

## Microbiome modulates intestinal homeostasis against inflammatory diseases

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### Abstract:

Eliminating prophylactic antibiotics in food animal production has exerted pressure on discovering antimicrobial alternatives (e.g. microbiome) to reduce elevated intestinal diseases. Intestinal tract is a complex ecosystem coupling host cells with microbiota. The microbiota and its metabolic activities and products are collectively called microbiome. Intestinal homeostasis is reached through dynamic and delicate crosstalk between host immunity and microbiome. However, this balance can be occasionally broken, which results in intestinal inflammatory diseases such as human Inflammatory Bowel Diseases, chicken necrotic enteritis, and swine postweaning diarrhea. In this review, we introduce the intestinal immune system, intestinal microbiome, and microbiome modulation of inflammation against intestinal diseases. The purpose of this review is to provide updated knowledge on host-microbe interaction and to promote using microbiome as new antimicrobial strategies to reduce intestinal diseases.

**Keywords:** Intestinal microbiome | Animal | Intestinal diseases | Inflammation | Metabolites

### Article:

#### 1. Introduction

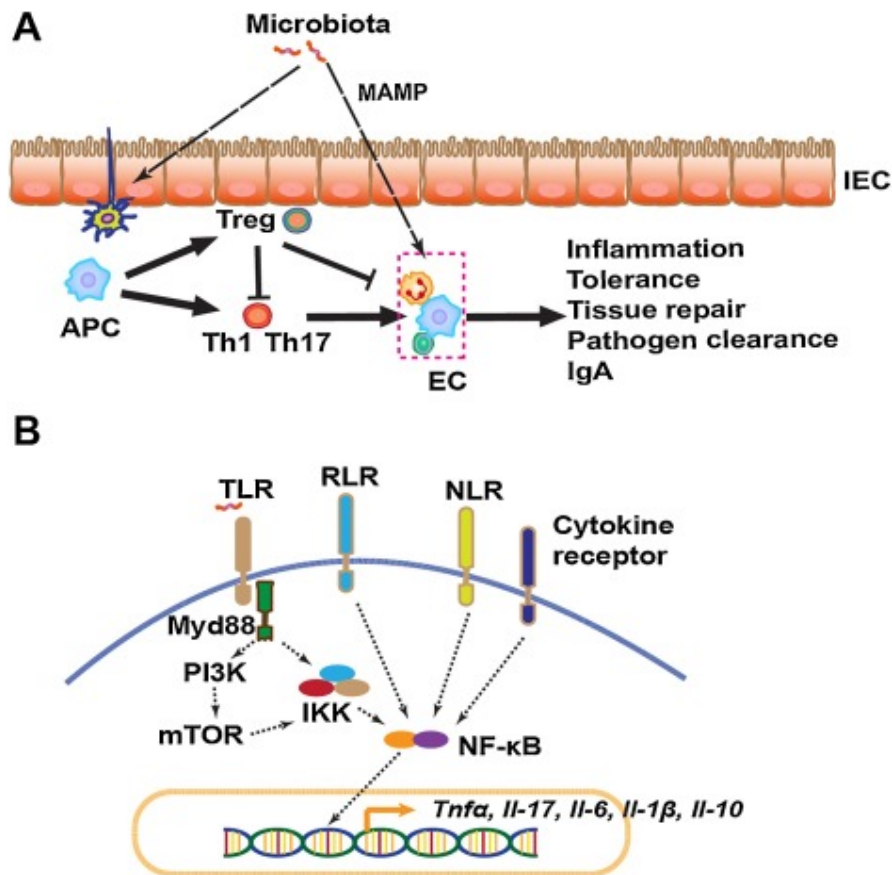
World Health Organization (WHO) defines antimicrobial resistance as “the ability of a microorganism (like bacteria, viruses, and some parasites) to stop an antimicrobial (such as antibiotics, antivirals, and antimalarials) from working against it” (WHO, 2018a). Urgency is mounting to reduce antimicrobial resistance from agriculture to healthcare because of the emergency of “superbug” bacteria resistant to antibiotics (e.g. colistin) in treating multidrug-resistant (MDR) infections (CDC, 2018; McGann et al., 2016). It is estimated that 558,000 new tuberculosis (TB) worldwide in 2017 were resistance to rifampicin, which is the most effective first-line antibiotics (WHO, 2018b). Among them, 82% were MDR-TB. Overuse and misuse of antimicrobial agents in medical and agricultural practice contribute to exacerbating the episodes of emerging antimicrobial resistant microbes (Makary et al., 2018; Martens and Demain, 2017; Neu, 1992; Van Puyvelde et al., 2018). A recent systematic review found that restricting the use

of antibiotics reduces antibiotic-resistant bacteria by 10–15% in animal studies or by 24% in human studies (Tang et al., 2017).

