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REVIEW

The journey of gut microbiome – An introduction and its influence on metabolic disorders

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BACKGROUND: Metabolic disorders such as Obesity, Diabetes Type 2 (T2DM) and Inflammatory Bowel Diseases (IBD) are the most prevalent globally. Recently, there has been a surge in the evidence indicating the correlation between the intestinal microbiota and development of these metabolic conditions apart from predisposing genetic and epigenetic factors. Gut microbiome is pivotal in controlling the host metabolism and physiology. But imbalances in the microbiota patterns lead to these disorders via several pathways. Animal and human studies so far have concentrated mostly on metagenomics for the whole microbiome characterization to understand how microbiome supports health in general. However, the accurate mechanisms connecting the metabolic disorders and alterations in gut microbial composition in host and the metabolites employed by the microorganisms in regulating the metabolic disorders is still vague.
OBJECTIVE: The review delineates the latest findings about the role of gut microbiome to the pathophysiology of Obesity, IBD and Diabetes Mellitus. Here, we provide a brief introduction to the gut microbiome followed by the current therapeutic interventions in restoration of the disrupted intestinal microbiota.
METHODS: A methodical PubMed search was performed using keywords like "gut microbiome," "obesity," "diabetes," "IBD," and "metabolic syndromes." All significant and latest publications up to January 2018 were accounted for the review.
RESULTS: Out of the 93 articles cited, 63 articles focused on the gut microbiota association to these disorders. The rest 18 literature outlines the therapeutic approaches in maintaining the gut homeostasis using probiotics, prebiotics and faecal microbial transplant (FMT).
CONCLUSION: Metabolic disorders have intricate etiology and thus a lucid understanding of the complex host-microbiome inter-relationships will open avenues to novel therapeutics for the diagnosis, prevention and treatment of the metabolic diseases.

Keywords gut microbiome, metabolic disorders, obesity, diabetes type 2, inflammatorybowel diseases, probiotics, prebiotics, FMT

Introduction

Humans are teeming with around 10 times more (hundred trillion) microbial cells than their own (ten trillion) cells, symbiotically (Qin et al., 2010). There are about 22000 genes in humans which are surpassed by two million genes (Savage, 1977; Qin et al., 2010) of microbial origin. The ecological population of mutualistic, commensal and pathogenic microorganisms occupying a specific niche in the body is defined as the Microbiota (Lederberg and McCray, 2001; Peterson et al., 2009). It is mainly composed of bacteria but also harbours fungi, archaea, viruses, and some single-celled eukaryotes(Ho and Ross, 2017). The complete assemblage of the genes and genomes found within the Microbiota make up the Microbiome. Joshua Lederberg first used the word "Microbiome" (Lederberg and McCray, 2001) to emphasize the relevance of the microbiota inhabiting the human body in a normal, healthy and a diseased condition. Recently, there has been a rise in the publications in the field of microbiome and promotion of several microbiome projects (Ho and Ross, 2017) to comprehend the role that these intestinal microbial tenants have on our health (Qin et al., 2010).

How does our body acquire their microbiota? It was long thought that as a neonate slides through the mother's vaginal canal, the process of inhabitation of one's gut with the microbiota is initiated at birth (Donnet-Hughes et al., 2010; D'Argenio and Salvatore, 2015; Bäckhed et al., 2015; Ho and

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Ross, 2017). However, it was found that the gut microbial colonization may commence even earlier before birth as evident from the current study in premature babies, where both their meconium and placenta possess their own distinct microbiomes (Slattery et al., 2016). The seeding process of the human gut by the microbiota continues post birth. The nature of microbiota population and functions of the microbiome in the gut is influenced by multiple elements like heredity, age, delivery mode either by vaginal (natural) or by Caesarean section, diet [breast-feeding or cup/bottle feeding for new-borns] (Sharon et al., 2013), medication, antibiotics, sanitation (Koenig et al., 2011; Palmer et al., 2007; Perez-Cobas et al., 2012), illness and devoid of exercise (Allen et al., 2017; Boulangé et al., 2016; Ho and Ross, 2017). One study (Dominguez-Bello et al., 2010) assessed the meconium of new-born babies and reported a strong association between the first population of the intestinal microbiota and the microbiota present in either the skin of the mother *(Staphylococcus, Corynebacterium, Micrococcus* and *Propionibacterium)* of infants born by Caesarean section (CS) or mother's vagina (*Gardnerella vaginalis, Lactobacillus, Sneathia* or *Prevotella*) in babies delivered naturally. Additionally, it has been found that in babies born by CS mode of delivery, there is reduced diversity in their intestinal microbiota; Bacteroidetes colonization is delayed and Th1 cells show minimum immune responses (Jakobsson et al., 2014). The food type and the conditions of the environment to which the baby is exposed during the initial 3 years of life are crucial in establishing an adult-like microbial population. The first microbial colonizers are members of Enterobacteriaceae and *Enterococci*; followed by *Bacteroides, Clostridium* and *Bifidobacterium* sp. (strict anaerobes) once the initial oxygen supply is exhausted (Adlerberth and Wold, 2009). The main features of a stable adult microbiota in the gut are formed in the infant of 2 and 5 years of age (Rodrı et al., 2015) until old age when there is a decline in the variety and microbiota constitution (Claesson et al., 2011). This results in the elderly people being more vulnerable to repeated *Clostridium difficile* infections (D'Argenio and Salvatore, 2015) and other health disorders.

Microbiome: Then and now

The area of Microbiome is as ancient as the field of microbiology itself. The study on microbiome initiated as early as the 1680s, when Antoine van Leeuwenhoek had compared his oral and faecal microbiota. He noted differences in the nature of the microbes found in these two sites. Also, when he analyzed the oral and faecal samples from healthy and diseased individuals, he observed distinguishing features (Leeuwenhoek, 1684; Dobell, 1920). Initially, isolation and direct culturing of microbes on simple media was employed to study different microorganisms. Gram staining and other morphological and biochemical tests were carried out for the in-vitro identification of the individual microbial members. Even though these culture-based techniques are nowadays commonly used for diagnostics, they face some constraints. First of all, as the conditions for the growth of various microbes differ, the growth conditions employed may favor one or more microbial species over other species. These methods could separate many broad bacterial taxa but were non-specific at lower taxa (Morgan and Huttenhower, 2012; Human Microbiome Project Consortium et al., 2012). Besides, about 99% of the microorganisms are currently uncultivable (Li and Qin, 2005). Thus, there were certain demerits in the qualitative and quantitative studies of the uncultured microorganisms.

