The Roles of Inflammation, Nutrient Availability and the Commensal Microbiota in Enteric Pathogen Infection

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ABSTRACT The healthy human intestine is colonized by as many as 10^{14} bacteria belonging to more than 500 different species forming a microbial ecosystem of unsurpassed diversity, termed the microbiota. The microbiota’s various bacterial members engage in a physiological network of cooperation and competition within several layers of complexity. Within the last 10 years, technological progress in the field of next-generation sequencing technologies has tremendously advanced our understanding of the wide variety of physiological and pathological processes that are influenced by the commensal microbiota [1, 2]. An increasing number of human disease conditions, such as inflammatory bowel diseases (IBD), type 2 diabetes, obesity and colorectal cancer are linked with altered microbiota composition [3]. Moreover, a clearer picture is emerging of the composition of the human microbiota in healthy individuals, its variability over time and between different persons and how the microbiota is shaped by environmental factors (i.e., diet) and the host’s genetic background [4].

A general feature of a normal, healthy gut microbiota can generate conditions in the gut that disfavor colonization of enteric pathogens. This is termed colonization-resistance (CR). Upon disturbance of the microbiota, CR can be transiently disrupted, and pathogens can gain the opportunity to grow to high levels. This disruption can be caused by exposure to antibiotics [5, 6], changes in diet [7, 8], application of probiotics and drugs [9], and a variety of diseases [3]. Breakdown of CR can boost colonization by intrinsic pathogens or increase susceptibility to infections [10]. One consequence of pathogen expansion is the triggering of inflammatory host responses and pathogen-mediated disease. Interestingly, human enteric pathogens are part of a small group of bacterial families that belong to the Proteobacteria: the Enterobacteriaceae (E. coli, Yersinia spp., Salmonella spp., Shigella spp.), the Vibrionaceae (Vibrio cholerae) and the Campylobacteriaceae (Campylobacter spp.). In general, members of these families (be it commensals or pathogens) only constitute a minority of the intestinal microbiota. However, proteobacterial “blooms” are a characteristic trait of an abnormal microbiota such as in the course of antibiotic therapy, dietary changes or inflammation [11].

It has become clear that the gut microbiota not only plays a major role in priming and regulating mucosal and systemic immunity, but that the immune system also contributes to host control over microbiota composition. These two ways of mutual communication between the microbiota and the immune system were coined as “outside-in” and “inside-out,” respectively [12]. The significance of those interactions for human health is particularly evident in Crohn’s disease (CD) and Ulcerative Colitis (UC). The symptoms of these recurrent, chronic types of gut inflammation are caused by an excessive immune response against one’s own commensal microbiota [13]. It is assumed that deregulated immune responses can be caused by a genetic predisposition, leading to, for example, the impairment of intestinal barrier function or disruption of mucosal T-cell homeostasis.

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In CD or UC patients, an abnormally composed microbiota, referred to as “dysbiosis,” is commonly observed (discussed later). This is often characterized by an increased relative abundance of facultative anaerobic bacteria (e.g., Enterobacteriaceae, Bacilli) and, at the same time, depletion of obligate anaerobic bacteria of the classes Bacteroidia and Clostridia. So far, it is unclear whether dysbiosis is a cause or a consequence of inflammatory bowel disease (IBD). In fact, both scenarios are equally conceivable.

Recent work suggests that inflammatory immune responses in the gut (both IBD and pathogen-induced) can alter the gut luminal milieu in a way that favors dysbiosis [14]. In this chapter, I present a survey on our current state of understanding of the characteristics and mechanisms underlying gut inflammation-associated dysbiosis. The role of dysbiosis in enteric infections and human IBD is discussed. In addition, I will focus on competition of enteric pathogens and the gut microbiota in the inflamed gut and the role of dysbiotic microbiota alterations (e.g., "Enterobacterial blooms" [11]) for the evolution of pathogenicity.

CHARACTERISTICS AND MECHANISMS OF INFLAMMATION-MEDIATED DYBSIOSIS

Characteristics of the Inflammation-Associated Gut Microbiota

Genetic susceptibility, the mucosal immune system, and environmental factors such as the microbiota, stress, and diet, contribute to the pathogenesis of inflammatory bowel disease (IBD) [15]. Involvement of the microbiota has been proposed early on, as microbiota manipulation by antibiotics or probiotics can treat or alleviate IBD symptoms in humans. In experimental animal models, the gut luminal microbiota is required for the induction of chronic inflammation [16]. Different theories about how the microbiota is involved in the pathogenesis of IBD have been proposed. (1) Mutations that lead to a defective mucosal barrier function (e.g., mucus layer, innate killing, antimicrobial peptides) involve excessive translocation of commensal bacteria and triggering of proinflammatory signalling cascades. (2) Abnormal host immune regulation induces an overshooting immune response against intrinsic commensal bacteria. (3) The presence of an unidentified pathogen leads to induction of the disease or (4), a dysbiotic microbiota, characterized by an imbalance between “beneficial” and “potentially harmful” commensal bacteria, acts as a trigger or driver of the disease. The latter theory has been challenged by studies conducted in experimental rodent models: inflammatory disease conditions in the course of chronic colitis or enteropathogen infection can disrupt normal microbiota composition, induce dysbiosis, and favor overgrowth of pathogens and commensals with an increased virulence potential [10, 14, 17]. Therefore, dysbiosis may not only be considered as a cause but also a consequence of gut inflammation.

