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MINIREVIEW

What a Dinner Party! Mechanisms and Functions of Interkingdom Signaling in Host-Pathogen Associations

Melissa M. Kendall,[a] Vanessa Sperandio[b,c]

Department of Microbiology, Immunology, and Cancer Biology, University of Virginia School of Medicine, Charlottesville, Virginia, USA[a]; Department of Microbiology, University of Texas Southwestern Medical Center, Dallas, Texas, USA[b]; Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, Texas, USA[c]

ABSTRACT **Chemical signaling between cells is an effective way to coordinate behavior within a community. Although cell-to-cell signaling has mostly been studied in single species, it is now appreciated that the sensing of chemical signals across kingdoms can be an important regulator of nutrient acquisition, virulence, and host defense. In this review, we focus on the role of interkingdom signaling in the interactions that occur between bacterial pathogens and their mammalian hosts. We discuss the quorum-sensing (QS) systems and other mechanisms used by these bacteria to sense, respond to, and modulate host signals that include hormones, immune factors, and nutrients. We also describe cross talk between these signaling pathways and strategies used by the host to interfere with bacterial signaling, highlighting the complex bidirectional signaling networks that are established across kingdoms.**

Chemical and nutritional signaling are at the interfaces among the mammalian host, beneficial microbiota, and invading pathogens. Mammalian and bacterial cells employ cell-to-cell signaling to regulate the expression of traits that enable rapid adaptation to environmental changes. Hormones are a major type of signaling molecule in multicellular organisms. In bacteria, chemical signaling is generally referred to as quorum sensing (QS) (1) and is akin to hormonal signaling in mammalian systems (2). Chemical signaling between bacterial cells coordinates population behavior, allowing the maximization of resources within a community. Significantly, bacteria have evolved to sense host signaling molecules, including hormones. This process has been called interkingdom signaling, whereby bacterial pathogens co-opt host signaling molecules as cues of the local environment, as well as to gauge the physiological status of the host and respond by modulating the expression of genes important for pathogenesis (2). Moreover, bacterial signaling molecules modulate the host immune system and several mammalian signaling pathways (3), demonstrating that interkingdom signaling is complex and not one sided.

Human beings have their cells outnumbered by bacterial cells by 1 order of magnitude. These microbial communities constitute the microbiota that populates the gastrointestinal (GI), genitourinary, and respiratory tracts and the skin. The GI microbiota plays an important role in nutrient assimilation, the development of the innate immune system, and a barrier to limit pathogen colonization (4, 5). Recently, the intestinal microbiota has also been shown to promote enteric virus replication and systemic disease (6). Given the high bacterial population density and diversity within the GI tract, many studies were devoted to understanding how these microorganisms communicate with each other, as well as with the host, in order to maintain a homeostatic GI environment. However, bacterial pathogens exploit molecules integral to the host and commensal cell-to-cell signaling systems as cues to recognize their colonization niche and precisely control spatiotemporal expression of virulence genes (7). Additionally, pathogens sense the availability of nutritional sources such as carbon and nitrogen as cues to outgrow the resident microbiota and regulate gene expression. Integration of interkingdom and nutrient sensing is necessary for successful bacterial colonization of the GI tract, as well as to ensure survival.

In this review, we discuss recent advances in the elucidation of the pathways of interkingdom signaling that occur between bacterial pathogens and their mammalian hosts. In particular, we examine the mechanisms, such as QS systems, that bacterial pathogens use to sense mammalian hormones, immunity factors, and metabolites as cues to modulate growth, virulence, and metabolism. We also describe cross talk between these pathways that integrate hormonal signaling with nutrition, as well as interkingdom manipulation of intrinsic signaling pathways, in which mammalian factors interfere with bacterial signaling to modulate virulence, or bacterial factors that inhibit components of the host immune system to compromise host defense. Furthermore, we discuss interkingdom signaling in bacterial-nonmammalian host interactions and highlight that interkingdom signaling contributes to symbiotic relationships between bacteria and their host. Finally, we consider future avenues for progress, including translational research for the development of antimicrobial drugs and the study of the transkingdom signaling events that establish symbiotic interactions between commensal microbiota and mammalian hosts.

CROSS SIGNALING BETWEEN QS AND HORMONES.

Mammalian hormones belong to three broad categories: protein (or peptide), steroid, and amino acid derivatives (amine). Protein and peptide hormones constitute the majority of the hormones. These signaling molecules are prohormones that are processed and exported out of the cell. This is an extremely diverse group of hormones that includes the epidermal growth factor (EGF), insu-

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Address correspondence to Vanessa Sperandio, vanessa.sperandio@utsouthwestern.edu.

lin, and glucagons. Steroid hormones are derived from cholesterol, and amines are synthesized from tyrosine. Amine hormones include the catecholamines adrenaline, noradrenaline (NA), and dopamine (8). All of these hormones serve as cues for microorganisms to modulate gene expression and thus function in interkingdom signaling. The location of these hormone receptors in mammalian cells is dictated by whether or not they can cross the cell membrane. Some examples of cell surface receptors are receptor kinases (tyrosine or threonine) and G protein-coupled receptors (GPCRs) that recognize a variety of amine and peptide hormones, whereas intracellular receptors largely recognize steroid hormones, which can cross plasma membranes (8).

Adrenergic signaling in bacteria. Adrenaline and NA are the most abundant catecholamines in the human body and are primarily involved in the fight-or-flight response. Adrenaline and NA contribute important functions to intestinal physiology, including modulation of intestinal smooth muscle contraction, submucosal blood flow, and chloride and potassium secretion (9). Several sources contribute to the pool of intestinal adrenaline and NA, which can reach micromolar concentrations (10). In addition to the central nervous system and adrenal medulla, the adrenergic neurons that are present in the enteric nervous system are major sources of NA in the intestine (11, 12). Furthermore, the resident microbiota, as well as pathogens, influences adrenaline/NA concentrations in the colon. The resident commensal microbiota stimulates the production of NA and, to some extent, adrenaline in the GI tract through an as-yet-unknown mechanism (13). Additionally, T cells, macrophages, and neutrophils generate and secrete adrenaline and NA (14). Therefore, pathogens may augment adrenaline and NA concentrations in the GI tract, not only because of the stress of infection but also by stimulating an immune response.

Adrenaline and NA were the first hormones recognized as influencing bacterial growth and virulence gene expression. Notably, these studies were conducted with bacteria that colonize the human GI tract (7, 15–28), such as enterohemorrhagic *Escherichia coli* (EHEC). Adrenaline and NA have been reported to enhance the growth of EHEC (19, 22, 24), possibly by functioning as siderophores that aid in iron uptake or by upregulation of iron uptake systems (19, 29). More recent work supports this idea, as NA was shown to induce enterobactin expression and iron uptake in *E. coli* (15).

