Review Article

Human microbiome and its association with health and diseases †

Running title: Human microbiome and diseases

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Abstract

Human microbiota aredistinctcommunities of microorganisms that resides at different body niches. Exploration of the human microbiome has become a reality due to the availability of powerful metagenomics and metatranscriptomic analysis technologies. Recent advances in sequencing and bioinformatics over the past decade help providea deep insight into the nature of the host-microbial interactions and identification of potential deriver genes and pathways associated with human health, well-being, and predisposition to different diseases.

In the present review, we outline recent studies devoted to elucidate the possible link between the microbiota and various type of diseases. The present review also highlights the potential utilization of microbiota as a potential therapeutic option to treat a wide array of human diseases.

Keywords Human microbiome; host-microbial interactions, dysbiosis, cancer, metabolism; obesity;neurodegenerative, gut microbiome; global health; prebiotics, probiotics, synbiotics; diseases, health, virome

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Introduction

Humans are viewed as composites of human and microbial cells. Human microbiotaare complex and dynamic microbial communitiescomposed mainly ofbacteria, but also includes protozoa, archaea, viruses, and fungi that resides in and on different body niches such as oral cavity, throat, esophagus, stomach, colon, urogenital tract, respiratory tract, and skin[1]. The number of microbial cells inhabiting human body is estimated to exceed the *H.sapiens* cells by 10-fold and estimated at 350 trillion microbial cells[2]. The colonic microbiota constitutes the most abundant microbial domain within the human body with the vast majority belonging to bacterial phyla; *Firmicutes* and *Bacteroidetes*[3]. The collective genomes of the complete human microbiota located at the different body sitesare referred to as human microbiome[4]. Metagenome and metatranscriptome refers to the study of collective genes and RNA derived from a specific microbiome respectively. The term virome is used to describe the viral components (bacterial, archeal, eukaryotic virome, and virus-derived elements) while mycobiome refers to fungal organisms within human microbiota[5-8]. As shown in figure (1), the human microbiome is composed of complex communities of viral (virome), bacterial (microbiota) and fungal (mycobiota) and their associated genetic material. The interplay among human microbiome and host cells affects human health and contribute in the pathogenesis of various diseases.

Marked differences in the abundance and diversity of microbiota are observed in healthy human individuals along with the presence of a strong niche specialization both within and among individuals[9]. These difference may be explained due to a number of factors including differences in host genetics, feeding habits, life style, and early life microbial exposure[10-12]. Moreover, changes in the composition of human microbiota have profound impacts on health and may predispose to different immunological and pathological conditions[9,13,14]. These microbial

communities have a profound impact on human health and well-being, and each person's microbiome is thought to be unique. Differences in the microbiome composition can help explain why some people are more susceptible or resistant to certain diseases.

Exploration of the human microbiome has recently become possible due to the availability of powerful metagenomics and metatranscriptomic analysis protocols. Using these protocols, it become possible to have a better insight on the nature of the host-microbial interactions, and to identify potential deriver genes, and pathways associated with human health and diseases.

This review highlights the recent advances in human microbiome and explores possible uses of different microbial genetic signaturesin identifying possible disease risks. The exploration of novel therapeutic targets to improve human health, well-being, and to treat various diseases associated with microbiome dysbiosis are also mentioned.

Role of human microbiome in health

Accumulating evidence reveals that the gut microbiota plays a major role in promoting health, as a result of which it is often referred to as the 'forgotten organ'[15]. The relationship between the host and microbiota is symbiotic and mutualistic, each deriving benefits from the other. These two terms are similar but mutualism is defined as 'an interaction between species that is beneficial to both of them' and symbiosis as 'the living together of two organisms in close association'[16]. While the host provides the microbiota with a protected and nutrient-rich environment, the microbiota enhance, e.g., digestion, immunity and neuronal development.

Microbiota are key to maintaining homeostasis where it confers many benefits for the host such as pathogen displacement, development of the immune system, vitamin production and absorption of nutrients[17]. The influence of microbiota on health extends beyond the GI tract affecting almost every organ of the body[18,19]. In the intestine, microbiota affect angiogenesis[20]

and improve gut immunity and motility, as well as decreasing the permeability of the intestinal barrier. In distant organ such as the lungs, microbiota regulate immunological defense against viral infection[21]. Microbiota also influence behavior by reducing synaptic connectively and elevating anxiety[22,19] and perception of pain[23]. In the liver, microbiota modulate hepatic metabolism in such a way as to decrease energy expenditure and promote adiposity[24]. In addition, absence of gut microbiota leads to more bone mass in association with fewer osteoclasts surface area of bone[25]. Recent studies also showed that microbiota are involved in the development of personalized medicine[26], in xenobiotic metabolism[27] and in regulating blood-tissue barriers[28-30].

