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IL-33 Signaling in Lung Injury

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Abstract

Interleukin (IL)-33, a member of the IL-1 cytokine super-family, acts as both a traditional cytokine and an intracellular nuclear factor. It is generally released from damaged immune cells and signals through its receptor ST2 in an autocrine and paracrine fashion, plays important roles in type-2 innate immunity, and functions as an “alarmin” or a danger signal for cellular damage or cellular stress. Here, we review recent advances of the role of IL-33 in lung injury and explore its potential significance as an attractive therapeutic target.

Keywords

interleukin-33 (IL-33); lung injury; ventilator-induced lung injury (VILI)

Introduction

Interleukin (IL)-33, previously known as “DVS27” [1], is a cytokine protein and ligand of the receptor ST2, a member of the Toll-like receptor (TLR)/IL-1 receptor (IL-IR) super-family[2]. Although ST2 was first reported in 1989 in both mice[3] and rats[4], IL-33 wasn't identified and named until 2005 based on a computer database search for genes homologous to IL-1 family members[2].

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IL-33 is an member of IL-1 cytokine family with ~32 kD and 18 kD molecules that in the past represented uncleaved and mature IL-33 proteins, respectively[2, 5], but now represent the bioactive and cleavage forms [6, 7], respectively. IL-33 appears to be a cytokine with dual functions: first, it acts as a conventional cytokine via activation of the ST2 receptor complex, and second, it performs as an intracellular nuclear factor with properties of transcriptional regulatory [8, 9]. IL-33 plays an important role in type-2 innate immunity and induces production of IL-5 and IL-13 by activating intracellular molecules via NF-κB and MAP kinase signaling pathways [10-12]. IL-33 is also considered an “alarmin” which is promptly discharging from its producing cells upon cellular damage or cellular stress [11].

The function of IL-33 in different immune diseases has been well examined and reviewed. The role of IL-33 in lung injury was first identified mainly in lung inflammation and allergic diseases such as viral infection and asthma [13, 14]. In recent years, IL-33 has also been found to take part in other types of lung diseases such as ventilator-induced lung injury[15], acute lung injury, chronic obstructive pulmonary disease [16], lung cancer[17], and other clinical conditions. The purpose of the current review is to highlight the crucial role of IL-33 in lung injury and explore its potential as an attractive therapeutic target.

IL-33 receptor activation and its signaling pathway

IL-33 receptor is a complex that requires the expression of both ST2L, which is a member of the TLR/IL-1R superfamily, and also the IL-1 receptor accessory protein (IL-1RAP) [18, 19]. There are at least two other forms of ST receptors in addition to ST2L, including secreted soluble ST2 (sST2) that can serve as an allurement receptor for IL-33[20] and a ST2V variant that is present primarily in the human gut [21]. Soluble ST2 is considered a biomarker of several diseases, including cardiac disease[22], ulcerative colitis[23], and others.

IL-33 signaling starts from activation of cytoplasmic Toll-interleukin receptor domain which attracts the adaptor molecule myeloid differentiation primary response gene 88 (MyD88)[10, 24]. Then interleukin receptor-associated kinase 4 (IRAK4) is gathering to MyD88, followed by the interaction of myddosome which is composed of IRAK1, IRAK2, and/or IRAK3 [25, 26]. This myddosome then combines with tumor necrosis factor receptor-associated factor 6 (TRAF6), which is crucial for signal propagation [27] and further activates transcription factors NF-κB or mitogen-activated protein kinase (MAPK) [2, 9]. (Figure 1).

As a traditional cytokine, IL-33 stimulates Th2 cells, eosinophils, basophils and mast cells, to produce IL-4, IL-5, IL-13 and some other type 2 cytokines , which stimulate the proliferation of B cells, T cells and have other critical immune-modulatory functions[24, 28, 29]. Function as a nuclear factor, IL-33 could also bind to NF-κB directly, sequestering it and diminishing its ability to turn on gene transcription [9].

Release and cellular sources of IL-33 in the lung

Even though it is well known that IL-33 expression is increased in inflamed tissue, controversy still exists regarding the active form of IL-33 and its releasing mechanism. Mature IL-33 (18kD) may be released during cellular necrosis, thereby acting as an “alarmin” [11, 30, 31], whereas other studies showed that unlike IL-1 super-family

members, full-length IL-33 does not need proteolysis for activation [6]. IL-33 is not activated by caspase 1 cleavage, but is processed into a mature bioactive form in neutrophils by elastase and cathepsin G [7]. The bioactivity of IL-33 is diminished in apoptotic cells through caspase-dependent proteolysis [6, 32].

