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The Release of Norepinephrine in C57BL/6J Mice Treated with 6-Hydroxydopamine (6-OHDA) is Associated with Translocations in Enteric *Escherichia coli* via the QseC Histidine Kinase Receptor

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: We aimed to investigate the effects of norepinephrine (NE) released from endogenous stores on bacterial translocation of *Escherichia coli* in mice by administration of 6-hydroxydopamine (6-OHDA), which selectively destroys noradrenergic nerve terminals.

Material/Methods: *E. coli* strain BW25113 and its derivatives (BW25113Δ*qseC* and BW25113Δ*qseC* pQseC) were used in this study. The serum concentrations of endotoxin were analyzed. The strains BW25113, BW25113Δ*qseC*, and BW25113Δ*qseC* pQseC were detected respectively in tissue specimens harvested from mice treated with 6-OHDA.

Results: Mice treated with BW25113Δ*qseC* showed reduced levels of bacterial translocation following administration of 6-OHDA compared with mice treated with BW25113. The defect of *E. coli* QseC receptor caused the norepinephrine-QseC signal chain to be interrupted, and the invasiveness and penetrating power of the bacteria on the intestinal mucosa was weakened, eventually leading to a significant decrease in the incidence of bacterial translocation.

Conclusions: NE modulates the interaction of enteric bacterial pathogens with their hosts via QseC. The blockade of the QseC receptor-mediated effects may be useful to attenuate bacterial translocation.

MeSH Keywords: **Bacterial Translocation • *Escherichia coli* • Norepinephrine**

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Background

Escherichia coli is an *Escherichia* bacterium that lives in the gut of humans and animals and is a widely distributed conditional pathogen. In stressful conditions such as severe trauma and shock, bacterial translocation occurs in bacteria in the intestine, leading to gut origin sepsis (GOS) [1–3]. Among the bacteria displaced from the intestine, *E. coli* accounts for more than half. In recent years, it has been recognized that stress causes neuroendocrine changes in the gastrointestinal tract, and bacteria can sense and recognize human signaling molecules, which in turn cause a series of phenotypic changes in intestinal bacteria, such as accelerated growth and increased virulence [4,5]. This is also one of the causes of intestinal bacterial translocation and intestinal sepsis [6].

The gastrointestinal tract of mammals is rich in catecholamine hormones, especially when exposed to stressful situations. Stress-related catecholamines such as norepinephrine (NE), epinephrine (EPI), and dopamine have been previously shown to decrease the immune effectiveness and increase the infection ability of enteric bacterial pathogens to their hosts [7,8]. QseC is a homolog of the adrenergic sensor kinase and acts as an important bacterial adrenergic receptor in this interkingdom interaction [9]. Previous researches have shown that *E. coli* and *Salmonella enterica* sensed and responded to NE via QseC signaling [10–12]. It was also found that flagellar motor genes were induced by QseC-like receptor [13], suggesting that *E. coli* may also be regulated by the host during bacterial translocation.

6-hydroxydopamine (6-OHDA) is a neurotoxic agent that selectively destroys sympathetic nerve terminals [12,14]. Since the sympathetic nerve terminals are destroyed, a large amount of NE in the postganglionic neurons of the sympathetic nervous system is immediately released into the circulating blood, resulting in a dramatic increase in the concentration of NE in the blood. In this study, an animal model of transient release of norepinephrine was established by intraperitoneal injection of 6-OHDA to investigate the role of *E. coli* QseC in intestinal bacterial translocation.

Material and Methods

Strain

The experiments involving strains and primers are shown in Table 1. *E. coli* K-12 BW25113 was obtained from our laboratory and was confirmed by genome sequencing to contain the complete *qseC* gene. *E. coli* K-12 BW25113Δ*qseC* strain, which is a *qseC* gene deletion strain of BW25113 strain, was constructed by our laboratory. Its *qseC* gene was replaced by kanamycin resistance gene, and primer B1 and B2 were designed on the outside of the homologous region of *E. coli* chromosome *qseC* gene. *E. coli* K-12 BW25113 and BW25113Δ*qseC* colony PCR were used to identify the *qseC* gene deletion strain. *E. coli* K-12 BW25113Δ*qseC* pQseC, a *qseC* gene complementary strain of BW25113Δ*qseC* strain, was also constructed by our laboratory, and the *qseC* complementary vector pGFPuv-QseC was transformed into *E. coli qseC* negative mutant strain to obtain BW25113Δ*qseC* pQseC. P1 and P2 are sense and antisense primers respectively for the complementary vector pGFPuv-QseC, and the *qseC* gene complementary strain was identified by P1 and P2 *E. coli* K-12 BW25113Δ*qseC* pQseC colony PCR. Primers were synthesized by Invitrogen (Carlsbad, CA, USA).

