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REVIEW

Regulatory roles of mast cells in immune responses

Hideaki Morita[1,2] · **Hirohisa Saito**[1] · **Kenji Matsumoto**[1] · **Susumu Nakae**[3,4]

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Abstract Mast cells are important immune cells for host defense through activation of innate immunity (via toll-like receptors or complement receptors) and acquired immunity (via FcεRI). Conversely, mast cells also act as effector cells that exacerbate development of allergic or autoimmune disorders. Yet, several lines of evidence show that mast cells act as regulatory cells to suppress certain inflammatory diseases. Here, we review the mechanisms by which mast cells suppress diseases.

Keywords Mast cell · Rejection · Graft-versus-host disease · Contact hypersensitivity · Innate-type allergic airway inflammation

Introduction

Mast cells are derived from hematopoietic stem cells and are distributed in various tissues, especially the airways, skin, and gastrointestinal tract, where various antigens are encountered. Mast cells are thus considered to be sentinel immune cells in host defense. Indeed, mast cells can contribute to host defense against pathogens via innate immune systems such as toll-like receptors or complement receptors [1]. Binding of antigen-specific IgE to FcεRI on the surface of mast cells primes them to release various mediators upon subsequent exposure to the specific Ag [1]. IgE-mediated mast cell activation is important for host defense against certain parasites [2]. Mast cells also influence functions of various types of immune cells such as dendritic cells (DCs), macrophages, T cells, and B cells [3], contributing indirectly to host defense via such cells. However, inappropriate or excessive activation of mast cells is generally known to aggravate development of various diseases such as allergic and autoimmune diseases [4]. On the other hand, mast cells also play a suppressive role in development of certain diseases. Thus, mast cells can act not only as effector cells but also as suppressor cells, in certain immune responses, and those various roles are described in the following sections.

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✉ Susumu Nakae
snakae@ims.u-tokyo.ac.jp

[1] Department of Allergy and Clinical Immunology, National Research Institute for Child Health and Development, Tokyo 157-8535, Japan

[2] Swiss Institute of Allergy and Asthma Research, University of Zurich, Davos 7270, Switzerland

[3] Laboratory of Systems Biology, Center for Experimental Medicine and Systems Biology, The Institute of Medical Science, The University of Tokyo, Tokyo 108-8639, Japan

[4] Precursory Research for Embryonic Science and Technology (PRESTO), Japan Science and Technology Agency, Saitama 332-0012, Japan

Regulatory role of mast cells in skin allograft rejection

The number of mast cells is increased at the local sites of allografts such as the liver [5], kidney [6], and lung [7] in humans, which suggested that mast cells may contribute to the pathogenesis of allograft rejection. Mast cell-deficient $Kit^{W\text{-}sh/W\text{-}sh}$ mice were used to elucidate the roles of recipient mast cells in acute and chronic cardiac allograft rejection [8]. In this model, recipient mast cells were not required for acute or chronic cardiac allograft rejection [8]. On the other hand, mast cells played an immune-suppressive role in a murine model of skin allograft transplantation [9]. Compared with in naïve mice, long-term skin allograft survival was observed in mice rendered tolerant to alloantigens by co-injection of

allogenic cells and anti-CD154 blocking Abs [9]. In the setting, the numbers of regulatory T cells (Tregs), which are important for tolerance to alloantigens [10], and mast cells were increased in the skin allografts of the tolerized mice compared with the non-tolerized mice [9]. Remarkably, the long-term skin allograft survival seen in tolerized wild-type mice was not observed in tolerized mast cell-deficient $Kit^{W\text{-}sh/W\text{-}sh}$ mice [9], suggesting that mast cells somehow contribute to Treg-mediated skin allograft tolerance. In addition to Tregs and mast cells, IL-9, which is a potent cytokine that enhances growth and recruitment of mast cells [11–13], was also crucial for skin allograft tolerance in this model [9]. Tregs were a potential source of IL-9 in skin allografts, and treatment of wild-type mice with anti-IL-9 neutralizing Abs resulted in failure of skin allograft tolerance and accumulation of mast cells in the skin allografts [9]. Although direct evidence that Treg-derived IL-9 is involved in skin allograft tolerance was not generated (i.e., by adoptive transfer analysis using IL-9-deficient and IL-9-sufficient Tregs), these observations suggest that Treg-derived IL-9 may control mast cell function (Fig. 1). Likewise, Tregs and mast cells (especially their interaction) were crucial for protection in a Th1- and Th17-dependent model of nephrotoxic serum nephritis [14]. Transfer of wild-type Tregs prevented nephrotoxic serum nephritis and accumulation of mast cells in kidney-draining lymph nodes in wild-type, but not mast cell-deficient $Kit^{W/W\text{-}v}$, recipient mice [14]. On the other hand, transfer of IL-9-deficient Tregs failed to protect wild-type recipient mice against nephrotoxic serum nephritis and mast cell accumulation in kidney-draining lymph nodes [14]. Therefore, these observations in the two models of skin allograft and nephrotoxic serum nephritis suggested that Treg-derived IL-9 promotes mast cell function, and the mast cells somehow subsequently contribute to immune suppression.

