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 secrets 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).

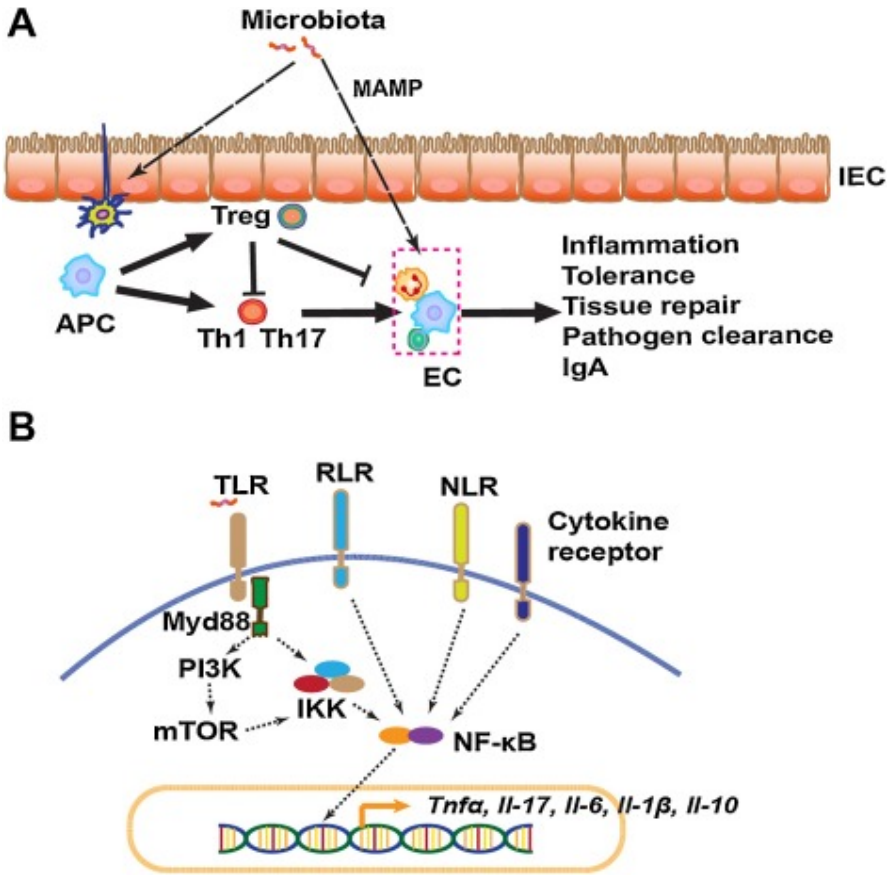

Fig. 1. Schematic intestinal immunity. (A) Microbe induces immune response. APC: antigen presenting cells including dendritic cells (DC) and macrophage. Treg: regulatory T help cell. EC: effect cells including effector T help cells (Th) of Th1 and Th17, innate cells of Granulocytes (neutrophil/heterophil, 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. $CD8^+$ T cells migrate to the intestinal epithelium, while $CD4^+$ 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 $CD4^+$ 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 $CD4^+$ 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 $Foxp3^+$ 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-β (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-1β (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, $CX3CR1^+$ macrophages up-regulate CCR7 and migrate to mesenteric lymph nods, 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 IL1a, 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)/ IκB kinase (IKK)/nuclear factor κ light chain enhancer of activated B cells (NF-κB) signaling, TAK1/p38α 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-κB, p38α, 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-κB activation through Nucleotide-binding oligomerization domain-containing protein (NOD)1 and NOD2 or regulate secretion of the pro-inflammatory cytokines IL1β 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-1β 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 $CD103^+$ DCs sense microbiota and its products, become tolerogenic and induce FoxP3+ Tregs by stimulating CCR7 and integrin-$\alpha_{IV}\beta_7$ on T cells resided in mesenteric lymph nods (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 $CD4^+$ 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; Vaishnava 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; Yatsunenko et al., 2012). Various factors influence infant microbiota development including preterm bird, 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; Koboziev 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.

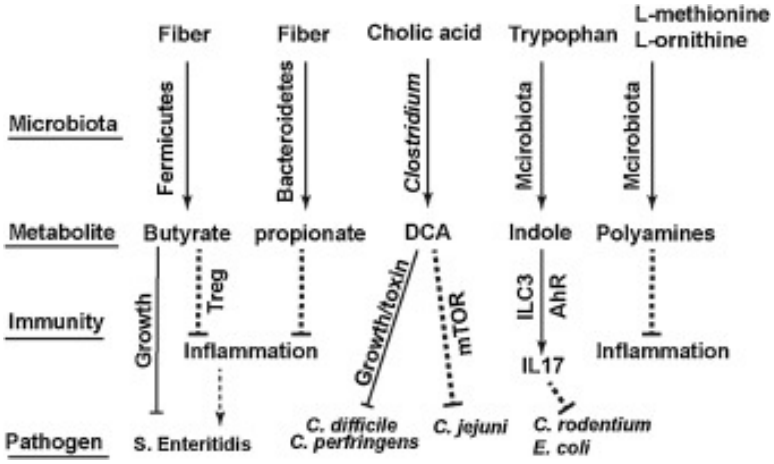

Fig. 2. Intestinal microbiome on immunity and pathogen. Solid/dotted arrow: direct/indirect induction; blunt end dotted line: indirect inhsibition; blunt end solid line: direct inhibition. AhR: aryl hydrocarbon receptor.

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/EBPβ 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 sun 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 RORγt + 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 Spreeuwel 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*$^{-/-}$ 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 discuss in previous sections, microbiota and it 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 regiments, 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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References

Agace, W.W., 2008. T-cell recruitment to the intestinal mucosa. Trends Immunol. 29, 514–522.

Ahmadi, N., Brewer, C.C., Zalewski, C., King, K.A., Butman, J.A., Plass, N., Henderson, C., Goldbach-Mansky, R., Kim, H.J., 2011. Cryopyrin-associated periodic syndromes: otolaryngologic and audiologic manifestations. Otolaryngol. Head. Neck Surg. 145, 295–302.

Akira, S., Uematsu, S., Takeuchi, O., 2006. Pathogen recognition and innate immunity. Cell 124, 783–801.