Human microbiome and diseases (Dysbiosis)

Alterations in the composition of microbiota can result from exposure to various environmental factors such as diet, xenobiotics, drugs, and pathogens as shown in figure (2), which eventually contribute to the pathogenesis of various metabolic, neurological, immunological, and cancer promoting diseases. The collective microbiota of the gut whose DNA contributes to the metagenome have links with inflammatory bowel disease (IBD), liver disorders, ankylosing spondylitis, neurodegenerative diseases, obesity and associated noncommunicable diseases (NCDs) including diabetes mellitus, hypertension, atherosclerosis, coronary heart disease, and neurodegenerative diseases beside other condition[31-35].

IntestinalDiseases

Due to the direct contact between the intestine and microbiota, it is predictable that alteration in the composition of microbiota could be involved in the pathogenesis of many intestinal disease such asCrohn's disease (CD) and ulcerative colitis (figure 3).

In CD, metagenomic analysis revealed a decrease in *Firmicutes*, in particular *F. prausnitzii*, and an increase in *Enterobacteriaceae*, especially the virulent invasive *E. coli*[36]. Alteration of gut microbiotamay affect mucosal health and immune system by acting on the epithelial barrier function, and regulation of the innate immune system[37].Reduction in the number of *F. prausnitzii* is associated with an increasing risk for the recurrence of ileal CD [38], another study confirmed an increase in the number of *F. prausnitzii*in pediatric CD [39]. Ott and colleagues demonstrated that CD was associated with altered fungal profile with a marked increase in the diversity of fungal community.In pediatric inflammatory bowel disease (IBD), dominance of *Basidiomycota*species was recorded [40].

Viruses associated with gut bacteria may affect the pathogenesis of CD and disease-specific viromes had been related to CD and ulcerative colitis (UC)[41]. Previous studies demonstrated a significant increase of *Caudovirales* bacteriophages concomitant with a reduction in the relative abundance of bacterial species, indicating a possible involvement of virome in bacterial dysbiosis associated with CD and UC[42].

Alterations in the homeostasis of gut microbiota may induce low-grade intestinal inflammation associated with irritable bowel syndrome (IBS)[43,44]. IBS was associated with an increase in the numbers of *Ruminococcus, Clostridium*, and *Dorea*, with a marked reduction in *Bifidobacterium* and *Faecalibacterium* spp.[45]. In comparison to normal population, an increase in the *Firmicutes* to *Bacteroidetes* ratio was evident in patients with IBS[46]. Dysbiosis of the gut microbiota is thought to play a crucial role in the development of mucosal lesions[47]and intestinal inflammation is generally believed to be associated with a specific reduction in the Bacteroidetes and Firmicutes phyla specially reductions in the *Clostridium leptum* and *Clostridium coccoides*

groups[48]. All of the aforementioned studies have certainly outlined a link between the gut microbiota and IBD.

Association between colorectal cancer (CRC) and the presence of specific causative organism has been suggested. For instance, the presence of high numbers of *Fusobacterium* in the gut microbiota has been linked to CRC[49,50]. Interestingly, members of *Fusobacterium* has been associated with IBS[51]. The initiation of chronic inflammatory condition due to dysbiosis of gut microbiota lead to impairment of intestinal barrier, induction of inflammation through a host immune response, and in turn, increase in tumor growth[52].

E. coli had been implicated in the initiation of CRC through polyketide synthase (pks) and mice mutants lacking the pks island had a decreased tumor growth and invasion compared to their wild-type pks+ counterparts[49]. Although there were strong correlations between inflammation induced by the presence of specific types of microorganisms and CRC, it was clear that further investigations were required to further explore the role of bacterial induced inflammation in tumorigenesis and CDC.

Gastric diseases

Although gastric pH, peristalsis and mucus layer play an essential protective role in preventing bacterial colonization in the stomach, maintenance of gastric microbiota homeostasis is essential for the stomach health. Five major phyla have been detected in the stomach including *Bacteroidites, Actinobacteria, Fusobacteria* and *Proteobacteria*. Healthy human stomach is dominated by *Prevotella, Streptococcus,Veillonella, Rothia*,and *Haemophilus*; however, the composition of the gastric microbiota is dynamic and is affected by diet, drugs, and diseases[53].

