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Emerging Trends in Systems Biology: Multi-Omics Integration and Beyond

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Abstract This study analyzes the framework and key technologies of multi-omics integration, including the combination of genomics, transcriptomics, proteomics, metabolomics, and epigenomics. It also discusses the computational tools and data analysis methods used in multi-omics integration, such as network construction, machine learning, and big data visualization, which are essential for processing and interpreting multi-omics data. With the rapid advancement of multi-omics technologies, data integration offers a holistic view of biological systems, enabling a deeper understanding of complex biological processes. Through case studies in fields such as personalized medicine and agriculture, this study demonstrates the practical applications of these integrative approaches, highlighting the importance of multi-omics in advancing personalized medicine, agriculture, and environmental research. Additionally, it aims to address the technical challenges in multi-omics data integration and provide insights into future directions, including real-time integration and the application of artificial intelligence.

Keywords Systems biology; Multi-omics integration; Data visualization; Personalized medicine; Artificial intelligence (AI)

1 Introduction

Systems biology is a holistic approach to understanding the complex interactions within biological systems. Unlike traditional biological research, which often focuses on individual components, systems biology aims to integrate various biological data to model and understand the dynamic interactions within a system. This approach is crucial for deciphering the intricate networks of genes, proteins, and metabolites that drive cellular functions and organismal phenotypes (MacLeod and Nersessian, 2016; Veenstra, 2020). The field has evolved significantly over the past few decades, driven by advancements in high-throughput technologies and computational methods, enabling researchers to analyze thousands of molecules simultaneously and understand their interdependencies.

The advent of multi-omics technologies has revolutionized systems biology by providing comprehensive datasets that encompass various biological layers, including genomics, transcriptomics, proteomics, and metabolomics. These technologies allow for the large-scale quantification of biomolecules, facilitating a deeper understanding of biological processes and interactions (Dhillon et al., 2020). The integration of these diverse datasets, although challenging due to their heterogeneity, has become essential for revealing novel insights into complex biological systems (Huan et al., 2017). Techniques such as network analysis, machine learning, and pathway enrichment are increasingly employed to integrate and interpret multi-omics data, thereby enhancing our understanding of biological functions and disease mechanisms (Pazhamala et al., 2021).

This study will explore emerging trends in systems biology, with a particular focus on the integration of multi-omics data. By reviewing recent advancements and methodologies in this field, it aims to highlight the potential of multi-omics integration in providing a holistic view of biological systems. This approach not only enhances our understanding of fundamental biological processes but also holds significant implications for various applications, including disease prediction, biomarker discovery, and crop improvement. The study emphasizes the importance of multi-omics integration in advancing systems biology and its potential to transform both biological research and its applications.

2 Framework and Key Technologies of Multi-Omics Integration

2.1 Integration of genomics and transcriptomics

The integration of genomics and transcriptomics is fundamental in understanding the flow of genetic information from DNA to RNA. Genomic data provides insights into the genetic blueprint, while transcriptomic data reveals gene expression patterns under different conditions. Combining these datasets helps in identifying regulatory elements and understanding gene function and regulation. For instance, genome-scale models (GEMs) have been employed to interpret and integrate genomics and transcriptomics data, enabling the modeling of metabolic, transcriptional, and translational reactions within an organism (Dahal et al., 2020). High-throughput strategies such as SPOT (Sample Preparation for Multi-Omics Technologies) facilitate the simultaneous analysis of genomic and transcriptomic data, enhancing throughput and resource efficiency (Gutierrez et al., 2018).

2.2 Integration of proteomics and metabolomics

Proteomics and metabolomics integration is crucial for linking protein function with metabolic pathways. Proteins act as catalysts and regulators of metabolic reactions, and their expression levels can significantly impact metabolite concentrations. Integrating these datasets provides a holistic view of cellular responses and metabolic states. For example, proteomic profiles can reflect cellular responses to genomic and environmental changes, and integrating these with metabolomic data can reveal novel biological insights and potential clinical applications (Zhang and Kuster, 2019). Moreover, metabolomics-centric approaches have been highlighted for their potential to combine metabolomics data with other omics layers, providing a global depiction of complex biological relationships (Wörheide et al., 2021). Tools like XCMS Online facilitate the integration of metabolomic data with transcriptomic and proteomic data, superimposing raw data onto metabolic pathways for comprehensive analysis (Huan et al., 2017).