Certain subsets of DCs, so-called tolerogenic DCs, are known to be crucial for induction of Tregs in draining lymph nodes, thereby contributing to allograft tolerance [15, 16]. Indeed, long-term skin allograft survival seen in wild-type mice tolerized by co-injection of allogenic cells and anti-CD154 blocking Abs was diminished in tolerized DC-depleted mice as well as mast cell-deficient $Kit^{W\text{-}sh/W\text{-}sh}$ mice [9, 16]. In the setting, mast cell-deficient $Kit^{W\text{-}sh/W\text{-}sh}$ mice showed impaired DC migration from the skin grafts to draining lymph nodes [16]. Mast cell-derived TNF and GM-CSF were, respectively, crucial for migration of DCs from skin grafts to draining lymph nodes and survival of DCs in draining lymph nodes [16] (Fig. 1). Taken together, mast cells control tolerogenic DCs, resulting in induction of Tregs in draining LNs during skin allograft tolerance.

Regulatory role of mast cells in graft-versus-host disease

Mast cells may contribute to the pathogenesis of acute graft-versus-host disease (GVHD) in humans [17]. Acute GVHD induced in irradiated DBA/2 mice (H-2^d) transplanted with T cells and bone marrow cells from B10.D2 mice (H-2^d) by mismatching minor histocompatibility antigens [18] was suppressed by treatment with peptide antagonists of binding of IgE to FcεR1 [19], suggesting that IgE/Ag-stimulated mast cells can enhance development of acute GVHD. In addition, the onset of acute GVHD in irradiated WBB6F1-$Kit^{W/W\text{-}v}$ mast cell-deficient mice was significantly delayed compared with in irradiated WBB6F1-$Kit^{+/+}$ mice (H-$2^{ja/b}$) after transplantation of $CD8^+$ T cells and T cell-depleted bone marrow cells

