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LETTER

Substrate Binding in Free Methionine-*R*-sulfoxide Reductase

Recently, the group of Chi and co-workers published the crystal structures of the reduced, substrate-bound, and oxidized forms of fRMsr from *Staphylococcus aureus* (1). In parallel, our group proposed a catalytic mechanism of free methionine-*R*-sulfoxide (Met-*R*-O) reductase (fRMsr) from *Neisseria meningitidis* based on crystal structure and biochemical data (2). Superimposition of the crystal structures of the substrate-bound forms of *N. meningitidis* and *S. aureus* enzymes show significant differences; specifically, the sulfoxide in the *S. aureus* fRMsr occupies the position of the carboxylate in the *N. meningitidis* fRMsr and vice versa; in addition, the conformation of the flap, which contains the catalytic Cys¹¹⁸, is not superimposable (Fig. 1).

Four arguments favor a competent positioning of Met-*R*-O in the active site of the crystal structure of the *N. meningitidis* fRMsr. Firstly, the presence of an oxyanion hole rather excludes the productive binding of the sulfoxide function within the oxyanion hole as the sulfoxide reduction step requires protonation of the oxygen of the sulfurane transition state (3). Secondly, the *S. aureus* fRMsr complex was obtained with C84S fRMsr. Therefore, a single turnover catalytic event was expected to occur in the crystal, unless a noncompetent binary complex has been formed between fRMsr and Met-*R*-O. Thirdly, in the structure of the *N. meningitidis* fRMsr, the positioning of the catalytic cysteine is appropriate to allow a nucleophilic attack on the sulfur atom of the sulfoxide. Fourthly, all the residues of the *N. meningitidis* active site impose constraints geometrically on the L-Met-*R*-O, which is tightly bound.

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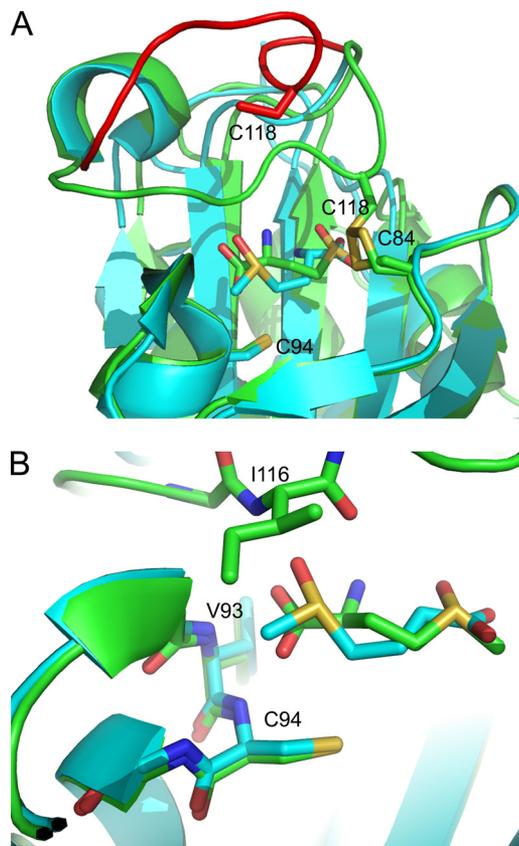


FIGURE 1. Ribbon representation of fRMsr from *N. meningitidis* (in green) and *S. aureus* (in cyan) in complex with L-Met-*R*-O. A, the conformation of a portion of the flap (residues 107–124, according to the numbering of the sequence of *Escherichia coli* fRMsr), between amino acids 113 and 120, which contains the catalytic Cys¹¹⁸, is not superimposable (in red for the structure of fRMsr of *S. aureus*). The side chains of Cys⁸⁴, Cys⁹⁴, and Cys¹¹⁸ are shown in stick representation. The L-Met-*R*-O is represented in stick with the oxygen atoms in red, nitrogen in blue, sulfur atoms in yellow, and carbon atoms in green (*N. meningitidis*) or in cyan (*S. aureus*). B, the main chain peptidic nitrogens of invariant residues Val⁹³, Cys⁹⁴, and Ile¹¹⁶ are shown in stick. The role of the oxyanion hole is to stabilize the binding of the carboxylate of the Met-O, whose negative charge is completely delocalized.

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