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Epigenetics and its role in development and regulation of allergy — a systematic review

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Abstract

BACKGROUND: Epigenetic mechanisms involving DNA methylation, histone modifications, and non-coding RNAs have more recently been highlighted as important regulatory elements of gene expression in allergic diseases. Such mechanisms mediate interactions between predisposing genetic determinants and environmental exposures, with subsequent influences on immune response as well as on susceptibility to conditions such as asthma, allergic rhinitis, atopic dermatitis, and food allergies.

MATERIALS AND METHODS: This systematic review integrated evidence from studies exploring the role of epigenetic modifications in allergic diseases. The databases were searched systematically and relevant studies as per predefined PECOS criteria were included. All data regarding epigenetic mechanisms, the target loci involved, environmental influences, and allergic outcomes were extracted and analyzed. The studies were evaluated for risk of bias using the RoB 2.0 and ROBINS-I tools, and the certainty of evidence was appraised using the GRADE framework.

RESULTS: It was observed that DNA methylation at such loci, including *FOXP3* and *IL-4Rα*, was invariably associated with immune dysregulation in allergic diseases across the 11 studies included. Exposure to pollutants and microbial exposure has shown associations with alterations in epigenetic profiles that have resulted in significant impacts on immune tolerance and allergic inflammation. Quantitative results: in specific immunotherapy settings, 95% suppression of effector T-cell proliferation (p <0.0001), and identification of 956 CpG sites associated with the risk of allergic rhinitis Fixed drug reaction (FDR) <5%. The studies together showed that epigenetic modifications are central to the pathogenesis of allergic diseases and may be used as biomarkers and therapeutic targets.

CONCLUSION: This review highlighted how epigenetics played a crucial role in the development and regulation of allergic diseases and underlined the interactions between these entities and environmental exposures. Findings indicated that epigenetic mechanisms promise a wide potential in precision medicine, mainly concerning biomarker discovery and treatment stratification. However, study methodology heterogeneity and variability of results should be pursued further for homogenization of methodologies and thus increasing the applicability in clinics.

Keywords: epigenetics; DNA methylation; allergic disease; immune regulation; environmental exposure; biomarker; precision medicine.

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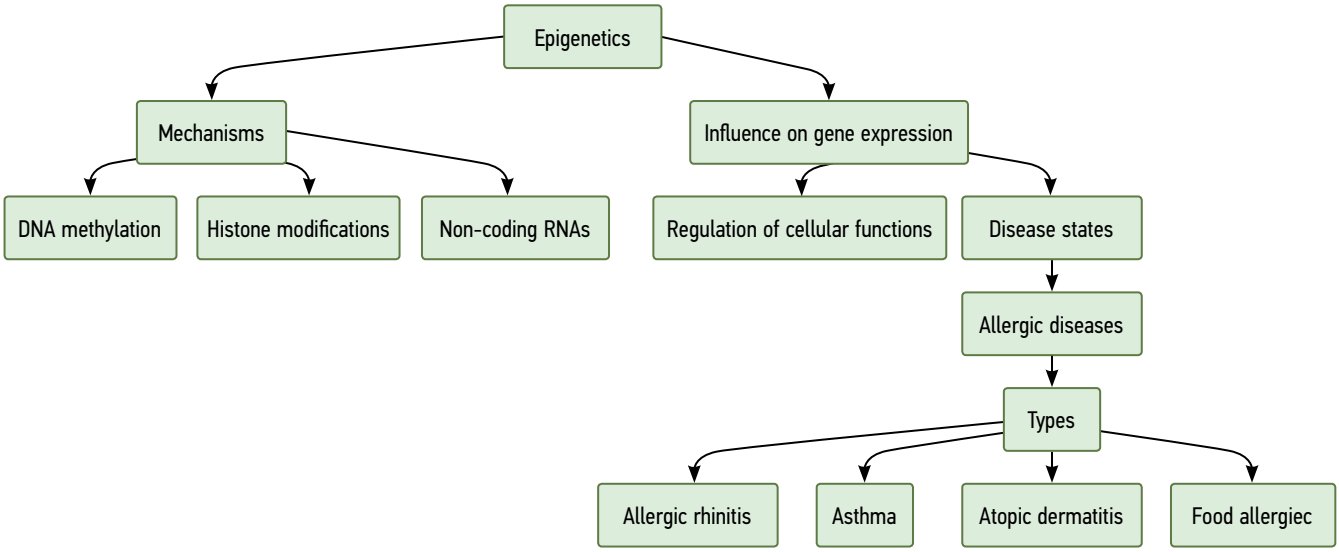

Fig. 1. Overview of epigenetics and allergic diseases.

Background

Epigenetics refers to the study of heritable modifications in gene expression without alterations to the underlying DNA sequence. This has emerged as a critical area of research regarding how genetic and environmental factors converge to regulate cellular functions and disease states. These have been shown to dynamically influence chromatin architecture and gene transcription through mechanisms including DNA methylation, histone modifications, and non-coding RNA activity, which provides a rather versatile framework for gene-environment interactions. Epigenetic changes are not fixed genetic mutations and thus are reversible. They therefore become key targets in understanding mechanisms of disease and the development of novel therapeutic approaches (Fig. 1) [1–3].

Allergic diseases include allergic rhinitis, asthma, atopic dermatitis, and food allergies. It represents a significant and growing health burden across all ages of millions of individuals worldwide [4, 5]. These diseases have rapidly increased in prevalence over the past few decades, especially in the urbanized and industrialized area. It is hypothesized that environmental factors such as pollution, dietary changes, microbial exposure, and sedentary lifestyle exacerbate allergic responses [6]. The sharp rise in disease over the previous decades, therefore, cannot be explained by predisposition alone, bringing into particular relevance epigenetic mechanisms as mediators of the impacts of environmental exposures on immunity and susceptibility to disease [7].

Dysregulated immune responses are central in allergic diseases (Fig. 2). Here, these relate to T helper (Th) and regulatory T cells (Treg) interactions with B cells. There are skewed Th2-mediated responses, that involve the overexpression of interleukins (IL) such as IL-4, IL-5, and IL-13, hence orchestrating the allergic inflammatory cascades [8]. These processes significantly appear to be modulated through epigenetic alterations. For instance, the DNA methylation patterns of the promoter regions of Th2 cytokine genes are associated with higher Th2 responses, whereas TSDRs in the *FOXP3* gene are associated with Treg function and immune tolerance [9]. Histone acetylation and methylation further modulate chromatin accessibility and thus the expression of genes involved in allergic inflammation and resolution [10]. Non-coding RNAs, especially microRNAs, have more recently emerged as important regulators targeting messenger RNAs to fine-tune immune cell signaling and cytokine production in allergic diseases [11].

