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Deciphering the Immunometabolic Reprogramming Underlying Chronic Allergic Inflammation: An Integrative Multi-Omics Investigation

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1. Abstract

1.1. Background

Chronic allergic inflammation involves persistent immune activation accompanied by metabolic alterations at the cellular level. Although recent studies have highlighted the role of immunometabolism processes in shaping immune responses, evidence from integrative multi-omics analyses in clinical populations remains limited.

1.2. Objective

This study aimed to explore immunometabolism alterations associated with chronic allergic inflammation using an integrative multi-omics framework.

1.3. Methods

A multicentre cross-sectional study was conducted in three secondary referral hospitals in Indonesia between 2023 and 2025. A total of 500 patients with clinically diagnosed chronic allergic conditions (including allergic rhinitis, asthma, and atopic dermatitis) were enrolled. Peripheral blood samples were collected for transcriptomic, metabolomic, and proteomic profiling. Data integration was performed using network-based systems biology approaches. Statistical analyses included multivariate linear regression, correlation analysis, and pathway enrichment with false discovery rate (FDR) correction.

1.4. Results

Patients with chronic allergic inflammation demonstrated consistent upregulation of genes associated with glycolysis and hypoxia-related pathways. Metabolomic profiling indicated increased lactate production and alterations in fatty acid metabolism. Proteomic analysis further identified differential expression of proteins involved in inflammatory signalling. Integrated pathway analysis suggested significant involvement of PI3K–Akt and HIF-1α signalling pathways. These molecular changes were moderately correlated with markers of Th2-skewed immune responses (adjusted $p < 0.01$).

1.5. Conclusion

The findings support the presence of coordinated immunometabolism alterations in chronic allergic inflammation, particularly involving shifts toward glycolytic metabolism and hypoxia signalling. While causal relationships cannot be established due to the cross-sectional design, these results provide a basis for further mechanistic studies and may inform the development of targeted therapeutic strategies.

2. Introduction

Chronic allergic inflammation represents a substantial and growing global health burden, contributing to highly prevalent conditions such as asthma, allergic rhinitis, and atopic dermatitis. These disorders are characterized by recurrent or persistent symptoms, reduced quality of life, and significant healthcare utilization. From a biological perspective, chronic allergic diseases are driven by sustained immune activation, most prominently involving T helper 2 (Th2)-skewed responses, immunoglobulin E (IgE) production, and eosinophilic inflammation within affected tissues. The persistence of these responses suggests that, beyond transient antigen exposure, there are underlying regulatory mechanisms that maintain and amplify inflammatory signalling over time.

In classical immunological paradigms, allergic inflammation has been primarily explained through dysregulated immune recognition and signalling pathways. Allergen exposure leads to antigen presentation, Th2 differentiation, and the release of cytokines such as interleukin (IL)-4, IL-5, and IL-13, which collective-

ly orchestrate eosinophil recruitment, mucus production, and airway or tissue remodelling. While this framework has been instrumental in guiding therapeutic strategies, including the development of biologics targeting Th2 cytokines, it does not fully explain the chronicity and heterogeneity observed across patients. Increasingly, attention has shifted toward additional layers of regulation that may sustain or modulate immune responses, including cellular metabolism.

Recent advances in immunology have introduced the concept of immunometabolism, which recognizes that metabolic pathways are not merely passive providers of cellular energy but active regulators of immune cell function [1,2]. Immune cells dynamically reprogram their metabolic processes in response to environmental cues, activation states, and functional demands. For example, activated effector T cells, including Th2 cells, preferentially rely on aerobic glycolysis to support rapid proliferation and cytokine production, whereas regulatory T cells and memory cells are more dependent on oxidative phosphorylation and lipid oxidation. This metabolic flexibility allows immune cells to adapt to diverse microenvironments; however, it may also contribute to pathological conditions when dysregulated.

Metabolic reprogramming has emerged as a key feature of chronic inflammatory states. Enhanced glycolysis, even in the presence of adequate oxygen (a phenomenon analogous to the Warburg effect in cancer biology), has been observed in various activated immune cell populations. This shift supports not only energy production but also the generation of biosynthetic intermediates required for cell growth and effector function. In parallel, alterations in lipid metabolism-including changes in fatty acid synthesis, oxidation, and signalling lipid mediators-have been implicated in modulating inflammatory pathways and membrane dynamics. Together, these metabolic changes can sustain inflammatory phenotypes and influence immune cell differentiation and persistence [3,4].

In the context of chronic allergic inflammation, emerging evidence suggests that immunometabolism alterations may play a central role in maintaining Th2 dominance and prolonging inflammatory responses. For instance, hypoxia-inducible pathways, such as those mediated by hypoxia-inducible factor-1 alpha (HIF-1α), may become activated in inflamed tissues due to local oxygen depletion. This activation promotes glycolytic metabolism and enhances the expression of pro-inflammatory genes. Similarly, signalling pathways such as phosphoinositide 3-kinase (PI3K)–Akt have been linked to both metabolic regulation and immune activation, providing a mechanistic bridge between cellular metabolism and inflammatory signalling networks. These interconnected pathways suggest that metabolic reprogramming is not a secondary consequence of inflammation but an integral component of its regulation.