What are the characteristics of IBD associated dysbiosis? Before methods for culture-independent microbiota analysis became available, several studies revealed alterations in mucosal and fecal microbiota composition in IBD patients. Some surveys already revealed an increase in the aerobic members of the microbiota [18–20]. These early investigations using bacterial culturing methods were confirmed and extended by numerous recent studies in patient and control cohorts as well as in animal models using molecular, culture-independent techniques such as 16S rRNA gene-sequencing [21] and metagenomics [22]. A general picture on the nature of inflammation-induced dysbiosis is gradually emerging: Most studies report a significantly decreased microbial diversity in active IBD, decreased abundance of particular obligate anaerobic Gram-positive bacteria (e.g., Ruminococcaceae, Lachnospiraceae), and a concomitant increase in facultative anaerobic bacteria such as Enterococci and Streptococci [23, 24] as well as Gram-negative Proteobacteria (in particular members of the Enterobacteriaceae) [21, 25, 26]. A decrease of Faecalibacterium prausnitzii [27, 28], an abundant butyrate-producer in the human gut [29], has been proposed as a microbial marker for active disease. Reports on changes in other bacterial groups are somewhat contradictory. Some studies observe depletion of Bacteroidetes [21, 25], while others report enrichment [30, 31]. No consistent changes in the abundance of the “probiotic” Lactobacilli and Actinobacteria (i.e., Bifidobacteria) in IBD were observed. In any case, most studies agree in terms of a significant enrichment of Enterobacteriaceae, particularly E. coli, in mucosa-associated and fecal microbiota of IBD patients. In Crohn’s disease patients, a disease-specific novel E. coli pathotype, termed adherent invasive E. coli (AIEC) was described [32, 33]. Numbers of AIEC are not only elevated in the inflamed gut lumen, but they were also found to exacerbate the disease (second section). Similarly, enrichment of E. coli is also observed in experimental rodent colitis models based on genetic defects [34, 35], chemical induction [36, 37], or pathogen infection [38–40]. This condition is termed Enterobacterial “blooms” [11].

A number of enteric pathogens are also able to exploit inflammatory responses for their own benefit. In the healthy intestine, the complex anaerobic microbiota efficiently blocks colonization and infection of the major human enteric pathogens. This “colonization resistance” is alleviated in the presence of gut inflammation and
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enables pathogen overgrowth. Prominent examples include *Citrobacter rodentium*, the agent of murine transmissible colonic hyperplasia; *Campylobacter jejuni*; and *Salmonella enterica* serovar Typhimurium (*S. Typhimurium*), which causes enterocolitis in humans (36, 38). A number of studies suggest that other pathogens such as *Klebsiella pneumoniae*, *Proteus mirabilis* (35), *Vibrio cholerae* (41), *Clostridium difficile* (42), and *Enterococcus* spp. (38, 43), may also benefit from an inflammatory milieu in the gut. Thus, an inflammatory milieu in the gut can alter survival, attachment, or growth of enteric pathogens and related commensal species.

**Mechanisms triggering inflammation-induced dysbiosis and Enterobacterial “blooms”**

Why do inflammatory conditions in the gut provide an advantage to facultative anaerobes and suppress many of the normally abundant anaerobic members of the microbiota? Different explanations have already been proposed: The “food hypothesis” suggests that inflamed intestine offers an altered nutrient spectrum or adhesion receptor sites that can be exploited only by a subset of bacteria. Alternatively (or additionally), antibacterial effector mechanisms released by the inflamed mucosa may selectively inhibit or kill a large part of the intrinsic microbiota, while the more “hardy” enteric pathogens and their close relatives among the commensals would remain unaffected (“differential killing hypothesis”). Over the past years, key studies in the field uncovered a number of underlying mechanisms about how mucosal inflammation supports overgrowth of resident or experimentally introduced facultative anaerobic members, in particular the family members of the *Enterobacteriaceae*. These mechanisms are illustrated later in the chapter.

**Physiology of facultative anaerobic members of the microbiota**

*Enterobacteriaceae*, *Enterococcus* spp., *Streptococcus* spp., and *Staphylococcus* spp. are prominent facultative anaerobes of the human fecal microbiota. Right after birth, these species are among the first colonizers of the infant gut and continue to be dominant during early life (44–46). In contrast, they represent only a minor fraction of the microbiota of adults, because facultative anaerobes are suppressed by the obligate anaerobic microbiota (47, 48). Interestingly, enrichment of facultative anaerobes is not only observed upon inflammation-induced dysbiosis but also upon broad-spectrum antimicrobial chemotherapy (antibiotic treatment). Antibiotic-caused disruption of the microbiota and depletion of its obligate anaerobic members lead to overgrowth of γ-Proteobacteria and Gram positive cocci (49, 50). This suggests that facultative anaerobic members of the microbiota share common physiologic properties that allow them to overgrow if the microbiota is disturbed.

What are the characteristics of these facultative anaerobic bacteria? *E. coli* can be considered the “work horse” of fundamental and molecular microbiology. This model organism enabled the discovery of a number of metabolic pathways of which homologues exist in many other species (51). The species *E. coli* includes commensal and different pathogenic strains (pathotypes) exhibiting different lifestyles. Accordingly, more than 20% of an *E. coli* genome represents strain-specific genes (degradation processes, virulence factors) (52, 53). Variable genes show to a great part an ancestry of horizontal gene transfer (i.e., plasmids, genomic islands, prophages and transposons). The conserved genes (core genome) comprise the pathways for central biosynthetic metabolism. *E. coli* can use a wide variety of carbon sources that are abundantly available in the mammalian intestine (54). In terms of energy metabolism, *E. coli* is a facultative anaerobic, chemoorganotrophic organism with the ability to switch between fermentative and respiratory metabolism. Under aerobic conditions, *E. coli* uses oxygen as a terminal electron acceptor. NADH, formate, and hydrogen can be used as electron donors. In the absence of oxygen, *E. coli* can switch to anaerobic respiration and use (in the order of preference) nitrate, nitrite, trimethylamine-N-oxide (TMAO), dimethyl sulfoxide (DMSO) and fumarate as electron acceptors (55). The expression of terminal oxidases is, at the transcriptional level, regulated by the O2 and NO3− sensing regulators FNR, ArcA/B, NarX/L, and NarP/Q.

In the absence of exogenous electron acceptors *E. coli* shifts to mixed acid fermentation, producing acetate, formic acid, succinic acid, lactic acid, and ethanol at different stoichiometric ratios (56).

In terms of the characteristics discussed above, *Enterococcus* spp. can be considered a Gram-positive “equivalent” of *E. coli*. Enterococci are opportunistic pathogens and cause a great portion of fatal nosocomial infections in humans in Europe and the United States. The dominant isolated species are *E. faecalis* and *E. faecium*. Often, strains exhibit multiple resistances to antibiotics. As *E. coli*, *Enterococcus* spp. exhibits an open pangenome structure featuring a large fraction of horizontally acquired DNA (57). In terms of energy metabolism, *Enterococci* belong to the lactic acid bacteria (Lactobacillales) and use the homolactic fermentative pathway for energy production (58). Some species
were reported to harbor cytochrome-oxidases and have the capacity to perform oxidative phosphorylation and respire O2. This property seems to depend on the external supplementation of heme (59). Besides, E. faecalis may be able to perform anaerobic respiration as suggested by the presence of a periplasmic nitrate reductase (napA) in the genome of strain OG1RF (ATCC 47077) (60).