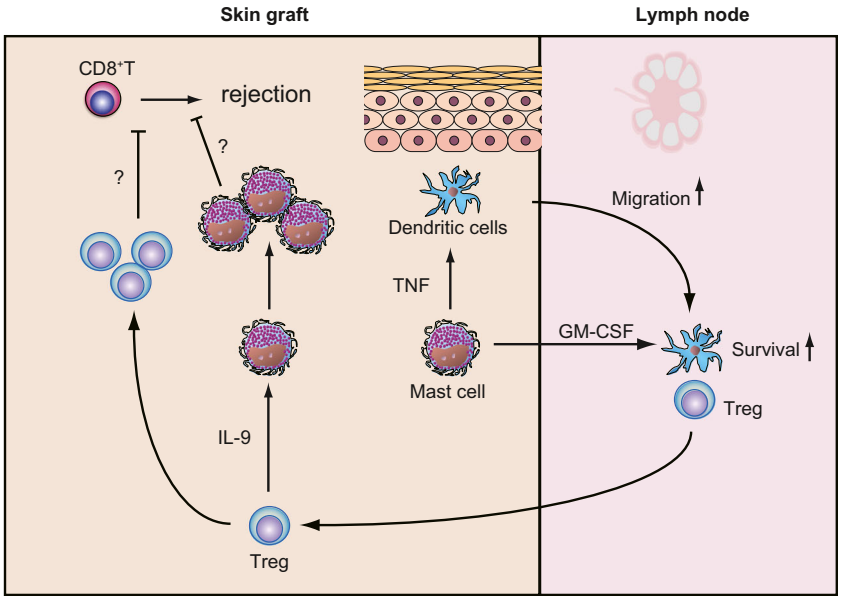

Fig. 1 Regulatory role of mast cells in skin allograft rejection. Mast cell-derived TNF and GM-CSF, respectively, enhance migration of dendritic cells (DCs) from the skin to draining lymph nodes and survival of DCs in draining lymph nodes. Then, DCs induce regulatory T cell (Treg) expansion in draining lymph nodes, after which the Tregs move to the skin allograft and produce IL-9, resulting in enhanced growth and recruitment of mast cells. Tregs and mast cells somehow suppress $CD8^+$ T cell-mediated allograft rejection

from C3H.SW mice (H-2^b) [20]. These observations suggest that mast cells act as effector cells in the development of acute GVHD induced by mismatching minor histocompatibility antigens in mice. Conversely, the development of acute GVHD by mismatching MHC antigens was significantly exacerbated in C57BL/6J mast cell-deficient $Kit^{W\text{-}sh/W\text{-}sh}$ mice (H-2^b) transplanted with T cell-depleted bone marrow cells from FVB/N mice (H-2^q) compared with C57BL/6J wild-type mice transplanted with T cell-depleted bone marrow cells from FVB/N mice [21], suggesting that mast cells play an immunoregulatory role in this setting. The exacerbated acute GVHD seen in C57BL/6J mast cell-deficient $Kit^{W\text{-}sh/W\text{-}sh}$ recipient mice was independent of Tregs, because the number, frequency, and suppressive function of Tregs were normal in the liver, spleen, and lymph nodes of those mice during the acute GVHD [21]. The exacerbated acute GVHD recovered to the level seen in the wild-type recipient mice when wild-type, but not IL-10-deficient, mast cells were administered [21]. These observations suggest that mast cell-derived IL-10 is crucial for inhibition of acute GVHD due to mismatched MHC antigens, independently of Tregs in mice, although it remains unknown what triggers mast cells to produce IL-10 in the setting.

Regulatory role of mast cells in contact hypersensitivities

Delayed-type hypersensitivity (DTH), which is experimentally elicited in mice by immunization with exogenous antigens such as cells (i.e., sheep red blood cells [SRBC] and allogenic splenocytes), protein antigens (i.e., ovalbumin [OVA], methylated bovine serum albumin [mBSA], and keyhole limpet hemocyanin), and pathogens (*Mycobacterium*, *Leishmania*, and viruses), is considered to be a Th1 cell-mediated cellular immune response [22]. Mast cells were not essential for development of DTH induced by immunization of mice with methylated human serum albumin (mHSA) emulsified in complete Freund's adjuvant (CFA) or SRBC emulsified in incomplete Freund's adjuvant (IFA) or CFA [23]. On the other hand, mast cell-deficient $Kit^{W/W\text{-}v}$ mice and $Kit^{Wf/Wf}$ mice showed reduced DTH when immunized with mHSA emulsified in IFA [23], SRBC without adjuvant [24], or OVA emulsified in CFA [25]. Therefore, mast cells must function as effector cells in such models of DTH.

Classically, contact hypersensitivity (CHS), which is induced by epicutaneous exposure to haptens, was considered to be a form of DTH reaction. However, studies using gene-deficient mice showed that the molecular mechanism of development of CHS differs from that of DTH [26]. Mast cells are involved [24, 27–33] or not involved [34–39] in development of acute CHS (Table 1). This apparent discrepancy in the contribution of mast cells to DTH and acute CHS may have been due to different experimental protocols. Likewise, the role of mast cells in development of OVA-induced allergic airway inflammation differed between immunization protocols (i.e., in the presence or absence of adjuvant) [40, 41]. On the other hand, mast cells play a regulatory role in development of certain CHS models in mice. It is known that ultraviolet B (UVB) irradiation suppresses systemic immune responses including CHS [42]. After exposure to UVB, induction of acute CHS by 2,4,6-trinitrochlorobenzene (TNCB) was suppressed in $Kit^{+/+}$ mice, but not in mast cell-deficient $Kit^{W\text{-}f/W\text{-}f}$ mice [43]. In this model, UVB-induced production of histamine by mast cells is considered to be important for UVB-induced immune suppression during acute CHS [43].

