

Critical roles of interleukin-33/suppression of tumorigenicity 2 (IL-33/ST2) in pulmonary disorders

Jiao Xu¹, Jianlei Tang²

¹Department of Respiratory Medicine, Wu-Jin Hospital Affiliated to Jiangsu University, Wu-Jin Clinical College of Xuzhou Medical University, Changzhou, Jiangsu 213017, China;

²Department of Intensive Care Unit, Wu-Jin Hospital Affiliated to Jiangsu University, Wu-Jin Clinical College of Xuzhou Medical University, Changzhou, Jiangsu 213017, China.

To the Editor: Interleukin (IL)-33, also named IL-1F11 is the 11th member of IL-1 family. The human IL-33 gene is located on the short arm of chromosome nine at 9p24.1. As a 31-kDa cytokine, IL-33 is constitutively expressed in endothelial and epithelial cells of barrier tissues. IL-33 cleaved by caspase-1 or caspase-3 is passively released from necrotic cells to maintain homeostasis and eliminate threats. IL-33 can also be cleaved by chymases, tryptases, and serine proteases, a process that converts IL-33 into various bioactive isoforms in different cell types.

Suppression of tumorigenicity 2 (ST2) is a member of the toll-like receptor (TLR)/IL-1 receptor (IL1R) superfamily, the gene of which is located on chromosome 2. Membrane type of suppression of tumorigenicity 2 (ST2L), which is a membrane-anchored receptor, binds to IL-33 to induce ligand-based signaling activation with the help of a co-receptor protein named IL-1R accessory protein (IL-1RACp). Binding of IL-33 to soluble type of suppression of tumorigenicity 2 (sST2) can block IL-33 biotic activity. In this review, the critical roles of the IL-33/ST2 pathway in pulmonary disorders will be discussed.

IL-33 from endothelial cells or other cells binds to the ST2L/IL-1-RACp heterodimer receptor, which induces signaling via the Toll/IL-1 receptor domain of ST2L/IL-1-RACp and recruits myeloid differentiation primary response 88, followed by IL-1 receptor-associated kinase 1/4 and tumor necrosis factor receptor-associated factor 6. This further induces mitogen-activated protein kinase (MAPK), which activates P38, extracellular regulated protein kinase (ERK), and C-jun N-terminal kinase (JNK), and/or activates nuclear transcription factor- κ B (NF- κ B). Alternatively, binding of IL-33 to sST2 neutralizes the pro-inflammatory effect of IL-33 [Supplementary Figure 1, <http://links.lww.com/CM9/A943>].

Asthma: In patients with asthma, an increase in IL-33 and ST2 in airway epithelial cells has been reported. In IL-33 or ST2 knockout mice, airway hyperresponsiveness and eosinophilic airway inflammation induced by IL-33 and ovalbumin (OVA) were both significantly attenuated without auto-amplification of the IL-33/ST2 pathway compared with wild-type mice, which suggests that endogenous IL-33 and auto-amplification of the IL-33/ST2 pathway play an important role in the induction of asthma.^[1]

The IL-33/ST2 pathway participates in asthma through inflammatory cells and mediators. In asthma, naive T helper (Th) 0 cells respond to IL-33, causing them to differentiate into Th2 cells and express pro-inflammatory cytokines, such as IL-4, IL-5, IL-6, and IL-13. Both basophils and mast cells express ST2, which binds to IL-33, causing basophils to release IL-4, IL-5, IL-8, and IL-13. Moreover, by upregulating cluster of differentiation (CD) 11b expression, IL-33 can recruit eosinophils from the circulation into the lung bronchoalveolar space to participate in asthma. A rare variant of *IL-33* (rs146597587-C) reduces the number of eosinophils in blood and protects against asthma. By increasing co-stimulatory molecules, such as CD40, CD80, OX40L, CD86, and major histocompatibility complex class II molecules, IL-33 can regulate maturation of bone marrow-derived dendritic cells and shift the immune response from Th1 cells toward Th2 cells. In a mouse model of asthma, IL-33 binds to ST2, activating downstream NF- κ B, MAPK, and other signaling pathways, resulting in the increased release of IL-4, IL-5, and IL-13, as well as other Th2 cytokines. Also, through ST2 on eosinophils, IL-33 can induce inflammatory mediators, including C-C motif chemokine ligand 2/ monocyte chemoattractant protein-1 and C-X-C motif chemokine ligand 8/IL-8.