In summary, the facultative anaerobic Enterobacteriaceae and Enterococci exhibit similar physiologic and metabolic properties that may enable them to bloom in the inflamed gut.

The “Oxygen-Hypothesis”

Degradation and fermentation of complex carbohydrates is the main metabolic strategy employed by anaerobic microbial communities (i.e., Bacteroidetes, Firmicutes) in the mammalian large intestine. Levels of facultative anaerobic Enterobacteriaceae and Enterococci are only minor constituents of a healthy microbiota (47), which might be due to a relative deficiency in anaerobic e-acceptors in the lower gut. Inspired by the observation that, under inflammatory conditions, the microbial community is characterized by a shift from obligate to facultative anaerobes, it was suggested that an increased oxygen tension may be a feature of the inflamed gut mucosa. O2 would serve facultative anaerobes as electron acceptor and at the same time inhibit growth of highly oxygen-sensitive commensals (“The Oxygen-Hypothesis” (61)). A steep O2 gradient reaches from the vascularised intestinal epithelium to the anaerobic gut lumen (62). Intestinal inflammation was shown to lead to mucosal tissue hypoxia. It is technically challenging to accurately determine pO2 in the gut lumen. Spectral electron paramagnetic resonance (EPR) imaging has been established to measure oxygenation in living mice (63). As an alternative method, Pd-porphyrin can be used to quantify local O2-tension using an intravital phosphorescence assay (64). Because oxidative (O2-dependent) respiration is thermodynamically more favorable than anaerobic respiration or fermentative metabolism, it is conceivable that increased oxygen levels, derived from blood and hemoglobin, reach the gut lumen via the damaged mucosa and foster growth of the facultative anaerobes. As a matter of fact, oxygen intake as a consequence of small bowel transplantation leads to a local increase in abundance of facultative anaerobic Enterobacteriales and Lactobacillales, which rapidly decrease after surgical closure (65). Clearly, an increase of oxygen concentration may play a role in intestinal dysbiosis. However, no studies have measured O2 levels in the gut lumen in the course of acute or chronic colitis to confirm the “Oxygen Hypothesis.”

Electron donors for anaerobic respiration

Apparently, introduction of a respiratory electron donor supports growth of facultative anaerobic bacteria in the gut lumen. While an elevated abundance of oxygen in the gut lumen upon acute or chronic colitis has not yet been experimentally verified, other electron donors supporting anaerobic respiration were shown to play a role. E. coli and S. Typhimurium can use a variety of oxidized substrates as terminal electron acceptors for anaerobic respiration. The substrate spectrum includes (in the order of preference): nitrate (NO3–), nitrite (NO2–), DMSO, TMAO, and fumarate (55). In addition, S. Typhimurium can respire on tetrathionate, a product of the oxidation of thiosulfate (66).

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) play a major role in the antibacterial immune defense of mice and men (67). Proinflammatory cytokine signalling induces the activation of intestinal epithelial ROS-generating enzymes such as Nox-1 and Duox2 (68–69). In addition, neutrophils transmigrating into the gut lumen upon severe inflammation can produce additional superoxide radicals (O2–) via the inducible phagocyte NADPH oxidase Phox (70). Neutrophils convert superoxide radicals to hydrogen peroxide and hypochlorite (OCl–) by the enzymes myeloperoxidase (MPO) and superoxide-dismutase (SOD). RNS are also produced by the inducible nitric oxide synthase (iNOS, Nos2) by epithelial cells and neutrophils in the inflamed gut mucosa. Further, NO can react with a superoxide radical to form peroxynitrite (ONOO–). In human IBD patients, elevated production of ROS and RNS was reported (71, 72). Likewise, in a mouse model for acute S. Typhimurium-induced colitis, increased expression of NADPH oxidase complex (Cybb) and the inducible nitric oxide synthase (Nos2) were measured (73).

Seminal work by Winter et al. first revealed that gut inflammation leads to the generation of electron acceptors, which boost anaerobic respiration of Enterobacteriaceae (74). They demonstrated that, in the course of S. Typhimurium-induced colitis, tetrathionate (S4O62–) is generated from thiolsulfate (S2O32–) via ROS-mediated oxidation. Thiosulfate is produced by epithelial cells upon detoxification of hydrogen sulphide (H2S), which is a product of anaerobic sulphate-reducing bacteria (SRB), which are members of the normal microbiota (75).

In contrast with many commensal Enterobacteriaceae, S. Typhimurium harbours the genes for tetrathionate respiration (ttrBCA operon and the two-component
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regulatory system ttrRS), which are encoded on the Salmonella pathogenicity island 2 (SPI-2) (66). By respiring on tetrathionate, S. Typhimurium can gain a competitive advantage over the competing microbiota in the inflamed gut (74). In contrast, in the absence of inflammation, no tetrathionate is produced, and tetrathionate respiration is dispensable for the fitness of S. Typhimurium. In the same way, the ttr operon does not confer any benefit for systemic infection (66).

Later, it was shown that other electron acceptors such as NO₃⁻ but also DMSO and TMAO are formed as a side effect of ROS and RNS production in the gut. NO₃⁻ is generated in an iNOS-dependent fashion by conversion of peroxynitrite (76), while DMSO and TMAO are produced by oxidation of organic sulfides and tertiary amines derived from host cell building blocks. S. Typhimurium, as well as commensal E. coli, produce NO₃⁻, NO₂⁻, DMSO, and TMAO reductases (section 2.2.1). All these respiratory reductases contain a molybdopterin cofactor (77). Therefore, growth of an E. coli moaA mutant, which is deficient in molybdopterin biosynthesis and anaerobic respiration, is severely attenuated in the gut upon dextran-sulfate sodium (DSS)-induced colitis (78). In the absence of colitis, gut colonization of E. coli moaA is not attenuated. This data revealed that anaerobic respiration of diverse substrates confers a major fitness benefit to E. coli—and other related facultative anaerobic bacteria—in the inflamed gut. Presumably, successful competition for external anaerobic electron acceptors against host intrinsic commensal E. coli strains defines the fitness of the pathogen S. Typhimurium. Both commensal and pathogenic E. coli strains as well as S. Typhimurium often harbour even several genes encoding NO₃⁻, NO₂⁻, DMSO, and TMAO reductases. Apparently, the ability to reduce tetrathionate also gives S. Typhimurium a competitive edge against E. coli. However, localization of the ttr-operon on a mobile genetic element makes it likely to be transmitted horizontally to other Enterobacteriaceae, which may also benefit from this function in inflammation-induced blooms. Indeed, similar sequences (∼70% identity) are present in the genomes of other Enterobacteriaceae, namely Klebsiella spp., Morganella spp., Enterobacter spp. and Serratia spp.

