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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 development[14] 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-

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-18Rα, CD218a	M	F4, F7
R6	IL-1RL2	IL-1Rrp2	M	F5, F6, F8, F9
R7	IL-18Rap	IL-18Rβ, 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-1α	LAF	R1/R3, R2/R3
F2	IL-1β	LAF	R1/R3, R2/R3
F3	IL-1Ra	-	R1, R2
F4	IL-18	IGIF, IL-1γ	R5/R7
F5	IL-1F5	IL-1Hy1, IL-1H3, FIL1δ, IL-1L1, IL-1δ, IL-1RP3	R6
F6	IL-1F6	FIL1ε	R6/R3
F7	IL-1F7	FIL1ζ, IL-1H4, IL-1RP1, IL-1H1	R5/R7
F8	IL-1F8	FIL1η, IL-1H2	R6/R3
F9	IL-1F9	IL-1H1, IL-1RP2, IL-1ε	R6/R3
F10	IL-1F10	IL-1Hy2, FKSG75	?
F11	IL-33	NF-HEV, DVS27	R4/R3, R10/R3

1β,[18] IL-1Ra,[18,21-23] IL-1R1[24,25] and IL-1RAcP[26] 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[27,28] and overexpressing transgenic (Tg) mice[29] 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.[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-γR1-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-
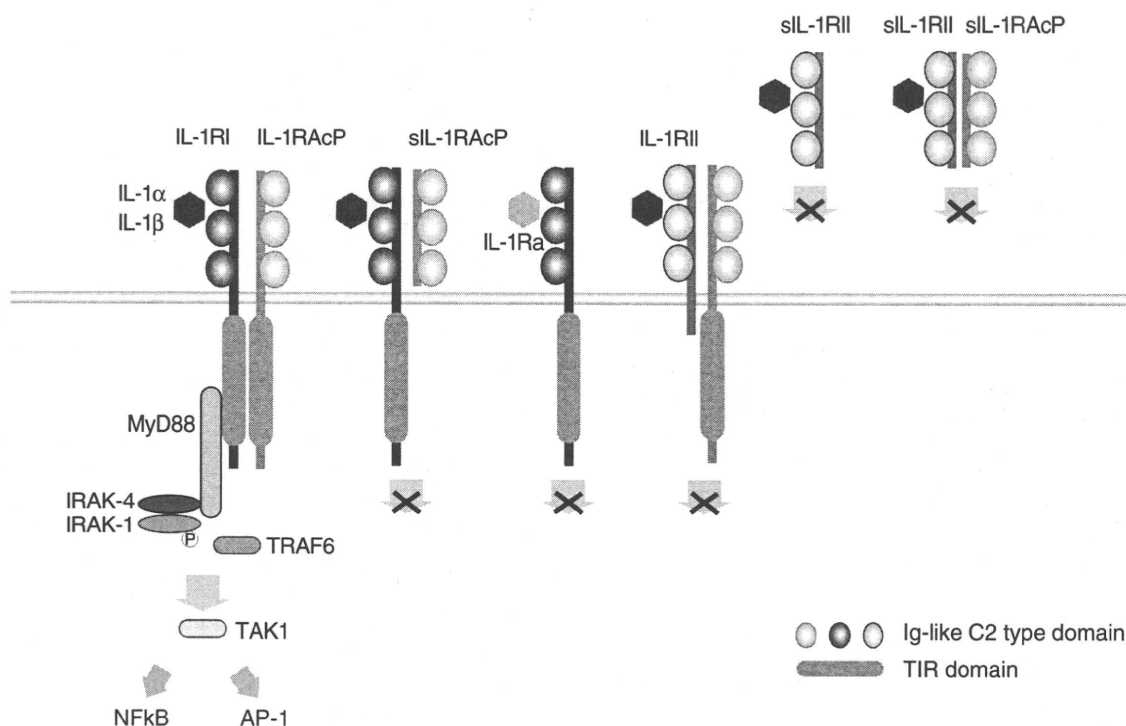
Fig. 1 IL-1 and IL-1R system.

Table 2 Role of IL-1 in DTH responses

Mice treatment with:	Mouse strain	Antigen	DTH	References
rIL-1α	C3H/He	*Listeria monocytogenes*	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 humans[44] 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-1β-deficient mice,[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).[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 immunology[54] 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 E[60] and neurokinin-1 receptor[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).[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.[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 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-trinitrochlorobenzen (TNCB), 4-ethoxymethylene-2-phenyloxazol-5-one (oxazolone) and fluorescein isothiocyanate (FITC) developed normally in IFN-γ- and/or IFN-γR1-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-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.[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-1α and/or rIL-1β 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-1α-, IL-1β- 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-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),[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).[83]

In spite of the importance of IL-1β for LC migration after oxazolone sensitization,[83] oxazolone-induced CHS developed normally in IL-1β-deficient mice[19] as well as mice treated with rIL-1Ra[88] and keratinocyte-specific IL-1R2-overexpressing Tg mice (Table 4).[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