2.3 Epigenomics integration

Epigenomics integration involves combining data on epigenetic modifications, such as DNA methylation and histone modifications, with other omics layers to understand their impact on gene expression and cellular function. Epigenetic changes can regulate gene activity without altering the DNA sequence, and their integration with genomics, transcriptomics, and proteomics data can elucidate mechanisms of gene regulation and disease progression. For instance, integrating epigenomic data with proteomic and transcriptomic data has been shown to provide insights into the regulatory effects of epigenetic modifications on protein expression and cellular functions. Systems genomics approaches have been employed to integrate epigenomic data with other omics layers, enhancing our understanding of complex traits and diseases in animal production and health (Suravajhala et al., 2016).

3 Computational Tools and Data Analysis for Multi-Omics Integration

3.1 Network construction and regulatory analysis

Network construction and regulatory analysis are pivotal in understanding the complex interactions within biological systems. Multi-omics data integration often involves constructing networks that represent relationships between various biological entities, such as genes, proteins, and metabolites. One approach to this is the use of heterogeneous multi-layered networks (HMLNs), which can integrate diverse biological data to represent the hierarchy and interactions within a biological system. HMLNs have been successful in inferring novel biological relations and understanding the environmental impact on organisms (Lee et al., 2020). Tools like KiMONo have been developed to handle missing data in multi-omics studies, allowing for robust network inference even when data is incomplete (Henao et al., 2023). These network-based approaches are essential for identifying key nodes and subnetworks that drive physiological and pathological mechanisms.

3.2 Application of machine learning in multi-omics analysis

Machine learning has become an indispensable tool in the analysis of multi-omics data. It offers novel techniques to integrate and analyze various omics data, enabling the discovery of new biomarkers and aiding in disease prediction, patient stratification, and precision medicine (Reel et al., 2021). Different machine learning methods, such as Bayesian models, tree-based methods, kernel methods, and deep neural networks, have been employed to handle the complexity and heterogeneity of multi-omics data. These methods can transform and map omics data into new representations, facilitating downstream analysis and improving the understanding of biological systems.

In oncology, machine learning methodologies have been crucial for patient phenotyping, biomarker discovery, and drug repurposing, demonstrating the potential of multi-omics data to drive precision medicine (Nicora et al., 2020).

3.3 Big data processing and visualization

The integration of multi-omics data generates large, multidimensional datasets that require advanced computational tools for processing and visualization. High-throughput omic approaches can produce tera- to peta-byte sized data files, posing significant challenges in data cleaning, normalization, and storage (Misra et al., 2019). Effective data integration strategies, such as early, mixed, intermediate, late, and hierarchical integration, are essential for managing these large datasets and extracting meaningful insights. Visualization tools and portals are also critical for interpreting multi-omics data, allowing researchers to explore complex biological processes and interactions. The development of standardized analytical pipelines and visualization frameworks is necessary to handle the increasing volume and complexity of multi-omics data, ultimately leading to a holistic understanding of biological systems (Joshi et al., 2020).

4 Applications of Multi-Omics Integration in Personalized Medicine

4.1 Multi-omics in cancer personalized treatment

4.1.1 Integrating genomic and transcriptomic data for cancer therapy

The integration of genomic and transcriptomic data has significantly advanced the field of cancer therapy by enabling a deeper understanding of tumor biology and heterogeneity. By combining these data types, researchers can identify driver mutations and their downstream effects on gene expression, which is crucial for developing targeted therapies. For instance, multi-omics approaches have been used to classify tumors more accurately, predict patient prognosis, and identify novel therapeutic targets (Figure 1) (Zhao et al., 2020; Menyhárt and Győrffy, 2021; Vlachavas et al., 2021). These integrated analyses help in understanding the complex molecular mechanisms underlying cancer, thereby facilitating the development of personalized treatment strategies.

4.1.2 Role of proteomics in identifying cancer biomarkers

Proteomics plays a pivotal role in the identification of cancer biomarkers, which are essential for early diagnosis, prognosis, and treatment monitoring. The integration of proteomic data with other omics layers, such as genomics and transcriptomics, enhances the sensitivity and specificity of biomarker discovery. Recent studies have shown that proteomics can reveal protein expression patterns and post-translational modifications that are not detectable at the genomic or transcriptomic levels (Hristova and Chan, 2019; Ivanisevic and Sewduth, 2023). This multi-omics approach has led to the identification of several potential biomarkers that could be translated into clinical practice, although challenges remain in their validation and implementation.

