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REVIEW

Inter-kingdom signaling between gut microbiota and their host

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Abstract

The crosstalk between prokaryotic bacteria and eukaryotic gut epithelial cells has opened a new field for research. Quorum sensing system (QS) molecules employed by gut microbiota may play an essential role in host–microbial symbioses of the gut. Recent studies on the gut microbiome will unveil evolved mechanisms of the host to affect bacterial QS and shape bacterial composition. Bacterial autoinducers (AIs) could talk to the host's gut by eliciting proinflammatory effects and modulating the activities of T lymphocyte, macrophage, dendritic cells, and neutrophils. In addition, the gut mucosa could interfere with bacterial AIs by degrading them or secreting AI mimics. Moreover, bacterial AIs and gut hormones epinephrine and noradrenaline may be interchangeable in the crosstalk between the microbiota and human gut. Therefore, inter-kingdom signaling between gut microbiota and host may provide a novel target in the management of gut microbiota-related conditions or diseases in the future.

Keywords Acylhomoserine lactone · Intestinal microflora · Mimic · Mucosa · Tumor immunity

Introduction

Microbiota contribute a lot to human beings, especially in the gut, where one hundred billion microorganisms reside [1]. In the gastrointestinal tract, the quantity of gut microbiota far exceeds the number of intestinal epithelium cells by one order of magnitude [2]. The commensal relationship between gut microbiota and intestinal cells is of extreme benefit to both partners [3]. Communication between microbiota and host is very important for homeostasis of host physiology, the responses to environmental change, and host survival [4]. There is growing evidence showing that changes in the composition and function of intestinal bacteria are associated with human disease [5], including obesity [6], diabetes [7], colorectal cancer (CRC) [8, 9], neurogenic disease like Alzheimer's disease [10], and atherosclerotic cardiovascular disease [11].

Gut microbiota can promote the maturation of the immune system [12], thereby playing a key role in establishing mucosal immunity [4, 13]. They have the ability to protect against colonization of pathogens by producing antimicrobial substances [14]. In addition, the metabolites derived from bacteria may act as important signals that mediate subsequent action of immune cells and the epithelial barrier in the intestine [15]. Some intestinal microbiota play an essential role in the initiation and development of gut tumors by invading the gut mucosa (Fig. 1a, b) [16]. However, the exact underlying mechanism of action between gut microbiota and the host intestine is currently not well understood.

Prokaryotes signal through quorum sensing (QS), while eukaryotic cells communicate with each other through hormones [17]. Bacteria and host have co-evolved for billions of years, which have exposed prokaryotic bacteria to host hormones in the gut, and gut epithelial cells to the bacterial QS [2]. The crosstalk between prokaryotic bacteria and eukaryotic gut epithelial cells has opened a new field for research.

