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A *meta-metabolome* network of carbohydrate metabolism: Interactions between gut microbiota and host

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ABSTRACT

With the current knowledge of the multitude of microbes that inhabit the human body, it is increasingly clear that they constitute an integral component of the host. The gut microbiota community is principally involved in the metabolism of dietary constituents such as carbohydrates which account for majority of the energy intake from diet. Diet has gained an important role in shaping the composition of gut inhabitants. The quantity and type of food consumed is recognized as a causal factor for metabolic disorders such as obesity and diabetes. Analysis of host–microbe interactions can thus contribute to the understanding of such metabolic disorders. In this study, data from Kyoto Encyclopedia of Genes and Genomes and Carbohydrate Active EnZYmes Database was utilized as a starting point. Enzyme information from the host *Homo sapiens* coupled with details of the three predominant phyla of gut bacteria, namely *Firmicutes*, *Bacteroidetes* and *Actinobacteria* were used in the creation of a comprehensive metabolic network, which we refer to as '*meta-metabolome*'. This '*meta-metabolome*' provides a perspective of the degree to which microbes influence carbohydrate metabolism, in conjunction with host specific enzymes. Analysis of reactions in the network reveals the amplification of monosaccharide content brought about by microbial enzyme activity. The framework outlined in this study provides a holistic approach to assess host–microbe symbiosis. It also provides us with a means of analyzing how diet can be modulated to provide beneficial effects to the host or how probiotics can potentially be used to relieve certain metabolic disorders.

1. Introduction

The human gastrointestinal tract is densely populated with an aggregate of microorganisms that is commonly known as the microbiota, whose genomes collectively contain a hundred times more number of genes than the host itself. It is referred to as a supplementary organ that is engaged in metabolic activities, which the host is, otherwise, incapable of [1]. Majority of the interactions between the host and microbes are essentially symbiotic and assist the host in deriving maximum nutritional value from the components in the diet. This is done by breaking down complex substances that can then be easily absorbed by the host and also by modifying the metabolic machinery of host cells. The gut microbial community is dependent on host genotype as well as environmental factors and is considered a dynamic ecosystem [2,3]. Through 16S ribosomal RNA gene sequencing, fragment restriction length polymorphism (RFLP) mapping, quantitative polymerase chain reaction, and shotgun DNA sequencing, it is possible to identify the type of microorganisms that inhabit the gut. The predominant species of bacteria that reside in the gut belong to three phyla, namely, the Gram-negative *Bacteroidetes*, the Gram-positive *Actinobacteria* and *Firmicutes* [3].

Carbohydrates form a bulk of the nutritional component of human diet. Simple monosaccharides such as glucose can be directly absorbed by the host. Disaccharides such as maltose, lactose and sucrose can be hydrolyzed to their respective monosaccharides, but the ability to digest complex plant polysaccharides such as inulin, pectin and xylan is very limited [3,4]. Certain class of bacteria can shift between the substrates freely, while others are more specific to a particular substrate. Microbial fermentation of the carbohydrates under anaerobic conditions results in the production of short chain fatty acids (SCFA) like butyrate, propionate, acetate which can be utilized by the host [4].

Butyrate is converted to ketone bodies or carbon dioxide in the epithelial cells of the colon [5]. Propionate and acetate reach the hepatic cells where they are used for gluconeogenesis and lipogenesis respectively. Because the quantity of carbohydrates consumed in the human diet varies from one individual to another, the amount and type of SCFA produced and also the composition of the bacterial species in the gastrointestinal tract differs [3].

Gut microbiota colonization and their interaction with diet are also known to influence expression of host genes that are linked to

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the immune system [6]. The gut microbiota has also been associated with inflammatory diseases such as obesity and diabetes. Studies analyzing the relative proportion of the major microbial players in the gut show that obese individuals have a higher *Firmicutes* to *Bacteroidetes* ratio. When subjected to a low carbohydrate or low fat diet, there was significant increase in the proportion of *Bacteroidetes*, accompanied by weight loss. Humans who were given a high protein diet and reduced carbohydrate intake were observed to have decreased populations of *Eubacterium* and *Roseburia* spp. and *Bifidobacterium* with corresponding decrease in fecal butyrate quantity [7]. The gut microbiota is variable between individuals, but family members share more gut species than unrelated persons. Though there is considerable interpersonal variation in gut species, a potential core set of genes can be identified that represent certain functional features expressed by the microbial population [11].

