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MINI REVIEW

Multiomics: Concepts, Methods and Applications

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ABSTRACT

Multiomics is a high-throughput technology with multilayered system biology approach incorporating bioinformatic analysis of the data. At present it includes genomics, epigenomics, transcriptomics, proteomics, metabolomics, and gut microbiomics with advancement to the level of single cell analysis. Multiomics is an advancing approach (1) to understand the pathobiology of disease, (2) to identify sensitive biomarkers for the diagnosis of diseases as well as in monitoring and (3) to identify disease specific targets to treat the patient in the context of precision medicine as targeted therapeutics. In the present review, a brief account of various multiomic techniques is considered and relevant examples are pondered to reflect their applications in both preclinical and clinical translational research.

Keywords: Multiomics; Genomics; Proteomics; Metabolomics; Pathobiology

Multiomics comprises several multilayered system biology techniques thereby enabling high throughput screening thus providing better insight into the pathobiology of human disease states. Examples of these are genomics, transcriptomics, single cell-transcriptomics, proteomics, metabolomics and spatial multiomics, epigenomics, and microbiomics[1–6]. The analysis components of these techniques have made significant progress in recent years including machine learning and artificial intelligence[7–12].

Genomics is system biology of whole genome comprising high of high-throughput DNA sequencing, sequence assembly, and genome annotation. Human genome project is an example for this[12]. Genome-wide association study (GWAS) is a typical application of genomics to find out the existing sequence variation in the whole human genome, namely, single nucleotide polymorphism (SNP)[13,14]. Transcriptomics comprises the studies on the expression of RNAs and reflects dynamic changes during the pathobiology of initiation and progression of disease and response to therapeutic strategies[15–18]. In these, protein-coding RNAs (mRNAs), long noncoding RNAs, short noncoding RNAs (microRNAs, small-interfering RNAs, small nuclear RNAs, piwi-interacting RNAs, and enhancer RNAs), and circular RNAs are studied[2]. Although RNA-seq, is usually used for quantifying RNA transcripts, the single-cell transcriptome (single-cell RNA sequencing [scRNA-seq]) is increasingly used to the role of different cells in causing organ injury in disease states[16,19]. In epigenomics, reversible modifications of DNA methylation and or histone modifications comprising methylation, phosphorylation and acetylation are studied[20–23].

Proteomics has been used to identify and study the role of specific proteins in normal and diseasesd states. Although earlier studies have commonly used two-dimensional gel electrophoresis, recent studies have advanced with advent of mass spectrometry with table isotope labeling proteomics and label-free proteomics[24–28]. In addition, additional techniques to identify post translational modification of proteins such as phosphorylation, acetylation, methylation and palmitoylation enabled studies on regulatory mechanisms of different proteins and changes in the levels of these post translationally modified proteins for the diagnosis and therapeutic monitoring of diseases especially different types

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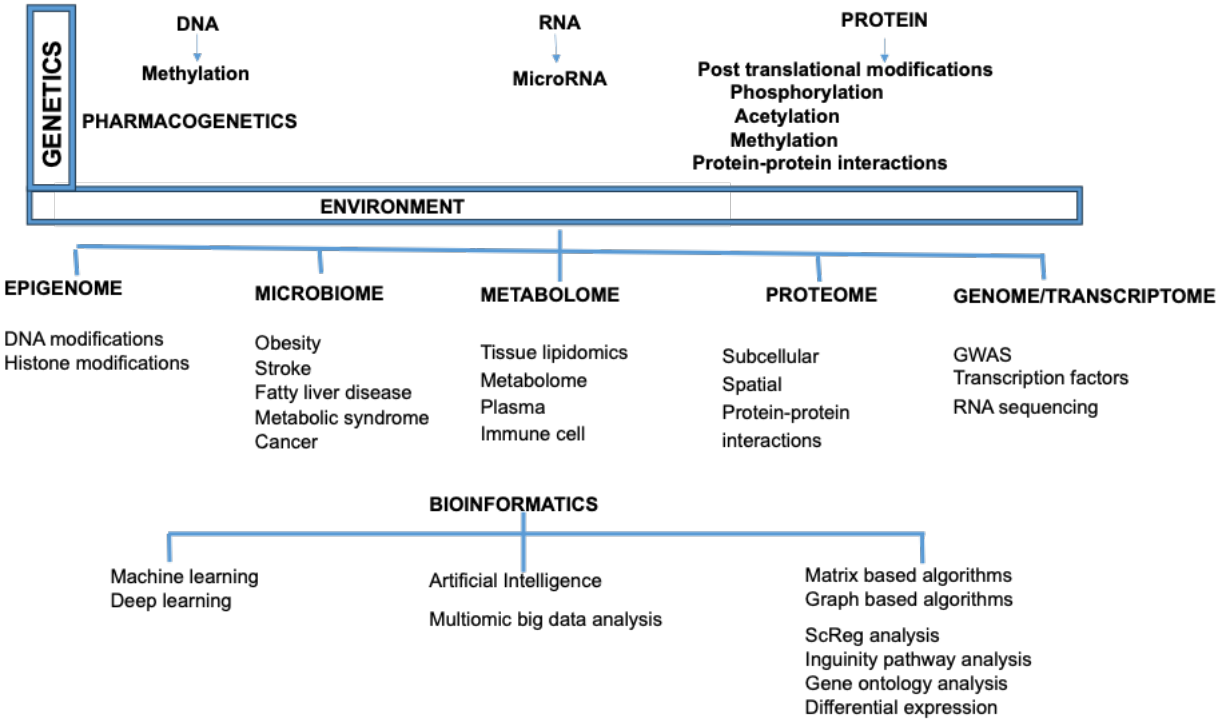