Mice treatment with:	Mouse strain	Specimen	Sensitizer	LC release/migration	References
rIL-1α	C57BL/6	epidermal sheet	N/A	no effect	81
rIL-1β	BALB/c	epidermal sheet	N/A	enhanced	82
		draining LN	N/A	enhanced	
rIL-1β	BALB/c	draining LN	Ox	enhanced	82
anti-IL-1α				no effect	
anti-IL-1β				reduced	
rIL-1α	BALB/c	epidermal sheet	N/A	enhanced	83
rIL-1β				enhanced	
anti-IL-1α	BALB/c	epidermal sheet	Ox	no effect	83
anti-IL-1β				reduced	
anti-IL-1α	BALB/c	epidermal sheet	SLS	reduced	83
anti-IL-1β		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-1α	C57BL/6	draining LN	FITC	reduced	85
IL-1β				reduced	
IL-1α/β				reduced	
IL-1β	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-1α	BALB/c	TNCB	normally developed	80
anti-IL-1β			attenuated	
Mice-deficient in:	Mouse strain	Hapten	CHS	References
IL-1β	129 x B6	Ox	normally developed	19
IL-1β	129 x B6	TNCB (high dose)	normally developed[†]	20
		TNCB (low dose)	attenuated[†]	
IL-1α	C57BL/6 & BALB/c	TNCB	attenuated	85
IL-1β		(low & high dose)	normally developed	
IL-1α/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-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 DNFB (Table 4).[80,90] 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).[85] 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

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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.[80] 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^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-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.[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-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 human 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 trachea[122] 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 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 mice[129] 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-

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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 mice[129] and -IL-1α/β double-deficient mice,[5] and exacerbated in BALB/c-IL-1Ra-deficient mice.[5] Both IL-1α and IL-1β 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-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.[132,133] On the other hand, IL-1α-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), hezamethylene 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-1α and/or anti-IL-1β 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-1α, IL-1β and IL-1Ra genes of patients with allergic rhinitis is associated with susceptibility to the disease.[140] IL-1α and IL-1β, 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-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

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REVIEW ARTICLE ▬▬

IL-33 and IL-33 Receptors in Host Defense and Diseases

Keisuke Oboki[1], Tatsukuni Ohno[1], Naoki Kajiwara[1,2], Hirohisa Saito[1,2] and Susumu Nakae[1,2,3]

ABSTRACT

Interleukin-33 (IL-33) is a member of the IL-1 cytokine family, which includes IL-1 and IL-18. IL-33 is considered to be crucial for induction of Th2-type cytokine-associated immune responses such as host defense against nematodes and allergic diseases by inducing production of such Th2-type cytokines as IL-5 and IL-13 by Th2 cells, mast cells, basophils and eosinophils. In addition, IL-33 is involved in the induction of non-Th2-type acute and chronic inflammation as a proinflammatory cytokine, similar to IL-1 and IL-18. In this review, we summarize and discuss the current knowledge regarding the roles of IL-33 and IL-33 receptors in host defense and disease development.

KEY WORDS

allergy, autoimmunity, basophil, chronic disease, eosinophil, host defense, IL-33, mast cell, ST2

REDISCOVERY OF IL-33

Interleukin-33 (IL-33) was originally identified as "DVS27," a gene which was upregulated in vasospastic cerebral arteries after subarachnoid hemorrhage,[1] and as a "nuclear factor from high endothelial venules (NF-HEV)," which is expressed in endothelial cell nuclei.[2] In 2005, DVS27 was rediscovered as IL-33 by using computational tools to search for sequences containing the β-trefoil structure seen in IL-1- and FGF-like proteins. IL-33 (also called IL-1F11) is now regarded as the 11th member in the IL-1 family of cytokines, which includes IL-1α, IL-1β and IL-18.[3] Expression of IL-33 mRNA/protein is observed in various organs and types of cells (Table 1). In the literature, relatively high levels of IL-33 mRNA expression are observed in the brain and spinal cord of mice.[3]

IL-33 AS A NUCLEAR FACTOR

IL-33 has the closest amino acid sequence homology to IL-18 among the members of the IL-1 cytokine family.[3] In striking contrast to the other IL-1-related cytokines except for IL-1α, IL-33 is localized in the nucleus of human epithelial and endothelial cells[2] and mouse bone-marrow derived cultured mast cells (BMCMCs)[4] by binding to chromatin via a homeodomain (helix-turn-helix-like motif) and nuclear localization signal in its amino-terminus (Fig. 1).[5,6] Although the pathophysiological role of IL-33 as a nuclear factor is not fully understood, IL-33 is known to bind to the acidic pocket of a dimeric histone, H2A-H2B, on the surface of nucleosomes, resulting in suppression of gene transcription, at least in the in vitro reporter assay system.[6]

IL-33 RECEPTOR AND SIGNAL TRANSDUCTION

Schmitz et al. first identified the orphan receptor "ST2" (also called IL-1R4) as a receptor for IL-33.[3] As in the case of receptors for the other IL-1-related cytokines, IL-33 receptor (IL-33R) is formed from heterodimeric molecules, consisting of ST2 and IL-1R accessory protein (IL-1RAcP).[7,8] IL-1RAcP is a shared component of receptors for IL-1α, IL-1β, IL-1F6, IL-1F8 and IL-1F9.[9-11] In this review, the complex of ST2 and IL-1RAcP is designated as "IL-33R1."

Two major products of ST2 genes (transmembrane form ST2 [ST2 or ST2L] and soluble form ST2 [sST2]) are produced by alternative splicing under the control of two distinct promoters.[12] In addition, ST2LV and sST2V, which are other splicing variants for ST2L and sST2, respectively, have also been iden-

