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A Systematic Review on Exploring the Role of MicroRNAs as Diagnostic and Prognostic Biomarkers in Elderly-Onset Asthma

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Abstract

MicroRNAs (miRNAs) are small, non-coding RNA molecules that function as significant post-transcriptional regulators of gene expression, influencing a wide range of biological processes, including immune modulation, inflammation, and cellular remodeling. Their dysregulation has been implicated in diverse chronic diseases, including asthma. Elderly-onset asthma (EOA) presents substantial clinical challenges due to its distinct immunopathophysiology, heterogeneous phenotypic presentations, and differential response to standard therapies. Emerging evidence underscores the integral role of miRNAs in asthma pathogenesis, modulating inflammatory cascades, immune dysregulation, and airway remodeling. This systematic review explores the significance of miRNAs as diagnostic and prognostic biomarkers in EOA, emphasizing their differential expression profiles and involvement in disease progression. Key regulatory miRNAs, including miR-21, miR-155, miR-140-3p, and miR-221, modulate molecular pathways implicated in Th_2-driven inflammation, epithelial-to-mesenchymal transition, and immune homeostasis. Dysregulated expression of miRNAs correlates with disease severity, therapeutic responsiveness, and long-term pulmonary outcomes, highlighting their clinical relevance in precision medicine. However, the translational applicability of miRNA-based biomarkers is constrained by methodological inconsistencies in miRNA profiling, including sample variability and the need for standardized protocols. Despite these challenges, the non-invasive nature and disease-specific expression patterns of miRNAs present a compelling case for their integration into biomarker-driven diagnostics and personalized treatment strategies. Future research should prioritize the validation of miRNA markers in diverse cohorts and explore their functional implications in EOA. By developing the regulatory networks governed by miRNAs, this review sets the stage for molecular asthma diagnostics and therapeutics, underscoring the potential of miRNA-targeted interventions in optimizing disease management and clinical outcomes in elderly populations.

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1. Introduction

Asthma, a chronic inflammatory disease of the airways, causes symptoms such as cough, wheezing, shortness of breath, and chest tightness. Mucus hypersecretion, remodeling of the airway wall, bronchial hyper-responsiveness, and reversible airflow obstruction, which stimulate the symptoms of asthma, occur due to inflammation of the airways (Hammad and Lambrecht, 2021; Maddox and Schwartz, 2002; Chapman and Irvin, 2015). Globally, respiratory conditions remain a significant health challenge, with chronic respiratory diseases like asthma being among the most prevalent. Asthma, in particular, has affected approximately 262

million people worldwide and caused an estimated 455,000 deaths in 2019 (WHO, 2024). The prevalence of asthma varies by region, with higher rates observed in urbanized and industrialized areas due to factors such as air pollution, allergens, and lifestyle changes. Most asthma-related deaths occur in low- and middle-income countries where underdiagnosis and insufficient treatment are common challenges. The death rate from asthma has seen a decline, but remains a concern in older populations and marginalized communities (American Lung Association, 2024).

Asthma usually manifests as early-onset asthma (childhood-onset asthma) or late-onset asthma (elderly-onset asthma). Childhood-onset asthma is predominantly an IgE-mediated allergic disorder, driven by heightened immune responses to allergens, which are more reversible and responsive to treatment. In contrast, late-onset asthma arises from non-IgE-mediated inflammatory processes, often linked to neutrophilic inflammation, which is more resistant to corticosteroids (Trivedi and Denton, 2019). Over time, cumulative environmental exposures contribute to more persistent and severe airway remodeling in adults, further exacerbating late-onset asthma's severity (Trivedi and Denton, 2019). The severity of asthma spans from intermittent to persistent and is classified into mild, moderate, or severe levels depending on how often symptoms occur (Padem and Saltoun, 2019). In asthma, complex etiology, influenced by multifactorial conditions can be identified as there is an interaction between patient-related factors (obesity, nutrition, infections, and allergic sensitization), genetic vulnerability, and environmental stimuli, including air pollution, pollens, mold, and tobacco smoke (Maddox and Schwartz, 2002; Sharma *et al.*, 2022). The variations in *ORMDL3*, *GSDMB*, *ZPBP2*, and *IKZF3* genes contribute to the pathogenesis of asthma (Mims, 2015). Airway obstruction, activation and infiltration of mast cells, and histopathological changes such as smooth muscle hypertrophy and hyperplasia, goblet cell hyperplasia and metaplasia, collagen deposition, subepithelial fibrosis, and submucosal gland hypertrophy are the key pathophysiological features of asthma (Hammad and Lambrecht, 2021; Mims, 2015). Remarkably, microRNAs have become important regulators that alter gene expression in several physiological and pathological processes, including inflammation, tissue remodeling, and immunological responses (Habib *et al.*, 2022). These molecules serve as both potential therapeutic agents and drivers of disease development, as their dysregulation can either regulate or worsen the chronic inflammatory nature of asthma.

MicroRNAs (miRNAs) are small, single-stranded RNAs that are produced by hairpin-shaped precursors (Wahid *et al.*, 2010). A miRNA strand is composed of approximately 19-25 nucleotides. miRNAs are classified as non-coding RNAs and can be found in both animals and plants. Mainly, they contribute to regulating genes or proteins in plants and animals. This regulation is carried out by miRNAs targeting mRNAs, which results in degradation or inhibition of protein translation. In humans, more than 2000 miRNAs have been discovered (Kai *et al.*, 2014). The biogenesis of miRNAs involves a sequential process. There are two main miRNA biogenesis pathways; the canonical pathway and the non-canonical pathway. In the canonical pathway, microRNAs are transcribed as structured primary miRNAs (pri-miRNAs), as they undergo processing into precursor miRNAs (pre-miRNAs) and mature miRNA duplexes by RNA polymerase II enzyme (Lucas *et al.*, 2015). A smaller group of miRNA genes linked to Alu repeats, which refers to the short repetitive DNA sequences that act as transposable elements, is transcribed by RNA polymerase III (Pol III). The produced pri-miRNA is cleaved, releasing a hairpin structure that is around 60–70 nt long and referred to as pre-miRNA (Wahid *et al.*, 2010). The RNase III enzyme Drosha and the protein DiGeorge syndrome critical region 8 (*DGCR8*) make up a large complex referred to as the 'Microprocessor complex'. ssRNA junction at the hairpin base is recognized by Drosha, while *DGCR8* connects with the ssRNA segment guiding Drosha to slice the pri-miRNA (Wahid *et al.*, 2010). Isomers are created once Drosha performs cleavage on RNA duplexes. After identifying the overhang of the hairpin by the RanGTP-dependent nuclear transport receptor exportin-5 (*EXP5*), it exports the pre-miRNA into the cytoplasm, for them to become mature miRNAs. The RNase III enzyme Dicer recognizes the 5′ phosphate, 3′ overhang, and loop structure of the pre-miRNA and binds to it in the cytoplasm. Dicer cleavage produces about a 22-nucleotide miRNA duplex, and it is integrated into an AGO family protein complex. One strand of the miRNA is primarily broken down, whereas the other strand stays attached to AGO protein complex (O'Brien *et al.*, 2018). The removal of the miRNA passenger strands is accomplished by the endonucleolytic enzyme activity of the AGO protein. The majority of miRNAs have middle mismatches, and certain AGO proteins don't have 'slicer' activity, which prevents the miRNA's passenger strand from being cut. Following loading, the miRNA directs the RNA-induced silencing complex (RISC) to the target mRNA, which is repressed, or degraded to silence it (Wahid *et al.*, 2010).

