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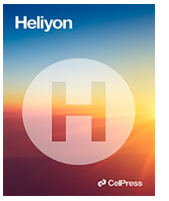

Research article

Bioinformatics analysis revealed underlying molecular mechanisms associated with asthma severity and identified GABAergic related pathway as a potential therapy for Th2-high endotype asthma

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ABSTRACT

Background: Asthma, a principally T helper 2 (Th2) cell mediated immunological disease, is categorized into Th2-high and Th2-low endotypes. The influence of these endotypes on clinical characteristics and treatment responsiveness in asthma is yet to be completely understood. This study delves into the underlying molecular mechanisms of Th2 endotypes on asthma.
Methods: Transcriptomics data of airway epithelial and corresponding clinical information were sourced from the GEO. The co-expression modules were established by WGCNA. Cytoscape was applied to construct PPI networks, and hub genes were determined via the Cytohubba plugin. Additionally, a functional enrichment analysis was conducted on the co-expressed genes from the relevant modules. The relative abundances levels of 22 different types of immune cells in asthma patients were evaluated by CIBERSORT algorithm.
Results: There were 471 genes in the pink module significantly correlated with Th2 endotype. Overall, 151 DEGs were identified in the various Th2 endotypes, and 66 were obtained through intersection with the pink module. In the PPI network, the ten most important genes that regulate Th2 endotypes were selected as hub genes. In Th2-high endotype asthma, the hub genes were significantly related to γ-aminobutyric acid (GABA) pathways, indicating that hub genes can mainly regulate Th2-high endotype asthma through GABAergic system.
Conclusions: The severity of asthma is influenced by different Th2 endotypes. GABAergic related hub genes may provide innovative insights for the treatment of Th2-high asthma.

1. Introduction

Asthma is a complex and highly heterogeneous disease defined by chronic inflammation of the airways, predominantly triggered by allergens [1]. Chronic inflammation often culminates in airway remodeling, causing dyspnea, wheezing, and hypoxia due to narrowed airways [2]. While most asthmatic patients can effectively relieved symptoms by medication, a subset of approximately 5–10% suffer from uncontrolled asthma [3]. A deeper understanding of the influencing factors in disease severity and the mechanisms of different asthma endotypes may lead to improved therapeutic strategies.

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Recent advances have deepened our understanding of the immunological processes involved, in particular the role of T helper 2 (Th2) cells in the pathophysiology of asthma. Th2 cells play a central role in coordinating immune responses and have been implicated in driving the inflammatory process that characterizes asthma [4]. Asthma has traditionally been viewed as a Th2-mediated disease, with its endotypes Th2-high and Th2-low distinguished by the influence of Th2 cells and related cytokines [5]. Th2-high asthma is frequently linked with inflammation of the eosinophils [6], while Th2-low comprises other forms such as neutrophilic asthma and paucigranulocytic asthma [7]. This classification into endotype groups is advantageous as it allows for targeted therapy through distinct pathogenic molecular mechanisms [8]. However, further investigation is required to determine how these asthma endotypes affect disease severity and which treatments are optimal for each endotype.

In this context, our research aims to identify key genes and pathways that are strongly correlated with different asthma endotypes. Although the phenotypic features of asthma have been extensively studied, the specific gene expression profiles that dictate these features remain to be fully elucidated. We expect to uncover novel biomarkers that could serve both diagnostic and therapeutic purposes, thus advancing the field towards more personalized management strategies for asthma.

2. Materials and methods

2.1. Data retrieval

Transcriptomic data and corresponding patient information were obtained from the GEO (http://www.ncbi.nlm.nih.gov/geo/) [9]. After exhaustive data filtering in the GEO, GSE43696 and GSE67472 dataset were selected in the study (Supplementary Table 1). The GSE43696 dataset, based on the Agilent-014850 Whole Human Genome Microarray 4 × 44 K G4112 F platform, discloses gene expression patterns of bronchial epithelial cells samples collected from 20 normal controls, 50 mild to moderate asthmatics, and 38 severe asthmatics. Furthermore, 105 gene expression profiles from the GSE67472 dataset were acquired from the GEO using the Affymetrix Human Genome U133 Plus 2.0 Array platform. Asthmatic subjects in this dataset were categorized into Th2-high and Th2-low. The above data were obtained from diverse platforms using different methodologies; hence, the R package sva was used to eliminate batch effects within each group.

2.2. Construction analysis of co-expression module of asthma

The WGCNA was employed to identify co-expression modules in tandem with the clinical variables of asthma. The WGCNA includes a set of functions designed to facilitate various facets of weighted correlation network analysis [10]. The power value β for soft-thresholding was computed for each module using the pickSoftThreshold function within WGCNA, which offers a spectrum of power values (1–20) appropriate for network construction. A soft threshold of six was chosen due to it meeting the degree of independence of 0.90 at the minimum power value ($R^2 = 0.90$). Subsequently, hierarchical clustering using dynamic tree-cutting techniques separated gene clusters into distinct modules. The correlation strength of the modules was evaluated and depicted using a heatmap. Module-trait interactions were assessed by Pearson correlations between module eigengenes and endotypes, with the goal of identifying the specific gene set (module) that correlates highly with the endotypes [11].

2.3. Functional enrichment analysis

The online resource DAVID was used to conduct functional annotation and pathway enrichment analysis, including GO enrichment and KEGG pathway analysis [12–14]. Statistical significance was ascribed to a *P*-value threshold of less than 0.05.

2.4. Identification of DEGs between Th2-high and Th2-low endotypes

The DEGs between Th2-high and Th2-low groups were identified by use of the limma package [15]. To adjust for potential false discoveries, we applied the Benjamini-Hochberg procedure, setting the FDR threshold below 0.01 and selecting for |fold change (FC)| greater than 2. Furthermore, functional annotation and pathway enrichment analyses were conducted on the DEGs using the WebGestaltR package [13,14,16]. An FDR below 0.05 was regarded as statistically significant.

