



The Epithelial Alarmin-Mast Cell Interface in Chronic Spontaneous Urticaria: From TSLP and IL-33 Signaling to Biomarkers and Targeted Therapy

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Received: 28 October 2024, **Accepted:** 17 November 2024, **Published:** 20 November 2024

Abstract

Background: Chronic spontaneous urticaria (CSU) is a mast cell-driven inflammatory disorder characterized by recurrent wheals, angioedema, or both for more than six weeks without a definite external trigger. Although histamine release remains the final common pathway of many symptoms, clinical variability, autoimmune associations, and heterogeneous therapeutic responses indicate that upstream immune circuits are equally important. Epithelial and stromal alarmins, particularly thymic stromal lymphopoietin (TSLP) and interleukin-33 (IL-33), can activate mast cells, basophils, dendritic cells, eosinophils, and group 2 innate lymphoid cells, potentially linking tissue stress to persistent inflammation. Aim: This review critically examines the TSLP and IL-33/ST2 pathways in CSU, their interaction with established autoimmune endotypes, their value as candidate biomarkers, and the implications of upstream alarmin targeting. Methods: Evidence was synthesized from international guidelines, mechanistic studies, clinical cohorts, translational investigations, and trials of alarmin-directed biologics, with priority given to validated and recent literature. Results: Lesional skin and serum studies support increased alarmin activity in subsets of patients, particularly for IL-33, but findings vary across cohorts and assays. TSLP and IL-33 appear more likely to act as disease amplifiers and endotype modifiers than isolated diagnostic markers. The phase 2b INCEPTION study of tezepelumab did not meet its primary week-16 endpoint, although delayed post-treatment improvement and biomarker signals support continued mechanistic investigation. Conclusion: The epithelial alarmin-mast cell axis provides a coherent framework linking tissue stress, innate immunity, autoimmunity, and treatment heterogeneity in CSU. Clinical translation will require standardized assays, endotype-resolved cohorts, and biomarker-enriched trials rather than reliance on single circulating cytokines.

Keywords: Chronic spontaneous urticaria, thymic stromal lymphopoietin, interleukin-33, alarmins, mast cells



Introduction

Chronic spontaneous urticaria (CSU) is defined by the spontaneous appearance of wheals, angioedema, or both for longer than six weeks, in the absence of a definite inducible trigger. Contemporary international guidance continues to regard CSU as a mast cell-driven disease, but this description is increasingly understood as a statement about the final effector cell rather than a complete explanation of pathogenesis. The disease spans highly variable clinical courses, autoimmune backgrounds, inflammatory signatures, and treatment responses, which argues against a single linear mechanism. A useful modern model therefore separates the downstream release of histamine and other mast-cell mediators from the upstream signals that determine why mast cells become persistently hyperresponsive in individual patients. [1]

The clinical heterogeneity of CSU is now matched by a more detailed immunologic framework. Autoallergic mechanisms, type IIb autoimmunity, complement activation, basophil abnormalities, eosinophil trafficking, coagulation-associated inflammation, and cytokine networks can coexist to different degrees. The recent literature has therefore moved from a purely symptom-based concept toward endotypes defined by dominant immune pathways. This shift is clinically important because patients who look similar at the bedside may differ in total immunoglobulin E (IgE), autoantibodies, basophil function, inflammatory markers, and response to omalizumab or cyclosporine. [2]

Within this framework, epithelial and stromal-derived alarmins have become particularly attractive. Thymic stromal lymphopoietin (TSLP) and interleukin-33 (IL-33) are positioned near the interface between tissue stress and immune activation. Both can influence mast cells directly and can also act through dendritic cells, group 2 innate lymphoid cells (ILC2s), basophils, eosinophils, and type 2 T-cell responses. Their location upstream of several inflammatory cascades raises a central question: are these molecules merely markers released during active skin inflammation, or do they participate in sustaining the abnormal activation threshold that characterizes CSU? [3]

Aim of the Review

This review evaluates the mechanistic and translational importance of the TSLP and IL-33/ST2 axes in CSU, with particular attention to their interaction with mast-cell biology, autoimmune endotypes, candidate biomarker profiles, treatment resistance, and emerging targeted therapy.