Non-canonical miRNA biogenesis may be broadly classified into routes that are Dicer-independent and those that are Drosha/*DGCR8*-independent. Pre-miRNAs generated by the route independent of Drosha and *DGCR8* resemble substrates of the Dicer enzyme. Without requiring Drosha cleavage, exportin 1 transports these developing RNAs straight to the cytoplasm. The m7G cap's ability to inhibit 5p strand loading into Argonaute is most likely the cause of the severe 3p strand bias (O'Brien *et al.*, 2018). Conversely,

Drosha processes endogenous short hairpin RNA (shRNA) transcripts to produce Dicer-independent miRNAs. These pre-miRNAs are too short to be Dicer-substrates, hence, *AGO2* is necessary for them to finish maturing in the cytoplasm. Consequently, this encourages the whole pre-miRNA to be loaded into AGO2 and AGO2-dependent 3p strand slicing. Their maturation is finished by cutting the 5p strand from 3′ to 5′ (O'Brien *et al.*, 2018). The sequence signatures generated by biogenesis processes ensure miRNAs' ability to fine-tune gene expression with strong precision and notable accuracy.

miRNAs are involved in a wide range of biological processes, including cell differentiation, proliferation, apoptosis, and immune response. Their dysregulation has been implicated in various pathological conditions, including cancer, cardiovascular diseases, neurodegenerative disorders, and inflammatory diseases (Ha *et al.*, 2011). miRNAs serve as core regulators of cellular function by modulating gene expression networks with high precision, thereby maintaining cellular homeostasis. In the context of asthma, miRNAs are emerging as key regulators in disease pathogenesis by regulating multiple pathways involved in airway inflammation, remodeling, cell proliferation, and immune responses (Sharma *et al.*, 2022). Moreover, miRNAs not only contribute to airway hyperresponsiveness but also offer potential as biomarkers for disease severity and therapeutic targets, highlighting their importance in asthma research.

Asthma was selected as the focus of this review due to the notable increase in post-COVID-19 respiratory complications, with asthma-like symptoms and disease exacerbations being increasingly observed among recovering patients. This emerging trend emphasizes the pressing need for more effective diagnostic and prognostic strategies, particularly in elderly populations where late-onset asthma exhibits complex pathophysiological features and diminished responsiveness to conventional treatments. MicroRNAs were chosen as the primary biomarkers of interest in this study due to their fundamental role in regulating gene expression and modulating key molecular pathways involved in asthma pathogenesis. These include mechanisms such as immune dysregulation, chronic inflammation, epithelial remodeling, and Th2-mediated responses. Investigating the fluctuations in these pathways driven by miRNA dysregulation offers valuable insight into the onset and progression of asthma. To ensure the relevance and reliability of this review, we focused on miRNAs that were recurrently reported in the literature to be significantly associated with asthma. Performing a systematic review on this topic is imperative to consolidate existing information on the diagnostic and prognostic value of miRNAs, specifically in elderly-onset asthma—a phenotype that remains underexplored despite its growing prevalence. This review holds significant implications for the healthcare sector and patient outcomes by potentially enabling early detection, guiding personalized therapeutic interventions, and enhancing disease management strategies for the aging populations.

Based on these guiding principles, this review aims to achieve the following objectives;

- To explore the relevance of microRNAs in the context of elderly-onset asthma and
- To identify and evaluate specific microRNAs associated with asthma pathogenesis and severity.

2. Methodology

This systematic review (PROSPERO registration number: CRD420251058950) was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) 2020 guidelines statement (Page *et al.*, 2021).

2.1 Search strategy

This systematic review was conducted to explore the role of miRNAs as diagnostic and prognostic biomarkers in elderly-onset asthma. Literature searches were carried out using PubMed database, while Google Scholar was only used for supplementary literature. Key terms such as 'asthma', 'microRNA ', 'biomarkers', and 'elderly-onset asthma' were used to retrieve studies from the databases. Additionally, references from relevant literature were reviewed to ensure comprehensive topic coverage. The following search string was used in PubMed.

("asthma"[Title/Abstract]) OR ("asthma"[MeSH Terms])) AND ("elderly"[Title/Abstract])) OR ("Aged"[MeSH Terms])) OR ("older adults"[All Fields])) OR ("elderly-onset"[All Fields])) AND ("microRNA"[Title/Abstract])) OR ("microRNAs"[MeSH Terms])) OR ("miRNA"[Title/Abstract])) AND ("biomarkers"[Title/Abstract])) OR ("diagnostic biomarkers"[All Fields])) OR ("prognostic biomarkers"[All fields])

2.2 Study Selection and Eligibility

The study selection process was carried out through manual screening. Three independent reviewers collected articles separately, and all identified articles were listed in Microsoft Excel spreadsheets to conduct study selection and duplicate removal manually. Duplicates were identified and removed. Titles and abstracts were manually screened against the inclusion and exclusion criteria by each reviewer independently. In cases where disagreements arose regarding the inclusion or interpretation of studies, discussions were held between authors to reach a consensus. This

approach aimed at ensuring the accuracy and reliability of the findings presented in this review.

2.2.1. Inclusion criteria

Full-text manuscripts published between 2008 and 2024 were reviewed for relevance. Studies were included if they involved patients diagnosed with asthma based on internationally recognized guidelines. To ensure relevance, studies were required to report at least one miRNA associated with asthma diagnosis and severity, or provide insights into miRNAs as diagnostic or prognostic biomarkers. Studies addressing elderly-onset asthma specifically or comparing this subset with early-onset asthma were prioritized.

2.2.2. Exclusion criteria

Studies were excluded if they met any of the following criteria: (1) the study was not published in English; (2) the research type was a case report, editorial, or conference abstract; (3) the publication focused solely on miRNAs related to asthma diagnosis in animal models without validation in human participants; (4) the study compared miRNA levels exclusively between asthma and other respiratory diseases, such as Chronic Obstructive Pulmonary Disease (COPD), without specific emphasis on asthma diagnosis or severity; (5) the study focused exclusively on childhood asthma; (6) the publication date was prior to the year 2008; (7) the publication lacked clear diagnostic criteria for asthma or failed to distinguish between early-onset and elderly-onset asthma.

The PRISMA flow diagram was used to present the study selection process, including record identification, duplication removal, and screening for eligibility based on inclusion and exclusion criteria (Figure 01).

A total of 208 publications were initially identified through the database searching and reference mining, including 133 from PubMed, 58 from Google Scholar, and 17 records through the backward citation tracking. 46 duplicates were removed before title and abstract screening. After the title and abstract screening of 162 records, 61 articles were excluded for the following reasons: non-English publication (n = 7), publication year (n = 21), no reference to miRNA (n = 11), non-diagnostic or prognostic approach (n = 14), and case reports/editorials, book chapters or conference abstracts (n = 8). While the remaining 101 articles were sought for retrieval, 5 articles were excluded for the following reasons: non-full-text articles (n = 4) and insufficient details for eligibility assessment (n = 1). During the eligibility assessment of 96 full-text articles, 53 articles were excluded for the following criteria, including animal studies without human validation (n = 31), studies comparing asthma with other diseases (n = 6), articles with unclear asthma diagnostic criteria or lacking distinction between early and elderly-onset asthma (n = 11), and studies focused on childhood asthma (n = 5). Finally, a total of 43 studies were included for the review.