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Table 1 Expression of IL-33

Reference	Spices	Detected form	Specimens	Detail information
Schmitz et al. Immunity. 2005	mouse	mRNA	organ	High level: stomach, lung, spinal cord, brain, and skin / Lower level: lymph node, spleen, pancreas, kidney, and heart
		mRNA	cell	Bone marrow cell-derived cultured dendric cells / Bone marrow cell-derived cultured macrophages: with LPS
	human	mRNA	cell	Bronchial smooth muscle cell and bronchial and small airway epithelial cell / Primary lung and dermal fibroblasts and keratinocytes: with TNF and IL-1
Carriere et al. Proc Natl Acad Sci U S A. 2007	human	mRNA	cell	Tonsil endothelial cells, endothelial cells from Crohn's disease intestine and RA synovium
Sanada et al. J Clin Invest. 2007	rat	mRNA	cell	Cardiac fibroblasts
Hayakawa et al. J Biol Chem. 2007	mouse	mRNA	organ	Thymus, lung, lymph node, ovary and testis (OVA-induced asthmatic model)
Verri et al. Proc Natl Acad Sci U S A. 2007	mouse	mRNA	organ	Plantar tissue (methylated BSA-induced cutaneous and articular mechanical hypernociception model)
Miller et al. J Exp Med. 2007	mouse	mRNA	organ	Thoracic aorta (ApoE-deficient mice fed a high-fat diet)
		protein	organ	Adventitia of the aorta (ApoE-deficient mice)
	human	mRNA	cell	Primary cultured HUVECs, saphenous vein endothelial cells, saphenous vein and coronary artery smooth muscle cells
		protein	cell	Heart small vessel endothelial cells
Hudson et al. J Leukoc Biol. 2008	mouse	mRNA	cell	Glia cells: with dsRNA, LPS, PAM3Cys or IL-1
		protein	cell	Glia cells and astrocytes: with dsRNA, LPS, LPS + ATP and/or PAM3Cys
Xu et al. Proc Natl Acad Sci U S A. 2008	human	mRNA	cell	Synovial fibroblasts from RA patients: with TNF or TNF + IL-1
		protein	cell	Synovial fibroblasts from RA patients: with TNF or TNF + IL-1
		protein	organ	Synovial membranes from RA patients
Küchler et al. Am J Pathol. 2008	human	protein	organ	Endothelial cells in vessels of skins, small intestines, umbilical veins and lungs and HUVECs
Kurowska-Stolarska et al. J Immunol. 2008	mouse	protein	cell	F4/80+ CCR3- alveolar macrophages
Moussion et al. PLoS One. 2008	human	protein	cell	Large vessel endothelial cells (colons, small intestines, stomachs, kidneys, lungs, livers, fallopians and prostates) / Small vessel endothelial cells (livers, skeletal muscles, kidneys, prostates and skins) / Epithelial cells (stomach, tonsillar crypts and salivary glands) / HEV endothelial cells, fibroblastic reticular cells (interfollicular T cell area) and keratinocytes
Goh et al. Immunology. 2009	mouse	mRNA	cell	Bone marrow cell-derived cultured macrophages: with LPS
Sakashita et al. Clin Exp Allergy. 2008	human	protein	serum	Japanese cedar pollinosis
Bartunek et al. J Am Coll Cardiol. 2008	human	mRNA	organ	Hearts
		protein	organ	Coronary artery endothelium

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Reference	Species	Detection	Sample	Description
Chapuis et al. Mol Psychiatry. 2009	human	mRNA	organ	Brain from Alzheimer's disease patients< control group
		protein	cell	Small meningeal and superficial cortical small vessels
				Brain endothelial and vascular smooth muscle cells
Palmer G et al. Arthritis Rheum. 2009	mouse	mRNA	organ	Artiritic inflammed lesions (collagen-induced arthritis model)
	human	mRNA	cell	Synovial fibroblasts: with IL-1, TNF or TNF + IL-1
		protein	organ	RA synovium
			cell	HEV endothelial cells and synovial lining cells from synovium of RA patients
				Synovial fibroblasts: with TNF and IL-1
Wood et al. Biochem Biophys Res Commun. 2009	human	mRNA	organ	White adipose tissue
			cell	Preadipocytes and adipocytes: with TNF, Preadipocytes: hypoxia (1% O2)
Matsuda et al. Invest Ophthalmol Vis Sci. 2009	human	mRNA	cell	Immortalized conjunctival cell lines and conjunctival fibroblasts: with IL-1
		protein	organ	Giant papillae from atopic keratoconjunctivitis patients
			cell	Giant papillae vascular endothelial and epithelial cells from atopic keratoconjunctivitis patients
				Conjunctival fibroblasts: with IL-1 or IL-1 + IFN-g (pro-IL-33)
				Immortalized conjunctival cell lines and conjunctival fibroblasts (mature-IL-33)
Pushparaj et al. Proc Natl Acad Sci U S A. 2009	human	mRNA	organ	Skin from atopic dermatitis patients
		protein	serum	Atopic patients with anaphylactic shock
			organ	Skin from atopic dermatitis patients
Lüthi et al. Immunity. 2009	human	protein	cell	THP-1 cells: with LPS, necrotic cells
Préfontaine, J Immunol. 2009	human	mRNA	organ	Lungs from asthmatic patients
			cell	Airway smooth muscle cells from asthmatic patients, primary airway smooth muscle cells: with TNF
		protein	cell	Airway smooth muscle cells from asthmatic patients, primary airway smooth muscle cells: with TNF
Kurowska-Stolarska et al. J Immunol. 2008	human	protein	cell	Lung epithelial cells from asthmatic patients
Seidelin et al. Immunol Lett. 2009	human	mRNA	cell	Colonocytes from patients with ulcerative colitis
		protein	cell	Colonocytes from patients with ulcerative colitis
Matsuyama et al. J Rheumatol. 2010	human	protein	serum	RA patients
			organ	Synovila fluids from RA patients
			cell	Fibroblast like synoviocytes from RA patients
Ohno et al. J Immunol. 2009	mouse	mRNA	cell	Peritomeal macrophages, splenic dendritic cells: with LPS
		protein		Bone marrow cell-cultured mast cells: with IgE, IgE + antigen
			cell	Peritomeal macrophages: with LPS, bone marrow cell-cultured mast cells: with IgE + antigen
Nishida et al. Gut. 2009	human	protein	cell	Myofibroblasts: with IL-1, TNF and LPS
				Pancreatic myofibroblasts: with IL-1, TNF and LPS

HEV, high endothelial venules; HUVEC, human umbilical vein endothelial cells; RA, rheumatoid arthritis.

