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Review article

DNA Methylation and microRNA regulation of the IL-33/TSLP–Th2 Axis in Virus-Associated Asthma

A.Shahimurtov[1], G.Salykova[2], O.Bulgakova[3], A.Kussainova[4], R.Bersimbaev[5], A.Aripova*[6]

[1,2,3,4,5,6] *Department of General Biology and Genomics,*

L.N. Gumilyov Eurasian National University, Astana, Kazakhstan
(E-mail:[1]a.shahi@mail.ru, [2]guka.kikymbaeva@mail.ru, [3]ya.summer13@yandex.kz,

*[4]assya.kussainova@gmail.com, [5]ribersim@gmail.com , *[6]aripova001@gmail.com*)

Abstract. Bronchial asthma is a heterogeneous chronic inflammatory disease of the airways that results from a complex interaction between genetic predisposition and environmental factors. Among these, respiratory viral infections—including rhinovirus, respiratory syncytial virus, influenza virus, and SARS-CoV-2—are recognized not only as the leading cause of asthma exacerbations but also as major contributors to persistent airway inflammation. A central role in virus-induced immune responses is played by the epithelial alarmin axis comprising interleukin-33 (IL-33) and thymic stromal lymphopoietin (TSLP), whose activation drives Th2-mediated inflammation, resulting in eosinophilic infiltration, airway hyperresponsiveness, and bronchial remodeling. The aim of the present review is to examine the relationship between the epithelial alarmins IL-33 and TSLP and epigenetic modifications, particularly DNA methylation and microRNA expression, in asthma pathogenesis, with special emphasis on respiratory viral infections as triggers of these molecular events. Current evidence on the mechanisms by which respiratory viruses modulate IL-33- and TSLP-dependent signaling through epigenetic regulations are summarized. Particular attention is given to DNA methylation and microRNA-mediated regulation of genes encoding epithelial alarmins and their downstream signaling pathways. Aberrant epigenetic regulation contributes to persistent Th2-driven inflammation, enhanced production of pro-inflammatory cytokines, and increased susceptibility to recurrent viral infections and non-infectious triggers. In addition, microRNAs can regulate the expression of epithelial alarmins and serve as potential biomarkers of asthma activity and response to treatment. Studying their role in the interaction between viruses and epigenetic mechanisms broadens our understanding of the pathogenesis

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*Corresponding author

of asthma and opens up new possibilities for precision therapy.

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Introduction

Asthma is one of the most common chronic non-communicable diseases among children and adults, the diagnosis of which presents significant challenges [1]. Currently, it is considered a heterogeneous condition encompassing various phenotypes and endotypes, triggered by factors such as allergens, weather changes, and respiratory viral infections [1-3].

Respiratory viruses can act as a contributing factor to asthma exacerbations. The most common viruses include rhinovirus, respiratory syncytial virus, influenza virus, parainfluenza virus, adenovirus, coronavirus, human bocavirus, and metapneumovirus. These viruses play a significant role in the development of wheezing, bronchiolitis, and asthma. In children under 12 months of age, rhinovirus accounts for approximately 20–40% of bronchiolitis cases or acute wheezing episodes in the emergency department, second only to respiratory syncytial virus [4]. Severe bronchiolitis is associated with a high risk of developing asthma in the future [5]. Long-term follow-up studies have shown that patients who experienced respiratory infections caused by respiratory syncytial virus exhibited airway hyperreactivity and persistent airway obstruction lasting up to 30 years later [6].

A key molecular link between viral injury to the airway epithelium and the development of asthmatic inflammation is represented by the epithelial-derived alarmin cytokines IL-33 and thymic stromal lymphopoietin (TSLP). Following viral infection, epithelial cells release IL-33 and TSLP, which activate group 2 innate lymphoid cells (ILC2s), dendritic cells, and mast cells, thereby initiating a Th2-mediated inflammatory cascade characterised by the production of IL-4, IL-5, and IL-13. This pathway is widely recognized as a central mechanism connecting acute viral insult to persistent allergic inflammation in the bronchial mucosa. For many years, asthma was regarded predominantly as a Th2-driven disease, characterised by elevated IgE levels and eosinophilia in response to allergen exposure [7]. For many years, asthma was considered predominantly a Th2-driven disease, marked by elevated IgE levels and eosinophilia after allergen exposure. Excessive Th2 cytokine production may partly reflect selective infiltration of T cells with a Th2 functional phenotype, but asthma is now known to involve additional T-helper subsets, including Th1, Th9, and Th17 cells [8].

In parallel with growing insights into the role of cytokines and IL-33/TSLP signalling pathways, considerable interest has emerged in epigenetic regulatory mechanisms — most notably small non-coding RNAs (microRNAs) and DNA methylation. MicroRNAs are endogenous single-stranded molecules of approximately 22 nucleotides in length that mediate post-transcriptional gene regulation by binding to the 3' untranslated region (3'UTR) of target messenger RNAs, resulting in translational repression or transcript degradation [9,10,11]. Evidence indicates that viral infections, including those caused by respiratory syncytial virus and rhinovirus, are capable of reprogramming microRNA expression profiles and DNA methylation patterns in bronchial epithelial cells, thereby altering the responsiveness of these cells to IL-33 and TSLP and consolidating a pro-inflammatory phenotype on a long-term basis.

The aim of the present review is to examine the relationship between the alarmin cytokines IL-33 and TSLP and epigenetic modifications, specifically DNA methylation and microRNA expression, in the pathogenesis of asthma, with particular emphasis on respiratory viral infections as initiating stimuli for these molecular events.

IL-33/TSLP–Th2 axis in asthma and viral infections

The IL-33/IL-25/TSLP–Th2 mechanism plays a key role in the development of bronchial asthma, particularly in virus-triggered exacerbations. The airway epithelium not only provides protection but also actively participates in immune responses [12, 13]. When exposed to allergens or viruses, epithelial cells release “alarmins” — IL-33, IL-25, and TSLP — which trigger a Th2-type immune response. [14, 15, 16, 17].

