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Uropathogenic *Escherichia coli* employ a previously unrecognized detoxification system for protection from reactive chlorine species

Abstract:
Neutrophils eliminate invading pathogens through the production of reactive oxygen and chlorine species (ROS/RCS), with hypochlorous acid (HOCl) representing the most abundant and bactericidal oxidant produced during host defense and inflammation. Compared to bacterial defenses against ROS, which are better understood, little is known about how pathogens respond to and counter RCS, including HOCl. Here, we identify and mechanistically characterize RcrB, a protein of the uncharacterized DUF417 protein family, for which no role in oxidative stress defense has been described yet. We report a previously unrecognized role as an RCS detoxification system that confers high-level resistance to uropathogenic *Escherichia coli* (UPEC). We show that RcrB is an inner membrane protein and strongly induced during RCS exposure and phagocytosis. Loss of RcrB results in profound HOCl hypersensitivity, accompanied by elevated macromolecular damage and severe metabolic perturbations, establishing RcrB as a central determinant of UPECs RCS stress resistance. In contrast, heterologous expression of RcrB in HOCl-sensitive intestinal *E. coli* strains is sufficient to restore resistance but requires functional glutathione biosynthesis. Quantitative HOCl trapping assays demonstrate that RcrB expression protects the bacterial population by significantly reducing extracellular HOCl, indicating active chemical quenching rather than passive membrane protection. Structure-function analyses reveal that conserved, redox-active amino acids facing the periplasm are essential for this activity, because their substitution abolishes HOCl detoxification without affecting protein expression and disrupting membrane localization. Our findings define a novel bacterial strategy for mitigating RCS and reveal a distinct mechanism by which UPEC may succeed during host defense.

Bio sketch:
My interest in microbial physiology was amplified during my graduate MS and PhD graduate training at Potsdam University (Germany) when I discovered two novel sulfur carrier proteins and characterized their role for molybdenum cofactor biosynthesis. While most of my work was biochemical in nature at the time, I realized the significance of validating results in an *in vivo* context and thus completed an internship at the CNRS Laboratoire de Chimie Bactérienne in Marseille (France), where I was trained in transcriptomics. During my postdoctoral training at the University of Michigan (US), I gained expertise in redox biology by using the genetic toolboxes available for *E. coli* and *P. aeruginosa.* I studied novel bacterial stress response systems, e.g. an acid-activated chaperone with effective protein-protective properties under low pH conditions. Moreover, I studied polyphosphate (polyP), an ancient and highly conserved inorganic biopolymer, and its unrecognized role as protein stabilizing scaffold which protects bacteria against a wide range of physiologically relevant protein-unfolding stress conditions. I discovered the first inhibitor of prokaryotic polyP synthesis (i.e. the FDA-

approved drug mesalamine) and demonstrated that inhibition of polyP synthesis by mesalamine decreases biofilm formation, stress resistance, and colonization. In my own lab at Illinois State University, we have continued to explore novel bacterial stress defense systems and identified an essential component for the increased HOCl resistance of uropathogenic *Escherichia coli*. Moreover, we investigate bacterial defenses towards ROS-producing antimicrobials as well as their mode of killing as well as continue to study the physiological role of the biopolymer polyphosphate (polyP).