Colonization of germ free mice by microorganisms is associated with stimulation of glycogenesis in the liver and increase in hepatic triglyceride synthesis. These changes are evidence of the degree of importance of mechanisms that regulate host–gut microbiota interactions [8]. A systems level framework to understand the community network in obese and inflammatory bowel disease conditions also establishes the impact of the microbiome on human health [9].

In this study, the extended carbohydrate metabolism capabilities conferred by the microbial community in the gut, in addition to innate host carbohydrate metabolic activity are analyzed through information accessed from well recognized biological databases and a network is built, encompassing all the appropriate data.

2. Methods

Different online databases used were: NCBI (National Center for Biotechnology Information) Genome, GOLD (Genome Online Database) [10], CAZy (Carbohydrates Active enZymes database) [11], and KEGG (Kyoto Encyclopedia of Genes and Genomes) [12,13]. The Food and Agriculture Organization of the United Nations website (http://www.fao.org/docrep/W8079E/w8079e0h.htm) [14] was utilized to obtain information regarding food sources of different carbohydrates. The ggplot2 tool of the R statistical software was used to generate a heatmap.

2.1. Extracting data from biological databases

Using the NCBI Genome database, GOLD (http://www.genomesonline.org/), and KEGG database, a catalogue of commensal, non-pathogenic organisms, with completely sequenced genomes, that inhabit the human gastrointestinal tract was recorded. *Bacteroidetes* and *Firmicutes* constitute a majority of the microbial population in the gut, hence these phyla were selected. *Actinobacteria* which are less abundant were also selected. The sample size in this study included 5 species of *Bacteroidetes*, 18 species of *Firmicutes* and 5 species of *Actinobacteria* (Table 1). From the KEGG database, the carbohydrate metabolism pathways of these groups of microorganisms were taken and a record of all of the reactions involved in each pathway was made, comprising details of the substrate, enzyme and product. In addition, the reactions from the human carbohydrate metabolism pathways were also considered.

The carbohydrate pathways included in the study were: glycolysis/gluconeogenesis, citrate cycle (TCA cycle), pentose phosphate pathway, pentose and glucuronate interconversions, fructose and mannose metabolism, galactose metabolism, ascorbate and aldarate metabolism, starch and sucrose metabolism, amino sugar and nucleotide sugar metabolism, pyruvate metabolism, glyoxylate and dicarboxylate metabolism, propanoate metabolism, butanoate metabolism, C5-Branched dibasic acid metabolism, and Inositol phosphate metabolism.

The Carbohydrate Active Enzyme database (CAZy) (http://www.cazy.org/) consists of four classes of enzymes – (i) Glycoside hydrolases hydrolyze the glycosidic bond between two or more carbohydrates or between a carbohydrate and a non-carbohydrate moiety. (ii) Glycosyl transferases catalyze the transfer of sugar moieties from activated donor molecules to specific acceptor molecules, forming glycosidic bonds. (iii) Polysaccharide lyases cleave uronic acid-containing polysaccharide chains via a β-elimination mechanism to generate an unsaturated hexenuronic acid residue and a new reducing end. (iv) Carbohydrate esterases catalyze the de-O or de-N-acylation of substituted saccharides [11].

The enzymes highlighted in KEGG carbohydrate pathway reactions of the selected species of *Bacteroidetes*, *Firmicutes* and *Actinobacteria* were compared with the enzymes from each class in the CAZy database (Table 2). Comparisons were also made with the enzymes listed in the KEGG human carbohydrate pathways. The enzymes which areshared by both host and gut microorganisms were recorded along with enzymes that were unique only to the gut microbial species.

Table 1
List of *Firmicutes*, *Bacteroidetes* and *Actinobacteria* with their 3 letter abbreviations.