Fig. 1: Summary of different types of multiomics

of cancer[29,30].

Further studies on subcellular proteomics helps to reveal pathobiology of different subcellular components in disease states. Moreover, using antibody for isolated specific proteins in complex with other proteins by immunoprecipitation enables study of protein-protein interactions[31,32].

In metabolomics, a set of small molecule metabolites form different sources including different tissues, circulating immune cells, plasma and urine[33–37]. They comprise both targeted and non-targeted metabolites. These molecules comprise metabolites that pre produced during the intermediary metabolism including metabolism of carbohydrates, proteins and lipids. Those are also useful to understand biochemistry in the context of other multiomics such as genomics, transcriptomics and proteomics. In this regard, the Human Metabolome Database (https://hmdb.ca/) is a free database containing detailed information of small molecule metabolites in the human body and MetaboAnalyst 5.0 (https://www.metaboanalyst.ca/, a free platform for metabolomics analysis) is now available. Nuclear magnetic resonance (NMR), mass spectrometry (MS)-based methods gas chromatograph–mass spectrometer (GC-MS), liquid chromatography tandem mass spectrometry(LC-MS), and capillary electrophoresis–mass spectrometry (CE-MS) are some of the techniques available for metabolomics study[37–41].

Recent advances in the isolation techniques made significant progress in multiomics that are helpful to understand the pathobiology of specific cell types in the context of single cell genomics, single cell transcriptomics and single cell proteomics. Some of the platforms that are available for single cell analysis are 10×Chromium Single Cell Gene Expression Solution and BD Rhapsody™ Single-Cell Analysis System[42–46].

Spatial transcriptomics and proteomics in which spatial location of tissues are being used in tissue sections. The techniques such as next-generation sequencing (NGS)-based techniques, and imaging-based methods of *in situ* sequencing, and *in situ* hybridization (ISH)-based methods, are used. Spatial omics techniques combined with proteomics will be more useful to understand role and regulation of specific proteins[15,47–51].

Microbiomics is to study the composition of gut microbial flora comprising both microorganisms that symbiotically exist or pathologically live. Therefore, studying the gut microbiome has been utilized to understand the mechanisms and mediators that cause systemic effects of pathological gut flora. The technique is 16S rRNA gene sequencing that is most commonly employed[52–56]. Different types of multiomics are summarized in Figure 1 .

Bioinformatics Network analysis is a set of tools available to analyze the data obtained by multiomics. Examples include G & T seq, DR-seq for Genome-transcriptome

and PEA/STA for transcriptome-proteome[8,9,57–62]. Several open-source tools are available to analyze the data obtained by multiomics studies. Examples are omicsAnalyst for Transcriptomics, proteomics, metabolomics and microbiome and OmicsNet 2.0 for genomics, transcriptomics, metabolomics, microbiome. Examples of bioinformatics analysis include correlation network analysis, cluster het heat map analysis, web based multioomic analysis platform that supports 2D and 3D network visualization exploration, Ingenuity Pathway Analysis (IPA), Gene Ontology (GO) analysis, Differential expression analysis, matrix-based algorithms. In addition, bioinformatics analysis also includes use of artificial intelligence, multiomic big data analysis, machine learning and deep learning.

