A bacterial inflammation sensor regulates c-di-GMP signaling, adhesion, and biofilm formation

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The reactive oxygen species produced during inflammation through the neutrophilic respiratory burst play profound roles in combating bacterial pathogens and regulating the microbiota. Among these, the neutrophilic oxidant bleach, hypochlorous acid (HOCl), is the most prevalent and strongest oxidizer and kills bacteria through non-specific oxidation of proteins, lipids, and DNA. Thus, HOCl can be viewed as a host-specific cue that conveys important information about what bacterial physiology and lifestyle programs may be required for successful colonization. Nevertheless, bacteria that colonize animals face a molecular challenge in how to achieve highly selective detection of HOCl due to its reactive and transient nature and chemical similarity to more benign and non-host-specific oxidants like hydrogen peroxide (H2O2). Here, we report that in response to increasing HOCl levels E. coli regulates biofilm production via activation of the diguanylate cyclase DgcZ. We show the molecular mechanism of this activation to be specific oxidation of a conserved cysteine that coordinates the zinc of its regulatory chemoreceptor zinc-binding (CZB) domain, forming a zinc-cysteine redox switch 685-fold more sensitive to oxidation by HOCl over H2O2. Dissection of the signal transduction mechanism through quantum mechanics, molecular dynamics, and biochemical analyses reveal how the cysteine redox state alters the delicate equilibrium of competition for Zn++ between the CZB domain and other zinc binders to relay the presence of HOCl through activating the associated GGDEF domain to catalyze c-di-GMP. We find biofilm formation and HOCl-sensing in vivo to be regulated by the conserved cysteine, and point mutants that mimic oxidized CZB states increase production of the biofilm matrix polymer poly-N-acetylglucosamine and total biofilm. We observe CZB-regulated diguanylate cyclases and chemoreceptors in phyla in which host-associated bacteria are prevalent and are possessed by pathogens that manipulate host inflammation as part of their colonization strategy. A phylogenetic survey of all known CZB sequences shows these domains to be conserved and widespread across diverse phyla, suggesting CZB origin predates the bacterial last universal common ancestor. The ability of bacteria to use CZB protein domains to perceive and thwart the host neutrophilic respiratory burst has implications for understanding the mechanisms of diseases of chronic inflammation and gut dysbiosis.