Review

The Role of YKL-40 and Dipeptidyl Peptidase-4 in Asthma: A Narrative Review

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Abstract

Background: Asthma is a complex and heterogeneous disease characterized by chronic inflammation, airway remodeling, and variable clinical manifestations. Despite advances in asthma management, there is a need for novel biomarkers to improve diagnosis, predict disease severity, and monitor treatment responses.

Objective: To review the current evidence on the role of YKL-40 and dipeptidyl peptidase-4 (DPP-4) in asthma, including their potential as biomarkers for disease severity, treatment responses, and genetic predisposition.

Methods: A comprehensive literature search was conducted to identify studies investigating the relationship between YKL-40, DPP-4, and asthma. Relevant articles were selected based on their relevance to the topic and study design.

Results: The review highlights the association of YKL-40 with airway remodeling, inflammation, and disease severity in asthma. Elevated YKL-40 levels have been linked to poor prognosis, increased exacerbations, and reduced lung function. Genetic variations in the CHI3L1 gene, which encodes YKL-40, have been associated with asthma susceptibility and severity. DPP-4 has been implicated in the regulation of inflammation and immune responses in asthma, with studies suggesting its potential role in modulating airway inflammation and remodeling.

Conclusion: YKL-40 and DPP-4 are promising biomarkers for asthma, with potential applications in disease diagnosis, severity assessment, and treatment monitoring. Further research is needed to fully elucidate their roles in asthma pathophysiology and to explore their clinical utility in asthma management.

Keywords: Asthma; YKL-40; Dipeptidyl Peptidase-4; Biomarkers; Airway Remodeling; Inflammation; Genetic Predisposition; Disease Severity; Treatment Responses.

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Introduction

Asthma is a complex disease that affects millions of people worldwide. The prevalence of asthma varies across different regions, age groups, and demographics, with racial disparities observed in some populations. For instance, a study found that Black children have the highest prevalence of asthma, followed by White and Asian children [1-3]. Asthma can have a significant impact on an individual's quality of life, causing symptoms such as wheezing, coughing, and shortness of breath. The disease can also have a substantial economic burden, with costs associated with healthcare utilization, lost productivity, and medication. In terms of epidemiology, asthma is a significant public health concern, with a global prevalence of approximately 340 million people [4,5]. The disease is more common in developed countries, but the prevalence is increasing in developing countries due to urbanization and changes in lifestyle [6]. Asthma can be triggered by a variety of factors, including allergens, respiratory infections, and air pollution [6]. T2-high asthma is a type of asthma characterized by the presence of type 2 inflammation, which is associated with increased levels of eosinophils, exhaled nitric oxide, and serum inflammatory factors. This type of asthma is more common in adults and is associated with a higher risk of asthma exacerbations and reduced lung function [7-8]. T2-high asthma can be predicted to some extent from raised levels of FeNO, blood and sputum eosinophil counts, but serum IgE or serum periostin were poor predictors [9]. The diagnosis and management of T2-high asthma involve the use of biomarkers such as sputum and blood eosinophils, exhaled nitric oxide, and airway gene expression markers [8-10]. Monoclonal antibodies are now available to treat individuals with T2-high asthma and these medications significantly reduce asthma exacerbation rates [10]. A study found that T2-high asthma was more common in females and was associated with a higher prevalence of asthma severity grade 5, more frequent rhinitis, and chronic rhino sinusitis with or without nasal polyps [9]. A real-world study investigated whether phenotyping patients with asthma using non-invasive parameters could be feasible to characterize the T2-low and T2-high asthma phenotypes in clinical practice [8]. The study found that T2-high asthma was associated with a higher prevalence of asthma severity grade 5, more frequent rhinitis, and chronic rhino sinusitis with or without nasal polyps [8]. A comprehensive characterization of difficult-to-treat asthma revealed a near absence of T2-low status, with 93% of patients meeting criteria for T2-high asthma [11]. The study found that body mass index, inhaled corticosteroid dose, asthma exacerbations, and common comorbidities did not differ by T2 status [11]. YKL-40 is a biomarker that has been associated with various types of cancer, including breast cancer (12), colorectal cancer (13), and pancreatic cancer (14). High levels of YKL-40 have been linked to poor prognosis and shorter survival rates in patients with cancer (12-16). YKL-40 is also involved in inflammation and tissue remodeling, and has been found in breast carcinomas associated with short disease-free survival and in glioblastomas with increased resistance to radiotherapy and decreased overall survival (12). YKL-40 has also been identified as a potential biomarker for asthma [17]. Dipeptidyl peptidase-4 (DPP-4) has been implicated in the pathophysiology of asthma, with studies suggesting its potential role in modulating airway inflammation and remodeling. DPP-4 inhibitors, commonly used in the treatment of type 2 diabetes, have been found to have no association with asthma control [18]. However, DPP-4 has been shown to regulate the Th17/IL-17 axis and accelerate epithelial mesenchymal transition, promoting ovalbumin-induced asthma in mice. Furthermore, DPP-4 has been identified as a potential biomarker for interleukin 13 pathway activation in asthma and allergy [19]. As previous studies have highlighted the potential of YKL-40 and DPP-4 as a biomarker for asthma, with associations with airway remodeling, inflammation, and disease severity, yet with inconsistent findings and limited understanding of its genetic regulation, we aimed to investigate the relationship between these biomarkers and asthma, including its genetic variants and potential interactions. Furthermore, we sought to explore the novelty of YKL-40 and DPP4 as a biomarker for asthma, particularly in the