Antharam, V.C., Li, E.C., Ishmael, A., Sharma, A., Mai, V., Rand, K.H., Wang, G.P., 2013. Intestinal dysbiosis and depletion of butyrogenic bacteria in Clostridium difficile infection and nosocomial diarrhea. J. Clin. Microbiol. 51, 2884–2892.

Antoni, L., Nuding, S., Weller, D., Gersemann, M., Ott, G., Wehkamp, J., Stange, E.F., 2013. Human colonic mucus is a reservoir for antimicrobial peptides. J. Crohns Colitis 7, e652–e664.

Antonissen, G., Eeckhaut, V., Van Driessche, K., Onrust, L., Haesebrouck, F., Ducatelle, R., Moore, R.J., Van Immerseel, F., 2016. Microbial shifts associated with necrotic enteritis. Avian Pathol. 45, 308–312.

Archer, R.H., Chong, R., Maddox, I.S., 1982. Hydrolysis of bile acid conjugates by Clostridium bifermentans. Eur. J. Appl. Microbiol. Biotechnol. 14, 41–45.

Begley, M., Gahan, C.G., Hill, C., 2005. The interaction between bacteria and bile. FEMS Microbiol. Rev. 29, 625–651.

Bennett, C.L., Christie, J., Ramsdell, F., Brunkow, M.E., Ferguson, P.J., Whitesell, L., Kelly, T.E., Saulsbury, F.T., Chance, P.F., Ochs, H.D., 2001. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat. Genet. 27, 20–21.

Brown, J., Wang, H., Hajishengallis, G.N., Martin, M., 2011. TLR-signaling networks: an integration of adaptor molecules, kinases, and cross-talk. J. Dent. Res. 90, 417–427.

Brucklacher-Waldert, V., Carr, E.J., Linterman, M.A., Veldhoen, M., 2014. Cellular plasticity of CD4+ t cells in the intestine. Front. Immunol. 5, 488.

Buffie, C.G., Bucci, V., Stein, R.R., McKenney, P.T., Ling, L., Gobourne, A., No, D., Liu, H., Kinnebrew, M., Viale, A., et al., 2015. Precision microbiome reconstitution restores bile acid mediated resistance to Clostridium difficile. Nature 517, 205–208.

Busbee, P.B., Rouse, M., Nagarkatti, M., Nagarkatti, P.S., 2013. Use of natural AhR ligands as potential therapeutic modalities against inflammatory disorders. Nutr. Rev. 71, 353–369.

Caballero, S., Pamer, E.G., 2015. Microbiota-mediated inflammation and antimicrobial defense in the intestine. Annu. Rev. Immunol. 33, 227–256.

Carulli, A.J., Samuelson, L.C., Schnell, S., 2014. Unraveling intestinal stem cell behavior with models of crypt dynamics. Integr. Biol. (Camb) 6, 243–257.

Casewell, M., Friis, C., Marco, E., McMullin, P., Phillips, I., 2003. The European ban on growth-promoting antibiotics and emerging consequences for human and animal health. J. Antimicrob. Chemother. 52, 159–161.

Caso, F., Galozzi, P., Costa, L., Sfriso, P., Cantarini, L., Punzi, L., 2015. Autoinflammatory granulomatous diseases: from Blau syndrome and early-onset sarcoidosis to NOD2-mediated disease and Crohn's disease. RMD Open 1 e000097.

CDC, 2018. Newly Reported Gene, mcr-1, Threatens Last-Resort Antibiotics. Centers for Disease Control and Prevention. https://www.cdc.gov/drugresistance/solutions-initiative/stories/gene-reported-mcr.html.

Chaudhry, A., Samstein, R.M., Treuting, P., Liang, Y., Pils, M.C., Heinrich, J.M., Jack, R.S., Wunderlich, F.T., Bruning, J.C., Muller, W., et al., 2011. Interleukin-10 signaling in regulatory T cells is required for suppression of Th17 cell-mediated inflammation. Immunity 34, 566–578.

Chiang, J.Y., 2004. Regulation of bile acid synthesis: pathways, nuclear receptors, and mechanisms. J. Hepatol. 40, 539–551.

Chiang, J.Y., 2009. Bile acids: regulation of synthesis. J. Lipid Res. 50, 1955–1966.

Cipriani, S., Mencarelli, A., Chini, M.G., Distrutti, E., Renga, B., Bifulco, G., Baldelli, F., Donini, A., Fiorucci, S., 2011. The bile acid receptor GPBAR-1 (TGR5) modulates integrity of intestinal barrier and immune response to experimental colitis. PLoS One 6 e25637.

Coelho, L.P., Kultima, J.R., Costea, P.I., Fournier, C., Pan, Y., Czarnecki-Maulden, G., Hayward, M.R., Forslund, S.K., Schmidt, T.S.B., Descombes, P., et al., 2018. Similarity of the dog and human gut microbiomes in gene content and response to diet. Microbiome 6, 72.

Collison, L.W., Workman, C.J., Kuo, T.T., Boyd, K., Wang, Y., Vignali, K.M., Cross, R., Sehy, D., Blumberg, R.S., Vignali, D.A., 2007. The inhibitory cytokine IL-35 contributes to regulatory T-cell function. Nature 450, 566–569.

Correa-Oliveira, R., Fachi, J.L., Vieira, A., Sato, F.T., Vinolo, M.A., 2016. Regulation of immune cell function by short-chain fatty acids. Clin. Transl. Immunology 5, e73.

Cummings, J.H., Pomare, E.W., Branch, W.J., Naylor, C.P., Macfarlane, G.T., 1987. Short chain fatty acids in human large intestine, portal, hepatic and venous blood. Gut 28, 1221–1227.

Darfeuille-Michaud, A., Boudeau, J., Bulois, P., Neut, C., Glasser, A.L., Barnich, N., Bringer, M.A., Swidsinski, A., Beaugerie, L., Colombel, J.F., 2004. High prevalence of adherent-invasive Escherichia coli associated with ileal mucosa in Crohn's disease. Gastroenterology 127, 412–421.

Darkoh, C., Lichtenberger, L.M., Ajami, N., Dial, E.J., Jiang, Z.D., DuPont, H.L., 2010. Bile acids improve the antimicrobial effect of rifaximin. Antimicrob. Agents Chemother. 54, 3618–3624.