Environmental exposures are powerful epigenetic modulators of allergic diseases (Fig. 3). Inhaled pollutants such as diesel exhaust particles can lead to the hypermethylation or hypomethylation of immune-related genes, changing immune cell function and aggravating the disease [12]. Furthermore, diet and, importantly, gut microbiota profiles during early development significantly impact the epigenetic programming of either immune tolerance or susceptibility to allergens. Hence, this evidence emphasizes the part of the life exposome cumulative lifetime environmental exposure that drives these epigenetic changes predisposing people to allergy diseases [13, 14].

Much progress has been made so far, but significant translation to clinical practice has yet to be achieved. There is still much heterogeneity of allergic diseases, differences in the methodologies applied, and variability in environmental

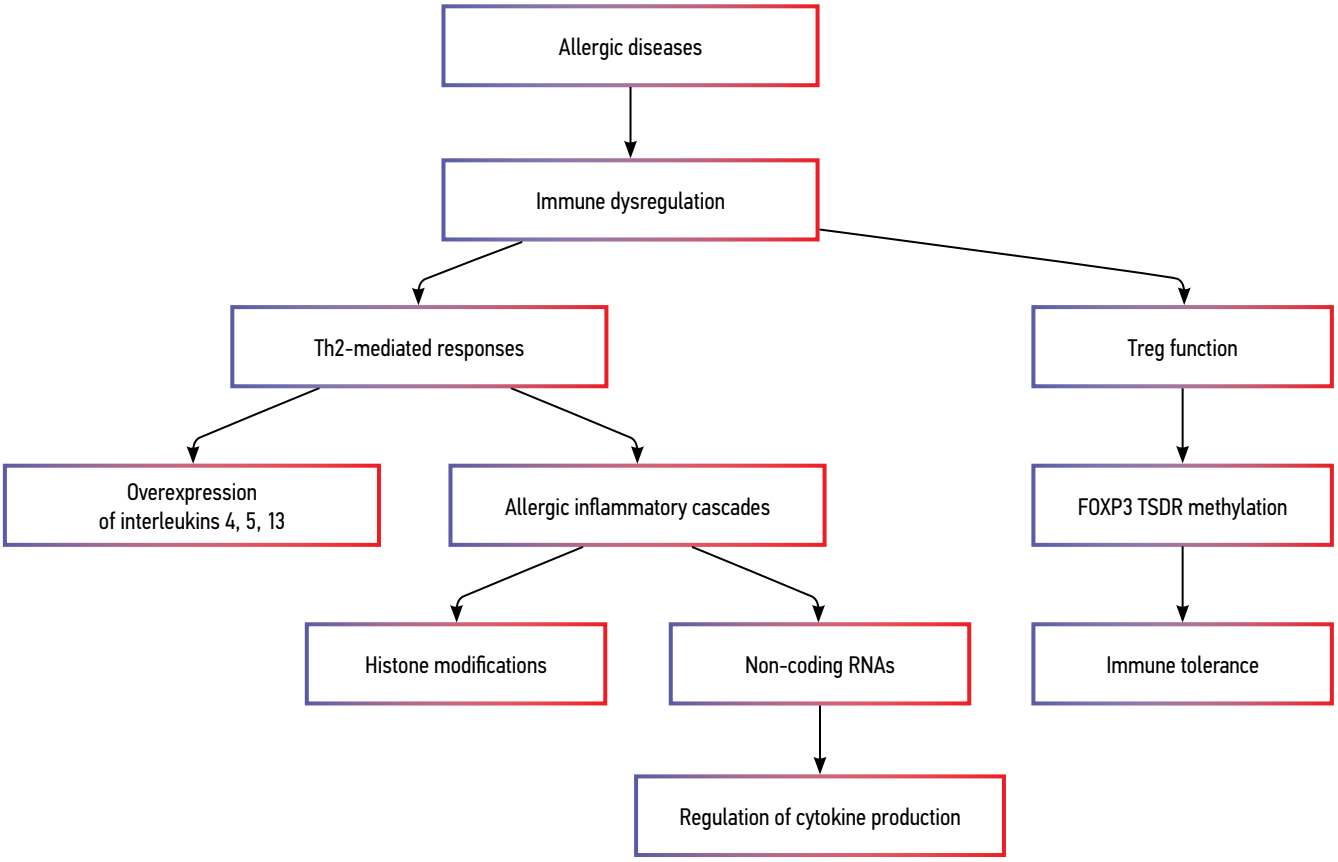

Fig. 2. Role of epigenetics in allergic diseases.

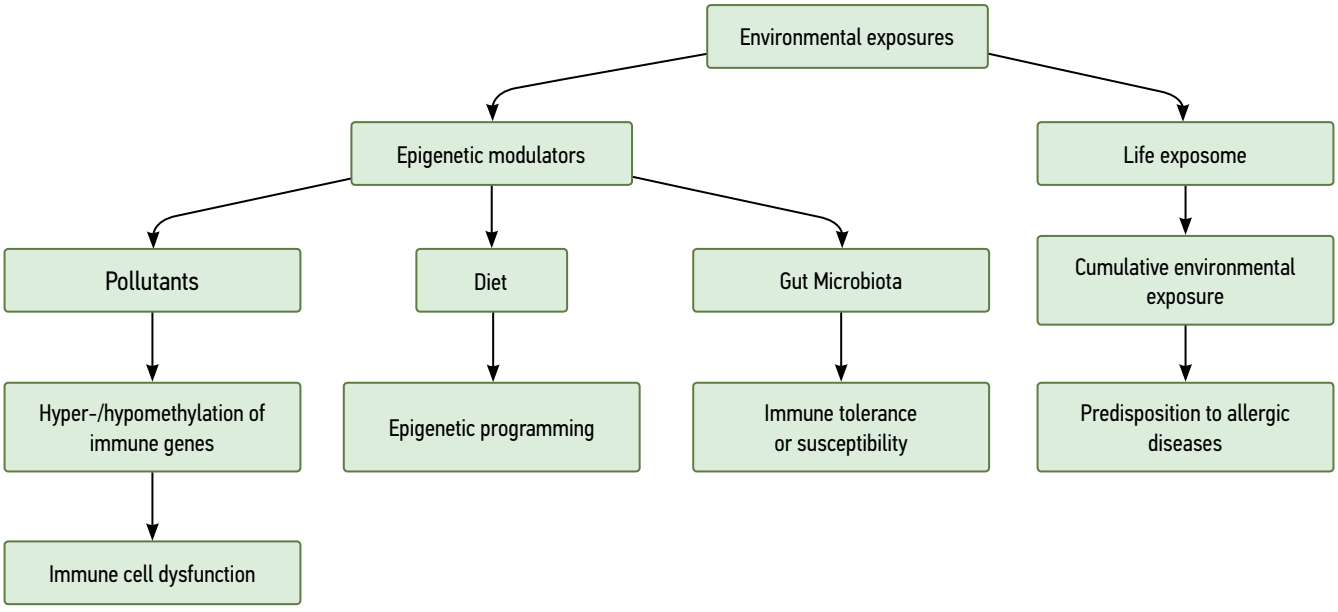

Fig. 3. Environmental modulation of epigenetics.

exposures to identify a consistent epigenetic biomarker. Moreover, understanding functional consequences requires integrated approaches that consider molecular, environmental, and clinical data. Efforts have been eased by recent developments in high-throughput sequencing and bioinformatics to identify disease state and treatment response epigenetic signatures. Against this backdrop, this systematic review and meta-analysis aims to synthesize current evidence on the role of epigenetic mechanisms in the development and regulation of allergic diseases.