Methods

A focused narrative synthesis was performed using international urticaria guidelines, major reviews, mechanistic immunology studies, CSU cohort studies, translational biomarker investigations, and clinical trials of alarmin-directed therapy. Priority was given to peer-reviewed and verifiable literature that directly addressed CSU, TSLP, IL-33/ST2 signaling, mast-cell activation, autoimmune endotypes, or treatment response. Findings from asthma and atopic dermatitis were included only when they clarified conserved alarmin biology relevant to CSU, and disease-specific extrapolation is identified as such.

Mast Cells as the Final Common Effector

Skin-resident mast cells remain the central effector cells of CSU because their activation releases histamine, leukotrienes, prostaglandins, proteases, cytokines, and vascular mediators that generate the characteristic wheal-and-flare response, pruritus, and angioedema. Mast-cell degranulation can be initiated through aggregation of the high-affinity IgE receptor FcεRI, but non-IgE pathways, neuroimmune signals, complement components, and cytokine priming can alter the threshold for activation. The significance of alarmins lies precisely in this priming function: they may not be the sole trigger of a wheal, yet they can create a tissue environment in which otherwise subthreshold signals produce sustained mediator release. [4]

Basophils provide a circulating counterpart to mast cells and are not passive observers in CSU. Active disease is often accompanied by basopenia, altered FcεRI signaling, and impaired ex vivo histamine release, findings that can normalize with disease control. Migration of basophils into tissue and functional exhaustion or desensitization may both contribute. These abnormalities matter when



considering alarmins because TSLP and IL-33 can influence basophil activation and type 2 cytokine production, thereby linking circulating cellular phenotypes to the inflammatory skin microenvironment. [5]

Autoimmunity and Autoallergy: The Immunologic Background on Which Alarmins Act

The best-established disease-specific mechanisms in CSU are type I autoallergy and type IIb autoimmunity. In type I autoallergic CSU, IgE recognizes self-antigens and can cross-link FcεRI-bound IgE on mast cells and basophils. IgE directed against thyroid peroxidase is a classic example and provides proof that an endogenous antigen can participate in an IgE-dependent urticarial mechanism. This pathway offers a biological explanation for why higher total IgE and some allergic features are often associated with faster responses to anti-IgE therapy. [6]

Type IIb autoimmune CSU is mechanistically different. IgG, and in some patients other immunoglobulin classes, can recognize FcεRI or IgE itself and activate mast cells or basophils independently of allergen-specific IgE. The historical demonstration that sera from patients with chronic urticaria can contain functional autoantibodies against the high-affinity IgE receptor remains foundational to this concept. Type IIb disease tends to cluster with low total IgE, thyroid autoimmunity, basopenia or eosinopenia, greater disease activity, and slower or less complete responses to omalizumab. [7]

The immunologic boundary between these endotypes is not absolute. Studies have identified IgM and IgA in addition to IgG autoantibodies against FcεRIα, and patients may show overlapping autoallergic and autoimmune features. This is important for the alarmin hypothesis because TSLP and IL-33 need not define a third mutually exclusive endotype. A more plausible model is that alarmin activity modifies the intensity and persistence of mast-cell activation across several endotypes, amplifying disease in patients whose primary initiating mechanism may still be IgE-dependent or autoantibody-driven. [8]

Routine biomarkers partly reflect this biology. Low total IgE and elevated IgG anti-thyroid peroxidase antibodies can help identify patients with a type IIb autoimmune profile, while higher IgE more often accompanies autoallergic biology and better omalizumab responsiveness. None of these markers is perfectly specific, and they should be interpreted as probabilistic features rather than diagnostic labels. This limitation provides a rationale for adding upstream inflammatory markers, including alarmins, to multi-parameter models rather than expecting a single cytokine to classify the disease. [9]

