

Distinctive properties of *Staphylococcus aureus* mevalonate kinase 3D structure: modeling of substrate binding sites

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One of the main directions of molecular pharmacology is searching for vulnerable links of enzyme systems of the general metabolic pathways of microorganisms. Mevalonate kinase (MK) is one of key enzymes of the mevalonate route of isoprenoid biosynthesis that provides formation of many essential substances in *S. aureus* cells that implicates *S. aureus* MK as promising target for the action of specific inhibitors that can be used as antibiotal drugs.

Flux through the mevalonate pathway is regulated at the mevalonate kinase (MK) step, which is strongly feedback inhibited by farnesylpyrophosphate (FPP) in most organisms [1] and by diphosphomevalonic acid (DPM) so far observed only for *Streptococcus pneumoniae* MK [2]. Recent appearance of 3D apo-structure for *S. aureus* MK [3] makes it possible to gain insight into substrate binding centers by overlay the binary complexes of MKs with appropriate ligands.

Using BioEdit computer program [4], we performed the protein sequence alignment of MKs from 6 different species. Mammalian MK chains are longer than prokaryotes' MK chains as a result of additional regions at both N- and C-termini. The extra region of N-terminal domain has to be shown to be a structural component of the FPP binding pocket.

Using PyMol computer program [5], we did pair-wise overlay of 3D structures of 3 MKs (*S. aureus*, *S. pneumoniae* and rat). MK molecules from different sources differ from each other by interdomain angle and spatial domain organization. It has been found that there was the interdomain angle difference of 30° between *S. pneumoniae* and rat MKs [6]. A similar situation was expected for other bacterial MKs. But it has been shown that interdomain angle in *S. aureus* MK was surprisingly closer to mammalian MKs than to *S. pneumoniae* MK. Apparently such a spatial domain organization is the distinctive feature of *S. pneumoniae* MK.

Since the structures of apo-MKs do not change upon a ligand binding, it can be assumed that the *S. aureus* MK structure remains the same in apo- and ligand binding state. On the basis of this assumption we did the substrate positions of *S. aureus* MK modeling using PyMol computer program by overlay of apo-form *S. aureus* MK on binary complexes of ATP-rat MK and mevalonate-*Leishmania major* MK.

Comparison of *S. aureus*, *S. pneumoniae* and rat MKs for the ATP and properly feedback inhibitor (FPP) binding sites demonstrated that *S. pneumoniae* MK exhibits the most solvent exposure for ATP and feedback inhibitor binding sites and consequently lack of binding for FPP. We have also compared mevalonate binding sites of three studied MKs. *S. aureus* MK has a very deep pocket for mevalonate compared to other two MKs. It might be specific for mevalonate binding to *S. aureus* MK, especially, in respect of previously shown substrate inhibition of this enzyme by mevalonate [1] that was not the case for MKs isolated from other species.

We compared previously published data on the amino acids involved in FPP and mevalonate binding: of FPP binding center of mammalian MK [6], of mevalonate binding center of *L. major* MK [7] and of DPM binding center of *S. pneumoniae* MK [8].

We conclude that the substrate binding sites of prokaryotes' MKs have some distinctive properties compared to eukaryotes' MKs. Furthermore these sites of different bacterial MKs differ from each other and this fact means that there is no single inhibitor for bacterial MKs. Our observations can be used as the basis in molecular modeling for development of new antibiotoxic drugs.

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