REFERENCES

1. Wei S, Tang W, Chen D, Xiong J, Xue L, Dai Y. Multiomics insights into the female reproductive aging. *Ageing Res Rev*. 2024;95(102245). Available from: https://doi.org/10.1016/j.arr.2024.102245.
2. Chen C, Wang J, Pan D, Wang X, Xu Y, Yan J. Applications of multi-omics analysis in human diseases. *MedComm*. 1931;4(4):e315. Available from: https://doi.org/10.1002/mco2.315.
3. MoTrPAC Study Group; Lead Analysts; MoTrPAC Study Group . Temporal dynamics of the multiomic response to endurance exercise training. *Nature*. 2024;629(8010):174–183. Available from: https://doi.org/10.1038/s41586-023-06877-w.
4. Liang G, Cao W, Tang D, Zhang H, Yu Y, Ding J, et al. NanomedomicsClick to copy article link. *ACS Nano*. 2024;18(17):10979–11024. Available from: https://doi.org/10.1021/acsnano.3c11154.
5. Lopez-Lee C, Torres E, Carling G, Gan L. Mechanisms of sex differences in Alzheimer's disease. *Neuron*. 2024;112(8):1208–1221. Available from: https://doi.org/10.1016/j.neuron.2024.01.024.
6. Mackowiak B, Fu Y, Maccioni L, Gao B. Alcohol-associated liver disease. *J Clin Invest*. 2024;134(3):e176345. Available from: https://doi.org/10.1172/jci176345.
7. Yan C, Bao J, J J. Exploring the interplay of gut microbiota, inflammation, and LDL-cholesterol: a multiomics Mendelian randomization analysis of their causal relationship in acute pancreatitis and non-alcoholic fatty liver disease. *J Transl Med*. 2024;22(1):179–179. Available from: https://doi.org/10.1186/s12967-024-04996-0.
8. Cui H, Wang C, Maan H, Pang K, Luo F, Duan N. scGPT: toward building a foundation model for single-cell multi-omics using generative AI. *Nat Methods*. 2024;21(8):1470–1480. Available from: https://doi.org/10.1038/s41592-024-02201-0.
9. Ewald JD, Zhou G, Lu Y, Kolic J, Ellis C, Johnson JD, et al. Web-based multi-omics integration using the Analyst software suite. *Nature Protocol*. 2024;19(5):1467–1497. Available from: https://doi.org/10.1038/s41596-023-00950-4.
10. Roehrig A, Hirsch TZ, Pire A, Morcrette G, Gupta B, Marcaillou C, et al. Single-cell multiomics reveals the interplay of clonal evolution and cellular plasticity in hepatoblastoma. *Nature Communications*. 2024;15(1):3031. Available from: https://doi.org/10.1038/s41467-024-47280-x.
11. Wang C, Qiu J, Liu M, Wang Y, Yu Y, Liu H, et al. Microfluidic Biochips for Single-Cell Isolation and Single-Cell Analysis of Multiomics andExosomes. *Adv Sci (Weinh)*. 2024;11(28):e2401263. Available from: https://doi.org/10.1002/advs.202401263.
12. Lim J, Park C, Kim M, Kim H, Kim J, Lee DS. Advances in single-cell omics and multiomics for high-resolution molecular profiling. *Exp Mol Med*. 2024;56(3):515–526. Available from: https://doi.org/10.1038/s12276-024-01186-2.
13. Madden EB, Hindorff LA, Bonham VL, Akintobi TH, Burchard EG, Baker KE, et al. Advancing genomics to improve health equity. *Nat Genet*. 2024;56(5):752–757. Available from: https://doi.org/10.1038/s41588-024-01711-z.
14. Scarano C, Veneruso I, Simone RRD, Bonito GD, Secondino A, D'Argenio V. The Third-Generation Sequencing Challenge: Novel Insights for the Omic Sciences. *Biomolecules*. 2024;14(5):568. Available from: https://doi.org/10.3390/biom14050568.
15. Jain S, Eadon MT. Spatial transcriptomics in health and disease. *Nat Rev Nephrol*. 2024;20(10):659–671. Available from: https://doi.org/10.1038/s41581-024-00841-1.
16. Zhang T, Zhao F, Lin Y, Liu M, Zhou H, Cui F, et al. Integrated analysis of single-cell and bulk transcriptomics develops a robust neuroendocrine cell-intrinsic signature to predict prostate cancer progression. *Theranostics*. 2024;14(3):1065–1080. Available from: https://doi.org/10.7150/thno.92336.
