The filtering mechanism in *Enterobacteraceiae*

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Abstract

The evolution and widespread of resistant bacterial pathogens along with the failure in antibacterial drug discovery have turned simple treatable infections into deadly ones again. In this adverse scenario, a new molecular framework for identifying and developing new antibiotics is absolutely needed. The situation is particularly critical for Gram-negative bacteria where the presence of the additional outer membrane (OM) represents an extra physical barrier for any antibiotic to access its internal target. In the OM, general diffusion porins are expressed to facilitate the entry of polar molecules as ions, vitamins and nutrients; therefore, they are the main entrance for polar antibiotics to overcome the OM barrier. Nevertheless, little is know about the rules governing the pore filtering mechanism, due to the lack of experimental techniques to quantify molecular permeability. We present an extensive study of small molecules permeability through the two major outer membrane porins of E.coli (OmpF, OmpC) and its ortologs in E. aerogenes (Omp35, Omp35), E. cloacae (OmpE35, OmpE36) and K. pneumonia (OmpK35, OmpK36). Using liposome swelling techniques and all-atom simulations we revealed the common filtering mechanism in Enterobacteriaceae and propose a theoretical score function for ranking molecules in terms of permeability through OM porins filling an important gap in antibiotic drug discovery.