To overcome these problems, the culture-independent procedures were developed in the late 1980s et al. In such methods, extraction of DNA occurs directly from a sample rather than from individually cultivated microbes. This has enabled the researchers to have a broad understanding and in investigating the various features of the microbial population. These include taxonomic level diversity, like the number and category of microbes present in a community and functional metagenomics, which elucidates the biochemical functions encoded in the microbiome (Pace et al., 1986; Morgan and Huttenhower, 2012). The DNA-based procedures initially evaluated the isolated DNA of the microbial group for the targeted genes by hybridization, or PCR amplification of specific genes of interest before DNA sequencing (Jovel et al., 2016). But, these procedures could impart very less information of the vast taxonomic diversity or detect the presence or absence of metabolic functions of the individual microorganisms (Morgan and Huttenhower, 2012; Jovel et al., 2016). One of the significant aspects of these procedures includes Next Generation Sequencing (NGS) technologies which have received a special attention over the past ten years. NGS allowed sequencing of several molecules of DNA simultaneously from multiple individuals at a time. These led to the reduction in the sequencing cost and also displayed high throughput of bases sequenced. These technologies are comparatively fast, precise and reproducible than direct cultivation methods. Unlike conventional techniques, NGS has allowed the characterization of the complex microbiome both qualitatively and quantitatively without the selection bias. Moreover, these technologies have resulted in the sequencing of Human Microbiome Project (The NIH HMP Working Group, 2009) the aim of which is to obtain the entire sequence of the genome of the microbes found in the various parts of the human body along with their functions (Gevers, 2012; Methé et al., 2012) .

Although NGS has been revolutionary in broadening our knowledge in the microbiome arena and had a great impact in metagenomics, they have disadvantages. One of the problems of the second generation sequencing technology is that it mostly read short sequences. This complicates further

splicing, assembly, location, and analysis of the sequence by Bioinformatics software (D'Argenio and Salvatore, 2015). These approaches rely mostly on continuously updated databases, Bioinformatics tools, and functional data. Using both culture-independent and conventional procedures for the whole genomic characterization of specific microorganism will provide deep comprehension into the role of intestinal microbiota. This in turn will help in the identification of novel gene targets for diagnosis and treatment of many incurable diseases (D'Argenio and Salvatore, 2015).

Gut microbiome–The most forgotten and neglected organ

The most abundant and varied microbiota population exists in the gut within the human body. Firmicutes and Bacteroidetes are the two predominant phyla that dominate the gut microbiota. They represent more than 98% of the 16S rRNA sequences observed in the intestinal microbiota (Backhed et al., 2004; Marchesi, 2010; Hinzey et al., 2016). As far as our health is concerned, these intestinal minions direct many normal host physiologic activities such as digestion, synthesis of essential vitamins, detoxification, maintenance of epithelial integrity, regulation of the immune and endocrine system, influencing behavioral responses and defend against possible pathogens thereby enabling in comprehending the consequences of metabolic imbalances (D'Argenio and Salvatore, 2015). The information for all these physiologic processes is contained in the gut microbial genes and this resembles that of an organ but lacks within the genome of humans. This resulted in the gut microbiome being referred to as the "neglected" organ (O'Hara and Shanahan, 2006).

Humans are known as "superorganisms" (Walsh et al., 2014) due to the fact that they possess two types of genome: one inherited from their parents and the other acquired through the microbiome. The genome inherited from the parents is stable throughout one's lifetime while the microbiome, the second genome is dynamic and influenced by alterations in the environmental parameters. Gut microbiome dysbiosis has led to a wide range of health issues like asthma, functional bowel disorders, allergies, obesity, diabetes, anxiety, depression etc. (Slattery et al., 2016).

Imbalances in the gut microbiome linked to obesity, diabetes mellitus and inflammatory bowel disease

Obesity

Not only the lifestyle and heredity are to be blamed for a person to be obese, recent literature shows that variation in the intestinal microbiome may be related with the risk for obesity (Komaroff, 2017; Boulangé et al., 2016). Owing to its link to heart diseases, cancer, type 2 diabetes etc. obesity is one of the most talked research topics. There is a strong impact of the gut minions on obesity, than simply dysbiosis in the gut microbial composition as evident from the several experiments conducted on mice models (Clarke et al., 2012; Cani, 2013; Ridaura et al., 2014; Barlow et al., 2015). For instance,

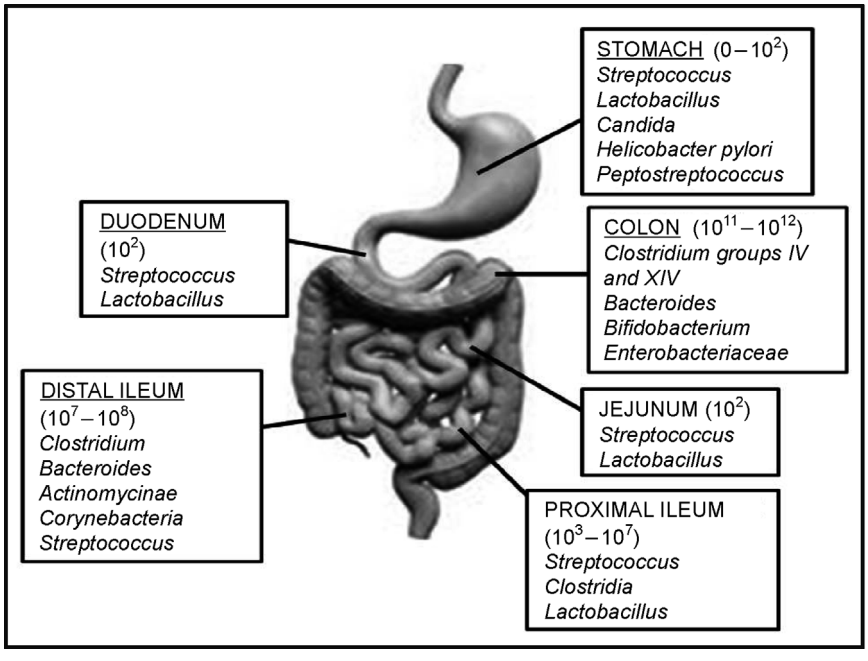

Figure 1 Distribution of the gut microbiota in gastrointestinal tract of humans (Sartor, 2008) [Numbers in bracket shows microbial load per mL].