context of its genetic predisposition and potential correlations with disease severity and treatment responses, which has not been fully elucidated in previous studies.

Results

YKL-40

YKL-40, also known as Chitinase-3-like protein 1 (CHI3L1), is a protein that has gained significant attention in medical research due to its potential as a biomarker for various diseases. Chitinase-3-like protein 1 (CHI3L1) is a member of the family 18 glycosyl hydrolases, which are characterized by their ability to bind and degrade chitin, a polysaccharide found in the exoskeletons of insects and crustaceans. Structurally, CHI3L1 is composed of a catalytic domain and a chitin-binding domain, which allows it to recognize and interact with chitin-containing molecules. It is a 40 kDa glycoprotein. Despite its name, it does not have chitinase activity [20-21].

YKL-40 and asthma

A series of studies have investigated the potential of serum YKL-40 as a biomarker in various respiratory and inflammatory conditions. Zhang et al. (2024) found no significant association between serum YKL-40 and T2-high asthma, but noted a positive correlation with fractional exhaled nitric oxide, especially in females over 40 with reduced lung function [21]. Zhu et al. (2024) reported that higher serum levels of YKL-40, LXRα, LXRβ, and TGF-β1 were linked to increased airway wall thickness and percentage of wall area, while lower PPM1A levels were associated with decreased lung function in bronchial asthma [22]. Kim et al. (2024) observed significantly higher levels of periostin and YKL-40 in pediatric asthma patients, suggesting YKL-40 as a marker for airway remodeling [23]. El-Ghoneimy et al. (2024) found that serum YKL-40 levels were significantly higher in asthmatic children and correlated with inflammatory markers, predicting exacerbations with high accuracy [24]. Wang et al. (2024) demonstrated that YKL40 promotes the overexpression of inflammatory cytokines in tonsils via the NF-κB pathway in children with obstructive sleep apnea syndrome [25]. Liang et al. (2024) suggested that serum YKL-40 and KL-6 could serve as useful biomarkers for diagnosing and assessing the severity of rheumatoid arthritis-associated interstitial lung disease [26]. Lai et al. (2015) found that serum YKL-40 levels in asthmatic patients significantly decreased after treatment, correlating with improved lung function and asthma control test (ACT) scores [27]. Pan et al. (2021) conducted a meta-analysis showing that serum YKL-40 levels were higher in asthmatic patients compared to healthy controls, with significant elevations in both pediatric and adult patients, and particularly in those with acute exacerbations [28]. Jin et al. (2022) performed a systematic meta-analysis indicating that serum YKL-40 levels are significantly higher in asthmatic patients compared to healthy individuals, and these levels increase with disease severity and acute exacerbations, suggesting its potential as a biomarker for diagnosis, severity assessment, and differential diagnosis of asthma, chronic obstructive pulmonary disease (COPD), and asthma-COPD overlap syndrome (ACO) [29]. Kimura et al. (2015) found that circulating YKL-40 levels were significantly associated with proximal wall area percentage and airway fractal dimension in patients with severe asthma, providing further evidence for the association of YKL-40 with airway remodeling [30]. Specjalski et al. (2019) reported that mean serum YKL-40 levels were significantly higher in asthmatic patients compared to healthy controls, and these levels were higher in poorly controlled and obese asthmatics, suggesting its correlation with severe asthma phenotypes and exacerbations [31]. Liu et al. (2019) demonstrated that serum YKL-40 levels were significantly elevated in non-eosinophilic asthma and predicted negative responses to anti-asthma treatments, indicating its potential as a biomarker for non-type 2 inflammatory phenotypes and poor treatment responses [32].