Withdrawing antimicrobials in food animal production, however, has caused new problems for the food animal industries including reducing production efficiency and increasing intestinal diseases, such as necrotic enteritis (NE) in poultry (Casewell et al., 2003) and postweaning diarrhea in piglets (Rhouma et al., 2015). Doubling of incidences in subclinical NE (cholangiohepatitis) from 2013 to 2014 in south-eastern Norway were associated with reduced in-feed antimicrobial usage (Kaldhusdal et al., 2016), although no major worldwide clinical NE outbreak has recently been reported. Although the use of antibiotics as antimicrobial growth promoter (APG) in food animal production is thought to inhibit intestinal microbial overgrowth, it has been suggested that antibiotics may also act as direct anti-inflammatory agents (Niewold, 2007). Interestingly, antibiotics have limited effect on treating human inflammatory intestinal diseases, such as Inflammatory Bowel Disease (IBD) and refractory *Clostridium difficile* infection (CDI). Recently, reconstituting intestinal microbiome has shown promise on preventing and treating some intestinal diseases. For example, refractory CDI patients who can't be cured with antibiotics have been successfully treated with fecal microbiota transplantation (FMT) (Silverman et al., 2010). A recent meta-analysis showed that 92% of CDI patients have clinically resolved the symptoms after FMT without serious adverse events (Quraishi et al., 2017). The introduction of donor fecal microbiota increases the diversity of the microbiome and alters the metabolic pathways active in the intestinal microbiota (Shankar et al., 2014). FMT against IBD remains controversial with some reporting remission in active ulcerative colitis (UC) patients at clinical and endoscopic levels (Jeon et al., 2018; Moayyedi et al., 2015), while others show little to no efficacy (Ianiro et al., 2014; Kump et al., 2013; Rossen et al., 2015). The underlying mechanisms of microbiome manipulation treating intestinal diseases are multiple facets involving delicate interactions between microbiome, immunity, and pathogens. Here, we will summarize recent progress on the intestinal microbiome, the intestinal immune system, and microbiome modulation against intestinal diseases. The aim of this review is to promote the use of microbiome as a new antimicrobial strategy to reduce intestinal diseases.

## **2. Intestinal immune system**

The gastrointestinal tract is essential for providing the nutritional needs of a body through digesting food/feed and absorbing nutrients. Luminal food and microbes are separated from the internal tissue by a single layer of intestinal epithelial cells (IEC), including enterocytes, goblet cells, Paneth cells, enteroendocrine cells, microfold cells (M cells), and stem cells (Carulli et al., 2014). Besides as a physical barrier, IEC also secretes antimicrobial peptides (AMPs) and mucin to control luminal microbes (Antoni et al., 2013). Underneath IEC is the intestinal lamina propria containing a diverse array of immune cells. These immune cells generally are classified into two main categories of adaptive and innate immune cells (Fig. 1A).



**Fig. 1.** Schematic intestinal immunity. (A) Microbe induces immune response. APC: antigen presenting cells including dendritic cells (DC) and macrophage. Treg: regulatory T help cell. EC: effect cells including effector T help cells (Th) of Th1 and Th17, innate cells of Granulocytes (neutrophil/heterophil, eosinophil, basophil), master cell, NK cell, macrophage, DC, ILC (ILC1, ILC2, ILC3), intestinal epithelial cell (IEC), intestinal epithelial lymphocyte (IEL). MAMP: pathogen-associated molecular patterns. (B) Enlargement of pink rectangle of A.

Cellular signaling pathways with emphasis on TLR/Myd88 pathway. TLR: toll-like receptor. NLR: NOD like receptor. RLR: RIG-I like receptor. Myd88: myeloid differentiation primary response 88. IKK: IκB kinase. NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells. PI3K: phosphatidylinositol 3-kinase. mTOR: mammalian target of rapamycin. Dotted arrow: indirect induction; solid arrow: direct induction; blunt end line: inhibition.

Adaptive immune cells in intestine include T and B lymphocytes which are constantly shaped by intestinal microbiota. Naive T and B cells migrate and accumulate in gut-associated lymphoid tissues (GALT), including Peyer's patches (PPs), isolated lymphoid follicles, and mesenteric lymph nodes (MLN) (Koboziev et al., 2010; Severson et al., 2010). The T cells then undergo antigen-driven priming/activation, polarization, and expansion (Agace, 2008) and the antigens come from microbiota, nutrients, metabolites, pollutants, and harmful pathogens. Upon priming within GALT, activated T cells acquire the ability to home to the intestine. CD8<sup>+</sup> T cells migrate to the intestinal epithelium, while CD4<sup>+</sup> T and B cells (mainly IgA-producing plasma cells) enter into the lamina propria (Mowat, 2003). It is evident that microbiota influence adaptive immunity. For instance, deficiency of intestinal IgA secreting plasma B cells in germ-free (GF) mice is

