Structural and Physiological Basis of Salmonella YfdX-driven Regulation of Antibiotic Tolerance and Virulence

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Typhoid fever, caused by *Salmonella* Typhi, exhibits severe symptoms: fever, hepatitis, lymph node necrosis, and intestinal perforation and bleeding. Antibiotics such as ciprofloxacin and ceftriaxone are now widely used for the treatment of this illness. In addition, newly available antibiotics with variable mechanism of action are in a continuous development. However, repeated exposure to antibiotics has resulted in steadily increasing of antibiotic-resistant *S*. Typhi. Therefore, uncovering mechanisms behind antibiotic-resistance and handling the properties are attractive approaches to successful antimicrobial treatment against the disease. YfdX is a downstream regulator of the EvgAS two-component system, which induces transcription of genes involved in acid and multidrug resistance. Even though previous reports suggested a possibility that YfdX is associated with recognition of diverse antibiotics, its precise functional role and molecular properties remained to be elucidated. In this study, we investigated structural, biochemical, and physiological uncovered issues of YfdX. We determined the tetrameric crystal structure of *S*. Typhi YfdX, and identified a dimeric form as a smallest functional unit. An unexpected pH-dependent dynamic conversion of YfdX in solution between dimeric and tetrameric states was identified, which was further verified by biochemical analysis using structure-based mutant proteins. We also demonstrated that *Salmonella* YfdX induces tolerance of living bacteria to antibiotics such as penicillinG and carbenicillin, and it reduces bacterial virulence toward the *Salmonella* infection animal model, *Galleria mellonella*. Our studies therefore provide novel insights for determining association between YfdX and responses against environmental stresses, especially antibiotics, in *Salmonella*.

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