in a particular study (Komaroff, 2017), germ-free thin mice, obese and thin mice were given a high fat rich diet for 2 weeks and then the intestinal microbiota from the obese mice and lean mice were transplanted into germ-free lean mice. The germ free mice inoculated with the cecal content of obese mice became obese, while when inoculated with the cecal matter from the lean mice made them leaner (Komaroff, 2017; Turnbaugh et al., 2008). Similarly, when the gut microbiota from conventionally raised mice was introduced into lean germ free mice, within 10-14 days the lean animals weighed 60% heavier than the control animals (Hartstra et al., 2015). These mice were also found to be insulin resistance even when there was no increase in daily food intake (Turnbaugh et al., 2006; Turnbaugh et al., 2008). Ridaura et al. studied monozygotic human twin pairs in which one of them was obese and the other lean. The faecal matter from the obese twins and faeces from the skinny twins were fed to the normal weight germ-free mice. There was gain in the bodyweight and obesity like phenotype in the mice fed faeces from the obese human twins while the mice remained thin which were fed faeces from the twins who were lean. Further, when the obese and lean mice were cohoused, they ate each other's faecal matter and gradually, the fat mice displayed lean phenotype with their gut microbiota resembling that of the skinny mice. This indicates that the gut microbial flora of the lean mice may be able to dominate the microbiota of the fat mice. Also there may be subsequent entry of the specific members of the Bacteroidetes from the lean to fat mice microbiota (Ridaura et al., 2013; Komaroff, 2017).These studies reveal that not just the gut microbial dysbiosis but the basic composition of gut microflora also play a key role in determining bodyweight. Bacteroidetes and Firmicutes are the two main phyla linked to the obesity related changes. The intestinal microbial community exerts influence on the amount of calories absorbed by the body rather than the calories ingested, leading to Obesity. Humans are unable to digest many dietary carbohydrates as they are devoid of the enzymes for turning the complex starches into simple sugars easily. However, the enzymes derived from the microbes can convert these polysaccharides into digestible energy sources like short-chain fatty acids (SCFAs) and monosaccharides(Holleran et al., 2017). The phylum *Firmicutes* could harvest more energy from the food rich in fats as compared to *Bacteroidetes* (Turnbaugh et al., 2006). High fat food containing fatty acids results in elevation of the *Firmicutes* and a resulting decrease in the *Bacteroidetes* population (Ley et al., 2005; Ley et al., 2006; Turnbaugh et al., 2006; Tang et al., 2017). Thus, obese people with high level of *Firmicutes* are more efficient in deriving energy from the diet than the lean people (Ley et al., 2006; Turnbaugh et al., 2006; Ridaura et al., 2013; Tang et al., 2017). The gut microbiome from the stool samples of 30 obese and 13 lean subjects were analyzed before and after Roux-en-Y gastric bypass surgery in one of the studies (Furet et al., 2010). The obese individuals displayed lower levels of *Prevotella* and *Bacteroides* than the skinnier individuals before surgery. But there was elevation in *Prevotella*, *Escherichia coli* and *Bacteroides* after surgery showing inverse relation to the bodyweight irrespective of changes in the diet (Furet et al., 2010; Fluitman et al., 2017). Moreover, decline in the abundance of the anaerobe *F. prausnitzii* was seen in obese diabetic patients compared to the non-diabetic obese and skinnier individuals (Fluitman et al., 2017). *F. prausnitzii* with its anti-inflammatory characteristics is associated with decreased inflammation in obesity and type 2 diabetes (Furet et al., 2010; Fluitman et al., 2017). There are various mechanisms by which the intestinal microbiome could cause weight gain. This variation in the phylum of the microbiota decreases the GLP2 (glucagon-like peptide-2) production endogenously (D'Aversa et al., 2013). The role of this peptide is to strengthen the tight junctions of the cell and prevents LPS (Lipopolysaccharide) influx into the plasma (D'Aversa et al., 2013). But decreased GLP2 production causes an increase in the permeability of the gut and LPS concentration in the plasma (Cani and Delzenne, 2009). Large amount of LPS in plasma triggers TLR4, upregulating the pro-inflammatory cytokines causing a series of the inflammatory reactions (Fessler at al., 2009) eventually leading to obesity (Catalán et al., 2007). The intestinal microbiota regulates the energy metabolism of the host via transcription of several mediators. Under normal physiologic conditions, the levels of fasting induced adipose factor (*Fiaf*) in the gut epithelial cells increases in the fasting individuals (Wolf and Lorenz, 2012). Lipoprotein lipase (Lpl) is an enzyme that elevates the fatty acids absorption and causes the accumulation of the adipocyte triglyceride but is inhibited by *Fiaf* (Bäckhed et al., 2005; Wolf and Lorenz, 2012). Normal mice and the germ-free mice fed with high fat food were compared and a 9-fold decrease in the *Fiaf* expression was seen in the presence of the gut microbes (Bäckhed et al., 2004). This implies that changes in the microbial communities in the gut due to consumption of the high fat food enhance Lpl enzyme levels and fat build-up in the body by reduced *Fiaf* expression (Bäckhed et al., 2004). Researchers at the Emory University of Medicine recently studied a mouse that had been engineered to not have a toll-like receptor 5 (TLRS) which recognizes flagellin from the invading bacteria and aid in innate immunity (Hinzey et al., 2016). The mice missing toll-like receptor 5 have an abnormal Firmicutes population. It was found that the obese mouse was never satiated due to its inability to synthesize leptin. It has a 50% reduction in Bacteroidetes and an increase in Firmicutes. It is possible that obesity leads to an abnormal level of Firmicutes. Some researchers believe that excessive levels of Firmicutes activate certain enzymes that promote the storage of fat-mass. All these findings are indicative that gut microbiota has a pivotal role in regulation of obesity.

Type 2 Diabetes Mellitus (T2DM)

A person with type 2 Diabetes Mellitus has high glucose levels in the blood and is insulin resistant as the cells cannot

