Review Paper:

Role of Gut Microbiota in Human Health

Bisht Neha[1] and Garg Amar P.[2*]
1. Department of Microbiology, C.C.S. University, Meerut-250004, INDIA
2. Shobhit Institute of Engineering and Technology (Deemed to-be University), NH-58, Modipuram, Meerut- 250110, INDIA
*amarprakashgarg@yahoo.com

Abstract

Over the last 15 years, microbiome has attracted the attention of medical scientist and microbiologists. Human gastro intestinal tract harbors a complex and dynamic population of microorganism which exerts influence on the host during homeostasis and diseases. Establishment of human gut microbiota during infancy depends on multiple factors. One of the main drives in shaping the gut microbiota across the lifetime is the quality of diet. Gut bacteria play a crucial role in maintaining the immunity and metabolic homeostasis and help in protection against various enteric pathogens.

Advancement in computational biology and DNA sequence technology has revolutionized the quality research in the field of microbiome. Alteration in microbiome is associated with disease including inflammatory bowel disease, cardiovascular disease, asthma, obesity, metabolic syndrome and immune mediated conditions.

Keywords: Microbiome, gastrointestinal tract, diet, pathogens and disease.

Introduction

More than trillions of symbiotic microorganisms live on within human beings and play an important role in human health. Microorganisms inhabit in various forms as a community and in close association with complex organisms by establishing ammensal, commensal, mutualistic, parasitic or pathogenic relationships with hosts.[20,70,96] The collection of such microorganisms is called microbiota/microbiome. The human microbiome comprises of collective genomes of microbiota inhabiting within host, namely protozoa, archaea, eukaryotes, viruses and predominantly bacteria that live symbiotically on and within various sites of the human body.[22,61]

Oral cavity, genital organs, respiratory tract, skin and gastrointestinal system all are examples of occupied habitats.[72,91,115] The human microbiota is estimated to harbour $10^{13}$to 10^{14} microbial cells that is approximately 10 times more than the number of human cells and over 100 times the amount of genomic content than the human genome.[94,103,111] These numbers are derived from the total bacterial cells in colon i.e. 3.8×10^{13} bacteria to the organ that harbors the densest number of microbes.[94] Various reports indicated that several parts of human body occupy over 10,000 microbial species.[13,28,67,76]

One of the largest interfaces between the host, environmental factors and antigens in the human body is represented by human gastrointestinal (GI) tract.[46,103] Around 60 tons of foods in average life span pass through the human GI tract along with an abundance of microorganisms from the environment which impose a huge threat on gut integrity.[58] The diverse GI microbiota is predominantly composed of bacteria from three major phyla i.e. *Firmicutes, Bacteroidetes and Actinobacteria.*[102] Complex and diverse microbiome serves as a functional expansion of host genomes and harbors about 50 to 100 fold more genes as compared to the host i.e. human genome has 23000 genes and microbial genome harbour 100,000 genes.[61,115]

The extra genes add various types of enzymatic proteins which are non-encoded by the host and play an important role in facilitating host metabolism and regulate host physiology.[55] The microbiota offers many benefits to the host such as protecting them against pathogens,[10] regulating host immunity,[22,50] harvesting energy[32] and strengthening gut integrity or shaping the intestinal epithelium.[84] Imbalance in normal gut microbiota leads to GI conditions such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) and wider systemic manifestations of disease i.e. type II diabetes, atopy and obesity.[16,45]

Development, structure and composition: Microbial colonization begins in human gut at the time of birth. The infant's intestine is believed to be sterile and contains very low level of microbes at birth, but the GIT is quickly colonized during and after delivery.[46] At delivery, the oral and nasopharyngeal membrane as well as skin and gut of the baby colonize with microorganisms. As a neonate passes through the birth canal, it acquires microbial populations that are similar to maternal vaginal flora and dominated by *Lactobacillus, Prevotella* and *Sneathia* spp.[33]

It has been observed that babies delivered through cesarean have lesser number of gut microbiome than those delivered through normal mode and face several immunological complications in their lifetime.[96] This process influences the development of an infant's intestinal microbiota similar to the maternal vaginal microbiota (Fig. 1). Infants who were born through cesarean section (C- section) mainly possess microbiota that naturally harbor on skin namely *Staphylococcus*, *Corynebacterium*and *Propionibacterium* s pp and differ from maternal skin microbiota.[34,95]

