Multi-omics insights into uveitis: From mechanisms to precision medicine (Review)

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Abstract. Uveitis encompasses a group of intraocular inflammatory disorders that notably contribute to global visual morbidity. Persistent challenges include early diagnosis, accurate subtype classification and individualized treatment. Recent advances in omics technologies, including genomics, epigenetics, transcriptomics, single-cell omics, proteomics, metabolomics, lipidomics and microbiome profiling, have reshaped the current understanding of uveitis pathogenesis by uncovering disease-associated genetic variants, dynamic transcriptional landscapes, inflammatory proteins, metabolic alterations, and microbe-host interactions. Notably, single-cell RNA sequencing offers unprecedented insights into retinal immune cell heterogeneity and functional states, while radiomics is emerging as a valuable platform for imaging biomarkers. The present review summarizes key findings from multi-omics studies in uveitis, described the sample sources and analytical strategies employed, and highlighted the transformative potential of integrative omics in precision ophthalmology. Multi-omics approaches hold promise for identifying novel biomarkers and therapeutic targets, refining disease classification, and enabling tailored interventions for patients with uveitis.

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1. Introduction

Uveitis is a group of intraocular inflammatory diseases that affect the uvea, retina, and its vasculature, as well as the optic nerve and vitreous (1). It may cause serious complications, including macular edema, vitreous hemorrhage, retinal detachment, cataracts and glaucoma, making it one of the leading causes of blindness, accounting for 10-15% of severe visual impairment. Uveitis has a notable impact on public health, primarily affecting individuals aged 20-50 years (2,3). According to the Standardization of Uveitis Nomenclature (SUN), uveitis is classified into anterior uveitis (affecting the iris and anterior ciliary body), intermediate uveitis (involving the posterior ciliary body, vitreous and pars plana), posterior uveitis (affecting the retina and choroid) and panuveitis (involving the entire uveal tract and associated tissues) (4,5). In addition, uveitis can also be categorized as either infectious or non-infectious. Specifically, bacterial, viral, fungal, or parasitic infections, including *Mycobacterium tuberculosis*, *Treponema pallidum*, *Toxoplasma gondii* and cytomegalovirus, cause infectious uveitis (6). Non-infectious uveitis is primarily autoimmune or autoinflammatory and includes Vogt-Koyanagi-Harada (VKH) disease, Behçet's disease (BD) uveitis, HLA-B27-associated uveitis, birdshot chorioretinopathy (BSCR), sympathetic ophthalmia, Fuchs uveitis syndrome, multifocal choroiditis and juvenile idiopathic arthritis-associated uveitis (3,7). Idiopathic uveitis refers to uveitis of unknown origin after considerable investigation. As the cause of idiopathic uveitis remains unclear, treatment can be challenging. However, the term 'unclassified uveitis' is preferred by modern ophthalmologists, as some cases of idiopathic uveitis may potentially be linked to immune system disorders or systemic diseases that are not yet fully understood (8,9).

Over the past decade, notable progress has been made in molecular profiling across various diseases, driving more precise and personalized clinical decision-making. Advances

in multi-omics technologies, including genomics, transcriptomics, proteomics and metabolomics, have facilitated the identification of informative biomarkers and their translation into clinical practice (10,11). By integrating these omics approaches, researchers have gained deeper insights into disease mechanisms, ultimately enhancing early diagnosis and treatment strategies (12). The present review explores the recent applications of multi-omics strategies in uveitis research. Key findings are summarized and integrated, highlighting the contributions of multi-omics technologies in improving diagnostic accuracy and therapeutic interventions. Furthermore, the future potential of these approaches in uveitis is discussed, offering novel perspectives for advancing precision medicine and optimizing patient care.

2. Main pathological processes in uveitis

The development of uveitis is driven by complex immune imbalances, with T cell-mediated autoimmunity recognized as the central pathological mechanism. The main pathological features include disruption of the blood-retinal barrier (BRB) and infiltration of immune cells (13). This section briefly reviews the current understanding of the underlying immune mechanisms. Anatomically, the uvea is richly vascularized, characterized by slow blood flow, and exhibits lymph node-like functions, making it particularly susceptible to immune cell infiltration and inflammation. Normal ocular tissues contain several potential autoantigens, including retinal S-antigen (S-Ag), interphotoreceptor retinoid-binding protein (IRBP) and melanin-associated antigens (14,15). Under physiological immune tolerance, these autoantigens do not elicit immune responses. However, when immune regulation is disturbed, due to infection, drugs, or genetic predisposition, tolerance may break down. Antigen-presenting cells (APCs), including dendritic cells (DCs) and macrophages, can then capture and process these self-antigens, presenting them to naïve $CD4^+$ T cells via major histocompatibility complex (MHC) class II molecules, thereby initiating autoimmune activation. Under the influence of antigenic stimulation and the local cytokine milieu, naïve $CD4^+$ T cells differentiate into Th1 and Th17 effector subsets (16-18). Th1 cells, activated primarily by interleukin (IL)-12, secrete interferon-γ (IFN-γ), which enhances macrophage activation and promotes antigen presentation and cytotoxic responses. By contrast, Th17 cells differentiate under the combined action of IL-6 and transforming growth factor-β (TGF-β), producing cytokines such as IL-17 and IL-22 that recruit neutrophils and amplify inflammation. Both Th1 and Th17 cells can cross the BRB, infiltrating intraocular tissues, where they disrupt barrier integrity and promote local inflammatory damage (19,20). Within the inflammatory microenvironment, monocytes/macrophages and neutrophils are continuously recruited, releasing reactive oxygen species, proteases, and additional proinflammatory cytokines that exacerbate uveal and retinal injury (21,22). Meanwhile, the levels of anti-inflammatory cytokines such as IL-10 and TGF-β decline, further aggravating the immune imbalance. Regulatory T cells (Tregs) normally maintain immune tolerance and intraocular homeostasis by secreting IL-10 and TGF-β to suppress excessive effector T-cell activation (15,23). In uveitis, however, Treg numbers are reduced or their function impaired, disrupting the balance between Th1/Th17 cells and Tregs. This imbalance results in sustained immune activation and chronic inflammation. Persistent activation of Th1/Th17 cells and proinflammatory pathways involving TNF-α, IFN-γ and IL-17 leads to progressive ocular tissue damage, while Treg dysfunction prevents effective suppression of inflammation (24,25). Collectively, these immune processes form the pathological basis of uveitis and provide a rationale for therapeutic strategies targeting cytokines and immune regulatory pathways (Fig. 1).

Leveraging these immunological insights, researchers have established experimental uveitis models. In the classic experimental autoimmune uveitis (EAU) model, mice are immunized with retinal antigens (including IRBP or its peptide fragments) in combination with complete Freund's adjuvant, with pertussis toxin administered to enhance the inflammatory response (26). The EAU model serves as a critical research platform for investigating the immune mechanisms of uveitis, providing insights into the role of T cells in disease pathogenesis (27,28). In addition to EAU, endotoxin-induced uveitis (EIU) is another widely used experimental model for studying ocular inflammation. Unlike EAU, which is primarily driven by antigen-specific adaptive immune responses, EIU is induced by systemic administration of lipopolysaccharide (LPS) and predominantly reflects innate immune activation. The model is characterized by a rapid onset of inflammation, breakdown of the blood-aqueous barrier, infiltration of neutrophils and macrophages, and increased production of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6. Due to its simplicity, reproducibility and acute inflammatory nature, EIU has been extensively employed to investigate early inflammatory responses, innate immune signaling pathways, and the therapeutic effects of anti-inflammatory agents (29). Together, EAU and EIU provide complementary platforms for elucidating the complex immunopathological mechanisms underlying uveitis. Immunotherapy for uveitis primarily includes glucocorticoids, immunosuppressants and biologics. Glucocorticoids are the first-line anti-inflammatory agents and can be administered either locally or systemically. Immunosuppressants modulate pathogenic immune responses and are a cornerstone in the management of non-infectious uveitis, particularly in severe, chronic, or vision-threatening cases and in specific entities such as BD or VKH. Major classes include antimetabolites (methotrexate, azathioprine), calcineurin inhibitors (cyclosporine A, tacrolimus), and alkylating agents (cyclophosphamide). These agents serve as essential steroid-sparing therapies for long-term inflammation control and, in selected conditions, may be used as first-line treatment. Additionally, biologics, including TNF-α inhibitors, including adalimumab, and IL-6 inhibitors, such as tocilizumab, play a crucial role in managing refractory autoimmune uveitis (30-32). Although significant progress has been made in the immune pathogenesis of uveitis in recent years and new immune-targeted drugs have been introduced, the disease still faces numerous challenges in clinical diagnosis and treatment, especially in early identification, efficacy evaluation, and the formulation of individualized treatment strategies (33).

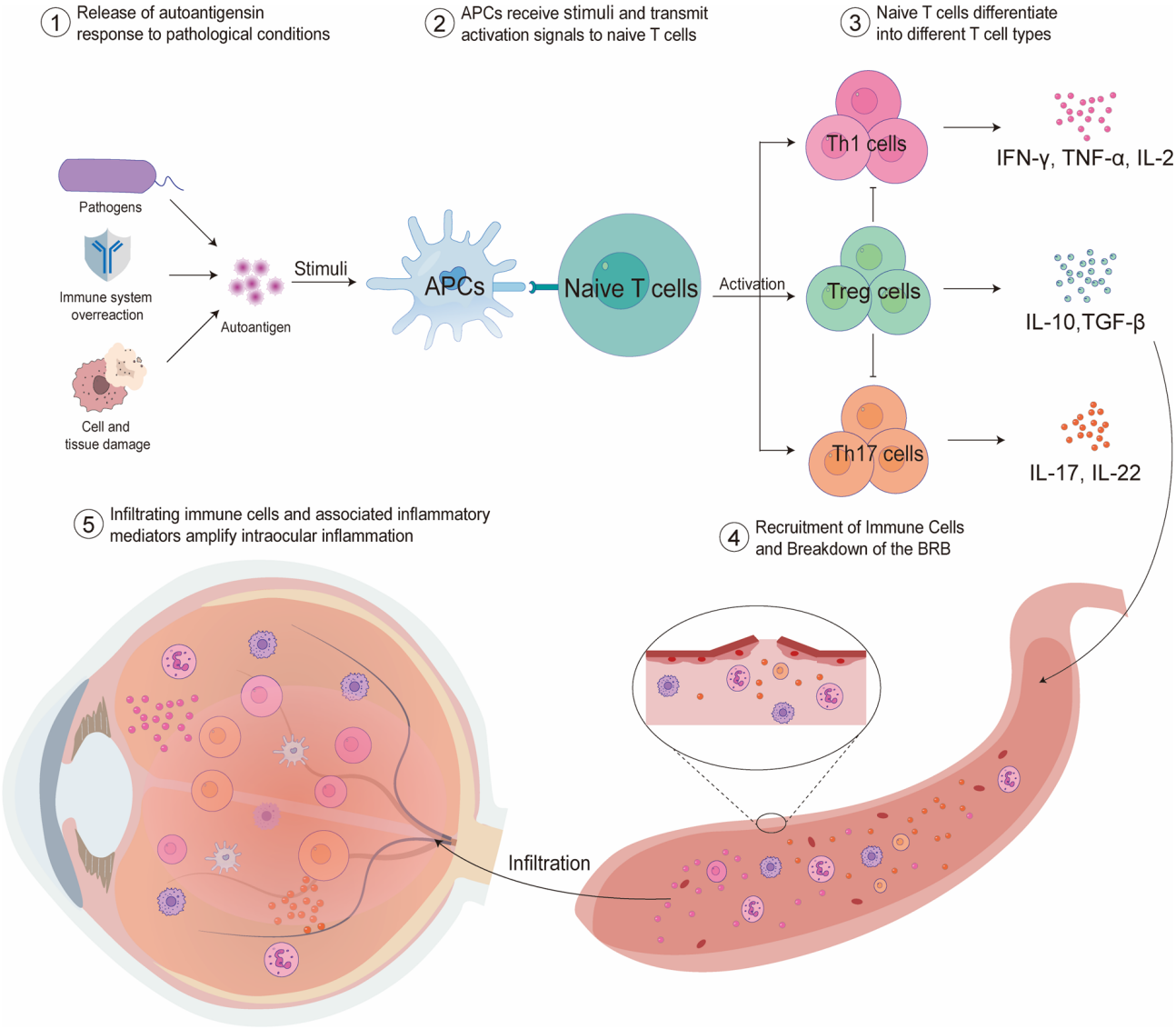

Figure 1. Schematic illustration of the immunopathogenesis of uveitis. Environmental, infectious, or autoimmune triggers promote the release and presentation of ocular autoantigens by APCs. APCs activate naïve $CD4^+$ T cells through MHC-mediated antigen presentation, leading to their differentiation into Th1, Th17 and Treg cell subsets. Activated Th1 and Th17 cells produce pro-inflammatory cytokines, IFN-γ, IL-17 and TNF-α, which disrupt the BRB and promote the recruitment of additional immune cells into ocular tissues. The resulting inflammatory cascade amplifies retinal and choroidal inflammation, ultimately contributing to tissue damage and visual impairment. APC, antigen-presenting cell; MHC, major histocompatibility complex; Th, T helper cell; Treg, regulatory T cell; IFN-γ, interferon-γ; IL-17, interleukin-17; TNF-α, tumor necrosis factor-α; BRB, blood-retinal barrier.

3. Omics in ophthalmology research

To understand the mechanisms by which multi-omics technologies uncover the pathogenesis of uveitis, aid in classification, and support personalized treatment, it is important to examine both their technical foundations and sample requirements. In the present review, first, the principles, focuses, and typical biomedical applications of major omics approaches are introduced, followed by a discussion of the sample types and acquisition methods relevant to ophthalmic research. This dual perspective will provide a basis for exploring the role of multi-omics in uveitis.

Overview of omics approaches. Omics refers to the systematic acquisition, analysis and interpretation of large-scale biological data on a specific class of biomolecules to elucidate the structure, function, and regulatory mechanisms of complex life systems (34,35). Omics technologies serve as powerful platforms in modern biomedical research, enabling comprehensive and high-throughput profiling of biological molecules across multiple regulatory layers. The foundational concept underlying most omics approaches is the central dogma of molecular biology, which describes the directional flow of genetic information from DNA to RNA to protein (36). Based on this framework, several major omics disciplines have been developed. Genomics investigates the complete structure, variation and function of the genome, helping to identify disease-associated genetic variants and susceptibility loci (37). Transcriptomics focuses on the entire set of RNA transcripts, including coding and non-coding RNAs (ncRNAs), to examine gene activity in different tissues or disease states (38). Proteomics analyzes protein abundance,

modifications and interactions, offering insights into signaling pathways and immune responses (38). Metabolomics assesses low-molecular-weight metabolites, which reflect downstream cellular processes and metabolic changes associated with disease progression (39).

However, with advances in molecular biology, the central dogma has been increasingly expanded and refined. For example, retroviruses utilize reverse transcriptase to convert RNA back into DNA, challenging the unidirectional nature of information flow. Furthermore, an increasing number of ncRNAs, including microRNAs (miRNAs) and long ncRNAs (lncRNAs), have been found to play critical roles in gene regulation without encoding proteins. In addition, processes including RNA splicing, alternative splicing, and epigenetic modifications are now recognized as essential contributors to protein synthesis and functional regulation (40). Epigenomics, in particular, investigates heritable modifications to DNA or chromatin that influence gene expression without altering the underlying DNA sequence (41).

In addition to omics disciplines grounded in the central dogma, the field has expanded to include non-central dogma-based omics. For instance, radiomics extracts high-dimensional quantitative features from medical imaging modalities, including optical coherence tomography (OCT) and magnetic resonance imaging (MRI), enabling the identification of subtle patterns associated with disease phenotypes and therapeutic responses (42,43). Microbiomics characterizes microbial communities in environments including the gut, skin or ocular surface, offering novel insights into host-microbe interactions and their roles in immune regulation (44).

These diverse omics layers provide complementary perspectives on disease mechanisms. When integrated, multi-omics approaches allow for a more complete understanding of complex conditions, including uveitis, improving biomarker discovery, therapeutic target identification, and precision medicine strategies (Fig. 2). Despite challenges related to sample availability, data integration and analytical complexity, the continued development and application of omics technologies are expected to transform uveitis research and clinical care (45,46). In the subsequent sections, each omics discipline is systematically presented, and its specific contributions to understanding the pathogenesis, diagnosis and treatment of uveitis are explored.

