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ALARMINS TSLP, IL-25, IL-33 AS A TARGET FOR THE DIAGNOSIS AND TREATMENT OF CHRONIC RECURRENT HERPETIC STOMATITIS

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Chronic recurrent herpetic stomatitis is one of the most prevalent viral diseases of the oral mucosa, with incompletely understood pathogenesis. This review systematizes current evidence on the role of epithelial alarmins – thymic stromal lymphopoietin, interleukin-33, and interleukin-25 – in the pathogenesis of chronic reccurent herpetic stomatitis. A concept of a self-perpetuating alarmin-driven pathogenetic cycle is proposed, along with immunological rationale for optimizing CRHS treatment by combining antiviral therapy with zinc supplementation and diode laser photobiomodulation.

Key words: herpes simplex virus infection, herpetic stomatitis, interleukin-33, interleukin-25, alarmins, thymic stromal lymphopoietin.

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АЛАРМІНИ TSLP, IL-25, IL-33 ЯК МІШЕНЬ ДІАГНОСТИКИ ТА ЛІКУВАННЯ ХРОНІЧНОГО РЕЦИДИВУЮЧОГО ГЕРПЕТИЧНОГО СТОМАТИТУ

Хронічний рецидивуючий герпетичний стоматит є одним із найпоширеніших вірусних захворювань слизової оболонки рота, патогенез якого досі недостатньо вивчено. У статті систематизовано сучасні дані щодо ролі епітеліальних алармінів – тимусного стромального лімфопоетину, інтерлейкіну-33 та інтерлейкіну-25 – у патогенезі хронічного рецидивуючого герпетичного стоматиту. Обґрунтовано концепцію самопідтримувального алармінового патогенетичного циклу та імунологічне підґрунтя для оптимізації лікування хронічного рецидивуючого герпетичного стоматиту шляхом поєднання противірусної терапії з прийомом препаратів цинку та опроміненням діодним лазером.

Ключові слова: герпетична інфекція, герпетичний стоматит, інтерлейкін 33, інтерлейкін 25, аларміни, тимусний стромальний лімфопоетин.

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Chronic recurrent herpetic stomatitis (CRHS) is one of the most prevalent infectious diseases of the oral mucosa, caused by herpes simplex virus type 1 (HSV-1). According to epidemiological studies, 60–95% of the adult population are seropositive for HSV-1, whereas clinically significant recurrences develop in 20–40% of infected individuals [14]. The clinical presentation of CRHS is characterized by a cyclical course with alternating phases of remission and exacerbation, which substantially impairs patients' quality of life and constitutes a considerable sociomedical burden [14, 29].

Despite extensive research into herpetic infection, the molecular mechanisms underlying susceptibility to recurrence, chronification of the inflammatory process, and the characteristics of local immune defense of the oral mucosa remain incompletely elucidated.

The purpose of the study was to synthesize available data characterizing the current state of knowledge regarding the molecular mechanisms of inflammation in herpetic infection, with particular focus on the role of alarmins and the cytokine network – specifically TSLP, IL-33, and IL-25 – in the pathogenesis of chronic recurrent herpetic stomatitis.

Materials and methods. The study employed bibliosemantic, comparative, and systematic analysis methods. The analysis included publications containing original data from clinical and experimental studies, systematic reviews, and meta-analyses addressing the molecular mechanisms of alarmin activity in viral infections, the pathogenesis of herpetic infection of the oral mucosa, and current therapeutic approaches to chronic recurrent herpetic stomatitis. Publications concerning exclusively allergic diseases without association with viral pathology, as well as studies for which full-text access was unavailable, were excluded from the analysis.

Literature searches were conducted across three databases using standardized search queries.

Database 1 – PubMed. Search query: ("thymic stromal lymphopoietin" OR "TSLP" OR "sfTSLP" OR "lfTSLP") AND ("herpes simplex virus" OR "HSV-1" OR "herpetic stomatitis" OR "recurrent herpes") AND ("alarmin" OR "IL-33" OR "IL-25" OR "epithelial barrier" OR "innate immunity"). Additional query: ("zinc" OR "low-level laser therapy" OR "diode laser" OR "photobiomodulation") AND ("herpes simplex" OR "oral mucosa"). Date of last search: May 1, 2025. Inclusion period: 2021–2026 (foundational studies: no date restriction). Exclusion period: publications prior to 2021 where more recent sources with equivalent content were available.

Database 2 – Scopus. Search query: TITLE-ABS-KEY ("TSLP" OR "thymic stromal lymphopoietin" OR "IL-33" OR "IL-25") AND TITLE-ABS-KEY ("herpes simplex" OR "HSV-1" OR "herpetic stomatitis" OR "oral epithelium") AND TITLE-ABS-KEY ("alarmin" OR "cytokine" OR "innate immunity" OR "Th2"). Date of last search: May 1, 2025. Inclusion period: 2021–2026.

Database 3 – Web of Science. Search query: TS=("alarmin" OR "TSLP" OR "IL-33" OR "IL-25") AND TS=("herpes simplex virus" OR "recurrent herpetic stomatitis" OR "oral mucosa") AND TS=("epithelial barrier" OR "innate immunity" OR "Th2 polarization"). Date of last search: May 1, 2025. Inclusion period: 2021–2026.

Study Selection and Characteristics

Inclusion criteria: publications from 2021–2026 containing original data from clinical and experimental studies, systematic reviews, and meta-analyses addressing the molecular mechanisms of alarmin activity in viral infections, the pathogenesis of herpetic infection of the oral mucosa, and current therapeutic approaches to CRHS; foundational studies from earlier periods where no contemporary equivalents were available.

Exclusion criteria: publications exclusively addressing allergic diseases without association with viral pathology; studies for which full-text access was unavailable; publications from before 2021 where more recent sources with equivalent content existed.