IL-33 (DVS-27, NF-HEV)

N- [   ] -C

Helix-turn-helix domain   IL-1-like domain
(Homeodomain-like)
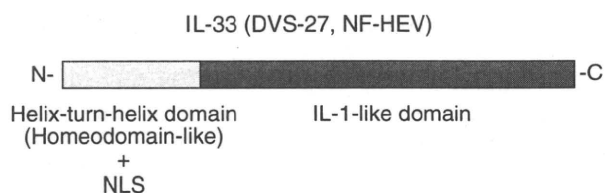   +
          NLS

Fig. 1 IL-33, a 270-amino-acid protein, consists of two domains: a homeodomain and a cytokine (IL-1-like) domain. The homeodomain contains a nuclear localization signal (NLS).

tified in chickens and humans.[13,14] ST2 is considered to be the functional component for induction of IL-33 bioactivities, while sST2 acts as a decoy receptor for IL-33, similar to soluble IL-1Rs for IL-1.[9-11]

The signal transduction downstream of IL-33R1 is mediated by adapter molecules that are shared by other IL-1 receptor family members such as IL-1R and IL-18R. The binding of IL-33 to IL-33R1 results in recruitment of MyD88 to the Toll-interleukin-1 receptor (TIR) domain in the cytoplasmic region of ST2, leading to induction of inflammatory mediators by activating transcription factors such as NF-κB and AP-1 through IRAK, TRAF6 and/or MAP kinases (Fig. 2).[3]

Recently, it has been shown that IL-33 binds to another IL-33R different from IL-33R1. In addition to IL-1RAcP, ST2 forms a complex with another IL-1R family molecule, "single Ig IL-1R-related molecule (SIGIRR) (also called Toll IL-1R8 [TIR8])".[15] In this review, the complex of ST2 and SIGIRR is designated as "IL-33R2". SIGIRR/TIR8 is considered to act as a negative regulator for IL-1R- and Toll-like receptor (TLR)-mediated immune responses.[16] Indeed, SIGIRR/TIR8-deficient dendritic cells showed hyper-responsiveness to stimulation with IL-1, IL-18 and TLR agonists.[17] In addition, SIGIRR/TIR8-deficient Th2 cells showed augmented Th2-type cytokine production in response to IL-33.[15] In contrast to IL-33R1 (ST2/IL-1RAcP), IL-33R2 seems to act as a negative regulator of IL-33.

TARGET CELLS OF IL-33

Th2 CELLS
It is well established that IL-4 is a key cytokine for the differentiation of Th2 cells from naïve CD4+ T cells. ST2 is predominantly expressed on Th2 cells but not naïve T cells, Th1 cells, Th17 cells or regulatory T cells.[18-20] On the other hand, ST2 is not essential for Th2 cell differentiation, as shown in studies using ST2-deficient mice: ST2-deficient mice showed normal development of Th2 cells.[21,22] In support of that, although IL-33 did not induce differentiation of Th2 cells from naïve CD4+ T cells *in vitro*,[23,24] it enhanced IL-5 and IL-13, but not IL-4, production by *in vitro*-skewed Th2 cells which highly express ST2.[3,7,23,25,26] In humans, IL-33 potentiates not only Th2-type cy-
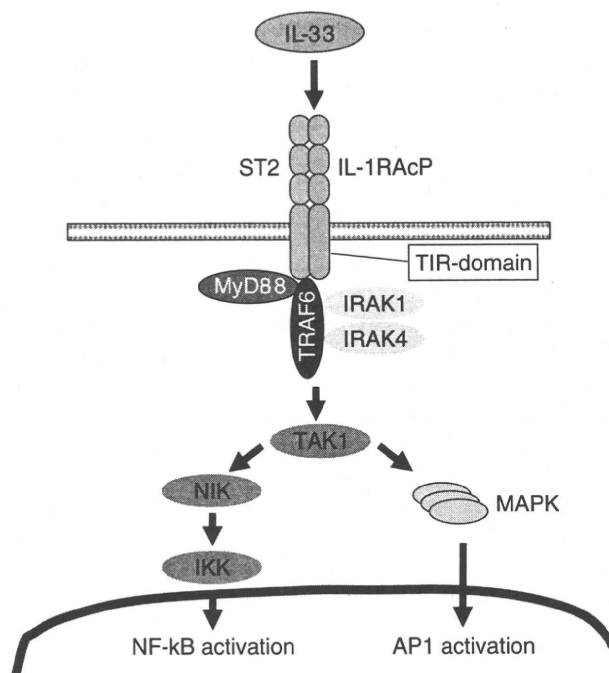

Fig. 2 IL-33 binds to IL-33 receptor, which is a dimer of ST2 and IL-1RAcP. The TIR-domain of IL-33 receptor recruits MyD88 and TRAF6, and the receptor signal results in activation of NF-kB or AP-1.

tokine production but also production of a Th1-type cytokine, IFN-γ, by peripheral blood-derived Th2 cells,[27] although IFN-γ production is only slightly increased by peripheral blood-derived human Th1 cells.[26] In addition, IL-33 acts as a chemoattractant for Th2 cells, but not Th1 cells, in both humans and mice.[28]

In contrast to the role of IL-33 in Th2 cell differentiation, Kurowska-Stolarska *et al.* reported that IL-33 induces differentiation of IL-5-positive IL-4-negative CD4+ T cells (IL-5+IL-4- Th cells) from naïve CD4+ T cells independently of IL-4, STAT-6 and GATA-3, which are important factors for the typical Th2 cell differentiation.[24] While ST2-expressing Th cells are also observed in IL-4-, IL-5- or IL-10-deficient mice,[19,29] two distinct populations of IL-4-producing Th cells were found: ST2-positive Th2 cells, which produce IL-4, IL-5 and IL-10, and ST2-negative Th2 cells, which produce IL-4 and IL-10, but not IL-5, in mice during *Leishmania major* infection.[30] Further evidence regarding the role of IL-33 in the differentiation of typical and atypical Th2 cells may provide new insight into the molecular mechanisms in Th2-type cytokine-mediated disorders such as allergic asthma.

