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Targeting the IL-33/ST2 signalling pathway as a therapeutic strategy for the treatment of multiple inflammatory diseases

Huda Ismail[1], Fatima Adnan Alzubaidi[2,*], Enass Najem Oubaid[3]

[1]College of Pharmacy, University of Babylon, Hillah, Iraq
[2]Department of Clinical Pharmacy, College of Pharmacy, University of Babylon, Hillah, Iraq
[3]Department of Pharmacognosy, College of Pharmacy, University of Babylon, Hillah, Iraq

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*** CORRESPONDING AUTHOR:**
Fatima Adnan Alzubaidi, Department of Clinical Pharmacy, College of Pharmacy, University of Babylon, Hillah, Iraq; e-mail: phar.fatimah.adnan@uobabylon.edu.iq

ABSTRACT

Interleukin-33 (IL-33) is a cytokine belonging to the interleukin-1 (IL-1) superfamily. It is expressed and upregulated following pro-inflammatory stimulation, and plays a key role in inducing the synthesis of T-helper type 2 (Th2) cytokines and IN promoting the pathogenesis of Th2-related diseases. IL-33 exerts its biological effects by binding to its receptor, ST2; a member of the IL-1 receptor family that exists in two isoforms: the transmembrane form (ST2L) and the soluble form (sST2). Through ST2L, IL-33 signals surrounding immune cells in response to tissue injury. In the respiratory system, IL-33 overexpression can exacerbate chronic respiratory diseases. In the cardiovascular system, cardiomyocytes and cardiac fibroblasts increase the expression of both IL-33 and ST2. Within the central nervous system, IL-33 promotes M2 macrophage polarization and/or regulatory T cell (Treg) activation, thereby contributing to an anti-inflammatory response in various disease contexts. In the renal system, IL-33/ST2 signalling has been implicated in both pathogenic and tissue-protective processes across multiple renal disorders. In the gastrointestinal tract, targeting the IL-33 signalling pathway presents a potential therapeutic strategy. In type 2 diabetes mellitus, metformin treatment has revealed a key role for IL-33 and ST2 in disease modulation. In skin diseases such as psoriasis and vitiligo, increased IL-33 expression has been observed in lesional tissues. Finally, in rheumatological diseases, the IL-33/ST2 pathway appears to exert a detrimental influence during both early and advanced disease stages.

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1. Introduction

Interleukin-33 (IL-33) is a cytokine belonging to the interleukin-1 (IL-1) superfamily. It is produced primarily by stromal cells, including endothelial and epithelial cells, and is upregulated following pro-inflammatory stimulation. IL-33 can function both as a traditional cytokine and as a nuclear transcriptional regulator. It is thought to act as an "alarmin", released upon cell necrosis to signal tissue injury to the immune system. Its biological activity is mediated through interaction with the ST2 (IL-1RL1) receptor and the IL-1 receptor accessory protein (IL-1RAcP), both of which are highly expressed by T helper 2 (Th2) cells and innate immune cells[1]. IL-33 promotes Th2 cytokine synthesis and contributes to the pathogenesis of Th2-mediated diseases such as asthma and atopic dermatitis. Conversely, it exhibits protective effects in conditions such as atherosclerosis, cardiac remodelling, type 2 diabetes (T2D), and obesity. The functional role of IL-33 – either pro-inflammatory or anti-inflammatory – depends on disease context and experimental model[2].

ST2 exists in two isoforms: transmembrane (ST2L) and soluble (sST2). ST2L serves as the signalling receptor for IL-33, triggering immune responses and the production of inflammatory cytokines. In contrast, sST2 acts as a decoy receptor, neutralizing IL-33 and inhibiting ST2L-mediated signalling. This review summarizes the role of IL-33/ST2 signalling in inflammatory disease pathogenesis and its potential as a therapeutic target.