Sample sources for omics study in uveitis. Biomarkers in ocular and systemic fluids serve as important indicators of pathological processes associated with uveitis, reflecting their critical role in disease development (Fig. 3). Ocular samples include the retina, choroid, aqueous humor, vitreous, tears and conjunctiva (47). While retinal and uveal tissues are most directly relevant to the disease, obtaining such samples from humans is not feasible. Thus, related omics studies typically rely on animal models or postmortem donor tissues to explore disease pathogenesis. In clinical practice, aqueous humor and vitreous samples are commonly used for omics analyses. Aqueous humor paracentesis is a well-established and generally safe procedure when performed under sterile conditions, whereas vitreous sampling is more invasive and usually reserved for selected cases. In both settings, sample volumes are carefully limited to minimize procedure-related complications, including hypotony (48). Optimizing the collection, storage, processing, and analysis of these limited samples is essential to maximize their utility (49). Tears and conjunctival samples are more easily accessible and primarily reflect anterior segment pathology. However, due to anatomical proximity, intraocular inflammation can influence tear composition, making tears a promising, non-invasive source of biomarkers for active intraocular inflammation (50,51).

Beyond ocular samples, researchers are investigating systemic biomarkers in blood, lymph nodes, feces, sweat, and other body fluids using omics approaches. Blood offers several advantages, including large sample volumes, accessibility, standardized collection protocols, established analytical techniques, and the opportunity for repeated measurements (10). Lymph nodes are crucial in immune cell interactions and in initiating autoimmune responses. Cervical draining lymph nodes (CDLN), as the primary drainage nodes of the central nervous system (CNS), play a crucial role in the pathogenesis of autoimmune diseases of the CNS, effectively receiving macromolecules and immune cells from the CNS (52). The gut microbiome, assessed through fecal analysis, has also been increasingly recognized for its influence on diseases beyond the intestine, including ocular and systemic autoimmune conditions (53).

4. Omics in uveitis

The present review summarizes recent advances in omics research in uveitis. To ensure comprehensive coverage of the literature, a systematic search was conducted in PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://clarivate.com/academia-government/scientific-and-academic-research/research-discovery-and-referencing/web-of-science/) and Scopus (https://www.scopus.com) for articles published. The search strategy combined relevant keywords and Medical Subject Headings terms, including 'uveitis', 'multi-omics', 'genomics', 'epigenomics', 'transcriptomics', 'single-cell sequencing', 'spatial omics', 'proteomics', 'metabolomics', 'lipidomics', 'microbiome', 'radiomics' and 'precision medicine'. Reference lists of relevant articles were also screened to identify additional studies. Priority was given to original research articles, high-quality reviews, and recent publications focusing on autoimmune and infectious uveitis. Studies lacking sufficient methodological details, those not directly related to ocular inflammatory diseases, or publications with limited relevance to the scope of the present review were excluded (Fig. 4). The selected literature was synthesized narratively to provide an overview of current omics technologies, key biological insights, and emerging applications in precision medicine for uveitis.

Genomics. The exact pathogenesis of uveitis remains unclear. However, it is widely acknowledged that a combination of genetic or epigenetic predispositions, environmental risk factors, and dysregulated immune responses contributes to disease development, particularly in autoimmune uveitis, including acute anterior uveitis (AAU), BD, VKH, BSCR, and sarcoid uveitis (54). In addition, several monogenic autoinflammatory disorders, including but not limited to Blau

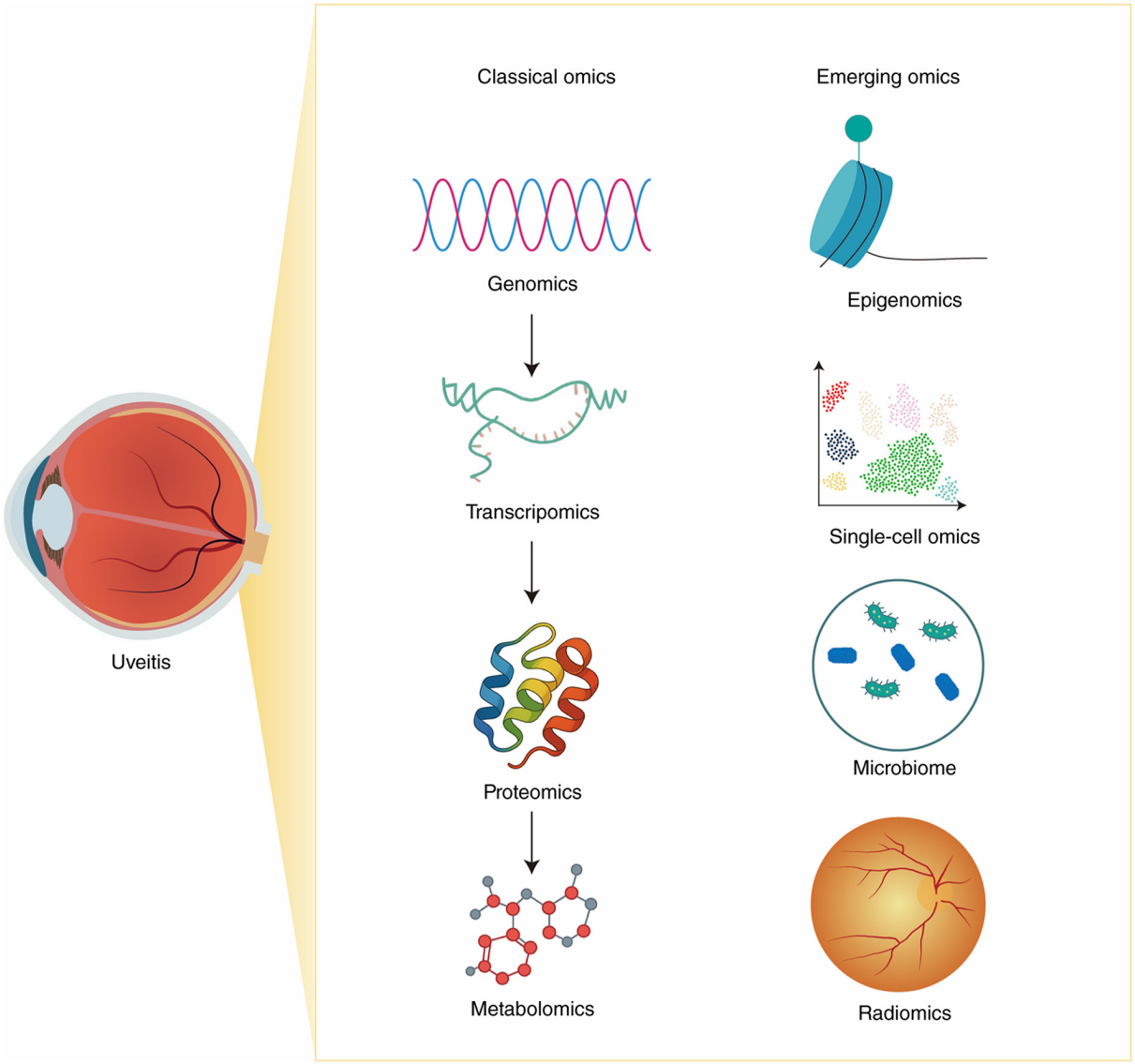

Figure 2. Overview of classical and emerging omics approaches in uveitis research. The figure summarizes the major omics technologies currently applied in uveitis research and their corresponding biological information layers. Classical omics approaches include genomics, which investigates genetic variants and disease susceptibility; transcriptomics, which characterizes gene expression patterns; proteomics, which profiles protein abundance and signaling pathways; and metabolomics, which analyzes small-molecule metabolites associated with cellular and immune functions. Emerging omics technologies include epigenomics, single-cell omics, spatial omics, lipidomics, microbiome analysis, and radiomics. These approaches provide complementary insights into gene regulation, cellular heterogeneity, spatial organization, host-microbe interactions, metabolic alterations, and imaging-derived biomarkers. Together, these technologies facilitate a comprehensive understanding of uveitis pathogenesis, biomarker discovery, disease stratification, therapeutic target identification and precision medicine.

syndrome, haploinsufficiency of A20 (HA20), and familial Mediterranean fever, have been identified as rare but important causes of uveitis (55,56).

Genomics is the comprehensive study of the entire genetic material of an organism, encompassing the structure, function, evolution, mapping and editing of genomes. The term genomics was first coined by geneticist Thomas H. Roderick in 1986 and gained prominence with advances in molecular biology and the landmark completion of the Human Genome Project (37). Since then, the field has expanded rapidly, driven by the advent of high-throughput sequencing technologies and the development of genome-wide association studies (GWAS), which have enabled the identification of genetic variants associated with complex traits and diseases (57). Genomics has broad applications ranging from the identification of disease-associated genetic variations, including single-nucleotide polymorphisms (SNPs) and copy number variations (CNVs), to advancements in personalized medicine, biotechnology and evolutionary biology (58,59). SNPs are point mutations involving the substitution of a single base at a specific genomic position, typically occurring at a frequency of >5% in the population. SNPs account for >90% of human genetic variation and are a major determinant of individual differences in drug metabolism and therapeutic response. CNVs refer to structural alterations in the genome involving deletions, insertions, duplications, or inversions of DNA segments ranging from 1 kilobase to 3 megabases in length. These variations can influence gene dosage and contribute to both normal phenotypic diversity and disease susceptibility (60). As sequencing becomes

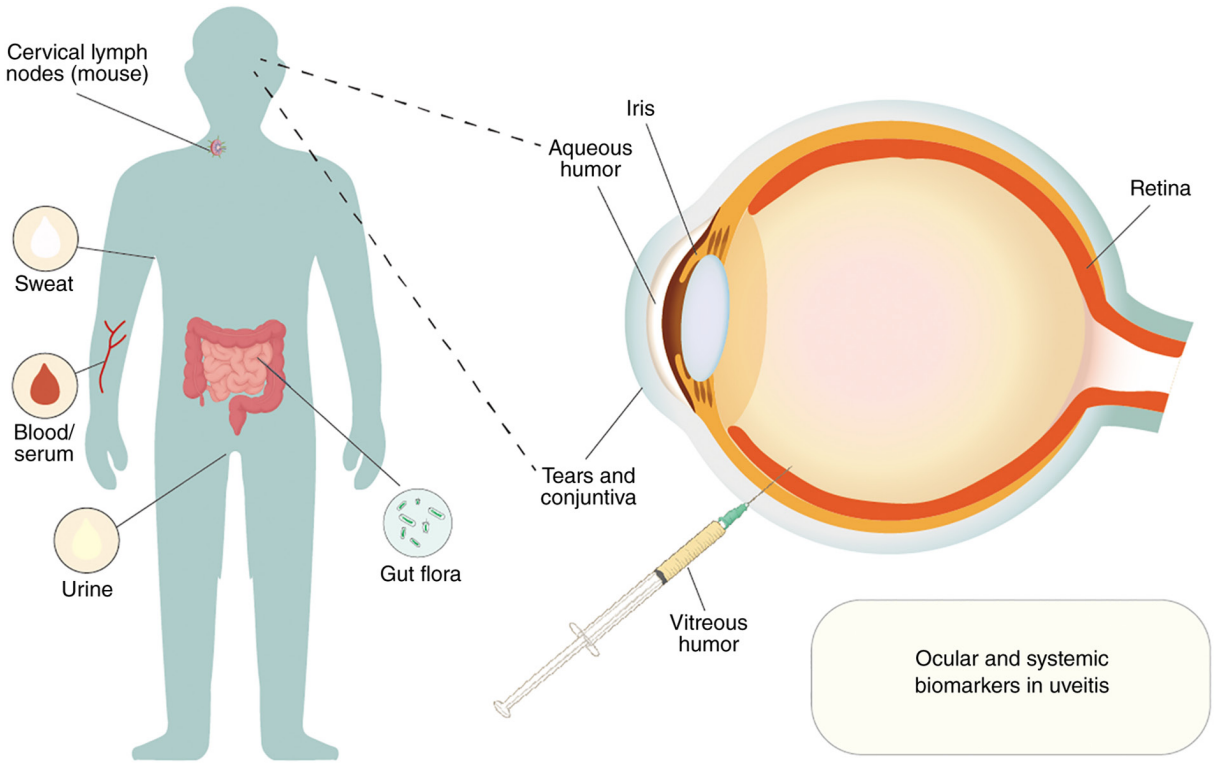

Figure 3. Biological sample sources used in multi-omics studies of uveitis. Systemic and ocular biological samples are widely used to investigate both local and systemic molecular alterations associated with uveitis pathogenesis. Systemic sample sources include peripheral blood, serum, urine, gut microbiota, and cervical lymph nodes in animal models, providing information on systemic immune responses and host-microbiome interactions. Ocular sample sources include tears, conjunctival swabs, aqueous humor, vitreous humor obtained through aqueous or vitreous paracentesis, as well as retinal and iris tissues, which more directly reflect the local inflammatory microenvironment. Each sample type presents distinct advantages and limitations. Peripheral blood and tears are readily accessible and suitable for longitudinal monitoring but may not fully capture intraocular disease activity. By contrast, aqueous humor and vitreous humor provide more disease-relevant molecular information but are obtained through invasive procedures and are often limited by small sample volumes. Retinal and iris tissues offer valuable mechanistic insights but are rarely available in clinical settings. Therefore, the selection of biological samples represents an important consideration in study design and influences the translational applicability of omics-based biomarkers in uveitis.

faster and cheaper, genomics continues to deepen the current understanding of life at a molecular level and revolutionize biomedical research (61).

Human leukocyte antigen (HLA) polymorphisms in uveitis. Early genetic studies of uveitis primarily focused on associations with HLA polymorphisms (54,62). HLAs are a group of highly polymorphic genes located on the short arm of chromosome 6, encoding glycoprotein allo-antigens involved in immune regulation. Identification of specific HLA alleles has proven valuable not only for disease diagnosis, risk prediction and population-based genetic epidemiology, but also for uncovering the potential immunogenetic basis of uveitis (63). Notably, these associations often exhibit ethnic specificity, underscoring the importance of population-based studies in understanding HLA-disease correlations (64). One of the most well-established examples is AAU, which shows a strong association with HLA-B27, particularly among patients with ankylosing spondylitis (AS) (65). In BD, HLA-B51 has been consistently linked to disease susceptibility across multiple populations, especially in those of Mediterranean and East Asian descent (66). VKH syndrome is associated with HLA-DR4 and specific DRB1/DQA1 haplotypes, implicating a T cell-mediated autoimmune response; these associations have been observed in various Asian populations (67,68). Among all uveitis subtypes, BSCR demonstrates the strongest HLA linkage, with >95% of patients carrying the HLA-A29 allele (69).