David, L.A., Maurice, C.F., Carmody, R.N., Gootenberg, D.B., Button, J.E., Wolfe, B.E., Ling, A.V., Devlin, A.S., Varma, Y., Fischbach, M.A., et al., 2014. Diet rapidly and reproducibly alters the human gut microbiome. Nature 505, 559–563.

Deaglio, S., Dwyer, K.M., Gao, W., Friedman, D., Usheva, A., Erat, A., Chen, J.F., Enjyoji, K., Linden, J., Oukka, M., et al., 2007. Adenosine generation catalyzed by CD39 and CD73 expressed on regulatory T cells mediates immune suppression. J. Exp. Med. 204, 1257–1265.

Deguine, J., Barton, G.M., 2014. MyD88: a central player in innate immune signaling. F1000Prime Rep. 6, 97.

Diehl, G.E., Longman, R.S., Zhang, J.X., Breart, B., Galan, C., Cuesta, A., Schwab, S.R., Littman, D.R., 2013. Microbiota restricts trafficking of bacteria to mesenteric lymph nodes by CX(3)CR1(hi) cells. Nature 494, 116–120.

DiNatale, B.C., Murray, I.A., Schroeder, J.C., Flaveny, C.A., Lahoti, T.S., Laurenzana, E.M., Omiecinski, C.J., Perdew, G.H., 2010. Kynurenic acid is a potent endogenous aryl hydrocarbon receptor ligand that synergistically induces interleukin-6 in the presence of inflammatory signaling. Toxicol. Sci. 115, 89–97.

Dominguez-Bello, M.G., Costello, E.K., Contreras, M., Magris, M., Hidalgo, G., Fierer, N., Knight, R., 2010. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc. Natl. Acad. Sci. U.S.A. 107, 11971–11975.

Dou, S., Gadonna-Widehem, P., Rome, V., Hamoudi, D., Rhazi, L., Lakhal, L., Larcher, T., Bahi-Jaber, N., Pinon-Quintana, A., Guyonvarch, A., et al., 2017. Characterisation of Early-Life Fecal Microbiota in Susceptible and Healthy Pigs to Post-Weaning Diarrhoea. PLoS One 12 e0169851.

Eastaff-Leung, N., Mabarrack, N., Barbour, A., Cummins, A., Barry, S., 2010. Foxp3+ regulatory T cells, Th17 effector cells, and cytokine environment in inflammatory bowel disease. J. Clin. Immunol. 30, 80–89.

Eberl, G., Colonna, M., Di Santo, J.P., McKenzie, A.N., 2015. Innate lymphoid cells. Innate lymphoid cells: a new paradigm in immunology. Science 348 aaa6566.

Feng, T., Wang, L., Schoeb, T.R., Elson, C.O., Cong, Y., 2010. Microbiota innate stimulation is a prerequisite for T cell spontaneous proliferation and induction of experimental colitis. J. Exp. Med. 207, 1321–1332.

Fouhy, F., Guinane, C.M., Hussey, S., Wall, R., Ryan, C.A., Dempsey, E.M., Murphy, B., Ross, R.P., Fitzgerald, G.F., Stanton, C., et al., 2012. High-throughput sequencing reveals the incomplete, short-term recovery of infant gut microbiota following parenteral antibiotic treatment with ampicillin and gentamicin. Antimicrob. Agents Chemother. 56, 5811–5820.

Franchi, L., Warner, N., Viani, K., Nunez, G., 2009. Function of Nod-like receptors in microbial recognition and host defense. Immunol. Rev. 227, 106–128.

Furusawa, Y., Obata, Y., Fukuda, S., Endo, T.A., Nakato, G., Takahashi, D., Nakanishi, Y., Uetake, C., Kato, K., Kato, T., et al., 2013. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature 504, 446–450.

Gilliland, S.E., Speck, M.L., 1977. Deconjugation of bile acids by intestinal lactobacilli. Appl. Environ. Microbiol. 33, 15–18.

Gomez-Arango, L.F., Barrett, H.L., McIntyre, H.D., Callaway, L.K., Morrison, M., Dekker Nitert, M., Group, S.T., 2016. Increased systolic and diastolic blood pressure is associated with altered gut microbiota composition and butyrate production in early pregnancy. Hypertension 68, 974–981.

Gondek, D.C., Lu, L.F., Quezada, S.A., Sakaguchi, S., Noelle, R.J., 2005. Cutting edge: contact-mediated suppression by CD4+CD25+ regulatory cells involves a granzyme B-dependent, perforin-independent mechanism. J. Immunol. 174, 1783–1786.

Grzeskowiak, L., Gronlund, M.M., Beckmann, C., Salminen, S., von Berg, A., Isolauri, E., 2012. The impact of perinatal probiotic intervention on gut microbiota: double-blind placebo-controlled trials in Finland and Germany. Anaerobe 18, 7–13.

Harrison, O.J., Powrie, F.M., 2013. Regulatory T Cells and Immune Tolerance in the Intestine. Cold Spring Harbor perspectives in biology.

Hoet, P.H., Nemery, B., 2000. Polyamines in the lung: polyamine uptake and polyamine-linked pathological or toxicological conditions. Am. J. Physiol. Lung Cell Mol. Physiol. 278, L417–L433.

Hu, L., Geng, S., Li, Y., Cheng, S., Fu, X., Yue, X., Han, X., 2017. Exogenous fecal microbiota transplantation from local adult pigs to crossbred newborn piglets. Front. Microbiol. 8, 2663.

Huang, G., Shi, L.Z., Chi, H., 2009. Regulation of JNK and p38 MAPK in the immune system: signal integration, propagation and termination. Cytokine 48, 161–169.

Hubbard, T.D., Murray, I.A., Bisson, W.H., Lahoti, T.S., Gowda, K., Amin, S.G., Patterson, A.D., Perdew, G.H., 2015. Adaptation of the human aryl hydrocarbon receptor to sense microbiota-derived indoles. Sci. Rep. 5, 12689.

Huber, S., Gagliani, N., Flavell, R.A., 2012. Life, death, and miracles: Th17 cells in the intestine. Eur. J. Immunol. 42, 2238–2245.

