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Enterohemorrhagic *Escherichia coli* outwits hosts through sensing small molecules

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Abstract

Small molecules help intestinal pathogens navigate the complex human gastrointestinal tract to exploit favorable microhabitats. These small molecules provide spatial landmarks for pathogens to regulate synthesis of virulence caches and are derived from the host, ingested plant and animal material, and the microbiota. Their concentrations and fluxes vary along the length of the gut and provide molecular signatures that are beginning to be explored through metabolomics and genetics. However, while many small molecules have been identified and are reviewed here, there are undoubtedly others that may also profoundly affect how enteric pathogens infect their hosts.

Introduction

Enterohemorrhagic *Escherichia coli* (EHEC) is a non-invasive intestinal pathogen that adeptly senses small molecules to infect the human large intestine. After consuming contaminated food or water, EHEC causes hemorrhagic colitis, and in severe cases, hemolytic uremic syndrome or death [1]. EHEC is a problematic, common pathogen because of its low infectious dose (< 100 cells) [1]. In addition, EHEC skillfully utilizes a plethora of small molecules to tightly regulate expression of its type III secretion system (T3SS) encoded on the locus of enterocyte effacement (LEE), a pathogenicity island that harbors 41 genes the majority of them being organized on five operons [2–4]. The LEE is needed for EHEC to colonize the gut by forming attaching and effacing (AE) lesions on enterocytes. AE lesions are associated with the dynamic remodeling of the host's cytoskeleton leading to the formation of a pedestal-like structure underneath the adherent bacterium. Expression of the LEE is energetically costly, and thus, tightly regulated to be deployed in microhabitats where it can help EHEC compete for a niche. Recent data about

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the type and role of these small molecules in EHEC pathogenesis will be explored in this review (summarized in Figure 1).

Host and microbiota signal: Ethanolamine

Bacterial and host membranes constantly release ethanolamine into the intestines, providing a reliable gut signal. Ethanolamine is useful as both a carbon or nitrogen source. EHEC uses ethanolamine as a nitrogen source to compete with the microbiota and colonize their host [5,6]. However, ethanolamine also activates expression of the LEE through the EutR transcription factor, a known ethanolamine receptor, independently of activating the *eut* operon [5,6] (Figure 1). Ethanolamine and choline also promote expression of several fimbrial operons which helps EHEC attach to cells [7]. These data suggest sensing of ethanolamine and choline is important for the initial stages of EHEC adherence to epithelial cells.

Host signals: Epinephrine and Norepinephrine

The host-derived signals epinephrine and norepinephrine play important roles in gut physiology and motility [8]. The host inactivates epinephrine and norepinephrine using glucuronidation; however, the gut microbiota encoded enzymes to cleave glucuronic acid from epinephrine and norepinephrine, thus making them biologically active in the lumen [9]. To sense these neurotransmitters, EHEC uses two bacterial adrenergic histidine sensor kinases, QseC and QseE. Upon sensing these signals, these kinases initiate a signal cascade phosphorylating three response regulators (RRs). QseE only phosphorylates the QseF RR, while QseC phosphorylates QseF, KdpE and QseB [10–15] (Figure 1). Phosphorylated KdpE then works in concert with the catabolite repressor activator (Cra), a global regulator of genes involved in gluconeogenesis, to activate expression of the LEE [14,16]. Recent data in the EHEC murine surrogate model, *Citrobacter rodentium*, highlight how *qseC, qseE*, and *qseEC* mutants are attenuated for murine infection because they fail to correctly sense epinephrine and norepinephrine [9]. In addition, in mice lacking dopamine β-hydroxylase, which do not produce epinephrine or norepinephrine, *C. rodentium* has colonization defects and reduced expression of the LEE [9]. In an infant rabbit model of infection, EHEC mutants in *qseC* [12] or the *qseEC* double mutant are attenuated [9]. It is important to note that QseC also senses the microbiota-produced signal autoinducer-3 [10,17] and QseE senses SO_4 and PO_4 [11].