Polygenic risk score (PRS) in uveitis. Recent GWAS conducted in China, Japan, Turkey, and other countries have expanded the current understanding of the genetic basis of uveitis. These studies have shown that, in addition to HLA gene variants, polymorphisms in several non-HLA genes, including IL10, IL23R/IL12RB2, and signal transducer and activator of transcription 4, are also associated with uveitis, further supporting the hypothesis that genetic factors contribute to disease susceptibility (70-72). Hou *et al* (54,62) provided a comprehensive summary of these findings. These insights suggest that, beyond uveitis caused by rare monogenic autoinflammatory disorders with defined etiologies, including Blau syndrome and HA20, common forms of non-infectious uveitis may involve multiple genetic susceptibility loci. In this context, the PRS model has emerged as a valuable tool, aggregating the effects of numerous genetic variants across the genome into a single risk score. PRS allows for quantitative assessment of the genetic susceptibility of an individual and can be applied to elucidate disease pathogenesis, stratify population risk, identify disease subtypes, and support early clinical intervention. Previous studies have supported the potential application of PRS in uveitis. A large GWAS in the UK involving 2,752 European participants with AS and AAU, and 3,836 patients

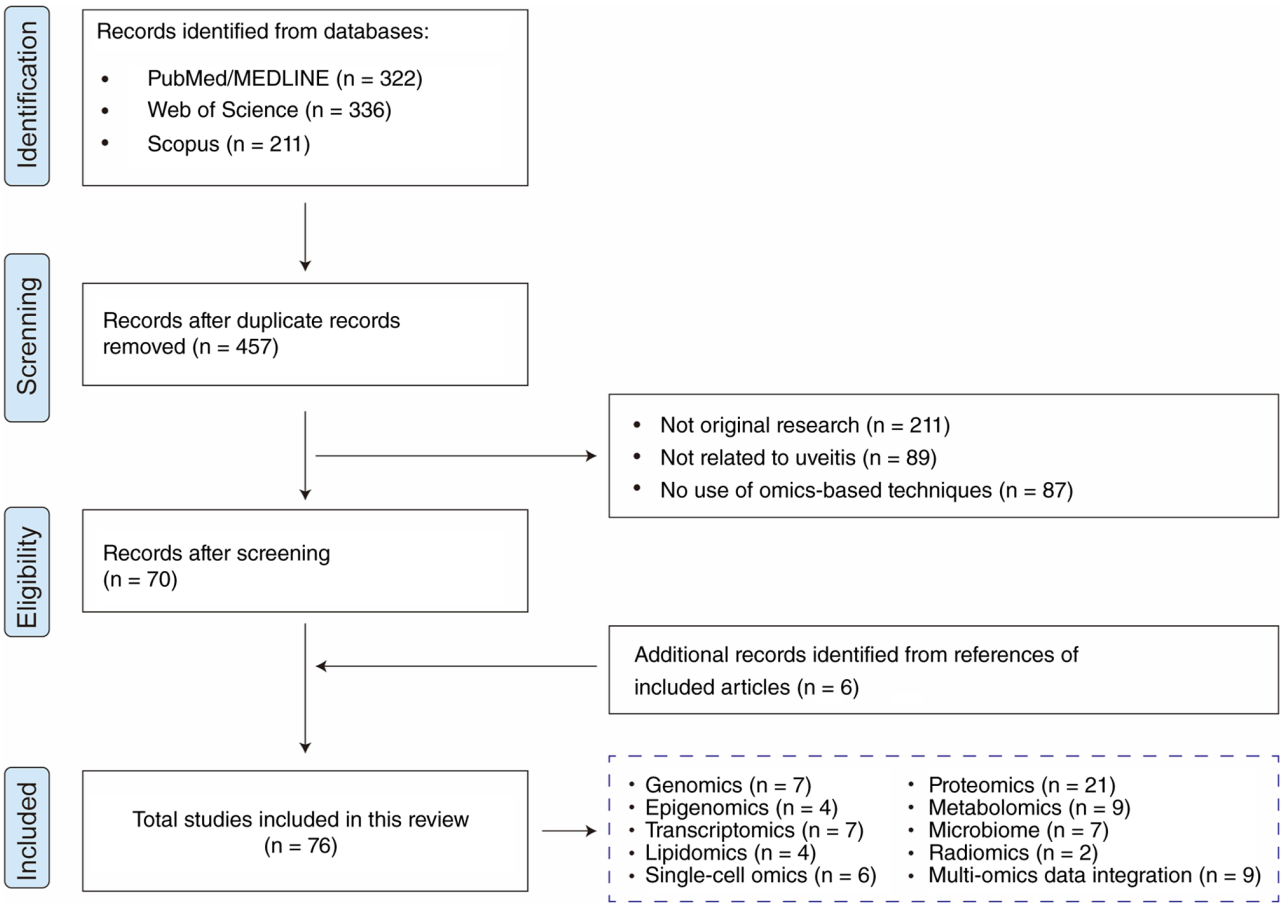

Figure 4. PRISMA flow diagram of the literature search and study selection process.

with AS without AAU, identified a genome-wide significant association at the rs9378248 locus near HLA-B ($P=2.69x10^{-8}$; OR=0.78). In addition, several suggestive loci were reported, including established AS-associated genes (ERAP1 and NOS2) and novel candidates (MERTK, KIFAP3, CLCN7 and ACAA2). Notably, the estimated SNP-based heritability of AS with AAU was 0.7, significantly higher than the 0.5 observed in AS without uveitis, indicating that PRS may be particularly effective in identifying high-risk individuals (72). Similarly, a GWAS conducted in Taiwan through the Taiwan Precision Medicine Program analyzed 468 patients with AS, including 90 with non-infectious anterior uveitis. This study identified two novel SNPs, rs1736952 and rs17354984 ($P<5x10^{-8}$), and developed an optimal PRS model incorporating 19 SNPs, achieving an area under the curve (AUC) of 0.907, demonstrating strong discriminatory power. Pathway enrichment analysis revealed that these genetic variants were associated with key biological processes, including antigen presentation, IFN signaling, immune regulation, ciliary movement and neurodegeneration (73).

Despite these promising findings, several important limitations currently restrict the broader clinical application of genomics in uveitis. First, numerous existing GWAS studies have been conducted within relatively homogeneous ethnic populations, which limits the generalizability and universal applicability of these genetic risk prediction models across diverse populations (73). Furthermore, although common susceptibility variants identified through GWAS have provided valuable insights into immune-related pathways involved in uveitis, they remain insufficient to explain rare monogenic and autoinflammatory forms of the disease, including Blau syndrome and HA20. Therefore, larger multi-center and multi-ethnic studies, together with standardized analytical pipelines and external validation cohorts, are still required to improve the robustness and translational applicability of genomics-based precision medicine approaches in uveitis.

Epigenomics. Several mechanisms underlying uveitis cannot be fully explained by genetic variation alone, underscoring the need for further research into epigenetic modifications to address the gap in heritability (74). Epigenetics investigates reversible mechanisms that regulate gene expression without changing the underlying DNA sequence. It serves as a vital link between genes and the environment, enabling the same gene to display distinct expression patterns across tissues, developmental stages or environmental conditions (75). The primary mechanisms of epigenetic regulation include DNA methylation and histone modifications. Additionally, ncRNAs, including miRNAs, lncRNAs and circular RNAs, regulate gene expression at the post-transcriptional level by modulating mRNA stability and translation efficiency (76,77).

DNA methylation. DNA methylation, a stable and heritable epigenetic mark, typically occurs at cytosine residues in CpG dinucleotides, forming 5-methylcytosine. This modification

plays a key role in regulating gene expression, maintaining genomic stability and guiding cellular differentiation. Promoter hypermethylation is often linked to gene silencing, whereas global hypomethylation can contribute to genomic instability (78). In a study by Hughes *et al* (79), 383 differentially methylated CpG sites were identified in monocytes and 125 in $CD4^+$ T cells from patients with BD compared with healthy controls. These changes were enriched in genes related to cytoskeletal regulation, implicating altered DNA methylation in BD pathogenesis. Notably, a number of these aberrant methylation patterns were reversed following disease remission, suggesting their dynamic and treatment-responsive nature (79).

ncRNAs. miRNAs are small (18-25 nucleotides), endogenous ncRNAs that regulate gene expression post-transcriptionally by binding to target mRNAs, thereby inhibiting translation or promoting degradation. Due to their stability in body fluids, resistance to degradation, and ease of detection, miRNAs hold promise as non-invasive biomarkers for autoimmune diseases (80). In a study involving serum samples from 10 patients with BD, 17 with sarcoidosis, 13 with VKH disease and 11 healthy controls, microarray analysis revealed widespread miRNA dysregulation. Specifically, 281 upregulated and 137 downregulated miRNAs were identified in BD, 35 upregulated and 86 downregulated in sarcoidosis, and 153 upregulated and 35 downregulated in VKH. A number of these miRNAs were associated with mitogen-activated protein kinase (MAPK) signaling and inflammatory cytokine pathways. Notably, miR-4708-3p (BD), miR-4323 (sarcoidosis) and let-7g-3p (VKH) emerged as top disease-specific biomarkers. A machine learning-based miRNA panel further demonstrated diagnostic potential across these uveitis subtypes (81). In addition to miRNAs, lncRNAs play crucial roles in autoimmune inflammation. Bioinformatics analysis of peripheral blood from patients with AS, BD and sarcoidosis by Lu and Lu (82) identified dysregulated lncRNAs and mRNAs, with XIST and MIAT as potential hub lncRNAs and FCGBP, CD247, CTSW, AES, NCR3, TIGIT, CASP5, DUSP2 and TBX21 as hub mRNAs. These genes were enriched in MAPK signaling and inflammatory cytokine pathways, suggesting that aberrant lncRNA expression may contribute to noninfectious uveitis and could serve as potential biomarkers or therapeutic targets (82).

Histone modifications. Histone modifications are among the most extensively studied epigenetic mechanisms and play a central role in regulating chromatin structure and gene transcription. Histone proteins form the core of nucleosomes around which DNA is wrapped, and post-translational modifications occurring on histone tails can alter chromatin accessibility and influence the recruitment of transcription factors and regulatory complexes. Common histone modifications include acetylation, methylation, phosphorylation, ubiquitination, and the recently identified lactylation (83). In general, histone acetylation, such as H3K27ac and H3K18ac, is associated with transcriptional activation and open chromatin states, whereas certain methylation marks, including H3K27me3 and H3K9me3, are linked to gene repression and chromatin compaction (84). Through these mechanisms, histone modifications dynamically regulate immune cell differentiation, inflammatory signaling pathways, and cytokine production. Emerging evidence suggests that aberrant histone modifications contribute to immune dysregulation (85) and ocular inflammation (86). Using data-independent acquisition-based lactyl-proteomics, researchers systematically profiled the lactylome in acute uveitis and identified widespread lactylation of nuclear proteins. Among these modifications, histone H3 lysine 18 lactylation (H3K18la) was found to be closely associated with chromatin decondensation during neutrophil extracellular trap (NET) formation. Combined with metabolic analyses and functional validation experiments, the study further demonstrated that HIF-1α-driven glycolytic reprogramming increased intracellular lactate production, thereby promoting H3K18la modification and NET release. The present study not only identifies histone lactylation as a novel epigenetic regulator in uveitis but also highlights the value of integrating lactyl-proteomics, epigenomics, and immuno-metabolic profiling to elucidate the molecular mechanisms underlying ocular inflammation (87).

Chromatin accessibility. Chromatin accessibility refers to the degree to which genomic DNA is accessible to transcription factors, RNA polymerases, and other regulatory proteins. As a fundamental component of epigenetic regulation, chromatin accessibility reflects the dynamic organization of chromatin and plays a critical role in controlling gene expression. Regions of open chromatin are generally associated with active promoters, enhancers, and transcription factor binding sites, whereas closed chromatin regions are typically linked to transcriptional repression (88). Alterations in chromatin accessibility can influence immune cell differentiation, activation and inflammatory responses, thereby contributing to the pathogenesis of immune-mediated diseases. Recent advances in high-throughput sequencing technologies have enabled genome-wide profiling of chromatin accessibility. Among these methods, Assay for Transposase-Accessible Chromatin using Sequencing (ATAC-seq) has become the most widely used approach due to its high sensitivity and low sample requirements (89). More recently, single-cell ATAC-seq (scATAC-seq) has allowed the characterization of chromatin landscapes at single-cell resolution, providing unprecedented insights into cellular heterogeneity and gene regulatory networks. By identifying accessible regulatory elements and transcription factor binding motifs, chromatin accessibility analyses complement transcriptomic studies and facilitate the reconstruction of molecular pathways underlying disease progression. Notably, the present literature search identified two studies that integrated single-cell ATAC-seq with single-cell RNA sequencing (scRNA-seq) to simultaneously characterize chromatin accessibility and transcriptional programs in uveitis-related immune cells. Given their relevance to multi-layer molecular profiling and data integration, these studies will be discussed in detail in Section 5, 'Multi-Omics Data Integration'.

Despite the growing promise of epigenomics, several important limitations remain. Numerous current studies are based on peripheral blood samples with relatively small cohort sizes, and epigenetic signatures may vary substantially across tissues, disease stages and treatment conditions. In addition, the dynamic and reversible nature of epigenetic modifications may complicate reproducibility and longitudinal interpretation (90). Therefore, larger multi-center studies integrating epigenomics with transcriptomics, proteomics, and clinical

phenotyping are still needed to improve the translational applicability of epigenetic biomarkers in uveitis.

Transcriptomics. Transcriptomics refers to the study of all RNA transcripts within a particular species, including mRNA and ncRNA. It examines RNA levels across the genome from a qualitative perspective, including identifying present transcripts, novel splicing events and RNA editing sites, and a quantitative perspective, including measuring transcript abundance (91). Unlike the genome, which statically presents the genetic blueprint of an organism, the transcriptome is dynamic and varies across different tissues, developmental stages and disease states. Therefore, transcriptional analysis plays a crucial role in elucidating genome structure and function, decoding the genetic networks underlying disease, and identifying sensitive molecular biomarkers for diseases, drugs and pathogens (92). The field of transcriptomics has evolved notably with the development of new technologies that redefine possibilities approximately every decade, rendering previous methods largely obsolete. Currently, two key technologies dominate: i) Microarrays, which quantify a predefined set of transcripts; and ii) RNA sequencing (RNA-Seq), which uses high-throughput sequencing to capture the complete range of RNA transcripts (93,94).

Transcriptomic profiling of idiopathic uveitis. In the study by Rosenbaum *et al* (95), RNA-Seq was used to analyze peripheral blood gene expression profiles from patients with the following four systemic non-infectious diseases associated with uveitis: i) Axial spondyloarthritis; ii) inflammatory bowel disease; iii) sarcoidosis; and iv) tubulointerstitial nephritis with uveitis. The researchers conducted KEGG and GO pathway analyses, which identified several shared pathways or GO terms ($P<0.0001$). These pathways were primarily related to immune response and/or infectious response. Based on the analysis, 119 transcripts were upregulated by at least 1.5-fold, while 61 transcripts were downregulated using the same criteria (False discovery rate <0.05). The following 10 common gene transcripts were identified: i) ICAM1; ii) IL15RA; iii) IL15; iv) IRF1; v) IL10RB; vi) GSK3A; vii) TYK2; viii) MEF2A; ix) MEF2B; and x) MEF2D (95). To explore whether gene expression profiles could assist in investigating the etiology of idiopathic uveitis, a classification algorithm was created using a gradient boosting tree model with 5-fold cross-validation. The mRNA from patients with idiopathic uveitis was analyzed to investigate whether any gene expression patterns matched the systemic diseases previously diagnosed. The gene expression profiling model achieved an overall accuracy of 85% ($P<0.001$) in associating uveitis with a diagnosable systemic disease. Although most patients with idiopathic uveitis did not have these four systemic diseases, the gene expression profiling helped reclassify 11 of the 38 patients (96). This suggests that gene expression profiling could play a notable role in understanding the pathogenesis of idiopathic uveitis and may aid in the improvement of diagnosis and treatment strategies.

Transcriptomic detection of intraocular infections. RNA-seq offers notable advantages over traditional targeted PCR testing for detecting intraocular infections, and with technological advancements, its cost is no longer prohibitive (97). PCR testing relies on a predefined list of pathogens and can only detect specified microorganisms, making it easy to miss atypical or unknown infections. By contrast, RNA-seq is a hypothesis-free, high-throughput technology that can identify all established and potentially novel pathogens present in a sample in a single test, offering broader diagnostic coverage (98). A study comparing RNA-seq and targeted PCR testing in samples from 41 patients with suspected ocular infections found that RNA-seq achieved complete positive concordance with PCR (positive agreement rate, 100%; 95% confidence interval, 78.5-100%) and a negative concordance rate of 92.6% (95% confidence interval, 76.6-97.9%). Notably, RNA-seq also identified four additional pathogens missed by PCR, including rubella virus and *Pithomyces chartarum*, and these findings were confirmed by orthogonal testing. The study concluded that RNA-seq can accurately detect both common and rare pathogens in intraocular fluid samples, expanding the diagnostic capabilities for ocular infections (99). In the future, further research is needed to establish its clinical utility fully.

Transcriptomic insights from EAU models. The retina is an ideal tissue for investigating the underlying mechanisms of uveitis, as it directly reflects pathological changes occurring during disease progression. However, obtaining retinal tissue from human patients is impractical and ethically challenging (100). Therefore, animal models, including EAU, have become essential tools for studying the pathogenesis of uveitis. EAU closely mimics numerous key features of human non-infectious uveitis, including immune-mediated retinal inflammation and tissue damage (101,102). With the advancement of high-throughput RNA-Seq technologies, transcriptomic profiling of retinal cells in EAU models has enabled researchers to systematically explore gene expression changes during disease progression. These studies have provided critical insights into the molecular mechanisms underlying uveitis, including inflammatory responses, immune activation, complement system involvement and cellular stress pathways. The application of transcriptomics in EAU thus provides a valuable platform for identifying novel therapeutic targets and enhancing the current understanding of ocular autoimmune diseases. The current studies utilizing transcriptomic approaches to investigate gene expression changes in the retina during EAU are summarized in Table I.