rectified by introducing commensal bacteria (Shroff et al., 1995), suggesting the important role of microbiota on shaping B cell development. The main cell types of intestinal CD4<sup>+</sup> T cells are T help cell 1 (Th1), Th17, and regulatory T cell (Treg, Foxp3-expressing) cells, although Th2, Th9, Th22, follicular helper T (Tfh), iTreg, and type 1 regulatory T cell (Tr1) are also reported (Brucklacher-Waldert et al., 2014; Kreisman and Cobb, 2011). Treg cells maintain tolerance to self-antigens and prevent an inflammatory response. In the gut, Treg cells maintain homeostasis at steady-state where the cells play an important role in the regulation of inflammation against intestinal microbes (Harrison and Powrie, 2013). Indeed, adoptive transfer of CD4<sup>+</sup> T cells to specific pathogen free (SPF) mice in the absence of Tregs, but not in their presence, elicit commensal microbiota-induced colitis (Powrie et al., 1993). Thus, Tregs are critical for the prevention of spontaneous inflammation against commensal microbes.

The importance of Treg is also evident in the case of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, where *FOXP3* is mutated. IPEX patients develop autoimmune enteropathy in the intestine (Bennett et al., 2001). Depletion of Foxp3<sup>+</sup> Treg cells in SPF mice leads to intestinal-associated autoimmune and inflammatory disorders (Lahl et al., 2007), while GF mice are healthy under Tregs depletion (Feng et al., 2010). Treg cells induce immunosuppressive functions through various mechanisms, namely, secreting anti-inflammatory cytokines of IL-10, IL-35, and TGF- $\beta$  (Chaudhry et al., 2011; Collison et al., 2007; Powrie et al., 1996), metabolic pathway disruption (Deaglio et al., 2007), induction of apoptosis in target cells (Gondek et al., 2005), and modulating DC maturation and function (Mahnke et al., 2007). These actions limit the expansion of antigen-specific effector T cells including Th1 and Th17 cells, which induce an inflammatory response, mucosal barrier protection, and tissue repair (Huber et al., 2012). Th17 cell differentiation depends on the presence of a pro-inflammatory microenvironment of IL-23, IL-6, and IL-1 $\beta$  (Zuniga et al., 2013). A specific microbiota modulates Th17 cell differentiation in the mucosa of the small intestine, and one group of bacteria are specific species of Clostridia-related bacteria, named segmented filamentous bacteria (SFB) (Ivanov et al., 2009, 2008).

The activation of adaptive cells is achieved by innate cells presenting antigens (Taams et al., 1999) and some of the most important antigens are derived from intestinal microbiota. Innate immune cells include dendritic cells, macrophage, neutrophil, and innate lymphoid cells (ILCs). Macrophages and dendritic cells (DC) are antigen presenting cells (APC), and they sample luminal content of food and microbiota and coordinate both innate and adaptive immune responses (Kayama et al., 2013). Hence, macrophage and DC determine the difference between innocuous and pathogen-derived antigens and induce either pro- or anti-inflammatory processes. In mice with antibiotics-induced dysbiosis, CX3CR1<sup>+</sup> macrophages up-regulate CCR7 and migrate to mesenteric lymph nodes, where the cells present antigens to induce T-cell responses and the differentiation of IgA-producing B cells (Diehl et al., 2013). Colonic macrophages from GF mice have enhanced proinflammatory cytokine responses (Ueda et al., 2010). Microbiota metabolizing bile acids mediates liver tumor growth through mobilizing natural kill T cells (Ma et al., 2018). These findings highlight the critical role of microbiota shaping innate immunity. Another important group of innate cells is ILCs which have been classified into three subtypes of ILC1, ILC2, and ILC3, based on their cytokine production and expression of determined transcription factors (Eberl et al., 2015). Because of their similarities, ILCs are considered the innate counterpart of T helper cells of Th1, Th2, and Th17 (von Burg et al.,

2015). The activity of these ILCs is modulated by many tissue-specific cues, including nutrients, environmental xenobiotics, and microbiota (Kiss et al., 2011; Spencer et al., 2014; van de Pavert et al., 2014). Notably, IL-22 secretion from ILC3 is negatively influenced by intestinal microbiota-promoted IL-25 secretion from epithelia cells (Sawa et al., 2011). IL-17 promotes local chemokine production to recruit monocytes and neutrophils to sites of inflammation to mediate protection against pathogens, especially against extracellular pathogens (Korn et al., 2009).