2.5. Construction of PPI network and identification of hub genes

We mapped the genes from the key module that correlated with Th2 endotypes to the STRING database (http://string-db.org) to assess their functional relationships, with a combination score above 0.4 was deemed significant [17]. Visualization of the PPI network, which outlines the interaction topology among genes, was facilitated using Gephi software. GO enrichment were done with the ClueGO plug-in of Cytoscape [18]. An FDR <0.05 was considered significant.

2.6. Gene set variation analysis (GSVA)

GSVA was applied to ascertain the molecular pathways most significantly enriched within the Th2 endotype [19]. A comparative enrichment score analysis for KEGG pathways of the two Th2 endotypes was conducted using the limma package [15]. KEGG pathways exhibiting a |log2FC| greater than 0.1 and FDR below 0.05 were designated as the most differentially enriched molecular pathways

between the two groups.

2.7. Correlation analysis of immune microenvironment and Th2 endotypes

To quantify the composition of 22 immune cell types from gene expression patterns, we applied CIBERSORT [20]. The correlations between immune cells and the two Th2 endotypes were explored to identify the most relevant immune cell. Further analysis was conducted to probe the associations between these immune cells and the identified hub genes.

2.8. Connectivity map (CMap) analysis

The CMap (https://clue.io/) was leveraged to investigate potential compounds that may modulate molecular pathways and genes implicated in the Th2 endotypes of asthma [21]. This resource enables drug prediction according to gene expression profiles and discloses the mode of action (MoA) of compounds aimed at specific molecular pathways. The DEGs between the Th2-high and Th2-low groups were used to interrogate the CMap, with an emphasis on the most significantly overexpressed genes in each endotype as potential drug targets. Compound enrichment scores were calculated, identifying compounds with a negative enrichment score and a *P*-value of less than 0.05 as putative therapeutic agents for each asthma endotype.

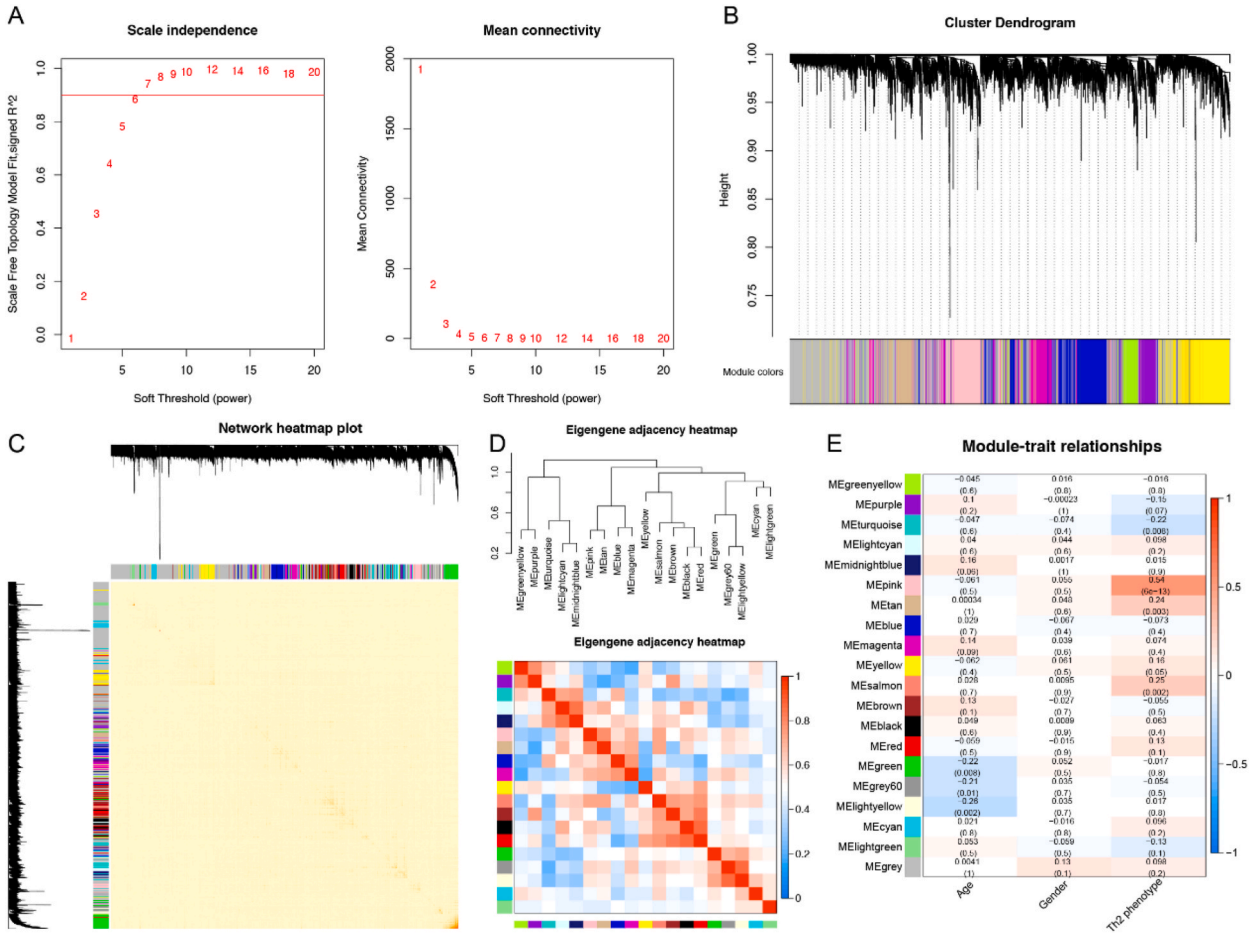

Fig. 1. Identification of the Th2-related gene module in asthma via WGCNA. (**A**) Analysis of network topology for a range of soft-thresholding powers. (**B**) Clustering dendrograms of genes. Different colors represent various co-expression modules. (**C**) Heatmap illustrated the interactions among co-expressed genes, which depicted the Topological Overlap Matrix (TOM) across all analyzed genes. (**D**) Upper panel: Hierarchical clustering of module genes. Lower panel: Heatmap of the adjacencies in the module gene network. (**E**) Module-trait plot displayed the correlations between module eigengenes and the clinical traits of asthmatic patients. The table displays module eigengenes and their corresponding correlations and *P*-values for each trait. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