2.3 Data extraction

Two key components were considered during the data extraction process. Selected data first component which includes the authors, year of publication, sample size, characteristics of participants, expressed specific miRNA types (Such as OncomiRs, tumor suppressor miRNAs, Pro-inflammatory miRNAs, Anti-inflammatory miRNAs, etc.), variations of miRNA expression between control and experimental groups, source of miRNAs, and detection methods. The second component differentiated the specific miRNAs according to their specific contribution as biomarkers for diagnosing elderly-onset asthma, specifying the severity or allergic/non-allergic asthma.

2.4 Data analysis

Data were analyzed qualitatively based on the information reported in the included publications. No quantitative analysis was conducted. Two reviewers independently assessed each of the studies for the risk of bias. The discrepancies between the reviewers were discussed and resolved by the involvement of a third reviewer.

3. Results and Discussion

MicroRNAs have emerged as important regulators of gene expression, playing significant roles in various biological processes, including immune response, inflammation, and tissue remodeling, key aspects of asthma pathology (Taka *et al.,* 2020). Recent studies have highlighted the involvement of specific miRNAs in modulating pathways that contribute to the inflammatory response, airway remodeling, and immune regulation in asthma. This study aims to provide a comprehensive overview of the roles of common miRNAs in asthma, exploring their regulatory functions in different cellular and molecular pathways, and discussing their potential as therapeutic targets or biomarkers for disease management. There are numerous miRNAs involved in the complex pathophysiology of asthma, each playing distinct roles. However, based on specific selection criteria, as their relevance to asthma pathogenesis and their potential as therapeutic targets, the following miRNAs have been discussed in detail below, focusing on their impact on inflammation, airway remodeling, and immune regulation.

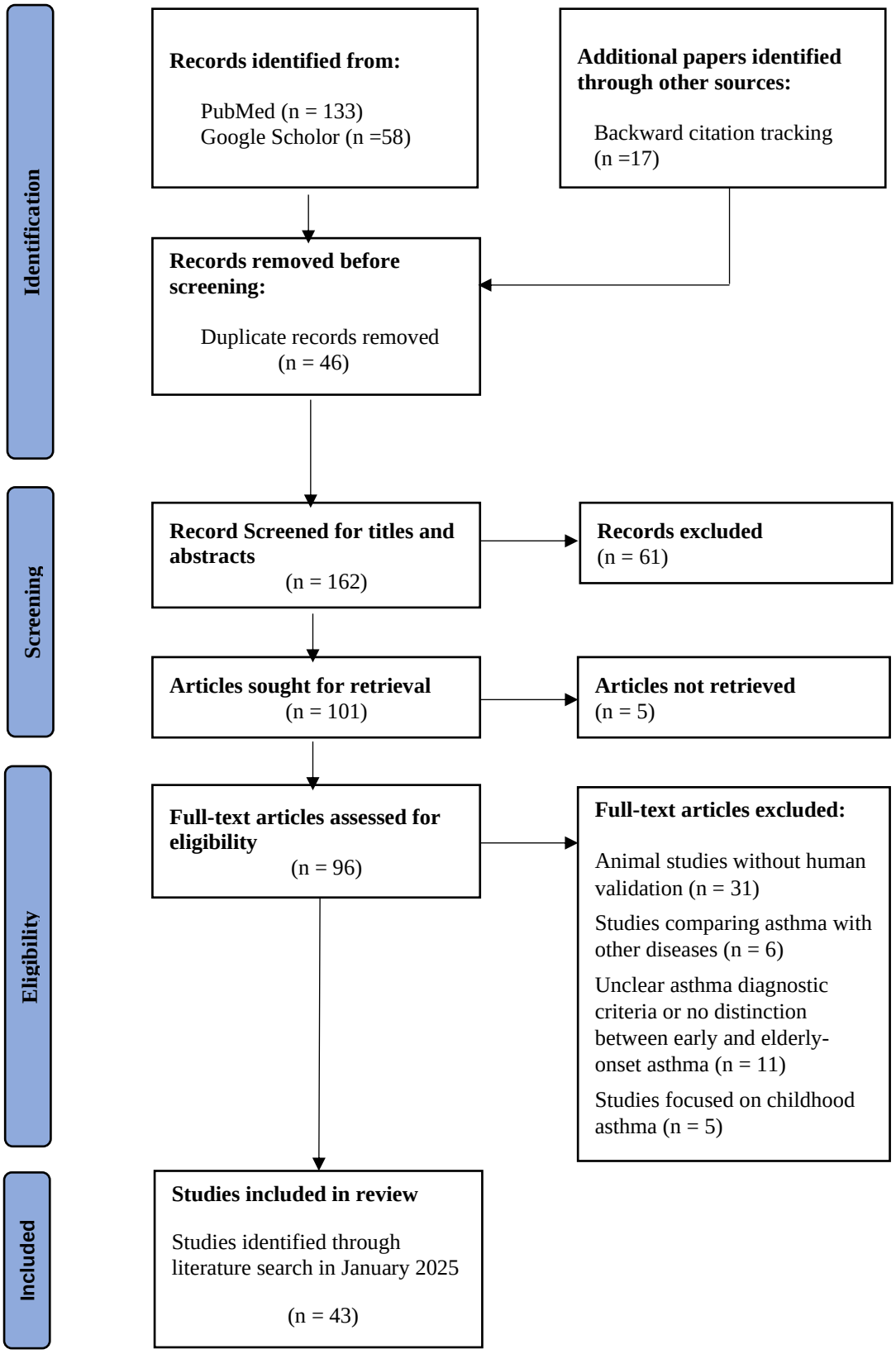

Figure 01: PRISMA flow diagram, representing study selection process through the manual screening

miR-21 is a regulatory RNA that is essential for many biological processes and illnesses, such as inflammation, cancer, cardiovascular disease, and development (Kumarswamy *et al.*, 2011). It is up-regulated in asthma, and it is involved in several inflammatory and immune pathways associated with asthma, primarily through its

promotion of a Th_2-dominant immune response, by up-regulating pro-inflammatory cytokines such as IL-4, IL-5, and IL-13, miR-21 amplifies the Th_2-driven immune response, which is central to the inflammation and allergic responses in asthma (Thomas *et al.,* 2009). This pathway is triggered by miR-21, leading to increased inflammation. Furthermore, miR-21 facilitates the differentiation of naive T cells into Th_2 cells, via post-transcriptional regulation, which further drives the production of cytokines that exacerbate allergic inflammation and contribute to airway hyper-reactivity (Kumarswamy *et al*, 2011). This differentiation pathway is activated by miR-21, increasing the overall inflammatory response in asthma. Additionally, miR-21 upregulates *STAT3*, a transcription factor that increases Th_2 responses while suppressing regulatory T cell (*Tregs*) functions, which are responsible for maintaining immune tolerance, thereby shifting the immune balance towards a Th_2-dominant response (Kumarswamy *et al.*, 2011). This pathway increases inflammation and reduces anti-inflammatory activity, thereby exacerbating the risk and severity of asthma. The overall effect of miR-21 upregulation is an increase in inflammatory processes, which elevates the probability of developing or worsening asthma. Finally, miR-21 downregulates *PDCD4*, a tumor suppressor that normally promotes apoptosis and inhibits pro-inflammatory cytokine production. By suppressing *PDCD4*, miR-21 enhances the survival of inflammatory cells and increases cytokine production, triggering an increase in inflammation in the asthmatic airway (Wu *et al.*, 2014).