Innate immune cells recognize microbial pathogen invasion or host cell damage with intracellular or surface-expressed pattern recognition receptors (PRR) (Fig. 1B). PRR detect microbe-associated molecular patterns (MAMP), such as microbial nucleic acids, lipoproteins, and carbohydrates or damage-associated molecular patterns (DAMP) released from injured cells including ATP, the cytokine IL1 $\alpha$ , uric acid, the calcium-binding cytoplasmic proteins S100A8 and S100A9, and the DNA-binding nuclear protein HMGB1 (Akira et al., 2006; Schaefer, 2014). Members of the toll-like receptor (TLR) family are major PRR in cells. Upon activation by microbial components, all TLRs except TLR3 recruit Myeloid differentiation primary response 88 (MyD88) with/without Toll/interleukin-1 receptor (TIR) domain-containing adapter protein/MyD88 adapter-like (TIRAP/Mal) (Deguine and Barton, 2014). Intestinal microbiota even drives systemic neutrophil inflammatory response through MyD88 signaling pathways (Karmarkar and Rock, 2013). In turn, MyD88 signaling in T cell modulates IgA secretion and controls gut microbiota composition to protect host (Kubinak et al., 2015). TLR/MyD88 downstream targets include transforming growth factor beta-activated kinase 1 (TAK1)/ I $\kappa$ B kinase (IKK)/nuclear factor  $\kappa$  light chain enhancer of activated B cells (NF- $\kappa$ B) signaling, TAK1/p38 $\alpha$  and JNK, and Phosphatidylinositol 3-kinase (PI3K)/ mammalian target of rapamycin (mTOR) (Brown et al., 2011; Jobin and Sartor, 2000; Kawasaki and Kawai, 2014). Transcription factors of NF- $\kappa$ B, p38 $\alpha$ , and JNK regulates various intestinal cell homeostasis and inflammation in response to host activities and microbial stimuli (Huang et al., 2009; Jobin et al., 1999).

Another family of PPR includes retinoic acid-inducible gene 1 (RIG-I) like receptor (RLR) including RIG-I, melanoma differentiation-associated protein 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2) (Loo and Gale, 2011). (Loo and Gale, 2011). RLR induces production of pro-inflammatory cytokines and type I IFN in response to viral and bacterial nucleic acids in the cytoplasm (Takeuchi and Akira, 2010). Intestinal microbiota of virus activates RIG-I signaling and reduces colitis-associated colorectal cancer (Zhu et al., 2017). (Takeuchi and Akira, 2010). Members of the Nod-like receptor (NLR) family of cytosolic PRR mediate NF- $\kappa$ B activation through Nucleotide-binding oligomerization domain-containing protein (NOD)1 and NOD2 or regulate secretion of the pro-inflammatory cytokines IL1 $\beta$  and IL18 through inflammasomes such as NLR family pyrin domain containing 3 (NLRP3) (Franchi et al., 2009). (Franchi et al., 2009). NOD2 mutations are associated with Crohn's Disease (one type of IBD) and Blau syndrome (Caso et al., 2015), whereas mutations in the CIAS1 (encoding NLRP3) are associated with familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (Ahmadi et al., 2011). Intestinal microbiota sensed by NOD2 is essential for maintaining the homeostasis of intestinal intraepithelial lymphocytes (Jiang et al., 2013). Hyperactive NLRP3 induced IL-1 $\beta$  production

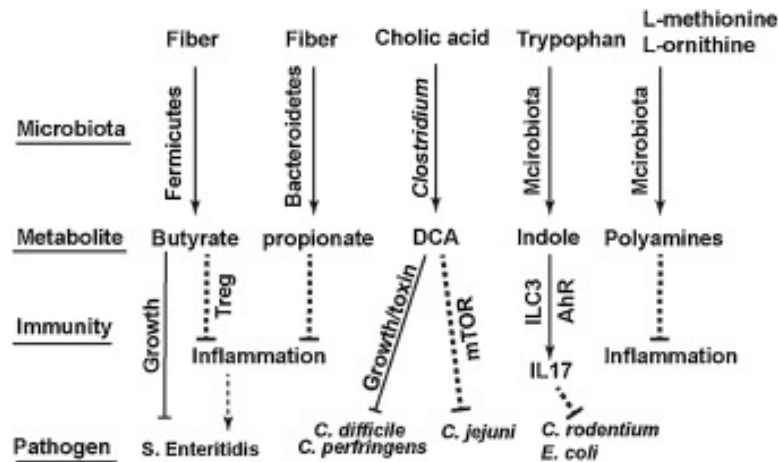
shapes intestinal microbiota to boost Tregs in intestinal lamina propria and resists against intestinal inflammation (Yao et al., 2017).

