Allergology International. 2013;62:13-20
DOI: 10.2332/allergolint.13-RAI-0538

REVIEW ARTICLE

Role of Interleukin-33 in Innate-Type Immune Cells in Allergy

Susumu Nakae[1,2], Hideaki Morita[3], Tatsukuni Ohno[4], Ken Arae[3,5], Kenji Matsumoto[3] and Hirohisa Saito[3]

ABSTRACT

Interleukin-33 (IL-33), a member of the IL-1 cytokine family, is preferentially and constitutively expressed in epithelial cells, and it is especially localized in the cells' nucleus. The nuclear IL-33 is released by necrotic cells after tissue injury and/or trauma, and subsequently provokes local inflammation as an alarmin, like high-mobility group box protein-1 (HMGB-1) and IL-1α. IL-33 mainly activates Th2 cells and such innate-type immune cells as mast cells, basophils, eosinophils and natural helper cells that express IL-33R (a heterodimer of IL-1 receptor-like 1 [IL-1RL1; also called ST2, T1, Der4, fit-1] and IL-1 receptor accessory protein [IL-1RAcP]). That activation causes the cells to produce Th2 cytokines, which contribute to host defense against nematodes. On the other hand, excessive and/or inappropriate production of IL-33 is also considered to be involved in the development of such disorders as allergy. In this review, we summarize current knowledge regarding the pathogenic roles of IL-33 in the development of allergic inflammation by focusing on its effects on innate-type immune cells.

KEY WORDS

allergy, basophil, interleukin-33, mast cell, natural helper cell

IL-33

IL-33, a ligand for IL-1RL1 (also called ST2, T1, Der4 and fit-1), which is a member of the Toll/IL-1 receptor superfamily,[1] is produced/expressed by various types of immune cells such as mast cells, macrophages and dendritic cells (DCs), and non-immune cells such as endothelial, epithelial and smooth muscle cells and fibroblasts[2] (Fig. 1). IL-33 is also known to be identical to DVS27, a gene transcript that is upregulated in vasospastic cerebral arteries after subarachnoid hemorrhage,[3] and nuclear factor from high endothelial venules (NF-HEV), a transcript expressed in the nucleus of endothelial cells.[4] IL-33 is localized in the nucleus—due to its association with heterochromatin via a helix-turn-helix motif within the N-terminal part—where it acts as a transcriptional repressor, at least *in vitro*.[5,6] Thus, like IL-1α and high-mobility group box 1 (HMGB1),[7,8] IL-33 is considered to act not only as a proinflammatory cytokine but also a nuclear factor. However, the pathophysiological roles of IL-33 as a nuclear factor remain unclear.

IL-1β and IL-18, members of the IL-1 family of cytokines, are initially synthesized as precursor forms—which lack the amino acid sequences of signal peptides—in the cytosol and fail to induce cell activation.[9,10] After exposure to certain stimuli in cells, the IL-1β and IL-18 precursors are proteolytically cleaved by caspase-1 through activation of inflammasomes, after which the cleaved forms become biologically active and are secreted.[9,10] In an early study, IL-33 was similarly considered to be biologically activated by cleavage by caspase-1 and then secreted via an unconventional secretion mechanism.[1] Unlike IL-1β and IL-18, however, full-length IL-33—which does not have a typical caspase-1 cleavage site such as seen in IL-1β and IL-18—is bioactive even without

[1]Laboratory of Systems Biology, Center for Experimental Medicine and Systems Biology, The Institute of Medical Science, The University of Tokyo, [3]Department of Allergy and Immunology, National Research Institute for Child Health & Development, [4]Department of Molecular Immunology, Graduate School of Medical and Dental Science, Tokyo Medical and Dental University, [5]Department of Immunology, Faculty of Health Sciences, Kyorin University, Tokyo and [2]Precursory Research for Embryonic Science and Technology (PRESTO), Japan Science and Technology Agency, Saitama, Japan.
Conflict of interest: No potential conflict of interest was disclosed.
Correspondence: Susumu Nakae, PhD, Laboratory of Systems Biology, Center for Experimental Medicine and Systems Biology, 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
Received 14 January 2013.