Table 1

Simplified PRISMA Flow

Stage	Description	Number of Records/Studies
1. Identified	Total number of records identified through database searching and other sources	300
2. Duplicates Removed	Number of records removed before screening (e.g., duplicates)	202
3. Screened (Title/Abstract)	Number of records screened after duplicates were removed	98
4. Assessed for Eligibility (Full-text)	Number of full-text articles assessed for eligibility against the inclusion/exclusion criteria	98
5. Included in Review	Total number of primary studies finally included in the systematic review	40

The findings of this study are presented in accordance with current literature data, conclusions of randomized trials, and meta-analyses devoted to the molecular mechanisms of inflammation in herpetic infection, with specific emphasis on the role of alarmins and the cytokine network.

Results of the study and their discussion. Traditionally, the pathogenesis of CRHS has been considered predominantly through the lens of antiviral immunity, with primary focus on the role of cytotoxic T lymphocytes, neutralizing antibodies, and the interferon response [27]. Considerably less attention, however, has been devoted to the early epithelial signals that initiate and modulate the inflammatory cascade prior to the formation of a specific immune response.

The concept of alarmins – endogenous danger molecules released by epithelial cells in response to damage, stress, or pathogenic invasion – has opened fundamentally new avenues for understanding the pathogenesis of chronic inflammatory diseases of the mucous membranes [22, 36]. Among epithelial alarmins, a particularly prominent role is attributed to three cytokines – thymic stromal lymphopoietin (TSLP), interleukin-33 (IL-33), and interleukin-25 (IL-25/IL-17E) – which function as "sentinel signals" at the interface between the epithelial barrier and the immune system [30, 36]. These molecules act at the apex of the inflammatory cascade, activating group 2 innate lymphoid cells (ILC2s), dendritic cells, and mast cells, thereby determining the nature and direction of subsequent immune responses [17].

In contrast to the well-established role of TSLP, IL-33, and IL-25 in allergic diseases of the airways and skin [6, 17, 24], their involvement in the pathogenesis of viral lesions of the oral mucosa remains insufficiently investigated.

An equally important aspect of this problem is the search for effective therapeutic strategies for CRHS. Standard antiviral therapy (acyclovir and its analogues), while reducing the duration of exacerbations, does not prevent recurrences and does not address systemic immune dysregulation. In this context, investigation of adjunctive therapeutic approaches is warranted – in particular, the use of zinc-containing preparations and diode laser irradiation (wavelength 630–980 nm), both of which have documented immunomodulatory and anti-inflammatory effects [10].

The term "alarmins" was proposed by Oppenheim and Yang in 2005 to designate a group of endogenous molecules released from cells in response to tissue damage, stress, or infection, capable of rapidly activating innate immunity. Unlike pathogen-associated molecular patterns (PAMPs), which are structural components of microorganisms, alarmins are host-derived molecules that normally perform intracellular functions but acquire immunostimulatory properties upon release into the extracellular space [36]. Both groups of molecules are collectively referred to as damage-associated molecular patterns (DAMPs), although a number of authors consider alarmins a distinct subcategory of DAMPs with more precisely defined functional characteristics [22].

Depending on the mechanism of release, two principal types of alarmin secretion are distinguished. Passive release occurs as a consequence of necrotic cell death, disruption of cell membrane integrity, or the direct cytopathic effect of a pathogen – as occurs,

in particular, during primary HSV-1 infection of oral mucosal epithelial cells [27]. Active alarmin release is a regulated process occurring from viable cells under conditions of activation or sublethal stress. It is mediated through several secretory mechanisms, including vesicular transport, the exosomal pathway, and, in certain cases, lysosome-associated secretion. Induction of this process is associated with the action of inflammatory mediators, activation of innate immune receptors recognizing pathogen-associated molecular patterns, and other stress signals that do not result in immediate cell death [36].

A distinct subcategory is represented by "stressorins" – nuclear alarmins (HMGB1, heat shock proteins) that are actively secreted from intact cells in response to oxidative stress, hypoxia, mechanical stimulation, and viral antigens, thereby sustaining the inflammatory response in the absence of massive cytolysis [22, 36].

Among alarmins, a special position is occupied by the so-called "epithelial barrier alarmins" – TSLP, IL-33, and IL-25 – which are produced by epithelial cells of barrier tissues, released in response to damage, and act at the apex of the immune cascade [24, 30].

Classically, TSLP, IL-33, and IL-25 were regarded as inducers of type 2 immune responses (Th2 responses), associated with allergic diseases and helminth infections [17]. However, accumulating evidence strongly indicates that the functions of these alarmins are considerably broader, encompassing regulation of antiviral immunity, control of tissue homeostasis, participation in regenerative processes, and even oncogenesis [30]. Notably, in chronic allergic conditions such as allergic rhinitis and bronchial asthma, alarmin-mediated dysregulation of the epithelial barrier represents a key pathogenetic mechanism that determines disease severity and therapeutic response [4, 9]. In particular, it has been demonstrated that, depending on the microenvironmental context and the nature of the damaging stimulus, the same alarmins may exhibit either pro-inflammatory or anti-inflammatory and regenerative properties [22].

The primary cellular targets of TSLP, IL-33, and IL-25 are group 2 innate lymphoid cells (ILC2s), which express receptors for all three alarmins and play a central role in the initiation and maintenance of the inflammatory response in barrier tissues [30]. In addition to ILC2s, alarmins directly activate dendritic cells, mast cells, basophils, eosinophils, and resident macrophages, forming a complex network of intercellular interactions that determines the phenotype and duration of the inflammatory response [17].

The oral mucosa constitutes the primary site of HSV-1 reactivation, where epithelial cells are the first to respond to viral invasion through alarmin release, mediated by activation of Toll-like receptors (TLRs), RIG-I (retinoic acid-inducible gene I) receptors, and the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and IRF (interferon regulatory factor) signaling cascades [27, 38].