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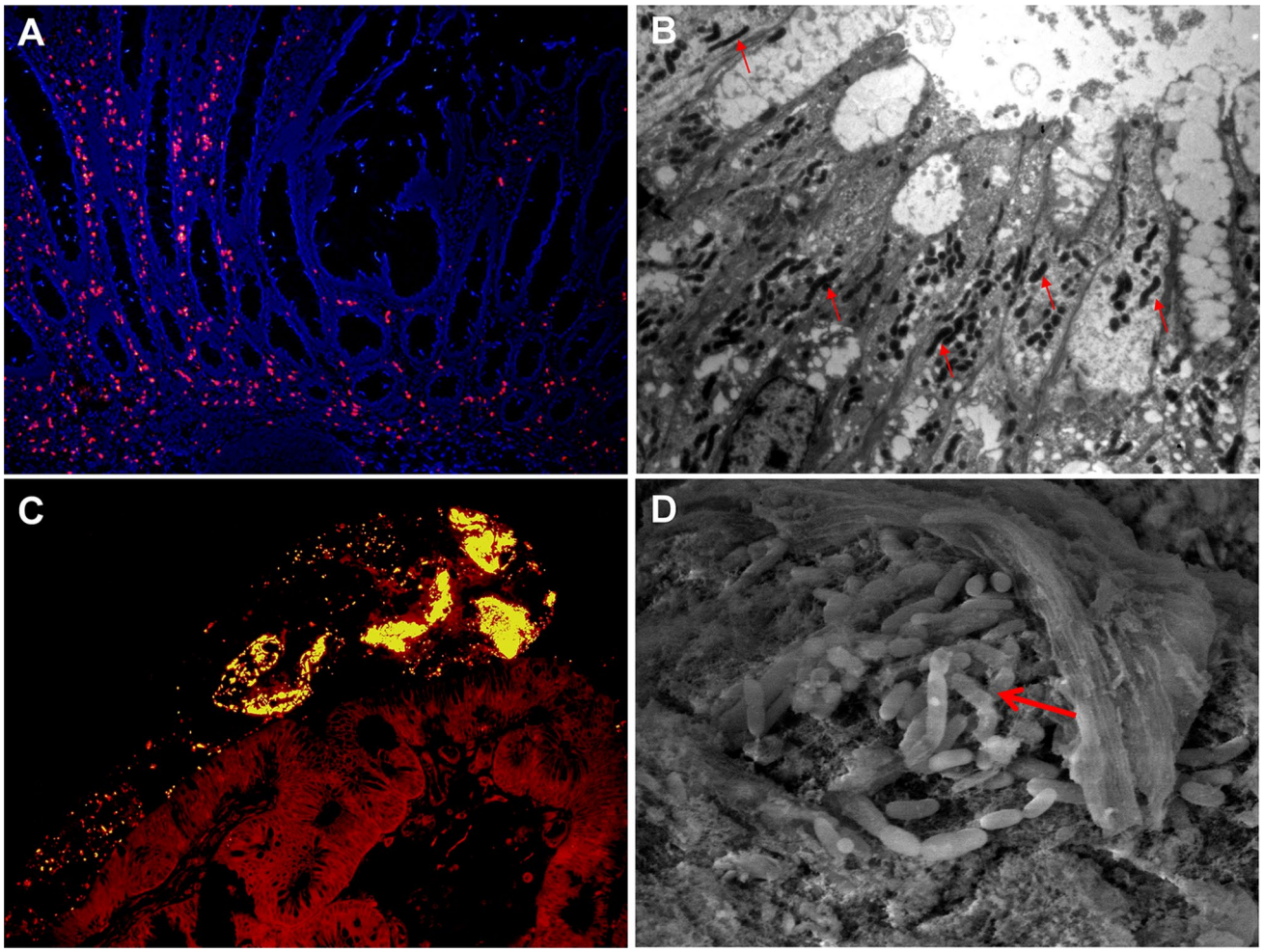

Fig. 1 Gut microbiota and colorectal tumor. Large number of invasive bacteria in a colon tumor detected by fluorescence in situ hybridization (FISH) (**a**) and transmission electron microscopy (TEM) (**b**). Bacterial biofilms on the surface of a colon adenoma detected by FISH (**c**) and scanning electron microscopy (SEM) (**d**). FISH, ×100 magnification; TEM, ×3000 magnification; SEM, ×7000 magnification Modified from Ref. [35]

The quorum sensing system of gut microbiota

Employed by large numbers of bacteria, QS is an important mechanism of intercellular communication among both intra- and interspecies [18], which enables bacteria to act as a group rather than an individual cell [19]. QS plays an indispensable role in bacterial biofilm formation, antibiotic production, virulence, symbiosis, bacterial cell density, and gene expression of those bacteria [20].

QS is mediated by small diffusible signal molecules termed autoinducers (AIs). Many Gram-negative bacteria use acylhomoserine lactones [AHL; also called AI-1, mainly including *N*-3-oxo-dodecanoyl-l-homoserine lactone (3O-C12-HSL)] for intraspecies communication. Gram-positive bacteria utilize small peptides for intraspecies communication. AI-2 has been described as being shared by both Gram-positive and Gram-negative bacteria [21]. It is a nonspecies-specific AI that mediates the communication among interspecies [22]. AI-2 is a family of molecules, and a major signal-type molecule of QS, which is a derivative of 4,5-dihydroxy 2,3-pentanedione synthesized by AI-2 synthetase (LuxS) enzymes [23]. Its levels modulate the abundance of major phyla of intestinal microbiota [24]. In the mammalian gastrointestinal tract, AI-2 mediated communication among bacteria, thereby shaping the structure of the microbial community [24]. In the last few years, accumulated evidence has suggested that the AI-2 system is closely related with the pathogenicity of various microorganisms [25].

Autoinducers of gut microbiota elicit proinflammatory effects

Recent studies have shown that QS molecules play an important role in microbiota–host interactions [25, 26]. QS molecules can elicit responses in mammalian cells [17]. AI-1 are fatty-acid-based signaling molecules, and many lipid-based hormones such as eicosanoid families, lipidic and steroid hormones, are involved in hundreds of biological functions in eukaryotes [17]. They are chemically analogous and it is supposed that bacterial AIs can enter the host cell, regulating gene transcription [3].