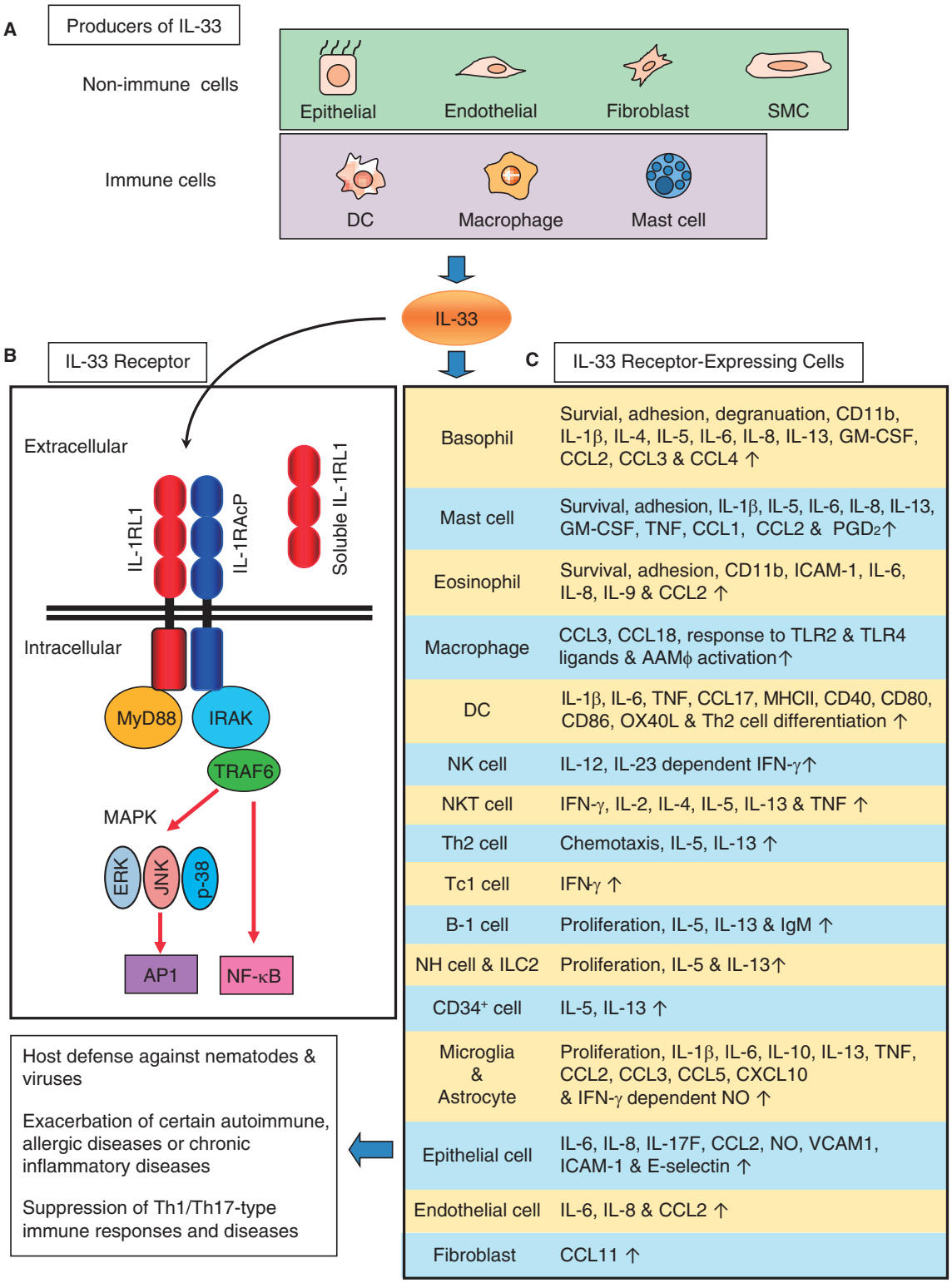

Fig. 1 The IL-33-IL-33R pathway and bioactivities of IL-33. **A.** Producers of IL-33. **B.** IL-33R and signal transduction. **C.** Bioactivities of IL-33 on various types of cells. DC, dendritic cell; SMC, smooth muscle cell; NK, natural killer; NKT, natural killer T; Th, helper T; Tc, cytotoxic T; NH, natural helper; ILC, innate lymphoid cell; AAMφ, alternative activated macrophage.