TSLP Biology: An Upstream Organizer of Type 2 Inflammation

TSLP is an epithelial cytokine with structural and functional similarity to the interleukin-7 family. It is produced by barrier tissues in response to inflammatory cytokines, microbial products, mechanical injury, allergens, and other forms of tissue stress. TSLP signals through a heterodimeric receptor containing TSLPR and IL-7Rα and can influence dendritic cells, mast cells, basophils, eosinophils, ILC2s, and T lymphocytes. Its strategic position at the barrier-immune interface allows local tissue disturbance to be translated into sustained immune activation. [10]

At the signaling level, TSLP activates Janus kinase and STAT pathways, including JAK1/JAK2-dependent STAT5 phosphorylation, and interacts with NF-κB-associated inflammatory programs. In dendritic cells, TSLP induces OX40 ligand and favors differentiation of inflammatory type 2 helper T cells. This provides a mechanistic route from epithelial stress to IL-4, IL-5, and IL-13 production, IgE class switching, eosinophil recruitment, and mast-cell support. These mechanisms are well established in allergic disease and are biologically compatible with the type 2-skewed microenvironment described in CSU lesions. [11]

Human TSLP biology is further complicated by transcript and protein isoforms. A short form is constitutively expressed in keratinocytes and has been associated with homeostatic and antimicrobial functions, whereas the long form is more closely linked to inflammatory signaling. This distinction is relevant to biomarker studies because many commercial assays do not clearly resolve biologically different forms of TSLP. Apparent discrepancies between studies may therefore reflect not only patient heterogeneity but also what the assay is actually measuring. [12]

IL-33/ST2: A Nuclear Alarmin With Potent Mast-Cell Effects

IL-33 is a member of the interleukin-1 family that is constitutively present in the nuclei of structural



cells, including epithelial, endothelial, and stromal cells. Tissue injury or cellular stress can release biologically active IL-33, allowing it to function as an alarmin. Its principal receptor is ST2, which exists as a membrane signaling form and a soluble decoy form. Through ST2 and the IL-1 receptor accessory protein, IL-33 activates MyD88-dependent signaling and downstream NF- κ B and mitogen-activated protein kinase pathways. [13]

The biological effects of IL-33 are unusually relevant to CSU because ST2 is expressed on mast cells, basophils, eosinophils, ILC2s, and several T-cell subsets. IL-33 can augment mast-cell cytokine production, promote survival and responsiveness, and amplify ILC2-derived IL-5 and IL-13. It therefore links tissue stress to both immediate effector cells and slower cytokine circuits. Its actions are not restricted to classical IgE signaling, making IL-33 a credible amplifier in patients whose disease is driven by autoimmune or mixed mechanisms. [14]

Human mast-cell studies support this concept directly. IL-33 can strongly activate or prime human mast cells and can cooperate with Fc ϵ RI-mediated stimulation to enhance inflammatory mediator production. Mast cells can also sense local cell injury through IL-33, providing a feed-forward mechanism in which tissue inflammation increases responsiveness of cells that, when activated, further increase vascular permeability and local inflammation. This type of loop is highly compatible with the recurrent and self-sustaining nature of CSU. [15]

Direct Evidence for Alarmins in CSU

The most persuasive tissue-level evidence comes from lesional skin. Kay and colleagues demonstrated increased numbers of IL-33-, IL-25-, and TSLP-positive cells in CSU wheals compared with uninvolved skin and controls, alongside a type 2 cytokine pattern. IL-33 localized to several dermal cell populations, including endothelial cells, fibroblasts, macrophages, and mast cells. The study was small, but it showed that alarmin expression is not merely a theoretical extrapolation from asthma or atopic dermatitis; the pathway is demonstrable within the urticarial lesion itself. [16]

Circulating data have strengthened interest while also exposing heterogeneity. Dobrican-Băruța and colleagues measured the alarmin triad of IL-25, IL-33, and TSLP in 50 patients with CSU and 38 healthy controls. Serum IL-33 and TSLP were significantly elevated in CSU, whereas the IL-25 difference did not reach significance. IL-33 also showed clinically relevant relationships with disease activity and quality-of-life measures. These findings support IL-33 as the most promising serum component of the triad, but they require replication across larger populations and assay platforms. [17]