Firmicutes	Bacteroidetes	Actinobacteria
Eubacterium rectale (ere)	*Bacteroides thetaiotaomicron* (bth)	*Bifidobacterium adolescentis* (bad)
Eubacterium eligens (eel)	*Bacteroides fragilis YCH46* (bfr)	*Bifidobacterium longum*
Anaerococcus prevotii (apr)	*Bacteroides fragilis NCTC9343* (bfs)	*NCC 2705* (blo)
Veillonella parvula (vpr)	*Bacteroides vulgatus* (bvu)	*Bifidobacterium bifidum S17* (bbi)
Enterococcus faecalis V583 (efa)	*Parabacteroides distasonis* (pdi)	*Bifidobacterium animalis* subsp.
L. crispatus (lcr)		*lactis AD 011* (bla)
L. rhamnosus GG (lrh)		*Eggerthella* sp. *YY7918* (eyy)
L. reuteri JCM1112 (lrf)		
L. reuteri DSM20016 (lre)		
L. reuteri SD2112 (lru)		
L. gasseri (lga)		
L. casei BL23 (lcb)		
L. salivarius UCC118 (lsl)		
L. plantarum subsp.		
plantarum ST-III (lps)		
L. plantarum JDM1 (lpj)		
L. acidophilus NCFM (lac)		
L. johnsonii NCC533 (ljo)		
Roseburia hominis (rho)		

Table 2
CAZy enzymes (E.C. Numbers) that are found in *Bacteroidetes*, *Firmicutes* and *Actinobacteria*.

Enzyme name	Present in *Bacteroidetes*	Present in *Firmicutes*	Present in *Actinobacteria*
Glycoside hydrolases	2.4.1.8, 2.4.1.18, 2.4.1.25, 3.2.1.4, 3.2.1.10, 3.2.1.14, 3.2.1.20, 3.2.1.21, 3.2.1.22, 3.2.1.23, 3.2.1.52, 3.2.1.65, 3.2.1.78	2.4.1.-, 2.4.1.5, 2.4.1.7, 2.4.1.8, 2.4.1.10, 2.4.1.18, 3.2.1.1, 3.2.1.4, 3.2.1.10, 3.2.1.20, 3.2.1.21, 3.2.1.22, 3.2.1.23, 3.2.1.26, 3.2.1.31, 3.2.1.52, 3.2.1.54, 3.2.1.55, 3.2.1.85, 3.2.1.86, 3.2.1.93, 3.2.1.122	2.4.1.18, 2.4.1.25, 2.4.1.7, 3.2.1.1, 3.2.1.10, 3.2.1.20, 3.2.1.21, 3.2.1.22, 3.2.1.23, 3.2.1.26, 3.2.1.37, 3.2.1.52, 3.2.1.55, 3.2.1.58, 3.2.1.86
Glycosyl transferases	2.4.1.15, 2.4.1.21	2.4.1.–, 2.4.1.1, 2.4.1.12, 2.4.1.21	2.4.1.1, 2.4.1.15
Carbohydrate esterases	3.1.1.11, 3.2.1.4, 3.5.1.–, 3.5.1.25	2.3.1.–, 2.4.1.–, 3.1.1.–, 3.1.1.11, 3.2.1.4, 3.5.1.–, 3.5.1.25	3.5.1.25, 3.5.1.–
Polysaccharide lyases	4.2.2.6		

3. Results and discussion

3.1. Construction of a meta-metabolome network

On observing the sets of enzymes that are unique to the microbes and those that are common to microbes and host, it is found that in some cases, the gut microbe enzymes and host carbohydrate metabolism enzymes act on the same substrate. A few breakdown products from the microbe metabolism reactions are in turn used as substrates by host enzymes and vice versa, i.e. a cross-feeding is observed, while other reactions are exclusive either to the host or gut flora. A total of 64 enzymes that span 87 reactions are available, out of which, 7 enzymes are unique to the host and 27 enzymes are exclusive to gut bacteria. 11 of these enzymes are present only in *Firmicutes*, 5 enzymes exist only in *Bacteroidetes* and 2 enzymes are found only in *Actinobacteria*. The set of reactions that form this nexus were tabulated in the Supplementary Table (Table S1) and a metabolic map was generated (Fig. 1). To arrive at a more comprehensive network, some non-CAZy enzymatic reactions were also added to the map. The pathway reactions in the network map follow the KEGG annotation for reversible and irreversible reactions.