There are various cellular sources of IL-33 in the lung. IL-33 expression in different cell types has been confirmed in individual studies and has been well-reviewed by Mirchandani *et al*[10]. Recent studies by Pichery *et al.*, who generated an Il-33 Gt/ Gt which means Il-33–LacZ gene trap reporter strain, showed that using this innovative tool to examine expression of endogenous IL-33 *in vivo* revealed that an endogenous IL-33 protein was highly expressed in mouse lung cuboidal epithelium and other epithelial barrier tissues[33]. Importantly, they demonstrated that IL-33 protein was localized mainly in the cell nucleus, but not in the cytoplasm of producing cells [33]. Mirchandani *et al.* showed that IL-33 protein increased in whole lung homogenates of BALB/c mice after 6-12 hours of chitin challenge[34] and further demonstrated that this expression of IL-33 was mainly from alveolar type II cells [35]. A recent study by Kaur D *et al.* showed that bronchial epithelium, airway smooth muscle (ASM), and mast cells expressed IL-33 correlating with airway hyper-responsiveness (AHR) in latter asthma. Thus, it seems that IL-33 acts via autocrine and paracrine pathways and may function as an important target to modulate the crosstalk between mast cells and ASM [36].

Role of IL-33 in lung injury

Inflammation and allergy in the lung

Lung inflammation and allergies activate the innate immune response. Immune cells, along with macrophages, monocytes, and neutrophils, migrate into the lungs and further activate the pro-inflammatory response by releasing cytokines and chemokines, leading to the immune response[37].

Considering IL-33 as an “alarmin” of Th2 immune responses, its role in lung inflammation and allergy has been well-studied. In virus-induced lung inflammation and the cysteine protease-induced lung inflammation model, there will always be an obvious increase in the production of IL-33 with an enhanced expression of ST2 Mrna [38-41]. These results show that IL-33/ST2 signaling participates in Th2-mediated airway inflammation. As a pro-inflammation “alarmin”, IL-33 itself could also induce airway inflammation, followed by group 2 innate lymphoid cell activation, eosinophil infiltration[42], and IL-8 up-regulation[43]. IL-33 can activate both ERK and p38 MAPK in primary endothelial cells, however it can only stimulate ERK in epithelial cells *in vitro* [43].

Asthma is considered as a common life-long chronic disease and is classically characterized by serum IgE levels elevation, airway hyper-responsiveness, allergic inflammation, and increased Th2 cytokine production[14]. The roles of IL-33 in asthma have been well studied [13, 14]. More recent research has implicated additional roles for IL-33 in asthma. It is plausible that IL-33 drives airway hyper-responsiveness (AHR) through directly stimulating mast cell activation and airway smooth muscle (ASM) wound repair and indirectly promoting ASM contraction via upregulation of mast cell-derived IL-13. The receptor for

advanced glycation end-products (RAGE) was found to drive asthma/allergic airway inflammation by stimulating IL-33 expression in response to allergen and by directing the inflammatory response downstream of IL-33[44]. To clarify distinctions between the functions of IL-25 and IL-33 in asthma, the IL-33-induced response was identified by more sustained laying down of extracellular matrix protein, neo-angiogenesis, and T helper type 2 (Th2) cytokine expression and elevation of tissue damping compared with IL-25[45]. IL-33 also plays a significant role in pediatric asthma. Severe asthma with fungal sensitization (SAFS) was associated with higher levels of airway IL-33, and alternate exposure induced increasing IL-3-mediated ILC2 numbers, steroid-resistant AHR and Th2 cell numbers. IL-33 might be considered as a unique therapeutic target for SAFS [46]. Elevated innate cytokines interleukin IL-33 and IL-25 and peculiar molecular responses in the interferon pathway are associated with rhinoviral infections in children. IL-33 also increased in fungal allergen-induced exacerbations, highlighting it as an attractive therapeutic target[47].