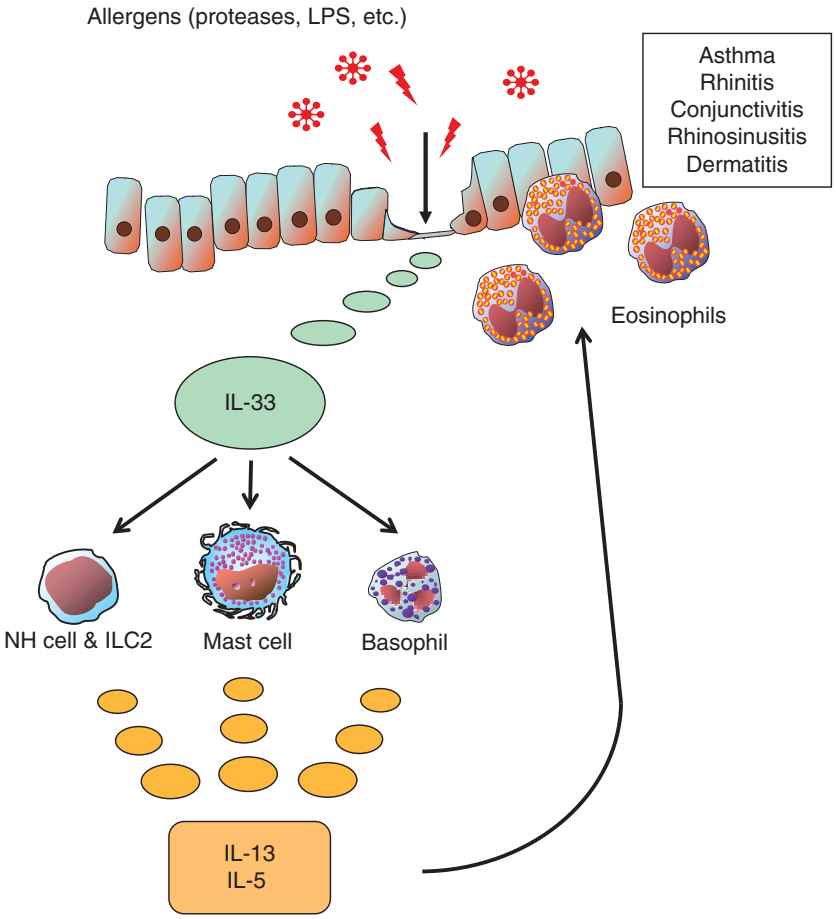

Fig. 2 IL-33-mediated allergic inflammation by innate-type immune cells. IL-33 is released by epithelial cells in response to protease allergens such as Der f1/p1 and papain and/or LPS. Epithelial cell-derived IL-33 induces production of IL-5 and IL-13 by innate-type immune cells such as NH cells/ILC2 cells, mast cells, and basophils. Subsequently, such innate-type immune cell-derived IL-5 and IL-13 provoke recruitment of eosinophils in the local sites, contributing to the development of various allergic disorders.

caspase-1-dependent cleavage[11-13] Thus, the caspase-mediated proteolytic cleavage during apoptosis associated with activation of inflammasomes is not necessary for activation and secretion/release of IL-33. Conversely, IL-33 released by necrotic cells without cleavage by caspases or calpain, which is required for IL-1α, has biological activity.[13,14] In addition, in contrast to cleaved-form IL-33 generated by caspase, cleaved-form IL-33 generated by neutrophil elastase and cathepsin G from full-length IL-33 released by cells during tissue injury has ~10 fold higher biological activity than full-length IL-33.[15] Thus, like HMGB-1 and IL-1α, IL-33 is considered to be an alarmin or a damage-associated molecular pattern (DAMP) molecule that is released by necrotic cells after tissue injury and/or trauma.

IL-33 RECEPTOR (IL-33R)

IL-33R is a heterodimer comprised of IL-1RL1 and IL-1 receptor accessory protein (IL-1RAcP).[16-18] It is expressed on various types of cells and induces activation of those cells by activation of transcription factors such as NF-κB and AP-1 via a signal pathway [consisting of recruitment of myeloid differentiation factor 88 (MyD88) to the Toll/IL-1R domain in the cytoplasmic region of IL-1RL1, IL-1R-associated kinase (IRAK), TNF receptor-associated factor 6 (TRAF6) and/or mitogen-activated protein kinase (MAPK)] after binding of IL-33, in a similar manner with other IL-1R family members such as IL-1R and IL-18R[1,19] (Fig. 2).

Regarding IL-1RL1, two major forms, i.e., transmembrane- and soluble-forms, are produced from the IL-1RL1 gene as a result of alternative splicing under

the control of two distinct promoters.[2,20,21] The transmembrane-form IL-1RL1 is considered to be a functional component of IL-33R, whereas soluble-form IL-1RL1 is regarded as a decoy receptor for IL-33, like soluble IL-1R for IL-1α and IL-1β.[2,20,21]

IL-33 ON MAST CELLS

Human peripheral blood or cord blood progenitor cell-derived mast cells (MCs) and mouse peritoneal and bone marrow-derived cultured MCs constitutively express IL-1RL1[16,18,22-25] and produce various cytokines and chemokines (i.e., IL-1β, IL-6, IL-13, TNF, GM-CSF, CXCL8, CCL1 and CCL2) that induce expression of mouse mast cell protease-6, prolong survival and promote adhesion of naïve human and murine MCs without inducing degranulation in response to IL-33[22-24,26,27] (Fig. 2). IL-33 can enhance IgE/Ag-, monomeric IgE-, C5a-, stem cell factor (SCF)- and nerve growth factor (NGF)-mediated cytokine production in human and mouse MCs, and a human mast cell line, HMC-1.[2,21,28] On the other hand, long-term exposure of human and mouse MCs to IL-33 resulted in attenuation of IgE/Ag-FcεRI-mediated degranulation due to down-regulation of PLCγ1 and Hck expression, although short term exposure to IL-33 did not influence that degranulation directly.[29]

IL-33 ON BASOPHILS

IL-33 can induce production of such cytokines and chemokines as IL-4, IL-5, IL-6, IL-8, IL-13, GM-CSF, CCL2, CCL3 and CCL4 and cell adhesion by promoting CD11b expression—without inducing degranulation or migration—in human and/or mouse naïve basophils that constitutively express IL-1RL1.[30-33] IL-33 enhances IgE-mediated degranulation and migration as well as IgE- and IL-3-mediated cytokine and chemokine production in human and mouse basophils[28,30-32,34] (Fig. 2). IL-33 also enhances the receptor for leptin—which is an adipokine and a member of the IL-6 family of cytokines—on human basophils, suggesting that IL-33 may be involved in metabolic abnormalities associated with inflammation via basophil activation.[35]

IL-33 ON EOSINOPHILS

Human eosinophils also express IL-1RL1,[36,37] and IL-33 enhances eosinophils' survival, cell adhesion accompanied by increased expression of CD11b and ICAM-1, and production of such cytokines and chemokines as IL-6, IL-8, IL-9 and CCL2, as well as superoxide[31,36-38] (Fig. 1). The role of IL-33 in degranulation of human eosinophils is controversial. IL-33 failed to induce degranulation as assessed by release of eosinophil-derived neurotoxin (EDN) and leukotriene C4,[36] but others conversely found it to induce degranulation as assessed by EDN release.[37] In humans, IL-33-stimulated basophils enhanced IL-17 production by $CCR6^+$ $CD4^+$ T cells and by effector and central memory T cells, suggesting basophil involvement in development of Th17-mediated inflammatory disorders such as inflammatory bowel disease.[39]