Hugon, P., Dufour, J.C., Colson, P., Fournier, P.E., Sallah, K., Raoult, D., 2015. A comprehensive repertoire of prokaryotic species identified in human beings. Lancet Infect. Dis. 15, 1211–1219.

Ianiro, G., Bibbo, S., Scaldaferri, F., Gasbarrini, A., Cammarota, G., 2014. Fecal microbiota transplantation in inflammatory bowel disease: beyond the excitement. Medicine (Baltimore) 93, e97.

Inagaki, T., Moschetta, A., Lee, Y.K., Peng, L., Zhao, G., Downes, M., Yu, R.T., Shelton, J.M., Richardson, J.A., Repa, J.J., et al., 2006. Regulation of antibacterial defense in the small intestine by the nuclear bile acid receptor. Proc. Natl. Acad. Sci. U. S. A. 103, 3920–3925.

Insull Jr, W., 2006. Clinical utility of bile acid sequestrants in the treatment of dyslipidemia: a scientific review. South. Med. J. 99, 257–273.

Islam, K.B., Fukiya, S., Hagio, M., Fujii, N., Ishizuka, S., Ooka, T., Ogura, Y., Hayashi, T., Yokota, A., 2011. Bile acid is a host factor that regulates the composition of the cecal microbiota in rats. Gastroenterology 141, 1773–1781.

Ivanov, I.I., Atarashi, K., Manel, N., Brodie, E.L., Shima, T., Karaoz, U., Wei, D., Goldfarb, K.C., Santee, C.A., Lynch, S.V., et al., 2009. Induction of intestinal Th17 cells by segmented filamentous bacteria. Cell 139, 485–498.

Ivanov, I.I., Frutos Rde, L., Manel, N., Yoshinaga, K., Rifkin, D.B., Sartor, R.B., Finlay, B.B., Littman, D.R., 2008. Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine. Cell Host Microbe 4, 337–349.

Jeon, S.R., Chai, J., Kim, C., Lee, C.H., 2018. Current evidence for the management of inflammatory bowel diseases using fecal microbiota transplantation. Curr. Infect. Dis. Rep. 20, 21.

Jiang, W., Wang, X., Zeng, B., Liu, L., Tardivel, A., Wei, H., Han, J., MacDonald, H.R., Tschopp, J., Tian, Z., et al., 2013. Recognition of gut microbiota by NOD2 is essential for the homeostasis of intestinal intraepithelial lymphocytes. J. Exp. Med. 210, 2465–2476.

Jobin, C., Bradham, C.A., Russo, M.P., Juma, B., Narula, A.S., Brenner, D.A., Sartor, R.B., 1999. Curcumin blocks cytokine-mediated NF-kappa B activation and proinflammatory gene expression by inhibiting inhibitory factor I-kappa B kinase activity. J. Immunol. 163, 3474–3483.

Jobin, C., Sartor, R.B., 2000. The I kappa B/NF-kappa B system: a key determinant of mucosalinflammation and protection. Am. J. Physiol. Cell Physiol. 278, C451–462.

Johansson-Lindbom, B., Svensson, M., Pabst, O., Palmqvist, C., Marquez, G., Forster, R., Agace, W.W., 2005. Functional specialization of gut CD103+ dendritic cells in the regulation of tissue-selective T cell homing. J. Exp. Med. 202, 1063–1073.

Jones, B.V., Begley, M., Hill, C., Gahan, C.G., Marchesi, J.R., 2008. Functional and comparative metagenomic analysis of bile salt hydrolase activity in the human gut microbiome. Proc. Natl. Acad. Sci. U.S.A. 105, 13580–13585.

Kaldhusdal, M., Benestad, S.L., Lovland, A., 2016. Epidemiologic aspects of necrotic enteritis in broiler chickens - disease occurrence and production performance. Avian Pathol. 45, 271–274.

Karmarkar, D., Rock, K.L., 2013. Microbiota signalling through MyD88 is necessary for a systemic neutrophilic inflammatory response. Immunology 140, 483–492.

Kawasaki, T., Kawai, T., 2014. Toll-like receptor signaling pathways. Front. Immunol. 5, 461.

Kayama, H., Nishimura, J., Takeda, K., 2013. Regulation of intestinal homeostasis by innate immune cells. Immune Netw. 13, 227–234.

Keyburn, A.L., Boyce, J.D., Vaz, P., Bannam, T.L., Ford, M.E., Parker, D., Di Rubbo, A., Rood, J.I., Moore, R.J., 2008. NetB, a new toxin that is associated with avian necrotic enteritis caused by Clostridium perfringens. PLoS Pathog. 4, e26.

Kiss, E.A., Vonarbourg, C., Kopfmann, S., Hobeika, E., Finke, D., Esser, C., Diefenbach, A., 2011. Natural aryl hydrocarbon receptor ligands control organogenesis of intestinal lymphoid follicles. Science 334, 1561–1565.

Koboziev, I., Karlsson, F., Grisham, M.B., 2010. Gut-associated lymphoid tissue, T cell trafficking, and chronic intestinal inflammation. Ann. New York Acad. of Sci. 1207 (Suppl 1), E86–93.

Koenig, J.E., Spor, A., Scalfone, N., Fricker, A.D., Stombaugh, J., Knight, R., Angenent, L.T., Ley, R.E., 2011. Succession of microbial consortia in the developing infant gut microbiome. Proc. Natl. Acad. Sci. U. S. A. 108 (Suppl 1), 4578–4585.

Kongsted, H., Jonach, B., Haugegaard, S., Angen, O., Jorsal, S.E., Kokotovic, B., Larsen, L.E., Jensen, T.K., Nielsen, J.P., 2013. Microbiological, pathological and histological findings in four Danish pig herds affected by a new neonatal diarrhoea syndrome. BMC Vet. Res. 9, 206.

Korn, T., Bettelli, E., Oukka, M., Kuchroo, V.K., 2009. IL-17 and Th17 cells. Annu. Rev. Immunol. 27, 485–517.

Kreisman, L.S., Cobb, B.A., 2011. Glycoantigens induce human peripheral Tr1 cell differentiation with gut-homing specialization. J. Biol. Chem. 286, 8810–8818.