AIs can activate inflammatory pathways of host cells [23, 27, 28]. It is reported that AI-1 injection induced inflammation by stimulating the expression of a number of cytokines including IL-1α and IL-6 in mice [29]. In HCT-8 colon cancer cells, interleukin-8 expression was regulated by AI-2 [28]. AI-2 synthetase (LuxS) has the ability to affect the host's proinflammatory responses to *Porphyromonas gingivalis*, an anaerobic oral pathogen [30]. In another study, it was demonstrated that the proliferation of gingival epithelial cells was enhanced after treatment with dihydroxy-2,3-pentanedione (DPD) (the precursor of AI-2) [27]. In addition, AI-2 was involved in the process of *Avian pathogenic Escherichia coli*-induced cellular damage of chicken type II pneumocytes [31]. Together, these findings indicate that AIs are involved in the inflammatory processes of host cells as a response to a challenge with bacterial pathogens.

In recent studies, it was demonstrated that QS contributed to the formation of bacterial biofilm [32]. Bacterial biofilms are widely present on the root surface of human teeth, respiratory epithelial cells, the epithelial surface of patients with inflammatory bowel disease, and colorectal tumors [30, 32–34]. Colon mucosal biofilms may be associated with an increased risk for sporadic CRC (Fig. 1c, d) [34, 35]. Thus, it would be interesting to hypothesize that AIs produced by gut microbiota contribute to the inflammation and carcinogenesis of intestinal mucosa.

Autoinducers talking to the gut immune system

Gut contains the majority of immune cells in the body. The mucosal immune system provides immune surveillance against foreign pathogens [36]. Gut microbiota and host immune systems co-evolve during host's lifespans [37]. Bacterial QS signaling has been demonstrated to be involved in immune responses in the host's tissue [38, 39]. AI-1 was found to have immunomodulatory activities on T lymphocyte, macrophage and antibody responses in mammalian cells [40]. AI-1 has immune suppressive activity by inhibiting cytokine production and lymphocyte proliferation [41, 42]. It is reported that 3O-C12-HSL entered mammalian immune cells by passive mechanism; and decreased the ability of bone marrow-derived dendritic cells (BM-DCs) to induce T-cell proliferation and activation in vitro, thereby impaired the adaptive immune against bacterial pathogen [43, 44]. Moreover, 3O-C12-HSL has critical roles in the modulation of the host immune system by inducing cytotoxicity in macrophages and neutrophils [38]. 3O-C12-HSL was shown to attenuate innate immune responses via disruption of NF-kB signaling, thereby potentially maintaining persistent infection in host [45].

It is reasonable that eukaryotic hosts have receptors that sense bacterial AI molecules; however, the receptors remain to be identified [21]. Some AI peptides can signal through the epidermal growth factor receptor (EGFR), activating intracellular signaling cascade and leading to tumor metastasis [46]. It is hypothesized that the eukaryotic receptor for AI-1 is a nuclear hormone receptor (NHR), such as peroxisome proliferators-activated receptor (PPAR), a transcription factor-modulating the expression of proinflammatory genes [47]. Identifying the exact receptors and associated signaling cascade in the host gut responding to microbiota AIs will enhance our understanding of crosstalk mechanism between microbiota and their host gut.

Host responses to gut microbiota autoinducers

During long-term interaction between microorganisms and the host, a series of reactions of the host to inhabiting microorganisms may occur. The host's immune system has control over the localization and community of resident microbiota by secreting antibacterial substance such as α-defensin [48]. What's more, the host's intestinal microenvironment could affect AI-2 activity, including pH, bile acid, temperature, osmotic pressure, and starvation [49]. This means that changes in the host intestinal conditions can affect AIs' activity, and influence the density and structure of gut microbiota, thereby affecting the health of the host in return.

Moreover, host cells could have developed the abilities to disrupt QS signaling, fighting against bacterial infection [2]. For example, human airway epithelia can fight back AIs by degrading them by the production of paraoxonases [50, 51]. Interestingly, plants have mastered the art of secreting bacterial AI mimics and thus have the potential to lead to disrupt QS in associated bacteria [52]. It has recently been reported that mammalian epithelial cells of tumor produced AI-2 mimics, which have AI-2 activity [26]. Communication between host cells and bacteria occurs via generating AI-2 mimics by the epithelium, which affects gene expression of bacteria through the AI-2 pathway in return [26].

