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REVIEW

Roles of basophils and mast cells in cutaneous inflammation

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Abstract Mast cells and basophils are associated with T helper 2 (Th2) immune responses. Newly developed mast cell-deficient mice have provided evidence that mast cells initiate contact hypersensitivity via activating dendritic cells. Studies using basophil-deficient mice have also revealed that basophils are responsible for cutaneous Th2 skewing to haptens and peptide antigens but not to protein antigens. Recently, several studies reported the existence of innate lymphoid cells (ILCs), which differ from classic T cells in that they lack the T cell receptor. Mast cells and basophils can interact with ILCs and play some roles in the pathogenesis of Th2 responses. Basophil-derived interleukin (IL)-4 enhances the expression of the chemokine CCL11, as well as IL-5, IL-9, and IL-13 in ILC2s, leading to the accumulation of eosinophils in allergic reactions. IL-33-stimulated mast cells can play a regulatory role in the development of ILC2-mediated non-antigen-specific protease-induced acute inflammation. In this review, we discuss the recent advances in our understanding of mast cells and basophils in immunity and inflammation.

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Introduction

Both mast cells and basophils produce the same effector molecules, including histamine, various cytokines, pro-inflammatory chemokines, and lipid mediators. Mast cells and basophils are associated with T helper 2 (Th2) immune responses. Mast cells are involved in the protection of the host against a range of parasitic and bacterial infections, the induction of tolerance to skin transplants, and tumor rejection [1, 2]. Basophils contribute to the pathogenesis of allergic skin and airway inflammation and contribute to immunity against parasites in both the gut and the skin [3, 4]. Mast cells also cause detrimental inflammatory responses to allergens and may exacerbate autoimmunity [5].

Recently, newly developed mast cell-deficient mice have provided evidence that mast cells initiate contact hypersensitivity via activating dendritic cells. In addition, studies using basophil-deficient mice have revealed that basophils are responsible for cutaneous Th2 skewing to haptens and peptide antigens but not to protein antigens. Moreover, human basophils infiltrate different skin lesions and have been implicated in the pathogenesis of a variety of skin diseases ranging from atopic dermatitis (AD) to autoimmune diseases [3, 4].

Recent studies have reported the existence of innate lymphoid cells (ILCs) in both mice and human subjects, which differ from classic T cells in that they lack the T cell receptor [6]. Mast cells and basophils can interact with ILCs and play some roles in the pathogenesis of Th2 responses. In this review, we summarize these recent studies on mast cells and basophils and focus on their role in immunity and inflammation.

Newly generated mast cell-specific depletion model

The selective depletion of mast cells in vivo is a useful tool to address the role of these cells in immune responses. Classic models for the investigation of mast cell functions are based on Kit-mutant mouse strains. In addition to their mast cell defect, $Kit^{W/Wv}$ mice that are *Kit*-mutant mouse strains have multiple hematopoietic abnormalities that include compromised fitness of the hematopoietic stem and progenitor cells [7], severe macrocytic anemia [8], impaired T development in the thymus [8], and a shift in intraepithelial T cells in the gut in favor of T cell receptor (TCR) $\alpha\beta^+$ cells and against TCR $\gamma\delta^+$ cells [9]. In addition, the *Kit* mutant is neutropenic, and this may be a major factor affecting immune responses in this strain [10].