In addition to CD4+ Th2 cells, it has been shown that type II CD8+ cytotoxic T cells (Tc2 cells) and IL-10-producing Tr1 cells also express ST2 on their cell surface.[31,32] However, the precise roles of IL-33 in Tc2 and Tr1 cells remain unclear.

MAST CELLS (MCs)

MCs, which express c-Kit and high-affinity IgE receptors (FcɛRI) and are predominantly localized in mucosal and connective tissues, are major effector cells in the induction of IgE-mediated immune responses. After binding of antigens (Ags) to IgE-bearing MCs via FcɛRI, MCs rapidly release a large variety of inflammatory mediators from their granules, thereby provoking local and systemic inflammation. Mouse MCs (i.e., BMCMCs and connective tissue-type MCs from the peritoneal cavity) and MC/basophil precursor cells and human MCs (i.e., cord blood and peripheral blood stem cell-derived cultured MCs) constitutively express ST2.[33-36] Except for IL-3 and stem cell factor (SCF, a ligand for c-kit), which are required for mast cell development at least in mice, IL-33 is the only cytokine among 45 different cytokines which can directly induce cytokine and chemokine (IL-1β, IL-6, IL-13, TNF and MCP-1) secretion from mouse BMCMCs without effecting their degranulation.[37,38] Like its murine counterpart, human IL-33 can induce cytokine and chemokine production, prolong survival and promote cell-adhesion in human cord blood stem cell-derived cultured MCs.[35,36] In addition, IL-33 can augment IgE-mediated cytokine production and degranulation by mouse BMCMCs and/or human cord blood stem cell-derived cultured MCs.[35-37,39] IL-33-mediated cytokine production by mouse BMCMCs and human cord blood stem cell-derived cultured MCs is enhanced in the presence of IL-3 and thymic stromal lymphopoietin (TSLP), respectively.[23,36]

Although the levels of phorbol ester + ionophore-induced IL-4 production and IgE + antigen-mediated histamine release from ST2-deficient BMCMCs are comparable to those from wild-type BMCMCs,[21] ST2-deficient BMCMCs do not produce cytokines in response to IL-33.[23] Therefore, IL-33-induced mast cell-derived cytokines are not involved in IL-4 production or IgE-dependent histamine release.

BASOPHILS

Basophils, which express FcɛRI, but not c-Kit, on their cell surface, are considered to be a potential primary source of IL-4 in certain allergic immune responses.[40,41] Supporting this, it was recently reported that basophils express MHC class II and present Ags to naïve T cells as an Ag-presenting cell, inducing Ag-specific Th2 cell differentiation in lymph nodes that is dependent on IL-4 production and Ag-presentation by activated basophils.[42-44]

In comparison with Th2 cells and MCs, human and mouse basophils constitutively express ST2 at a relatively low level on their cell surface.[23,26,45,46] On the other hand, expression of ST2 on the cell surface of basophils is promoted by stimulation with IL-3.[26] Like the effect of IL-33 on Th2 cells and MCs, IL-33 alone can induce production of cytokines, including Th2-type cytokines, and chemokines by basophils and promote cell-adhesion and CD11b expression by human and murine basophils.[26,27,45,46] IL-33 does not induce degranulation of basophils directly, but it synergistically enhances IgE-mediated degranulation of human basophils.[26,45] In addition, IL-33 augments immune responses of human and murine basophils in humans and mice: eotaxin-mediated migration,[45] cytokine secretion in the presence of IL-3, which is a growth factor for basophils as well as mast cells,[23,26,27,45-47] and prolonged survival in the presence of IL-3 or GM-CSF.[45-47] These observations suggest that IL-33 is a potential activator of basophils by enhancing their cytokine and chemokine secretion, recruitment and adhesion.

EOSINOPHILS

Eosinophilia is found in local inflammatory sites in patients with certain IgE-mediated allergic disorders, such as asthma. Although ST2 expression was barely detectable on the cell surface of human peripheral blood eosinophils, ST2 mRNA and intracellular ST2 protein were detectable in them.[26,48,49] IL-33 can directly induce production of superoxide and IL-8 and enhance IL-3-, IL-5- or GM-CSF-mediated IL-8 production by human eosinophils.[26,48] As in the case of MCs and basophils, IL-33 enhances adhesion of eosinophils by promoting CD11b expression and survival independently of IL-4, IL-5 and GM-CSF.[49] Unlike the case of basophils, IL-33 does not influence eotaxin-mediated migration of eosinophils.[49] The role of IL-33 in the degranulation of eosinophils remains controversial. One group demonstrated that IL-33 alone could enhance degranulation (EDN release) of human eosinophils,[48] whereas another showed that IL-33 could not (assessed by EDN and LTC4 release).[49] These observations strongly suggest that IL-33 may contribute to the pathogenesis of certain allergic disorders accompanied by marked accumulation of eosinophils.

