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Interleukin-33 and Mast Cells Bridge Innate and Adaptive Immunity: From the Allergologist's Perspective

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Interleukin (IL) 33, a member of the IL-1 superfamily, is an "alarmin" protein and is secreted in its active form from damaged cells undergoing necrotic cell death. Mast cells are one of the main effector cell types in allergic disorders. They secrete a variety of mediators, including T helper 2 cytokines. As mast cells have high-affinity IgE receptors (FcεRI) on their surface, they can capture circulating IgE. IgE-bound mast cells degranulate large amounts of histamine, heparin, and proteases when they encounter antigens. As IL-33 is an important mediator of innate immunity and mast cells play an important role in adaptive immune responses, interactions between the two could link innate and adaptive immunity. IL-33 promotes the adhesion of mast cells to laminin, fibronectin, and vitronectin. IL-33 increases the expression of adhesion molecules, such as intracellular adhesion molecule-1 and vascular cell adhesion molecule-1, in endothelial cells, thus enhancing mast cell adhesion to blood vessel walls. IL-33 stimulates mast cell proliferation by activating the ST2/Myd88 pathway; increases mast cell survival by the activation of survival proteins such as Bcl-XL; and promotes the growth, development, and maturation of mast cell progenitors. IL-33 is also involved in the activation of mature mast cells and production of different proinflammatory cytokines. The interaction of IL-33 and mast cells could have important clinical implications in the field of clinical urology. Epithelial dysfunction and mast cells could play an important role in the pathogenesis of interstitial cystitis. Urinary levels of IL-33 significantly increase in patients with interstitial cystitis. In addition, the number of mast cells significantly increase in the urinary bladders of patients with interstitial cystitis. Therefore, inhibition of mast cell activation and degranulation in response to increase in IL-33 is a potential therapeutic target in the treatment of interstitial cystitis.

Keywords: Interleukin-33, Mouse; Mast Cells; Cystitis, Interstitial; Allergy and Immunology

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INTRODUCTION

The Role of IL-33 and Mast Cells in the Immune Response

Interleukin (IL) 33 is a member of the IL-1 superfamily and has molecular properties similar to those of related cytokines such as IL-1 and IL-18 [1]. IL-33 is released in its active, uncleaved form from damaged cells undergoing necrotic cell death. Conversely, caspases cleave IL-33 to its inactive form in apoptotic cells [2,3]. Therefore, IL-33 functions as an "alarmin," particularly in cells that form an epithelial or endothelial barrier and are thus exposed to environmental damage [4,5].

IL-33 induces the production of T helper 2 (Th2) cytokines in Th2 lymphocytes, eosinophils, basophils, and mast cells [6-9]. Consequently, it is quite probable that IL-33 induces and

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promotes Th2 allergic inflammation [10]. IL-33 has been implicated in allergic asthma, conjunctivitis, and anaphylactic reactions [8,9,11,12].

Mast cells are innate immune cells that are preferentially located in highly vascularized tissues. They are one of the main effector cells in a number of allergic disorders. Mast cells secrete a variety of mediators, including Th2 cytokines such as IL-4, IL-5 and IL-13, in response to IL-33, independent of IgE crosslinking [7,13]. As they have high-affinity IgE receptors (FcεRI) on their surface, they can capture circulating IgE. IgE-bound mast cells degranulate large amounts of histamine, heparin, and proteases when they encounter antigens [14]. The presence of many cell surface receptors, including the IL-33 receptor, also enables mast cells to respond to microbial invasion, tissue damage, and inflammation [14]. Engagement of receptors with their ligands promotes the expression of several proinflammatory genes [6,15,16].

Patients with allergic disorders such as allergic rhinitis, asthma, and atopic dermatitis or with autoimmune disorders show an increased number of mast cells in their affected target organs, indicating a possible role of mast cells in these disorders [16,17].

IL-33 is one of the most crucial factors in innate immunity, while mast cells play an important role in adaptive immune responses. Therefore, exploring the relationship between IL-33 and mast cells could help identify potential links between innate and adaptive immunity. Here, we have reviewed studies investigating the relationship between IL-33 and mast cells. Furthermore, there is increasing evidence that IL-33 and mast cells are involved in the pathophysiology of interstitial cystitis (IC). We have also reviewed studies on the effects and potential clinical implications of IL-33 and mast cells in the field of clinical urology.