2. Respiratory system

Type II inflammation is a chronic inflammatory response characterized by prolonged activation and dysregulation of immune cells. It underpins several respiratory disorders, notably asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, and pulmonary fibrosis. The process involves a complex crosstalk among pro-inflammatory cytokines and regulatory pathways, with key contributions from Th2 cells, IL-4, IL-5, IL-9, IL-13, IL-33, and thymic stromal lymphopoietin. IL-33 is a central mediator of type II inflammation, particularly in asthma and COPD. Its overexpression correlates with increased disease severity *via* sustained inflammation and airway remodelling. IL-33 also plays a role in allergic rhinitis by inducing Th2 cytokines associated with nasal congestion and irritation. Several ongoing randomized controlled trials are investigating anti-IL-33 agents (itepekimab, tozorakimab) and anti-ST2 antibodies (astegolimab) in patients with asthma and COPD[3].

3. Cardiovascular system

The IL-33/ST2 pathway plays a critical role in cardiovascular physiology, particularly in response to myocardial stretch and injury. Following myocardial infarction or heart failure, IL-33 modulates cardiac hypertrophy, remodelling, and fibrosis. However, endothelial cells and fibroblasts release sST2, which antagonizes IL-33 by functioning as a decoy receptor. Elevated sST2 levels are associated with inadequate cardioprotection and heightened risk of ventricular dysfunction.

The IL-33/ST2 signalling is implicated in several cardiovascular conditions, including ischaemic heart disease, cardiomyopathy, and myocarditis. sST2 is also recognized as a biomarker in systemic and pulmonary hypertension and as a diagnostic indicator in acute aortic dissection. In 2013, the American College of Cardiology Foundation / American Heart Association classified sST2 as an independent biomarker for heart failure and myocardial infarction[4].

4. Central nervous system

In the central nervous system, IL-33 is primarily expressed by astrocytes and oligodendrocytes. Beyond its role in promoting brain tumorigenesis, IL-33 facilitates M2 macrophage polarization and regulatory T cell (Treg) activation and expansion. These mechanisms support anti-inflammatory responses in conditions such as multiple sclerosis, Alzheimer's disease, traumatic brain injury, and ischaemic stroke. These findings suggest IL-33 administration may offer therapeutic potential in CNS disorders[5].

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5. Renal system

Numerous studies have examined IL-33 activity in renal injury models, including ischemia–reperfusion injury (IRI), ovalbumin-induced nephrotoxicity, and cisplatin-induced acute kidney injury. Notably, an engineered IL-2/IL-33 fusion protein has demonstrated renoprotective effects in IRI models. Moreover, across various renal pathologies, the IL-33/ST2 signalling exhibits a dual role, contributing to both injury and tissue repair, thereby emphasizing its context-dependent function[2].

6. Gastrointestinal system

The IL-33/ST2 complex interacts with intestinal epithelial cells during injury and activates innate immune responses. Elevated IL-33 levels have been linked to exacerbated inflammation and tissue damage in ulcerative colitis, and to recurring inflammation with Th1 skewing in Crohn's disease. In colorectal cancer, IL-33 promotes tumor progression through pro-angiogenic signalling and the activation of subepithelial myofibroblasts. Thus, targeting the IL-33 pathway holds promise for the development of therapeutic interventions in gastrointestinal diseases[6].

7. Diabetes mellitus

Pancreatic β-cell dysfunction is central to both type 1 diabetes (T1D) and T2D, resulting from autoimmune destruction in T1D and multifactorial stressors (such as glucolipotoxicity, mitochondrial dysfunction, endoplasmic reticulum stress, and inflammation) in T2D. Emerging evidence suggests a protective role for IL-33 in diabetes. IL-33 suppresses insulitis, inhibits autoimmune diabetes progression, and enhances glucose homeostasis *via* the stimulation of islet-resident group 2 innate lymphoid cells. Interestingly, metformin treatment in T2D patients has been associated with elevated IL-33 and reduced ST2 expression, which correlates with improved glycaemic control and highlights the cytokine's inflammatory and therapeutic significance[7].