NATURAL KILLER (NK) CELLS AND NKT CELLS

As in the case of Th2 and Tc2 cells, ST2 expression was observed on the cell surface of IL-4-producing NK cells (NK2 cells), but not IFN-γ-producing NK cells (NK1 cells), which were derived in vitro from a freshly-isolated NK cell population of human PBMCs under Th1/Th2 cytokine-skewed culture conditions.[31] Smithgall et al. demonstrated that freshly-isolated NK cells from human PBMCs could produce IFN-γ in response to IL-33 in the presence, but not absence, of IL-12 or IL-23, since IL-12 and/or IL-23 enhanced the expression of ST2 mRNA in NK cells.[27] However, that study did not elucidate the role of IL-33 in Th2-type cytokine secretion by NK cells.

Smithgall et al. also detected ST2 mRNA expression in human invariant NKT (iNKT) cells and demonstrated a role for IL-33 in these cells: IL-33 en-

hanced TCR-dependent cytokine production (i.e., IFN-γ, IL-2, IL-4, IL-5, IL-13 and TNF) by iNKT cells after stimulation with α-galactosylceramide (α-GalCer).[27] Moreover, IL-33 enhanced IFN-γ, but not IL-4, production by iNKT cells in the presence, but not absence, of IL-12, independently of TCR stimulation.[27] As in the case of NK cells, IL-12 enhances ST2 mRNA expression in human iNKT cells.[27]

Administration of IL-33 to mice results in increased expansion of iNKT cells in the spleen and liver.[50] Thymic iNKT cells constitutively express ST2 on their cell surface, and IL-33 enhances IL-7-mediated thymic iNKT cell proliferation.[50] IL-33 alone could not induce cytokine secretion by naïve mouse iNKT cells. On the other hand, similar to the study in human iNKT cells,[27] IL-33 enhanced both IL-4 and IFN-γ production by TCR-stimulated mouse iNKT cells and IFN-γ, but not IL-4, production by mouse iNKT cells in the presence of IL-12, independently of TCR stimulation.[50] In contrast to the findings for human iNKT cells,[27] IL-12 could not enhance ST2 expression in mouse iNKT cells. These observations suggest that IL-33 may have a non-Th1/Th2 cytokine-restricted role in certain NK cell- and NKT cell-mediated immune responses.

DENDRITIC CELLS (DCs)

IL-33 is considered to promote the development of DCs from bone marrow cells.[51] It has been shown that DCs derived by cultivation of murine bone marrow cells in the presence of GM-CSF and IL-4 (that is, bone marrow-derived DCs; BMDCs) express ST2.[52] IL-33 enhances the production of IL-6, but not IL-12, by BMDCs and augments the expression of MHC class II and CD86, but not CD80, CD40 and "OX40 ligand (OX40L)", on the cell surface of BMDCs.[52] When naive CD4+ T cells were co-cultured with BMDCs in the presence of IL-33 for 6 to 10 days, IL-5 and IL-13, but not IL-4 or IFN-γ, were detected in the culture supernatant even without TCR engagement. Since such cytokine secretion was not induced by IL-33 in the culture of naïve CD4+ T cells alone, the effect of IL-33 seemed to be mediated by factors derived from IL-33-stimulated BMDCs through a TCR/Ag-MHC class II-independent pathway. However, the secreted cytokine profiles (IL-5 and IL-13, but not IL-4, production) in the setting (BMDCs + naïve CD4+ T cells + IL-33, no Ag) are similar to those by the IL-5-positive, IL-4-negative atypical Th2 cell population observed in the culture of naïve CD4+ T cells stimulated by TCR engagement plus IL-33, as described above. Thus, these observations suggest that IL-33 can enhance induction of an IL-5-positive, IL-4-negative atypical Th2 cell population from naïve CD4+ T cells directly and/or indirectly from DCs via the effects of certain factors.

Like IL-33, IL-25 and TSLP are known to be Th2-prone cytokines and contribute to the induction of Th2-type cytokine-mediated immune responses.[53] In contrast to the case of IL-33, TSLP-activated DCs promote IL-4-producing Th2 cell differentiation from naïve CD4+ T cells in the presence of TCR engagement through OX40L-OX40 interaction, at least in part.[54,55] IL-25 can enhance TSLP-stimulated DC-mediated Th2 cell expansion.[56] Unlike IL-33, both TSLP and IL-25 can induce differentiation of IL-4-producing Th2 cells from naïve CD4+ T cells after TCR engagement, dependent on the IL-4-IL-4Rα-STAT6 pathway.[57,58] Therefore, these observations suggest that the roles of IL-33, TSLP and IL-25 in T cells and DCs may be different in Th2-type cytokine-mediated immune responses. That is, TSLP and IL-25 may be preferentially involved in the induction of antigen-specific IL-4/IL-5/IL-13-producing Th2 cell-mediated immune responses, while IL-33 may contribute, at least in part, to the induction of antigen-non-specific Th2 cell-mediated immune responses by inducing IL-5/IL-13-, but not IL-4-, and thereby producing atypical Th2 cells.

MACROPHAGES

Constitutive expression of ST2 mRNA/proteins was detected in mouse bone marrow cell-derived cultured macrophages and mouse alveolar macrophage cell lines.[59,60] Soluble ST2 expression was increased in macrophages in response to LPS and proinflammatory cytokines such as TNF, IL-1 and IL-6.[60-62] IL-33 promoted the expression of LPS receptor components, such as MD2, TLR4, soluble CD14 and MyD88.[63] Although IL-33 alone did not induce TNF, IL-1 or IL-6 production by thioglycolate-induced mouse peritoneal macrophages, it did in the presence of LPS.[63] Such effects of IL-33 on LPS-mediated activation were abolished in anti-ST2 Ab-treated and ST2-deficient macrophages. Therefore, IL-33 may be a potential activator of macrophages during bacterial infections.