Despite the substantial advances enabled by transcriptomic technologies, several important limitations remain in current uveitis transcriptomics research. First, numerous transcriptomic studies rely heavily on EAU animal models, which, although valuable, cannot fully recapitulate the complexity and heterogeneity of human uveitis. Notable differences in immune regulation, retinal structure and disease progression between experimental models and human disease may limit translational applicability. In addition, human intraocular samples remain difficult to obtain due to ethical and technical constraints, resulting in relatively small clinical cohort sizes and limited validation studies. Transcriptomic profiles may also vary substantially depending on sample source, including peripheral blood, aqueous humor, vitreous fluid, tears and retinal tissue, thereby complicating cross-study comparisons and biomarker interpretation. Furthermore, technical factors such as batch effects, RNA degradation, sequencing depth and differences in bioinformatic pipelines may influence

Table I. Summary of transcriptomic studies investigating retinal and microglial gene expression changes during uveitis.

Authors, year	Species	Tissue/cell	Findings	(Refs.)
Busch *et al*, 2019	Mouse	Retina	478 DEGs were identified (log |FC| >1), among which 406 genes were upregulated, and 72 genes were downregulated in the EIU group. GO/KEGG analysis showed that these genes were related to biological processes, including inflammatory response, complement system activation, fibrinolytic system changes, and cellular stress.	(212)
de Hoog *et al*, 2019	Mouse	Retina	52 DEGs were identified (log |FC| >1). 37 genes were upregulated, and 15 genes were downregulated in the EIU group compared with the DEX treatment group. DEX treatment significantly suppressed the RIG-I-like receptor signaling pathway as well as several immune- and inflammation-related genes, including Ifit1, H2-T24, Mx2, and Eif2ak2.	(213)
Eidet *et al*, 2019	Mouse	Microglia	During the early activation phase (4 h), 613 DEGs were identified. A total of 537 DEGs were observed at the peak of cell infiltration (18 h), whereas no DEGs were detected at 2 weeks. C5AR1 was identified and validated as a robust marker for distinguishing microglial subsets during the LPS response.	(214)
Liang *et al*, 2020	Mouse	Retina	Compared with the TMP-treated group, 407 DEGs were identified in the untreated control group (log |FC| > 1), of which 356 were upregulated, and 51 were downregulated. There were 12 upregulated gene ontology terms enriched and 27 upregulated pathways. Seven DEGs were validated using quantitative PCR, including inflammation-related, complement system-related, and interferon-related genes.	(215)
Sepah *et al*, 2020	Mouse	Retinal cells and endothelial cells	RNA-Seq analysis of total retinal cells revealed a predominant upregulation of genes involved in antigen presentation and T cell activation during EAU. Targeted transcriptome analysis of retinal endothelial cells identified 82 genes that were differentially regulated during EAU development. The protein expression of five of these genes (Serpina3n, Lcn2, Ackr1, Lrg1, and Lamc3) was validated in cells located within the BRB.	(216)
Eidet *et al*, 2021	Zebrafish	Retina	Four gene clusters were identified via enrichment analysis, which were related to Toll-like receptor signaling pathway, cytokine-cytokine receptor interaction, NOD-like receptor signaling pathway, and extracellular matrix (ECM)-receptor interaction, respectively in EIU model.	(217)
Zheng *et al*, 2021	Mouse	Retina	KEGG and Reactome enrichment analysis of RNA-seq data revealed associations with chemokine signaling pathways and cytokine-cytokine receptor interactions in EAU model.	(218)

EIU, endotoxin-induced uveitis; EAU, experimental autoimmune uveitis; DEGs, differentially expressed genes; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; DEX, dexamethasone; TMP, tetramethyl-pyrazine; RIG-I, retinoic acid-inducible gene I; LPS, lipopolysaccharide; PCR, polymerase chain reaction; qPCR, quantitative polymerase chain reaction; RNA-seq, RNA sequencing; BRB, blood-retinal barrier; ECM, extracellular matrix; TLR, Toll-like receptor; NLR, nucleotide-binding oligomerization domain-like receptor; FC, fold change; C5AR1, complement component 5a receptor 1; Ifit1, interferon-induced protein with tetratricopeptide repeats 1; H2-T24, histocompatibility 2, T region locus 24; Mx2, MX dynamin-like GTPase 2; Eif2ak2, eukaryotic translation initiation factor 2 alpha kinase 2; Serpina3n, serine protease inhibitor A3N; Lcn2, lipocalin 2; Ackr1, atypical chemokine receptor 1; Lrg1, leucine-rich alpha-2-glycoprotein 1; Lamc3, laminin subunit gamma 3.

data reproducibility and contribute to inconsistencies among studies (103). Therefore, larger multi-center studies integrating transcriptomics with proteomics, metabolomics and clinical phenotyping are needed to improve the robustness, reproducibility and clinical translational potential of transcriptomic biomarkers in uveitis.

Single-cell omics. Single-cell omics aims to profile molecular information, including genes, transcripts, proteins, metabolites and epigenetic modifications at the resolution of individual cells, providing deep insights into cellular functional states, heterogeneity and developmental trajectories (104). This approach represents a notable advancement in spatial

resolution over traditional bulk omics technologies. By integrating multidimensional data across various omics layers, single-cell sequencing enables precise cell clustering, enhances analytical resolution, and effectively addresses intercellular heterogeneity (105). Among these technologies, scRNA-seq is the earliest and most widely adopted method, first introduced in 2009. Although single-cell approaches have since expanded to other omics layers and integrative frameworks (106), scRNA-seq remains the primary tool applied in uveitis research to date, with no reported studies utilizing other types of single-cell omics. This highlights the foundational role of transcriptomic profiling in current single-cell investigations of ocular inflammation. The following section focuses on the application of scRNA-seq in uveitis.

As a high-throughput technique, scRNA-seq enables comprehensive analysis of gene expression at the single-cell level, offering a powerful means to uncover cellular heterogeneity and to delineate distinct cell types and their dynamic changes (107). Compared with bulk RNA-seq, which averages gene expression across cell populations and obscures individual cell variations, scRNA-seq provides a more granular view. This is particularly important in complex tissues, including the retina, where multiple cell types coexist in varied physiological states. The advantages of scRNA-seq extend beyond structural characterization. It allows for the identification of transcriptional changes within specific cell subpopulations under disease conditions or therapeutic interventions, thereby deepening the current understanding of disease mechanisms and drug responses. Additionally, it supports an unbiased evaluation of tissue composition by capturing shifts in the relative abundance of all cell types under different pathological states (108,109). These features underscore the value of scRNA-seq as a key tool for dissecting the cellular basis of uveitis and related ocular disorders.

Applications of scRNA-seq in EAU models. Heng *et al* (110) were the first to apply scRNA-seq to the retina of Aire-deficient mice, a spontaneous uveitis model characterized by impaired central tolerance due to the failure to express self-antigens in the thymus. These mice develop chronic and progressive autoimmune uveitis. The study revealed a significant increase in immune cell infiltration in the retina of Aire-deficient mice compared with controls, with T cells, NK cells and monocyte-derived cells being the predominant populations, alongside smaller numbers of B cells and plasma cells (PCs). Further classification of T cells identified Th1 cells as the principal effector subset. Notably, the Th1 population could be divided into two distinct clusters, with one expressing Il10 and the other expressing Cd40lg (CD40 ligand), representing regulatory ($Il10^+$) and activated ($Cd40lg^+$) states, respectively. These findings suggest a self-regulatory mechanism within the Th1 compartment. In addition, enrichment analysis demonstrated that IFN-γ-responsive genes were upregulated across all major resident retinal cell types, indicating a widespread transcriptional response to IFN-γ during the autoimmune process. Furthermore, in the EAU mouse model, researchers performed clinical and histopathological assessments at days 7, 14, 21 and 28, in parallel with scRNA-seq of retinal tissues. Day 14 was identified as the peak of inflammation and disease severity, corresponding with the highest number of differentially expressed genes (DEGs). At this stage, microglia were markedly elevated, comprising 73.9% of all immune cells. Inflammatory-associated microglia showed significant enrichment of DEGs involved in antigen processing and presentation, as well as responses to type II IFN (111). In the study by Quinn *et al* (112), scRNA-seq of the EAU model revealed a widespread upregulation of IFN-γ and IFN-α response genes. Furthermore, Müller glia and retinal pigment epithelial cells were found to upregulate the expression of chemokines, complement factors, leukocyte adhesion molecules and MHC class II molecules, highlighting their active roles in immune cell recruitment and antigen presentation both within and beyond the BRB (112). The study by Li *et al* (113) focused on ocular-infiltrating PCs and found that these cells expressed multiple pro-inflammatory factors, particularly TNF-α, which contributed to the induction of α-synuclein-expressing microglia. Further subtyping of the heterogeneous PC population revealed that $MUC1^+$ PCs constituted the dominant pathogenic subset. These cells secreted various cytokines, exhibited long-lived properties, and produced IgG and IgM antibodies, thereby sustaining inflammation and contributing to prolonged disease progression.

Clinical translation and future perspectives of single-cell omics in uveitis. A recent study attempted to classify uveitis using single-cell omics approaches, which applied scRNA-seq combined with immune receptor profiling to ocular fluid samples from 23 patients with various clinical forms of uveitis. The analysis revealed subtype-specific immune signatures, including HLA-B27-associated AAU, which was characterized by an enrichment of myeloid cells and activation of innate immune pathways, and chronic uveitis, which showed a predominance of adaptive immune cells and related transcriptional programs. Furthermore, the observation of clonal expansion among T cells in some patients suggests antigen-driven pathogenesis. These findings highlight the potential of single-cell omics in uncovering immune endotypes and improving the molecular classification of uveitis, paving the way for personalized therapeutic strategies (114). In addition, single-cell sequencing holds notable promise for drug development in uveitis. A single-cell perspective is essential for advancing the current understanding of cellular and molecular targets, thereby improving the identification and prioritization of therapeutically effective candidates. The integration of single-cell protocols with advanced multiplexing strategies further enhances the scalability and resolution of these assays, enabling more precise and comprehensive drug screening (115). Li *et al* (52) investigated the effects of IL-38 on immune cells in the CDLN of EAU mice using single-cell analysis. Their findings revealed that IL-38 attenuated the expansion of effector T cells and the decline of Tregs, while also preventing the upregulation of numerous DEGs, particularly those associated with the IL-17 signaling and Th17 differentiation pathways, both of which are known to play pivotal roles in the pathogenesis of uveitis.

Spatial omics. Single-cell sequencing has played a pivotal role in providing high-resolution insights at the individual cell level. By enabling the detection of cellular heterogeneity, single-cell approaches allow detailed characterization of cellular behaviors, molecular mechanisms, and intercellular interactions. The high resolution of these technologies has

greatly facilitated large-scale exploration and characterization of cellular diversity. However, despite these advantages, conventional single-cell sequencing often fails to preserve critical spatial information within tissues, resulting in the loss of important spatial context (116). To overcome this limitation, spatial multi-omics has emerged as a transformative technology that enables precise spatial localization of cells and quantitative mapping of gene expression within intact tissue architecture (117).

Compared with conventional dissociative single-cell sequencing approaches, spatial omics preserves tissue morphology and regional cellular organization, thereby enabling simultaneous characterization of molecular alterations and their anatomical localization within ocular tissues. This advantage is particularly important in uveitis, where BRB disruption, inflammatory cell infiltration and retinal/choroidal immune microenvironment remodeling often exhibit strong spatial heterogeneity (118). Although only a limited number of spatial omics studies have been reported in uveitis to date, recent advances have enabled the integration of spatial transcriptomics with scRNA-seq. This combined approach preserves spatial context while providing high-resolution cellular characterization, allowing a more comprehensive understanding of tissue architecture, immune-cell localization, and intercellular interactions within inflamed ocular tissues. A representative study that applies this strategy to uveitis is discussed in the 'Multi-Omics Data Integration' section.

Despite its substantial promise, several challenges currently limit the widespread application of spatial omics in uveitis research, including limited ocular tissue availability, high technical complexity, elevated costs, and difficulties in computational integration and data interpretation (119,120). Nevertheless, as spatial transcriptomics and spatial proteomics technologies continue to evolve, their integration with single-cell sequencing, proteomics and imaging modalities is expected to provide deeper mechanistic insights into ocular inflammation and promote the development of precision medicine strategies for uveitis.

Proteomics. Proteomics is the study of protein composition, structure, function and interactions within organisms, and it plays a vital role in elucidating biological processes and disease mechanisms (38). Proteomics encompasses the complete workflow of protein separation, identification, quantification and analysis of post-translational modifications. Modern approaches rely on high-performance liquid chromatography coupled with mass spectrometry (MS) for high-resolution, high-throughput protein analysis (121). Quantitative strategies include stable isotope labeling methods, such as SILAC, iTRAQ, TMT and label-free techniques, enabling comparative analysis of protein expression across conditions. Post-translational modifications, including phosphorylation and ubiquitination, are analyzed via enrichment methods and high-resolution MS. Combined with systems biology and bioinformatics, proteomics provides a powerful platform for deciphering complex protein networks and identifying disease-related biomarkers (122,123).

Proteomics studies can be broadly categorized based on their objectives into assay-based (analytical) and discovery-based approaches (124). Assay-based studies focus on the quantification of a predefined set of proteins or peptides and are particularly advantageous for investigating specific classes of proteins. For instance, one study isolated mitochondrial components from the retina and utilized two-dimensional difference gel electrophoresis to examine changes in mitochondrial protein levels in response to oxidative stress during the early stage of EAU (125). Protein spots with differential expression were excised and analyzed using matrix-assisted laser desorption/ionization time-of-flight MS for peptide identification. The findings revealed the presence of mitochondrial-specific oxidative stress-related proteins and a downregulation of ATP synthase, providing early evidence of stress-induced retinal damage in EAU.

Discovery-based proteomics aims to analyze a broad, unbiased proteome to identify novel biomarkers or elucidate underlying biological pathways and has been widely applied in the study of uveitis (126). In the EAU model, researchers have examined a variety of samples, including plasma and granulocytes, to uncover disease-related targets. Guo *et al* (127) identified 62 upregulated and 106 downregulated proteins in the plasma of EAU rats using label-free liquid chromatography-tandem MS (LC-MS/MS). Notably, plasma levels of complement component 3 increased from 92.32 μg/ml in saline-treated rats to 168.92 μg/ml in EAU rats, while levels of IL-1 receptor accessory protein decreased from 1,120.97 to 798.39 pg/ml. In another study, primary granulocytes from healthy and equine recurrent uveitis (ERU) horses were stimulated with IL-8, and their responses were analyzed using differential proteomics. This revealed significant differences in the abundance of 170 proteins in ERU samples. Subsequent Ingenuity Pathway Analysis identified three activated canonical pathways: i) PKA signaling; ii) PTEN signaling; and iii) leukocyte extravasation. Notably, MMP25, a membrane-type GPI-anchored protease involved in the leukocyte extravasation pathway, was upregulated in IL-8-stimulated ERU granulocytes. These findings suggest that MMP25 may play a regulatory role in granulocyte extravasation and contribute to the disruption of the BRB in uveitis (128). In addition, proteomics has been increasingly applied to rare forms of uveitis to identify disease-specific biomarkers that may serve as diagnostic indicators or potential therapeutic targets (Table II).

Metabolomics. Metabolomics focuses on the identification and quantification of small-molecule metabolites, typically <1,500 Da, in biological systems. These metabolites, including amino acids, peptides, sugars, nucleic acids and exogenous compounds, reflect the metabolic state of the body under various physiological, pathological or environmental conditions (129). As the end products of cellular activity, metabolites provide a direct link to phenotypic changes, giving metabolomics a unique advantage among omics technologies (130). Depending on the research aim, metabolomics can be non-targeted, targeted or broad-targeted. Non-targeted approaches capture a wide range of metabolites for exploratory analysis and biomarker discovery, while targeted approaches focus on specific metabolites or pathways with high sensitivity and quantitative precision. Broad-targeted metabolomics combines both strategies to enable high-throughput, quasi-quantitative

Table II. Summary of key findings from proteomic studies in uveitis.