17. Cilento MA, Sweeney CJ, Butler LM. Spatial transcriptomics in cancer research and potential clinical impact: a narrative review. *J Cancer Res Clin Oncol*. 2024;150(6):296. Available from: https://doi.org/10.1007/s00432-024-05816-0.
18. Li H, Li D, Ledru N, Xuanyuan Q, Wu H, Asthana A, et al. Transcriptomic, epigenomic, and spatial metabolomic cell profiling redefines regional human kidney anatomy. *Cell Metab*. 2024;36(5):1105–1125. Available from: https://doi.org/10.1016/j.cmet.2024.02.015.
19. Armingol E, Baghdassarian HM, Lewis NE. The diversification of methods for studying cell-cell interactions and communication. *Nat Rev Genet*. 2024;25(6):381–400. Available from: https://doi.org/10.1038/s41576-023-00685-8.
20. Mathur R, Wang Q, Schupp PG, Nikolic A, Hilz S, Hong C, et al. Glioblastoma evolution and heterogeneity from a 3D whole-tumor perspective. *Cell*. 2024;187(2):446–463. Available from: https://doi.org/10.1016/j.cell.2023.12.013.
21. Villiger L, Joung J, Koblan L, Weissman J, Abudayyeh OO, Gootenberg JS. CRISPR technologies for genome, epigenome and transcriptome editing. *Nat Rev Mol Cell Biol*. 2024;25(6):464–487. Available from: https://doi.org/10.1038/s41580-023-00697-6.
22. Kiri S, Ryba T. Cancer, metastasis, and the epigenome. *Mol Cancer*. 2024;23(1):154. Available from: https://doi.org/10.1186/s12943-024-02069-w.
23. Wu Z, Qu J, Zhang W, Liu GH. Stress, epigenetics, and aging: Unraveling the intricate crosstalk. *Molecular Cell*. 2024;84(1):34–54. Available from: https://dx.doi.org/10.1016/j.molcel.2023.10.006.
24. Pietzner M, Uluvar B, Kolnes KJ, Jeppesen PB, Frivold SV, Skattebo Ø, et al. Systemic proteome adaptions to 7-day complete caloric restriction in humans. *Nature Metabolism*. 2024;6(4):764–777. Available from: https://dx.doi.org/10.1038/s42255-024-01008-9.
25. Tholey A, Schlüter H. Top-down proteomics and proteoforms - special issue. *Proteomics*. 2024;24(3-4):2200375. Available from: https://doi.org/10.1002/pmic.202200375.
26. Shen L, Zhang Z, Wu P, Yang J, Cai Y, Chen K, et al. Mechanistic insight into glioma through spatially multidimensional proteomics. *Science Advances*. 2024;10(7):1721. Available from: https://dx.doi.org/10.1126/sciadv.adk1721.
27. Strauss MT, Bludau I, Zeng WFF, Voytik E, Ammar C, Schessner JP, et al. AlphaPept, a modern and open framework for MS-based proteomics. *Nat Commun*. 2009;15(1):2168. Available from: https://doi.org/10.1038/s41467-024-46485-4.
28. Fedorov II, Protasov SA, Tarasova IA, Gorshkov MV. Ultrafast Proteomics. *Biochemistry (Moscow)*. 2024;89(8):1349–1361. Available from: https://dx.doi.org/10.1134/s0006297924080017.
29. Tao J, Li J, Fan X, Jiang C, Wang Y, Qin M, et al. Unraveling the protein post-translational modification landscape: Neuroinflammation and neuronal death after stroke. *Ageing Research Reviews*. 2024;101:102489. Available from: https://dx.doi.org/10.1016/j.arr.2024.102489.
30. Zhang N, Wu J, Zheng Q. Chemical proteomics approaches for protein post-translational modification studies. *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics*. 2024;1872(4):141017. Available from: https://dx.doi.org/10.1016/j.bbapap.2024.141017.
31. Greenblatt JF, Alberts BM, Krogan NJ. Discovery and significance of protein-protein interactions in health and disease. *Cell*. 2024;187(23):6501–6517. Available from: https://dx.doi.org/10.1016/