IL-33 is considered one of the earliest mediators of respiratory epithelial damage. It is released from epithelial and endothelial cells following viral infection or cellular stress and binds to the ST2 receptor — a member of the IL-1 receptor family expressed on the surface of type 2 innate lymphoid cells (ILC2s), mast cells, eosinophils, and Th2 cells [18]. ILC2s represent a population of innate immune cells capable of rapidly producing large amounts of IL-5 and IL-13 without involvement of an antigen-specific immune response. Activation of the IL-33/ST2 signaling pathway leads to enhanced production of IL-5 and IL-13, promoting eosinophilic inflammation, mucus hypersecretion, and bronchial hyperreactivity [19, 20]. The role of IL-33 is particularly pronounced in respiratory viral infections, including rhinovirus and influenza virus, where elevated IL-33 levels are accompanied by enhanced Th2 inflammation and airway remodeling [20,21,22,23].

IL-25 (IL-17E) is likewise produced by epithelial cells in response to viruses and allergens. Its primary function is the activation of ILC2s and the support of Th2 cells [24]. IL-25 enhances the synthesis of IL-4, IL-5, and IL-13, promotes eosinophil migration, and increases IgE production by B lymphocytes. It is particularly important in the early stages of allergic sensitization and can amplify chronic inflammation in asthma, notably by potentiating ILC2 activity during viral infections [25].

TSLP (thymic stromal lymphopoietin) is an interleukin-7-like cytokine produced by epithelial cells. TSLP is primarily expressed in the lungs, skin, and stroma and bridges innate and adaptive immunity. Under the influence of viruses and allergens, it activates dendritic cells, thereby promoting the differentiation of naïve T lymphocytes into Th2 cells. TSLP also sustains ILC2 activity [26,27]. In the airways of asthmatic patients, TSLP is markedly elevated and correlates with disease severity and eosinophilic inflammation. During viral infections, TSLP amplifies the production of IL-4, IL-5, and IL-13, thereby contributing to asthma exacerbations [27, 28].

A key link in the IL-33/IL-25/TSLP–Th2 cascade is represented by ILC2s (Figure 1). These cells respond rapidly to alarmins and synthesize IL-5 and IL-13 in the absence of an antigen-specific immune response [29]. IL-33 is a potent activator of pulmonary ILC2s, TSLP sustains their survival, and IL-25 amplifies their activity. Together, these mediators establish and maintain persistent Th2 inflammation in asthma [30].

In respiratory viral infections, activation of this axis becomes particularly critical. Viruses such as rhinovirus, and influenza damage the airway epithelium and activate pattern-recognition receptors, leading to rapid release of alarmins, including IL-33, IL-25, and TSLP. This amplifies eosinophil recruitment, ILC2 and Th2 cell activation, mucus production, and airway hyperreactivity, thereby making viral infections frequent precipitants of asthma exacerbations [30, 31, 32]

Furthermore, alarmins drive chronic airway remodeling. IL-13 stimulates goblet cell hyperplasia and fibrosis, IL-5 sustains eosinophil survival, and IL-4 increases IgE production. Thus, the IL-33/IL-25/TSLP–Th2 axis not only initiates inflammation but also perpetuates the chronic course of asthma [33].

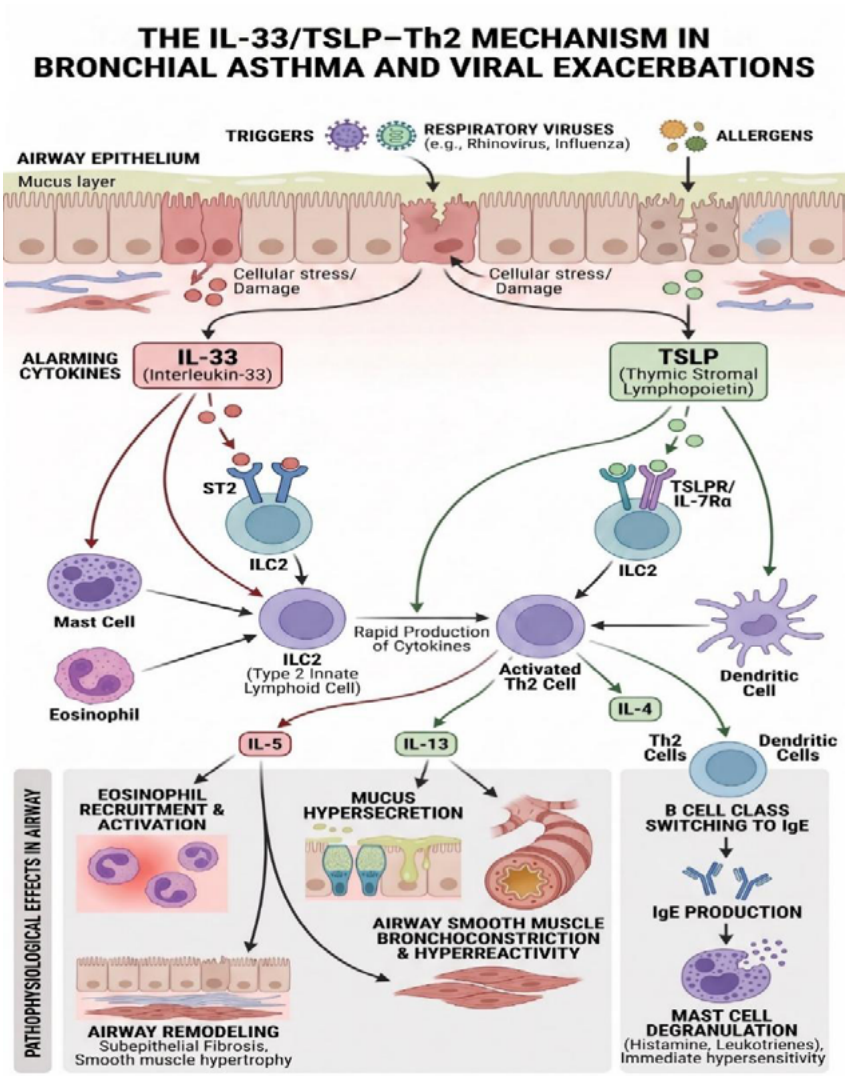

Figure1. The IL-33/IL-25/TSLP–Th2 signaling cascade in bronchial asthma (https://sci-draw.com/ru)

