

[REVIEW ARTICLE]

Current Overview of Multi-omics Analyses in Microscopic Polyangiitis and Granulomatosis with Polyangiitis

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Abstract:

Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) is an autoimmune disease characterized by autoantibodies against neutrophil cytoplasmic antigens such as myeloperoxidase (MPO) and proteinase 3 (PR3). AAV affects small blood vessels, leading to systemic inflammation and multiorgan damage. Recent advances in multi-omics analyses, including genomics, epigenomics, transcriptomics, proteomics, and metabolomics, have significantly improved our understanding of AAV complex pathophysiology. Genome-wide association studies (GWASs) have revealed robust genetic associations, especially within the human leukocyte antigen (HLA) region. Epigenomic analyses have elucidated regulatory mechanisms that affect autoantigen gene expression and disease activity. Transcriptomic approaches, particularly single-cell RNA sequencing (scRNA-seq), have identified distinct gene expression profiles and cellular interactions, which have been further enriched by the recent application of spatial transcriptomics of diseased tissues. Proteomic and metabolomic approaches have been used to identify potential biomarkers. This review discusses recent advances in multi-omics research aimed at developing personalized diagnostic and therapeutic strategies based on the molecular and genetic profiles of AAV.

Key words: ANCA-associated vasculitis, genomics, transcriptomics, scRNA-seq, spatial transcriptomics, proteomics

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Background

Vasculitis is a heterogeneous group of immune-mediated disorders characterized by inflammation that affects blood vessels of varying sizes, resulting in diverse clinical manifestations. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic autoimmune disease characterized by autoantibodies against neutrophil cytoplasmic antigens such as myeloperoxidase (MPO) and proteinase 3 (PR3) (1). Clinical subtypes of AAV include microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA), which are predominantly associated with

MPO-ANCA and PR3-ANCA, respectively. Patients with AAV frequently present with systemic inflammatory symptoms, such as fever and fatigue, accompanied by organ-specific injury involving small vessels, notably in the kidneys, lungs, and peripheral nerves. Renal involvement is characterized by pauci-immune glomerulonephritis, which lacks immune complex deposition in glomeruli. This pathological feature differentiates AAV from immune complex-mediated nephritis observed in systemic lupus erythematosus (SLE) (2-5).

“Omics” refers to the comprehensive and large-scale analysis of molecular entities within biological systems. With the completion of the Human Genome Project in the

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Table. Omics in ANCA-associated Vasculitis.

	Year	Disease	Omics technique	Key findings	Ref
a) Genomics	2012	MPA/GPA	GWAS	Variants in <i>HLA-DQ</i> are implicated in MPA Variants in <i>HLA-DP</i> are implicated in GPA	(7)
	2013	GPA	GWAS	Variants in <i>SEMA6A</i> are implicated in GPA	(9)
	2017	MPA/GPA	GWAS	SNPs at the <i>HLA-DPB1</i> locus are associated with AAV	(8)
b) Epigenomics	2010	MPA/GPA	Epigenomics (quantitative ChIP analysis)	Decreased trimethylation of H3K27 in neutrophils is observed in AAV patients	(14)
	2017	MPA/GPA	Epigenomics (EpiTyper MassARRAY)	Reduced methylation of PR3 is associated with an increased risk of relapse	(13)
c) Transcriptomics	2023	MPA/GPA (white blood cells)	scRNA-seq	The active phase of AAV is characterized by pathways related to cell cycle checkpoints and metabolic processes	(19)
	2023	MPA (white blood cells)	scRNA-seq, CITE-seq	Transcriptomic-based classification of MPA identifies two types: MPA-MONO and MPA-IFN	(21)
	2025	MPA (white blood cells)	scRNA-seq, Abseq	A type II IFN-related neutrophil subset (Neu_T2ISG) is associated with MPA; serum IFN- γ predicts relapse risk	(22)
	2023	MPA/GPA (kidney)	scRNA-seq	Clonally proliferating cytotoxic T cells infiltrate crescentic glomerulonephritis lesions	(23)
	2023	MPA/GPA (kidney)	Spatial transcriptomics (GeoMx DSP)	piFNGN glomeruli exhibit varying expression profiles with the morphological evolution of lesions	(27)
	2024	MPA/GPA (kidney)	Spatial transcriptomics (Visium)	Th1 and Th17 cells infiltrate inflamed glomeruli; targeting IL-12 and IL-23 represents a potential therapeutic strategy	(29)
d) Proteomics	2017	MPA/GPA	Proteomics (LC-MS/MS)	Serum biomarkers for detecting active AAV; TNC, CRP, and TIMP1	(35)
	2021	MPA/GPA	Proteomics (antibody microarray)	EV biomarkers for characterizing AAV; C1q and IL-18	(36)
	2021	MPA/GPA (urinary EV)	Proteomics (LC-MS/MS)	MAN1A1 levels in urinary EVs are reduced during active AAV	(37)
e) Metabolomics	2023	MPA/GPA	Metabolomics (LC-MS/MS)	Serum 1-methylhistidine predicts risk of end-stage renal disease and mortality	(42)