Chronic CHS is induced by repeated epicutaneous exposure to haptens. Development of chronic CHS induced by 2,4-dinitrofluorobenzene (DNFB) or urushiol was exacerbated in mast cell-deficient $Kit^{W\text{-}sh/W\text{-}sh}$ and $Kit^{W}/Kit^{W\text{-}v}$ mice compared with $Kit^{+/+}$ mice, suggesting that mast cells suppress the development of chronic CHS [44]. The exacerbated DNFB-induced chronic CHS was attenuated by intradermal engraftment of bone marrow cell-derived cultured mast cells from wild-type, but not IL-10-deficient, mice [44]. In this model, IL-10 production by IgG1/FcγR-mediated mast cells is crucial for suppression of chronic CHS [44] (Fig. 2). Likewise, development of chronic CHS induced by oxazolone was exacerbated in mast cell-deficient $Kit^{W\text{-}sh/W\text{-}sh}$ mice compared with $Kit^{+/+}$ mice [45]. The exacerbated oxazolone-induced chronic CHS was similarly attenuated by engraftment of bone marrow cell-derived cultured mast cells from wild-type, but not IL-2-deficient, mice [45]. These results suggested that IL-2 production by mast cells in response to IgE/Ag in the spleen, but not local skin, enhances Treg expansion in the inflamed skin, but not in the spleen, following suppression of skin inflammation during chronic CHS by Tregs [45] (Fig. 2).

By contrast, mast cell-depleted mice (diphtheria toxin (DT)-injected Mcpt5-Cre^+ $iDTR^+$ mice or Mcpt5-Cre^+ Rosa-DTA^+ mice, in which connective tissue-type mast cells are depleted but mucosal-type mast cells are present) showed attenuated development of DNFB-induced chronic CHS as well as DNFB- and/or FITC-induced acute CHS [32], suggesting that mast cells are potent effector cells in induction of acute and chronic CHS. The reason for the discrepancy between mast cell-deficient Kit mutant mice and mast cell-depleted mice remains unclear, but it may be due to mast cell-independent Kit signaling in mast cell-deficient Kit mutant mice ($Kit^{W\text{-}sh/W\text{-}sh}$ mice, $Kit^{W}/Kit^{W\text{-}v}$ mice, etc.) or some effect of mucosal-type mast cells in mast cell-depleted mice (DT-injected Mcpt5-Cre^+ $iDTR^+$ mice and Mcpt5-Cre^+ Rosa-DTA^+ mice). Also, since a commercial database (NextBio, Illumina Inc.) indicates that Mcpt5 mRNA is expressed in certain types of macrophages, B cells and NK cells, and mast cells, we can not rule out the possibility that depletion of such cells as well as mast cells also influences the phenotypes seen of DT-injected Mcpt5-Cre^+ $iDTR^+$ mice and Mcpt5-Cre^+ Rosa-DTA^+ mice.

Table 1 Roles of mast cells in contact hypersensitibity; analysis of different mast cell-deficient mice