Current research identifies IL-33, IL-25, and TSLP as promising therapeutic targets. Agents directed against TSLP and IL-33 have shown reductions in asthma exacerbation frequency and attenuation of Th2 inflammation. Of particular interest is TSLP blockade with tezepelumab, which appears capable of suppressing a broad range of Th2 responses regardless of asthma phenotype. [30].

Methylation of TSLP in Asthma

Epigenetic modifications play a key role in regulating the activity of genes that are specific to particular tissues and developmental stages. They can also serve as mediators of gene–environment interactions, influencing the onset and progression of various diseases [34]. Asthma is a complex disease that develops from a combination of genetic and environmental factors [35,36]. Research has shown that both inherited traits and external influences play a role in the development of atopic asthma. A key player in this process is DNA methylation, an epigenetic mechanism that helps bridge genetic and environmental interactions [37]. This process can

affect how prone individuals are to allergic conditions like asthma. DNA methylation influences how T-helper (Th) cells develop, steering them towards either the Th1 or Th2 type, which in turn impacts immune responses linked to asthma [38]. In mammals, DNA methylation is driven by enzymes called DNA methyltransferases (DNMTs) — specifically DNMT1, DNMT3A, and DNMT3B. These enzymes work together to create, maintain, and regulate the methylation patterns across the genome, which are vital for proper cell function and a balanced immune system [39].

Previous studies have demonstrated that, in asthmatic mice, the mRNA levels of DNMT1, STAT3, IFN-γ, and IL-6 in lung cells, tracheal tissue, and bronchoalveolar lavage fluid are significantly reduced compared with those in healthy controls, whereas the expression of SOCS3, IL-4, and IL-5 is markedly increased [40].

DNA hypomethylation and overexpression of TSLP have been identified in skin lesions from patients with atopic dermatitis, with promoter hypomethylation shown to contribute directly to this overexpression [41]. Consistently, in asthmatic airway epithelial cells, DNMT1 mRNA and protein levels are markedly decreased compared with controls, while TSLP mRNA and protein expression are significantly elevated, accompanied by demethylation of the TSLP promoter, collectively suggesting that DNA demethylation plays a key role in driving TSLP overexpression in asthma [42]. Some studies have also confirmed that DNMT1 is essential for the regulation, differentiation, proliferation, and survival of T cells [40, 43].

Prenatal tobacco smoke exposure has been shown to alter DNA methylation levels at the TSLP gene, with TSLP methylation levels negatively correlating with TSLP protein expression [44]. Similarly, exposure to benzyl butyl phthalate (BBzP) in settled dust may increase respiratory symptoms in children through decreased TSLP methylation, suggesting that BBzP exposure should be minimized, particularly in children with existing allergic diseases [45]. Furthermore, phthalate exposure was found to shift the TH1/TH2 cytokine balance toward TH2 responses, with in vivo evidence indicating that phthalate in combination with FITC may trigger TSLP production via activation of the NF-κB signaling pathway [46].

Regarding T-cell differentiation, naive CD4+ T lymphocytes can differentiate into Th1 or Th2 lineages, with Th2 cells expressing IL-4, IL-5, and IL-13, cytokines implicated in asthma. In naive cells, the DNA at the IL-4 and IL-13 loci is predominantly methylated, whereas Th2 differentiation is accompanied by the appearance of DNase I hypersensitive sites and CpG demethylation at regions coinciding with binding sites for the Th2-specific transcription factor GATA-3, indicating that chromatin remodeling and DNA demethylation are tightly coupled to cytokine gene activation in a tissue-specific manner [47]. Pendrin expression is upregulated in pathological respiratory conditions such as asthma and COPD, contributing to inflammation and mucus production [48,49,50, 51,52, 53]. This upregulation is mediated by phosphorylated STAT6, activated by IL-4, which binds to a functional N4 GAS motif in the pendrin promoter. Accordingly, IL-4 has been shown to induce site- and cell-specific CpG demethylation of the human pendrin promoter in primary bronchial epithelial cells, with methylation at CpG sites 90 and 90bis proposed to influence the magnitude and speed of the pendrin mRNA response to IL-4 [54].

Together, these findings suggest that epigenetic dysregulation may play a critical role in aberrant TSLP expression; however, the precise molecular mechanism responsible for TSLP overexpression in asthma remains incompletely understood.

MicroRNAs Regulating the IL-33/TSLP Axis

IL-33 represents a pivotal “alarmin” mediator that initiates the inflammatory cascade in asthma. The mechanisms of post-transcriptional regulation of its expression — particularly those involving microRNAs - are of considerable interest as potential therapeutic targets.

The most direct evidence for microRNA-mediated regulation of IL-33 has been obtained

for the miR-200 family [55]. miR-200b and miR-200c directly bind to the 3′ untranslated region (3′UTR) of IL-33 mRNA in bronchial epithelial cells. Both microRNAs were significantly down-regulated in the bronchoalveolar lavage fluid of young adults with bronchial asthma compared to healthy controls; an analogous pattern was reproduced in two distinct murine models of allergic airway inflammation [56]. Reduced expression of miR-200b/c relieved inhibitory constraints on the IL-33 3′UTR, resulting in elevated IL-33 levels and augmented type 2 inflammation. The down-regulation of the miR-200 family in asthma is further corroborated by additional data: decreased expression of family members was also detected in vesicular fractions of bronchoalveolar lavage fluid and exhaled breath condensate from allergic asthmatic patients, with investigators attributing this finding to impaired epithelial-to-mesenchymal transition and airway remodeling [56].