MPA: microscopic polyangiitis, GPA: granulomatosis with polyangiitis, GWAS: genome-wide association study, PR3: proteinase 3, scRNA-seq: single-cell RNA sequencing, CITE-seq: cellular indexing of transcriptomes and epitopes by sequencing, IFN: interferon, GeoMx DSP: GeoMx digital spatial profiler, piFNGN: pauci-immune focal necrotizing glomerulonephritis, IL: interleukin, TNC: tenascin C, EV: extracellular vesicle, LC-MS/MS: liquid chromatography-tandem mass spectrometry, MAN1A1: mannosidase alpha class 1a member 1

early 2000s, omics technologies have rapidly evolved, providing novel insights into complex disease mechanisms. Translational research employing omics data has revealed novel immune pathways implicated in the pathogenesis of autoimmune diseases. In addition, omics technologies have facilitated the discovery of biomarkers and therapeutic targets for personalized treatment strategies.

In recent years, AAV research has benefited substantially from advancements in multi-omics analyses, including genomics, epigenomics, transcriptomics, proteomics, and metabolomics. This review focuses on multi-omics studies that provide comprehensive insights into AAV pathogenesis, thereby guiding diagnostic and therapeutic strategies.

1. Genomics

Genomics involves a comprehensive study of the entire genome with the aim of identifying genetic variations associated with disease susceptibility and pathogenesis. Since the completion of the Human Genome Project in 2003 and the

International HapMap Project in 2005, genome-wide association studies (GWASs) have expanded our understanding of complex and polygenic diseases by linking genetic variants, particularly single nucleotide polymorphisms (SNPs), to specific disease phenotypes (6). It is widely recognized that genetic variants, particularly those within the human leukocyte antigen (HLA) locus, play critical roles in determining susceptibility to autoimmune diseases (Table a).

In AAV research, three major GWASs have significantly advanced our understanding of genetic risk factors. These studies have identified associations between AAV and genetic loci within the HLA region, showing the importance of antigen presentation in disease pathogenesis (7-9). A study of 1,223 cases from the United Kingdom demonstrated subtype-specific genetic susceptibility, revealing that MPA is strongly associated with variants in *HLA-DQ*, whereas GPA is closely linked to variants in the *HLA-DP* region as well as genes encoding serpin A1 (SERPINA1) and proteinase 3 (PRTN3) (7). A large European cohort study of 1,986 cases highlighted significant associations between AAV risk and

SNPs at the *HLA-DPB1* locus (rs141530233 and rs1042169). These SNPs are correlated with a reduced expression of *HLA-DPB1* in B cells and monocytes and an increased frequency of PR3-reactive T cells (8). Furthermore, robust associations were found with loci, such as *SERPINA1*, *PTPN22*, and *PRTN3*. Another GWAS involving 492 European GPA cases highlighted the crucial role of the HLA region, implicating variants in the *SEMA6A* gene (9). These genomic findings emphasize the genetic heterogeneity underlying AAV and facilitate the stratification of patients based on genetic susceptibility.

2. Epigenomics

Epigenomics investigates the regulatory mechanisms that influence gene expression without altering the underlying DNA sequence, primarily through DNA methylation and histone modifications (10). These epigenetic modifications play crucial roles in gene regulation, and are closely linked to cellular differentiation, development, and disease progression. In malignancies and lifestyle-related diseases, epigenomic alterations have been increasingly recognized as essential contributors to disease pathogenesis (11, 12) (Table b).

Epigenomic analyses of AAV have focused on DNA methylation and histone modifications. A longitudinal study involving 82 patients with AAV (42 PR3-ANCA-positive and 40 MPO-ANCA-positive) analyzed DNA methylation profiles in white blood cells and revealed significant demethylation at the MPO and PR3 gene promoters during active disease phases, resulting in increased gene expression. Methylation levels are elevated during disease remission (13). Specifically, increased methylation of the PR3 promoter during remission was correlated with a significantly reduced risk of relapse, while decreased methylation was associated with a 4.5-fold increased risk of relapse. In addition, a study investigating histone modifications in 15 AAV patients demonstrated decreased H3K27 trimethylation at the MPO and PR3 loci in neutrophils from AAV patients, providing a mechanism for the aberrant upregulation of these autoantigen genes (14). These findings suggest that epigenetic dysregulation plays a pivotal role in AAV disease activity and progression and that epigenetic modifications may serve as potential biomarkers for disease monitoring.

