



Metabolomic Interactions: An Insight into Health and Disease

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Authors' contributions

This work was carried out in collaboration among all authors. Author MRM conceived and designed the study. Author SMA and SSK were responsible for data collection and acquisition of data. Authors SPA and KRG analyzed, interpreted the data and wrote the initial manuscript. Author SV and AAM critically revised the manuscript. All authors have read the final manuscript.

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ABSTRACT

Over the past decade, metabolic engineering has emerged as an active and distinct discipline characterized by its over-arching emphasis on integration. In practice, metabolic engineering is the directed improvement of cellular properties through the application of modern genetic methods. The concept of metabolic regulations deals with the varied and innumerable metabolic pathways that are present in the human body. A combination of such metabolic reactions paves the way to the proper functioning of different physiological and biological processes. Dealing with the adversities of a disease, engineering of novel metabolic pathways showcases the potential of metabolic

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engineering and its application in the therapeutic treatment of diseases. A proper and deeper understanding of the metabolic functions in the human body can be known from simulated yeast models. This review gives a brief understanding about the interactions between the molecular set of metabolome and its complexity.

Keywords: Metabolome; metabolic engineering; microbiota; microbiome; metagenomics.

1. INTRODUCTION

As a central hub or an area concentrated with majority of metabolic reactions, it can be understood from the studies of the gut that systemic metabolism in human is not just regulated by their genes and their personal dietary habits but also by gut microbes [1]. If the gut microbiota present in the body is in a state of intestinal dysbiosis, certain micro-organisms like *E.coli* can be engineered and modelled metabolically to improve the functioning and growth of the indigenous microbiome [2]. The role of microorganism is widely being known and explored in the recent years due to their exploitable advantages and disadvantages that are meant to be kept in check [3]. Apart from different cohorts and divisions of microbiota present, a decent understanding and knowledge about the gut microbiota present in the human digestive system is required to evaluate, explore and treat the different diseases related to the human intestine tract [4]. A proper balance in the growth and bioactivity of different intestinal flora is required for the homeostasis of the human biological system [5]. A metabolic pathway is basic for every disease or any biological function that takes place in the body [6]. So, study about these metabolic pathways and identifying the metabolites involved in them as markers helps in easy diagnosis and treatment of different diseases [7] like Non-small cell lung cancer and Anaplastic large cell lymphoma (ALK), Alpha-fetoprotein (AFP) - Liver cancer and germ cell tumours, Beta-2 – microglobulin (B2M) - Multiple myeloma, chronic lymphocytic leukemia, and some lymphomas and problems faced by the organism [8].

2.1 Role of Metabolites in Precision Medicine

It is known from statistics that out the many people who are being treated with a disease only few of them are responding to the treatment and some are not. As an example when it comes to the radiotherapy and immunotherapy for the treatment of different cancers, only a handful people are being cured. This is because not

every individual's body responds in the same way. So this is where the concept of precision medicine comes in to picture [9]. With the required biomarkers and companion (diagnostic tests used as a companion to a therapeutic drug to determine its applicability to a specific patient), researchers based on the patients disease progression and other key factors can stratify patients in to subsets [10]. This facilitates in the better prediction of disease outcomes so that appropriate treatment regimes can be formulated for the different sub groups identified. In turn, stratified medicine can give rise to precision medicine, where treatment is tailored for each patient according to their medical history, results from other tests, their response to medication and other clinical features [11]. In this respect there are a set of plant derived secondary metabolites like Vinblastine [12], Capsaicin [13], Curcumin [14] which are of medicinal importance. These metabolites can be harnessed by modifying their respective metabolic pathways so that these metabolites are produced in large amounts. As a result they can be commercially produced in large amounts and aid in the treatment of different diseases [15]. Transcriptomics and proteomics have produced tremendous amounts of comprehensive data on life. Additionally, analysis of the experimental data by bioinformatics has also generated clusters and networks that are composed of many links connecting genes, proteins, and chemical substances.

2.2 Gut Microbiota – Impacting Flora in Human Body

The fluctuation seen in the growth of different gut microbiota can be due to host genotypes, physiological status, diet, drugs, and living conditions. The system formed as a combination of both the gut microbiota and the human system is called a “Super organism” [16]. Based on the effects they induce, gut microbiota can be divided into 3 groups: - 1) beneficial bacteria 2) conditional pathogenic bacteria 3) pathogenic bacteria. As per the growth and functioning of different classes of gut microbiota listed above it results in the different diseases and ill effects of

the gut and organs concerned to it like the liver and the gall bladder.