Authors, year	System/Disease	Sample type	Methodology	Study design	Key findings	(Refs.)
Isenberg *et al*, 2018	OT	Serum	2D-GE, SELDI-MS, SDS-PAGE, MS	Case-control proteomic biomarker discovery and validation study (first-episode OT, n=9; recurrent OT, n=9; toxoplasmosis IgG-positive without uveitis, n=9; non-toxoplasmosis uveitis, n=9)	PPIA was identified as a serum biomarker for recurrent ocular toxoplasmosis; it can distinguish active recurrent OT from other uveitis types or infections.	(200)
Busch *et al*, 2019	JIA-associated uveitis	Iris, ciliary body, retina	2D gel electrophoresis, MS	Case-control immunoproteomic study (JIAU, n=23; JIA without uveitis, n=14; healthy controls, n=10)	Patients with JIAU exhibited a broad spectrum of serum autoantibodies targeting ocular antigens, primarily within the iris proteome. These antibodies were directed against proteins, including keratin and heat shock proteins, suggesting that autoantibodies may contribute to iris inflammation in JIAU.	(212)
de Hoog *et al*, 2019	PVRL vs. uveitis	Vitreous	Flow cytometry, multiplex immunoassay	Prospective diagnostic immune-profiling study ((P)VRL, n=10; non-(P)VRL uveitis/vitritis, n=43)	Combined cellular and soluble mediator profiles distinguished PVRL from non-PVRL cases; key markers include IL-10/IL-6 ratio, IL-1RA, and $CD19^+$ B cells.	(213)
Eidet *et al*, 2020	Unilateral acute anterior uveitis	Tear fluid	LC-MS/MS	Paired-eye proteomic study (unilateral AAU patients, n=5; fellow healthy eyes, n=5)	Ipsilateral changes in tear proteome identified; LXR/RXR pathway implicated; APOBEC3A increased, TGM2 decreased in affected eyes.	(214)

Table II. Continued.

Authors, year	System/Disease	Sample type	Methodology	Study design	Key findings	(Refs.)
Liang *et al*, 2020	Unilateral BDU	Tear fluid	DIA proteomics	Paired-eye proteomic study (unilateral relapsed BDU patients, n=15)	51 proteins were differentially expressed between active and quiescent eyes; Alpha-1-acid glycoprotein 1 increased, and Annexin A1 decreased in active eyes; potential tear biomarkers for BDU activity.	(215)
Sepah *et al*, 2020	Intermediate uveitis	Vitreous	LC-MS/MS	Case-control vitreous proteomic study (IU, n=4; controls, n=4)	A total of 233 proteins were differentially expressed; IL-23 and MYD88 were implicated in myeloid cell recruitment, revealing potential biomarkers and therapeutic targets.	(216)
Bansal *et al*, 2021	Tubercular uveitis	Vitreous	Shotgun LC-MS/MS	Case-control vitreous proteomic study (TBU, n=13; non-TBU uveitis, n=7; non-uveitic controls, n=9)	Compared with controls, 32 differentially expressed proteins were identified, related to complement, coagulation, and glycolysis pathways, suggesting diagnostic potential for tubercular uveitis.	(199)
Eidet *et al*, 2021	Acute anterior uveitis	Tear fluid	LC-MS/MS, laser flare measurement	Case-control tear proteomic biomarker discovery and validation study (AAU, n=13; bacterial keratitis, n=7; healthy controls, n=14)	SERPINA3 is a potential tear biomarker for AAU. SERPINA3 levels were elevated in unaffected fellow eyes, correlated with intraocular inflammation, and showed good diagnostic performance (85% sensitivity, 71% specificity).	(217)

Table II. Continued.

Authors, year	System/Disease	Sample type	Methodology	Study design	Key findings	(Refs.)
Zheng *et al*, 2021	VKH disease	Plasma exosomes	Isobaric tagging, LC-MS/MS, ELISA	Case-control exosomal proteomic biomarker discovery and validation study (active VKH, unstable VKH, stable VKH, and healthy controls)	43 proteins were upregulated during the active phase; CA2 and Rap-1b were identified as potential biomarkers correlating with inflammation severity.	(218)
Choi *et al*, 2022	CMV-positive HAU	Aqueous humor	LC-MS/MS, GO enrichment, network analysis	Case-control aqueous humor proteomic study (CMV-HAU, n=10; cataract controls, n=10)	Complement-associated inflammation and immunoglobulin pathways were upregulated; increased GDF-15 and decreased vasorin suggest inflammatory mechanisms in CMV-HAU.	(219)
Komatsu *et al*, 2022	Ocular sarcoidosis vs. VRL	Vitreous	LC-MS/MS, pathway analysis	Case-control vitreous proteomic biomarker discovery and validation study (ocular sarcoidosis, n=28; VRL, n=25; Behçet's disease-associated uveitis, n=7; ERM/MH controls, n=30)	Compared with controls and VRL, 290 and 174 DEPs were detected in the vitreous of sarcoidosis eyes, respectively. NGAL and JAMB were identified as auxiliary diagnostic biomarkers	(220)
Kuiper *et al*, 2022	Non-infectious uveitis	Serum	Aptamer-based proteomics, bioinformatics, and Cox analysis	Multicenter prospective proteomic prognostic cohort study (discovery cohort, n=78; validation cohorts, n=111 and n=67; healthy controls, n=26)	A network of 85 serum proteins predicted the need for systemic immunosuppressive therapy. Serum protein signatures associated with neutrophil levels are highly predictive for the use of IMT in non-infectious uveitis.	(221)
Schrijver *et al*, 2022	PVRL vs. uveitis	Vitreous	TMT, LC-MS/MS	Discovery-validation vitreous proteomic stratification study (training cohort, n=47; validation cohort, n=22)	The diagnostic value of ISOLD and the IL-10/IL-6 ratio for identifying (P)VRL has been validated, and CD70 has emerged as a potentially valuable target for (P)VRL stratification. Additionally, elevated	(222)

Table II. Continued.

Authors, year	System/Disease	Sample type	Methodology	Study design	Key findings	(Refs.)
					CCL17 levels may aid in distinguishing sarcoid uveitis from tuberculosis-associated uveitis.	
Wu *et al*, 2023	Ankylosing spondylitis-associated uveitis, Behçet's uveitis, Vogt-Koyanagi-Harada syndrome, and posterior scleritis	EVs	SWATH-MS	Discovery-validation plasma and extracellular vesicle proteomic study (AS-associated uveitis, n=16; BDU, n=16; VKH, n=16; posterior scleritis, n=16; healthy controls, n=16)	A total of 3,668 proteins were identified, and over 3,000 proteins were quantitatively profiled across 278 samples. When comparing disease groups to healthy controls, the proteomic signatures of both EV subgroups showed stronger disease association than those derived from plasma.	(223)
Achten *et al*, 2024	dupilumab-related uveitis	Aqueous humor	PEA	Case-control aqueous humour proteomic profiling study (dupilumab-associated uveitis, n=3; non-infectious uveitis, n=27; cataract controls, n=11)	The molecular characteristics of dupilumab-related uveitis are similar to those of non-infectious uveitis	(224)
Galozzi *et al*, 2024	Blau syndrome	Tear fluid	MS	Case-control tear proteomic biomarker discovery study (Blau syndrome patients with *NOD2* mutation, n=4; healthy familial controls, n=3; healthy controls, n=7)	A2M and IGHG4 were overexpressed. Bioinformatics analysis linked differentially expressed proteins to the acute phase response, exosome formation, and protein binding. Notably, neutrophil granule proteins (AZU1, MPO, DEFA3) were highly expressed in severely affected individuals, suggesting neutrophil involvement in ocular severity.	(225)

Table II. Continued.

Authors, year	System/Disease	Sample type	Methodology	Study design	Key findings	(Refs.)
Kouwenberg *et al*, 2024	Non-infectious pediatric uveitis patients diagnosed with nonanterior uveitis, idiopathic chronic anterior uveitis, or JIA-associated uveitis	Serum	Serum Proteomic Olink Analysis	Case-control serum proteomic biomarker discovery study (nonanterior uveitis, n=74; idiopathic chronic anterior uveitis, n=36; juvenile idiopathic arthritis-associated uveitis, n=44; noninflammatory pediatric controls, n=22)	Serum proteins involved in coagulation and complement cascades are associated with retinal vascular involvement in pediatric uveitis.	(226)
Qin *et al*, 2024	BDU	Urine	Label-free data-dependent acquisition and TMT-labeled quantitative proteomics methods	Discovery-validation urinary proteomic biomarker study for disease activity monitoring in Behçet's disease-associated uveitis (active BDU and quiescent BDU patients; discovery cohort analyzed by label-free DDA and TMT proteomics, followed by DIA validation cohort, n=50)	79 DEPs were significantly changed in other active BDU urine samples compared with quiescent BDU urine samples. GO and PPI analyses showed that DEPs were associated with multiple functions, including immune and neutrophil activation responses. Finally, 7 proteins were identified as candidate biomarkers for BDU monitoring and relapse prediction, namely CD38, KCRB, DPP4, FUCA2, MTPN, S100A8, and S100A9.	(227)
Zhang *et al*, 2024	VH and BDU	aqueous humor-derived exosomes	label-free quantitative proteomics	Case-control aqueous humor-derived exosomal proteomic biomarker discovery study (VKH, n=45; BDU, n=39; senile cataract controls, n=45)	65 and 40 DEPs were detected in the VKH and BU groups, respectively. GO and KEGG analyses showed that DEPs were mainly enriched in complement-related pathways. C1QB was identified as a key exosomal protein	(228)

OT, ocular toxoplasmosis; 2D-GE, two-dimensional gel electrophoresis; SELDI-MS, surface-enhanced laser desorption/ionization mass spectrometry; SDS-PAGE, sodium dodecyl sulfate-polyacrylamide gel electrophoresis; MS, mass spectrometry; PPIA, peptidyl-prolyl cis-trans isomerase A; IgG, immunoglobulin G; JIA, juvenile idiopathic arthritis; JIAU, juvenile idiopathic arthritis-associated uveitis; PVRL, primary vitreoretinal lymphoma; VRL, vitreoretinal lymphoma; IL, interleukin; IL-1RA, interleukin-1 receptor antagonist; CD, cluster of differentiation; AAU, acute anterior uveitis; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LXR, liver X receptor; RXR, retinoid X receptor; APOBEC3A, apolipoprotein B mRNA editing enzyme catalytic subunit 3A; TGM2, transglutaminase 2; BDU, Behçet's disease-associated uveitis; DIA, data-independent acquisition; IU, intermediate uveitis; MYD88, myeloid differentiation primary response protein 88; TBU, tubercular uveitis; SERPINA3, serpin family A member 3; VKH, Vogt-Koyanagi-Harada disease; ELISA, enzyme-linked immunosorbent assay; CA2, carbonic anhydrase II; CMV, cytomegalovirus; HAU, hypertensive anterior uveitis; GO, Gene Ontology; GDF-15, growth differentiation factor 15; NGAL, neutrophil gelatinase-associated lipocalin; JAMB, junctional adhesion molecule B; DEPs, differentially expressed proteins; IMT, immunomodulatory therapy; TMT, tandem mass tag; ISOLD, interleukin score for lymphoma diagnosis; CCL17, C-C motif chemokine ligand 17; EV, extracellular vesicle; SWATH-MS, sequential window acquisition of all theoretical fragment ion spectra mass spectrometry; PEA, proximity extension assay; NOD2, nucleotide-binding oligomerization domain-containing protein 2; A2M, alpha-2-macroglobulin; IGHG4, immunoglobulin heavy constant gamma 4; AZU1, azurocidin 1; MPO, myeloperoxidase; DEFA3, defensin alpha 3; DDA, data-dependent acquisition; PPI, protein-protein interaction; CD38, cluster of differentiation 38; KCRB, creatine kinase B-type; DPP4, dipeptidyl peptidase 4; FUCA2, alpha-L-fucosidase 2; MTPN, myotrophin; S100A8, S100 calcium-binding protein A8; S100A9, S100 calcium-binding protein A9; BU, Behçet's uveitis; KEGG, Kyoto Encyclopedia of Genes and Genomes; C1QB, complement C1q subcomponent subunit B.

analysis based on established metabolite libraries (131). MS and nuclear magnetic resonance (NMR) are the core analytical platforms. MS, often combined with chromatography, including GC-MS for volatile compounds and LC-MS for polar, thermally unstable metabolites, offers high sensitivity and resolution, especially when coupled with advanced techniques such as ultra-high-performance liquid chromatography and high-resolution MS (including TOF-MS and Orbitrap). NMR, although less sensitive, provides notable reproducibility and structural information with minimal sample preparation. Capillary electrophoresis-MS also complements these methods in analyzing highly polar, charged metabolites (132). The integration of multiple platforms enhances metabolite coverage and improves the depth of metabolic profiling.

Recent advances in metabolomics have notably contributed to the understanding of the pathogenesis and biomarker discovery in various forms of uveitis. Chu *et al* (133) used untargeted metabolomics via LC-MS/MS to examine the effects of green tea extract (GTE) in a rat model of EIU. GTE treatment increased systemic phosphorylcholine lipids and reduced plasma prostaglandin E1 and other inflammatory lipid metabolites, correlating with improved retinal function, as shown by enhanced electroretinography responses. In the retina, GTE suppressed inflammatory mediators, including tetranor-PGAM and kynuramine, while elevating antioxidative selenopeptides, suggesting that its anti-inflammatory and antioxidative effects are mediated through modulation of lipid metabolism both systemically and locally. Chistyakov *et al* (134) developed a novel rabbit model of recoverin-induced EAU, closely mimicking human posterior uveitis. Metabolomic and targeted lipidomic analysis of aqueous humor in early EAU revealed elevated lactate and decreased ascorbate levels, along with increased levels of pro-inflammatory lipid mediators including PGE_2, TXB2, 11-HETE and Lyso-PAF. In the late stage, levels of the anti-inflammatory fatty acid docosahexaenoic acid (DHA) were reduced. Additionally, the presence of recoverin in AH indicated BRB and photoreceptor disruption.

To comprehensively understand the metabolic alterations associated with various types of uveitis, recent metabolomics studies focusing on different uveitis subtypes, sample types, analytical methods and key findings were summarized (Table III). By integrating metabolomic profiling from diverse biological fluids, including aqueous humor, plasma, serum, urine, feces and sweat, researchers have identified potential diagnostic biomarkers and elucidated disease-specific metabolic pathways that may offer new insights into uveitis pathogenesis and therapeutic targets.

Lipidomics. Lipids have traditionally been regarded as the primary structural components of cell membranes and as reservoirs for energy storage. However, accumulating evidence indicates that lipids also serve as bioactive signaling molecules that regulate diverse cellular processes, including proliferation, apoptosis and inflammation (135,136). According to the LIPID MAPS® Structure Database, lipids are categorized into eight major classes: i) Fatty acyls; ii) glycerolipids; iii) glycerophospholipids; iv) sphingolipids; v) sterol lipids; vi) prenol lipids; vii) saccharolipids; and vii) polyketides (137,138). These structurally diverse molecules not only constitute essential components of cellular membranes and lipid droplets, but also play critical roles in signal transduction, molecular transport and the spatial distribution of biomacromolecules (139,140). In uveitis, multiple lipid subclasses contribute notably to immune regulation. Phospholipids, once considered simply structural membrane constituents, are now recognized as signaling mediators that modulate a broad range of cellular responses. Various lysophospholipids have been shown to regulate neutrophil and macrophage activation and to facilitate the phagocytosis and clearance of apoptotic cells, thereby maintaining immune homeostasis. Similarly, sphingolipids, key components of cellular and extracellular membranes, act as signaling molecules involved in stress responses and inflammatory cascades (135,136). Moreover, several endogenous lipid mediators, including prostaglandins and leukotrienes, have attracted increasing attention for their roles in modulating inflammation and coordinating lipid signaling pathways (141,142). Specialized pro-resolving mediators (SPMs), including lipoxins, resolvins, protectins and maresins, have emerged as promising endogenous regulators of inflammation resolution in uveitis. Unlike conventional anti-inflammatory therapies that primarily suppress immune responses, SPMs actively promote the termination of inflammation and restoration of tissue homeostasis without inducing broad immunosuppression (143,144). Experimental studies have demonstrated that SPMs can attenuate ocular inflammation by reducing leukocyte infiltration, suppressing Th1/Th17-mediated immune responses, promoting macrophage polarization toward a pro-resolving phenotype, and enhancing the clearance of inflammatory cells (145,146). Moreover, eicosanoids are a diverse family of bioactive lipid mediators derived primarily from arachidonic acid (AA), a 20-carbon ω-6 polyunsaturated fatty acid released from membrane phospholipids by phospholipase A2. Once liberated, AA is metabolized through three major enzymatic pathways: The cyclooxygenase, lipoxygenase and cytochrome P450 pathways. These pathways generate a wide range of lipid mediators, including prostaglandins, thromboxanes, leukotrienes, lipoxins, hydroxy-eicosatetraenoic acids and epoxy-eicosatrienoic acids. Eicosanoids play pivotal roles in regulating vascular permeability, leukocyte recruitment, cytokine production, immune cell activation and tissue repair, thereby orchestrating both the initiation and resolution phases of inflammation (147-149).