Kubinak, J.L., Petersen, C., Stephens, W.Z., Soto, R., Bake, E., O'Connell, R.M., Round, J.L., 2015. MyD88 signaling in T cells directs IgA-mediated control of the microbiota to promote health. Cell Host Microbe 17, 153–163.

Kump, P.K., Grochenig, H.P., Lackner, S., Trajanoski, S., Reicht, G., Hoffmann, K.M., Deutschmann, A., Wenzl, H.H., Petritsch, W., Krejs, G.J., et al., 2013. Alteration of intestinal dysbiosis by fecal microbiota transplantation does not induce remission in patients with chronic active ulcerative colitis. Inflamm. Bowel Dis. 19, 2155–2165.

Lahl, K., Loddenkemper, C., Drouin, C., Freyer, J., Arnason, J., Eberl, G., Hamann, A., Wagner, H., Huehn, J., Sparwasser, T., 2007. Selective depletion of Foxp3+ regulatory T cells induces a scurfy-like disease. J. Exp. Med. 204, 57–63.

Levy, M., Thaiss, C.A., Zeevi, D., Dohnalova, L., Zilberman-Schapira, G., Mahdi, J.A., David, E., Savidor, A., Korem, T., Herzig, Y., et al., 2015. Microbiota-Modulated Metabolites Shape the Intestinal Microenvironment by Regulating NLRP6 Inflammasome Signaling. Cell 163, 1428–1443.

Lin, L., Zhang, J., 2017. Role of intestinal microbiota and metabolites on gut homeostasis and human diseases. BMC Immunol. 18, 2.

Lippert, E., Karrasch, T., Sun, X., Allard, B., Herfarth, H.H., Threadgill, D., Jobin, C., 2009. Gnotobiotic IL-10; NF-kappaB mice develop rapid and severe colitis following Campylobacter jejuni infection. PLoS One 4, e7413.

Loo, Y.M., Gale Jr, M., 2011. Immune signaling by RIG-I-like receptors. Immunity 34, 680–692.

Louis, P., Flint, H.J., 2017. Formation of propionate and butyrate by the human colonic microbiota. Environ. Microbiol. 19, 29–41.

Luo, Y., Van Nguyen, U., de la, Fe, Rodriguez, P.Y., Devriendt, B., Cox, E., 2015. F4+ ETEC infection and oral immunization with F4 fimbriae elicits an IL-17-dominated immune response. Vet. Res. 46, 121.

Lupp, C., Robertson, M.L., Wickham, M.E., Sekirov, I., Champion, O.L., Gaynor, E.C., Finlay, B.B., 2007. Host-mediated inflammation disrupts the intestinal microbiota and promotes the overgrowth of Enterobacteriaceae. Cell Host Microbe 2, 204.

Ma, C., Han, M., Heinrich, B., Fu, Q., Zhang, Q., Sandhu, M., Agdashian, D., Terabe, M., Berzofsky, J.A., Fako, V., et al., 2018. Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. Science 360.

Macfarlane, S., Macfarlane, G.T., 2003. Regulation of short-chain fatty acid production. Proc. Nutr. Soc. 62, 67–72.

Mahnke, K., Ring, S., Johnson, T.S., Schallenberg, S., Schonfeld, K., Storn, V., Bedke, T., Enk, A.H., 2007. Induction of immunosuppressive functions of dendritic cells in vivo by CD4+CD25+ regulatory T cells: role of B7-H3 expression and antigen presentation. Eur. J. Immunol. 37, 2117–2126.

Makary, M.A., Kaczmarski, K., Nachman, K., 2018. A call for doctors to recommend antibiotic-free foods: agricultural antibiotics and the public health crisis of antimicrobial resistance. J. Antibiot. 71, 685–687.

Makishima, M., Lu, T.T., Xie, W., Whitfield, G.K., Domoto, H., Evans, R.M., Haussler, M.R., Mangelsdorf, D.J., 2002. Vitamin D receptor as an intestinal bile acid sensor. Science 296, 1313–1316.

Martens, E., Demain, A.L., 2017. The antibiotic resistance crisis, with a focus on the United States. J. Antibiot. 70, 520–526.

Maruyama, T., Miyamoto, Y., Nakamura, T., Tamai, Y., Okada, H., Sugiyama, E., Nakamura, T., Itadani, H., Tanaka, K., 2002. Identification of membrane-type receptor for bile acids (M-BAR). Biochem. Biophys. Res. Commun. 298, 714–719.

Matricon, J., 2010. [Immunopathogenesis of inflammatory bowel disease]. Med. Sci. (Paris) 26, 405–410.

Matsumoto, M., Kibe, R., Ooga, T., Aiba, Y., Kurihara, S., Sawaki, E., Koga, Y., Benno, Y., 2012. Impact of intestinal microbiota on intestinal luminal metabolome. Sci. Rep. 2, 233.

McCormack, U.M., Curiao, T., Wilkinson, T., Metzler-Zebeli, B.U., Reyer, H., Ryan, T., Calderon-Diaz, J.A., Crispie, F., Cotter, P.D., Creevey, C.J., et al., 2018. Fecal microbiota transplantation in gestating sows and neonatal offspring alters lifetime intestinal microbiota and growth in offspring. mSystems 3.

McGann, P., Snesrud, E., Maybank, R., Corey, B., Ong, A.C., Clifford, R., Hinkle, M., Whitman, T., Lesho, E., Schaecher, K.E., 2016. Escherichia Coli Harboring mcr-1 and blaCTX-M on a Novel IncF Plasmid: First Report of mcr-1 in the USA. Antimicrobial agents and chemotherapy.

Mencarelli, A., Renga, B., Migliorati, M., Cipriani, S., Distrutti, E., Santucci, L., Fiorucci, S., 2009. The bile acid sensor farnesoid X receptor is a modulator of liver immunity in a rodent model of acute hepatitis. J. Immunol. 183, 6657–6666.

Mezrich, J.D., Fechner, J.H., Zhang, X., Johnson, B.P., Burlingham, W.J., Bradfield, C.A., 2010. An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. J. Immunol. 185, 3190–3198.

Moayyedi, P., Surette, M.G., Kim, P.T., Libertucci, J., Wolfe, M., Onischi, C., Armstrong, D., Marshall, J.K., Kassam, Z., Reinisch, W., et al., 2015. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. Gastroenterology 149 102-109 e106.