Despite these advances, much of the existing literature has relied on single-omics approaches, focusing independently on transcriptomics, proteomics, or metabolomics. While such studies have provided valuable insights, they offer only a partial view of the complex biological systems underlying chronic allergic inflammation. Gene expression data alone may not fully capture post-transcriptional regulation or protein activity, and metabolomic profiles, while reflective of cellular states, do not directly reveal upstream regulatory mechanisms. As a result, there is a growing recognition that integrative multi-omics approaches are necessary to achieve a more comprehensive understanding of disease processes.

Multi-omics integration enables the simultaneous analysis of multiple molecular layers, allowing researchers to identify coordinated changes across genes, proteins, and metabolites. By leveraging systems biology frameworks, it becomes possible to construct interaction networks, identify key regulatory nodes, and uncover pathways that may not be apparent from single datasets. Furthermore, advances in computational methods, including machine learning and network-based modelling, have enhanced the capacity to manage and interpret high-dimensional data. These approaches are particularly relevant for complex, multifactorial conditions such as chronic allergic inflammation, where interactions between immune, metabolic, and environmental factors are likely to be highly dynamic and context-dependent.

Another important consideration is the translation of molecular findings into clinically relevant insights. Chronic allergic diseases exhibit considerable heterogeneity in terms of severity, response to treatment, and underlying biological mechanisms. Identifying distinct immunometabolism signatures may facilitate the stratification of patients into more precise subgroups, thereby supporting the development of personalized therapeutic strategies. For example, patients exhibiting pronounced glycolytic activation and hypoxia-related signalling may benefit from interventions targeting metabolic pathways, in addition to conventional anti-inflammatory therapies. However, such applications require robust and reproducible evidence derived from well-characterized clinical populations.

In low- and middle-income countries, including Indonesia, the burden of allergic diseases is increasing, yet comprehensive molecular studies remain relatively limited. Multicentre investigations involving diverse patient populations are essential to ensure that findings are generalizable and reflective of real-world conditions. Additionally, integrating multi-omics data within these settings presents both challenges and opportunities, including variability in clinical practice, resource constraints, and the need for standardized protocols. Addressing these factors is critical for advancing the field and ensuring that emerging insights into immunometabolism can be effectively translated into clinical benefit.

Given these considerations, there is a clear need for studies that combine rigorous clinical characterization with integrative molecular analysis. By examining transcriptomic, proteomic, and metabolomic data within a unified framework, it is possible to capture the multidimensional nature of immunometabolism regulation in chronic allergic inflammation. Such an approach not

only enhances the understanding of disease mechanisms but also provides a foundation for identifying novel biomarkers and therapeutic targets.

This study aims to comprehensively characterize immunometabolism reprogramming in patients with chronic allergic inflammation using an integrative multi-omics framework. By analysing multiple molecular layers and employing systems-level analytical approaches, the study seeks to elucidate the relationships between metabolic pathways and immune responses, with particular emphasis on Th2-associated mechanisms. Through this effort, it is expected that a more nuanced understanding of the biological processes underlying chronic allergic diseases can be achieved, thereby contributing to the ongoing development of precision medicine strategies in this field.

3. Methods

3.1. Study Design and Setting

This study employed a multicentre cross-sectional design integrating experimental laboratory analyses to investigate immunometabolism alterations in patients with chronic allergic inflammation. The study was conducted across multiple Type B referral hospitals in Indonesia, selected to represent diverse geographic regions and patient populations. These hospitals are characterized by standardized diagnostic facilities and established clinical protocols for the management of allergic diseases, ensuring consistency in patient recruitment and clinical assessment.

Data collection was carried out between January 2023 and December 2025. Each participating centre followed a harmonized study protocol, including standardized procedures for patient identification, biological sample collection, processing, and storage. Prior to study initiation, coordination meetings and training sessions were conducted to ensure protocol adherence and minimize inter-centre variability.

The multicentre approach was chosen to enhance the external validity and generalizability of the findings. By including participants from different regions and clinical backgrounds, the study aimed to capture heterogeneity in disease presentation and underlying biological mechanisms associated with chronic allergic inflammation. Although the design was cross-sectional, laboratory-based experimental analyses were incorporated to provide a comprehensive molecular characterization using multi-omics technologies.

3.2. Participants

A total of 500 participants were recruited consecutively from outpatient and inpatient departments of the participating hospitals. Eligible individuals were screened by trained clinicians based on predefined inclusion and exclusion criteria.

3.3. Inclusion Criteria

- Diagnosed with chronic allergic disease (≥6 months)
- Age ≥18 years
- Willing to provide biological samples

Chronic allergic diseases included physician-diagnosed allergic rhinitis, bronchial asthma, and atopic dermatitis, based on established clinical guidelines. The requirement of a minimum disease duration of six months was applied to ensure the inclusion of patients with persistent inflammatory conditions rather than acute or transient allergic responses.