In recent years, lipidomics has rapidly emerged as a vital branch of metabolomics. Unlike conventional metabolomics, which encompasses a broad spectrum of small-molecule metabolites, lipidomics specifically focuses on the comprehensive analysis of lipid composition, dynamics and functional networks in biological systems. Given that lipids account for ~70% of plasma metabolites, lipidomics offers distinct advantages for elucidating mechanisms of energy metabolism, signal transduction, and inflammatory regulation (150,151). A recent study identified six differentially expressed lipid metabolites in the plasma of patients with active BD, including two triglyceride (TAG) subtypes that were significantly elevated. TAGs are generally associated with autoimmune activation and inflammatory processes. In subsequent *in vitro* experiments, TAG stimulation of $CD4^+$ T cells isolated from healthy donors resulted in increased cytokine production and enhanced proliferation and differentiation of Th1 and Th17

Table III. Summary of metabolomics studies in uveitis.

Authors, year	System/Disease	Sample type	Methodology	Study design	Key findings	(Refs.)
Guo *et al*, 2014	AAU	Plasma	UPLC-MS, PCA, PLS-DA	Cross-sectional aqueous humor metabolomics biomarker discovery study (ocular sarcoidosis n=28; VRL n=25; Behçet's disease-associated uveitis n=7; ERM/MH controls n=30)	33 metabolites identified; 10 pathways involved; metabolomics effective for AAU diagnosis.	(229)
Wang *et al*, 2019	PSS	Aqueous humour	GC-TOF-MS	Aqueous humor metabolomics case-control study in Posner-Schlossman syndrome (PSS n=12; control n=12)	Identified 14 differential metabolites; pathways including lysine degradation and TCA cycle were disturbed; glycine and homogentisic acid were proposed as biomarkers.	(230)
Shimizu *et al*, 2020	BD, Sarcoidosis, VKH	Serum	LC-TOF-MS	Serum metabolomics case-control and disease-stratification study in non-infectious uveitis (BD n=19; sarcoidosis n=20; VKH n=15; healthy controls n=16)	24 metabolites significantly differed; logistic regression models achieved AUCs of 0.72-0.84 for disease discrimination.	(231)
Chen *et al*, 2020	VKH	Plasma	LC-MS/MS	Plasma metabolomics case-control study in VKH disease (active VKH n=28; inactive VKH n=27; healthy controls n=30)	D-mannose, stearic acid, and L-lysine were identified as diagnostic biomarkers (AUC >0.91); sarcosine indicated inactive VKH.	(232)
Cui *et al*, 2020	VKH	Sweat	LC-MS/MS	Sweat proteomics and metabolomics case-control multi-omics study in VKH disease (VKH patients n=30; healthy controls n=30)	Amino acid metabolism abnormalities were identified in the sweat samples of VKH patients.	(233)
Chang *et al*, 2021	VKH	Urine	UHPLC-Q-TOF/MS	Case-control urine metabolomic biomarker discovery and disease activity stratification study (VKH active vs. inactive vs. controls; VKH active n=28, inactive n=27, healthy controls n=30)	Urinary acetylglycine and γ-glutamylalanine differentiated VKH from controls; active VKH was associated with altered lysine and biotin metabolism.	(234)

Table III. Continued.

Authors, year	System/Disease	Sample type	Methodology	Study design	Key findings	(Refs.)
Xu *et al*, 2021	VKH and BD	Aqueous humor	UHPLC-Q-TOF/MS	Case-control aqueous humor metabolomic profiling study in Vogt-Koyanagi-Harada disease and Behçet's disease (VKH n=28 differential metabolites vs. controls; BD n=29 differential metabolites; controls included)	28-29 differential metabolites per group; pathways involved included amino acid and fatty acid metabolism, aminoacyl-tRNA biosynthesis.	(235)

AAU, acute anterior uveitis; UPLC-MS, ultra-performance liquid chromatography-mass spectrometry; PCA, principal component analysis; PLS-DA, partial least squares discriminant analysis; VRL, vitreoretinal lymphoma; ERM, epiretinal membrane; MH, macular hole; PSS, Posner-Schlossman syndrome; GC-TOF-MS, gas chromatography-time-of-flight mass spectrometry; TCA cycle, tricarboxylic acid cycle; BD, Behçet's disease; VKH, Vogt-Koyanagi-Harada disease; LC-TOF-MS, liquid chromatography-time-of-flight mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; AUC, area under the receiver operating characteristic curve; UHPLC-Q-TOF/MS, ultra-high-performance liquid chromatography quadrupole time-of-flight mass spectrometry; tRNA, transfer ribonucleic acid.

subsets. These findings suggest that TAGs exert proinflammatory effects and may contribute to the immunopathogenesis of active BD (20). Additionally, Wang *et al* (152) identified elevated levels of lysophospholipids and sphingolipids, including ceramides (Cer_{240} and Cer_{241}) and sphingomyelins (SM_{240}), during the acute inflammatory phase. Notably, the ratio of lysophospholipids to total phospholipids was markedly increased, accompanied by a 6.4-fold and 3.8-fold rise in 18:0 lysophosphatidylcholine in the aqueous humor and retina, respectively. Several ceramide-1-phosphate (C-1-P) species, including C12 C-1-P, C16 C-1-P and C24 C-1-P, were also upregulated, suggesting their involvement in the regulation of local inflammatory response. Although C1P is hypothesized to promote homeostasis by inhibiting NF-κB activation, elevated NF-κB levels were still observed, suggesting a dysregulated compensatory mechanism. These findings highlight that distinct lipid subclasses may exert both pro-inflammatory and protective effects in uveitis. Modulating these lipid pathways, either by inhibiting pathogenic lipid mediators or supplementing protective lipid species, may represent a promising therapeutic strategy for controlling ocular inflammation. In a mouse model of *Staphylococcus aureus* (*S. aureus*)-induced bacterial endophthalmitis, Ahmad *et al* (153) performed untargeted and temporal lipidomic profiling of retinal tissues, identifying dynamic alterations across multiple lipid classes. The levels of sphingolipids, glycerolipids, sterols and non-esterified fatty acids increased progressively during infection, whereas phospholipids, particularly phosphatidylcholine, declined markedly. Oxylipin analysis demonstrated elevated prostaglandin E_2, hydroxy-eicosatetraenoic acids, and polyunsaturated fatty acids such as DHA and AA, indicating enhanced lipid peroxidation and proinflammatory lipid mediator synthesis. *In vitro* experiments using bone marrow-derived macrophages further confirmed increased lipid droplet accumulation and lipid-peroxide formation following *S. aureus* exposure. Collectively, these findings suggest that bacterial infection disrupts retinal lipid metabolism, promoting oxidative stress and inflammatory lipid signaling that may contribute to the pathogenesis of endophthalmitis. Additionally, in a targeted LC-MS/MS study, Ben-Fradj *et al* (154) analyzed plasma polyunsaturated fatty acids (PUFAs) and oxylipins in patients with BD and identified a distinct lipidomic signature characterized by reduced circulating n-3 and n-6 PUFAs together with increased levels of both pro-inflammatory mediators (for example, prostaglandin E2, thromboxane B2 and leukotriene B4) and pro-resolving lipid mediators (for example, lipoxin A4, resolvin D5 and protectin X). These findings suggest an imbalance between inflammatory activation and resolution pathways, highlighting oxylipin metabolism as a potential biomarker source and therapeutic target in BD (154).

Together, these findings highlight the pivotal role of lipid metabolism in ocular inflammation. Dysregulated lipid pathways appear to contribute to both autoimmune and infectious forms of uveitis by modulating immune activation, cytokine production, oxidative stress, and inflammatory resolution within ocular tissues. Different lipid subclasses may exert divergent biological effects, with certain mediators amplifying inflammatory cascades while others promote inflammation resolution and tissue repair. Therefore, characterization of context-dependent lipid signatures may facilitate the identification of disease-specific biomarkers and novel therapeutic targets. Further studies are still needed to clarify the temporal dynamics and cell-specific functions of lipid mediators in uveitis and to evaluate the therapeutic potential of lipid-modulating strategies in inflammatory eye diseases.

Despite the rapid advancement of proteomics, metabolomics and lipidomics in uveitis research, several important challenges continue to limit their clinical translation. Molecular profiles identified through these approaches may vary substantially depending on sample source, including tears, aqueous humor, vitreous fluid, serum, plasma and retinal tissues, thereby complicating cross-study comparisons and biomarker interpretation. In addition, pre-analytical variables, including sample collection, storage conditions, extraction procedures, and batch effects, may influence molecular measurements and reduce reproducibility across studies. Technical heterogeneity among analytical platforms, including differences in MS instruments, chromatographic separation methods, and bioinformatic pipelines, further contributes to inconsistencies in identified biomarkers and molecular signatures (155,156). Moreover, numerous currently available studies remain limited by relatively small sample sizes, single-center designs, and the lack of independent external validation cohorts, reducing the robustness and generalizability of reported findings. Although numerous candidate biomarkers and dysregulated inflammatory pathways have been identified, relatively few have progressed to clinical validation or therapeutic application. Therefore, future studies should prioritize standardized experimental protocols, larger multi-center cohorts, and integrated multi-omics approaches combining proteomics, metabolomics, and lipidomics with genomics, transcriptomics, and clinical phenotyping to improve reproducibility and facilitate precision medicine applications in uveitis.

Microbiome. The microbiome, often referred to as the second human genome, encompasses the composition, functions, and host interactions of microbial communities and constitutes a vital component of the immune system (157). Functionally, the microbiome plays critical roles in metabolic regulation and drug response modulation. To explore its diversity and functionality, microbiome research utilizes a suite of high-throughput omics technologies. Amplicon-based sequencing, including 16S rRNA for bacteria and internal transcribed spacer for fungi, facilitates taxonomic profiling (158,159). Shotgun metagenomics offers species- and strain-level resolution while enabling functional gene annotation (160). Meta-transcriptomics captures active gene expression patterns, providing insights into microbial activity under specific conditions (161). Meta-proteomics assesses expressed proteins to uncover functional phenotypes, whereas metabolomics focuses on small-molecule metabolites, elucidating microbe-host metabolic interactions (162).

Gut microbiota in uveitis. Studies have shown that in EAU models, alterations in intestinal morphology and microbial gene expression occur even before the onset of ocular inflammation. Notably, multiple studies have demonstrated that depletion or absence of the gut microbiota can attenuate disease severity in animal models of uveitis (163,164). For example, Nakamura *et al* (165) reported that oral administration of broad-spectrum antibiotics significantly reduced the severity of EAU, whereas intraperitoneal antibiotic treatment had no protective effect, highlighting the importance of intestinal microbial modulation rather than direct systemic antibiotic exposure. This protection was accompanied by an increase in Tregs within the gut lamina propria and peripheral lymphoid tissues, along with reduced effector T-cell responses and inflammatory cytokine production. Additionally, Heissigerova *et al* (166) demonstrated that germ-free mice or conventionally housed mice subjected to broad-spectrum antibiotic-induced microbiota reduction exhibited significantly reduced retinal inflammation, characterized by decreased infiltration of macrophages and T cells, as well as lower frequencies of IFN-γ- and IL-17-producing T cells in draining lymph nodes, together with an increase in regulatory T-cell populations, indicating that the presence of gut microbiota during antigen priming is a key determinant of autoimmune susceptibility in EAU. However, more recent studies have highlighted that the relationship between gut microbiota depletion and uveitis is not strictly linear but is influenced by treatment duration. Salvador *et al* (167) showed that short-term oral antibiotic treatment before immunization delayed and attenuated EAU, whereas long-term antibiotic exposure abolished this protective effect. This paradoxical finding was associated with a progressive loss of microbiota-dependent $CD4^+CD8^+$ intraepithelial lymphocytes in the gut, which possess regulatory functions and suppress autoreactive T-cell activation, suggesting that prolonged microbiota depletion may disrupt intestinal immune homeostasis and thereby reverse the beneficial effects of microbial reduction in EAU. Furthermore, 16S rRNA sequencing revealed distinct microbial community structures associated with protection from uveitis, suggesting that specific commensal microbes may either promote or suppress ocular inflammation. For the eye, peripheral immune activation appears to be a critical step, as the retinal autoantigens targeted in uveitis are typically sequestered within the immune-privileged environment of the healthy eye. To initiate pathology, retinal antigen-specific lymphocytes must first be activated in the periphery to breach the BRB. The gut microbiota may function as an 'adjuvant', providing innate immune signals that enhance and direct the host immune response, thereby contributing to the initiation and progression of uveitis (168). A summary of the current microbiome studies related to uveitis is provided in Table IV.

Ocular and intraocular microbiomes: Emerging insights. Microbiome research has largely centered on the gut due to its rich microbial diversity and notable systemic influence on metabolism, immunity and disease (169). In comparison, an increasing number of studies relating to the ocular surface microbiome have emerged, driven by increasing evidence that resident microbes play a role in maintaining ocular surface homeostasis and may be involved in conditions including dry eye, blepharitis and keratitis (170). Research on intraocular fluids, including aqueous humor and vitreous humor, remains limited. Previously considered sterile except during infection, these compartments were considered to harbor microorganisms only under pathological conditions. However, advancements in deep metagenomic sequencing have challenged this theory, revealing the presence of bacterial DNA even in these traditionally considered immune-privileged sites, thus opening new avenues for understanding ocular immunity and disease pathogenesis (171). Advances in sequencing technologies have enabled more precise characterization of these low-biomass communities, highlighting their potential relevance in ocular health and disease.

Despite the growing interest in microbiome research in uveitis, several important limitations remain. A study relies

Table IV. Summary of microbiome studies in uveitis.

Authors, year	System/Disease	Sample type	Methodology	Study design	Key findings	(Refs.)
Ye *et al*, 2018	BD	Feces, Saliva	Metagenomics, 16S rRNA	Case-control gut metagenomic and fecal microbiome functional profiling study with experimental fecal microbiota transplantation (BD active n=32; healthy controls n=74; additional EAU mouse model validation)	Patients with BD had more sulfate-reducing bacteria and pathogens, including *Bilophila*, *Parabacteroides*, and fewer butyrate-producing bacteria; fecal transplants exacerbated EAU in mice.	(236)
Ye *et al*, 2020	VKH	Feces	Metagenomics	Case-control gut microbiome metagenomic sequencing study with treatment response evaluation (VKH patients n=32 active; healthy controls n=74)	Patients with VKH had lower butyrate/lactate producers and methanogens; microbial changes were partially reversible by immunosuppressants.	(237)
Li *et al*, 2022	VKH and non-infectious anterior scleritis	Feces	16S rDNA	Case-control 16S rDNA gut microbiome sequencing study comparing active VKH patients, non-infectious anterior scleritis patients, and healthy controls (VKH n=11; scleritis n=20; controls n=11)	At the genus level, three microbes (*Stomatobaculum*, *Pseudomonas*, *Lachnoanaerobaculum*) were uniquely enriched, and two (*Gordonibacter*, *Slackia*) depleted in VKH patients. Additionally, 10 genera were enriched and 12 depleted in both VKH and non-infectious anterior scleritis.	(238)
Wang *et al*, 2023	BDU, VKH	Feces	Metagenomics	Case-control integrated gut metagenomic comparative analysis of Behçet's uveitis and Vogt-Koyanagi-Harada disease within a multi-disease cohort framework, including autoimmune and inflammatory controls (BU + VKH + AS + RA + CD + UC +	In BU patients, *Dorea*, *Blautia*, *Coprococcus*, *Erysipelotrichaceae*, and *Lachnospiraceae* were depleted, while *Bilophila* and *Stenotrophomonas* were enriched. In VKH patients, *Alistipes* was enriched and *Dorea* was reduced.	(239)

Table IV. Continued.