Sequencing of the small subunit 16S rRNA revealed that *Helicobacter pylori* was the predominant phylotype in the stomach of chronic gastritis patients[54]. The interaction between *H.*

pylori and other species within the gut microbiota might increase the risk of gastric cancer. Other bacterial genera such as Streptococcus, Prevotella, Neisseria, Haemophilus and Porphyromonas may also contribute to the development of gastritis. In this regard, the high number of Streptococcus genus was associated with antral gastritis [55].

Modifications of gastric microbiota have been associated with gastric cancer or precancerous conditions. Although gastric cancer is known to be a multifactorial disease, *H. pylori* infection was found to actively contribute to its progression, probably by induction of chronic atrophic gastritis leading to reduction of gastric acid secretion and initiation of inflammatory cytokines[56,57].

The exact role of microbiota in the origination of gastric cancer is not clear and is poorly understood. Using culture-based protocol, a comparatively large number of anaerobic bacteria such as *Clostridium* and *Bacteroides* was identified in patients with gastric cancer. Elevation of the pH in in the gastric lumen due to reduction of acid-secreting cell number may influence colonization of microbiota within the gastric mucosa[58]. Subsequent studies have cast doubts on the existence of significant differences in gastric microbiota between control and gastric cancer patients, and that the microbiota in gastric cancer patients was dominated by different species of the genera *Streptococcus, Lactobacillus, Veillonella*, and *Prevotella*[57].

Liver diseases

Disturbance tothe gut microbiota as a result of extrinsic factors such as unbalanced diet and alcohol consumption had been reported to contribute to nonalcoholic fatty liver disease (NAFLD), steatohepatitis, alcoholic liver disease, and cirrhosis. Identifying specific microbial alterations associated with different liver diseases could improve our understanding of the role of

microbiota in the development of liver diseases, and hence could lead to the discovery of novel fecal biomarkers.

Nonalcoholic steatohepatitis (NASH) is characterized by the development of liver inflammation and fibrosis. Microbiota samples from NASH patients often yield areduced number of *Ruminococcaceae* and a significantly higher percentage of *Clostridium coccoides*[59]. The proportion of *Bacteroidaceae* was lower in samples from alcoholic patients than from nonalcoholic individuals[60]. Aerobic and anaerobic bacterial cultures of jejunal aspirates from patients who chronically abuse alcohol were found to be associated with dysbiosis of jejunal microflora[61].

At the preclinical level, ethanol intakein rats was associated with dysbiosis, overgrowth of bacteria along almost the entire gastrointestinal tract, and significant reductions in proportions of probiotic bacteria; *Lactobacillus*, *Pediococcus*, *Leuconostoc*, and *Lactococcus*[62]. The use of probiotics in patients of alcohol-induced liver injury lead to a marked improvement in liver functions[63]. Modulation of the gut microbiome in response to alcohol intake might be supported by various factors including inhibition of intestinal motility, alterations in acid secretion, and modulation of the intestinal immune response[64,65].

Extensive research has been devoted to explain the phylogenetic analysis of gut microbiota associated with liver cirrhosis[66-71].Liver cirrhosis was associated with reduction in the number of beneficial bacteria with a concomitant increase of pathogenic microorganisms. Members of the *Prevotellaceae* family have significantly increased in patients with alcoholic cirrhosis compared with healthy individual[68]. Factors contributing to modulation of intestinal microbiome includeimpaired motility of the small intestine, reduced bile flow, altered secretion of immunoglobulin A, and antimicrobial molecules[72].

There has been a reciprocal interplay between gut microbiota and liver, where alcohol-induced liver diseaseswere reported to impair intestinal barrier by increasing systemic levels of IL1b or tumor necrosis factor (TNFα), which disrupt tight junctions[73]. Increasing intestinal leakage might facilitates the movement of microbial products from the lumen of the gut into other distal organs including the liver [73]. In this respect, reduction of Gram-negative bacteria in the intestine due to the use of antibiotics has been associated with decrease in the levels of endotoxins and protection against liver disease after ethanol consumption[74].

