Structural and Kinetic Analysis of Methicillin-resistant Staphylococcus aureus MenE, an acyl-CoA Synthetase of the Bacterial Menaquinone Biosynthesis Pathway as a Novel Antibacterial Target

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The increasing drug resistance among Gram-positive bacteria such as methicillin-resistant Staphylococcus aureus (MRSA) has become a growing threat and thus the necessity for novel antibacterial targets is as imperative as ever. Bacterial menaquinone biosynthesis and the enzymes within its pathway are promising targets for novel drug discovery and development against drug-resistant bacteria because menaquinone functions as the lipid-soluble electron carrier in the electron transport chain of bacteria and humans lack this biosynthetic pathway. This study focused on MenE, the o-succinylbenzoate-CoA Synthetase of menaquinone biosynthesis. In order to gain insight on the structure and function of the domains and specific residues of the enzyme, S. aureus MenE was compared to other ANL superfamily enzymes, and steady-state kinetics and isothermal titration calorimetry was ran with saMenE mutants. Structural alignment and analysis of saMenE and ANL enzymes identified a potential function of the C-terminal domain of ANL enzymes to be that of an adenylate binding domain and ITC results of a C-terminal truncation of saMenE confirmed that the C-terminal domain is necessary for ligand binding. Steady-state kinetics of site-directed saMenE mutants discovered important catalytic residues in the active site of MenE, elucidating the molecular details of each catalytic half reaction. Therefore, the C-terminal domain and key conserved catalytic residues can serve as novel targets for antibacterial drug development against MenE and the entire ANL superfamily of enzymes.

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