IL-33 ON NATURAL HELPER CELLS AND OTHER TYPE II INNATE LYMPHOID CELLS

Recently, a number of IL-5- and IL-13-producing Lin^- $c\text{-}kit^+$ $Sca\text{-}1^{-/+}$ innate lymphoid cells, such as natural helper (NH) cells, multi-potent progenitor type 2 cells (MPP^{type2} cells), nuocytes and innate helper type 2 (Ih2) cells, were identified as populations that are distinct from lymphoid progenitors, lymphoid tissue inducer cells and $ROR\gamma t^+$ ILCs.[40-46] Also, GATA-3 was found to be a key transcription factor for development of those cells[47] (Table 1). Lin^- $c\text{-}kit^+$ $Sca\text{-}1^+$ NH cells, found in fat-associated lymphoid clusters in visceral adipose tissue, constitutively express IL-1RL1 and produce larger amounts of IL-5, IL-6 and IL-13, but not IL-4, than basophils and mast cells in response to IL-33 alone or IL-2 + IL-25, but not IL-25 alone. They are involved in host defense against helminths such as *Nippostrongylus brasiliensis* (*N. brasiliensis*) via IL-5- and IL-13-dependent eosinophilia and goblet cell hyperplasia.[40,48] IL-1RL1-expressing Lin^- $c\text{-}kit^+$ $Sca\text{-}1^+$ nuocytes and IL-1RL1-expressing Lin^- $c\text{-}kit^+$ $Sca\text{-}1^-$ Ih2 cells accumulate in the mesenteric lymph nodes, spleen and liver of mice injected with IL-25 or IL-33 and infected with *N. brasiliensis*. Both nuocytes and Ih2 cells as well as NH cells are known to be crucial for host defense against *N. brasiliensis*[41,43,49] and the development of allergic airway inflammation.[50,51] Expansion of Lin^- $c\text{-}kit^+$ $Sca\text{-}1^+$ MPP^{type2} cells, which do not express IL-1RL1, is observed in mesenteric lymph nodes and gut-associated lymphoid tissues, including Peyer's patches, of mice injected with IL-25 or infected with helminths such as *N. brasiliensis* and *Trichuris muris*, contributing to host defense against such pathogens.[42] Although IL-33 and/or IL-25 are key cytokines for expansion of IL-5- and IL-13-producing ILCs such as NH cells, nuocytes, Ih2 cells and MPP^{type2} cells in mice, except for NH cells it is unclear whether these cells produce IL-5 and/or IL-13 in response to IL-33 or IL-25.

Brickshawana *et al*. reported that IL-33-responsive c-Kit-negative $Sca\text{-}1^+$ $CD25^+$ cells differed from c-Kit-positive NH cells, nuocytes and Ih2 cells.[52] Monticelli *et al*. identified Lin^- $c\text{-}Kit^+$ $Sca\text{-}1^+$ $CD90^+$ $CD25^+$ $CD127\ (IL\text{-}7R\alpha)^+$ $IL\text{-}1RL1^+$ cells, which produce IL-5 and IL-13 in response to IL-33, among resident cells in human and mouse lungs, and found that differentiation of those cells requires expression of a transcription factor, Id2.[53] Ikutani *et al*. found two types of $c\text{-}Kit^+$ ILCs, which produce IL-5 alone or IL-13 alone in response to IL-33 or IL-25, in the peritoneal cavity, lung and gut of mice.[54] Bartemes *et al*. also found Lin^- $c\text{-}Kit^+$ $Sca\text{-}1^+$ $CD25^+$ ILCs that produced IL-5 and

Table 1 Natural helper cells and other type 2 innate lymphoid cells

		Natural helper	Nuocyte	MPP^{type2}	Ih2
Induction		Resident	IL-25 &/or IL-33 injection *Nb* infection	IL-25 injection *Nb* infection *Tm* infection	IL-25 &/or IL-33 injection *Nb* infection
Location		FALC	Mesentric LNs, spleen & bone marrow	GALT	Mesentric LNs, spleen, liver, bone marrow & lung
Surface phenotype	Lin	-	-	-	-
	c-Kit	+	+	+	+
	Sca-1	+	+	+	-
	CD45	+	+	+	+
	IL-7Rα/CD127	+	+	-/lo	?
	Thy-1/CD90	+	+	?	+
	CD34	-	-	-/lo	?
	CD25/IL-2Rα	+	-	?	+
	CD44	+	+	?	+
	CD69	+	?	-	+
	CD62L	-	?	-/lo	?
	FcεRIα	-	-	-	?
	IL-1RL1	+	+	-/lo	?
	MHCII	-	+	?	?
	IL-17RB	?	+	?	?
	Others	GITR$^+$ CD27$^+$ CD38$^+$	CD43$^+$ CD132$^+$ Itgb7$^+$ ICOS$^+$ CD49d$^+$ CCR9$^+$		CD122^{lo}
Transcription factor	GATA-3	+	?	?	+
	ROR-α	?	+	?	?
Responsivity to IL-25		○ (+IL-2)	×	?	?
Responsivity to IL-33		○	○ (+IL-7)	?	?
Reference		40, 47	41	42	43

MPP^{type2}, multipotent progenitor type 2; Ih2, innate helper type 2; *Nb*, *Nippostrongylus brasiliensis*; *Tm*, *Trichuris muris*; LN, lymph node; FALC, fat-associated lymphoid cluster; GALT, gut-associated lymphoid tissue.