The dysbiosis of gut microbiota lead to increase in the level of endotoxin and production of ammonia which has been implicated in the development of hepatic encephalopathy associated with liver cirrhosis[75]. Interestingly, the number of bacterial species members of *Enterobacteriaceae* including *E. coli*, *Klebsiella*, *Proteus*, and *Enterobacter* surge in the microbiota of patients with cirrhosis[67].

Metabolic disorders

The gut microbiota plays important rolesin modulatinghost metabolism, extraction of energy from ingested food, and synthesis of various metabolites and vitamins.Gut microbiota are also essential in the modulation of lipid absorption and deposition, polysaccharide content and the production of short-chain fatty acids which have a marked impact on food intake, inflammatory tone, or insulin signaling. Recent findings suggested that an altered gut microbial composition was associated with metabolic diseases including obesity, diabetes, or non-alcoholic fatty liver disease (figure 3)[76].

Changes to the gut microbiota play a critical role in the pathogenesis of obesity and diabetes. In humans it has been shown that gut microbiota composition differs between obese and lean subjects. Remarkably, inoculation of germ-free (GF) animals with gut microbiota derived from

obese controls significantly increase the deposition of fat, and wasassociated with increase in the insulin resistance[77]. Leptin-deficient ob/ob obese mice displayed an alteration in the gut microbiota represented by a decrease in *Bacteroidetes* and a corresponding increase in *Firmicutes*[78].

Recent metagenomics studies showed the presence of reduced numbers of butyrate-producing *Clostridiales* and greater numbers of non-butyrate-producing ones in type 2 diabetes (T2DM), suggesting a protective role of butyrate-producing bacteria against T2DM[79,80]. Furthermore, disruption of the gut barrier and microbiota-derived endotoxemia may contribute to the pathophysiology of T2DM and obesity. In this regard, modulation of the gut microbiota with antibiotics or prebiotics reduces the metabolic endotoximia, decreases inflammatory markers, enhances gut permeability, and alleviates glucose intolerance. Moreover, the microbiome signature may act as an early diagnostic marker for T2DM, and may provide a novel therapeutic target against T2DM and obesity[81-83].

Lately, fecal microbiota transplantation (FMT) was reported to be highly successful therapeutic approach for the treatment of recurrent *Clostridium difficile* infection, a finding that might suggest a potential therapeutic protocol for metabolic syndrome[84]. Inoculation of fecal microbiota via gastroduodenal tube from lean donors into obese subjects resulted in an increase in the abundance (2.5 fold increase) and diversity of gut microbiota, improvement of insulin sensitivity, increase in the proportion of butyrate producer *Roseburia intestinalis*, and decrease in the level of short chain fatty acids[85].

Dysbiotic gut microbiota has been found to play a role in obesity, other obesity related disorders such as type 2 diabetes (T2D), and metabolic syndrome[86-88].The role ofmicrobiota to weight gain and host metabolism is not completely understood. It was suggested that in obese individual, the

presence of specific microbial communities may increase the energy harvest and thus predispose to obesity[86,88].Other studies asserted that there can be several other mechanisms in which the microbial populations can influence weight gain and alteration of host metabolism [89].

Neurodegenerative diseases

Aging is associated with progressive changes in the gastrointestinal motility, defective gut-blood barrier, weakness in the immune function, and improper protein folding. Such age-related changes appear to have a great impact on the diversity of gut microbiota and may be linked to the age-relatedness of the neurodegenerations[90].

Amyloid protein has been linked to neurodegeneration particularly to Alzheimer's disease (AD) and the possibility of production of amyloid protein by human microbiota might raise great concerns about the possible role of microbiota in the induction of AD and other neurodegenerative diseases (NDD) including behavioral changes and autism[91-95].Nonfunctional amyloids is found in yeast and bacteria[93]. There is paucity of information in literature on the potential role of amyloid protein in the pathogenesis of NDD. It was hypothesized that amyloids may induce or influence human neurodegeneration by three possible mechanisms including misfolding, neruroinflammation, and oxidative stress[96].

Antigen presenting cells such as epithelial microfold (M) cells and dendritic cells may uptake proteins produced by gut microbiota and transmit them into neurons in the myenteric plexus providing a means of communication between gut microbiota and CNS tissue[97]. One misfolded molecule may elicit the misfolding of a different molecule to cause cross-seeding of Aβ-aggregation *in vitro*[98] Cross-seeding of neurodegenerative disorder proteins may be induced by environmental amyloids such as those produced by bacteria[99].

