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MINI-REVIEW

Structural diversity, functional aspects and future therapeutic applications of human gut microbiome

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Abstract

The research on human gut microbiome, regarded as the black box of the human body, is still at the stage of infancy as the functional properties of the complex gut microbiome have not yet been understood. Ongoing metagenomic studies have deciphered that the predominant microbial communities belong to eubacterial phyla *Firmicutes, Bacteroidetes, Proteobacteria, Fusobacteria, Cyanobacteria*, *Verrucomicrobia* and archaebacterial phylum *Euryarchaeota*. The indigenous commensal microbial flora prevents opportunistic pathogenic infection and play undeniable roles in digestion, metabolite and signaling molecule production and controlling host's cellular health, immunity and neuropsychiatric behavior. Besides maintaining intestinal health via short-chain fatty acid (SCFA) production, gut microbes also aid in neuro-immuno-endocrine modulatory molecule production, immune cell differentiation and glucose and lipid metabolism. Interdependence of diet and intestinal microbial diversity suggests the effectiveness of pre- and pro-biotics in maintenance of gut and systemic health. Several companies worldwide have started potentially exploiting the microbial contribution to human health and have translated their use in disease management and therapeutic applications. The present review discusses the vast diversity of microorganisms playing intricate roles in human metabolism. The contribution of the intestinal microbiota to regulate systemic activities including gut–brain–immunity crosstalk has been focused. To the best of our knowledge, this review is the first of its kind to collate and discuss the companies worldwide translating the multi-therapeutic potential of human intestinal microbiota, based on the multi-omics studies, i.e. metagenomics and metabolomics, as ready solutions for several metabolic and systemic disorders.

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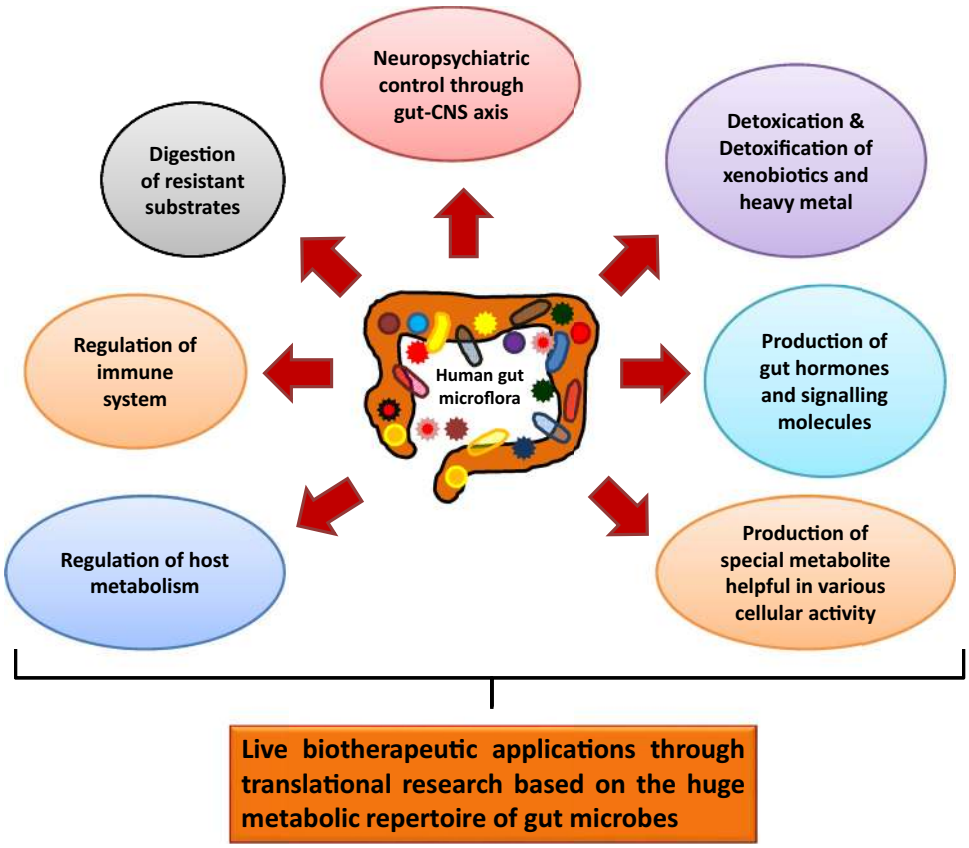
Graphic abstract



Keywords Gut microbiome · Short chain fatty acids · Xenobiotic degradation · Immune system and gut–CNS axis · Therapeutic applications

Introduction

Human gut microbiome refers to the total microbial population in the human gastrointestinal tract (GIT) that includes bacteria and other microorganisms. The human body is the host to approximately 500–1000 species of gut microbes that encode 100-fold more unique genes than the host human genome (Ley et al. 2006). The huge diversity of gut microbiota remained unknown until culture independent high-throughput sequencing technology and powerful analytical and bioinformatics tools were developed. With the development and advancement of next generation sequencing technology, the long unexplored black box of the human body, i.e. the gut microbiome came into light and a deeper understanding of the same was designated as the second human genome (Mosca et al. 2016). Although the first one is inherited from the parents of an individual and is highly stable, the second genome is adapted from the environment after birth and remains continuously dynamic (D'Argenio and Salvatore 2015). The second genome, i.e. the acquired microbiome is therefore, highly dependent and subject to change upon several environmental factors, such as i) host genotype and ethnicity, ii) age and sex, iii) diet, iv) hormonal cycles, v) illness and therapies, and vi) travel history. Establishment of a microbial community is therefore, consequent to varied range of ecological interactions classified under five different heads: i) mutualism—beneficial interaction for both the partners), ii) amensalism—one impacts the other negatively, iii) commensalism—one impacts the other positively, iv) competition—both the competitors harm each other, v) predation and parasitism—one gets benefitted out of the other (Faust and Raes 2012; Mosca et al. 2016).

Mounting evidences indicate that the trillions of bacteria and archaea residing in the human gut are extensively related to host health regulating various metabolisms, such as fermentation and digestion of various biomolecules, xenobiotic degradation and heavy metal biotransformation, production of various immune regulators and special metabolites, energy production, epithelial homeostasis, short-chain fatty acid (SCFA) production and so on (Bäckhed et al. 2015; Li

et al. 2019). The gut microbiome comprising thousands of bacterial species interact and crosstalk with the host cells in various ways and comprehensively with the host genome to determine human health. Disturbed ecology of the gut microbiome has been frequently reported to be associated with various human diseases, such as obesity and metabolic syndromes, non-alcoholic fatty lever disease, coronary heart disease, irritable bowel syndrome, inflammatory bowel disorders, allergy, asthma, etc. (Holmes et al. 2011; Mosca et al. 2016). Extensive research on gut microbiome through various alterations have shown that the secondary metabolites produced by the bacterial flora can signal the activity of distal tissues, such as liver, brain, muscle and adipose tissues. A healthy and normal microbiota not only maintains the gastrointestinal activities, but also controls various central nervous systemic activities, perturbation of which might trigger neuropsychiatric effects, such as anxiety, depression, schizophrenia and autism (Yarandi et al. 2016). The nature of microbial composition of human gut is increasingly being documented through various microbiome projects, such as the International Human Microbiome Consortium, the European Commission's Metagenomics of the Human Intestinal Tract Project, the US National Institutes of Health's Human Microbiome Project, the Human Microbiome Project (HMP) the Human Gastrointestinal Bacteria Genome Collection (HGG) and the Canadian Microbiome Initiative which finally converge into a single global network (Bäckhed et al. 2015; Gevers et al. 2012; Huttenhower et al. 2012). Several recent research findings that are intriguing yet very promising could pave the way for filling the knowledge gaps in microbiome–host interactions and their role in disease pathogenesis as well as potential therapeutic applications.

In view of the existing knowledge on gut microbiome the present review discusses an integrated approach to understand the diversity of the complex black box of our body and the specific roles of particular bacterial taxa related to human metabolism under varying environmental or physiological conditions. It further discusses as to how the extraordinarily diverse microbial community participates in the functioning of innate and adaptive immune responses and is also involved in the crosstalk with central nervous system where brain commands several gut functions like mucin production, peristalsis and gut immune functions. The potential use of gut microbiota by several start-up companies for therapeutic applications and commercialization is also discussed.

Diversity in the gut microbiome

Microbial colonization on the human body starts immediately following birth and the community composition is shaped by various environmental factors. Various molecular techniques have been employed to analyze the microbial diversity and abundances (Table 1). The infant gut microbiota is majorly predominated by members of *Actinobacteria, Proteobacteria, Firmicutes* and *Bacteroidetes* and the abundance of the phylum detected are according to the order of their appearance. However, in adults, the abundance shifts to *Firmicutes* followed by the members of *Bacteroidetes* and *Actinobacteria.* Although members of *Proteobacteria, Fusobacteria, Cyanobacteria* and *Verrucomicrobia* are present in adults, but are less represented (Eckburg 2005; Ley et al. 2006; Winston and Theriot 2020; Zhernakova et al. 2016). Trillions of bacteria belonging to thousands of different species majorly fall under the above mentioned phyla (D'Argenio and Salvatore 2015; Li et al. 2008). Human metabolic phenotypes are found to be modulated by the symbiotic intestinal gut microbiome. Moreover, their ratio of abundance might act as biomarkers indicating sex, age or diseased conditions. Li et al. (2008) in their study showed that a low ratio of *Bacteroidetes* to *Firmicutes* correlate with obesity and could be elevated by restricting the dietary calorific intake.

DGGE fingerprint study to identify the key OTUs of specific and dominant intestinal bacterial groups provided a deeper level understanding (Li et al. 2008). The major OTUs were found to be predominated by *Bacteroides coprocola, B. thetaiotaomicron* and *B. uniformis.* These were shown to be important metabotypes which displayed correlation with various urinary metabotypes (Li et al. 2008). Studies on gut microbiome in an European population through fluorescence in situ hybridization (FISH) and flow cytometry is also found to be sex dependent as gender specific differences in ratio of *Bacteroides* to *Prevotella* were found to be higher for males than females (Mueller et al. 2006). Among these, *B. thetaiotaemicron* was found to be more abundant in males than in females which may serve as a potential marker for sex-discrimination (Li et al. 2008). Another study documented the prominent differences in the microbial community composition in obese and non-obese individuals through metagenomic high-throughput sequencing (Chatelier et al. 2013). Individuals with low gene count (LGC), i.e. < 480,000 genes were found to be associated with inflammatory bowel disorder (IBD), inflammation and obesity and were detected with low richness of gut microbiota. Others were considered as high-gene count (HGC) group, i.e. with > 480,000 genes who were non-obese and with little reported gut disorder. They could detect that 46 bacterial genera differed significantly in abundance. The phylogenetic shift showed an abundance of phyla *Proteobacteria* and *Bacteroidetes* encompassing genera *Bacteroides, Parabacteroides, Ruminococcus* (*R. torques, R. gnavus*), *Campylobacter, Dialister, Porphyromonas, Staphylococcus* and *Anaerostipes* in LGC individuals. Concurrently, HGC individuals were found to be highly associated with members of phyla, *Verrucomicrobia,*

Table 1 List of microbiological, biochemical and molecular techniques applied to analyze the microbiome components of an environment

