Impact of Hfq on the intrinsic drug resistance of Salmonella enterica serovar Typhimurium

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SUMMARY

Salmonella enterica is an important enteric pathogen, and its various serovars cause both systemic and intestinal diseases in humans and domestic animals. The emergence of multidrug-resistant strains of Salmonella, leading to increased morbidity and mortality, has further complicated its management. Hfq is an RNA chaperone that mediates the binding of small RNAs to mRNA and assists in post-transcriptional gene regulation in bacteria. Although Hfq is related to important phenotypes including virulence in Salmonella, its role in the drug resistance of this organism is unknown. The aim of this study was to investigate the role of Hfq in intrinsic drug resistance of S. enterica serovar Typhimurium. hfq Mutant was susceptible to acriflavine. Although there is a relationship between the production of the AcrB multidrug efflux pump and Hfq in Escherichia coli, the deletion of the drug efflux acrB did not impair the effect of hfq deletion on Salmonella susceptibility. In contrast, the deletion of another drug efflux gene, smvA, impaired the effect of hfq deletion on acriflavine susceptibility. These results indicate that Hfq regulates the intrinsic drug resistance, and it may influence drug susceptibility by regulating SmvA in Salmonella.

KEYWORDS: drug efflux system, drug resistance, Hfq, Salmonella, small RNA
the ability of *Salmonella* to invade epithelial cells, secrete virulence factors, infect mice, and survive inside cultured macrophages (Sittka et al., 2007). Transcrip
tomic analysis revealed that Hfq controls the expression of *Salmonella* genes in several horizontally acquired pathogenicity islands (SPI-1, -2, -4, -5), two sigma factor regulons, and the flagellar gene cascade (Sittka et al., 2008). However, the role Hfq in the drug resistance of *Salmonella* is unknown.

In this study, we demonstrate that Hfq affects drug suscepti
tibilities in *Salmonella*. In addition, we reveal that SmvA and not the AcrB drug efflux system contributes to the Hfq-mediated drug resistance of *Salmonella*, whereas it has been reported that AcrB contributes to the Hfq-mediated drug resistance of *Escherichia coli*. Our data suggest that Hfq plays an important role in controlling drug susceptibility against acriflavine and that the SmvA efflux pump is involved in this susceptibility in *Salmonella*.

**MATERIALS AND METHODS**

**BACTERIAL STRAINS, PLASMIDS, AND GROWTH CONDITIONS**

The bacterial strains and plasmids used in this study are listed in Table 1. The strains of *S. enterica* serovar Typhimurium used in this study were derived from the wild-type strain ATCC 14028s (Fields et al., 1986). Bacterial strains were grown at 37°C in Lysogeny Broth (LB). Ampicillin was added to the growth medium at a final concentration of 100 μg/ml for plasmid maintenance.

**CONSTRUCTION OF GENE DELETION MUTANTS**

The ΔacrB (NKS148) and ΔtolC (NKS174) mutants were conconstructed as described previously (Horiyama et al., 2010). To construct Δhfq and ΔsmvA mutants, gene disruption was performed as described by Datsenko and Wanner (2000). The following oligonucleotide primers were used for the construction of the mutants: hfq-P1 (GAAAGCTTCAGCTTTTACGGAAGAAAGAGGTAGGTGAGCTGAGCCTTC); hfq-P2 (ATTATCCGAGCCCGAGCTTATGATGAAACAGCGTGA ACCATATGATATATCCCTCTTAA); smvA-P1 (CTGGACAAGCG

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**Table 1 | *Salmonella* strains and plasmids used in this study.**

| Strain or plasmid | Characteristics | Source or reference |
|-------------------|----------------|---------------------|
| ATCC 14028s       | *Salmonella enterica* serovar Typhimurium wild-type | Fields et al. (1986) |
| NKS798            | Δhfq           | This study          |
| NKS148            | ΔacrB          | This study          |
| NKS799            | ΔacrB Δhfq     | This study          |
| NKS174            | ΔtolC          | This study          |
| NKS802            | ΔtolC Δhfq     | This study          |
| NKS771            | ΔsmvA          | This study          |
| NKS1390           | ΔsmvA Δhfq     | This study          |
| NKS1396           | ΔsmvA Δhfq/ΔpsmA | This study          |
| NKS1395           | ΔsmvA Δhfq/ΔpsmA | This study          |
| Vector            | pBR322, ColE1-type vector, TCR, ApR | Takara Bio, Inc. |
| Plasmid           | psmvA, smvA gene cloned into pBR322, ApR | This study          |

TCCAAATTTGAGTTTGAAGGGAGAGTTGTTAGGCTGG AGCTGGCTTC; and smvA-P2 (CCAGCTAGGGCATTAAGGG CTTATCACCAGGGCTTATGATGAAATATCCCTTAA). The chloramphenicol resistance gene cat, flanked by Flp recognition sites, was amplified by PCR using the primers listed above. The resulting PCR products were used to transform the recipient ATCC 14028s strain that harbors the plasmid pKD46, which expresses Red recombinase. The chromosomal structure of the mutated loci was verified by PCR. cat was eliminated using the plasmid pCP20, as described previously (Datsenko and Wanner, 2000). To construct the ΔacrBΔhfq, ΔtolCΔhfq, and ΔsmvAΔhfq double mutants, the deletions were transferred to strains by P22 transduction as described by Davis et al. (1980).