Recently, new mouse models have been developed, which have marginal effects on other immune cells. These studies have reported the generation of mice expressing Cre recombinase under the control of mast cell protease genes [11–13]. Several groups developed their mice or generated lines to obtain Kit-independent mast cell-deficient mouse strains [14–17]. The differences among these strains are the selected gene loci and the methods used to drive ectopic gene expression in mast cells (targeted knock-in or transgenic overexpression) and depletion mechanisms. Dudeck et al. generated a mast cell depletion model in which *mast cell protease* (*Mcpt*)*5-Cre* transgenic mice were crossed to *inducible diphtheria toxin receptor* (*iDTR*) line [13]. In these mice, peritoneal mast cells were completely depleted by a single injection of diphtheria toxin (DT), but skin-resident mast cells were not. For the depletion of mast cells in the skin, $Mcpt5\text{-}Cre^+ iDTR^+$ mice require an additional local injection of DT [14]. Using *Mcpt5-Cre* mice crossed with the *R-DTA* line, the constitutive mast cell depletion model was generated [18]. These models do not have any effects on other cell types. Lilla et al. crossed mice carrying the *Cpa3-Cre* transgene with mice in which the first exon of myeloid cell leukemia sequence 1 (Mcl-1) is flanked by LoxP sites [16] and generated constitutive mast cell deficiency. Although these mice exhibit reductions in mast cell number in all tissues, they also exhibit a marked reduction in basophils, splenic neutrophilia, and macrocytic anemia. Using *Cpa3-Cre* transgenic mice, Feyerabend et al. also generated a mast cell deficiency model [15]. These mice exhibit reductions in mast cells and basophils. Considering the phenotype of these mast cell depletion models, Cpa3 may play some roles in the development of both mast cells and basophils. We also generated Mas-TRECK Tg mice using the DTR transgene under the control of 5′ enhancer, promoter, and intronic enhancer of interleukin (IL)-4 and demonstrated the role of mast cells in contact hypersensitivity [17]. Both mast cells and basophils in Mas-TRECK Tg mice are depleted after DT treatment, but basophils are restored sooner than mast cells.

Newly generated basophil-specific depletion model

Although no natural mouse mutants with basophil deficiencies have been reported yet, antibodies have often been used to study the contribution of basophils in different experimental settings. MAR-1 and Ba103 antibodies recognize FcεRI and the orphan activating receptor CD200 receptor 3 (CD200R3), respectively. They are both mainly expressed by basophils and mast cells. Both antibody clones can efficiently deplete basophils, and they can also activate mast cells [19, 20]. Furthermore, the depletion of basophils by Ba103 is FcR-dependent and has a potential to activate myeloid cells and natural killer (NK) cells [21]. In addition, MAR-1 also depletes a subset of FcεRI-expressing dendritic cells (DCs) [22]. Recently, several new mouse strains with a constitutive or inducible depletion of basophils have been generated. *Mcpt8* is a basophil-specific gene in the conserved chymase locus [23]. Taking advantage of this gene regulation, three groups generated basophil depletion models [19, 24, 25]. Basophils, but not mast cells or other cell types, were depleted in the blood and spleen in these mice. Another group generated a different basophil depletion model [26] in which the N-terminal sequences for P1-Runx were replaced with the neo^r gene, resulting in the absence of both P1-Runx1 transcriptions and protein. A severe reduction in basophils was observed in these mice without any effects on eosinophils, neutrophils, or mast cells. Bas-TRECK Tg mice using the DTR transgene under the control of 5′ enhancer, promoter, and intronic enhancer of IL-4 were reported by another group [27]. New mast cell depletion models exhibited marginal effects on basophil depletion, while new basophil depletion models seemed to have no effect on the depletion of other immune cells.

The role of mast cells and basophils in contact hypersensitivity

Contact hypersensitivity (CHS) has been widely used as a model to study cutaneous immune responses, as a prototype of delayed-type hypersensitivity [28, 29]. CHS is classified into a sensitization phase and an elicitation phase. An essential step in the sensitization phase of CHS is the migration of hapten-bearing cutaneous DCs, such as epidermal Langerhans cells (LCs) and dermal DCs, into the skin-draining lymph nodes (LNs). In the draining LNs, mature DCs present antigens to naïve T cells, thus establishing the sensitization phase. In the elicitation phase, re-exposure to the same hapten induces the recruitment of antigen-specific T cells and other non-antigen-specific leukocytes into the lesional skin.