The microbiota of neonates substantially differs. During the first year of life, the distinct feature of gut microbiota composition is relatively simple and maintained, it shows wide inter individual variations.[16,101] Microbial diversity seems important for the well-balanced interaction between microbiota and host and also on the other hand shaping the composition of adult GI microbiota. During 2–3 years, the gut microbiota stabilizes and totally resembles the bacterial composition as the adult gut.[14,15] Studies have shown that, during the first two years babies born by C section more often suffer from allergic sensitization and wheezing.[48,96]

C-section has been associated with an increased risk to food allergy, allergic rhinitis, asthma and intestinal bacterial infections to neonates at the age of 1–2 years.[95] However the causality of C-section for bacterial infection or allergic reactions is marginal and thus the mode of delivery seems to play only a minor role in the establishment of a robust microbiota.[6,7,33,96] The monozygotic twins microbiota are more similar to each other as compared to unrelated individuals.[105] Twins showed similar sequential variations of their microbiota profile and underline the importance of environmental conditions for establishing gut microbiota.[58,87]

The infant's gut flora is strongly impacted by diet i.e. breastfeeding or formula-feeding to weaning and solid food. Breast-feeding diet favors the gut flora diversity, richness and colonization of *Lactobacillus*, *Staphylococcus*, *Megasphaera* and class of *Actinobacteria* in the intestine.[16] Formula feeding leads to the enrichment of *Clostridiales* and phylum *Proteobacteria*[14]. In the first year of life, the application of antibiotics affects the bacterial community in early babyhood which causes alteration and delay in gut bacterial colonization with the depletion of *Enterobacteriaceae*, *Lachnospiraceae* and *Erysipelotrichaceae*.[77,114]

GI microbiota is also influenced by various external and internal host-related factors. External factors include the type of food eaten, microbial load of the immediate environment, feeding habits and the composition of the maternal microbiota (Fig. 2).[115] The successions of microbes are influenced by dietary and temperature-related stresses. Internal factor includes intestinal pH, microbial interactions, environmental temperature, physiological factors like peristalsis, bile acids, host secretions and immune responses (drug therapy and bacterial mucosal receptors).[96] Other than delivery mode, infant diet, antibiotics and other factors like host genetics, age, life style, hygiene factors, allergen contact, diets and consumption of pro- or prebiotics or infections might influence the complexity of gut microbiota.[3,48,98]