### 3. Specific members of the microbiome on gut function and immunity

The intestine harbors a complex community of trillions of microbes including bacteria, archaea, virus, and eukarya. These microbes called microbiota, and their metabolic activities and products are collectively defined as the microbiome. The hosts tolerate and form a symbiosis relationship the microbiome (Neish, 2009). The tolerance is mediated through suppressing host immune inflammatory response toward the microbiome. In gut lamina propria, intestinal CD103<sup>+</sup> DCs sense microbiota and its products, become tolerogenic and induce FoxP3<sup>+</sup> Tregs by stimulating CCR7 and integrin- $\alpha_{IV}\beta_7$  on T cells resided in mesenteric lymph nodes (Johansson-Lindbom et al., 2005; Sun et al., 2007; Worthington et al., 2011). The important role of Tregs on sustaining tolerance to microbiome is clearly demonstrated where colitis is developed in CD4<sup>+</sup> transferred SPF mice without Tregs, while no colitis occurs with Tregs (Powrie et al., 1993). The host also actively interacts with microbiome to maintain friendly microbiota composition through secretion of mucin, IgA, and antimicrobial peptides (Caballero and Pamer, 2015; Shapiro et al., 2014; Vaishnavi et al., 2011). Specific members of microbiota play an important role in shaping host health and disease at the local gut and extraintestinal systematic levels. A human commensal bacterium *Bacteroides fragilis* induces Tregs development in the mouse intestine (Round et al., 2011). Clostridia-related bacteria SFB promote Th17 cell differentiation in the mucosa of mouse small intestine, and the cells protect host against enteropathogenic and enterohemorrhagic (EPEC) *Citrobacter rodentium* (counterpart of human pathogen EPEC *E. coli*) infection in the intestine (Ivanov et al., 2009). At a systematic level, higher abundance of intestinal butyrate-producing genus *Odoribacter* has been found to associate with lower blood pressure in overweight and obese pregnant women (Gomez-Arango et al., 2016). Clinical severity of rheumatoid arthritis is associated with the abundance of *Lactobacillus salivarius* in the patients' intestine and oral cavity (Zhang et al., 2015).

Besides gut microbiota modulates host immune response, its constituents are influenced by a variety of factors such as host, age, diet, and others. Despite of mice are frequently utilized to model human microbiota, the similarity of microbiota population between humans and other animals is dog > pig > mice (Coelho et al., 2018). Host T cells modulate IgA secretion through MyD88 and shapes gut microbiota to protect itself (Kubinak et al., 2015). The composition of the healthy adult human microbiota is identified with 2172 prokaryotic species, and 12 different phyla and 93.5% of phyla are Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria (Hugon et al., 2015). Diets influence the spatial distribution of microbiota by providing available nutrients. At ileum, microbiota is colonized with microbes capable of utilizing simple sugars such as *Streptococcus* sp., *Escherichia coli*, *Clostridium* sp. and high G + C organisms (Zoetendal et al., 2012). Colonic microbiota is driven by the availability of microbiota-accessible polysaccharides in dietary fiber. Short term animal-based diet increases the abundance of bile-tolerant microorganisms of *Alistipes*, *Bilophila*, and *Bacteroides* but decreases the ratio of Firmicutes of *Roseburia*, *Eubacterium rectale* and *Ruminococcus bromii* that metabolize dietary plant polysaccharides (David et al., 2014). The constituents of microbiota evolve with aging. The intestinal microbiota of neonates has low diversity and is mainly phyla Proteobacteria and Actinobacteria, but Firmicutes and Bacteroidetes become dominant with aging (Koenig et al.,

2011; Yatsunenکو et al., 2012). Various factors influence infant microbiota development including preterm birth, mode of delivery, infant diet, antibiotic use, environment and lifestyle, host genetics (Dominguez-Bello et al., 2010; Fouhy et al., 2012; Grzeskowiak et al., 2012; Koboziyev et al., 2010; Turnbaugh et al., 2009; Wang et al., 2009). The microbiota of a 2.5-year-old toddler is comparable to that of an adult in terms of composition and diversity (Koenig et al., 2011), suggesting a relatively quick and regulated assembly of infant microbiota.



**Fig. 2.** Intestinal microbiome on immunity and pathogen. Solid/dotted arrow: direct/indirect induction; blunt end dotted line: indirect inhibition; blunt end solid line: direct inhibition. AhR: aryl hydrocarbon receptor.

The intestinal microbiota generates a variety of bioactive metabolites after metabolizing nutrients from diets and host secretion (Fig. 2). These microbial metabolites are actively engaged with gastrointestinal function and immunity. For example, short chain fatty acids (SCFA) are the early finding of microbiota metabolic products with level as high as 131 mM in human colon content (Cummings et al., 1987; Macfarlane and Macfarlane, 2003). The most abundant SCFA is propionate, butyrate, and acetate typically at a ratio of 1:1:3 (Tazoe et al., 2008). Intestinal epithelial cells rapidly absorb the SCFA which regulates a variety of cellular events including gene expression, chemotaxis, differentiation, proliferation and apoptosis (Correa-Oliveira et al., 2016). For regulating immunity, butyrate induces colonic Treg cells (Furusawa et al., 2013) and protects against inflammatory response and tumorigenesis (Lin and Zhang, 2017; Morrison and Preston, 2016). Specifically, intestinal macrophages and DCs sense butyrate via the niacin receptor GPR109a, and lead to elevated IL-10 production, up-regulated retinaldehyde dehydrogenase enzymes, and enhanced Treg cell differentiation (Singh et al., 2014). For supporting intestinal epithelial growth, butyrate was used by colonocytes as an important energy source (Correa-Oliveira et al., 2016). SCFA also attenuates bacterial invasion by modulating gut barrier function, mucin secretion, and inflammatory response (Morrison and Preston, 2016). Besides SCFAs directly interact with and benefit host, they inhibit microbial growth. Various short-chain carboxylic acids are used as food/feed preservative, and butyrate reduces *Salmonella* Enteritidis invasion into epithelial cells (Van Immerseel et al., 2004). SCFAs are metabolites of specific members of intestinal microbiota. Propionate is mainly produced in human gut by Bacteroidetes such as species of *Bacteroides uniformis*, *Prevotella copri*, and *Alistipes putredini*, while the majority of butyrate is generated by Firmicutes including species of *Roseburia intestinalis*, *Eubacterium rectale*, *Coprococcus eutactus*, and *Subdoligranulum variabile* (Louis