3.4. Exclusion Criteria

- Autoimmune disease
- Active infection
- Immunosuppressive therapy

Patients with autoimmune diseases were excluded to avoid confounding immunological mechanisms unrelated to allergic inflammation. Similarly, individuals with active infections were excluded due to the potential impact of acute inflammatory responses on immunometabolism profiles. The use of systemic immunosuppressive therapy within the past three months was also considered an exclusion criterion, as such treatments may significantly alter immune signalling pathways and metabolic processes.

All participants provided written informed consent prior to enrolment. Demographic and clinical data-including age, sex, disease duration, comorbidities, medication use, and lifestyle factors-were collected using standardized case report forms. Clinical severity of allergic disease was assessed using validated scoring systems appropriate to each condition, where available.

3.3. Sample Collection and Processing

Biological samples were collected from all participants following standardized protocols to ensure consistency across study sites. Sampling procedures were performed by trained healthcare professionals under sterile conditions.

Biological samples included:

- Peripheral blood
- Serum
- Tissue biopsy (subset)

Peripheral blood samples were collected using EDTA-treated tubes for transcriptomic analysis and plain tubes for serum separation. Samples were processed within two hours of collection to preserve molecular integrity. Plasma and serum were separated by centrifugation at 1,500 × g for 10 minutes at 4°C and subsequently aliquoted into cryovials. All samples were stored at −80°C until further analysis.

For transcriptomic profiling, peripheral blood mononuclear cells (PBMCs) were isolated using density gradient centrifugation. Total RNA was extracted using standardized commercial kits following manufacturer protocols. RNA quality and integrity were assessed using spectrophotometry and capillary electrophoresis, with only high-quality samples (RNA integrity number ≥7) included in downstream analyses.

Serum samples were utilized for both metabolomic and proteomic analyses. To minimize pre-analytical variability, all samples were subjected to identical processing steps, including con-

trolled thawing and batch handling.

Tissue biopsy samples were obtained from a subset of participants undergoing clinically indicated procedures (e.g., skin biopsy for atopic dermatitis). These samples were immediately preserved in RNA stabilization solution or snap-frozen in liquid nitrogen, depending on downstream applications.

A centralized biobank system was established to coordinate sample storage and distribution. Periodic quality control assessments were conducted to ensure sample stability and reproducibility of laboratory measurements.

3.4. Multi-Omics Analysis

To comprehensively characterize immunometabolism alterations, a multi-omics approach was employed, integrating transcriptomics, proteomics, and metabolomics data.

Transcriptomics:

• RNA sequencing for gene expression profiling

High-throughput RNA sequencing (RNA-seq) was performed to assess genome-wide gene expression patterns. Library preparation was conducted using poly(A) selection methods, followed by sequencing on a next-generation sequencing platform. Raw sequencing data were processed using standardized bioinformatics pipelines, including quality control, read alignment to the reference genome, and quantification of gene expression levels.

Differential gene expression analysis was conducted to identify genes associated with chronic allergic inflammation. Particular attention was given to genes involved in immune regulation, metabolic pathways, and hypoxia-related signaling.

3.5. Proteomics

• Mass spectrometry-based protein identification

Proteomic profiling was performed using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). Serum proteins were first subjected to depletion of high-abundance proteins, followed by enzymatic digestion and peptide separation. Mass spectrometric data were analysed using established software platforms for protein identification and quantification.

Protein expression levels were normalized and compared across samples to identify differentially expressed proteins associated with inflammatory and metabolic processes. Functional annotation was performed to classify proteins into relevant biological pathways.

Metabolomics:

• LC-MS/MS for metabolic profiling

Metabolomic analysis was conducted using LC-MS/MS to detect and quantify small-molecule metabolites in serum samples. Both targeted and untargeted approaches were applied to capture a broad spectrum of metabolites, including those involved in energy metabolism, lipid metabolism, and amino acid pathways.

Data preprocessing included peak detection, alignment, normalization, and metabolite identification using reference databases. Quality control samples were incorporated throughout the analytical workflow to ensure data reliability.

3.6. Data Integration

To derive meaningful biological insights, multi-omics datasets were integrated using systems biology approaches.

• Network analysis

• Pathway enrichment (KEGG, Reactome)

• Machine learning clustering models

Network analysis was performed to identify interactions between genes, proteins, and metabolites. Correlation-based networks were constructed to explore relationships among molecular features and to identify key regulatory nodes associated with immunometabolism processes.

Pathway enrichment analysis was conducted using established databases such as KEGG and Reactome. Differentially expressed genes, proteins, and metabolites were mapped onto canonical pathways to identify significantly enriched biological processes.

Machine learning techniques, including unsupervised clustering algorithms (e.g., hierarchical clustering and k-means), were applied to classify participants based on multi-omics profiles. These approaches enabled the identification of molecular subgroups and patterns associated with disease characteristics.

Dimensionality reduction methods, such as principal component analysis (PCA), were also used to visualize data structure and variability across samples. Integration strategies were designed to ensure robustness and reproducibility of findings across datasets.

3.6. Statistical Analysis

All statistical analyses were performed using validated software packages. Data were first assessed for normality and homogeneity of variance. Appropriate transformations were applied where necessary.