miR-155 is a microRNA that has a significant role in modulating immune responses and is a key biomarker for comprehending molecular processes, particularly in the context of asthma. miR-155, which is transcribed from the B-cell integration cluster (*BIC*) gene and discovered on chromosome 21, promotes inflammation. The thymus and spleen are the primary sites of miR-155 expression (Hu *et al.,* 2022). This miRNA up-regulation in allergic asthma is largely triggered by exposure to allergens like pollen, and it follows a seasonal pattern, being most significant during periods of heightened allergen exposure, where it influences several key pathways. miR-155 targets and down-regulates *SOCS1* to promote Th2 cell differentiation. The *JAK/STAT* pathway, which transduces cytokine signals, is negatively regulated by *SOCS1*. As a result of this signaling, transcription factors that control immune responses, including Th2 differentiation, are activated. By reducing *SOCS1* levels, miR-155 enhances Th_2 responses, which are central to allergic inflammation in asthma. This pathway is triggered due to miR-155 activity, leading to a Th_2-dominant immune response typical in allergic asthma (Mahesh *et al.,* 2019). By promoting Th_2 differentiation, miR-155 indirectly suppresses the differentiation of Th_1 cells. This suppression is a consequence of the Th_2-dominant environment, which miR-155 helps establish. The Th_2 pathway is thus triggered, while the Th_1 pathway is suppressed, contributing to the characteristic allergic inflammation in asthma. miR-155 also impacts the function of regulatory T cells (*Tregs*) by targeting *FOXP3*, a transcription factor essential for the development and function of regulatory *Tregs*. By down-regulating *FOXP3*, miR-155 impairs *Treg* activity, reducing immune tolerance and leading to increased inflammation (Hu *et al.,* 2018). The pathway involving *Treg* function is suppressed due to miR-155, which exacerbates inflammatory responses in asthma. The up-regulation of miR-155 thus switches on inflammatory pathways, increasing the probability of developing asthma (Zhu *et al.,* 2021). Moreover, miR-155 targets *SHIP1*, a negative regulator of the *PI3K/AKT* pathway, which is important for cell survival and proliferation. By down-regulating *SHIP1*, miR-155 promotes the activation of the *PI3K/AKT* pathway, leading to enhanced survival and proliferation of inflammatory cells in the airways. The up-regulation of miR-155 thus switches on inflammatory pathways, increasing the probability of developing asthma. This pathway is triggered, contributing to the persistence of inflammation in the asthma-affected airways (Zhu *et al.,* 2021).

miR-140-3p has a significant impact on bronchial smooth muscle cells by controlling the expression of various proteins involved in asthma pathology. When miR-140-3p is down-regulated, it leads to the up-regulation of CD38 protein, which is involved in calcium signaling by converting NAD^+ into cyclic ADP-ribose that promotes calcium release from the endoplasmic reticulum. This enhanced calcium signaling increases muscle contractility, contributing to bronchoconstriction, a hallmark of asthma (Chiba *et al.,* 2020). Here, the pathway triggered by CD38 activation is escalated due to the low levels of miR-140-3p. In airway smooth muscle cells (ASMCs), miR-140-3p is up-regulated, leading to the downregulation of *HMGB1*, a protein involved in inflammation. By targeting and reducing *HMGB1* expression, miR-140-3p inhibits the *JAK2/STAT3* signaling pathway. This inhibition results in decreased airway inflammation and remodeling, which are key aspects of asthma pathogenesis (Meng *et al.*, 2022). Since miR-140-3p effectively downregulates *HMGB1*, the *JAK2/STAT3* pathway is not triggered; therefore, this mitigates the inflammatory response and showcases a protective role, contributing to the reduction of asthma risk and severity.

miR-223-3p has a significant role in regulating inflammation and airway remodeling, particularly in the context of asthma. By targeting components of the NF-κB signaling pathway, which is central to the regulation of inflammation, miR-223-3p can inhibit the expression of NF-κB-dependent inflammatory genes. This down-regulation reduces inflammation, suggesting that miR-

223-3p is generally up-regulated as a protective mechanism to suppress excessive inflammatory responses that could otherwise contribute to asthma pathogenesis (Martinez *et al.*, 2023). Furthermore, miR-223-3p targets genes involved in cell cycle progression, such as cyclins and cyclin-dependent kinases (CDKs). By down-regulating these genes, miR-223-3p reduces the proliferation of airway smooth muscle cells, a process that contributes to airway remodeling and thickening, both hallmarks of chronic asthma (Rofell *et al*, 2020). In addition, miR-223-3p can target and downregulate proteins involved in cell migration, such as matrix metalloproteinases (MMPs) and integrins, thereby inhibiting the migration of inflammatory cells and fibroblasts to sites of airway injury. This action reduces tissue damage and remodeling, further protecting against the progression of asthma (Rofell *et al.*, 2020). Therefore, when miR-223-3p is up-regulated, it can potentially reduce the severity of asthma by mitigating inflammation and airway remodeling. **miR-200** is involved in maintaining epithelial integrity and regulating inflammation and extracellular matrix (ECM) homeostasis, all of which are key factors in asthma (Johansson *et al*., 2021). The extracellular matrix (ECM) acts as a significant regulator of cellular and tissue functions in the body since organ development, wound healing, and homeostasis of normal body organs can depend on tightly regulated ECM homeostasis. As well as having persistent dysregulation of ECM homeostasis causes fetal disorders (Cox and Erler, 2011). Zinc finger E-box binding homeobox 1 (*ZEB1*) (also referred to as *AREB6*, *TCF8*, *δEF-1*, *BZP*, and *ZFHEP*) and Zinc finger E-box binding homeobox 2 (*ZEB2*) (also referred to as *KIA0569*, *SIPS1*, *SMADIP-1*, *ZEB-2*, and *Zfhx1b*) belong to the family of *ZEB* transcription factors (Wang *et al*., 2021; Sánchez-Tilló *et al.*, 2011). *ZEB1* and *ZEB2* act as both transcriptional repressors and activators based on the targeted tissue or gene (Sánchez-Tilló *et al.*, 2011). By down-regulating *ZEB1* and *ZEB2*, miR-200 prevents the epithelial-to-mesenchymal transition (EMT), a process that leads to the loss of epithelial characteristics and the gain of mesenchymal properties. This pathway is effectively switched off by miR-200, preventing the transition of epithelial cells to mesenchymal cells and thus preserving the epithelial barrier, which is vital in protecting the airways from environmental triggers (Johansson *et al.*, 2021). Additionally, miR-200 downregulates pro-inflammatory cytokines such as IL-6 and TNF-α, both of which are central to chronic airway inflammation in asthma. By modulating these cytokines, miR-200 reduces the inflammatory response, potentially lessening the severity of asthma symptoms (Duan *et al.*, 2020). Furthermore, miR-200 helps maintain ECM homeostasis by regulating the balance between matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs), preventing pathological remodeling that can lead to airway stiffness and obstruction. Notably, in moderate to severe asthmatic patients, miR-200b and miR-200c are significantly reduced, suggesting that the downregulation of these miRNAs may contribute to increased inflammation, disrupted epithelial function, and pathological airway remodeling, all of which enhance asthma severity (Usman *et al.*, 2021).