4.1.3 Metabolomics for understanding cancer metabolism

Metabolomics provides insights into the metabolic alterations associated with cancer, which are critical for understanding tumor biology and developing metabolic-targeted therapies. By integrating metabolomic data with genomic, transcriptomic, and proteomic information, researchers can map out the metabolic pathways that are dysregulated in cancer. This comprehensive view helps in identifying metabolic vulnerabilities that can be targeted for therapy. For example, metabolomics has been used to study the Warburg effect and other metabolic reprogramming events in cancer cells, offering new avenues for therapeutic intervention (Raufaste-Cazavieille et al., 2022).

4.2 Cardiovascular disease risk assessment

Multi-omics integration is also being applied to assess the risk of cardiovascular diseases (CVD). By combining genomic, transcriptomic, proteomic, and metabolomic data, researchers can identify biomarkers and molecular pathways associated with CVD risk. This holistic approach allows for a more accurate prediction of disease risk and the development of personalized prevention and treatment strategies. Studies have shown that multi-omics data can reveal novel biomarkers that are not detectable by single-omics approaches, thereby improving the precision of CVD risk assessment (Olivier et al., 2019).

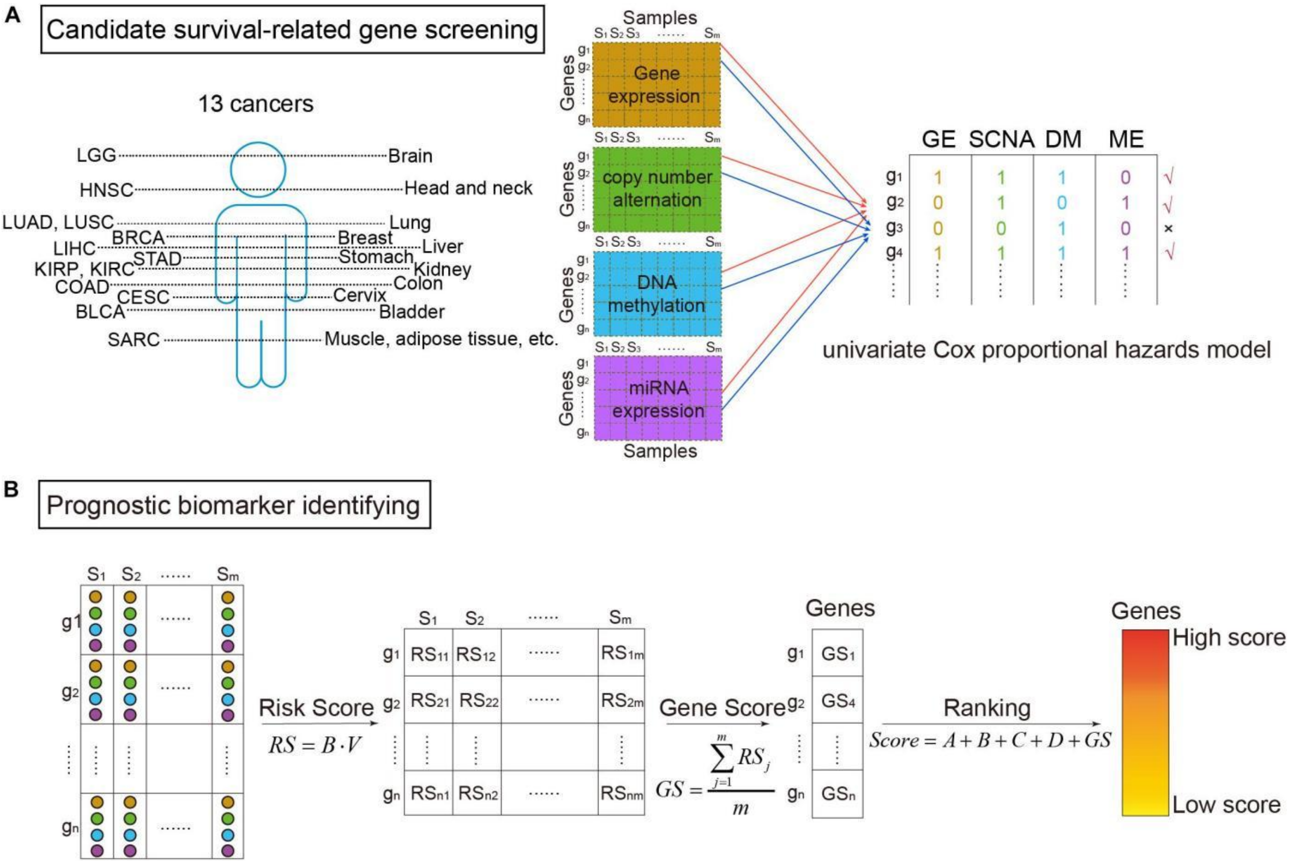

Figure 1 The workflow of survival-related genes identification (Adopted from Zhao et al., 2020)

Image caption: (A) Candidate survival-related gene screening. (B) Prognostic biomarker identifying (Adopted from Zhao et al., 2020)

4.3 Drug metabolism and toxicity prediction

The integration of multi-omics data is crucial for predicting drug metabolism and toxicity, which are key factors in the development of safe and effective therapies. By combining genomic, transcriptomic, proteomic, and metabolomic data, researchers can gain a comprehensive understanding of the molecular mechanisms underlying drug response and adverse effects. This approach helps in identifying biomarkers for drug metabolism and toxicity, which can be used to tailor treatments to individual patients, thereby minimizing adverse effects and improving therapeutic outcomes. For instance, machine learning methods applied to multi-omics data have been shown to predict drug toxicity with high accuracy, facilitating the development of safer drugs (Reel et al., 2021; Karaman and Işik, 2023; Xiang and Wu, 2024).

5 Applications of Multi-Omics Integration in Agriculture

5.1 Multi-omics in crop breeding

