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Gut microbiota and the human gut physiological changes

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Abstract

Background: The human gut can be colonized by number of microorganisms. The most studied are bacteria, which changes from birth to newborn born into adult-like gut microbiota. Much is known about the effects of dietary, medications, and lifestyles on the bacterial composition. However, the host physiological changes influencing the gut microbiota, the immediate consequences, and the possible gut microbiota therapy are not studied at length. This review is based profoundly on animal model studies through experimentation and some human clinical trials for the past 20 years.

Forward: The physiological factors studied to influences gut microbiota are bacterial mucosal receptors, mucin glycosylation, mucus, epithelial microvilli, and tight junction. Host secretions and immune response such as immunity, secretory A (sIgA), inflammasome, innate immunity, immune response, glycans, bile acids, peristalsis, microRNA, and adhesion to intestinal glycans are as well found to confer variety of alterations on gut microbial flora.

Conclusion: Despite the resilience of the gut microbiota in response to changes, chain of events causes the imbalance microbiota. Increased pro-inflammatory potential with the help of cell barriers, host secretions, and immune response mediate gut recovery.

Keywords: Intrinsic factors, Intestinal mucosa, Gut microbes, Dysbiosis, Mucins, Glycans

Introduction

Diversity of bacterial population in the gut is associated with gut microbiota of healthy individuals. In contrast, reduced diversity is seen among diseased individuals and those with some abnormal physiological changes. The snowball effect of these physiological changes are seen when commensals are dominated by pathogonic strains. These might pose pathogenic futures and change the bacterial function metabolically in the gut (Qiu et al., 2020a, b).

Natural variations such as genes and mutation influence gut microbiota. The immune system, the intestinal mucosa, microbiota itself, diet, stress, chemotherapy, abuse of alcohol, and ingested antibiotics are the major factors influencing gut bacterial population (Bajinka et al. 2020). Ingested antibiotics might be either for medication or through the consumption of antibiotic-treated animal products. Probiotics and prebiotics supplementations and fecal microbiota transplantation (FMT) are studied to be promising interventions to restore gut microbiome (Bajinka et al. 2020).

Despite many previous efforts, the mechanisms underpinning dysbiosis still remain unclear (Bajinka et al. 2020). These are due to the limited microbial characterizing techniques (Bajinka and Secka, 2017). Also, the intricate interactions between interspecies such as the role of parasites, virus, bacteriophages, and fungi are not explored. In addition, combination with natural variations such as gene and mutations in the host, stress, secretions of bacterial toxins are yet to be deciphered (Thaiss et al. 2016). Until the knowledge gap of these effects is bridged to the role they play towards dysbiosis, the

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explicit role of microbiota on health and disease would not be better understood (Thaiss et al. 2016; Marques et al. 2010).

The trillions of microorganism residing in the gut are dispersedly distributed. These are not uniformly based on the biochemical and physiological properties in the human body. Acidophilic genera such as *Streptococcus*, *Lactobacillus*, *Helicobacter pylori*, *Candida*, and *Peptostreptococcus* are found in the stomach. The study of gut microbiome in health and disease are based on clusters of bacteria forming genera and rarely on the specific strain. The entire human body, with the exception of sterile organs harbors different bacterial populations. Studies have found *Firmicutes* and *Bacteriodetes* with 64% and 23% respectively as the most common in human gut. *Actinobacteria* and *Proteobacteria* are also occurring in varying percentages (Kasai et al. 2015). These microbes residing in the intestinal tract influence local and systemic process such as supplying vitamin, maturation of mucosal immunity, nutrient transformation, and influence the brain dopaminergic neurotransmitter (Marques et al. 2010; Arumugam et al. 2011).

The normal functioning of gut microbiota is more stable with diverse microbiota composition. Based on the recent Metagenomics analysis, a healthy human gut comprises mainly *Bacteriodetes*, *Firmicutes*, *Actinobacteria*, and *Proteobacteria* (Kasai et al. 2015).

Due to the biochemical niches in the gut, microbes developed resiliency in response to the host's lifestyle. For example, the time and type of food consume by the host influence the group of distinct phyla or class. The more abundant they are with respect to phyla, the more adaptable to any biochemical changes (Saha et al. 1983). The energy of the specific phyla or family of these bacteria is generally derived via fermentation and sulfate reduction of dietary and host carbohydrates. The 'survival of the fittest' existing among the microbes can be observed through their phenotypic traits (Ley et al. 2008; Saha et al. 1983).

