Allergy

WILEY

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI

POSITION PAPER OPEN ACCESS

Molecular Signatures and Functional Pathways of Human Monocytes and Macrophages in Allergy: An EAACI AllergoOncology Scoping Review

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Received: 11 March 2025 | **Revised:** 23 June 2025 | **Accepted:** 14 July 2025

Funding: This work was supported by European Academy of Allergy and Clinical Immunology.

Keywords: AllergoOncology | allergy | data-driven bioinformatics | macrophages | monocytes

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Rodolfo Bianchini and Andrea Escolar-Peña contributed equally to this work.

Rocio Rebollido-Rios and Elena Izquierdo contributed equally to this work.

[Correction added on 16 September 2025, after first online publication: The punctuation errors in author names have been corrected, and missing ORCID IDs are now included.]

Allergy, 2025; 80:2710–2725
https://doi.org/10.1111/all.16672

ABSTRACT

AllergoOncology explores the intersection of allergic diseases and cancer, focusing on shared immune mechanisms. While monocytes and macrophages are extensively studied in cancer, their roles in allergic diseases remain underexplored. To address this gap, we conducted a scoping review to systematically characterize the molecular landscape and related pathways of human monocytes and macrophages in allergy. An automated search of PubMed and Web of Science databases retrieved 4668 unique articles, which were manually curated based on predefined inclusion and exclusion criteria, yielding 138 eligible studies. From these, we identified 451 molecules associated with monocyte and macrophage responses across allergic disorders. Data analyses revealed a research bias towards blood-derived monocytes, underrepresentation of tissue-resident macrophages, and limited inclusion of miRNAs. Semantic similarity and pathway enrichment analyses highlighted a common molecular signature across major allergic disorders, with consistent enrichment in interleukin signaling and immune activation pathways. To enhance reproducibility and translational utility for researchers and clinicians, we developed ALO•HA, a web application for interactive data exploration. This overview of monocyte and macrophage molecular responses in human allergy underscores the need for integrative, human-focused approaches to better define their roles, and to guide future therapeutic strategies in allergic diseases and at the interface with oncology.

1 | Introduction

AllergoOncology is an emerging interdisciplinary field investigating the complex relationships between allergic responses and cancer, focusing on immune cells and mechanisms central to both conditions [1, 2]. Allergic diseases involve exaggerated immune responses to harmless substances, often requiring immunomodulatory treatments, whereas cancer progression is driven by immune evasion, allowing tumor cells to escape detection and suppress immune responses.

Monocytes and macrophages, key components of the innate immune system, play critical roles in maintaining tissue homeostasis, mediating inflammation, and influencing disease evolution [3–5]. However, research in both allergy and cancer has traditionally targeted T cells and other adaptive immune components, with comparatively less attention given to innate immune cells, despite their critical regulatory functions. Investigating their roles could provide novel insights into disease mechanisms and therapeutic strategies.

These cells exhibit notable heterogeneity and functional diversity shaped by distinct developmental pathways from embryogenesis to postnatal life. Tissue-resident macrophages, such as microglia in the central nervous system and Kupffer cells in the liver, originate from embryonic precursors established during development and are maintained throughout life by local self-renewal. In contrast, macrophage populations in tissues continuously exposed to environmental stimuli, including the lung, gut, and skin, are primarily replenished from circulating monocytes during postnatal life, especially under inflammatory conditions [6] (Figure 1).

Macrophages demonstrate remarkable plasticity, transitioning along a continuum of activation states in response to cytokines, pathogens, and tissue-specific signals. Rather than adhering to strict M1-like (pro-inflammatory) or M2-like (anti-inflammatory) classifications (Figure 2A), these dynamic states enable macrophages to fulfill specialized roles in allergy and cancer (Figure 2B) [7–10].

Numerous studies of monocyte and macrophage characteristics in human diseases rely on murine models to clarify cellular features. While these experiments are invaluable for generating hypotheses and dissecting mechanisms, they do not fully recapitulate human monocytes and macrophages [11, 12]. This divergence originates from genetic and transcriptional differences, distinct marker expression and polarization signatures, and variations in disease manifestation and progression between species. For example, the murine pan-macrophage marker EMR1 (F4/80) is broadly expressed on mouse macrophages, whereas its human homolog EMR1 is largely restricted to eosinophils. Likewise, classic murine polarization markers, inducible nitric oxide synthase (NOS2/iNOS) and arginase-1 (ARG1), exhibit inconsistent and often controversial expression in human polarized macrophages, limiting their validation as canonical markers [5, 11–15].

Macrophages have been extensively studied in cancer, where they often acquire immunosuppressive phenotypes that promote tumor growth, tissue remodeling, and immune evasion [16]. In allergic conditions such as asthma, atopic dermatitis, and allergic rhinitis, the inflammatory cascade is orchestrated by a complex network of immune cells and mediators. Monocytes play a pivotal role in the effector phase by rapidly migrating to sites of allergen exposure, where they secrete chemokines including CCL13, CCL17, CCL18, and CCL24. These signals promote the recruitment of key effector cells, mainly eosinophils and memory T lymphocytes, thus amplifying and sustaining the local inflammatory response [6, 17–19]. As inflammation progresses, monocyte-derived or tissue-resident macrophages play an important role in initiating and maintaining chronic inflammation in allergic responses. This role has largely been inferred from in vitro models and animal studies [20–23]. However, data derived from primary human samples, particularly in direct comparison to healthy individuals, remain scarce [24, 25], highlighting the need for human-focused studies investigating the functions and molecular profiles of monocytes and macrophages in allergy [12–15].

To address this gap, the MacTooL Task Force, under the AllergoOncology Working Group of the European Academy of Allergy and Clinical Immunology (EAACI), prioritized the systematic analysis of human-based studies. We conducted a scoping review to examine the molecular landscape and related pathways of human monocytes and macrophages in allergy, a field where these cells remain under investigated compared to their well-characterized roles in cancer. Automated searches in PubMed and Web of Science (WOS) were followed by manual screening and annotation using predefined inclusion and

