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The Crystal Structure of MarR, a Regulator of Multiple Antibiotic Resistance, at 2.3Å Resolution.

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Beamline(s): X8C

Introduction: MarR is a regulator of multiple antibiotic resistance (MAR) in *E. coli*. It is the prototype for a family of such regulatory proteins, members of which exist in a wide range of bacteria. In *E. coli*, MarR acts to repress the expression of MarA, a transcription factor which leads to the production of a wide range of response elements, which in turn give rise to antibiotic resistance. The binding of certain phenolic ligands to MarR inhibits the binding of the repressor to DNA, triggering the MAR response. The solved crystal structure includes one such ligand, salicylate. This is the first reported structure of a member of this protein family.

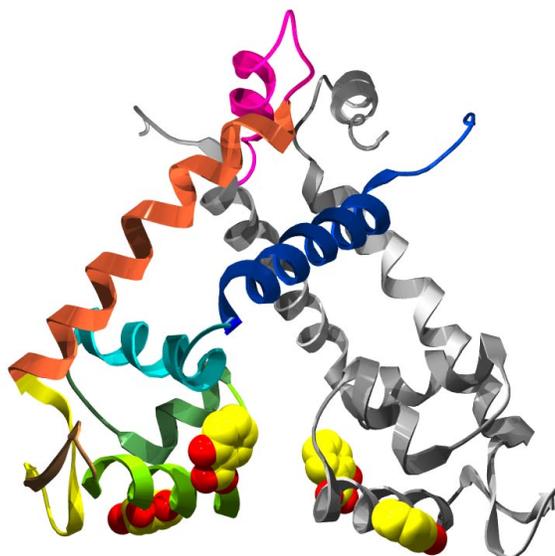
Methods and Materials: Crystals of MarR were grown in the presence of salicylate, both as the native protein and as the selenomethionine form. The structure was solved using MAD data collected from the selenomet crystals at the NSLS, beamline X8C. The structure was refined against data collected at the same source from native protein. The crystals of both forms of the protein grow in space group I4₁22, a=b=62.0 Å c= 132.9 Å, with a single monomer in the asymmetric unit.

Results: MarR consists of a dimer with the N and C termini interdigitating to form a lobe that holds the subunits together. This lobe is connected by a pair of helices in each subunit leading to a DNA binding domain. The DNA-binding domain is in the form of a “winged-helix” motif. Density believed to correspond to bound salicylate is found at two surface sites in each subunit, one on either side of the prospective DNA binding helix, where it might be expected to interfere with DNA binding.

Conclusions: The present structure shows that the two DNA-binding lobes in the MarR dimer have very few interactions between them and they appear free to interact relatively independently. To accommodate the concurrent binding of both lobes to DNA, it seems likely that the protein would have to undergo a conformational reorientation of the lobes. This would in turn require alterations in the two helices leading to the dimerization domain. Apparent flexibility in the present structure near the middle of one of these linker helices and at a turn leading to the C-terminal helix suggest that these might be sites which could accommodate such a change.

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References: M.N. Alekshun, S.B. Levy, T.R. Mealy, B.A. Seaton, and J.F. Head, “The crystal structure of MarR, a regulator of multiple antibiotic resistance, at 2.3Å resolution”. *Nature Structural Biology*, **8**, 710-714.



Ribbon Diagram of MarR showing space-filling representation of bound salicylate.