Host and microbiota signals: Mucin and diet derived sugars

Exploitation of non-preferred carbon sources helps pathogens gain a niche advantage. In the gut, *E. coli* prefers monosaccharides that feed into the Embden-Meyerhof-Parnas pathway (classical glycolysis), but also metabolizes sugars using the pentose phosphate pathway and the Entner-Doudoroff (ED) pathway [18–22]. These sugars are liberated by glycophagic bacteria, such as *Bacteroides thetaiotaomicron*, degrading ingested food as well as mucus [23] (Figure 2). The GI mucus layer is composed of mucins, glycoproteins composed of 80% carbohydrates, and provides a barrier between the microbiota and host epithelial cells [23]. Recently, it has been shown in *C. rodentium* infections that diet affects the amount of

mucus degradation in the intestine [24] (Figure 2). Mice colonized with a synthetic human microbiota and fed diets devoid of fiber had eroded mucus layers compared to mice fed a fiber-rich diet. In addition, the fiber deprived mice, with diminished mucus layers, were more susceptible to *C. rodentium* infection and had more aggressive colitis [24]. In another study, mice colonized with *B. thetaiotaomicron* exacerbates *C. rodentium* infections by increasing gluconeogenic substrates such as succinate [25]. *C. rodentium* uses the gluconeogenic master regulator Cra to metabolize succinate and activate expression of the LEE [25]. *B. thetaiotaomicron* also enhances EHEC infection using another sugar utilization pathway. *B. thetaiotaomicron* liberates fucose from mucin, which is sensed by the histidine sensor kinase FusK that phosphorylates its response regulator FusR [26] (Figure 1). FusR represses LEE expression to avoid assembling the T3SS in the intestinal lumen where the microbiota would be cleaving terminal mucin sugars [26].

The mucus layer and the diet provide nutrients for the microbiota but also signals for EHEC (Figure 2). Mucin-derived sugars available for *E. coli* to utilize in the gut include: glucose, fucose, galactose, N-acetyl-galactosamine, N-acetyl-glucosamine, N-acetylneuraminic acid, fructose, xylose, and mannose [27,28]. Some diet derived sugars in the large intestine include those involved in pectin degradation. Pectin is constructed of long chains of α-1,4-glycoside-linked D-galacturonic acid which can be decorated with other terminal sugars such as rhamnose, D-xylose, L-fucose, D-glucuronic acid, and others [29]. Expression of the T3SS is affected when EHEC is grown with these mucin-derived and pectin-derived sugars as a sole carbon source. The ED pathway sugars galacturonic acid, glucuronic acid, and gluconic acid all increase secretion of EspB, which is needed to form the pore in mammalian cells for the needle apparatus of the T3SS to inject effectors into the cytosol [16]. N-acetyl-galactosamine, N-acetyl-glucosamine, N-acetylneuraminic acid, and mannose also increased secretion of EspB [16]. These sugars are important building blocks in O-linked and N-linked glycosylation of attached and secreted mucins in the large intestine [30,31]. Pyruvate, a glucoenogenic sugar, also increased secretion of EspB as well as increased expression of the LEE [16]. This increased secretion is not from a growth advantage, except potentially in the case of galacturonic acid where EHEC grows almost twice as quickly as on glucose, but suggests EHEC is regulating its virulence genes via catabolite repression [16] (Figure 2).

Host and microbiota signals: Electron acceptors

In the GI tract, *E. coli* use different electron acceptors depending on the location of their environmental niche, health of the host, and presence of the microbiota. Both aerobic respiration of oxygen (via cytochrome *bd* oxidase) and anaerobic respiration of nitrate and fumarate are needed for EHEC colonization in the intestine [32,33]. Oxygen and nitrate are both limited in the large intestine, but fumarate is more readily available and helps with longer term colonization [32]. Recent data suggest there is a radial oxygen gradient in the large intestine that varies depending on atmospheric pressure, the host's ability to sequester oxygen, and the aerotolerant members of the microbiota that consume oxygen in the outer mucosal layer [34–36]. While the lumen is predominately anaerobic, near the epithelial surface microaerobic conditions exist because of diffusion across the microvillus capillary network [34,36–38]. If the microbiota is absent or in dysbiosis, then oxygen levels can increase further [39–41]. If there is a breach in the epithelium and blood infiltrates into the

large intestine, as is common in EHEC infections, then the amount of oxygen can dramatically increase [42] (Figure 2).