Materials and methods

Review design

The PECOS (Population, Exposure, Comparison, Outcomes, Study design) protocol of this systematic review followed the reporting guidelines of PRISMA to allow it to be made transparent and reproducible (Table 1) [15]. The population included individuals diagnosed with allergic diseases, including asthma, allergic rhinitis, atopic dermatitis, and food allergies. The exposure involved epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNAs. The comparator comprised individuals without allergic conditions or with normal epigenetic profiles. The outcomes focused on the association of epigenetic alterations with immune dysregulation, disease severity, and therapeutic responses. The study design included observational, cohort, case-control, and clinical studies that assessed the role of epigenetics in allergic diseases.

Database search protocol

To ensure an all-inclusive capture of literature, a database search strategy was conceptualized. It was performed in seven databases: PubMed, Embase, Scopus, Web of Science, Cochrane Library, CINAHL, and PsycINFO. Boolean operators and MeSH keywords maximized the precision of the search. It included combinations such as:

- (“Epigenetics” OR “DNA methylation” OR “Histone modification” OR “non-coding RNA”) AND (“Allergic diseases” OR “Asthma” OR “Rhinitis” OR “Atopic dermatitis” OR “Food allergy”);
- (“Immune regulation” OR “T-helper cells” OR “Regulatory T cells” OR “Inflammation”) AND (“Allergy pathogenesis” OR “Environmental exposures”);
- (“Epigenetic biomarkers” AND “Allergic inflammation”).

Data extraction protocol and data items

Application of data extraction was conducted by using a form of pre-designed data-extraction. Data extraction used two independent reviewers to limit error and bias. Included are study characteristics such as: author; year; location; study design; samples of size; demographics; epigenetic mechanisms involved; genes or loci of interest; the implicated biological pathways; the method applied for the analysis of epigenetics; major findings; the statistical outputs that included odd ratios or beta coefficients; environmental exposures examined. Third reviewers compared and resolved inconsistencies from cross checking in consensus.

Table 1. Inclusion and exclusion criteria devised for this review

Criteria	Inclusion	Exclusion
Population	Studies involving individuals with confirmed allergic diseases, such as asthma, rhinitis, dermatitis, or food allergies	Studies involving non-allergic conditions, autoimmune diseases, or non-human populations
Exposure	Studies reporting epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNAs	Studies without explicit evaluation of epigenetic modifications
Comparator	Studies with controls including healthy individuals or those with normal epigenetic profiles	Studies without appropriate comparators or unclear control group characteristics
Outcomes	Studies evaluating immune dysregulation, disease severity, therapeutic response, or biomarker potential	Studies without measurable outcomes related to epigenetics and allergic disease
Study design	Observational studies, cohort studies, case-control studies, and clinical trials	Reviews, editorials, letters, commentaries, animal studies, or in vitro studies without human data
Publication language	Articles published in English	Articles published in languages other than English
Publication year	Studies published from 2000 onwards to ensure relevance to current epigenetic methodologies	Studies published prior to 2000

Bias assessment protocol

Bias was determined by ROBINS-I for non-randomized studies, while Cochrane's RoB 2.0 was used to determine bias in randomized studies [16, 17]. ROBINS-I evaluates biases across confounding, participant selection, classification of interventions, and outcome measurement domains. Cochrane's RoB 2.0 assessed randomized studies by considerations in the randomization process, deviations from intended interventions, missing data, outcome measurement, and reporting bias. For every included study, a risk of bias was rated as low, moderate, or high, and all discrepancies between the reviewers were solved by consensus.

Results

The database search retrieved an initial number of 407 records, which were from seven databases: CINAHL (*n* = 44), PubMed (*n* = 51), Cochrane Library (*n* = 63), Embase (*n* = 68), Web of Science (*n* = 60), PsycINFO (*n* = 70), and Scopus (*n* = 51). After excluding 38 duplicate records, 369 unique records were screened. No records were excluded during this round. Then, an order was placed for 369 reports to retrieve those. Out of them, 21 reports could not be retrieved. After retrieval, 348 reports were screened for eligibility. Among the reports, 337 were excluded because they consisted of literature reviews (*n* = 49), *in vitro* studies (*n* = 62), cross-sectional