IL-13 in response to IL-33 in the murine lung.[55] However, unlike Ikutani *et al*., these cells did not respond to IL-25.[55]

IL-33 IN INNATE-TYPE CELLS DURING ALLERGY

Genetic polymorphism of IL-33 and IL-1RL1 is suspected of causing susceptibility to development of asthma in certain patients.[56] In support of that, increased expression/production of IL-33 and/or IL-1 RL1 was shown in specimens from asthma patients.[57-60] Treatment of mice with IL-33 resulted in development of eosinophil-associated inflammation in the lung and gut dependent on IL-13, but independently of B cells (that is, IgE), T cells and NKT cells.[1,61] However, airway eosinophilia after IL-33 inhalation was observed even in mast cell-deficient mice and mice whose NK-cell and basophil populations were depleted[61] by injection of anti-asialo GM1 mAb.[62] These observations suggest that mast cells and basophils are not essential for IgE-independent IL-33-mediated airway eosinophilia. Rather than mast cells and basophils, lung NH cells are suggested to be involved in development of IL-33-mediated airway eosinophilia. A plant-derived cysteine protease, papain, which is homologous to Der P1 and Der f1 from house dust mites and human cathepsin B,[63] induces airway inflammation by disrupting tight junctions between epithelial cells in mice[64] and is a cause of occupational asthma in humans.[65] In mice, papain inhalation increased IL-33 expression in the lung, and subsequently IL-33 induced airway eosinophilia de-

pendently of IL-13 even in the absence of acquired immune cells such as T cells, B cells and NKT cells.[64] In addition to IL-33-deficient mice,[64] NH cell-depleted mice showed attenuated airway eosinophilia after papain inhalation.[66] Thus, lung natural helper cells are crucial for development of papain-induced IL-33-mediated innate-type acute airway eosinophilia. As in mice, resident IL-1RL1-expressing Lin^- $CD127^+$ $CD25^+$ NH cells/innate lymphoid cells have been identified in lung parenchymal tissue from healthy humans,[53] suggesting that resident NH cells/innate lymphoid cells also may be important for human pulmonary immune responses.

As in asthma, genetic polymorphism of IL-1RL1 has also been identified in patients with atopic dermatitis, and expression of IL-33 is increased in inflamed skin from these patients,[21,67,68] suggesting involvement of IL-33 in the development of atopic dermatitis. Intradermal injection of IL-33 to mice caused development of skin inflammation accompanied by accumulation of neutrophils.[69] In contrast to IL-33-induced airway eosinophilia, the IL-33-induced neutrophilic skin inflammation was dependent on dermal mast cell activation via IL-1RL1.[69] The possible roles of basophils and NH cells in IL-33-induced skin inflammation remain poorly understood.

Genetic polymorphism of IL-1RL1 and IL-33 and increased IL-33 levels in specimens are found in certain patients with rhinitis, conjunctivitis and/or rhinosinusitis.[70-73] Ovalbumin-induced or ragweed pollen-induced allergic rhinitis is attenuated in anti-IL-33-Ab-treated mice,[74] IL-33-deficient mice and FcεRI-deficient mice.[73] In ragweed pollen-induced allergic rhinitis, IL-33 enhances release of histamine and chemoattractant factors for eosinophils and basophils by mast cells and basophils, contributing to local inflammation in the early and late phases of diseases.[73] IL-1RL1-expressing Lin^- $CD127^+$ $CD161^+$ $CRTH2^+$ NH/innate lymphoid cells, which produce IL-13 in response to IL-33 or IL-25 in the presence of IL-2, were identified in the human fetal gut and observed to be accumulated in inflamed, but not non-inflamed, nasal polyps from adult patients with chronic rhinosinusitis.[75] Those findings suggest a contribution of IL-33-activated NH/innate lymphoid cells—in addition to mast cells and basophils—to the pathogenesis of allergic diseases.

CONCLUSION

IL-33 released by such cells as epithelial cells and macrophages after tissue injury during infection plays important roles in host defense against pathogens such as nematodes and viruses by activating various cell types, especially innate-type immune cells, including mast cells, basophils, eosinophils and NH cells/innate lymphoid cells. In addition, dysregulation of IL-33 is suspected to be involved in development of various allergic disorders, such as asthma, dermatitis and rhinitis. Thus, neutralization of IL-33 may be a new therapeutic approach for allergic diseases.

ACKNOWLEDGEMENTS

This work was supported by Grants-in-Aid for Young Scientists (A) (S.N.), from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and, PRESTO, JST (S.N.). We also thank Lawrence W. Stiver (Tokyo, Japan) for his critical reading of the manuscript.