**Alternative nutrient sources in the inflamed gut**

Besides anaerobic electron acceptors, the inflamed gut offers several other nutrient niches that could selectively foster bacterial growth. Inflammatory mediators lead to disruption of the mucosal epithelium and an increased shedding of dead epithelial cells. Epithelial cell membranes contain lipids and phospholipids such as phosphatidylcholine and phosphatidylethanolamine. The latter is converted to ethanolamine by microbial activity. Ethanolamine is an abundant substrate in the bovine and murine intestine (79, 80), and S. Typhimurium can use it as sole source of carbon and nitrogen. Ethanolamine is converted to ammonia, acetaldehyde (ethanol), and acetyl-coA in a vitamin B₁₂-dependent manner; in Salmonella, the pathway is encoded by a 17-gene cluster, the eut operon (81). Yet, ethanolamine can only be used as a sole energy source in the presence of oxygen or upon anaerobic tetrathionate respiration (82, 83). Conversely, S. Typhimurium benefits from ethanolamine-degradation in the inflamed gut upon concomitant use of tetrathionate (80). The ability to use ethanolamine is restricted to certain bacteria among the Firmicutes, Actinobacteria, and Proteobacteria (84, 85). Of note, Enterococcus faecalis, E. coli, and Clostridium difficile, which all “bloom” in an inflamed gut, can also degrade ethanolamine (86–88).

Intestinal mucins form a gel-like structure that contributes to protection against invasion of both commensals and enteric pathogens. On top, mucins shield the epithelium from damage by intestinal contents (89, 90). The goblet cell is a specialized cell type of the intestinal epithelium that mediates production and secretion of intestinal mucins. MUC2, the major colonic mucin in humans and mice, is a large protein rich in proline, serine, and threonine, which is processed by extensive O-glycosylation. N-acetyl-D-galactosamine, N-acetyl-D-glucosamine, N-acetylneuraminic acid (sialic acid), L-fucose, and D-galactose are the five major mucin-derived sugars (91). This makes the mucus layer an attractive bacterial habitat and nutrient source. Increased mucus production and its secretion is another hallmark of enteric pathogen infection (92–94). Mucus secretion by intestinal goblet cells in response to Salmonella infection is controlled IFN-γR-signalling (95). Mucus-associated bacteria are increased in IBD, and a number of known mucin-degrading bacteria were shown to be enriched in the inflamed gut. For instance, Ruminococcus gnavus and Ruminococcus torques were more abundant in UC/CD patients, while Akkermansia muciniphila was decreased (96). In mice, bacterial families like the Enterobacteriaceae, Verrucomicrobiaeae (mainly Akkermansia spp.), Erysipelotrichaceae, Deferribacteraceae (mainly Mucispirillum spp.), and Bacteroides acidofaciens were enriched in DSS colitis (37). Moreover, an enrichment of transcripts for genes related to mucin-degradation was detected upon development.
of DSS colitis (97). Mucispirillum schaedleri and Akkermansia muciniphila are two species that have been isolated from mouse and human intestinal mucus, respectively (98, 99). A recent study confirmed in vivo mucin-degrading activity for both species, as well as for B. acidifaciens (100). Thus, enrichment of mucolytic bacteria supports the notion that increased mucin production in the course of intestinal inflammation expands this ecological niche and positively selects for mucin-degrading bacteria. Accordingly, in human CD patients, glycosidase activity in fecal samples was significantly higher than in healthy controls (101). Along the same lines, accumulation of sugar moieties (lactose, galactinol, melibiose, raffinose) was detected in the Salmonella-infected, inflamed gut (102). Accumulation of these metabolites may be causally linked to depletion of commensal bacteria. Further, increased levels of sugars might be exploited by the pathogen for growth. A similar scenario has been described after antibiotic-mediated disruption of the microbiota: Disturbance of commensal microbial food webs gives rise to free microbiota-liberated monosaccharides in the gut, which can promote growth of enteropathogenic bacteria such as S. Typhimurium and Clostridium difficile (103). Motility and chemotaxis were essential for S. Typhimurium to move towards the epithelium and benefit from mucin-derived sugars such as D-galactose (92). Moreover, S. Typhimurium employs aerotaxis to benefit from the anaerobic electron acceptors nitrate and tetrathionate, which are generated in close proximity to the mucosa (104). Lastly, blood, serum, and erythrocytes are leaking into the gut lumen from damaged mcosa. Besides antimicrobial effector molecules (e.g., complement, antimicrobial peptides), serum contains proteins, ions, and glucose, which may also promote growth of many “serum-resistant” bacteria (e.g., E. coli and S. Typhimurium) (105).

Antimicrobial effector mechanisms of the inflamed mucosa

The purpose of an inflammatory response is to eliminate infectious agents or attenuate their replication. Therefore, the release of antimicrobial mediators is a hallmark of intestinal inflammation in order to kill pathogens, impede their growth in close vicinity to the epithelium, and prevent invasion. As a matter of fact, the innate immune system can, for the most part, not distinguish between co-colonizing pathogens and commensals in the gut lumen. Therefore, acute inflammation in the gut may damage both beneficial and harmful members of the microbiota (106).

