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Selective Permeability of Antimicrobial Agents through the Protein Nanopore of the Highly-Drug Resistant Melioidosis Bacterium Burkholderia pseudomallei
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BpsOmp38 is a trimeric β-barrel protein abundantly located on the outer membrane of the ultra-drug resistant Melioidosis bacterium Burkholderia pseudomallei. Each barrel of BpsOmp38 has a diameter of about 1.2 to 1.5 nm and contains 16 β-strands connected with each other in an antiparallel fashion. This biological nanopore acts a molecular entry, allowing small, hydrophilic molecules, such as monosaccharides, amino acids, and antimicrobial agents, to pass through the bacterial membranes by passive diffusion. In our study, we determined the rates of sugar permeation, using liposome swelling assays and found that the permeability rates decreased as the molecular sizes of sugar increased. The permeation rates of the selected neutral sugars were in the order: L-arabinose (Mr 150) > D-galactose = D-glucose = D-mannose (Mr 180) > D-GlcNAc (Mr 221) > D-sucrose (Mr 342). Slight permeation of D-melezitose (Mr 522) or D-raffinose (Mr 504) was observed, suggesting the size exclusion limit of the molecules to pas through the BpsOmp38 nanopores to be < 500 kDa. The permeability of antimicrobial agents through the BpsOmp38 channel was further investigated and found to be barely correlated with molecular sizes, since most antimicrobial compounds carried net charge(s) that affected their relative mobility. For example, ceftazidime and cefoxitin with a net charge of -1 showed significantly higher permeating rates than the rates for meropenem and imipenem with a net charge of 0. The results emphasized the importance of ionizable groups lying inside the pore interior in controlling the molecular passage of BspOmp38. The data provide an implication for the strategic drug design that may help to improve the susceptibility of this highly drug resistant pathogen towards new drug molecules.

Keywords: Biological nanopore, outer membrane protein; melioidosis, antimicrobial resistance, Burkholderia pseudomallei

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