Sl. No	Technique	Principle	References
Microbiological and Biochemical Techniques			
1	Plate counts	Direct cultivable bacterial count upon growth on media plates based on morphological differences	Kirk et al. 2004
2	Community Level Physiological Profiling (CLPP)	Physiological profiling based on sole carbon source utilization properties of microbial communities helpful in detecting copiotrophic organisms	Lladó and Baldrian 2017
3	Fatty Acid Methyl Ester analysis (FAME)	Gas chromatographic analysis of cellular fatty acids through	Ghosh et al. 2020
4	Guanine plus Cytosine (GC)	GC content of the genomic DNA, a taxon level characteristic feature, is analyzed through melting temperature curve of DNA renaturation studies	Kirk et al. 2004
Molecular Techniques			
1	16S rDNA sequencing approach	a. 16S rRNA gene amplification, preparation of clone libraries (for metagenomic samples), forming operational taxonomic units (OTUs) upon Amplified Ribosomal DNA Restriction Analysis (ARDRA), selection of representative members and sequencing b. 16S rRNA gene amplicon library preparation, next generation high-throughput sequencing, OTU formation and bioinformatic analysis for phylogenetic classification	Ghosh and Sar 2013 Dutta et al. 2018
2	Polymorphism based techniques	a. Denaturing Gradient Gel Electrophoresis (DGGE): 16S rRNA gene amplicon from bacterial genomic DNA differing in sequence composition is resolved electrophoretically based on their difference in denaturation at increasing concentrations of the denaturant in the gel b. Temperature Gradient Gel Electrophoresis (TGGE): Electrophoretic separation of 16S rRNA gene amplicon based on the varying melting temperature on a temperature gradient gel c. Amplified ribosomal DNA restriction analysis (ARDRA) or restriction fragment length polymorphism (RFLP) Terminal restriction fragment length polymorphism (T- RFLP): Polymorphism of restriction sites of 16S rRNA gene for a particular restriction enzyme is utilized to differentiate the microbial communities d. Single strand conformation polymorphism (SSCP): Separation based on the electrophoretic mobility of secondary structures formed out of DNA single strands under non-denaturing conditions	Kirk et al. 2004 Theron and Cloete 2000 Schwieger et al., 1998
3	Nucleic acid reassociation and hybridization techniques	a. DNA-DNA hybridization: Genomic DNA hybridization with known microbial taxa to analyze distinctness of the taxon to species level with 70% as cornerstone b. DNA microarray: Microscopic DNA slides with spots of known DNA sequences to which the unknown DNA sequences are hybridised and fluorescence measured c. DNA Reassociation: Lower the DNA reassociation kinetics of a microbial community, higher is the diversity d. Reciprocal Hybridization of Community DNA: Reciprocal hybridization of total community DNA indicates the presence of same kinds of organisms in two samples based on the idea that only identical or very closely related species would show significant cross-hybridization of pure culture DNA	Theron and Cloete 2000 Cho and Tiedje 2001

Table 1 (continued)

Sl. No	Technique	Principle	References
4	Ribosomal Intergenic Spacer Analysis (RISA)/ Automated Ribosomal Itergenic Spacer Analysis (ARISA)	DNA fingerprinting technique based on the amplification of the intergenic region between *16* and *23S rRNA* genes in the rRNA operon. Different microbial taxon has characteristic and significant variability in the length and nucleotide sequence of this region. ARISA is an updated and more efficient technique to get high-resolution data involving a fluorescence-tagged oligonucleotide primer for PCR amplification and subsequent electrophoresis in an automated system	Ciesielski et al. 2013
5	Flow cytometry	Flow cytometry conjugated with fluorescence-activated cell sorting (FACS) relying on fluorescent dyes for detection helps quantify and fractionate complex bacterial communities	Park et al. 2005
6	Fluorescence In Situ Hybridization (FISH)	Fluorescently labelled DNA probes are used to target rRNA of defined taxonomic or phylogenetic groups for microbial identification. Recently, an updated technique named live-FISH combined with FACS has been developed to sort specific taxonomic groups of bacteria and culture them for their further taxon level identification	Batani, et al. 2019

Actinobacteria and *Euryarchaeota* with genera *Faecalibacterium*, *Bifidobacterium, Lactobacillus, Butyrivibrio, Alistipes, Akkermansia, Coprococcus* and *Methanobrevibacter.* Evidently, high richness of the gut microbiome diversity is associated with healthy host metabolism.

Another factor that plays the most crucial role in maintaining the diversity of the bacterial taxa found in gut microbiome is the presence of predator bacterial communities. Predators are the key species that limits the population of the dominant species, preventing it from overgrowing and building up a high biomass which will directly hamper the species diversity. Mathematical simulation based on Lotka Voltera model suggested that the predators can drastically reduce the population of their preys helping in maintenance of the species diversity (Mosca et al. 2016). One of the best-known predatory bacteria are the members of *Bdellovibrio* and *Bdellovibrio*—like organisms (BALO). These have shown the best sensitivity towards gram-negative bacteria like *Salmonella enteritidis* and *Pseudomonas fluorescens* and have also been found to impact the growth of gram-positive *Staphylococcus aureus.* Besides, predation upon dominant species of the gut microbiome has also been reported through protists and bacteriophages.

A mini microbiome was constructed considering reference genomes in level of phyla obtained from Integrated Microbial Genomes–Human Microbiome Project (IMG/HMP) online platform was built to represent a healthy adult gut microbiome (Kaoutari et al. 2013). A list of 177 genomes was predominated by the members of *Firmicutes* ($n = 104$), *Bacteroidetes* (mostly *Bacteroides* spp. $n = 29$), *Proteobacteria* ($n = 22$) and *Actinobacteria* ($n = 12$). The mini microbiome also contained members of *Fusobacteria* ($n = 2$) and *Cyanobacteria, Elusimicrobia, Lentisphaerae, Spirochaetes, Synergistetes, Tenericutes, Thermotogae* and *Verrucomicrobia,* ($n = 1$ of each phylum).

The human gut is segregated and partitioned so that the first shot of digestive activity on the food ingested is the host's own. The gut is partitioned into stomach, duodenum, jejunum, ilium and colon, the environment of which is in the ascending order of pH and anaerobic from stomach to colon. The stomach is highly acidic (pH ~ 1.5) and was considered as sterile until *Helicobacter pylori* was discovered to be able to survive this hostile environment (Marshall and Warren 1984). Later investigations on possibility of existence of other microbial life in this acidic environment revealed that the gastric fluid was predominated by the members of *Firmicutes, Bacteroidetes* and *Actinobacteria* (Minalyan et al. 2017). The gastric mucosa was rather found to be richer in diversity with bacterial members belonging to *Firmicutes, Bacteroidetes, Proteobacteria, Fusobacteria* and *Actinobacteria.* In most individuals *Streptococcus* and *Prevotella* were found to be predominating apart from *H. pylori.* Other allochthonous species were found to belong to *Gamella, Granulicatella, Veillonella, Porphyromonas, Rothia, Neisseria, Fusobacterium* and *Lactobacillus* (Walter and Ley 2011). The microbial biomass in the gastric environment remains up to $10^{2–3}$ cells/ml. This increases up to 10^8 cells/ml in the small intestine (SI). The SI mucosa is associated with members of phyla, *Bacteroidetes* and *Firmicutes.* The SI is partitioned into three sections—the duodenum with pH 5–7 and bacterial load of $10^{3–4}$ cells/ml where Gram positive aerobes predominate, followed by jejunum and ileum with

pH 7–9 and cell density of $10^{4–8}$ cells/ml comprising strict to facultative anaerobic Gram-positive and Gram-negative bacteria. The microbiome composition of the intestinal lumen, known as mucosal and epithelial spaces of the gut (Swidsinski et al. 2005), is highly diverse and comprises members of *Verrucomicrobia, Fusobacteria, Asteroplasma, Cyanobacteria, Actinobacteria, Lentisphaera, Spirochaetes, Bacteroidetes, Proteobacteria, Bacilli, Clostridial clusters I, IV, IX, XI, XIII, XIVa, XV, XVI, XVII, XVIII* and uncultured *Clostridiales* and *Mollicutes* (Zoetendal et al. 2012). The predominating genera are *E. coli, Klebsiella, Enterococcus, Bacteroides, Ruminococcus, Dorea, Clostridium, Coprococcus, Weisella* and *Lactobacillus.* Allochthonous populations include *Granulicatella, Streptococcus, Veilonella and Lactobacillus.* The large intestine (LI) or the colon is strictly anaerobic with pH varying from 5 to 7. This area of the gut is the fermentation hub where various amino acids and butyrate–an SCFA, are fermented and production of various phenolic and indolic compounds take place (Smith and MacFarlane 1996, 1998). This compartment of the gut is home to the most complex bacterial diversity where the cell density reaches 10^{11} cells/ml. The high-bacterial diversity and abundance in the LI is due to several factors, such as i) larger volume, ii) moderate or less acidic pH, iii) low concentration of biliary salts and iv) longer retention time due to relatively slower peristalsis. Five major phyla- *Firmicutes, Bacteroidetes, Actinobacteria, Verrucomicrobia* and *Proteobacteria* covering a wide range of bacterial genera *Clostridium, Fusobacterium, Bacteroidetes, Actinomyces, Propionibacterium* are associated with the LI. Other Gram-positive cocci- micrococci, peptococci, peptostreptococci and ruminococci have been also reported to play crucial roles in the LI (Ramakrishna 2013; Walter and Ley 2011). These are majorly responsible for the SCFA production, i.e. acetate, butyrate and propionate. The specific bacteria responsible for particular SCFA synthesis have been discussed later in this review.

Apart from eubacterial members, archaebacterial members also constitute the LI microbiota with *Methanobrevibacter smithii* and *Methanosphaera stadtmanae* as the predominating species. *M. smithii* alone makes 10% of the colonic anaerobic bacterial population (Walter and Ley 2011; Jhangi et al. 2014) (Fig. 1). Archaeal growth is syntrophic with eubacterial H_2, C, acetate, formate or methanol production in mammalian gut where these are incorporated as precursor materials by methanogens in their methanogenesis and energy production process playing a crucial role in energy balance (Hoffmann et al. 2013; Matarazzo et al. 2012; Ishaq et al. 2015). In contrast to these species, *Methanomassiliicoccus luminyensis* was found to significantly increase with age having remarkable metabolic properties, such as trimethylamine degradation with low immunogenic properties (Bang et al. 2017). Besides methanogens, members of halophilic archaea, *Crenarchaeota* and *Thaumarchaeota* have also been detected to colonize human intestinal tract through metagenomic investigations (Gaci et al. 2014). Archaeal diversity has been found to be maximum in the age group 25–60 years where apart from the predominant spp., abundance of *M. oralis, M. arboriphilus, M. millerae, M. ruminantium, Methanosalsum zhilanaea, Methanomassiliicoccus luminyensis, Methanoculleus chikugoensis* have been found (Nkamga et al. 2017; Guindo et al. 2021). Occurrence of *Nitrososphaera,* a member of *Thaumarchaeota,* although at a low abundance, have been found to be antagonistic with *Methanobrevibacter* (Hoffmann et al. 2013). However, the diversity is less in the age group below 15 years and above 70 years old. Predominant taxa in the former age group are *Methanobreviibacteriales* and *Methanomassiliicocales* and that in the later age group are *M. smitthii, M. stadtmanae, M. luminyensis* and *Candidatus M. intestinalis.* Representative taxa of halophillic archaea identified in human fecal samples of populations with higher intake of salty and sea foods have been found to be *Halorubrum koreense, H. alimentarium, H. saccharovorum, Halococcus morrhuae* and *Halopherax massiliense* (Nkamga et al. 2017). A recent study on the Korean gut archaeom revealed abundance of archaeal genera, *Halolamina, Haloplanus, Halorubrum, Halobacterium, Haloterrigena, Natronomonas, Halarchaeum, Haloarcula, Halonotius* and *Halorussus* (Kim et al. 2020).