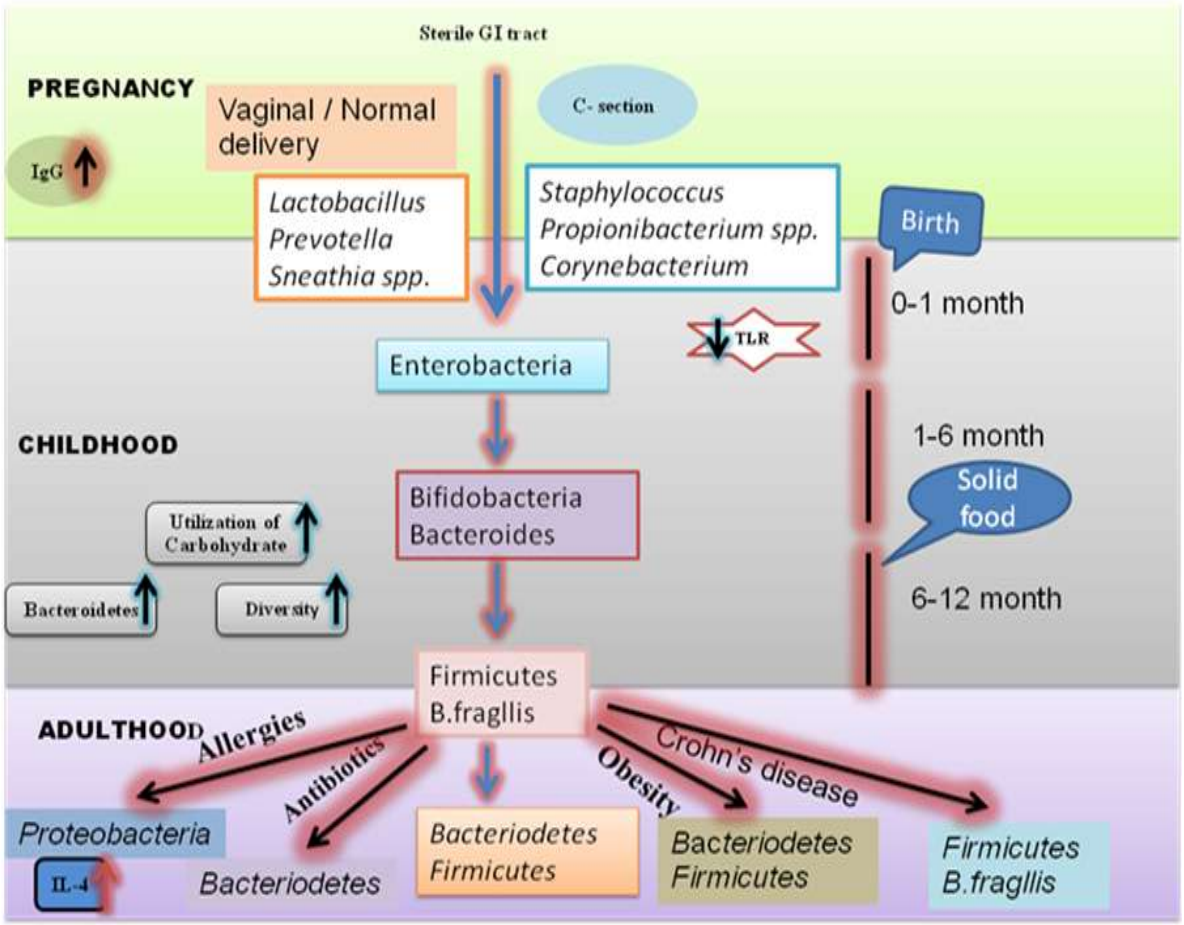

Figure 1: Development of gut microbiome

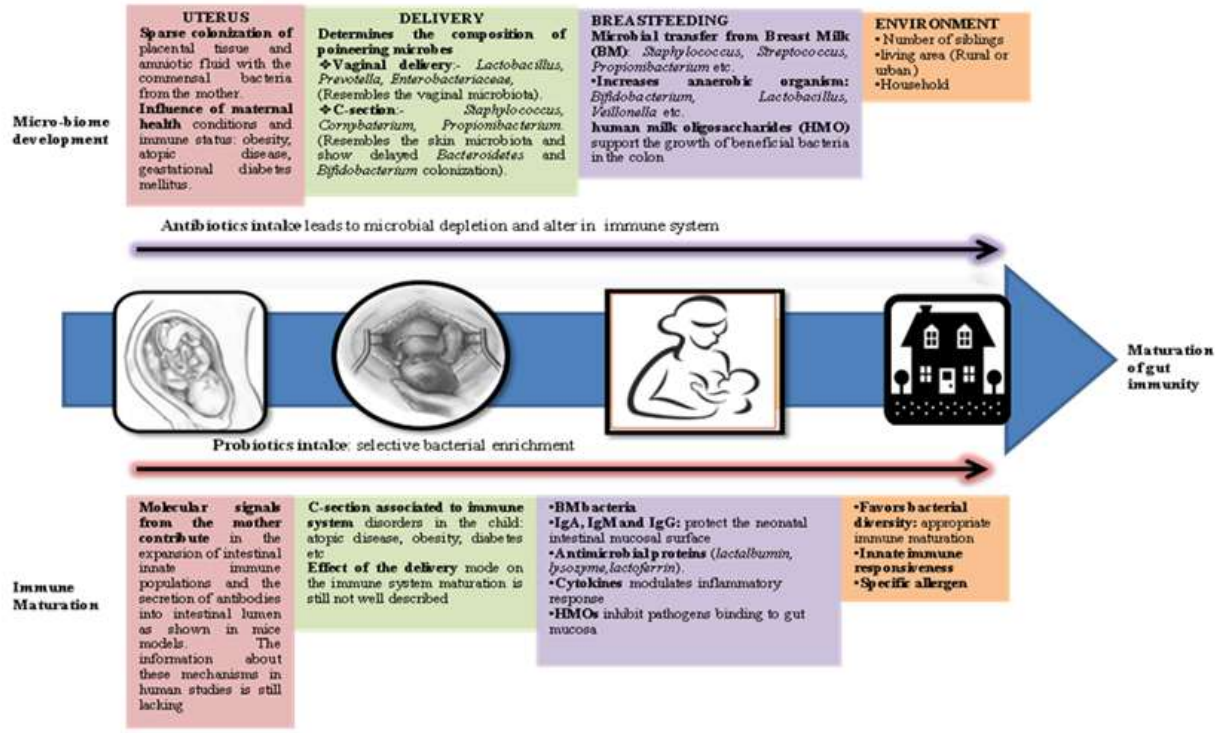

Figure 2: Various factors influencing micro-biota development and maturation of the immune system modification from Dzidic et al[39]