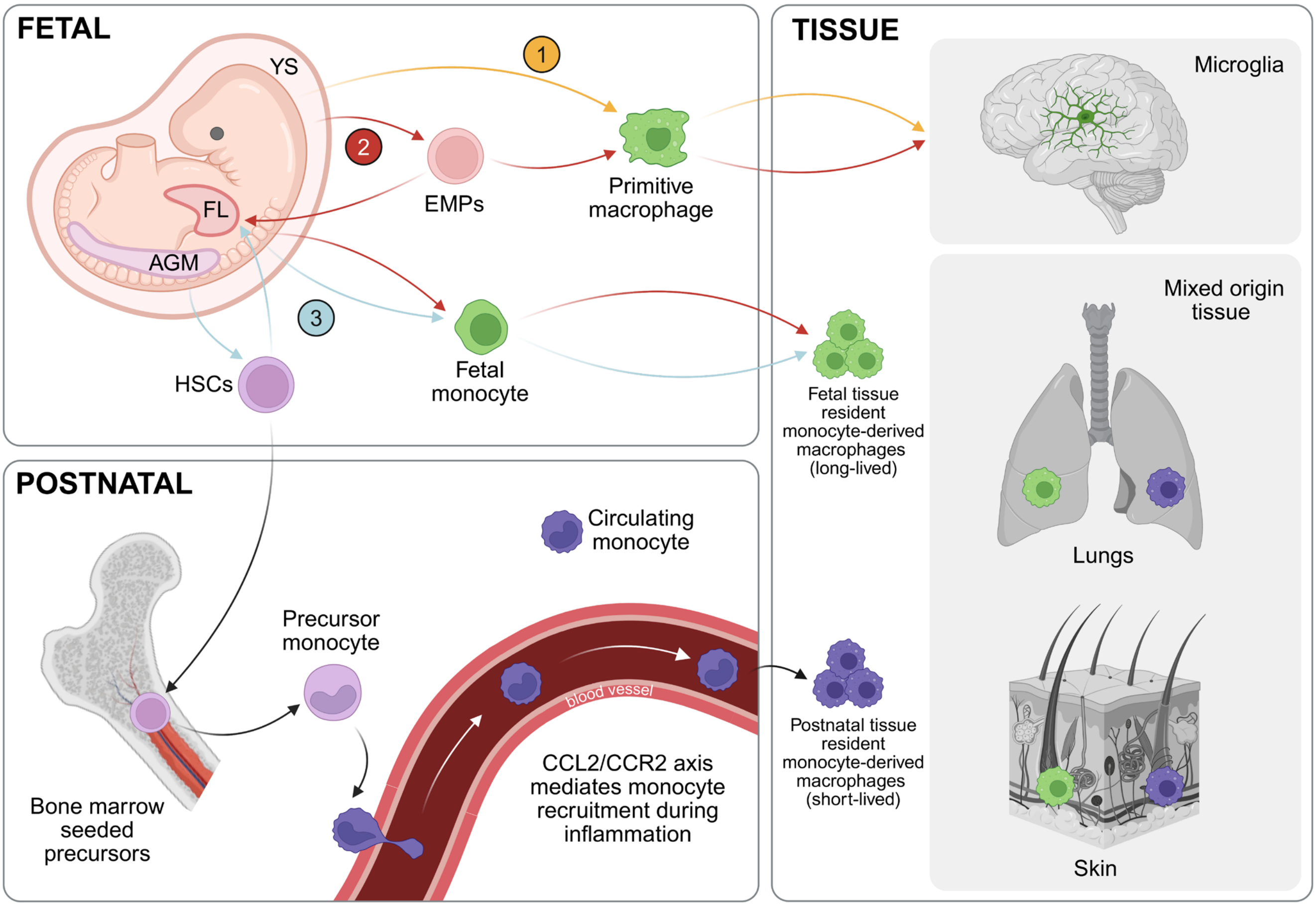


FIGURE 1 | Ontogeny of monocytes and macrophages during embryogenesis and postnatal life. The three overlapping developmental waves of monocytes and macrophages in the human embryo are illustrated, referenced to Carnegie stages (CS) and days post-conception (dpc), together with the postnatal bone marrow pathway. In the first wave (1, orange lines): CS7-CS10, ~16–22 dpc), yolk sac (YS) hemogenic endothelium generates primitive macrophage progenitors that migrate directly into tissues (e.g., brain), differentiating into microglia and extra-embryonic macrophages such as Hofbauer cells, prior to the emergence of hematopoietic stem cells (HSCs). The second wave (2, red lines): CS11-CS23, ~23–56 dpc) arises from erythro-myeloid progenitors (EMPs) in the YS at CS11 (~23 dpc), which enter the circulation, colonize the fetal liver at CS12-CS13 (~28–30 dpc), and differentiate into fetal monocytes. These monocytes seed tissues (lungs, skin, liver), establishing long-lived, tissue-resident macrophage populations. The third wave (3, blue lines): CS14-CS17, ~30–42 dpc onward) originates from hemogenic endothelium in the aorta-gonad-mesonephros (AGM), generating HSCs that seed the fetal liver and, later, the bone marrow, producing fetal monocytes and contributing postnatally to monocyte/macrophage pools. In postnatal life (gray line), bone marrow–derived HSCs generate circulating monocyte subsets: Classical ($CD14^{++}CD16^{-}$), intermediate ($CD14^{++}CD16^{+}$), and non-classical ($CD14^{+}CD16^{++}$). Each of them with distinct roles in immune surveillance and inflammation. Classical monocytes ($CCR2^{+}$) are recruited to inflamed tissues via the CCR2/CCL2 axis, where they differentiate into short-lived monocyte-derived macrophages or dendritic cells (key points: Long-lived, fetal-origin macrophages seed tissues prenatally, short-lived, postnatal-origin macrophages derive from circulating monocytes during inflammation. Figure created with BioRender.

exclusion criteria. This approach provides a comprehensive overview of monocyte and macrophage molecular responses in human allergy, supports future allergy-focused therapeutic strategies and data exploration through our interactive web application, ALO•HA, and contributes to advancing research questions within the field of AllergoOncology.

2 | Methods

2.1 | Search Strategy

The study was conducted following the PRISMA extension for scoping reviews [26]. A pipeline is illustrated in Figure 3A. This study was guided by the following research question: "What are the key molecular characteristics and functional roles of monocytes and macrophages in human allergic diseases?". To address this, we searched for research articles in two databases, PubMed and WOS, focusing on original research articles published in English between 2000 and mid-2024.

Eligible studies investigated in vivo and/or ex vivo primary human monocytes and macrophages obtained from allergic patients, comparing their characteristics to those of healthy individuals. Only studies based on Hypersensitivity Type I Asthma were included in asthma-related articles. Exclusion criteria included studies conducted on animals, those using human cell lines, or involving in vitro differentiated or stimulated monocytes and/or macrophages. Additionally, reviews, books, and case reports were also excluded (Figure 3B).

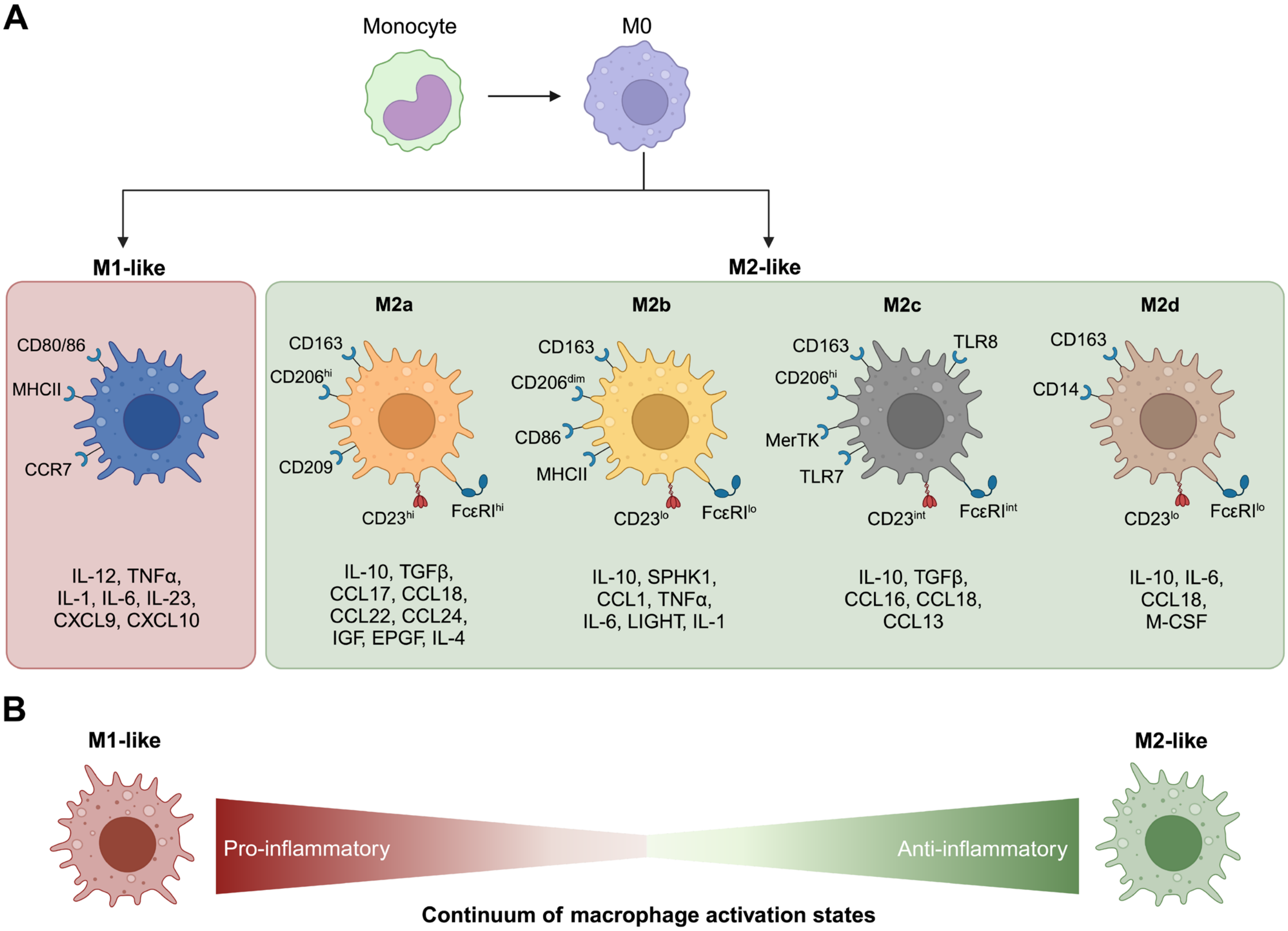


FIGURE 2 | The human macrophage polarization spectrum and functional diversity. (A) In vitro polarization spectrum of monocyte-derived macrophages (M0), in two main phenotypic extremes: M1-like (pro-inflammatory) and M2-like (anti-inflammatory and tissue repair). M1-like macrophages are activated by stimuli such as IFN-γ, lipopolysaccharide (LPS), or microbial products, leading to the production of cytokines (e.g., IL-12, TNFα, IL-1, IL-6, and IL-23), and chemokines (e.g., CXCL9 and CXCL10), along with the expression of surface markers such as CD80/86, MHCII, and CCR7, reflecting their role in immune activation and pathogen elimination. In contrast, M2-like macrophages display functional diversity across distinct subtypes: M2a, induced by IL-4 or IL-13, is characterized by high CD206/CD209 expression, and are CD23^{hi} and FcεRI^{hi}, mediating tissue repair and anti-inflammatory responses. M2b, driven by immune complex stimulation with TLR ligands or IL-1R agonists, produces IL-10, TNFα, and IL-6 and expresses CD86 and CD206^{dim}, contributing to immunoregulation. M2c, stimulated by IL-10 and TGFβ, express markers like CD163, MerTK, TLR7, and TLR8, contributing to tissue remodeling and resolution of inflammation. M2d, induced by exposure to adenosine or hypoxia-inducible factors (HIFs), is linked to angiogenesis and immunosuppression, with intermediate expression of FcεRI (FcεRI^{int}) and CD23 (CD23^{int}), alongside IL-10 and IL-6 production. The figure highlights the dynamic functional plasticity of macrophages in response to distinct microenvironmental signals, shaping their roles in immunity, inflammation, and tissue homeostasis. (B) Representation of the continuum of macrophage activation states. Monocytes differentiate into macrophages displaying a remarkable plasticity, as they transition along a dynamic continuum of activation states rather than fitting into the rigid M1/M2 dichotomies. Figure created with BioRender.