A neighbor-joining phylogenetic tree based on the 16S rRNA sequences of all the microbial species detected in human gut microbiome has been constructed which reflects that the predominant phyla are *Firmicutes, Proteobacteria, Bacteroides* and *Actinobacteria* in eubacterial group and *Euryarchaeota* in the archaeal group (Fig. 2). Other phyla are moderately to sparsely represented.

Role of gut microbiome in human metabolic activities

a. Digestion

Gut microbes and microbial enzymes play pivotal roles in digestion of human diet; however, the specific contributions of different species are not well understood. Many substrates in human diet are resilient to host enzymes and their digestion solely depends on gut microbial enzymes. Dietary resistant starch, a complex carbohydrate composed of amylase and amylopectin, is one such example which is essentially broken down to small chain fatty acids like butyrate, propionate, valerate and isovalerate, etc. Amylopectin, a polymer of glucose, is readily hydrolysed by amylase at 1–6 glycosidic bonds. However, amylose, a more linear glucose polymer with 1–4 glycosidic bonds, is the one that show resistance to degradation. The varying propor-

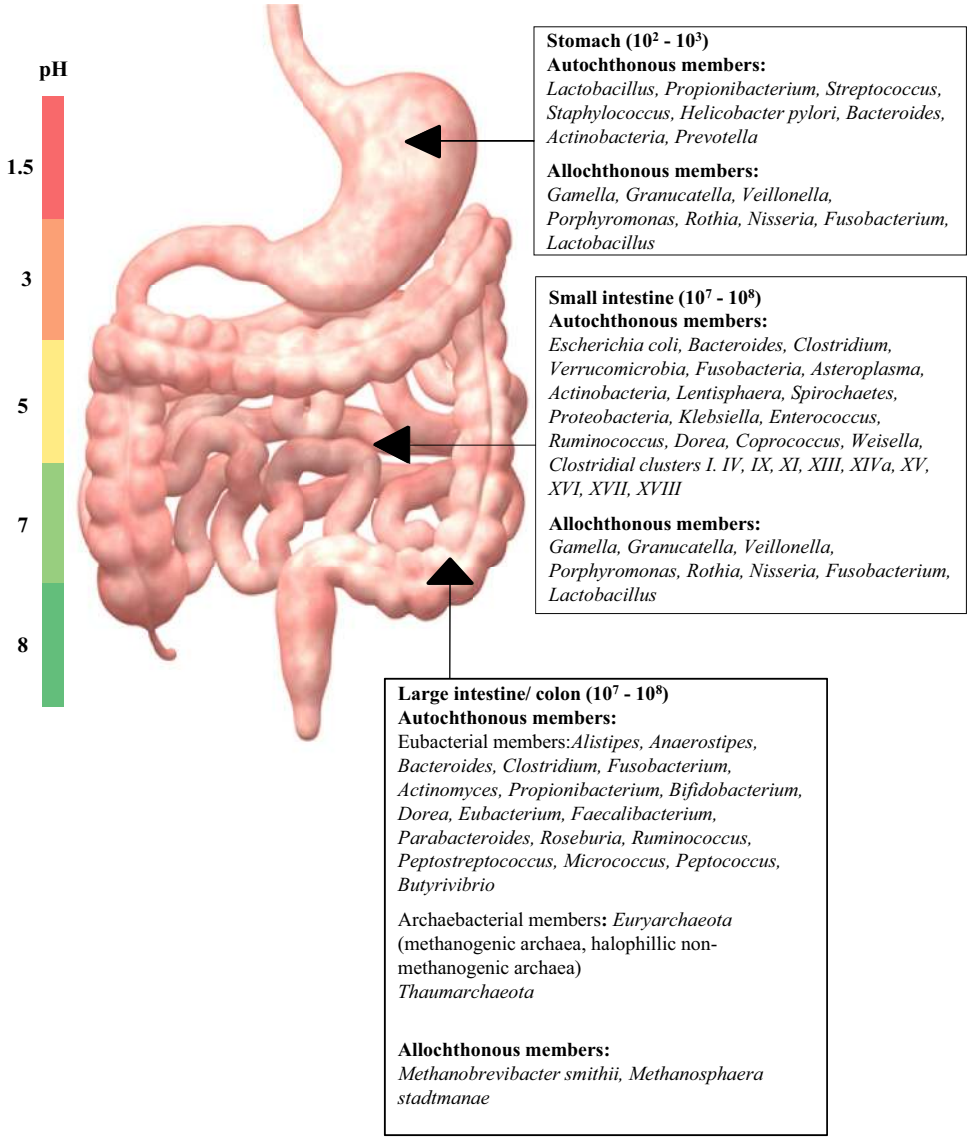


Fig. 1 Autochthonous and allochthonous members of bacterial taxa distributed in different compartments of GIT. The colour bar indicates pH range corresponding to the pH of the GIT compartment lying beside, respectively

tions of amylose to amylopectin that a starch molecule contains increases the degree of resistance to degradation. Besides, digestibility of starch molecule in the diet vastly depends on the structure, crystallinity, particle size and cooking. Depending on digestibility, Resistant Starch (RS) has been classified into 5 different types: RS type 1 (physically inaccessible), RS type 2 (native granular starch consisting of ungelatinized granules), RS type 3 (retrograded amylose) and RS type 4 (indigestible *i.e.* chemically modified) and RS type 5 (amylase- lipid complexes- often considered as slowly digested starch and not a true RS) (DeMartino and Cockburn 2020). Digestion of resistant starch has been found to be mainly associated with the members of *Clostridium* cluster IV- *Faecalibacterium prausnitzii, Clostridium leptum* and *Ruminococcus bromii* and XIV- *Eubacterium rectal, Clostridium coccoides, Butyrivibrio fibrisolvens* and *Roseburia* sp. whereas members of *Bacteroidetes* were found to be downregulated upon administration of high-resistant starch (HRS) diet (Maier et al. 2017; Ramakrishna 2013). *F. prausnitzii, Ruminococcus, Prevotellaceae*, *Eubacterium rectale*, *Roseburia faecis* and *Akkermansia muciniphila* are the specific taxa that were found to increase upon HRS diet (Maier et al. 2017). *R. bromii,* has been regarded as the keystone species in RS degradation. They have been found to possess special structures called amylosomes in which the amylolytic enzymes are uniquely arranged bound through cohesin and dockerin modules (DeMartino and Cockburn 2020). These multi-enzyme complexes remain attached to the cell surface via scaffolding proteins as found in cellulosomes (DeMartino and Cockburn 2020; Ze et al. 2012, 2015). Metaproteomic study has also reflected that most of the carbohydrate metabolizing enzymes and

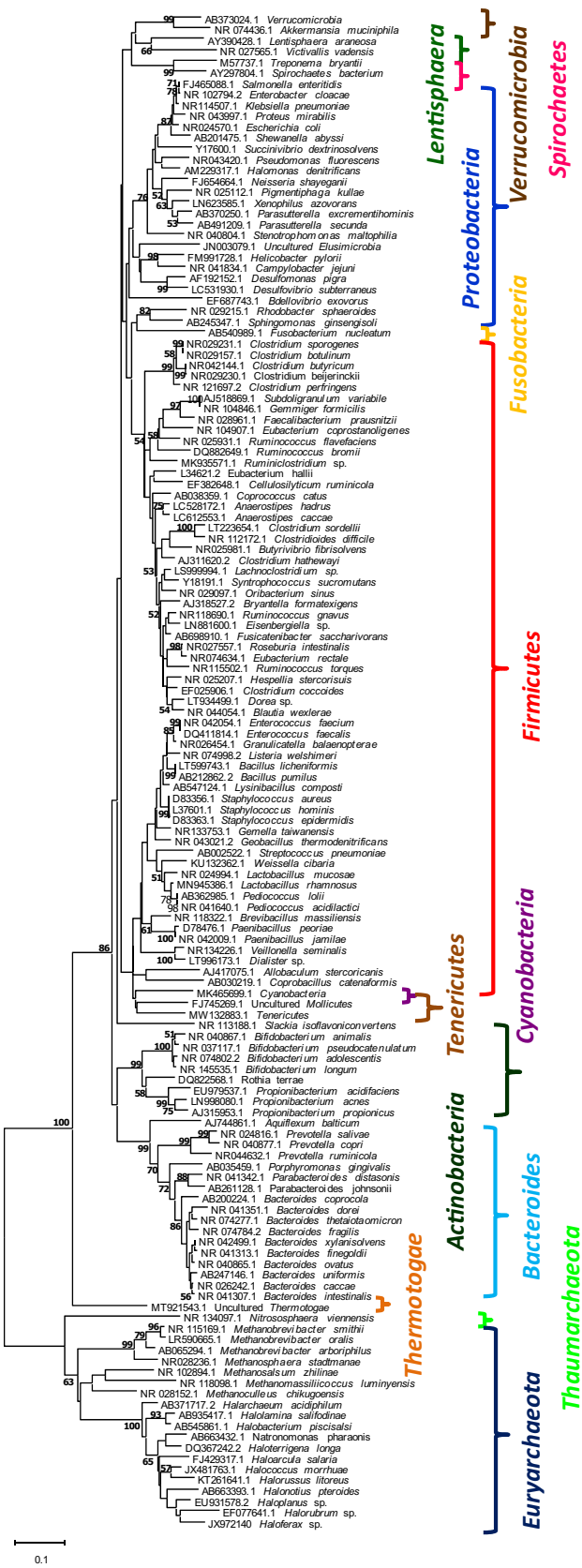


Fig. 2 Neighbour joining tree showing phylogenetic relatedness among human gut bacterial and archaeal 16S rRNA genes based on Jukes Cantor model. Nucleotide sequences were retrieved from NCBI database and the values at the branches denote bootstrap values obtained upon 1000 iterations. Coloured brackets indicate various phyla Evolutionary analyses were conducted in MEGAX (Felsenstein 1985; Jukes and Cantor 1969; Kumar et al. 2016; Saitou and Nei 1987)

transportational molecular systems were affiliated to *F. prausnitzii* and *Coprococcus comes,* following an HRS diet. An HRS diet has shown upregulation in human enzymes related to lipid metabolism, such as colipase, pancreatic triglyceride lipase and bile salt-stimulated lipase while downregulating human α-amylase. Thus, an HRS diet would promote the growth and abundance of microbial taxa involved in resistant starch digestion and SCFA production in colon and is a coherent phenomenon with human lipid metabolism (Maier et al. 2017). On the contrary, a diet rich in starch and other easily digestible carbohydrates has been found to be associated with methanogenic archaeal members, *M. smithii* (Carberry et al. 2014; Hoffmann et al. 2013) which has shown to improve polysaccharide digestion and promote the production of acetate or formate for its own use. *M. stadtmanae,* found in omnivores, helps in pectin fermentation to produce methanol required to carry out its methanogenesis pathway (Dridi et al. 2009; Ishaq et al. 2016; Moses et al. 2015). Among various dietary lipids, cholesterol (majorly in Western diets) is one of the major components that poses serious health threats related to cardiovascular diseases. Upon ingestion followed by enterohepatic absorption, biliary excretion and circulation, cholesterol is subjected to gut microbial reduction to produce co-prostanol- a major (50%) steroid found in human feces. *Eubacterium coprostanoligenes* have been documented to be a cholesterol reducing coprostanol synthesizing gut bacteria (Gérard et al. 2004; Kenny et al. 2020; Koppel et al. 2017).