Adrenaline and NA influence virulence gene expression in EHEC, independently of their influence on growth. Adrenaline and NA do not cross the cellular membrane; therefore, EHEC relies on the two-component systems (TCSs) QseBC and QseEF to relay the adrenergic signals to the intracellular environment. TCSs are typically composed of a histidine sensor kinase (HK) located in the cytoplasmic membrane that senses a specific signal and a cytoplasmic response regulator (RR) that controls the output (30). Upon sensing a particular environmental cue, the kinase autophosphorylates and subsequently transfers this phosphate to its cognate RR. The majority of RRs are transcription factors that, upon phosphorylation, mediate the output of this signaling cascade by binding DNA to promote or repress gene expression (30).

The sensor kinase QseC senses adrenaline and NA (17) and is a global regulator that influences the expression of more than 400 genes (31), including a second QS TCS, QseEF. To mediate these responses, QseC phosphorylates its cognate RR QseB, as well as the RRs QseF and KdpE (31–33). These RRs coordinate the expression of genes encoding flagella and motility, attaching-and-effacing (AE) lesion formation on enterocytes, stress responses, potassium uptake, and osmolarity (16, 26, 31–36) (Fig. 1).

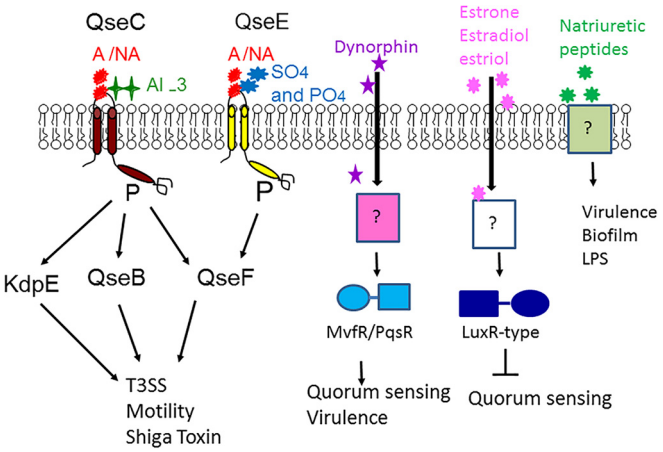

FIG 1 Bacterial receptors of mammalian hormones. The host hormones adrenaline (A) and NA are sensed by the membrane-bound bacterial histidine kinases QseC and QseE. QseC also senses the bacterial signal AI-3, while QseE senses sources of SO_4 and PO_4. QseC and QseE phosphorylate KdpE, QseB, and/or QseF (as indicated), and this signaling activates the expression of the T3SS, motility, and Shiga toxin. The stress signal dynorphin has been reported to enter bacterial cells, and its signaling involves the MvfR/PqsR receptor, although it is not clear if MvfR/PqsR directly senses dynorphin. Dynorphyn activates QS and virulence. The estrogen hormones (estrone, estriol, and estradiol) are lipid molecules that enter bacterial cells and influence LuxR-type QS signals, although LuxR-type regulators are great candidates to sense these steroid hormones, there is no evidence that this is the receptor for them. Estrogen hormones inhibit QS. Natriuretic peptides promote virulence, biofilm formation, and LPS modifications; their bacterial receptor is unknown.

QseC is critical for EHEC virulence *in vivo*, as a *qseC* deletion strain was highly attenuated in rabbit and bovine infection models (17, 37) and, significantly, QseC has been identified in at least 25 animal and plant pathogens and contributes to virulence in all of the examples characterized. QseC signaling enhances the expression of type III secretion systems (T3SSs), adhesins, biofilm formation, toxin production, intramacrophage replication by intracellular pathogens, and iron uptake, among others (38–45) (Table 1; Fig. 1). Although, QseC-dependent regulation has been directly linked to adrenaline/NA in only a subset of these studies, the cumulative results of these findings suggest that this interkingdom signaling is a conserved trait that allows bacteria to modulate virulence gene expression.

QseEF is a second TCS that plays a role in adrenaline- and NA-dependent interkingdom signaling (26). This TCS was discovered through experiments that demonstrated that inhibition of QseC-dependent signaling was effectively inhibited only by an α-adrenergic antagonist (phentolamine) (17), whereas AE lesion formation was also blocked by a β-adrenergic antagonist (propranolol) (7). Adrenergic receptors in mammalian cells are GPCRs that belong to two broad categories, α and β, and can be specifically blocked by α-adrenergic and β-adrenergic antagonists. Further examination confirmed that QseEF influences EHEC formation of AE lesions on epithelial cells (36). Additionally, QseEF regulates the expression of genes involved in the SOS response and Shiga toxin production, as well as genes encoding other TCSs, including RcsBC and PhoPQ (26, 46, 47). The QseC

TABLE 1 Bacterial receptors of mammalian signals

Signal	Bacterial receptor	Species	Function(s)	*In vivo*[a]	Reference(s)
Gastrin	Unknown	*H. pylori*	Growth		50
Somatostatin	Unknown	*H. pylori*	Growth		51
Insulin	Unknown	*B. pseudomallei*	Growth, virulence		54
EGF	Unknown	*Providencia stuartii*	Unknown		53, 54
Dynorphin	Unknown	*P. aeruginosa*	QS, virulence	Mouse	62
Natriuretic peptides	Unknown	*P. aeruginosa*, *P. fluorescens*	Virulence, biofilm, LPS modifications	Worm	55, 56
Estrogen steroid hormones	Unknown	*A. tumefaciens*, *P. aeruginosa*	QS		64
IL-1	Caf1A	*E. coli*, *Y. pestis*	Growth		66
IL-2	Unknown	*E. coli*	Growth		65
TNF-α	Unknown	*E. coli*, *Shigella*, *S. enterica*	Virulence, invasion, intracellular replication		67
IFN-γ	OprF	*P. aeruginosa*	QS, lectin PA1, pyocyanin,		68
CAMPs	PhoQ	*S. enterica*	LPS modification, T3SS, invasion, intramacrophage replication	Mouse	72, 163
Glutathione	PrfA	*L. monocytogenes*	Cellular invasion, phagosome escape, cell-to-cell spread	Mouse	143
EA	EutR	*S. enterica*	Growth, T3SS activation, intramacrophage survival	Mouse	104, 113
		EHEC	Growth, T3SS activation, fimbrial and toxin expression		102, 110, 114, 115
	EutW	*E. faecalis*	Growth	Worm	103
		L. monocytogenes	Growth	Mouse	105
Fucose	FusK	EHEC	T3SS, growth	Rabbit	126
Adrenaline/noradreline	QseC	*E. coli*	T3SS activation, motility, toxin expression, iron uptake, virulence, growth,QS, biofilm formation	Rabbit	7, 15–24, 28, 29, 31, 32, 46
		S. enterica	Cell invasion, intracellular replication, virulence gene expression	Mouse	41, 152
		F. tularensis	Biofilm formation, intramacrophage replication, serum resistance	Mouse	153–155
		Edwardsiella tarda	Motility, intracellular virulence	Zebrafish	45
		Legionella pneumophila	Replication within amoebae	Amoebae	156
		Haemophilus influenzae	Biofilm		157
		Actinobacillus pleuropneumoniae	Adhesion		158
		Aeromonas hydrophila	Motility, biofilm, protease, cytotoxic enterotoxin	Mouse	39, 159
		Pectobacterium carotovorum	Biofilm	Cabbage	160
		Aggregatibacter actinomycetemcomitans	Iron storage, biofilm		161, 162
QseE		*E. coli*	AE lesion formation, toxin expression, stress response		26, 36, 46
		S. enterica	Cell invasion, intracellular replication, virulence gene expression		152