3. Transcriptomics

Transcriptomics is an approach that allows the comprehensive characterization of RNA molecules and provides detailed insights into gene expression profiles within cells or tissues (15). RNA sequencing (RNA-seq) can quantitatively measure gene expression, identify transcriptomic diversity, and detect alternative splicing variants. Single-cell RNA sequencing (scRNA-seq), initially developed in 2009 for the transcriptome profiling of single blastocysts and oocytes (16), has evolved rapidly over the past decade. Since

the late 2010s, this technology has been applied to patient-derived samples of autoimmune diseases, facilitating the identification of novel immune cell subsets and personalized treatment strategies (17, 18) (Table c).

In the context of AAV, an RNA-seq analysis of whole blood from 30 patients identified 1,982 differentially expressed genes involved in leukocyte degranulation and cytokine signaling (19). A pathway enrichment analysis highlighted cell cycle checkpoints and metabolic pathways during active disease phases. Humoral immune pathways were prominent in the ANCA-positive cases. Subtype-specific analyses revealed distinct transcriptomic signatures between GPA and MPA. The interferon (IFN)- γ pathway was associated with GPA, whereas MPA showed distinct alterations in autophagy and mRNA splicing pathways. We performed scRNA-seq and cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq) (20) of peripheral blood mononuclear cells (PBMCs) from eight newly diagnosed MPA patients (21) (Figure a). Compared with healthy controls, CD14⁺ monocytes were significantly increased in patients with MPA. Patients were stratified into two groups: MPA-MONO type, characterized by a high proportion of activated CD14⁺ monocytes; and MPA-IFN type, characterized by increased interferon-stimulated genes. Clinical evaluations indicated that the MPA-MONO subtype is associated with increased monocyte proportions and a high relapse risk. The MPA-IFN subtype is associated with elevated serum IFN- α levels and a better therapeutic response. Thus, scRNA-seq analyses may predict clinical outcomes in individual patients. In a study exploring neutrophil diversity in MPA (22), the distinct neutrophil subset Neu_T2ISG, characterized by type II interferon (IFN- γ) signature genes, was identified. This subset emerges upon IFN- γ and tumor necrosis factor (TNF) stimulation and is prone to ANCA-induced neutrophil extracellular trap formation (Figure b). Patients with an increased proportion of Neu_T2ISG cells showed persistent disease activity, and elevated serum IFN- γ levels at the diagnosis were strongly associated with a risk of relapse. These findings highlight Neu_T2ISG as a pathogenic subset and propose serum IFN- γ as a predictive biomarker for MPA relapse (Figure c). Further application of scRNA-seq combined with a T-cell receptor repertoire analysis on renal biopsy specimens identified clonally expanded cytotoxic T cells expressing high levels of granzyme B (GzmB) (23). These T cells induce apoptosis in the renal parenchymal cells and exacerbate glomerular injury in AAV nephritis. Animal model experiments have confirmed that infiltration of CD8⁺ T cells secreting GzmB contributes to glomerular injury, with amelioration of disease observed in mice deficient in either CD8 or GzmB.

Spatial transcriptomics, a cutting-edge technique that preserves spatial information while assessing gene expression at a cellular resolution, has recently been employed in autoimmune disease research (24). Spatial transcriptomics emerged in the early 2010s and has rapidly evolved to address the loss of spatial information due to cell dissociation in