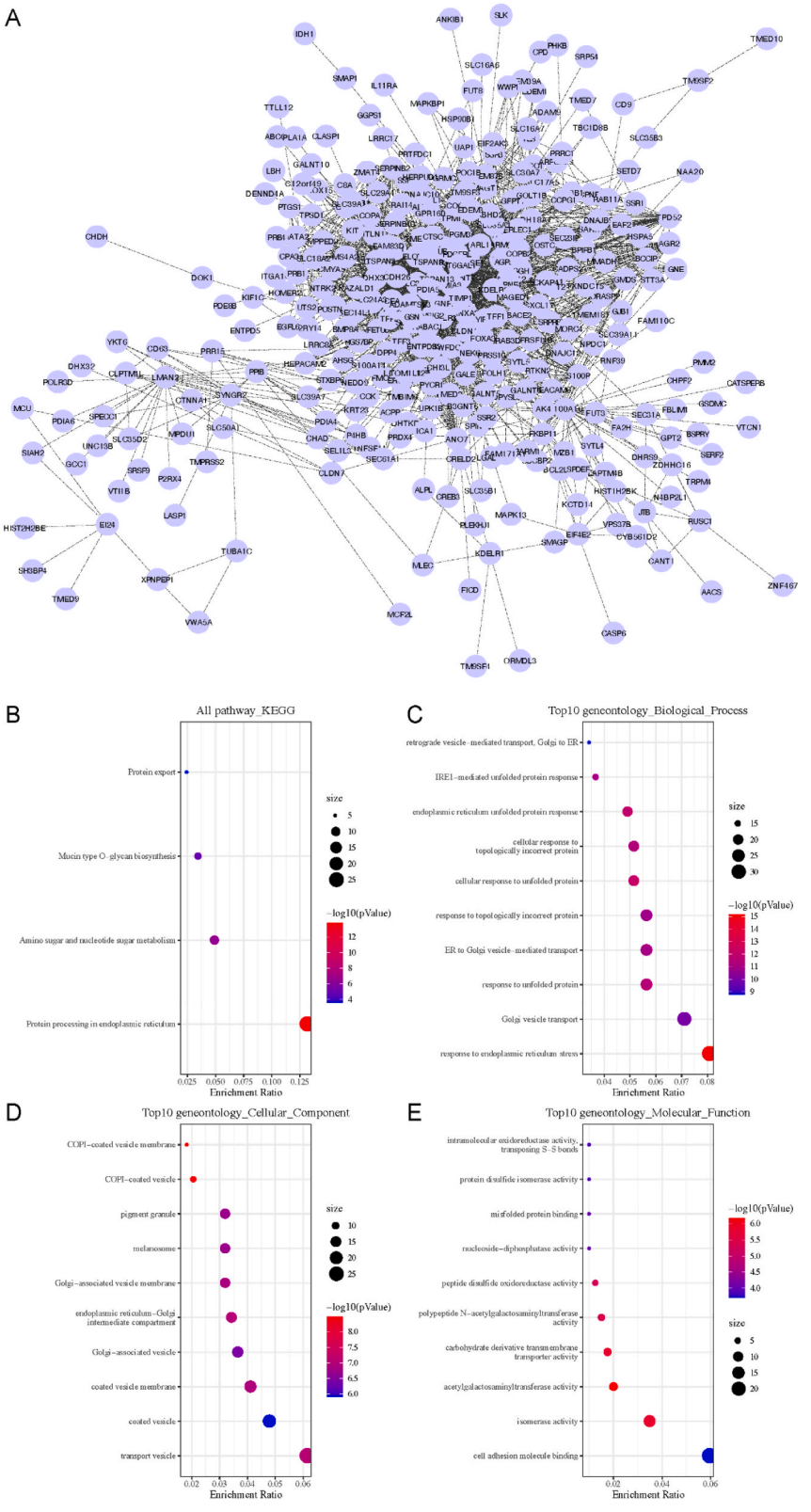

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Fig. 2. Functional and pathway enrichment analysis of the Th2-related genes. (**A**) PPI network of the pink module genes. (**B**) KEGG pathways analysis for Th2-related genes. (**C**) Enriched Biological Processes (BP) of Th2-related genes. (**D**) Enriched Cellular Components (CC) of Th2-related genes. (**E**) Enriched Molecular Functions (MF) of Th2-related genes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