Several studies have demonstrated that mast cells modulate the DC function. It has been reported that activated human cord blood-derived mast cells induce DC maturation in vitro

[30]. In addition, IgE-stimulated mast cell-derived histamine induces murine LC migration in vivo [31]. Furthermore, mast cell-derived tumor necrosis factor (TNF)-α promotes cutaneous murine DC migration in vivo in an IgE-independent manner [32], and coculture of mast cells and DCs results in upregulation of DC maturation markers, such as CD40, CD80, and CD86 [33]. Moreover, mast cells were required for the migration of plasmacytoid and $CD8^+$ subsets of DCs into the draining LNs [34]. In contrast, prostaglandin (PG) D_2 is abundantly produced by mast cells in response to allergens [35] and inhibits LC migration [36]. Therefore, mast cells might have bi-directional effects on DC activity in a context-dependent manner.

While basophils are essential to CHS development [37], the role of mast cells in CHS is controversial. Although mast cell-deficient mice have exhibited reduced inflammation in trinitrochlorobenzone (TNCB)-induced CHS in several studies [38, 39], other studies showed undiminished CHS induced with TNCB or 2, 4-dinitrofluorobenzene (DNFB) [40, 41]. To date, the reason for this discrepancy between reports using stem cell factor-deficient or c-Kit-deficient models and those using conditional mast cell ablation models is unknown. One of the differences between these two models is the existence of melanocytes and hematopoietic stem cells. Recently, melanocytes were shown to express toll-like receptors (TLRs) to modulate immune responses and to produce IL-1α and IL-1β [42, 43]. In addition, because of the congenital absence of mast cells in $Kit^{W/Wv}$ and $Kit^{W-sh/W-sh}$ mice, a compensatory mechanism may exist such as the repopulation of the skin with basophils [44]. Therefore, $Kit^{W/Wv}$ and $Kit^{W-sh/W-sh}$ mice may not necessarily be appropriate for evaluating the exclusive roles of mast cells.

Newly mast cell-deficient mice were developed as mentioned previously [14, 37]. Using these mice, it was reported that the CHS response induced by several haptens was attenuated [14, 37]. Using Mas-TRECK Tg mice, we demonstrated that the skin DC migration and/or maturation and T cell priming in the sensitization phase were impaired [17]. Consistently, the CHS response was reduced in DT-treated *Mcpt5-Cre*$^+$*iDTR*$^+$ mice [14], which showed attenuation of the CHS response using DNFB and FITC as haptens. Thus, newly generated mast cell depletion mouse models provided evidence that mast cells promote the development of CHS irrespective of the type of haptens. Mast cell-derived TNF-α is considered to play an essential role in the modulation of DC function. A recent study showed the critical role of mast cell-derived TNF in $CD8^+$ DC maturation, migration, and T cell-priming efficiency and, consequently, in efficient hapten-specific skin inflammation using the *Mcpt5-CreTNFFL/FL* mouse line [45]. Our studies showed that mast cells stimulated DCs via ICAM-1 or lymphocyte function-associated antigen 1 interaction and by membrane-bound TNF-α on mast cells [17]. Interestingly, activated DCs in turn increased Ca^{2+} influx in mast cells [17], suggesting that mast cells and DCs interact to activate each other. In the elicitation phase, mast cell deficiency resulted in an impaired CHS response, probably as a result of reduced vascular permeability caused by a loss of histamine release from mast cells [14].

The role of basophils in cutaneous allergic response

Recent studies reported that basophils migrate into draining LNs from the site of papain injection or helminth infection and act as antigen-presenting cells (APCs) by taking up and processing antigens [46–48]. Basophils are capable of expressing MHC class II and costimulatory molecules such as CD40, CD80, and CD86. They also secrete several cytokines critical for Th2 development, including IL-4 and thymic stromal lymphopoietin (TSLP). In addition, it has been demonstrated that basophils are capable of inducing Th2 upon exposure to ovalbumin (OVA) proteins complexed with specific IgE [48]. Thus, under certain conditions, basophils alone, without DCs, can cause Th2 induction from naïve T cells. However, the role of basophils in Th2 skewing has once more been questioned since several of the above experiments used bone marrow-derived basophils (BMBaso) containing FcεRI-expressing inflammatory DC [22].