j.cell.2024.10.038.
32. Si S, Liu H, Xu L, Zhan S. Identification of novel therapeutic targets for chronic kidney disease and kidney function by integrating multi-omics proteome with transcriptome. *Genome Medicine*. 2024;16(1):84. Available from: https://dx.doi.org/10.1186/s13073-024-01356-x.
33. Zhang S, Wang Z, Wang Y, Zhu Y, Zhou Q, Jian X, et al. A metabolomic profile of biological aging in 250,341 individuals from the UK Biobank. *Nat Commun*. 2024;15(1):8081. Available from: https://doi.org/10.1038/s41467-024-52310-9.
34. Luo YQ, Zhang CY, Nong XZ, Gao Y, Wang L, Ji G, et al. Metabolomics incirrhosis: Recent advances and opportunities. *Clin Chim Acta*. 2024;557:117886. Available from: https://doi.org/10.1016/j.cca.2024.117886.
35. Yang S, Liu R, Xin Z, Zhu Z, Chu J, Zhong P, et al. Plasma Metabolomics Identifies Key Metabolites and Improves Prediction of Diabetic Retinopathy: Development and Validation across Multinational Cohorts. *Ophthalmology*. 2024;131(12):1436–1446. Available from: https://doi.org/10.1016/j.ophtha.2024.07.004.
36. Berrell N, Sadeghirad H, Blick T, Bidgood C, Leggatt GR, O'Byrne K, et al. Metabolomics at the tumor microenvironment interface: Decoding cellular conversations. *Med Res Rev*. 2024;44(3):1121–1146. Available from: https://doi.org/10.1002/med.22010.
37. Vicari M, Mirzazadeh R, Nilsson A, Shariatgorji R, Bjärterot P, Larsson L, et al. Spatial multimodal analysis of transcriptomes and metabolomes in tissues. *Nat Biotechnol*. 2024;42(7):1046–1050. Available from: https://doi.org/10.1038/s41587-023-01937-y.
38. Johnson CH, Ivanisevic J, Siuzdak G. Metabolomics: beyond biomarkers and towards mechanisms. *Nat Rev Mol Cell Biol*. 2016;17(7):451–459. Available from: https://doi.org/10.1038/nrm.2016.25.
39. Wang R, Li B, Lam SM, Shui G. Integration of lipidomics and metabolomics for in-depth understanding of cellular mechanism and disease progression. *J Genet Genomics*. 2020;47(2):69–83. Available from: https://doi.org/10.1016/j.jgg.2019.11.009.
40. Bujak R, Struck-Lewicka W, Markuszewski MJ, Kaliszan R. Metabolomics for laboratory diagnostics. *J Pharm Biomed Anal*. 2015;113:108–120. Available from: https://doi.org/10.1016/j.jpba.2014.12.017.
41. Khamis MM, Adamko DJ, El-Aneed A. Mass spectrometric based approaches in urine metabolomics and biomarker discovery. *Mass Spectrom Rev*. 2017;36(2):115–134. Available from: https://doi.org/10.1002/mas.21455.
42. Papalexi E, Satija R. Single-cell RNA sequencing to explore immune cell heterogeneity. *Nat Rev Immunol*. 2018;18(1):35–45. Available from: https://doi.org/10.1038/nri.2017.76.
43. Han X, Zhou Z, Fei L, Sun H, Wang R, Chen Y, et al. Construction of a human cell landscape at single-cell level. *Nature*. 2020;581(7808):303–309. Available from: https://doi.org/10.1038/s41586-020-2157-4.
44. Collin J, Queen R, Zerti D, Bojic S, Dorgau B, Moyse N, et al. A single cell atlas of human cornea that defines its development, limbal progenitor cells and their interactions with the immune cells. *Ocul Surf*. 2021;21:279–298. Available from: https://doi.org/10.1016/j.jtos.2021.03.010.
45. Ferchen K, Song B, Grimes L, H. A primer on single-cell genomics in myeloid biology. *Curr Opin Hematol*. 2021;28(1):11–17. Available from: https://doi.org/10.1097/MOH.0000000000000623.
46. Chang JG, Tu SJ, Huang CM, Chen YC, Chiang HS, Lee YT, et al. Single-cell RNA sequencing of immune cells in patients with acute gout. *Sci Rep*. 2022;12:22130. Available from: https://doi.org/10.1038/s41598-022-25871-2.
47. Shiao SL, Gouin KH, Ing N, Ho A, Basho R, Shah A, et al. Single-cell and spatial profiling identify three response trajectories to pembrolizumab and radiation therapy in triple negative breast cancer. *Cancer Cell*. 2024;42(1):70–84. Available from: https://doi.org/10.1016/j.ccell.2023.12.012.