Establishment of tracer bacteria

pEGFP, a plasmid containing an ampicillin resistance gene and a gene encoding green fluorescent protein (GFP), was obtained

Table 1. Strains and primers used in this study.

Strains or primers	Description or relevant genotype	Source
Strains		
BW25113	*E. coli* K-12	This lab
BW25113Δ*qseC*	BW25113 mutant with the deletion of *qseC* gene	This lab
BW25113Δ*qseC* pQseC	*qseC* complemented strain (in HindIII/XbaI pGFPuv)	This lab
Primers		
B1	CGACGCAAACTCGGTAGTGA	This study
B2	TTGGGGACGGTTTATATTTT	This study
P1	CAGCAAGCTTGAAATGAAATTTACCC	This study
P2	AGACAGTCTAGATACCAGCTTACCT	This study

The underlined sequences are the restriction sites of HindIII and XbaI respectively.

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commercially (Clontech, Tokyo, Japan). To establish the tracer bacteria, pEGFP was transformed into *E. coli* BW25113 and *qseC* negative mutant strain BW25113Δ*qseC* to facilitate bacterial resistance and fluorescent labeling in later animal experiments (*E. coli* K-12 BW25113Δ*qseC* pQseC already has an ampicillin resistance gene and a GFP gene when constructing a *qseC* complementary vector). The 3 strains were expanded in LB liquid medium containing 100 mg/L of ampicillin to a bacterial concentration of 5 x 10^{10} CFU/mL, and subsequently used.

Experimental animals

The Imperial Cancer Research Fund (ICRF) specific pathogen-free (SPF) male C57BL/6J mice provided by Hunan Slack Jingda Experimental Animal Co., Ltd., animal license number: SCXK (Xiang) 2016-0002, weight 18~20 g, 42 days old, were used for experiments adaptive feeding: mice were housed in a peaceful, temperature and humidity-controlled room (ambient temperature, ~22°C; relative humidity, ~64%) with a 12 hour light/dark cycle, and a standard mouse diet and water was available ad libitum. Forty-two ICR mice with no ampicillin-resistant bacterial growth were randomly divided into 7 groups: blank+sham group (blank-S), BW25113+sham group (B-S), Δ*qseC*+sham group (Δ-S), Δ*qseC* pQseC+sham group (C-S), BW25113+6-OHDA group (B-6OH), Δ*qseC*+6-OHDA group (Δ-6OH), and Δ*qseC* pQseC+6-OHDA group (C-6OH), each group of 6 mice. Animal studies were performed in strict accordance with the Declaration of Helsinki and the recommendations in the Guidelines for Care and Use of Laboratory Animals accepted by the National Institutes of Health (NIH, Publication No. 80-23). All experiments were approved by the institutional Ethics Committee of the First Affiliated Hospital of Kunming Medical University. Every effort was made to reduce the animals suffering during the experiment.

Colonization of tracer bacteria in the intestine

All mice were free to drink a sterile aqueous solution containing 300 mg/L ampicillin for 3 consecutive days to inhibit the intrinsic flora in the intestine. The blank group was started on the fourth day, and the mice were given sterile physiological saline (1 mL/10 g, once a day) for 3 consecutive days. On the fourth day of the other groups, mice were fed with *E. coli* BW25113, BW25113Δ*qseC*, or BW25113Δ*qseC* pQseC (1 mL/10 g, once a day) for 3 consecutive days. During the feeding period, all animals continued to drink a sterile aqueous solution containing 300 mg/L ampicillin for 3 days. From the fifth day, fecal specimens were collected for 3 consecutive days and cultured on LB agar plates containing 100 mg/L ampicillin. The growth of resistant bacteria confirmed that the experimental strains had been colonized in the intestine.