Basophils contribute to the strength of the Th2 response in the lungs, but they cannot present the antigens or express the chaperones involved in antigen presentation [22]. Therefore, it was suggested that DCs are necessary and sufficient for inducing Th2 immunity to house dust mites in the lungs, and basophils are not required. Recently, we demonstrated that basophils play a role in Th2 skewing in response to haptens and peptide antigens, but not protein antigens because of the lack of processing ability [37]. Because basophils are not able to take up or process protein antigens efficiently, DCs may prepare peptides from protein antigens for antigen presentation by basophils or may promote IL-4 production from basophils to skew Th2. Consistently, we had previously demonstrated that LCs, an epidermal DC subset, plays an essential role in epicutaneous sensitization with OVA protein antigen to induce Th2-type immune responses through TSLP production [49].

Recently, two different groups have shown that Th2 skewing in response to infection with a gastrointestinal nematode parasite depends on dermal $CD301b^+$ DCs [50, 51]. Depletion of $CD301b^+$ DCs prior to infection reduces the number of IL-4-producing $CD4^+$ T cells [50, 51]. $CD301b^+$ DCs also express programmed death ligand-2 (PDL2), and a subset of $PDL2^+CD301b^+$ DCs that express the transcription factor interferon regulatory factor 4 (IRF4) was shown to be required for Th2 induction in vivo [51]. Based on these findings, $CD11c^+$MHC class II^+ dermal DCs expressing PDL2 and CD301b were identified as a Th2-inducing DC subset in

gastrointestinal nematode parasite infection [52]. However, CD301b$^+$ DCs alone cannot induce Th2 response in vitro [51] or in vivo [50]. Furthermore, basophils were found in the vicinity of T cells in the T cell zone of draining LNs by epicutaneous sensitization with haptens [53]. In addition, reactive oxygen species (ROS) were generated in dermal DCs and in LN DCs upon subcutaneous exposure to papain plus antigen. ROS promoted the Th2 response via the formation of oxidized lipids that triggered TSLP production by epithelia cells. In addition, ROS enhanced Th2 induction by inducing the release of CCL7 from DCs, leading to the recruitment of basophils to the draining LNs [54]. These studies support the hypothesis that DCs prepare peptides from protein antigens for antigen presentation by basophils and promote Th2 skewing.

Several studies show that murine basophils can serve as APCs, although the situation is less clear for human basophils. Human basophils express MHC class II [55, 56] but are not able to induce antigen-specific T cell activation or proliferation in response to exposure to house dust mite allergen [56]. Another group reported that human leukocyte antigen—antigen D related (HLA-DR) in human basophils—is upregulated by IL-3 and interferon (IFN)-γ, but that the basophils cannot work as APCs for pollen allergen [57]. It has been confirmed that human basophils lack some features of APCs [58, 59]. Additional studies are needed to determine whether human basophils can act as APCs under various pathophysiological conditions.

Cooperation of basophils and ILC2

Recent studies have reported the existence of ILCs in both mice and human subjects, which differ from classic T cells in that they lack the TCR [60]. ILCs can be distinguished into the three groups, ILC1, ILC2, and ILC3, according to their cytokine production (Fig. 1a) [60]. ILC2s produce type 2 cytokines including IL-5 and IL-13 and are responsive to IL-25 or IL-33 [61, 62]. These cells express the IL-7R, CD25, IL-33 receptor (T1/ST2), and the IL-25 receptor [61, 63]. In humans, ILC2s also express CRTH2 and CD161 (Fig. 1b) [64]. ILC2 development requires GATA-3 and RORα [64] and has been identified in various tissues such as the skin, lungs, and intestine [63]. ILC2s in the gut produce both IL-5 and IL-13, which are regulated in response to feeding. On the contrary, ILC2s in the lungs produce IL-13 only after cytokine stimulation and helminth infection [65]. IL-25, IL-33, and TSLP are the main cytokines produced by epithelial cells after certain stimuli, such as tissue damage, allergic inflammation, and helminth infections. These cytokines promote cytokine production from ILC2 [61, 63]. ILC2s have the potential to produce IL-4, especially in response to TSLP and leukotriene D_4 rather than IL-33 (Fig. 1b) [66].