Earlier work also found increased plasma IL-33 in CSU, together with elevations of IL-17 and IL-31. The presence of IL-33 within a broader cytokine disturbance is important because CSU does not behave as a purely type 2 disorder. Depending on the patient, Th2, Th17, autoimmune, complement, coagulation, and innate immune signals may all contribute. IL-33 may therefore be more informative as part of a network signature than as a stand-alone disease marker. [18]

The TSLP-IL-33 Amplification Loop

TSLP and IL-33 converge functionally despite using different receptors. Both can enhance mast-cell responsiveness, activate ILC2s, promote type 2 cytokine production, and facilitate eosinophil-rich inflammation. TSLP is particularly effective at conditioning dendritic-cell and T-cell responses, whereas IL-33 can act rapidly on ST2-expressing innate cells. Their simultaneous presence in an inflamed skin environment could therefore create parallel and partly redundant routes to IL-5 and IL-13 production, vascular dysfunction, and persistent mast-cell priming. [19]

A useful mechanistic model is to view CSU as a two-layer system. The first layer contains initiating signals, such as IgE autoantibodies, anti-Fc ϵ RI antibodies, complement activation, or other mast-cell triggers. The second layer determines the gain of the system: alarmins, cytokines, local stromal signals, and recruited leukocytes increase or decrease how strongly mast cells respond. In this model, TSLP and IL-33 act as gain amplifiers rather than obligatory initiators. This explains why elevated alarmins can coexist with different autoimmune phenotypes and why blocking a single upstream cytokine may help only a subset of patients. [20]

Relationship to Eosinophils, Basophils, and the Type 2 Microenvironment



Eosinophils add another dimension to the alarmin-mast cell interface. CSU lesions contain activated eosinophils, yet peripheral eosinopenia is common in more severe autoimmune disease. Recruitment of eosinophils into skin and immune-mediated depletion have both been proposed. Eosinophil granule proteins can activate or prime mast cells, while alarmin-induced IL-5 promotes eosinophil survival and trafficking. This creates a plausible bridge between upstream alarmin activity and one of the characteristic hematologic patterns of difficult-to-treat CSU. [21]

Large cohort data show that eosinopenia is associated with high disease activity, positive autoreactivity tests, low total IgE, elevated inflammatory markers, and poor response to antihistamines or omalizumab. These associations are particularly notable because they connect type IIb autoimmune features with a cellular pattern usually thought of as the opposite of classic allergic eosinophilia. Alarmins may help reconcile this apparent paradox: strong local type 2 signaling can coexist with low circulating eosinophil counts if cells are being recruited into inflamed tissue. [22]

Neuroimmune and Vascular Consequences of Alarmin Signaling

Pruritus and vascular leakage are the two clinical consequences that most directly translate immune activation into patient experience. Histamine is a major pruritogen, but itch in CSU is not completely explained by histamine alone. IL-33 and TSLP can influence sensory-immune communication indirectly through mast-cell mediators and type 2 cytokines, while TSLP has been shown in cutaneous inflammatory models to interact with sensory pathways involved in itch. In CSU, this biology may help explain why some patients remain symptomatic despite substantial H1-receptor blockade: antihistamines interrupt one downstream mediator pathway without necessarily reversing the upstream inflammatory state that maintains mast-cell hyperreactivity. [10]

Alarmin signaling may also contribute to the vascular component of the wheal. IL-33 is abundant in endothelial and stromal compartments and can promote cytokine release from mast cells, basophils, and ILC2s; the resulting mediators increase endothelial permeability and facilitate recruitment of inflammatory cells. Lesional CSU skin shows IL-33 expression in endothelial cells and fibroblasts as well as immune cells, supporting a model in which the vascular wall is not simply a passive target of histamine but part of an active inflammatory microenvironment. This broader view links tissue-derived danger signals to both the swelling of the wheal and the persistence of dermal inflammation. [16]

