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Application of (multi-)omics approaches for advancing food allergy: an updated review

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Food allergy (FA) has become a significant food safety and public health issue, with evidence of increasing prevalence worldwide. Considering the complexity and multifactorial nature of FA, the use of high-throughput technologies, collectively called omics, would benefit the in-depth understanding of the disease etiology and clinical management. This short review provides updates of the application of omics, especially advanced and multi-omics approaches in the research of FA, including exploration of the susceptible factors, distinct adaptive immune responses, biomarkers and metabolic changes, and the role of microbiome dysbiosis. The use of (multi-)omics to identify potential therapeutic targets of FA was also discussed. With the burgeoning advances of omics sciences, a detailed and systematic framework illustrating the biological landscape of the disease is to be allowed. To develop efficacious preventive, diagnostic, and therapeutic tools of FA in the future, the integration of multi-omics data into comprehensive models is highly deserved.

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Introduction

Food allergy (FA), as defined by the National Institute of Allergy and Infectious Diseases, is a group of IgE-mediated and non-IgE-mediated "adverse immune responses that occurs reproducibly on exposure to a given food and is distinct from other adverse responses to food, such as food intolerance, pharmacologic reactions, and toxin-mediated reactions". Growing evidence has shown that the prevalence of FA keeps increasing in the past 2–3 decades, which affects approximately 8% of children and 5% of the adult population worldwide [1]. Despite significant advances in FA, the in-depth pathophysiological understanding, accurate diagnostic markers, and efficacious therapeutic options are still demanding, ascribed to the complexity and heterogeneity of allergic pathogenesis [2•].

Like most chronic diseases, the etiology of FA is associated with a multilevel combination of genomic, biological, and environmental factors, resulting in a highly verified disease development and response to the therapy. Considering the complex and multifactorial nature of FA, the potential use of high-throughput technologies, collectively called omics, would greatly benefit the research of FA by interrogating the totality of different biological molecules and their modifications. These methods include the (epi)genomics, transcriptomics, proteomics, metabolomics and microbiomics, and so on. In recent years, the use of omics has generated valuable insights into a systematic construction of the disease network and clinical management. Several reviews have discussed the application of omics sciences in FA, with a focus on the basis of each method and their respective targeted biological processes [3,4••]. In this scenario, the individual omics layer does not act in isolation, and a holistic, multiscale approach is required for a deep, mechanistic understanding of the disorders. Additionally, advanced omics such as single-cell omics measure molecules at the individual cell level, which enables a deeper understanding of the key biological processes and hidden mechanisms. With the advances of FA research, and the parallel development of cell isolation/barcoding and computational techniques, there is a need to revisit the potency of omics, especially advanced and multi-omics applications, in the field of FA from different key aspects of the disease.

In this mini-review, we aimed to provide the most updated information of omics sciences in FA from diverse aspects of the disease itself, including the etiology, diagnosis, and treatment. A specific emphasis was put on the studies using advanced and multi-omics approaches, with the purpose of fully leveraging the strength of those methods to advance FA. Last, the future trend of multi-omics data integration was introduced, and the remaining challenges at the experimental and data analysis levels were critically discussed.

Updates of (multi-)omics sciences in food allergy

An overview of each omics technology is shown in Figure 1, and their individual strengths and limitations are summarized in Table 1. For the generality of each method, readers can refer to several reviews [3–5]. We would therefore focus on the most updated application of these approaches in advancing FA from different aspects.

Omics and the development of food allergy

Genomic heterogeneity

Similar to other chronic diseases, the etiology of FA is related to genetics, environment, and genome-environment interactions (e.g. epigenetic effects) [1,6]. At the DNA level, genome-wide association studies (GWAS) enable us to identify genetic architectures in certain diseases and have been applied for the investigation of genetic variations in FA. Earlier GWAS have pointed to peanut allergy-specific loci in the human leukocyte antigen (*HLA*)-*DR*/-*DQ* region, which is part of the major histocompatibility complex locus and is involved in antigen presentation to T cells [7–9]. Later, large-scale GWAS identified several novel loci apart from the HLA region as risk factors for FA in general and peanut allergy in particular. These include the clade-B serpin (*SERPINB*) gene, a cytokine gene cluster in chromosome 5, the filaggrin gene, and the *C11orf30/LRRC32* locus, and so on [10–12]. Functional annotation implies that these located loci are involved in the immunological regulation and epidermal/epithelial barrier function, implying the role of relevant mechanisms in the etiology of FA.