House dust mites (HDMs) are a leading source of allergens in patients with allergic disorders such as atopic dermatitis, asthma, and rhinitis [48], and administration of HDM extracts to mice induces allergic airway inflammation with similarities to asthma [49]. Full-length and bioactive IL-33 expression increased in caspase-1-deficient mice exposed to HDM, followed by a marked eosinophil recruitment. Using soluble ST2 receptor to neutralize IL-33 inhibited the enhanced allergic inflammation, while administering recombinant IL-33 enhanced allergic inflammation in caspase-1-deficient mice[50]. IL-33 was also needed to induce a humoral immune reaction to a single inhalational challenge to a HDM-pulsed dendritic cell-derived Th2 response [51-53]. Other research using chitin, a component of the exoskeleton of many organisms including HDM, indicates that uncleaved chitin promotes IL-33 release, whereas cleaved chitin could induce the activation of caspase-1 and caspase-7, which promotes IL-33 inactivation and further results in the resolution of type 2 immune responses[54].

Acute lung injury and ventilator-induced lung injury

Although mortality from acute lung injury (ALI) or its severe form, acute respiratory distress syndrome (ARDS) has decreased substantially over the past 30 years, it still remains a high rate of morbidity and mortality[55, 56]. Surviving patients in intensive care units have long term disability and high mortality rates years after discharge. Mechanical ventilation, acting as a most significant supportive measure in ALI[57], may produce an iatrogenic complication called ventilator-induced lung injury (VILI). Nonetheless, the etiology of VILI remains unclear. Very few studies have focused on this aspect of IL-33. One recent study[15] investigated IL-33/ST2 signaling in rat VILI model. Ventilation at 10 cmH_2O of inspiratory pressure for four hours elicited a high expression of IL-33 expression in lung tissues with increased membrane ST2L but decreased cytosol ST2L, indicating translocation of ST2L from the cytosol to the cell membranes of lung tissue. Using a mechanical stretch model for lung epithelium, we found that lung epithelial cells were able to release IL-33 following mechanical stretch (unpublished data). These results indicated that IL-33/ST2 signaling might participate in the process of VILI. Further experiments should need to confirm the role and significance of IL-33 in VILI.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is considered as one of the major concerns in public health and is estimated to rank as the third worldwide for mortality[58]. Cigarette smoke exposure is considered the leading causative agent of COPD. There is no effective treatment for COPD, and the mechanism by which the interaction between smoking and infection aggravate COPD remains poorly understood[16]. Kearley *et al.*[59] showed that cigarette smoke altered the lung microenvironment to facilitate an alternative IL-33-dependent magnified pro-inflammatory response to infection, leading to exacerbated COPD. They first exposed ST2- or IL-33-deficient mice or wild-type control mice to cigarette smoke and subsequently infected them with influenza A virus. Significantly enhanced weight loss and exaggerated lung inflammation occurred compared to viral infection alone in ST2- or IL-33 deficient mice, indicating that administration of ST2 could protect mice from exacerbated inflammation. These results showed that IL-33 is an essential trigger of COPD aggravation in mice by augmenting the inflammatory response. Other studies also demonstrated that increasing IL-33 expression in COPD [60] and altered IL-33 expression and release in airway epithelial cells is induced by cigarette smoke [61].

Lung cancer and pulmonary sarcoidosis

Immunoregulatory cytokines may play an important role in the metastases and growth of tumor. Sarcoidosis is also characterized as a multisystem immunologic disorder. As an “alarmin” in type-2 innate immunity and innate lymphoid cells (ILC2), IL-33 plays a significant role in lung cancer and pulmonary sarcoidosis. Kim *et al.*[17] evaluated the role of plasma IL-33 levels in the development of lung cancer and showed that cancer patients have lower levels of IL-33 than normal control subjects and that IL-33 decreased in a stage-dependent manner. Moreover, plasma IL-33 levels gradually reduced after surgical resection of malignant lesions, but were unchanged after chemotherapy. Together with cytokines IL-4 and IL-10, IL-33 may also be considered a potential immunotherapy biomarker in cancer research [62]. Moreover, because strongly correlation with systemic disease has been shown only between IL-33 expression and sarcoidosis but not other granulomatous diseases, IL-33 appears to be a new marker of pulmonary sarcoidosis[63, 64] and might serve as an adjunct diagnostic marker [64,65].