In addition, human hormones epinephrine and noradrenaline (NE) are abundantly present within the human gastrointestinal tract [53]. NE has been shown to promote bacterial growth [54]. AIs and hormones may be interchangeable in the crosstalk between prokaryotes and eukaryotes [55]. It is reported that AI-3 and epinephrine may signal through the same pathway. Epinephrine can mimic the activity of AI-3, and this effect is inhibited by adrenergic antagonists [56]. A recent study suggested that the mammalian stress hormone dynorphin released from the mice intestinal mucosa activated the QS signaling in an opportunistic pathogen *P. aeruginosa,* and enhanced its virulence [57]. Taken together, these findings provide evidences of crosstalk between host hormone signaling and bacterial QS system in the gut (Table 1; Fig. 2).

Personal experience

We have demonstrated that *Fusobacterium nucleatum (Fn)* was enriched within CRC tissues and metastatic lymphnodes [35]. Furthermore, we have revealed that high abundance of *Fn* in CRC tissue is associated with a lower density of $CD4^+$ T cells [58]. In addition, *Fn* had an immunosuppressive effect by promoting M2 polarization of macrophages in *Fn*-related CRCs [59].

Concluding remarks

Gut microbiota has recently been found to play an important role in many human diseases. QS is an important mechanism of intercellular communication among both intra- and interspecies of the gut microbiota. Coevolution of gut microbiota and host has exposed prokaryotic bacteria to host hormones, and gut epithelial cells to the bacterial AIs. The crosstalk between prokaryotic bacteria and eukaryotic gut cells has opened a new field for research. AIs of gut microbiota could elicit proinflammatory effects by stimulating the expression of a number of cytokines, and inducing cellular proliferation or damage of the host. Moreover, AIs could talk to the gut immune system by modulating the activities of T lymphocyte, macrophage, dendritic cells and neutrophils. However, the exact receptors of bacterial AIs and associated signaling cascade in the host gut remain to be unraveled. In addition, the epithelium and immune cells of the gut could fight back bacterial AIs by

Table 1 Signals and biological functions involved in crosstalk between bacteria and mammalian hosts

Prokaryotic signals	Eukaryotic cell	Eukaryotic function	References	Eukaryotic signals	Prokaryotic function	References
3O-C12-HSL	Skin cells	Stimulates the expression of cytokines including IL-1α and IL-6	[29]	α-Defensin	Controls bacterial localization	[48]
3O-C12-HSL	Macrophage, B cells, T cells, spleen cells	Modulates cell activities and antibody responses	[40]	Bile acid	Affects AI activity	[49]
3O-C12-HSL	Lymphocytes	Inhibits cytokine production and lymphocyte proliferation	[41, 42]	Paraoxonases	Degrading AIs	[50, 51]
3O-C12-HSL	BM-DCs	Decreases the ability of BM-DCs to induce T-cell proliferation and activation	[43, 44]	AI-2 mimics	Affect gene expression of bacteria	[26]
3O-C12-HSL	Macrophages, neutrophils	Cytotoxicity	[38]	Noradrenaline	Promotes bacterial growth	[54]
3O-C12-HSL	BM-DMs	Disruption of NF-kB signaling	[45]	Epinephrine	Mimic the activity of AI-3	[56]
AI-2	Colon cancer cells	Regulates Interleukin-8 expression	[28]	Dynorphin	Activates QS signaling and enhanced bacterial virulence	[57]
AI-2	Pneumocytes	Cellular damage	[31]			
DPD	Gingival epithelial cells	Enhances cell proliferation	[27]			
AI peptides	Colon cancer cells	Tumor metastasis	[46]			
AI-3	HeLa cells	Produces AE lesions	[56]			

AE attaching and effacing, *AI* autoinducer, *BM-DCs* bone marrow-derived dendritic cells, *BM-DMs* bone marrow-derived macrophages, *DPD* dihydroxy-2,3-pentanedione (precursor of AI-2), *QS* quorum sensing