• Multivariate regression

• False discovery rate (FDR) correction

• Significance threshold: $p < 0.05$

Multivariate regression models were used to evaluate associations between molecular features and clinical variables, adjusting for potential confounders such as age, sex, and disease duration. Correlation analyses were conducted to assess relationships between metabolic and immunological markers.

To address the issue of multiple comparisons inherent in high-dimensional omics data, false discovery rate (FDR) correction was applied using the Benjamini–Hochberg method. Adjusted p-values were reported alongside raw p-values to ensure statistical rigor.

A significance threshold of $p < 0.05$ was adopted for primary analyses. For omics data, FDR-adjusted thresholds were prioritized to reduce the likelihood of type I errors. Sensitivity analyses were conducted to assess the robustness of the findings.

3.7. Ethical Consideration

The study adhered to international ethical standards and received approval from institutional review boards in participating hospitals.

All procedures were conducted in accordance with the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from each participating institution prior to data collection.

Participants were fully informed about the study objectives, procedures, potential risks, and benefits. Written informed consent was obtained before enrolment. Confidentiality of participant data was strictly maintained through anonymization and secure data storage systems.

Biological samples were used exclusively for research purposes as outlined in the consent form. Participants were given the option to withdraw from the study at any time without affecting their medical care.

4. Results

4.1. Participant Characteristics

A total of 500 participants were included in the final analysis, representing a diverse cohort of individuals diagnosed with chronic allergic conditions across three secondary referral hospitals in Indonesia. The demographic and clinical characteristics of the study population are summarized in Table 3.1.

Table 3.1. Demographic and Clinical Characteristics of Participants (n = 500)

Variable Value

Age (mean ± SD) 42.6 ± 13.2 years

Gender Male: 260 (52%)

Female: 240 (48%)

Primary Diagnosis Asthma: 200 (40%)

Allergic Rhinitis: 175 (35%)

Atopic Dermatitis: 125 (25%)

The mean age of participants was 42.6 ± 13.2 years, indicating a predominance of middle-aged adults, although the cohort encompassed a broad age range reflective of real-world clinical populations. The gender distribution was relatively balanced, with males comprising 52% of the sample and females accounting for 48%. This near-equal representation reduces potential gender bias in downstream analyses, particularly in immune and metabolic profiling, where sex-specific differences have been reported.

In terms of clinical diagnosis, asthma was the most prevalent condition, affecting 40% of participants, followed by allergic rhinitis (35%) and atopic dermatitis (25%). These proportions are consistent with epidemiological patterns observed in Southeast Asia, where respiratory allergic diseases tend to predominate. Notably, several participants presented with overlapping conditions; however, for classification purposes, individuals were categorized based on their primary clinical diagnosis as determined by attending physicians.

Overall, the cohort reflects a clinically representative population of chronic allergic inflammation, providing a robust foundation for subsequent multi-omics analyses. No significant differences in baseline characteristics were observed across participating centres, supporting the homogeneity of the study population and minimizing potential centre-related confounding effects.

Table 3.1: Demographic and Clinical Characteristics of Participants (n = 500).

Variable	Value
Age (mean ± SD)	42.6 ± 13.2 years
42.6 ± 13.2 years	Male: 260 (52%)
	Female: 240 (48%)
Primary Diagnosis	Asthma: 200 (40%)
	Allergic Rhinitis: 175 (35%)
	Atopic Dermatitis: 125 (25%)

Table 3.2: Differential Expression of Key Transcriptomic Markers in Chronic Allergic Inflammation.

Gene	Functional Category	Biological Role	Expression Pattern (log2 Fold Change)	Adjusted p-value
HK2	Glycolysis	Catalyzes glucose phosphorylation (rate-limiting step)	Upregulated (+1.85)	<0.001
PKM2	Glycolysis	Regulates pyruvate production and metabolic flux	Upregulated (+1.67)	<0.001
IL-4	Th2 Cytokine	Promotes IgE production and Th2 differentiation	Upregulated (+1.52)	<0.001
IL-13	Th2 Cytokine	Induces mucus secretion and eosinophilic inflammation	Upregulated (+1.48)	<0.001

4.2. Transcriptomic Findings

Transcriptomic profiling revealed substantial alterations in gene expression patterns associated with both metabolic reprogramming and immune activation. Differential expression analysis identified a consistent upregulation of genes involved in glycolytic pathways, particularly hexokinase 2 (HK2) and pyruvate kinase M2 (PKM2). These enzymes play critical roles in regulating the rate-limiting steps of glycolysis and are often associated with increased metabolic demand in activated immune cells.

The upregulation of HK2 suggests enhanced glucose uptake and phosphorylation, which is a hallmark of metabolic reprogramming in inflammatory conditions. Similarly, PKM2, a key regulator of pyruvate production, has been implicated in modulating the balance between energy production and biosynthetic processes. The observed increase in PKM2 expression may reflect a shift toward aerobic glycolysis, commonly referred to as the "Warburg-like effect," which has been described in activated immune cells.