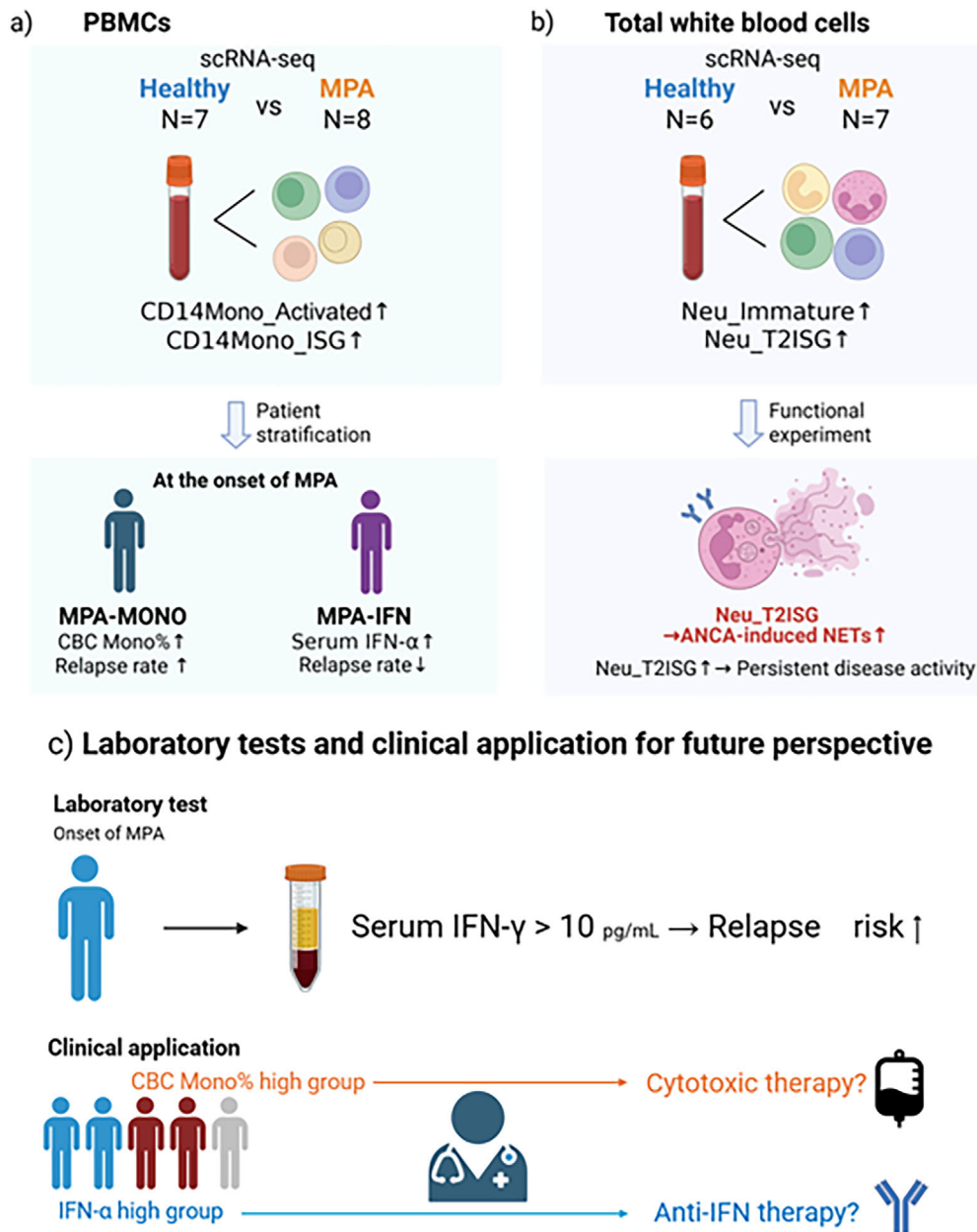


Figure. Insights and potential clinical applications of single-cell transcriptomics for MPA. a) Single-cell RNA sequencing (scRNA-seq) of peripheral blood mononuclear cells (PBMCs) from patients with new-onset microscopic polyangiitis (MPA). Distinct patient stratification was proposed based on the differences in cell subtype composition. MPA-MONO is characterized by activated CD14⁺ monocytes and is associated with a poor response to treatment. MPA-IFN is characterized by the increased expression of interferon-stimulated genes (ISGs) in various cell types and corresponds to favorable treatment outcomes (21). b) scRNA-seq of whole white blood cells from patients with MPA. A Neu_T2ISG subset, characterized by type II interferon (IFN-γ) signature genes, emerges upon IFN-γ and tumor necrosis factor (TNF) stimulation. This subset of cells is prone to ANCA-induced neutrophil extracellular trap (NET) formation. Patients with a high proportion of Neu_T2ISG cells show persistent disease activity (22). c) Potential clinical applications of the scRNA-seq results. A serum IFN-γ concentration >10 pg/mL at the onset of MPA can predict relapse risk for each patient. As a potential treatment strategy, cytotoxic therapy and anti-IFN therapy could be considered for the high CBC monocyte % and high IFN-α groups, respectively. Mono: monocytes, ANCA: anti-neutrophil cytoplasmic antibody, CBC: complete blood count

scRNA-seq methodology (25, 26). NanoString's Digital Spatial Profiling (DSP) of kidney biopsies from 18 patients with AAV revealed distinct molecular profiles within the affected

tissue regions (27, 28). CD44 and CD45 expression was consistently high in fibrotic glomeruli. Transforming growth factor beta 1 (TGFB1) was overexpressed in epithelial cell