The nodes in the network denote the metabolites of enzyme catalyzed reactions. The edges between the nodes denote the dif-

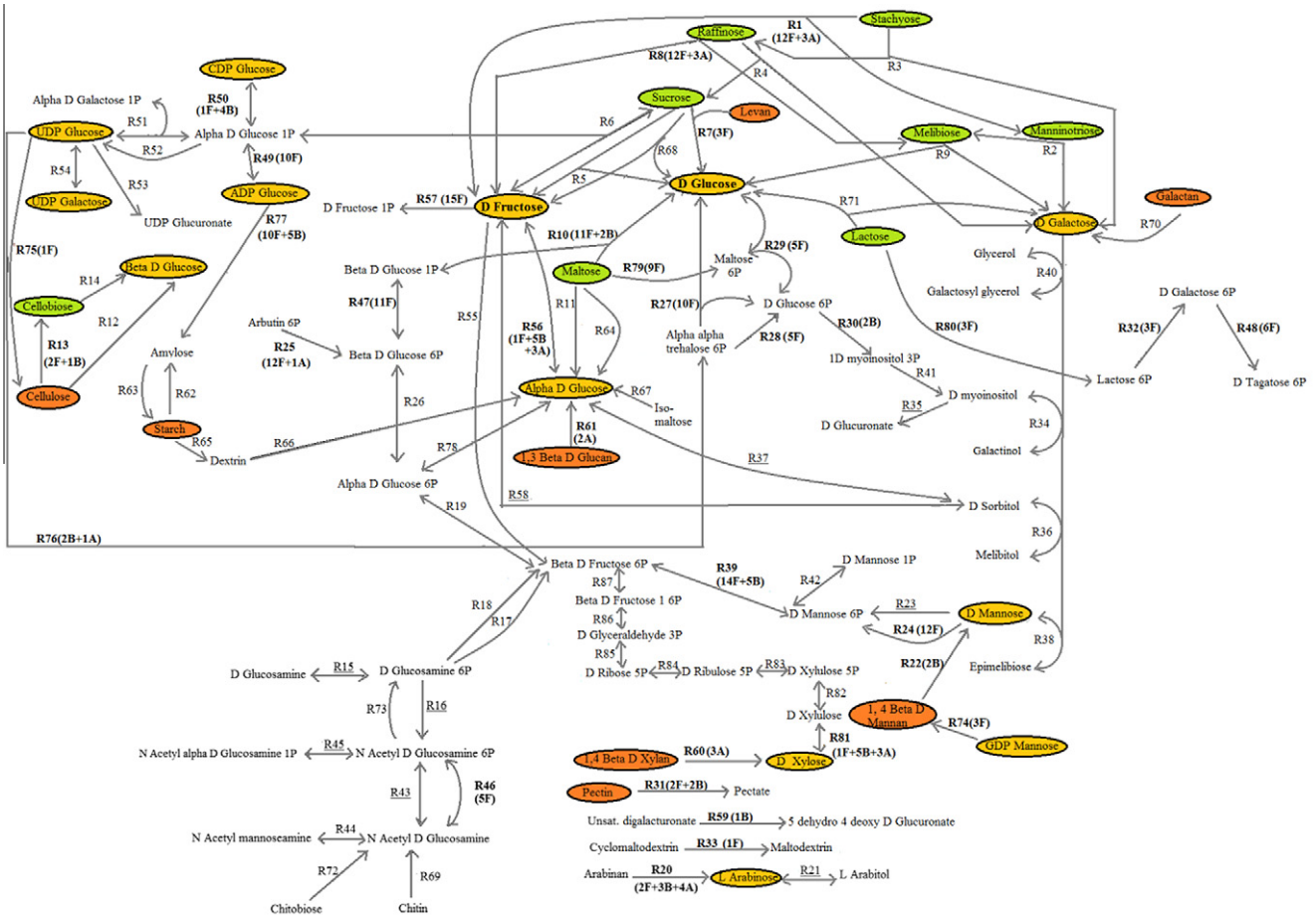

Fig. 1. Meta-metabolome – A metabolic map representing metabolism of carbohydrates aided by microbes of the gut. Reactions numbers shown in **bold** are those catalyzed only by gut microbial enzymes, reactions underlined are those catalyzed by host enzymes, other reactions are undertaken by enzymes common to both microbes and host. Reactions follow KEGG annotation for reversibility and irreversibility. Color codes – Orange for polysaccharides, Green for oligosaccharides and Yellow for monosaccharides. A – *Actinobacteria*, B – *Bacteroidetes*, F – *Firmicutes*.(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ferent enzymes that catalyze the reaction. The edge weightsrepresent the number of species of microorganisms that carry out the particular reaction. The map provides an alternate perspective on how a series of gut microbes effectively collaborate to metabolize carbohydrates that are obtained in diet, in addition to the activity of host enzymes. The network created in this study is not absolute, and is restricted only to carbohydrate metabolism; however it helps to understand the activities in an ideal human gut environment that would be colonized by a composite collection of microbes from the three major bacterial phyla.