The Role of IL-33 in Allergic Inflammation

Release of active IL-33 from damaged epithelial cells is a key step in the initiation and maintenance of allergic inflammation. Haenuki et al. [18] induced murine allergic rhinitis to ragweed allergen by intraperitoneal and intranasal challenge in wild-type and IL-33-knockout mice. Compared to wild-type mice, IL-33-knockout mice were found to show significantly reduced sneezing, lower serum titers of total and ragweed-specific IgE, lower titers of Th2 cytokines (IL-4, IL-5, and IL-13), reduced eosinophilic infiltration into the nasal mucosa, and lesser goblet hyperplasia [18]. The authors also performed an intranasal IL-33 challenge with a ragweed challenge to induce allergic rhinitis in IL-33-knockout mice. IL-33-knockout mice that underwent the ragweed challenge only did not display typical clinical features of murine allergic rhinitis. However, intranasal instillation of IL-33 and the ragweed challenge together induced typical Th2 responses. Therefore, both IL-33 and FcεRI crosslinking are essential for the development of allergic rhinitis [18].

Single nucleotide polymorphisms in the region of the *IL33* gene or the IL-33 receptor gene *IL1RL1* are associated with several allergic disorders, such as atopic dermatitis, allergic rhinitis, and asthma [19-30]. A clinical study showed that IL-33 levels were significantly elevated in the bronchoalveolar lavage fluid and bronchial epithelial biopsy samples of patients with allergic asthma. IL-33 levels were found to be highly correlated with clinical severity [31]. In addition, patients with allergic rhinitis had elevated IL-33 levels in serum and nasal secretions. Therefore, it is highly probable that IL-33 is a marker of disease severity in allergic rhinitis [32,33]. In patients with atopic dermatitis, IL-33 was also significantly higher in serum and skin biopsy samples after allergen challenge [34,35].

Psoriasis is a common autoimmune disorder of the skin, characterized by elevated levels of proinflammatory cytokines and epidermal keratinocyte hyperplasia. Hueber et al. [36] showed that ST2 (IL-33 receptor)-knockout mice had a reduced inflammatory response in their skin compared to wild type mice, in a murine model of skin inflammation using phorbol ester. They also observed that inflammatory skin lesions were aggravated by injection of IL-33 into the ears of mice. Finally, they investigated the skin lesions of patients with psoriasis and observed significantly increased IL-33 expression compared to that in the skin of healthy volunteers [36]. These results suggest that damage to the epithelial or endothelial barrier and subsequent release of alarmins such as IL-33 may be an important mechanism in the initiation of an allergic response. Thus, IL-33 is a potential target for treating allergic disorders.

IL-33 has been suggested as a therapeutic target in several allergic and autoimmune disorders [37-39]. Murine splenocytes incubated with soluble ST2 (sST2, a decoy receptor for IL-33) showed significantly inhibited production of Th2 cytokines [40]. In a murine model of cigarette smoking-induced pulmonary inflammation, intranasal instillation of anti–IL-33 antibody significantly ameliorated lung lesions, that is, it decreased pulmonary infiltration of neutrophils and macrophages and decreased levels of inflammatory cytokines such as IL-1β, IL-17, and tumor necrosis factor (TNF)-α [41]. Ovalbumin-challenged mice treated with anti–IL-33 antibody or sST2 had significantly reduced allergic pulmonary inflammation, along with decreased levels of Th2

cytokines in their bronchoalveolar lavage fluid and fewer eosinophils [42]. Therefore, blocking the IL-33/ST2 signaling pathway could be a target for the development of novel antiallergy treatments [43,44].

However, careful consideration must be given to the systemic administration of anti–IL-33 as a therapeutic agent, as the IL-33/ST2 signaling pathway may play very different roles in different organs and tissues. In other words, while blocking the IL-33/ST2 pathway may be quite beneficial for allergic disorders, it could aggravate clinical features in other disorders. For example, IL-33 reduces atherosclerosis in ApoE-knockout mice. When these mice were treated with sST2 to block IL-33/ST2 signaling, they developed large atherosclerotic plaques [45]. Some authors also argue that IL-33 could promote metastasis in gastric and colorectal cancers [46,47]. However, others researchers suggest that IL-33 could be used as an adjunct in enhancing antitumor antigen-specific immunity [48]. In contrast, IL-33 has been also reported to promote functional recovery after contusion spinal cord injury in a murine model [49]. IL-33 is also related to improvement of experimental autoimmune uveitis [50]. Therefore, systemic blocking of the IL-33/ST2 pathway is a double-edged sword.