Knowledge of adult human gut microbiota stemmed from labor intensive culture-based methods Due to the advent of culture independent approaches, the breadth of the gut microbiota has greatly improved.[28,103] DNA sequence technology coupled with advances in bioinformatics has totally revolutionized the field of microbiomics.[62] The methods involve amplification and sequencing of targeted microbial DNA regions followed by statistical analysis for the identification and diversity of microbes based on sequence similarity and comparisons to genomic databases.[63] 16S ribosome gene (16S rDNA) is a most popular approach for targeting the bacteria present in all bacteria and archaea and contains nine hyper variable sequences (V1–V9) that differ between species.[54,79,90]

More recently, investigators shifted the focus from 16S rRNA sequencing gene to shorter sub regions of the gene in greater depth. Whole-genome shotgun metagenomics is the more reliable method of estimating microbiota composition and diversity due to the higher resolution and sensitivity of this technique.[28,75,113] Difference in methods of sample processing techniques, sequencing technologies and statistical methods complicates any direct comparison between different sequencing studies. It has been reported that 2172 species isolated from human beings are classified into 12 different phyla belonging to *Proteobacteria, Firmicutes, Actinobacteria* and *Bacteroidetes* that are estimated to be around 93.5%.[68]

Three of the 12 identified phyla contained only one species isolated from humans' i.e. *Akkermansia muciniphila*, the only known representative of the phyla *Verrucomicrobia*. In humans, 386 of the identified species are strictly anaerobic and found in mucosal regions such as the oral cavity and the GI tract.[56,115]

Functions of the Gut Microbiota

Metabolism: Using metagenomic sequencing and 16S ribosomal RNA techniques, sample analysis of human fecal significantally reveals enrichment in metabolism of amino acid, xenobiotics, polysaccharides and micronutrients conferred by gut microbiota strongly suggesting that these indigenous microbes facilitate host energy harvesting and metabolic efficiency.[51,81,99] The end products of fermentation exist in the form of a short-chain fatty acids (SCFAs) which act as one of the energy substrates for the host contributing extra 10% daily dietary energy for utilization by the host for other metabolic processes.[61,88] 70% of ATP production in colon is contributed when microbially-synthesized SCFAs with a preferred fuel for colonocytes (butyrate).[26,28,36,42,44]

Anti-inflammatory and anticancer activities are attributed to the production of butyrate that causes happiness.[71,80] SCFAs are the ligands for G protein-coupled receptor 41 (GPR41) expressed in a subset of epithelial entero endocrine cells, the gut regulates energy of homeostasis by stimulating GPR41-mediated leptin production in mouse adipocytes which affects on a vast range of host physiological functions such as appetite, energy metabolism, sympathetic nerve activity, immune response, interactive host-microbe signaling.[20,82,93,112]

Micronutrients such as vitamins are synthesized by gut microbiotas which manifest beneficial effects on both host and microbial metabolisms. Gut microbiota synthesise vitamin K, riboflavin, biotin, nicotinic acid, pantothenic acid, pyridoxine and thiamine in human.[65,76] It has been reported that gut bacteria namely *Eubacterium lentum*, *Enterobacter agglomerans*, *Serratia marcescens*, *Enterococcus faecium* and *Bacteroides fragilis* (Table 1) produce vitamin-K.[25,43,53,114]

Anaerobically synthesis of menaquinone i.e. vitamin K2 is vital in elevating HDL, decreasing vascular calcification, lowering cholesterol levels, decreasing the risk of cardiovascular and coronary heart diseases.[37,49,60] Gut microbiota are the vital source of vitamins B also[31], especially vitamins B5 and B12 act as coenzyme for various host biochemical processes such as production of cortisol and acetylcholine required for normal nervous system functioning synthesized by intestinal microbiota.[19,61]

Several disorders such as insomnia, gastrointestinal discomfort, neuropsychological and hematological disorders are due to the deficiency of vitamins B5 and B12.[41,52,81] Cometabolism of bile acids with the host is also maintained by gut microbiota. Both the primary and secondary bile acids activate host nuclear farnesoid X receptor (FXR) signaling which regulates the production of bile, glucose metabolism and potentially hepatic autophagy.[66,85] Nie et al[85] have stated that secondary bile acids also have antimicrobial effects on microbial cell membrane integrity which cause spillage of intracellular contents and inhibiting the growth of bile acid-intolerant microbes, shaping the composition of the gut microbiota and protecting the host from pathogenic agents.[3,11,12,24,47]