MicroRNA miR-146a exerts a predominantly anti-inflammatory role in asthma and modulates IL-33 expression through several mechanisms. miR-146a-deficient mice demonstrated exacerbated airway inflammation and enhanced Th2 responses in a house dust mite-induced asthma model [56]. In humans, a polymorphism within the miR-146a gene has been associated with susceptibility to asthma [56].

From a clinical perspective, miR-146a is upregulated in plasma and serum of asthmatic patients and correlates with markers of poor disease control, including the Asthma Control Questionnaire (ACQ) score [57]. Furthermore, miR-146a has been shown to suppress cyclooxygenase-2 and IL-1β expression upon induction by inflammatory stimuli in airway smooth muscle cells [56], thereby reducing the substrate for potential epithelial injury and subsequent IL-33 release. In bronchial epithelial cells, miR-146a has been reported to potentiate the anti-inflammatory effects of glucocorticoids [57], which may serve to attenuate IL-33-mediated inflammation in treated patients. Notably, miR-146a is consistently included in both diagnostic panels and asthma severity-risk assessment panels [57], underscoring its significance in the regulation of the IL-33-dependent inflammatory cascade (Figure 3).

MicroRNA-21 (miR-21) is among the most extensively investigated microRNAs in the context of asthma. It is upregulated across a variety of biological fluids and tissues, augmenting the Th2 inflammatory response in synergy with IL-33. miR-21 modulates the Th1/Th2 balance by suppressing IL-12p35 expression, thereby attenuating IFN-γ production and promoting Th2 cell differentiation [56]. Furthermore, miR-21 directly induces Th2 differentiation by upregulating GATA-3 and IL-4 expression [57], converging on the same pro-inflammatory pathway activated by IL-33(Figure 3).

In asthmatic children, plasma levels of miR-21-5p are positively correlated with IL-13 concentrations and the percentage of eosinophils, and inversely correlated with pulmonary function as assessed by forced expiratory volume in one second (FEV_1) [58]. Given that IL-33 promotes IL-13 production by ILC2s and Th2 cells, while miR-21 amplifies the Th2 response, a functional synergism between miR-21 and IL-33 may be postulated: IL-33 activates immune effector cells, whereas miR-21 sustains their pro-inflammatory phenotype. In airway smooth muscle cells, miR-21 additionally suppresses PTEN, thereby activating the PI3K signalling pathway [58] - the same pathway engaged in downstream IL-33 signal transduction.

A notable direct regulator of IL-33, specific to asthmatic airway and nasopharyngeal inflammation, is miR-181a-5p. Experimental evidence reviewed by Gu et al. demonstrates that miR-181a-5p directly targets IL-33 mRNA and suppresses the IL-33/ST2/p38 MAPK axis in nasal epithelial cells (RPMI-2650 cell line), thereby exerting an anti-inflammatory effect [59]. This finding is of considerable therapeutic relevance, as it describes a mechanism by which a single microRNA can simultaneously inhibit both IL-33 expression and its downstream signal transduction. The p38 MAPK pathway is of critical importance in asthma, regulating IL-33 expression in

the airway epithelium particularly during viral infections that precipitate disease exacerbations [59]. Downregulation of miR-181a-5p in nasopharyngeal inflammation and asthma may thus permit unrestricted activation of the IL-33/ST2/p38 MAPK signalling cascade.

A novel mechanism of IL-33 production regulation involving miR-206 has recently been described. The miR-206/CD39/ATP axis governs the expression of IL-33, IL-25, and TSLP in the airways under conditions of type 2 inflammation [59]. CD39, an ectonucleotidase responsible for the degradation of extracellular ATP, activates purinergic receptors on epithelial cells, thereby mediating IL-33 release. miR-206 is capable of modulating CD39 expression, consequently influencing extracellular ATP levels and the purinergic stimulation of IL-33 secretion. Elevated extracellular ATP activates purinergic receptors to promote IL-33 secretion, whereas reduced ATP levels suppress the release of IL-33, IL-25, and TSLP, as well as downstream ILC2 expansion [59]. This mechanism represents an indirect yet functionally significant pathway through which microRNAs regulate IL-33 expression.

Members of the let-7 family are downregulated in asthma and function as regulators of IL-13 — a key downstream effector of the IL-33 signalling pathway. let-7 microRNAs have been shown to directly target the 3′UTR of IL-13 mRNA, with IL-13 levels in T cells inversely correlating with let-7 abundance [56]. In murine models of allergic asthma, let-7 family members were downregulated, whereas intranasal administration of let-7 mimics reduced IL-13 expression and promoted resolution of allergic airway inflammation [56]. In clinical studies, downregulation of the let-7 family has been detected in bronchoalveolar lavage fluid, serum, exhaled breath condensate, and lymphocytes of asthmatic patients [57]. Since IL-33 is a potent inducer of IL-13 production via ILC2 and Th2 cell activation, the reduction in let-7 potentially amplifies the IL-33-initiated inflammatory cycle by sustaining elevated IL-13 levels.

MicroRNA-145 (miR-145) is upregulated in the airway wall in asthma, stimulating IL-5 and IL-13 secretion by Th2 cells and contributing to eosinophilia, mucus hypersecretion, and bronchial hyperresponsiveness [56,58]. Its inhibition in murine models attenuated allergic inflammation and since IL-33 promotes Th2 differentiation and ILC2 expansion, the upregulation of miR-145 in asthma likely reflects IL-33-driven inflammatory changes that miR-145 itself mediates [56]. In airway smooth muscle cells, miR-145 regulates proliferation via the EGFR pathway [58], while IL-33 signalling may additionally contribute to airway remodelling and smooth muscle hypertrophy in severe asthma.