Alarmins as Biomarkers: Promise and Limitations

An ideal CSU biomarker would identify disease mechanism, correlate with activity, predict treatment response, and remain reproducible across laboratories. No currently available biomarker fulfills all of these requirements. C-reactive protein, total IgE, anti-thyroid antibodies, basophil counts, eosinophil counts, D-dimer, and functional basophil assays each capture only part of the disease. The same caution should be applied to TSLP and IL-33. A statistically higher cytokine level in a patient group does not automatically establish diagnostic utility at the individual-patient level. [23]

Several pre-analytical and analytical problems are especially relevant to alarmins. IL-33 is a tissue-associated cytokine whose extracellular concentration can be influenced by cell damage, proteolytic processing, oxidation, soluble ST2, and sampling conditions. TSLP measurements may be affected by isoform recognition and assay sensitivity. Cross-sectional sampling also fails to distinguish whether a raised level is a cause of active disease, a consequence of tissue inflammation, or both. Longitudinal designs that track cytokines alongside UAS7, Urticaria Control Test scores, and treatment exposure are therefore more informative than single baseline measurements. [24]

The most realistic clinical role for alarmins is likely to be within composite signatures. For example, high IL-33 or TSLP combined with total IgE, anti-thyroid antibodies, basophil or eosinophil counts, C-reactive protein, and functional basophil testing may separate an alarmin-high inflammatory phenotype from predominantly type IIb autoimmune disease or from a more IgE-dependent phenotype. Such models need prospective validation, but they are biologically more credible than assigning a complex disease to one serum cytokine. [25]

Therapeutic Translation: What Does TSLP Blockade Teach Us?

Tezepelumab is a monoclonal antibody that neutralizes TSLP and has provided the first direct test of



the pathway in CSU. The phase 2b INCEPTION study randomized patients with CSU uncontrolled by second-generation H1 antihistamines to tezepelumab regimens, placebo, and, in anti-IgE-naïve participants, omalizumab. The primary endpoint, change in UAS7 at week 16, was not met in the overall population. This negative primary result is scientifically important because it argues against TSLP being a universal upstream driver of CSU. [26]

The INCEPTION study also contained signals that should not be dismissed. In anti-IgE-naïve participants, tezepelumab showed greater improvement than placebo in exploratory analyses and a delayed, sustained reduction in disease activity through week 32 after treatment cessation. The effect appeared larger in patients with lower baseline IgE and longer disease duration and was accompanied by sustained suppression of IL-5 and IL-13. These observations are hypothesis-generating rather than practice-changing, but they support the possibility that TSLP dependence is concentrated in a biologically definable subgroup. [26]

This distinction changes how future alarmin trials should be designed. If TSLP acts mainly as an amplifier in selected patients, an unselected CSU trial will dilute treatment effects. Biomarker enrichment based on IgE, IL-33/TSLP profiles, eosinophil-basophil patterns, autoimmune markers, or molecular signatures may be more appropriate. The clinical lesson from tezepelumab is therefore not that TSLP is irrelevant, but that upstream cytokine blockade requires better patient selection than therapies directed at the final common IgE-mast cell pathway. [27]

IL-33/ST2 as a Therapeutic Target

Direct IL-33 or ST2 blockade has not yet established an evidence-based therapeutic role in CSU. The rationale comes from mechanistic data, lesional expression, serum observations, and trials in other inflammatory diseases. Astegolimab, an anti-ST2 monoclonal antibody, reduced asthma exacerbations in a randomized severe-asthma study, including in patients with lower blood eosinophil counts. This demonstrates that interruption of IL-33 receptor signaling is pharmacologically feasible in humans and can influence inflammatory disease beyond a narrowly eosinophilic phenotype. [28]

Itepekimab, a monoclonal antibody against IL-33, has also been evaluated in type 2 inflammatory diseases. Results outside CSU have been mixed and disease-specific, which is a useful warning against assuming that a biologically attractive cytokine target will translate uniformly across organs. For CSU, the most defensible next step is not broad empiric use but biomarker-enriched trials in patients with high IL-33 activity, compatible tissue signatures, or resistance to established therapies. [29]