REFERENCES

1. Schmitz J, Owyang A, Oldham E *et al*. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity* 2005;**23**:479-90.
2. Oboki K, Ohno T, Kajiwara N, Saito H, Nakae S. IL-33 and IL-33 receptors in host defense and diseases. *Allergol Int* 2010;**59**:143-60.
3. Onda H, Kasuya H, Takakura K *et al*. Identification of genes differentially expressed in canine vasospastic cerebral arteries after subarachnoid hemorrhage. *J Cereb Blood Flow Metab* 1999;**19**:1279-88.
4. Baekkevold ES, Roussigne M, Yamanaka T *et al*. Molecular characterization of NF-HEV, a nuclear factor preferentially expressed in human high endothelial venules. *Am J Pathol* 2003;**163**:69-79.
5. Carriere V, Roussel L, Ortega N *et al*. IL-33, the IL-1-like cytokine ligand for ST2 receptor, is a chromatin-associated nuclear factor in vivo. *Proc Natl Acad Sci U S A* 2007;**104**:282-7.
6. Roussel L, Erard M, Cayrol C, Girard JP. Molecular mimicry between IL-33 and KSHV for attachment to chromatin through the H2A-H2B acidic pocket. *EMBO Rep* 2008; **9**:1006-12.
7. Werman A, Werman-Venkert R, White R *et al*. The precursor form of IL-1α is an intracrine proinflammatory activator of transcription. *Proc Natl Acad Sci U S A* 2004;**101**: 2434-9.
8. Andersson U, Tracey KJ. HMGB1 is a therapeutic target for sterile inflammation and infection. *Annu Rev Immunol* 2011;**29**:139-62.
9. Dinarello CA. Interleukin-1 beta, interleukin-18, and the interleukin-1 beta converting enzyme. *Ann N Y Acad Sci* 1998;**856**:1-11.
10. Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol* 2009;**27**: 519-50.
11. Luthi AU, Cullen SP, McNeela EA *et al*. Suppression of interleukin-33 bioactivity through proteolysis by apoptotic caspases. *Immunity* 2009;**31**:84-98.
12. Talabot-Ayer D, Lamacchia C, Gabay C, Palmer G. Interleukin-33 is biologically active independently of caspase-1 cleavage. *J Biol Chem* 2009;**284**:19420-6.
13. Cayrol C, Girard JP. The IL-1-like cytokine IL-33 is inactivated after maturation by caspase-1. *Proc Natl Acad Sci U S A* 2009;**106**:9021-6.
14. Ohno T, Oboki K, Kajiwara N *et al*. Caspase-1, caspase-8, and calpain are dispensable for IL-33 release by macrophages. *J Immunol* 2009;**183**:7890-7.
15. Lefrancais E, Roga S, Gautier V *et al*. IL-33 is processed into mature bioactive forms by neutrophil elastase and cathepsin G. *Proc Natl Acad Sci U S A* 2012;**109**:1673-8.