Th_2-mediated inflammatory response can be identified as an essential component of the pathophysiology of allergic asthma. A variety of pro-inflammatory cytokines are secreted by Th_2-predominant T-lymphocytes in order to regulate allergic diseases. IL-4, IL-5, and IL-13 are the canonical cytokines associated with Th_2-mediated responses. Increased expression of **miR-1248** can be identified in allergic asthmatic subjects. Generally, miR-1248 binds to the 3'UTR (3' untranslated region) of IL-5 mRNA, increasing the expression of IL-5 via post-transcriptional regulation of the 3'UTR of the IL-5 mRNA. IL-5 can act as a strong signaling factor for eosinophil survival, growth, differentiation, and recruitment (Panganiban *et al.*, 2012). Although miRNAs usually repress the expression of genes by acting as a post-transcriptional regulator of their mRNAs (Catalanotto *et al.*, 2016), the physical interaction between miR-1248 3'UTR of the IL-5 transcript may relieve repression to increase the IL-5 expression, which means miR-1248 can act as a positive regulator to promote IL-5 expression (Panganiban *et al.*, 2012). As a result of enhancing the IL-5 expression, eosinophils are recruited, activated, and survive by miR-1248 in the airway. Accumulation of eosinophils occurs in the airways, while they are prone to release inflammatory mediators and cytokines in eosinophilic asthmatic conditions. Those inflammatory mediators and cytokines are capable of causing severe airway inflammation, tissue damage, airway hyperresponsiveness, mucus hypersecretion, and airway remodeling (Hussain *et al.*, 2024; McBrien and Menzies-Gow, 2017).

While asthma is closely associated with the Th_1/Th_2 imbalance, deregulated **miR-145** can regulate the *RUNX3* gene by directly targeting the 3'-UTR of *RUNX3* and changing the Th_1/Th_2 balance in asthma. Various transcription factors such as *GATA-3*, *STAT3*, *STAT5a*, *STAT6*, *c-Maf*, *notch*, *SOCS-3* and *SOC5-5* involve in regulating the Th_1/Th_2 balance. While Th_1 cells, which produce IFN-γ and IL-12, are able to antagonize the Th_2-induced immune responses and help limit the progression of asthma, IL-4, IL-5, and IL-13 are primarily secreted by Th_2 cells. IL4, IL-5, and IL-13 are responsible for elevating the serum IgE levels and attracting eosinophils in order to increase airway reactivity (Qiu *et al.*, 2017). A higher number of miR-145 and a lower level of expression of *RUNX3* can be identified in $CD4^+$ cells in asthmatics (Fan *et al.*, 2016). Although *RUNX3* encourages Th_1 responses and suppresses Th_2 responses, miR-145 can shift immune responses towards the Th_2 phenotype since miR-145

downregulates the *RUNX3* gene by targeting the 3'-UTR of *RUNX3* (Qiu *et al.,* 2017). That indicates the negative correlation between miR-145 and *RUNX3* in asthma (Fan *et al.,* 2016). Therefore, the level of IFN-γ^+ $CD4^+$ T cells is decreased, and IL-4^+ $CD4^+$ T cells are decreased. Furthermore, decreasing the IL-2 and IFN-γ and enhancing the level of IL-4 and IL-10 can be identified in asthmatic conditions. These fluctuations indicate Th_1 hyperactivity and Th_2 deficiency. Ultimately, Th_1/Th_2 imbalance is central to the allergic inflammation seen in asthma. Instead, the interaction between miR-145 and miR-371, miR-138, miR-544, and miR-214 can be identified, meaning that the knockdown of only one candidate miRNA leads to an enhancement of another miRNA's level (Qiu *et al.,* 2017).

A significant increase of **miR-221** can be identified in the bronchial epithelial cells (BEAS2B cells) of severe asthmatic patients, while the reduction of *SIRT1* mRNA in the bronchial epithelial cells of asthma patients is the ultimate target of miR-221 (Zhang *et al*., 2018). *SIRT1* miRNAs are responsible for controlling cell growth, cell differentiation, aging, energy metabolism, and inflammatory responses (Taka *et al*., 2020). The transfection of *BEAS2B* cells with miR-221 has occurred; the process that tends to upregulate miR-221. While the miR-221 binds with *SIRT1*'s 3'UTR, this process gives the ability to miR-221 to target directly on *SIRT1* in the *BEAS2B* cells. This upregulation of miR-221 leads to preventing *SIRT1* from being expressed at the miRNA and protein level in the bronchial epithelial cells. Furthermore, inhibition of cell proliferation and induction of apoptosis of miR-221 mimic-transfected bronchial epithelial cells occur due to the processes of miR-221 up-regulation and *SIRT1* knockdown (Zhang *et al*., 2018). As a conclusion, when miR-221 is up-regulated, it can potentially damage the *BEAS2B* cells by targeting *SIRT1* (Taka *et al*., 2020). Type 2 low and high asthma can be identified as another classification of asthma, while type 2-high asthma is characterized by airway eosinophilic inflammation.

A significant correlation between **miR-221-3p** expression and airway eosinophilic inflammation, and the biomarker for type 2 status, including blood eosinophil count and epithelial gene signature (*CLCA1*, *SERPINB2*, *POSTN*) of type-2 asthmatic conditions, has been identified. Since miR-221-3P is recognized as an epithelial miRNA, miR-221-3P can differentiate the airway epithelial cells, and it also contributes to promoting airway eosinophilic inflammation through the up-regulation of inflammatory cytokines such as chemokine (C-C motif), ligand (CCL) 24 (eotaxin-2), and CCL26 expressed in the airway epithelial cells. Those inflammatory cytokines recruit the eosinophils into the airway (Zhang *et al.,* 2018). The expressions of CCL24 (eotaxin), CCL26 (eotaxin-3), and POSTN are also increased through the p38 *MAPK* pathway (Taka *et al.,* 2020). The control of the proliferation of airway smooth muscle cells is also regulated by the miR-221-3P in severe asthmatic conditions. Furthermore, miR-221-3P has been identified as a miRNA that upregulates the activation of mast cells, IL-4 expression in mast cells, and stimulation of the degranulation, migration, and adherence of mast cells. This also suggests that miR-221-3P may promote airway eosinophilic inflammation in asthma. The reduction of epithelial, sputum, and plasma miR-221-3P expression has been identified in asthma, while epithelial and sputum miR-221-3P are more belong to airway eosinophilic inflammation than plasma miR-221-3P. Moreover, sputum miR-221-3P correlates with airway eosinophilic inflammation when sputum miR-221-3P is compared with epithelial miR-221-3P. *In vitro*, suppression of miR-221-3P expression has been shown to inhibit both basal and IL-13-induced CCL24, CCL26, and *POSTN* in the airway epithelial cells. Additionally, miR-221-3p has been found to enhance the expression of anti-inflammatory cytokine ligand 17 (CXCL17) (Zhang *et al.,* 2018).

