Title: **An EAACI Task Force Scoping Review: Human Monocytes and Macrophages in Allergy – Implications for AllergoOncology**

**Running title:** Scoping review of monocyte and macrophage features in allergy.

**Authors:** Rodolfo Bianchini1,2\*, Andrea Escolar-Peña3\*, Vanda Pick4,5, Aurélie Poli6, Rebecca Adams7, José Basílio1,8, Luigi Cari9, Jitesh Chauhan7, Tomás Chivato3,  Leticia de las Vecillas10, María Isabel Delgado-Dolset3,11, María M Escribese3, Melanie Grandits7, Heather J Bax7, Isabel Adoración Martín-Antoniano3,12,13, Leticia Martín-Cruz14,15, Hanna Mayerhofer1,2, Alessandro Michelucci6, Giuseppe Nocentini10, Gabriel Osborn7, Carmela Pablo-Torres3,16, Oscar Palomares Gracia14, Mariona Pascal17,18,19, Urszula Radzikowska20,21, Nataliya Rohr-Udilova22, Milena Sokolowska20,21, Christoph Bergmann23, Erika Jensen-Jarolim1,2,  Sophia N Karagiannis,7,24, Rocio Rebollido-Rios,4,5&, Elena Izquierdo3&.

1. Institute of Pathophysiology and Allergy Research, Center of Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna, Austria.
2. The Interuniversity Messerli Research Institute, University of Veterinary Medicine Vienna, Medical University of Vienna, and University of Vienna, Vienna, Austria.
3. Institute of Applied Molecular Medicine Instituto de Medicina Molecular Aplicada Nemesio Díez (IMMA), Department of Basic Medical Sciences, Facultad de Medicina, Universidad San Pablo-CEU, CEU Universities, Urbanización Montepríncipe, 28660 Boadilla del Monte, Madrid, Spain.
4. University of Cologne, Faculty of Medicine and Cologne University Hospital, Department I of Internal Medicine; Center for Integrated Oncology Aachen, Bonn, Cologne, Düsseldorf, Cologne, Germany.
5. CECAD Cologne Cluster of Excellence on Cellular Stress Responses in Aging-Associated Diseases, Cologne, Germany. Center for Molecular Medicine Cologne, Cologne, Germany.
6. Neuro-Immunology Group, Department of Cancer Research, Luxembourg Institute of Health, Luxembourg, Luxembourg.
7. St. John's Institute of Dermatology, School of Basic & Medical Biosciences & KHP Centre for Translational Medicine, King's College London, Guy's Hospital, London, UK.
8. INESC-ID, Instituto Superior Técnico, Universidade de Lisboa, Lisboa, Portugal
9. Section of Pharmacology, Department of Medicine and Surgery, University of Perugia, Perugia, Italy.
10. Department of Allergy, La Paz University Hospital - IdiPAZ, Madrid, Spain.
11. Centro de Metabolómica y Bioanálisis (CEMBIO), Facultad de Farmacia, Universidad San Pablo-CEU, CEU Universities, Boadilla del Monte, España.
12. Genetic and Molecular Epidemiology Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain.
13. Instituto de Estudios de las Adicciones IEA-CEU, Universidad San Pablo-CEU, CEU Universities, Madrid, Spain.
14. Department of Biochemistry and Molecular Biology, School of Chemistry, Complutense University, Madrid, Spain.
15. Department of Biochemistry and Molecular Biology, School of Pharmacy, Complutense University, Madrid, Spain.
16. Department of Environmental Health, Harvard T. H. Chan School of Public Health, Boston, MA 02115, USA
17. Immunology Department, Centre de Diagnòstic Biomèdic, Hospital Clínic de Barcelona, Barcelona, Spain.
18. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain.
19. Department of Medicine, Faculty of Medicine, Universitat de Barcelona, Barcelona, Spain.
20. Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland.
21. Christine Kühne - Center for Allergy Research and Education (CK-CARE), Davos, Switzerland.
22. Division of Gastroenterology and Hepatology, Internal Medicine III, Medical University of Vienna, Vienna, Austria.
23. Department of Otorhinolaryngology, RKM740 Interdisciplinary Clinics, Düsseldorf, Germany.
24. Breast Cancer Now Research Unit, School of Cancer & Pharmaceutical Sciences, King's College London, Innovation Hub, Guy's Cancer Centre, London, UK

\*& Equal contribution

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**Corresponding Author:**

Elena Izquierdo, PhD

Department of Basic Medical Sciences

Facultad de Medicina Universidad San Pablo-CEU

Campus Montepríncipe. Crtra. Boadilla del Monte km 5.3.