The microRNA-mediated regulation of TSLP is closely linked to that of IL-33, together forming a coordinated molecular network that governs the alarmin cascade. The most detailed experimental evidence for direct microRNA-mediated regulation of TSLP has been obtained for miR-19b. Ye et al., employing an ovalbumin (OVA)-induced murine model of asthma, demonstrated that TSLP constitutes a direct target of miR-19b, as confirmed by bioinformatic analyses and dual-luciferase reporter assays [60].

A fundamentally novel mechanism of indirect TSLP and IL-25 regulation via purinergic signalling was described by Zhang et al. Microarray profiling of bronchial epithelial microRNAs identified differentially expressed microRNAs between patients with type 2-high and type 2-low asthma [61]. miR-206 emerged as the most highly expressed microRNA in the bronchial epithelium of type 2-high asthma relative to type 2-low asthma; however, its levels were reduced in both subgroups compared to healthy subjects. CD39, an ectonucleotidase responsible for extracellular ATP degradation, was identified as a direct target of miR-206 and exhibited upregulated expression in asthma. Allergen exposure of cultured human bronchial epithelial cells induced rapid extracellular ATP accumulation, which was accompanied by downregulation of miR-206 and upregulation of CD39, forming a negative feedback loop directed at the elimination of excess

extracellular ATP [61].

In vivo studies employing allergic rhinitis models demonstrated that miR-375 enhances ILC2 function through regulation of TSLP [62]. Although the majority of relevant investigations have been conducted in allergic rhinitis models, the underlying mechanism retains its significance for bronchial asthma, given that both conditions engage the same ILC2 and TSLP-dependent pathways. These findings suggest that miR-375 may potentiate TSLP-dependent ILC2 activation, thereby representing a potential therapeutic target in upper and lower airway diseases sharing a common pathogenic mechanism.

A further important aspect concerns the participation of mast cells in TSLP–ILC2 crosstalk. miR-103a-3p, markedly upregulated in extracellular vesicles (EVs) derived from FcεRI-aggregated mast cells, was shown to enhance IL-5 production by human ILC2s in co-culture experiments, acting through arginine methylation of GATA3 residues [62]. This mechanism represents an indirect pathway whereby mast cells, in response to IgE-mediated signalling, may augment ILC2 function via miRNA-loaded EVs in a manner synergistic with TSLP-mediated priming.

Bioinformatic analysis conducted using the miRNet platform, a set of microRNAs capable of targeting the IL-33 and TSLP genes in the context of asthma was identified on the basis of HITS-CLIP, microarray, and RNA-Seq experimental datasets derived from exosomal and peripheral blood samples. The analysis revealed 8 microRNAs predicted to regulate IL-33 (hsa-miR-146a-5p, hsa-miR-9-5p, hsa-miR-148b-3p, hsa-miR-21-3p, hsa-miR-221-5p, hsa-miR-148a-3p, hsa-miR-152-3p, and hsa-miR-34a-5p) and 3 microRNAs predicted to regulate TSLP (hsa-miR-34a-5p, hsa-let-7b-5p, and hsa-miR-155-5p). Notably, hsa-miR-34a-5p was identified as a shared regulatory target of both genes simultaneously (Figure 2).