Authors, year	System/Disease	Sample type	Methodology	Study design	Key findings	(Refs.)
				healthy controls), with functional integration analysis.		
Essex *et al*, 2024	SpA, AAU, CD	Feces	16S rRNA sequencing	Case-control 16S rRNA stool microbiome profiling study with multi-disease comparative analysis of immune-mediated conditions, including spondyloarthritis (SpA, n=102), AAU (n=103), CD (n=72), and back pain controls without inflammatory disease (n=62).	Shared microbial dysbiosis was marked by decreased *Lachnospiraceae*, while disease-specific changes included increased *Collinsella* in SpA and elevated *Faecalibacterium* in HLA-B27+ individuals, suggesting overlapping but distinct microbial mechanisms.	(240)
Liu *et al*, 2024	BU and Fuchs Syndrome	Feces	16S rRNA	Case-control integrated gut microbiome (16S rRNA) and fecal metabolomics (LC-MS/MS) comparative study of BDU (n=11), Fuchs uveitis syndrome (n=15), and healthy controls (n=18), aimed at identifying differential microbial and metabolic signatures associated with distinct uveitis phenotypes.	Compared with controls, BU patients showed specific changes in *Fusicatenibacter* and Fuchs patients showed specific changes in *Pantoea*.	(195)
Morandi *et al*, 2024	HLA-B27-associated AAU	Feces	Shotgun metagenomics	Case-control whole metagenome shotgun gut microbiome study of HLA- B27-associated non-infectious anterior uveitis, including patients with AU (n=20), HLA-B27-negative healthy controls (n=21), and HLA-B27-positive	In AAU, Lipid IV(A) biosynthesis was increased, *E. ramulus* was reduced in patients, and microbiome alterations were functionally associated with HLA-B27 status.	(241)

Table IV. Continued.

Authors, year	System/Disease	Sample type	Methodology	Study design	Key findings	(Refs.)
				healthy controls without uveitis (n=6), with additional subgroup analysis based on disease activity and MaAsLin-based multivariate association analysis of taxonomic and functional microbial features.		
Li *et al*, 2025	VKH vs. AS-related AAU	Feces	16S rDNA + LC-MS/MS	Case-control integrated 16S rDNA gut microbiome and LC-MS/MS metabolomics profiling study of uveitis, including Vogt-Koyanagi-Harada disease (VKH, n=16), acute anterior uveitis (AAU, n=11), and healthy controls (n=18), with multi-omics correlation analysis and biomarker evaluation for disease discrimination.	VKH had more distinct microbial and metabolic changes; biomarkers (for example, pyrimidine, *Pediococcus*) distinguished disease types with high AUC.	(194)

BD, Behçet's disease; VKH, Vogt-Koyanagi-Harada disease; AAU, acute anterior uveitis; EAU, experimental autoimmune uveitis; AS, ankylosing spondylitis; RA, rheumatoid arthritis; CD, Crohn's disease; UC, ulcerative colitis; SpA, spondyloarthritis; HLA-B27, human leukocyte antigen B27; rRNA, ribosomal ribonucleic acid; rDNA, ribosomal deoxyribonucleic acid; LC-MS/MS, liquid chromatography-tandem mass spectrometry; AUC, area under the receiver operating characteristic curve; MaAsLin, Multivariate Association with Linear Models.

primarily on 16S rRNA sequencing, which provides limited taxonomic resolution and insufficient functional characterization (172). In addition, although microbial dysbiosis has been associated with uveitis, the causal relationship between microbiome alterations and intraocular inflammation remains unclear. Microbiome profiles may also be influenced by geographic region, diet, ethnicity, disease subtype and immunosuppressive therapies, contributing to inconsistencies among studies. Furthermore, the low microbial biomass of ocular samples increases the risk of contamination and false-positive findings (173). Therefore, larger standardized multi-center studies integrating microbiomics with other omics approaches are still needed to improve reproducibility and clarify the translational potential of microbiome-based biomarkers in uveitis.

Radiomics. Imaging modalities, including fundus photography, OCT, OCTA, MRI and CT, are essential tools for the diagnosis, monitoring and management of a wide range of ophthalmic diseases. However, inter-observer variability and the potential for human error due to subjective interpretation remain notable challenges. Radiomics is an emerging technique that addresses these limitations by extracting a large number of quantitative features from medical images.

The standard radiomics workflow typically involves feature extraction, feature selection and data processing (42). By providing objective, reproducible and quantitative assessments, radiomics helps reduce subjectivity in ophthalmic image interpretation and enhances clinical decision-making (174). With the rapid advancement of artificial intelligence (AI), medical imaging has evolved beyond traditional diagnostic applications to encompass disease risk prediction, differential diagnosis, treatment response evaluation and prognostic assessment (42). The eye serves as a unique and accessible window into systemic health, offering insights into disease mechanisms and progression. Over the past decade, growing evidence has shown that ocular structure and function closely reflect systemic conditions, including cardiovascular disease, neurodegenerative disorders and renal dysfunction. This convergence has led to the emergence of oculomics, a field dedicated to leveraging ophthalmic imaging biomarkers to elucidate disease mechanisms, improve early detection and refine predictive modeling (175,176).

Several recent studies have explored the application of radiomics in diagnosing and monitoring uveitis and related posterior segment disorders using OCT-based imaging. In a post-hoc analysis of the HAWK trial focusing on cases involving intraocular inflammation, endophthalmitis and retinal vascular occlusion, Sil Kar *et al* (177) extracted 481 texture-based radiomic features from the vitreous compartment of spectral-domain OCT images and identified early inflammatory signals associated with intraocular inflammation, achieving AUCs of 0.76 and 0.81 at pre- and post-event time points, respectively. In another study on Behçet's uveitis (BU), Lu *et al* (178) employed OCTA combined with radiomic analysis to develop a neural network classifier. From 837 extracted features, the top 20 were used to train a model that achieved an AUC of 0.90, which increased to 0.908 with the inclusion of clinical variables. These findings underscore the potential of radiomic signatures in enhancing the diagnostic accuracy for BU.

Despite these promising findings, several important limitations currently restrict the broader clinical application of radiomics in uveitis. Numerous existing studies are based on relatively small, single-center cohorts with limited external validation, which may reduce the reproducibility and generalizability of radiomic models. In addition, variations in imaging devices, acquisition protocols, image quality, and feature extraction pipelines may substantially influence radiomic results across studies. The 'black-box' nature of certain AI algorithms also limits interpretability and clinical trust (179). Therefore, larger standardized multi-center studies integrating radiomics with clinical and multi-omics data are needed to improve model robustness and facilitate the development of precision medicine approaches in uveitis.

5. Multi-omics data integration

Uveitis is a multifactorial disease driven by complex interactions among immune, genetic, metabolic and environmental factors. While single-omics studies have significantly advanced our understanding of its pathogenesis, each approach offers only a partial view of the disease (180). Abdel-Aziz *et al* (181) metaphorically compares disease to a puzzle: A single biomarker represents just one puzzle piece, insufficient to reveal the complete picture. Only by assembling multiple biomarkers can the full image emerge, providing a clearer understanding of the disease's size, shape and complexity, which ultimately guides precise clinical decisions (181). Multi-omics integration, which combines and analyzes data from genomics, epigenomics, transcriptomics, proteomics, metabolomics, and other omics layers, offers a powerful strategy for comprehensively characterizing biological systems and complex diseases. By integrating molecular omics data with clinical phenotypic information, researchers can uncover intricate relationships between molecular alterations and disease manifestations, identify disease-driving mechanisms, construct detailed patient profiles, and improve the accuracy of diagnosis, prognosis and treatment stratification. Furthermore, multi-omics approaches enable the identification of novel biomarkers and therapeutic targets while supporting the development of personalized medicine through monitoring of disease progression and treatment responses. Consequently, the transition from single-omics investigations to integrated multi-omics analyses has become an essential trend in contemporary biomedical research and holds great promise for advancing precision medicine in uveitis (182,183). To achieve a more comprehensive understanding of disease biology, various multi-omics integration strategies have been developed by combining complementary omics layers. By integrating these complementary datasets, researchers can construct molecular networks across different biological layers, identify key regulatory pathways, and gain a systems-level understanding of disease pathogenesis.

Integrated genomics and transcriptomics. The integration of genomic and transcriptomic data provides a powerful framework for linking genetic susceptibility to downstream cellular and molecular mechanisms. While GWAS have identified numerous susceptibility loci for autoimmune and inflammatory diseases, most disease-associated variants are located within non-coding regions of the genome, making their functional interpretation challenging. By combining genomic data with transcriptomic profiling, researchers can map genetic risk variants to specific cell populations, identify their downstream target genes, and elucidate the biological pathways through which genetic variation contributes to disease pathogenesis (184). Such approaches are particularly valuable in uveitis, where the relationship between genetic susceptibility and immune-cell dysfunction remains incompletely understood.

A study was reported by Chen *et al* (185), who combined genomic and single-cell transcriptomic analyses to investigate the pathogenesis of HLA-B27-associated anterior uveitis. Using plasma protein quantitative trait loci data, GWAS datasets, Mendelian randomization, and colocalization analyses, the authors identified several proteins causally associated with disease risk, including allograft inflammatory factor-1 (AIF1) and valyl-tRNA synthetase. Subsequent scRNA-seq analysis revealed that AIF1 was predominantly expressed in myeloid cells, particularly monocytes, macrophages, and DCs, and that HLA-B27-positive patients exhibited altered myeloid-cell differentiation trajectories characterized by increased DC abundance and reduced AIF1 expression. Cell-cell communication analyses further identified enhanced DC-mediated

signaling pathways, including APP, SELPLG and CADM pathways, suggesting a central role of DCs in disease initiation and propagation (185). By integrating genetic association signals with cellular transcriptomic data, the aforementioned study linked disease-associated molecular markers to specific immune-cell populations and identified AIF1 as a potential biomarker and therapeutic target for HLA-B27-associated uveitis.

Integrated transcriptomics and proteomics. Transcriptomics and proteomics provide complementary perspectives on biological processes. Transcriptomics characterizes gene-expression patterns and regulatory programs at the mRNA level, whereas proteomics directly reflects protein abundance and post-translational regulation, which more closely represent cellular function and disease phenotypes (10). Because mRNA abundance does not always correlate with protein expression due to translational control, protein degradation, and post-translational modifications, integration of transcriptomic and proteomic datasets can provide a more comprehensive understanding of disease mechanisms than either modality alone. In inflammatory and autoimmune diseases, such integrative approaches have proven particularly valuable for identifying dysregulated pathways, validating molecular signatures across multiple biological layers, and uncovering clinically relevant therapeutic targets.

Integrated transcriptomic and proteomic analyses have provided important insights into the local immune microenvironment and pathogenic mechanisms of juvenile idiopathic arthritis-associated uveitis (JIAU). Using iris tissues and aqueous humor samples from patients with JIAU, Wildschütz *et al* (186) combined RNA-seq with proteomic profiling and identified 136 DEGs and 56 differentially expressed proteins compared with controls. Multi-omics integration revealed coordinated upregulation of immunoglobulin-related molecules and B-cell-associated factors, including *ID1*, *ID3*, *EBF1* and *MZB1*, together with elevated aqueous humor levels of BAFF, APRIL and IL-6, supporting a central role for B-cell activation and plasma-cell survival in disease pathogenesis (186). Building upon this dataset, Baquet-Walscheid *et al* (187) further investigated angiogenesis-related mechanisms and found that angiogenesis was the most significantly enriched biological process among DEGs. Proteomic analyses additionally identified dysregulated angiogenesis-associated proteins, including angiopoietin, lumican and decorin, while aqueous humor profiling demonstrated increased ANGPT-2 levels. Moreover, multimodal iris angiography revealed vascular leakage, hypoperfusion and neovascularization in patients with severe disease. By integrating transcriptomic, proteomic, aqueous humor and imaging data, these studies demonstrated that both aberrant B-cell-mediated immunity and angiogenesis-related pathways contribute to chronic ocular inflammation and tissue remodeling in JIAU, highlighting potential therapeutic targets and illustrating the value of integrated multi-omics approaches in elucidating uveitis pathogenesis (187).

Beyond identifying differentially expressed molecules, these studies underscore the ability of integrated transcriptomic-proteomic analyses to connect immune activation with downstream tissue-level alterations. The coordinated upregulation of B-cell-related genes and proteins provides convergent evidence that humoral immune responses may play a more prominent role in uveitis pathogenesis than previously appreciated. Meanwhile, the discovery of angiogenesis-associated molecular signatures suggests that vascular remodeling may represent an important component of chronic ocular inflammation, potentially contributing to persistent tissue damage, leukocyte recruitment and disease progression. Together, these findings highlight the complex interplay between immune dysregulation, inflammatory signaling, and tissue remodeling in uveitis.

Despite these advances, several challenges remain. Most existing studies have been conducted in relatively small patient cohorts and have primarily focused on advanced or treatment-refractory disease stages, limiting the ability to capture dynamic molecular changes throughout disease evolution. Furthermore, bulk transcriptomic and proteomic analyses may obscure cellular heterogeneity within ocular tissues. Future studies integrating transcriptomics and proteomics with single-cell sequencing, spatial omics, and longitudinal clinical data are expected to provide a more comprehensive understanding of disease mechanisms. Such multidimensional approaches may facilitate the identification of robust biomarkers for disease activity, prognosis and therapeutic response, while enabling the development of precision medicine strategies tailored to individual patients with uveitis.

Integrated single-cell omics. Single-cell omics technologies have revolutionized the study of complex diseases by enabling the characterization of cellular heterogeneity at unprecedented resolution. However, individual single-cell modalities capture only specific aspects of cellular biology. For instance, scRNA-seq reveals transcriptional states, whereas scATAC-seq provides insights into chromatin accessibility and gene regulatory mechanisms. Likewise, spatial transcriptomics preserves tissue architecture and cellular localization, while emerging multimodal platforms can simultaneously profile gene expression, chromatin accessibility, protein abundance and immune receptor repertoires within the same cell. The integration of these complementary datasets enables a more comprehensive characterization of cellular identity, functional states, developmental trajectories, and intercellular communication than any single modality alone. In uveitis research, integrated single-cell omics approaches have begun to uncover previously unrecognized immune-cell subsets, transcriptional regulatory networks, and cellular interactions involved in ocular inflammation. By combining transcriptomic, epigenomic, proteomic and spatial information at single-cell resolution, these technologies provide unprecedented insights into disease pathogenesis while creating new opportunities for biomarker discovery and precision therapeutics.

In VKH disease, Shi *et al* (188) integrated transcriptomic and chromatin accessibility profiles of PBMCs and identified extensive immune-cell heterogeneity, widespread inflammatory activation, and disease-specific regulatory programs. Their analyses demonstrated that conventional DCs exhibited enhanced NF-κB-associated chromatin accessibility and transcriptional activity, suggesting a central role for these cells in coordinating immune responses through antigen presentation, cytokine production and intercellular communication. Furthermore, the combined analysis of scRNA-seq and scATAC-seq data enabled the assignment

of VKH-associated genetic risk loci to specific immune-cell populations and identified key transcription factors, including RELA and HIF1A, that may drive pathogenic immune activation (188). These findings illustrate how integrated single-cell multi-omics can bridge gene expression, epigenetic regulation, genetic susceptibility and cell-cell communication, thereby providing mechanistic insights into immune dysregulation and highlighting potential therapeutic targets in uveitis. The translational value of integrated single-cell multi-omics was further demonstrated by Huang *et al* (189), who combined scRNA-seq analysis of cervical draining lymph node cells from EAU mice with scATAC-seq profiling of peripheral blood mononuclear cells from patients with VKH disease to investigate the role of JAK/STAT signaling in autoimmune uveitis. Across multiple immune-cell populations, including B cells, $CD4^+$ T cells, $CD8^+$ T cells, monocytes and other myeloid cells, both transcriptomic and chromatin accessibility analyses consistently revealed activation of JAK/STAT, TNF, NF-κB and Th17-associated inflammatory pathways. Moreover, cell-type-specific epigenomic alterations were identified at key signaling genes, including increased chromatin accessibility of *JAK1* in $CD4^+$ T cells, *JAK3* in monocytes, *STAT4* in $CD8^+$ T cells, and *STAT1* in B cells, highlighting widespread dysregulation of JAK/STAT signaling in uveitis (189).