Immune-system Development and Host Protection: The mucus and epithelial layer (junctional protein structures that regulate barrier integrity and para-cellular permeability) are the gut barriers which serve as the interface between the outside and internal environments.[24] Disruption in gut barrier function leads to aberrant immune-inflammatory response such as inflammation, allergy and autoimmune disorder which are mediated by molecular mimicry and dysregulated T-cell response.[9,41] SCFAs confer the protection of the gastrointestinal barrier integrity against the disruptive effects i.e. proinflammatory cytokines which results due to aberrant immune-inflammatory axis.[21,42,89]

Table 1
Taxonomy and phylogeny of common constituents of the gastrointestinal microbiome (https://www.ncbi.nlm.nih.gov)[8]

Phylum	Class	Order	Family	Genus
Frimicutes	*Bacilli*	*Lactobacilliales*	*Lactobacillaceae*	*Lactobacillus*
			Streptococcaceae	*Streptococcus* *Enterococcus*
	Clostridia	*Clostridiales*	*Clostridiaceae*	*Clostridium*
			Ruminococcaceae	*Ruminococcus* *Faecalibacterium*
			Eubacteraceae	*Eubacterium*
	Erysiphelotrichia	*Erisophelotrichales*	*Erysiphelotrichaceae*	*Turicibacter* *Catenibacterium* *Coprobacillus* *Allobaculum*
	Negativicutes	*Veillonellales*	*Veillonellaceae*	*Dialister* *Megasphaera* *Veillonella*
Bacteroidetes	*Bacteroidia*	*Bacteroidales*	*Prevotellaceae*	*Prevotella*
			Bacteroidaceae	*Bacteroides*
Actinobacteria	*Coriobacteriia*	*Coriobacteriales*	*Coriobacteriaceae* *Atopobiaceae*	*Collinsella* *Olsenella*
		Eggerthellales	*Eggerthellaceae*	*Slacika* *Eggerthella*
	Actinobacteria	*Bifidobacteriales*	*Bifidobacteriaceae*	*Bifidobacterium*
Fusobacteria	*Fusobacteria*	*Fusobacteriales*	*Fusobacteriaceae*	*Fusobacterium*
Proteobacteria	*Gammaproteobacteria*	*Enterobacteriales*	*Enterobacteraceae*	*Escherichia* *Shigella*
		Aeromonadales	*Succinivibrionaceae*	*Succinivibrio* *Anerobiospirillum*

The segmented filamentous bacteria (SFB) induces intestinal T helper (T_H) 17 cells which results in the production of pro-inflammatory interleukin (IL) 17 and IL-22 that enhances antimicrobial defense and mucosal immunity against intestinal pathogens as *Citrobacter rodentium* in case of gnotobiotic mice model.[31]

ATP by gut microbiota is capable to activate differentiation of lamina propria cells [(cluster of differentiation) CD70 and CD11c] into T_H17[5]. Tight regulation of Treg/T_H17 is critical in preventing aberrant immune inflammatory response by healthy host-gut microbiota interactions.[42]

Modulatory role of gut microbiota in the enteric nervous system (ENS) has already been studied. The ENS is crucial for life in regulating the physiology and functions of the GIT and bidirectionally communicate with the central nervous system CNS via vagal pathways leading to the formation of "gut-brain axis".[81] Enteric glial cell (EGC) is the major component of ENS which resembles astrocyte in the CNS. EGCs regulate various GI functions including blood flow, exocrine/endocrine secretions, gut motility and immune-inflammatory reactions (*via* calcium-dependent signaling).[86] Dysfunctioning of ENS and EGC leads to various GI disorders (Inflammatory Bowel Disease (IBD), irritable bowel syndrome (IBS), postoperative ileus), motility disorder (constipation), neuro-degenerative disorder (Parkinson's Disease (PD)) and infection-inducing gut inflammation.[45,61] Toll like receptors (TLRs) from microorganism sensing play a critical role in maintaining gut microbiota host symbiotic relationship and intestinal homeostasis.[2,81]