New data exploring the role of oxygen on Enterobacteriaceae blooms and how oxygen regulates expression of EHEC virulence factors shed light on the dynamic processes taking place in the gut. For EHEC and *C. rodentium*, oxygen plays a strong role in regulating infection [40,42]. In mice with an inflamed gut, expression of *E. coli* genes involved in respiratory pathways are overrepresented [41,42]. Microbiota-derived formate concentrations also increase during dysbiosis and *E. coli* use it as an electron donor and oxygen as an electron acceptor to compete and proliferate in this environment [41,42] (Figure 2). For EHEC, oxygen availability also affects LEE expression. When oxygen is present, LEE expression is activated through Cra and KdpE, and when oxygen is absent, KdpE and FusR strongly repress the LEE [16] (Figure 1). However, if oxygen and pyruvate are present, then FusR represses the LEE [16]. Together, EHEC uses these three transcriptional regulators to express the T3SS when oxygen is present, which is consistent with EHEC being near the epithelial surface [16].

Host and microbiota signals: Short and long chain fatty acids, bicarbonate, and pH

Short chain fatty acids (SCFAs) vary throughout the gut and can regulate EHEC virulence genes. Concentrations of SCFAs acetate, propionate, and butyrate are affected by the microbiota and the diet (reviewed in [43]). Butyrate, a preferred food source for colonocytes, also affects EHEC colonization. In mice fed high-fiber diets with floras producing more butyrate, EHEC colonizes the mice better compared to their low fiber diet counterparts, presumably because fewer *Escherichia* species are present to outcompete incoming pathogens [44] (Figure 2). EHEC senses butyrate through the leucine-responsive regulatory (LRP) protein, which promotes transcription of *pchA*, a positive regulator of the LEE [39]. SCFAs also affect EHEC flagella and motility. Low concentrations of SCFAs, characteristic of the large intestine where EHEC forms AE lesions, reduce flagella gene *fliC* expression and motility [45].

SCFAs production affects the overall pH of the large intestine. The host uses bicarbonate to neutralize the proton byproducts of SCFAs production. EHEC can sense bicarbonate through *rscB* and *grvA* [46,47]. RscB forms a heterodimer with GadE to activate the glutamate-dependent acid resistance (GDAR) pathway and repress LEE expression when EHEC is in acidic environments such as the stomach [47]. However, once EHEC is in the intestine, it senses bicarbonate through GrvA [47]. GrvA represses the GDAR pathway, promoting expression of the LEE and increased adherence to epithelial cells [46–48] (Figure 1). EHEC also uses CpxA to sense pH changes, copper, alterations in the membrane, and overexpression of envelope proteins such as NlpE [49]. If such stimuli are present, the histidine kinase sensor CpxA phosphorylates CpxR, which modulates transcription of LEE activators *ler* and *grlA* [49]. CpxR activates *rpoH*, which then activates transcription of the *lon* protease (Figure 1). Mutants in *cpxA* or *lon* are attenuated in a *Galleria mellonella* infection model [49].

Long chain fatty acids (LCFAs), cysteine, and D-serine also affect EHEC virulence (Figure 1). The cysteine utilization regulator, CutR, was recently found to sense exogenous cysteine and promote LEE expression (Pifer submitted). CutR also activates expression of the D-serine transporter, YhaO, and long chain fatty acid transporter, FadL (Pifer submitted). D-serine concentrations are low in the large intestine, but high in other body locations [50,51]. When D-serine concentrations are low, YhaO can promote YhaJ to bind to the *LEE1* promoter and activate LEE transcription and repress the LEE when D-serine concentrations are high [50,51]. If LCFAs are unavailable, FadL can signal through the transcription factor FadR to promote fatty acid synthesis; FadR can also bind upstream of the *LEE1* promoter to repress LEE transcription (Pifer submitted). In a *C. rodentium* model, both *cutR* and *fadR* were attenuated (Pifer submitted).