**PLASMID CONSTRUCTION**

smvA was amplified from ATCC 14028s genomic DNA by using the primers GGCGATGGAATCCGTTTCAACCTGAGGG and GGCGCTCGGAAATGCACTTCCCCTGACCC, which introduced SpfI and SalI sites (underlined in the primer sequences above). The fragment was cleaved with SpfI and SalI and then cloned into the corresponding sites of pBR322, resulting in psmvA (Table 1).

**DETERMINATION OF THE MINIMUM INHIBITORY CONCENTRATION OF TOXIC COMPOUNDS**

The antibacterial activities of various agents were determined on LB agar (1% tryptone, 0.5% yeast extract, 0.5% NaCl) plates containing nalidixic acid, acriflavine, rhodamine 6G, benzalkonium, oxacillin, cefamandole, sodium dodecyl sulfate, or norfloxacine (Sigma, St. Louis, MO, USA) at various concentrations as indicated in Table 2. Agar plates were made by the twofold agar dilution technique, as described previously (Horiyama et al., 2010). To determine minimum inhibitory concentrations (MICs), bacteria were grown in LB broth at 37°C overnight, diluted into the same medium, and then tested at a final inoculum size of 1 × 10^5 cfu/μl using a multipoint inoculator (Sakuma Seisakusyo, Tokyo, Japan) after incubation at 37°C for 20 h. The MIC was the lowest concentration of a compound that inhibited cell growth.

**RESULTS AND DISCUSSION**

**Hfq AFFECTS THE INTRINSIC DRUG SUSCEPTIBILITY OF *SALMONELLA***

To investigate the role of Hfq in drug susceptibilities, hfq was deleted from *S. enterica* serovar Typhimurium strain ATCC 14028s, as described in the Section "Materials and Methods." Δhfq mutant was more sensitive to acriflavine (64-fold) than the wild-type strain (Table 2). The MICs of nalidixic acid, rhodamine 6G, benzalkonium, oxacillin, cefamandole, sodium dodecyl sulfate, and norfloxacine were the same for Δhfq mutant as those for the wild-type strain. These data indicate that Hfq affects the intrinsic acriflavine resistance of *Salmonella*.

**AcrB IS NOT INVOLVED IN Hfq-MEDIATED DRUG SUSCEPTIBILITY OF *SALMONELLA***

In *E. coli*, it has been demonstrated that the AcrB multidrug efflux pump is involved in Hfq-mediated multidrug resistance (Yamada et al., 2010). To investigate whether AcrB in *Salmonella* is also involved in Hfq-mediated drug susceptibility of this organism, we measured MICs of several toxic compounds against ΔacrB
Table 2 | Susceptibility of Salmonella strains to toxic compounds.

| Strain          | MIC (µg/ml) |
|-----------------|------------|
|                 | NAL   | ACR   | R6G   | BENZ  | OXA   | FAM   | SDS   | NFLX  |
| Wild-type       | 4     | 4096  | 4096  | 64    | 1024  | 0.5   | >32768| 0.25  |
| Δhfq            | 4     | 64    | 4096  | 64    | 1024  | 0.5   | >32768| 0.25  |
| ΔacrB           | 1     | 64    | 8     | 4     | 2     | 0.125 | 128   | 0.031 |
| ΔacrB Δhfq      | 1     | 16    | 8     | 4     | 2     | 0.125 | 128   | 0.031 |
| ΔtolC           | 0.5   | 32    | 8     | 4     | 0.5   | 0.125 | 32    | 0.031 |
| ΔtolC Δhfq      | 0.5   | 8     | 8     | 4     | 0.5   | 0.125 | 32    | 0.031 |
| ΔsmvA           | 4     | 64    | 4096  | 64    | 1024  | 0.5   | >32768| 0.25  |
| ΔsmvA Δhfq      | 4     | 64    | 4096  | 64    | 1024  | 0.5   | >32768| 0.25  |
| ΔsmvA Δhfq/psmvA| 4     | 64    | 4096  | 64    | N.D.  | N.D.  | >32768| 0.25  |

NAL, nalidixic acid; ACR, acriflavine; R6G, rhodamine 6G; BENZ, benzalkonium; OXA, oxacillin; FAM, cefamandole; SDS, sodium dodecyl sulfate; NFLX, norfloxacin.

Values in bold are smaller than those of the wild-type strain.

MIC determinations were repeated at least three times. Shown is one of the three experiments, which gave same results.

N.D., not determined, because vectors have an ampicillin resistance cassette.