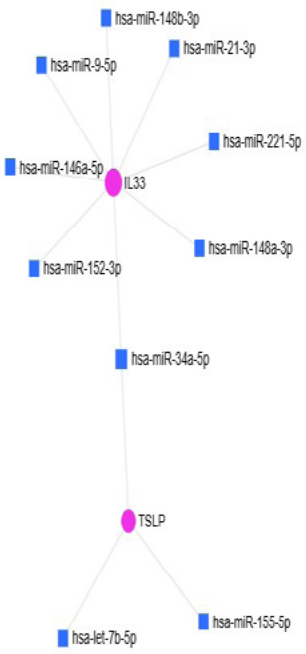

Figure 2. MicroRNA–target gene interaction network for IL-33 and TSLP in asthma

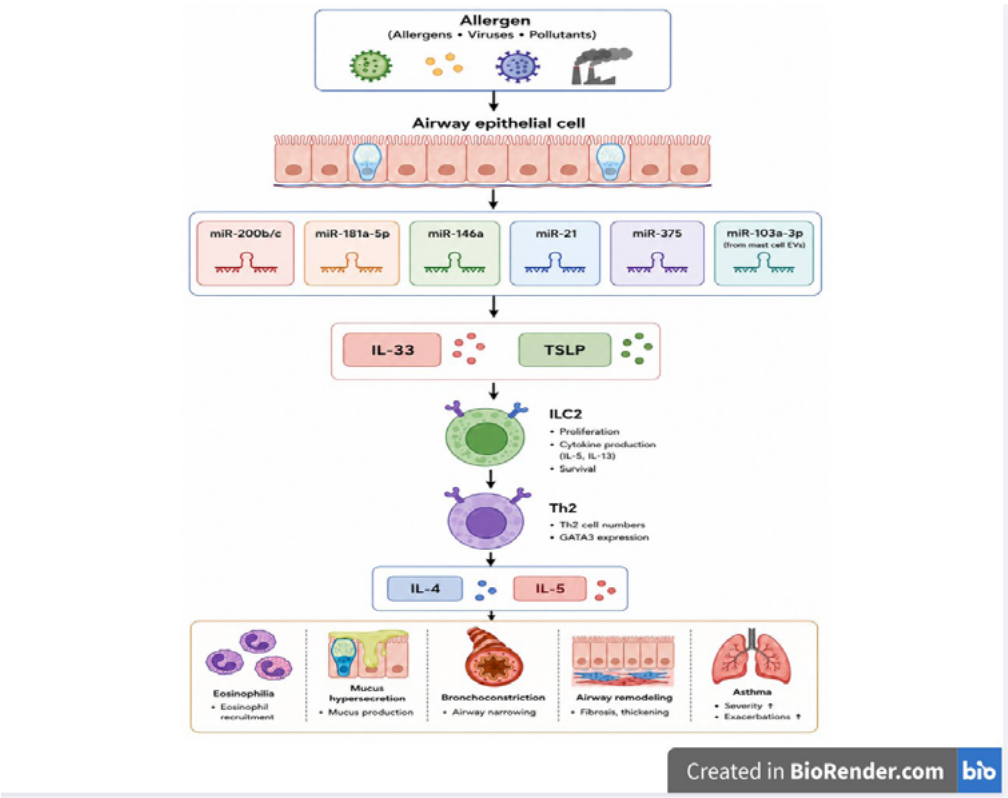

Figure 3. Epigenetic regulation of the IL-33/TSLP axis by microRNAs in bronchial asthma (https://app.biorender.com)

Viruses and Epigenetic Regulation of Asthma

Viral infections are closely associated with epigenetic mechanisms that can alter both the intensity and character of the host inflammatory response. Such mechanisms include DNA methylation, histone modifications, and non-coding RNA-mediated regulation; viruses are capable of exploiting these processes to attenuate innate and adaptive immunity and thereby modify the course of inflammation [63].

Epigenetic regulation is of particular importance because inflammatory activity depends not solely on the genetic programme of the cell, but also on the accessibility of chromatin regions for transcription. During viral infection, this can result either in the suppression of antiviral genes or, conversely, in the sustained hyperactivation of inflammatory pathways. Consequently, the inflammatory response may become either insufficient — thereby facilitating viral persistence — or excessive, leading to amplified tissue injury [63, 64].

Respiratory viruses, including coronaviruses and influenza viruses, exemplify this phenomenon, as they can influence antigen presentation and immune response regulation through alterations in DNA methylation and histone modifications. Such epigenetic shifts modify the expression of genes involved in inflammation and may contribute to more severe disease courses [63].

Herpesviruses also actively interact with the host epigenome. In the context of human cytomegalovirus (HCMV) and Epstein–Barr virus (EBV) infection, viral and cellular proteins engage chromatin-modifying complexes, influencing viral latency, reactivation, and the inflammatory background of infection. This is of particular relevance in chronic infections, wherein prolonged

inflammation sustains tissue damage and may increase the risk of complications [63, 64].

From a translational perspective, elucidating these processes opens avenues for epigenetically targeted therapy. The conceptual basis of such an approach involves acting upon chromatin-regulatory enzymes to correct virus-induced inflammation, attenuate viral replication, and reduce pathological inflammatory activity. This strategy is regarded as a promising therapeutic direction for a number of viral diseases, including HIV, HCMV, HBV, HCV, and herpesvirus infections [64].

Viral infections are capable of inducing epigenetic alterations in airway epithelial cells, including disruption of DNA methylation patterns and changes in microRNA expression profiles. These processes lead to upregulated expression of pro-inflammatory genes and activation of IL-33/TSLP-dependent Th2 inflammation. Virus-induced alterations in miRNA profiles further amplify the production of IL-4, IL-5, and IL-13, sustaining chronic airway inflammation and remodelling in asthma. Moreover, virus-induced epigenetic mechanisms may impair epithelial barrier function and heighten airway susceptibility to allergens and infectious agents [65, 66,67,68].

In viral infections, the inflammatory response is mainly shaped by the balance among Th1, Th2, and other immune pathways, with microRNAs serving an important regulatory role. Among the microRNAs most relevant to Th2 immunity are miR-21, miR-27, and miR-128: elevated miR-21 promotes Th2 differentiation, whereas miR-27 and miR-128 inhibit the production of the Th2 cytokines IL-4 and IL-5 by activated CD4+ T cells. This implies that viruses may indirectly affect allergic or anti-inflammatory immune responses by changing microRNA expression patterns [69].

Virus-induced inflammation is also associated with activation of Toll-like receptor (TLR) signalling, which triggers the expression of several microRNAs that regulate the duration and intensity of the inflammatory response. Among these, miR-155 amplifies the pro-inflammatory response, while miR-146a, miR-132, miR-9, miR-21, and miR-147 participate in its attenuation or transition to an anti-inflammatory phase. In the context of Th2 immunity, alterations in the levels of these microRNAs may shift the immunological balance towards more pronounced inflammation or, alternatively, towards a more controlled response [69].

Viral infections, including SARS-CoV-2, are capable of inducing epigenetic changes in airway epithelial cells, including disruption of DNA methylation and altered microRNA expression. These changes result in upregulation of pro-inflammatory gene expression and activation of IL-33/TSLP-dependent Th2 inflammation. Furthermore, viruses can alter the miRNA profiles of both epithelial and immune cells, accompanied by increased production of IL-4, IL-5, and IL-13, thereby sustaining chronic airway inflammation in asthma. In SARS-CoV-2, elevated expression of IL-33 and TSLP is associated with augmented inflammatory responses, epithelial barrier disruption, and airway remodelling. Impairment of the antiviral interferon response further amplifies the activation of IL-33 and TSLP signalling pathways, contributing to the development of virus-induced asthma exacerbations [70, 71, 72, 73, 74].

In SARS-CoV-2, changes in DNA methylation have also been observed that may influence the duration and character of airway inflammation. During the acute phase of infection, numerous differentially methylated regions were identified in SARS-CoV-2 patients: hypomethylated regions involved genes associated with immune regulation, while hypermethylated regions affected genes related to epithelial ciliary function. This is of direct relevance to asthma, as disruption of the epithelial barrier and persistent inflammation may exacerbate bronchial hyperresponsiveness and impair disease control [64, 75]

For patients with bronchial asthma, SARS-CoV-2 may act as a factor that intensifies the epigenetic reprogramming of the immune response, rendering inflammation more prolonged or more severe. Thus, DNA methylation serves as a mechanistic link between SARS-CoV-2 infection

and exacerbation of asthmatic inflammation, particularly in airway tissues.