Gene expression and regulation

The epigenomic studies give us valuable information about how gene-environment interactions contribute to the development of diseases. Though limited, the first retrospective epigenome-wide association study (EWAS) targeting FA unveiled differentially methylated probes in the CD4+ T cells of infants diagnosed at 12 m, and pathway analysis noticed enrichment of several genes in the mitogen-activated protein kinase signaling pathway [13]. Another two cross-sectional EWAS in children with cow's milk allergy profiled hypo-/hypermethylated probes involved in the Th1/Th2 balance and, interestingly, some novel candidates, such as butirosin and neomycin biosynthesis, and carbohydrate metabolism [14,15]. In this scenario, research into other epigenetic changes, such as those mediated by histone modifications, will be insightful to enlarge our understanding of the molecular evolution of FA.

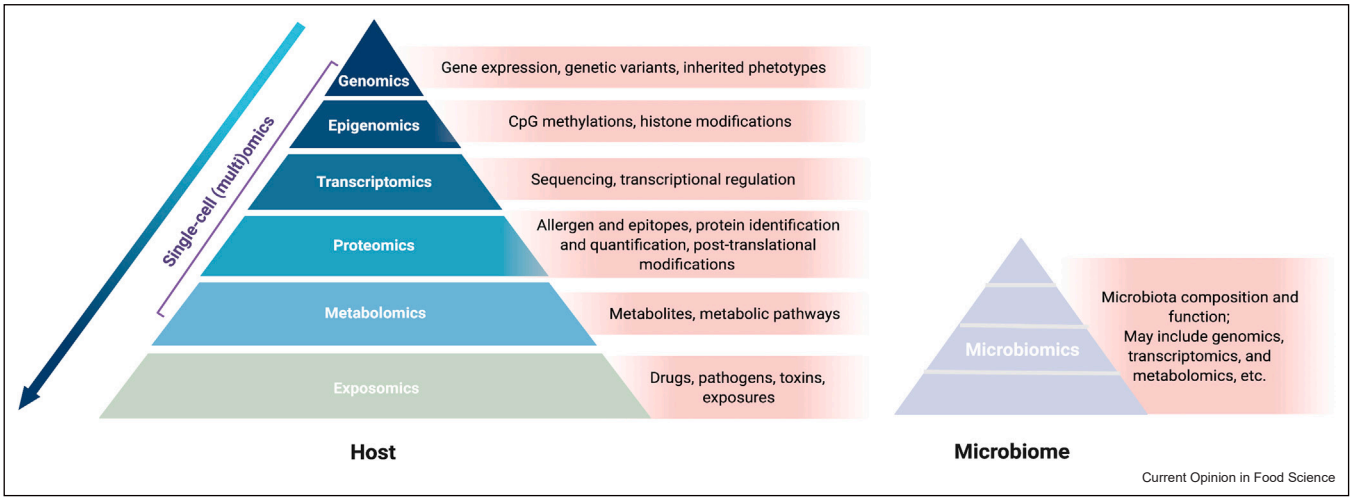
At the RNA level, a longitudinal whole-blood transcriptomic study of pediatric peanut allergy revealed 6 genes (*LTB4R*, *PADI4*, *IL1R2*, *PPP1R3D*, *KLHL2*, and *ECHDC3*) as causally modulators of the state of response to peanut, and further, by leukocyte deconvolution, changes in the subpopulations of neutrophils, macrophages, and CD4+ T cells were observed during the course of peanut-triggered acute reactions [16]. In more targeted cell populations, earlier investigations reported genes differentially expressed in the purified CD4+ T cells from subjects with IgE-mediated FA, which were in association with the T-cell activation and function [17]. More recently, the dual use of transcriptomics and epigenomics in isolated B cells from adolescents with single- and multifood allergies highlighted the hypermethylation near three S100 genes and an enhanced myeloid-cell activation in multiallergic individuals [18]. Another well-designed integrated study using both cross-sectional and longitudinal designs in an egg-allergic infant cohort found that, subjects with persistent FA displayed increases in the epigenetic disruption at T-cell activation genes and poorer lymphoproliferative responses, indicating pathways affected by the gene-environment interactions in FA [19••]. Similar integration of both omics sciences was later applied in peanut-allergic children to identify molecular signatures of the reaction severity [20••]. Combining gene expression and methylation profiles, the integrated use of transcriptomics with epigenomics is showing a paramount role for a mechanistic understanding of the immunological and cellular basis driving FA (multi-omics studies listed in Table 2, and typical workflow for multi-omics sciences shown in Figure 2).