Gut microbiome and diseases

Dysbiosis in gut microbiome is induced by external factor which includes consumption of antibiotic, dietary component, psychological and physical stress and host factors. Dysbiosis impairs the normal functioning of gut microbiota in maintaining host wellness leading to production of microbial-derived products or metabolites which might be harmful to the host causing diverse range of diseases (Fig. 3).[81] Some of the diseases and their respective microbiome-based therapy are discussed as follows:

- **Inflammatory Bowel Disease (IBD):** IBD encompass 2 common forms Crohn's disease (CD) and ulcerative colitis (UC). Inflammation can occur anywhere in the whole GIT in case of CD whereas UC is restricted only to the large intestine.[16] CD and UC are associated with fever, relapsing diarrhea and abdominal pain. The mechanism of action of pathogensis for this disease is still lacking but the crosstalk between host factor and gut microbiota shows great potential in development of disease (Fig. 4).[11] The culprit in causing severe inflammation is the immune system against GI microbiota. IBD is due to the hyper-responsiveness of T-lymphocyte in the gut microbiota towards non-pathogenic antigens.[45]

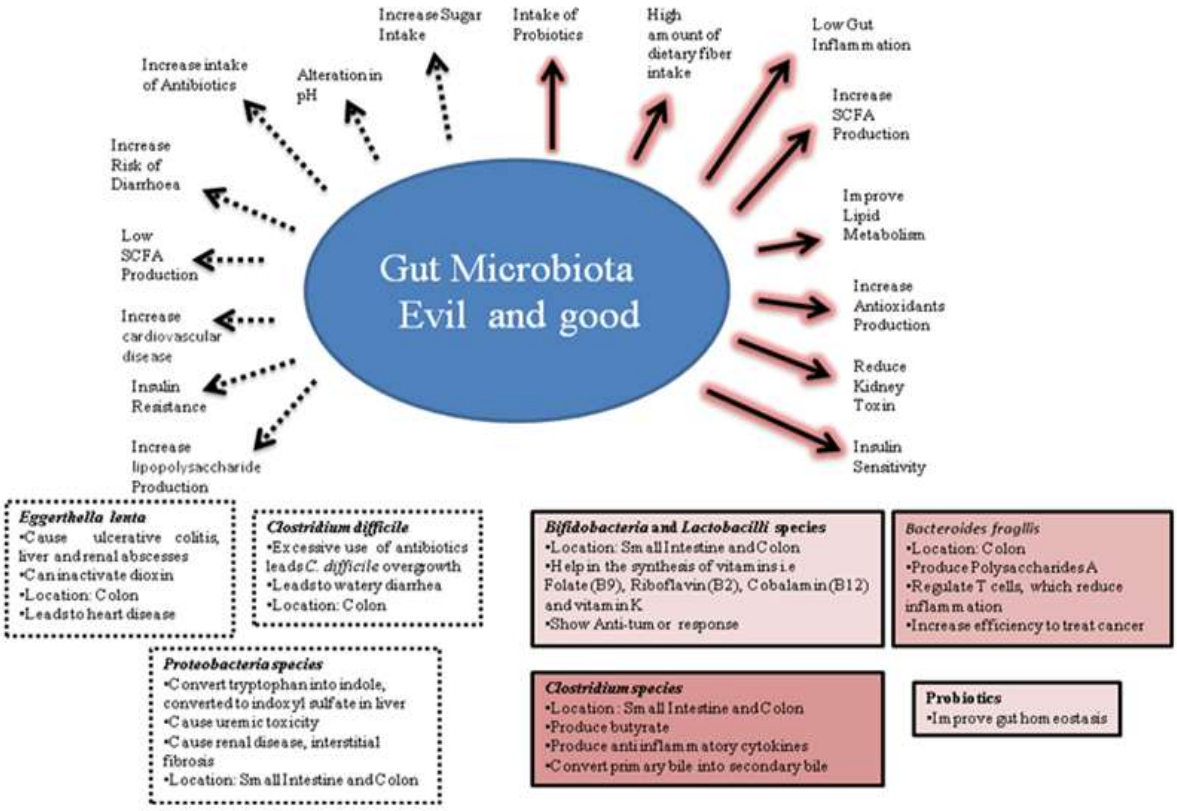

Figure 3: Attributes of good and evil gut microbiota their functions and microorganism

Several studies have reported development of antibodies against antigens of commensal microbes and autoantigens like anti-*Saccharomyces cerevisiae*, perinuclear anti-neutrophil cytoplasmic antibody and anti-*Pseudomonas fluorescens*-associated sequence 12.[38,64,76] Loss of tolerance towards gut microbiota in IBD patient totally with aberrant immune response leads to dysbiosis and also to loss of microbiota which is responsible in maintaining the gut mucus barrier integrity. Impaired functions increase the exposure between gut microbiota and epithelial cells which lead to the stimulation of local immunity and contributing to severe gut inflammation.