Preparation of an animal model of transient release of norepinephrine

After the experimental strain was colonized in the intestine, an animal model was prepared. 6-OHDA (100 mg/kg body weight) was intraperitoneally injected, and 6-OHDA was temporarily prepared to 0.96 mmol/L with physiological saline before use, and sterilized by filtration through a 0.22 μm filter. The control group was intraperitoneally injected with an equal amount of physiological saline. All mice were fasted for 12 hours before the experiment, but they were allowed to drink. They were free to eat 6 hours after the experiment.

Bacterial culture

After 24 hours, the mice were intraperitoneally injected with pentobarbital sodium 60 mg/kg, and the mesenteric lymph nodes (MLN), spleen and liver specimens were obtained under strict aseptic conditions. The tissues were ground and homogenized with sterile physiological saline (0.5 mL/0.2 g tissue weight), and then the homogenate samples were all applied to an LB agar plate containing 100 mg/L ampicillin and cultured at 37°C for 18 hours. The bacterial translocation rate and the number of colonies were counted and converted to the total number of colonies per gram of tissue (CFU/g) based on tissue weight.

Fluorescence microscopy

We applied 5 μL of the bacterial culture solution to a glass slide, and a fluorescent image of the bacteria was observed under a fluorescence microscope (Zeiss Axiplan 2 microscope; Zeiss, Jena, Germany), and a fluorescent image was acquired using Axiovision 3.1 software.

Plasma endotoxin content

Portal vein blood samples were taken, and the endotoxin content of plasma was determined by *Limulus* quantitative azo color test (LQACT): 0.1 mL plasma was fully mixed with 0.2 mL non-thermal normal saline solution and 0.2 mL Tris-HCl buffer. This mixture was placed in 100°C water bath for 10 minutes and was centrifuged at 3000 rpm for another 10 minutes. Then, 0.1 mL of the supernatant was mixed with 0.05 mL *Limulus* lysate reagent lightly, placed in 37°C water bath for 25 minutes, followed by addition of 0.05 mL *Limulus* tripeptide at 37°C for 3 minutes. After removing from the water bath, 0.5 mL sodium nitrite solution was added and followed by homogenous and complete mixing. After 10 minutes, 0.5 mL amino-sulphonamide was added. After 10 minutes, 0.5 mL naphthalene acetamide was added to the mixture. Absorbance was measured at 545 nm and was checked against the standard curve to obtain the plasma endotoxin content.

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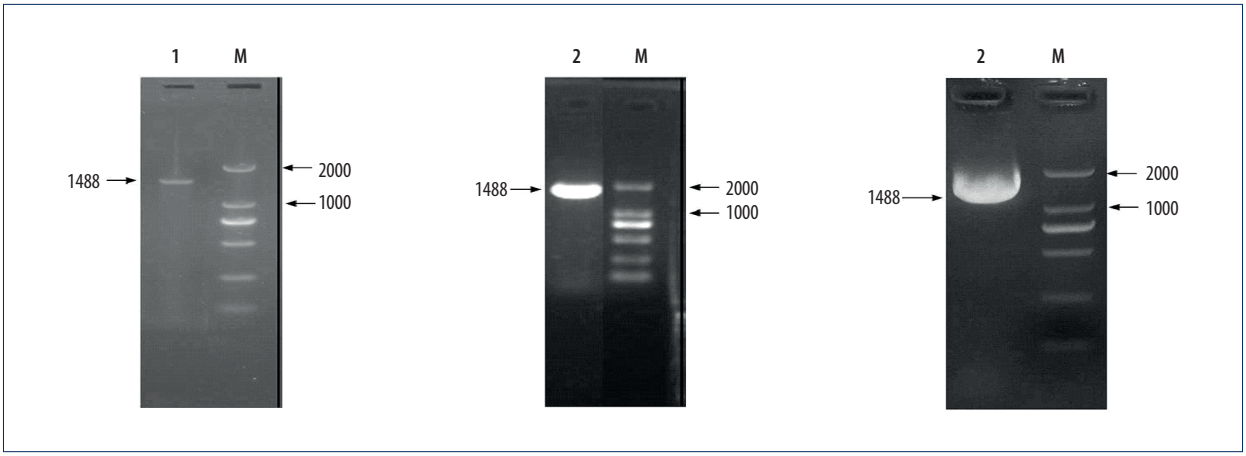

Figure 1. The genotype of the BW25113, BW25113Δ*qseC*, and BW25113Δ*qseC* pQseC was identified by polymerase chain reaction (PCR). M – DL2000 DNA Marker; 1 – BW25113; 2 – BW25113Δ*qseC*; 3 – BW25113Δ*qseC* pQseC.

