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•Commentary•

Reverse metabolomics as a novel strategy to annotate the human metabolome

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Identifying chemical structures in human-derived samples presents significant challenges due to limited structural data obtained from untargeted metabolomics studies. When the chemical structures of molecules are closely related to the phenotypic status of human ecosystems, it becomes invaluable to devise a method for efficiently and systematically determining structures that correlate with the pathophysiological status of humans in a high-throughput approach.

Recently, advanced repository-scale analyses employing Mass Spectrometry Search Tool (MASST) [1] and reanalysis of data user interface (ReDu) [2] serve as key tools for searching and reanalyzing public mass spectrometry data. These tools enable researchers to confirm the presence of generated tandem mass spectrometry (MS/MS) spectra within human-derived metabolites [3]. Specifically, MASST facilitates the search for MS/MS fragmentation patterns within public MS/MS spectral databases, while ReDu allows for the filtering of public data according to organism, disease state, phenotype, sample descriptors, or other metadata. Utilizing these methods, Gentry and coworkers introduced a novel approach termed "reverse metabolomics" in their publication in *Nature*. This strategy integrates combinatorial chemistry with repository-scale analyses to faciliate the discovery process of the human metabolome [4].

Classical metabolomics seeks to identify a comprehensive list of differentiated metabolite ions associated with a known phenotype, followed by structural validation using chemically synthesized standards (Fig. 1A). Reverse metabolomics introduces an innovative concept whereby researchers synthesize a vast array of suspected compounds as standards. They then utilize public metabolomics databases to determine whether these synthesized structures are present and how they relate to specific phenotypes (Fig. 1B). Similarly, reverse pharmacokinetics focuses on identifying the targets of clinically effective and safe natural medicines, as opposed to classical pharmacokinetics, which assesses the safety and efficacy of target-identified compounds [5].

To assess the efficacy of reverse metabolomics, Gentry et al. synthesized a large array of structurally diverse compounds using combinational synthesis. This process involved the systematic, repetitive covalent linkage of various "building blocks", including free bile acids, fatty acids, amines, and hydroxy acids, resulting in four metabolite classes: N-acyl amides, fatty acid esters, bile acid esters, and bile amidates, which served as compound standards. Subsequent MS/MS spectral analysis of these compound mixtures was conducted, followed by using the MASST and ReDu platforms to search existing MS/MS databases to verify the presence of synthesized structures. Interestingly, more than 100 synthesized structures were newly identified in human ecosystems, with several microbial bile amidates showing correlations with the inflammatory bowel disease (IBD) phenotype. Further experimental work elucidated the biological functions of various bile amidates in immunoregulation and PXR activation, both of which are involved in IBD phenotype [6-9].

Reverse metabolomics, in theory, is suited for the study of synthetically accessible metabolites capable of ionizing and fragmenting within a mass spectrometer at detectable concentrations. This method hypothesizes the existence of specific compound classes based on existing biochemical

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These authors have no conflict of interest to declare.

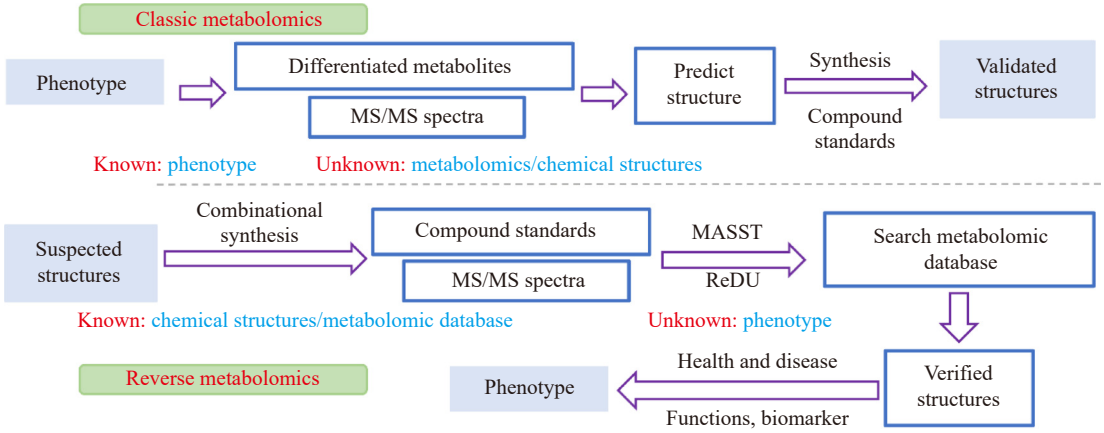

Fig. 1 Reverse metabolomics insights into structure verification of human-derived samples. (A) workflow of classical metabolomics. (B) Workflow of reverse metabolomics.

knowledge of metabolome formation. This approach mirrors an earlier strategy that expanded metabolic pathways to map the metabolome from initial metabolites and metabolic reactions, grounded in the principle that the entire metabolome is constructed from a finite set of initial metabolites through diverse biochemical reactions [10]. By linking combinatorial synthesis with biochemical reaction knowledge, reverse metabolomics bridges the gap for high-throughput identification of metabolites within public metabolomic datasets. This shift from passively identifying metabolomic-derived structures to actively searching for them using a large array of standards represents a significant paradigm shift, poised to significantly expedite the discovery of human-derived structures.

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