Access this article online	
Quick Response Code:	Website: www.cmj.org
	DOI: 10.1097/CM9.0000000000002007

Correspondence to: Jianlei Tang, Department of Intensive Care Unit, Wu-Jin Hospital Affiliated to Jiangsu University, Wu-Jin Clinical College of Xuzhou Medical University, Changzhou, Jiangsu 213017, China
E-Mail: tangjianlei@163.com

Copyright © 2022 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2022;135(12)

Received: 18-04-2021; Online: 03-08-2022 Edited by: Peifang Wei

The IL-33/ST2 pathway is necessary for virus-induced asthma exacerbation in both humans and mice. Moreover, inhibition of IL-33 or ST2 eases airway inflammation, mucus hypersecretion, and airway hyperresponsiveness in murine asthma. When IL-33 was administered into the respiratory tract by nasal application, airway eosinophilic mucosal infiltration, hyperresponsiveness, and neo-angiogenesis were induced. However, binding of IL-33 to sST2 can reduce the expression of Th2 cytokines and inflammatory cell counts in bronchoalveolar lavage fluid (BALF) of mice with OVA-induced asthma. One study showed that IL-33 decreased and sST2 increased in asthmatic mice after acupuncture, suggesting that acupuncture through sST2 has an inhibitory effect on the IL-33/ST2 pathway to control asthma.^[21] The serum concentration of sST2 is higher during exacerbation of asthma in humans. It may thus be an accurate predictor of exacerbation occurring within 3 months. The findings mentioned above suggest that the IL-33/ST2 pathway promotes asthma through various immune cells and via a shift from Th1- to Th2-regulated immune responses. The host tries to attenuate IL-33 signaling by increasing sST2 in a feedback circuit. IL-33 and ST2 have emerged as promising new drug targets and treatments, including IL-33 antibodies and sST2. Moreover, vaccines against IL-33 are under investigation for the treatment of asthma.

Pulmonary arterial hypertension (PAH): In patients with PAH, sST2 expression was significantly higher compared with healthy individuals, while there were no differences in IL-33 between cases and controls. PAH patients with higher sST2 expression had a significantly worse World Health Organization functional class, right ventricular volume, and systolic function, as well as myocardial fibrosis, which suggests that sST2 may be a candidate biomarker in PAH. Moreover, nuclear IL-33 was markedly diminished in the vessels of patients with idiopathic PAH (iPAH), but serum levels of IL-33 were unchanged compared with healthy subjects. However, serum sST2 was enhanced in patients with iPAH. Shao *et al*^[3] proved that through recruitment of transcriptional repressor proteins, IL-33 regulated the expression of IL-6 and sST2 in primary human endothelial cells and may thus play an important role in the pathogenesis of PAH. IL-33 and ST2 were significantly increased in lung tissue from mice with hypoxia-induced pulmonary hypertension (HPH). Moreover, hypoxia-inducible factor (HIF)-1 α and vascular endothelial growth factor (VEGF) signaling, which occurs downstream of IL-33/ST2 signaling, was activated and contributed to hypoxic pulmonary vascular remodeling. Knockdown of endogenous IL-33 or ST2 significantly suppressed vascular remodeling initiated by HIF-1 α and VEGF in HPH. In IL-33-induced arterial hypertrophy animal models, group 2 innate lymphoid cell (ILC2) cells and eosinophils have been reported to leave hypertrophied arteries in the later stages. Moreover, the anti-IL-5(R α) antibody effectively prevented the development of arterial hypertrophy in an animal model of IL-33-induced arterial hypertrophy.^[4]

Acute lung injury (ALI): In a previous study, the level of serum IL-33 was higher in patients with ALI compared with healthy controls. In mice with lipopolysaccharide (LPS)-induced ALI,

the expression of IL-33 and ST2 in the serum and BALF was upregulated by LPS, and the LPS receptor toll-like receptor can be induced by IL-33 in macrophages with the activation of NF- κ B, which increased the production of pro-inflammatory cytokines. The recent study proved that IL-33 induced the expressions of interstitial matrix proteins matrix metalloproteinase (MMP) 2 and MMP9, which mediated degradation of proteins in the alveolar epithelial-endothelial unit, correlated with the alveolar-arterial oxygen gradient and activated signal transducer and activator of transcription 3 during LPS-induced ALI. In addition, neutralizing IL-33 using antibodies inhibited the LPS-induced MMP2/9 expression and ALI.^[5] The mechanism has been explored recently; it is thought that after viral infection, IL-33 stimulates ST2⁺ regulatory T cells to upregulate amphiregulin during lung repair. The level of IL-33 in mice with LPS-induced ALI could be altered by changes in autophagy caused by rapamycin or 3-methyl adenine, in part as a result of NF- κ B-mediated inflammatory pathways. Thus, IL-33 has potential as a promising new target for the treatment of ALI.