Bacterial amyloid has been demonstrated to activate a wide array of inflammatory molecules such as toll-like receptor-2 (TLR2), NFκB, TLR1, and CD14[100]. Cerebral amyloid may mimic viral or bacterial infection resulting in glial cell activation through TLRs[101]. TLR2 activation lead to upregulation of Notch1which play a crucial role in the development of AD[102]. It has been established that there is sterile inflammation in the brain in neurodegenerative disorders[103].

Peripheral inflammatory conditions may be involved in the induction of different form of neurodegeneration[104]. It was reported that peripherally-induced inflammation induced damage of dopaminergic neurons as a response to the activation of complement pathway of microglial cells[105]. CD14, which is involved in the activation of the TLR2/TLR1 complex lead to upregulation of NFκB expression and induction of oxidative toxicity that has been implicated in all neurodegenerative disorders[106]. Bacterial amyloids are recognized through TLR2 mediated pathway leading to inflammation and oxidative toxicity that are the main induction factors to AD and PD[107].

Conclusion

Recent advances in metagenomics and metatranscriptomics tools coupled with the availability of rapid and cost-effective sequencing platforms have revolutionized the field of microbiome research. However, it remains imperative to completely understand the strengths and limitations of current genetic methods used to study the human gut microbiome.Advances in bioinformatics and high-throughput sequencing techniques facilitate the identificationof the abundance and diversity of human microbiota in the different body niches, andhelp to decipher the possible link betweenmicrobiomeand different disease conditions. Such goals are important prerequisites to identify novel diagnostic and therapeutic targets that will help to alleviate and cure different microbiome-associated diseases.

Deciphering the possible inter-individual variations in the microbial composition within different body regions and identification ofthe potential role of these human microbiota in the induction of different disease conditions is expected to hasten the application of microbiota-driven personalized medicine. In addition, it is possible to identifynovel antibiotics againstthe emerging antibiotic resistantmicrobiota that may be present in different human body niches. Altogether, this comprehensive picture on human microbiome will help understand the current therapeutics available for modulating the gut microbiome composition for the prevention and treatment of various NCDs and determine whether the dysbiosis and reduced microbial diversity seen in many NCDs is causal or a consequence of those diseases.

Current status of microbiome research discloses the need to map the different types and complexity of microbiota among different human populationsglobally and to demonstrate the possible reciprocal interplay between some developmental factors, different environmental factors such as food, lifestyle, exposure to different environmental hazards and microbiota.

Research has shown the possible role of microbiota in induction of different disease conditions and inexploringpossible noveltherapeutic and preventative strategies to improveand reversethe microbiome-associated diseases as well as promote global human health.

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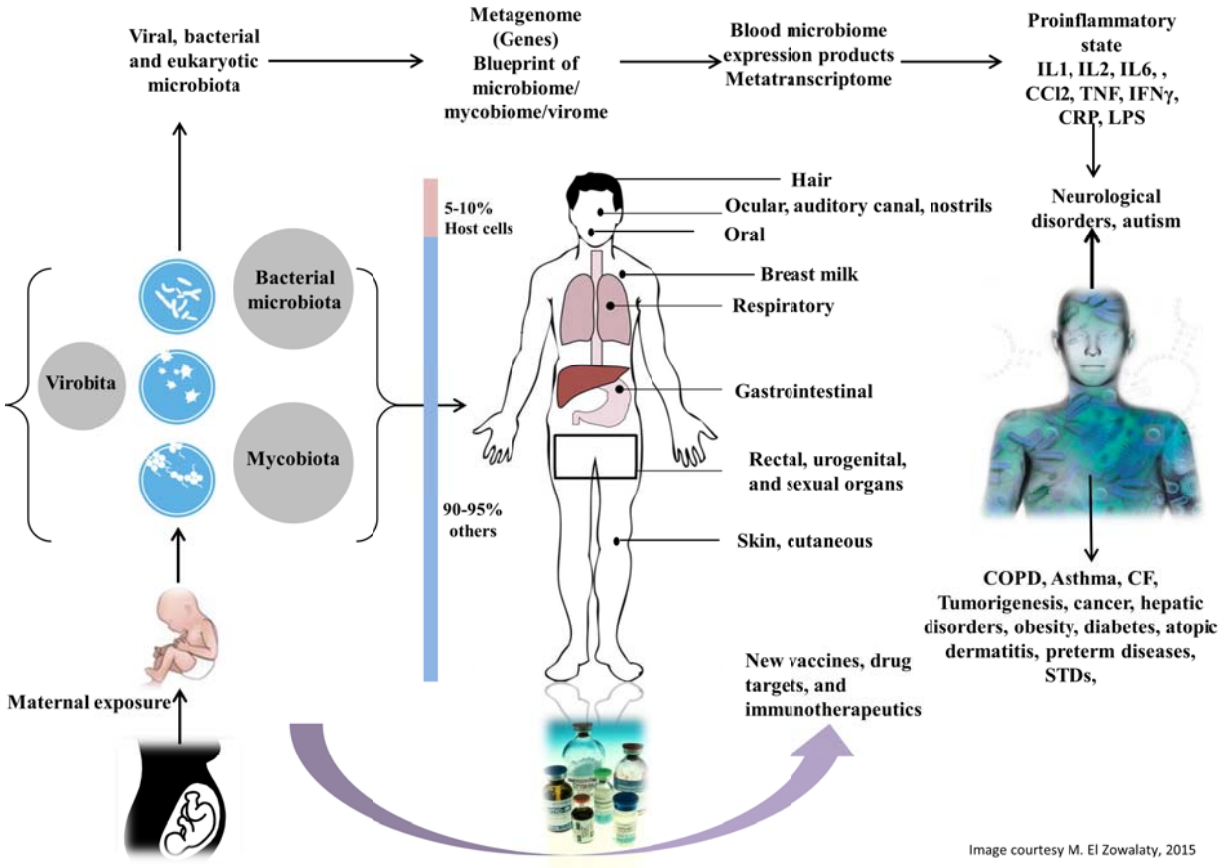