The network displays the different stages where the gut microbiota intervenes in the overall carbohydrate metabolism process and significantly, the existence of a '*meta-metabolome*' where microbial and host enzymes are in sync. As is known from animal studies and also from human cases, there is a large division wise increase in the population of *Firmicutes* of obese individuals [15]. A large population of *Firmicutes* would mean an amplified effect of the enzymes responsible for carbohydrate breakdown. The metabolic pathways enriched in a Western diet microbiome [15] include phosphotransferase system, fructose and mannose metabolism, glycolysis/gluconeogenesis apart from others. The *meta-metabolome* network created in this study also points to enzymes of these pathways to be of importance:

3.2. Carbohydrate metabolism and phosphotransferase system in Firmicutes

The phosphoenolpyruvate–carbohydrate phosphotransferase system in bacteria such as *Firmicutes*, is involved in the coupled transport and phosphorylation of disaccharides, monosaccharides and other sugar derivatives [16]. In contrast, the *B. thetaiotaomicron* microbe from *Bacteroidetes* phyla is thought to be deficient in a complete PTS system [17]. In the network, reactions, R24, R57, R79, R80 (Fig. 1) describe the phosphorylation and transport of mannose, fructose, maltose and lactose via the PTS system, where the Enzyme II complex of the PTS is specific to the particular carbohydrate. Thus, it can be inferred that, more amount of carbohydrates are transported with the aid of *Firmicutes*, hence they contribute to an increase in the levels of carbohydrates that are metabolized. Also, in recent studies, it has been identified that the enzymes enriched in obesity and inflammatory bowel disease states belong to the phosphotransferase system or nitrate reductase [9].

The metabolism of lactose takes two directions according to the network generated. One includes breakdown by enzymes common to host and gut microbes (R71), while the other path is exclusive to enzymes found in *Firmicutes*. The path through *Firmicutes* leads to the conversion of lactose to tagatose. The first two steps (R80 & R32) in the conversion of lactose to tagatose are carried out by a common set of three species, namely, *Lactobacillus rhamnosus GG*, *L.gasseri*, and *L.casei BL23*. The enzyme utilized is 6-phospho beta galactosidase (EC No. 3.2.1.85). Conversion of galactose to tagatose (R48) is aided by three additional species, namely, *Anaerococcusprevotii*, *Enterococcus faecalis V583* and *L.crispatus*. Tagatose is a monosaccharide, that is considered to have an anti-hyperglycemic effect, and hence useful in the control of type 2 diabetes [18]. Unabsorbed tagatose is largely converted to SCFA, by fermentation from gut bacteria [19]. This example serves to highlight the use of a combination of these microbial species as probiotics to enhance tagatose absorption.

In the metabolism of maltose, the path exclusive to degradation by enzymes from *Firmicutes* leads to glucose (R79 & R29), this occurs with the help of the PTS system. In addition to this, maltose is also metabolized by enzymes from *Bacteroidetes* and host (R11 & R64). These cases underline instances where bacterial enzymes from *Firmicutes* confer extended metabolic capabilities and hence play an important role in shaping the metabolite pool of the human gut.

3.3. Accumulation of glucose from diet by microbial agents

Glucose is the primary source of energy for living cells and a balance in the levels of glucose is necessary to maintain the integrity of the cells. It is observed from the network that several paths exist to reach glucose and its phosphate derivatives using complex carbohydrates as points of origin.