This approach was adopted to focus specifically on macrophages and monocytes directly isolated from allergic patients, in order to capture their native in vivo characteristics. Although in vitro studies can offer mechanistic insights, they typically involve cells from healthy individuals subjected to artificial stimulation protocols, which may not accurately reflect the immune environment or disease-specific alterations observed in allergic patients.

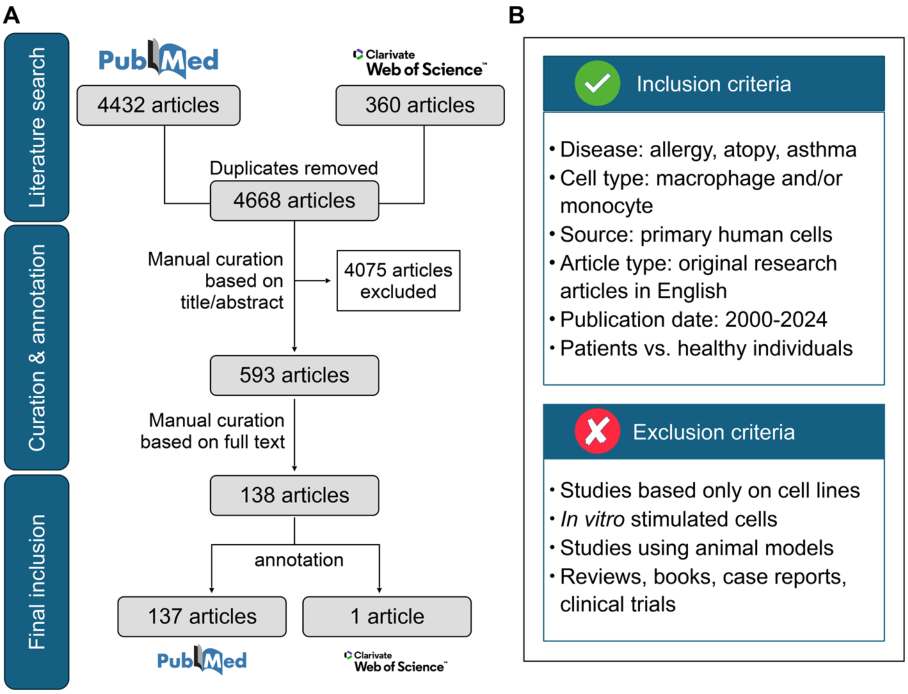
The search terms were optimized to capture studies focusing exclusively on monocytes and macrophages. Broader or overlapping terms referencing these cell types were intentionally excluded to maintain the scope of the review. This ensured that studies involving other cell types or mixed populations, which could introduce heterogeneity, were not considered.

The most recent article search was conducted on 14 July 2024. For PubMed, articles were retrieved automatically using the easyPubMed R package [27], whereas for WOS, articles were collected manually by downloading a text file containing all results for the specified query.

The database search queries were as follows:

PubMed: (((macrophag*[tw]) OR (monocyt*[tw])) AND ((allerg*[tw]) OR (atop*[tw]) OR (asthm*[tw]) OR (dermatitis)) AND (humans[mh])) NOT (review*[ptyp]) AND (2000:2024[dp]).

WOS: ((TS = ("macrophag*" OR "monocyt*")) AND (TS = ("allerg*" OR "atop*" OR "asthm*" OR "dermatitis"))) AND (TS = ("Humans") AND (PY = (2000–2024))).



Inclusion criteria

- Disease: allergy, atopy, asthma
- Cell type: macrophage and/or monocyte
- Source: primary human cells
- Article type: original research articles in English
- Publication date: 2000-2024
- Patients vs. healthy individuals

Exclusion criteria

- Studies based only on cell lines
- *In vitro* stimulated cells
- Studies using animal models
- Reviews, books, case reports, clinical trials

FIGURE 3 | Schematic representation outlining the literature search, screening, and selection processes. (A) Systematic pipeline used in this study. (B) Inclusion and exclusion criteria applied during the literature search and full-text review.

2.2 | Manual Curation and Annotation of Articles

The article selection and analysis process involved systematic screening followed by detailed manual curation and annotation. A total of 4792 articles retrieved from the two databases were cross-referenced to remove duplicates, resulting in 4668 unique articles. These articles were divided into 15 groups, with each group assigned to two independent reviewers for initial screening. Reviewers evaluated the same articles to ensure consistency, and inter-reviewer agreement was assessed and incorporated into subsequent screening steps.

The Metagear R package [28] was used to classify articles based on their titles and abstracts into three categories: “YES”' (retain), “MAYBE”' (uncertain), or “NO”' (discard). Articles labeled “NO” by both reviewers were excluded, while those labeled “YES” by both were retained for further curation. Articles with conflicting labels or marked “MAYBE”' were re-evaluated by a third independent reviewer using the same package. Following the secondary review, articles labeled “YES” were advanced to the curation phase, resulting in a total of 593 articles selected for detailed manual annotation.

To ensure a comprehensive analysis, 593 articles were redistributed among expert reviewers. Each reviewer thoroughly examined the main text and Supporting Information of their assigned articles to annotate relevant information, including the disorders, sample sources, and molecules of interest. The term “molecules” collectively encompasses proteins, protein-coding genes, and miRNAs, offering a comprehensive perspective on the changes associated with allergic conditions. The cell type studied in each article was inferred based on the sample source: articles with blood-derived samples were classified as focusing on monocytes, whereas those derived from other sources were categorized as macrophage-based studies. This curation process refined the dataset to 138 articles that met all inclusion criteria.

To harmonize terminology across studies, disorders were mapped to their corresponding Medical Subject Headings (MeSH) 2025 unique identifiers, providing a standardized framework for annotation. Hypersensitivity Type I Asthma studies were categorized as “Allergic Asthma.” Moreover, in cases where studies compared allergic patients to healthy individuals without specifying the type of allergy, they were classified under “Immediate Hypersensitivity”. A full list of disorders and corresponding MeSH terms is provided in Table S1.

2.3 | Data Processing and Analysis

The raw text from annotations was preprocessed using a standard text processing pipeline. This included data cleaning and formatting, such as removing punctuation, special characters, extra whitespaces, and correcting spelling errors. Annotated molecules were standardized and converted to gene symbols. These symbols were mapped to their corresponding ENTREZ IDs using the limma and AnnotationDbi R packages [29, 30]. This procedure yielded a total of 451 unique molecules.

To focus on diseases with sufficient data for meaningful analysis, only those represented in at least three articles and associated with more than five molecules were included in further analyses.

2.4 | Inter-Rater Agreement

To evaluate the reliability of article screening between reviewers, the agreement coefficient (AC) Gwet's AC1 was calculated using the irrCAC R package [31]. Reliability was further assessed using the Fleiss benchmark scale, which categorizes the strength of agreement to enhance interpretability (Table S2) [32].

2.5 | Semantic Similarity Analysis

Molecules were grouped based on their associated diseases, and a semantic similarity analysis was performed on the resulting clusters using Disease Ontology with the DOSE R package [33]. This analysis used the Wang and the Best Match Average (BMA) methods, as implemented in the clusterProfiler R package [34].

Subsequently, molecules were categorized based on the cell types studied in their respective articles, distinguishing between monocytes and macrophages, and also grouped according to their associated diseases. For each cell type, a semantic similarity analysis was conducted on the resulting clusters using Gene Ontology Molecular Function terms from the GOSemSim R package [35]. The same Wang measure and BMA combine method were applied to identify functional similarities both within cell type-specific molecule clusters.