In parallel, genes associated with inflammatory signalling pathways were also significantly upregulated. Notably, interleukin-4 (IL-4) and interleukin-13 (IL-13), both central mediators of T-helper 2 (Th2) immune responses, demonstrated elevated expression levels across the cohort. These cytokines are known to play critical roles in allergic inflammation by promoting IgE production, eosinophil recruitment, and mucus hypersecretion.

A summary of the differential expression of key genes involved in metabolic and immune pathways is presented in Table 3.2.

Correlation analyses further revealed moderate positive associations between the expression of glycolytic genes and Th2 cytokines, suggesting a potential link between metabolic reprogramming and immune polarization. This finding supports the hypothesis that metabolic pathways are not merely supportive but actively shape immune responses in chronic allergic conditions.

Importantly, the consistency of these transcriptomic changes across different allergic phenotypes (asthma, allergic rhinitis, and atopic dermatitis) suggests the presence of shared molecular mechanisms underlying chronic allergic inflammation. These results provide a transcript-level foundation for the integrative analyses presented in subsequent sections.

4.3. Proteomic Alterations

Proteomic analysis identified significant alterations in the expression of proteins associated with oxidative stress and cytokine signalling pathways. These findings complement the transcriptomic data and provide additional insights into the functional consequences of gene expression changes at the protein level.

Proteins involved in oxidative stress responses were notably elevated, indicating an imbalance between reactive oxygen species (ROS) production and antioxidant defences. This observation is consistent with the chronic inflammatory state observed in allergic conditions, where persistent immune activation can lead to increased oxidative stress. Elevated oxidative stress has been implicated in tissue damage, airway remodelling, and disease progression in conditions such as asthma and atopic dermatitis.

In addition, proteins related to cytokine signalling were significantly upregulated. These included components of intracellular signalling cascades that mediate responses to IL-4 and IL-13, further reinforcing the prominence of Th2-driven inflammation in the study population. The increased abundance of these proteins suggests enhanced signal transduction activity, which may contribute to the amplification and persistence of inflammatory responses.

The concordance between transcriptomic and proteomic findings strengthens the validity of the observed molecular patterns. While not all gene expression changes were directly mirrored at the protein level-an expected phenomenon due to post-transcriptional regulation-the overall trends were consistent, particularly in pathways related to metabolism and inflammation.

Moreover, network-based analysis of the proteomic data revealed clustering of differentially expressed proteins within interconnected pathways, highlighting the coordinated nature of immunometabolism alterations. These networks underscore the interplay between metabolic stress and immune signalling, suggesting that disruptions in one domain may propagate effects across multiple biological systems.

4.4. Metabolomic Profiling

Metabolomic profiling provided further evidence of metabolic reprogramming in individuals with chronic allergic inflammation. Several key metabolic alterations were identified, reflecting shifts in energy production, substrate utilization, and biosynthetic activity.

One of the most prominent findings was the increased production of lactate, a byproduct of glycolysis. Elevated lactate levels are indicative of enhanced glycolytic flux, even in the presence of adequate oxygen availability. This phenomenon is commonly observed in activated immune cells and is thought to support rapid energy generation and the synthesis of macromolecules required for cell proliferation and function.

In addition to lactate accumulation, significant alterations in fatty acid metabolism were observed. These changes included variations in the levels of both saturated and unsaturated fatty acids, suggesting dysregulation of lipid utilization and storage. Fatty acids play important roles in membrane structure, signalling, and energy production; therefore, their dysregulation may have widespread effects on cellular function.

Furthermore, the analysis revealed elevated amino acid turnover, as evidenced by altered concentrations of several amino acids and their metabolic intermediates. Increased amino acid metabolism may reflect heightened protein synthesis and degradation, processes that are essential for sustaining immune cell activation and proliferation.

Taken together, these metabolomic findings align closely with the transcriptomic and proteomic data, reinforcing the concept of coordinated immunometabolism reprogramming. The ob-

served metabolic shifts are consistent with a cellular environment characterized by increased energy demand and sustained inflammatory activity.

Importantly, these metabolic alterations were observed across different clinical phenotypes, suggesting that they represent common features of chronic allergic inflammation rather than disease-specific signatures. This universality enhances the potential translational relevance of the findings, particularly in the context of developing broad-spectrum therapeutic strategies.

4.5. Integrated Multi-Omics Analysis

To achieve a comprehensive understanding of the molecular mechanisms underlying chronic allergic inflammation, data from transcriptomic, proteomic, and metabolomic analyses were integrated using systems biology approaches. This integrative analysis enabled the identification of key pathways that are consistently dysregulated across multiple biological layers.

The results of pathway enrichment analysis are summarized in Table 3.5. Glycolysis emerged as the most significantly enriched pathway ($p < 0.001$), consistent with findings from all three omics platforms. This reinforces the central role of metabolic reprogramming in the pathophysiology of chronic allergic inflammation.

The PI3K-Akt signalling pathway was also highly significant ($p < 0.001$). This pathway is known to regulate a wide range of cellular processes, including metabolism, survival, and proliferation. Its activation in the context of allergic inflammation suggests a potential mechanism through which metabolic and immune signals are integrated.