Discussion

Genetics of YKL-40 and asthma:

The genetic variation in CHI3L1, particularly the SNP rs12141494, is associated with higher YKL-40 expression in the airway and severe asthma, suggesting a predisposing role of YKL-40 in asthma severity and airway remodeling [33]. The study by Ober et al. (2008) found that a promoter SNP (−131C→G) in the CHI3L1 gene, which encodes YKL-40, is associated with elevated serum YKL-40

levels, asthma, bronchial hyper responsiveness, and reduced lung function [34]. The study by Usemann et al. (2016) found that the SNP rs10399805 in the CHI3L1 gene was significantly associated with asthma development at 6 years of age, with an odds ratio of 4.5 per T-allele. However, cord blood YKL-40 levels at birth were not significantly associated with asthma [35]. The study by Specjalski et al. (2018) highlights that YKL-40 is overexpressed in asthma and correlates with exacerbation rate, therapy resistance, and poor symptom control, while inversely correlating with FEV1. YKL-40 is involved in allergen sensitization, IgE production, and bronchial remodeling. While it shows associations with blood eosinophilia and FeNO, indicating a role in T2-high inflammation, the highest levels of YKL-40 are found in severe neutrophilic asthma and obesity-associated asthma [36]. The study by Rathcke et al. (2009) found that the G allele of the rs4950928 polymorphism in the CHI3L1 gene was associated with an increased risk of asthma and atopic asthma in a large population-based sample of Danish adults. Additionally, other SNPs in the CHI3L1 gene were associated with atopy and FEV1/FVC ratio, suggesting a role of CHI3L1 in asthma and lung function [37]. The study by Kanazawa et al. (2019) identified a cis-eQTL allele (rs946261) in the CHI3L1 gene that is associated with reduced expression of CHI3L1 mRNA and late-onset adult asthma in Japanese cohorts. Specifically, the C allele at rs946261 was significantly associated with late-onset asthma (≥41 years) and a specific asthma phenotype characterized by late onset, less atopy, and mild airflow obstruction [38].

Dipeptidyl peptidase-4

Dipeptidyl peptidase-4 (DPP-4) is a serine protease that plays a crucial role in the regulation of glucose metabolism and inflammation. It is a cell-surface protease that belongs to the prolyloligopeptidase family and selectively removes the N-terminal dipeptide from peptides with proline or alanine in the second position. DPP-4 is also involved in the degradation of incretin peptides, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are important for glucose homeostasis [39-42]. In addition to its catalytic activity, DPP-4 interacts with several proteins, including adenosine deaminase, the HIV gp120 protein, fibronectin, collagen, the chemokine receptor CXCR4, and the tyrosine phosphatase CD45 [41-42].