Conclusions and Future Directions

Pathogens need information on their environments to control their virulence armamentariums. Through recently published data in EHEC and its mouse surrogate *C. rodentium*, it is clear enteric pathogens like EHEC must sense multiple small molecules to avoid constructing its T3SS in unfavorable niches. In addition, the advancements in visualizing intact mucus layers and infection environments *in vivo* will no doubt show the effect of other host, microbiota, or diet derived signals on EHEC virulence. Regardless of how healthy or inflamed the host environment is, EHEC can outwit the host defense systems to colonize, grow, and eventually relocate to other microhabitats.

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• of special interest

•• of outstanding interest

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Highlights

- Enterohemorrhagic *Escherichia coli* (EHEC) tightly controls expression of its type III secretion system to compete for favorable microhabitats in the large intestine.
- EHEC co-opts metabolites derived from the host or the microbiota found in the gut to promote attachment to epithelial cells.
- EHEC senses oxygen concentrations to regulate virulence gene expression, which may be indicative of gut dysbiosis.
- Different combinations of small molecules can reflect the health of the host and potential competition from the microbiota.

Highlights

- Enterohemorrhagic *E. coli* (EHEC) exploits microbiota and host derived signals and metabolites to recognize the gut environment and properly regulate expression of its virulence repertoire.
- The host hormones epinephrine and norepinephrine acts through QseC and QseE to increase EHEC virulence.
- Several host and microbiota-derived metabolites such as SCFAs, succinate, ethanolamine, fucose and aminoacids are also sensed as signals to regulate virulence gene expression

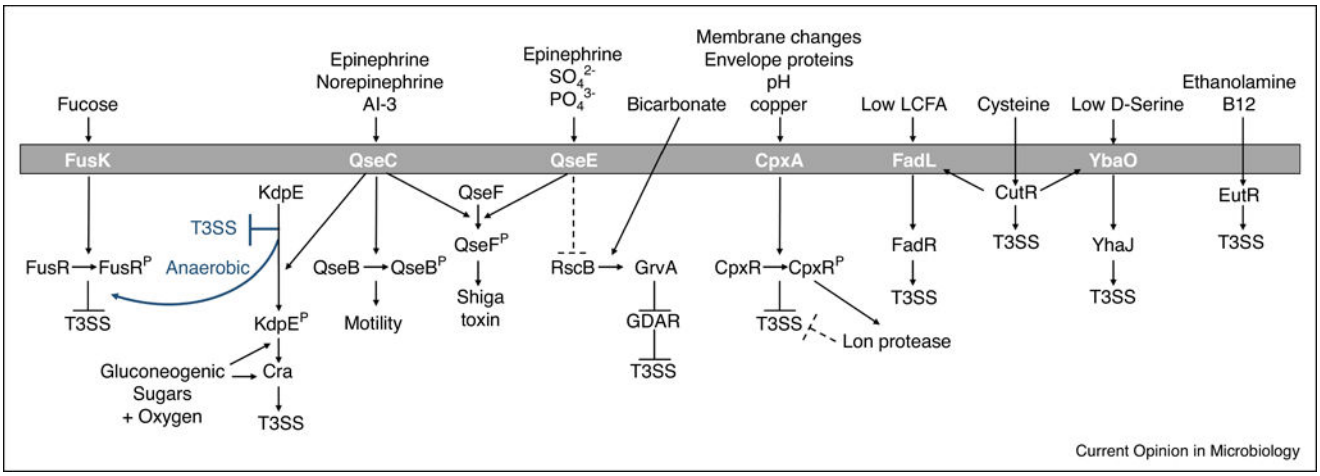

Figure 1.