It is important to emphasize that in the chronic recurrent course of herpetic infection, a persistent dysregulation of alarmin signaling develops, which simultaneously sustains subclinical inflammation during the inter-recurrence period and reduces the efficacy of the antiviral response upon subsequent viral reactivation [30]. Analogous patterns of cytokine dysregulation in chronic inflammatory diseases of the mucous membranes have been described for other interleukins – notably, elevated IL-26 levels in induced sputum have been associated with the degree of systemic inflammation and impaired barrier epithelial function in chronic obstructive pulmonary disease [26], underscoring the universality of cytokine-mediated chronification mechanisms across mucosal surfaces regardless of the specific nosological entity. This gives rise to the so-called "alarmin vicious cycle" characteristic of many chronic inflammatory diseases of barrier tissues, including atopic dermatitis, bronchial asthma, and chronic rhinosinusitis [21, 30].

Alarmins TSLP, IL-33, and IL-25 are key regulators of the oral mucosal immune response in HSV-1 infection, influencing disease course, chronification, and therapeutic efficacy.

Thymic stromal lymphopoietin (TSLP) is a pleiotropic cytokine of the interleukin-2 family, produced predominantly by epithelial cells of barrier tissues – the skin, respiratory mucosa, gastrointestinal tract, and oral mucosa [28]. Initially described as a B-cell survival factor in the mouse thymus, TSLP is now regarded as one of the key regulators of immune responses at the level of the epithelial barrier, capable of initiating and sustaining a broad spectrum of inflammatory reactions [24].

The human TSLP gene is located on chromosome 5q22 and encodes two protein products – the long form (lfTSLP) and the short form (sfTSLP) – arising from alternative use of distinct promoters and differing in both size and functional properties (Fig. 1) [28]. The long form, lfTSLP, comprises 159 amino acids and serves as the principal mediator of type 2 pro-inflammatory reactions; its expression markedly increases in response to allergic inflammation, mechanical epithelial injury, microbial products, and cytokines – notably TNF-α, IL-1β, and IFN-γ [24]. The short form, sfTSLP, consists of only 58 amino acids, is constitutively expressed in epithelial cells under physiological conditions, and has traditionally been associated with maintenance of homeostasis and anti-inflammatory effects [28].

TSLP acts through a heterodimeric receptor complex composed of the TSLP receptor (TSLPR) and the alpha chain of the interleukin-7 receptor (IL-7Rα). Binding of TSLP to this complex activates JAK1/JAK2 and STAT5 signaling pathways, resulting in transcription of target genes involved in immune regulation, cell survival, and proliferation (Rochman et al., 2010). The TSLPR receptor is expressed on a broad spectrum of immune cells, including dendritic cells, mast cells, basophils, ILC2s, as well as T and B lymphocytes, which

explains the pleiotropic nature of the biological effects of this cytokine [24].

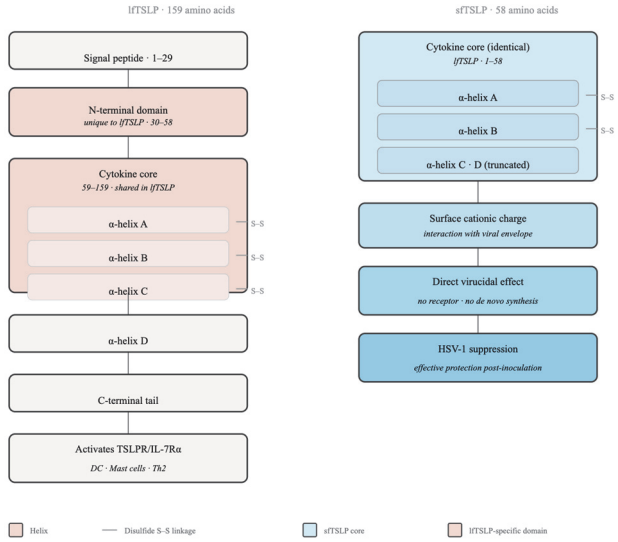

Fig. 1. Domain organization of thymic stromal lymphopoietin (TSLP) isoforms.

Left: long form lfTSLP (159 amino acids) – signal peptide (aa 1–29), unique N-terminal domain (aa 30–58), cytokine core with four α-helices (A–D) and two disulfide bonds (S–S), C-terminal loop; interacts with the TSLPR/IL-7Rα receptor complex and activates the pro-inflammatory Th2 cascade.

Right: short form sfTSLP (58 amino acids) – contains only the cytokine core without the N-terminal domain; the cationic charge of the exposed surface confers direct virucidal activity against HSV-1 independent of receptor engagement and de novo protein synthesis.

Domain boundaries are shown schematically according to Smolinska et al. (2023) and Zeitvogel et al. (2024); the spatial organization of the cytokine core corresponds to the crystal structure PDB 5J11 (Verstraete et al., Nat Commun, 2017).

The long form lfTSLP is a potent activator of dendritic cells, which, under its influence, acquire the capacity to stimulate differentiation of naive T helper cells toward a Th2 phenotype with production of IL-4, IL-5, and IL-13 [17]. Moreover, lfTSLP directly activates ILC2s, mast cells, and basophils, amplifying and sustaining allergic inflammation even in the absence of antigenic stimulation [24].

During viral infection development, it is important to note that lfTSLP can be induced by Toll-like receptors TLR3 and TLR7/8 upon recognition of viral RNA, making it one of the early mediators of innate immune responses to viral pathogens [30].

