Structural characterization of intramolecular interactions of a metallochaperone domain in the mercuric reductase MerA

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Microbes have naturally evolved to deal with heavy metal toxicity resulting in elaborate heavy metal resistance mechanisms. Bacterial mercury resistance is mediated by the *mer* operon. It encodes specific genes that facilitate removal of toxic mercury species from the cell. Here, we apply experimental biophysics and high performance computer simulation to investigate molecular mechanisms of bacterial resistance to mercury.
Reduction of Hg(II) to Hg(0) is catalyzed by mercuric reductase, MerA. MerA is an NADPH-dependent flavin-disulfide oxidoreductase and catalyzes the reduction of Hg(II) to Hg(0), which is relatively inert and passively diffuses from the bacterial cell. All MerA proteins consist of a homodimeric catalytic core domain, and many also possess an N-terminal metallochaperone-like domain NmerA, which is tethered to the core by a ~30 amino acid linker of unknown fold. Prior studies using separately expressed NmerA and core domains showed that NmerA acquires Hg(II) from other *mer* proteins such as the organomercurial lyase, MerB, and the membrane transport protein, MerT, and delivers it to the MerA catalytic core for reduction. Here, we have applied small-angle X-ray scattering (SAXS), small-angle neutron scattering (SANS) and molecular dynamics simulations to characterize the interactions of NmerA and the core in full-length MerA in solution. Our data reveals the extent of spatial sampling of the two NmerA domains relative to the homodimeric catalytic core and identifies the inter-domain docking orientation that occurs during transient handoff of Hg(II) from a pair of cysteine residues on NmerA to a pair of cysteines on the C-terminus of the catalytic core.