2.3 Scfa and Gut Microbiota

In general the food that enters into the digestive system is partly digested by the digestive enzymes and partly by the gut microbiota. The complex carbohydrates that entering the human gut is fermented into SCFA (small chain fatty acids) via the gut microbiota which further promotes the process of intestinal gluconeogenesis, and the formation of lipids [17]. This SCFA produced is known to play certain significant role in host organisms by improving the intestinal functioning, increases the resistance against pathogenic microorganisms, fight tumours, maintaining the electrolyte balance of the host and they also provide energy to the host epithelial cells [18]. Another intriguing factor about the gut microbiota is found out through a study that the peroxisome proliferation receptor- γ (PPAR- γ) signal induced by them is the one responsible for maintaining homeostasis. The compound that is responsible for the transduction of PPAR- γ is butyrate which is mainly produced by the metabolism of Clostridia. Butyrate also decrease the production of TGF- β 1 and IL-6, increases the activity of cytokines (anti-inflammatory) and by inducing the T cells enhances body immunity through anti-inflammatory effects [19].

It was further known that the *Bifidobacteriaceae* in the intestine of the mice have started to increase in number after the treatment with oligofructose weakened the weight gain, fat accumulation and ameliorated metabolic disorders induced due to high fat diet in mice [20]. *Akkermansia muciniphila* is microbe whose abundance in the gut is closely related with the health of the host. It majorly survives on the intestinal mucin as the only carbon and nitrogen source with its main metabolite being propionate (SCFA) and its intestinal abundance is around 1-3%. These bacteria with its metabolite are seen to have their effect in the inflammatory responses of obese and diabetic patients, improve adverse symptoms such as insulin resistance and glucose tolerance [21].

2.4 Gut Microbiota- A Regulative Biome for Many Diseases

A comprehensive study on gut microbiota can give us a idea about different diseases on which the gut microbiota can have their effect [22]. If seen every disease has its own specific microbial

markers for the targeted treatment of diverse diseases. In this point of view Louis et al. found out that, in a weight loss problem conducted the *Firmicutes/Bacteroidetes* was high in obese patients [23] and the *Akkermansia* an intestinal microbiota abundance was found in successful weight loss patients [24]. Additionally it was also found that the *Lactobacillus* additives maintain homeostasis and reduced body weight considerably [25]. Similarly when it comes to liver diseases and liver cirrhosis, compared to healthy individuals the significant increase in the number of *Enterobacteriaceae*, *Enterococcus* species and *Proteus* species were found in patients with liver cirrhosis [26]. Seen at the pathogenesis of gastrointestinal diseases the microorganisms like Enterotoxigenic *B. fragilis* induced inflammatory responses in colorectal cancer (CRC) mouse models [27]. In this disease model it was also found out that the colon epithelial regeneration was hindered to an extent due to the low availability or absence of *Bifidobacterium* [28].

2.5 Role of Metagenomics: Gut Microbiota

A complex and dynamic environment is established in human gastrointestinal tract. Its known fact that the microbial microflora plays an important role in the host immune response (Fig. 1). The microbiota number is 10 times of the total human cells and the microbiota is referred as an important organ. The effects brought by the microflora is due the host genome as well as microbial genome [29]. It was found that over 100,000 bacterial species were found and metagenomics proved that 99% of the harbored microbiota are bacteria. By applying the metagenomics fecal samples were analyzed, surprisingly it was found that millions of non-redundant genes were traced and the entire gene set is larger than of humans [30]. Metagenomics was first explained in 1998 by Handelsman and Rodonand and this became useful approach to study the complex gut microflora. The random sequencing of all genes from the complex environment of microbiota is carried out and before being sequenced the samples are sheared by short gun approach [31].