As an example, a dietary intake of soybeans and other soy related products would result in release of components such as stachyose and raffinose; these oligosaccharides are known to cause gastrointestinal uneasiness [20]. The gut microbes possess the enzyme alpha-galactosidase that act upon stachyose and raffinose, which gives rise to intermediates manninotriose and melibiose. Melibiose is then further broken down to D-glucose with both host and microbial enzymes. It is seen that the beta-fructofuranosidase enzyme from 12 different species of *Firmicutes* and 3 species of *Actinobacteria* is involved in the conversion of stachyose to manninotriose and D-fructose (R1). Conversion of raffinose to melibiose and D-fructose (R8) is again carried out by beta-fructofuranosidase from 12 species of *Firmicutes* and 3 species of *Actinobacteria*. Raffinose is also converted to sucrose and galactose (R4) via alpha-galactosidase enzymes that are common to host and microbes. Sucrose conversion to D-glucose can occur through different reactions, one reaction (R7) being exclusive to levansucrase enzymes from *L.crispatus*, *L.reuteri SD2112* and *L.johnsonii NCC533* strains of *Firmicutes*. The reactions concur with the biochemistry of the oligosaccharides, where stachyose and raffinose comprises of units of galactose, glucose and fructose. These reactions are part of the galactose metabolism pathway listed in the KEGG database. The number of microbial enzymes involved in each reaction is high and the pool of glucose is thus increased with this augmentation provided by the microbial population.

Mannose obtained in the diet through foods such as blueberries, eggplants, broccoli are reduced to metabolites such as epimelibiose and other mannose phosphate derivatives, which is chained back to the fructose pools. Breakdown of mannan to D-mannose (R22) is accomplished only by two species of *Bacteroidetes*.D-Mannose is phosphorylated to D-mannose 6 phosphate (R24) by the PTS system of 12 different species of *Firmicutes*. These reactions are part of the fructose and mannose metabolism pathway listed in the KEGG database.

Table S2 gives details about the reaction number, enzyme name and bacterial strains for all 87 reactions considered in this network. Fig. 2 provides an overview of the number of different bacteria involved in each biochemical reaction. It is seen that the reactions, R2, R3, R4, R5, R9, R11, R12, R14, R17, R34, R36, R38, R40, R62, R63, R64, R65, R66, R67, R70, R71, R72, R73, R78, R82, R83, R84, R85, R86 and R87 take place with enzymes, belonging mainly to glycoside hydrolases and glycosyl transferases classes of CAZy enzymes, which are ubiquitous to organisms from the three phyla as well as the host. From Fig. 2 and Table S2, it is seen that a majority of the metabolic reactions are accomplished by organisms of the *Firmicutes* phyla, this could be attributed to the fact that the sample population used, consisted of more number of *Firmicutes* than *Bacteroidetes* and *Actinobacteria* put together.

3.4. Heatmap representation of carbohydrate enzymes among Bacteroidetes and Firmicutes

A graphical representation of the carbohydrate enzymes found in the gut microbial community of *Firmicutes* and *Bacteroidetes* is shown in Fig. 3. The heatmap generated shows the presence (colored black) or absence (colored white) of an enzyme in a particular

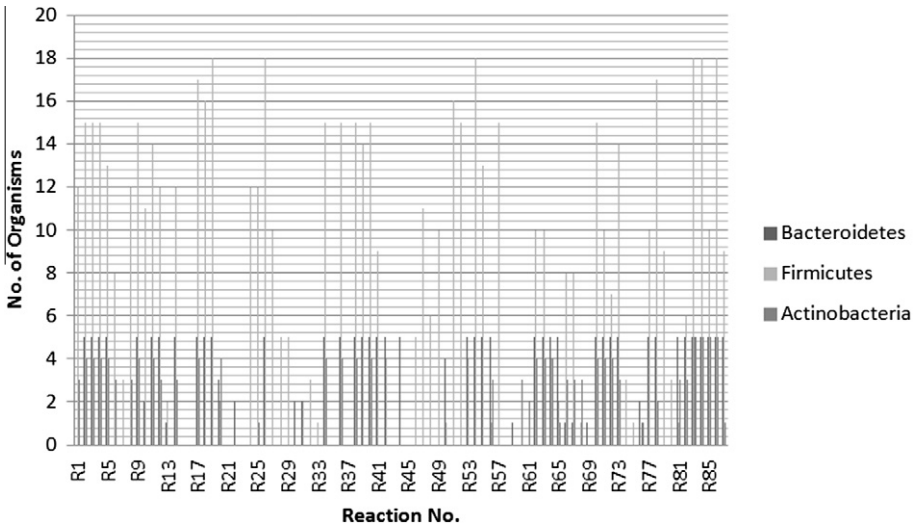

Fig. 2. Number of microbial species from each phyla of gut bacteria involved in the biochemical reactions of carbohydrate metabolism.