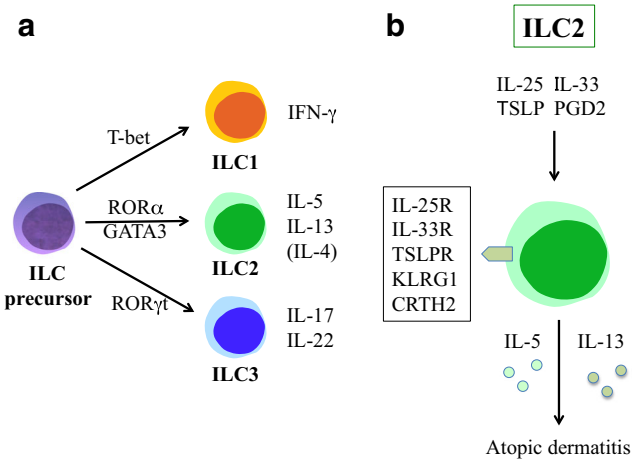

Fig. 1 Three groups of innate lymphoid cells (ILCs). **a** ILCs can be distinguished into three groups, ILC1, ILC2, and ILC3, according to their cytokine production. ILC2 development requires GATA-3 and RORα. **b** ILC2 produces type 2 cytokines such as IL-5 and IL-13 and is responsive to IL-25 or IL-33. These cells express the IL-7R, CD25, IL-33 receptor (T1/ST2), and the IL-25 receptor. In humans, ILC2s also express CRTH2 and CD161

Recent studies have demonstrated that basophils and ILC2s infiltrated the atopic dermatitis (AD)-like lesional skin in a TSLP-dependent manner and play an essential role in Th2-type inflammation in a murine model [63, 67]. Basophils produced IL-4 and TNF-α in contact with fibroblasts and promoted the expression of eotaxin/CCL11 from fibroblasts, which promotes the infiltration of innate cells such as eosinophils [68]. In contrast, ILC2s express IL-5 and IL-13 [61, 63]. The differential effector cytokine expression profiles of basophils and ILC2s define their specialized functions in vivo [69]. IL-13 production was largely confined to Th2 cells and ILC2 cells in the lungs and was associated with large amounts of cellular transcription factor GATA-3. Conversely, follicular helper T cells (T_{FH} cells) and basophils produced only IL-4 in vivo and did not have a high expression of GATA-3 [69]. In addition, recent studies have demonstrated that basophils and ILC2s accumulate in close proximity to each other in the dermis of lesional skin in AD patients and in AD-like murine lesions [67]. Basophil–ILC2 clusters significantly accumulated in AD-associated skin compared to those in healthy control skin. In murine AD-like inflammation, basophils accumulated into the lesional skin and then eosinophils infiltrated there. Basophils and IL-4 were necessary for the accumulation of ILC2s and the induction of AD-like inflammation. In addition, ILC2s expressed IL-4Rα and depended on the IL-4 produced by basophils for their proliferation in AD-like inflammation. Collectively, these studies demonstrate that basophils are early regulators of ILC2 responses in the AD-like inflammation.

Although ILC2s have been reported to be at least IL-33-independent [67], another study demonstrated that the skin-

specific expression of IL-33 in transgenic mice causes AD-like cutaneous manifestations with the accumulation of eosinophils and ILC2s [70]. IL-33 stimulates the production of IL-4 by eosinophils [71], which in turn can promote the proliferation of ILC2 via IL-4Rα.