2.6 Functional Genomics- Paving A Path to Discover Novel Genes, Metabolic Pathways and Identification of Antibiotic Resistant Genes

E.coli is commonly used bacteria for studying functional metagenomics, it is because genes from other species of bacteria can also be

expressed in *E.coli*. The human gut microbiota produces CAZymes (Carbohydrate active enzymes) which help in degrading the complex fiber into absorbable monosaccharide and disaccharides. The metagenomics revealed the role of CAZymes and its diversity among the species in gut. Recent studies also revealed the butyrate producing pathways and it's found that genomes of 225 bacteria are capable of producing butyrate and most of them belonged to families of Firmicutes [32]. Novel β -glucuronidase activity was found dominant in healthy adults and children was revealed by functional screening of metagenomic libraries of *E.coli* clones. It is important to understand the contribution of gut microbiota towards the resistance attained by the host organism. Diseases due to bacterial infections it is becoming difficult to treat and the disease occurs when the pathogenic microbial population outnumbers the non-pathogenic ones [33]. The resistance is attained by host because the gut harbors the microflora with antibiotic resistant genes (ARGs). It has become possible to predict the phenotype of resistance by knowing the genome set of microorganism and to reveal the novel ARGs in both microflora and host. The findings also demonstrated that fecal resistomes are of higher diversity in healthy children [34].

2.7 Metagenomics in Finding Functional Dysbiosis

Intestinal Gut microbiota dysbiosis is associated with the diseases within the host because the metabolism is not only regulated by the genes of host but also by its close interaction with gut microbiota [35]. The diseases associated with the microbiota dysbiosis are illustrated below and other incidences of occurrence of other diseases such as Cholesterol gall stone, Diarrhea, nonalcoholic steatohepatitis, cardio vascular associated and neurological disorders are also

prevalent [36]. The changes in microbial functions can also be understood from the metagenomics. Novel plasmids are also identified in gut microbiota and these elements help in the co-evolution of host and microorganism. Based on the results of the metagenomic analysis the chances of horizontal gene exchange between phylogenetically distant bacterial species [37].

2.8 Shotgun Sequencing – for Predicting Function of Microbiome

The whole genome can be analyzed using this method by using continuous overlapping sequences (contigs) which are obtained from fragmented sequences and assembled from whole purified genome set using references data bases like SEED, KEGG and NCBI [38]. In this method the sequences are submitted to different methods like endonucleases, nebulization for the fragmentation and alignment of sequences. The method gives the detailed understanding of the polymorphisms that helps to know information of gut microbiota. These metagenomic studies revealed the relationship between digestion and microbiota. Sometimes small undigestible compounds are formed into small chain fatty acids (SCFAs) and they play an important role in maintaining immune response within gut. When a diabetic patient takes insulin, it is being found that certain species like *Faecalibacterium* and *bifidobacterium* species in human are more dominant. These species are important for metabolic regulation and immune function because they produce folate. Folate is also the precursor of the nucleic acids. The identified genes were submitted in databases which lead to the creation of Human Microbiome Project which has helped in forming the microbiome database. [39].

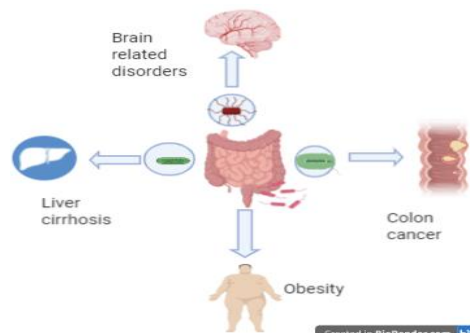


Fig. 1. Understanding the human gut microbiome

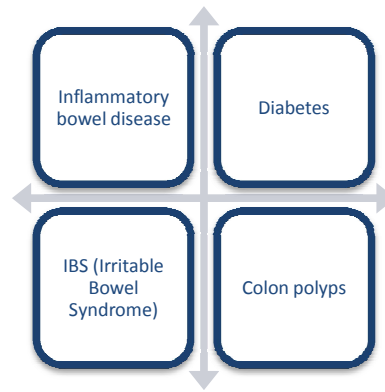


Fig. 2. Etiology of functional dysbiosis.

3. CONCLUSION

From above mentioned strategies using metagenomics it is clear that it has become a powerful technology in analyzing the gut microbiota and in understanding its relationship with host. But there are some limitations. It is not an easy task to know the expression of microbial systems and it also requires higher sequence coverage. The time and cost are also considerable constraints for limitations. Among above all limitations mentioned above getting highly purified and high-quality DNA samples is important because there may be 50% of human contaminants in DNA sample selected.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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