Investigation of the Ligand Binding Characteristics of Staphylococcus aureus NorA Efflux Pump

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Staphylococcus aureus is a gram-positive bacterial pathogen which is highly adaptive to environmental conditions and causes various disorders. Excessive usage of antibiotics may result in development of antibiotic resistance in S. aureus. One of the resistance mechanisms is increase in the activity of transmembrane multi-drug efflux pumps. NorA is the most studied efflux pump in S. aureus, which belongs to Major Facilitator Superfamily (MFS). NorA has been shown to contribute to resistance against a variety of small molecules, such as hydrophilic fluoroquinolone antibiotics, antiseptics, dyes as ethidium bromide, and biocides. Moreover, a variety of small molecule inhibitors of NorA have also been found as well. However, the molecular mechanism and structural aspects underlying this ligand promiscuity of NorA is not yet well understood. Here, we aimed to characterize ligand specificity and promiscuity of NorA by identifying potantial ligand binding sites within the internal cavity of of NorA. For this purpose, a list of known NorA inhibitors and non-inhibitors were docked into detected ligand binding pockets on an ensemble of modelled NorA structures generated via molecular dynamics simulations. A clustering analysis based on molecular similarity and binding fingerprints indicated that binding sites of different ligands were not consistent, in line with the promiscuous nature of NorA. On the other hand, residues 47-PHE, 19- ILE, 98-ARG, were found to play a prominent role in ligand binding. Our findings may guide further research on discovery of novel NorA inhibitors.