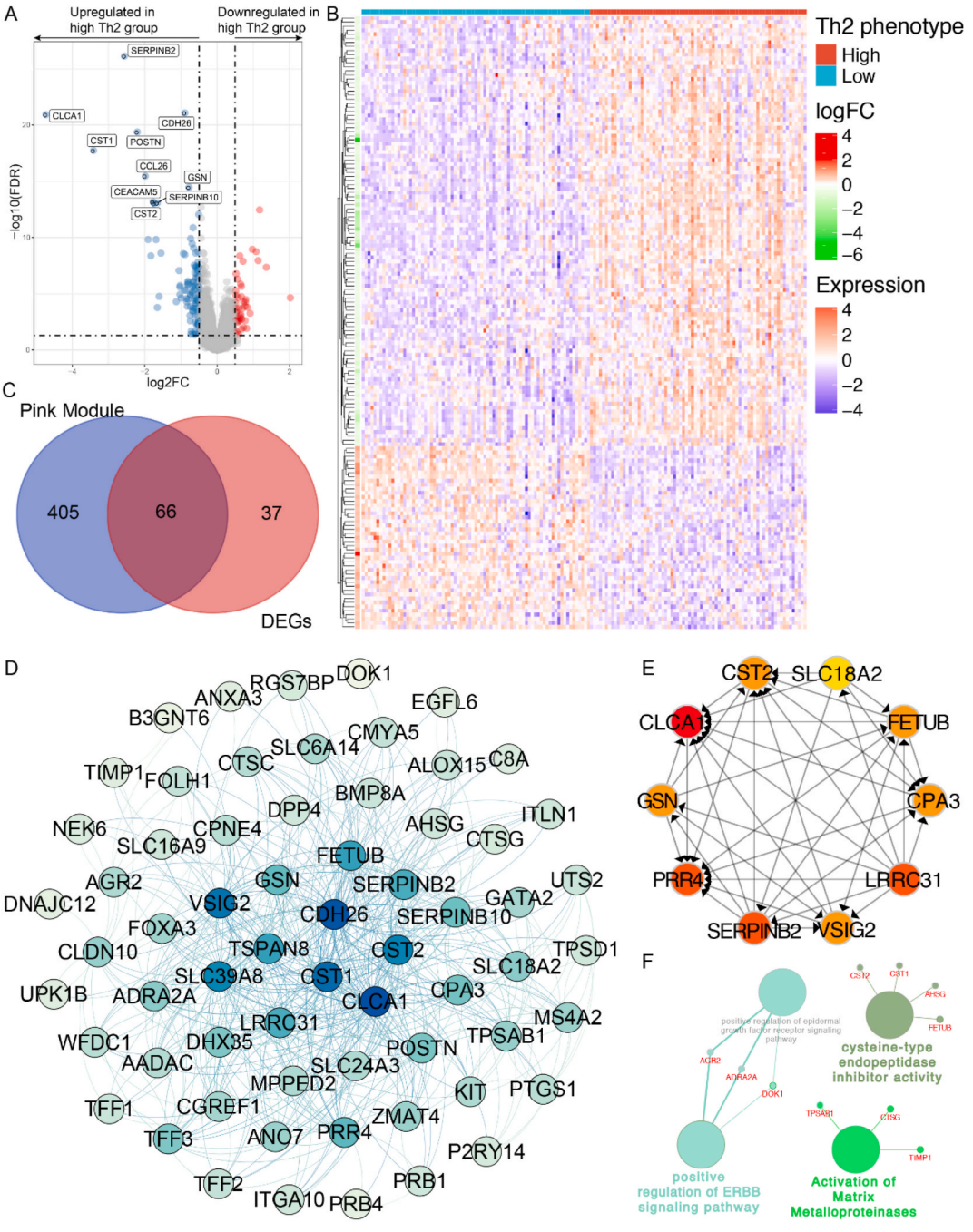

Fig. 3. Identification of DEGs and construction of PPI and hub genes network. (**A**) Volcano plot delineating the DEGs between Th2-high and Th2-low endotypes. (**B**) Heatmap illustrating the Th2 endotype in asthmatic patients. (**C**) Venn diagram depicting the intersection of DEGs and pink module genes. (**D**) PPI network including 66 intersecting genes. (**E**) Hub gene network focusing on the top ten genes pivotal in regulating the Th2 endotype. (**F**) Functional enrichment analysis performed on the aforementioned 66 genes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

