Data article

MagMD: Database summarizing the metabolic action of gut microbiota to drugs

Jiajia Zhou a, Jian Ouyang a, Zihao Gao a, Haipeng Qin a, Wu Jun a,b,⇑, Tieliu Shi a,b,c,⇑,*

⇑ Co-Corresponding authors.
E-mail addresses: jwu@bio.ecnu.edu.cn (W. Jun), tlshi@bio.encu.edu.cn (T. Shi).

⇑ Corresponding authors.

a Center for Bioinformatics and Computational Biology, and the Institute of Biomedical Sciences, School of Life Sciences, East China Normal University, Shanghai 200241, China
b School of Statistics, Key Laboratory of Advanced Theory and Application in Statistics and Data Science-MOE, East China Normal University, Shanghai 200062, China
c Beijing Advanced Innovation Center for Big Data-Based Precision Medicine, Beihang University & Capital Medical University, Beijing 100083, China

Article history:
Received 14 August 2022
Received in revised form 8 November 2022
Accepted 8 November 2022
Available online 12 November 2022

A R T I C L E  I N F O

Article info

Article history:
Received 14 August 2022
Received in revised form 8 November 2022
Accepted 8 November 2022
Available online 12 November 2022

A B S T R A C T

An increasing number of studies have reported that microbiome can affect drug response by altering pharmacokinetics and pharmacodynamics of formation of toxic metabolites. With the development of metagenomic sequencing, gut microbial composition as well as the metabolic function are drawing more and more attention for the patient stratification. The established microbiota databases provide useful information about the gut microbe-drug interactions. However, these databases generally lacked the detailed effects on substance and the metabolites, which are helpful in elucidating the mechanisms underlying drug biotransformation and personalized medicine. To address these issues, in this study, we developed Metabolic action of gut Microbiota to Drugs (MagMD), a database and a web-service covering 32,678 records of interactions between 2,146 gut microbes, 36 enzymes and 219 substrates (mainly drugs). The detailed annotations for each entry, including the taxonomic level of microbes, the molecular form and PubChem ID of drugs from PubChem Compound Database, types of microbial secreted enzymes and the original reference links can also be accessed from the web service.

Availability and implementation: MagMD is a publicly available resource, constantly updated. It has an intuitive web interface and can be freely accessed at http://www.unimd.org/magmd.

© 2022 The Authors. Published by Elsevier B.V. on behalf of Research Network of Computational and Structural Biotechnology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

The drug-gut microbiota interactions are bidirectional, and the drug can reduce microbial fitness or alter drug availability through biotransformation. The microbes, in turn, can induce either a positive or a negative effect on drug activity and efficacy [2,25]. The gut microbiota could impact drug activity and efficacy through three main ways, including secreting microbial metabolites to interfere with drug metabolism, producing microbial enzymes to transform drug molecules and modifying drug metabolizing genes or enzymes in host liver or intestinal tissues [1]. So far it has been reported over 180 drugs are regarded as substrates for gut bacterial enzymes, and can be directly transformed by microbes in vivo [5,26]. Gut microbiota can directly metabolize drugs through enzymatic transformation or indirectly affect drugs through some special metabolites or pathways [4]. For example, Eggerthella lenta secretes cardiac glycoside reducense enzyme to reduce Lactone ring of Digoxin, forming an inactive metabolite (dihydrodigoxin) leading to the bioavailability reduction of Digoxin's [5,6]. Clostridium scindens cleavages the sidechain of Dexamethasone, liberating an androgen metabolite, reducing drug concentration in the caecum, and increasing androgen metabolite concentration in the caecum and serum [3]. Enright et al. found that the activity of microbial enzyme affects the solubilisation capacity of bile salts to dissolve nine oral drugs including the antiepileptic phenytoin [7]. The microbiome can also change the epithelial permeability [8], gut motility [9] and other new mechanisms mediated drug absorption [10,11]. Hence, the mechanistic elucidation of gut microbiota in drug metabolism and toxicity will facilitate the rational drug design and provide important evidence for gut microbiota-target therapeutic.

