

Homology study between human drug metabolizing enzymes and intestinal microbial metabolizing enzymes

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Abstract: Pharmacology is a very crucial element in the science of human health and diseases. Since this field is mainly involved in the development, testing and availing of human drugs, critical studies are often made in order to ensure that medicine in all markets are safe for each intended purpose of use in humans. It is therefore basically important to understand the relationship between drugs and the human body and by this we mean how pharmaceutical products react within the human body when it comes to fighting diseases and boosting immunity. In order to get this, researchers take into consideration the manner in which human bodies interact with various kinds of medicine. How drugs get absorbed and utilised within the body involves a number of metabolic processes and the process of metabolism is greatly driven by a number of enzymes. Enzymes can either be microsomal with the hepatic enzyme playing the greatest role and often called drug enzyme or non-microsomal enzymes which are quite specific in such a way that they only metabolise drugs with certain structure and content composition. For this study, we shall be looking at how to develop human immunity within the intestinal system considering that there have been a number of viral organisms in the human gut identified by scientists over the last years of research. Microbes evidently determine the level of individual health and wellbeing since how they interact with host cells determines their level of positive or negative effectiveness.

Keywords: Pharmacology, Enzymes, Immunity, Intestinal, Metabolism, Microbes, Cells

1. Introduction

Drug metabolism has become an important part of pharmacological research. The study of the metabolic process of drugs in the body and its chemical changes is important for the elaboration of pharmacological effects, toxicity studies, structural modifications, etc. The most important players in the process of drug metabolism are the various enzymes involved, and there are two major categories of enzymes: microsomal enzymes and non-microsomal enzymes. Microsomal enzymes are mainly found in the liver, lung, kidney and other parts of the body, with the highest activity of hepatic microsomal enzymes, which mainly catalyze the metabolism of drugs and other exogenous substances, so they are also known as drug metabolizing enzymes, or drug enzymes for short. Microsomal drug-metabolizing enzymes are the most important mixed-function oxidases, of which cytochrome P450 is the most important. Non-microsomal enzymes are present in plasma, cytosol and mitochondria. These enzymes are highly specific and act only on drugs of specific structure, such as cholinesterase in plasma and monoamine oxidase in mitochondria, etc. The drugs biotransformed by these enzymes are less, but their effect on drug action is equally important. In recent years, there are many studies on drug metabolism enzymes in human body, such as drug toxicity mechanism and clinical rational drug use based on drug metabolism/transport, drug metabolism of intestinal flora, drug metabolism of traditional

Chinese medicine, etc.

The intestinal microbiota is an important component of the developing intestinal immune system, and intestinal immune homeostasis is influenced by host-microbe interactions¹. Scientists have identified more than 140,000 viral species in the human gut. In recent years, we have come to observe how microbes affect human health and how interactions between microbes and host cells control infectious diseases.

It is becoming increasingly apparent that microbiome dysfunction is associated with a wide range of diseases, such as chronic inflammation, metabolic diseases, neurological disorders, and cancer. Such microbiome disruptions may occur locally at the site of disease or at mucosal sites or organ systems distant from the lesion, thereby stimulating altered metabolism and immunity in the host.

At the same time, scientists have found that gut microbes are closely associated with drugs: some metabolic enzymes in the gut are homologous to human genes, so as proteins formed by transcription of gene sequences, some drug-metabolizing enzymes in the human body will correlate with gut metabolic enzymes. For example, CYP2D6 is a protein of the CYP450 family of human drug metabolizing cytochromes, whose homologous metabolic enzyme in intestinal microbes is: GUT_GENOME096372_2, which catalyzes many reactions involving drug metabolism and synthesis of cholesterol, steroids and other lipids. This protein is localized in the endoplasmic reticulum and is known to metabolize up to 25% of commonly used drugs. Its substrates include antidepressants, antipsychotics, analgesics and anticonvulsants, beta-adrenergic blockers, antiarrhythmics and antiemetics. The gene is highly polymorphic in humans; certain alleles result in a poor metabolism phenotype characterized by a reduced ability to metabolize the enzyme's substrates. In addition, the researchers found that at least 2/3 of the 271 clinical drugs selected could be metabolized by one and more strains, and experimentally validated 30 enzymes encoded by microorganisms with drug-metabolizing abilities that were able to convert 20 drugs into 59 candidate metabolites. However, the homology between human drug metabolizing enzymes and metabolizing enzymes in gut microorganisms has not been systematically investigated. Based on online public data, we have made the first systematic study to compare the homology between human drug metabolizing enzymes and gut microorganisms and found a large number of microbial metabolizing enzymes with homologous phenotypes, and we hope that our study can provide a theoretical basis for subsequent studies of gut microorganisms and drugs.