In chronic mucosal inflammation, elevated lfTSLP expression establishes a so-called "pro-allergic microenvironment" characterized by lowered activation thresholds for immune cells, enhanced production of pro-inflammatory cytokines, and progressive epithelial barrier dysfunction [17]. This mechanism is regarded as key in the pathogenesis of chronic recurrent inflammatory diseases of barrier tissues, including atopic dermatitis and bronchial asthma, and may hold similar importance in CRHS [21, 30].

A principally significant discovery in recent years has been the identification of antiviral properties of the short form sfTSLP against HSV-1. In the study by Zeitvogel et al., it was demonstrated that sfTSLP significantly reduces HSV-1 infectivity in primary human keratinocytes, whereas lfTSLP exhibited no such effect [37]. Specifically, under the influence of sfTSLP, reduced expression and replication of HSV-1 genes were observed, whereas initial virion binding to the cell surface and nuclear transport of the capsid were unimpaired, indicating an intracellular mechanism of action of this isoform [28, 37]. Notably, the antiviral effect of sfTSLP was independent of de novo protein synthesis and was not mediated by induction of innate cytokines, pointing to a direct mechanism of viral replication suppression fundamentally distinct from classical antiviral pathways [28].

The highest efficacy of sfTSLP was demonstrated when administered prior to or immediately after HSV-1 inoculation, underscoring its role specifically as a prophylactic barrier factor rather than a therapeutic agent in established infection [28]. These data acquire particular significance in the context of CRHS, as they suggest that reduced constitutive expression of sfTSLP in the oral mucosa epithelium may be a contributing factor to HSV-1 reactivation and recurrence development.

A clinically significant model of TSLP interaction with herpetic infection is herpetic eczema (eczema herpeticum, ADEH+) – disseminated HSV-1 infection in patients with atopic dermatitis. Elevated lfTSLP levels suppress antimicrobial peptides (β-defensins, LL-37) and natural killer (NK) cell function, establishing susceptibility to severe herpetic disease, as confirmed by significantly higher TSLP and IL-25 levels in the skin epithelium of ADEH+ compared with ADEH− patients [32]. Pathogenetic parallels between ADEH+ and CRHS allow extrapolation of these findings to mechanisms of chronification in herpetic oral mucosal disease.

Data concerning TSLP expression and function directly in oral mucosal tissues remain limited compared with respiratory airways and skin. Nevertheless, oral mucosal epithelial cells are capable of producing TSLP in response to mechanical irritation, microbial stimuli, and cytokine-mediated inflammation [38]. HSV-1 infection in human gingival fibroblasts is accompanied by extensive transcriptome remodeling with activation of TLR, NF-κB, and interferon response signaling pathways, creating a microenvironment conducive to induction of epithelial alarmins, including TSLP [37].

Given that the oral mucosa is the primary site of both primary HSV-1 infection and recurrence [14], and sfTSLP exhibits direct antiviral properties against this virus [37], it may be hypothesized that the balance between the two TSLP isoforms in the oral epithelium plays an important regulatory role in determining susceptibility to CRHS recurrence. The shift in the balance between TSLP isoforms toward pro-inflammatory lfTSLP in CRHS is mediated through differential regulation of two alternative

promoters of the TSLP gene: Th2 cytokines (IL-4, IL-13), accumulated as a result of repeated HSV-1 reactivations, activate the NF-κB-dependent long promoter while simultaneously suppressing the constitutive short promoter – resulting in progressive reduction of protective sfTSLP and elevation of pro-inflammatory lfTSLP during inter-recurrence periods [31, 34, 36].

Interleukin-33 (IL-33) is a member of the IL-1 family and functions as a nuclear alarmin, serving a dual role – as an intranuclear transcriptional regulator under physiological conditions and as an extracellular alarm cytokine upon cell damage or viral invasion [33]. Unlike most cytokines, IL-33 is not secreted through the classical endoplasmic reticulum–Golgi pathway but is released passively during necrosis or mechanical cell damage, and actively through inflammatory cell death pathways including [30]:

– Pyroptosis – programmed lytic cell death with release of pro-inflammatory mediators [8];

– Necroptosis – regulated form of necrosis accompanied by release of intracellular contents, including IL-33 [8];

– NETosis – neutrophil death with formation of extracellular neutrophil traps (NETs) associated with IL-33 release into the inflammatory focus [7].

It is precisely this feature that makes IL-33 particularly important in the context of viral infections accompanied by cytopathic effects – in particular, in HSV-1 infection.

The human IL-33 gene is located on chromosome 9p24 and encodes a 270-amino-acid protein containing an N-terminal nuclear localization domain and a C-terminal cytokine domain homologous to other members of the IL-1 family [15].

Full-length IL-33 acquires full biological activity following proteolytic cleavage by caspases or extracellular proteases (notably neutrophil elastase and cathepsin G), generating mature cytokine forms [30]. The receptor for IL-33 is a heterodimeric complex composed of the ST2 chain (Suppression of Tumorigenicity 2), also known as IL1RL1 (Interleukin-1 Receptor-Like 1), and the co-receptor IL-1RAcP (Interleukin-1 Receptor Accessory Protein). ST2 exists in two forms – membrane-bound (ST2L), which transduces the signal, and soluble (sST2), which functions as a natural decoy receptor, neutralizing free IL-33 and limiting its pro-inflammatory action [16, 36]. Binding of IL-33 to ST2L/IL-1RAcP activates the MyD88 (Myeloid Differentiation Primary Response 88) / IRAK (Interleukin-1 Receptor-Associated Kinases) / TRAF6 (TNF Receptor-Associated Factor 6) cascade with subsequent activation of NF-κB and mitogen-activated protein kinases (MAP kinases) – p38, ERK (Extracellular Signal-Regulated Kinase), and JNK (c-Jun N-terminal Kinase) – and transcription of pro-inflammatory cytokine genes [40]. An important feature of IL-33 biology is auto-amplification: IL-11, produced by inflammatory fibroblasts, stimulates IL-33 expression through STAT3 (Signal Transducer and Activator of Transcription 3), creating a positive feedback loop and sustaining chronic inflammation [33]. This mechanism may be of fundamental importance for chronification of herpetic stomatitis, since fibroblasts are among the principal sources of IL-33 in oral tissues.