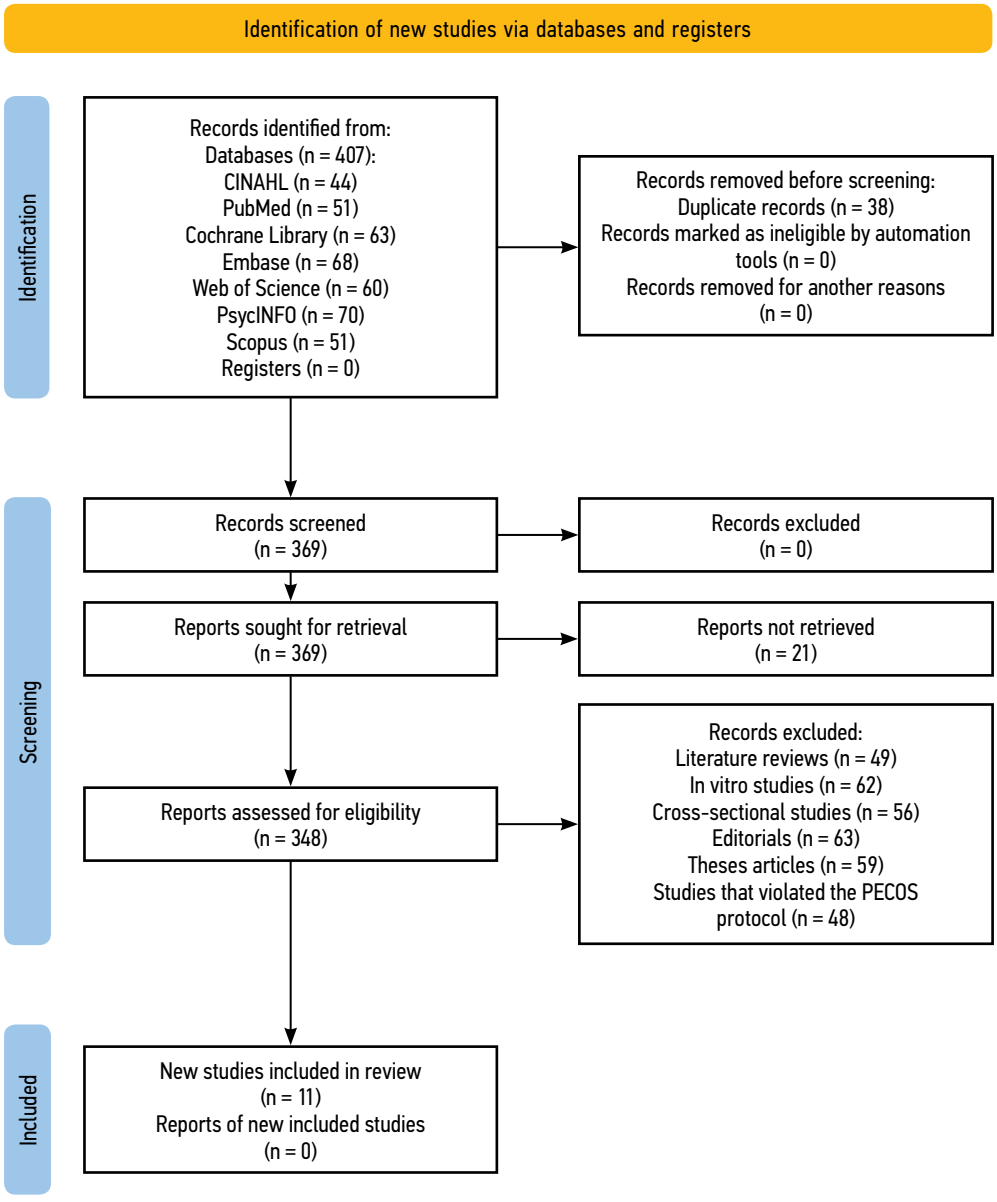

Fig. 4. Study selection process for this review.

studies (n = 56), editorials (n = 63), theses articles (n = 59), and studies violating PECOS protocol (n = 48). Finally, 11 studies were included in the review (Fig. 4) [18–28].

Demographic characteristics

It incorporates geographically varied research locations and studies within them (Table 2). Most of the works were carried out in locations in California, USA; Australia; Copenhagen, Denmark; Naples, Italy; and China [18, 19, 21, 22, 28]. By doing so, it reflects wider geographical spread in the review studies. Moreover, the varied types of designs which featured in these reviewed studies ensured strength in methodology. This consisted of observational cohort studies, genome-wide studies, randomized controlled trials, prospective birth cohort studies, as well as the single-site work [18–21, 26]. Sample sizes varied between smaller cohorts, 16 participants in controlled trials and larger cohorts, up to 700 participants, in birth cohort studies [21, 23]. The average age of participants was neonates and infants and adults [19, 22, 23, 28], and is an indicator of the effects that epigenetic mechanisms may play at various ages. Some research studies included an equal gender split, as in infant and children studies, but some comprised mostly males, like in the case of patients with peanut allergy [21, 27]. Lengths of follow-up ranged from six hours after exposure to six years of longitudinal follow-up, thus incorporating both acute and chronic epigenetic modifications related to allergic diseases [21, 23].

Epigenetic mechanisms and target genes

The included studies focused on DNA methylation as the core epigenetic mechanism and highlighted the central role in controlling immune responses in allergic diseases (Table 3). Key loci included *FOXP3*, *HLA-DQB1*, and *IL-4Rα* [18, 19, 22, 25, 28]. The methylation and demethylation patterns of these

Table 2. Demographic characteristics observed across the included studies

Author ID	Year	Location	Study design	Sample size	Mean age	Male female ratio	Follow-up period
K.M. Hew et al. [18]	2015	California, USA	Observational cohort study	256	Children (10–21 years)	171:85	Up to 1 year
D.J. Martino et al. [19]	2013	Australia	Genome-wide study	60	Neonatal to 12 months	Not reported	Not reported
R.L. Miller et al. [20]	2017	USA	Randomized control trial	200	5.2–17.5 years	Not reported	12 months
A. Morin et al. [21]	2020	Copenhagen, Denmark	Prospective birth cohort study	700	Infants and Children (up to 6 years)	236:232	6 years
L. Paparo et al. [22]	2016	Naples, Italy	Clinical observational study	40	3–18 months	Not reported	4 weeks
N. Rabinovitch et al. [23]	2021	USA	Randomized controlled study	16	Adults with Asthma	Not reported	6 hours post-exposure
B.J. Schmiedel et al. [24]	2018	La Jolla, USA	Database study	91	Adult	Balanced	Longitudinal
R.S. Swamy et al. [25]	2012	Stanford, USA	Phase I randomized controlled trial	30	5–40 years	Not reported	12 months
A. Syed et al. [26]	2014	Stanford, USA	Phase I single-site study	43	Peanut-allergic patients	Not reported	27 months
L.L. Tan et al. [27]	2025	Singapore	Retrospective study	41	20 months	73.2 % male	35 months (median)
Y. Zhao et al. [28]	2024	China	Phase IIb randomized controlled trial	120	18–70 years	Not reported	24 weeks

Table 3. Studies included in the review and their observed correlation between epigenetics and allergies

Author ID	Epigenetic mechanism	Target gene(s)/ locus	Biological pathway implicated	Allergy type/ subtype	Methodology for epigenetic analysis	Key findings/ association strength	Tissue type analyzed	Environmental/ trigger exposure considered	Conclusion assessed
K.M. Hew et al. [18]	DNA methylation	*FOXP3*	Treg dysfunction and immune suppression	Asthma and allergic rhinitis	Sodium bisulfite conversion and pyrosequencing	Beta-coefficients for Treg function increased threefold (asthmatics)	Tregs from blood	Polycyclic aromatic hydrocarbons	Chronic polycyclic aromatic hydrocarbons exposure leads to *FOXP3* methylation and immune dysfunction
D.J. Martino et al. [19]	DNA methylation	*HLA-DQB1*	T-cell differentiation	Food allergy	Genome-wide methylation profiling	85 loci differentially methylated	$CD4^+$ T-cells	Not applicable	Epigenetic changes in T-cells linked to allergy
R.L. Miller et al. [20]	DNA methylation	*FOXP3*, *IFNÎ³*	Regulatory genes and allergy suppression	Mouse allergen-induced asthma	Pyrosequencing	Mouse allergen reduction associated with reduced *FOXP3* methylation	Buccal DNA	Mouse allergen	Environmental allergen changes influence epigenetics
A. Morin et al. [21]	DNA methylation	956 CpGs linked to allergic rhinitis	Immune modulation via microbial exposure	Allergic rhinitis	Illumina 850k EPIC array	956 CpGs associated with allergic rhinitis risk (FDR <5%)	Upper airway mucosal cells	Early life microbial exposure	Microbial diversity influences allergic rhinitis through epigenetic modifications
L. Paparo et al. [22]	DNA demethylation	*FOXP3* TSDR	Treg immune regulation	IgE-mediated CMA	High-resolution melting polymerase chain reaction	TSDR demethylation correlates with tolerance	PBMCs	Dietary treatment	*FOXP3* demethylation linked to CMA tolerance
N. Rabinovitch et al. [23]	DNA methylation	*CysLTR1*, *GPR17*	Cysteinyl leukotriene pathway	Asthma	Pyrosequencing	r = –0.51 (p = 0.04, FEV1 *vs* LTE4)	PBMCs	Diesel exhaust	Exposure to Diesel exhaust alters *CysLTR1* methylation, linked to asthma severity