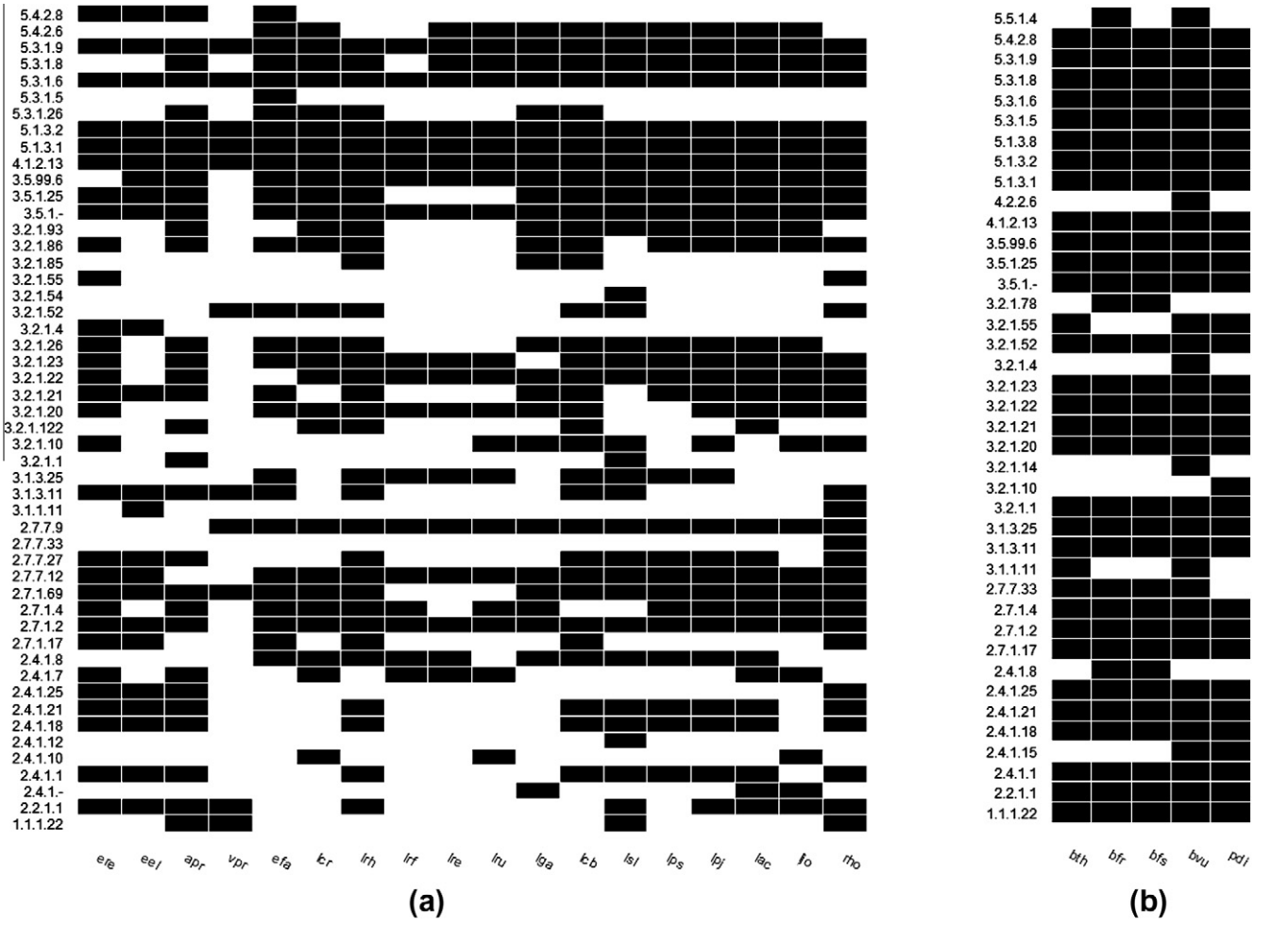

Fig. 3. Heatmap showing the occur1rence of enzymes from the carbohydrate metabolism (a) different strains of *Firmicutes* and (b) different strains of *Bacteroidetes*. Black color indicates the presence of the enzyme, while white color denotes the absence of the enzyme in the particular strain.

microbial species. Fig. 3(a) shows the enzymes among *Firmicutes*, while Fig. 3(b) shows the enzymes among *Bacteroidetes*. Among *Firmicutes*, *L.rhamnosus GG* and *L.casei BL23* have a majority of the enzymes that are required in the metabolism of carbohydrates, while *Veillonella parvula* consists of the least number of enzymes. Certain enzymes such as alpha L-arabinofuranosidase (EC No.