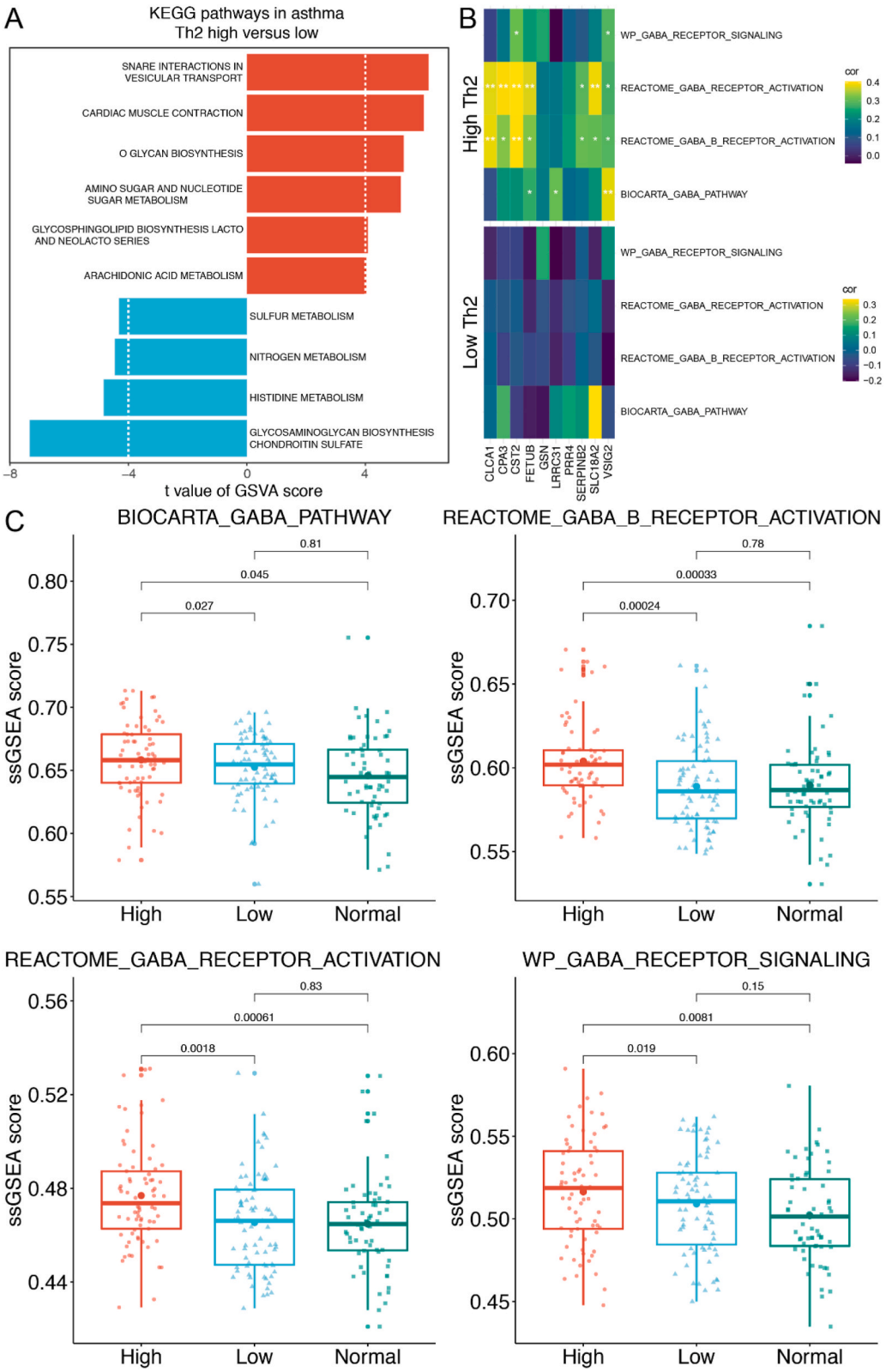

Fig. 4. Distinguishing features between Th2-high and Th2-low endotypes and their relationship with γ-aminobutyric acid (GABA). (**A**) Comparative analysis of KEGG pathways associated with Th2-high and Th2-low endotypes. (**B**) Correlation analysis between γ-aminobutyric acid (GABA)-related signaling pathways and identified hub genes. (**C**) Differences in the GABA-related signaling pathway among Th2 endotypes and normal samples.

3. Results

3.1. Identification of the Th2-related gene module in asthma via WGCNA

The WGCNA tool was utilized to generate the co-expression module, using expression values of 15,603 genes from 213 asthma samples, and the impact of batch effect removal is illustrated in Supplementary Fig. 1. The power value, an important parameter influencing the independence and average connectivity of the co-expression modules, was set to six. This threshold ensured an independence degree of up to 0.9 and facilitated enhanced connectivity within modules. This power value aided in constructing the co-expression module, leading to the identification of 20 unique gene co-expression modules in asthma (Fig. 1A). Each module represented by a distinct color (Supplementary Table 2). The clustering dendrogram, produced using the Dynamic Tree Cut package, showcased the hierarchical arrangement of gene modules (Fig. 1B). Modules not part of this array, denoted in gray, were omitted from further analysis. The network heatmap plot revealed strong intramodular correlations, implying that genes with high co-expression may share analogous biological significance and function. The dendrogram and module assignment were depicted on the heatmap's left side, with the top representing different genes. The intensity of the yellow hue denoting the strength of the connection (Fig. 1C). Moreover, an analysis of the modules' co-expression similarity was visualized, with modules clustered into two main groups based on their intercorrelations (Fig. 1D). The module-trait heatmap indicated the pink module as having the most substantial correlation, with a Pearson correlation coefficient of 0.54 and $P = 6 \times 10^{-13}$, identifying it as the pivotal module associated with the Th2 endotype in asthma (Fig. 1E).

3.2. Functional and pathway enrichment analysis

The Cytoscape software's 'Network Analyzer' application was utilized to create a PPI network, which identified the genes of the pink module (Fig. 2A). GO analysis—encompassing Biological Process (BP), Cellular Component (CC) and Molecular Function (MF), was conducted on the key genes related to Th2. This functional and pathway enrichment analysis revealed 76 significantly enriched BPs, 42 CCs, 23 MFs, and four KEGG pathways (Supplementary Table 3). The KEGG pathway implicated Th2-related genes in vital cellular processes, such as protein processing within the endoplasmic reticulum, amino sugar and nucleotide sugar metabolism, mucin type O-glycan biosynthesis, and protein export (Fig. 2B). The overlapping genes were mainly enriched in the response to endoplasmic reticulum stress, golgi vesicle transport, response to unfolded protein, and others among the BP categories; the transport vesicle, coated vesicle, coated vesicle membrane, etc. in the CC categories; and cell adhesion molecule binding, isomerase activity, acetylgalactosaminyltransferase activity, etc. among the MF categories (Fig. 2C–E).

3.3. Identification of DEGs between Th2-high and Th2-low endotypes, construction of PPI and hub genes network

A total of 151 DEGs were identified between Th2-high and Th2-low endotypes, comprising 103 upregulated and 48 downregulated genes in asthma. These findings are represented in a volcano plot where red dots indicate downregulated genes, and blue dots indicate upregulated ones (Fig. 3A). The classification of asthmatic patients into Th2-high and Th2-low endotypes is depicted in the accompanying heatmap (Fig. 3B). Intersection analysis of DEGs and pink module genes yielded 66 genes that were both DEGs and associated with Th2 expression (Supplementary Table 4) (Fig. 3C). The PPI network was built to depict the functional associations and interaction topology of these 66 genes, with the intensity of the dots shifting from lighter to darker shades indicating increasing gene connectivity (Fig. 3D). Ten hub genes were screened out including CLCA1, CST2, SLC18A2, FETUB, CPA3, LRRC31, VSIG2, SERPINB2, PRR4, GSN. These are the most important genes in regulating the Th2 endotype and can be detected via PCR and Western blot (Fig. 3E). Further functional annotation of these 66 genes highlighted their enrichment across four GO clusters, denoting respective GO terms, with varying dot colors indicating different clusters (Fig. 3F).

