Molecular bases of antibiotic translocation across outer membrane porins

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Hydrophilic antibiotics preferentially use non-specific porins, channel-forming proteins in the outer membrane of Gram-negative bacteria, to gain access to the cell interior. Two major porin-based mechanisms for antibiotic resistance have been reported: alterations of the porin expression or altered function due to specific mutations reducing permeability.

In *Escherichia coli*, OmpF is considered a major pathway for the translocation of ß-lactam antibiotics and newer generations of quinolone antibiotics. The X-ray structure of OmpF reveals a homotrimer, with each monomer forming a separate ß-barrel composed of sixteen ß-strands spanning the outer membrane (Fig. 1A and 1B). A key feature in the structure of OmpF is the presence of a constriction region due to loop L3, which folds back into the channel, forming both a steric and electrostatic hindrance (Fig. 1C). This zone is characterized by a strong transversal electric field, generated by the negatively charged residues D113 and E117 on the L3 side facing a cluster of positively charged arginines (R42, R82, and R132). In this work, we investigated the impact of porin structure on antibiotic permeability by using complementary *in vivo* and *in vitro* approaches. Specifically, we characterized translocation of ß-lactam antibiotics across the three porins (Omp35, Omp36 and Omp37) of *Enterobacter aerogenes*, a Gram-negative “superbug”.

Improved understanding of porin specificity, the nature of porin-antibiotic interactions, and the structure-kinetics of porin translocation would facilitate the design of new antibiotics that can reach high intracellular concentration.