Table 3. Studies included in the review and their observed correlation between epigenetics and allergies

End of ***Table 3.***

Author ID	Epigenetic mechanism	Target gene(s)/ locus	Biological pathway implicated	Allergy type/ subtype	Methodology for epigenetic analysis	Key findings/ association strength	Tissue type analyzed	Environmental/ trigger exposure considered	Conclusion assessed
B.J. Schmiedel et al. [24]	Cis-eQTL analysis	Multiple genes (>12,000)	Immune cell transcriptomics	General immune conditions	RNA-Seq, eQTL mapping	41 % of genes showed cell-specific cis-eQTLs	Immune cells	None (baseline analysis)	eQTLs reveal cell-specific gene expression patterns
R.S. Swamy et al. [25]	DNA demethylation	*FOXP3*	Immune modulation by Tregs	Respiratory allergies	Bisulfite sequencing	*FOXP3* methylation reduced (p <0.01)	Tregs	Allergen exposure (TG/ DM)	SLIT induces *FOXP3* modifications, improves tolerance
A. Syed et al. [26]	DNA hypomethylation	*FOXP3* CpG sites	Treg suppression and clinical tolerance	Peanut allergy	Flow cytometry and methylation analysis	95 % suppression of Teff proliferation in IT group (p <0.0001)	PBMCs and Treg Subsets	Peanut protein	Peanut oral immunotherapy enhances Treg function and induces *FOXP3* hypomethylation
L.L. Tan et al. [27]	Not reported	Not applicable	IgE-mediated allergy	Coconut allergy	SPT, PPT, sIgE testing	Anaphylaxis: 9.8 %, tolerance: eare	Skin	Coconut products	Coconut allergy is persistent and uncommon
Y. Zhao et al. [28]	Not reported	*IL-4Ra*	Th2 cytokine pathway	Atopic dermatitis	Not applicable	EASI-75 improvement: 50 % *vs.* placebo	Serum and skin	Not reported	CM310 is effective and safe for atopic dermatitis treatment

Note. *Treg — regulatory T cells; Ig — immunoglobulin; CMA — cow's milk allergy; PBMCs — peripheral blood mononuclear cells; Th — T helper.*

loci influenced immune regulatory pathways; *FOXP3* was the center of Treg function and immune tolerance [18, 22, 25]. For example, TSDR demethylation at *FOXP3* was associated with enhanced Treg function and tolerance in immunoglobulin (Ig) E-mediated allergies [22]. Hypomethylation at *FOXP3* CpG sites was also associated with clinical tolerance in peanut allergies [26].

Besides *FOXP3*, several other loci, such as *HLA-DQB1*, were also involved in T-cell differentiation with 85 statistically differentially methylated loci identified in food allergy contexts [19]. Another locus, *IL-4Rα*, was also of prime importance for Th2-mediated responses, elucidating the role of the cytokine pathway in atopic dermatitis [28]. Finally, 956 CpG sites have been associated with allergic rhinitis risk, indicating the impact of microbes on epigenetic programming during early life [21].

Biological pathways and allergy subtypes

Epigenetic alterations were highly correlated with biological pathways that regulate immune responses. Treg dysfunction and Th2 cytokine dysregulation was identified to be the dominant mechanisms in asthma and allergic rhinitis [18, 28]. For example, *CysLTR1* and *GPR17* gene methylation aberrantly altered cysteinyl leukotriene pathways in asthma patients to the high levels of expression [23]. Histone acetylation and noncoding RNA activities were associated with modulation of chromatin accessibility that further modulated allergic inflammation [19, 26].

Allergy subtypes investigated included asthma, allergic rhinitis, atopic dermatitis, and IgE-mediated disorders like peanut allergy and cow's milk allergy (CMA) [18, 21–23, 26, 28]. For instance, in the scenario of peanut oral immunotherapy, there was the enhancement of Treg function and a reduction of Teff proliferation, correlating with *FOXP3* hypomethylation [26]. Dietary interventions caused IgE mediated CMA to induce TSDR demethylation, which promoted immune tolerance [22].

Methodologies and key findings

The other methods with higher resolution are the sodium bisulfite conversion of pyrosequencing, genome-wide methylation profiling, and Illumina 850k EPIC arrays [18, 19, 21, 23]. Using these methods, authors identified locus-specific epigenetic alterations linked to allergic phenotypes, with some of the observations mentioned below:

- chronic polycyclic aromatic hydrocarbons exposure was associated with methylation of *FOXP3* and resulted in impaired Treg cell function in asthmatics;
- epigenetic modifications in *CysLTR1* and *GPR17* were inversely correlated with lung function measures, such as FEV1, in asthma [23];
- epigenetic demethylation of *FOXP3* CpG sites decreased Teff proliferation by 95% in peanut allergies, which is a crucial therapeutic scope of epigenetic modulation [26];
- in genome-wide analysis, 956 CpG sites showed significant correlation with allergic rhinitis, and it emphasizes the significance of microbial diversity in immune regulation [21].

Environmental exposures and epigenetic modulation

Determinative factors for the epigenetic alteration are linked to environmental exposure. The polluting agents including diesel exhaust emitted hypermethylation of immune-associated genes and increased the severity of asthma [23]. Early-life microbiota exposure in humans has influenced epigenetic changes that strengthen immune tolerance or allergic susceptibility, respectively [21]. Interventions with diets during infancy altered profoundly epigenetic signatures, including the demethylation of TSDR in *FOXP3*, facilitating immune tolerance within IgE-associated CMA [22]. Thus, these findings reinforced the concept of the exposome as a cumulative environmental exposures interacting with the epigenome to shape immune responses and disease outcomes.