Chronic obstructive pulmonary disease (COPD): A previous study showed that the level of IL-33 in patients with exacerbated COPD was significantly higher compared with healthy controls.^[6] An IL-33 polymorphism (rs1891385 [A/C]) was proven to be correlated with COPD onset. Patients with COPD with genotype AA exhibited a higher IL-33 level, but a lower forced expiratory volume in 1 s (FEV₁)/forced vital capacity ratio (%) and FEV₁/predicted value ratio (%) compared with those with genotypes AC and CC. In a mouse model of COPD, after viral infection or cigarette smoking, IL-33 expression increased in airway epithelial cells. In addition, treatment with an antioxidant N-acetylcysteine decreased the expression of IL-33 in human bronchial epithelial cells (HBECs) from patients with COPD, which suggests that oxidative stress is involved in the regulation of IL-33 production in COPD. MAPK, JNK, and ERK1/2 inhibitors significantly decreased the expression of IL-33 in HBECs from patients with COPD, which suggests that the MAPK-JNK-ERK1/2 signaling pathway involves hydrogen peroxide (H₂O₂)-augmented IL-33 expression in COPD. Jiang *et al*^[7] proved that ST2⁺ ILC2 cells and IL-33 in the peripheral blood of patients with COPD were significantly higher compared with healthy individuals. IL-33 also promoted the differentiation of peripheral blood ILC2 cells in patients with COPD and induced ILC2 cells to produce Th2 cytokines, including IL-4, IL-5, and IL-6, through the IL-33/ST2 signaling pathway.

Lung cancer: IL-33/ST2 expression was detected in the tumor microenvironment of non-small-cell lung cancer (NSCLC). Specifically, IL-33 was elevated in serum and BALF of patients with NSCLC. IL-33 activated A549 cells via ST2 to enhance tumor outgrowth and metastasis. Meanwhile, IL-33 and ST2 expression in NSCLC tissues correlated with tumor progression, while knockdown of IL-33 or ST2 blockade limited NSCLC progression. IL-33 promoted the effector functions of CD8⁺ T cells, which play a critical role in the antitumor immune response. IL-33 upregulates T-cell receptor-like CD107a, granzyme B, CC chemokine ligand 20, and through ST2 on CD8⁺ T

cells, can promote effector CD8⁺ T cells to express interferon- γ in mice with lung cancer. IL-33 promoted proliferation, activation, and recruitment of CD8⁺T cells and NK cells by NF- κ B signaling to block lung cancer metastasis. However, Kim *et al*^[8] proved that the level of IL-33 was significantly lower in patients with cancer compared with healthy individuals and was inversely associated with lung cancer progression. The role of IL-33 should be explored in lung cancer.

Idiopathic pulmonary fibrosis: A previous study showed that IL-33 was elevated in a bleomycin-induced murine model of lung fibrosis. In detail, mouse IL-33 production was induced in macrophages by bleomycin, which polarized macrophages toward the M2 phenotype, accelerating pulmonary fibrosis. Mato *et al*^[9] demonstrated that the increase of neutrophils was suppressed in BALF from ST2-overexpressing bleomycin-treated mice. The pro-inflammatory factors tumor necrosis factor alpha (TNF- α) and IL-1 β increased immediately on the day of treatment, while after 3 days of bleomycin treatment, endogenous ST2 and IL-33 messenger RNA expression in lung tissue increased significantly, and the concentrations of TNF- α , IL-6, and albumin in BALF were reduced. The structure of lung tissue from ST2-overexpressing mice treated with bleomycin remained almost normal. Therefore, ST2 can inhibit bleomycin-induced lung damage at an early stage by inhibiting the release of inflammatory cytokines and neutrophil aggregation, in turn alleviating the degree of pulmonary fibrosis. Tajima *et al*^[10] found that the level of serum ST2 in patients with stable IPF was not significantly different compared with healthy controls, while the level of serum ST2 in patients with acutely exacerbated IPF increased significantly. In addition, sST2 levels are associated with lactate dehydrogenase and C-reactive protein. Tajima *et al*^[10] believe that ST2 plays a role in the development of IPF.