Statistical analysis

Using the SPSS 13.0 statistical software package, and date were expressed as mean±standard deviation (SD). The visceral bacterial content was expressed in median and range, using the Mann-Whitney U test. Bacterial translocation rates were expressed as relative numbers using chi-square test (χ^2 test) and other results using one-way analysis of variance (ANOVA). The difference was statistically significant at $P<0.05$.

Results

Polymerase chain reaction (PCR) identification of 3 strains

Primers B1 and B2 were identified on the outside of the *qseC* gene, the sequence between them was 1488 bp in wild bacteria, and the sequence of *qseC* gene replaced by kanamycin resistance gene was 1659 bp. The genotype of the strain was identified by this primer. P1 and P2 are the primers of the complementary vector pGFPuv-QseC. The product obtained by PCR is the HindIII-Qsec-XbaI gene fragment (HindIII and XbaI are the cleavage sites when constructing the vector pGFPuv-QseC), and its size is 1363 bp, which was consistent with the theoretical value (Figure 1).

Animal visceral bacterial culture and identification

The MLN, spleen, and liver specimen homogenates of each group of mice were cultured on the LB agar plate containing ampicillin. As a result, the grown colonies were found to have the following characteristics: uniform size and shape, yellow-white, round and moist, and were initially considered to be resistant to ampicillin (Figure 2A). In order to further determine that the positive colonies are from the intestine, the smears were observed under a fluorescence microscope and the results showed that the bacteria emitted intense green fluorescence (Figure 2B).

Bacterial culture results of MLN, spleen, and liver tissue

Bacterial translocation was not detected in the blank-S group (Table 2). In addition, bacterial translocation occurred in the saline control group (B-S group, Δ-S group, and C-S group), but the visceral bacteria content was not high (Table 2). The bacterial translocation rate and visceral bacterial contents of the B-6OH group were significantly higher than those of the saline control group ($P<0.01$, Table 2). The bacterial translocation rate and bacterial content of MLN, spleen, and liver in the Δ-6OH group were significantly lower than those in the B-6OH group ($P<0.01$, Table 2). Furthermore, the bacterial contents of MLN, spleen, and liver of the C-6H group were significantly increased compared with the Δ-6H group ($P<0.01$, Table 2).

Plasma endotoxin levels

The plasma endotoxin level in the B-6H group was significantly higher than that in the saline control group (B-S group, Δ-S group, and C-S group), and the difference was statistically significant ($P<0.01$, Table 3). The plasma endotoxin level in the Δ-6OH group was significantly lower than that in the B-6H group ($P<0.01$, Table 3). Similarly, the plasma endotoxin level in the C-6OH group was increased compared with the Δ-6OH group, and the difference was statistically significant ($P<0.01$, Table 3).

Discussion

The *E. coli qseC* gene is about 1.3 kb in size, and the encoded protein QseC is a histidine protein kinase located on the plasma membrane of the cell, which is responsible for recognizing