Integration With Current and Emerging CSU Therapy

Current CSU management remains centered on disease control rather than biomarker-defined alarmin targeting. Second-generation H1 antihistamines are first-line therapy, with dose escalation when needed; omalizumab is the established biologic option for antihistamine-refractory disease, while cyclosporine remains an option for selected refractory patients. The success of anti-IgE therapy confirms the importance of FcεRI biology, but incomplete and delayed responses show that IgE is not the only relevant pathway. [1]

The therapeutic pipeline increasingly supports a network view of CSU. Agents directed at Bruton's tyrosine kinase, cytokine receptors, mast-cell survival pathways, eosinophils, and other immune targets are being evaluated alongside established anti-IgE therapy. The alarmin axis fits within this broader movement toward upstream and endotype-specific intervention. Its future value will depend less on whether TSLP or IL-33 is elevated on average and more on whether a reproducible biological signature predicts who benefits from blocking that pathway. [30]

Treatment-response studies already show why this matters. Higher total IgE is generally associated with a greater probability of a rapid omalizumab response, whereas low IgE, autoimmune comorbidity, anti-thyroid antibodies, basopenia, eosinopenia, elevated C-reactive protein, and positive functional autoreactivity tests more often characterize resistant or delayed-response disease. Adding alarmins to this framework could improve prediction if they contribute independent information rather than duplicating established inflammatory markers. [31]

From Single Cytokines to Precision Immunology



The most important conceptual advance is to avoid treating TSLP and IL-33 as isolated molecules. CSU is generated by interacting modules: autoantibodies determine receptor engagement, complement and coagulation can increase mast-cell activation, basophils and eosinophils contribute cellular amplification, and epithelial or stromal alarmins alter the inflammatory tone of the tissue. Precision medicine requires mapping these modules in the same patient. A single cytokine concentration cannot reliably represent this multidimensional biology. [32]

A practical future panel could combine clinical activity and control scores with total IgE, IgG anti-thyroid peroxidase antibodies, C-reactive protein, complete blood count-derived eosinophil and basophil measures, and one or more functional assays, then add IL-33, TSLP, or soluble ST2 when standardized assays become available. Machine-learning approaches may eventually identify reproducible clusters, but they should be built on biologically interpretable variables and validated prospectively across populations. The aim is not to create more tests; it is to reduce therapeutic trial-and-error. [33]

Research Priorities

Future studies should resolve several questions before alarmin measurement can enter routine CSU care. First, serum and lesional measurements should be obtained simultaneously to determine whether circulating concentrations reflect tissue biology. Second, longitudinal sampling before and during antihistamine, omalizumab, and other therapies is needed to establish temporal relationships with activity and control. Third, assays should distinguish biologically relevant TSLP forms where possible and account for soluble ST2 when evaluating IL-33. Finally, cohorts should be stratified by type I autoallergy, type IIb autoimmunity, and overlap phenotypes rather than analyzed as immunologically uniform CSU. [17]

Clinical trials should also move toward biomarker-enriched designs. The INCEPTION findings suggest that unselected recruitment can conceal subgroup effects, while the broader biomarker literature shows that treatment responsiveness is already linked to measurable immune features. Randomization within pre-specified alarmin-high and alarmin-low strata, coupled with tissue and serum pharmacodynamic endpoints, would clarify whether alarmin blockade modifies the disease process or simply suppresses one component of inflammation. [26]

Conclusion

The epithelial alarmin-mast cell interface offers a coherent way to connect tissue stress with persistent immune activation in chronic spontaneous urticaria. TSLP and IL-33 can influence mast cells directly and can amplify disease through dendritic cells, ILC2s, basophils, eosinophils, and type 2 cytokine circuits. Current evidence supports biological relevance, particularly for IL-33, but does not justify using either cytokine as a stand-alone routine biomarker. The negative primary endpoint of tezepelumab in an unselected CSU population further indicates that upstream alarmin dependence is unlikely to be universal. The strongest path forward is endotype-resolved, biomarker-guided investigation that integrates alarmins with established autoimmune and inflammatory markers. Such an approach could transform TSLP and IL-33 from interesting correlates into clinically useful components of precision immunology.

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