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Emerging Applications of Metabolomics in Drug Development

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Abstract

Metabolomics has been increasingly applied in biomedical research and drug efficacy evaluation in the context of rapid advances in analytical instrumentation and bioinformatics. Metabolomics-based discovery will potentiate the drug development in many ways such as novel biomarkers discovery, precise clinical trial by stratifying patients, and evaluation of drug metabolism or toxicity. More translational metabolomic results will be available with the technological innovation in the near future.

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Introduction

Metabolomics is a relatively new discipline in contrast to other well-established omics such as genomics, transcriptomics, and proteomics. However, metabolomics has drawn tremendous attention in both biomedical research and drug development areas in recent years because of its capacity of global profiling either the endogenous or exogenous metabolites. The human body is a complex "superorganism" which consists of over at least 100 times of microbiome than human genome [1]. As a result, the variations of metabolites are consequence of interactions between genetic and environmental factors including the contribution of gut microbiota. The metabolic insights on diseases and drug efficacy could facilitate the discovery of novel therapeutic biomarkers of diseases that are of critical significance for drug discovery.

Metabolomics technologies

Metabolomics is defined as "the comprehensive and quantitative analysis of all metabolites" [2]. In reality, the "metabolic window" usually varies greatly due to the limitation of metabolomics instrumentation that is used. Among all tools for analytical platforms, mass spectrometry (MS) has the highest sensitivity and selectivity, leading toits best identification capabilities for analysis of the metabolites in urine, currently, MS-based techniques has been the most prevalent platform in metabolomics studies [3]. MS always combined with other related technologies, followed by various mass spectrometry-based platforms appeared gradually, such as gas chromatography mass spectrometry (GC-MS) and liquid chromatography mass spectrometry (LC-MS). Inaddition, metabolomics researches areal so mainly conducted with nuclear magnetic resonance (NMR).Notably, due to the diversity and complexity of the metabolic profile, different analytical tools must be adopted individually orin combination according to the properties of different metabolites [4].

Given the universal presence of 1H in most metabolites and the numerous advantages, 1H NMR-based platform has been adopted for metabolomic study in many groups. However, the application of NMR-based platform is also limited because of its disadvantage in sensitivity compared to MS-based approaches. GC-MS is primarily used in metabolomics due to the facts of relatively low-cost, high reproducibility in metabolite identification with commercial or in-house compounds databases. Nevertheless, since GC-MS is only suitable for detection of volatile or derivatized compounds, it is particularly necessary to combine GC-MS with other analytical approaches (e.g LC-MS) to broaden its "metabolic window" [5]. LC-MS is the most widely used platform for metabolomic study nowadays which provides comprehensive coverage of metabolites and the super higher sensitivity than other analytical approaches, as well as its obvious advantages in sample preparation, automation and sample volume. More detailed comparisons among metabolomic platforms have been reviewed [6-8].

Metabolomics potentiates novel drug target discovery

Over the past decades, tremendous efforts have been paid to discovery of novel drug targets by over whelmingly focus on genetic aspect, however, the successful cases were far less than expected because most diseases are consequences of complicated interactions between genetic and environmental factors (e.g gut microbiome and epigenome). Since the profiling of metabolites are the final "readout" of cell, organ or even whole body metabolism, the metabolic insights acquired with metabolomics usually reveal both the environmental and genetic contributions to disease development, which are of vital significance for identifying novel drug targets.

2-hydroxyglutarate (2-HG) is a well-evidenced oncometabolite that is accumulated in several types of tumor patients with isocitrate dehydrogenase 1/2 (IDH1/2) mutations including acute myeloid leukemia patients, gliomas, chondrosarcoma, enchondromaand intrahepatic cholangiocarcinoma [9]. Recent investigation indicates that 2-HG can also extend the lifespan in C. elegans by suppressing ATP synthase and mTOR signaling similar to α-ketoglutarate (α-KG) [10]. This discovery highlights the potential of tumor therapy by targeting aging pathways through metabolic modulation. Since it is variable in survival range in patients with or without IDH1 mutation

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in different kinds of tumors, the elevation of 2-HG is postulated as not only a functional biomarker of IDH mutation, but also may play important roles in tumor development via the competition with α-KG-dependent enzymes [11]. As a result, the identification of oncometabolites opens a new avenue for seeking novel drug target of tumor therapy.

Another good example of novel drug target discovery is the elucidation on the roles trimethylamine N-oxide (TMAO) in atherosclerosis, which is traditionally attributed to genetic and cholesterol factors. However, the application of metabolomics has revealed the elevation of TMAO in atherosclerosis, which is derived from dietary choline by co-metabolism of gut microbiota with hepatic enzyme, flavinmonoxygenase 3 (FMO3) [12,13]. Further investigations indicate that the higher plasma TMAO is correlated with the adverse myocardial events in humans, as well as the causative role of TMAO in atherosclerosis [14,15]. Accordingly, it is postulated that the novel drug target of anti-atherosclerosis could be explored by modulating intestinal bacteria and hepatic FMO3 enzyme [16]. These two examples highlight the great potential of metabolomics-based discovery of novel drug targets in the context of integrative insights on disease mechanism. Much more evidence is accumulating in respect to the metabolomics-based novel drug target discovery in various diseases.