[a] Only studies that used intact, whole animals were included (i.e., studies using primary cells in tissue culture and/or animal tissue extracts are not listed).

and QseE regulatory cascades have distinct, as well as overlapping, targets (46). Thus, adrenaline/NA signaling through QseC and QseE may lead to the enhanced expression of certain virulence genes, or perhaps QseC and QseE are important for EHEC to effectively coordinate virulence gene expression in response to distinct microenvironments within the host. EHEC colonizes the human colon, and it has to sense when it reaches this GI compartment, as well as whether it is in the lumen or at the interface with the epithelium, where it forms AE lesions. Different compartments of the GI tract have different concentrations of adrenaline and NA. Hence, the ability to sense these adrenergic hormones may be important for the optimal expression of EHEC's virulence repertoire to ensure colonization of its host.

Peptide hormones. Peptides constitute an extremely diverse class of hormones. They are processed from a prohormone and exported out of the cell (8). Bacteria sense several of these hormones (Table 1). *Helicobacter pylori* colonizes the stomachs of 50% of the human population. This bacterium can cause duodenal ulcers and gastric cancer (48). Gastrin, a peptide hormone secreted by stomach cells, stimulates the release of gastric acid (49) and has been shown to increase the growth rate of *H. pylori*, and this gastrin-induced phenotype can be outcompeted by the synthetic analogue pentagastrin and another peptide hormone, cholecystokinin. Although the sensor for gastrin in *H. pylori* has not yet been identified, the fact that this response can be blocked by gastrin analogs suggests the presence of a bacterial receptor for this

hormone. It is also noteworthy that this response is restricted to human gastrin, and this may explain the specificity of *H. pylori* to humans (50). Conversely, another gastric peptide hormone, somatostatin, which inhibits the secretion of gastric acid, suppresses *H. pylori* growth. Somatostatin has been shown to directly bind to bacteria, and this binding can be blocked by an antisomatostatin antibody, again suggesting that *H. pylori* harbors an as-yet-unidentified receptor for this peptide (51). Moreover, *H. pylori* infection also changes the levels of these two hormones, increasing and decreasing the levels of gastrin and somatostatin, respectively (52, 53).

Burkholderia pseudomallei is the causative agent of melioidosis, and the most common risk factor for melioidosis is diabetes mellitus. *B. pseudomallei* and the related species *B. cepacia* are both capable of binding and responding to insulin, the peptide hormone secreted by the pancreas that is responsible for the regulation of blood glucose levels, to increase growth and virulence by reducing the activity of phospholipase C and acid phosphatase (54). However, the bacterial insulin receptor remains unknown.

Another class of peptide hormones sensed by bacteria is natriuretic peptides, which are involved in the osmoregulation of blood. This family contains three structurally related peptides, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP), which in mammalian cells signal through membrane-bound guanylyl cyclase receptors. *Pseudomonas aeruginosa* and *P. fluorescens* increase their cytotoxicity and modify their lipopolysaccharide (LPS) in response to BNP and CNP. This LPS modification causes it to be more necrotic to eukaryotic cells than the unmodified LPS is. These hormones increase the levels of cyclic GMP (cGMP) and cyclic AMP (cAMP) in *Pseudomonas* through two cytoplasmic adenylate cyclases, and cAMP binds to Vfr to engender this response. Cyclic nucleotides are important intracellular signaling molecules that promote biofilm formation and the expression of virulence traits in *P. aeruginosa*. Vfr bound to cAMP activates the expression of virulence genes that promote acute *P. aeruginosa* infection, while cGMP signaling represses the genes involved in acute infection and facilitates the expression of genes involved in biofilm formation, which causes chronic infections. The sensing of these natriuretic peptides may allow *Pseudomonas* to sense the blood environment. The receptor(s) that senses these peptides has not yet been identified, but the shared use of cyclic nucleotides as second messengers downstream of natriuretic peptides converges in both prokaryotes and eukaryotes (55, 56) (Fig. 1).

Another example of interkingdom signaling that involves peptide hormones is the sensing of EGFs, which are small proteins widely used as signals by animal cells (57). Secretion of EGFs requires proteolytic activation by the eukaryotic membrane serine protease rhomboid (RHO). RHO homologues in prokaryotes, such as the Aar protein encoded by *Providencia stuartii*, provide a link between eukaryotic signaling and host-microorganism communication. Aar can functionally substitute for RHO in *Drosophila melanogaster*; moreover, eukaryotic RHO can complement a *P. stuartii* aar mutant. RHO is involved in signaling in animal cells, and Aar is also required for the production of a bacterial QS signal whose structure is still unknown (58, 59). QS in *P. stuartii* represses the expression of an acetyltransferase that acetylates peptidoglycan (an intrinsic component of the bacterial cell wall). The increased acetylation of peptidoglycan changes the morphology of cells, causing them to round up as coccobacilli and form chains (60, 61). Although eukaryotic RHO and prokaryotic Aar are interchangeable, suggesting an interkingdom signaling link, it is unknown whether *P. stuartii* responds to the EGF eukaryotic signal or whether the *P. stuartii* Aar-dependent signal influences eukaryotic cells.

A final class of peptide reported to mediate interkingdom signaling comprises opioid hormones. Intestinal damage that may occur during surgery or biopsy-related procedures causes the opioid dynorphin to be released into the intestinal lumen. The opportunistic pathogen *P. aeruginosa* can internalize dynorphin, which activates the QS pathway through the *Pseudomonas* quinolone signal (PQS). The PQS is a QS signal that binds to the multiple virulence factor regulator (MvfR) or PQS regulator (PqsR) to enhance the expression of genes necessary for its own production, as well as promote virulence gene expression. MvfR/PqsR is involved in the action of dynorphin (Fig. 1) (62).

Steroid hormones. Steroid hormones control metabolism, immunity, sexual development, and many other physiological functions in mammals. They are generally synthesized from cholesterol and are lipids that can pass through the cell membrane. Their receptors are usually located within the nucleus or in the cytosol (8). It is noteworthy that one of the best-characterized classes of bacterial QS signals, the acyl-homoserine lactones (AHLs), are themselves lipidic and are also known to cross membranes, with their bacterial receptors, the LuxR-type family of proteins, being cytosolic (63). While screening *Agrobacterium tumefaciens* and *P. aeruginosa* for AHL-based-QS inhibitors, Beury-Cirou et al. identified three mammalian estrogen steroid hormones (estrone, estriol, and estradiol) as QS inhibitors (Fig. 1). They decreased AHL accumulation and the expression of QS-dependent genes (64).