Moinard, C., Cynober, L., de Bandt, J.P., 2005. Polyamines: metabolism and implications in human diseases. Clin. Nutr. 24, 184–197.

Morrison, D.J., Preston, T., 2016. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. Gut Microbes 7, 189–200.

Mowat, A.M., 2003. Anatomical basis of tolerance and immunity to intestinal antigens. Nat. Rev. Immunol. 3, 331–341.

Neish, A.S., 2009. Microbes in gastrointestinal health and disease. Gastroenterology 136, 65–80.

Neu, H.C., 1992. The crisis in antibiotic resistance. Science 257, 1064–1073.

Niewold, T.A., 2007. The nonantibiotic anti-inflammatory effect of antimicrobial growth promoters, the real mode of action? A hypothesis. Poult. Sci. 86, 605–609.

Ogura, Y., Bonen, D.K., Inohara, N., Nicolae, D.L., Chen, F.F., Ramos, R., Britton, H., Moran, T., Karaliuskas, R., Duerr, R.H., et al., 2001. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature 411, 603–606.

Ohkusa, T., Sato, N., Ogihara, T., Morita, K., Ogawa, M., Okayasu, I., 2002. Fusobacterium varium localized in the colonic mucosa of patients with ulcerative colitis stimulates species-specific antibody. J. Gastroenterol. Hepatol. 17, 849–853.

Olkowski, A.A., Wojnarowicz, C., Chirino-Trejo, M., Drew, M.D., 2006. Responses of broiler chickens orally challenged with Clostridium perfringens isolated from field cases of necrotic enteritis. Res. Vet. Sci. 81, 99–108.

Oostenbrug, L.E., Drenth, J.P., de Jong, D.J., Nolte, I.M., Oosterom, E., van Dullemen, H.M., van der Linde, K., te Meerman, G.J., van der Steege, G., Kleibeuker, J.H., et al., 2005. Association between Toll-like receptor 4 and inflammatory bowel disease. Inflamm. Bowel Dis. 11, 567–575.

Pereira, G.Q., Gomes, L.A., Santos, I.S., Alfieri, A.F., Weese, J.S., Costa, M.C., 2018. Fecal microbiota transplantation in puppies with canine parvovirus infection. J. Vet. Intern. Med. 32, 707–711.

Perino, A., Pols, T.W., Nomura, M., Stein, S., Pellicciari, R., Schoonjans, K., 2014. TGR5 reduces macrophage migration through mTOR-induced C/EBPbeta differential translation. J. Clin. Invest. 124, 5424–5436.

Powrie, F., Carlino, J., Leach, M.W., Mauze, S., Coffman, R.L., 1996. A critical role for transforming growth factor-beta but not interleukin 4 in the suppression of T helper type 1-mediated colitis by CD45RB(low) CD4+ T cells. J. Exp. Med. 183, 2669–2674.

Powrie, F., Leach, M.W., Mauze, S., Caddle, L.B., Coffman, R.L., 1993. Phenotypically distinct subsets of CD4+ T cells induce or protect from chronic intestinal inflammation in C. B-17 scid mice. Int. Immunol. 5, 1461–1471.

Qiu, J., Heller, J.J., Guo, X., Chen, Z.M., Fish, K., Fu, Y.X., Zhou, L., 2012. The aryl hydrocarbon receptor regulates gut immunity through modulation of innate lymphoid cells. Immunity 36, 92–104.

Quraishi, M.N., Widlak, M., Bhala, N., Moore, D., Price, M., Sharma, N., Iqbal, T.H., 2017. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory Clostridium difficile infection. Aliment. Pharmacol. Ther. 46, 479–493.

Rhouma, M., Beaudry, F., Theriault, W., Bergeron, N., Laurent-Lewandowski, S., Fairbrother, J.M., Letellier, A., 2015. Gastric stability and oral bioavailability of colistin sulfate in pigs challenged or not with Escherichia coli O149: F4 (K88). Res. Vet. Sci. 102, 173–181.

Ridlon, J.M., Kang, D.J., Hylemon, P.B., 2006. Bile salt biotransformations by human intestinal bacteria. J. Lipid Res. 47, 241–259.

Ridlon, J.M., Kang, D.J., Hylemon, P.B., Bajaj, J.S., 2014. Bile acids and the gut microbiome. Curr. Opin. Gastroenterol. 30, 332–338.

Rossen, N.G., Fuentes, S., van der Spek, M.J., Tijssen, J.G., Hartman, J.H., Duflou, A., Lowenberg, M., van den Brink, G.R., Mathus-Vliegen, E.M., de Vos, W.M., et al., 2015. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. Gastroenterology 149 110-118 e114.

Round, J.L., Lee, S.M., Li, J., Tran, G., Jabri, B., Chatila, T.A., Mazmanian, S.K., 2011. The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. Science 332, 974–977.

Sawa, S., Lochner, M., Satoh-Takayama, N., Dulauroy, S., Berard, M., Kleinschek, M., Cua, D., Di Santo, J.P., Eberl, G., 2011. RORgammat+ innate lymphoid cells regulate intestinal homeostasis by integrating negative signals from the symbiotic microbiota. Nat. Immunol. 12, 320–326.

Schaefer, L., 2014. Complexity of danger: the diverse nature of damage-associated molecular patterns. J. Biol. Chem. 289, 35237–35245.

Seekatz, A.M., Young, V.B., 2014. Clostridium difficile and the microbiota. J. Clin. Invest. 124, 4182–4189.

Severson, K.M., Mallozzi, M., Driks, A., Knight, K.L., 2010. B cell development in GALT: role of bacterial superantigen-like molecules. J. Immunol. 184, 6782–6789.

Shankar, V., Hamilton, M.J., Khoruts, A., Kilburn, A., Unno, T., Paliy, O., Sadowsky, M.J., 2014. Species and genus level resolution analysis of gut microbiota in Clostridium difficile patients following fecal microbiota transplantation. Microbiome 2, 13.

Shapiro, H., Thaiss, C.A., Levy, M., Elinav, E., 2014. The cross talk between microbiota and the immune system: metabolites take center stage. Curr. Opin. Immunol. 30, 54–62.