Figure 1

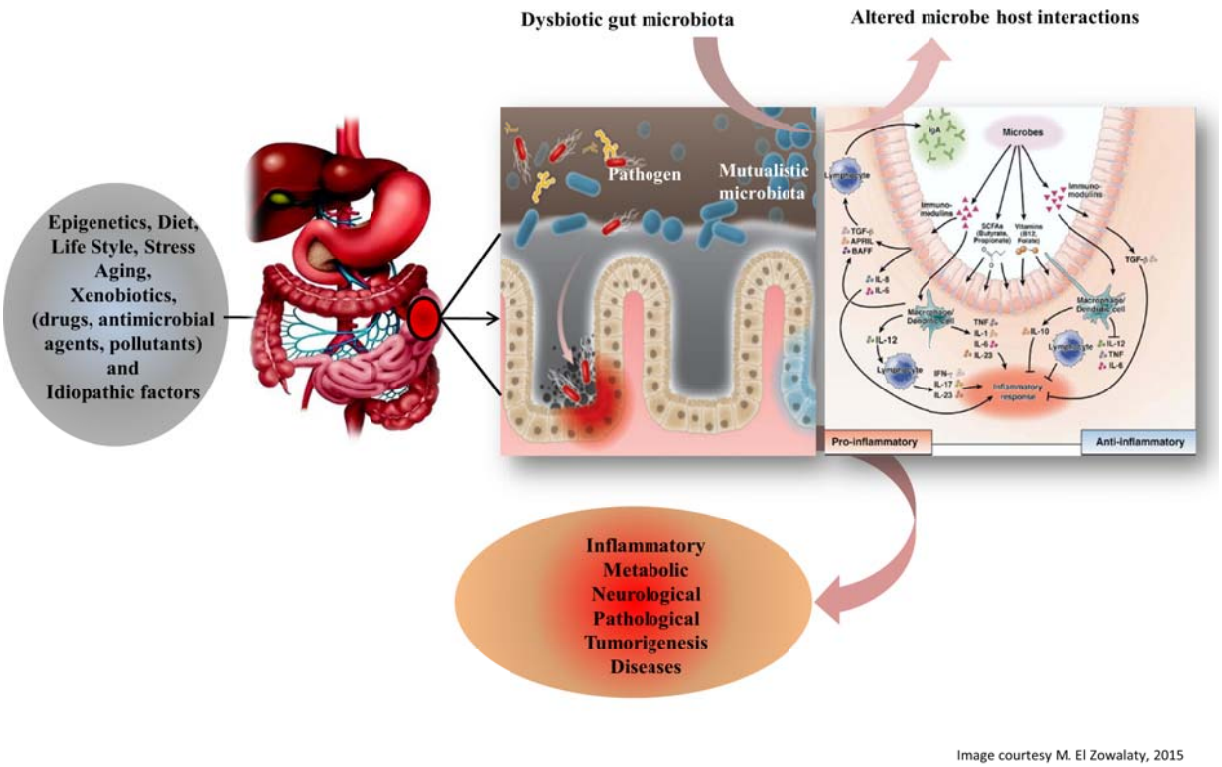

Image courtesy M. El Zowalaty, 2015

Figure 2