IL-33 demonstrates a fundamentally dichotomous role in viral infections, determined by microenvironmental context, type of target cells, and phase of the infectious process [30]. On one hand, IL-33 is a potent activator of pro-inflammatory reactions: it activates ILC2s, mast cells, eosinophils, and Th2 lymphocytes, induces production of IL-4, IL-5, and IL-13, and enhances vascular permeability and tissue edema [17]. On the other hand, numerous studies demonstrate the capacity of IL-33 to stimulate antiviral and neuroprotective mechanisms, especially in herpetic infection [21]. Early release of IL-33 upon tissue damage serves a protective function, activating innate immunity and accelerating epithelial repair, whereas chronic excessive activation of the IL-33–ST2 axis promotes pathological inflammation and tissue destruction [30]. The balance between these two vectors determines whether an effective antiviral response with recovery develops or a chronic recurrent disease is established.

Gingival fibroblasts are one of the principal sources of IL-33 in the oral mucosa; transcriptomic and proteomic analysis of their response to HSV-1 revealed sequential activation of TLR, NF-κB, and interferon response pathways, establishing a microenvironment favorable for IL-33 release and its action on resident immune cells [38, 39].

It is important to emphasize that in the chronic recurrent course of HSV-1 infection in the oral cavity, repeated cycles of cytopathic damage to epithelial cells and fibroblasts result in a cumulative effect with progressive exhaustion of protective mechanisms and formation of sustained pro-inflammatory IL-33-mediated activation of tissue macrophages and mast cells [36].

This mechanism may explain the phenomenon characteristic of CRHS – progressive shortening of inter-recurrence intervals in a subset of patients.

The balance between membrane-bound ST2L and soluble sST2 is a critical regulator of IL-33-mediated inflammation intensity. Elevation of sST2 levels in serum and tissue fluids is considered a compensatory mechanism aimed at limiting excessive IL-33 activation [30]. Nevertheless, chronic viral persistence and repeated episodes of tissue damage may exhaust this regulatory mechanism, leading to increased IL-33 bioavailability and intensification of its pro-inflammatory effects [22]. From a therapeutic perspective, the described neuroprotective and antiviral properties of IL-33 in herpetic infection open opportunities for development of approaches aimed at modulating the IL-33–ST2 axis in CRHS treatment. However, the dichotomous nature of this cytokine requires caution: non-selective suppression of IL-33 may weaken its protective antiviral effects, whereas excessive activation may intensify tissue inflammation. The optimal therapeutic strategy should be directed at restoring the physiological balance

between pro- and anti-inflammatory functions of IL-33 in specific tissue conditions [22, 25].

Interleukin-25, also known as IL-17E, is a unique member of the IL-17 family occupying a special place among epithelial alarmins due to its capacity to potently induce type 2 immune responses while simultaneously modulating antiviral defense of barrier tissues [6]. Despite its structural membership in the IL-17 family, IL-25 is fundamentally distinct from other family members in its biological functions: whereas IL-17A and IL-17F are classical pro-inflammatory cytokines with antibacterial and antifungal activity, IL-25 is the sole family member that potently and specifically activates Th2-dependent inflammatory reactions [35].

Human IL-25 is a secretory glycoprotein with a molecular weight of approximately 17 kDa, encoded by the IL17E gene located on chromosome 14q11.2 (Yuan et al., 2018). Unlike IL-33 and TSLP, IL-25 is a classically secreted cytokine released through the conventional endoplasmic reticulum–Golgi pathway, although a certain amount of IL-25 may also be released upon mechanical damage or apoptosis of epithelial cells [6]. The receptor for IL-25 is a heterodimeric complex consisting of IL-17RB (the IL-25-specific receptor) and IL-17RA (a shared co-receptor for several IL-17 family members) [6]. Binding of IL-25 to this complex activates the intracellular adaptor protein Act1 (NF-κB activator 1, also known as CIKS; encoded by the TRAF3IP2 gene), resulting in activation of NF-κB and mitogen-activated protein kinase (MAP kinase) signaling pathways (ERK, JNK, p38) with subsequent transcription of IL-4, IL-5, and IL-13 genes – key cytokines of the Th2 response [35]. Unlike IL-33, the IL-25 signaling cascade does not utilize MyD88, determining a distinct spectrum of biological effects of these two alarmins despite certain functional similarity [6].

The principal cellular producers of IL-25 in barrier tissues are epithelial cells, notably specialized epithelial cells with brush borders (tuft cells) of the intestine and respiratory airways, which are regarded as "chemosensory" cells capable of being the first to respond to the presence of parasites and other triggers [13]. Additionally, IL-25 is produced by dendritic cells, mast cells, basophils, and T cells, attesting to its role not only as a primary epithelial signal but also as a mediator amplifying an already-initiated immune response [35]. A key feature of IL-25 as a "barrier surface cytokine" is the dependence of its expression on external environmental factors – allergens, microbial products, mechanical irritation, and viral stimuli [19]. Upregulation of IL-25 under these conditions leads to activation of group 2 innate lymphoid cells (ILC2s), which produce large quantities of IL-4, IL-5, and IL-13, establishing the Th2-dominant microenvironment characteristic of allergic and parasitic diseases (von Moltke et al., 2016). In CRHS, this mechanism may play a role in sustaining chronic subclinical inflammation during inter-recurrence periods, creating conditions favorable for HSV-1 reactivation.

