The dynamic nature of mercuric ion reductase MerA

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Mercury (Hg) is a ubiquitous contaminant in the environment of particular interest as its conversion to methyl mercury leads to bioaccumulation and toxicity in higher organisms. Some bacteria have naturally evolved elaborate resistance mechanisms to deal with heavy metal toxicity. Bacterial mercury resistance is mediated by the *mer* operon, a set of genes encoding proteins that specifically facilitate cellular uptake of Hg(II) species, cleavage of organomercurials to hydrocarbons and Hg(II), and the key step in the resistance pathway, reduction of Hg(II) to Hg(0). With its intracellular location, the enzyme catalyzing the reduction, mercuric ion reductase (MerA), not only needs to be an efficient catalyst but also must acquire Hg(II) efficiently from other cellular and pathway proteins. All MerA proteins have a conserved homodimeric catalytic core (~100 kDa), homologous with the NADPH-dependent flavin disulfide oxidoreductases, and many have an N-terminal metallochaperone-like domain, NmerA, which acquires Hg(II) and transfers it using pairs of cysteine residues to an active site in the core homodimer for reduction. Here we have applied small angle neutron and X-ray scattering and molecular dynamics simulations to explore the structure and dynamics of full length MerA and to identify the docking site of NmerA with the core. We have characterized two functionally relevant states of MerA: (1) MerA in the absence of Hg(II) and (2) a multiple Cys to Ala mutant that traps the transient intermediate that would occur during handover of Hg(II) between NmerA and the catalytic core. Our data show first that the two N-terminal domains in dimeric MerA can sample a large number of conformations, consistent with the hypothesis that NmerA serves as a shuttle removing Hg(II) from distant donors in the cytoplasm for delivery to the core. In addition, the results identify the site of interaction between NmerA and the catalytic core during the transient Hg(II) handoff, providing insight into structural features that lead to efficient transfer. The high specificity of NmerA for mercuric mercury facilitates efficient acquisition and directed transport of Hg(II) to the catalytic core of MerA, which actively reduces Hg(II) to less harmful Hg(0).