Model	Strain	Phenotype	Hapten	Concentration of hapten (%)		Solvent of hapten		Reference
				Sensitization phase	Challenge phase	Sensitization phase	Challenge phase	
Acute	W/W^v, Sl/Sl^d	Suppressed	TNCB	5.0	0.8	EtOH/Ac (3:1)	OO	24
	W/W^v, Sl/Sl^d		TNCB	5.0	5.0	EtOH/Ac (3:1)	OO	27
	W/W^v, Sl/Sl^d		TNCB	5.0	1.0	EtOH/Ac (3:1)	OO	28
	W/W^v, Sl/Sl^d		Oxazolone	3.0	1.0	EtOH/Ac (3:1)	EtOH/Ac (3:1)	28
	W/W^v		Oxazolone	1.6	0.8	EtOH	EtOH	29
	$Kit^W/Kit^{W\text{-}v}$		TNCB	2.0	1.0	Ac/OO (4:1)	Ac/OO (1:9)	30
	W/W^v		DNFB	0.5	0.2	EtOH	EtOH	31
	W/W^v		Oxazolone	2.0	1.0	EtOH	EtOH	31
	Mcpt5-Cre+ iDTR+		DNFB	0.5	0.2	Ac/OO (4:1)	Ac/OO (4:1)	32
	Mas-TRECK		DNFB	0.5	0.3	Ac/OO (4:1)	Ac/OO (4:1)	33
	Mas-TRECK		Oxazolone	2.0	1.0	Ac/OO (4:1)	Ac/OO (4:1)	33
Acute	W^f/W^f, W/W^v	No change	TNCB	5.0	0.5	Ac/DP (1:1)	Ac/DP (1:1)	34
	Wf/Wf, *W/Wv*		Oxazolone	3.0	0.5	Ac/DP (1:1)	Ac/DP (1:1)	34
	W^f/W^f, W/W^v		Oxazolone	3.0	1.0	Ac/DP (1:1)	Ac/DP (1:1)	34
	W/W^v, Sl/Sl^d		TNCB	5.0	0.5	EtOH	EtOH	35
	W/W^v, Sl/Sl^d		Oxazolone	3.0	0.3	EtOH	EtOH	35
	W/W^v, Sl/Sl^d		Oxazolone	3.0	2.5	EtOH	EtOH	35
	W/W^v, Sl/Sl^d		DNFB	0.5	0.2	Ac/OO (4:1)	Ac/OO (4:1)	36
	W/W^v, Sl/Sl^d		Oxazolone	3.0	0.5	Ac/OO (4:1)	Ac/OO (4:1)	37
	W/W^v, Sl/Sl^d		DNFB	0.5	0.2	Ac/OO (4:1)	Ac/OO (4:1)	37
	W/W^v		TNCB	2.5	1.0	Ac/OO (4:1)	Ac/OO (4:1)	38
	W/W^v, Sl/Sl^d		Oxazolone	3.0	0.5	Ac/OO (4:1)	Ac/OO (4:1)	39
Chronic	$Kit^{W\text{-}sh/W\text{-}sh}$	Exacerbated	Oxazolone	1	0.5	Ac	Ac	45
	$Kit^{W\text{-}sh/W\text{-}sh}$, $Kit^{W/W\text{-}v}$		DNFB	0.5	0.5	Ac	Ac	44
	$Kit^{W/W\text{-}v}$, $Kit^{W\text{-}sh/W\text{-}sh}$		DNFB	0.5	0.2	Ac/OO (4:1)	Ac/OO (4:1)	32
Chronic	Mcpt5-Cre+ iDTR+	Suppressed	DNFB	0.5	0.2	Ac/OO (4:1)	Ac/OO (4:1)	32

EtOH ethanol, *Ac* acetone, *OO* olive oil, *DP* dibutyl phthalate

Regulatory role of mast cells in innate-type allergic airway inflammation

It is thought that, in the sensitization process to allergens during allergic airway inflammation such as asthma, the allergens have to invade hosts beyond the epithelial cell barrier in the airway. House dust mites (HDMs) are considered as a major source of allergens in various allergic diseases such as atopic asthma, dermatitis, and rhinitis [46]. HDM-derived cysteine proteases such as Der p1 and Der f1 can disrupt the tight junctions between epithelial cells [47–49], allowing invasion of allergens into hosts. In addition to disrupting the tight junctions, such proteases also induce necrosis of epithelial cells, following induction of antigen-non-specific inflammation by damage-associated molecular patterns (DAMPs). Supporting this, inhalation of Der p1 and papain, which is a plant-derived cysteine protease and homologous to Der p1/Der f1 and human cathepsin B [50], in mice resulted in induction of airway inflammation in the absence of acquired immune systems [51, 52]. In the setting, papain damaged airway epithelial cells, after which epithelial cell-derived DAMP "IL-33," which is a member of the IL-1 cytokine family and binds to IL-33R (a heterodimer of ST2 and IL-1R accessory protein), activated group 2 innate lymphoid cells (ILC2) to secrete IL-5 and IL-13 in the lung, leading to development of eosinophilic airway inflammation [51–53] (Fig. 3). IL-33 can activate both mast cells and basophils even in the absence of IgE/Ag-FcεRI cross-linking [54–56]. During the papain-induced innate-type airway inflammation, IL-33-dependent basophil-derived IL-4 was important for type 2 cytokine production by ILC2, indicating that basophils are potent effector cells [52] (Fig. 3). On the other hand, mast cell-deficient $Kit^{W\text{-}sh/W\text{-}sh}$ mice showed exacerbated development of papain-induced innate-type airway inflammation, suggesting that mast cells normally play a suppressive role [57]. In the setting, IL-33-dependent mast cell-derived IL-2 induced expansion of Tregs, after which