In addition, both naïve and thioglycolate-induced mouse peritoneal macrophages produced IL-33 upon LPS stimulation,[4] suggesting that macrophage-derived IL-33 may autocrinely enhance LPS-mediated macrophage activation. Supporting this, LPS-mediated production of cytokines, such as IL-1, IL-6, IL-12 and/or TNF, by mouse bone marrow cell-derived cultured macrophages or mouse alveolar macrophage cell lines was inhibited by addition of soluble ST2-Fc fusion proteins.[59,60]

It is well known that macrophages are key effector cells during septic shock. It was shown that mice treated with polyclonal anti-ST2 antiserum, which had potential activity to deplete ST2-expressing cells, including macrophages,[64] were highly susceptible to LPS-induced endotoxin shock,[59] suggesting the importance of ST2-expressing macrophages for protection against this event. Consistent with the effect of soluble ST2-Fc fusion proteins on macrophage activa-

tion by LPS, mice treated with soluble ST2-Fc fusion proteins were resistant to endotoxin shock and showed reduced serum IL-6 and TNF levels after intraperitoneal LPS injection.[59]

However, in contrast with the effect of soluble ST2-Fc fusion proteins,[59,60] IL-6, IL-12 and TNF productions by ST2-deficient thioglycolate-induced peritoneal macrophages were increased in response to LPS.[65] In addition, ST2-deficient mice showed high susceptibility to LPS-induced endotoxic shock.[65] The apparent discrepancy between the results using macrophages treated with soluble ST2-Fc fusion proteins and macrophages deficient in ST2 may be explained as follows. Perhaps ST2-deficiency results in increased formation of other IL-1R family molecules, such as IL-1R (IL-1R1 and IL-1RAcP), due to the failure of formation of IL-33R1 (ST2 and IL-1RAcP), causing cytokine hyperproduction by ST2-deficient macrophages in response to IL-1, which can be produced by these macrophages after LPS stimulation. Indeed, ST2-deficient macrophages produced larger amounts of cytokines than wild-type macrophages after IL-1β treatment.[65] Although IL-1R1-deficient mice showed normal susceptibility to LPS-induced endotoxic shock,[66] IL-1R antagonist-deficient mice, which have excessive IL-1-signaling, showed high susceptibility.[67] This suggests that IL-1 is not required for induction of LPS-induced endotoxic shock, but excessive IL-1 production leads to amplified susceptibility to LPS, as seen in ST2-deficient mice.

Macrophages are phenotypically divided into two distinct populations: "classically activated macrophages (CAMφ)/type 1 macrophages (M1)" and "alternatively activated macrophages (AAMφ)/type 2 macrophages (M2)." CAMφ/M1s are generated in response to IFN-γ and LPS (or TNF induced by bacterial components) and are involved in Th1-type immune responses such as host defense against viral and bacterial infections and tumor rejection by producing IL-12, IL-23 and nitric oxide. M2 macrophages are further subdivided into at least three populations by in vitro stimulation with distinct factors: IL-4- and/or IL-13-stimulated M2a (also called AAMφ), immune complex plus IL-1β- or LPS-stimulated M2b (also called typeIIMφ) and IL-10-, TGF-β- or glucocorticoid-treated M2c (also called deactivated Mφ).[68-71]

IL-13 enhances ST2 expression in mouse bone marrow cell-derived cultured macrophages, and IL-33 amplifies polarization of M2a/AAMφs in the presence, but not absence, of IL-13, contributing to the induction of Th2-type immune responses.[72]

CD34-POSITIVE HEMATOPOIETIC PROGENITOR CELLS

CD34+ hematopoietic progenitor cells are capable of differentiating into various types of cells in the bone marrow and peripheral tissues. Recently, it was shown that mRNA and cell surface expression of ST2

as well as TSLPR were found in CD34+ hematopoietic progenitor cells derived from human umbilical cord blood cells.[73] IL-33 enhances the production of various cytokines and chemokines, including IL-5, IL-13, CCL17 and CCL22, by human umbilical cord blood cell-derived CD34+ hematopoietic progenitor cells in cooperation with TSLP in the presence of IL-3 and SCF.[73] Interestingly, the number of CD34+ hematopoietic progenitor cells was increased in peripheral blood from allergic patients.[73] In addition, IL-5- and IL-13-producing CD34+ hematopoietic progenitor cells were also detected in sputum from patients with asthma. These observations suggest that CD34+ hematopoietic progenitor cells may themselves be potential effector cells by responding to IL-33 and TSLP even in the undifferentiated state and contributing to the development of allergic diseases.

NATURAL HELPER CELLS

Adipose tissue-associated Lin- c-Kit+ Sca-1+ natural helper cells are a newly identified population distinct from lymphoid progenitors and lymphoid tissue inducer cells.[74] Natural helper cells constitutively express ST2 and can produce larger amounts of IL-5 and IL-13 than basophils and mast cells in response to IL-33. IL-33-mediated natural helper cell activation was shown to be important for development of goblet cell hyperplasia during Nippostrongylus brasiliensis infection.[74]

PRODUCERS AND RELEASE OF IL-33 AS "Alarmin"

During host defense against pathogens, innate immune cells recognize pathogen-associated molecular patterns (PAMPs) directly via Toll-like receptors (TLRs), resulting in induction of local and/or systemic inflammation. In addition, endogenous proinflammatory factors called "damage associated molecular patterns (DAMPs)" (also called "alarmin"), which are released by necrotic cells in injured tissues during trauma and/or infection, also provoke local and/or systemic inflammation by acting as an endogenous danger signal that often promoting immune responses.[75] For example, high-mobility group box 1 (HMGB1), which was initially identified as a nuclear factor acting as a transcriptional regulator, is released by macrophages in response to LPS, leading to induction of inflammation.[76] Like HMGB1, several recent lines of evidence suggest that IL-33, which is also localized in the nucleus, may also act as a DAMP/alarmin.[77]

