

The LytM structure: Implications for lysostaphin and for the definition of a new group of metallopeptidases

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Lysostaphin is under development as a protein drug to eradicate nasal *Staphylococcus aureus* infections. In spite of the strong practical interest in lysostaphin-type enzymes, no structure of any lysostaphin-type enzyme was available prior to our work. We have recently solved the structure of LytM, the first structure of a metallopeptidase of this family. The structure generated several surprises: Firstly, and contrary to the prior literature on the enzyme, it showed that full length LytM is a latent enzyme, most likely the proform of the enzyme, a finding that could be confirmed biochemically. Secondly, and more importantly, it showed that sequence based assumptions about the architecture of the active site of the enzyme have to be revised. Finally, the structure showed an unexpected similarity between the active sites of lysostaphin-type peptidases of a large group of peptidases with specificity for the peptidoglycan building block D-Ala-D-Ala. As a similar arrangement of residues is also present in the N-domain of sonic hedgehog, a peptidase without known substrate so far, we propose for this group of enzymes the term “LAS (lysostaphin/D-Ala-D-Ala/sonic hedgehog)” enzymes according to the initials of three main families.

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