Another recalcitrant substrate is gluten which resists complete digestion via human enzymes. Gluten, rich in amino acids like proline and glutamine, is a crucial source of dietary protein derived from wheat and wheat-based diets (Fernandez-Feo et al. 2013; Helmerhorst et al. 2010; Zamakhchari et al. 2011). Human digestive proteases release incompletely digested metastable Pro/Gln-rich gliadin peptides, 30–40 residues long, into the gut lumen. Sometimes these induce abnormal immune responses in some individuals with genetic predisposition eliciting intestinal symptoms and severe mucosal damage, a condition known as coeliac disease (CD). However, upon arrival to large intestine after escaping digestion in the stomach and the small intestine, gluten proteins and peptides act as dietary compounds from

which gut microbiota derive energy. The specific taxa found to show glutenasic activity are *Bacillus licheniformis, B. subtilis, B. pumilus, Bacteroides fragilis, Bifidobacterium longum, Clostridium sordellii, C. perfringens, C. botulinum/sporogenes, C. butyricum/beijerinckii, Enterococcus faecalis, E. faecium, Propionibacterium acnes, Pediococcus acidilactici, Paenibacillus jamilae, Staphylococcus epidermidis, S. hominis and Stenotrophomonas maltophilia* (Caminero et al. 2014; Herrán et al. 2017). The hydrolysis of gliadin peptide is again found to be a specific peptidase activity for a group of microbial taxa. The 33-mer peptidase activity was found to be higher in *Lactobacillus mucosae*, *L. rhamnosus* and *Clostridium botulinum/sporogenes* than other bacteria belonging to *Enterococcus faecalis* or *Bacillus licheniformis* (Caminero et al. 2014).

Other highly complex and variable plant cell wall polysaccharides, such as xylans, xyloglucans and pectins require the concerted action of different glycosidases to produce fermentable monosaccharides. For example, the breakdown of type I and type II rhamnogalacturonan that are two different components of pectin, requires at least a dozen enzymes or more for complete breakdown. Role of gut microbial enzymes have also been found in degradation of animal glycans, such as glycosaminoglycan substrates, such as hyaluronan, heparin and chondroitin (Cantarel et al. 2012; Stam et al. 2006). Other glycosylated proteins such as mucins (produced by intestinal epithelial cells) and peptidoglycans (bacterial cell wall component) also act as alternative energy source for the distal gut microbiota. Degradation of the total dietary carbohydrates is not solely possible through human enzymes as human produces only 17 active enzymes for digestion of food glycans. Hence, the huge and complex repertoire of our dietary polysaccharides are digested into fermentable compounds through the microbial carbohydrate active enzymes (CAZymes) produced in our gut. The CAZyme family of the gut microbiome encodes 15,882 enzymes and is composed of glycoside hydrolases (GH = 57%), polysaccharide lyases (PL = 2%), glycosyl transferases (GT = 35%) and carbohydrate esterases (CE = 6%) (Kaoutari et al. 2013). Majority of the CAZymes constituting GHs and PLs are produced by the members of *Bacteroides caccae*, *B. dorei*, *B. finegoldii*, *B. fragilis*, *B. intestinalis*, *B. ovatus*, *B. thetaiotaomicron*, *B. uniformis*, *B. xylanisolvens*, *Bryantella formatexigens*, *Butyrivibrio fibrisolvens, Clostridium hathewayi*, *Enterobacter cloacea*, *Escherichia coli*, *Faecalibacterium prausnitzii*, *Klebsiella pneumoniae*, *Parabacteroides distasonis*, *Prevotella copri*, *P. salivae*, *Roseburia intestinalis*, *Ruminococcus flavefaciens*, *R. gnavus*, *Subdoligranulum variabile*, *Victivallis vadensis* (Oliphant and Allen-Vercoe 2019). Archaeal members are also associated with a healthy digestion process and the relationship among the archaeal and eubacterial members are metabolically interdependent. *Methanobrevibacter ruminantium* is associated with diet high in fiber and structural carbohydrates, such as cellulose, hemicelluloses, lignin that majorly remains recalcitrant to animal and human digestive enzymes (Zhou et al. 2010). On the contrary, a diet rich in starch and readily digestable carbohydrates is associated with *M. smithii* which has also been shown to improve polysaccharide digestion and influence the production of acetate or formate for its own use (Hoffmen et al. 2013; Carberry et al. 2014; Ishaq et al. 2015). The archaeal diversity of an omnivore is comprised of *Msp. stadtmanae* as it requires methanol, a by-product of pectin fermentation, for its methanogenesis pathway (Ishaq et al. 2015).

b. Production of special metabolites

Degradation of dietary carbohydrates, lipids and proteins by the gut microbiome give rise to multitude of biochemical metabolites of both local and systemic action. These metabolites can be either potentially beneficial or harmful to the host depending on the concentration and site of action. Generally, a wide variety of metabolites are produced, such as SCFAs and alcohols from monosaccharides, ammonia, branched chain fatty acids, amines, sulfur compounds, phenols and indoles from amino acids, glycerol and choline derivatives from lipids and tertiary cycling of CO_2 and hydrogen. Production of SCFAs like butyrate, acetate and propionate upon degradation of pyruvate are the most abundant faecal metabolites. These are extremely important for host health as butyrate apart from serving as the primary energy source for colonocytes, also improves the integrity of intestinal epithelial cells (IECs) by promoting tight junctions and cell proliferation, increases mucin production by Goblet cells, production of cytokines, TGF-β, IL-10 and IL-8 and induces differentiation of naïve T-cells. Both acetate and propionate also aid in anti-inflammatory process and cytokine production. Excess SCFAs can be incorporated in gluconeogenic and lipogenic process. (Oliphant and Allen-Vercoe 2019). *F. prausnitzii, Eubacterium rectale, Eubacterium hallii* and *R. bromii* are well known n-butyrate producers (Li et al. 2008; Louis et al. 2010). *Bacteroides, Veillonella, Dialister* and *Salmonella* (gram-negative bacteria) as well as gram-positive bacteria *Coprococcus, Roseburia* and *Ruminococcus* are key propionate producers (Covasa et al. 2019; Morrisson 2016) whereas, *Akkermansia municiphilla, Bacteroides, Clostridium* and *Bifidobacterium longum* and *Bifidobacterium adolescentis* are profound acetate producing bacteria (Derrien et al. 2004; Frost et al. 2014; Fukuda et al. 2011; Russell et al. 2013).

Eubacterium halii—an SCFA producer and *Clostridium sporogenes* is known to produce indole-3-propionic acid and *Clostridium difficile* has been known to produce 4-cresol, cholesterol and coprostanol (Wang et al. 2017). Pyruvate fermentation can also result in production of small amount of alcohols, such as ethanol, propanol, 2,3- butane-di-ol. Gut microbiota can also produce toxic methanol by processes other than fermentation. Members of *Proteobacteria* are known to be alcohol producers. Besides, members of genera *Bifidobacterium, Clostridium, Eubacterium, Blautia, Coprococcus, Dorea, Lachnoclostridium, Roseburia, Lactobacillus, Faecalibacterium, Ruminiclostridium*, *Ruminococcus, Streptococcus, Veilonella* and *Escherichia* are well-known alcohol producers including ethanol, propanol, 1,2- propanediol.

2,3-butanediol production. These species also produce various other SCFAs like formate, acetate, lactate, propionate, succinate, valerate, etc. (Oliphant and Allen-Vercoe 2019).

Dietary protein after digestion by pancreatic proteases and other proteolytic enzymes move to the small intestine where the peptides and amino acids that are generated during proteolysis, are further subjected to microbial fermentation. Microbes have lesser diverse enzymatic apparatus to degrade amino acids due to the obvious fact that the complex steps involved consume more energy than actually generated. Incorporation of the available amino acids in their anabolic processes rather than utilizing them as their energy substrates, however, is more preferred by the gut microbes. However, series of Stickland reactions take place by members of *Clostridium* sp. produces variety of SCFAs and branched chain fatty acids (BCFAs) like isovalerate, isobutyrate, 2- methyl butyrate. Members of *Bacilli* are capable of producing other SCFAs and BCFAs (Oliphant and Allen-Vercoe 2019). These processes may give rise to indolic and phenolic metabolites, which are otherwise not produced by human cells and may exert deleterious effects in the host. Degradation products of α-amino acids like tyrosine and phenylalanine include 4-hydroxyphenylpyruvate, 4-hydroxyphenylacetate, 4-hydroxyphenylpropionate and 4-hydroxyphenylacetate, phenol, p-cresol and 4-ethylphenol as well as phenylpyruvate, phenyllactate, phenylacetate and phenylpropionate, respectively. Degradation of tryptophan generates indole, 3-methyl indole (skatole), indole acetate and indole propionate (Windey et al. 2012). These metabolites have been found to be produced by bacterial members belonging to *F. prausnitzii, Subdoligranulum variabile* and *Bifidobacterium pseudocatenulatum* (Li et al. 2008). Production of toxic metabolites, such as indoxyl sulfate, p-cresyl sulfate, amines and ammonia have been shown to be related to nephrological issues, cardiovascular diseases in chronic kidney disease (CKD) in human host (Mafra et al. 2014; Oliphant and Allen-Vercoe 2019; Windey et al. 2012). The predominant proteolytic bacteria with strong peptidase activity in human faeces are the members of *Bacteroides* spp. and *Clostridium* spp., whereas members of *Desulfomonas* spp. and *Desulfovibrio* spp. are capable of oxidizing sulfur containing amino acids like cystine, cysteine, taurine and methionine to producing H_2S. Depending on the concentration of H_2S produced, it may act as "friend or foe" to the host (Blachier et al. 2019). Polyamines, such as putrescine, spermidine, agmatine, cadaverin, tyramine and histamine are small polycationic molecules with multitude of functions including gene regulation, stress resistance, cell growth and proliferation and differentiation (Mafra et al. 2014; Tofalo et al. 2019). Members of *Bacteroides, Fusobacterium, Escherichia coli, Enterococcus faecalis, Bifidobacterium animalis* sub sp. *lactis* and *Lactobacillus rhamnosus* have been shown to play profound roles in production of various polyamines (Tofalo et al. 2019).

c. Production of signaling molecules

The gut microbiome is capable of playing a multitude of functions related to host metabolism through its ability to produce extremely diverse repertoire of metabolites and gene products (D'Argenio and Salvatore 2015; Olivares et al. 2018; Yano et al. 2015). Depending on the dietary exposure, it also produces signaling molecules which contribute in controlling neuro-immuno-endocrine activities as well as peripheral metabolism (Turnbaugh et al. 2007). The inaccessible carbohydrates like resistant starch and plant polysaccharides in the host diet are utilized by the intestinal microbiota, the products of which in turn aid in release of several gut hormones by the enteroendocrine (EE) cells of the GI tract which are important peripheral host metabolism regulators. The microbial structural components, such as flagella and membrane-bound lipopolysaccharide (LPS), can also act as signaling molecules (Gordon 2002). The cell wall LPS of Gram-negative bacteria, e.g. *Bacteroidetes* phylum, is a potent ligand for toll like receptor 4 (TLR4). The activation of TLRs induce strong immunity- and inflammation effects (Lancaster et al. 2018; Takeuchi and Akira 2010), along with secretion of multitude of metabolically active hormones, such as glucagon-like peptide-1 (GLP-1) (Lebrun et al. 2017), 5-hydroxytryptamine (5-HT) (Kidd et al. 2008) and peptide tyrosine tyrosine (PYY) (Larraufie et al. 2017).