use insulin properly (Scott et al., 2007; Brunkwall and Orho-melander, 2017; Aw and Fukuda, 2018) Diabetes Mellitus is a chronic metabolic disorder of global concern which is affected by both genetics and epigenetic factors, with obesity-linked metabolic changes being one of the consequence (Scott et al., 2007). However, new findings have shown that disturbances in the gut microbiome can also contribute to Diabetes Mellitus (Nadia et al., 2010; Qin et al., 2013; Brunkwall and Orho-melander, 2017). The levels of Firmicutes, and mainly *Clostridium* species were lower, while there was elevation in the proportion of Beta-proteobacteria and Bacteroidetes population in patients diagnosed with T2D compared to non-diabetic, control individuals (Larsen at al., 2010). Two metagenomic studies have shown that diabetic patients had lower abundance of butyrate-producer *Clostridiales* (*Faecalibacterium prausnitzii* and *Roseburi*) and greater proportions of non-butyrate producing *Clostridiales* in comparison to control groups (Qin et al., 2012; Karlsson et al., 2013). Thus, it can be inferred that bacteria producing butyrate provide some protection against Diabetes Mellitus (Karlsson et al., 2013; Qin et al., 2012).According to these two studies, the gut microbiome of diabetes mellitus cohort includes *Clostridium ramosum, Eggerthella lenta*, *Bacteroides caccae*, *E. coli* and *C. hathewayi* which cause opportunistic infections in human beings. While the cohort of non-diabetics was found to be enriched with the microbiome of numerous butyrate producers like *F. prausnitzii, Roseburia intestinalis, Clostridiales* sp., *Roseburia inulinivorans, and E. rectale* (Aw and Fukuda, 2018). In another study, the analysis of the faecal samples of postmenopausal obese Caucasian females in Sweden displayed high concentrations of proximal intestine flora such as *Streptococcus mutans* and *Lactobacillus gasseri* in addition to *E.coli.* This predicts the development of insulin resistance in these postmenopausal obese females (Hartstra et al., 2015). Moreover, the by-products of the gut microbiota also have a role in the pathophysiology of Diabetes Mellitus. The dietary plant fibers which are difficult to digest by humans are fermented by the gut microbiota in them producing short-chain fatty acids (SCFAs) like acetate, butyrate, propionate etc. These SCFAs are absorbed in the intestine and act as energy substrates for the host. Butyrate is mainly involved in energy metabolism while the other short chain fatty acids enter the portal venous circulation (Donohoe et al., 2012; Hartstra et al., 2015; Tang et al., 2017) Regulation of inflammation, increased satiety and decreased intake of food are some of the functions of these SCFAs (Cani et al., 2006). Studies on animal models have indicated that acetate act as a substrate for synthesis of cholesterol and propionate is involved in gluconeogenesis and hepatic lipogenesis (Delaere et al., 2013). SCFAs generated by the intestinal microbiota affect the host metabolism in several ways as depicted in the Fig. 2. Any variation in the production of short-chain fatty acids due to elevated Firmicutes to Bacteroidetes ratio may be related to Type 2 Diabetes (Aw and Fukuda, 2018)**.**It is observed that high acetate levels in the blood leads to insulin resistance and elevation of the appetite-activating hormone, ghrelin levels in the stomach (Perry et al., 2016). Reduced butyrate concentrations in the gut stimulate low-level inflammation which induces insulin-resistance (Devaraj et al., 2013). Gut inflammation in rodents weakens the tight junction proteins of epithelial cells in the mucosal layer. This facilitates endotoxemia, and results in enhanced innate immune response, ultimately leading to insulin resistance and gain in the bodyweight (Forslund et al., 2015).

Inflammatory bowel diseases (IBD)

IBD refers to a class of many chronic inflammatory conditions of the part or whole of the GI tract. It includes ulcerative colitis (UC) and Crohn's disease (CD) as the main types (Cénit et al., 2014). The major distinction between these two is that UC is localized to the large intestine while Crohn's disease (CD) can cause damage to any part of the digestive tract. IBD is a relapsing disorder affected by environmental and genetic elements. From genetics point of view, many IBD susceptible genes were known that controls the microbial-host interactions (Khor et al., 2011). For example, Nod2 gene maintains the gut homeostasis by sensing the peptidoglycan layer of the microbiota and activates a series of inflammatory reactions. This in turn stimulates the release of antimicrobial peptides and mucin which prevent the contact of microbiota from the gut epithelial cells (Bevins and Salzman, 2011). Nod2 is recognized as a Crohn's disease susceptibility gene (Ogura et al., 2001; Inohara et al., 2003). Nod2 mutations in Crohn's may modify these inflammatory reactions and cause gut barrier breakdown and thus dysbiosis. Mice lacking Nod2 exhibited reduced ability to kill the pathobionts and harbours increased proportion of commensal microflora (Petnicki-Ocwieja et al., 2009). This indicates the crucial role of Nod2 in the regulation of gut commensal microbiota (Petnicki-Ocwieja et al., 2009; Couturier-Maillard et al., 2013). The impairment of the microbial community caused by the Nod2 deficiency in mice appears to be a risk element for ileal colitis (Petnicki-Ocwieja et al., 2009). It is observed from other studies that there is low diversity and change in the intestinal microbiota composition in individuals diagnosed with IBD compared to unaffected individuals (Frank et al., 2007; Tong et al., 2013). Bacteroidetes and Firmicutes population was found to decrease and Proteobacteria and Actinobacteria levels showed an increase in their population in IBD patients (Frank et al., 2007; Morgan et al., 2012). Various literatures have reported that the reduction in the Firmicutes levels mainly contributes to the low intestinal microbiota diversity in IBD sufferers (Scanlan et al., 2006; Sokol et al., 2008; Sokol et al., 2010). The proportion of *F. prausnitzii* of the *Clostridium* cluster IV was reduced among the Firmicutes. The composition of the gut microbiota differs between CD