2.6 | Pathway Enrichment Analysis

A Reactome pathway enrichment analysis with all molecules was performed using the ReactomePA R package [36]. A false discovery rate (FDR) threshold of 0.001, calculated using the Benjamini-Hochberg (BH) method, was applied to identify significantly enriched pathways.

2.7 | Interactive Data Analysis and Visualization

The **A**llergy **L**inking • **O**ncology **H**uman **A**nalyses (ALO•HA) https://rebollidorioslab.shinyapps.io/aloha/ Shiny app was developed to enable interactive exploration of the results. This application provides a user-friendly platform for analyzing data and exploring molecule- and disease-level information. Data visualization was performed using the following R packages: circlize [37], ComplexHeatmap [38], GGally [39], ggplot2 [40], ggsankey [41], and network [42]. A CSV file summarizing the 451 molecules identified across the 138 included studies, along with associated study identifiers, sample sources, cell types, and diseases, is available within the application and on the GitHub repository at https://github.com/RebollidoRiosLab/ALO-HA, where a lightweight version of the app documentation and selected assets is also provided.

3 | Results

3.1 | Study Selection and Temporal Trends in Monocytes and Macrophage Research

A comprehensive literature search was conducted to identify research articles investigating the roles of monocytes and macrophages in allergic disorders, focusing on comparisons between healthy individuals and allergic patients. The search encompassed PubMed (4432 articles) and WOS (360 articles), yielding a total of 4668 unique entries after duplicates were removed (Figure 3A). During the initial manual curation phase, 4075 articles were excluded based on title and abstract review, narrowing the selection to 593 articles for full-text evaluation.

Predefined inclusion and exclusion criteria were meticulously applied to the full text (Figure 3B). This rigorous selection process resulted in 138 articles, used as the primary source for annotations and subsequent analyses. The extracted data are summarized in Table S1.

The rigor of the screening process was validated through inter-rater reliability assessment, detailed in Table S2. The Gwet's AC1 values ranged from 0.485 to 0.930 across different groups, with a median value of 0.728, indicating substantial agreement in most cases. This high level of reliability demonstrates the consistency and objectivity of the reviewers, although moderate agreement was observed in a few groups.

To evaluate temporal trends, we analyzed the yearly distribution of the 138 selected articles, focusing on the number of publications, the study approach used, the investigated cell type, and the number of molecules analyzed (Figure 4). Between 2000 and 2010, fewer than 10 studies were published annually, reflecting limited attention to the field. Research activity increased after 2020 and reached a peak of 13 publications in 2023 (Figure 4A). By mid-2024, 8 additional studies were published, highlighting the growing recognition of the importance of monocytes and macrophages in allergic disorders. Among the selected articles, 115 employed targeted methods such as RT-qPCR, flow cytometry, ELISA, or Western blot to investigate specific molecules or cellular markers (Figure 4B). In contrast, only 23 studies employed untargeted approaches, including bulk RNA-seq and other omics techniques. Although omics approaches hold the potential to uncover novel insights, the lack of open-access data availability in some studies limits their broader applicability and impact on research efforts.

The selected studies exhibited variability in the immune cell types analyzed (Figure 4C). We categorized cell types based on the reported sample source, in line with the terminology used by the original authors: blood-derived cells were typically referred to as monocytes and tissue-derived cells as macrophages, often without additional experiments to confirm their identity. We followed this reporting practice, acknowledging that further phenotypic characterization was not conducted in most studies. Monocytes were investigated in 69 articles, macrophages in 62 articles, and both cell types in seven articles. This diversity highlights the multifaceted roles of these immune cells in allergic disorders and the complexity of their involvement in disease mechanisms.

Across the 138 selected articles, a total of 451 molecules were identified as associated with monocytes and macrophages. As shown in Figure 4D, there was a notable increase in the number of molecules analyzed over the years, particularly in recent studies. Earlier, research typically focused on fewer than 10 molecules, whereas more recent studies have broadened their scope using high-throughput or next-generation sequencing techniques. The adoption of untargeted methodologies has likely driven this growth, which reflects the progression of the field toward a more holistic understanding of the molecular profiles underlying allergic disorders.

FIGURE 4 | Legend on next page.

FIGURE 4 | Trends in allergy research covering publications, study approaches, cell types, and identified molecules. (A) Annual publication trends highlighting the number of articles investigating monocyte and/or macrophage features in allergic disorders. (B) Proportions of studies employing targeted vs. untargeted methods reveal the predominant use of targeted approaches. (C) Distribution of studies by cell type, categorizing them as focusing on monocytes, macrophages, or both. (D) Annual trends in the number of molecules studied showed a substantial increase in molecular investigations in recent years, particularly with the adoption of high-throughput methodologies. The star next to 2024 indicates that only studies published until July of that year were included in the search.

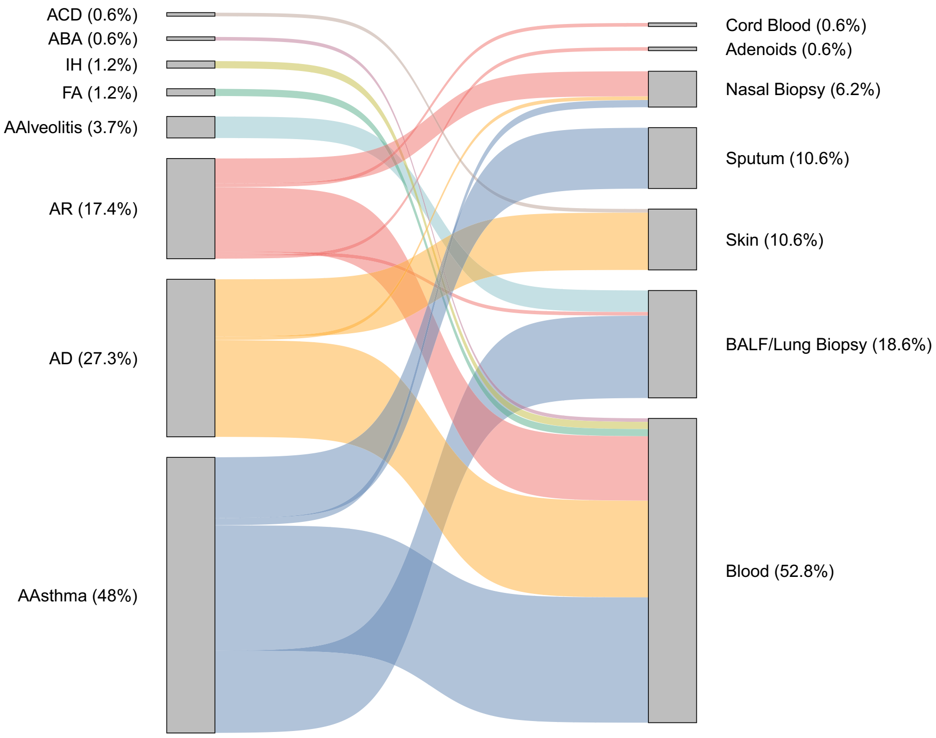


FIGURE 5 | Associations between allergic disorders and sample sources. Sankey diagram shows the relationships between allergic disorders (left) and their corresponding sample sources (right). The thickness of each link and the associated percentages indicate the frequency of specific disorders and sample source combinations within the 138 selected articles. Disorder abbreviations and corresponding MeSH terms in parentheses: Allergic Alveolitis (AAlveolitis, D000542), Allergic Asthma (AAsthma, D001249), Allergic Bronchopulmonary Aspergillosis (ABA, D001229), Allergic Contact Dermatitis (ACD, D017449), Atopic Dermatitis (AD, D003876), Allergic Rhinitis (AR, D065631), Food Allergy (FA, D005512), and Immediate Hypersensitivity (IH, D006969).

3.2 | Sample Sources and Disorder Associations in Monocytes and Macrophages in Allergy

Monocytes and macrophages were studied in the context of eight allergic disorders: Allergic Asthma, Atopic Dermatitis, Allergic Rhinitis, Allergic Alveolitis, Food Allergy, Allergic Bronchopulmonary Aspergillosis, and Allergic Contact Dermatitis (Table S1). Two articles compared monocytes and macrophages in allergic patients versus healthy individuals without specifying the type of allergy, and these were categorized as Immediate Hypersensitivity. Among the disorders, Allergic Asthma was the most frequently studied (48% of articles), followed by Atopic Dermatitis (27.3%) and Allergic Rhinitis (17.4%). In contrast, Allergic Alveolitis (3.7%), Food Allergy (1.2%), Allergic Bronchopulmonary Aspergillosis (0.6%), and Allergic Contact Dermatitis (0.6%) received comparatively less attention (Figure 5).