2. Methods

2.1. Human drug metabolizing enzymes summary and sequence download

Currently, drug metabolizing enzymes mainly include phase I drug metabolizing enzymes and phase II drug metabolizing enzymes. Phase I drug metabolizing enzymes include cytochrome P450 enzymes and non-cytochrome P450 enzymes. We mainly studied CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, CYP4F2, ALDH, DPYD, NAT1, NAT2, GST, TPMT, UGT1A1. The protein and gene sequences of drug metabolizing enzymes were downloaded from the GENE database of NCBI.

2.2. Gut microbial genome sequence download and identification of homologous drug metabolizing enzymes

The human gut microbial genome (UHGG) database was downloaded and the sequences of human drug-metabolizing enzymes were matched to the gut microbial genome by blast to find homologous proteins ($1e-5$ && identity > 25%) of all human drug-metabolizing enzymes from different bacterial genomes. Subsequently, the homologous proteins matched to human drug-metabolizing enzymes were validated by blast comparison with the nr library of NCBI. The homologous proteins as well as the corresponding genomic sequences were used to construct a microbial genomic drug-metabolizing enzyme database.

2.3. Identification of intestinal drug-metabolizing enzyme species and their abundance

Homologous genes containing drug metabolizing enzymes were Blast matched against the human gut microbial genome (UHGG) database to identify the corresponding species of gut microbial genome sequences containing drug metabolizing enzymes ($1e-5$ && identity > 90% && besthit). Find the abundance of gut microbes (flora) in the Human High Quality Gut Microbial Database

(<https://gmrepo.humangut.info/taxon>).

2.4. Diseases of human and intestinal microbial drug metabolizing enzymes and drug research

Find human drug-metabolizing enzyme-associated diseases on Genecard (<https://www.genecards.org/>) and pharmgkb (<https://www.pharmgkb.org/>), and in the Human High Quality Gut Microbes database (<https://gmrepo.humangut.info/taxon>) for diseases associated with gut microbes containing drug-metabolizing enzymes.

3. Result and Discussion

3.1 Summary of human drug metabolizing enzymes

We have summarized the human drug metabolizing enzymes based on literature reports and divided them into two main groups: phase I drug metabolizing enzymes and phase II drug metabolizing enzymes. phase I enzymes (CYP450) are composed of the pigment cell riboflavin protein. They are mainly oxidation, reduction and hydrolysis reactions, producing a series of hepatocytotoxic products, including electrophile and oxygen radicals. Among the phase I drug metabolizing enzymes, it contains cytochrome enzyme P450 and non-cytochrome enzyme P450. cytochrome enzyme P450 contains: CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, CYP4F2, etc. and is represented by CYP3A4, which is mainly found in the liver and small intestine. It oxidizes exogenous organic small molecules (xenobiotics), such as toxins or drugs, in order to get them out of the body. The non-cytochrome enzymes P450 contain: ALDH and DPYD. represented by ALDH, a type of aldehyde dehydrogenase, which is responsible for catalyzing the oxidation of acetaldehyde to acetic acid. ethanol dehydrogenase in the liver is responsible for the oxidation of ethanol (a component of wine) to acetaldehyde, and the resulting acetaldehyde is further converted to harmless acetic acid as a substrate catalyzed by acetaldehyde dehydrogenase. Phase II enzymes perform binding reactions, i.e., drug detoxification processes. phase II reactions, in which the prodrug or its metabolites after phase I reactions contain certain chemical functional groups, often readily combine with endogenous substances azoic or conjugated to form conjugates, which are often polar molecules and are often inactive, and thus can be excreted from the body relatively quickly. Phase II drug metabolizing enzymes include: NAT1, NAT2, GST, TPMT, UGT1A1, etc., with GST as the representative, it is one of the most important phase II metabolizing enzymes for in vivo biotransformation and is the main detoxification system for cellular anti-damage and anti-carcinogenesis.