Gut dysbiosis potentially contributes in IBD pathogenesis.[83] Common feature observed in IBD patients is the reduction in gut *Firmicutes* such as *Faecalibacterium prausnitzii* and *Roseburia sp*.[53,74,97,108] These bacteria play an important role as anti-inflammatory in reducing pro-inflammatory cytokines (IL-12, IFN-g) and increasing anti-inflammatory IL-10.[97]

Butyrate is produced by *Firmicutes* which is the primary energy substrate for colonocytes. Reduction in *Firmicutes* could elicit local inflammation by decreasing anti-inflammatory cytokine which is an important factor in regulation of mucosal immunity and induced impairment in colonic barrier function due to SCFA-deficiency.[42,74,89]

The therapeutic use of probiotic *F. prausnitzii* is used in managing IBD. Elevation of virulent gut microbes such as species of *Enterobacteriaceae* and *Bacteroides fragilis*, both having high endotoxic LPS in their outer membranes, are the dysbiotic features observed in IBD patients.[29,92] Feagan et al[40] and Christensen et al[23] have stated that the anti-inflammation therapy like Ab (antibodies) which targets pro-inflammatory cytokines (such as anti-TNF-alpha, anti-IL12, anti-IL23).

Employing a4b7-integrin antagonist leads to the inhibition by trafficking of T-lymphocytes in gut tissue.[19,45] Administration of fermented polysaccharides i.e. prebiotics which leads to stimulate on at the growth and metabolic activities of gut microbes such as butyrate-synthesizing bacteria, an attractive notion to treat GI inflammation in IBD.[30,59,81]

- **Obesity:** WHO[109] stated that obesity is a worldwide health hazard, affecting ≥ 600 million people. It is correlated with aloft energy intake and reduces in energy expenditure which leads to the excessive accumulation of fat with increases body mass index (BMI ≥ 30kg/m^2) linked to metabolic disease. Individuals develop a high risk of developing obesity associated disorders which include cardiovascular disease, type- II diabetes and liver abnormalities, premature mortality and low-grade inflammation.[18,35,37,39] The gut microbiota is fully associated with obesity when metabolically obese mice with leptin gene having mutation showed a significantly different microbiota as compared with mice without having mutation in the gene.[17,61] Lozupone et al[73] indicated that the ratio of *Firmicutes* to *Bacteroidetes* in the obese mice gut microbiota shifted in favored of *Firmicutes* whereas *Bacteroidetes* favour in lean mice.