Blood-derived samples (53.4%) dominated as the source for most allergic conditions, except for Allergic Contact Dermatitis and Allergic Alveolitis (Figure 5). This preference indicates a stronger emphasis on circulating monocytes, whereas the modulation of tissue-specific macrophages in allergy remains less frequently investigated.

Tissue-specific samples, while less commonly used, provided important insights into localized immune responses. Among these, bronchoalveolar lavage fluid (BALF) and lung biopsies were used in 18.6% of studies, primarily in Allergic Asthma (23 articles), Allergic Rhinitis (1 article), and Allergic Alveolitis (6 articles), with no other diseases associated with this sample source. Skin biopsies featured in studies of Atopic Dermatitis (16 articles) and Allergic Contact Dermatitis (1 article), with the latter exclusively relying on this sample type. Sputum samples were only analyzed in Allergic Asthma (17 articles), while nasal biopsies were employed in Allergic Rhinitis (7 articles), Allergic Asthma (2 articles), and Atopic Dermatitis (1 article). Other sample types, such as Adenoids (0.6%) and Cord Blood (0.6%), were only used in Allergic Rhinitis research (Figure 5).

Despite the valuable insights provided by tissue-specific samples, which aimed to investigate macrophage behavior in situ, many studies did not clearly differentiate between monocytes and macrophages across allergic disorders (Figure S1). For example, the focus was nearly evenly divided between monocytes and macrophages in Allergic Asthma and Atopic Dermatitis, the most extensively studied disorders. This highlights the need for a more detailed characterization of these immune cells to elucidate their distinct roles in allergic diseases (Figure S1).

3.3 | Key Molecular Alterations in Monocytes and Macrophages Across Allergy

Among the identified 451 molecules, only nine were miRNAs, reflecting the limited study of non-coding RNAs in this context (Table S3). The relevance of the studied molecules was assessed by quantifying their occurrence across studies, providing insight into those more frequently associated with allergic conditions. Table S3 provides a detailed summary of these molecules, sorted in descending order of their occurrence, along with annotations such as UniProt IDs, protein families, pathways, subcellular localization, and Gene Ontology terms, offering a comprehensive view of their biological context.

Based on their occurrence, the top 20 molecules were selected to further investigate the allergic disorders they were associated with, and the sample sources used in their studies (Figure 6, Table S4). Surface markers such as CD14, CD68, CD206 (MRC1), and HLA-DRA were prominently represented among the frequently studied molecules. Several of these, including HLA-DRA, IL-4R, and CD86, were observed across multiple conditions such as Allergic Asthma, Allergic Rhinitis, and Atopic Dermatitis, suggesting shared molecular mechanisms underlying these disorders. In contrast, only IL-12A and IL-12B were associated with Allergic Contact Dermatitis, and IL-10 with Allergic Bronchopulmonary Aspergillosis, which were the least represented disorders among the top 20 molecules.

Pro-inflammatory cytokines and chemokines, such as IL-12A/B, TNF, IL-1B, CCL17, CXCL8, IL-6, and IL-18, were also frequently studied alongside the anti-inflammatory mediator IL-10. Molecules strongly associated with allergic responses, including the IL-4 receptor (IL-4R) and FCGR3A, were notable among the top 20. Molecules such as IL-4R, IL-12A, and CD14 were associated with multiple sample sources and disorders, underscoring their relevance in shared allergic processes.

The molecular profile varied by sample type, highlighting the influence of the biological source on the observed patterns. Molecules such as TNF, CXCL8, and TLR4 were predominantly identified in blood-derived cells, whereas CCL17 was specifically associated with tissue samples like BALF and lung biopsies, emphasizing the importance of localized immune responses.

3.4 | Molecular and Functional Insights of Monocyte and Macrophage Responses in Allergy

A detailed understanding of the molecular profiles of monocytes and macrophages in allergic disorders is essential, especially since many studies do not clearly distinguish between these cell types. This limitation does not hinder their involvement in disease mechanisms but rather limits our ability to understand their distinct contributions. Semantic similarity analysis is a useful computational approach to uncover shared and unique molecular features. To ensure a more robust analysis, we excluded disorders with limited representation, such as Immediate Hypersensitivity (four genes, two articles), Allergic Bronchopulmonary Aspergillosis (two genes, one article), and Allergic Contact Dermatitis (two genes, one article), which were each examined in fewer than three articles or involved fewer than five molecules. Importantly, this exclusion did not reduce the overall number of molecules analyzed, as those associated with the excluded conditions were also present in other, better-represented disorders.

Using the 451 molecules, a semantic similarity analysis based on Gene Ontology molecular function terms was performed (Figure S2). Molecules were categorized based on the cell types studied, distinguishing between monocytes (Figure S2A) and macrophages (Figure S2B), and grouped according to their associated diseases. The analysis revealed significant functional overlaps for both cell types, with similarity scores ranging from 0.76 to 0.90 for Allergic Asthma, Allergic Rhinitis, and Atopic Dermatitis. A Disease Ontology semantic similarity analysis was further conducted where the molecules were grouped according to their associated diseases only. The results supported the above findings and showed high similarity scores (≥ 0.96) among the most well-represented disorders (Figure 7A). Together, these analyses suggest the existence of a shared molecular signature in monocytes and macrophages across allergic disorders.

The extent of the molecular overlap was quantified using a Venn diagram (Figure 7B). Allergic Asthma, Allergic Rhinitis, Atopic Dermatitis, and Food Allergy shared six molecules, while Allergic Asthma, Allergic Rhinitis, and Atopic Dermatitis shared 23 molecules. However, less-studied conditions such as Allergic Alveolitis shared just two molecules with Allergic Asthma and Atopic Dermatitis and one molecule with Allergic Rhinitis, reflecting its underrepresentation in the studies.

Figure 7C depicts a network of shared molecules with at least two connections across the five allergic disorders, highlighting central hubs such as IL-4R, CD14, and IL-12A, with strong interconnectivity across multiple conditions. These molecules highlight potential common immune mechanisms underlying allergic responses, while condition-specific hubs reflect the complexity and heterogeneity of allergic disorders. These results underscore the need to balance generalized and condition-specific research strategies and suggest a shared molecular signature in monocytes and macrophages across allergic conditions.