As noted earlier, Schmitz et al. demonstrated that IL-33 shows the closest amino acid sequence homology to IL-18 among the members of the IL-1 family of cytokines.[3] Like IL-1β and IL-18, IL-33 is not considered to be secreted via the conventional vesicle transport pathway because its amino-terminus lacks the necessary signal sequence. Also like IL-1β and IL-18,
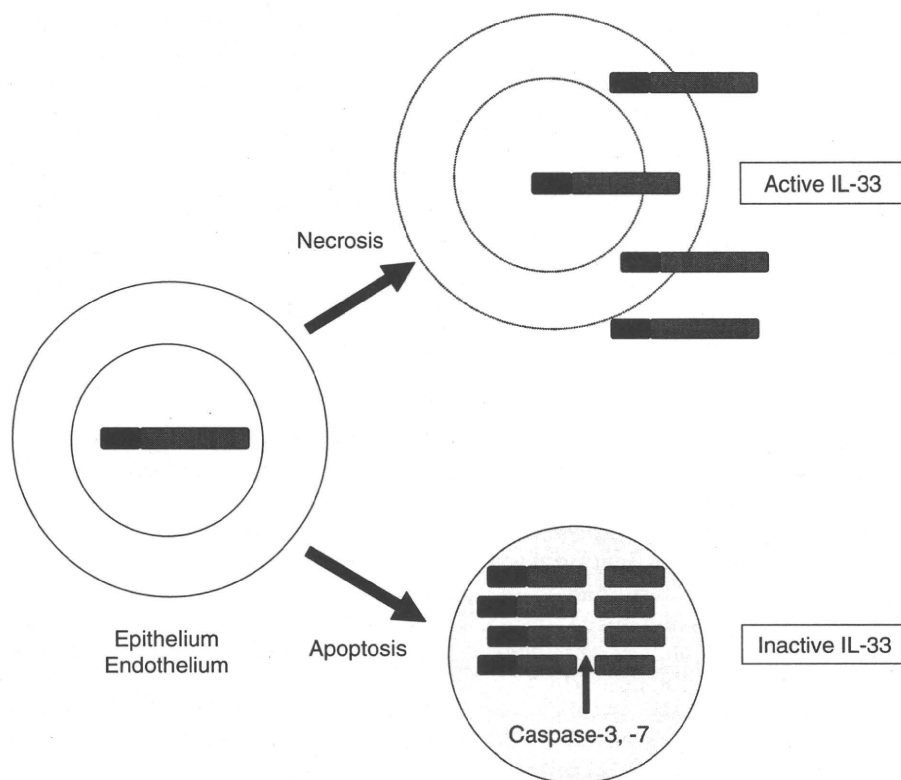
Fig. 3 Modes of cell death and IL-33 release. IL-33 is thought to be passively released by necrotic cells. On the other hand, caspases cleave IL-33, resulting in inactivation of IL-33 during apoptosis.

it was reported that IL-33 was cleaved from pro-IL-33 by caspase-1 *in vitro*,[3] suggesting that IL-33 may be secreted by activation of NACHT, LRR and PYD-containing protein (NLRP)-mediated inflammasomes. However, pro-IL-33 does not have a typical cleavage site such as seen in pro-IL-1β and pro-IL-18, and caspase-1 proteolytically cleaved pro-IL-33 in the cytokine motif, not the intermediate region between the helix-turn-helix and cytokine motifs, resulting in inactivation of IL-33.[77-79] Like caspase-1, both caspase-3 and caspase-7 are able to cleave pro-IL-33 during apoptosis, although apoptotic cells do not generally induce inflammation, and IL-33 processed by these caspases does not express biological activities via IL-33R1 (Fig. 3).[77,78] On the other hand, it is known that pro-IL-33 is released by necrotic cells without any processes by proteases such as caspase-1, -3, -7 and -8 and/or calpain.[4,77-79] In addition, like pro-IL-1α, pro-IL-33 has biological activity[78]: pro-IL-33 can induce mouse mast cell activation so that they produce cytokines via IL-33R1.[79] Therefore, these observations suggest that pro-IL-33 released by necrotic cells during tissue injury may play a DAMP/alarmin-like role in induction of inflammation. However, it remains unclear whether IL-33 can act as a potent adjuvant profoundly promoting acquired immune responses compared to other alarmin adjuvants such as ATP which

are also released during necrosis.

IL-33-IL-33R IN INFECTIONS

LEISHMANIA MAJOR
It is well established that host protection against a protozoan, *Leishmania major*, is mediated by Th1 cell-mediated immune responses, but reciprocally aggravated by Th2 cell-mediated immune responses.[80]

ST2-expressing CD4+ T cells accumulate in local lesions of *L. major*-infected mice.[81] Administration of polyclonal anti-ST2 antiserum, which has potential activity to-deplete ST2-expressing cells, including Th2 cells, reduced lesion development and Th2 cytokine production and increased Th1 cytokine production during *L. major* infection in female BALB/c mice, a strain that is susceptible to this pathogen.[64] On the other hand, BALB/c mice treated with anti-ST2 mAb (clone DJ8), which did not deplete ST2-expressing cells, or ST2-Fc fusion proteins showed lesion development, parasite replication and antigen-specific ST2+ Th2 cell differentiation that were similar to in mice treated with control Ab, although their IFN-γ production was increased.[30] These observations suggest that ST2-expressing immune cells, but not IL-33-ST2-mediated signaling, contribute to the pathogenesis of leishmaniasis in mice.