IL-4 from basophils is also considered to play an essential role in allergic asthma. Proteases such as papain cause barrier disruption in epithelial cells, leading to the production of multiple cytokines including IL-25, IL-33, and TSLP due to the stress of tissue injury. A recent study showed that the conditional deletion of basophils caused a resolution of the papain-induced eosinophilia and mucus production in an allergic asthma model [72]. Basophil-derived IL-4 enhanced the expression of the chemokine CCL11, as well as IL-5, IL-9, and IL-13 in ILC2s, leading to the accumulation of eosinophils. IL-33-deficient mice, but not TSLP receptor-deficient mice, failed to develop papain-induced lung inflammation [73]. Furthermore, antibody neutralization of IL-33 blocked IL-13 production [74]. Therefore, it has been speculated that lung ILC2 cells respond to the IL-33 produced by activated lung stromal cells, which directly induces IL-5 and IL-13 production by ILC2 cells, resulting in lung eosinophilia, goblet cell hyperplasia, and mucus production [73, 74]. Above all, basophil-derived IL-4 seems to be the main regulator of ILC2s in allergic conditions (Fig. 2). The mechanism of the induction or accumulation of ILC2s may depend on the organ specificity or the stimuli.

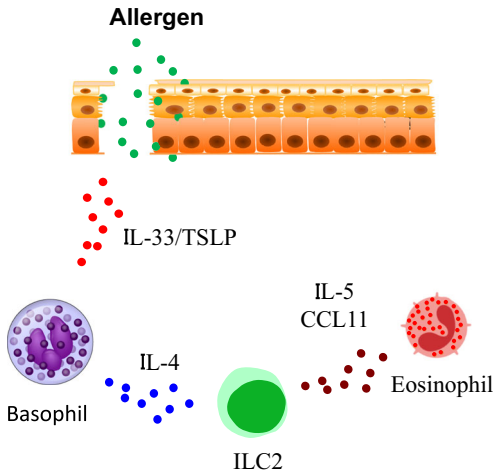

Fig. 2 Both basophils and ILC2s play essential roles in allergic inflammation. Proteases such as papain cause barrier disruption in epithelial cells, leading to the production of multiple cytokines including IL-33 and TSLP due to the stress of tissue injury. These cytokines promote IL-4 production from basophils. Basophil-derived IL-4 enhanced the expression of the chemokine CCL11, as well as IL-5, IL-9, and IL-13 in ILC2s, leading to the accumulation of eosinophils. ILC2s expressed IL-4Rα and depended on the IL-4 produced by basophils for their proliferation in allergic inflammation

Bi-directional effects of mast cells and ILC2

Original studies have reported that ILC2 exists in fat-associated lymphoid tissue and mucosa-associated tissues [62, 75–77]. A recent study identified dermal ILC2s as producing IL-13 in steady-state conditions and depending on IL-7 for their survival [78]. Dermal ILC2 preferentially interacts with skin-resident mast cells [78]. In addition, dermal ILC2 responds to IL-2–anti-IL-2 complexes to proliferate and produce IL-5, leading to the promotion of eosinophil influx [78]. Collectively, dermal ILC2s are considered to play some roles with other immune cells in cutaneous immune reactions.

Activated mast cells produce prostaglandin D_2 (PGD_2), which binds to their receptor, a chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2), on eosinophils, basophils, and Th2 cells [79]. The allergic response mediated by mast cells was significantly attenuated in mice in which CRTH2 is genetically ablated [80]. A recent report showed that PGD_2 promoted IL-13 production from ILC2s through activation of CRTH2 in a synergistic manner with IL-25/IL-33 [76]. Another study showed that CRTH2 also played an essential role in the proinflammatory responses of ILC2s, including cell migration and diverse cytokine production [81]. Therefore, ILC2s can contribute to adaptive type 2 immunity via IgE-mediated mast cell degranulation. In addition, it has been reported that IL-25-mediated collaborations between ILC2s and Th2 cells can enhance the allergic reactions to ingested antigens in the effector phase of IgE-mediated food allergy through mast cells [82, 83].