CP 28668 Boadilla del Monte. Madrid, Spain

Phone: +34 91 372 47 00 ext. 14686   
E-mail: [elena.izquierdoalvarez@ceu.es](mailto:elena.izquierdoalvarez@ceu.es)

Rocio Rebollido-Rios, PhD

Department I of Internal Medicine, University of Cologne, and Cologne University Hospital

CECAD Research Center.   
Joseph-Stelzmann-Str. 26, 50931 Cologne, Germany   
Phone: +49 221 478 42151

E-mail: [rocio.rebollido-rios@uk-koeln.de](mailto:rocio.rebollido-rios@uk-koeln.de) 

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**Abstract** (197/200 words)

AllergoOncology explores the intersection of allergic diseases and cancer, focusing on shared immune mechanisms mediated by monocytes and macrophages. These cells exhibit high heterogeneity, plasticity, and functional diversity across tissues and disease progression, yet their roles in allergic disorders remain unclear. This scoping review systematically analyzed 138 articles, identifying 451 molecules associated with monocyte and macrophage responses in allergic diseases, including Allergic Asthma, Atopic Dermatitis, and Allergic Rhinitis. Our findings revealed a research bias toward blood-derived samples, underrepresentation of tissue-resident macrophages and limited inclusion of non-coding RNAs. Semantic similarity and pathway enrichment analyses identified shared molecular signatures across major allergic disorders, highlighting interleukin signaling and immune activation pathways. Less-studied conditions, such as Allergic Alveolitis and Food Allergy, displayed distinct molecular profiles, emphasizing the need for broader investigations. To enhance data accessibility, we developed [ALO•HA](https://rebollidorioslab.shinyapps.io/aloha/), a web application for interactive analysis. [ALO•HA](https://rebollidorioslab.shinyapps.io/aloha/) fosters reproducibility and translational potential for both researchers and clinicians. Our findings highlight the need for integrative approaches, combining omics technologies and human-based studies, to better characterize monocyte and macrophage phenotypes in allergy. This work advances the understanding of allergy-immunity interactions, bridges allergy and oncology, addresses critical gaps and opens new opportunities for therapeutic development.

**Keywords:** AllergoOncology, allergy, data-driven bioinformatics, macrophages, monocytes

**(4482/4500 words)**

**INTRODUCTION (513 words)**

AllergoOncology is an emerging interdisciplinary field investigating the complex relationships between allergic responses and cancer, focusing on immune cells and mechanisms central to both conditions1,2. 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 evolution3-5. However, research in allergy and cancer has traditionally targeted T cells and other adaptive immune components, with 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.

Monocytes and macrophages exhibit notable heterogeneity and functional diversity shaped by distinct developmental pathways from embryogenesis to adulthood. In humans, monocytes differentiate into tissue-resident macrophages with specialized functions influenced by the microenvironment5 (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)6-9.

While murine models provide valuable insights into their biology, they do not fully replicate human disease contexts. Murine monocyte subsets roughly correspond to human classical and non-classical monocytes10,11. Transcriptional and phenotypic differences, along with the absence of direct human equivalents for markers such as EGF-like module-containing mucin-like hormone receptor-like 1 (EMR1 - F4/80), Inducible Nitric Oxide Synthase (NSO2 – iNOS), and Arginase-1 (ARG1), underscore the importance of studying human monocytes and macrophages to deepen our understanding of disease biology and guide treatment development 5,11-14.

In allergic conditions such as asthma, atopic dermatitis, and allergic rhinitis, macrophages have been implicated as key drivers of chronic inflammation, primarily based on *in vitro* and animal studies.15-18. Conversely, in cancer, they often acquire immunosuppressive phenotypes that promote tumor growth, tissue remodeling, and immune evasion, ultimately influencing patient outcomes19. Understanding these dual roles presents an opportunity to reprogram macrophages for therapeutic applications. Research on primary human macrophages in allergic individuals, particularly in comparison to healthy controls, remains limited20,21 reinforcing the need for human-focused studies11-14.