Other kinds of lung injury

IL-33 also plays an essential role in other types of lung injuries such as interstitial lung disease, idiopathic pulmonary fibrosis, and malaria-associated lung injury. Luzina *et al.*[65] demonstrated that bleomycin injury combined with full-length IL-33 expression exerted a synergistic pulmonary lymphocyte effect and collagen accumulation. In addition, the expressions of several heat shock proteins were increased with full-length IL-33 treatment. Li *et al.*[66] showed that IL-33 was mainly expressed in lung epithelial cells, but was induced in macrophages by bleomycin. Deficiency of ST2, treatment with anti-IL-33 antibody, or attenuated alveolar macrophage depletion, as well as exogenous IL-33 enhanced bleomycin-inducing lung inflammation and fibrosis. Ampawong *et al.*[67] compared the histopathological specialties of lung injury in Southeast Asian patients who died from severe malaria and investigated whether a correlation to pulmonary edema was present. They

showed that IL-33 expression in bronchial cells was dramatically increased in severe malaria patients who also suffered from pulmonary edema. These results suggest that IL-33 may take part in the pathogenic process of lung injury during severe malaria.

Summary

As stated above, IL-33 seems to function as a potent activator in various types of lung injury (Figure 2). IL-33/ST2 signal transduction could be considered as a molecular target to treat human diseases such as asthma [45, 47], ALI/ARDS [68], and so forth. Considering IL-33 as an “alarmin” cytokine, studies have tried to modulate the IL-33/ST2 signal, including both IL-33/ ST2L (membrane receptor and IL-33 complex) and IL-33/sST2 (soluble form and IL-33 complex). For example, vitamin D upregulated the sST2 production in a dose-dependent fashion, leading to inhibit the IL-33 cytokine response [69]. Endogenous IL-33 can be released from the respiratory epithelium upon stimulation to elicit an immune response. However, secreted, biologically-active IL-33 can be inactivated rapidly via the formation of a disulphide bonded form of IL-33. Such a mechanism limits the duration, rang of immunological responses to airway stimuli which dependent on ST2 [70]. RAGE recognizes ligands such as high-mobility group box 1, and its pathway has been reported to play an important role in ALI. RAGE-deficient mice demonstrated increased IL-33 levels in the lung, leading to enhanced innate AHR, whereas blockade of IL-33 receptor ST2 suppressed innate AHR [71]. Vaccination against IL-33 has already been used in research to inhibit hyper-responsiveness and inflammation [72, 73]. Rebamipide, a widely-used medication for mucosal protection, showed an inhibitory effect on IL-33 production and an improving mite-induced asthma conditions[74], as did dietary galacto-oligosaccharides on IL-33[75].

In conclusion, IL-33 appears to be a crucial cytokine in modulating immune responses in several lung diseases, particularly in hyper-responsiveness and inflammation. Further research on its role in VILI is worth further pursuing. IL-33 has shown potential as an attractive therapeutic target.

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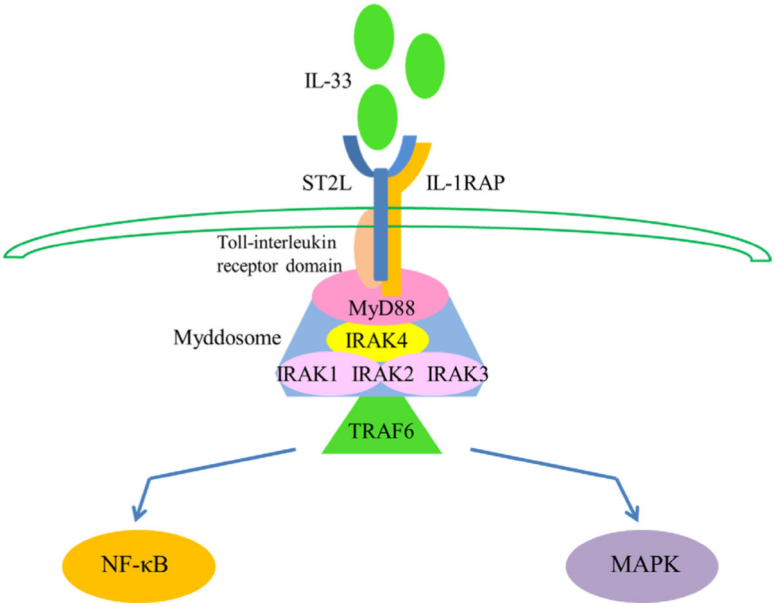

Figure 1.

IL-33 signaling pathway. IL-33 first binds to a receptor complex, which is composed of ST2L and IL-1RAP. Signaling is induced through the cytoplasmic Toll-inter-leukin receptor domain and leads to the recruitment of MyD88; IRAK4 is then recruited to MyD88, followed by interaction between IRAK1, IRAK2, and/or IRAK3 to form a complex known as the myddosome. This myddosome then interacts with TRAF6 and further activates the transcription factors NF-κB or MAPK.