Dipeptidyl peptidase-4 (DPP4) and asthma

Research has shown that DPP4 is involved in the recruitment of T cells to the lungs in a rat model of asthma. Additionally, studies have found that DPP4-deficient rats exhibit a less pronounced inflammation and increased Treg cell influx into the lung compared to wild-type rats. However, the degree of OVA-induced Th2-driven pulmonary inflammation was similarly pronounced in both wild-type and DPP4-deficient Dark Agouti (DA) rats [43]. The study of Vázquez-Mera et al. revealed that CD4+CD26−/lo T cells, which express proteins typically found in granulocytes, are expanded in eosinophilic asthma and may play a significant role in sustaining long-term inflammation in atopic asthma [44].

Conclusion

Multiple studies have linked elevated serum YKL-40 levels to asthma severity, airway wall thickness, and exacerbations, particularly in specific subgroups such as females over 40, pediatric patients, and those with non-eosinophilic asthma. Genetic variations in the CHI3L1 gene, such as SNPs rs12141494 and rs4960928, are associated with higher YKL-40 expression and an increased risk of severe asthma and atopy. Additionally, the literature touches on the role of DPP-4 in asthma, noting its involvement in T cell recruitment and inflammation, with DPP4-deficient rats showing reduced inflammation and increased Treg cell influx. Overall, YKL-40 and DPP-4 are emerging as important biomarkers and potential therapeutic targets in the management of asthma.

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The author contributed to the data analysis. Drafting, revising and approving the article, responsible for all aspects of this work.

Ethical Consideration

None

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phenotype and severity: A novel CD4+ T cell subset expressing archetypical granulocyte proteins. Allergy. 2024 Sep 25.

Tables

Table 1: Studies included in the narrative review

Study	Year	Key Findings
Zhang et al.	2024	No significant association with T2-high asthma; positive correlation with FeNO in females >40 with reduced lung function
Zhu et al.	2024	Higher YKL-40, LXRα, LXRβ, TGF-β1 linked to increased airway wall thickness and wall area; lower PPM1A with decreased lung function
Kim et al.	2024	Higher periostin and YKL-40 in pediatric asthma; marker for airway remodeling
El-Ghoneimy et al.	2024	Higher YKL-40 in asthmatic children; correlates with inflammatory markers; predicts exacerbations
Wang et al.	2024	YKL-40 promotes inflammatory cytokine overexpression via NF-κB in children with OSA
Liang et al.	2024	YKL-40 and KL-6 as biomarkers for rheumatoid arthritis-associated interstitial lung disease
Lai et al.	2015	YKL-40 levels decreased after treatment; correlates with improved lung function and ACT scores
Pan et al.	2021	Higher YKL-40 in asthmatic patients; significant in pediatric and adult patients; higher in acute exacerbations
Jin et al.	2022	Higher YKL-40 in asthmatic patients; increases with severity and acute exacerbations; potential biomarker for asthma, COPD, and ACO
Kimura et al.	2015	YKL-40 levels associated with proximal wall area percentage and airway fractal dimension in severe asthma
Specjalski et al.	2019	Higher YKL-40 in asthmatic patients; higher in poorly controlled and obese asthmatics; correlates with severe asthma phenotypes and exacerbations
Liu et al.	2019	Higher YKL-40 in non-eosinophilic asthma; predicts negative treatment responses
Ober et al.	2008	Promoter SNP (−131C→G) associated with elevated YKL-40, asthma, bronchial hyperresponsiveness, and reduced lung function
Usemann et al.	2016	SNP rs10399805 associated with asthma development at 6 years; cord blood YKL-40 not significantly associated
Specjalski et al.	2018	Overexpressed in asthma; correlates with exacerbation rate, therapy resistance, poor symptom control, and inversely with FEV1; involved in allergen sensitization, IgE production, and bronchial remodeling
Rathcke et al.	2009	G allele of rs4950928 associated with increased risk of asthma and atopic asthma; other SNPs associated with atopy and FEV1/FVC ratio
Kanazawa et al.	2019	Cis-eQTL allele (rs946261) associated with reduced CHI3L1 mRNA and late-onset adult asthma; C allele associated with late-onset, less atopy, and mild airflow obstruction