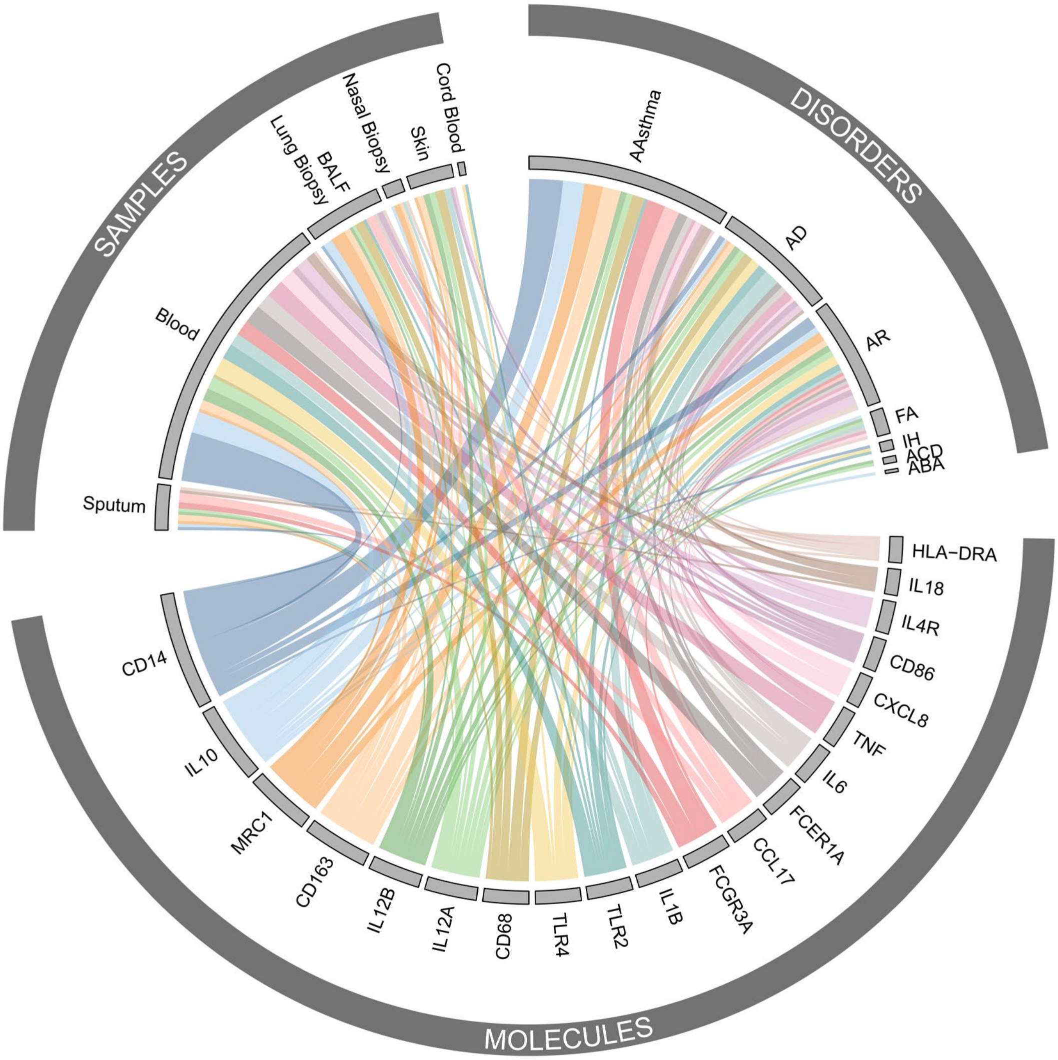


FIGURE 6 | Interconnections among the most studied molecules, allergic disorders, and sample sources. Chord diagram visualizing the associations between top 20 molecules selected based on their occurrence across the analyzed articles, along with allergic disorders and sample sources. Molecules are sorted within the plot according to their total number of associations with disorders and sample sources, ranked from highest to lowest. The width of the links represents the frequency of co-occurrence, while gray sections adjacent to molecules, disorders and samples summarize the aggregated connections, highlighting their significance in allergy research. Disorder abbreviations: AAlveolitis, Allergic Alveolitis; AAsthma, Allergic Asthma; ABA, Allergic Bronchopulmonary Aspergillosis; ACD, Allergic Contact Dermatitis; AD, Atopic Dermatitis; AR, Allergic Rhinitis; FA, Food Allergy; and IH, Immediate Hypersensitivity.

To further investigate the biological relevance of the 451 molecules, we conducted a Reactome pathway enrichment analysis (Table S5). Figure 7D presents a heatmap of the enriched pathways with more than five associated genes. The analysis revealed significant enrichment of immune-related pathways, including “Signaling by Interleukins”, “Interleukin-10 signaling”, “Neutrophil degranulation”, “Interleukin-4 and Interleukin-13 signaling”, and “Interferon-gamma signaling.” These findings align with the central role of cytokine signaling pathways in allergic inflammation and their influence on immune responses mediated by monocytes and macrophages. Beyond immune-specific pathways, the analysis identified enrichment in cellular communication and signal transduction processes. Key pathways included “Chemokine receptors binding chemokines”, “GPCR ligand binding”, “Class A/1 (Rhodopsin-like receptors)”, and “Peptide ligand-binding receptors”. These processes emphasize the importance of cell-environment interactions and signaling dynamics in allergic responses. Pathways related to programmed cell death, such as “Caspase activation through Death Receptors”, were also enriched. This suggests a secondary, though relevant, role for apoptotic mechanisms in shaping allergic responses mediated by monocytes and macrophages.

Our findings underscore the diversity of biological processes involved in allergic responses, connecting monocyte and macrophage activation to broader cellular mechanisms, such as signal transduction and apoptosis, while shedding light on shared and disorder-specific pathways.

3.5 | A User-Friendly Web Platform for Dynamic Exploration of Study Findings

ALO•HA was developed to facilitate the analysis of the articles and 451 molecules and their associations with allergic disorders,

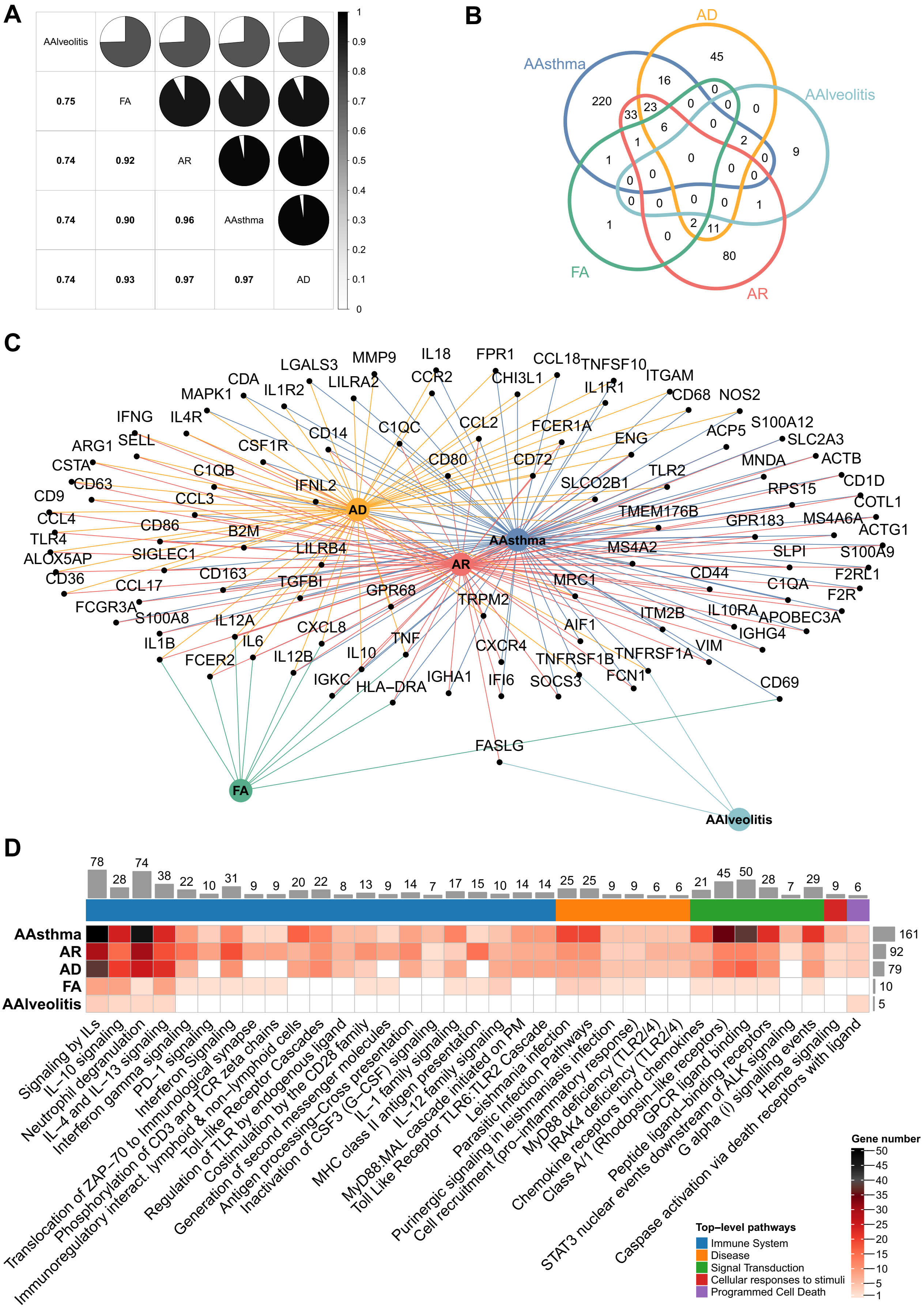


FIGURE 7 | Legend on next page.

FIGURE 7 | Shared and unique molecular and functional features in monocyte and macrophage responses across the most represented allergic disorders. (A) Disease Ontology semantic similarity matrix showing similarity scores among Allergic Asthma (AAsthma), Allergic Rhinitis (AR), Atopic Dermatitis (AD), Food Allergy (FA) and Allergic Alveolitis (AAlveolitis). (B) Venn diagram visualizing the number of shared and unique molecules among the 5 main disorders. (C) Network illustrating molecules associated with multiple disorders, where nodes represent molecules and disorders; edges indicate molecule-disorders associations, and node size reflects the degree of interconnectivity. Colored nodes and edges correspond to specific allergic conditions. (D) Heatmap of Reactome enrichment analysis showing enriched pathways across disorders. Gray bars on the top represent the total number of unique genes per enriched pathway. Gray bars on the right show the total number of unique genes present in each disorder. The top bar annotation categorizes pathways into 5 top-level Reactome pathways.