This review aims at digging into the knowledge gap regarding physiological factors influencing gut microbes, the alterations caused in the gut, the immediate consequences and their alternative gut therapy. We focus mainly on mucus layers, epithelial microvilli, and tight junctions (TJs), immune factors, inflammasome, and host secretions. The review dwells on studies centered on a wide range of microbiota associated based on animal model. In addition, this review has much evidence on randomized clinical trials over the last 20 years. We deciphered on the varying dysbiosis caused by specific physiological changes.

Mucus layers and bacterial mucosal receptors

Human small intestine comprises duodenum, jejunum and ileum. It helps in digestion and nutrient absorption. Large intestines are cecum, colon and rectum for the absorption of digested food and formation of feces. These anatomies are specific to their functions. The layers that are in contact with the intestinal activity are muscularis propria, the submucosa, and the most concentrated mucosa. The concentration of enterocytes coming from the villi on the surface of the small intestinal wall gives rise to microvilli. Microvilli are specific for absorption of nutrients as part of the digestive process. Colonocytes absorb water in the colon while lubricating the intestinal contents. Through the direct competition for nutrients, microbiota increase mucus layer on the intestinal mucosa. This process stimulates the immune system of the gut with the help of gut-associated lymphatic tissue (GALT) (SorgJA, 2008).

Mucus layer are made up of inner, stratified, and are firmly adhered to the epithelial cells. They produce digestive juices and other biochemical products like enzymes. In addition to the protective effects to the gut, these biochemical products are crucial in distributing nutrients between the host cells and the resident microbes (SorgJA, 2008). Transmembrane mucins found on the apical surface of microvilli such as MUC3, MUC12, MUC13, and MUC17 functionally form a layer. This is protective in nature and works as diffusion barrier in the gut. They maintain the integrity of the surface epithelial layer and in interaction with different PDZ-proteins; they regulate the membrane channels and signal proteins (Hooper, 2010). The protective mechanisms for epithelium from direct contact with microbes are accomplished when goblet cells secrete mucus that lines the gastrointestinal tract.

Instead of the microbes to feed on the epithelium, the intestinal mucus serves as sources of carbohydrates from the mucins (glycan chains) (SorgJA, 2008). Moreover, the daily production of mucus, which is regulated through transcriptional regulation of MUC2 expression is influenced with increased MUC2 transcription by multiple of factors. These factors are only expressed when the metabolic output of resident bacteria dominate the prebiotic effects on total microbiome composition (Hibberd et al., 2019). During inflammation, mucin glycosylation alters the influences of cytokines production and hormones (Hooper, 2010). Lipopolysaccharide (LPS) and lipoteichoic acid; interleukin (IL)-4 and IL-13; and vasoactive intestinal peptide hormone and cytokines such as tumor necrosis factors (TNF) all increase MUC2 transcription (SorgJA, 2008; Carter and Rood, 2012). The expression of the fucosyltransferase 2 (FUT2) in the intestine that accelerates fucosylation of intestinal mucins is induced by LPS and cytokine IL-23 (Van Maele et al. 2010). Once the changes in glycosylation are effected, the supply of carbohydrates for bacterial utilizing mucin glycans as the only source of carbon is equally

obstructed; dysbiosis in the gut microbiota is the resulting consequences (Qiu et al., 2020a, b). An increased concentration of free fucose in the colon gives rise to Locus of Enterocyte Effacement (LEE) virulence genes produced by enterohaemorrhagic *E. coli* (Wells et al. 2011).

Once the gut bacterial composition is distorted, the bacterial diversity is lost. Extinction in number of species results in (Bajinka et al. 2020). Normalizing these diversities is not an easy intervention. One instance is seen in the intestinal mucus layer. It requires long-term microbial re-colonization (Hooper 2009). Gel-forming mucins are packed in the lumen for forming mucus wall. This layer is divided into inner firm and outer loose layer. While the former forms a coat for segregating microbes, the latter provides habitat for residence. Both play a role in penetration of mucosal integrity by bacteria. This dense impermeability of the inner layer enables the layer to be virtually sterile (Justesen et al. 1984). However, just as the national border chaos, mucin proteins, which are produced by the enormous rich and diverse O-glycans, will supply energy. In addition, they provide preferential binding sites for the commensal bacteria against pathogens (Kim and Ho, 2010) (Table 1). Unlike in the lumen, where species display is reduced, the outer mucus layer is a complex and unique niche. It shows a very organized bacterial species displaying different patterns of proliferation and utilization of resources. In the Golgi apparatus, glycosyltransferases is expressed and this determined the type of O-glycosylation. Any little changes in this complex will have an effect on the gut microbiota (Kim et al. 2014; Theriot et al. 2014). Two of the key proteins that are crucial in shaping the microbiota and hence mediating a normal health conditions are mucin glycosylation and mucus. These enable the selection of the highly microbial species to mediate host health.