Beyond transcriptomic and epigenomic integration, recent advances in spatial transcriptomics have enabled the investigation of retinal inflammatory responses within their native tissue context. A recent study integrating scRNA-seq with spatial transcriptomics in non-human primate retinas following adeno-associated virus-mediated retinal gene therapy provided important insights into localized retinal immune responses. Using the 10X Genomics Visium platform, the authors generated spatially resolved transcriptomic maps of full-thickness retinal tissues and integrated these data with single-cell transcriptomic profiles to characterize inflammatory microenvironments within the retina. This approach revealed region-specific immune activation characterized by T-cell infiltration, chemokine upregulation, microglial activation and glial reactivity in treated retinal regions. Importantly, integration of spatial and single-cell transcriptomic datasets enabled simultaneous identification of inflammatory cell populations and their precise spatial localization, providing a cell-type- and location-resolved view of retinal inflammation (190). These findings underscore the substantial spatial heterogeneity of retinal immune responses and suggest that inflammatory signaling is concentrated within localized retinal niches rather than being uniformly distributed throughout ocular tissues. Furthermore, spatial transcriptomics preserves retinal layer architecture and local tissue context, facilitating more precise investigation of inflammatory signaling pathways and immune-cell interactions within specific retinal regions. Such approaches may enable the identification of spatially restricted biomarkers and therapeutic targets that cannot be fully resolved through bulk tissue analyses or dissociative single-cell sequencing alone. Collectively, integrated single-cell and spatial multi-omics technologies are providing increasingly comprehensive insights into the cellular, molecular and spatial mechanisms underlying uveitis and are expected to play an increasingly important role in advancing precision medicine for ocular inflammatory diseases.

Integrated microbiome and metabolomics. Microbiome and metabolomic analyses are highly complementary and are particularly well suited for integrated investigations. Both approaches can be performed using non-invasively collected fecal samples, facilitating patient recruitment and longitudinal monitoring. Moreover, while microbiome profiling characterizes the composition and diversity of microbial communities, metabolomics captures the downstream biochemical products and functional consequences of host-microbe interactions (191). The integration of these datasets therefore provides a more comprehensive view of the intestinal ecosystem, linking microbial alterations with metabolic changes and their potential effects on host physiology and immune regulation. Accordingly, the integration of microbiome and metabolomic data has emerged as a powerful strategy for elucidating the gut-eye axis in uveitis. By simultaneously characterizing microbial communities and host metabolic profiles, this approach enables the identification of complex interactions between intestinal dysbiosis, metabolic reprogramming and immune-mediated ocular inflammation.

Recent studies have demonstrated the value of this strategy in both mechanistic investigations and disease stratification. Using a vitamin D-deficient EAU model, Chen *et al* (192) combined gut microbiota profiling with untargeted metabolomics and showed that vitamin D deficiency profoundly altered both microbial composition and host metabolism. These changes were associated with impaired intestinal barrier integrity, increased circulating LPS levels, enhanced inflammatory responses, and aggravated disease severity. Notably, the vitamin digestion and absorption pathway was consistently disrupted in both microbiome and metabolomic analyses, suggesting coordinated dysregulation of vitamin-associated metabolic processes and highlighting a potential gut microbiota-metabolism-immune axis involved in uveitis pathogenesis (192).

One of the earliest studies applying this strategy in uveitis was conducted by Huang *et al* (193), who combined 16S rDNA sequencing with GC-MS-based fecal metabolomics in patients with AAU. Although only modest alterations in gut microbial composition were observed, significant differences in fecal metabolic profiles were identified between AAU patients and healthy controls. Several metabolites, including linoleic acid, palmitoleic acid and shikimic acid, were significantly increased in AAU, and correlation analyses revealed associations between altered metabolites and specific bacterial genera such as *Roseburia* and *Veillonella*. These findings suggested that metabolic alterations may be more prominent than taxonomic microbial changes in AAU and highlighted the importance of integrating microbiome and metabolomic data to better understand disease-associated host-microbe interactions (193). Microbiome-metabolomics integration has also provided insights into the heterogeneity of different uveitis subtypes. Li *et al* (194) compared patients with active VKH disease, AS-associated AAU, and healthy controls using 16S rDNA sequencing and LC-MS/MS-based metabolomics. VKH exhibited more pronounced alterations in both microbial and metabolic profiles than AAU, with disease-specific metabolites primarily associated with nicotinamide and biotin metabolism, whereas AAU-related metabolites were mainly enriched in AA metabolism. Furthermore, integrated analyses

identified microbial and metabolic biomarkers capable of distinguishing VKH from AAU and healthy controls with high diagnostic accuracy, demonstrating the potential of multi-omics approaches for disease classification and biomarker discovery (194). Similarly, Liu *et al* (195) integrated gut microbiome and metabolomic analyses to compare BU and Fuchs syndrome. Distinct microbial and metabolic signatures were observed between the two disease entities. BU was characterized by alterations in *Fusicatenibacter* and metabolites related to delta-tocopherol, palmitic acid and serotonin metabolism, whereas Fuchs syndrome showed enrichment of *Pantoea* and disturbances in linoleic acid metabolism. In addition, elevated serum zonulin levels in both groups suggested impaired intestinal barrier function, further supporting the involvement of the gut-eye axis in uveitis. Importantly, metabolite-based biomarkers demonstrated superior discriminatory performance compared with microbial markers, highlighting the complementary value of integrating multiple omics layers (195).

Microbiome-metabolomics integration offers several unique advantages over single-omics approaches. While microbiome analyses identify alterations in microbial composition and diversity, metabolomics provides functional information regarding the biochemical consequences of these changes. The combination of these two approaches enables researchers to move beyond descriptive taxonomic profiling and establish links between specific microbial taxa and their metabolic outputs, thereby providing a more comprehensive understanding of host-microbe interactions (196). In uveitis, this strategy has facilitated the identification of disease-specific microbial and metabolic signatures, improved disease stratification, and generated novel mechanistic hypotheses regarding the gut-eye axis. However, several limitations should also be acknowledged. Firstly, microbial abundance does not necessarily reflect microbial activity, and correlations between microbial taxa and metabolites do not prove direct functional relationships. Secondly, metabolomic profiles are influenced by numerous confounding factors, including diet, medications, geographic location and lifestyle, which may obscure disease-specific signals. In addition, methodological heterogeneity across studies, including differences in sample collection, sequencing platforms, metabolomic techniques and bioinformatic pipelines, complicates comparisons and reproducibility. Therefore, although microbiome-metabolomics integration provides valuable insights into uveitis pathogenesis, further validation through larger longitudinal cohorts, functional experiments and integration with additional omics layers is required before these findings can be translated into routine clinical applications.

6. Omics-guided precision medicine in uveitis

Recent advances in omics technologies have significantly expanded the understanding of the molecular mechanisms underlying uveitis and have created new opportunities for precision medicine. By characterizing disease-associated alterations at the genomic, transcriptomic, proteomic, metabolomic, microbiome and single-cell levels, omics studies have begun to identify molecular signatures associated with specific disease subtypes, treatment responses and pathogenic pathways (197). Although most findings remain at the discovery stage, these approaches provide an important foundation for improving disease classification, risk stratification, prognostic assessment and individualized therapeutic intervention in uveitis.

Precision diagnosis and disease subtyping. Current classification of uveitis relies primarily on clinical manifestations, anatomical location and etiological assessment. However, considerable heterogeneity exists within clinically defined disease entities, and overlapping clinical features may complicate differential diagnosis. Omics technologies provide complementary molecular information that may facilitate more accurate disease classification and patient stratification.

Recent studies have demonstrated that omics-based technologies can also enhance the characterization of infectious uveitis, complementing clinical and anatomical assessments. For example, metagenomic deep sequencing of intraocular fluids has successfully identified fungal, parasitic and viral pathogens, including *Cryptococcus neoformans*, *Toxoplasma gondii*, *Herpes simplex virus 1* and *Rubella virus*, in cases where conventional diagnostics were inconclusive (198). These sequencing-based approaches not only improve pathogen detection but also enable molecular profiling of host immune responses, providing insights into disease activity, inflammatory pathways, and potential therapeutic targets. Emerging applications of transcriptomics, proteomics and metabolomics further allow evaluation of host-pathogen interactions and biomarker discovery for monitoring treatment response (199,200). Collectively, these advances suggest that integrating multi-omics data may enhance disease classification and patient stratification for both non-infectious and infectious uveitis.

Accumulating evidence indicates that distinct uveitis subtypes exhibit characteristic molecular signatures revealed by different omics platforms. For example, integrated single-cell transcriptomic and epigenomic analyses of VKH disease have demonstrated activation of Th17-associated inflammatory pathways, dysregulated JAK/STAT signaling, and a disease-specific transcriptional regulatory network (188,201). In BD-associated uveitis, transcriptomic, proteomic and metabolomic studies have consistently identified enhanced neutrophil activation, innate immune dysregulation and altered inflammatory metabolic pathways. In HLA-B27-associated anterior uveitis, integrated genomic, proteomic and single-cell transcriptomic analyses have revealed altered DC differentiation trajectories and AIF1-related signaling networks (185,202). Meanwhile, integrated transcriptomic and proteomic analyses of JIA-associated uveitis have highlighted the importance of B-cell activation, plasma-cell survival, and BAFF/APRIL-mediated immune responses (186). Collectively, these findings suggest that multi-omics-derived molecular endotypes may complement traditional clinical classifications and facilitate more precise disease subtyping.

Precision prediction of treatment response and prognosis. Precision medicine aims to tailor therapeutic strategies to individual patients based on their molecular, cellular and clinical profiles. In uveitis, significant heterogeneity exists in disease mechanisms, severity and response to therapy, making it challenging to predict which patients will benefit from a given treatment (203). Traditional clinical parameters alone are often insufficient to guide personalized therapy, highlighting

the need for molecular biomarkers that can reliably forecast therapeutic efficacy and disease prognosis.

High-throughput proteomic analyses have begun to provide such predictive biomarkers in non-infectious uveitis. For example, Rodríguez-Martínez *et al* (204) performed tear proteomics in patients receiving adalimumab therapy and identified 29 differentially expressed proteins distinguishing responders from non-responders. The proteins upregulated in non-responders were associated with enhanced neutrophil effector functions and redox imbalance. Among these, defensin-1/3 (DEF-1,3), biotinidase, and ATP-binding cassette transporter A1 were highlighted as potential biomarkers for predicting treatment response. These findings suggest that molecular signatures in easily accessible biological fluids, such as tears, may provide non-invasive predictors of therapeutic efficacy, inform individualized treatment decisions, and identify alternative therapeutic targets, including IL-6, JAK signaling, or complement pathway modulation, for patients who do not respond to anti-TNF therapy (204).

Therapeutic target discovery. Omics technologies have provided a powerful platform for identifying novel therapeutic targets in uveitis by interrogating multiple molecular layers simultaneously, uncovering disease-driving pathways that are often not evident in traditional hypothesis-driven studies. Integrated genomics and transcriptomics analyses in VKH disease have implicated RELA and HIF1A as central regulators of pathogenic immune activation, highlighting potential upstream nodes for targeted intervention. Single-cell multi-omics studies further revealed dysregulated JAK1-, JAK3- and STAT-mediated signaling pathways across multiple immune-cell populations, suggesting the utility of JAK inhibition in modulating autoimmune responses. Preclinical and translational studies have begun to validate these insights. For example, in patients with VKH, tofacitinib treatment was shown to restore Th17/Treg balance, inhibit STAT1/3 phosphorylation, and reduce pathogenic $CD4^+$ T cell proliferation, while also attenuating inflammatory cell-cell interactions, particularly in dendritic cells and monocytes (201). Similarly, upadacitinib, a selective JAK1 inhibitor, effectively alleviated EAU in mice and modulated pathogenic immune networks in patients with VKH. Upadacitinib suppressed aberrant $CD4^+$ T cell proliferation, promoted Treg expansion, restored $CD8^+$/B cell ratios, downregulated inflammatory gene expression, and inhibited CXCR4-mediated migratory pathways, revealing both mechanistic targets and translational therapeutic potential (189).

Although most candidate targets remain at the preclinical or early translational stage, these multi-omics investigations collectively illustrate how integrating genomics, transcriptomics, proteomics and single-cell analyses can uncover actionable molecular targets, guide mechanism-based therapeutic strategies, and advance precision medicine approaches in uveitis. Future studies focusing on independent cohort validation, longitudinal monitoring, and *in vivo* functional assessment are required to translate these discoveries into clinical practice.

7. Future perspectives

Despite the rapid advancement of omics technologies in uveitis research, several important challenges continue to hinder their clinical translation. A critical concern is the limited reproducibility of numerous published omics studies. Most currently available studies are single-center investigations with relatively small sample sizes, lacking independent external validation cohorts and standardized experimental or bioinformatic pipelines. These limitations may contribute to inconsistencies across studies and reduce the reliability and generalizability of identified biomarkers and molecular signatures. In addition, substantial heterogeneity in patient populations, disease subtypes, sample sources, sequencing platforms and analytical methods further complicates cross-study comparison and data integration.

To address these limitations, future research should prioritize large-scale, multi-center and standardized clinical studies that can generate robust multi-omics datasets across diverse patient populations. Such initiatives would enhance reproducibility, facilitate subtype classification and support the discovery of universally applicable biomarkers. In addition, establishing harmonized data standards and open-access platforms, including uveitis-specific ontologies, curated databases and knowledge graphs, will be critical for cross-study comparability and global collaboration (183,205). Building upon this, the SUN Project has provided a robust framework for disease classification by developing validated, expert-driven criteria for 25 common uveitic conditions through a rigorous, multi-phase process involving informatics, case curation and machine learning. This landmark effort demonstrates the feasibility and necessity of achieving global consensus on disease definitions, which is essential for integrating heterogeneous multi-omics datasets and ensuring consistency across studies (5,206).

The sheer complexity and high dimensionality of multi-omics data necessitate the development of advanced computational tools, including machine learning, network analysis and AI-powered predictive models (207,208). These approaches can accelerate the identification of diagnostic and prognostic biomarkers, optimize treatment regimens and support the development of personalized therapeutic strategies. In the era of data-driven medicine, future paradigms of uveitis care will increasingly rely on intelligent, integrative and individualized models capable of translating multi-omics insights into actionable clinical decisions (209).

Ultimately, multi-omics integration holds transformative potential for decoding the immunopathogenesis of uveitis, enhancing disease monitoring and refining therapeutic strategies (210). Future efforts should also aim to translate research findings into routine clinical practice, bridging the gap between discovery and application through rigorous validation, regulatory frameworks, and clinician-friendly decision support systems (211). By embracing the full potential of omics-driven precision medicine, more effective, personalized and preventive care may be achieved for patients with uveitis.

8. Conclusion

Uveitis is a multifactorial disease characterized by immune dysregulation, genetic predisposition and environmental triggers. Traditional diagnostic and therapeutic strategies have a limited capacity to address the heterogeneity and complexity of this condition. The emergence of multi-omics technologies has revolutionized the current ability to interrogate the molecular underpinnings of uveitis. Genomics, transcriptomics,

proteomics, metabolomics and microbiome studies have each provided unique insights into immune pathways, metabolic shifts and microbial influences. Furthermore, single-cell omics and radiomics offer fine-resolution perspectives on cellular behavior and disease phenotypes. While current research has largely focused on single-layer omics, the integration of multi-omics data stands to transform the present understanding and management of uveitis. Future efforts should prioritize large-scale, standardized and collaborative studies incorporating multi-dimensional data and AI to achieve actionable biomarkers and therapeutic targets. Ultimately, the convergence of omics and clinical practice paves the way for precision medicine in uveitis, offering the opportunity for earlier detection, more accurate classification and individualized treatment strategies.

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Authors' contributions

CL wrote the original draft, conceptualized the study, visualized and curated data. QW, MY, ML, XW and JS wrote, reviewed and edited the manuscript. XC wrote, reviewed and edited the manuscript, acquired funding and conceptualized the study. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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