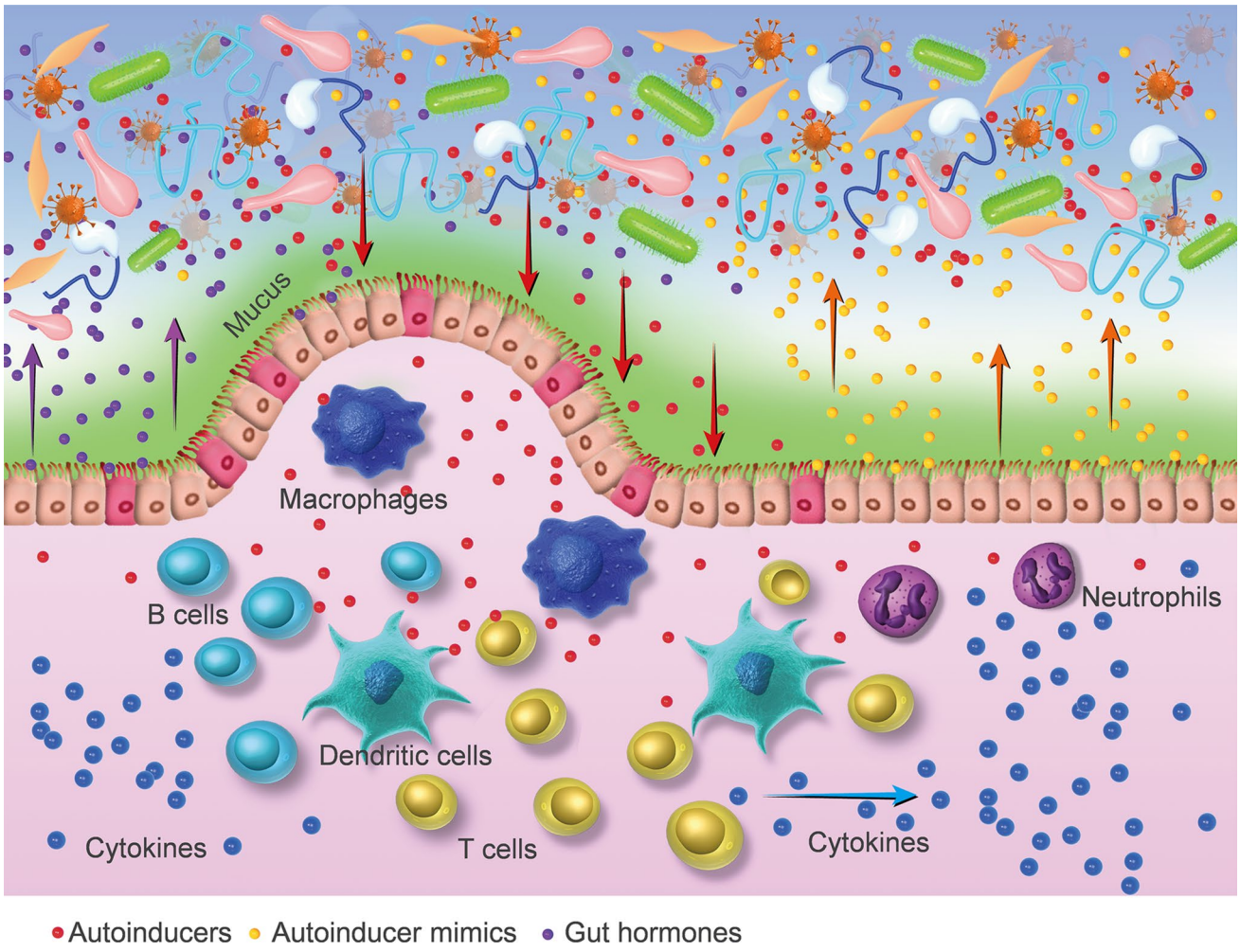

Fig. 2 Inter-kingdom signaling between gut microbiota and their host. Autoinducers of gut microbiota talk to the host's gut by eliciting proinflammatory effects and modulating the activities of T lymphocyte, macrophage, dendritic cells and neutrophils. The gut mucosa interferes with bacterial autoinducers by secreting autoinducer mimics. Bacterial autoinducers and gut hormones epinephrine and noradrenaline may be interchangeable in the crosstalk between the microbiota and human gut

degrading them or secreting AI mimics. Interestingly, bacterial AIs and gut hormones may be interchangeable in the crosstalk between prokaryotes and eukaryotes. Therefore, inter-kingdom signaling between gut microbiota and host may provide a novel target in the management of gut microbiota-related conditions or diseases.

Compliance with ethical standards

Conflict of interest Authors declare no conflict of interests for this article.

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