An effective instrument of the host’s innate response is restriction of iron availability. Free iron in blood and mucosal secretions are kept at low levels, which is mediated by host proteins such as lactoferrin, transferrin, ferritin, and heme (107). Upon infection, the host can limit free iron concentration in the blood by different mechanisms, including secretion of the hormone hepcidin, which downregulates the iron transporter ferroportin 1 in the intestinal epithelium and prevents discharge of iron into the bloodstream (108, 109). To overcome iron starvation, bacteria can produce iron-scavenging molecules, termed siderophores, which are released from the bacteria and have a high affinity for iron (mostly FeIII). Specific surface receptors serve the reabsorption of iron-siderophore complexes. Enterobacteriaceae can produce an arsenal of different catecholate-type and hydroxamate-type siderophores (110). Prominent examples are the siderophore enterochelin and the hydroxamate-type siderophore aerobactin. Enterochelin is synthesized by all Enterobacteriaceae, including E. coli and S. Typhimurium. The host, in turn, counteracts enterochelin by expressing lipocalin-2 (LCN2), an antibacterial protein that tightly binds the ferric enterochelin and thus blocks siderophore-mediated iron uptake. S. Typhimurium on the other hand, can evade LCN2-mediated inhibition by synthesizing the enterochelin variant salmochelin. Salmochelin-synthesis is mediated by the iroBCDE iroN gene cluster. IroN encodes a salmochelin-specific outer membrane receptor. IroB codes for a glucosyltransferase that modifies enterochelin to produce salmochelin; iroC encodes an ABC transporter required for transport of salmochelins; and iroD, and iroE code for a cytoplasmic esterase and a periplasmic hydrolase, respectively (111). Salmochelin-mediated resistance to LCN2 conferred a competitive advantage to S. Typhimurium when colonizing the inflamed intestine of wild-type but not of LCN2-deficient mice (112). LCN2 is produced by epithelial cells but also neutrophils, which transmigrate into the gut lumen upon S. Typhimurium-triggered inflammation and engulf bacteria (113, 114).

Moreover, the antimicrobial repertoire of neutrophils includes proteases and ROS produced by the NADPH oxidase complex. Further, neutrophils produce myeloperoxidase, calprotectin, and elastase and release lactoferrin at the site of infection (70). Neutrophil elastase mediates changes of microbiota composition observed in response to S. Typhimurium infection in the mouse colitis model (115). Specifically, neutrophil elastase activity is linked to loss of bacterial families such as Lachnospiraceae and Ruminococcaceae and an increase in Barnesiellae and S. Typhimurium. Antibody-mediated
depletion of neutrophils reverts these changes, while application of recombinant elastase to mice partially recapitulates *Salmonella*-induced dysbiosis (115). This suggests that elastase may differentially inhibit/kill *S.* Typhimurium and the commensal microbiota and thereby contribute to inflammation-induced pathogen overgrowth.

Calprotectin is one of the most abundant antimicrobial proteins in neutrophils and is secreted during inflammation at high levels. Calprotectin binds metal ions such as Zn$^{2+}$ and Mn$^{2+}$ and thereby contributes to inhibition of bacterial replication by inducing nutrient starvation (116). Interestingly, it was shown that manganese depletion increases bacterial susceptibility to ROS, as Mn$^{2+}$ is an essential cofactor of superoxide dismutases (117). *S.* Typhimurium is somewhat resistant to calprotectin by expressing a high-affinity Zn$^{2+}$ transporter, *zymA* (118). Accordingly, an *S.* Typhimurium *zymA* mutant was outcompeted by the microbiota, demonstrating that competition for Zn$^{2+}$ is important for efficient colonization of the inflamed intestine, which is depleted by calprotectin. Indeed, in calprotectin-deficient mice (*S100a9*−/−), *zymA* did not confer a competitive advantage to *S.* Typhimurium.

Recently, it was shown that neutrophil transmigration into the gut lumen during *Toxoplasma gondii* infection results in the formation of organized intraluminal structures (“casts” or pseudomembranes), which encapsulate bacteria and thus prevent them from contacting the epithelium and invading the mucosa (40). *Fpr1*−/− mice, lacking the neutrophil N-formyl peptide receptor Fpr1, showed reduced “cast” formation, which suggests that neutrophil transmigration is chemotactically guided by bacterial patterns within the gut lumen, because the N-formyl peptides are products of bacterial growth.

In addition to antibacterial effectors of neutrophils, epithelial and paneth cells produce a number of antimicrobial mediators. In the small intestine, Paneth cells produce *α*-defensins (cryptdin-1 to cryptdin-6 in mice, HD5, and HD6 in humans) and the *C*-type lectins of the RegIII family (RegIIIβ, RegIIIγ). Several studies have demonstrated that antimicrobial peptides can indeed significantly influence gut microbiota composition: transgenic mice overexpressing *α*-defensin HD5 show altered microbiota composition in the ileal lumen (119).

Similarly, changes in microbiota composition were reported for mice expressing a human alpha-defensin gene (DEFA5) as well as for MMP7−/− mice (lacking alpha-defensins) (120). However, alpha-defensins are not regulated by proinflammatory stimuli. While human beta defensin 1 (HBD-1) is constitutively expressed in the colonic and ileal epithelium, expression of human and mouse beta defensins (beta defensin HBD2-4, mouse beta defensin-3) is induced in the colon of IBD patients in response to infections and chronic colitis (121, 122). Broad-spectrum antimicrobial activity of beta defensins and significant variability in MICs has been reported. Aerobic bacteria generally exhibited higher susceptibility than anaerobes (123). Defensins were shown to effectively target pathogens, including *S.* Typhimurium, *Shigella flexneri,* and *E. coli* (124–126). Yet, their activity spectrum against the vast and diverse number of commensal bacteria has not been investigated in detail. Finally, it remains to be shown whether alpha- or beta-defensins contribute to inflammation-induced differential killing of microbiota and pathogens.

Expression of the *C*-type lectins RegIIIγ and RegIIIβ is upregulated during mucosal colonization with symbionts as well as upon pathogen infection. The lectins are released into the gut lumen and possess potent antimicrobial activity *in vitro*. Differential bacterial killing has been demonstrated both for RegIIIγ and RegIIIβ (127, 128). *In vitro*, RegIIIβ kills diverse commensal gut bacteria but not *S.* Typhimurium (128). Feeding of RegIIIβ to mice showed suppression of a RegIIIβ-sensitive commensal *E. coli*, while *S.* Typhimurium was not inhibited. These data suggest that RegIIIβ production by the host could promote *S.* Typhimurium infection by eliminating inhibitory members of the gut microbiota. Afterwards, a growth-phase-dependent antimicrobial activity against *S.* Typhimurium was revealed (129). Therefore, *in vivo* experiments involving RegIII-deficient mice will be necessary to further elucidate the mechanisms of differential killing of microbiota and pathogens in the inflamed gut.