Shen, A., 2012. Clostridium difficile toxins: mediators of inflammation. J. Innate Immun. 4, 149–158.

Shroff, K.E., Meslin, K., Cebra, J.J., 1995. Commensal enteric bacteria engender a self-limiting humoral mucosal immune response while permanently colonizing the gut. Infect. Immun. 63, 3904–3913.

Silverman, M.S., Davis, I., Pillai, D.R., 2010. Success of self-administered home fecal transplantation for chronic Clostridium difficile infection. Clin. Gastroenterol. Hepatol. 8, 471–473.

Singh, N., Gurav, A., Sivaprakasam, S., Brady, E., Padia, R., Shi, H., Thangaraju, M., Prasad, P.D., Manicassamy, S., Munn, D.H., et al., 2014. Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. Immunity 40, 128–139.

Spencer, S.P., Wilhelm, C., Yang, Q., Hall, J.A., Bouladoux, N., Boyd, A., Nutman, T.B., Urban Jr., J.F., Wang, J., Ramalingam, T.R., et al., 2014. Adaptation of innate lymphoid cells to a micronutrient deficiency promotes type 2 barrier immunity. Science 343, 432–437.

Strober, W., Fuss, I.J., 2011. Proinflammatory Cytokines in the Pathogenesis of Inflammatory Bowel Diseases. Gastroenterology 140 1756-1767.e1751.

Studer, E., Zhou, X., Zhao, R., Wang, Y., Takabe, K., Nagahashi, M., Pandak, W.M., Dent, P., Spiegel, S., Shi, R., et al., 2012. Conjugated bile acids activate the sphingosine-1-phosphate receptor 2 in primary rodent hepatocytes. Hepatology 55, 267–276.

Sun, C.M., Hall, J.A., Blank, R.B., Bouladoux, N., Oukka, M., Mora, J.R., Belkaid, Y., 2007. Small intestine lamina propria dendritic cells promote de novo generation of Foxp3 T reg cells via retinoic acid. J. Exp. Med. 204, 1775–1785.

Sun, X., Jobin, C., 2014. Nucleotide-binding oligomerization domain-containing protein 2 controls host response to Campylobacter jejuni in Il10-/- mice. J. Infect. Dis. 210, 1145–1154.

Sun, X., Liu, B., Sartor, R.B., Jobin, C., 2013. Phosphatidylinositol 3-kinase-gamma signaling promotes Campylobacter jejuni-induced colitis through neutrophil recruitment in mice. J. Immunol. 190, 357–365.

Sun, X., Threadgill, D., Jobin, C., 2012. Campylobacter jejuni induces colitis through activation of mammalian target of rapamycin signaling. Gastroenterology 142 86-95 e85.

Surawicz, C.M., Brandt, L.J., Binion, D.G., Ananthakrishnan, A.N., Curry, S.R., Gilligan, P.H., McFarland, L.V., Mellow, M., Zuckerbraun, B.S., 2013. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am. J. Gastroenterol. 108, 478–498 quiz 499.

Taams, L.S., van Eden, W., Wauben, M.H., 1999. Antigen presentation by T cells versus professional antigen-presenting cells (APC): differential consequences for T cell activation and subsequent T cell-APC interactions. Eur. J. Immunol. 29, 1543–1550.

Takeuchi, O., Akira, S., 2010. Pattern recognition receptors and inflammation. Cell 140, 805–820.

Tamboli, C.P., Neut, C., Desreumaux, P., Colombel, J.F., 2004. Dysbiosis in inflammatory bowel disease. Gut 53, 1–4.

Tang, K.L., Caffrey, N.P., Nobrega, D.B., Cork, S.C., Ronksley, P.E., Barkema, H.W., Polachek, A.J., Ganshorn, H., Sharma, N., Kellner, J.D., et al., 2017. Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. Lancet Planet. Health 1, e316–e327.

Tazoe, H., Otomo, Y., Kaji, I., Tanaka, R., Karaki, S.I., Kuwahara, A., 2008. Roles of short-chain fatty acids receptors, GPR41 and GPR43 on colonic functions. J Physiol Pharmacol 59 Suppl 2, 251–262.

Turnbaugh, P.J., Hamady, M., Yatsunenko, T., Cantarel, B.L., Duncan, A., Ley, R.E., Sogin, M.L., Jones, W.J., Roe, B.A., Affourtit, J.P., et al., 2009. A core gut microbiome in obese and lean twins. Nature 457, 480–484.

Uda, K., Tsujikawa, T., Fujiyama, Y., Bamba, T., 2003. Rapid absorption of luminal polyamines in a rat small intestine ex vivo model. J. Gastroenterol. Hepatol. 18, 554–559.

Ueda, Y., Kayama, H., Jeon, S.G., Kusu, T., Isaka, Y., Rakugi, H., Yamamoto, M., Takeda, K., 2010. Commensal microbiota induce LPS hyporesponsiveness in colonic macrophages via the production of IL-10. Int. Immunol. 22, 953–962.

Vaishnava, S., Yamamoto, M., Severson, K.M., Ruhn, K.A., Yu, X., Koren, O., Ley, R., Wakeland, E.K., Hooper, L.V., 2011. The antibacterial lectin RegIIIgamma promotes the spatial segregation of microbiota and host in the intestine. Science 334, 255–258.

van de Pavert, S.A., Ferreira, M., Domingues, R.G., Ribeiro, H., Molenaar, R., Moreira-Santos, L., Almeida, F.F., Ibiza, S., Barbosa, I., Goverse, G., et al., 2014. Maternal retinoids control type 3 innate lymphoid cells and set the offspring immunity. Nature 508, 123–127.

Van Immerseel, F., De Buck, J., De Smet, I., Pasmans, F., Haesebrouck, F., Ducatelle, R., 2004. Interactions of butyric acid- and acetic acid-treated Salmonella with chicken primary cecal epithelial cells in vitro. Avian Dis. 48, 384–391.

Van Puyvelde, S., Deborggraeve, S., Jacobs, J., 2018. Why the antibiotic resistance crisis requires a one Health approach. Lancet Infect. Dis. 18, 132–134.

van Spreeuwel, J.P., Duursma, G.C., Meijer, C.J., Bax, R., Rosekrans, P.C., Lindeman, J., 1985. Campylobacter colitis: histological immunohistochemical and ultrastructural findings. Gut 26, 945–951.