The proportion of various SCFAs, such as acetate, propionate and butyrate, produced by the intestinal microbes upon degradation of dietary fibers and resistant starch although depends on the diet, microbial

composition and intestinal transit time, yet maintains a ratio of 3:1:1 in the intestinal lumen (Cummings et al. 1987; Mowat & Agace 2014; Topping & Clifton 2001). These SCFAs are found to be important neuro-immuno-endocrine regulators and play significant roles in microbiota-gut-brain crosstalk like motility, secretion and blood flow. SCFAs also controls peripheral activities like brown adipose tissue activation, regulation of liver mitochondrial function, body energy homeostasis and control over appetite and sleep (De Vadder et al. 2014; Éva et al. 2019; Li et al. 2008, 2019; Mollica et al. 2017; Silva et al. 2020; Bhattacharya et al. 2002). Following their production, colonocytes absorb SCFAs mainly via H^+-dependent or sodium-dependent monocarboxylate transporters (MCTs and SMCTs, respectively) (Vijay and Morris 2014). While acetate is readily absorbed by the circulatory tissue for peripheral distribution, propionate is metabolized by hepatocytes and butyrate acts as fuel for colonocytes (Koh et al. 2016; Martin et al. 2019). Not much has yet been elucidated regarding the specific role of different taxa in metabolite production, however, members of *Bacteroidetes* are found to be enriched with carbohydrate metabolism genes and *Firmicutes* have been reported to harbor bile acid metabolism genes (David et al. 2014; Martin et al. 2019). These SCFAs, thus produced, act as important signaling molecules for enteroendochrine cells by i) inhibiting nuclear histone deacetylase (HD) and ii) stimulating G-protein coupled free fatty acid receptors 2 & 3 (FFAR2 and FFAR3) (Fellows et al. 2018; Larraufie et al. 2017; Offermans et al. 2014; Rooks and Garrett 2016; Waldecker et al. 2008).

Secondary bile acids, such as lithocholate (LCA) and deoxycholate (DCA) are important signaling molecules that have profound roles in peripheral metabolism through their action on two bile acid receptors expressed on EE cells, the G- protein coupled receptor TGR5 and the nuclear farnesoid receptor FXR (Ramírez-Pérez et al. 2018; Winston & Theriot 2020). These are more hydrophobic than the bile acids and are produced by deconjugation and dehydroxylation of bile salts by microbial bile salt hydrolases (BSH). Metagenomic studies have revealed that BSHs are expressed majorly within three phyla, i.e. *Firmicutes* (30%), *Bacteroidetes* (14.4%) and *Actinobacteria* (8.9%) (Jones et al. 2008; Winston and Theriot 2020). Members of genera *Clostridium, Bacteroides, Lactobacillus, Bifidobacterium* and *Enterococcus* and their roles in BSH expression have been vividly studied (Begley et al. 2005; Jones et al. 2008). The BSH of *Firmicutes* and *Actinobacteria* metabolizes all conjugated bile salts, whereas those of *Bacteroidetes* are specific to tauro-conjugated bile acids (Jones et al. 2008). The importance of secondary bile acids lies in the fact that being more hydrophobic help in better reabsorption of the bile salts through passive diffusion, thus limiting faecal loss (Martin et al. 2019; Winston and Theriot 2020).

The gut microbiota also exerts its control over host metabolism by regulating the release of an array of gut hormones and peptides like 5-HT, GLP-1, PYY, glucose-dependent insulinotropic peptide (GIP), cholecystokinin (CCK), ghrelin, leptin, pancreatic polypeptide (PP), oxyntomodulin and neurotensin (Bliss and Whiteside 2018; Covasa et al. 2019; Dockray 2014; Fukui et al. 2018) (Table 2). Serotonin or 5-HT is one among several other important regulatory factors which not only acts as a brain neurotransmitter, but also regulates diverse functions like platelet aggregation, bone development, immune responses, cardiac functions, promote homeostasis and control enteric motor and secretory reflexes. Serotonin is known to be secreted by the enterochromaffin cells upon sensing the nutrient condition in the intestinal lumen (Yano et al. 2015). Cultivable bacterial isolates have been shown to produce 5-HT under laboratory conditions. Therefore, it is still ambiguous if microbial de-novo synthesis of 5-HT by indigenous members of gut microbiota contribute to host 5-HT levels. However, the gut microbiota comprising spore forming microbes have been specifically found to promote 5-HT production in adult mice. The 5-HT concentrations in serum, colon and fecal samples were low for germ-free mice as compared to conventionally colonized specific pathogen-free controls (Wikoff et al. 2009). Glucagon like peptide, an incretin hormone and the neuroendocrine hormone PYY are the two regulatory hormones secreted by L-cells of ileum and colon. GLP-1 is released in response to glucose to augment insulin and impede the secretion of insulin. On the other hand, PYY is secreted postprandially from illeal and colonic endocrine cells inducing feeling of satiety and reducing food intake. This is therefore, directly related to obesity (Muller et al. 2007). The enzyme dipeptidyl peptidase IV (DPP-IV) can cleave GLP-1 as well as PYY leading to potentially anti-diabetic effects. The dynamic relation among the L-cells and microbial DPP like activity, SCFA signaling, bacterial lipopolysaccharide and indole production by gut microbes can exert potential influence on levels of host GLP-1 and PYY levels, thereby controlling glucose metabolism. This, in turn may also influence the microbial composition and microbial metabolite compositions. Indole, another major bacterial metabolite, derived from tryptophan metabolism stimulates GLP-1 (Chimerel et al. 2014). Another gastric inhibitory peptide GIP secreted from K-cells significantly contributes to insulin secretion postprandially. While DPP-IV and microbial DPP-

Table 2 List of signaling molecules, secretory cells and bacterial genera aiding in secretion of specific signaling molecule

Gut hormones	Secretory cells	Aiding microbes	References
Serotonin	Enterochromaffin cells	*Clostridium spp., Escherichia, Enterococcus, Truchuris, Candida, Streptococcus*	Covasa et al. 2019; Yano et al. 2015
Glucagon like peptide 1	Colonic L-cells	*Bifidobacteria, Lactobacillus, Akkermansia muciniphila*	Everard and Cani 2014; Greiner and Bäckhed 2016
Peptide YY	Colonic L- cells	*Bifidobacteria, Lactobacillus, Akkermansia muciniphila, Escherichia, Enterococcus and Truchuris*	Covasa et al. 2019; Everard and Cani 2014; Greiner and Bäckhed 2016; Xu et al. 2015
DPP 4	Enterocytes, epithelial cells and immune cells	*Prevotella* and *Lactobacillus*	Klemann et al. 2016; Olivares et al. 2018; Zhong et al. 2015
Glucose dependent insulinotrophic peptide	K- cells	NK	Fukui et al. 2018
Cholecystokinin	I- cells	NK	Dockray 2014; Fukui et al. 2018
Leptin	adipocyte	NK	Queipo-Ortuño et al. 2013
Pancreatic polypeptide	F or PP cells	NK	Bliss and Whiteside 2018
Ghrelin	cardiomyocytes	NK	Iglesias et al. 2004
Oxyntomodulin	Pancreatic cells	NK	Bliss and Whiteside 2018
Neurotensin	Gastrointestinal endocrine N cells	NK	Bliss and Whiteside 2018
Motilin	Endocrine M- cells	NK	Chapman et al. 2016
Insulin	B- cells	*Lactobacillus, Bifidobacterium, Blautia coccoides, Eubacterium rectale, Prevotella*	Zhang et al. 2015
Glucagon	A cells	NK	Kelly et al. 2010
Somatostatin	D cells	NK	Giloteaux et al. 2012
Dopamine or noradrenaline	Nerve cells	*Escherichia, Bacillus and Saccharomyces*	Covasa et al. 2019
Acetylcholine	Nerve cells	*Lactobacillus*	Covasa et al. 2019
GABA	B- cells	*Lactobacillus, Bifidobacterium*	Covasa et al. 2019
Indole	NK	*Escherichia, Bacteroides, Clostridium*	Covasa et al. 2019
Bile acids	Hepatocytes	*Acetatifactor and Bacterroides*	Covasa et al. 2019

NK not known

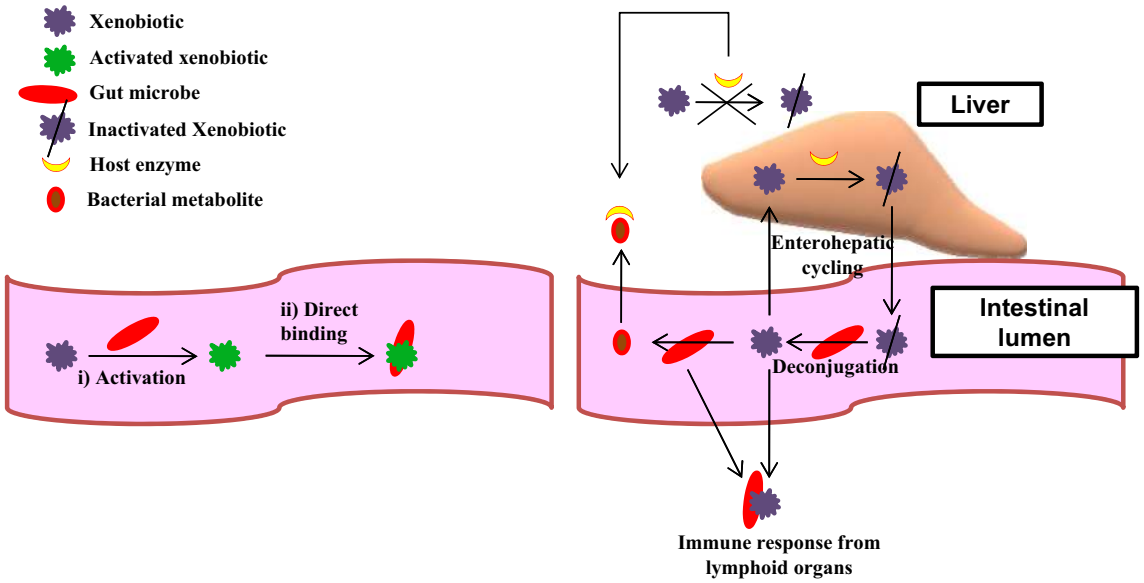
IV like activity, such as in *Prevotella* or *Lactobacillus* (Olivares et al. 2018) attenuates the biological activity of GIP and GLP-1, it stimulates that of PYY by breaking down it to PYY_{3-36}. Cholecystokinin, secreted by I—cells, is released in response to fat and protein content of the host diet. It acts by activation of CCK1 and CCK2 receptors located all over the tissues of GIT and CNS. Although, abundance of certain gut bacteria like commensal *Bifidobacterium* and *Lactobacillus* strains have been negatively correlated to the decreased levels of cholecystokinin and ghrelin in germ-free mice, yet no strong association has yet been found among the intestinal bacteria and levels of these hormones (Covasa et al. 2019; Martin et al. 2019; Pen & Welling 1983; Perry et al. 2016; Queipo-Ortuño et al. 2013), etc.

d. Xenobiotic degradation and heavy metal transformation

Xenobiotics are chemicals or synthetic substances metabolically extrinsic to host system which might accumulate within host extraneously or may be produced as a defense mechanism by certain host microbes (Atashgahi et al. 2018; Koppel et al. 2017). These include environmental pollutants produced in large volumes for industrial, agricultural and domestic use (Atashgahi et al. 2018) which might enter the environment at macro (µg/L to mg/L range) or micro levels (ng/L to µg/L range) (Meckenstock et al. 2015; Schwarzenbach et al. 2006). Pharmaceutical compounds like metformin, methotrexate, proton-pump inhibitors (PPIs), opioids, non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics, etc. immensely affect the gut microbiome structure. Other xenobiotic compounds, such as persistent organic compounds (POPs), pesticides, pharmaceuticals, e.g. psychotropic agents like olanzapine, personal care products (PPCPs), food additives, disinfection by-products (DBPs) (Atashgahi et al. 2018) can also potentially alter the gut microbiome diversity. Dietary

compounds including polyphenolic phytochemicals like resveratrol and flavonoids, polyunsaturated fatty acids, artificial sweeteners and plant sterol esters have also been associated with changes in structural diversity of gut microbiome. Variety of other environmental and industrial chemicals, such as endocrine disrupting chemicals, heavy metals, pesticides and pollutants majorly impact the structural composition as well as functionality of the gut microbiome (Clarke et al. 2019).