IL-33 and Mast Cells: Mechanisms of Interaction

Mast cells have several properties that are quite important for their role in bridging the innate immune response at epithelial or endothelial cell barriers with the adaptive immune response [51]. First, mast cells are particularly abundant near epithelial cells, where several alarmins, including IL-33, are released following cellular damage [51]. Furthermore, mast cells have abundant IL-33 receptors (ST2) on their cell surface [52]. Thus, IL-33 and ST2 crosslinking at the mast cell surface can significantly affect mast cell development, survival, and functions, including adhesion, maturation, activation, and release of mediators [51].

IL-33 promotes adhesion of mast cells to laminin, fibronectin, and vitronectin [51]. Stem cell factor (SCF) mediates adhesion of mast cells to fibronectin via IL-33 [13,53]. IL-33 also increases the expression of adhesion molecules such as intracellular adhesion moldeule-1 and vascular cell adhesion molecule-1 on endothelial cells via activation of the nuclear factor-kappa B (NF-κB) pathway, thus enhancing mast cell adhesion to blood vessel walls [54]. IL-33 enhances mast cell proliferation via activation of the ST2/Myd88 pathway [55]. IL-33 increases mast cell survival by activating survival proteins such as Bcl-XL [56].

IL-33 is involved in the growth, development, and maturation of mast cell progenitors. IL-33 promotes the maturation of CD34+ progenitor cells to tryptase-producing cells [57]. IL-33 also promotes the maturation of mast cell progenitors *in vitro* and induces secretion of Th2-attracting chemokines and Th2 cytokines [57].

IL-33 is also related to the activation of mature mast cells. It promotes the production of various Th2 cytokines and chemokines, which play a pivotal role in allergic inflammation. IL-33 also induces the production of prostaglandins and leukotrienes [57-59]. IL-33 promotes autoantibody-mediated degranulation of mast cells in synovial tissue [60]. High numbers of mast cells

Table 1. Effects of IL-33 on the adhesion, proliferation, survival, development, and activation of mast cells in allergic inflammation

Process	Effects reported in the literature
Adhesion	Promotes adhesion to laminin, fibronectin, and vitronectin [51] Promotes SCF-mediated adhesion of mast cells to fibronectin [13] Increases expression of adhesion molecules, such as ICAM-1 and VCAM-1, in endothelial cells [54]
Proliferation	Enhances proliferation of mast cells through activation of the ST2/Myd88 pathway [55]
Survival	Activates survival proteins such as Bcl-XL [56]
Growth, development, and maturation	Promotes maturation of CD34+ progenitor cells to tryptase-producing cells [57] Promotes maturation of mast cell progenitors *in vitro* [57]
Activation	Promotes production of Th2 cytokines and chemokines, prostaglandins, and leukotrienes [57–59] Promotes autoantibody-mediated degranulation of mast cells in synovial tissue [60]
Production of cytokines and chemokines	Promotes production of IL-4, IL-6, IL-13, TNF-a, and GM-CSF, and chemokines MIP-2 (CXCL2), KC (CXCL1), MCP-1 (CCL2), MIP-1a (CCL3), and MCP-3 (CCL7) [58,62-64,66]

IL, interleukin; ICAM, intracellular adhesion molecule; VCAM, vascular cell adhesion molecule; Th2, T helper 2; TNF, tumor necrosis factor; GM-CSF, granulocyte macrophage-colony stimulating factor; MIP, macrophage inflammatory protein; KC, keratinocyte chemoattractant; MCP, monocyte chemoattractant protein.

were observed in the synovium of patients with rheumatoid arthritis. The degree of mast cell degranulation in the synovium correlates well with disease severity [61].