Epithelial microvilli and tight junction (TJ)

On each of the thousands of microvilli, the epithelial harbors enterocytes. They form the brush border. The microvilli facilitate absorption of nutrients and defense luminal microbes, thereby restricting microbial adhesion.

Table 1 Bacterial mucosal receptors

Bacterial mucosal receptors	Observations in the gut	Physiological changes in the gut	Alternative remedies or mechanisms
E. coli binding to Neu5Gc-containing glycans	Influence the gut microbiota population and metabolism.	Cause stomach disorders (Sreevalsan and Safe, 2013) and loss of short chain fatty acids (SCFAs).	Diet rich in fibre promotes the growth of bacteria that generate SCFAs.
Changes in mucosal glycosylation (due to inflammation)	Affects a low number among bacteriophages and less eradicating effects on bacteria specific for mucus-penetrating (Kamada et al., 2013).	The resulting dysbiosis is associated with intestinal permeability (Kamada et al., 2013).	*Akkermansia muciniphila* is a promising probiotics, improving metabolic functions and immune response (Zhang et al., 2019)
Increased free fucose in the colon	Confers locus of Enterocyte Effacement (LEE) virulence genes produced by *Enterohaemorrhagic E.coli* (Wells et al., 2011).	LEE effacing lesion, leading to a brush border or lumen and microvili destruction, loss of ion and induce severe diarrhea.	Eat diet rich in fibre to supply SCFAs and fermented food to heal the gut.
Thinner mucus in the distal colon (diet with Microbiota-accessible carbohydrates (MACs depletion)	Increases the proximity of microbes to the epithelium.	The expression of an inflammation marker REGIIIβ is increased (Gebhart et al., 2015).	*Faecalibacterium prausnitzii* has anti-inflammatory effects partially via the elevation of IL-10 production (Yan et al., 2008). TGF-β also suppresses an inflammatory response and mediates immune tolerance (Hornung et al., 2009).
Shiga, bacterial toxins of type AB5 and pertussis toxins	Get adhered to the surface of intestinal glycan (Sreevalsan and Safe, 2013).	Influence the gut microbiota population and metabolism. Eventually cause stomach disorders (Sreevalsan and Safe, 2013).	*Akkermansia muciniphila* is a promising probiotic, improving metabolic functions and immune response (Zhang et al., 2019)
Monosaccharide (from intestinal glycans)	Utilized by bacteria devoid of glycosidases.	Mediate a strong proliferating response leading to dysbiosis (Rahman et al., 2016).	Same intervention as above.
Obstructed mucin glycosylation	Obstruction of carbohydrates for bacterial utilizing mucinglycans as source of carbon (Rahman et al., 2016)	Dysbiosis in the gut microbiota is the resulting consequences.	Same intervention as above.
The junctional adhesion molecule A (JAM-A) knockout	Increase of *Desulfovibrionaceae* and decrease of *Akkermansia* (Kashiwagi et al., 2015)	Wound-induced inflammation and angiogenesis.	Probiotics, dietary fiber, antioxidants, mucosal nutrients stimulating digestive enzymes.

Mucosa-associated microbes are repelled by the negative charge on the luminal surface of the epithelial microvilli and shapes gut microbiota (Chan et al. 2013). The exact phyla mediating this mechanism, causing alteration or the diversity of gut microbiota is yet to be studied.