The human gut microbiota homes genetic information for multiple xenobiotic detoxification and sequestration and is capable of encoding a broad diversity of enzymes (Haiser and Turnbaugh 2013; Spanogiannopoulos et al. 2016). Factors, such as host genetics, age, geographical location of the host, diet, administration of drugs, hormonal status, gender, stress and circadian rhythm immensely control microbial metabolism of xenobiotic compounds (Clarke et al. 2019; Das et al. 2016). A cyclic metabolic interaction takes place between microbes and host cells. The anoxic environment of the gut facilitates a reductive and hydrolytic metabolism generating non-polar, low-molecular weight by-products that are readily absorbed by the host cells. These by-products are transported to the liver where the hepatic cells metabolize them to generate hydrophilic, polar metabolites via a diverse repertoire of oxidative and conjugative enzymes. These high-molecular weight polar metabolites are secreted through the bile and again reach the gut where they are further subjected to reductive and hydrolytic metabolism (Claus et al. 2017; Koppel et al. 2017; Sousa et al. 2008). Two mechanisms are involved in xenobiotic metabolism, i.e. direct mechanism which includes production of active compounds which are microbially detoxified in the gut lumen. In indirect mechanism the xenobiotic undergoes enterohepatic cycling where the host physiology is manipulated by the gut bacteria. Here, xenobiotic compounds are inactivated by conjugation in the liver; the conjugated compound then enters the intestinal lumen through bile where, microbial enzymes release the conjugate group, reactivating the compound. This active compound may now re-enter the circulation or may undergo microbial transformation to form microbial metabolite which now competes with the active xenobiotic compound for binding sites on the enzyme. These microbial metabolites may in turn stimulate immune responses through translocation or inflammation (Fig. 3) (Carmody and Turnbaugh 2014). The host may face beneficial, detrimental or even lethal outcomes of xenobiotic metabolism (Okuda et al. 1998; Satoh-Takayama et al. 2008; Shin et al. 2013). Exposure to xenobiotics may lead to significant alteration in gut microbiota composition and metabolic activity (Maurice et al. 2013) and, may increase predisposition to various diseases (Lee & Hase 2014; Lu et al. 2015; Šrut et al. 2018; Wang et al. 2011). Metabolism of xenobiotic in human occurs in two phases, i.e. Phase I—wherein, polar functional groups are exposed and Phase II—wherein, phase I groups are



(a) Direct mechanism of xenobiotic detoxification

(b) Indirect mechanism of xenobiotic detoxification

Fig. 3 Direct (**a**) and indirect (**b**) mechanisms of xenobiotic detoxification

Table 3 List of microbial enzymes involved in specific group of xenobiotic metabolism and the organisms producing the enzymes

Enzymes used	Xenobiotic detoxified	Organism	References
Cytochrome P450	fatty acids, 4-n-nonylphenol, pharmaceutical agents, such as S-mephenytoin, phenytoin, S-warfarin, tolbutamide, arachidonic acid, steroids and non-steroidal anti-inflammatory substances	*Sphingomonas* sp. strain KSM1, *Bacillus megaterium,* *Nocardia farcinica IFM 10152* *Actinoplanes* sp.	Bracco et al. 2013; Di Nardo and Gilardi 2012; Eleftherios Venizelos Bezirtzoglou 2012
Monoamine oxidase	biogenic amines like histamine, benzyl amines, tyramine, dopamine, octopamine or norepinephrine, etc	Lactic acid bacteria, *Klebsiella, Enterobacter, Escherichia, Salmonella, Serratia and Proteus, Pseudomonas aeruginosa* IFO 3901*, Sarcina lutea, Micrococcus luteus* IFO 12708 *and Brevibacterium ammoniagenes* IAM 1641	Murooka et al. 1996; Murooka et al. 1979
Epoxide hydrolase	Epichlorohydrin, epibromohydrin, epoxyoctane, styrene epoxide and, lipids	*Rhodococcus, Nocardia* spp., *Mycoplana rubra* and *Methylobacterium* spp., *Alternaria alternata*	Krenn et al. 1999; Morisseau 2013; Theisen and Berger 2005
Alcohol dehydrogenase	2- chloroethanol	*Acetohalobium, Acholeplasma, Achromobacter, Acidovorax, Anaerococcus, Coprococcus, Coprothermobacter, Coraliomargarita, Desulfarculus, Desulfatibacillum, Desulfitobacterium, Desulfobacca, Desulfobacterium, Gemmatimonas Geobacillus, Geobacter, Geodermatophilus, Geopsychrobacter, Haemophilus, Hafnia, Marinobacter, Marinomonas, Streptococcus gordonii*	Das et al. 2016; Pavlova et al. 2013
Aldehyde dehydrogenase	Acetaldehyde, folate, aromatic aldehydes, Fatty aldehydes, Glutamate γ-semialdehyde, Succinic semialdehyde, Methylmalonate semialdehyde and, Aminoaldehydes	*Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli*	Nosova et al. 1998; Vasiliou et al. 2000
Thiopurine methyltransferase	thiopurine drugs, such as 6-mercaptopurine	*Acetobacter, Acetohalobium, Acholeplasma, Achromobacter, Acidaminococcus, Acidimicrobium, Acidiphilium, Acidithiobacillus, Acidobacterium,*	Das et al. 2016
N-acetyl transferase	5-Aminosalicylate, sulfapyridine, mesalamine and sulfasalazine, etc	*Helicobacter pylori, Klebsiella pneumoniae, Pseudomonas aeruginosa,*	Chen et al. 2012; Chung et al. 2001; Ricart et al. 2002; Westwood et al. 2005
Glutathione S-transferase	organophosphorus pesticides and cytotoxic aldehydes produced during lipid peroxidation	*Acidiphilium, Acidithiobacillus, Enterobacter, Enterococcus, Pseudoanabaena, Pseudoalteromonas, Thiomicospira, Thiomonas,* etc	Booth and O'Halloran 2001
Azo reductase	dimethoxybenzidine-based dye- Direct Blue 15, acid yellow, amaranth, azodisalicylate, chicago sky blue, congo red, direct black 38, direct blue 6, direct brown 95, fast yellow, lithol red, methyl orange, methyl red, methyl yellow, naphthalene fast orange 2G, neoprontosil, new coccine, orange ii, phenylazo-2-naphtho1, ponceau 3R, ponceau SX, red 2G, red 10b, salicylazosulphapyridine, sunset yellow, tartrazine, trypan blue, brilliant black	*Acidaminococcus, Aerococcus, Bacillus, Butyrivibrio* sp., *Bacteroides* sp., *Brevibacillus, Clostridium clostridiiforme., C.paraputrificum, C. nexile, Escherichia, Enterococcus faecalis, E. faecium, E. avium, E. durans, E. gallinarum, E. hirae Eubacterium hadrum, Fusobacterium, Halomonas, Lactobacillus, Lysinibacillus, Peptostreptococcus, Pigmentiphaga, Pneumococcus, Pseudomonas, Rhodobacter, Rhodococcus, Ruminococcus, Salmonella, Shigella, Shewanella, Sphingomonas, Staphylococcus, Streptococcus, Veillonella, Xenophyllus*	Chung et al. 1992; Rafii et al. 1990; Zahran et al. 2019

Table 3 (continued)

Enzymes used	Xenobiotic detoxified	Organism	References
Alkane hydroxylase	Norcarane, n-Hexane, Iso-hexane, Cyclopentane, etc	*Pseudomonas oleovorans, Pseudomonas aerofaciens, P. putida. Acinetobacter, Rhodococcus and Alcanivorax borkumensis, Hydrocarboniphaga effusa*	Janssen et al. 2005
Haloalkane dehalogenase	1,2-dibromoethane, 1,3-dichloropropene, 1-chlorobutane-, 1-chlorohexane- and, 1,6-dichlorohexane,	*Xanthobacter autotrophicus, Rhodococcus erythropolis, Mycobacterium, Pseudomonas pavonaceae*	Janssen et al. 2005
Oxalate	an oxalate:formate antiporter; formyl-CoA transferase and oxalyl-CoA decarboxylase	*Oxalobacter formigenes*	Carmody and Turnbaugh 2014

conjugated to more-polar metabolites. While the oxidative, reductive or hydrolytic reactions are performed by Phase I enzymes to generate hydroxyl groups, epoxides, thiols and amines; in Phase II, the xenobiotic molecule or the phase I metabolites are appended with glucuronyl, methyl, acetyl, sulfonyl and glutathionyl groups (Koppel et al. 2017; Pellock and Redinbo 2017). Enzymes used and reactions catalysed in xenobiotic degradation have been listed in Table 3.

Gut microbiome has been found to play profound roles in increasing or decreasing the activity of various pharmaceutical drugs when incubated with respective cell lines. Structural modification of anti-cancerous drugs by tumor-associated bacteria, such as *E. coli* or *Listeria welshimeri* have been experimentally found to be responsible for inter-individual differences in response to anti-cancerous chemotherapy. Likewise, many anti-inflammatory prodrugs rely on gut microbial activity to be transformed into active drugs, such as sulfasalazine containing azo linkages. Various gut associated azoreductases have been characterized till date, which are mainly involved in detoxification of various azo dyes, nitro-aromatic and azoic drugs. Diverse group of azoreductase enzymes with varying co-factor dependence, structure and functional mechanism, catalytic activity and aerobic or anaerobic microbial source have been isolated and characterized with a common potential to reduce azo compounds (Bryant and DeLuca 1991; Bürger and Stolz 2010; Matsumoto et al. 2010; Misal and Gawai 2018; Morrison et al. 2012; Vijay and Morris 2014) Aerobic bacterial strains belonging to genera *Pseudomonas, Bacillus, Escherichia, Xenophillus, Pigmentiphaga, Rhodobacter, Enterococcus, Staphylococcus, Geobacillus, Brevibacillus, Lysinibacillus, Aquiflexum, Shewanella, Rhodococcus* and *Halomonas* along with anaerobic members of *Clostridium, Eubacterium, Butyrivibrio, Sphingomonas* produce a large array of azoreductases varying in their temperature and pH optima, flavin/nicotinamide requirement, with aerobic/anaerobic natures (Misal and Gawai 2018).

Exposure to heavy metals have also been reported to perturb the gut microbiome significantly. A study by Li et al. (2019) on the effect of heavy metal exposure on gut metabolic health suggested that several metabolically important genera like *Blautia, Eisenbergiella, Clostridium* showed a decline in metabolic interactions. A significant decline in butyrate producing organism, such as *Fusicatenibacter, Eisenbergiella, Syntrophococcus, Blautia, Clostridium* XIVb*, Cellulosilyticum, Oribacterium, Coprococcus, Anaerostipes, Hespellia and Lachnospiracea incertae sedis* was found upon exposure to both As and Cd. Exposure was also found to affect bile acids, amino acids and taxa associated with metabolic

health. Butyrate besides being the major energy source for the colonic epithelium, is also capable of improving insulin sensitivity and increase energy expenditure (Gao et al. 2018; Roediger 1980). Consequently, these downregulated genera along with *Parasutterella* and *Gemmiger*, are also associated with alleviation of T2DM (Helmerhorst et al. 2010; Li et al. 2018; Xu et al. 2015). Exposure to lead has been found to be associated with *Succinivibrionaceae* and *Gammaproteobacteria* in children (Bisanz et al. 2014) and Gammaproteobacterial members in adults (Eggers et al. 2019).