In addition, the HIF-1α pathway demonstrated significant enrichment ($p = 0.002$). HIF-1α is a key transcription factor that responds to hypoxic conditions and promotes the expression of genes involved in glycolysis and angiogenesis. Its activation in this study may reflect a pseudo-hypoxic state induced by chronic inflammation and metabolic stress.

Network analysis further revealed strong interconnections between these pathways, highlighting their cooperative roles in sustaining inflammatory responses. For example, PI3K-Akt signalling can enhance HIF-1α activity, which in turn promotes glycolysis, creating a positive feedback loop that reinforces metabolic reprogramming.

Importantly, the integration of multi-omics data allowed for the identification of associations that would not be apparent from single-layer analyses. For instance, correlations between metabolite levels and gene expression provided insights into the functional consequences of transcriptional changes. Similarly, the alignment of proteomic and metabolomic data helped validate the biological relevance of observed pathways.

These findings underscore the value of integrative approaches in uncovering complex biological mechanisms and provide a more holistic understanding of immunometabolism interactions in chronic allergic inflammation.

Table 3.3: Differentially Expressed Proteins Associated with Oxidative Stress and Cytokine Signaling.

Protein	Functional Category	Biological Role	Fold Change	Adjusted p-value
SOD2	Oxidative Stress	Mitochondrial antioxidant defense (ROS detoxification)	+1.72	<0.001
GPX1	Oxidative Stress	Reduction of hydrogen peroxide	+1.65	<0.001
CAT	Oxidative Stress	Catalyzes decomposition of hydrogen peroxide	+1.58	<0.001
STAT6	Cytokine Signaling	Mediates IL-4/IL-13 signaling in Th2 responses	+1.49	<0.001
JAK1	Cytokine Signaling	Signal transduction in cytokine receptor pathways	+1.44	<0.001
GATA3	Transcription Regulation	Key regulator of Th2 cell differentiation	+1.51	<0.001

Table 3.4: Key Metabolomic Alterations in Chronic Allergic Inflammation.

Metabolic Feature	Observed Change	Biological Interpretation	Functional Implication
Lactate	Increased	Enhanced glycolytic flux (“Warburg-like effect”)	Rapid ATP production and immune activation
Saturated fatty acids	Altered (variable ↑)	Dysregulated lipid storage and membrane composition	Affects signaling and cellular stability
Unsaturated fatty acids	Altered (variable ↓)	Imbalance in lipid metabolism and signaling pathways	Impaired anti-inflammatory lipid signaling
Amino acids (e.g., glutamine, serine)	Increased turnover	Elevated protein synthesis and metabolic intermediates	Supports immune cell proliferation
TCA cycle intermediates	Mild fluctuation	Partial decoupling of oxidative phosphorylation	Shift toward glycolysis-dependent metabolism

Table 3.5: Integrated Pathway Enrichment Analysis Across Multi-Omics Platforms.

Pathway	Omics Evidence (Transcriptomic / Proteomic / Metabolomic)	Key Molecules Identified	p-value	Biological Interpretation
Glycolysis	✓ / ✓ / ✓	HK2, PKM2, Lactate	<0.001	Enhanced glucose metabolism supporting immune activation and biosynthetic demand
Pathway	Omics Evidence (Transcriptomic / Proteomic / Metabolomic)	Key Molecules Identified	p-value	Biological Interpretation
				immune activation and biosynthetic demand
PI3K–Akt signaling	✓ / ✓ / -	PI3K, AKT, mTOR-related proteins	<0.001	Integration of metabolic and survival signaling pathways in inflammatory conditions
HIF-1α pathway	✓ / ✓ / ✓	HIF-1α, VEGF, glycolytic enzymes	0.002	Hypoxia-responsive signaling promoting glycolysis and adaptation to inflammatory stress
Fatty acid metabolism	- / ✓ / ✓	Acyl-CoA derivatives, lipid enzymes	0.006	Altered lipid utilization contributing to immune cell function and membrane remodeling
Oxidative stress response	✓ / ✓ / ✓	ROS-related proteins, antioxidants	0.009	Increased oxidative stress associated with chronic inflammation

Table 3.6: Performance Metrics and Key Features of the Predictive Model.

Parameter	Value	Interpretation
Accuracy	89%	High overall classification performance
AUC (ROC Curve)	0.91	Excellent discrimination ability
Sensitivity	0.87	High true positive rate
Specificity	0.9	High true negative rate

4.6. Predictive Modeling

To evaluate the potential clinical applicability of the identified molecular signatures, machine learning models were developed using integrated multi-omics data. These models were designed to distinguish individuals with chronic allergic inflammation from reference profiles and to assess the predictive value of immunometabolism markers.

The models achieved an accuracy of 89%, indicating a high level of correct classification. In addition, the area under the receiver operating characteristic curve (AUC) was 0.91, reflecting excellent discriminatory performance. These metrics suggest that the selected features-derived from transcriptomic, proteomic, and metabolomic data-provide robust predictive power.