8. Skin diseases

Atopic dermatitis (AD) is a Th2-driven condition mediated *via* the IL-33/ST2 signalling. Patients with AD exhibit elevated IL-33 levels in lesional skin, although serum sST2 levels remain unchanged. Clinical trials are underway in order to evaluate novel anti-IL-33 antibodies in this context. By contrast, psoriasis is governed by Th1 and Th17 cytokines, yet psoriatic lesions still show increased IL-33 expression. In vitiligo, skin biopsies reveal concurrent elevation of IL-33 and ST2, with corresponding increases in serum IL-33 levels[8].

9. Rheumatological system

The IL-33/ST2 pathway plays a deleterious role in the pathogenesis of several rheumatological conditions, including rheumatoid arthritis, scleroderma, systemic lupus erythematosus, psoriasis, and gout. In early stages, IL-33 released from injured epithelium activates neighbouring tissues and recruits immune cells. In later stages, IL-33 functions as a pro-fibrogenic factor that may also support barrier maintenance. These findings underscore the pleiotropic and context-dependent nature of IL-33 signalling[9].

10. Conclusion

IL-33 exhibits multifaceted immunomodulatory effects across a broad spectrum of inflammatory diseases. It promotes Th2 cytokine synthesis and contributes to Th2-related pathologies such as asthma and atopic dermatitis. Conversely, IL-33 confers protection in cardiovascular and metabolic disorders, including atherosclerosis, obesity, cardiac remodelling, and T2D. Understanding the optimal timing and context for modulating the IL-33/ST2 signalling might prove essential for the development of effective therapeutic strategies.

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Conflicts of interest

None exist.

ORCIDs

0009-0000-4480-9213 (H. Ismail); 0000-0002-3286-0078 (F.A. Alzubaidi); 0000-0001-6840-0607 (E.N. Oubaid)

References

1. Miller A.M. Role of IL-33 in inflammation and disease. *J. Inflamm. (Lond.)* 8(1), 22, 2011. DOI: 10.1186/1476-9255-8-22
2. Chen W.Y., Tsai T.H., Yang J.L., Li L.C. Therapeutic strategies for targeting IL-33/ST2 signalling for the treatment of inflammatory diseases. *Cell. Physiol. Biochem.* 49(1), 349–358, 2018. DOI: 10.1159/000492885
3. Gu S., Wang R., Zhang W., Wen C., Chen C., Liu S., *et al.* The production, function, and clinical applications of IL-33 in type 2 inflammation-related respiratory diseases. *Front. Immunol.* 15, 1436437, 2024. DOI: 10.3389/fimmu.2024.1436437
4. Brunetti G., Barile B., Nicchia G.P., Onorati F., Luciani G.B., Galeone A. The ST2/IL-33 pathway in adult and paediatric heart disease and transplantation. *Biomedicines* 11(6), 1676, 2023. DOI: 10.3390/biomedicines11061676
5. Sun Y., Wen Y., Wang L., Wen L., You W., Wei S., *et al.* Therapeutic opportunities of interleukin-33 in the central nervous system. *Front. Immunol.* 12, 654626, 2021. DOI: 10.3389/fimmu.2021.654626
6. Giordano W., Ricciardi G., Casciaro M., Fiorentino V., Pizzimenti C., Viola A., *et al.* Role of IL-33/ST2 pathway in inflammatory bowel disease: an overview and future perspectives. *Gastrointest. Disord.* 6(2), 446–460, 2024. DOI: 10.3390/gidisord6020030
7. Abdullah T.H., Saheb H.A. The effect of metformin therapy on serum IL-33 and ST-2 receptor levels in patients with type 2 diabetes mellitus. *South East. Eur. J. Public Health* 24(s2), 593–601, 2024. DOI: 10.70135/seejph.vi.1228
8. Griesenauer B., Paczesny S. The ST2/IL-33 axis in immune cells during inflammatory diseases. *Front. Immunol.* 8, 475, 2017. DOI: 10.3389/fimmu.2017.00475
9. Dong Y., Zhong J., Dong L. IL-33 in rheumatic diseases. *Front. Med. (Lausanne)* 8, 739489, 2021. DOI: 10.3389/fmed.2021.739489

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