3.2 Identification of intestinal microbial drug-metabolizing enzymes

Using bioinformatic methods, we identified a total of 20 drug-metabolizing enzyme homologs in the gut microbes, all of which were derived from the cytochrome P450 of phase I drug-metabolizing enzymes, such as CYP3A4, CYP2D6, CYP2C19 and others. We found that CYP3A4, a human drug enzyme, is homologous to three gut microbial sequences, GUT_GENOME096290, GUT_GENOME096372 and GUT_GENOME141763. CYP3A4 is generally expressed in Liver, Epithelial Cells, Amnion, and Intestine and leads to the expression of CYP3A4 in human. CYP3A4 is generally expressed in the Liver, Epithelial Cells, Amnion, and Intestine and causes the following diseases: heart transplantation, Kidney Transplantation, laparoscopic sleeve gastrectomy, liver transplantation, lung transplantation. Similar examples are CYP2C9, a human drug enzyme that is expressed in Liver; Epiblast; Amnion; Epithelial Cells; Intestine and causes the following diseases: Coumarin Resistance, Diffuse A total of three gut microbial sequence homologs, GUT_GENOME142457, GUT_GENOME141763 and GUT_GENOME096089, were identified in the gut microbial genome.

3.3 Gut microbial drug-metabolizing enzyme species and their abundance

Based on the results of bioinformatic analysis, we learned that the 20 drug-metabolizing enzyme homology sequences, mainly from three intestinal microorganisms were *Helicobacter canadensis*, *Bacillus subtilis*, and *Paenibacillus*. we performed a predictive analysis of the three microorganisms using the human high-quality intestinal microbial database (<https://gmrepo.humangut.info/taxon>). We found that *Helicobacter canadensis* causes Severe Acute Malnutrition, which occurs at a frequency of about 0.019%, and *Bacillus subtilis* causes HYPERTENSION as well, which occurs at a frequency of

0.213%. *Paenibacillus* causes Kidney Diseases, with a frequency of about 1.204%.

3.4 Study of intestinal microbial drug-metabolizing enzymes and human drug-metabolizing enzyme-related diseases

To investigate whether metabolic enzymes in gut microbes are associated with diseases, we investigated the diseases associated with microbial species containing drug-metabolizing enzyme homologs and the diseases associated with human drug-metabolizing enzymes. We found that CYP3A4 was associated with hypertension, heart transplantation and other diseases by reviewing the genecard database, while *Bacillus subtilis* was associated with hypertension in the human intestine by reviewing the NCBI, which may indicate that *Bacillus subtilis* has the potential ability to digest drugs in hypertension diseases. The presence of large amounts of CYP3A4 in human intestinal microorganisms has been reported, which suggests that intestinal microorganisms have the ability to break down drug molecules.

4. Conclusion

Based on this study, we have preliminarily demonstrated the presence of homologs of drug-metabolizing enzymes in gut microbes and identified which species may carry these homologs. Interestingly, only members of the cytochrome P450 family of phase I drug-metabolizing enzymes were found to be present in the gut microbes, and it is unknown whether other types of drug-metabolizing enzymes are present in the gut microbes, which may require further exploration. Frankly speaking, there are many shortcomings in this study, for example, the sample size of the data used is not large, and the homologous genes of drug-metabolizing enzymes need to be further verified. However, in the future, we believe that the research on gut microorganisms will become hot with the development of technology, especially in the aspect of clinical typing of drugs, and the performance of gut microorganisms will be especially outstanding.

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