IL-25 and its receptor are constitutively expressed on the apical surface of epithelial cells, and viral infection further enhances their expression. In the study by Williams et al., blockade of IL-25 with monoclonal antibody resulted in a recalibrated immune response – a significant increase in type I and III interferon expression and a reduction in type 2 cytokine levels, whereas exogenous IL-25 administration, conversely, increased viral load and suppressed antiviral immunity in vivo [34, 35]. Thus, elevated IL-25 levels in the oral mucosal epithelium may substantially reduce the effectiveness of local antiviral defense and promote development of CRHS recurrences [6].

Notably, IL-25 is among the alarmins whose levels are significantly elevated in patients with atopic dermatitis complicated by herpetic eczema (ADEH+) compared with patients without herpetic complications [32]. This observation is significant as it indicates that elevated IL-25 levels not only accompany allergic inflammation but are also associated with substantially increased susceptibility to severe disseminated herpetic infection – likely through the mechanism of antiviral interferon defense suppression described above [34].

Furthermore, IL-25 participates in regulating the balance between Th17 and Th2 responses, which play important roles in anti-herpetic immunity. Specifically, IL-17A, produced by Th17 cells, is involved in protection against herpetic infection at mucosal surfaces [25], and IL-25, suppressing the Th17 response in favor of Th2, may indirectly reduce mucosal resistance to HSV-1 [35].

TSLP, IL-33, and IL-25 function not as independent mediators but as an integrated signaling network in which each component amplifies and modulates the effects of others [30]. Upon HSV-1 infection in the oral mucosal epithelium, the three alarmins are activated through distinct mechanisms. IL-33 is released passively during necrosis of infected cells and actively during inflammatory cell death – pyroptosis [8, 15]. TSLP is induced through TLR3- and TLR7/8-mediated recognition of viral RNA by epithelial cells [30]. IL-25, in turn, is upregulated in response to viral stimuli and maintains Th2 skewing of the tissue microenvironment [6].

The common result of all three alarmins' action is ILC2 activation, leading to massive production of IL-4, IL-5, and IL-13 and maintenance of a Th2-dominant microenvironment [30]. Simultaneously, in contrast to IL-33, which may stimulate antiviral mechanisms through neuroprotection and reprogramming of tissue macrophages toward an antiviral phenotype [18, 21], IL-25 consistently suppresses the antiviral response of epithelial cells [34], and TSLP through its sfTSLP isoform directly blocks HSV-1 replication in epithelial cells (Yuan et al., 2018). Thus, there is reason to believe that excessive IL-25 activation against the background of TSLP isoform dysbalance may nullify the protective effects of IL-33 and sfTSLP, establishing a vulnerable microenvironment for CRHS recurrences [7, 17].

A comparative characterization of the molecular organization, receptor mechanisms, and roles of TSLP, IL-33, and IL-25 in the pathogenesis of viral infections and CRHS is summarized in Table 2.

Table 2

Comparative characteristics of epithelial alarmins TSLP, IL-33, and IL-25 (compiled on the basis of [6, 17, 28, 30, 40])

Parameter	TSLP / sfTSLP / lfTSLP	IL-33	IL-25 (IL-17E)
Gene/ chromosome	TSLP 5q22; isoforms through alternative promoters	IL33 9p24; 270 aa; N-terminal nuclear localization domain	IL17E 14q11.2; 17 kDa; secretory glycoprotein
Receptor	TSLPR / IL-7Rα → JAK1/JAK2/STAT5	ST2L / IL-1RAcP → MyD88/IRAK/TRAF6 → NF-κB, MAPk; sST2 = soluble decoy-receptor	IL-17RB / IL-17RA → Act1 → NF-κB, MAPk; (independent from MyD88)
Primary sources	Keratinocytes, oral cavity and respiratory epithelium, fibroblasts; lfTSLP: induced by damage, TLR3/7/8, cytokines; sfTSLP: constitutive expression	Epithelial cells, fibroblasts, endothelial cells, mast cells; released during necrosis and pyroptosis; nuclear active form	Tuft cells, dendritic cells, mast cells, basophils, T-cells; secreted through conventional ER/Golgi pathway
Role in viral infection	sfTSLP: direct antiviral effect against HSV-1 (independent of de novo protein synthesis); lfTSLP: induced by HSV-1, viral RNA (TLR3) → dendritic cell activation → Th2; Balance sfTSLP/lfTSLP critical	Dual cleavage mechanisms; NK cell activation; neuroprotection (HSK); pathological: chronic ST2 activation → inflammation; IL-33 modulates macrophage phenotype via CD169+/LPL markers	Suppresses IFN-I/III type response in epithelial cells; upregulated on apical epithelial surface during viral infection; exogenous IL-25 increases viral load
Role in CRHS	↑ lfTSLP → Th2-microenvironment in inter-recurrence period; ↓ sfTSLP → reduction of barrier antiviral protection; genetic variants of TSLP promoters determine recurrence susceptibility; ADEH+ phenotype associated with lfTSLP genetic risk	Host phase → IL-33 release during necrosis → ILC2 activation; IL-11 via fibroblasts → STAT3 → IL-33 (positive feedback loop); repeated epithelial damage → cumulative IL-33 accumulation → exhaustion of sST2 regulatory mechanism; progressive shortening of inter-recurrence intervals	↑ IL-25 → suppression of IFN-I/III → impaired barrier protection; elevated IL-25 in ADEH+ (severe disseminated herpetic infection); suppression of Th17-response → reduced mucosal resistance to HSV-1; IL-25 blocks protective antiviral mechanisms
Therapeutic potential	Restoration of constitutive sfTSLP production via NF-κB modulation; selective lfTSLP inhibition; anti-TSLP monoclonal antibodies for systemic use; topical sfTSLP application (non-systemic) – promising for barrier restoration; genetic stratification by TSLP promoter variants	Modulation of ST2L/sST2 balance; selective IL-33 inhibition with preservation of neuroprotective and antiviral mechanisms; anti-IL-33 / anti-ST2 monoclonal biological therapeutics for clinical use; challenges: dual role requires context-specific targeting	Blockade of IL-25 → restoration of IFN-I/III response → enhanced antiviral immunity; IL-25 / anti-IL-17RB monoclonal antibodies; clinical IL-25-neutralizing strategies ongoing; at CRHS: blockade strategy superior to lfTSLP modulation alone; combination approach with IL-33 modulation may be optimal

TSLP, IL-33, and IL-25 function as an integrated signaling system in which the action of each component is determined and modified by the presence of the others [30].