and Flint, 2017). Hence, it is possible that colonizing the butyrate-producing bacteria such as *Roseburia intestinalis* may increase IL-17 production against intestine bacterial (e.g., *E. coli*, *Salmonella*) infection in human and animals.

Another group of microbial metabolites with high intestinal concentration are bile acids at 3–30 mM in the human small intestine (Darkoh et al., 2010). Bile acid generation is the primary pathway for cholesterol catabolism and accounts for 50% daily cholesterol turnover (Insull, 2006). Primary bile acids of cholic acid (CA) and chenodeoxycholic acid (CDCA) are synthesized from cholesterol in hepatocytes and conjugated with glycine or taurine (Chiang, 2004). In the intestine, the conjugated primary bile acids are deconjugated by bacterial bile salt hydrolase (BSH) and further altered by microbiota to produce secondary bile acids including lithocholic acid (LCA), deoxycholic acid (DCA), and ursodeoxycholic acid (UDCA). Besides emulsification of lipid for digestion, bile acids are implicated in various signaling pathways including nuclear receptors of farnesoid X receptor (FXR) (Wang et al., 1999), pregnane X receptor (PXR) (Xie et al., 2001), and vitamin D receptor (VDR) (Makishima et al., 2002), as well as G protein-coupled receptors of G-protein-coupled bile acid receptor (TGR5) (Maruyama et al., 2002) and sphingosine-1-phosphate receptor 2 (S1P2) (Studer et al., 2012). CDCA in humans or CA in mice is the most potent FXR ligand, while DCA and LCA are preferential ligands for TGR5 and membrane-type receptor for bile acids (Chiang, 2009; Maruyama et al., 2002). DCA and LCA also activate PXR and VDR (Chiang, 2009). These signaling pathways regulate hepatic lipid, glucose, and energy homeostasis and maintain metabolic homeostasis. Both TGR5 and FXR are expressed by circulating monocytes and macrophages isolated from intestine and liver, and activation of the signaling pathways attenuates inflammatory response (Cipriani et al., 2011; Mencarelli et al., 2009; Vavassori et al., 2009). DCA and LCA induced TGR5 signaling reduces the accumulation and activation of macrophages in aortic plaques and adipose tissues through mechanisms of mTOR-induced C/EBP $\beta$  differential translation (Perino et al., 2014). However, it remains elusive how important it is during health and diseases that host responds to different bile acid species such as CA vs. DCA or LCA vs. DCA. Besides bile acids influence host response, their level is associated with microbial community dynamics in the gut (Ridlon et al., 2014). Bile acids directly inhibit gut microbes (Begley et al., 2005) and indirectly modulate microbiota through FXR-induced antimicrobial peptides (Inagaki et al., 2006). Mice fed CA have increased class Clostridia (70 vs. 39%) compared to control mice, and genus Blautia (including Ruminococcus spp. and *Clostridium* cluster XIVa) expands from 8.3 to 55–62% (Islam et al., 2011). Deconjugating enzyme BSH is present in all major bacterial divisions and archaeal species in the human gut including members of genus *Lactobacilli*, *Bifidobacteria*, *Clostridium*, and *Bacteroides* (Archer et al., 1982; Gilliland and Speck, 1977; Jones et al., 2008; Ridlon et al., 2006). Secondary bile acid producing bacteria consist of a small population of genus *Clostridium*, including *C. scindens*, *C. hiranonis*, *C. hylemonae* (*Clostridium* cluster XVIa), and *C. sordelli* (*Clostridium* cluster XI) (Ridlon et al., 2006). The bile acid-metabolizing bacteria such as *Lactobacilli* and *Bifidobacteria* are probiotics and they enhance health by promoting host immune homeostasis (Vlasova et al., 2013).