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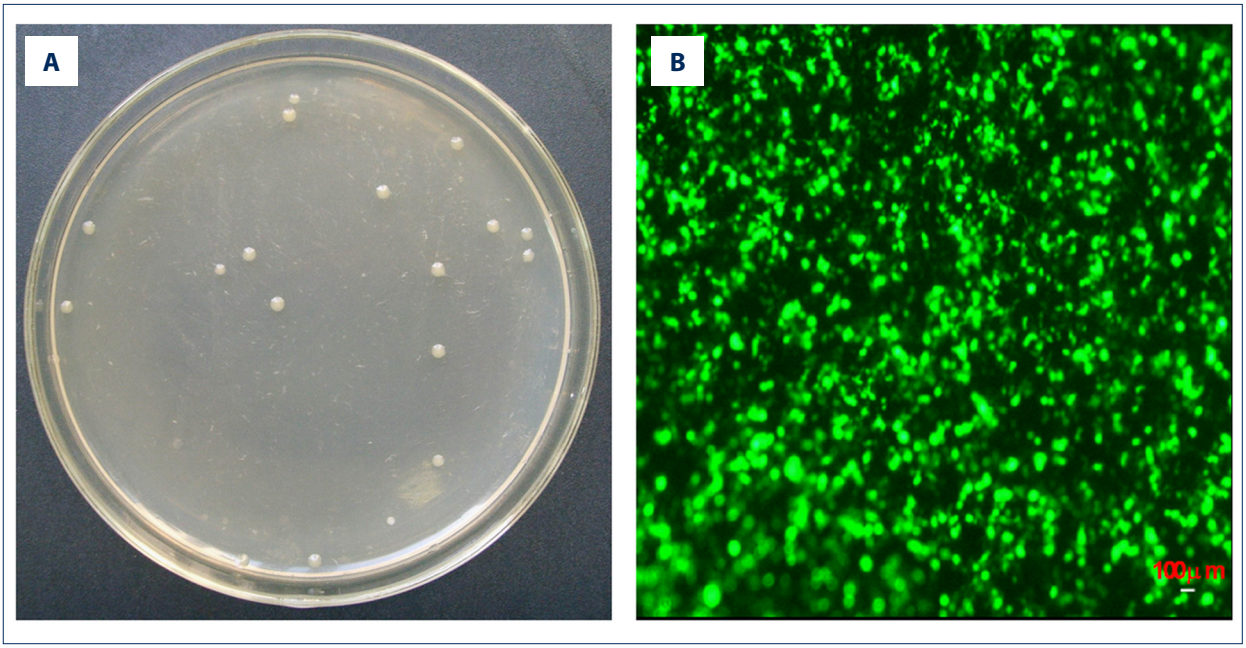

Figure 2. The ampicillin-resistant bacteria isolated from viscera. (**A**) The morphological characteristics of ampicillin-resistant bacteria. (**B**) The fluorescence microscopy image of the ampicillin-resistant bacteria. The photomicrograph was taken at 200× magnification.

Table 2. Bacterial translocation after administration of 6-hydroxydopamine.

	Bacterial translocation rate	CFU/g (median, range)		
		MLN	Spleen	Liver
Blank-S	0/6	0 (0)	0 (0)	0 (0)
B-S	1/6	0 (0~98)	0 (0)	0 (0~77)
Δ-S	1/6	0 (0~62)	0 (0)	0 (0)
C-S	1/6	0 (0~72)	0 (0)	0 (0~55)
B-6OH	5/6**	240 (0~590)**	113 (0~270)**	120 (0~290)**
Δ-6OH	3/6*	38 (0~300)*	0 (0~150)*	0 (0~208)*
C-6OH	4/6	135 (0~500)***	85 (0~250)***	64 (0~300)***

Blank-S – blank+sham group; B-S – BW25113+sham group; Δ-S – Δ*qseC*+sham group; C-S – Δ*qseC* pQseC+sham group; B-6OH – BW25113+6-OHDA group; Δ-6OH – Δ*qseC*+6-OHDA group; C-6OH – Δ*qseC* pQseC+6-OHDA group. MLN – mesenteric lymph nodes. * $P<0.01$ compared with the B-6OH group; ** $P<0.01$ compared with the saline control groups (blank-S, B-S, Δ-S and C-S groups); *** $P<0.01$ compared with the Δ-6OH group.

the receptor protein of an external signal molecule. It activates the signal chain downstream of *qseC* by sensing autoinducer 3 (AI-3), thereby promoting the expression of flagellum genes and increasing bacterial viability [15]. Previous studies found that AI-3 can highly recognize EPI and NE [16]. Moreover, *qseC* can also recognize the human hormone molecules EPI and NE [17], and is capable of sensing and recognizing the signal molecule AI-3 produced by bacteria. Previous studies have confirmed that the exercise ability of *qseC*-negative mutant strains is significantly weaker than that of wild-type strains, while the complementary strains partially restore the exercise capacity of gene-deficient strains compared to the *qseC*-deficient strains [18–20]. The QseC receptors can significantly increase the activity of wild strains, but it has little effect on *qseC*-negative mutant strains [21]. This indicates that the *qseC* gene is associated with the motility of *E. coli*. In order to simulate the release of NE in the gastrointestinal tract during trauma, this study established an animal model that achieves

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Table 3. The serum concentrations of endotoxin detected in the groups.