In conclusion, as an important Th2 cytokine inducer, IL-33, acting via ST2, has been documented to play an important role in pulmonary diseases. However, thus far, its role has not been fully understood. The IL-33/ST2 pathway is a critical pathway to induce related immune mechanisms, while IL-33/sST2 appears to neutralize IL-33/ST2 signaling. Therefore, further studies are needed to elucidate these pathways in pulmonary diseases, either as novel biomarkers or as therapeutic targets.

Funding

This work was supported by grants from the Young Talent Development Plan of Changzhou Health Commission

(No. CZQM2021025), the Science and Technology Project of Changzhou Health Commission (No. QN202140), and the Clinical Technology Development Foundation of Jiangsu University (Nos. JLY2021023 and JLY2021031).

Conflicts of interest

None.

References

- Magat JM, Thomas JL, Dumouchel JP, Murray F, Li WX, Li J. Endogenous IL-33 and its autoamplification of IL-33/ST2 pathway play an important role in asthma. *J Immunol* 2020;204:1592–1597. doi: 10.4049/jimmunol.1900690.
- Dong M, Ma C, Wang WQ, Chen J, Wei Y. Regulation of the IL-33/ST2 pathway contributes to the anti-inflammatory effect of acupuncture in the ovalbumin-induced murine asthma model. *Acupunct Med* 2018;36:319–326. doi: 10.1136/acupmed-2017-011377.
- Shao D, Perros F, Caramori G, Meng C, Dormuller P, Chou PC, *et al*. Nuclear IL-33 regulates soluble ST2 receptor and IL-6 expression in primary human arterial endothelial cells and is decreased in idiopathic pulmonary arterial hypertension. *Biochem Biophys Res Commun* 2014;451:8–14. doi: 10.1016/j.bbrc.2014.06.111.
- Ikutani M, Ogawa S, Yanagibashi T, Nagai T, Okada K, Furuichi Y, *et al*. Elimination of eosinophils using anti-IL-5 receptor alpha antibodies effectively suppresses IL-33-mediated pulmonary arterial hypertrophy. *Immunobiology* 2018;223:486–492. doi: 10.1016/j.imbio.2017.12.002.
- Liang Y, Yang N, Pan G, Jin B, Wang S, Ji W. Elevated IL-33 promotes expression of MMP2 and MMP9 via activating STAT3 in alveolar macrophages during LPS-induced acute lung injury. *Cell Mol Biol Lett* 2018;23:52. doi: 10.1186/s11658-018-0117-x.
- Kim SW, Rhee CK, Kim KU, Lee SH, Hwang HG, Kim YI, *et al*. Factors associated with plasma IL-33 levels in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2017;12:395–402. doi: 10.2147/COPD.S120445.
- Jiang M, Tao S, Zhang S, Wang J, Zhang F, Li F, *et al*. Type 2 innate lymphoid cells participate in IL-33-stimulated Th2-associated immune response in chronic obstructive pulmonary disease. *Exp Ther Med* 2019;18:3109–3116. doi: 10.3892/etm.2019.7924.
- Kim MS, Kim E, Heo JS, Bae DJ, Lee JU, Lee TH, *et al*. Circulating IL-33 level is associated with the progression of lung cancer. *Lung Cancer* 2015;90:346–351. doi: 10.1016/j.lungcan.2015.08.011.
- Mato N, Fujii M, Hakamata Y, Kobayashi E, Sato A, Hayakawa M, *et al*. Interleukin-1 receptor-related protein ST2 suppresses the initial stage of bleomycin-induced lung injury. *Eur Respir J* 2009;33:1415–1428. doi: 10.1183/09031936.00084307.
- Tajima S, Bando M, Ohno S, Sugiyama Y, Oshikawa K, Tominaga S, *et al*. ST2 gene induced by type 2 helper T cell (Th2) and proinflammatory cytokine stimuli may modulate lung injury and fibrosis. *Exp Lung Res* 2007;33:81–97. doi: 10.1080/01902140701198583.

How to cite this article: Xu J, Tang J. Critical roles of interleukin-33/suppression of tumorigenicity 2 (IL-33/ST2) in pulmonary disorders. *Chin Med J* 2022;135:1508–1510. doi: 10.1097/CM9.0000000000002007