48. Bandyopadhyay S, Duffy MP, Ahn KJ, Sussman JH, Pang M, Smith D, et al. Mapping th cellular biogeography of human bone marrow niches using single-cell transcriptomics and proteomic imaging. *Cell*. 2024;187(12):3120–3140. Available from: https://doi.org/10.1016/j.cell.2024.04.013.
49. Hu J, Wang SG, Hou Y, Chen Z, Liu L, Li R, et al. Multiomic profiling of clear cell renal cell carcinoma identifies metabolic reprogramming associated with disease progression. *Nat Genet*. 2024;56(3):442–457. Available from: https://doi.org/10.1038/s41588-024-01662-5.
50. Desai TA, Åsa K Hedman, Dimitriou M, Koprulu M, Figiel S, Yin W, et al. Identifying proteomic risk factors for overall, aggressive, and early onset prostate cancer using Mendelian Randomisation and tumour spatial transcriptomics. *eBioMedicine*. 2024;105:105168. Available from: https://dx.doi.org/10.1016/j.ebiom.2024.105168.
51. Patel AG, Ashenberg O, Collins NB, Åsa Segerstolpe, Jiang S, Slyper M, et al. A spatial cell atlas of neuroblastoma reveals developmental, epigenetic and spatial axis of tumor heterogeneity. *bioRxiv*. 2024. Available from: https://doi.org/10.1101/2024.01.07.574538.
52. Sul WJ. Host-Associated Microbiome. *J Microbiol*. 2024;62(3):135–136. Available from: https://doi.org/10.1007/s12275-024-00135-y.
53. Ratiner K, Ciocan D, Abdeen SK, Elinav E. Utilization of the microbiome in personalized medicine. *Nat Rev Microbiol*. 2024;22(5):291–308. Available from: https://doi.org/10.1038/s41579-023-00998-9.
54. Li R, Li J, Zhou X. Lung microbiome: new insights into the pathogenesis of respiratory diseases. *Signal Transduct Target Ther*. 2024;17(1):19. Available from: https://doi.org/10.1038/s41392-023-01722-y.
55. White MT, Sears CL. The microbial landscape of colorectal cancer. *Nat Rev Microbiol*. 2024;22(4):240–254. Available from: https://doi.org/10.1038/s41579-023-00973-4.
56. Verdegaal AA, Goodman AL. Integrating the gut microbiome and pharmacology. *Sci Transl Med*. 2024;16(732):eadg8357. Available from: https://doi.org/10.1126/scitranslmed.adg8357.
57. Matsuoka T, Yashiro M. Bioinformatics Analysis and Validation of Potential Markers Associated with Prediction and Prognosis of Gastric Cancer. *Int J Mol Sci*. 2024;25(11):5880. Available from: https://doi.org/10.3390/ijms25115880.
58. Li C, Lin X, Lin Q, Lin Y, Lin H. Jiangu granules ameliorate postmenopausal osteoporosis via rectifying bone homeostasis imbalance: A network pharmacology analysis based on multi-omics validation. *Phytomedicine*. 2024;122:155137.
59. Yang S, Wei Z, Luo J, Wang X, Chen G, Guan X, et al. Integrated bioinformatics and multiomics reveal Liupao tea extract alleviatin NAFLD via regulating hepatic lipid metabolism and gut microbiota. *Phytomedicine*. 2024;132:155834. Available from: https://doi.org/10.1016/j.phymed.2024.155834.
60. Gu Y, Li Z, Li H, Yi X, Liu X, Zhang Y, et al. Exploring the efficacious constituents and underlying mechanisms of sini decoction for sepsis treatment through network pharmacology and multi-omics. *Phytomedicine*. 2024;123:155212. Available from: https://doi.org/10.1016/j.phymed.2023.155212.
61. Chen J, Ruan X, Sun Y, Lu S, Hu S, Yuan S. Multi-omic insight into the molecular networks of mitochondrial dysfunction in the pathogenesis of inflammatory bowel disease. *EBioMedicine*. 2024;99:104934. Available from: https://doi.org/10.1016/j.ebiom.2023.104934.
62. Daskalakis NP, Iatrou A, Chatzinakos C, Jajoo A, Snijders C, Wylie D, et al. Systems biology dissection of PTSD and MDD across brain regions, cell types, and blood. *Science*. 2024;384(6698):3707–3707. Available from: https://doi.org/10.1126/science.adh3707.