The specific bacterial groups in the human intestinal lumen act for detoxication rather than detoxification of the xenobiotic or heavy metals to which human body is exposed. Detoxication is the mechanism by which the drugs, mutagens and other harmful agents like heavy metals are removed from the body (Monachese et al. 2012). This helps to prevent the harmful agents to enter and impair the important organs of human body. Heavy metals are largely removed from the intestinal lumen by gram-positive bacteria by binding of metals to their cell walls. Ion exchange reactions of the exposed metal with peptidoglycan and teichoic acid, precipitation through nucleation reactions and complexation with nitrogen and oxygen ligands are main mechanisms through which these gram-positive bacteria, particularly *Bacillus* spp., having high peptidoglycan and teichoic acid content in their cell walls absorb the heavy metals. However, gram-negative bacteria show poorer metal absorbing capacity due to presence of a thin cell wall with lower peptidoglycan content.

The abundance of xenobiotic metabolizing enzyme repertoire in specific groups of bacteria vary across different nationalities (Das et al. 2016). Depending on the abundance pattern of various bacterial genera, the microbial groups have been categorized accordingly. The first category includes genera like *Prevotella*, *Faecalibacterium*, *Dorea*, *Roseburia*, *Eubacterium*, *Ruminococcus*, *Bacteroides*, etc. which showed a high-specific abundance across all regions. The next category included genera like *Neisseria*, *Bacillus*, *Slackia*, *Coprobacillus*, *Treponema*, etc. which were highly abundant across the European and American populations, but depleted relatively in the gut microbiomes of individuals of Asian nationalities. Genera like, *Rhizobium*, *Rhodospirillum*, *Bradyrhizobium*, *Rhodopseudomonas*, *Methylobacterium*, etc. comprised the third group which could be sparsely detected in the gut microbiome of European and American populations and was absent in that of Asians. Asian gut microbiome rather showed the presence of *E. coli* as one of the genera harboring xenobiotic metabolizing gene repertoire.

Control over immune system

The extraordinarily diverse and complex microbial community of gut microbiome has been found to participate in maturation and functioning of innate as well as adaptive immunity (Cénit et al. 2014; Cheng et al. 2019). The diverse microbial flora also plays important role in host defense against pathogens by repairing intestinal mucosal damage, production of various anti-microbial peptides and induction of secretion of interleukins IL-22, IL-17 and, IL-10 by host immune cells.

The first line of defense provided by intestinal bacteria is by competing for attachment sites and nutrient in the gut lining, thus preventing attachment of non-commensals or pathogenic strains- a mechanism known as competitive-exclusion effect. Further, these bacteria are also equipped with ability to produce several bacteriocins and elicit production of various anti-microbial peptides, such as α-defensins, β- defensins, angiogenins, C-lectins and RegIIIγ and Reg IIIβ by intestinal epithelial cells (IECs) (Bull and Plummer 2014; Cheng et al. 2019; Guarner and Malagelada 2003; Lazar et al. 2018). An example of bacteriocin production has been found in *E.coli* competing for amino acids and producing bacteriocin against enterohemorrhagic strain of *E.coli* (Belkaid 2015; Momose et al. 2008). Induction of other anti-microbial peptides by *B. thetaiotaomicron,* targeting other intestinal microbe have also been reported (Lazar et al. 2018). Intestinal microbes can even exert immunomodulatory effects so that the environment becomes hostile for the pathogenic species, e.g. *Lactobacillus* creating an acidic environment unfit for pathogenic invasion. The α-defensins are produced by intestinal Paneth cells upon stimulation by both Gram-negative and Gram- positive bacteria and bacterial metabolites, such as lipopolysaccharides, lipoteichoic acids, lipid A and muramyl dipeptide. *Lactobacillus* induces production of α-defensins upon infection with *Helicobacter hepaticus.* β-defensins are involved in direct killing or attenuation of the pathogenic microorganisms by penetrating into their cell membrane and chemoattraction of immune cells. *Lactobacillus* and *E.coli* induce β-defensin production upon infection with *S. aureus, S. pyogenes, P. aeruginosa, E. coli* and *C. albicans* (Cheng et al. 2020; Islam et al. 2004; Schlee et al. 2007; Seo et al. 2012; Steubesand et al. 2009; Wehkamp et al. 2004). C-type lectins, i.e. RegIIIγ and Reg IIIβ also play key roles in innate immunity by providing protection against specific pathogens like *Enterococcus faecalis, Yersinia pseudotuberculosis* and *Listeria monocytogenes.* Several interleukins have been documented to be produced upon infection with particular pathogens by different innate immune response cells. *Enterobacteriaceae,* pathobiont *Proteus mirabilis,* gut microbe derived ATP and SCFAs have been reported to induce production of IL-1β

and IL-18. IL-22 is found to play central role in maintenance of mucosal barrier integrity produced in response to infection by diverse pathogens, such as *Klebsiella pneumonia, Citrobacter rodentium,* vancomycin resistant *Enterococcus, Plasmodium chabaudi.* Gut microbes like *Lactobacillus, Allobaculum* spp. *E.coli, Clostridium* and *Bacteroides* spp. utilize tryptophan and produce indole-3-aldehyde which in turn induce IL-22 production by innate lymphoid cells (ILCs) (Abt et al. 2016; Kinnebrew et al. 2010; Ota et al. 2011; Satoh-Takayama et al. 2008; Sellau et al. 2016; Xu et al. 2015; Zheng et al. 2008). IL-17 is another important cytokine produced by intraepithelial lymphocytes (IELs) modulated by commensal bacteria in response to pathogens like *Salmonella typhimurium*. IL-17 acts by both neutrophil recruitment and anti-microbial peptide production, thereby limiting invasion and dissemination of pathogenic microbes. Production of IL-17 is induced by *Bacteroides* in response to infection with *S. typhimurium.* IL-10 is an anti-inflammatory cytokine produced by macrophages in response to host damage by pathogens and play neutralizing roles to maintain intestinal homeostasis. *Clostridium butyricum* has been shown to induce IL-10 production in IL-10 deficient mice to prevent acute colitis. Probiotic strains of *Lactobacilli* and *Bifidobacterium* have been shown to modulate IL-10 production (Niers et al. 2005).

However, innate immune homeostasis is acquired by the intestinal macrophages through a mechanism called inflammation anergy (Smythies et al. 2005, 2010). This mechanism involves phenotypic modulation of intestinal macrophages with no or low innate response in contrast to the blood monocytes. This is due to the lack of or low expression of a key receptor CD14 protein involved in recognition of bacterial LPS or related antigens known as microbe-associated molecular proteins (MAMPs) (Smith et al. 1997, 2011). Other innate response receptors, such as CD 89, CD 64, CD 32, CD16, CD 11, CD 18, CD 25, CD 123 and proinflammatory cytokines, such as IL-1, IL-6, IL-12, RANTES, TNFβ, TNFα were found to be downregulated upon inflammatory stimulations (Cénit et al. 2014).

The adaptive immune response required for local and systemic homeostasis is highly regulated by the diverse composition of gut microbiota. Gut harbors an environment where continuous presence of microbes imposes a selective pressure on the gut-associated lymphoid tissue (GALT) to undergo dynamic remodeling. Intestinal CD4 + T cells present on the lamina propria of intestine are the key component of adaptive immunity which can differentiate into four major subtypes, i.e. T helper 1 cells (Th1), Th2, Th17 and regulatory T (T_{reg}) cells, The characteristics and roles of different subtypes of T cells have been summarized in Table 4 (Wu and Wu 2012)**.** Gut microbiota plays a major role in T cell differentiation, e.g. the polysaccharide A molecule of *Bacteroides fragilis* induces systemic Th1 response. Segmented Filamentous Bacteria (SFBs) influence TH17 cell differentiation through pro-inflammatory response and Th1 cells to a lesser extent. Overexpression of Th17 response may lead to auto-immune diseases. *Clostridia* spp. belonging to clusters XIVa and IV were found to be associated with IL-10 producing T_{reg} cells (Atarashi et al. 2011).

Microbiota-gut-central nervous system axis

The gut-brain axis is an integrated communication system that involves afferent and efferent neural, endocrine/hormonal, nutrient and immunological signals for the crosstalk of the gut microbiota and its metabolites with the central nervous system. It is a bidirectional communication system where in response to the gut microbial environment and its metabolite signaling, brain commands several gut functions, such as mucin production, peristalsis and gut immune functions. Factors, such as stress, variations in diet (Buffington et al. 2016), immune activation (Estes and McAllister 2016; Foley et al. 2014) and alterations in maternal microbiome during pregnancy due to use of antibiotics or probiotics (Russell et al. 2013; Tochitani et al. 2016), can modulate the microbiome, neurodevelopment and behavior of an individual (Baumgart and Carding 2007; Borre et al. 2014; Bull and Plummer 2014; Silva et al. 2020). Gut pathologies increase permeability of the intestinal barrier which leads to increase in translocation of bacterial products that can in turn, enhance the production of cytokines and impact the blood brain barrier (BBB). This leads to even more serious ill effects. Moreover, it is well documented that levels of several neurotransmitters are regulated by the gut microbes. These microbes have even been found to directly synthesize or modulate the synthesis of various other neurotransmitters like g-aminobutyric acid (GABA), serotonin (5-HT), dopamine (DA) and noradrenaline (NA) (Calvani et al. 2018; Fung et al. 2017; Sherwin et al. 2018) which can potentially influence microglial activation and several cerebral functions. Signal transducers, such as enterochromaffin cells can bind several microbial metabolites, secrete serotonin increasing its concentration in both blood and colon. Among other transducers are vagus nerve signaling involved in mediating satiety, stress and mood and microbial metabolites, such as SCFAs, the variation of which have shown various neuropathologies (Silva et al. 2020). There are speculations that SCFAs might have roles in the production of GLP-1, PYY and other gut hormones, such as 5-HT, GIP, ghrelin and CKK.

The microbiome-gut-brain axis involves multidirectional communication which includes metabolic, endocrine, neural and immune pathways (Joscelyn and Kasper 2014; Wang

Table 4 Subtypes of T-cells, role played, health impact due to overexpression of the T cells and gut microbial taxa influencing T cell differentiation

Subtype of T cell	Role played	Overexpression of T cells	Gut microbial taxa influencing T cell differentiation
Th1	Host defence against intracellular microbial infection	Autoimmune disease	*Bacillus fragilis*
Th2	Elimination of infection by parasites	Allergen specific IgE response	*Roseburia intestinalis*
Th 17	Produces IL-17; a crucial cytokine involved in limiting invasion and dissemination of pathogens, such as *Salmonella typhimurium*	Autoimmune disease	Segmented filamentous bacteria (SFB)
T reg	Immune tolerance; promotes class switching to IgA in presence of specific antigen	Autoimmune disorder	Clostridial clusters IV. XIVa

and Kasper 2014). The intrinsic nervous system of the GI tract is known as the enteric nervous system (ENS) and is a part of the autonomic nervous system. Due to its huge extent, degree of autonomy and capability to control gastric functions, such as absorption, secretions, integrity, proliferation, barrier function and defense alarm system in concert with CNS, it is also known as the 'second brain'. Enteric neurons have been known to be activated by various bacterial toxins and metabolites, e.g. *Lactobacillus rhamnosus*-(strain JB-1) and *B. fragilis*-specific polysaccharide A (PSA) activates intestinal primary afferent neurons of the ENS in mice (Ochoa-Repáraz and Kasper 2016). Gut commensals including *E. coli* have also been documented to show symbiotic host-microbiota relationships via production of inositol 1,4,5 triphosphate through phytate metabolism. Besides, inducing growth of human tissue derived intestinal organoids, inositol 1, 4, 5 triphosphate has been shown to stimulate histone deacetylase 3 (HDAC3)—dependent proliferation and counteract the inhibitory effect of abundantly present butyrate upon colonic growth. Thus, the gut microbiota-derived metabolite inositol 1,4,5 triphosphate has been shown to activate a mammalian HDAC to promote intestinal epithelial repair (Wu et al. 2020).