CROSS SIGNALING BETWEEN QS AND HOST DEFENSES

The function of the immune system is to recognize and clear pathogens. Consequently, an underlying theme of bacterial pathogenesis research pertains to how pathogens recognize and subvert the host's immune response. Bacteria have evolved multiple systems to sense several components of the immune system, including cytokines, apolipoprotein B (ApoB), Nox2, and antimicrobial peptides. Moreover, there seems to be an important intersection between bacterial QS and host immune signaling, with several bacterial signals modulating immune responses in mammalian cells.

Cytokine signaling in pathogen-mammalian interactions. Cytokines are the chief signaling molecules employed by the immune system, which makes them a prime target to be recognized as cues by pathogens. Several cytokines (such as interleukin-1 [IL-1], IL-2, and granulocyte macrophage colony-stimulating factor) increase the growth of pathogenic *E. coli*, suggesting that bacteria sense these cytokines and change their behavior (65). IL-1 was reported to bind to pathogenic *E. coli* and to *Yersinia pestis* (the causative agent of plague) (66). IL-1 binds to the F1 antigen of the *Y. pestis* capsule through the capsule antigen F1 assembly (Caf1A) protein, which is an outer membrane protein responsible for its assembly (66). Caf1A shows significant homology to the human IL-1β receptor, suggesting that the gene encoding Caf1A may have been horizontally acquired from mammals. Additionally, several Gram-negative bacteria, including *E. coli*, *Shigella*, and *Salmonella enterica*, bind to and alter their virulence in response to another proinflammatory cytokine, tumor necrosis factor alpha (TNF-α).

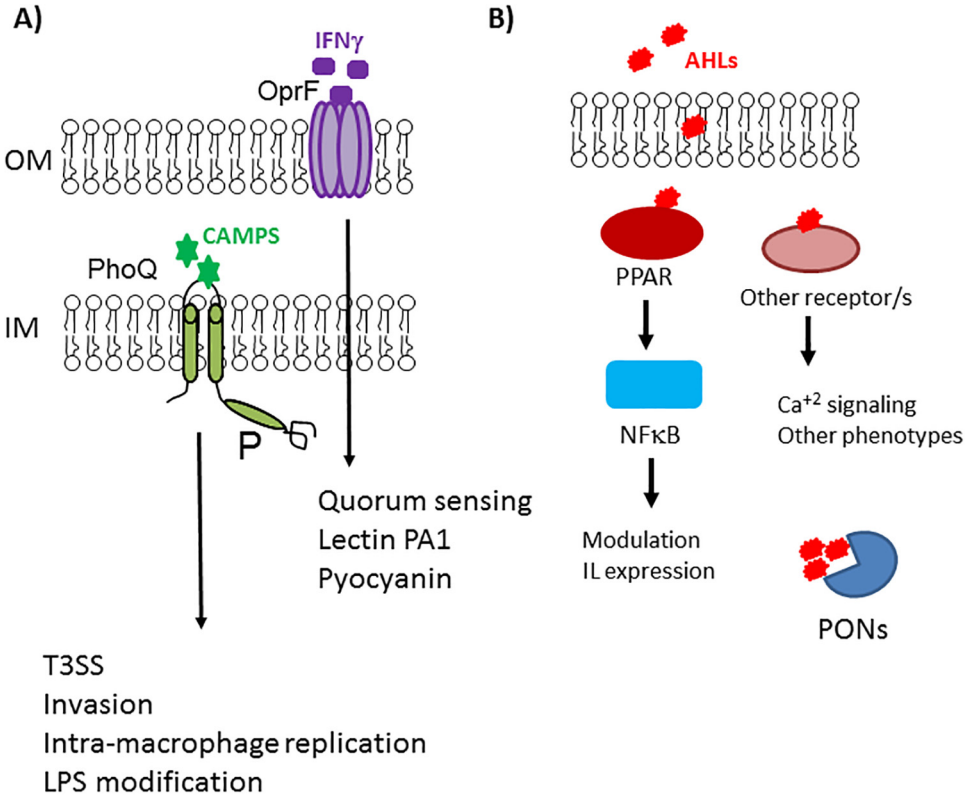

FIG 2 Cross signaling with host defenses. (A) The inner membrane (IM)-bound PhoQ histidine kinase from *S. enterica* directly binds to and responds to mammalian CAMPs and activates the T3SS and LPS modifications and promotes invasion of epithelial cells and intramacrophage replication. The outer membrane (OM) protein OpfR of *P. aeruginosa* interacts with the cytokine IFN-γ. This signaling promotes QS, induces lectin PA1 expression that causes intestinal damage, and induces pyocyanin expression. (B) The bacterial QS signals, AHLs, cross the mammalian plasma membrane and interact with the PPAR family of nuclear receptors to modulate NF-κB activity and the expression of different ILs. However, not all AHL signaling activity within mammalian cells occurs through PPARs, suggesting that other receptors exist. Additionally, mammalian PON lactonases degrade the AHL signals.

The exact mechanisms of TNF-α recognition by these bacteria are unknown. TNF-α binding to *Shigella* enhances the invasion of epithelial cells and uptake and replication within macrophages (67). Another cytokine that has been reported to be sensed by bacteria is gamma interferon (IFN-γ). IFN-γ binds to outer membrane porin F (OprF) (Fig. 2A) of *P. aeruginosa*, leading to activation of the QS gene *rhlI*, which synthesizes the signal C_4-homoserine lactone (C_4-HSL), resulting in induction of the expression of lectin PA-1, which leads to disruption of the intestinal barrier, and pyocyanin (68). This IFN-γ enhancement of *P. aeruginosa* pathogenesis is especially intriguing in light of the observation that IFN-γ treatment worsens *P. aeruginosa* infections in several mouse models and clinical studies (69).

Bacterial sensing of mammalian antimicrobial peptides. One of the front lines of defense of the innate immune system is the production of cationic antimicrobial peptides (CAMPs). CAMPs interact with and disrupt the bacterial membrane. Several bacterial pathogens modify the lipid A of their LPS to prevent CAMPs from binding to their outer membrane. One of the best-characterized examples of lipid A modifications that lead to CAMP resistance has been described in the intracellular pathogen *S. enterica*. These lipid A modifications are controlled by the PhoPQ TCS, where PhoQ is the HK and PhoP is the RR. PhoPQ regulation of genes encoding lipid A modification enzymes is vital for *S. enterica* virulence (70). PhoQ autophosphorylation is repressed by divalent metal ions such as Ca^{2+} and Mg^{2+}, and their depletion induces virulence gene expression. These ions act as bridges between acidic residues in the periplasmic domain of PhoQ and the negatively charged phospholipids on the membrane, locking the protein in a repressed state (71). Conversely, CAMPs activate PhoQ by directly binding to the same metal binding sites on PhoQ (Fig. 2A), even in the presence of physiologically relevant concentrations of divalent cations. CAMPs alter the conformation of PhoQ, activating its kinase activity, leading to the phosphotransfer to PhoP and the activation of downstream genes necessary for invasion of epithelial cells and intramacrophage replication (72).