Considering the importance of gut microbiota-drug interactions, several databases have been designed. PharmacoMicrobiom contains 131 records about the gut microbiota and drug interactions, yet most of them only describe the effects of drugs on the gut microbiota [12]. Sun et al. provided a Microbe-Drug Association Database (MDAD) including 5,055 entries involving 1,388 drugs and 180 microbes from drug databases and related publications [13]. Microbiota-Active Substance Interactions database (MASI) provides 3,694 entries about the active substance-
microbiota interactions with specific species name, whereas only 7.12% of which have the detailed effects on substance and 11.02% of which have the records of metabolites [14]. Since these details are helpful in elucidating the mechanisms underlying drug biotransformation and personalized medicine. A typical example is that co-administration of the antiviral drug solivudine with the antitumor drug 5-fluorouracil (5-FU) can increase circulating 5-FU levels, resulting in 5-FU-related death, as the gut microbiota can transform solivudine into (E)-5-(2-bromovinyl)uracil (BVU) which is an inhibitor of hepatic dihydropyrimidine dehydrogenase and hepatic dihydropyrimidine dehydrogenase is responsible for the detoxification of 5-FU [15,16]. Moreover, gaining the product information of microbial metabolic substrates can aid in drug development. Gut microbiota enzymes, such as β-glucosidase and endo-β-glucosidase, can convert quercetin to aglycone, exhibiting antiplatelet activity. Hesperetin and naringenin belong to flavonoids like quercetin, which can also be converted into aglycones by gut microbiota enzymes [17,18]. According to the efficacy of quercetin, we can infer that hesperetin and naringenin may also have antiplatelet activity.

To better address demands mentioned above, in this study, we developed a new and regularly updated database, MagMD, to provide detailed information about 32,695 entries about the metabolic action between 2,146 gut microbes and 219 substrates. The details about the enzymes, metabolites and effects on substrates involved in the metabolic processes were also included. Our MagMD provides a user-friendly interface allowing easy access to the data. This platform provides a quick search of the database via its website at http://www.unimd.org/magmd.

2. Materials and methods

2.1. Database sources and preprocessing

To collect the details involved in the drug-gut microbiota interactions, we first collected the publication using the PubMed ID recorded in the publicly available database (e.g. PharmacoMicrobomic and MASI), and then search the related literatures from the PubMed [19] with the keywords “gut microbiota”, “metabolism”, “gut microbiome”, “drug metabolism”, “gut microbiome” and “drug pharmacokinetics”. The literature-reported interaction entries were manually extracted from the collected publications and only the experimentally determined interactions were retained. After that 740 literature-reported records from 113 publications were included in the MagMAD, as well as the experimental details (e.g. Drug category, molecular formula and potential effects to the pharmaceutical efficacy) involved in the drug-gut microbiota interactions reported in the original publications were recorded if available. More details related to the drug metabolism were supplemented by integrating the information obtained from UniprotKB [20], ChemicalBook (https://www.chemicalbook.com/ProductIndex_EN.aspx), PubChem Compound [21] and Drugbank [22]. The potential effects to the pharmaceutical efficacy were further manually evaluated and grouped into 15 classes, such as toxicity increased, toxicity decreased, side effect, carcinogenic, activation, and activity decreased (more details can be found in the web server).

Moreover, as gut microbiota can affect drugs by secreting enzymes, we can build new interactions between the gut microbiota and drugs with the intermediary enzymes. We hypothesized a microbe can affect a drug if the microbe can secret the enzyme which was proved to metabolize the drug. Based on this hypothesis, we first collected information of the enzyme which can metabolize drugs and then the related protein sequences were retrieved from the UniProtKB database (https://www.uniprot.org). After that, we aligned the protein sequence of each enzyme against the Non-Redundant Protein Sequence Database (NR database) (https://www.ncbi.nlm.nih.gov/protein) using BLASTP. NR proteins with identity larger than 90% and coverage larger than 60% were regarded as matched. The taxonkit [23] was applied to assign the enzyme with microbes which were considered to be capable of secreting the enzyme. Hence, novel interactions between the microbes and the drugs were established using the enzymes as
intermediary agent and 31,770 records were supplemented to our database.