To address these gaps, the MacTooL Task Force, under the AllergoOncology Working Group of the European Academy of Allergy and Clinical Immunology (EAACI), has prioritized human-based studies. This scoping review examines allergic diseases and aims to characterize monocyte and macrophage profiles in this context. Systematic searches were conducted in PubMed and Web of Science (WOS) databases, followed by a customized pipeline to screen, select, and annotate key information from articles. By implementing a well-defined approach, we provide a comprehensive assessment of monocytes and macrophages in allergic diseases. This framework establishes a foundation for future research on novel therapeutic strategies for allergy, and potentially cancer, while also providing an interactive platform for data exploration through the developed web application, [ALO•HA](https://rebollidorioslab.shinyapps.io/aloha/). Additionally, it seeks to further elucidate the overlapping roles of these innate immune cells in AllergoOncology.

**METHODS (880 words)**

***Search strategy***

The scoping review was conducted following the PRISMA extension for scoping reviews22. 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 2 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. The 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).

The most recent article search was conducted on 14 July 2024. For PubMed, articles were retrieved automatically using the easyPubMed R package23, whereas for WOS, articles were collected manually by downloading a text file containing all results for the specified query.

The database search queries were:

**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)))

***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 4,792 articles retrieved from the two databases were cross-referenced to remove duplicates, resulting in 4,668 unique articles. These articles were divided into 15 groups, with each group assigned to 2 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 package24 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 supplementary materials of their assigned articles to annotate relevant information, including the disorders, sample sources, and molecules of interest. 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 studies. This curation process refined the dataset to 138 articles that met all inclusion criteria.

Disorders were categorized using their corresponding Medical Subject Headings (MeSH) unique IDs to standardize the annotated information. Hypersensitivity Type I Asthma studies were categorized as “allergic asthma.” Moreover, in the case of papers focusing on allergic patients versus healthy individuals without specifying the type of allergy, the studies were categorized as “Immediate Hypersensitivity.”

***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, proteins, and genes were standardized and converted to gene symbols. These symbols were mapped to their corresponding ENTREZ IDs using the limma and AnnotationDbi R packages25,26. 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 3 articles and associated with more than 5 genes were included in further analyses.

***Inter-Rater agreement***

To evaluate the reliability of data extraction between reviewers, the agreement coefficient (AC) Gwet’s AC1 was calculated using the irrCAC R package27. Reliability was further assessed using the Fleiss benchmark scale, which categorizes the strength of agreement to enhance interpretability (Table S2)28.

***Semantic similarity analysis***

Molecules were grouped according to their associated diseases, and a semantic similarity analysis was performed on Disease Ontology clusters using the DOSE R package29. This analysis used the Wang and the Best Match Average (BMA) methods, as implemented in the clusterProfiler R package30.

Subsequently, molecules were categorized based on the cell types studied in their respective articles, distinguishing between monocytes and macrophages. For each cell type, a semantic similarity analysis was conducted on the clusters annotated with Gene Ontology Molecular Function terms using the GOSemSim R package31. The same Wang measure and BMA combine method were applied to identify functional similarities both within cell type-specific molecule clusters.

***Pathway Enrichment Analysis***

A Reactome pathway analysis with all molecules was performed using the ReactomePA R package32. A false discovery rate (FDR) threshold of 0.001, calculated using the Benjamini-Hochberg (BH) method, was applied to identify significantly enriched pathways.

***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 gene- and disease-level information. Data visualization was performed using the following R packages: circlize33, ComplexHeatmap34, GGally35, ggplot236, ggsankey37, and network38.

**RESULTS (1943 words)**

**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 (4,432 articles) and WOS (360 articles), yielding a total of 4,668 unique entries after duplicates were removed (Figure 3A). During the initial manual curation phase, 4,075 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 texts (Figure 3B). This rigorous selection process resulted in 138 articles, used as the primary source for 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 (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). In line with the assumptions made by authors in the original studies, we categorized cell types based on the sample source, as they typically referred to cells in blood as monocytes and cells in tissue as macrophages without performing additional experiments to confirm their identity. We adhered to this reporting convention, recognizing that further characterization of these cell types was not conducted in the majority of studies. Monocytes were investigated in 69 articles, macrophages in 62 articles, and both cell types in 7 articles. This diversity highlights the multifaceted roles of these cells in allergic disorders.