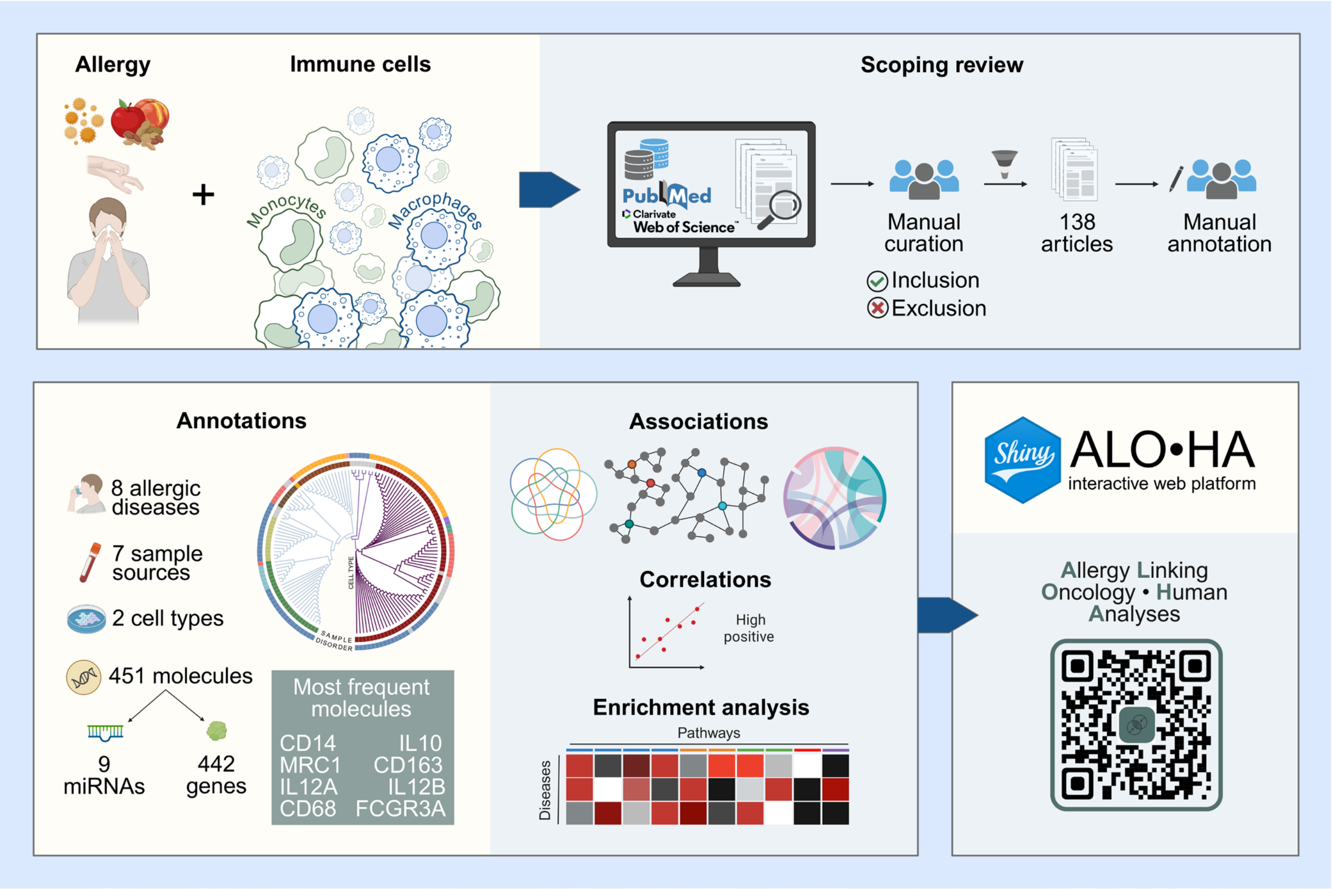


FIGURE 8 | Overview of the scoping review workflow and outcomes. The graphical summary illustrates the process from literature curation and annotation to molecular and immunological insights, highlighting key annotations, associations, and pathway analyses, as well as access to the interactive ALO•HA platform. [Correction added on 16 September 2025, after first online publication: A new figure 8 and caption have been added.]

sample sources, and temporal trends. Tailored for researchers and clinicians, ALO•HA integrates key study outputs, enabling interactive data exploration and providing options to download figures and datasets. This tool enhances accessibility, reproducibility, and the translational potential of the findings, advancing allergy research.

4 | Discussion

Monocytes and macrophages are critical players in immune regulation and inflammation and have been extensively characterized in cancer, where their diverse roles in tumor progression, tissue remodeling, and immune evasion have been elucidated [43–46]. However, their specific features and functions in allergic conditions remain unclear. To address this gap, we analyzed research articles focusing on human monocyte and macrophage characteristics in allergy compared to healthy individuals, examining their molecular and immunological profiles. As a result, we developed ALO•HA, a web application to facilitate interactive data exploration. An overview of the study design, key findings, and the integration of results into ALO•HA is presented in Figure 8.

From the initial 4668 articles, 138 met the inclusion criteria, highlighting substantial gaps in the literature on human monocytes and macrophages in allergic diseases. The limited number of studies underscores the need for further investigation, particularly in the context of primary human cells and the inclusion of healthy controls, which are crucial for identifying disease-specific features [24, 25, 47]. Despite these limitations, this review identified distinct differences in monocyte and macrophage profiles between healthy individuals and patients with allergic conditions, such as Allergic Asthma, Atopic Dermatitis, Allergic

Rhinitis, and Food Allergy, among others. Allergic Asthma emerged as the most studied disorder, reflecting a research bias toward respiratory conditions and highlighting the need to investigate other allergic diseases.

The analysis revealed a predominant reliance on peripheral blood monocytes, with relatively few studies examining tissue-resident macrophages, likely due to the greater accessibility of blood compared to tissue samples. This focus on circulating monocytes overlooks the ontogeny and functional diversity of macrophages, which are shaped by their tissue environment and pathological conditions [7, 43, 48–53]. Tissue-resident macrophages in the lungs, skin, and released from sputum play critical roles in local immune responses and disease pathology [22, 47]. Their underrepresentation highlights the limited understanding of macrophage behavior in the context of allergic disorders and the need for more strategies targeting shared immune pathways localized studies [8, 20, 50, 54–57].

The molecular profiling of monocytes and macrophages identified 451 molecules altered in allergic patients compared to healthy individuals. These included the most investigated molecules, such as CD14, IL-10, IL-12A/B, CD163, IL-6, CD206 (MRC1), and TNF, which are implicated in macrophage activation, inflammation, and immune regulation [5, 50, 58–61]. However, only 9 out of 451 molecules were miRNAs, reflecting limited research on these biological molecules in this context. Among the few studies addressing miRNAs, Rupani et al. identified 16 upregulated miRNAs in alveolar macrophages from asthmatic patients, including miR-150, miR-152, and miR-375, which target TLR7 [62]. Similarly, Wang Li et al. reported elevated miR-202-5p levels in macrophages from allergic rhinitis patients [63]. While the 451 molecules provide a broad molecular overview, their roles in allergy-specific contexts remain underexplored. Furthermore, the reliance on targeted methodologies restricts the ability to capture the full spectrum of molecular alterations, underscoring the need for unbiased approaches, including omics-based methodologies [14, 53, 64–66].

This review also revealed molecular similarities among Allergic Asthma, Allergic Rhinitis, and Atopic Dermatitis, the most well-represented atopic disorders. Semantic similarity analyses uncovered shared molecular and functional signatures, suggesting common immune mechanisms underlying these pathologies. Pathways such as “Interleukin-10 signaling”, “Interleukin-4 and Interleukin-13 signaling”, and “Interferon-gamma signaling” were consistently enriched, reflecting their central roles in allergic inflammation and modulation of myeloid cell phenotypes [1, 2, 59]. Beyond immune-specific pathways, enriched processes related to cellular communication, apoptosis, and response to external stimuli highlight broader regulatory mechanisms in allergic responses [7, 16]. Shared molecular features suggest potential avenues for therapeutic intervention, particularly in targeting core immune inflammatory pathways. However, molecules or pathways uniquely enriched in specific disorders may also reveal highly selective targets. Modulating these disease-specific elements could reduce the risk of off-target effects on fundamental immune processes, as illustrated by the distribution of pathways in Figure 7D. Thus, both common and disease-specific features warrant careful evaluation when prioritizing candidates for therapeutic development.

The emerging field of AllergoOncology explores parallels between immune processes in allergy and cancer, identifying shared, opposite, or unique mechanisms and cross-disciplinary opportunities [1–4, 67]. Molecules such as IL-10, IL-6, and TNF, identified as key features of monocytes and macrophages in allergic conditions, are also implicated in cancer biology, where they influence inflammation, tumor progression, immune evasion, and metastasis [1, 16, 22, 68]. For instance, IL-10 is an anti-inflammatory mediator, suppressing anti-tumor immunity while promoting tumor growth and metastasis in cancers such as melanoma, colorectal, and pancreatic carcinoma [1, 16]. Similarly, IL-6 supports both pro-inflammatory and tumor progression responses, contributing to therapeutic resistance and relapse in breast, ovarian, and hepatocellular carcinomas [16, 22]. TNF fosters a pro-inflammatory tumor microenvironment, which can either enhance anti-tumor immunity or promote tumor growth and metastasis, depending on the context [16]. While some of these molecules may play dual roles in allergy and cancer, others remain to be validated.

