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Enterohemorrhagic *Escherichia coli* outwits hosts through sensing small molecules

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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.

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

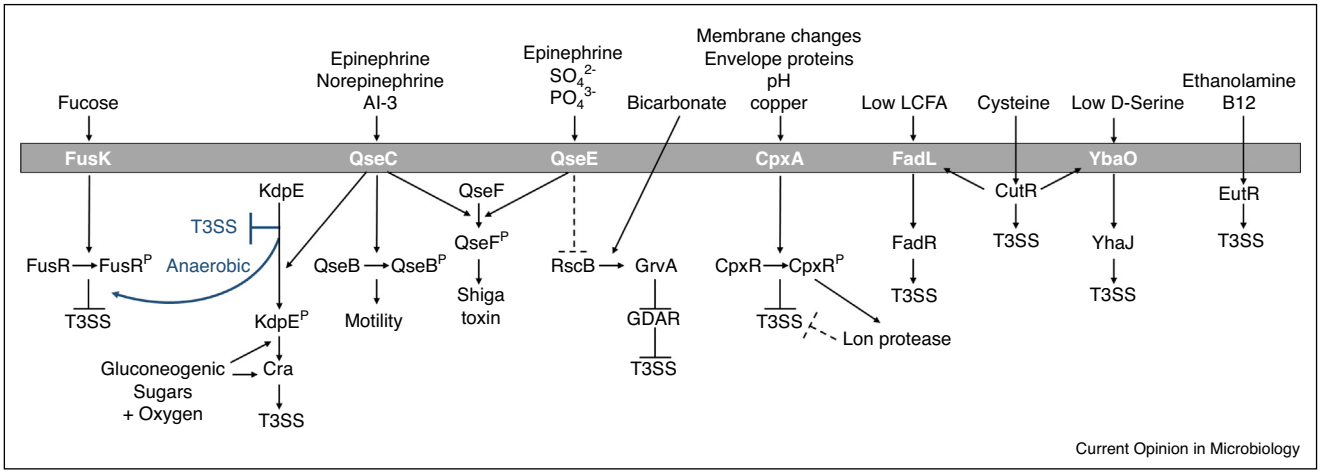
Host and microbiota signal: ethanolamine

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

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.

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