Mast cells can also negatively regulate innate or adaptive immune responses. Mast cells have been reported to promote

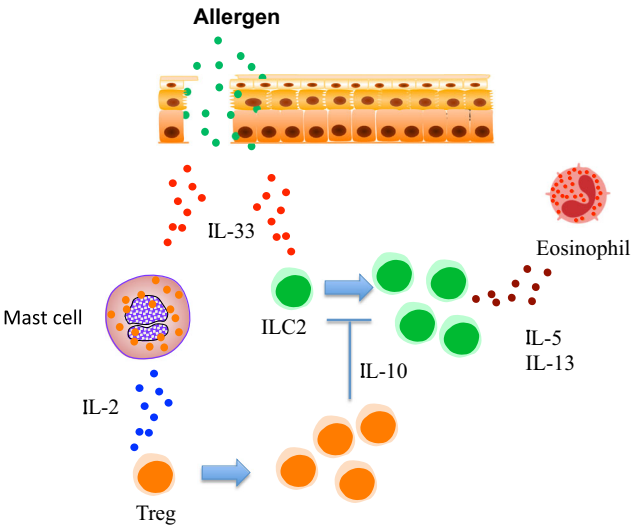

Fig. 3 Both mast cells suppress ILC2-induced allergic inflammation. Mast cell-deficient mice exhibited exacerbated protease-induced lung inflammation associated with a reduced number of Tregs. IL-33-activated mast cells produced IL-2 which suppressed the Treg expansion. IL-10 produced by Treg inhibited the proliferation of ILC2s which play an essential role in papain-induced lung inflammation

peripheral tolerance to skin allografts using mast cell-deficient *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice [84]. This research showed that IL-9 represents the functional link through which activated regulatory T cells recruit and activate mast cells to mediate regional immune suppression [84]. In addition, mast cells have been reported to exert anti-inflammatory or immunosuppressive effects via the production of histamine [85]. Furthermore, IgG-stimulated mast cell-derived IL-10 or IL-2 can suppress the chronic phase of local inflammation during CHS [86, 87]. A recent study identified another mechanism of mast cell-dependent negative regulation for inflammation. They showed that mast cell-deficient *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice exhibited exacerbated protease-induced lung inflammation associated with a reduced number of regulatory T (Treg) cells [88]. IL-33-activated mast cells produced IL-2 which suppressed the Treg expansion. The IL-10 produced by Treg inhibited the proliferation of ILC2s which play an essential role in papain-induced lung inflammation. Although IgE-stimulated mast cells are considered to have potent effector cell functions in the pathology of allergic disorders, the study provided multiple lines of evidence that IL-33-stimulated mast cells can play a regulatory role in the development of ILC2-mediated non-antigen-specific protease-induced acute inflammation (Fig. 3) [88].

Conclusion

The establishment of newly developed mast cell-deficient or basophil-deficient mice revealed the novel mechanisms of immunity and inflammation. However, several key questions remain unanswered, such as what role basophils play in pathogenic processes where they are detected in the lesional skin and how DCs present peptides to basophils during Th2 skewing. In addition, there remains a compelling need to determine whether these findings in mouse models are relevant to humans. Especially for basophils, most of the current knowledge in vivo is based on the murine model. Further studies are needed to investigate the counterpart in human skin diseases. In addition, recent studies have demonstrated the strong relationship between ILC2s and mast cells/basophils in allergic reactions. The newly developed mast cell-deficient and basophil-deficient models are expected to provide us with valuable information on the mechanisms of allergic diseases. Future studies focusing on these topics will enable the development of novel therapeutic approaches to controlling immunity and inflammation.

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