This review highlights the dysregulation of monocytes and macrophages in allergy and stresses the need for further studies to fully elucidate their molecular profiles and potential relevance to cancer biology. Advancing our understanding of monocyte and macrophage phenotypes in allergy offers opportunities for novel therapeutic strategies that extend beyond allergic conditions. The potential to reprogram macrophages, such as transforming pro-tumoral macrophages into tumor-killing macrophages or shifting pro-inflammatory strategies targeting shared immune pathway macrophages toward regulatory phenotypes in allergy, presents promising treatment avenues [1, 16, 22, 69]. For instance, anti-IgE therapies could be repurposed to re-educate patient-derived macrophages in both allergy and cancer [22]. This approach could mitigate chronic inflammation in allergy or enhance anti-tumor immunity in cancer [1, 2, 16, 22]. Strategies targeting shared immune pathways, such as IL-10, IL-6, and TNF, could simultaneously address allergic inflammatory responses and suppress tumor-promoting pathways in cancer [16, 22]. Furthermore, omics-based approaches may facilitate the discovery of novel biomarkers and therapeutic targets, enabling personalized treatments tailored to individual immune profiles [7, 14, 50, 53, 64–66, 70].

Despite its valuable insights, our study faced some limitations. The reliance on targeted methodologies, such as RT-qPCR and flow cytometry, inherently biases the findings toward predefined targets, limiting the capacity to capture broader molecular changes [12, 14]. In parallel, the selection of only in vivo studies (necessary to focus on cells directly isolated from allergic individuals) resulted in the exclusion of in vitro models, which often employ large-scale, untargeted approaches. Furthermore, the limited availability of studies including healthy controls and tissue-resident macrophages further restricts the generalizability of the results [24, 25]. The exclusion of certain allergic disorders due to insufficient data leads to critical gaps in our understanding of monocyte and macrophage features in underrepresented conditions. Addressing these gaps is crucial to uncover key drivers of immune processes in allergy and to explore their potential relevance to cancer biology. Notably, the inflammatory environment characteristic of allergy could provide valuable knowledge for overcoming immune evasion in cancer [2, 3, 22, 44, 46, 59, 60, 67, 69–72].

In conclusion, this scoping review identifies significant gaps and biases in the current literature regarding monocyte and macrophage characterization in allergy. Our findings emphasize the need for integrative studies that include tissue-resident macrophages, healthy controls, and omics-based approaches to uncover the full spectrum of molecular and functional alterations in these cells. The shared and specific molecular signatures across allergic disorders may facilitate the development of targeted therapies addressing common immune mechanisms.

Moreover, the development of ALO•HA represents an important step in enhancing the accessibility and practical use of these findings. This interactive web platform enables reproducible data exploration and provides researchers and clinicians with an intuitive framework to analyze molecule- and disease-specific features.

The parallels between macrophage and monocyte behavior in allergy and cancer point to promising opportunities for cross-disciplinary insight. A deeper understanding of their phenotypes in allergy may open new avenues for therapeutic innovation, bridging allergy and oncology within the emerging field of AllergoOncology and ultimately transforming patient care.

Author Contributions

Conceptualization: Rodolfo Bianchini, Andrea Escolar-Peña, Rocio Rebollido-Rios, and Elena Izquierdo. Data analysis: Andrea Escolar-Peña, José Basílio, Rocio Rebollido-Rios. Query design: Isabel Adoración Martín-Antoniano, Rodolfo Bianchini, and Elena Izquierdo. Shiny App Development: Andrea Escolar-Peña, Vanda Pick, and Rocio Rebollido-Rios. Screening of papers and manual data extraction: Rodolfo Bianchini, Aurélie Poli, Rebecca Adams, Luigi Cari, Jitesh Chauhan, Tomás Chivato, Leticia de las Vecillas, María Isabel Delgado-Dolset, Melanie Grandits, Heather J. Bax, Leticia Martín-Cruz, Hanna Mayerhofer, Giuseppe Nocentini, Gabriel Osborn, Carmela Pablo-Torres, Oscar Palomares, Mariona Pascal, Urszula Radzikowska, Nataliya Rohr-Udilova, Milena Sokolowska, and Elena Izquierdo. Writing original draft preparation: Rodolfo Bianchini, Andrea Escolar-Peña, Rocio Rebollido-Rios, and Elena Izquierdo. Review and editing: Rodolfo Bianchini, Andrea Escolar-Peña, Aurélie Poli, María M. Escribese, Alessandro Michelucci, Christoph Bergmann, Erika Jensen-Jarolim, Sophia N. Karagiannis, Rocio Rebollido-Rios, and Elena Izquierdo. All authors have read and agreed to the published version of the manuscript.

Acknowledgements

This scoping review was supported by the European Academy of Allergy and Clinical Immunology (EAACI) under the EAACI Task Force "Macrophage role in Allergy and Cancer: Novel therapeutic opportunities (MacTooL)" within the Working Group AllergoOncology, within the Basic Immunology Section; Budget code 40210 (Year 2023) and 40322 (Year 2024). A.E.-P. was a recipient of a Research Short-Term Fellowship 2024 funded by the European Academy of Allergy and Clinical Immunology (EAACI). The authors would like to thank the EAACI for its financial support to develop this scoping review.

Conflicts of Interest

All authors have read and approved the manuscript. Any potential conflicts of interest related to the manuscript are listed here: S.N.K. is the founder and shareholder of Epsilogen Ltd. (formerly IGEM Therapeutics Ltd.) and has received funds from IGEM Therapeutics Ltd/Epsilogen Ltd. H.J.B., and M.G. are employed through a fund provided by Epsilogen Ltd. J.C. has been employed through a fund provided by Epsilogen Ltd. S.N.K. and H.J.B. are inventors of patents on antibody technologies. S.N.K. reports grants from Worldwide Cancer Research (24-0087); Guy's and St Thomas's Foundation Trust Charity Melanoma Special Fund (573); the British Skin Foundation (006/R/22); the Biotechnology and Biological Sciences Research Council (BB/T008709/1); Cancer Research UK (C30122/A11527; C30122/A15774); the Cancer Research UK King's Health Partners Centre at King's College London (C604/A25135); the CRUK City of London Centre Award (C7893/A29290); Breast Cancer Now (147; KCL-BCN-Q3); the Medical Research Council (MR/L023091/1; MR/R015643/1; MR/V049445/1); Innovate UK (51746); S.N.K. has projects supported by the King's Health Partners Centre for Translational Medicine. The views expressed are those of the author(s) and not necessarily those of King's Health Partners. O.P. received research grants from MINECO, Ministerio de Ciencia e Innovación, CAM, Inmunotek S.L., Novartis, and AstraZeneca and fees for giving scientific lectures or participation in Advisory Boards from: AstraZeneca, Pfizer, GlaxoSmithKline, Inmunotek S.L., Novartis, Sanofi-Genzyme and Regeneron. E.J.J. is inventor in EP2894478; "LCN2 as a tool for allergy diagnostic therapy", EP 14150965.3, Year: 01/2014; US 14/204,570, immunoBON, owned by Biomedical International *R*+D GmbH, Vienna, Austria, of which E.J.J. is shareholder.

Data Availability Statement

The data that supports the findings of this study are available in the Supporting Information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Article-based disorder and cell type associations. The network depicts the associations between disorders and cell types addressed in the publications based on the sample sources described in each article. The classification of cell types is defined at the publication level. Nodes representing disorders are connected to article nodes which are colored based on one of three cell type classifications: monocytes, macrophages, or both. Disorder abbreviations: AAlveolitis, Allergic Alveolitis; AAsthma, Allergic Asthma; AD, Atopic Dermatitis; AR, Allergic Rhinitis; and FA, Food Allergy. **Figure S2:** Semantic similarity analysis of monocytes and macrophages across allergic disorders. Gene Ontology Molecular Function semantic similarity analysis of gene clusters associated with each disorder is presented for monocytes (A) and macrophages (B). Similarity scores among Allergic Asthma (AAsthma), Allergic Rhinitis (AR), Atopic Dermatitis (AD), Food Allergy (FA), and Allergic Alveolitis (AAlveolitis). **Table S1:** Summary of the 138 included articles, including all extracted data and manual annotations1-138. **Table S2:** AC1 coefficient values assessing inter-rater agreement for each group. **Table S3:** Gene occurrence across the 138 selected articles. **Table S4:** Associations of the 20 most-studied molecules with disorders and sample sources, used for the chord diagram. **Table S5:** Reactome enrichment analysis results, filtered to include pathways with at least six genes and their corresponding top-level categories.