Multi-omics integration has revolutionized crop breeding by providing comprehensive insights into the genetic and phenotypic traits of crops. Advances in next-generation sequencing (NGS) have enabled the development of various omics technologies such as genomics, transcriptomics, proteomics, metabolomics, phenomics, and ionomics. These technologies have been instrumental in understanding the growth, senescence, yield, and responses to biotic and abiotic stresses in crops like wheat, soybean, tomato, barley, maize, millet, cotton, Medicago truncatula, and rice. The integration of functional genomics with other omics approaches has highlighted the relationships between crop genomes and phenotypes under specific physiological and environmental conditions, thereby enhancing crop breeding science (Yang et al., 2021). The integration of omics databases is crucial for selecting and developing new plant varieties with desirable traits such as increased yield, improved disease resistance, and enhanced nutritional value, which is essential for global food security (Chao et al., 2023).

5.2 Multi-omics in plant-microbe interactions

Plants interact with a diverse array of microorganisms in their environment, and these interactions can significantly influence plant health and productivity. Multi-omics approaches have been pivotal in deciphering the complex interactions between plants and their associated microbiomes (Han, 2024). By integrating genomics, transcriptomics, proteomics, and metabolomics data, researchers can gain a comprehensive understanding of the microbial diversity associated with plants and the specific gene-by-gene interactions that occur. This knowledge can be applied to promote healthy plant growth with minimal agrochemical use, enhance nutrient acquisition, and improve stress resilience. The integration of host and microbial omics datasets has led to improved models of crop microbial community structure and function, which are crucial for sustainable agriculture (Kimotho and Maina, 2023; Kumar et al., 2023).

5.3 Multi-omics in food quality and safety

The application of multi-omics technologies extends beyond crop breeding and plant-microbe interactions to include food quality and safety. High-throughput omics approaches such as genomics, proteomics, and metabolomics provide detailed insights into the molecular composition of food products, enabling the identification of key factors that influence food quality and safety. For instance, the integration of omics data can help in understanding the metabolic pathways and functional gene patterns that contribute to the nutritional value and safety of food crops. This holistic approach ensures the development of nutrient-sufficient and safe food products that can meet the growing global demand (Pazhamala et al., 2021; Dikobe et al., 2023).