Assessment of bias

For studies evaluated using the RoB 2.0 tool, R.L. Miller et al. had high overall bias because of important concerns in several domains, including domain 3 (high bias) and domain 5 (some concerns) (Fig. 5) [20]. R.S. Swamy et al. also had high bias across most domains, indicating important methodological concerns [25]. In contrast, N. Rabinovitch et al. and Y. Zhao et al. showed less bias as a whole but had low bias in several domains with some concerns in specific areas, such as domain 5 [23, 28]. A. Syed et al. had a low overall risk of bias despite having some concerns in domains 2 and 4 [26].

A. Morin et al. and L. Paparo et al. had very low overall bias as appraised by ROBINS-I, with few concerns across the majority of domains, indicating robust methodologies (Fig. 6) [21, 22]. However, D.J. Martino et al. and L.L. Tan et al. were also found to be of moderate bias overall since domains 2, 6, and 7 possessed moderate concerns [19, 27]. K.M. Hew et al. were also moderate overall due to a general concern that the domains presented as moderate for domains 1 and domain 7 [18]. B.J. Schmiedel et al. had overall moderate bias while the issues occurred in the following domains 2, 3, and 4 [24].

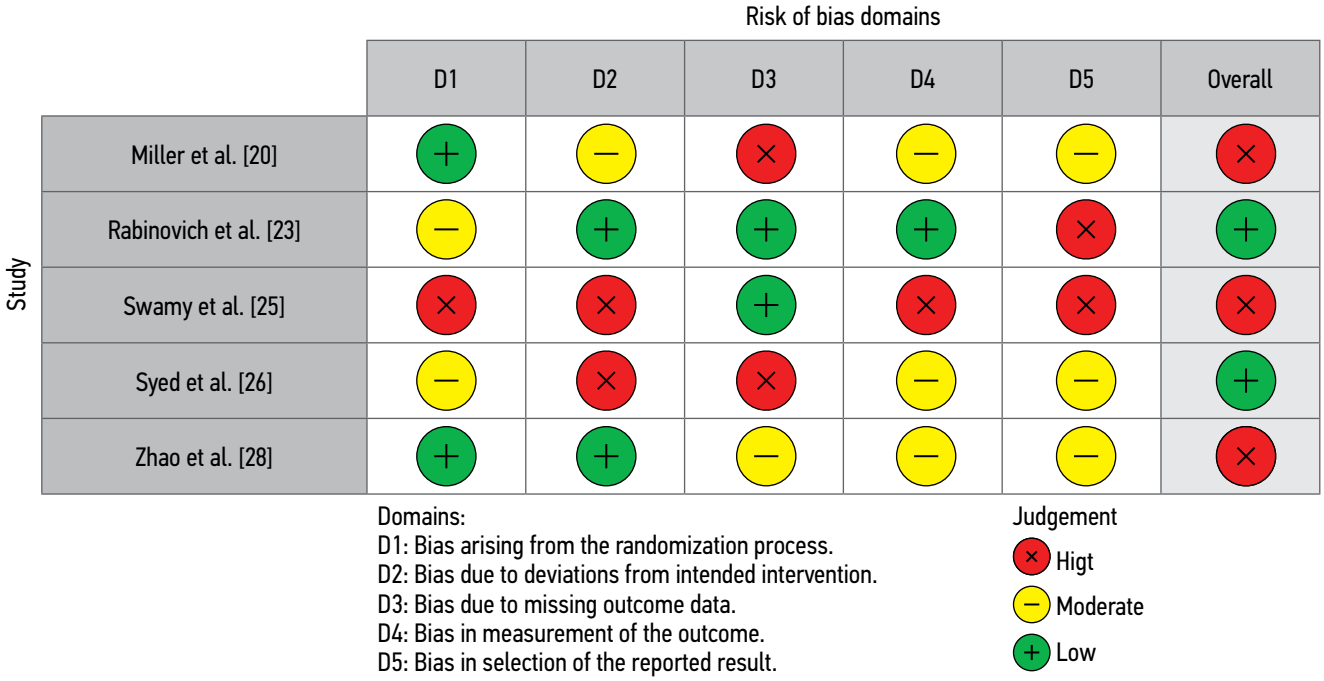

Fig. 5. Bias assessment using the RoB 2.0 tool.

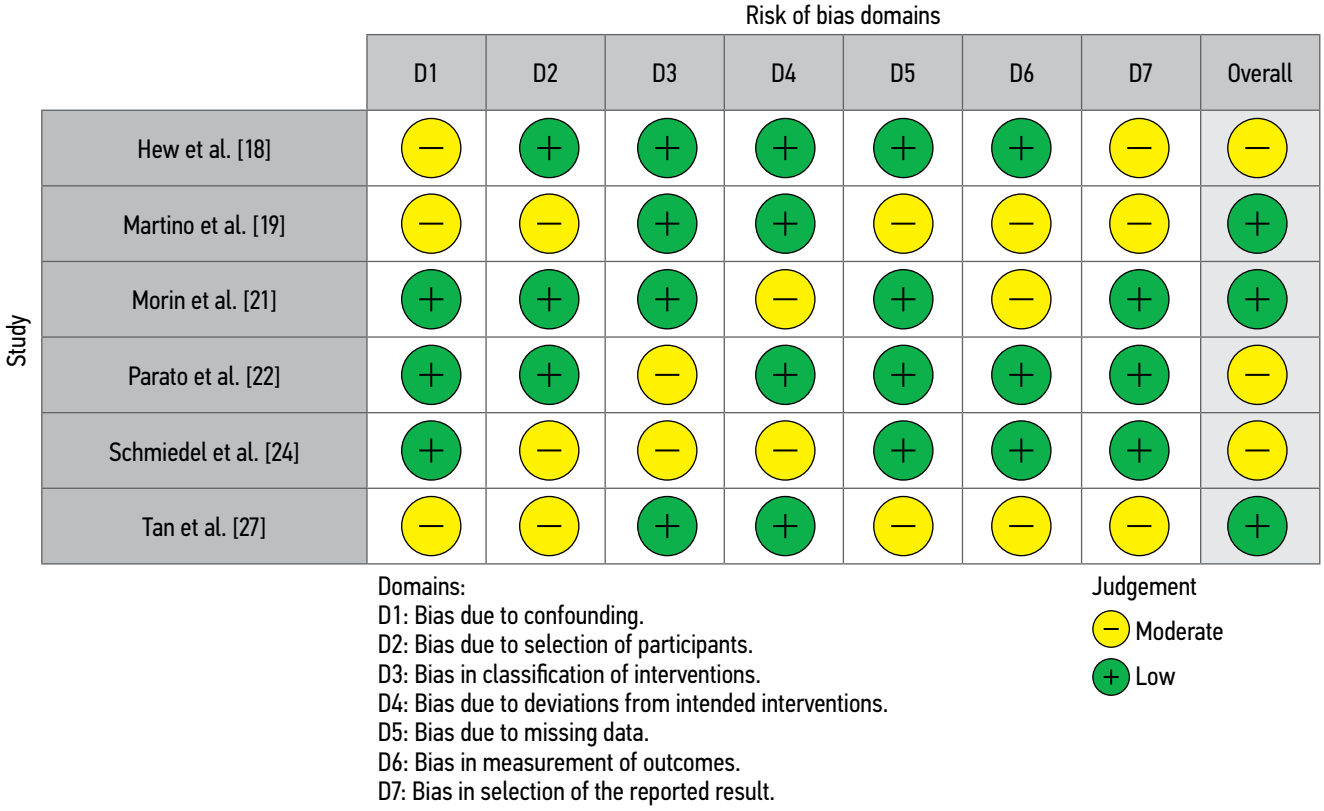

Fig. 6. Bias assessment using the ROBINS-I tool.