Besides being a nutrient source for intestinal bacteria, mucus can also act as a structural matrix for the retention of antimicrobial molecules (*e.g.*, defensins, cathelicidins, lysozymes, lectins). It was shown that mucin binding of the antibacterial lectin RegIIIγ strengthens the barrier function of the mucus layer in such a way that it is kept free of microbes (130). Therefore, increased mucus production upon inflammation may also augment antimicrobial activity and longevity of antimicrobial proteins by tethering them to mucins.

The Role of Dysbiosis in Enteric Infections and Human IBD

Inflammation creates conditions that can be better exploited or sustained by those bacteria, adapted to or resistant to immune defences (*such as pathogens*). Thereby, intestinal inflammation affects the microbiota
in a specific, stereotypic manner, and a pre-existing beneficial microbial community can be shifted towards a “facultative pathogenic” microbiota. This inflammatory microbiota may further promote disease and result in a “vicious circle” of microbiota alteration and induction of inflammation. In the inflamed gut, bacterial species, which are normally less abundant, become enriched (“blooming”). While these species are generally harmless, apathogenic commensals in a healthy host at low abundance, they can become pathogenic when enriched in an immune-compromised host. At high density, pathogenesis might be driven by the proinflammatory action of bacterial products (LPS, toxin production), cell adherence, tissue invasion (131), or increased resistance to phagocytosis. Members of the gut microbial community featuring these properties were termed “pathobionts” (132). For example, expansion of a specific multidrug-resistant Escherichia coli strain in the gut of immunodeficient mice occurred in the course of antibiotic therapy. Overgrowth in the gut facilitated tissue invasion and triggering of E. coli-induced sepsis (133). In fact, there is compelling evidence that bacteria with the ability to “bloom” in the inflamed gut can also trigger inflammation under these conditions.

The E. coli AIEC pathotype is a prominent example of such “pathobionts.” AIEC are isolated from healthy individuals, in which they do not trigger disease symptoms. In response to inflammatory conditions, AIEC are positively selected, grow to high numbers, and can further promote disease in human IBD. In CD patients, elevated AIEC levels have been reported consistently (25, 134). AIEC strains can invade epithelial cells, and they are detected in mucosal ulcers and granuloma (16). In vitro, AIEC show high-level adherence to intestinal epithelial cell lines and can invade and survive within cells (135). IBD patients sometimes harbor systemic antibodies against E. coli (136). This suggests that AIEC are “pathobionts” that can benefit from the compromised mucosal immune system of a CD susceptible individual (e.g., polymorphisms in NOD2, ATG16L1, reduced defensin production (137)) or pre-existing inflammation. Overgrowth of AIEC in CD patients might well be related to concomitant depletion of other commensals and their metabolites (e.g., Faecalibacterium prausnitzii, butyrate) (28) to pre-existing inflammation or other unknown factors.

In mouse models of chronic colitis, AIEC only triggers/promotes disease in combination with certain host genotypes. Upregulation of carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) on intestinal epithelium was reported for CD patients (138). The AIEC strain E. coli LF82 triggered colitis in CEABAC10 transgenic mice, which express human CEACAMs (139), a putative receptor for bacterial type 1 pili. Accordingly, induction of disease was found to depend on expression of type 1 pili by LF82. This supported the idea that CD patients express abnormally high CEACAM-levels, which act as receptor for AIEC and promote bacterial invasion and induction of inflammation. This may lead to a vicious circle of AIEC-induced inflammation and inflammation-induced upregulation of the AIEC-receptor. Furthermore, AIEC was also shown to trigger disease in a genetically predisposed host. TLR5-deficient mice, lacking the pattern-recognition receptor for bacterial flagellin, are highly susceptible to developing colitis (140). The incidence of colitis in TLR5-deficient mice was associated with transient microbiota instability and increased abundance of Proteobacteria in the post-weaning period (141). When the microbiota was experimentally disrupted (germfree or antibiotic-treated mice), AIEC colonization triggered colitis in TLR5⁺/⁻ but not WT mice. In conclusion, this data support the idea that AIEC are pathobionts, which are usually kept in check by the microbiota. If, for any reason, they grow to high levels, they can trigger or drive colitis in a genetically predisposed host.

IL-10-deficient mice have become a widely used tool to test the “inflammatogenic” potential of different commensals, such as species with the ability to “bloom” in the inflamed gut. IL-10–deficient mice spontaneously develop intestinal inflammation when colonized with a complex microbiota (142). Interestingly, monoaasociation of germfree IL-10–deficient mice with “nonpathogenic” strains of E. coli (mouse isolate) and Enterococcus faecalis (strain OG1RF) triggered colitis (143). Upon co-colonization of both strains, symptoms of intestinal disease are even more severe (144). What is known about the mechanisms as to how these bacteria induce disease? In the case of Enterococcus faecalis OG1RF, it was shown that it expresses a metalloprotease (gelatinase) that compromises epithelial integrity, which in turn triggers colitis in this model (145). Helicobacter hepaticus is one of the best characterized pathobionts in mice. It asymptotically colonizes immune-proficient mice while, in combination with a normal SPF microbiota, it causes disease in colitis-susceptible mouse models (146). In contrast with E. coli and E. faecalis, however, monoaasociation of IL-10–deficient mice with H. hepaticus does not lead to colitis (147). Under specific pathogen-free (SPF) conditions, mice from different SPF facilities display strong differences in their susceptibility to H. hepaticus-induced
pathology (148). Therefore, *H. hepaticus* seems to require the presence of a “colitogenic” microbiota to trigger or exacerbate colitis in IL-10–deficient mice. So far, it is unclear which members of a normal microbiota are necessary and how they influence disease progression. The remaining microbiota may affect the mucosal immune system of the mice or modulate environmental conditions in the intestine and, thereby, *H. hepaticus* colonization or virulence factor expression. So far, it is also unclear if an inflamed gut environment would support *H. hepaticus* growth.

In conclusion, bacterial “blooms” occurring as a consequence of intestinal inflammation may contain a high proportion of pathobionts, which engage in disease perpetuation. This might feed into a futile cycle of high proportion of pathobionts, which engage in disease perpetuation. This might feed into a futile cycle of pathogen titers and explains, at least in part, the mechanism of protection against *S. Typhimurium* infection conferred by *E. coli* Nissle (149).