5.4.2.8) is found in *Eubacterium rectale* and the enzyme pectin esterase (EC No. 3.1.1.11) is found only in *Roseburia hominis* and *Eubacterium eligens*. These *Firmicutes* are therefore considered to possess additional capabilities compared to other members of the group. Among *Bacteroidetes*, *Bacteroides vulgatus* consists of most of the enzymes required for carbohydrate metabolism.

3.5. Metabolism and association with short-chain fatty acids

The end products of metabolism are observed to be various derivatives of monosaccharides, which are intermediates in the glycolytic and pentose phosphate pathways leading to the production of SCFA, which can be absorbed via transporters in the intestinal lumen and then taken to the bloodstream. A particular kind of polysaccharide produces specific SCFA, for instance, breakdown of xylan and pectin gives acetate [26]. Some enzymatic reactions are found to be identical with microbial enzymes and human enzymes, suggesting that there is an escalation in the production of SCFA, due to the combined effect of native human enzymes and enzymes belonging to the diverse species of gut microbes. Sugar alcohols or polyols such as sorbitol and maltitol result in the enrichment of bacterial population and also contribute to increase in the levels of SCFA [21].

3.6. Carbohydrate metabolism linked to disease states

Consumption of a diet rich in carbohydrates includes activation of a wide range of microbial enzymes, and increased glucose flux to the hepatic cells in the liver. This leads to the over production of SCFA, and enhancement of *de novo* lipogenesis followed by triglyceride production and accumulation that could serve as a precursor for obesity [1]. Alterations in gut bacteria also influence intestinal permeability and inflammation, and hence, metabolic disorders such as diabetes [22].

Deficiency of certain carbohydrate enzymes can cause diseases, for example, deficiency in alpha-galactosidase causes Fabry disease. The disease is associated with accumulation of glycosphingolipid globotriaosylceramide in the body accompanied with gastrointestinal symptoms of diarrhea and abdominal pain. Enzyme replacement therapy is used as a means for treatment of the disease [23]. The enzyme alpha galactosidase is observed to catalyze reactions R2, R3, R4, R9, R34, R36, R38 and R40 in the *meta-metabolome* network. The enzyme is found in 15 strains of *Firmicutes*, 5 strains of *Bacteroidetes* and 4 strains of *Actinobacteria*. The option of using gut microbes that have alpha galactosidase as probiotics to compensate host deficiency of the enzyme can thus be explored. Hexosaminidases are known to cleave beta-glycosides of N-acetylglucosamine and *N*-acetyl-*d*-galactoseamine (R73) [24]. The enzyme catalyzing reaction R72 is found in all the 5 species of *Bacteroidetes* considered in this study, along with 7 species of *Firmicutes* and 4 strains of *Actinobacteria*. A deficiency in the hexoaminidase enzyme results in Tay-Sachs [25] and Sandhoff diseases. The information of such gut microbial enzymes can potentially be used to treat these diseases.

The right knowledge in the quantity and combination of carbohydrates to be taken on a daily basis can help achieve a balance in the amount of SCFA produced. Though genetic and environmental factors play an important role in the class of microbes existing in the gut [1,26], the diet of an individual is one that can be altered more readily and hence is of great interest to help sustain a good population of microbes in the gut, which impart favorable properties to the host. This study has underscored the importance of providing a framework to address carbohydrate metabolism in a holistic manner. Large scale metagenomic sequencing carried out under the Human Microbiome Project has been able to provide sufficient information on individual metabolic pathways of gut microorganisms that are deposited in public repositories. Recent studies, thus far, have considered microbial communities and their association with disease states [9]. We present an integrated network that includes host enzymatic activities in association with microbial enzymes. The inclusion of host enzymes is relevant to the systems biology top-down approach. A framework of this kind, could aid in the identification of microbial strains that have beneficial properties for the host under some conditions, and targeting of enzymes from strains that may benefit the metabolic process.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2012.10.045.

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