Discussion

As a collective, the studies demonstrated an important role of epigenetic mechanisms in the modulation of immune responses and their associations with allergic diseases and varying degrees of similarity and dissimilarity among the findings (Fig. 7). Studies by K.M. Hew et al. and N. Rabinovitch et al. have explored the impact of environmental pollutants on DNA methylation and immune dysfunction in humans, where K.M. Hew et al. examined methylation of *FOXP3* associated with chronic polycyclic aromatic hydrocarbons exposure, and N. Rabinovitch et al. investigated diesel exhaust (DE) exposure linked to altered methylation of *CysLTR1* in asthma [18, 23]. These studies were consistent in linking environmental exposures to epigenetic alterations but differed in the specific pathways and allergens studied. D.J. Martino et al. and A. Morin et al. showed agreement in studying the epigenetic modifications of immune cells, although D.J. Martino et al. discovered 85 loci associated with food allergies, whereas A. Morin et al. connected microbial diversity to the epigenetic changes occurring in allergic rhinitis [19, 21]. Both studies have highlighted the role of environmental and microbial effects on epigenetic immuneregulation with the involvement of T-cell modulation; however, the former study considered allergic conditions different from those described by the latter one.

L. Paparo et al. and A. Syed et al. shared the common theme of demethylation of *FOXP3*, which is involved in the induction of immune tolerance in IgE-mediated CMA and peanut oral immunotherapy, respectively [22, 26]. The studies differed in their therapeutic context but tended to have consistent findings regarding the importance of *FOXP3* for Treg-mediated immune regulation. R.S. Swamy et al. extended this in further proving a critical role of *FOXP3* demethylation in the process of immune modulation; hence, they proved an SLIT-enhanced tolerance through alteration of *FOXP3* [25]. L. Paparo et al. and A. Syed et al. revealed similar results, but only with regard to respiratory allergies [22, 26]. Therefore, R.S. Swamy et al. expanded its application to more comprehensive use via *FOXP3*-mediated epigenetic mechanisms [25].

B.J. Schmiedel et al. differed from others in using cis-eQTL analysis to identify cell-specific epigenetic expression profiles, rather than focusing on methylation or demethylation only [24]. This enabled a more extensive transcriptomic view of immune regulation, differing by methodology but concordant with the other studies in emphasizing the role of epigenetics in allergic diseases. L.L. Tan et al. was the only study that focused on coconut allergies, showing persistence and limited tolerance, which was different from the rest of the studies that highlighted therapeutic modulation [27]. Y. Zhao et al. discussed the use of CM310 in atopic dermatitis, where Th2 cytokine pathway

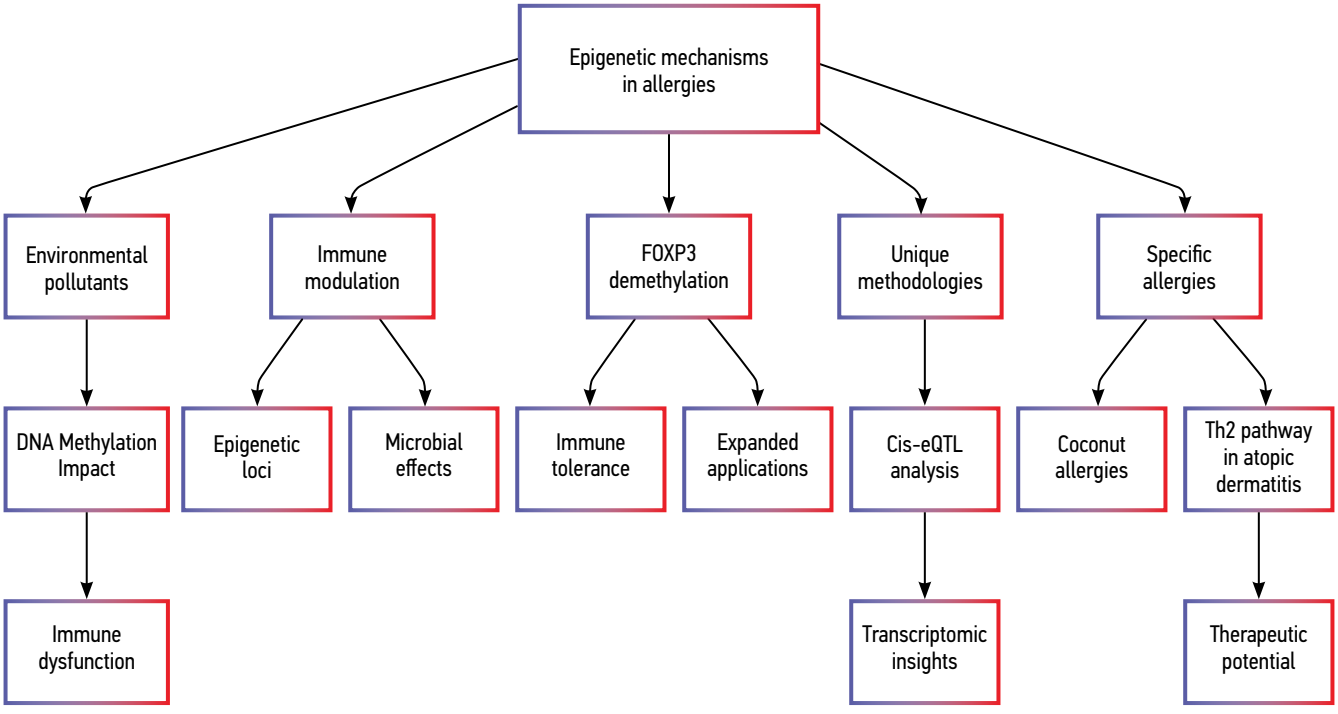

Fig. 7. Flowchart representing the overall findings of this review.

regulation was linked to clinical improvement [28]. Though the therapeutic focus was different, it was similar to D.J. Martino et al. and A. Morin et al. as it was related to epigenetic changes and allergic conditions [19, 21].

