REGIONAL CENTRE FOR BIOTECHNOLOGY
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# The 1.4 Å crystal structure of the ArsD arsenic metallochaperone and docking studies provide insights into its interaction with the ArsA ATPase


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Arsenic ranks first on the Superfund List of Hazardous Chemicals, in part because it is the most ubiquitous of all environmental toxic compounds. Bacterial resistance to arsenic is facilitated by ArsD, which delivers arsenite [As(III)] to ArsA ATPase, the catalytic subunit of the ArsAB pump. Here we report the first structure of an arsenic metallochaperone, ArsD dimer, at 1.4 Å resolution, and also present a model for its binding to a metalloid. ArsD binds one arsenic per monomer that is coordinated with the sulfur atoms of Cys12, Cys13 and Cys18. Based on data from structural homologues, ArsD was modeled with and without bound As(III). In this study, a combination of x-ray crystallography, in silico modeling and docking were used to examine the structure of ArsD and its interaction with the partner protein, ArsA. ArsA undergoes a number of conformational transitions during the catalytic cycle. It assumes an open form in the absence of MgATP and As(III), and a closed form when both are present. The closed form of ArsA structure is available, and an open form of ArsA structure was modeled based on the open Get3 structure. These structures were used for analysis of ArsA-ArsD interactions and docking studies. The open ArsA and metallated ArsD models were docked using the fully automated, web-based program ClusPro Version 2.0, which yielded 108 top-scoring solutions based on the balanced, electrostatic-favored, hydrophobic-favored, van der Waals plus electrostatic favored coefficients. Since biochemical analysis indicates that the three cysteines of ArsD and the three cysteines of ArsA must be in close proximity for the metalloid transfer, the 77 solutions that did not meet this constraint were discarded. This left 31 solutions in which ArsD fits into the cavity formed between the two halves of ArsA. One of these models demonstrated that, the ArsD sulfur atoms of Cys12 and Cys13 are within 4.1 - 7.5 Å of the sulfur atoms of ArsA Cys113 and Cys172. This model places 30 ArsD residues within 4 Å of 20 residues of ArsA and provides testable predictions of residues involved in ArsA-ArsD interactions.


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