

Investigations on the mechanism of the new class of methionine sulfoxide reductase: the fRMsr from *Neisseria meningitidis*.

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The methionine sulfoxide reductases (Msrs) catalyse the reduction of the sulfoxide function of methionine sulfoxide (MetSO) preferentially included into a polypeptide chain. Msrs are known to play a role 1) in cell resistance to oxidative stress, 2) as physiological virulence determinant of bacterial pathogens like *N. meningitidis*, and 3) in the anti-ageing processes. There exist two structurally-unrelated classes of Msrs, called MsrA and MsrB, with opposite stereoselectivity towards the *S* and *R* isomers of the sulfoxide function of MetSO, respectively. Both Msrs present a similar three-step catalytic mechanism of sulfoxide reduction by thiols *via* the sulfenic acid chemistry^{1,2}.

Recently, a novel Msr activity, named fRMsr, has been identified in *E. coli*³. It is carried by a GAF domain, which usually presents no enzymatic activity but is involved in cyclic nucleotide signaling. The fRMsr is specific for the free form of Met-*R*-SO and uses Trx as a reductant. Inspection of the known fRMsr X-ray structure⁴ suggests that: 1) fRMsrs use Cys residues for catalysis, and 2) the active site, which is enclosed in a small cavity, is probably responsible for the selectivity for free Met-*R*-SO against protein-bound MetSO. Although speculative, the binding and reduction of free Met-*R*-SO by the fRMsr GAF domain may function as a key element in cell signaling in response to oxidative stress and nutrients.

The study recently initiated on the *N. meningitidis* fRMsr, should decipher its catalytic mechanism and the nature of its residues involved in the catalysis and in the structural specificity. Biochemical and kinetics data will be presented which illustrate the nature of the limiting step and the role of the aminoacids which are involved in the mechanism of the fRMsr. The results will be discussed in relation to the known mechanism, catalysis and structural specificities of MsrA and MsrB⁵.

¹ Boschi-Muller *et al.*, 2000, *J. Biol. Chem.*; **275**, 35908-13

² Olry *et al.*, 2002, *J. Biol. Chem.*, **277**, 12016-22

³ Lin *et al.*, 2007, *P.N.A.S.*, **104**, 9597-9602

⁴ Badger *et al.*, 2005, *Proteins : Structure, Function, and Bioinformatics*, **60**, 787-796

⁵ Boschi-Muller *et al.*, 2008, *Arch. Biochem. Biophys.*, in press