3.4. Differences between Th2-high and Th2-low endotypes and the relationship with γ-aminobutyric acid (GABA)

The GSVA method was employed to probe the KEGG pathways and molecular mechanisms associated with Th2 endotype in asthma samples. Ten differentially enriched molecular pathways were revealed, including six pathways upregulated in the Th2-high endotype and four pathways downregulated in the same endotype. Notably, snare interaction in vesicular transport was the most significant KEGG pathway associated with Th2-high endotype asthma, suggesting a potential molecular mechanism underlying the Th2-high endotype (Fig. 4A). The hub genes within the Th2-high endotype exhibited a significant correlation with GABA-related signaling pathways, suggesting that these genes predominantly regulate the Th2-high endotype through such pathways. Thus, this finding implies that GABA-related therapeutic approaches might not yield the same efficacy in Th2-low endotype patients (Fig. 4B). The biocarta GABA pathway, reactome GABA B receptor activation, reactome GABA receptor activation, and wp GABA receptor signaling were highlighted as potential therapeutic targets for Th2-high endotype asthma, given their notably higher enrichment levels compared to the Th2-low endotype and the control group. This suggests an activation of these pathways in Th2-high endotype asthma and their potential roles in promoting Th2 expression of asthma (Fig. 4C).

3.5. Correlation analysis of immune microenvironment and Th2 endotypes

The CIBERSORT algorithm was applied to score the abundance of 22 immune cell types within Th2-high, Th2-low, and normal

groups, with different colors representing different types of immune cells (Fig. 5A). Then, the relative abundance of these cells, indicative of the immune activity in asthma, was quantified. Unsupervised hierarchical clustering grouped the 213 asthmatic patients into Th2-high, Th2-low, and normal categories. The results suggested significant differences among the three groups regarding the immune cells, including macrophages M2, eosinophils, T cells follicular helper, activated dendritic cells, activated mast cells, activated NK cells, macrophages M1, resting T cells CD4 memory, resting NK cell, activated T cells CD4 memory, T cells regulatory (Tregs), monocytes, resting mast cells ($P < 0.05$) (Fig. 5B). Furthermore, an in-depth correlation analysis was conducted between the expression levels of the ten hub genes and the diverse immune cells within the asthma context. This analysis unveiled strong associations, notably with resting mast cells in both Th2-high and Th2-low endotypes (Fig. 5C–D). In the Th2-high group, SERPINB2 ($r = 0.38$, $P = 0.008$) and VSIG2 ($r = 0.29$, $P = 0.033$) were remarkably relevant to resting mast cells, and the correlations between them were showed in Fig. 5E. Moreover, in the Th2-low group, CST2 ($r = 0.35$, $P = 0.007$) and PRR4 ($r = 0.32$, $P = 0.012$) exhibited the most