Bacterial signals modulating the host immune response. Inasmuch as bacteria sense host signaling molecules, it is not surprising that the host is also capable of sensing molecules important in bacterial signaling. The bacterial QS AHL signals have immunomodulatory effects (73). *P. aeruginosa* produces two AHLs, C_{12}-HSL and C_4-HSL. Extensive studies showed that C_{12}-HSL mediates both pro- and anti-inflammatory responses. To mediate an anti-inflammatory response, C_{12}-HSL inhibits the production of IL-4 and IFN-γ, thereby inhibiting the proliferation of both Th1 and Th2 T helper cells (74–76). Furthermore, C_{12}-HSL prevents LPS- or TNF-mediated activation of NF-κB, suggesting that this AHL modulates NF-κB-dependent gene expression induced by proinflammatory stimuli (77). In contrast, to

elicit a proinflammatory response, C_{12}-HSL acts as a chemotactic cue for polymorphonuclear leukocytes (78) and induces IL-8 production through the mitogen-activated protein kinase pathway via the NF-κB and AP-2 transcription factors (79). IL-8 is a potent chemokine for neutrophils, and C_{12}-HSL NF-κB activation also leads to the activation of cyclooxygenase (Cox-2), which is a proinflammatory enzyme responsible for the production of prostaglandin (80). The strong induction of inflammation assists in the clearance of *P. aeruginosa* by healthy individuals but exacerbates the disease in cystic fibrosis patients (81). The anti- and proinflammatory roles of AHLs are probably reflective of the complex interaction of these molecules with different sets of immune cells during the infection process.

In addition to immune modulation, AHLs (specifically, C_{12}-AHL) induce apoptosis in various mammalian cell types, including macrophages, neutrophils, and some epithelial cell lines. AHLs suppress signaling through the signal transducer and activator of transcription 3 (STAT3) pathway (82, 83) and by releasing calcium from the endoplasmic reticulum (84).

AHLs are lipidic signals; hence, it was shown that C_{12}-HSL enters mammalian cells across the cell membrane in a fashion similar to that of mammalian steroid hormones (85). The observation that AHLs penetrate the mammalian cell membrane, combined with comparative structural analyses of LuxR-type bacterial receptors, led to the speculation that intracellular nuclear receptor proteins may be AHL receptors (86). Indeed, the peroxisome proliferation activator receptor (PPAR) family of nuclear receptors was shown to be mammalian AHL receptors (87) (Fig. 2B). However, PPAR recognition of AHLs does not fully account for all of the biological effects of this bacterial signal on mammalian cells, suggesting that other receptors exist (87).

Another facet of this interkingdom communication includes the fact that mammals evolved means to interfere with bacterial AHL signaling through a family of enzymes called paraoxonases (PONs), which act as lactonases that degrade AHLs. These enzymes are not secreted into the extracellular environment, where they could interfere with QS signaling, but they degrade AHLs within mammalian cells (88–91). There are three PONs (PON1, PON2, and PON3), and studies using knockout mice have determined that PON2 is the most likely candidate for an active AHL-degrading enzyme (92). Interestingly, in these arms races of interkingdom chemical signaling, a C_{12}-HSL-mediated increase in cytoplasmic calcium in mammalian cells leads to the degradation of PON2 mRNA and a decrease in the hydrolytic activity of this enzyme (93) (Fig. 2B).

Mammalian Nox2 and ApoB interference with bacterial QS. ApoB is a component of low-density lipoprotein (LDL) and very LDL present in large concentrations in serum. Nox2 is an NADPH oxidase expressed in phagocytes that generates reactive oxygen species. Both Nox2 and ApoB antagonize the QS signal autoinducing peptide (AIP), which activates virulence gene expression in *Staphylococcus aureus* (94, 95). ApoB directly binds to AIP, sequestering this signal from its bacterial receptor AgrC and preventing QS and virulence activation in *S. aureus* (95). Nox2 oxidizes LDL, facilitating a conformational change in ApoB and allowing it to bind and sequester all classes of AIPs (there are four different AIPs, which differ in their amino acid sequences, that are produced by different *S. aureus* strains) (96). This constitutes an example of host defense by interference with bacterial QS.

INTERKINGDOM NUTRITIONAL SIGNALING

The mammalian GI tract provides a complex and competitive environment for the resident microbiota (97, 98). Successful intestinal colonization by pathogenic bacteria is thought to depend on their scavenging nutrients, sensing chemical signals present in the intestine, competing with the resident bacteria for space and nutrients, and precisely regulating the expression of virulence genes (99). The GI tract is heavily colonized by a complex and highly adapted microbiota composed of over 1,000 species of bacteria. The GI microbiota has an important symbiotic relationship with its host, providing and gaining nutrients in the form of carbon and nitrogen sources. Enteric pathogens have to compete with the residing microbes for these nutrient sources and find a suitable niche for colonization. Hence, precise coordination of the expression of virulence genes, which are competition tools for the microbiota, combined with metabolic adaptation to better exploit nutrient resources, is key for successful colonization of the host.

Ethanolamine signaling. Phosphatidylethanolamine (PE) is an essential membrane component of mammalian and bacterial cells. Besides contributing to membrane architecture (100), PE plays important roles in cell division and cell signaling and is also an important supplier of biologically active molecules (100, 101). The turnover and exfoliation of intestinal cells, including bacterial cells and enterocytes, provide a continuous supply of ethanolamine (EA) in the intestine that bacteria can use as a carbon and/or nitrogen source. Although EA is abundant in the GI tract, the resident microbiota does not efficiently metabolize EA (102), and thus, pathogens, including EHEC, *S. enterica*, and *Enterococcus faecalis*, exploit EA as a noncompetitive metabolite to outgrow the resident microbiota and establish infection (102–104). Notably, recent evidence suggests that EA metabolism confers a growth advantage on pathogens outside the intestinal environment, as both uropathogenic *E. coli* and *Listeria monocytogenes* rely on EA metabolism for robust growth during murine urinary tract and systemic infections, respectively (105, 106). Bacterial pathogens link the ability to sense EA with the genes required to catabolize EA. The EA utilization (*eut*) locus contains genes encoding the transport and breakdown of EA, as well as genes for a microcompartment that recycles cofactors and toxic intermediates generated during EA metabolism (reviewed in reference 107). Although EA metabolism is a trait associated with diverse bacterial phyla, the number and organization of the genes contained in the *eut* operon can vary considerably among species (44). The mechanism of regulating *eut* expression can broadly be categorized into the Gram-negative or Gram-positive classification scheme based on studies with *S. enterica* and EHEC (Gram negative) or *E. faecalis* and *L. monocytogenes* (Gram positive) (105, 108–112). In these examples, the *eut* locus is positively autoregulated not only in response to EA but also in response to the cofactor vitamin B_{12} (detailed in Fig. 3).