miR-16 is known to regulate the expression of pro-inflammatory cytokines such as TNF-α and IL-6. By targeting the mRNA of these cytokines, miR-16 helps to suppress their expression. When miR-16 levels are reduced, this regulatory control is lost, leading to the up-regulation of TNF-α, IL-6, and other inflammatory mediators (Martinez *et al.,* 2023). The increase in pro-inflammatory cytokines due to reduced miR-16 levels increases inflammation and structural changes in the airway, which contribute to airway obstruction and reduced lung function, as reflected by decreased FEV1 (Forced Expiratory Volume in 1 second) and FVC (Forced Vital Capacity) (Yu *et al.,* 2019). This up-regulation of inflammatory pathways contributes to the worsening of asthma symptoms. miR-16 also influences airway remodeling by targeting genes involved in extracellular matrix ECM production and tissue fibrosis, such as those encoding matrix metalloproteinases (MMPs) and collagen (Martinez *et al.,* 2023). When miR-16 is down-regulated, there is an increase in ECM production and fibrosis, leading to structural changes in the airways. Enhanced airway remodeling due to lower miR-16 levels leads to thickening of the airway walls and increased airway resistance, which further contributes to asthma severity and reduces lung function (Yao *et al.,* 2020).

Table 01: Role of the miRNA towards the elderly-onset asthmatic condition

miRNA name	**Target gene/ protein**	**Pathway/function**	**Regulation of miRNA (Up / Down)**	**Reference**
miR-21	*STAT3*	Promote Th_2 immune responses.	Up-regulated	(Kumarswamy *et al.*, 2011; Thomas *et al.*, 2009)
	PDCD4	Promote inflammatory cell survival and cytokine production.	Up-regulated	(Wu *et al.*, 2014)
miR-155	*SOCS1*	Promote Th_2 differentiation via the *JAK/STAT* pathway.	Up-regulated	(Mahesh *et al.*, 2019)
	FOXP3	Impair regulatory T cell activity.	Up-regulated	(Hu *et al.*, 2018)
	SHIP1	Enhance *PI3K/AKT* signaling by increasing cell survival and proliferation.	Up-regulated	(Zhu *et al.*, 2021)
miR-140-3p	*HMGB1*	Decrease airway inflammation and remodeling.	Up-regulated	(Meng *et al.*, 2022)
	CD38	Enhance calcium signaling and contribute to bronchoconstriction.	Down-regulated	(Chiba *et al.*, 2020)
miR-223-3p	NF-κB-dependent inflammatory genes	Reduce inflammation by suppressing excessive inflammatory responses.	Up-regulated	(Martinez *et al*., 2023)
	Cyclins and Cyclin-dependent kinases	Reduce airway smooth muscle proliferation.	Up-regulated	(Rofell *et al*., 2020)
	Matrix metalloproteinases (MMPs) and integrins	Inhibit cell migration and tissue remodeling.	Up-regulated	(Rofell *et al*., 2020)
miR-200	*ZEB1*and *ZEB2*	Prevent the epithelial-to-mesenchymal transition (EMT).	Up-regulated	(Johansson *et al.*, 2021; Sánchez-Tilló *et al.*, 2011)
	IL-6 and TNF-α	Reduce the inflammatory responses.	Up-regulated	(Duan *et al*., 2020)

miR-1248	IL-5	Eosinophil recruitment and activation.	Up-regulated	(Panganiban *et al.*, 2012; Hussain *et al.*, 2024; McBrien and Menzies-Gow, 2017)
miR-145	*RUNX3*	Regulate the Th_1/Th_2 balance.	Down-regulated	(Qiu *et al.*, 2017)
miR-221	SIRT1	Cell proliferation, apoptosis, and inflammation regulation	Up-regulated	(Zhang *et al*., 2018; Taka *et al*., 2020)
miR-221-3p	CCL24, CCL26, and *POSTN*	Promote airway eosinophilic inflammation.	Up-regulated	(Zhang *et al*., 2018; Taka *et al*., 2020)
	CXCL17	Anti-inflammatory cytokine regulation.	Up-regulated	(Zhang *et al*., 2018)
miR-16	TNF-α and IL-6	Increase inflammation and contribute to airway obstruction and reduced lung function.	Down-regulated	(Martinez *et al.*, 2023; Yu *et al.*, 2019)
	Matrix metalloproteinases (MMPs) and Collagen	Increase airway remodeling by thickening airway walls and increasing airway resistance.	Down-regulated	(Martinez *et al.*, 2023; Yao *et al.*, 2020)

4. Conclusion

The role of miRNAs is emerging as an important factor in the pathogenesis and management of elderly-onset asthma. Their dysregulated expression has established miRNAs as effective components, serving as diagnostic biomarkers to identify disease presence and differentiate between phenotypes, as well as prognostic markers to predict disease progression and response to therapy. The regulatory influence of miRNAs on inflammatory, immune, and tissue remodeling pathways offers compelling evidence for their significance as biomarkers and therapeutic targets. miRNAs can effectively manage elderly-onset asthma due to their ability to modulate Th2-driven inflammation, epithelial-to-mesenchymal transition, and immune homeostasis, addressing significant clinical challenges. Moreover, their stability in biological samples and their disease-specific expression profiles enhance their feasibility as non-invasive diagnostic and prognostic biomarkers.

Despite their potential, translating miRNAs into clinical practice faces challenges, including variability in miRNA expression among sample types, lack of standardization in methodologies, and limited studies focused on elderly-onset asthma. Their clinical applicability is further complicated by environmental variables and population-specific variations in miRNA expression. However, the stability of miRNAs in biological samples and their non-invasive detection methods enhance their viability as biomarkers.

Future research should prioritize addressing these limitations with the development of miRNA-based therapeutic approaches and explore the integration of miRNA profiling into clinical practice. Understanding the interplay between miRNA dysregulation and environmental factors in elderly-onset asthma will further enhance precision medicine approaches. By leveraging the therapeutic and diagnostic potential of miRNAs, we can advance personalized care for asthma patients, improving outcomes and quality of life, particularly in the older populations.

Conflict of interest

The authors declare that they have no conflicts of interest related to this article.

References

American Lung Association (2024). *Asthma Trends and Burden | American Lung Association*. [online] www.lung.org. Available at: https://www.lung.org/research/trends-in-lung-

disease/asthma-trends-brief/trends-and-burden (Accessed 30 Nov. 2024).

Catalanotto, C., Cogoni, C. and Zardo, G. (2016). MicroRNA in Control of Gene Expression: An Overview of Nuclear Functions. *International Journal of Molecular Sciences*, [online] 17(10), p.1712. doi: https://doi.org/10.3390/ijms17101712. (Accessed 29 Nov.2024).

Chapman, D.G. and Irvin, C.G. (2015). Mechanisms of airway hyper-responsiveness in asthma: the past, present and yet to come. *Clinical & Experimental Allergy*, [online] 45(4), pp.706–719. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC4386586/ (Accessed 30 Nov. 2024).