In addition to 2-HG and TMAO, bile acids (BAs) are also a large class of gut microbiota-derived metabolites associated with various metabolic diseases, including conjugated BAs and unconjugated BAs,which are now recognized as signaling molecules [17]. The emerging evidence has confirmed that BAs metabolisms play important roles in the formation or development of cardiovascular diseases (CVD) and nonalcoholic fatty liver diseases (NAFLD) [18,19]. In astudy, an increase of secondary and primary BAs ratio were found in patients with chronic heart failure, that is, primary BAs were decreased and secondary BAs were enhanced [20]. In another study, scientists quantitatively analyzed small molecule metabolites induced by gut microbial metabolism, suggesting that BA is an important factor shaping gut microbiota of obese mice [21]. Interestingly, they also demonstrated that BA reduction by farnesoid X receptor (FXR) agonist, GW4064, attenuated obese phenotype [21,22]. Moreover, a recent studyidentifiedlithocholicacid as a putative biomarker in Alzheimer's disease [23]. In summary, the confirmed links between BAs metabolisms and metabolic diseases highlighting the significance of BA-targeting therapeutic strategies in the future.

Metabolomics facilitates precise clinical trial in drug development

The clinical trial is a critical step in drug development, however, the high failure rate of novel drug candidates is very common because of unsatisfied therapeutic effect or severe toxicity in trialed subjects [24]. Given the heterogeneity of most diseases among patients, the precise clinical trial is urgently needed by stratifying patients into responders and nonresponders with omics approaches. Pharmacometabolomics (also pharmacometabonomics [25, 26]) has been aggressively applied in evaluating the correlation between baseline metabolic profiles and therapeutic outcomes or drug metabolism in several clinical drugs such as simvastatin [27], aspirin [28], sertraline [29] and acetaminophen [30]. Taken acetaminophen as an example, interindividual differences of acetaminophen-induced liver damage are commonly reported in clinic. Metabolomics-based investigation uncovers the association between predose urinary metabolite composition and extent of liver injury [25], moreover, their subsequent evidence demonstrates that the abundance of predose urinary metabolite p-cresol, a gut microbial-derived structural analog of acetaminophen, is inversely correlated with the postdose ratio of acetaminophen sulfate to acetaminophen glucuronide [30]. Generally, dual antiplatelet therapy (DAPT) is crucial for CAD patients undergoing percutaneous coronary intervention (PCI), whereas adverse reactions were also observed in clinical, for instance,clopidogrel high on treatment platelets reactivity. Subsequently, pharmacometabolomics analysis of plasma indicated that several pathways involved in this process, including metabolism of nitrogen and glycine-serine-threonine and biosynthesis of aminoacyl-tRNA [31]. The drug efficacy-related metabolites either serve as the metabolic biomarkers for stratifying patients who are sensitive or insensitive to certain therapies, or shed light on novel mechanisms of drug activity. Accordingly, the precise clinical trial is of highly promise in drug development by adopting metabolomics or pharmacometabolomics to assign "suitable" patients to the right medicines.

Conclusion

Taking the technological advances and increasing application of metabolomics in research of biomedicine into account, a large number of exiting evidence is accumulating in respect to the metabolic characteristics of various diseases and drug activities. Some well-confirmed disease-associated metabolites, as well as their metabolic pathways will be promising targets for designing of novel drug candidates. On the other hand, drug efficacy or metabolism-associated metabolic phenotypes open up an important window for performing precise clinical trial of either "old" or novel drug candidates.

Expert Opinion

The productivity of drug development is steadily declining in the context of limited recognition on the etiology and pathogenesis of most diseases. Metabolomics provides new insights on disease development and drug activity at the metabolic level, which is of vital significance for uncovering novel drug targets or stratifying patients to effective therapies. However, we are still encountered some big challenges in advancing the drug development by using metabolomics-based discovery. First of all, the reproducibility and reliability in metabolites identification and quantitation are critical for any subsequent investigation based on metabolomics discovery. Unfortunately, very few published metabolomic results have experienced strict validation from independent laboratories where different instrumental platforms or protocols are usually adopted. As the analytical instrumentation and technologies advance, absolute quantitation of metabolites in clinical samples is particularly important for designating them as potential diagnostic or prognostic biomarkers. Secondly, patient stratification is an ideal goal in clinic, however, there is a long way to go before it comes true. It is envisioned that the metabolic signatures associated with drug efficacy or toxicity could be adopted during the early stage in drug development, in which candidates with high potential of toxicity could be screened out. Finally, metabolomics data are much more eligible for translation from laboratory to clinic

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where researchers from laboratory or industry should step forward to collaborate with clinicians. With these in mind, a promising perspective could be expected that validated metabolic biomarkers would be efficiently measured with clinical-oriented instruments for diagnosis or patient stratification in the coming 5-10 years.

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