The oral mucosa is a unique microenvironment combining features of keratinized and non-keratinized epithelium and simultaneously serves as the primary site of HSV-1 replication and recurrence [16, 39]. Primary HSV-1 infection in epithelial cells triggers a cascade of molecular events with extensive remodeling of the tissue's cytokine profile [38].

Transcriptomic analysis of human gingival fibroblasts following HSV-1 infection revealed temporal dynamics: at the early stage (12 hours) IRF, TLR, and NF-κB-dependent mediators dominate; at the late stage (72 hours), chemokines and interleukins predominate [38]. TLR2/3/9 recognize viral glycoproteins and nucleic acids and through MyD88/TRIF activate IRF3/7 and NF-κB, whereas RIG-I/MDA5 through MAVS trigger analogous cascades in response to cytosolic viral RNA [12] – creating a microenvironment favorable for induction of all three alarmins [37]. HSV-1 also induces elevation of IL-6, IL-1, and TGF-β1 in the periodontal environment, which indirectly stimulates production of TSLP and IL-33 by fibroblasts and epithelial cells [38].

The acute phase of CRHS recurrence is characterized by rapid IL-33 release from necrotic epithelial cells, activating mucosal mast cells and ILC2s [15]. Simultaneously, TLR3-mediated recognition of double-stranded viral RNA stimulates production of lfTSLP by epithelial cells, which activates dendritic cells and initiates Th2 polarization [30]. Against the background of an escalating Th2 microenvironment, IL-25 levels increase, further

amplifying ILC2-dependent production of IL-4, IL-5, and IL-13 while suppressing antiviral interferon response [34].

A key mechanism of CRHS chronification is the establishment of a persistent Th2-dominant microenvironment during inter-recurrence periods, sustained by continuously elevated lfTSLP and IL-25 levels – analogous to patterns observed in atopic dermatitis and bronchial asthma [21, 36]. This microenvironment reduces constitutive sfTSLP production [5] and increases susceptibility to severe herpetic infection through suppression of antimicrobial peptides and NK cell dysfunction [32].

Repeated cycles of viral replication and cytopathic damage result in epithelial cell lysis, degradation of tight junctions, and intensified tissue inflammation [12], which collectively impair the barrier function of the oral mucosa. The compromised barrier, in turn, facilitates HSV-1 penetration upon subsequent reactivation and creates conditions for an amplified alarmin response at lower viral loads – a phenomenon analogous to that described in atopic dermatitis, where HSV-1 more readily penetrates epithelium damaged by Th2-associated inflammation [32]. Thus, a self-perpetuating pathogenetic loop is established: viral replication → epithelial damage → alarmin release → Th2 polarization → reduced antiviral defense → facilitated HSV-1 reactivation (Fig. 2).

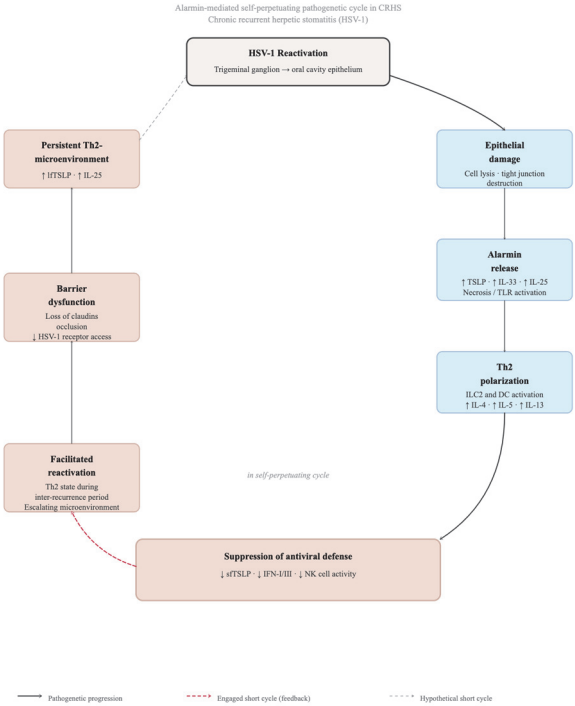

Fig. 2. Alarmin-mediated self-perpetuating pathogenetic cycle in CRHS.

HSV-1 reactivation induces the release of lfTSLP, IL-33, and IL-25 from epithelial cells, which through ILC2 activation form a sustained Th2-dominant microenvironment. This, in turn, suppresses antiviral defense and impairs the barrier function of the mucosa, thereby promoting the subsequent viral reactivation. Solid red arrows – mechanisms confirmed by evidence; dashed arrow – hypothetical feedback loop.

Therefore, CRHS is characterized by an imbalance in the cytokine profile, manifested by the predominance of the Th2 response, disruption of TSLP isoform ratio in favor of the pro-inflammatory lfTSLP, elevated IL-25 levels, and the dual role of IL-33, which collectively contribute to insufficient antiviral protection, maintenance of chronic inflammation, and increased risk of HSV-1 recurrences [17, 22, 28, 32].