Chiba, Y., Ando, Y., Kato, Y., Hanazaki, M. and Sakai, H. (2021). Down-regulation of miR-140-3p is a cause of the interleukin-13-induced up-regulation of RhoA protein in bronchial smooth muscle cells. *Small GTPases*, [online] pp.1–6. Available at: https://pubmed.ncbi.nlm.nih.gov/33427568/ (Accessed 9 Oct. 2024).

Cox, T.R. and Erler, J.T. (2011). Remodeling and homeostasis of the extracellular matrix: implications for fibrotic diseases and cancer. *Disease Models & Mechanisms*, 4(2), pp.165–178. doi: https://doi.org/10.1242/dmm.004077. (Accessed 30 Nov. 2024).

Duan, X.-J., Zhang, X., Li, L.-R., Zhang, J.-Y. and Chen, Y.-P. (2020). MiR-200a and miR-200b restrain inflammation by targeting ORMDL3 to regulate the ERK/MMP-9 pathway in asthma. Experimental Lung Research, [online] 46(9), pp.321–331. Available at: https://pubmed.ncbi.nlm.nih.gov/32820688/ (Accessed 1 Dec. 2024).

Fan, L., Wang, X., Fan, L., Chen, Q., Zhang, H., Hui, P., Xu, A., Wang, H. and Yu, Y. (2016). MicroRNA-145 influences the balance of Th1/Th2 via regulating RUNX3 in asthma patients. *Experimental Lung Research*, 42(8-10), pp.417–424. doi: https://doi.org/10.1080/01902148.2016.1256452. (Accessed 9 Oct. 2024).

Ha, T.-Y. (2011). MicroRNAs in Human Diseases: From Cancer to Cardiovascular Disease. *Immune Network*, [online] 11(3), p.135. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3153666/ [Accessed 24 Jan. 2025].

Habib, N., Pasha, M.A. and Tang, D.D. (2022). Current Understanding of Asthma Pathogenesis and Biomarkers. *Cells*, [online] 11(17), p.2764. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9454904/ (Accessed 30 Nov. 2024).

Hammad, H. and Lambrecht, B.N. (2021). The basic immunology of asthma. *Cell*, [online] 184(6), pp.1469–1485. Available at: https://pubmed.ncbi.nlm.nih.gov/33711259/ (Accessed 30 Nov. 2024).

Hu, J., Huang, S., Liu, X., Zhang, Y., Wei, S. and Hu, X. (2022). miR-155: An Important Role in Inflammation Response. *Journal of Immunology Research*, [online] 2022, p.7437281. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9007653/ (Accessed 21 Nov. 2024).

Hussain, M. and Liu, G. (2024). Eosinophilic Asthma: Pathophysiology and Therapeutic Horizons. *Cells*, [online] 13(5), p.384. doi: https://doi.org/10.3390/cells13050384. (Accessed 30 Nov. 2024).

Hussain, S., Bokhari, H., Fan, X., Malik, S.I. and Fatima, A. (2024). MicroRNAs modulation in lung cancer: exploring dual mechanisms and clinical prospects. BIOCELL, [online] 48(3), pp.403–413. Available at: https://www.researchgate.net/publication/379019577_MicroRNAs_modulation_in_lung_cancer_exploring_dual_mechanisms_and_clinical_prospects (Accessed 01 Dec. 2024)

Johansson, K., Woodruff, P.G. and Ansel, K.M. (2021). Regulation of airway immunity by epithelial miRNAs. Immunological Reviews, [online] 304(1), pp.141–153. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC9135676/ (Accessed 1 Dec. 2024).

Kai, W., Qian, X. and WU Zu Qun (2014). MicroRNAs and Asthma Regulation. *Iranian Journal of Allergy, Asthma and Immunology*, [online] pp.120–125. Available at: https://ijaai.tums.ac.ir/index.php/ijaai/article/view/403 (Accessed 30 Nov. 2024).

Kumarswamy, R., Volkmann, I. and Thum, T. (2011). Regulation and function of miRNA-21 in health and disease. *RNA Biology*, [online] 8(5), pp.706–713. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256347/ (Accessed 14 Nov. 2024).

Lu, T.X., Munitz, A. and Rothenberg, M.E. (2009). MicroRNA-21 Is Up-Regulated in Allergic Airway Inflammation and Regulates IL-12p35 Expression. *The Journal of Immunology*, [online] 182(8), pp.4994–5002. Available at: https://pubmed.ncbi.nlm.nih.gov/19342679/ (Accessed 29 Nov. 2024).

Lucas, K.J., Zhao, B., Liu, S. and Raikhel, A.S. (2015). Regulation of physiological processes by microRNAs in insects. *Current Opinion in Insect Science*, [online] 11, pp.1–7. Available at:

https://doi.org/10.1016/j.cois.2015.06.004 (Accessed 22 Nov. 2024).

Maddox, L. and Schwartz, D.A. (2002). The Pathophysiology of Asthma. *Annual Review of Medicine*, [online] 53(1), pp.477–498. Available at: https://pubmed.ncbi.nlm.nih.gov/11818486/ (Accessed 30 Nov. 2024).

Mahesh, G. and Biswas, R. (2019). MicroRNA-155: A Master Regulator of Inflammation. *Journal of Interferon & Cytokine Research*, [online] 39(6), pp.321–330. Available at: https://pubmed.ncbi.nlm.nih.gov/30998423/ (Accessed 30 Nov. 2024).

Meng, J., Zou, Y., Hou, L., He, L., Liu, Y., Cao, M., Wang, C. and Du, J. (2022). MiR-140-3p Ameliorates The Inflammatory Response of Airway Smooth Muscle Cells by Targeting HMGB1 to Regulate The JAK2/STAT3 Signaling Pathway. *DOAJ (DOAJ: Directory of Open Access Journals)*, [online] 24(11), pp.673–680. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC9663964/ (Accessed 30 Nov. 2024).

Mims, J.W. (2015). Asthma: Definitions and Pathophysiology. *International Forum of Allergy & Rhinology*, [online] 5(S1), pp.S2–S6. Available at: https://pubmed.ncbi.nlm.nih.gov/26335832/ (Accessed 30 Nov. 2024).

McBrien, C.N. and Menzies-Gow, A. (2017). The Biology of Eosinophils and Their Role in Asthma. *Frontiers in Medicine*, 4(93). doi: https://doi.org/10.3389/fmed.2017.00093. (Accessed 30 Nov. 2024).

O'Brien, J., Hayder, H., Zayed, Y. and Peng, C. (2018). Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. *Frontiers in Endocrinology*, [online] 9(402). Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6085463/ (Accessed 30 Nov. 2024).

Padem, N. and Saltoun, C. (2019). Classification of asthma. *Allergy and Asthma Proceedings*, [online] 40(6), pp.385–388. Available at: https://pubmed.ncbi.nlm.nih.gov/31690376/ (Accessed 30 Nov. 2024).

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S. and McGuinness, L.A. (2021). The PRISMA 2020 statement: an Updated Guideline for Reporting Systematic Reviews. British Medical Journal, [online] 372(71). Doi: https://doi.org/10.1136/bmj.n71. (Accessed 23 May 2025).