Summary of small molecules sensed by EHEC to regulate expression of the Type III secretion system (T3SS). Diagrams in blue are under anaerobic, gluconeogenic conditions. In general, molecules that are found near the epithelial surface such as oxygen, epinephrine, norepinephrine, gluconeogenic carbon sources (pyruvate, N-acetyl-galactosamine, N-acetyl-glucosamine, N-acetylneuraminic acid, mannose, galacturonic acid, gluconic acid, and glucuronic acid), and ethanolamine activate T3SS. Fucose, which is found in the lumen, inhibits T3SS. Cysteine concentrations increase with infection and can activate T3SS. Low concentrations of long chain fatty acids (LCFA) or D-Serine also activate the T3SS. Bicarbonate activates GrvA in an RscB dependent manner to inhibit the Glutamate-dependent acid resistance (GDAR) pathway, thereby activating T3SS.

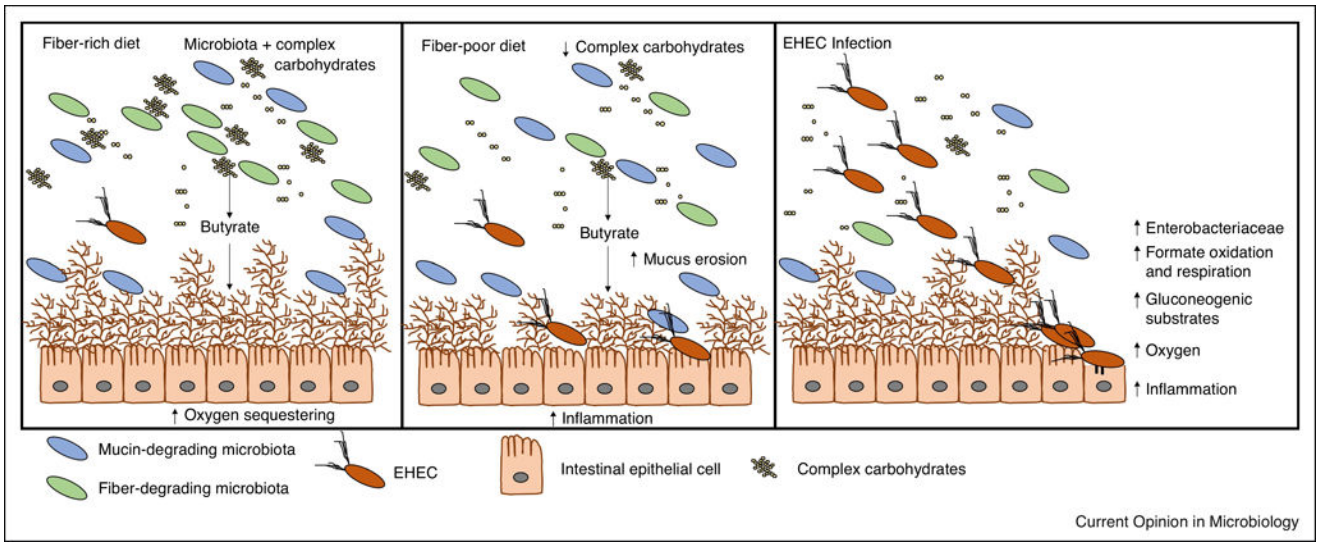

Figure 2.

EHEC hosts have varied diets and environmental conditions. In the left panel, the host has a fiber-rich diet where the microbiota digest complex carbohydrates to short chain fatty acids such as butyrate. These hosts have a normal mucus layer to keep infecting pathogens away from gut epithelial cells. In the center panel, the host has a fiber-poor diet. Fewer complex carbohydrates are available, and thus the proportion of mucin-degrading microbiota members increases. There is enhanced mucus erosion and an increase in inflammation that makes it easier for enteric pathogens to infect gut epithelial cells. In the right panel, EHEC is infecting the host by sensing different small molecules. The infection causes a bloom in Enterobacteriaceae, an increase in formate oxidization and respiration, gluconeogenic substrates such as succinate, oxygen, and inflammation.