Amino acid tryptophan is an important nutrient for both host and microbiota. Xenobiotic aryl hydrocarbon receptor (AhR) is an evolutionarily conserved receptor recognizing environmental compounds. AhR ligands include tryptophan metabolites of kynurenine (Mezrich et al., 2010)



and kynurienic acid (DiNatale et al., 2010) from hosts as well as indole-3-acetate, indole-3-aldehyde, indole, and tryptamine (Hubbard et al., 2015) from microbiota. Dietary ingredients from plants also contain AhR ligands such as flavonoids, stilbenes, carotenoids, and some indoles (Busbee et al., 2013). AhR expressed on ROR $\gamma$ t + ILC3 is essential for their expansion (Kiss et al., 2011). AhR ligands of microbiota tryptophan metabolites induce IL-22 production and the secretion of the anti-microbial peptides lipocalin-2, S100A8, and S100A9 against *Candida albicans* infection (Zelante et al., 2013). Other amino acid metabolites with immune bioactivity are polyamines including putrescine, spermidine, and spermine. Polyamines regulate differentiation of immune cells as well as inflammation (Moinard et al., 2005), and they suppress pulmonary immunologic and intestinal allergic responses (Hoet and Nemery, 2000). Diet ingredients of fruit, cheese, vegetable, meat, and milk are rich in polyamine contents. Most dietary polyamines are absorbed in the small intestine (Uda et al., 2003), while intestinal microbiota produces polyamines in the colon (Matsumoto et al., 2012). Spermine reduces inflammatory cytokine expression in immune cells (Zhang et al., 1997). Microbiota-associated metabolites, such as spermine, histamine, and taurine, regulates host response by activating NLRP6 inflammasome signaling, epithelial IL-18 secretion, and downstream anti-microbial peptides (Levy et al., 2015).

#### **4. Microbiome modulates immunity against intestinal inflammatory diseases**

Despite different etiologies, intestinal diseases in human and animals, such as human IBD, CDI, and campylobacteriosis, chicken necrotic enteritis, and swine postweaning diarrhea share common features of extensive intestinal inflammation (Lippert et al., 2009; Matricon, 2010; Olkowski et al., 2006; Shen, 2012; Xiao et al., 2014) and disturbed microbiota (Antharam et al., 2013; Antonissen et al., 2016; Dou et al., 2017; Lupp et al., 2007; Tamboli et al., 2004). The intestinal inflammation is often characterized by infiltration of immune cells into lamina propria, depletion of goblet cells, hyperplasia of the crypt, or epithelial cell death. At cellular and molecular levels, proinflammatory cytokines from Th1 and Th17 cells and TLR4 signaling pathway drive inflammation in IBD (Oostenbrug et al., 2005; Strober and Fuss, 2011), while Treg cells and NOD2 signaling attenuate the inflammatory response (Eastaff-Leung et al., 2010; Ogura et al., 2001). Inflammation in IBD patients disturbs intestinal microbiota and increases the abundance of Enterobacteriaceae, including *Escherichia coli* and *Fusobacterium* (Darfeuille-Michaud et al., 2004; Lupp et al., 2007; Ohkusa et al., 2002). However, FMT as a therapy for IBD remains uncertain. Some reports have showed little to no efficacy (Ianiro et al., 2014; Kump et al., 2013; Rossen et al., 2015), while others have found remission in active ulcerative colitis (UC) patients at clinical and endoscopic levels (Jeon et al., 2018; Moayyedi et al., 2015). Multiple factors may influence the outcome of FMT against IBD such as the composition of donor and recipient microbiota, age of IBD appearance, and health status of IBD patients. Moreover, IBD is collective diseases with limited understanding on its etiology and it would be more effective to treat IBD using microbiome by targeting specific and limited pathogenic factors.

The most successful case of microbiome treatment of intestinal disease comes from treating CDI by FMT. Recurrent or refractory CDI patients can't be cured with antibiotics but are successfully treated with FMT (Silverman et al., 2010). (Silverman et al., 2010). Later it has been found that secondary bile acids of *Clostridium scindens* metabolites contribute to the decrease of *C. difficile*

growth/colonization and toxin production (Buffie et al., 2015). The role of the microbiome on CDI intestinal inflammation remains to be determined, although CDI induce severe colitis with yellowish pseudomembranous lesions (Surawicz et al., 2013). Another human infectious enteritis is campylobacteriosis which features with severe intestinal inflammation in human (van Spreuwel et al., 1985) and animal model (Lippert et al., 2009). Innate signaling pathway of PI3K/mTOR induces campylobacteriosis (Sun et al., 2013, 2012), while NOD2 protects against it (Sun and Jobin, 2014). Remarkably, anaerobic microbiota and its metabolite DCA prevent campylobacteriosis through inhibiting mTOR signaling pathway in germ-free *Il10<sup>-/-</sup>* mice (Xiaolun Sun et al., 2018). The success of microbiome against CDI and campylobacteriosis is benefit from the available knowledge of the contributing pathogenic factors in the diseases (Seekatz and Young, 2014; Sun et al., 2012).