Conclusion

Epigenetic mechanisms thus constitute a form of molecular memory of prior viral exposure and may account for inter-individual differences in susceptibility to, and severity of, bronchial asthma. MicroRNAs and DNA methylation actively participate in the regulation of the IL-33/TSLP–Th2 inflammatory axis, and dysregulation of these epigenetic marks offers potential for their application as biomarkers for disease diagnosis and therapeutic monitoring. Given the pharmacological reversibility of epigenetic modifications, a deeper understanding of these mechanisms holds direct relevance for the development of targeted therapeutic strategies in asthma. Nevertheless, the role of epigenetic regulation of the IL-33/TSLP signalling pathway in the context of respiratory viral infections remains insufficiently characterised and warrants further investigation.

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Conflicts of Interest

All authors have no conflict of interest to declare.

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Вируспен байланысты астмадағы IL-33/TSLP–Th2 осінің ДНҚ метилденуі және микроРНҚ реттелуі

А.Д. Шаhимұратова[1], Г.Ш.Салыкова[2], О.В. Булгакова[3], А.А.Кусаинова[4], Р.И.Берсімбай[5], А.А.Арипова*[6]

[1,2,3,4,5,6] Жалпы биология және геномика кафедрасы,
Л.Н. Гумилев атындағы Еуразия ұлттық университеті, Астана, Қазақстан

Аннотация. Бронх демікпесі – генетикалық бейімділік пен қоршаған орта факторларының күрделі өзара әрекеттесуінен туындайтын тыныс алу жолдарының гетерогенді созылмалы қабыну ауруы. Олардың ішінде риновирус, респираторлық синцитиальды вирус, тұмау вирусы және SARS-CoV-2 сияқты респираторлық вирустық инфекциялар астманың өршуінің негізгі себебі ғана емес, сонымен қатар тыныс алу жолдарының тұрақты қабынуының негізгі факторлары ретінде де танылады. Вирус тудыратын иммундық реакцияларда интерлейкин-33 (IL-33) және тимус стромальды

лимфопоэтинінен (TSLP) тұратын эпителий дабыл осі орталық рөл атқарады, олардың белсенділігі Th2 арқылы қабынуды тудырады, бұл эозинофильді инфильтрацияға, тыныс алу жолдарының гиперреактивтілігіне және бронхтардың қайта құрылуына әкеледі.

Осы мақаланың мақсаты – астма патогенезіндегі эпителий дабыл осі IL-33 және TSLP мен эпигенетикалық модификациялар, әсіресе ДНҚ метилденуі мен микроРНҚ экспрессиясы арасындағы байланысты зерттеу, әсіресе респираторлық вирустық инфекцияларға осы молекулалық оқиғалардың қоздырғыштары ретінде ерекше назар аудару. Тыныс алу вирустарының IL-33 және TSLP-тәуелді сигнал беруді эпигенетикалық реттеулер арқылы модуляциялау механизмдері туралы қазіргі дәлелдер қорытындыланған. Эпителий дабылдарын кодтайтын гендердің ДНҚ метилденуіне және микроРНҚ арқылы реттелуіне және олардың сигнал беру жолдарына ерекше назар аударылады. Эпигенетикалық реттеудің бұзылуы Th2 тудыратын қабынудың тұрақты дамуына, қабынуға қарсы цитокиндердің өндірілуін арттыруға және қайталанатын вирустық инфекциялар мен инфекциялық емес триггерлерге сезімталдықтың артуына ықпал етеді. Сонымен қатар, жинақталған дәлелдер нақты микроРНҚ-лардың эпителий дабылының экспрессиясын реттейтінін және ауру белсенділігі мен терапиялық жауаптың сезімтал көрсеткіштері ретінде қызмет етуі мүмкін екенін көрсетеді. Тыныс алу вирустары, эпителий дабылдары және эпигенетикалық механизмдер арасындағы өзара әрекеттесуді анықтау астма патогенезі туралы жаңа түсініктер береді және микроРНҚ-ны перспективалы диагностикалық және болжамдық биомаркерлер, сондай-ақ дәл медицина мен мақсатты астма терапиясы үшін әлеуетті терапиялық нысаналар ретінде көрсетеді.

Кілт сөздер: бронх демікпесі, эпителий дабылдары, IL-33, TSLP, эпигенетика, микроРНҚ, тыныс алу вирустары

Метилирование ДНК и регуляция микроРНК оси IL-33/TSLP–Th2 при вирус-ассоциированной астме

А.Д. Шахимуратова[1], Г.Ш.Салыкова[2] , О.В. Булгакова[3], А.А.Кусаинова[4], Р.И.Берсимбаев[5], А.А.Арипова*[6]

[1,2,3,4,5,6] *Кафедра общей биологии и геномики, Евразийский национальный университет имени Л.Н. Гумилева, Астана, Казахстан*

Аннотация.Бронхиальная астма это гетерогенное хроническое воспалительное заболевание дыхательных путей, возникающее в результате сложного взаимодействия между генетической предрасположенностью и факторами окружающей среды. Среди них респираторные вирусные инфекции, включая риновирус, респираторно—синцитиальный вирус, вирус гриппа и SARS-CoV-2, признаны не только основной причиной обострений астмы, но и основными факторами, способствующими постоянному воспалению дыхательных путей. Центральную роль в иммунных реакциях, вызванных вирусом, играет эпителиальная алармин-система, включающая интерлейкин-33 (IL-33) и тимусный стромальный лимфопоэтин (TSLP), активация которых вызывает Th2-опосредованное воспаление, приводящее к эозинофильной инфильтрации, гиперчувствительности дыхательных путей и ремоделированию бронхов. Целью настоящего обзора является изучение взаимосвязи между эпителиальными аларминами IL-33 и TSLP и эпигенетическими модификациями, в частности метилированием ДНК и экспрессией микроРНК, в патогенезе астмы, с особым акцентом на респираторные вирусные инфекции как триггеры этих