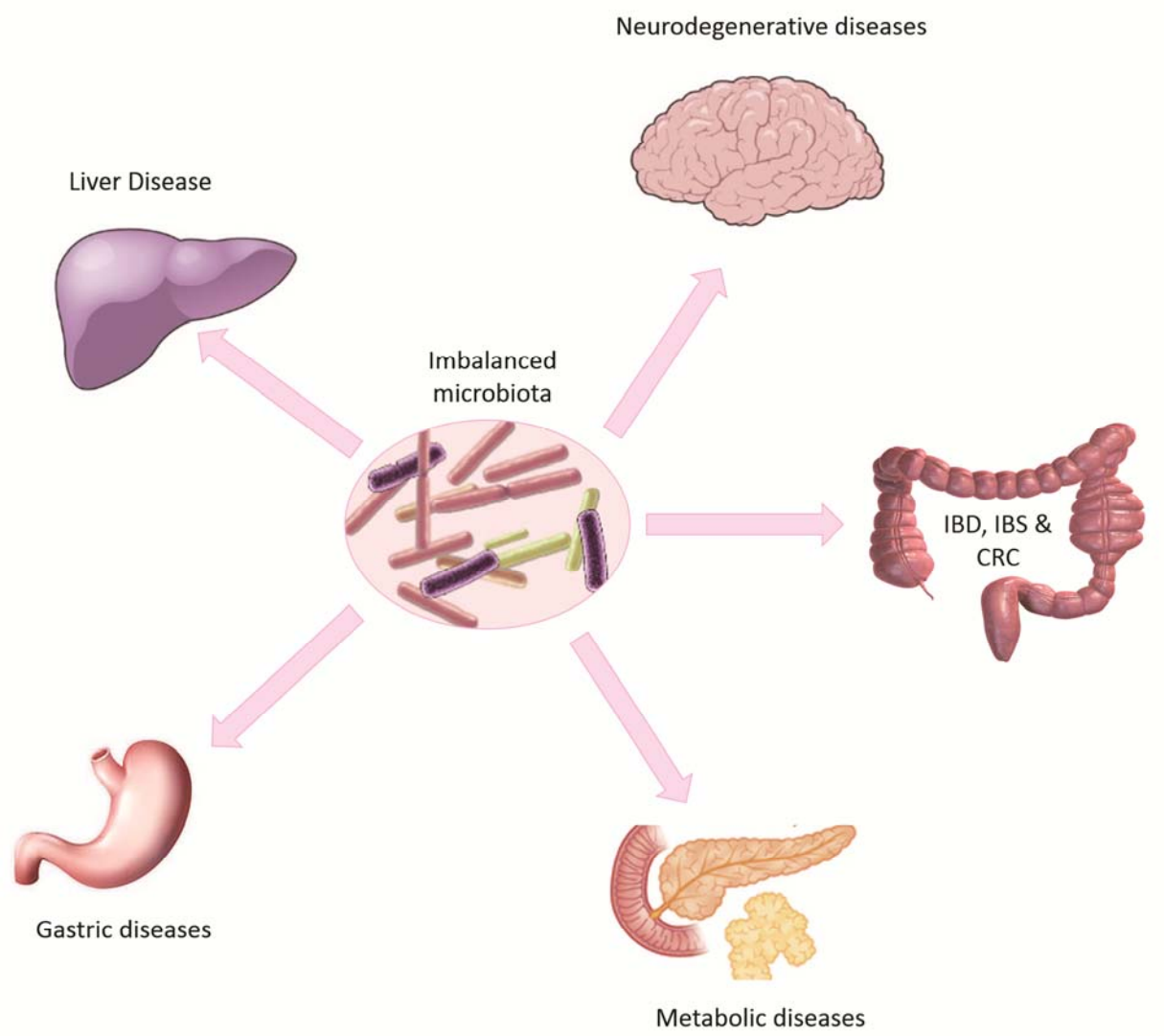

Figure 3: A diagram showing the microbiota and associated diseases has been added