To further expand our database, we tended to infer the association between the microbes and drugs with computational approach. With the detailed experimental results of 23 drugs metabolized by the gut microbiota of 20 healthy donors reported in Javadan et al.’s study [24], we retrieved the microbial composition (by relative abundance) of the 20 fecal samples as well as the normalized depletion of the 23 FDA approved drugs. For each drug, the key microbes involved in the drug metabolism were inferred using the stepwise linear regression method. Briefly, microbes with mean of relative abundance less than 5e-3 and variance less than 1e-4 across all the samples were filtered. The remained microbes were acted as variables and normalized depletion of the drugs were regarded as the response of the stepwise linear regression method. Microbes with a p value less than 0.05 were regarded as key microbes, and then 178 interactions were obtained.

Totally, 32,695 interactions between the microbes and drugs were established with these strategies. To facilitate users to distinguish predicted items, we included the source of each items in our database with the column named “the ways to obtain records”.

2.2. Webserver construction

We utilized the Apache HTTP server as a web server, developed by PHP (Version: 7.0.12, https://www.php.net/) programming. Data interaction was implemented by HTML5, JavaScript, jQuery. All data in MagMD are stored and managed in MySQL database (Version: 5.7.17, https://www.mysql.com/). Data analyses were mainly carried out by the R (Version 3.6.0, https://www.
3. Results and conclusion

In the current release, our MagMD database holds over 32,695 records describing the interactions between 2,146 gut microbes and 219 substances (94.06% were drugs), involving 195 types of diseases. These records consist of 747 items derived from public databases and literatures, 31,770 items established using enzymes as intermediary agent, and 178 items predicted using the data in Javdan et al.’s study. To provide more details about the interactions, we also included the information of 36 enzymes related to 97.59% of these interactions. Moreover, to give an intuitive description about the effect of gut microbiota to the drug, we grouped the effects of the metabolic action of gut microbes to drugs into 15 types, such as activation, activity decreased, activity increased, inactivation, toxicity decreased, and toxicity increased, according to the original description in the related publications. More details about our database were shown in Fig. 1. The results showed that the most frequently presented microbe was Bacteroides uniformis, which are clinically important species and important in numerous metabolic activities. Similarly, the most frequently presented substance and enzyme were stevioside and β-glucosidase.

The MagMD also provided a user-friendly interface allowing easy access to the data and also provides a quick search of the database for details via its website at http://www.unimd.org/magmd (Fig. 2). The webpage consists of four interfaces, which are Home, Browse, Search, Download and About (Fig. 1). In the Search interface, users can search for metabolic actions by typing any one of the types of bacteria, enzyme substrate or effect. The users can also download all the records from the Download interface in xlsx format. The Browse interface gives the brief summary about the database.

Although, there are several databases related to gut microbiota and drugs [12,14] it still necessary to develop a more comprehensive database including the gut microbiota alteration of active substances, along with information on enzymes and effects of drug efficacy after metabolizing by gut microbiota. We believe that the proposed MagMD database will provide a broader knowledge for interaction between gut microbiota and pharmaceutical and better serve the related communities for both basic research and clinical application, such as personalized evaluation of therapeutic efficacy with the gut microbial composition. We also realize clearly some shortcomings of MagMD. As most of the interactions recorded were predicted and the confidence should be further evaluated. Besides that, more details about the interactions are required and the amount of data is not large enough.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank ElRakaiby et al., Zeng et al and Javdan et al. for their wonderful research results.