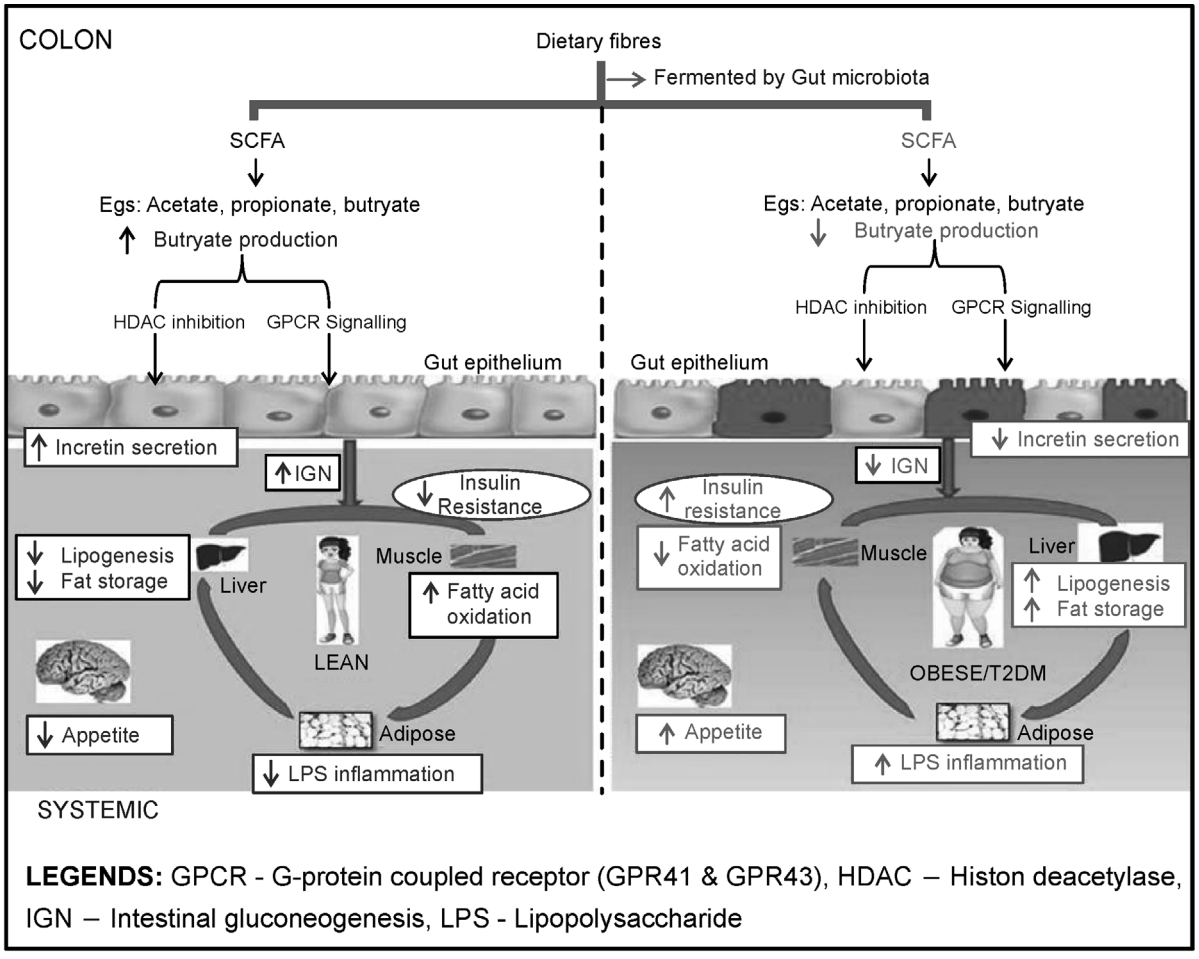

Figure 2 Mechanisms by which the gut microbiota produced SCFAs affect the host metabolism in lean and obese persons. {Adapted from Hartstra et al., 2015. Insights into the role of the microbiome in obesity and type-2 diabetes. *Diabetes Care*}.

and UC groups. In UC affected individuals, declined levels of the butyrate producer R*oseburia hominis* and *F. prausnitzii* was observed compared to healthy controls (Machiels et al., 2014) whereas contrary result was found in Crohn's disease with enhanced *F. prausnitzii* abundance patients and decrease in overall microbial diversity (Hansen et al., 2012). The studies so far have concentrated mainly on the role of intestinal bacteria in the pathophysiology of metabolic syndromes and the role of gut fungi has been relatively ignored. The two latest studies in murine and humans have reported the association of mycobiome (fungal community) to obesity (Heisel et al., 2017) and Crohn's disease (Hager and Ghannoum, 2017; Sheehan and Shanahan, 2017). When mice were fed diet rich in high fat, notable differences in the abundances of not only the gut bacteria but also in the fungal population were observed. Complex diet specific relationships were found to exist between certain bacterial and fungal groups and these inter-kingdoms in high-fat diet fed mice were significantly reduced (Heisel et al., 2017). This shows the effect of high fat enriched diet in alteration of the mycobiome and its potential role in obesity. In the humans study (Hager and Ghannoum, 2017), Crohn's disease (CD) affected individuals displayed higher levels of the fungus *Candida tropicalis* together with two bacteria, *Serratia marcescens* and *E. coli* of Enterobacteriaceae family compared to their healthy and normal relatives. In addition to that, these three pathogens worked together to form stable biofilms thereby worsening the gut inflammation. This is the first study that highlights the combined role of fungi and bacteria in aggravating the inflammation in CD. It also shows the influence of mycobiota in CD progression (Hager and Ghannoum, 2017). Even though, inflammation may result in these microbiome shifts, the alteration in the microbial community in the gut may be a factor for IBD pathogenesis. This could be due to imbalance between the useful and the deleterious microbes or intolerance to the commensal microflora (Frank et al., 2007; Lepage et al., 2011; Elson and Cong, 2012). Dysbiosis leads to some functional alterations in the intestinal microbiota which may be responsible for IBD pathogenesis. The overall mechanism employed by the gut microbiota in influencing IBD is represented in the Fig. 3. Metabolites of the intestinal