In addition to bulk RNA-seq, the use of single-cell RNA-seq (scRNA-seq) provides detailed information of individual immune cells in a biological system. With single-cell transcriptomics, Chiang and colleagues found that peanut-allergic patients possessed a highly biased Th2 response secreting related cytokines with a minor Treg cell deficit among allergen-responsive CD4+ T cells [21•]. Besides general immune responses and associated pathways [22], the scRNA-seq is unparalleled for the characterization of allergen-specific antibodies and T-cell receptors in FA patients, as well as the mechanisms leading to isotype switching to IgE in B cells [23,24]. This approach points us toward possibilities for a deeper understanding of the molecular processes that confer antigen specificity in FA individuals, and would also help to inform cell-type repertoire in the development of FA.

Proteomic and metabolomic markers

In addition to the characterization and discovery of food allergens, proteomic analysis has been used to explore disease endotypes and biomarkers in different FA populations. Leung et al. conducted a multi-omics study (lipidomics+microbiomics+ transcriptomics) in children with atopic dermatitis (AD) having FA, and found that patients with AD+FA presented an immature skin barrier and a Th2 immune activation in association with

Figure 1



Overview of omics technologies and their targeted applications. Created with BioRender.com. Adapted from Dhondalay et al. [3].

the multimorbidity [25••]. Later, a globally proteomic analysis of the same cohort confirmed that those highly expressed skin proteins in the AD+FA were associated with abnormal skin barrier integrity and a higher risk of epicutaneous sensitization [26]. In recent years, mass cytometry by time-of-flight (CyTOF), an advanced and in-depth proteomic technology, is gaining prosperity in the study of FA. By replacing traditional fluorophores with different stable metal isotope tags, more than 40 proteins can be multiplexed at a time, facilitating high-dimensional, quantitative analysis of cell populations and functional states at single-cell resolution. The use of CyTOF was lately reported in several FA cohorts for profiling of the immune cell signatures and specific responses [27•,28]. Christophersen et al. accomplished a multidimensional study using CyTOF with transcriptomics to unveil a distinct phenotype of CD4+ T cells in patients with celiac disease, an autoimmune disease driven by gluten intake in genetically susceptible subjects [29]. In addition to immune cell subset analysis, the CyTOF as a high-dimensional technique can also inform cell signaling and metabolic dysregulations, which warrants implementation in the future within FA.

On the other hand, the untargeted and targeted metabolomics, targeting low-molecular-weight compounds generated in cellular processes, offer us a powerful tool to dissect the disease mechanisms and discover biomarkers. Kong et al. earlier conducted an untargeted metabolomic analysis in peanut-allergic children, identifying uric acid as a serum biomarker for the induction of peanut allergy, possibly due to its ability to activate dendritic cells [30]. More recently, a similar approach was performed in serum samples of children with FA and asthma, and a disease-specific metabolomic signature in different subgroups was profiled. Of note, the FA subjects showed notably lower levels of sphingolipid and a series of other lipid metabolites [31]. The notification of sphingolipid metabolites as biomarkers of FA was also reported in another work, but with an opposite higher trend observed in FA when compared with the health control [32]. The lipid metabolism seems to be closely related to pediatric FA, but the underlying mechanisms warrant further investigations.

For targeted metabolomics, the short-chain fatty acids (SCFAs), produced from microbial fermentation in the intestine, are extensively studied due to their recognized anti-inflammatory and immunoregulatory abilities. In this context, the analysis of SCFAs in FA is always combined with microbiome approaches. For example, Ho et al. integrated SCFA metabolite assay with 16s rRNA sequencing and multiplex cytokine analysis to profile oral mucosal environment in peanut-allergic adolescents [33••]. Apart from individual marker analysis, the integrated use of proteomics and metabolomics constitutes a powerful tool for phenotyping and endotyping of allergic diseases, but its application to advance FA has been limited thus far.

Microbiota composition and function

Realization of the important role played by the human microbiome in allergic diseases has greatly promoted studies exploring how changes in the microbial communities contribute to the etiology of FA [34]. In this

Table 1

Principles, applications, strengths, and limitations of omics technologies in food allergy.