Groups	Serum endotoxin concentrations
B-S	0.062±0.04
Δ-S	0.066±0.03
C-S	0.063±0.06
B-6OH	0.323±0.15**
Δ-6OH	0.168±0.11*
C-6OH	0.216±0.08***

B-S – BW25113+sham group; Δ-S – Δ*qseC*+sham group; C-S – Δ*qseC* pQseC+sham group; B-6OH – BW25113+6-OHDA group; Δ-6OH – Δ*qseC*+6-OHDA group; C-6OH – Δ*qseC* pQseC+6-OHDA group. MLN – mesenteric lymph nodes. * $P<0.01$ compared with the B-6OH group; ** $P<0.01$ compared with the saline control groups (blank-S, B-S, Δ-S and C-S groups); *** $P<0.01$ compared with the Δ-6OH group.

a large release of NE by intraperitoneal injection of 6-OHDA. 6-OHDA selectively kills dopaminergic neurons and is a neurotoxic agent that does not cross the blood-brain barrier during peripheral application [22–25].

In this study, *E. coli* BW25113, BW25113Δ*qseC*, and BW25113Δ*qseC* pQseC strains were selected, which have the same genetic background except *qseC* gene, which can truly judge the function of *E. coli qseC* gene in intestinal bacterial translocation. In the experiment, ampicillin-resistant bacteria were isolated from the MLN, spleen, and liver tissues of mice. These bacteria were confirmed by fluorescence microscopy from the experimental strains fed into the intestine of mice, indicating that each group had intestinal bacterial translocations in the experiment. The bacterial translocation rate and visceral bacterial content in the saline groups (blank-S, B-S, Δ-S, and C-S groups) were low, while the bacterial translocation rate and visceral bacterial content in the B-6OH group were significantly increased, indicating that NE acts on the *E. coli* QseC receptor in the intestine tract, promoting intestinal bacterial translocation. QseC deletion strain-6-OHDA group *E. coli* QseC receptor deficiency, the bacterial translocation rate and visceral bacterial content were significantly lower than wild strain-6-hydroxydopamine group. QseC complementary strain-6-OHDA group *E. coli* QseC receptor function recovery, the bacterial translocation rate and visceral tissue bacteria content increased compared with the Δ-6OH group. These results indicated that the blockade of this pathway can inhibit intestinal bacterial translocation. Endotoxin is a lipopolysaccharide component of the cell wall of Gram-negative bacilli, and it is abundantly present in the intestinal lumen of animals [26]. When the intestinal bacteria translocation, it causes endotoxin to enter the blood and resulting in endotoxemia [27,28]. The results of plasma endotoxin levels in each group were consistent with the results of bacterial translocation. Therefore, the defect of *E. coli* QseC receptor causes the norepinephrine-QseC signal chain to be interrupted, and the invasiveness and penetrating power of the bacteria on the intestinal mucosa is weakened, eventually leading to a significant decrease in the incidence of bacterial translocation.

There were some limitations presented in our study. It is well known that intestinal pathogens such as enteric *E. coli* skillfully used redundant signaling molecules to tightly regulate the type III secretory system, and that the healthy intestinal environment of hosts is inevitably infected [7]. In the process of studying bacterial translocations, indeed, we should establish a more comprehensive network system, including not only other host-derived signals other than norepinephrine, such as epinephrine, long chain fatty acid and D-serine, but also other bacterial sensor kinases such as the histidine sensor FusK and QseE upstream and downstream of QseC. Moreover, the QseC is a conserved periplasmic sensing domain in many bacteria. Further studies are needed to investigate that whether in addition to pathogenic bacteria such as enteric *E. coli* and *Salmonella*, the blockade of the QseC affects the beneficial bacterial flora of the human gut or not.

Conclusions

In summary, this study provides evidence that the interkingdom signaling of QseC could be regulated by NE. Under various stress conditions, the body secretes a large amount of adrenaline and NE, and catecholamines. At this time, EPI (or NE) and *E. coli* QseC receptor interactions are bound to increase the incidence of intestinal bacterial translocation. Therefore, blocking the QseC-adrenergic signaling pathway will provide new ideas for the prevention and treatment of clinical bacterial translocation of enteric *E. Coli* and the treatment of critically ill patients.

Conflict of interest

None.

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