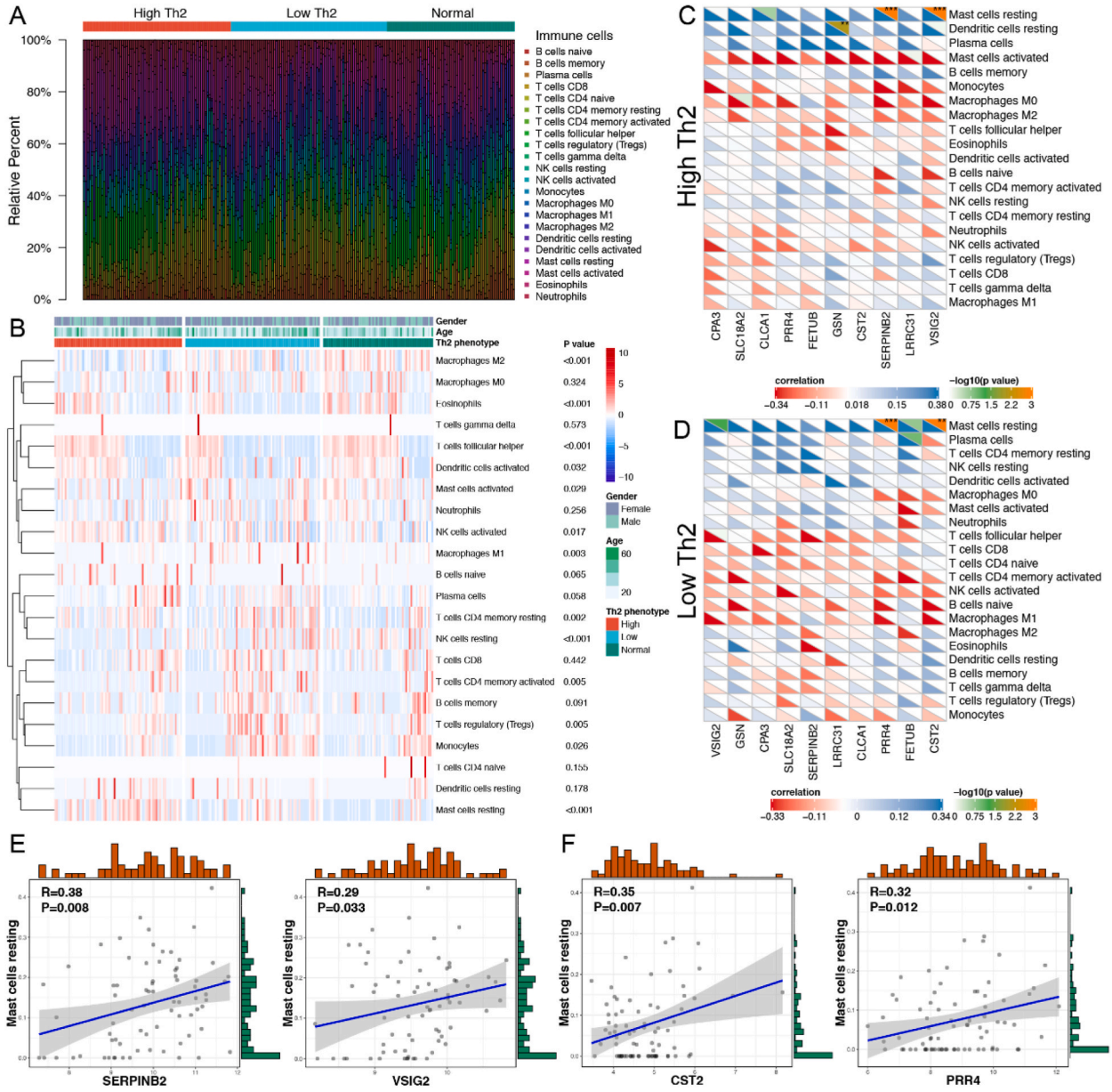

Fig. 5. Correlation analysis of immune microenvironment and Th2 endotypes. (**A**) Bar graph of the abundance of immune cells in Th2-high, Th2-low, and normal groups. (**B**) The heatmap displays the immune subtypes of asthmatics, categorized by the immune activity of asthma. (**C**) Relationships between identified hub genes and immune cells within the Th2-high group. (**D**) Relationships between identified hub genes and immune cells within the Th2-low group. (**E**) Correlations between positively related hub genes and the resting mast cells in the Th2-high group. (**F**) Correlations between positively related hub genes and the resting mast cells in the Th2-low group.

robust correlation with resting mast cells (Fig. 5F).

3.6. Prediction of asthma targeted therapy

Our exploration into Th2-related genes and associated pathways, conducted via CMap analysis, sought to identify potential compounds for asthma treatment. The MoA analysis elucidated 72 molecular pathways impacted by 154 compounds in asthma. Notably, 42 compounds were identified the same MoA as cyclooxygenase inhibitor, 16 compounds with the same MoA as serotonin receptor antagonist, and 15 compounds with the same MoA as adrenergic receptor agonist in asthma (Fig. 6).

4. Discussion

Asthma presents a significant global health challenge, affecting more than 300 million individuals with its characteristic airway hyperresponsiveness (AHR) and fluctuating airflow obstruction [22]. The disease complexity calls for robust research to dissect intricate asthma endotypes and uncover new, functional biomarkers to enhance diagnosis and therapeutic modalities. A crucial aspect of this pathophysiology involves Th2 lymphocytes, particularly post the initial sensitization phase [23], leading to the classification of asthma into Th2-high and Th2-low endotypes based on the Th2 inflammation status [7]. Unveiling distinctive biomarkers to identify these endotypes and predict treatment responsiveness has increasingly piqued scientific interest [24]. Through the strategic application of gene expression datasets and bioinformatics analysis, we seek to disentangle the elaborate mechanisms that underlie asthma, laying the groundwork for future personalized therapies [25].

WGCNA helps demystify asthma-related hub genes, gene networks, and associated pathogenesis. WGCNA's methodological focus on correlating co-expression modules with clinical traits bestows a higher level of reliability and biological significance to its outcomes [11]. In this research, WGCNA facilitated the construction of 20 co-expression modules from a cohort of 15,603 genes derived from 213 human asthmatic samples. The primary aim was to identify the gene module most relevant to the Th2 endotype, which led to the discovery of the pink module comprising 471 genes. The functional interconnection of the genes within this module, coupled with the proven efficacy of biological agents targeting the Th2 pathway in asthma treatment [26], positions these genes as potential biomarkers for both the diagnosis and treatment of asthma.

The PPI network among the pink module genes was constructed via the STRING database and visualized with the aid of Cytoscape. KEGG enrichment analysis disclosed the involvement of Th2-related genes in endoplasmic reticulum protein processing. In the GO analysis, the findings of BP showed the genes were implicated in the response to endoplasmic reticulum stress. Heightened endoplasmic reticulum stress is linked to severe eosinophilic and neutrophilic infiltration in asthma, mediating both airway inflammation and epithelial apoptosis, key factors in asthma's pathogenesis [27,28]. The CC terms demonstrated gene relation to transport vesicle. Extracellular vesicles are pivotal for instigating the immune response, releasing Th2 inflammatory cytokines that contribute to AHR and the pathophysiological development of asthma [29]. The MF terms indicated that the genes were related to cell adhesion molecule binding. Intercellular adhesion molecule-1 (ICAM-1)-mediated elevated inflammation is associated with asthma, and anti-ICAM-1 therapies offer a potential avenue to relieve asthma [30].

Most cases of severe asthma are caused by Th2-dependent inflammation [7], so the severity of asthma is related to the endotype of

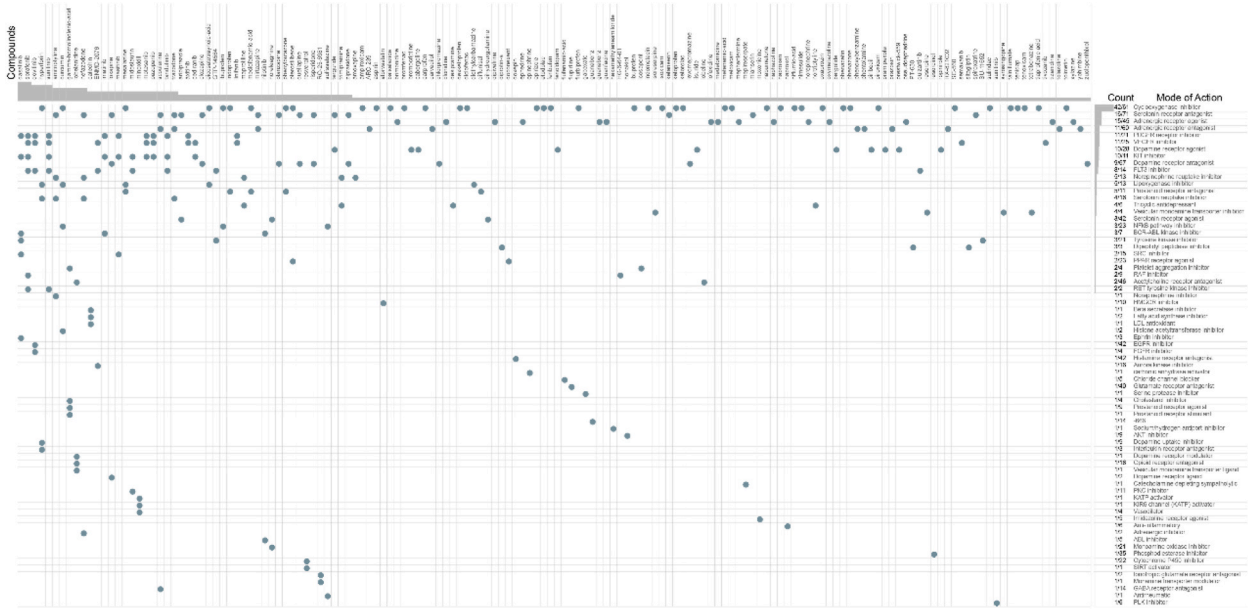

Fig. 6. CMap-based investigation of drug candidates and molecular pathways for the treatment of asthma.