Comparable to investigating human intestinal diseases, understanding the pathogenic factors and microbiota status is essential for successfully treating animal diseases using microbiome. It is still in the infantile stage of using antimicrobial alternatives such as microbiome to prevent and treat animal intestinal diseases. With the progress in the biomedical field, it is possible to “borrow” the experience from them for accelerating the findings in animal enteritis prevention and treatment. Compared to huge data on human microbiota and its metabolites, animal microbiome research is accelerating, and the results are mounting. For example, when searching for terms “chicken” and “microbiome” with “2014”, “2016” or “2018” on October 8, 2018 on Pubmed, 58, 108, or 133 papers/results, respectively, have been found. In contrast, 4792, 7191, and 6714 results, respectively, were showed when replacing “chicken” with “human”. These accumulating research results on animal microbiome will promote the advancement of using microbiome against animal diseases.

Necrotic enteritis at chicken ileum is reproduced with sequential infection of *Eimeria maxima* and *Clostridium perfringens* (Williams et al., 2003). Necrotic enteritis shows as necrosis intestinal cells and severe inflammation (Olkowski et al., 2006) and altered microbiota (Antonissen et al., 2016). It remains elusive whether the dysbiosis is just a correlation or cause/result of necrotic enteritis. *C. perfringens* expresses a number of toxins such as toxin A and *NetB* (Keyburn et al., 2008), but few reports in the US show that *NetB* positive *C. perfringens* alone induces necrotic enteritis. Inspired from bile acids against CDI and campylobacteriosis, our lab recently found that microbial metabolites primary bile acid CA and secondary bile acid DCA attenuated necrotic enteritis-induced body weight loss, ileal inflammation, and intestinal cell death (Wang et al., 2018). Inhibiting *C. perfringens* virulence (growth/toxin) and inflammatory COX2 signaling by DCA and CA may contribute to necrotic enteritis reduction. It is necessary to further identify additional factors of the precise virulence factors in *C. perfringens*, specific host inflammatory responses, and defined members of microbiome in necrotic enteritis.

Another food animal enteritis is swine postweaning diarrhea caused by infection and overgrowth of enterotoxigenic *Escherichia coli* (ETEC) in small intestine (Kongsted et al., 2013) and disturbed microbiota (Dou et al., 2017). It remains unclear whether the dysbiosis is the cause or result of the enteritis. *Il-17* gene accumulation is increased in piglet infected with ETEC (Luo et al., 2015). IL-17 secreting ILC3 cells protect against infection of *Citrobacter rodentium* (Qiu et al., 2012), a murine counterpart of human enteropathogenic *E. coli*. Furthermore, IL-17 protects

mice against adherent invasive *E. coli* strain LF82 colonization and its induction of colitis through promoting IL-22 (Zhang et al., 2018). As discussed in previous sections, microbiota and its metabolites increase IL-17 secretion (Ivanov et al., 2009; Kiss et al., 2011). Hence,

microbiome (e.g. SFB, indole) could be used to enhance ILC3 or Th17 cells for attenuating ETEC-induced postweaning diarrhea in piglets. Indeed, FMT has been used to improve swine growth performance. FMT increases average daily weight gain of recipient piglets, and reduces diarrhea incidence of the recipients during the trial (Hu et al., 2017). Interestingly, body weight gain and feed efficiency have been reduced in offspring when sows and/or neonatal offspring are treated with FMT using microbiota from high feed efficiency pigs (McCormack et al., 2018). More recently, FMT to treat canine parvovirus in dogs shows faster resolution of diarrhea and shorter hospitalization time, while mortality isn't improved (Pereira et al., 2018). With increasing understanding of the pathogenic factors in swine postweaning diarrhea, it is possible to formulate specific microbiome to attenuate the enteritis.

## 5. Conclusion

Given the pressure to eliminate antimicrobials in food animal regimens, it is ever more important than before to understand the mechanism of host-microbiota interaction and to use the knowledge to prevent and treat enteritis. The development and function of the intestinal immunity, such as adaptive and innate cell activation, is modulated by intestinal microbiota and its metabolic activities and products. Intestinal dysbiosis is often associated with various aberrant inflammatory diseases, including IBD, CDI, campylobacteriosis, chicken necrotic enteritis, swine postweaning diarrhea, and other diseases. Hence, it is possible to manipulate microbiota and/or its metabolic products for “correcting” the dysbiome and/or deviant inflammatory response to prevent and treat the intestinal diseases in animals and humans. Indeed, microbiota reconstitution by FMT is able to prevent or treat a number of intestinal disorders including human CDI, campylobacteriosis in mice, diarrhea in piglets, and canine parvovirus in dogs. Consistently, supplementing microbial metabolite of secondary bile acid DCA prevents campylobacteriosis in mice and necrotic enteritis in chickens. Based on the successful or failed examples of the microbiome intervention on intestinal diseases, it is logic to conclude that a better knowledge on disease etiology and microbiome status during health and the diseases are essential for specifically targeting the pathogenic driving factors to prevent and treat the intestinal diseases. With more and more recognition and participation in the field of microbiome and host response, the success to find antimicrobial alternatives against additional diseases should be within our reach.

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