Omics	Principles and methods	Applications in food allergy	Advantages	Limitations
Genomics	Identification of SNP and CVN by whole-genome sequencing or DNA microarray.	Detection of SNP and CVN variants linked to susceptibility and phenotype of FA.	Provide information on disease risk and guide personalized medicine; highly reproducible data.	High cost for genome-wide methods; associations with disease phenotype are indirect.
Epigenomics	Targeting DNA methylation and histone modification using methods such as microarray and ChIP-seq.	Assessment of nongenetic alterations in DNA that affect gene expression related to FA.	Give dynamic information about the gene-environment interactions in disease.	Represent one of many mechanisms of gene regulation; in-depth study prefers multi-omics uses.
Transcriptomics	RNA transcript detection and quantification via targeted expression assay, bulk RNA-seq, or single-cell RNA-seq.	Profiling cell- and tissue-specific regulation of gene expression in FA.	Gene expression is more closely related to the modified biological function.	Transcript levels may have variable correlations with other omics data; high cost for single-cell RNA-seq.
Proteomics	Measurements of protein expression and posttranslational modification by LC–MS and CyTOF, and so on.	Characterization of food allergens; discover cellular proteins related to allergen immune responses.	Expressed or modified proteins represent the real biological state of a system, compared with (epi)genomic and transcriptomic data.	Some proteins are liable analytes; the identification and quantification are challenging due to the large variety of analytes.
Metabolomics	Quantify low-MW molecules in cellular processes by LC–MS, GC/MS, and NMR.	Analyze changes in the host/microbiome-derived metabolic pathways and discover FA biomarkers.	Provides metabolic changes related to disease and treatment; samples easy to be collected and analyzed.	Some signatures of FA are likely indirectly related to the metabolic profiles.
Microbiomics	Determine microbial composition and associated function by 16s rRNA and shotgun metagenomic sequencing.	Profile microbial compositional and functional changes driving FA.	Minimally invasive methods; samples easy to be accessed, collected, and analyzed.	16s sRNA sequencing provides low-resolution data; high cost for shotgun metagenome.
Exposomics	Analysis of environmental exposure and related consequences by suitable methods.	Help to understand nongenetic external exposures as risk factors of FA.	Accurate analysis of nongenetic factors in the pathogenesis of a disease.	Integration and standardization of multiple analyses remain challenging.

Abbreviations: SNP, single-nucleotide polymorphisms; CVN, copy number variation; MW, molecular weight; LC–MS, liquid chromatography–mass spectrometry; GC–MS, gas chromatography–mass spectrometry; NMR, nuclear magnetic resonance.

context, the 16s rRNA and shotgun metagenomic sequencing are increasingly used. By 16s rRNA sequencing, a few cross-sectional and longitudinal studies have described the relationship between early-life gut microbiome (GM) composition and the development of FA [35–37]. The results highlighted an increased abundance of bacteria from the *Firmicutes* phylum (e.g. the *Clostridium*, *Oscillospira*, and *Lactococcus* genera) in healthy infants, which can be potential probiotic candidates to prevent FA. Our research group recently integrated 16s rRNA sequencing with quantitative proteomic approaches in allergic patients who were mono- or polysensitized to food and inhalant allergens, unveiling that polysensitization was a distinct clinical phenotype in association with dysbiosis of the oral microbiota and disturbances in local immunological status [38••]. The use of germ-free or microbiome-depleted mice further shed light on the critical role of GM dysbiosis in FA. Colonizing germ-free mice with feces from healthy infants could alleviate the signs of cow's milk allergy in mice, and the abundance of a *Clostridiale* species was correlated with unique transcriptome signatures in the ileal epithelium [39••]. In another study, germ-free mice colonized with feces from mice fed a high-fat diet showed exacerbated food-allergic responses, which suggested a pathogenic role of the western diet and obesity-associated GM signature in FA [40].

Compared with 16s rRNA sequencing, the shotgun metagenome is capable of providing high-resolution data at the subspecies level, as well as valuable information about gene functional potential. Currently, the use of shotgun metagenomic sequencing is far from being implemented in the research of FA. The most in-depth study in FA using metagenome sequencing was conducted by de Flippis et al., who identified a specific baseline signature in the GM of allergic children (FA and aeroallergen allergy), which had a pro-inflammatory potential with enrichment of genes involved in the production of bacterial lipopolysaccharides (LPS) and urease [41••]. Furthermore, changes in the GM composition are always accompanied by an altered microbial metabolism. Recent studies that analyzed the microbiome–metabolome axis in FA patients have unveiled a lower potential of the subjects to degrade complex polysaccharides into immunoregulatory metabolites, particularly, the SCFAs [41••].