The physical barrier consists of epithelial cells. These form intercellular TJs that check passage of the digested food and gut microbes to the deeper tissues. Paracellular permeability in the host is decreased with the help of gut commensal that can induce TJ protein expressions. However, in contrast to this positive effect, TJs are studied to be degraded by the decreased paracellular permeability conferred by the gut commensal. TJ proteins are internalized when disrupted via instigating the enterocytes. The molecular pathway of this process is not thoroughly studied. However, it is more likely the cause of luminal microbes to activate immunocytes in the lamina propria that shapes the microbiota (Hammer et al. 2014)

Immune factors

A non-inflammatory homeostasis involves mechanisms such as the secretion of anti-microbial proteins by the host cells, immunoglobulin A, and adequate mucus barrier as adherence to the epithelium. This ensures a symbiotic relationship between commensal in the gut (McGovern et al. 2010). In the absences of immunoglobulin-A, the immune system is studied to be associated with an increase in abundance of anaerobic bacteria in the gut. This includes mucosa-adherent segmented filamentous bacteria (SFB) from the phylum *Firmicutes*. Furthermore, components of the innate immune system affect gut microbiota. The inflammasome are all studied to be affecting the gut microbes (Table 2) (Zhu et al. 2017).

Innate immunity

Innate immunity of gut epithelium harbors enterocytes that express pattern recognition receptors (PRRs). PRRs sense microbes-associated molecular patterns (MAMPs) and promote the production of anti-microbial peptides, recruitment of immune cells and transportation of sIgAs as immune response (Liu et al. 2020). Various PRRs determine the sensing-response system of the host. The following will be looked into with respect to shaping the gut microbiota.

Toll-like receptors (TLRs), C-type lectin-like receptors (CLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) forms of PPRs are critically recapitulated (Salzman et al., 2010). Dysbiosis-associated obesity and insulin resistance are prominent but only if there is an inactivation of the pattern recognition receptor (PPRs) that recognize flagellin on the epithelial surface. TLR5 helps to maintain the balance of microbiota by stimulating IL-8 and TNFα in the epithelium and monocytes (Wells et al. 2011). They also induce the expression of IL-22 and IL-17 in the mucosa (Wehkamp et al. 2005). Much evidence arises from the mouse study. The microbial transfer of TLR5-deficient mice to wild type develops forms of metabolic syndromes. Blossoms of *E. coli* are seen with TLR5 deficiency in the intestine (Kumar et al. 2016).

In the terminal ileum, NOD2 receptor expressed monocytes and Paneth cells. It restricts colonization of pathogens and checked the number of bacteria to reside as commensal gut community (Sakaguchi et al. 2008). However, a polymorphisms occurring in the *NOD2* gene during the stages of Crohn's disease (CD) lower the expression of α-defensin in Paneth cells (Sokol et al. 2008). This is not good news for the gut community since loss of α-defensin promotes the increasing ratio of *Firmicutes* to *Bacteriodetes.* This in turn promotes the growth of SFB that initiate antimicrobial defense. Furthermore, expansion of SFB is inhibited with an increase in α-defensin expression of IL-17. Low number of IL-17-producing Th17 cells in the lamina propria signals loss of α-defensin and expansion of SFB (Elinav et al. 2011).

Treg cells are regulatory T cells that secrete anti-inflammatory IL-10.They also transform growth factor TGF-β that ensures mutualism relationship with the microbiota (Irrazábal et al., 2014). A reduced IL-10 from the mouse study was associated with an increased abundance of *Bacteriodetes*, *Proteobacteria*, and *Verrucomicrobia*. Inflammation in the caecum and colon is prominent due to this shift. One such bacterium from *Proteobacteria* is *E. coli,* seen with 100-fold increased (Arthur et al., 2012). Again *E. coli* are enriched in the absence of dendritic cells-specific (DC-specific) TGF-β signaling. Note TGF-β mediates immune tolerance by suppressing an inflammatory response. In addition to its occurring in Treg cells, it occurs in DC and other cells of intestinal mucosa (Wells et al. 2011).

Secretory IgA (sIgA)

Plasma cells in the lamina propria of gut produce IgA that is transported through the enterocytes into the lumen. The outermost layer harbors mucins and bacteria that interact with sIgA. Changes in gut microbiota are studied to be associated with reduction of sIgA levels in Rig-1 and lymphotoxin (LT)-α knockout mouse (Fadlallah et al. 2018). Bacteria-binding capacities that induce alteration in microbiota are reduced with the sIgAs inhibitory co-receptor programmed cell death-1 (PD-1) knockout mice. Establishing the role of the sIgAs in shaping gut microbiota and control of gut ecology homeostasis, individuals with IgA deficiency are as well studied to have alteration of gut microbiota (van den Elsen et al. 2019). Both the breast milk-derived sIgA and sIgA-

