol* 1994;**93**:1060-7.
142. Gosset P, Malaquin F, Delneste Y *et al*. Interleukin-6 and interleukin-1a production is associated with antigen-induced late nasal response. *J Allergy Clin Immunol* 1993;**92**:878-90.
143. Sim TC, Grant JA, Hilsmeier KA, Fukuda Y, Alam R. Proinflammatory cytokines in nasal secretions of allergic subjects after antigen challenge. *Am J Respir Crit Care Med* 1994;**149**:339-44.
144. Zhang HQ, Sun Y, Xu F. Therapeutic effects of interleukin-1 receptor antagonist on allergic rhinitis of guinea pig. *Acta Pharmacol Sin* 2003;**24**:251-5.
145. Asano-Kato N, Fukagawa K, Okada N *et al*. TGF-β1, IL-1b, and Th2 cytokines stimulate vascular endothelial growth factor production from conjunctival fibroblasts. *Exp Eye Res* 2005;**80**:555-60.
146. Keane-Myers AM, Miyazaki D, Liu G, Dekaris I, Ono S, Dana MR. Prevention of allergic eye disease by treatment with IL-1 receptor antagonist. *Invest Ophthalmol Vis Sci* 1999;**40**:3041-6.