Translation and commercialization of gut microbiome

Several investigators have proposed that the human microbiome should be used as an integral part of precision medicine approach as not only it could contribute to inter-individual variability in diseases but could also be a modifiable factor in terms of development of future therapeutics. Various researchers observed that personalized diets could be created through blood glucose response by integrating parameters, such as dietary habit, physical activity and gut microbiota for lowering blood glucose post-meal (Suez and Elinav 2017; Zeevi et al. 2015). Several promising research findings have documented the link between the gut microbiome, their therapeutic effects and various systemic diseases in recent times. Numerous start-up companies have initiated the translation of the research findings of several investigations on gut microbiome for fruitful therapeutic applications and subsequent commercialization. Companies developing microbiome therapy pipelines use various microbial approaches which include small molecule therapy (31%), e.g. prebiotics supporting growth of a particular group of bacteria of therapeutic importance; development and administration of single strain whole bacteria (26%). Few other approaches, such as application of microbial consortia and genetically modified single strain bacteria (12%) are also adopted. However, with increase in the number of bacterial populations number of factors playing role in cause and effect also increases. The least used approaches are phage cocktail (4%) and microbial ecosystems (4%) which call for several challenges including immune response, microbial succession and change in gut flora composition of an individual.

The microbiome therapeutic pipeline includes five stages of trials, i.e. preclinical, research, phase I, phase II and, phase III before commercialization of the product for public use. Several companies, such as SERES therapeutics have reported to meet the Phase 3 primary endpoint in developing oral microbiome therapeutic SER-109 to show statistically significant reduction in the rate of *Clostridium difficile* infection (CDI). Another company Rebiotix have also started Phase III trial for reduction of recurrent CDI. Faecal microbiota transplantation (FMT) has been found to be rigorously successful, with cure rates over 95%, in treating various infectious disease, such as recurrent CDI, ulcerative colitis, irritable bowel syndrome, etc. Cure for other diseases like obesity, autism, Alzheimer's and Parkinson's diseases are also being investigated with good prospects and highly expected to be successful through microbiome therapies.

Today around 200 companies are working across the globe to utilize the therapeutic capacity of the healthy gut microbiome to translate it for public use. Biomica is an emerging company working on microbiome-based therapeutics against immune mediated infectious diseases,

Table 5 List of companies working on translational research on gut microbiome, location and their research focus

Company	Location	Research focus
Adapsyn Bioscience	Canada	Production of novel bacterial metabolites
AOBiome	Boston	Restoration of ammonia oxidizing bacteria
A-Mansia	Louvain-la-Neuve	microbial products based on unique properties of the *Akkermansia muciniphila* bacterium
ActoBio Therapeutics	Ghent	Targeted and microbe-based therapeutic agents for locally delivering potential disease modifying therapeutics
4D Pharma	UK	Novel therapeutics
Artugen Therapeutics	Concord	Novel Live Biotherapeutic Products to help patients living with infectious, inflammatory and oncologic diseases
Biohm	Cleveland	Probiotic comprising bacteria, fungi and enzymes to remove digestive plaques
BioGaia	Stockholm	Developing probiotics for gut and immune system
BioMe	Oslo	High-throughput microbiome analysis and probiotic development
Biomica	Park Rehovot	Microbiome-based therapeutics for the treatment of immune-mediated and infectious diseases, with specific focus on Immuno-Oncology and GI-related disorders
BiomX	Ness Ziona	Phage cocktails containing natural and/or engineered phage developed through algorithm and experimental validation for targeted killing of specific pathogenic bacteria
Biosortia Pharmaceuticals	San Diego	Development of drugs/therapeutics based on the cell to cell communication chemistry from mining of microbiome in the field of immuno-oncology and immunology
Boehringer Ingelheim	Fremont	Small Molecules, Biologics, Microbiome
Carverr	Brooklyn	Developing traceable probiotics and custom microbiomes
CHAIN Biotechnology	Nottingham, Marlow	Develop live biotherapeutics—these are novel drugs based on living bacteria found in the gut but engineered to deliver specific therapeutic molecules
ClostraBio	Chicago	Developing new therapeutics to treat food allergies and provide protective immunity
Consortia Therapeutics	La Jolla CA	Develops microbial therapies to prevent and treat human disease and allergies
Da Volterra	Paris	Development of microbiota protective therapy during antibiotic treatments to help prevent and cure human diseases
Diagnostic Solutions Laboratory	Alpharetta	Provides diagnostic solutions for identifying pathogenic organisms in stool through PCR and comprehensive stool testing for assessing GI health through DNA-based studies
EnteroBiotix	UK	Full therapeutic potential of fecal microbiota transplantation (FMT) through a field-leading GMP-compliant minimally manipulated microbiome platform and an ex vivo microbiome engineering platform
Enterome	Cambridge and Paris	Discovery and development of novel therapeutics upon understanding the gut microbe and immune system interaction; production of small molecules and peptides with a focus on cancer, autoimmune, inflammatory and metabolic diseases
Evolve Biosystems	Davis	Developing the next generation of products to establish, restore and maintain a healthy newborn gut microbiome
Federation Bio	South San Francisco	Therapeutic approaches of using beneficial microbes for curing human diseases like secondary hyperoxaluria, metabolic disorders, cancer, immune diseases

Table 5 (continued)

Company	Location	Research focus
Finch Therapeutics	Somerville MA	Developing oral microbiome drugs for recurrent *C. difficile*, chronic hepatitis B, inflammatory bowel disease and children with autism and significant GI symptoms
Gusto Global	Morrisville NC	Development of novel live biotherapeutic products through advanced computational and microbiological tools for targeted immune modulation and optimization of metabolic pathways
Kaleido Biosciences	Bedford MA	Develop microbial metabolic therapies (MMT) to understand the disease pathways, such as the use of synthetic glycans, harnessing target enzymes across the microbial taxa, formulation of therapeutic products to mitigate serious complications of Covid-19, treat IBD, urea cycle disorders and hepatic encephalopathy
Locus Biosciences	Morrisville NC	Works on CRISPR-Phage (crPhage) platform combines the antibacterial power of CRISPR-Cas3 with the efficient, safe delivery of bacterial viruses called bacteriophage. The lead targets are *E. coli*, *Clostridium difficile* and organisms causing respiratory infections
MaaT	France	Patient specific biotherapeutics for improving the survival outcome of blood cancer through proprietary data collection and analysis on CGMP platform
Metabiomics	Aurora CO, Manassas VA, Chevy Chase MD; US	Developing a non-invasive microbiome test for the earlier and more accurate detection of colon polyps and colorectal cancer
Microbiotica Limited	Cambridge, UK	Identifies gut bacteria linked to phenotype with unprecedented precision in order to discover and develop live bacterial therapeutics and biomarkers
Novome Biotechnologies	South San Francisco CA; United States	Synthetic biology and microbial therapies; selecting potential bacteria from the human gut microbiome, engineering them to express therapeutic products to treat chronic disease
Oragenics	Florida, US	Production of lantibiotics helpful to recover microbial antibiotic resistance and prebiotics active in weight management in obese people
TargEDys	Rouen; France	Appetite regulation via molecular mimicry of pharmacological targets controlling gut brain axis involving bacterial, hormonal mimetic, proteins naturally occurring in the gut microbiome. They target to regulate/ moderate appetite in obese and/or old aged people
Sun Genomics	San Diego CA, USA	Customises probiotics constituting gut microbes, such as *Lactobacillus acidophillus, L. rhamnosus, Bifidobacterium lactis*
Synlogic	Cambridge, MA	Develop biotic medicines to treat various metabolic diseases like phenylketonuria, hyperoxaluria as well as immunomodulation therapies to treat diseases like cancer, IBS, etc
Sugarlogix	Berkeley CA, USA	Produces complex sugars with prebiotic functions which selectively feed the beneficial human gut bacteria strengthening the immune and nervous functions in turn
Seres Therapeutics	Cambridge, MA	Formulates and develops microbiome therapeutics to cure recurrent *C. difficile*, ulcerative colitis, metastatic melanoma and antibiotic resistant bacterial disease and graft versus host disease,
Vedanta BioSciences	Cambridge MA, United States	Leveraging live therapeutics made up of gut bacterial consortia which can stimulate immunoregulatory responses controlling allergic diseases as well as holds roles in cancer and vaccination

Table 5 (continued)

Company	Location	Research focus
Xeno Biosciences	Los Angeles CA, United States	Engineer gut bacterial consortia addressing obesity and metabolism-related diseases; oral formulation of probiotic composition to cause weight loss by mimicking the microbiome changes induced by gastric bypass surgery

immuno-oncology and, gastro-intestinal tract disorders. Finch therapeutics group is another concern that harnesses the gut microbiome. Companies adopting other approaches, i.e. on single strain cell development are A-mansia, BioGaia, Bio-Me, Ginkgo Bioworks, Next Biotix, etc. Others that focus on development of gut microbiome modulating drugs are Vedanta BioSciences, Snipr Biome, Ritter Pharmaceuticals, etc. The use of prebiotics/probiotics has been immensely adopted for the treatment of various gut related diseases affecting metabolism, immune system and CNS. Genetically modified *Escherichia coli* Nissle 1917 (EcN) is a well-known probiotic or Live Biotherapeutic Products (LBP) which is believed to impede the growth of opportunistic pathogens, including *Salmonella* spp. and other coliform enteropathogens, through the production of microcin proteins or production of iron-scavenging siderophores. It has been used to treat various gastrointestinal conditions, including inflammatory bowel disease and irritable bowel syndrome in its unengineered form. Besides, probiotics belonging to diverse genera *Lactobacillus*, *Lactococcus, Lysteria monocytogenes, Bifidobacterium, Staphylococcus, Salmonella typhii, Clostridium* and *Bacteroidetes* have also been engineered to be applied for biotherapeutic purpose to treat various therapeutic indications (Charbonneau et al. 2020). Companies like Acto Bio Therapeutics, Synlogic, Oragenics, Novome Biotechnologies and, CHAIN biotech, etc. are actively involved in bioengineering and production of various lantibiotics, immunomodulators and probiotics to treat systemic and metabolic disorders (Table 5). Several other companies have also worked on novel therapeutics based on small molecules, such as 4D Pharma, VAXIMM, Scioto Biosciences, etc. specially targeted to act as immunomodulators or live biotherapeutics to treat grave diseases as various cancers, neurodegenerative disorders and recurrent *C. difficile* prevention.

Concluding remarks

The complex and dynamic population of microorganisms in the human gut and its relationship with human health and disease has been the subject of extensive research in the last two decades. Several research studies have reported that the human gut microbiome contribute immensely in regulating human health including metabolic diseases, neuropsychological disorders and immunological response. Exciting discoveries on targeted roles of microbial communities on host metabolism, increasing knowledge on keystone species relating to particular disease states through high-throughput sequencing data, understanding links between the bacterial activation of host cells through expression of special metabolites and production of host signaling molecules in turn could open up new avenues to treat infectious and chronic diseases in a much healthy and chemical-free manner. Deeper understanding of the roles of gut microbial species in host immune activation and regulation of central nervous system would be highly rewarding in treating several autoimmune diseases and neuropsychiatric disorders which either remain untreated or suffer from various adverse side-effects upon chemical therapy. Researchers worldwide have started utilizing the knowledge excavated from microbiome mining studies into the translational pipeline to treat and prevent various human diseases. However, even deeper insights would be needed to completely unravel the complexity of human gut microbiome or the second genome and realize its enormous potential to serve mankind.

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