Table 2 Immune factors influencing gut microbes

Immunity	Observations in the gut	Alteration in the gut	Alternative remedies or mechanisms
Absences of immunoglobulin A	Increase in mucosa-adherent segmented filamentous bacteria (SFB) from the phylum *Firmicutes* (Wells et al. 2011).	This is linked with autoimmune diseases such as encephalitis and arthritis.	Enriching the gut with genera such as *Eubacterium, Prevetolla and Roseburia*(Qiu et al., 2020a, b)
Absence of dendritic cells-specific (DC-specific) TGF-β signaling	*E. coli* are enriched in the gut.	Non mediation of immune tolerance and inflammatory response is prominent (Wells et al. 2011).	The probiotic *Clostridium butyricum* is able to induce TGF-β signaling in DC, which in turn induces Treg cell generation (Hornung et al. 2009).
Polymorphisms in the NOD1 gene and NOD2 gene	Changes in the levels of Enterobacteriaceae in humans (Knights et al. 2014; Elinav et al. 2011).	The resulting dysbiosis is associated with intestinal permeability and onset of inflammation (Kamada et al. 2013).	The knockout of resistant-like molecule β (RELMβ) gives abundance of *Bacteroidetes*, *Firmicutes* and *Proteobacteria* (Bonder et al. 2016) and hence a healthy gut.
NOD2 knockout mice	Harbor a higher amount of *Bacteroides*, *Firmicutes* and *Bacillus* in the terminal ileum	Have downregulated expression of α-defensins and were more susceptible to *Listeria monocytogenes* infection (Dheer et al. 2016).	NLRP6 inflammasome deficient mice increased Prevotellaceae and TM7, and reductions of genus *Lactobacillus* in the *Firmicutes* phylum (Kobayashi et al. 2005)
Mice with intestinal epithelium over expression of TLR4	Abundance of *Fusobacteria* and *Proteobacteria* and lower abundances of *Firmicutes* in the colonic mucosa (Bereswill et al. 2014)	This condition is associated with the onset of colorectal cancer.	TLR2 in T cells has been proven to help the colonization of commensal *Bacteroides fragilis* in the gut (June et al., 2011).
TLR9 knockout mice	Lower *Enterobacteria* and *Bacteroidetes*, whereas levels of *Clostridium leptum* and *Bifidobacteria* expand (Xiao et al. 2019).	Increased prevalence of IgG2a and accelerated renal diseases (Albert et al. 2009).	Increase *Firmicutes* and *Proteobacteria* associated with higher level of miR-200a-3p (Johansson et al. 2011).
Mice deficient in TLR5	Higher abundance in *Bacteroidetes* and *Lachnospiraceae* (Suzuki et al. 2004)	Spontaneous intestinal inflammation and metabolic abnormalities, however not much evidence.	TLR4 knockout in mice decreased the abundance of *Bacteroidetes* (Suzuki et al., 2004), The mice lacking matrix metalloproteinase 7; **(**MMP7 displayed a significantly higher abundances of *Firmicutes* and a significantly lower abundances of *Bacteroidetes* (Mathias et al. 2010).
Inactivation of NLRP6 proteins	NLRP-6-deficiency affects the goblet cells in	Reduced mucus layer thereby enabling microbes to be more susceptible to dextran sulfate sodium-induced colitis and some forms of intestinal infections (Hooper, 2010).	TLR2 in T cells has been proven to help the colonization of commensal *Bacteroides fragilis* in the gut (June et al., 2011).
NLRP6 protein	Mediates IL-18 secretion via caspase-1	A pro-inflammatory cytokine that suppresses mucin production and promote ulcerative colitis among the type colitis (Hu et al. 2015).	IL-22-binding protein express antimicrobial peptides and induce tissue repair (Wells et al. 2011), hence playing an important function in intestinal homeostatic (Wang et al. 2014).
RIG-1 knockout	Altered microbiota in comparison with wild-type mice.	Microbial change could be linked to the downregulation of IgA, REGIIIγ, and PD-1 (Schroeder et al. 2011).	AIM2 mediation of antimicrobial peptides such as C-type lectins (REGIIIβ and REGIIIγ), calprotectin (S100A8 and S100A9) and lipocalin 2 (Lcn2) in gut epithelial cells (Schneeberger et al. 2018).
β-defensins, such as DEFB1, beta-defensin 1 (DEFB1)	Bactericidal effects against the gram-positive commensal of *Bifidobacterium* and *Lactobacillus* (Mathias et al. 2010).	Reduction in mucosal microbial community and likelihood of onset of insulin resistance.	Immunoglobulin receptor (pIgR), CD71, and CD89 on the epithelial cells may enable microbes to benefit from sIgA to build up a mucosal microbial community (Mathias et al. 2010;Vangay et al. 2018).

coated bacteria have demonstrated sIgAs binding affinity with gut bacteria. While the former helps in shaping the gut microbiota, the latter is found with protective effects on mice from diseases (Gersemann et al. 2009).