6 Case Studies: Multi-Omics Integration Across Different Fields

6.1 Multi-omics integration in cancer research

Multi-omics integration has revolutionized cancer research by providing a comprehensive understanding of the molecular complexity and heterogeneity of tumors. The integration of genomics, transcriptomics, proteomics, and metabolomics has enabled the classification of cancers beyond traditional histopathological methods, leading to the identification of novel biomarkers and therapeutic targets. For instance, multi-omics approaches have facilitated the pan-cancer molecular classification, which offers new therapeutic opportunities for precision medicine (Raufaste-Cazavieille et al., 2022). Tools like IOBR have been developed to decode the tumor microenvironment and signatures, enhancing our understanding of oncogenesis and immunotherapeutic sensitivity (Zeng et al., 2020). These advancements underscore the potential of multi-omics integration in improving cancer diagnosis, prognosis, and treatment.

6.2 Multi-omics in metabolic disorder research

In the realm of metabolic disorders, multi-omics integration has provided significant insights into the complex biochemical and physiological interactions underlying these conditions. For example, genome-scale metabolic modeling has been used to identify metabolic footprints of diseases and guide the design of personalized treatments. A notable finding from multi-omics studies is the identification of increased plasma mannose levels as a potential biomarker of early insulin resistance, highlighting the utility of these approaches in metabolic disorder research (Figure 2) (Son et al., 2020). Furthermore, the integration of various omics data, including genomics, transcriptomics, and metabolomics, has been instrumental in understanding the molecular underpinnings of metabolic disorders and developing targeted therapeutic strategies (Pinu et al., 2019; Wörheide et al., 2021).

6.3 Microbiome and host interactions

The interplay between the microbiome and host physiology is a burgeoning area of research that has greatly benefited from multi-omics integration. The holo-omic approach, which combines multi-omic data from both hosts and microbes, has been pivotal in untangling the bidirectional interactions between the two. This approach has applications across various fields, including biomedicine, biotechnology, and ecology, and has the potential to open new research avenues and discoveries (Nyholm et al., 2020). Multi-omics strategies have been employed to uncover host-pathogen interactions, providing insights into the genetic, immunologic, and metabolic mechanisms underlying infection and immune response (Khan et al., 2019). These studies underscore the importance of multi-omics integration in advancing our understanding of microbiome-host interactions and their implications for health and disease.

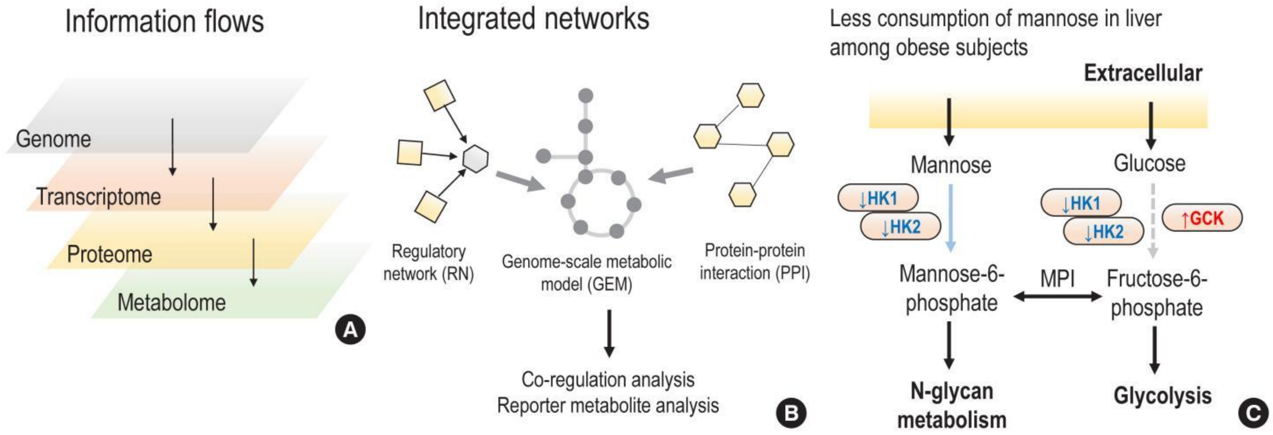

Figure 2 Multi-omics integration approaches (Adopted from Son et al., 2020)

Image caption: (A) Based on the central dogma, information flows could affect different omics from the upstream level (the genome) to the downstream level (the metabolome). (B) Integrating different biological networks into genome scale metabolic models, and explaining changes in metabolomics through studying integrated networks and multi-omics datasets. (C) Based on a co-regulation analysis of integrated networks, and together with a reporter metabolite analysis, less consumption of mannose in liver tissue was identified among obese subjects (Adopted from Son et al., 2020)