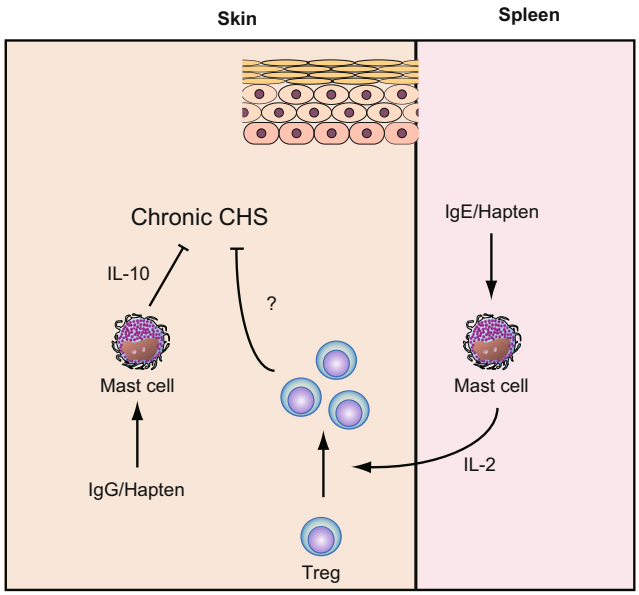

Figure 2 Regulatory role of mast cells in contact hypersensitivities. In chronic contact hypersensitivity (CHS) induced by DNFB, IgG/hapten-dependent mast cell-derived IL-10 suppresses skin inflammation independently of Tregs. In chronic CHS induced by oxazolone, mast cells produce IL-2 in response to IgE/hapten in the spleen, and IL-2 subsequently enhances expansion of Tregs in the skin, resulting in suppression of CHS

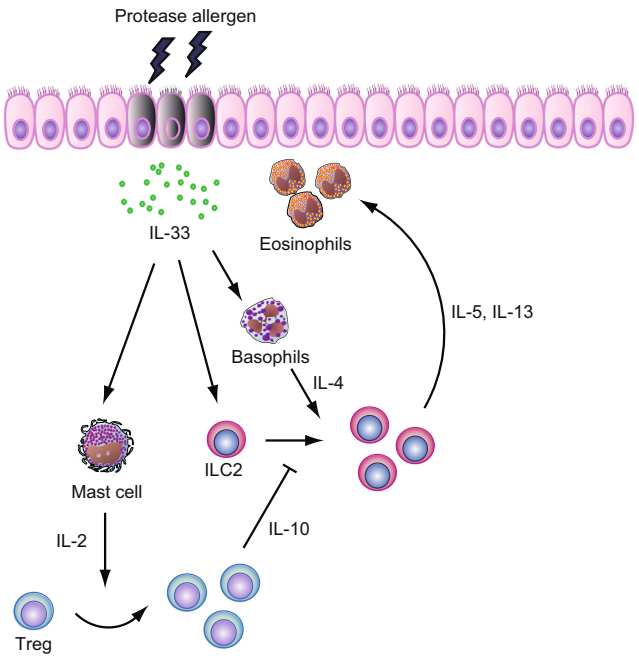

Fig. 3 Regulatory role of mast cells in innate-type allergic airway inflammation. After inhalation of protease antigens, epithelial cells release IL-33, followed by activation of group 2 innate lymphoid cells (ILC2) and basophils. IL-33-stimulated and/or IL-33-stimulated basophil-derived IL-4-dependent ILC2 produce type 2 cytokines such as IL-5 and IL-13, resulting in induction of airway eosinophilia in the absence of antigen-specific T cells and B cells. On the other hand, IL-33 stimulates mast cells to produce IL-2, after which IL-2 induces expansion of Tregs. Then, Treg-derived IL-10 suppresses ILC2-mediated airway eosinophilia

Treg-derived IL-10 inhibited ILC2 proliferation and type 2 cytokine production, resulting in suppression of ILC2-mediated papain-induced innate-type airway inflammation [57] (Fig. 3).

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Compliance with ethical standards

Conflict of interests The authors declare that they have no competing interests.

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