Omics and the treatment of food allergy

The clinical management of FA still remains challenging attributed to the complexity of allergic pathogenesis. Currently, the oral immunotherapy (OIT) and bacterial manipulation are two most investigated therapeutics to treat FA. The OIT refers to feeding an allergic individual increased amounts of certain allergen, with the goal of elevating the threshold that triggers a reaction. In this scenario, application of (multi-)omics methods would help to understand the mechanisms behind the development of immune tolerance during OIT, thus benefiting therapeutic strategies in FA. Epigenomics, metabolomics, and proteomics (CyTOF) have been recently used in peanut and cashew-allergic patients receiving OIT, which manifests that the successfully desensitized subjects harbor decreased allergen-specific T cells and a shift from the Th2-skewed immunity to a Th1/Th17 response [42–44].

On the other hand, the GM-immune axis serves as a promising therapeutic target for nutrition-mediated modulation of FA [45]. Using 16s microbial sequencing and SCFA analyses, Abdel-Gadir and coworkers demonstrated that bacteriotherapy with species from the order *Clostridiales* or *Bacteroidales* suppressed FA in a susceptible mouse model, where activation of the regulatory T-cell MyD88/RORγt pathway played an important part [46••]. In addition, the administration of probiotics and prebiotics is gaining positive outcomes in patients with allergic diseases. Despite limited evidence in FA cohorts, a series of studies using murine models have reported the biological role of probiotics/prebiotics in modulation of FA via the GM-immune axis [47,48].

Challenges in multiomics application and data integration

Compared with individual omics, the combined use of multiomics certainly allows for a more systematic analysis of biological problems leading to FA. Within the application of multiple omics methods, integrating data from several -omes into a comprehensive model will allow explanation of biological mechanisms driving complex diseases, known as the systems biology strategy. Despite the increasing availability of omics data sets and tools for analyses, the integration of multiomics data to inform on FA is limited thus far (Table 2). Some studies have begun to pave the way via integrating transcriptomics with epigenomics to define molecular signature and signal transduction [19••,20••], with proteomics [38••] to unveil biomarker and dysregulated pathways, or with metabolomics [33••] and microbiomics [25••,39••] to explore 'microbial-host immunity' interactions. In this scenario, accurately modeling the interactions between different omics layers into a biologically meaningful feature is a major issue to solve the challenge of data integration in systems biology. One such promising method is the network-based modeling, which possesses a great potential to identify interactions and co-expression modules from complex systems and has already been used in recent works aiming to unveil the mechanisms driving peanut allergy [20••,33••] and other atopic diseases [49]. The other unsupervised and supervised data-integrative methods such as matrix factorization and Bayesian framework can be also powerful tools for interrogation of

Table 2

Summary of in-depth studies using multi-omics data to advance food allergy (2019–2021).