*Enterobacteriaceae* might also “parasitize” on siderophores produced by close relatives cocolonizing in the same gut, respectively (151). Parasitism has to be prevented in order to ensure successful colonization of this niche by the siderophore producer. To this end, *E. coli* and relatives produce an arsenal of different bacteriocins, the colicins, to fight off phylogenetically close competitors (152). Colicin production is a common trait in *E. coli* populations (153). On average, 30% of natural *E. coli* populations produce one or more colicins (154). Colicins can kill bacteria by one of four general mechanisms: inner-membrane pore formation, DNAse or RNAse activity, and interference with cell wall synthesis. For cell entry, colicins first bind to a specific outer-membrane receptor. Thereafter, “group A” colicins (colicin A, E1-E9, K, N, U) pass through the periplasm via the Tol-dependent import pathway, while “group B” colicins (colicin B, D, Ia, Ib, M) exploit the TonB-pathway for entry. The colicin producer protects itself against self-killing by expressing a cognate immunity protein. In addition to the immunity protein, strains can become resistant to the colicin by mutations in the colicin-import pathway or the cellular target (referred to as “colicin-resistant,” as opposed to “immune”). Since this import pathways usually serve the uptake of key nutrients (e.g., iron), mutations conferring resistance to colicins might concommitantly decrease bacterial fitness.

In addition to porins (OmpA, OmpF) and the vitamin B12 receptor (BtuB), many colicins bind to iron-siderophore receptors on the outer bacterial membrane. Therefore, these colicins can also act as a “weapon” specifically directed against competitors for siderophores: On the one hand, colicins compete with siderophores for receptor binding. Receptor-binding of the colicin would block siderophore uptake regardless of the competitor exhibiting an additional intrinsic resistance to the colicin (e.g., by carrying a mutation in the import pathway). On
the other hand, colicins targeting siderophore-receptors can directly eliminate colicin-sensitive bacteria, which express the respective receptor. Indeed, the degree of sensitivity to colicin Ib increases with the quantity of CirA-receptor molecules on the bacterial surface, which is upregulated in response to iron limitation in a Fur-dependent manner (155). A vast number of colicin/siderophore-receptor couples follow the same principle: Colicin B and D target FepA (enterochelin-receptor); colicin M targets FhuA (ferrichrome-receptor); colicin Ia/Lb and microcin L both target CirA (binds breakdown products of enterochelin); pesticin targets FyuA (Yersiniaabactin) (156); and cloacin DF13 targets IutA (aerobactin receptor). Because all the named receptors are induced in response to iron-limiting conditions (157), it is highly likely that increased sensitivity to colicin-mediated killing under iron depletion may also apply to other colicins binding to TonB-dependent outer-membrane transporters. Further studies are needed to experimentally verify that colicins can prevent siderophore “parasitism” in vivo in the inflamed gut.

Colicin producers have to pay a certain cost for colicin expression. On one hand, colicin synthesis results in a higher metabolic load, which may affect physiology and growth rates of the bacteria. Moreover, colicin release is mediated by bacterial lysis and is therefore lethal for the bacteria (152). Colicin producers solve this problem by “division of labor”: Colicins are expressed by only a small subpopulation that sacrifices itself and releases colicins, which benefits the whole population and contributes to survival of the genotype. Colicin expression is repressed by LexA and is under the control of the bacterial SOS-response. DNA damage (e.g., induced by ultraviolet light, radicals, or antibiotics) leads to activation of the protease RecA, which in turn mediates LexA degradation and triggers the SOS-response (158). The SOS response is induced in a stochastic fashion (159). In vitro, in the absence of DNA-damaging agents, colicins are expressed only by a small fraction (<1%) of the total population (160). The rate of colicin-expression in vivo (e.g., in the mammalian gut) has never been addressed. Nevertheless, it is clear that bacteria have to tightly control expression of colicins to prevent excessive cell lysis. This implies that expression should be increased under conditions in which the chances are high to encounter closely related competitors.

Inflammation-inflicted Enterobacterial blooms can contain high loads of different closely related Enterobacteriaceae, which likely compete for the same resources (e.g., iron, anaerobic electron acceptors). The individual strains may hugely benefit from colicin production under this highly competitive situation. Recently, we have shown in a murine colitis model that colicin Ib (ColIb) provides a competitive advantage to S. Typhimurium against commensal E. coli strains (155). In fact, the benefit was apparent only in the inflamed gut. Expression of colicin Ib (cib), which is under negative control by Fur and LexA, was induced in the inflamed gut. This suggests that, under this condition, S. Typhimurium senses iron limitation as well as signals triggering the SOS response, which leads to increased cib expression. On the other hand, expression of the ColIb receptor cirA in E. coli was upregulated as well. Thus, physiological changes of the murine intestine in Salmonella-induced colitis are likely to provide the environmental cues required for upregulation of both colicins and their corresponding receptors. These findings shed new light on the role of colicins as important fitness factors providing a competitive advantage for bacterial growth in the inflamed gut.

Horizontal gene transfer and bacterial evolution

Owing to the enormous bacterial density, horizontal gene transfer (HGT) among bacteria in the mammalian gut is thought to occur at relatively high frequencies compared with other microbial ecosystems (161, 162). HGT enables bacterial evolution in quantum leaps rather than via stepwise adaptation by mutations to changing environments. Mechanisms of HGT occur via the uptake of naked DNA by natural transformation, phage-mediated transduction, and the exchange of plasmids by conjugation. Conjugation is an HGT mechanism which that direct physical contact between the donor and the recipient strain and thereby is a highly efficient way for bacteria to exchange DNA. Conjugative plasmids encode the machinery (conjugative pilus), which serves plasmid transfer from the donor to the recipient strain. When the bacteria involved are present at high densities (e.g., in the gut), conjugation is most effective. Indeed, intestinal metagenomes harbor a large variety of conjugative plasmids and transposons (163).