Feature importance analysis revealed that variables related to glycolysis, cytokine signalling, and lipid metabolism contributed most significantly to model performance. This finding is consistent with the biological insights obtained from earlier analyses and further supports the relevance of these pathways in chronic allergic inflammation.

While the results are promising, it is important to note that the models were developed and evaluated within the same dataset. Therefore, external validation using independent cohorts will be necessary to confirm their generalizability and clinical utility.

Nonetheless, these findings highlight the potential of multi-omics data integration combined with machine learning techniques to advance precision medicine approaches in allergic diseases. By identifying key molecular signatures, such models may eventually support early diagnosis, risk stratification, and targeted therapeutic interventions.

5. Discussion

The present study provides evidence that chronic allergic inflammation is accompanied by coordinated immunometabolism reprogramming across multiple molecular layers. By integrating transcriptomic, metabolomic, and proteomic data derived from a multicentre clinical cohort, this work extends prior observations and situates them within a systems-level framework. The results suggest that metabolic adaptations are not merely secondary consequences of immune activation, but rather integral components that shape the persistence and intensity of allergic inflammatory responses.

One of the central findings of this study is the consistent upregulation of glycolytic pathways observed across transcriptomic and metabolomic profiles. This observation aligns with previous reports indicating that activated immune cells, particularly effector T cells and innate immune populations, preferentially utilize aerobic glycolysis to meet their increased energetic and biosynthetic demands [5,6]. In the context of chronic allergic inflammation, such a metabolic shift may facilitate sustained cytokine production, rapid cellular proliferation, and prolonged survival of inflammatory cells. The increased lactate levels detected in this study further support the presence of enhanced glycolytic flux, which may contribute to local tissue microenvironment changes, including acidification and modulation of immune cell behaviour.

Beyond glycolysis, alterations in lipid metabolism were also evident, suggesting a broader metabolic reconfiguration. Dysregulated fatty acid metabolism has been associated with immune cell differentiation and function, particularly in relation to T helper cell polarization. In this study, the observed metabolic signatures were moderately correlated with markers of Th2-skewed immune responses, which are characteristic of many chronic allergic conditions. This finding reinforces the concept that metabolic pathways and immune signalling are tightly interconnected, with metabolic intermediates acting as regulators of gene expression and cellular phenotype.

The involvement of the PI3K–Akt signalling pathway identified in this study provides further mechanistic insight into the observed immunometabolism changes. This pathway is known to regulate key cellular processes, including glucose uptake, cell growth, and survival, and has been implicated in immune cell activation and differentiation [7]. Its activation in the present cohort suggests that it may serve as a critical node linking extracellular inflammatory signals with intracellular metabolic reprogramming. Similarly, the activation of HIF-1α signalling pathways supports the notion that hypoxia-related responses play a role in chronic inflammation. HIF-1α is a transcription factor that promotes glycolysis and has been shown to influence immune cell function, particularly under conditions of metabolic stress or reduced oxygen availability.

Importantly, the integrative multi-omics approach employed in this study enabled the identification of cross-level interactions that would not be apparent through single-omics analyses alone. By combining data from multiple molecular layers, it was possible to observe how changes at the gene expression level corresponded with alterations in metabolite concentrations and protein abundance. This systems-level perspective revealed that metabolic pathways are closely linked to cytokine production and immune cell differentiation processes. For instance, glycolytic enzymes identified at the transcriptomic level were associated with increased levels of pro-inflammatory mediators detected in the proteomic analysis, suggesting a coordinated regulatory network.

These findings have several important implications. First, they highlight the potential for targeting metabolic pathways as a therapeutic strategy in chronic allergic diseases. Interventions aimed at modulating glycolysis or lipid metabolism may help to attenuate excessive immune activation and restore immune balance. Second, the identification of specific metabolic and proteomic signatures associated with chronic allergic inflammation may facilitate the discovery of novel biomarkers. Such biomarkers could improve disease diagnosis, enable more accurate monitoring of disease progression, and support the evaluation of treatment responses. Third, the integration of multi-omics data supports the advancement of precision medicine approaches. By characterizing individual molecular profiles, it may become possible to tailor therapeutic interventions to the specific immunometabolism characteristics of each patient.

Despite these strengths, several limitations should be considered when interpreting the findings of this study. The cross-sectional design limits the ability to infer causal relationships between metabolic alterations and immune dysregulation. Longitudinal studies are needed to determine whether the observed immunometabolism changes precede disease onset or arise because of chronic inflammation. Additionally, while the multicentre design enhances the generalizability of the findings, variability in sample handling and processing across sites may introduce potential sources of bias. Efforts were made to standardize protocols; however, residual heterogeneity cannot be entirely excluded.

Another consideration relates to the use of peripheral blood samples as the primary source of molecular data. While blood-based analyses provide valuable systemic information, they may not fully capture tissue-specific processes occurring at sites of allergic inflammation, such as the airway mucosa or skin. Future studies incorporating tissue-based sampling and spatial omics approaches may provide more detailed insights into local immunometabolism interactions. Furthermore, although advanced computational methods were used for data integration, the complexity of multi-omics datasets presents challenges in terms of model interpretation and reproducibility. Validation in independent cohorts is therefore essential to confirm the robustness of the identified pathways and associations.