A total of 451 molecules were identified across the 138 selected articles as associated with monocytes and macrophages. The term “molecules” collectively encompasses proteins, coding, and non-coding genes (miRNAs), offering a comprehensive perspective on the changes associated with allergic conditions. As shown in Figure 4D, there has been a notable increase in the number of molecules analyzed over the years, particularly in more 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.

**Sample sources and disorder associations in monocytes and macrophages in allergy**

Across the full text of the 138 articles, monocytes and macrophages were studied in the context of 7 allergic disorders: Allergic Asthma, Atopic Dermatitis, Allergic Rhinitis, Allergic Alveolitis, Food Allergy, Allergic Bronchopulmonary Aspergillosis, and Allergic Contact Dermatitis (Figure 5). 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), where they were the sole sample types used. Skin biopsies featured in studies of Atopic Dermatitis (16 articles) and Allergic Contact Dermatitis (1 article), which exclusively relied on this sample type. Sputum samples were 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).

**Key molecular alterations in monocytes and macrophages across allergy**

Among the identified 451 molecules, only 9 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 were prominently represented among these frequently studied molecules, including CD14, CD68, CD206 (MRC1), and HLA-DRA. 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. Some molecules, such as HLA-DRA, IL4RIL-4R, and CD86, were also observed across several disorders, including allergic asthma, allergic rhinitis, and atopic dermatitis. These suggest shared molecular mechanisms underlying these conditions. Nevertheless, only IL-12A and IL-12B were associated with allergic contact dermatitis and IL-10 with allergic bronchopulmonary aspergillosis, clearly the least represented disorders among the top 20 molecules.

**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, particularly given that many studies do not clearly distinguish between these cell types. This limitation can hinder their distinct contributions to disease mechanisms. Semantic similarity analysis is a useful computational approach to uncover shared and unique molecular features. To ensure a more reliable analysis we excluded disorders with limited representation, such as Immediate Hypersensitivity (4 genes, 2 articles), Allergic Bronchopulmonary Aspergillosis (2 genes, 1 article), and Allergic Contact Dermatitis (2 genes, 1 article), which were studied in less than 3 articles or had less than 5 molecules. Importantly, this exclusion did not reduce the overall number of molecules, as those associated with 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). 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 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 6 molecules, while Allergic Asthma, Allergic Rhinitis, and Atopic Dermatitis shared 23 molecules. However, less-studied conditions such as Allergic Alveolitis shared just 2 molecules with Allergic Asthma and Atopic Dermatitis and 1 molecule with Allergic Rhinitis, reflecting its underrepresentation in the studies.

Figure 7C depicts a network of shared molecules with at least 2 connections across the 5 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.

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 5 genes across allergic disorders. 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.

**A user-friendly web platform for dynamic exploration of study findings**

[ALO•HA](https://rebollidorioslab.shinyapps.io/aloha/) was developed to facilitate the analysis of the ticles and 451 molecules and their associations with allergic disorders, sample sources, and temporal trends. Tailored for researchers and clinicians, ﷟HYPERLINK "https://rebollidorioslab.shinyapps.io/aloha/"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.

**DISCUSSION (1146 words)**

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 elucidated5,39-42. 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,](https://rebollidorioslab.shinyapps.io/aloha/) a web application to facilitate interactive data exploration.

From the initial 4,668 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 features20,21,43. 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 as sample sources, 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 conditions6,42,44-49. Tissue-resident macrophages in the lungs, skin, and liberated into sputum play critical roles in local immune responses and disease pathology15,43. Their underrepresentation highlights the limited understanding of macrophage behavior in the context of allergic disorders and the need for more strategies targeting shared immune pathway localized studies7,16,46,50-53.

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 regulation5,46,54-57. However, only 9 out of 451 molecules were miRNAs, reflecting limited research on non-coding RNAs 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 TLR758. Similarly, Wang Li et al. reported elevated miR-202-5p levels in macrophages from allergic rhinitis patients59. 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 methodologies13,49,60-62.

This review also revealed molecular similarities among Allergic Asthma, Allergic Rhinitis, and Atopic Dermatitis, the most well-represented atopic disorders. Semantic 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 phenotypes1,2,55. Beyond immune-specific pathways, enriched processes related to cellular communication, apoptosis, and response to external stimuli highlight broader regulatory mechanisms in allergic responses6,19. These shared molecular features present opportunities for therapeutic strategies targeting common pathways.