It was recently shown that inflammation can foster HGT by mediating a transient increase of total Enterobacteriaceae in the gut (11, 164). During the course of Salmonella infection in the mouse colitis model, pColIb, a conjugative colicin plasmid of the S. Typhimurium strain SL1344 (165), was transmitted at high frequency to commensal E. coli strains, which are part of the normal microbiota of the mice. Conjugation frequency was increased when the overall levels of donor and recipient strains were elevated, such as within inflammation-
inflicted *Enterobacteriaceae* blooms or in gnotobiotic mice, which do not exhibit colonization resistance against *Enterobacteriaceae* (166). In contrast, a complex microbiota supressed growth of *S. Typhimurium* and *E. coli*, alleviating conjugation. Interestingly, colicin loci are often associated with transposons, insertion sequences, and mobilizable or conjugative plasmids (167). This suggests that inflammation-inflicted blooms not only provide the environmental cues for colicin-dependent bacterial competition (section 2.4.1), they also enhance the spread of colicin plasmids among blooming *Enterobacteriaceae*. Therefore, inflammation-inflicted blooms play an important role in colicin ecology.

*Enterobacteriaceae* in general, and *E. coli* in particular, are highly “promiscuous” bacterial species. Their genomes contain a large proportion of horizontally acquired DNA (168–171). *S. Typhimurium* virulence and fitness factors are frequently associated with pathogenicity islands, prophages, transposons, and plasmids, pointing at a history of HGT. Because *E. coli* and *Salmonella* genomes exhibit high homology (>80%) (172), they presumably share a common ancestor (173) from which *S. Typhimurium* and *E. coli* strains evolved independently. Evolution has been driven in particular by the horizontal acquisition of virulence and fitness factors. Thus, we suggested that virulence of contemporary *Salmonella* spp. may have evolved in two stages (11). Because the property to bloom in the inflamed gut is a characteristic of both commensal *E. coli* and *S. Typhimurium*, the common ancestor of contemporary commensal *E. coli* and *Salmonella* spp., a commensal inhabitant of the mammalian intestine, may successively have acquired factors to profit from a pre-existing intestinal inflammation (e.g., genes for iron acquisition, resistance to antimicrobial mediators). Thereafter, commensal *E. coli* remained at this stage, while *Salmonella* spp. acquired an array of virulence factors (e.g., Salmonella pathogenicity islands, Type 3 secretion systems, and effector proteins, fimbriae/pili), which enabled it to trigger the inflammatory response by itself. From then on, overgrowth of *Salmonella* in episodes of inflammation-induced blooms with other *Enterobacteriaceae* led to a continuous exchange of “inflammation fitness factors” by HGT among the different species.

From the beginning of the antibiotic era, excessive and uncontrolled antibiotic use has led to the emergence of antibiotic (AB)-resistant strains. Because a large part of resistance can be transferred horizontally (e.g., conjugative transposons/plasmids), inflammation-induced blooms may also form the playground for exchange of antibiotic-resistance cassettes. Mainly in recent years, a number of multiple AB-resistant *S. Typhimurium* strains have emerged, causing an increasingly serious threat to global public health and leading to elevated morbidity, mortality, and treatment costs. The multidrug-resistant *S. Typhimurium* strain DT104, which caused a global epidemic in the 1990s, carries resistance to ampicillin, chloramphenicol, spectinomycin/streptomycin, sulfonamides, and tetracyclines (174, 175). Most of the AB resistance genes are clustered on a 13kb multidrug-resistant region within *Salmonella* genomic island 1, but some isolates carry additional AB-resistance plasmids (176). A recent study comparing the genome sequences of more than 300 DT104 isolates from humans and animals revealed that the AB resistance profile of the isolates is more diverse than core genome variability, pointing at a rather frequent horizontal exchange of AB-resistances (177). As a consequence of the HIV pandemic, a highly invasive disease caused by nontyphoidal *Salmonella* strains has become a serious public health problem in sub-Saharan Africa. *S. Typhimurium* causes a fatal systemic infection in immune-compromised HIV-infected patients. These African epidemic strains are often multidrug-resistant to ampicillin, cotrimoxazole, and chloramphenicol, complicating the clinical treatment of the disease (178). Here, the incidence of plasmid-encoded extended spectrum beta lactamase (ESBL) or AmpC betalactamase–producing strains is on the rise (179). This alarming increase in clinical MDR *Salmonella* isolates suggests that horizontal spread of AB resistances commonly occurs among virulent epidemic *S. Typhimurium* strains. It remains to be shown whether *Enterobacterial* blooms in the gut of infected patients play a role in driving transmission and remixing AB resistances.

Similar to *E. coli*, *Enterococcus* spp. also has an open pan-genome, which is shaped by HGT (57, 180). Genomic sequencing data have allowed the identification of the enterococcal “mobilome,” which includes plasmids, insertion sequences, transposons, and integrons that can be mobilized between cells (181). As for *E. coli*, Enterococcal plasmids encode AB resistances, virulence factors, and bacteriocins. Interestingly, a recent study revealed that the genomes of clinical *E. faecium* isolates were enriched in mobile elements, virulence factors, and AB resistance genes compared with environmental isolates (180). Although this interesting correlation was not seen for the other human pathogenic species, *E. faecalis*, it suggests that Enterococci adapt to the clinical setting by HGT. One could imagine that the ability of Enterococci to dwell in inflammation-triggered bacterial blooms may contribute to frequent HGT among the clinical strains.
CONCLUSION/OUTLOOK

For many years, the intestinal microbiota has been considered an insignificant ingredient of our body. However, research during the last decade has taught us numerous new functions of our commensals and how bacteria shape and modulate their host’s metabolism and immunity. An increasing number of human disease conditions were identified as having a correlative or causative association with specific microbiota alterations (3). Later, it was more and more appreciated that an inflammatory immune response in the gut (both IBD and pathogen-induced) can also directly shape the composition of the microbiota and trigger dysbiosis. This discovery has far-reaching consequences. It fundamentally changes our understanding of the pathogenesis of human IBD. Moreover, it sheds new light on the evolution of bacterial virulence. Currently, we are still getting a clearer picture of the “inflammiome” which is characterized by the environmental conditions bacteria encounter in an inflamed intestine and their response to it. Future research directed towards an in-depth characterization of this “inflammiome” will yield valuable insights into the metabolic pathways and virulence factors that are employed by pathogens and members of the microbiota in inflammation-triggered blooms. Interference with “blooming” by specific drugs or probiotics may offer an elegant strategy to revert a dysbiotic microbiota to a normal state. This may lead to the development of new therapies for the treatment of human IBD and infectious diseases. Further, prevention of “Enterobacterial blooms” in the hospital setting may decrease the rate of horizontal transfer of AB resistances and virulence factors.

REFERENCES

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