16. Ali S, Huber M, Kollewe C, Bischoff SC, Falk W, Martin MU. IL-1 receptor accessory protein is essential for IL-33-induced activation of T lymphocytes and mast cells. *Proc Natl Acad Sci U S A* 2007;**104**:18660-5.
17. Chackerian AA, Oldham ER, Murphy EE, Schmitz J, Pflanz S, Kastelein RA. IL-1 receptor accessory protein and ST2 comprise the IL-33 receptor complex. *J Immunol* 2007;**179**:2551-5.
18. Palmer G, Lipsky BP, Smithgall MD *et al*. The IL-1 receptor accessory protein (AcP) is required for IL-33 signaling and soluble AcP enhances the ability of soluble ST2 to inhibit IL-33. *Cytokine* 2008;**42**:358-64.
19. Akira S, Takeda K, Kaisho T. Toll-like receptors: critical proteins linking innate and acquired immunity. *Nat Immunol* 2001;**2**:675-80.
20. Smith DE. IL-33: a tissue derived cytokine pathway involved in allergic inflammation and asthma. *Clin Exp Allergy* 2010;**40**:200-8.
21. Ohno T, Morita H, Arae K, Matsumoto K, Nakae S. Interleukin-33 in allergy. *Allergy* 2012;**67**:1203-14.
22. Ho LH, Ohno T, Oboki K *et al*. IL-33 induces IL-13 production by mouse mast cells independently of IgE-FcεRI signals. *J Leukoc Biol* 2007;**82**:1481-90.
23. 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.
24. Allakhverdi Z, Smith DE, Comeau MR, Delespesse G. The ST2 ligand IL-33 potently activates and drives maturation of human mast cells. *J Immunol* 2007;**179**:2051-4.
25. Moritz DR, Rodewald HR, Gheyselinck J, Klemenz R. The IL-1 receptor-related T1 antigen is expressed on immature and mature mast cells and on fetal blood mast cell progenitors. *J Immunol* 1998;**161**:4866-74.
26. Moulin D, Donze O, Talabot-Ayer D, Mezin F, Palmer G, Gabay C. Interleukin (IL)-33 induces the release of pro-inflammatory mediators by mast cells. *Cytokine* 2007;**40**: 216-25.
27. Kaieda S, Shin K, Nigrovic PA *et al*. Synovial fibroblasts promote the expression and granule accumulation of tryptase via interleukin-33 and its receptor ST-2 (IL1RL1). *J Biol Chem* 2010;**285**:21478-86.
28. Silver MR, Margulis A, Wood N, Goldman SJ, Kasaian M, Chaudhary D. IL-33 synergizes with IgE-dependent and IgE-independent agents to promote mast cell and basophil activation. *Inflamm Res* 2010;**59**:207-18.
29. Jung MY, Smrz D, Desai A *et al*. IL-33 induces a hyporesponsive phenotype in human and mouse mast cells. *J Immunol* 2013;**190**:531-8.
30. Smithgall MD, Comeau MR, Yoon BR, Kaufman D, Armitage R, Smith DE. IL-33 amplifies both Th1- and Th2-type responses through its activity on human basophils, allergen-reactive Th2 cells, iNKT and NK cells. *Int Immunol* 2008;**20**:1019-30.
31. Pecaric-Petkovic T, Didichenko SA, Kaempfer S, Spiegl N, Dahinden CA. Human basophils and eosinophils are the direct target leukocytes of the novel IL-1 family member IL-33. *Blood* 2009;**113**:1526-34.
32. Suzukawa M, Iikura M, Koketsu R *et al*. An IL-1 cytokine member, IL-33, induces human basophil activation via its ST2 receptor. *J Immunol* 2008;**181**:5981-9.
33. Schneider E, Petit-Bertron AF, Bricard R *et al*. IL-33 activates unprimed murine basophils directly in vitro and induces their in vivo expansion indirectly by promoting hematopoietic growth factor production. *J Immunol* 2009; **183**:3591-7.
34. Kroeger KM, Sullivan BM, Locksley RM. IL-18 and IL-33 elicit Th2 cytokines from basophils via a MyD88- and p38α-dependent pathway. *J Leukoc Biol* 2009;**86**:769-78.
35. Suzukawa M, Nagase H, Ogahara I *et al*. Leptin enhances survival and induces migration, degranulation, and cytokine synthesis of human basophils. *J Immunol* 2011; **186**:5254-60.
36. Suzukawa M, Koketsu R, Iikura M *et al*. Interleukin-33 enhances adhesion, CD11b expression and survival in human eosinophils. *Lab Invest* 2008;**88**:1245-53.
37. Cherry WB, Yoon J, Bartemes KR, Iijima K, Kita H. A novel IL-1 family cytokine, IL-33, potently activates human eosinophils. *J Allergy Clin Immunol* 2008;**121**:1484-90.
38. Chow JY, Wong CK, Cheung PF, Lam CW. Intracellular signaling mechanisms regulating the activation of human eosinophils by the novel Th2 cytokine IL-33: implications for allergic inflammation. *Cell Mol Immunol* 2010;**7**:26-34.
39. Wakahara K, Baba N, Van VQ *et al*. Human basophils interact with memory T cells to augment Th17 responses. *Blood* 2012;**120**:4761-71.
40. Moro K, Yamada T, Tanabe M *et al*. Innate production of TH2 cytokines by adipose tissue-associated c-Kit$^+$Sca-1$^+$ lymphoid cells. *Nature* 2010;**463**:540-4.
41. Neill DR, Wong SH, Bellosi A *et al*. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. *Nature* 2010;**464**:1367-70.
42. Saenz SA, Siracusa MC, Perrigoue JG *et al*. IL25 elicits a multipotent progenitor cell population that promotes TH2 cytokine responses. *Nature* 2010;**464**:1362-6.
43. Price AE, Liang HE, Sullivan BM *et al*. Systemically dispersed innate IL-13-expressing cells in type 2 immunity. *Proc Natl Acad Sci U S A* 2010;**107**:11489-94.
44. Koyasu S, Moro K. Type 2 innate immune responses and the natural helper cell. *Immunology* 2011;**132**:475-81.
45. Saenz SA, Noti M, Artis D. Innate immune cell populations function as initiators and effectors in Th2 cytokine responses. *Trends Immunol* 2010;**31**:407-13.
46. Barlow JL, McKenzie AN. Nuocytes: expanding the innate cell repertoire in type-2 immunity. *J Leukoc Biol* 2011;**90**:867-74.
47. Hoyler T, Klose CS, Souabni A *et al*. The transcription factor GATA-3 controls cell fate and maintenance of type 2 innate lymphoid cells. *Immunity* 2012;**37**:634-48.
48. Koyasu S, Moro K. Innate Th2-type immune responses and the natural helper cell, a newly identified lymphocyte population. *Curr Opin Allergy Clin Immunol* 2011;**11**:109-14.
49. Liang HE, Reinhardt RL, Bando JK, Sullivan BM, Ho IC, Locksley RM. Divergent expression patterns of IL-4 and IL-13 define unique functions in allergic immunity. *Nat Immunol* 2011;**13**:58-66.
50. Wilhelm C, Hirota K, Stieglitz B *et al*. An IL-9 fate reporter demonstrates the induction of an innate IL-9 response in lung inflammation. *Nat Immunol* 2011;**12**:1071-7.
51. Barlow JL, Bellosi A, Hardman CS *et al*. Innate IL-13-producing nuocytes arise during allergic lung inflammation and contribute to airways hyperreactivity. *J Allergy Clin Immunol* 2012;**129**:191-8. e1-4.
52. Brickshawana A, Shapiro VS, Kita H, Pease LR. Lineage$^-$ Sca1$^+$c-Kit$^-$CD25$^+$ cells are IL-33-responsive type 2 innate cells in the mouse bone marrow. *J Immunol* 2011;**187**: 5795-804.
53. Monticelli LA, Sonnenberg GF, Abt MC *et al*. Innate lymphoid cells promote lung-tissue homeostasis after infection with influenza virus. *Nat Immunol* 2011;**12**:1045-54.
54. Ikutani M, Yanagibashi T, Ogasawara M *et al*. Identifica-