References

[1] Li H, He J, Jia W. The influence of gut microbiota on drug metabolism and toxicity. Expert Opin Drug Metab Toxicol 2016;12(1):31–40.
[2] Falony G et al. Population-level analysis of gut microbiome variation. Science 2016;352(6285):560–4.
[3] Zimmermann M et al. Mapping human microbiome drug metabolism by gut bacteria and their genes. Nature 2019;570(7762):462–7.
[4] McCoubrey LE et al. Predicting drug-microbiome interactions with machine learning. Biotechnol Adv 2022;54:107797.
[5] Haiser HJ et al. Predicting and manipulating cardiac drug inactivation by the human gut bacterium Eggerthella lenta. Science 2013;341(6143):295–8.
[6] Haiser HJ et al. Mechanistic insight into digoxin inactivation by Eggerthella lenta augments our understanding of its pharmacokinetics. Gut Microbes 2014;5(2):233–8.
[7] Enright EF et al. Impact of Gut Microbiota-Mediated Bile Acid Metabolism on the Solubilization Capacity of Bile Salt Micelles and Drug Solubility. Mol Pharm 2017;14(4):1251–63.
[8] Takashima S et al. Proton pump inhibitors enhance intestinal permeability via dysbiosis of gut microbiota under stressed conditions in mice. Neurogastroenterol Motil 2020;32(7):e13841.
[9] González-Sarrías A et al. The gut microbiota ellagic acid-derived metabolite urolithin A and its sulfate conjugate are substrates for the drug efflux transporter breast cancer resistance protein (ABCG2/BCRP). J Agric Food Chem 2013;61(18):4352–9.
[10] Wang H et al. Intestinal lysozyme releases Nod2 ligand(s) to promote the intestinal mucosal adjuvant activity of choleragen toxin. Sci China Life Sci 2021;64 (10):1720–31.
[11] Ding S et al. Potential role of Lactobacillus plantarum in colitis induced by dextran sulfate sodium through altering gut microbiota and host metabolism in murine model. Sci China Life Sci 2021;64(11):1506–16.
[12] ElRakaiby M et al. Pharmacobiomics: the impact of human microbiome variations on systems pharmacology and personalized therapeutics. OMICS 2014;18(7):402–14.
[13] Sun YZ et al. MDAD: A special resource for microbe-drug associations. Front Cell Infect Microbiol 2018;8:424.
[14] Zeng X et al. MASI: microbiota-active substance interactions database. Nucleic Acids Res 2021;49(D1):D776–82.
[15] Nakayama H et al. Intestinal anaerobic bacteria hydrolyse sorivudine, producing the high blood concentration of 5-(E)-(2-bromovinyl)uracil that increases the level and toxicity of 5-fluorouracil. Pharmacogenet Genomics 1997;7(1):35–43.
[16] Okuda H et al. Lethal drug interactions of sorivudine, a new antiviral drug, with oral 5-fluorouracil prodrugs. Drug Metab Dispos 1997;25(2):270–3.
[17] Yang B et al. New insights on bioactivities and biosynthesis of flavonoid glycosides. Trends Food Sci Technol 2018;79:116–24.
[18] Feng W et al. Targeting gut microbiota for precision medicine: Focusing on the efficacy and toxicity of drugs. Theranostics 2020;10(24):11278–301.
[19] Sayers EW et al. Database resources of the National Center for Biotechnology Information. Nucleic Acids Res 2011;39(Database issue):D38–51.
[20] Boutilé E et al. UniProtKB/Swiss-Prot. Methods Mol Biol 2007;406:89–112.
[21] Kim S et al. PubChem Substance and Compound databases. Nucleic Acids Res 2016;44(D1):D1202–13.
[22] Wishart DS et al. DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic Acids Res 2018;46(D1):D1074–82.
[23] Shen W, Ren H. TaxonKit: A practical and efficient NCBI taxonomy toolkit. J Genet Genomics 2021;48(9):844–50.
[24] Javdan B et al. Personalized mapping of drug metabolism by the human gut microbiome. Cell 2020;181(7):1661–1679.e22.
[25] Liu H et al. Microbiome technology empowers the development of traditional Chinese medicine. Sci China Life Sci 2020;63(11):1759–61.
[26] Hu P et al. A cyclin protein governs the infectious and sexual life cycles of Cryptococcus neoformans. Sci China Life Sci 2021;64(8):1336–45.