Inflammasome

TM7 bacteria (*Saccharibacteria*) and *Pretovella* spp.are expanded when the inflammasome complex NOD-like receptor family of pyrin domain containing NLRP6 proteins is inactivated (Davis, 1974). The goblet cells in

NLRP-6-deficiency from the mouse model of study confer a reduced mucus layer. This enables microbes to be more susceptible to dextran sulfate sodium-induced colitis causing intestinal infections (Kashiwagi et al. 2015). NLRP6 mediates IL-18 secretion via caspase-1. The exact role that IL-18 is playing in the intestinal homeostasis is not established. However, some studies on mouse model found it as a pro-inflammatory cytokine that suppresses mucin production. The mechanism is by inhibiting the maturation of goblet cells that protect and maintain mucus blanket through synthesizing mucin. In doing this, it promotes ulcerative colitis among the type colitis (McGovern et al. 2010). However, IL-22-binding protein is also studied to be induced by IL-18 through down regulating inflammasome. This protein will express antimicrobial peptides and induce tissue. Hence, playing an important function in intestinal homeostatic (Gebhart et al. 2015).

In addition, the presence and absences of H and ABO antigens in GI mucosa that is determined by the FUT2 genotype directly affects bacterial diversity. Remember FUT2 genotype is a gene expressing α 1, 2fucosyltransferase (Neu and Walker 2011). Also in some books, the presence and absence of H and ABO antigens will be found as 'secretor and non-secretor.' In one of studies using mouse model, diet with MACs depletion showed thinner mucus in the distal colon. This increases the proximity of microbes to the epithelium and the expression of an inflammation marker REGIIIβ is heightened (Gebhart et al. 2015). The heightening of inflammation marker REGIIIβ means regenerating gene family protein 3, lectins belonging to the antimicrobial proteins. This leads to alteration of gut microbiota.

Host secretions

Glycans

Bacteriodetes, when expanded inside the gut, signal increased carbohydrate-fermenting machineries such as hydrolase enzymes and transporters. These utilize monosaccharide as the carbon source (Vuille-dit-Bille et al., 2015). *Bacteriodetes* and some *Firmicutes*, such as *Ruminococcus gnavus*, *Ruminococcus flavefaciens*, *Ruminococcus intestinalis*, and *Akkermansia muciniphila* from Phylum *Verrucomicroiota* enable microbes to possess greater ability to extract carbohydrates from mucin glycans (Srinivasjois et al. 2013; Carter and Rood, 2012). When *Enterobacteriaceae* lost the enzymatic ability to degrade intestinal mucins, *Bifidobacterium* spp, which is prominent in the infant gut from breast milk ferments complex fucosylated oligosaccharides (Lawson et al., 2020). These can reduce pathogen adhesion to the gut by serving as decoy receptors, thus protecting infants (Kelly et al., 1994).

The differences in carbohydrate composition in the intestinal mucosa orient the various binding domains of bacterial species. Some of the adhesions earlier studied as binding domains to the intestinal glycans are but not limited to fimbriae, pili, and adhesins. While the pathogen *Campylobacter jejuni* express binding mechanism to fucosylated epitopes (blood group antigens H2, Lewis-b, Lewis-y and Lewis-x (Van Maele et al. 2010), another commensal in the gut such as *Lactobacilli* depend on mucus-binding proteins to colonize the gastrointestinal (GI) tract (Toyoda et al. 2015). In essence, the oligosaccharides found in human milk give higher density of fucosylated glycan in the lumen of the intestine and the inhibition to the adherence of *C. jejuni*. The binding specificity of *E. coli* K99 utilizes fimbriae as the domain of adhesion. This enables the bacteria to recognize gangliosides terminated with 2,3-linked NEu5Gc (Oliver et al. 2003). This is one of the ways in which intestinal glycans can regulate the binding mechanisms of the microbes in the gut. Strict consumption of red meat means gut rich in Neu5Gc. Since human cells cannot digest this, the SubAB toxin secreted by Shiga toxigenic *E. coli* use this opportunity and bind to Neu5Gc-containing glycans on human epithelial cells. Although the mechanisms are not studied at length, other toxins like cholera, Shiga, bacterial toxins of type AB5, and pertussis toxins all get adhered to the surface of intestinal glycans. They influence the gut microbiota population, metabolism, and eventually cause stomach disorders (Sreevalsan and Safe 2013).