The emerging field of AllergoOncology explores parallels between immune processes in allergy and cancer, identifying shared, opposite or unique mechanisms and cross-disciplinary opportunities1-4,63. 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 metastasis1,15,19,64. 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 carcinoma1,19. Similarly, IL-6 supports both pro-inflammatory and tumor progression responses, contributing to therapeutic resistance and relapse in breast, ovarian, and hepatocellular carcinomas15,19. TNF fosters a pro-inflammatory tumor microenvironment, which can either enhance anti-tumor immunity or promote tumor growth and metastasis, depending on the context19. 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 avenues1,15,19,65. For instance, anti-IgE therapies could be repurposed to re-educate patient-derived macrophages in both allergy and cancer15. This approach could mitigate chronic inflammation in allergy or enhance anti-tumor immunity in cancer1,2,15,19. 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 cancer15,19. Furthermore, omics-based approaches may facilitate the discovery of novel biomarkers and therapeutic targets, enabling personalized treatments tailored to individual immune profiles6,13,46,49,60-62,66.

Despite its valuable insights, this review faced several 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 changes11,13. The limited availability of studies including healthy controls and tissue-resident macrophages further restricts the generalizability of the results20,21. Additionally, 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 cancer2,3,15,39,41,55,56,63,65-68.

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 molecular signatures across allergic disorders may facilitate the development of targeted therapies addressing common immune mechanisms.

Moreover, the development of [ALO•HA](https://rebollidorioslab.shinyapps.io/aloha/) represents a major advancement in enhancing the accessibility and practical application of the study results. This interactive web platform enables reproducible data exploration and provides researchers and clinicians with an intuitive framework to analyze gene- and disease-specific features. Finally, the parallels between macrophage behavior in allergy and cancer suggest potential cross-disciplinary insights that could inform treatment strategies for both conditions. A deeper understanding of monocyte and macrophage phenotypes in allergy holds the potential to unlock novel therapeutic approaches, bridging the fields of allergy and oncology for transformative advancements in patient care.

**FIGURE LEGENDS**

**Figure 1. Development of monocytes and macrophages during embryogenesis and adulthood**. The figure illustrates the sequential waves of monocyte and macrophage development, highlighting their embryonic origins and adult differentiation pathways5. In the first wave (1: orange lines), the yolk sac (YS) gives rise to primitive macrophages at embryonic day 7.5 (E7.5 in mice); these cells are known to migrate to tissues such as the brain to form microglia. The second wave (2: red lines), driven by erythromyeloid progenitors (EMPs), begins at E8.25 and involves differentiation into macrophages or migration to the fetal liver (FL) to generate fetal monocytes that seed tissues like the lungs and skin before birth, forming long-lived tissue-resident macrophages. In the third wave (3: blue lines), hematopoietic stem cells (HSCs), emerging later from the aorta-gonad-mesonephros (AGM) and FL, contribute to fetal monocyte production. In adulthood, HSCs in the bone marrow generate monocyte precursors, giving rise to circulating monocyte subsets: classical (CD14++CD16-), intermediate (CD14++CD16+), and non-classical (CD14+CD16++), which fulfill distinct roles in immune surveillance and inflammation. Classical monocytes, the primary subset released from the bone marrow, express high levels of CCR2. The CCR2/CCL2 axis recalls classical monocytes that circulate in the blood to migrate into tissues, where they differentiate into short-lived tissue macrophages, dendritic cells, or undergo apoptosis.

**Figure 2. The macrophage polarization spectrum and functional diversity.** (A) Molecular and functional characteristics of macrophage subtypes. The figure depicts the polarization spectrum of macrophages in vitro, originating from monocyte-derived macrophages (M0), into two primaries 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, 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 CD23hi and FcεRIhi, 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 express CD86 and CD206dim, 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 (FcεRIint) and CD23 (CD23int), 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 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.

**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 versus 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 showing 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 visualizing 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 studies examining specific disorders and sample source combinations within the 138 selected articles. 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; IH, Immediate Hypersensitivity.

**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.

**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 genes associated with multiple disorders, where nodes represent molecules, edges indicate associations with disorders, and node size reflects the degree of interconnectivity. Node and edge colors 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 genes per enriched pathway. Gray bars on the right show the total number of genes present in each disorder. Top bar annotation categorizes pathways into 5 top-level Reactome pathways, including immune system processes, signal transduction, and programmed cell death.

**Figure S1. Article-based disorder and cell type associations.** The network depicts the associations between disorders and publication cell type 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; 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).

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