Th2.This study successfully identified the DEGs between Th2-high and Th2-low groups, extracting 66 genes by taking the intersection with the pink gene module. A PPI network was then constructed with these 66 genes, from which ten hub genes were selected (CLCA1, CST2, SLC18A2, FETUB, CPA3, LRRC31, VSIG2, SERPINB2, PRR4, GSN). These outcomes will contribute to the elucidation of the underlying molecular mechanisms associated with asthma severity, and they are congruous with earlier studies identifying key genes in asthma, such as CLCA1, CPA3, SERPINB2 [31]. The gene CLCA1 is recognized for its role as a secretory mediator, which regulates both airway mucus secretion and tissue inflammation response [32]. CPA3, found within a subset of mast cells alongside tryptase, is associated with Th2-high asthma [33]. SERPINB2 is highly expressed during inflammation and promotes the differentiation of Th2 cells [34]. Hence, these genes unveiled in our study might be potential therapeutic targets for asthma treatment, which warrants further rigorous research for verification.

The differentiation process of Th2 cells is a significant contributor to the pathogenesis of asthma. T cells possess a complete GABA intrinsic system and express GABA receptors (GABARs), which modulate T cells activation [35]. The presence of GABARs on both airway epithelium and smooth muscle contributes significantly to the prorelaxant effects on airway muscle force [36]. A previous study indicated that GABAR agonists mitigate asthmatic inflammation via inhibiting Th2 cell differentiation, inducing apoptosis, and/or suppressing proliferation [37]. Our analysis expands on this by indicating that hub genes predominantly regulate the Th2-high endotype via GABA-related signaling pathways, hinting that different targeted therapies may be suitable for asthmatic patients depending on their endotype.

The complexity of respiratory allergic diseases is typified by chronic airway inflammation and the infiltration of a multitude of immune cells [38]. Our study spotlighted mast cells as notably significant within the immune cell-asthma nexus. Not only are mast cells associated with allergic responses in conditions like asthma [39], but they also contribute to Th2 cytokine production [40] and synthesize and secrete substantial amounts of proinflammatory cytokines such as IL-4, IL-5, and IL-13 [41]. The results suggested that SERPINB2, VSIG2, CST2, and PRR4 are principal genes interacting with mast cells. SERPINB2 is IL-13 response gene, CST2 is upregulated in mild asthma [42], and PRR4 is involved in secreting airway surface fluids from submucosal glands [43]. Whereas VSIG2 was not found to be relevant to asthma and mast cell in previous studies, which deserves further study in diagnosis and targeted therapy.

Potential anti-asthma compounds were analyzed by CMap in this study. Dasatinib emerged as the highest-ranking compound, with its primary mode of action identified as cyclooxygenase (COX) inhibition. Earlier research has found that dasatinib can attenuate asthma exacerbation-associated airway inflammation in mice [44], suggesting it could be a novel drug candidate for asthma [45]. However, more detailed studies addressing aspects like drug dosage, administration methods, and potential side effects are imperative prior to its clinical application. The COX enzyme, a linchpin in the production of key inflammation mediators, was recognized as a potential target for asthma [46] —a notion supported by our findings.

There are some limitations in our research. The relatively small sample sizes of the GSE43696 and GSE67472 datasets (a total of 213 samples) may introduce bias. Additionally, the conclusions drawn are primarily grounded in transcriptomic data, underscoring the need for validation through future basic and clinical experimental studies.

5. Conclusions

In summary, our study identified the DEGs between Th2-high and Th2-low endotypes and discovered ten hub genes (CLCA1, CST2, SLC18A2, FETUB, CPA3, LRRC31, VSIG2, SERPINB2, PRR4, GSN) associated with Th2 expression. Then, our results indicated that the hub genes can regulate Th2-high endotype mainly through GABA-related signaling pathways, therefore, GABA-related therapy may be not effective in Th2-low endotype. Besides, we provided evidence that mast cells are the most relevant immune cells to asthma. Thus, a comprehensive exploration of these mechanisms of asthma will provide new theoretical basis and perspectives for the development of novel therapies for individualized treatment in the future.

Data availability statement

Public data used in this work can be acquired from the Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/).

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Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors consent to the publication of this article.

CRediT authorship contribution statement

Ruisong Gong: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis,

Conceptualization. **Zihao Wang:** Writing – review & editing, Visualization, Validation, Software, Methodology, Investigation, Formal analysis. **Gang Tan:** Supervision, Resources, Funding acquisition. **Yuguang Huang:** Project administration, Funding acquisition, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28401.

Abbreviations

Th2	T helper 2
GEO	Gene Expression Omnibus
WGCNA	weighted gene co-expression network analysis
PPI	Protein-protein interaction
DEG	differentially expressed gene
GABA	γ-aminobutyric acid
GABAR	γ-aminobutyric acid receptor
DAVID	Database for Annotation, Visualization and Integrated Discovery
GO	Gene Ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes
FDR	false discovery rate
GSVA	Gene set variation analysis
CMap	Connectivity map
MoA	mode of action
TOM	Topological Overlap Matrix
BP	Biological Process
CC	Cellular Component
MF	Molecular Function
AHR	airway hyperresponsiveness
COX	cyclooxygenase

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