reaction areas, suggesting early activation of TGF- β signaling and collagen synthesis during pauci-immune focal necrotizing glomerulonephritis. Another study using the Visium spatial transcriptomics platform revealed distinct inflammatory niches within the glomeruli and tubulointerstitial regions of the kidneys from 34 patients with ANCA-associated glomerulonephritis (29). This study highlighted the central role of Th1 and Th17 cells in the production of proinflammatory cytokines such as interleukin (IL)-12 and IL-23. Using digital pharmacology approaches, the monoclonal antibody ustekinumab, which targets IL-12 and IL-23, was identified as a potential therapeutic candidate. Thus, transcriptomic analyses of AAV, particularly using recent scRNA-seq and spatial transcriptomic technologies, have provided insights into novel pathologies and potential therapeutic interventions for AAV.

4. Proteomics

Proteomics involves the comprehensive analysis of protein expression profiles, offering critical insights into cellular function and disease phenotypes (30). This approach includes methods such as mass spectrometry, which identifies and quantifies proteins by measuring the mass-to-charge ratio of peptide ions, and protein microarrays, which analyze numerous proteins simultaneously (31). Extracellular vesicles (EVs) released by a variety of eukaryotic cells during cell activation and programmed cell death have emerged as key mediators of intercellular communication and represent promising sources of biomarkers (32-34) (Table d).

In a proteomic study of serum samples from 169 patients with AAV, 135 potential biomarkers were identified (35). Targeted mass spectrometry-based proteomic analyses of serum samples identified specific biomarkers, including tenascin C (TNC), C-reactive protein (CRP), and tissue inhibitor of metalloproteinase 1 (TIMP1), that effectively discriminated active phases from remission phases (six months post-treatment) or healthy conditions. TIMP1 serves as a highly reliable marker for detecting high disease activity. Proteomic analyses using antibody microarrays in 316 cases of SLE, rheumatoid arthritis (RA), Sjögren's syndrome (SS), and systemic vasculitis (36) demonstrated their ability to differentiate autoimmune diseases from control groups with high accuracy (area under the receiver operating characteristic curve values ranging from 0.96 to 0.80). Molecules such as the complement components C1q and IL-18 were highlighted as distinct markers of vasculitis ($n=82$). Recent urinary EV proteomics using liquid chromatography-mass spectrometry (LC-MS/MS) identified decreased levels of mannosyl-oligosaccharide 1,2- α -mannosidase IA (MAN1 A1), a Golgi enzyme involved in the glycosylation of N-glycans associated with T-cell activation in AAV (37). Altered glycosylation patterns of ANCA, particularly reduced sialylation and galactosylation, have been previously associated with macrophage activation and increased disease activity (38, 39). These findings highlight the utility of proteomic

analyses in elucidating biomarkers involved in the pathophysiology of AAV.

5. Metabolomics

Metabolomics involves the comprehensive analysis of metabolites (40) and small molecules that are indicators of biological processes and are thus closely linked to the phenotype. Metabolomics can provide insights into the gene function, metabolic pathways, disease mechanisms, and potential diagnostic biomarkers (41) (Table e).

A serum metabolomic study using LC-MS/MS revealed significant metabolic alterations in patients with AAV-associated nephritis (42). This analysis identified 135 differentially expressed metabolites, including amino acids, nucleotides, and their derivatives, of which 121 were upregulated and 14 were downregulated compared to healthy controls. Using machine learning approaches, metabolites such as N-acetyl-L-leucine, acetyl-DL-valine, and 5-hydroxyindole-3-acetic acid, as well as combinations of 1-methylhistidine and Asp-Phe, have demonstrated high accuracy in distinguishing AAV patients from healthy individuals. Among these metabolites, elevated levels of 1-methylhistidine are particularly associated with disease progression, predicting an increased risk of end-stage renal disease and mortality.

6. Conclusion

We reviewed current multi-omics research in AAV, highlighting the progress achieved through genomic, epigenomic, transcriptomic, proteomic, and metabolomic analyses. These integrative approaches have deepened our understanding of the complex pathophysiology underlying AAV, revealing the genetic susceptibilities, regulatory mechanisms of gene expression, distinct cellular profiles, and metabolic perturbations associated with the disease. Further integration of multi-omics data with clinical features is necessary to refine personalized medicine strategies tailored to specific molecular profiles. In particular, recent advances in single-cell technologies and spatial transcriptomics have the potential to enhance our understanding of individual patient molecular profiles and drive innovations in clinical management strategies for AAV. Translating omics-driven insights into clinical practice is expected to facilitate optimized diagnostic and therapeutic strategies.

The authors state that they have no Conflict of Interest (COI).

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