Human cohorts	Study purpose and design	Multi-omics approaches and data integration (if any)	Key findings	References
Children with challenge-confirmed peanut allergy (n = 21).Independent cohort with peanut allergy (n = 19).	Aim: Delineate the genetic and epigenetic variations underlying the reaction severity of peanut allergy. Design: Whole-blood transcriptome and CD4+ T-cell epigenome profiles before, during, and after oral peanut challenge.	Transcriptomics, epigenomics (DNA methylation). Integrated network analysis of peanut- severity genes and CpGs using xMWAS.	Identification of peanut-severity genes and CpGs related to the neutrophil-mediated immunity.The *NFKBIA* and *ARG1* are hubs in the networks and the key nodes encompassed immune response, chemotaxis, and regulation of macroautophagy.	[20••][a]
Children with AD with (n = 21) or without FA (n = 19).Healthy controls (n = 22)	Aim: Determine whether subjects with AD+FA had skin features that distinguished them from those with AD-FA and nonatopic ones. Design: Skin-tape stripping (lesional and nonlesional areas) collected from each subject, and analyzed for skin- barrier functions, related protein expressions, microbial composition, and transcriptome.	Targeted metabolomics (lipidomics), microbiomics, and transcriptomics. Correlation network and relative importance for prediction analyses of multi-omics and clinical variables.	The multimorbidity (AD+FA) is associated with a dysfunctioned nonlesional skin, which shows an immature skin barrier and Th2 immune activation.	[25••][a]
Adolescents with peanut allergy (challenge-confirmed or elevated serum sIgE levels; n = 56).Healthy controls (n = 49).	Aim: Characterize oral host-environment dynamics in food allergy. Design: Saliva collected at enrollment and applied for corresponding analyses.	Targeted metabolomics (SCFAs), microbiomics. Correlation and network analyses of OM, SCFAs, and cytokine profiles.	Subjects with FA had a distinct oral microbiome and reduced production of SCFAs, features of which are correlated to the local secretion of Th2-type cytokines.	[33••][a]
Adults with allergic diseases (mono- or polysensitized to food and aeroallergens; n = 19). Healthy controls (n = 11).	Aim: Explore links between OM and the host oral milieu in different sensitization patterns. Design: Saliva collected at enrollment and applied for indicated measurements.	Microbiomics, proteomics.Correlation analysis and unsupervised clustering of OM and proteomics data.	Polysensitization to food and inhalant allergens is a distinct clinical pattern in association with dysbiosis of OM and disturbances in the local secretory and immunological balances.	[38••][a]
Infants with confirmed CMA (n = 4).Healthy controls (n = 4).	Aim: Understand how commensal bacteria regulate FA in early life. Design: Colonizing germ-free mice with feces from healthy or CMA infants, and mice samples analyzed for immune responses, GM, and ileal epithelium transcriptome.	Microbiomics, transcriptomics. Correlation analysis of GM profile and DEGs in ileal epithelia.	Germ-free mice colonized with GM from CMA infants fail to protect against allergic responses to BLG.The abundance of a *Clostridiale* species correlates with unique transcriptome signatures in the ileal epithelium.	[39••][a]
Children with confirmed IgE-mediated allergy (n = 90; FA, N = 55).Age-matched healthy controls (n = 30)	Aim: Decipher imbalances in GM composition and function in relation to pediatric allergy. Design: Stool samples collected from subjects at enrollment and 3-year follow-up, followed by GM and metabolomic analyses.	Microbiomics, targeted metabolomics (SCFAs)	The allergic children possess specific GM signatures with a pro-inflammatory potential.The *R. gnavus* strains enriched in allergic children had a lower ability to degrade fiber but a higher capacity to produce LPS.GM signatures at baseline can be predictable of persistent allergy.	[41••]
Infants with confirmed FA (n = 56).Age-matched healthy controls (n = 98).	Aim: Explore GM dysbiosis associated with the development of FA, and the potential of bacteriotherapy to treat FA. Design: Stool samples collected from infants at 1–15 m and periodically sampled until 30 m for GM analyses.Therapeutic potential of GM species to treat FA was conducted in a susceptible mouse model.	Microbiomics, targeted metabolomics (SCFAs)	GM from FA subjects fails to protect against allergic symptoms in mice.Therapy with species from the order *Clostridiales* or *Bacteroidales* suppressed FA in a mouse model. Supplementation of SCFAs alone did not have a protective effect.Activation of the regulatory T-cell MyD88/RORγt pathway played a crucial part during microbiota therapy.	[46••]

Abbreviations: AD, atopic dermatitis; BLG, β-lactoglobulin; CMA, cow's milk allergy; DEGs, differentially expressed genes; OM, oral microbiome; PBMCs, peripheral blood mononuclear cells.
[a] Studies applied integrated analysis of multi-omics data.