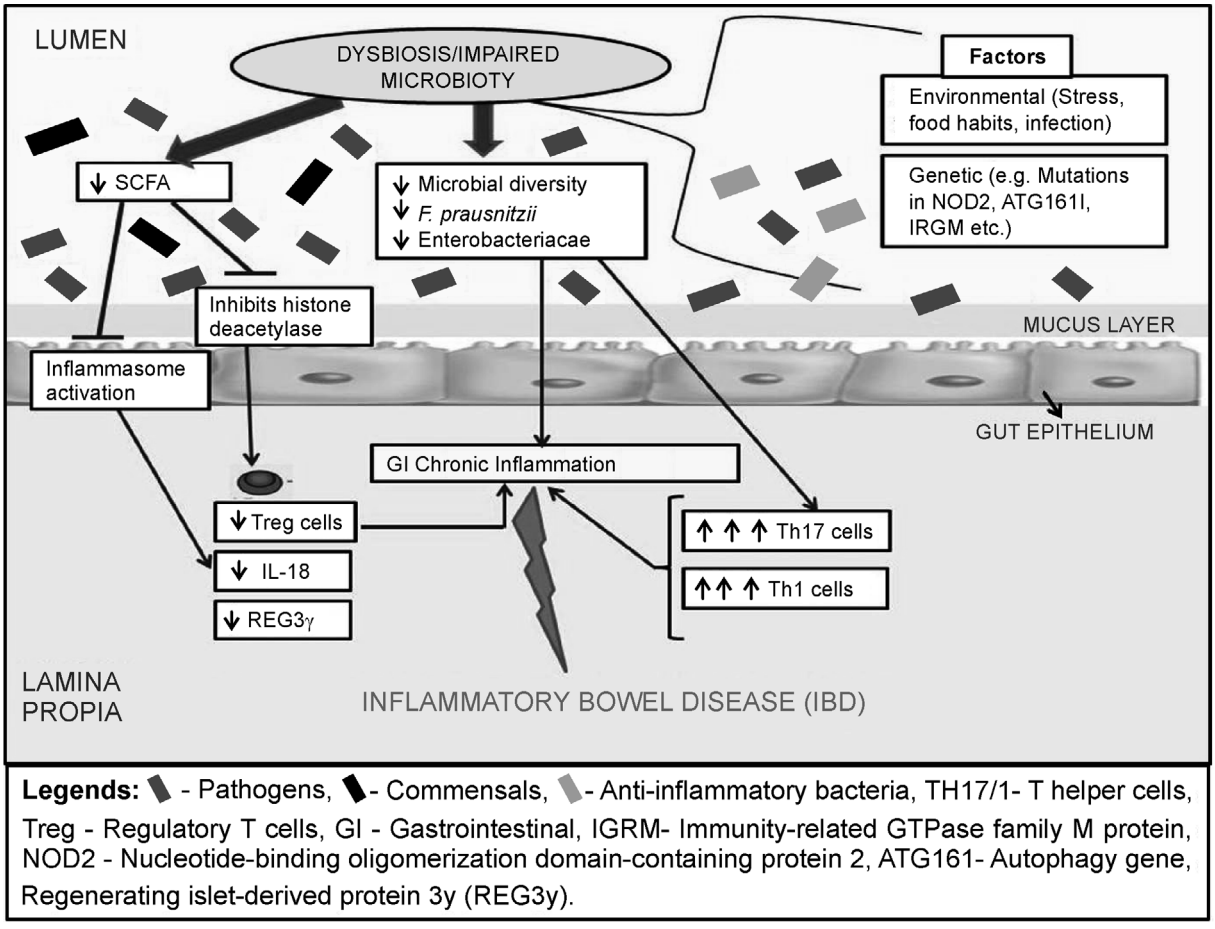

Figure 3 Diagram representing the mechanisms by which the gut microbiota contributes to IBD pathophysiology.

microbiota like SCFAs, dietary fibers etc. aid in the maintenance of the energy balance, functions of the epithelial cells and in shaping the host immune system. There is decline in the SCFA levels produced as by-products of the intestinal microbiota. This results in enhanced inflammation of the GI tract due to induction of T_{reg} cells by SCFA via inhibition of histone deacetylase activity. Besides, SCFA cause inflammasome activation which promote gut epithelial repair by IL-18 (Frank et al., 2007; Lepage et al., 2011). Metagenomics data of the gut microbiota of the IBD sufferers showed decrease in the genes involved in amino acid and carbohydrate metabolism and an increase in the genes involved in the oxidative stress pathway (Morgan et al., 2012). This suggests that the gut inflammation in IBD affected people may be caused by the oxidative stress from the intestinal microbiota (Matsuoka and Kanai, 2015). From the above studies it can be deduced that the combined effect of both environmental and genetic factors cause disturbances in the microbial population. As a result, there is rise in the colitogenic pathogen levels and suppression of the beneficial microflora due to dysbiosis. This induces chronic inflammation due to TH1 and TH17 cells hyper-activation, decrease in barrier integrity, REG3γ, regulatory T cells and IL-10, ultimately leading to IBD.

Novel curative approaches for the manipulation of intestinal microbiota for obesity, diabetes mellitus and IBD treatment

Manipulation by prebiotics

There are un-digestible but fermentable polysaccharides like fructo-saccharides, oligosaccharides, galacto-oligosaccharides, resistant starch, inulin that cause specific alterations in the composition and proliferation of the beneficial gut microbes and provide health benefits to the host (Roberfroid et al., 2010; Hur and Lee, 2015). These polysaccharides are termed as prebiotics. The end products like SCFAs and lactic acid formed during the fermentation of these unabsorbed polysaccharides by the gastrointestinal microbiota help in the modulation of the gut microbiota composition. Prebiotics stimulate SCFA production as well as favor the growth of

good bacteria, primarily *Lactobacillus and Bifidobacterium* sp. (Roberfroid et al., 2010; Fluitman et al., 2017). Many literature studies on humans and animal models have demonstrated that prebiotics intake mediate the immune system, supress the growth of pathogens, decrease blood ammonia, decrease hunger and induced satiety (Delzenne et al., 2011; Dahiya et al., 2017; Fluitman et al., 2017). Besides, these un-digestible carbohydrates also promote cellular differentiation, cell-cycle control and induce apotosis of transformed epithelial colon cells by inhibiting histone deacetylase (Cani et al., 2009). This manipulation is partly mediated via alterations in the intestinal peptide secretions induced by SCFAs and partly by favoring the growth of *Bifidobacterium* microbes. This results in ameliorating the function of the intestinal barrier (Cani et al., 2007). The overall mechanisms exhibited by the prebiotics in the treatment of metabolic disorders are illustrated in the Fig. 4.

Manipulation by probiotics

WHO defines probiotics as live, viable microbes that when administered or ingested in appropriate amounts, provide health benefits to the host. Probiotics strains, mainly those of the *Bifidobacterium* and *Lactobacillus* genera help in the treatment of metabolic disorders. Probiotics employ different ways for treatment. This includes: prevention pathogen adherence to the intestinal mucosa, restoration of the dysfunctional gut barrier, thereby reducing endotoxemia, activating the immune system, SCFAs production like butyrate or by alleviating low-level inflammation. There are many experiments that show the role of probiotics in modification of the gut microbiome and thus in the treatment of Obesity, T2DM and IBD (Tvede and Rask-Madsen, 1989; Aas et al., 2003; Park et al., 2013). In an experiment by Park et al. (2013), diet-induced obese mice were administered probiotic strains *Lb plantarum* KY1032 and *Lb curvatus* HY7601. Results exhibited reduction in their weight gain and fat build-up. Also, when compared with the group which was provided the same diet with a placebo, the mice showed decrease in their levels of cholesterol, insulin, liver toxicity and leptin (Park et al., 2013). Many mouse models were given the probiotic VSL#3 which was able to prevent and treat