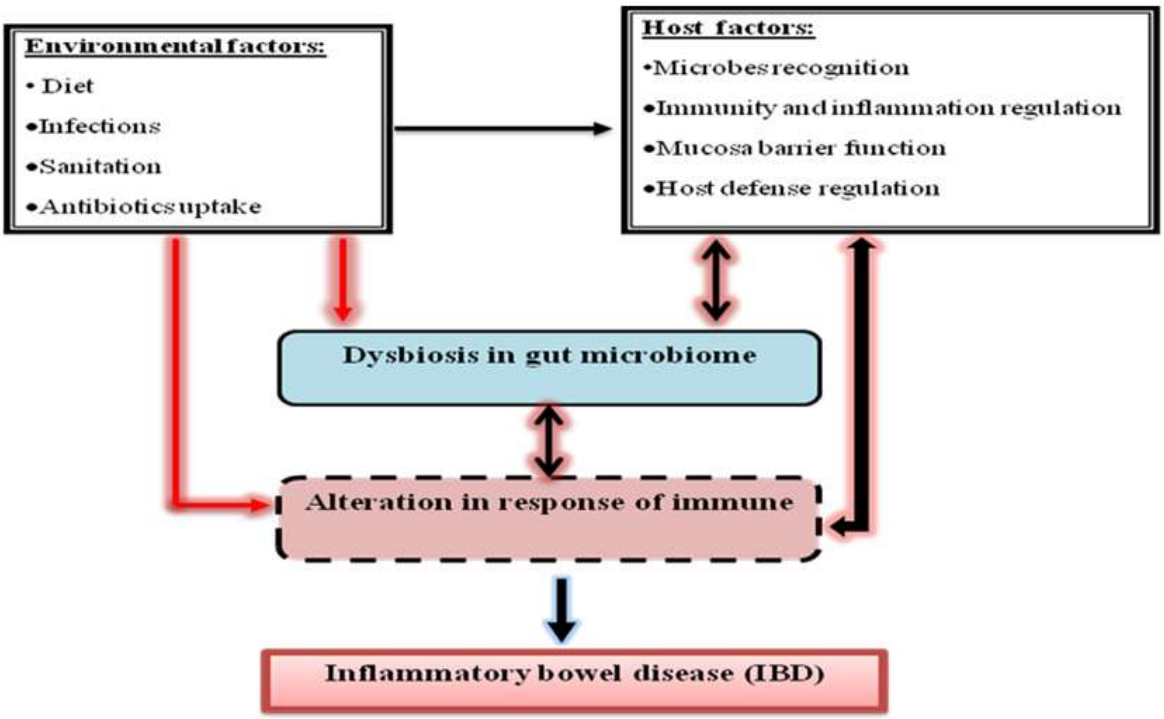

Figure 4: Interactive relationships among gut micro-biome, host factors and environmental factors in IBD

Tagliabue and Elli[100] in human reported that the gut microbiota composition altered in obese when it is compared with normal-weight individuals as their composition changes in response to changes in host body weight. Tremaroli and Bäckhed[104] stated that studies have also failed to demonstrate a relationship between obesity and the ratio of *Firmicutes* to *Bacteroidetes* till both the phylum and the species levels. Several studies suggest that gut bacteria, gram-negative increase in endotoxic LPS contribute to obesity associated metabolic syndrome. In obesity management, the application of probiotics and prebiotics is extensively used.[11,12,17,20]

- **Colorectal Cancer (CRC):** Worldwide mortality of colorectal cancer (CRC) is the fourth leading cause of cancer.[4] CRC is a multifaceted disease associated with both genetic and environmental factors. Kho and Lal[61] stated that gut microbiota plays an important role in the intersection of these factors which enhanced tumor-promoting environment. In the gut lumen tumor outgrowth damages the intestinal barrier which increases the infiltration of gut microbiota and allows the entry of harmful substrates in the tissue leading to immune-inflammatory response and disturbs the gut microbiome.[69] Fecal microbiota of CRC patients were analyzed using 16S rRNA sequencing that revealed a significant enrichment of *Bacteroides fragilis*.[107,110] Enterotoxigenic strains of *B. fragilis* (ETBF) contribute in CRC by enhancing the production of oncogenic *B. fragilis* enterotoxin (BFT).[28]

Ulger Toprak et al[106] reported the bft gene expression tremendously higher in CRC patients as compared to healthy person. BFT is cytopathic in intestinal epithelial cells leading to colitis and colonic tumor due to its capability of catalyzing proteolytic degradation of tight junction proteins (such as ZO-1 and E-cadherin) leading to petrub in intestinal para cellular barriers.[20,96,111] *Fusobacterium nucleatum* outer membrane protein i.e. Fap2 also mediates specific Fusobacterial attachment to Gal-GalNAc which is overexpressed in CRC patients and facilitating *F. nucleatum* invasion as well as colonization of CRC cells.[1]

Wu et al[111] stated that invasive *F. nucleatum* is employed by the involvement of Toll like Receptor (TLR4) /phosphorylated-p21-activated kinase, 1/phosphorylated-b-catenin S675 in a cascade manner[53]. Probiotics using lactic acid-producing bacteria (*Lactobacillus* and *Bifidobacterium*) shows protective effect against colon cancer by reducing tumor incidence and tumor loads and suggested directly anti proliferative effect on tumor cells by preventing carcinogen induced DNA damage, partly via inhibiting the carcinogen and mutagen formation, reducting the pro-carcinogenic enzyme (ornithine decarboxylase) activity as well as in enhancement of anti-tumor immunity due to increased natural killer cells, MHC class II antigen presenting cells and CD4–CD8C T cells.[39,96]

Conclusion

The gut microbiota is evolved throughout the life and plays an important role in both health and prevention of diseases. In a state of healthy gut, microbiota have positive functions which include energy recovery from the metabolism of non-digestible components present in the food protecting the host from pathogens and modulation of the immune-system. A dysbiotic gut microbiota state is recognized as an environmental factor which acts on host's metabolism and has a role in pathological conditions both in systemic-(obesity, atopy and diabetes) and gut-related IBS and IBD.

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