Figure 2

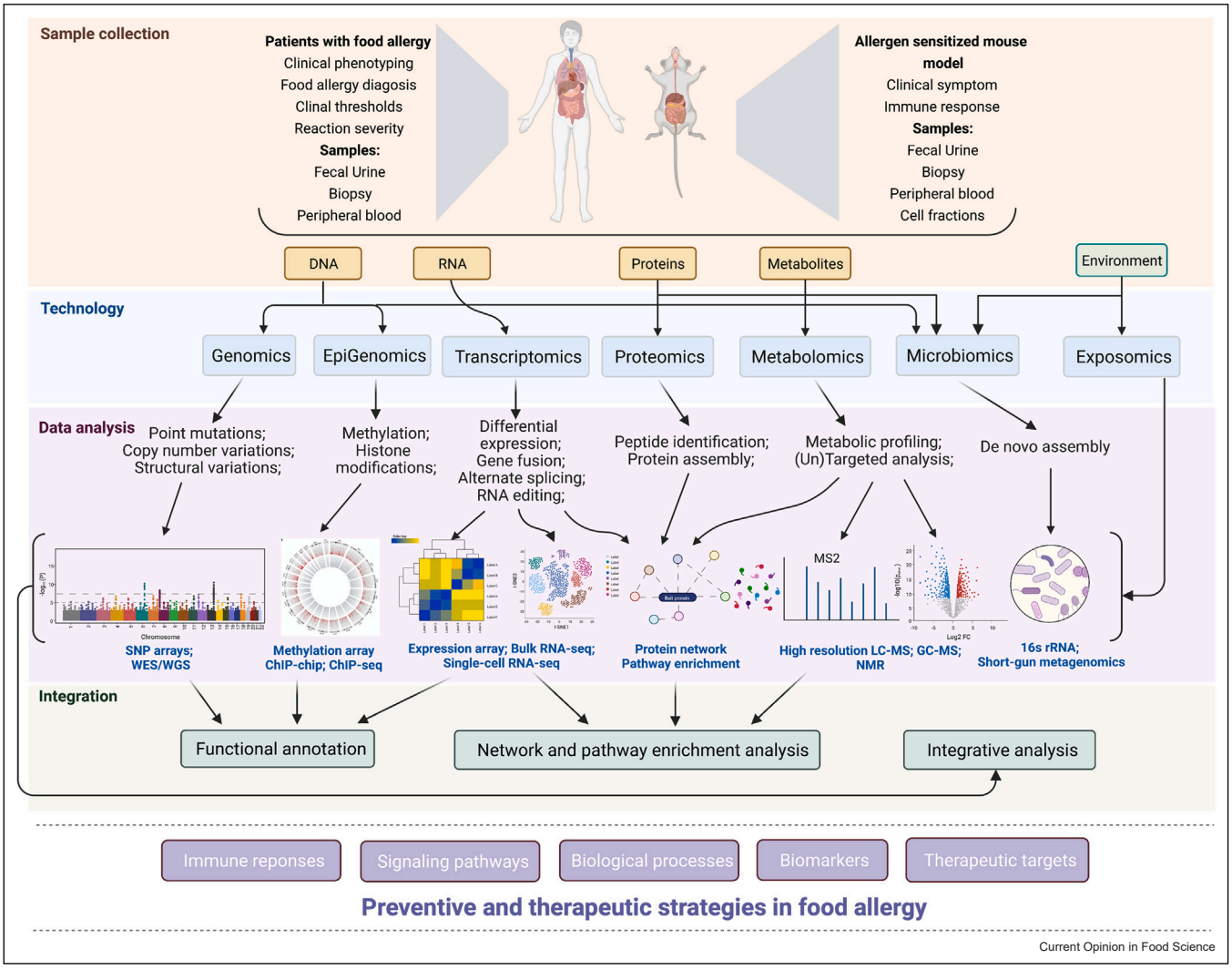


Illustration of the workflow of omics analyses in food allergy: from sample collection, data analysis, to multi-omics integration. Created with BioRender.com.
Adapted and improved from Dhondalay et al. [3], Patil et al. [51] and Irizar et al. [4••].

multitier data to study disease mechanisms and predict risks, whereas the use of such promising methods in FA remains limited [50]. In this regime, biological knowledge-guided integrative approaches are still desired, and a systems biology strategy with diverse computational tools would lead us to the next generation of the research of FA.

Conclusions and future directions

At present, the application of (multi-)omics technologies in biological sciences has greatly promoted the exploration of risk factors, molecular signatures, and potential therapeutic targets of FA. The enormous quantities of omics data from different patients and disease states have enabled us to create a detailed framework illustrating the physiological pathways related to the disease. However, due to the complexity and heterogeneity of FA, to-date omics studies are limited to common types of FA (e.g. peanut and egg allergies) and the pediatric populations. Further exploration of the general cohorts with FA and classification of the heterogeneous disease into endotypes and phenotypes warrant investigations. Furthermore, in addition to adaptive immune responses and associated processes, the pathological role of the innate immune system and the 'diet-microbiota-immunity' dynamics in FA need to be understood. In this regard, the great progress made in single-cell omics and multiomics data integration would lead us to a precise framework for the prevention and treatment of FA. We

are standing at the beginning of the journey of (multi-) omics sciences in FA and the path ahead remains encouraging.

Conflict of interest statement

The authors have no conflict of interest to declare.

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