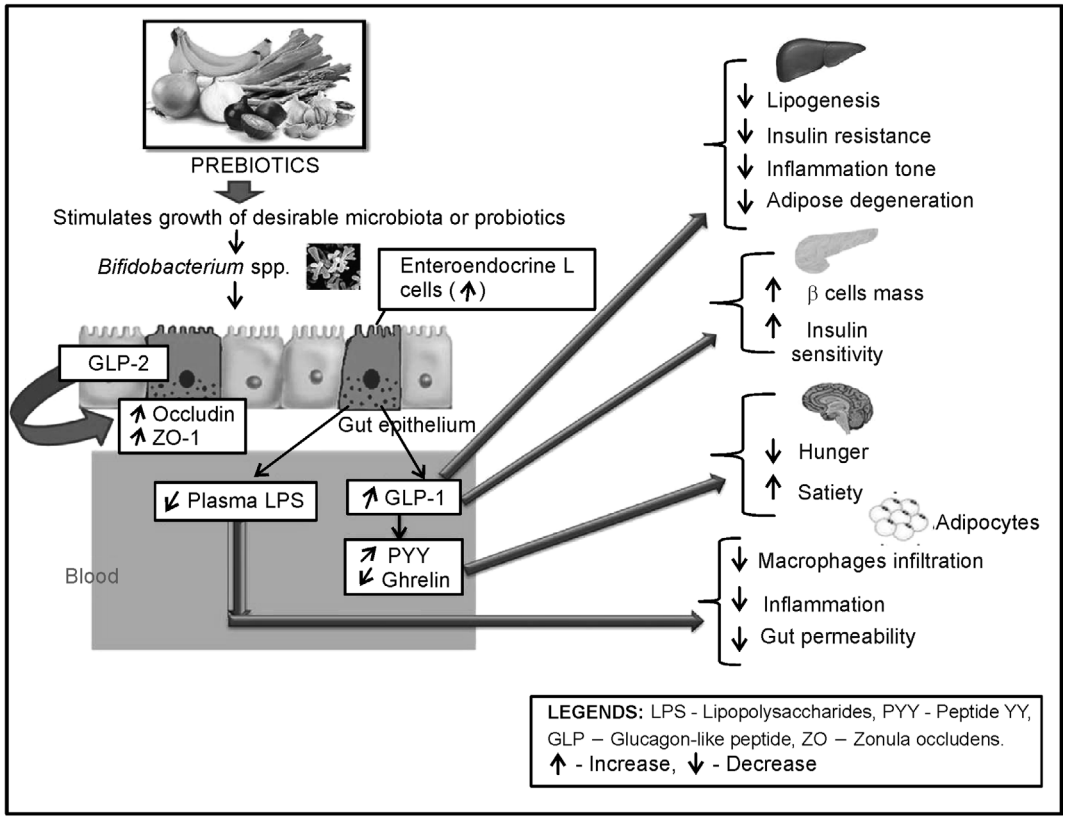

Figure 4 Diagram depicting the role of prebiotics in modifying the gut microbiome and treatment of metabolic disorders. Prebiotics modify the intestinal microbiota by promoting the growth and activity of probiotics (E.g. *Bifidobacterium* spp.). This induces the differentiation of precursor cells into entero-endocrine L cells in the gut epithelium. L cells increase the secretion of GLP-1 and PYY in the portal plasma and decrease Ghrelin and plasma LPS levels. This activates the endocannabinoid system in the gut and adipose tissue. L cells also secrete GLP-2 that improves the distribution of tight junction proteins ZO-1 and Occludin, thereby alleviating endotoxemia, and localized inflammation. All these processes lead to decreased gut permeability, reduced hunger, enhanced satiety, reduction in body fat accumulation, increased insulin sensitivity and pancreatic beta cell mass, and normalized low-level inflammation, indicating the usefulness of prebiotics in management of Obesity, T2D and IBD.

obesity and Type 2 diabetes via gut microbiome manipulation (Yadav et al., 2013).When IL-10 deficient mice was fed with *L. salivarius* UCC118, reduced inflammation of the gut mucosa was observed. Also, *Lactobacillus plantarum* 299v and VSL#3 precluded the start of colitis in IL-10 deficient mice. All advantages of probiotics were not linked to a universal strain but were mostly strain specific. A new study has emphasized the role of intestinal fungi in health and disease (Hager and Ghannoum, 2017; Heisel et al., 2017). It also provides information on novel therapeutic approaches in the treatment of IBD through combined use of antifungals and probiotics (Hager and Ghannoum, 2017). Antifungals will suppress the fungal growth and probiotics can restore beneficial microbes and maintain balance of the gut microbiota (Hager and Ghannoum, 2017).

Manipulation of the intestinal microbiota using heavy metal mediated editing

Disruption in the gut microbial community is linked to colitis. Some bacterial members of Enterobacteriaceae such as *E.coli*, *Proteobacteria* (Hager and Ghannoum, 2017) in the intestinal microbiota are known to cause inflammatory bowel disorders. In one of the latest study (Zhu et al., 2018) based on murine colitis model, the abnormal growth of Enterobacteriaceae members could be arrested by treatment with tungstate. When drinking water with sodium tungstate was administered to the affected mouse, a marked shift in the Enterobacteriaceae population from abnormal to normal state was observed. This shift led to decrease in the gut inflammation. Tungstate is mistakenly incorporated into a significant cofactor by Enterobacteriaceae members. The resulting toxic cofactor does not work properly and impairs their capacity to harvest energy in the inflamed GI tract. It hampers the respiratory pathways dependent on molybdenum cofactor in bacteria that operates only during inflammation. However, the composition of the gut microbiota in mouse with colitis in balanced conditions remains unaffected by tungstate. Therefore, accurate tungstate mediated editing of the microbiota in the gut could reduce the deleterious effects of colitis (Zhu et al., 2018).

Faecal Microbial transplant

Faecal Microbial transplantation (FMT) is a process in which the stool or faecal matter from a healthy donor is transplanted to an unhealthy recipient by endoscopy, enema, sigmoidoscopy, or colonoscopy (Hur and Lee, 2015). This procedure is currently becoming more effective approach in replenishing the disturbed gut microbiota and to lessen the symptoms of a disease (Walsh et al., 2014). FMT has been most commonly employed to treat repeated infections caused by *C. difficile* (Aas et al., 2003; McIlroy et al., 2018). It does so by re-establishing the commensal bacterial populations which have been obliterated by the overuse of antibiotics. Khoruts et al., 2010 compared the bacterial composition of *Clostridium difficile* infected patient's microbiota using terminal-RFLP and 16S rRNA sequencing method before and after Faecal Transplant treatment (Khoruts et al., 2010). It was observed that before FMT there was decline in the Firmicutes and Bacteroidetes levels in the patient but after 14 days of FMT, the microbiota was dominated by *Bacteroides* spp. The microbiota was restored and resembles that of the healthy donor's gut microbial community (Khoruts et al., 2010). Another report had shown that FMT from thin donors into obese individuals with obesity via gastroduodenal tube induced enhanced insulin sensitivity in the receiver (Vrieze et al., 2012). Also, post six weeks faecal transplant in another study showed increase in butyrate producing bacteria *Roseburia intestinalis* known to have protective role in T2DM but had reduced SCFA levels. The selection and screening of the donors is crucial for the success of FMT. Donors with no gastrointestinal diseases and who have not used antibiotics for the last two-six months are selected. They are screened for faecal pathogens and blood prior transplantation (Woodworth et al., 2017). Although there are no standard eligibility criteria, a few genetically unrelated healthy members and mostly family members or relatives (e.g. sisters/brothers, parents/grandparents, spouses, children/grandchildren) are preferred (Woodworth et al., 2017). In spite of some evidence that FMT could be effective, there is still uncertainty in the long-term benefits of the transplantation. A study was done in which unique SNV (Single nucleotide variation) patterns of the gut microorganisms were employed to specifically identify donor microorganisms and their persistence in stool samples of recipients with recurrent *C. difficile* infection after FMT (Kumar et al., 2017). The results showed close similarity between the donor and recipient (both early and two year samples) for *Bacteroides* spp. (*B. vugatus* and *B. ovatus*) three-six months post transplantation and for *P. merdae, B. intestinihominis* and *A. onderkondii* two years after FMT (Kumar et al., 2017). This provides some insights into the long-term persistence of the donor microorganisms after the faecal transplant and its potential therapeutic approach (Kumar et al., 2017; Woodworth et al., 2017).