молекулярных событий. В обзоре обобщены современные данные о механизмах, посредством которых респираторные вирусы модулируют IL-33- и TSLP-зависимую передачу сигналов через эпигенетическую регуляцию. Особое внимание уделяется метилированию ДНК и опосредованной микроРНК регуляции генов, кодирующих эпителиальные алармины, и их нижестоящих сигнальных путей. Эпигенетические сбои провоцируют хроническое Th2-воспаление, повышая чувствительность к инфекциям и внешним триггерам. Роль микроРНК в регуляции эпителиальных аларминов позволяет использовать их в качестве высокоточных индикаторов активности заболевания и ответа на проводимую терапию. Изучение взаимодействий между респираторными вирусами, эпителиальными аларминами и эпигенетическими механизмами открывает новые перспективы в понимании патогенеза астмы и выявляет микроРНК как перспективные диагностические и прогностические биомаркеры, а также потенциальные терапевтические мишени для персонализированной медицины и целенаправленной терапии астмы.

Ключевые слова: бронхиальная астма, эпителиальные алармины, IL-33, TSLP, эпигенетика, микроРНК, респираторные вирусы.

Авторлар туралы мәліметтер:

Шаhимұратова Айдана Досболқызы – жалпы биология және геномика кафедрасының білім алушысы, Л.Н. Гумилев атындағы Еуразия ұлттық университеті, Сәтбаев көш. 2, 010000, Астана, Қазақстан

Салыкова Гүлназ Шарыпқанқызы жалпы биология және геномика кафедрасының білім алушысы, Л.Н. Гумилев атындағы Еуразия ұлттық университеті, Сәтбаев көш. 2, 010000, Астана, Қазақстан

Кусаинова Асия Арыслановна – PhD, жалпы биология және геномика кафедрасының қауымдастырылған профессор м.а., Л.Н. Гумилев атындағы Еуразия ұлттық университеті, Сәтбаев 2, 010000, Астана, Қазақстан

Булгакова Ольга Владимировна – PhD, жалпы биология және геномика кафедрасының профессоры, Л.Н. Гумилев атындағы Еуразия ұлттық университеті, Сәтбаев көш. 2, 010000, Астана, Қазақстан

Берсімбай Рахметқажы Іскендірұлы – ҚР ҰҒА академигі, Клеткалық биология және биотех-нология ғылыми-зерттеу институтының директоры, Л.Н. Гумилев атындағы Еуразия ұлттық университеті, Сәтбаев көш. 2, 010000, Астана, Қазақстан

Арипова Акмарал Алтынбаевна – Хат-хабар авторы. PhD, жалпы биология және геномика кафедрасының қауымдастырылған профессор м.а., Л.Н. Гумилев атындағы Еуразия ұлттық университеті, Сәтбаев 2, 010000, Астана, Қазақстан

Сведения об авторах:

Шахимуратова Айдана Досболовна – докторант кафедры общей биологии и геномики, Евразийский национальный университет имени Л.Н. Гумилёва, ул. Сатпаева, 2, 010000, Астана, Қазақстан

Салыкова Гулназ Шарыпкановна – докторант кафедры общей биологии и геномики, Евразийский национальный университет имени Л.Н. Гумилёва, ул. Сатпаева, 2, 010000, Астана, Қазақстан

Кусаинова Асия Арыслановна – PhD, и.о. доцента кафедры общей биологии и геномики, Евразийский национальный университет имени Л.Н. Гумилёва, ул. Сатпаева, 2, 010000, Астана, Казахстан.

Булгакова Ольга Владимировна – PhD, профессор кафедры общей биологии и геномики, Евразийский национальный университет имени Л.Н. Гумилёва, ул. Сатпаева,

010000, Астана, Қазақстан

Берсимбай Рахметкажи Искендирович – академик НАН РК, директор Научно-исследовательского института клеточной биологии и биотехнологии, Евразийский национальный университет имени Л.Н. Гумилёва, ул. Сатпаева, 2, 010000, Астана, Қазақстан

Арипова Акмарал Алтынбаевна – Автор-корреспондент. PhD, и.о. доцента кафедры общей биологии и геномики, Евразийский национальный университет имени Л.Н. Гумилёва, ул. Сатпаева, 2, 010000, Астана, Казахстан.

Information about the authors:

Shahimuratova Aidana Dosbolkyzy – doctoral student at the Department of General Biology and Genomics, L.N. Gumilyov Eurasian National University, Satpayev Street, 2, 010000, Astana, Kazakhstan.

Salykova Gulnaz Sharypkankyzy– doctoral student at the Department of General Biology and Genomics, L.N. Gumilyov Eurasian National University, Satpayev Street, 2, 010000, Astana, Kazakhstan.

Kussainova Assiya – PhD, senior researcher, Research Institute of Cell Biology and Biotechnology, L.N. Gumilyov Eurasian National University, Satpayev str. 2, 010000, Astana, Kazakhstan.

Bulgakova Olga – PhD, Professor, Department of General Biology and Genomics, L.N. Gumilyov Eurasian National University, Satpayev str. 2, 010000, Astana, Kazakhstan.

Bersimbaev Rakhmetkazhy – Academician of the National Academy of Sciences of the Republic of Kazakhstan, Director of the Research Institute of Cell Biology and Biotechnology, L.N. Gumilyov Eurasian National University, Satpayev str. 2, 010000, Astana, Kazakhstan.

Aripova Akmaral – Corresponding author. PhD, Acting associate professor, Department of General Biology and Genomics, L.N. Gumilyov Eurasian National University, 2 Satpayev Street, 010000, Astana, Kazakhstan.