tion of innate IL-5-producing cells and their role in lung eosinophil regulation and antitumor immunity. *J Immunol* 2012;**188**:703-13.
55. Bartemes KR, Iijima K, Kobayashi T, Kephart GM, McKenzie AN, Kita H. IL-33-responsive lineage$^-$ CD25$^+$ CD44^{hi} lymphoid cells mediate innate type 2 immunity and allergic inflammation in the lungs. *J Immunol* 2012; **188**:1503-13.
56. Gudbjartsson DF, Bjornsdottir US, Halapi E *et al*. Sequence variants affecting eosinophil numbers associate with asthma and myocardial infarction. *Nat Genet* 2009; **41**:342-7.
57. Oshikawa K, Kuroiwa K, Tago K *et al*. Elevated soluble ST2 protein levels in sera of patients with asthma with an acute exacerbation. *Am J Respir Crit Care Med* 2001;**164**: 277-81.
58. Ali M, Zhang G, Thomas WR *et al*. Investigations into the role of ST2 in acute asthma in children. *Tissue Antigens* 2009;**73**:206-12.
59. Prefontaine D, Lajoie-Kadoch S, Foley S *et al*. Increased expression of IL-33 in severe asthma: evidence of expression by airway smooth muscle cells. *J Immunol* 2009;**183**: 5094-103.
60. Prefontaine D, Nadigel J, Chouiali F *et al*. Increased IL-33 expression by epithelial cells in bronchial asthma. *J Allergy Clin Immunol* 2010;**125**:752-4.
61. Kondo Y, Yoshimoto T, Yasuda K *et al*. Administration of IL-33 induces airway hyperresponsiveness and goblet cell hyperplasia in the lungs in the absence of adaptive immune system. *Int Immunol* 2008;**20**:791-800.
62. Nishikado H, Mukai K, Kawano Y, Minegishi Y, Karasuyama H. NK cell-depleting anti-asialo GM1 antibody exhibits a lethal off-target effect on basophils in vivo. *J Immunol* 2011;**186**:5766-71.
63. Chua KY, Stewart GA, Thomas WR *et al*. Sequence analysis of cDNA coding for a major house dust mite allergen, Der p 1. Homology with cysteine proteases. *J Exp Med* 1988;**167**:175-82.
64. Oboki K, Ohno T, Kajiwara N *et al*. IL-33 is a crucial amplifier of innate rather than acquired immunity. *Proc Natl Acad Sci U S A* 2010;**107**:18581-6.
65. Milne J, Brand S. Occupational asthma after inhalation of dust of the proteolytic enzyme, papain. *Br J Ind Med* 1975; **32**:302-7.
66. Halim TY, Krauss RH, Sun AC, Takei F. Lung natural helper cells are a critical source of Th2 cell-type cytokines in protease allergen-induced airway inflammation. *Immunity* 2012;**36**:451-63.
67. Shimizu M, Matsuda A, Yanagisawa K *et al*. Functional SNPs in the distal promoter of the ST2 gene are associated with atopic dermatitis. *Hum Mol Genet* 2005;**14**:2919-27.
68. Matsuda A, Okayama Y, Terai N *et al*. The role of interleukin-33 in chronic allergic conjunctivitis. *Invest Ophthalmol Vis Sci* 2009;**50**:4646-52.
69. Hueber AJ, Alves-Filho JC, Asquith DL *et al*. IL-33 induces skin inflammation with mast cell and neutrophil activation. *Eur J Immunol* 2011;**41**:2229-37.
70. Sakashita M, Yoshimoto T, Hirota T *et al*. Association of serum interleukin-33 level and the interleukin-33 genetic variant with Japanese cedar pollinosis. *Clin Exp Allergy* 2008;**38**:1875-81.
71. Castano R, Bosse Y, Endam LM, Desrosiers M. Evidence of association of interleukin-1 receptor-like 1 gene polymorphisms with chronic rhinosinusitis. *Am J Rhinol Allergy* 2009;**23**:377-84.
72. Asaka D, Yoshikawa M, Nakayama T, Yoshimura T, Moriyama H, Otori N. Elevated levels of interleukin-33 in the nasal secretions of patients with allergic rhinitis. *Int Arch Allergy Immunol* 2012;**158** (Suppl 1):47-50.
73. Haenuki Y, Matsushita K, Futatsugi-Yumikura S *et al*. A critical role of IL-33 in experimental allergic rhinitis. *J Allergy Clin Immunol* 2012;**130**:184-94.e11.
74. Kim YH, Yang TY, Park CS *et al*. Anti-IL-33 antibody has a therapeutic effect in a murine model of allergic rhinitis. *Allergy* 2012;**67**:183-90.
75. Mjosberg JM, Trifari S, Crellin NK *et al*. Human IL-25- and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CRTH2 and CD161. *Nat Immunol* 2011;**12**:1055-62.