Bacteriophages, which are virus that infect bacteria, help to control the number of mucus-penetrating bacteria through intestinal glycoprotein, which favors its higher density. In turn, they serve as a protective barrier for the host (Sokol et al. 2008). However, any changes in mucosal glycosylation due to inflammation affect a low number among bacteriophages. This means less eradicating effects on bacteria specific for mucus-penetration (Kamada et al. 2013). The resulting dysbiosis is also considered to be associated with intestinal permeability. Intestinal glycans are reviewed to be self-regulated for glycosylation and mucin secretion. The factors apart from the adhesion specificity, diet, and genes also increase the risk of diseases and hence dysbiosis. In fact, hypomorphic alleles expresses 1-2-fucosyltransferase FUT2 enzyme that is known to be associated with CD (Kuper, 2000).

Bile acids

Bile acids taurocholate and deoxycholate, secreted by gall bladder in the duodenum facilitates the germination of *C. difficile* (Liu et al. 2016). While the mechanism in which gut with its resilient effects suppress the vegetative growth of *C. difficile* in asymptomatic patients

remain elusive, competition for N-acetylglucosamine and Neu5Ac carbohydrate derived from intestinal mucins are established (Sakaguchi et al. 2008). Exhausting these nutrients is a means to stop the over growth of *C. difficile*. The competition to stop the overgrowth of *C. difficile* goes beyond depriving nutrients. Some microbes have the potential to transform the bile acids that would not favor the proliferation of *C. dificile.* With this, there will be no germination of clostridia spores in the gut (Srinivasjois et al. 2013).

Discussion

As humans require shelter to live a healthy life, so do the microbes. Microbes have the ability to shape and maintain their composition in a way to confer protections against any environmental selective pressures. These pressures might be external stimuli or internal aggression of combined microbial and cell physiology. The borderline controllers of our gut microbiota ensure that anything foreign to the body is screened at microscopic level, non-threat to the body and be physiologically symbiotic with the normal intestinal microbes. They do this by recruiting and using the host immune system and establishing a multi-factorial and dynamic intestinal barrier. It is interesting enough to know that the multifactorial intestinal barrier consists of immunological (Immunoglobulin A (IgA) and epithelia-associated immune cells), physical (mucus layers and the epithelial), and biochemical (enzymes and antimicrobial proteins) factors influence the balance of micro-organisms in the gut (Frank et al. 2007).

IgA being the principal antibody plays a crucial role in the immune functioning of mucosal membrane. It is the first line of defense mediating a variety of protective functions via the interaction with specific receptors and immune mediators. The intrinsic factors range from the pH of the intestine, host body temperature, and microbial interactions. In addition, physiological factors will be host secretions and immune response, bile acids, peristalsis and bacterial mucosal receptors (Lachnit et al. 2019). Gut as a complex organ composed of multilayer of tissues in shaping microbiota. It consists of epithelia that serve as the frontline in response to both direct and indirect response to luminal microbes. Epithelium-associated factors on gut microbes include epithelial tight junctions, epithelial microvilli, epithelial innate immune sensors, mucus barrier, epithelial metabolism, sIgAs, oxygen barrier, and microRNA. Description of the physiological factors influencing gut microbes, immediate consequences is worth exploring (Fig. 1).

Exogenous factor such as diet, antibiotics, and other used drugs while eliminating their targeted pathogens, will as well wash away number of commensal organisms. This gives chances for resistance pathogens to overgrow, consequently comprising of the pathobionts. The interplay of these pathobionts and dysbiotic community functionalities determine the pathogenic potential, called nososymbiocity. The host-microbes interplay and communicate through a space provided by the mucus layer. This is possible since epithelial cells composed of mucins/epithelial glycocalyx and secreted gel-forming mucins/mucus wall. Without the host physiological factors that include immune response and secretions due to the