Buccal epithelium is an accessible and minimally invasive material for molecular monitoring – cell collection by scraping is a simple, painless, and non-invasive procedure that allows obtaining sufficient RNA for further analysis [11]. Real-time PCR allows quantitative assessment of alarmin mRNA levels – namely TSLP (both isoforms sfTSLP and lfTSLP), IL-33, and IL-25 – using reference genes GAPDH and 18s rRNA for result normalization, which ensures correct comparison of indicators between patients and between different disease phases [11]. However, given the above, comprehensive analysis requires additional determination of the concentration of final protein products.

Treatment of chronic recurrent herpetic stomatitis remains one of the urgent tasks of clinical dentistry and infectology. Despite extensive experience with antiviral drugs, the problem of recurrences remains acute [23], which necessitates the search for new therapeutic approaches aimed not only at suppressing viral replication but also at correcting the immunological imbalance underlying disease chronification [30].

The basis of standard CRHS therapy consists of nucleoside analogues – acyclovir and its derivatives (valacyclovir, famciclovir), which inhibit viral DNA polymerase and block HSV-1 replication in the active phase of infection [23]. Clinical studies have confirmed that timely administration of antiviral drugs reduces the duration of recurrence by 1–2 days and decreases pain intensity, but their effect on the frequency of subsequent recurrences is minimal [12, 28].

A fundamental limitation of antiviral therapy is its inability to affect the latent viral reservoir in the trigeminal ganglion – the primary source of recurrences in CRHS [3]. Furthermore, standard therapy does not correct the alarmin profile imbalance described in previous sections – elevated lfTSLP and IL-25 levels, reduced sfTSLP production, and impaired epithelial barrier function. Thus, even with regular use of nucleoside analogues, the pathogenetic microenvironment promoting HSV-1 reactivation remains unchanged, which accounts for the recurrent nature of the disease [24].

Zinc is an essential microelement that plays a key role in maintaining the functional activity of the immune system and structural integrity of epithelial barriers [20]. In zinc deficiency, disruption of T-lymphocyte differentiation, decreased cytotoxic activity of NK cells, suppression of antimicrobial peptide production, and epithelial barrier dysfunction are observed – all these effects are directly related to the pathogenetic mechanisms of CRHS described in previous sections [20].

The link between zinc levels and herpetic infection was noted in early clinical observations: zinc deficiency is associated with prolonged recurrences and more severe CRHS course, whereas adequate zinc levels promote faster healing of lesions [20]. Notably, in the review by Gopinath et al., it was emphasized that zinc deficiency leads to prolonged duration of herpetic lesions and impaired mucosal regenerative processes [14].

From the perspective of molecular mechanisms, zinc is capable of modulating the alarmin profile of the mucosa through several interconnected pathways. First, zinc regulates NF-κB activity – a key transcription factor that controls lfTSLP and IL-33 production in epithelial cells during viral damage [20]. Second, zinc maintains the structural integrity of epithelial tight junctions through regulation of claudins and occludin, which directly affects the barrier function of the mucosa and accessibility of HSV-1 receptors [20]. Third, zinc stimulates the production of antimicrobial peptides – namely β-defensins and LL-37 – which synergize with sfTSLP in suppressing HSV-1 replication [16].

Low-level laser therapy (LLLT), in particular using diode lasers with a wavelength of 630–980 nm, has gained widespread application in dental practice for the treatment of recurrent herpetic lesions of the oral mucosa. Clinical data indicate that the use of diode lasers reduces the duration of recurrence, decreases pain syndrome, and prolongs inter-recurrence intervals [1].

The molecular mechanisms of the therapeutic effect of diode laser in CRHS are realized through photobiomodulation – a process in which photons of laser radiation are absorbed by mitochondrial chromophores (cytochrome c oxidase), which leads to increased ATP production, changes in membrane potential, and activation of a number of signaling cascades [1, 2]. From the perspective of the alarmin profile, photobiomodulation is capable of suppressing NF-κB-dependent transcription of pro-inflammatory cytokines – particularly IL-1β and TNF-α – which indirectly reduces the induction of lfTSLP and IL-33 in epithelial cells [1].

In addition, laser therapy stimulates the proliferation and migration of epithelial cells, collagen synthesis, and the restoration of tight junctions, which directly contributes to the restoration of the mucosal barrier function impaired by repeated herpetic recurrences [1]. Restoration of barrier function, in turn, reduces the accessibility of HSV-1 receptors and decreases the intensity of the alarmin response during subsequent viral reactivation [12].

Conclusion

Alarmins TSLP, IL-33, and IL-25 are key regulators of epithelial immunity in viral infections, exerting their influence through ILC2 activation, Th2 response polarization, and modulation of interferon-mediated defense. In CRHS, these molecules form a self-perpetuating pathogenetic cycle: HSV-1 reactivation induces the release of alarmins, which sustains the Th2-dominant microenvironment during the inter-recurrence period, suppresses constitutive production of protective sfTSLP, and impairs the epithelial barrier function, thereby creating conditions for subsequent viral reactivation.

Based on the analysis of literature data regarding the molecular mechanisms of inflammation, the role of alarmins, and the cytokine network in herpetic infection, it can be concluded that the problem has certain scientific advances but requires further study in order to develop new, effective, pathogenetically substantiated treatment regimens. Standard antiviral therapy with nucleoside analogues acts exclusively during the phase of active viral replication and is unable to correct the described immunological imbalance, nor does it affect the latent HSV-1 reservoir in the trigeminal ganglion, which accounts for the recurrent nature of the disease.

Prospects for further research. The presented data outline specific directions for further research. First and foremost, it remains unclear whether the alarmin profile of the buccal epithelium reflects the dynamics of CRHS – in particular, whether mRNA levels of lfTSLP, sfTSLP, IL-33, and IL-25 change between the exacerbation phase and the inter-recurrence period, and whether these changes correlate with clinical indicators of disease severity, which would allow verification or refutation of the concept of a self-perpetuating alarmin cycle.

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