Panganiban, R.P.L., Pinkerton, M.H., Maru, S.Y., Jefferson, S.J., Roff, A.N. and Ishmael, F.T. (2012). Differential microRNA expression in asthma and the role of miR-1248 in regulation of IL-5. *American journal of clinical and experimental immunology*, [online] 1(2), pp.154–65. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3714196/. (Accessed 30 Sep. 2024).

Qiu (2017). miR-371, miR-138, miR-544, miR-145, and miR-214 could modulate Th1/Th2 balance in asthma through the combinatorial regulation of Runx3. *American journal of translational research*, [online] 9(7). Available at: https://pubmed.ncbi.nlm.nih.gov/28804539/ (Accessed 24 Aug. 2024).

Roffel, M.P., Brandsma, C.-A., Den, V., Boudewijn, I., Bracke, K., Maes, T. and Heijink, I. (2019). Unraveling the role of miR-223-3p in the regulation of airway inflammation in asthma and COPD. 03.02 - Airway cell biology and immunopathology, [online] pp.OP07–OP07. Available at: https://doi.org/10.1183/23120541.lungscienceconference-2019.OP07 (Accessed 1 Dec. 2024).

Sinyor, B. and Concepcion Perez, L. (2023). *Pathophysiology of asthma*. [online] PubMed. Available at: https://pubmed.ncbi.nlm.nih.gov/31869060/ (Accessed 30 Nov. 2024).

Sharma, R., Tiwari, A. and McGeachie, M.J. (2022). Recent miRNA Research in Asthma. Current Allergy and Asthma Reports, [online] 22(12), pp.231–258. doi: https://doi.org/10.1007/s11882-022-01050-1. (Accessed by 30 Nov. 2024).

Seo, W. and Taniuchi, I. (2020). The Roles of RUNX Family Proteins in Development of Immune Cells. *Molecules and cells*, [online] 43(2), pp.107–113. doi: https://doi.org/10.14348/molcells.2019.0291. (Accessed 20 Aug. 2024).

Sánchez-Tilló, E., Siles, L., Barrios, O. de, Cuatrecasas, M., Vaquero, E.C., Castells, A. and Postigo, A. (2011). Expanding roles of ZEB factors in tumorigenesis and tumor progression. *American Journal of Cancer Research*, [online] 1(7), p.897. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC3196287/ (Accessed 1 Dec. 2024).

Taka, S., Tzani-Tzanopoulou, P., Wanstall, H. and Papadopoulos, N.G. (2020). MicroRNAs in Asthma and Respiratory Infections: Identifying Common Pathways. *Allergy, Asthma & Immunology Research*, [online] 12(1), p.4. Available at: https://pubmed.ncbi.nlm.nih.gov/31743961/ (Accessed 7 Nov. 2024).

Trivedi, M. and Denton, E. (2019). Asthma in Children and Adults—What Are the Differences and What

Can They Tell Us about Asthma? *Frontiers in Pediatrics*, [online] 7(256). Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6603154/ (Accessed 30 Nov. 2024).

Usman, K., Hsieh, A. and Hackett, T.-L. (2021). The Role of miRNAs in Extracellular Matrix Repair and Chronic Fibrotic Lung Diseases. Cells, [online] 10(7), p.1706. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC8304879/ (Accessed 1 Dec. 2024).

Wahid, F., Shehzad, A., Khan, T. and Kim, Y.Y. (2010). MicroRNAs: Synthesis, mechanism, function, and recent clinical trials. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*, [online] 1803(11), pp.1231–1243. Available at: https://www.sciencedirect.com/science/article/pii/S0167488910001837. (Accessed 30 Nov. 2024).

World Health Organization (2024). *Asthma*. [online] World Health Organisation. Available at: https://www.who.int/news-room/fact-sheets/detail/asthma. (Accessed 30 Nov. 2024).

Wu, X.-B., Wang, M.-Y., Zhu, H.-Y., Tang, S.-Q., You, Y.-D. and Xie, Y.-Q. (2014). Overexpression of microRNA-21 and microRNA-126 in the patients of bronchial asthma. *International Journal of Clinical and Experimental Medicine*, [online] 7(5), p.1307. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC4073748/ (Accessed 30 Nov. 2024).

Wang, J., Farkas, C., Benyoucef, A., Carmichael, C., Haigh, K., Wong, N., Huylebroeck, D., Stemmler, M.P., Brabletz, S., Brabletz, T., Nefzger, C.M., Goossens, S., Berx, G., Polo, J.M. and Haigh, J.J. (2021). Interplay between the EMT transcription factors ZEB1 and ZEB2 regulates hematopoietic stem and progenitor cell differentiation and hematopoietic lineage fidelity. *PLOS Biology*, 19(9), p.e3001394. doi: https://doi.org/10.1371/journal.pbio.3001394. (Accessed 01 Dec. 2024).

Yao, Q., Xing, Y., Wang, Z., Liang, J., Lin, Q., Huang, M., Chen, Y., Lin, B., Xu, X. and Chen, W. (2020). MiR-16-5p suppresses myofibroblast activation in systemic sclerosis by inhibiting NOTCH signaling. Aging, [online] 13(2), pp.2640–2654. Available at: https://www.aging-us.com/article/202308 (Accessed 1 Dec. 2024).

Yu, Y., Zhang, J., Wang, J. and Sun, B. (2019). MicroRNAs: The novel mediators for nutrient-modulating biological functions. Trends in Food Science & Technology, [online] 114, pp.167–175. Available at: https://www.sciencedirect.com/science/article/pii/S0924224421003502 (Accessed 1 Dec. 2024).

Zapata-Martínez, L., Águila, S., Lozano, M.L., Constantino Martínez and Rocío González-Conejero (2023). microRNAs as biomarkers of risk of major adverse cardiovascular events in atrial fibrillation. Frontiers in cardiovascular medicine, [online] 10. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC9988920/ (Accessed 10 Jul. 2024).

Zhang, H., Sun, Y., Rong, W., Fan, L., Cai, Y., Qu, Q., Gao, Y. and Zhao, H. (2018). miR-221 participates in the airway epithelial cells injury in asthma via targeting SIRT1. *Experimental Lung Research*, [online] 44(6), pp.272–279. doi: https://doi.org/10.1080/01902148.2018.1533051. (Accessed 20 Aug. 2024).

Zhang, K., Liang, Y., Feng, Y., Wu, W., Zhang, H., He, J., Hu, Q., Zhao, J., Xu, Y., Liu, Z. and Zhen, G. (2018). Decreased epithelial and sputum miR-221-3p associates with airway eosinophilic inflammation and CXCL17 expression in asthma. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, 315(2), pp.L253–L264. doi: https://doi.org/10.1152/ajplung.00567.2017. (Accessed 01 Dec. 2024).

Zhu, Y., Ye, F., Fu, Y., Zhu, X., Wang, Z., Wu, S., Guo, L., Zhang, Q., Mou, X. and Liu, Y. (2021). MicroRNA-155-5p regulates the Th1/Th2 cytokines expression and the apoptosis of group 2 innate lymphoid cells via targeting TP53INP1 in allergic rhinitis. International Immunopharmacology, [online] 101, p.108317. Available at: https://www.sciencedirect.com/science/article/abs/pii/S156757692100953X (Accessed 30 Nov. 2024).