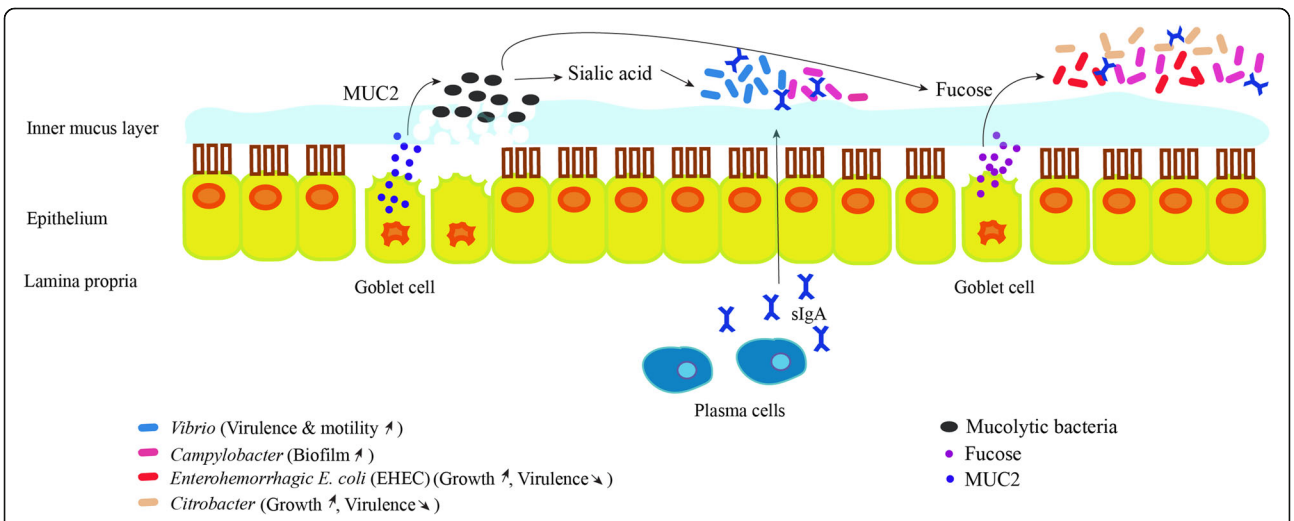

Fig. 1 Physiological factors influencing gut microbes and its immediate consequences. Enterobacteriaceae mediate sialic acid from MUC2 (main O-glycosylated product of or mcin genes) from cecal sialidase activity, which can uptake the sialic acid from synthesis of lipooligosaccharides and bacterial capsule. A regulated sIgA in normal healthy host can ensure and maintain a beneficial diverse microbiota in the gut. The binding of sIgA to the luminal bacteria support association of mucin layer and formation of biofilm, and prevent bacteria from direct access to the surface of intestinal epithelial cells

resilient homeostasis of the gut, inflammation and other diseases will be prominent among gut microbiota harboring organisms.

Conclusion

The physiological factors suppress these pathobionts and mediate gut recovery in respect to healthy gut by stabilizing the increased pro-inflammatory potential with the help of cell barriers, host secretions and immune response. The effective adaptive immune response that serves as defense and regulation of immune responses and inflammation does this by determining what will pass through the gut. The cells doing these tasks are epithelia-associated cells found in the lining of epithelium. Although first line defense against pathogens are provided by the innate immunity comprises antimicrobial peptides and proteins, the disruptive functions of microbial cells against pathogenic bacteria requires multiple and careful design of studies.

Abbreviations

CD: Crohn's disease; CLRS: C-type lectin-like receptors; DEFB1: Beta-defensin 1; DC-specific: Dendritic cells-specific; FMT: Fecal microbiota transplantation; FUT2: Fucosyltransferase 2; GALT: Gut-associated lymphatic tissue; GI: Gastrointestinal; IgA: Immunoglobulin A; LEE: Locus of enterocyte effacement; LPS: Lipopolysaccharide; LT: Lymphotoxin; MAC: Microbiota-accessible carbohydrates; MAMPs: Microbes-associated molecular patterns; MMP7: Matrix metalloproteinase **7**; NOD: Nucleotide-binding oligomerization domain; PRRs: Pattern recognition receptors; PD-1: Programmed cell death-1; sIgA: Secretory A; SFB: Segmented filamentous bacteria; TJ: Tight junction; TNF: Tumor necrosis factors; TLRs: Toll-like receptors

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OB wrote the manuscript. YT, KAA, LBC, and AD edited and reviewed the paper. The author(s) read and approved the final manuscript.

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The authors declare no competing interest.

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