Vavassori, P., Mencarelli, A., Renga, B., Distrutti, E., Fiorucci, S., 2009. The bile acid receptor FXR is a modulator of intestinal innate immunity. J. Immunol. 183, 6251–6261.

Vlasova, A.N., Chattha, K.S., Kandasamy, S., Liu, Z., Esseili, M., Shao, L., Rajashekara, G., Saif, L.J., 2013. Lactobacilli and bifidobacteria promote immune homeostasis by modulating innate immune responses to human rotavirus in neonatal gnotobiotic pigs. PLoS One 8 e76962.

von Burg, N., Turchinovich, G., Finke, D., 2015. Maintenance of immune homeostasis through ILC/T cell interactions. Front. Immunol. 6, 416.

Wang, H., Chen, J., Hollister, K., Sowers, L.C., Forman, B.M., 1999. Endogenous bile acids are ligands for the nuclear receptor FXR/BAR. Mol. Cell 3, 543–553.

Wang, H., Latorre Cardenas, J.D., Bansal, M., Al-Rubaye, B., Tellez, G., Hargis, B., Sun, X., 2018. Microbiota Metabolic Product Deoxycholic Acid Controls Chicken Necrotic Enteritis. bioRxiv.

Wang, Y., Hoenig, J.D., Malin, K.J., Qamar, S., Petrof, E.O., Sun, J., Antonopoulos, D.A., Chang, E.B., Claud, E.C., 2009. 16S rRNA gene-based analysis of fecal microbiota from preterm infants with and without necrotizing enterocolitis. ISME J. 3, 944–954.

WHO, 2018a. Antimicrobial Resistance. World Health Organization. http://www.who.int/en/news-room/fact-sheets/detail/antimicrobial-resistance.

WHO, 2018b. Tuberculosis. World Health Organization. http://www.who.int/newsroom/fact-sheets/detail/tuberculosis.

Williams, R.B., Marshall, R.N., La Ragione, R.M., Catchpole, J., 2003. A new method for the experimental production of necrotic enteritis and its use for studies on the relationships between necrotic enteritis, coccidiosis and anticoccidial vaccination of chickens. Parasitol. Res. 90, 19–26.

Worthington, J.J., Czajkowska, B.I., Melton, A.C., Travis, M.A., 2011. Intestinal dendritic cells specialize to activate transforming growth factor-beta and induce Foxp3+ regulatory T cells via integrin alphavbeta8. Gastroenterology 141, 1802–1812.

Xiao, D., Wang, Y., Liu, G., He, J., Qiu, W., Hu, X., Feng, Z., Ran, M., Nyachoti, C.M., Kim, S.W., et al., 2014. Effects of chitosan on intestinal inflammation in weaned pigs challenged by enterotoxigenic Escherichia coli. PLoS One 9 e104192.

Xiaolun Sun, K.W., Raad Z. Gharaibeh, Josee Gauthier, Zhen He, Prabhanshu Tripathi, Dorina Avram, Steven Bruner, Anthony A. Fodor, Christian Jobin (2018). Microbiota-derived Metabolic Factors Reduce Campylobacteriosis in Mice. Gastroenterology In Press.

Xie, W., Radominska-Pandya, A., Shi, Y., Simon, C.M., Nelson, M.C., Ong, E.S., Waxman, D.J., Evans, R.M., 2001. An essential role for nuclear receptors SXR/PXR in detoxification of cholestatic bile acids. Proc. Natl. Acad. Sci. U. S. A. 98, 3375–3380.

Yao, X., Zhang, C., Xing, Y., Xue, G., Zhang, Q., Pan, F., Wu, G., Hu, Y., Guo, Q., Lu, A., et al., 2017. Remodelling of the gut microbiota by hyperactive NLRP3 induces regulatory T cells to maintain homeostasis. Nat. Commun. 8, 1896.

Yatsunenko, T., Rey, F.E., Manary, M.J., Trehan, I., Dominguez-Bello, M.G., Contreras, M., Magris, M., Hidalgo, G., Baldassano, R.N., Anokhin, A.P., et al., 2012. Human gut microbiome viewed across age and geography. Nature 486, 222–227.

Zelante, T., Iannitti, R.G., Cunha, C., De Luca, A., Giovannini, G., Pieraccini, G., Zecchi, R., D'Angelo, C., Massi-Benedetti, C., Fallarino, F., et al., 2013. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. Immunity 39, 372–385.

Zhang, H.J., Xu, B., Wang, H., Xu, B., Wang, G.D., Jiang, M.Z., Lei, C., Ding, M.L., Yu, P.F., Nie, Y.Z., et al., 2018. IL-17 is a protection effector against the adherent-invasive Escherichia coli in murine colitis. Mol. Immunol. 93, 166–172.

Zhang, M., Caragine, T., Wang, H., Cohen, P.S., Botchkina, G., Soda, K., Bianchi, M., Ulrich, P., Cerami, A., Sherry, B., et al., 1997. Spermine inhibits proinflammatory cytokine synthesis in human mononuclear cells: a counterregulatory mechanism that restrains the immune response. J. Exp. Med. 185, 1759–1768.

Zhang, X., Zhang, D., Jia, H., Feng, Q., Wang, D., Liang, D., Wu, X., Li, J., Tang, L., Li, Y., et al., 2015. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. Nat. Med. 21, 895–905.

Zhu, H., Xu, W.Y., Hu, Z., Zhang, H., Shen, Y., Lu, S., Wei, C., Wang, Z.G., 2017. RNA virus receptor Rig-I monitors gut microbiota and inhibits colitis-associated colorectal cancer. J. Exp. Clin. Cancer Res. 36, 2.

Zoetendal, E.G., Raes, J., van den Bogert, B., Arumugam, M., Booijink, C.C., Troost, F.J., Bork, P., Wels, M., de Vos, W.M., Kleerebezem, M., 2012. The human small intestinal microbiota is driven by rapid uptake and conversion of simple carbohydrates. ISME J. 6, 1415–1426.

Zuniga, L.A., Jain, R., Haines, C., Cua, D.J., 2013. Th17 cell development: from the cradle to the grave. Immunol. Rev. 252, 78–88.