In addition to enhancing growth, EA controls virulence gene expression in EHEC and *S. enterica* serovar Typhimurium (*S.* Typhimurium) (110, 113–115). In EHEC, EA activates the expression of genes important for colonization of the GI tract, including those encoding fimbrial adhesins and the locus of enterocyte effacement (LEE) genes that promote AE lesion formation on enterocytes, as well as genes encoding Shiga toxin (114, 115). EHEC encodes 16 distinct fimbrial loci (116, 117), and these fimbriae may be crucial for the initial adherence of EHEC to epithelial cells

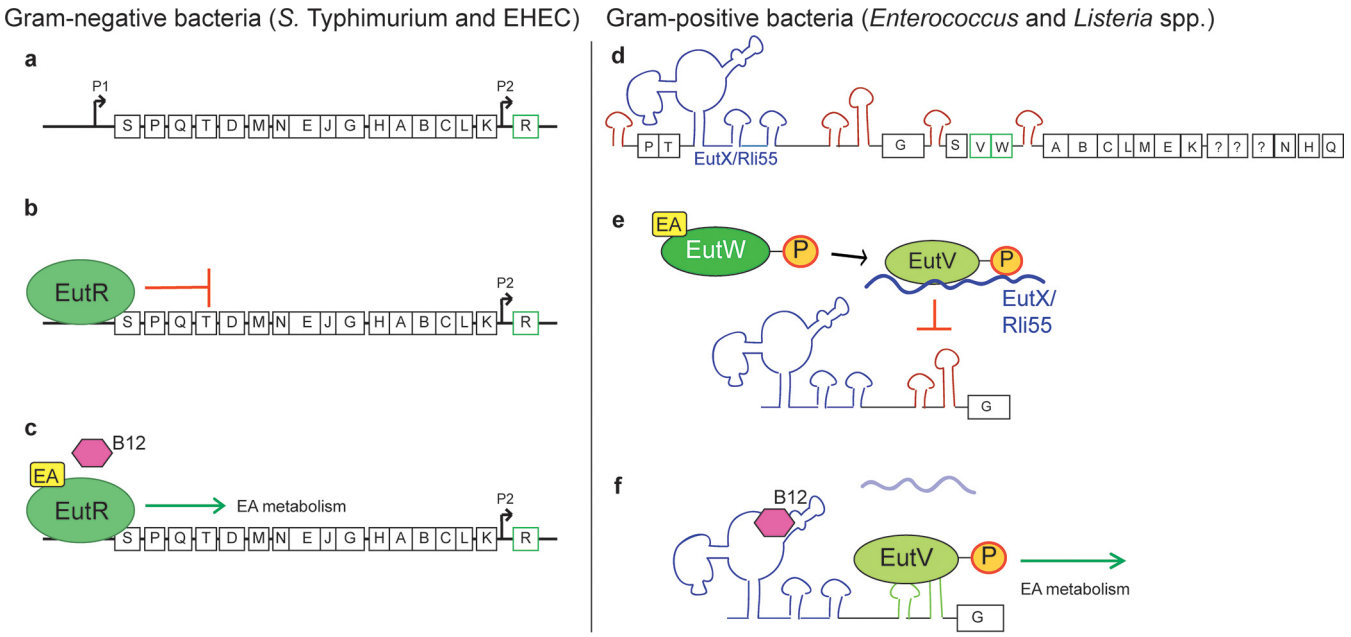

FIG 3 EA sensing and regulation of the *eut* operon. (A, B) Regulatory proteins are green, and RNA regulatory elements are blue. (A) In *S.* Typhimurium and EHEC, the *eut* locus contains 17 genes, including *eutR*, which encodes the transcription factor EutR. (B) In the absence of EA and vitamin B_{12}, EutR binds the *eut* promoter but cannot activate transcription. (C) EutR senses EA and vitamin B_{12} to activate transcription. (D) Schematic of the *eut* operon in *E. faecalis* and *L. monocytogenes*. (E) The sensor kinase EutW autophosphorylates in response to EA and then transfers this phosphate to the RR EutV. In the absence of vitamin B_{12}, the small RNA Rli55/EutX interacts with and sequesters EutV. (F) Vitamin B_{12} binds the Rli55/EutX mRNA and causes a conformational change that results in premature transcription termination, thereby enabling phosphorylated EutV to bind to and relieve transcriptional repression of the *eut* locus.

that precedes intimate, LEE-dependent adherence (118). However, many fimbrial loci have been hypothesized to be cryptic because of the difficulties of expressing fimbrial genes *in vitro* (119). Thus, the finding that the biologically relevant molecule EA promotes the expression of EHEC fimbriae suggests that these fimbriae play critical roles in the ability of EHEC to establish infection. The transcription factor EutR directly regulates LEE expression (110), and genetic data suggest that EutR also regulates a subset of EHEC fimbriae (114).

The *in vivo* importance and relevance of EA-dependent virulence gene regulation were recently demonstrated in *S. enterica*. *S. enterica* senses EA within macrophages to activate the expression of genes required for intracellular survival and replication and thus enhance dissemination. Importantly, EA-dependent virulence gene regulation is independent of EA metabolism, as a strain deficient in the EA catalytic enzymes is able to respond to EA and activate the expression virulence genes in EHEC and *S. enterica* (115, 113).

Signaling through sugars. The mammalian intestinal epithelium is protected from direct contact with bacteria by the mucus layer. This mucus is composed of mucin, antimicrobial peptides, glycoproteins, glycolipids, epithelial cell debris, and 50% polysaccharides (121). The major structural component of mucus is mucin, a glycoprotein that has a protein backbone connected to hydrophilic and hygroscopic oligosaccharide side chains that form a gel-like tridimensional structure (122). A diverse collection of monosaccharides decorates mucin: arabinose, fucose, galactose, gluconate, glucuronate, galacturonate, mannose, glucosamine, *N*-acetylglucosamine, galactosamine, *N*-acetylgalactosamine, *N*-acetylneuraminic acid, and ribose. These sugars are made available to the microbiota through the polysaccharide-degrading activity of glycolytic commensal anaerobes. Hence, the mucus layer is an important habitat and source of carbohydrates for bacterial communities that colonize mucosal surfaces, especially in the colon (122). Moreover, gut commensals influence the glycan composition of mucin, with the prominent member of the GI microbiota *Bacteroides thetaiotaomicron* inducing the fucosylation of host mucins (123).