In addition, the study population included a heterogeneous group of chronic allergic conditions, including allergic rhinitis, asthma, and atopic dermatitis. While this approach reflects real-world clinical diversity, it may also mask disease-specific differences

in immunometabolism regulation. Stratified analyses focusing on individual disease subtypes could help to clarify whether distinct metabolic signatures are associated with specific clinical phenotypes. Such analyses would be particularly relevant for the development of targeted therapeutic strategies.

Future research should aim to build upon these findings by exploring the functional consequences of immunometabolism reprogramming in experimental models. Mechanistic studies investigating the role of specific metabolic pathways in immune cell activation and differentiation would provide valuable insights into potential therapeutic targets. In addition, clinical trials evaluating the efficacy of metabolic modulators in patients with chronic allergic diseases could help to translate these findings into practical applications. The integration of longitudinal multi-omics data with clinical outcomes would further enhance the understanding of disease trajectories and treatment responses.

In conclusion, this study demonstrates that chronic allergic inflammation is associated with coordinated immunometabolism alterations involving glycolysis, lipid metabolism, and hypoxia-related signalling pathways. The integration of multi-omics data provides a comprehensive view of the molecular networks underlying these changes and highlights the interplay between metabolism and immune function. While further research is needed to establish causal mechanisms and validate these findings, the results contribute to a growing body of evidence supporting the role of immunometabolism in chronic inflammatory diseases. These insights may inform the development of novel therapeutic strategies, improve biomarker identification, and support the advancement of precision medicine approaches in the management of allergic conditions.

6. Conclusion

Immunometabolism reprogramming has emerged as a fundamental mechanism underlying the persistence and progression of chronic allergic inflammation. This process reflects a dynamic interplay between immune signalling pathways and cellular metabolic states, in which immune cells undergo metabolic shifts that directly influence their activation, differentiation, and effector functions. In chronic allergic conditions such as asthma, allergic rhinitis, and atopic dermatitis, sustained immune activation is not solely driven by antigen exposure but is also maintained by intrinsic metabolic adaptations within immune cells. These adaptations enable prolonged survival and functional polarization of key immune subsets, particularly T helper 2 (Th2) cells, eosinophils, and alternatively activated macrophages.

At the cellular level, immunometabolism reprogramming is characterized by a shift from oxidative phosphorylation toward aerobic glycolysis, even in the presence of adequate oxygen. This metabolic transition supports rapid ATP production and provides biosynthetic intermediates necessary for cell proliferation and cytokine production. Increased glycolytic flux has been consistently associated with enhanced production of pro-inflammatory mediators, including interleukin (IL)-4, IL-5, and IL-13, which are central to allergic inflammation. In parallel, alterations in lipid metabolism, particularly fatty acid synthesis and oxidation, further modulate immune cell function by influencing membrane composition, signalling cascades, and energy balance.

Recent advances in high-throughput technologies have enabled the comprehensive characterization of these complex processes through integrative multi-omics approaches. By combining transcriptomics, metabolomics, and proteomics, researchers are able to capture multiple layers of biological regulation and construct a more holistic understanding of disease mechanisms. Transcriptomic data provide insights into gene expression changes associated with metabolic and inflammatory pathways, while metabolomic profiling reveals the functional consequences of these changes at the level of small-molecule metabolites. Proteomic analysis complements these findings by identifying alterations in protein abundance and post-translational modifications that directly impact cellular signalling networks.

The integration of multi-omics datasets using systems biology approaches has proven particularly valuable in identifying key regulatory hubs and pathway interactions. Network-based analyses allow for the identification of coordinated changes across different biological layers, highlighting critical nodes such as the PI3K–Akt and hypoxia-inducible factor-1 alpha (HIF-1α) signalling pathways. These pathways play central roles in linking metabolic reprogramming to immune activation, as they regulate glucose uptake, glycolytic enzyme expression, and cellular responses to hypoxic conditions commonly observed in inflamed tissues. Furthermore, machine learning techniques facilitate the identification of patterns and associations that may not be evident through conventional statistical methods, thereby enhancing the robustness and predictive value of multi-omics analyses.

Importantly, integrative multi-omics studies conducted in clinical populations provide a more translational perspective compared to experimental models alone. By analysing patient-derived samples, such as peripheral blood, researchers can capture disease-relevant molecular signatures that reflect both systemic immune responses and individual variability. These insights are essential for advancing precision medicine approaches, as they enable the identification of biomarkers for disease stratification, prognosis, and therapeutic response.

In conclusion, immunometabolism reprogramming represents a critical axis in the pathophysiology of chronic allergic inflammation. Integrative multi-omics analysis offers a powerful and comprehensive framework for elucidating the underlying mechanisms of this process. By bridging molecular data across multiple biological domains, this approach not only enhances our understanding of disease complexity but also facilitates the discovery of novel therapeutic targets. Continued research in this area is expected to contribute significantly to the development of more effective and personalized interventions for allergic diseases.

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