Mutant (Table 2). The ΔacrB mutant was sensitive to nalidixic acid (fourfold), acriflavine (64-fold), rhodamine 6G (512-fold), benzalkonium (16-fold), oxacillin (512-fold), cefamandole (fourfold), sodium dodecyl sulfate (>256-fold), and norfloxacin (eightfold). Although ΔacrB mutant was as sensitive to acriflavine as Δhfq mutant, the drug susceptibility pattern for other compounds was very different among these mutants. ΔacrBΔhfq double mutant was more sensitive to acriflavine (fourfold) than ΔacrB mutant, indicating that the deletion of acrB did not impair the effect of hfq deletion on Salmonella susceptibility. Based on these data, it was suggested that factors other than AcrB may be involved in the Hfq-mediated drug susceptibility of Salmonella because the drug susceptibility pattern of ΔacrB was very different from that of Δhfq, and the deletion of hfq from ΔacrB mutant made this strain more sensitive to acriflavine.

ToIC IS NOT INVOLVED IN THE Hfq-MEDIATED DRUG SUSCEPTIBILITY OF SALMONELLA

ToIC is a major outer membrane channel, and a variety of inner membrane and accessory protein interact with ToIC to expel structurally diverse molecules. We previously identified that seven drug efflux systems, AcrAB, AcrD, AcrEF, MdsAB, MdtABC, EmrAB, and MacAB, in Salmonella that require TolC to function (Horiyama et al., 2010). To investigate whether ToIC-dependent type drug efflux systems are involved in Hfq-mediated drug susceptibility, we measured MICs of compounds against ΔtolC mutant (Table 2). ΔtolC mutant was sensitive to nalidixic acid (eightfold), acriflavine (128-fold), rhodamine 6G (512-fold), benzalkonium (16-fold), oxacillin (2048-fold), cefamandole (fourfold), sodium dodecyl sulfate (>1024-fold), and norfloxacin (eightfold). The susceptibilities of ΔtolC mutant to oxacillin and sodium dodecyl sulfate were higher than those of the ΔacrB mutant probably because ToIC-dependent type efflux systems other than AcrB are involved in the efflux of these compounds. The deletion of hfq from ΔtolC mutant made this strain more sensitive to acriflavine (fourfold), meaning that the ToIC-dependent type drug efflux systems are not involved in the Hfq-mediated drug susceptibility of Salmonella.

INVOLVEMENT OF SmvA EFFLUX PUMP IN THE Hfq-MEDIATED ACRIFLAVINE SUSCEPTIBILITY

Among the tested compounds, Δhfq mutant was specifically susceptible to acriflavine (Table 2) as mentioned above. Because it has been reported that SmvA is an important efflux pump for acriflavine (Villagrasa et al., 2008), we hypothesized that SmvA may be involved in the Hfq-mediated acriflavine susceptibility of Salmonella. Similarly, as Δhfq mutant, ΔsmvA mutant was more sensitive to acriflavine (64-fold) than the wild-type strain (Table 2). This phenotype is in good agreement with a previous report (Villagrasa et al., 2008). MIC of acriflavine against ΔsmvAΔhfq double mutant was similar to that against ΔsmvA mutant, indicating that deletion of smvA impaired the effect of hfq deletion on acriflavine susceptibility. Moreover, psmvA, which expressed smvA, conferred acriflavine resistance to ΔsmvAΔhfq double mutant. MIC of acriflavine against ΔsmvAΔhfq/psmvA strain is similar to that against the wild-type strain (Table 2). Taken together, these results indicated that Hfq regulates the intrinsic acriflavine resistance of Salmonella and SmvA plays an important role in this resistance because the drug susceptibility pattern of ΔsmvA was same as that of Δhfq, and the deletion of hfq from ΔsmvA mutant did not change the acriflavine susceptibility of this strain.

In this study, we investigated the role of Hfq in the drug susceptibility of S. enterica serovar Typhimurium ATCC 14028s and found that Hfq plays a role in its intrinsic acriflavine resistance and that SmvA efflux pump is involved in this resistance. Interestingly, Δhfq mutant of Salmonella was specifically sensitive to acriflavine among the tested compounds. This phenotype is very different from Δhfq mutant of E. coli W3104 or MC4100 (Yamada et al., 2010). In case of E. coli, Δhfq mutant was susceptible to various compounds including acriflavine, benzalkonium, cefamandole, chloramphenicol, crystal violet, nalidixic acid, novobiocin, oxacillin, and rhodamine 6G because Hfq positively

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regulates the production of the AcrB drug efflux pump (Yamada et al., 2010). However, AcrB was considered not to be involved in the Hfq-mediated intrinsic acriflavine resistance of *Salmonella*. These observations suggest the differential regulation of genes by Hfq between *E. coli* and *Salmonella*. Indeed, transcriptomic analysis revealed that Hfq controls the *Salmonella* gene expression in several horizontally acquired pathogenicity islands (SPI-1, -2, -4, -5) that are not present in *E. coli* (Sittka et al., 2008). Unlike the AcrAB drug efflux system, which is widely distributed throughout all Enterobacteriaceae, homologs of SmvA are not found in *E. coli* and *Shigella* spp. Villagrá et al. (2008) suggested that acriflavine is a substrate for both AcrB and SmvA efflux pumps, but SmvA pump plays the major role in the efflux of acriflavine in *Salmonella*. This may explain why SmvA and not AcrB drug efflux system contributes to the Hfq-mediated drug resistance of *Salmonella*.

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