Conclusion and future directions

Gut microbiome has an important contribution in regulating the host physiology and metabolism for survival. Nowadays, literatures on the correlation of the intestinal microbiome to the global and common metabolic syndromes like Obesity, Diabetes Mellitus and Inflammatory Bowel Diseases are on the rise. It is evident from several studies that Obesity, T2DM and IBD are not only nutrition associated metabolic disorders but dysbiosis in the gut microbiome also contribute to their pathophysiology. The gastrointestinal tract represents an intricate microbiota. The linkage between the metabolic

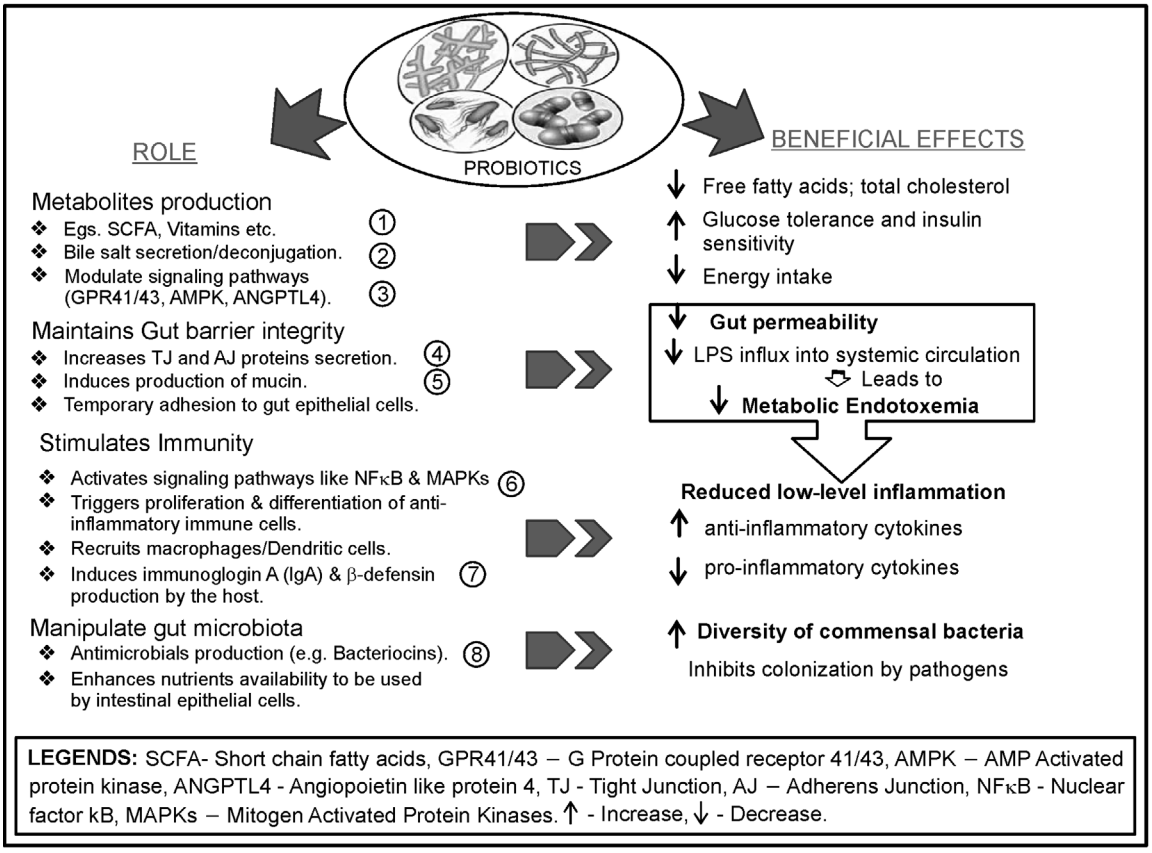

Figure 5 Overview of the mechanisms of modulation of the intestinal microbiota against metabolic disorders by probiotics(Figure adapted from Le Barz et al., 2015). 1) Intake of Probiotics stimulates metabolites like SCFAs (Butyrate, Propionate, acetate etc.) which act as energy sources and regulate host metabolism. SCFAs bind to G-protein coupled receptors (GPR41/43) and secrete GLP-1 that inhibits glucagon secretion, reduce hepatic gluconeogenesis thereby enhancing glucose tolerance and insulin sensitivity. 2) Bile salt hydrolase activity in probiotics aid in detoxification of the bile salts and increase their survival in the gut. Bile salt de-conjugation decreases serum cholesterol and fatty acids and their absorption through the lumen causing decrease in lipid accumulation. 3) Probiotics activates AMPK pathway that elevates fatty acid oxidation, inhibits glycogen storage and decreases insulin resistance. ANGPTL4 is modulated by probiotics that restricts LPL production and prevents accumulation of fatty acids in adipocytes; this in turn prevents obesity and related disorders. 4) Probiotics promote TJ and AJ junction proteins production that reduces intestinal permeability and inhibits the influx of LPS into systemic circulation, thereby reducing metabolic endotoxemia. 5) Induces production of mucin proteins that assembles to form a mucus layer, acting as physical barrier against pathogen establishment. 6) Probiotics stimulates signaling pathways such as NF-κB and MAPK that recruits dendritic cells/macrophages and trigger anti-inflammatory pathways (Plasma cells multiplication and T_{reg} cells). This results in decrease in pro-inflammatory cytokines and increase in anti-inflammatory cytokines and IgA immunoglobulins. 7) IgA mostly present in the mucus layer aid in maintaining the mucosal barrier. All these cause reduction in low-level inflammation and useful in colitis treatment. 8) Bacteriocin production by probiotics changes the gut microbial community and increases the commensal bacteria. It also prevents invasion by harmful microbes. Metabolites produced by the probiotics enhance the diversity of beneficial microbes and nutrients availability to be used by the surrounding colonocytes.

disorders and microbial composition patterns in host are not uniform among some studies and how the particular microbes in a microbiota stimulate the observed effects and the molecules used by them to regulate the metabolic disorders development is still uncertain. Thus, more research in this context is required to enhance our understanding of the complex host-microbiome inter-relationships. This will open new avenues to new therapeutic approaches for diagnosis, prevention and treatment of these disorders. Recent trend is now on the smart manipulation of the disturbed intestinal microbiota using probiotics, prebiotics, FMT and many more, which could be beneficial for the health. It can be said that the gut microbiome is the untapped reservoir in unlocking the different diagnostic strategies for prevention of many diseases.

Conflicts of interest

There are no conflicts of interest between the authors.

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