Conformational changes of nucleotide-bindings site for the antibiotics development against D-ala-D-ala ligase from Acinetobacter baumannii

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Acinetobacter baumannii, which is emerging as a multidrug-resistant nosocomial pathogen, causes a number of diseases, including pneumonia, bacteremia, meningitis, and skin infections. With ATP hydrolysis, the D-alanine-D-alanine ligase (DDL) catalyzes the synthesis of D-alanyl-D-alanine, an essential component of bacterial peptidoglycan. Structural studies showed the flexible conformational changes in the ATP-binding site, more specifically both the hydrophobic nucleotide base binding site and the hydrophilic triphosphate binding site with the movement of the central domain and serine-loop. The central domain of AbDDL (DDL from Acinetobacter baumannii) can have an ensemble of the open and closed conformations before the binding of substrate ATP. In other DDL structures from Xanthomonas oryzae pv. oryzae and Yersinia pestis, the serine-loop and the ω-loop showed flexible conformations, especially the serine-loop is mainly responsible for the conformational change in substrate nucleotide phosphates. Currently, computer-aided drug designing methods has been actively and efficiently used. The detailed catalytic mechanism and structural information will be helpful in applying the CADD method in drug discovery.

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