Enteric pathogens have evolved systems to exploit the metabolic properties of specific members of the microbiota as nutritional cues to gain a competitive advantage. *S. enterica* and *Clostridium difficile* exploit metabolic end products of *B. thetaiotaomicron*, including fucose, sialic acid, and succinate, and expand in the intestine following disturbances of the microbiota due to antibiotic treatment (124, 125). Furthermore, EHEC uses metabolic end products of *B. thetaiotaomicron* as nutritional cues to alter the expression of virulence genes important for host colonization. Specifically, glycophagic *B. thetaiotaomicron* generates fucose from host mucin, making fucose accessible to EHEC. EHEC senses fucose by using the TCS FusKR, which has been recently horizontally acquired by this pathogen, possibly from *E. faecalis*. Fucose sensing through the HK FusK initiates a signaling cascade through FusK's RR, FusR, that regulates the expression of virulence and metabolism genes (Fig. 4). This regulatory circuit may function as a cue for EHEC to sense its location in the lumen, where *B. thetaiotaomicron* resides and makes this sugar source available and where the expression of EHEC's virulence repertoire is onerous and not advantageous (126). Specifically, FusR represses the expression of the LEE genes, which are only necessary at the epithelial interface, and also the genes involved in fucose utilization. EHEC's main competition for carbon sources in the lumen is commensal *E. coli*, which favors fucose as a carbon source within the intestine (126). Repression of the fucose utiliza-

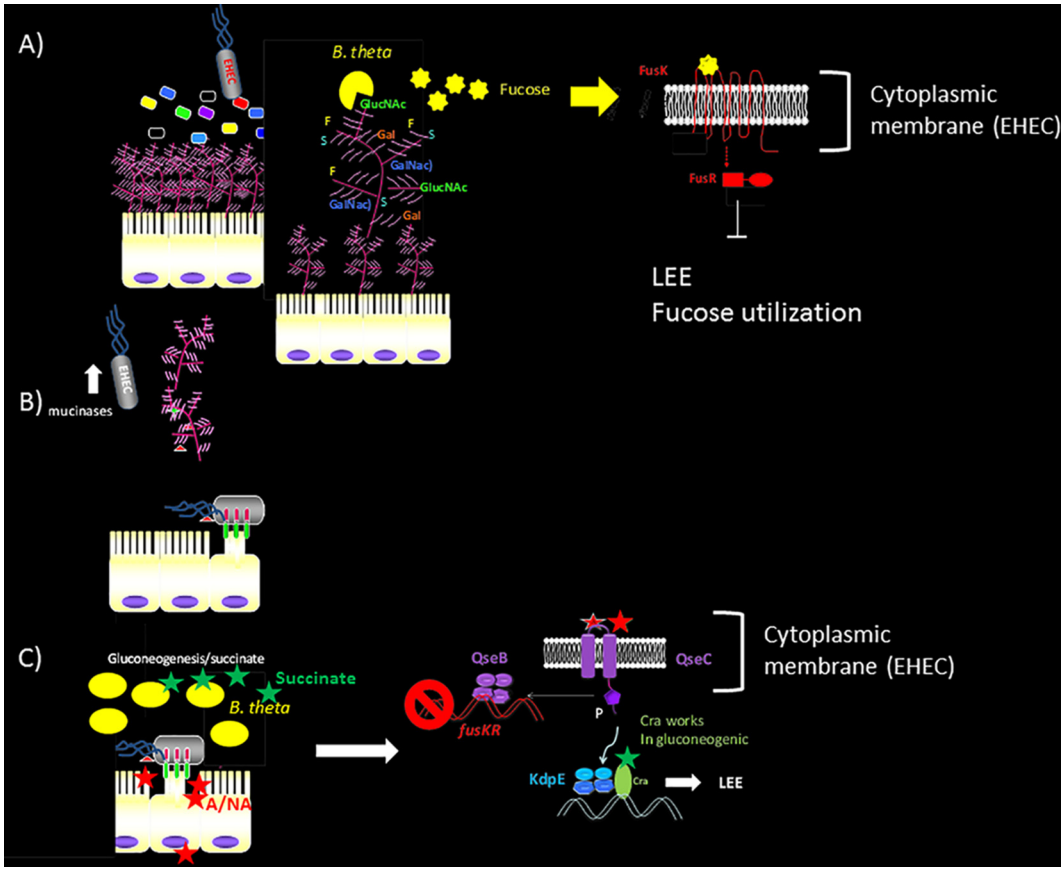

FIG 4 Sugar regulation at the interfaces among the host, microbiota, and enteric pathogens. (A) EHEC senses fucose cleaved from the mucus layer by *B. thetaiotaomicron* (*B. theta*) in the colon as a cue to recognize that it is in the intestinal lumen. Fucose is sensed by the histidine kinase FusK in EHEC to rewire transcription, repressing the expression of the LEE and fucose utilization genes to adapt to this intestinal compartment. (B) As disease progresses, EHEC produces mucinases that obliterate the mucus layer. EHEC gains access to the epithelium, as do *B. thetaiotaomicron* and other members of the microbiota. (C) However, without mucus as a carbon source, this is a carbon-poor environment where *B. thetaiotaomicron* starts to secrete succinate, which, upon being taken up by EHEC, is sensed by the Cra transcription factor as a clue to a gluconeogenic environment. Cra binds to another transcription factor, KdpE, which is an RR phosphorylated by the QseC adrenergic sensor, to integrate adrenergic and sugar sensing to activate virulence gene expression at the interface with the intestinal epithelium. QseC then also, through another RR, QseB, represses the expression of the *fusKR* genes, further derepressing the LEE (virulence genes).

tion genes by FusR in EHEC prevents competition with commensal *E. coli* for fucose and rewires EHEC's metabolism to favor D-galactose as a primary carbon source. Of note, D-galactose is also highly prevalent in this compartment, and EHEC utilizes this sugar source better than commensal *E. coli* does, gaining a metabolic competitive advantage (127). Thus, it is tempting to speculate that acquisition of FusKR enhances EHEC's ability to successfully compete for a niche in the colon.

Using yet another nutrient-based environmental cue, EHEC also regulates virulence gene expression through recognition of glycolytic and gluconeogenic environments. The lumen is more glycolytic (rich in sugar) because of predominant glycophagic members of the microbiota degrading complex polysaccharides into monosaccharides that can be readily utilized by nonglycophagic bacterial species such as *E. coli* and *Citrobacter rodentium* (a murine pathogen that models EHEC mammalian infection). In contrast, the tight mucus layer between the lumen and the epithelial interface in the GI tract is devoid of microbiota; it is known as a "zone of clearance." Enteric pathogens such as EHEC produce mucinases whose expression is enhanced by end products of *B. thetaiotaomicron* metabolism. As infection progresses, these mucinases completely degrade the mucus. In this scenario, both the pathogen and *B. thetaiotaomicron* are now closer to the epithelium in a gluconeogenic (poor sugar) microenvironment (no mucus left to extract sugar from), where *B. thetaiotaomicron* is producing and secreting succinate that is now sensed by the EHEC transcription factors Cra and KdpE to promote virulence gene expression, presumably at the interface with the epithelium. Importantly, succinate also influences host behavior, inhibiting polymorphonuclear leukocyte function (128, 129). Hence, the coupling of virulence regulation to optimal expression under gluconeogenic and low-fucose conditions mirrors the interface with the epithelial layer environment in the GI tract, suggesting a model in which EHEC will only express its virulence genes at optimal levels at the epithelial interface (35, 130) (Fig. 4).

Importantly, these sugar-sensing systems in EHEC are interconnected with the adrenergic sensing systems. The QseC and QseE kinases that sense adrenaline and NA through their RRs repress the expression of the *fusKR* genes, preventing FusKR's repression of LEE gene expression (126). Another level of integration occurs with the sensing of gluconeogenesis and succinate, given that the QseC-phosphorylated RR KdpE directly interacts

with the gluconeogenesis sensor Cra to promote virulence gene expression (35). Hence, at the epithelial interface, where adrenaline and NA are more likely to be found and the environment is gluconeogenic, QseC and QseE are triggered, and they promote LEE gene expression through the KdpE and Cra transcription factors and relieve the previous LEE repression by FusKR by repressing the expression of the *fusKR* genes.