IL-33 stimulates proinflammatory cytokine production by mast cells. In murine mast cells, IL-33 stimulated the production of IL-4, IL-6, IL-13, TNF-α, and granulocyte macrophage-colony stimulating factor, as well as chemokines such as macrophage inflammatory protein (MIP)-2 (CXCL2), keratinocyte chemoattractant (CXCL1), monocyte chemoattractant protein (MCP)-1 (CCL2), MIP-1α (CCL3), and MCP-3 (CCL7) [58,62-64]. Several agents can act synergistically to stimulate mast cell secretion of Th2 cytokines. In the presence of nerve growth factor, SCF, C5a, and 5′-N- ethylcarboxamidoadenosine (NECA), IL-33 significantly promoted secretion of IL-6 [65]. C5a, NECA, and IL-33 promoted IL-13 release [65]. IL-33 synergized with NECA and SCF to induce the release of chemokines such as CXCL8 and CCL4 [65]. IL-33 also promotes the production of IL-6, IL-13, TNF-α, MIP-1, MCP-1α, and MCP-3 in bone marrow-derived murine mast cells [66]. Conversely, mast cells in the maturation and differentiation stage had decreased IgE receptor crosslinking-mediated degranulation after long-term exposure to IL-33 [67]. The diverse effects of IL-33 on mast cells are summarized in Table 1.

REVIEW OF RECENT STUDIES

Chu et al. [68] developed a murine model of hyperactive mast cells by specifically ablating A20, a negative feedback regulator of NF-κB, in mast cells [69-73]. Unrestricted over-activation of NF-κB in mast cells induced IgE, IL1R1, and most importantly, IL-33R (ST2) expression [14]. Wild-type mast cells treated with IL-33 had significantly increased transcription of the *A20* gene [14]. A20-deficient mast cells treated with IL-33 showed increased expression of survival genes such as Bcl-XL, Bcl-2, and A1 [14]. The authors suggested that upregulation of these pro-survival genes is an antiapoptosis mechanism in A20-deficient mast cells [14].

Heger et al. [14] also induced allergic asthma using ovalbumin in an A20-deficient murine model of hyperactive mast cells. Compared to wild-type mice, A20-deficient mice had significantly more eosinophils, B and T lymphocytes, and elevated ovalbumin-specific IgE levels. These mice also had significantly increased influx of dendritic cells in the lung following intranasal instillation of IL-33. It was concluded that A20-deficient mice with hyperactive mast cells have increased sensitivity to IL-33, which contributes to an enhanced allergic response [14].

Many studies suggest that mast cells are involved in autoimmune diseases such as rheumatoid arthritis and multiple sclerosis [17,61]. Mast cells, A20, and IL-33 have all been reported to play a role in the pathogenesis of rheumatoid arthritis or collagen-induced arthritis [61,74-76]. Significantly increased severity of collagen-induced arthritis was also observed in mice with A20-deficient mast cells [14]. A20-deficient mast cells treated with IL-33 had significantly greater expression of proinflammatory cytokines such as TNF-α, IL-6, and IL-13 than wild-type mast cells. Stimulated mast cells demonstrated increased expression of the activation markers OX40L, CD30L, CD25, and Fas [14]. During the arthritis disease process, IL-33 released from fibroblasts activates mast cells. In turn, mast cells enhance IL-33 expression by secreting proinflammatory cytokines [76].

Recently, Kiss et al. [77] suggested that proteases derived from some pathogens or plants could initiate nonspecific allergic inflammation independent of antigen via activation of the innate immune system. This involves the release of alarmins from damaged cells [77]. In contrast, Morita et al. [78] suggested that mast cell-deficient mice ($Kit^{W\text{-}sh/W\text{-}sh}$) had exacerbated airway inflammation (more eosinophilic infiltration, increased IL-5 and IL-13 in bronchoalveolar lavage fluid) compared to wild-type mice following inhalation of low-dose (0.1 μg) IL-33. They also observed that mast cell-depleted (Mas-TRECK) mice had increased eosinophilic infiltration induced by low-dose IL-33 inhalation [78]. It was proposed that mast cells suppress airway eosinophilia induced by low doses of IL-33 [78].

IMPLICATIONS FOR CLINICAL UROLOGY

IC is characterized by vague bladder pain, increased frequency and urgency of urination, and dyspareunia [79]. The pathophysiology of IC has not yet been elucidated. However, many researchers agree that epithelial dysfunction and mast cells could play an important role in its pathogenesis [80]. In a recent study, urinary IL-33 levels were significantly higher in patients with IC than in the control group [81]. The authors suggested that elevated urinary alarmin in these patients indicates that an innate immune response is involved in the pathogenesis of IC. Therefore, immunomodulation by targeting the action of alarmins such as IL-33 could be a promising treatment strategy.

It is also likely that mast cells are involved in the pathogenesis of IC [82]. In fact, increase in mast cell numbers has been sug-

gested as an etiological factor [83,84]. Mast cells play an important role in responding to increased alarmin levels released from damaged epithelial cells [58]. In a rat model of IC, there was significantly more mast cell infiltration compared to that seen in control rats, and most of the cells were degranulated [85].

