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Adrenergic Regulation of Bacterial Virulence

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Complex interactions between pathogen and host occur during the course of most infectious diseases. Microbes sense the host environment and produce factors, such as toxins, that usually promote their growth and often lead to symptoms in the host. Hosts sense the microbe and respond in various ways, such as activation of the innate immune response, to eliminate the pathogen. The host molecules that microbes sense to trigger production of virulence factors are poorly understood. Accumulating observations made in the past few years suggest that host adrenergic agonists like norepinephrine (NE) can promote the virulence of enterohemorrhagic *Escherichia coli* (EHEC) [1-4]. In this issue of the *Journal*, there is an intriguing paper by Nakano et al. [5] that shows that the pathogenicity of another enteric pathogen, *Vibrio parahaemolyticus*, is also augmented by NE.

V. parahaemolyticus is an important cause of foodborne illness. In Japan, this gram-negative rod is the most common foodborne bacterial cause of gastroenteritis. In the United States, *V. parahaemolyticus* is the most frequent cause of *Vibrio*-associated gastroenteritis, and most cases are associated with consumption of undercooked shellfish [6]. This summer the Centers for Disease Control and Prevention issued a dispatch detailing elevations in the number of *V. parahaemolyticus*–associated cases of gastroenteritis in New York, Oregon, and Washington [7]. The mechanisms of *V. parahaemolyticus* pathogenicity are not well understood, in part because of the lack of a good animal model of infection. The *V. parahaemolyticus* thermostable hemolysin, Tdh, has long been considered one of its key virulence factors. The *V. parahaemolyticus* genome sequence revealed the unexpected finding that each of the 2 *V. parahaemolyticus* chromosomes codes for a type III secretion system (TTSS1 and TTSS2) [8]. TTSSs are found in many enteric pathogens such as *Salmonella enterica*, EHEC, and enteropathogenic *E. coli*, *Shigella* species, and *Yersinia* species. These specialized multiprotein component secretion systems mediate the transfer of protein effectors directly from the bacterial to the host cell cytoplasm. In many cases, the targets and activities of the translocated proteins are unknown. Functional studies have suggested that the 2 *V. parahaemolyticus* TTSSs may mediate distinct aspects of this organism's pathogenicity. TTSS1 appears to mediate the organism's cytotoxicity, whereas TTSS2 appears to account for its enterotoxicity [9].

In this issue of the *Journal*, Nakano et al. show that NE promotes the pathogenic effects of both *V. parahaemolyticus* TTSSs. They found that addition of NE to tissue-cultured cells shortly before the addition of *V. parahaemolyticus* augmented the pathogen's cytotoxic effects. Because either α- or *β*-adrenergic antagonists inhibited NE stimulation of *V. parahaemolyticus* cytotoxicity, they argue that NE is acting via adrenergic receptors on the

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cell line. However, recent work has demonstrated that NE can act directly on EHEC [10], and it is plausible that *V. parahaemolyticus* might also directly respond to this adrenergic agonist. The authors also show that *V. parahaemolyticus* TTSS1 and not TTSS2 was required for NE to promote the pathogen's cytotoxicity. Interestingly, this adrenergic agonist was found to increase the transcript levels of several TTSS1 loci but not of TTSS2 loci or *tdh*. The mechanism by which NE stimulates transcription of TTSS1 genes was not explored. Taken together, these observations suggest that NE either acts directly or indirectly to increase transcription of *V. parahaemolyticus* TTSS1 genes thereby augmenting its cytotoxicity.

The authors used a rat ileal loop model to investigate the influence of NE on *V. parahaemolyticus* enterotoxicity. They found that NE increased *V. parahaemolyticus* induced fluid accumulation in this model. Unlike the case for NE stimulation of *V. parahaemolyticus* cytotoxicity, NE stimulation of *V. parahaemolyticus*' enterotoxicity only required the pathogen's TTSS2 and not its TTSS1. α-adrenergic antagonists blocked this effect, but *β*-adrenergic antagonists did not, suggesting that NE-stimulation of *V. parahaemolyticus* enterotoxicity requires only host cell α-adrenergic receptors. NE does not appear to elevate transcripts of TTSS2 genes. Deciphering the mechanisms by which NE stimulates *V. parahaemolyticus* cytotoxicity and enterotoxicity is a key challenge for the future.

As in *V. parahaemolyticus*, NE induces expression of TTSS genes in EHEC [3]. In EHEC, NE has been shown to act directly on the pathogen. This adrenergic agonist directly binds to QseC, an EHEC sensor kinase, increasing its autophosphorylation and thereby initiating a complex signaling cascade that activates transcription of the genes encoding the TTSS, flagella, and Shiga toxin [3,10]. The binding of NE to QseC can be inhibited by the α-adrenergic antagonist phentolamine, suggesting that QseC functions as a bacterial adrenergic receptor analog [10]. Thus, even though *V. parahaemolyticus*, like EHEC, lacks a homologue of a mammalian adrenergic receptor, it may, like EHEC, encode a protein that can recognize and respond to host adrenergic agonists.

In both of these enteric pathogens, type III secretion is also regulated by quorum sensing signaling [3,11,12]. In EHEC, the QseC sensor responds to both the quorum sensing signal AI-3 and the host signal NE by increasing its autophosphorylation, leading to increased expression of the TTSS genes [10,13]. Exploration of the cross-talk between quorum sensing signaling and host adrenergic signaling has only just begun. Regardless of the mechanisms by which adrenergic agonists augment virulence, the observations of Nakano et al. provide a remarkable example of interkingdom signaling between host and pathogen. Furthermore, these observations suggest that andrenergic antagonists may someday become part of the therapeutic armamentarium to treat enteric infections.

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