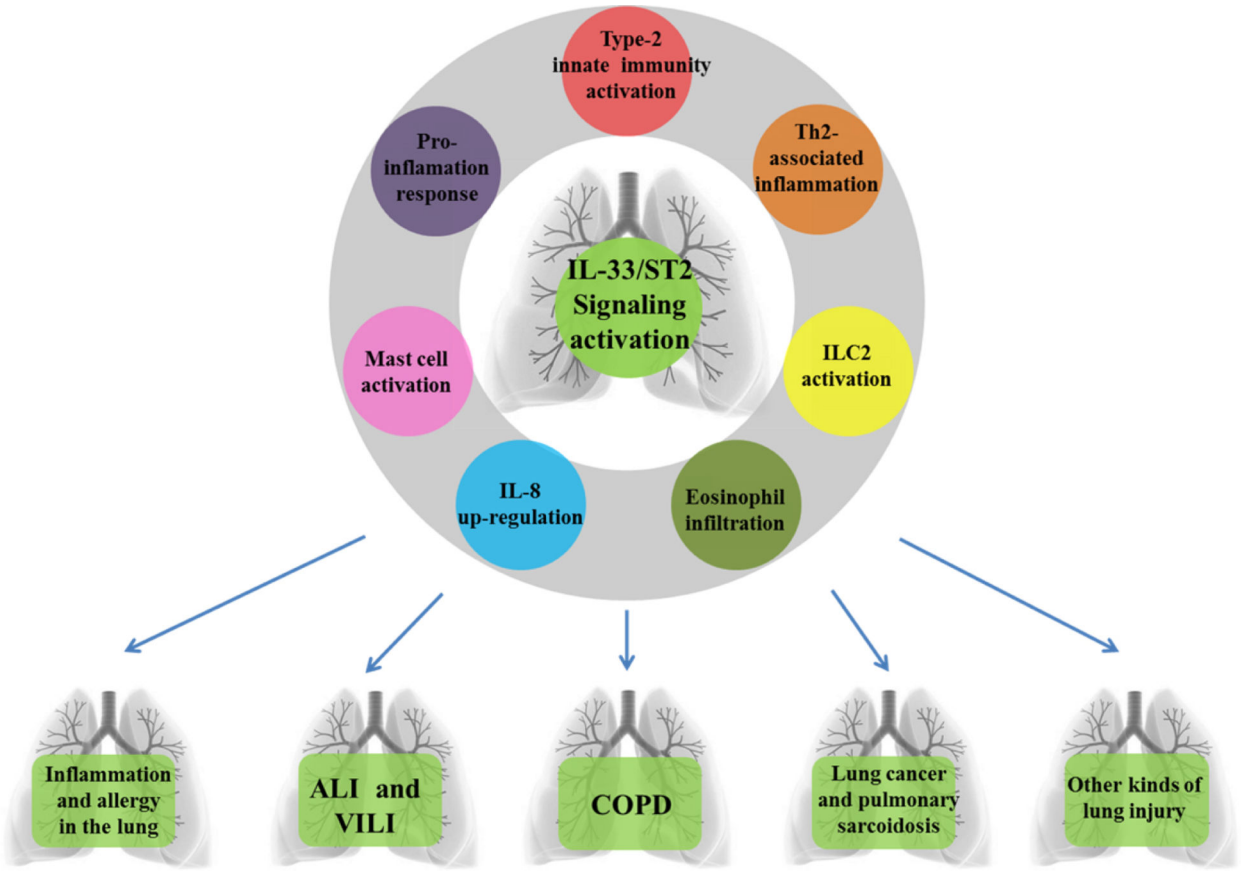

Figure 2. IL-33/ST2 signaling participates in various types of lung injury

IL-33 /ST2 signaling activation followed by type-2 innate immunity activation, Th2-associated airway inflammation, group 2 innate lymphoid cell (ILC2) activation, eosinophil infiltration, IL-8 up-regulation, mast cell activation and pro-inflammation response, further participates in lung inflammation and allergy, acute lung injury (ALI) and ventilator-induced lung injury (VILI), chronic obstructive pulmonary disease (COPD), lung cancer and pulmonary sarcoidosis and other kinds of lung injury.