Glutathione. The antioxidant glutathione (L-γ-glutamyl-L-cysteinyl-glycine; GSH) is a low-molecular-mass thiol that is involved in multiple physiological processes in plants and animals (reviewed in references 131 and 132). In prokaryotes, the ability to synthesize GSH is limited to cyanobacteria, proteobacteria, and a few strains of Gram-positive bacteria (133, 134). However, some bacterial pathogens that do not produce GSH, including *Francisella tularensis* (135) and *Helicobacter pylori* (136–138), have evolved mechanisms to scavenge and incorporate host-produced GSH into energy-generating or biosynthetic pathways. Moreover, the food-borne pathogen *Listeria monocytogenes* senses mammalian-produced GSH as an interkingdom signaling molecule. During infection, *L. monocytogenes* crosses the intestinal barrier and invades immune and epithelial cells, escapes from the phagosome, replicates in the host cell cytosol, and spreads from cell to cell, thereby escaping immune defenses. The transcription factor PrfA is a master regulator of virulence genes in *L. monocytogenes* and directs the expression of traits necessary for each of these steps of listerial infection (139–142). Recent genetic and biochemical data demonstrate that PrfA directly binds GSH to activate the expression of genes involved in *L. monocytogenes* pathogenesis. Importantly, PrfA binds to reduced GSH with higher affinity than oxidized GSH (143), demonstrating that sensing of GSH may be a mechanism for *L. monocytogenes* to specifically recognize the intracellular environment.

Interkingdom signaling with nonmammalian hosts. As signaling systems based on hormones, metabolites, and host defenses, which are used by mammalian pathogens, are discovered and characterized, additional research indicates that these interkingdom signaling mechanisms are conserved in bacteria that infect nonmammalian hosts. For example, in the fish pathogen *Edwardsiella tarda*, the QseBC TCS regulates the expression of genes encoding motility, fimbriae, and the T3SS (45) similarly to the role of interkingdom signaling in mammalian systems. Moreover, *E. tarda* responds to adrenaline to promote motility, and this effect was lost by a *qseB* or *qseC* deletion strain (45), suggesting that the mechanism of QseBC-dependent gene regulation is conserved in diverse pathogens. Additionally, the *eut* locus that encodes EA metabolism has been implicated as important to the infection strategies of the insect pathogen *Photorhabdus luminescens* and the plant pathogen *Erwinia chrysanthemi* (144, 145). Interestingly, a disruption of *eutR* in *E. chrysanthemi* results in impaired systemic infection of African violet plants (145). Whether this effect is due to the defect of EA metabolism and/or EA signaling through EutR-dependent regulation of virulence traits has not been reported. Finally, the coral pathogen *Vibrio coralliilyticus* senses the host metabolite dimethylsulfoniopropionate (DMSP) to regulate chemotaxis and chemokinesis in order to infect the mucus of its coral host, *Pocillopora damicornis* (146). Significantly, *V. coralliilyticus* does not metabolize DMSP, indicating that DMSP functions specifically as a signal for *V. coralliilyticus* to regulate virulence genes (146).

Although this review has focused on interkingdom signaling in host-pathogen interactions, interkingdom signaling also plays a role in mutualistic relationships between bacteria and hosts. One of the best-studied examples is that of rhizobia and host legume plants. The rhizobia are nitrogen-fixing bacteria that infect plant roots, eventually forming a new root organ or a nodule, under nitrogen-limiting conditions. In the nodule, the bacteria fix nitrogen that can be used by the host, and in return, the plant provides carbon that the bacteria use for growth. For this mutually beneficial relationship to be established, signals are exchanged between the bacteria and the host. Specifically, the legumes produce flavonoids that are sensed by the bacterial NodD protein. Subsequently, the NodD protein initiates a regulatory cascade essential for nodule formation. Furthermore, the bacteria also produce signals that influence the host response to infection. For example, the bacterial Nod factor may play a role in suppressing the plant immune response, thereby inducing nodule development (164). Studies on how the rhizobia influence plant innate immunity to establish symbiotic associations highlight that interkingdom signaling is not limited to host-pathogen interactions. Indeed, it is likely that additional studies that examine interkingdom signaling between a host and the resident microbiota will demonstrate that interkingdom signaling is a conserved mechanism shared by pathogens and commensal bacteria to form associations.

CONCLUSIONS

In this review, we have discussed how bacterial pathogens sense diverse mammalian hormones as cues to promote host colonization. We have also addressed the immune signaling interplay involved in pathogen-host associations and integrated these signaling systems with efficient nutrient sensing and utilization. While interkingdom chemical signaling systems are extremely diverse, there is a recurrent trend; i.e., they intersect with QS and nutritional cues. The intersection with QS may reflect the central role that QS plays in virulence regulation and coordination of population behaviors leading to successful association with a host. Bacteria produce many of the same small molecules as eukaryotes or molecules similar to them, suggesting that these behaviors may be an example of convergent evolution or that they have the same origin. After all, hormones and other signaling molecules employed by multicellular eukaryotes serve the same basic purpose as QS molecules, i.e., intercellular communication that mediates cooperative behaviors. The ability to sense and respond to host signals was identified in most major pathogens, suggesting that interkingdom signaling is extremely common and that these signaling pathways could be targets for the development of new antimicrobial drugs. One can envision the repurposing of hormonal analogs such as the gastrin analogue pentagastrin in controlling *H. pylori* infections (50). Another possibility is to exploit hormones such as somatostatin (51) and estrogen steroid hormones (64) to inhibit growth or virulence. Finally, there are examples of inhibitors of bacterial adrenergic receptors, such as QseC, that prevent virulence gene expression and act as promising antivirulence drugs to treat infections by many pathogens (147, 148). Future research will also unravel many classes of novel chemicals employed in these interactions.

In addition to the convergence with QS, interkingdom signaling obviously intertwines with nutrition. This is especially exciting given the renaissance of research on the chemistry of the microbiome and the recent appreciation that carbon and nitrogen sources are not only used as metabolites but are important signals

interpreted by enteric pathogens to regulate virulence and adjust their metabolism. Moreover, the engagement between host microbiota and pathogens is fascinating; with members of the microbiota inducing the host to decorate its mucus layer with different carbohydrates that can then be scavenged by members of the microbiota itself as carbon sources and exploited by enteric pathogens as nutritional and competition cues. The implications are that dietary changes, antibiotic treatments, and genetic trends causing shifts in the gut microbial populations may have important consequences regarding infection by pathogenic agents and host health and homeostasis. New powerful technologies are emerging to probe the chemistry within these microbiota-host-pathogen relationships. An especially powerful approach relies on imaging mass spectrometry, by which modifications of the chemical landscape in different microbe-microbe and microbe-host associations can be mapped (149, 150).

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