7 Technical Challenges of Multi-Omics Integration

7.1 Data standardization and integration difficulty

The integration of multi-omics data is fraught with challenges, primarily due to the vast differences in data types and nomenclature across various omics platforms such as genomics, transcriptomics, proteomics, and metabolomics. Each of these platforms generates large datasets that require extensive data cleaning, normalization, and biomolecule identification before they can be integrated into a cohesive biological context. The lack of standardized analytical pipelines further complicates this process, making it difficult to achieve a holistic systems biology understanding (Pinu et al., 2019). The differences in data dimensionality and the need for biological contextualization and statistical validation add layers of complexity to the integration process (Misra et al., 2019).

7.2 Computational demand and storage bottlenecks

The sheer volume of data generated by high-throughput omics technologies poses significant computational and storage challenges. Each omics analysis can produce tera- to peta-byte sized data files, necessitating robust computational frameworks and substantial storage capacities to handle and process these datasets efficiently (Miao et al., 2021). The computational demand is further exacerbated by the need for sophisticated algorithms capable of integrating and analyzing high-dimensional, heterogeneous data. Techniques such as deep learning and network-based methods have shown promise in addressing these challenges, but they also require considerable computational resources (Lee et al., 2020).

7.3 Challenges in integrating heterogeneous data

Integrating heterogeneous data from different omics platforms is another major challenge. The complexity, heterogeneity, and high-dimensionality of omics data make it difficult to develop universal integration strategies. Different omics data types often have varying levels of completeness, with missing data being a common issue due to experimental limitations or cost constraints (Flores et al., 2023; Henao et al., 2023). Moreover, the integration of matched (measured on the same cell) and unmatched (measured on different cells) data requires different strategies, each with its own set of computational and biological challenges. The development of methods that can handle these diverse data types and provide biologically interpretable results is crucial for advancing multi-omics integration (Nicora et al., 2020).

8 Future Directions in Multi-Omics Integration

8.1 Real-time multi-omics integration

Real-time multi-omics integration represents a significant advancement in systems biology, enabling the dynamic monitoring and analysis of biological processes as they occur. This approach leverages high-throughput sequencing technologies and bioinformatics tools to provide immediate insights into the interactions between various biomolecules. For instance, genome-resolved metagenomic approaches have been successfully applied in water engineering to link microbial community dynamics with system performance in real-time, facilitating more sustainable bioprocesses (McDaniel et al., 2021). The integration of real-time data from genomics, transcriptomics, proteomics, and metabolomics can enhance our understanding of complex biological systems and improve predictive models for various applications, including disease management and environmental monitoring.

8.2 AI and multi-omics integration

Artificial intelligence (AI) and machine learning (ML) are poised to revolutionize multi-omics integration by providing robust analytical frameworks capable of handling the complexity and volume of omics data. AI techniques can effectively interpret multi-omics data, offering meaningful predictions and insights that traditional methods may miss. In horticultural research, for example, the integration of multi-omics data with AI has shown promise in advancing plant phenotyping, predictive breeding, and sustainable crop management (Cembrowska-Lech et al., 2023). The use of AI in multi-omics integration can also facilitate the identification of biomarkers, disease subtyping, and the development of personalized medicine approaches (Abdullah-Zawawi et al., 2022). As computational tools and high-performance computing resources continue to evolve, the potential for AI-driven multi-omics integration will expand, offering new opportunities for scientific discovery and innovation.

8.3 Multi-omics applications in ecology and environmental research

The application of multi-omics technologies in ecology and environmental research is rapidly growing, providing comprehensive insights into the interactions between organisms and their environments. Multi-omics approaches have been employed to study microbial communities in various environmental settings, such as water engineering systems, where they have helped link microbial dynamics to process parameters and system performance. In plant systems, multi-omics integration has been used to understand the responses of crops to biotic and abiotic stresses, aiding in crop improvement and sustainable agriculture (Jamil et al., 2020; Yang et al., 2021). These technologies enable researchers to dissect complex ecological interactions and develop strategies for environmental conservation and resource management. The continued development and application of multi-omics in ecology and environmental research will enhance our ability to address global challenges related to biodiversity, climate change, and ecosystem health (Veenstra, 2020).

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Conflict of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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