Clinical manifestations vary even among diseases within the same organ system, because different phenotypes with distinct underlying pathophysiological and molecular endotypes occur. The examination of inflammatory profiles of these diseases aims to be used in guiding the implementation of personalized therapeutic approaches. The discovery of epigenetic marks, potentially related to allergic disease phenotypes and endotypes, may lead to improved allergic disease management, with a further understanding of the induction of tolerance following immunotherapy and potentially forecasting the outcome of the treatment when conducted early during intervention [1, 29–31].

These include both stable and dynamic epigenetic modifications such as DNA methylation, histone changes, and expression of non-coding RNAs that are thought to underlie the relationship between environmental triggers and asthma incidence and course of disease and determination of its phenotypic characterization [11]. Pharmacological intervention thus might impinge on pathogenesis of asthma primarily at an epigenetic level of regulation. For example, the inhaled corticosteroids, commonly used for decades to manage inflammation in both acute and chronic forms of asthma and chronic obstructive pulmonary disease, are believed to act partially through epigenetic pathways, such as histone acetylation and microRNA modulation [32, 33].

Corticosteroids work by binding to intracellular glucocorticoid receptors, which then activate glucocorticoid response elements located in the promoter regions of glucocorticoid-responsive genes. These drugs increase histone acetylation at anti-inflammatory gene sites, such as mitogen-activated protein kinase phosphatase-1, MKP-1, while also attracting histone deacetylases, HDAC2, to deacetylate and suppress pro-inflammatory genes, such as IL-8, NF-κB, and activator protein-1, AP-1. A new study published recently has shown that the asthma medication theophylline is capable of suppressing corticosteroid resistance. This is thought to happen through the reactivation of HDAC2 by inhibiting phosphoinositide 3-kinase-δ and subsequent phosphorylation of HDAC2-associated kinases [34, 35].

The results of our review have similarities with different investigations conducted in the same regard, such as the review by I. Agache et al., mainly concerning the epigenetic mechanisms, like DNA methylation and histone modifications, for the mediation of environmental impacts on allergic diseases [4, 11, 36–39]. These two reviews proved the necessity of integrating genetic data with environmental factors to enhance diagnostics and therapeutics of allergic diseases in the future. The review further emphasizes that tools such as the CRISPR/Cas9 may also contribute toward research and treatment approaches about this disease. A critical role in the shaping of epigenetic landscapes was continuously brought out throughout our findings as well as other studies, like S. Mijač et al. and A. Cardenas et al. [38, 39]. These other studies supported the findings that environmental exposures during prenatally as well as postnatally modify pollutants, maternal microbiota, diet, and contribute to immune regulation through epigenetic modifications involving *FOXP3* methylation and, therefore, influence Treg functions.

The mechanistic insights into immune modulation through DNA methylation of specific loci, such as *FOXP3* and *IL-4Rα*, were reflected in M. Kabesch et al. where large-scale epigenome-wide association studies (EWAS) emphasized that there was an interaction between epigenetic signatures and environmental factors on asthma and allergy phenotypes [11]. In the same way, findings and M. Kabesch et al. also put emphasis on the importance of pharmacogenetics in understanding and improving treatments of asthma and allergy [11]. Studies such as S. Barni et al. and B.S.D. Fiuza et al. paralleled our focus on immune regulation via epigenetic mechanisms, particularly in IgE-mediated conditions [36, 37]. For example, both have discussed how diet interventions and microbiota diversity impact epigenetic programming and tolerance to the immune system, which coincides with the demethylation of TSDR in *FOXP3* during CMA and oral immunotherapy against peanut.

While our review focused on specific loci, such as *FOXP3* and *HLA-DQB1*, A. Cardenas et al. highlighted broader epigenetic patterns through EWAS and proposed integration of genetic influences (meQTL) with DNA methylation studies [39]. This suggests a more generalized approach compared to the locus-specific investigations emphasized in our findings. The protective roles of early microbial exposure were further expanded on by S. Mijač et al. and maternal infection, propounding certain dietary supplements such as vitamin D and polyunsaturated fatty acids for the prevention of this condition [38]. The review showed the role of microbiota but less elaborate than that of S. Mijač et al. [38].

Our review did discuss the modulation of pro-inflammatory and anti-inflammatory gene expressions via DNA methylation and histone acetylation but neither focused much on compartment-specific epigenetic responses as highlighted in A. Cardenas et al., nor did it at all expand on the impacts of helminths and other parasitic exposures discussed in

B.S.D. Fiuza et al. [37, 39]. S. Barni et al. reported a much more clinically and diagnostically orientated paper on IgE-mediated food allergies and the present strategies to manage them [36]. It is definitely in contrast to our review, which discusses an understanding of the molecular epigenetic pathways for their potential as biomarkers or therapeutic targets.

Limitations

This heterogeneity in study design, population, and methodology confined the outcomes of this review, rendering them not comparable across studies directly. Further limitation was variability in the environmental exposures that were being measured and also in the standardized analysis techniques that epigenetics analyses required. Moreover, no longitudinal follow-up in some of the studies complicated it to infer a causal relationship between epigenetic modifications and allergic disease progression. Further limiting the scope of the analysis were the few studies that looked at particular subtypes of allergy, such as food allergies.

Clinical recommendations and future directions

Future studies should be oriented toward standardizing methodologies for epigenetic analysis, such as consistent use of high-throughput sequencing techniques and well-defined outcome measures. Longitudinal studies are necessary to elucidate causal relationships between environmental exposures, epigenetic modifications, and allergic disease development. Greater focus on the underrepresented allergy subtypes, such as food allergies, should be placed with regard to therapeutic targeting of epigenetic modifications in these conditions. Integrated approaches combining molecular, clinical, and environmental data should be prioritized for the development of precision medicine frameworks. There is also a need for public health strategies focusing on modifiable environmental exposures, such as pollution and dietary factors, to dampen their adverse effects on epigenetic regulation and allergic disease prevalence.

Conclusion

Together, the included studies have highlighted the epigenetic changes as significant mediators of allergic diseases, altering immune pathways, disease severity, and therapeutic outcomes. DNA methylation at these important loci, such as *FOXP3*, *HLA-DQB1*, and *IL-4Rα*, served as a central hub of research to understand allergic inflammation and immune dysregulation. These results suggest functional exploitation of epigenetic mechanisms toward the development of novel precision therapies in allergic diseases. Still, on the other hand, despite all these advances there is still a need to standardize methodologies and to identify biomarkers that can be applied universally to bridge the gap between research and the potential clinical application.

ADDITIONAL INFORMATION

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