Similarly, increased mast cell numbers are present in the urinary bladders of patients with IC. One study reported that the mean number of mast cells in the bladder muscularis was 62±8 cells/mm^2 in patients with IC, which was significantly more than that in the control group (6±8 cells/mm^2) [86]. In another study, patients with IC had more mast cells in the bladder submucosa (mean, 34.5 cells/mm^2) than healthy volunteers did (range, 11.7–19.4 cells/mm^2) [87]. Aldenborg et al. [88] compared mast cell infiltration in the bladder detrusor muscle of patients with ulcerative or nonulcerative IC and in healthy volunteers. Ulcerative IC patients had the most infiltration (120 cells/mm^2); nonulcerative IC patients had lesser infiltration (60 cells/mm^2) but the infiltration was higher than that in controls (40 cells/mm^2). Although the degree of mast cell infiltration was not correlated with the severity of clinical symptoms, it correlated well with the degree of submucosal inflammation [89].

Johansson and Fall [90] reported that the number of mast cells in the lamina propria and detrusor muscle in ulcerative IC patients was 164±12.7 cells/mm^2 and 99±10.6 cells/mm^2, respectively. Nonulcerative IC patients had significantly fewer mast cells in the lamina propria and detrusor muscle (93±5.7 cells/mm^2 and 46±6.8 cells/mm^2, respectively) than ulcerative IC patients, but these numbers were not significantly different from those for the control group (88±5.5 cells/mm^2 and 36±5.8 cells/mm^2, respectively). Therefore, there is increased mast cell infiltration into the bladder submucosa, muscularis, and lamina propria of patients with ulcerative IC (Hunner's ulcers) [91].

IC is also characterized by the ultrastructural activation of mast cells in the bladder [89]. A control group was found to have 6.6±4.8 mast cells/mm^2 in the bladder, of which 69.6% (4.6±3.7 cells/mm^2) had intact secretory granules; IC patients had 42.7±31.2 mast cells/mm^2, of which only 20.1% (6.6±9.2 cells/mm^2) had intact granules [79].

Murine experimental autoimmune cystitis, a mouse model of IC, displays mast cell proliferation [92]. Balb/cAN mice immunized with syngeneic bladder homogenate typically develop bladder edema and fibrosis and show accumulation of mast cells within 4 weeks [92]. Systemic sensitization and challenge using ovalbumin results in histamine release and mast cell degranulation in guinea pig bladders [93]. In rats systemically sensitized to ovalbumin, intravesical ovalbumin challenge induced extravasation of bladder plasma, which was blocked by degranulation of mast cells before the challenge [94]. Furthermore, bladder plasma extravasation caused by substance P or bacterial lipopolysaccharide could not be reproduced in mast cell-deficient mice [95].

Acute psychological stress may also be involved in mast cell activation. Rats experiencing acute stress showed increased activation of mast cells in their bladder [96,97]. Acute stress also caused increased urinary release of histamine, mast cell protease-1, and IL-6, which was blocked by intravesical pretreatment with 0.4% sodium hyaluronate.

Therefore, mast cell inhibition is a potential therapeutic target in IC. Hydroxyzine, a popular antihistamine, inhibits mast cell activation [98]. However, a recent systematic review of the effects of H1-antihistamine on mast cell activation was unable to come to a definitive conclusion due to limited available data [99]. The National Institutes of Health Interstitial Cystitis Clinical Trials Group is performing randomized, double-blinded, placebo-controlled clinical trials to determine its effects [79]. The plant pigment quercetin was found to be effective against chronic prostatitis, a clinical variant of IC [100].

As there is still much to be elucidated about the pathophysiologic mechanism underlying IC, the treatment strategy for this disease remains at the stage of symptomatic management. Based on our current knowledge about the roles of IL-33 and mast cells in the pathogenesis of IC, new innovative treatment strategies may be developed in the near future.

CONCLUSIONS

The interaction between IL-33 and mast cells plays a pivotal role in bridging innate and adaptive immune responses. In addition to involvement in a variety of allergic disorders such as allergic rhinitis, atopic dermatitis, and allergic asthma, IL-33 and mast cells are also involved in the pathogenesis of IC. Cooperative research between allergologists and urologists may yield more meaningful conclusions about the pathophysiologic mechanism and treatment strategies of IC.

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