Mechanistic approach to antibiotic resistance: Mode of action of daptomycin

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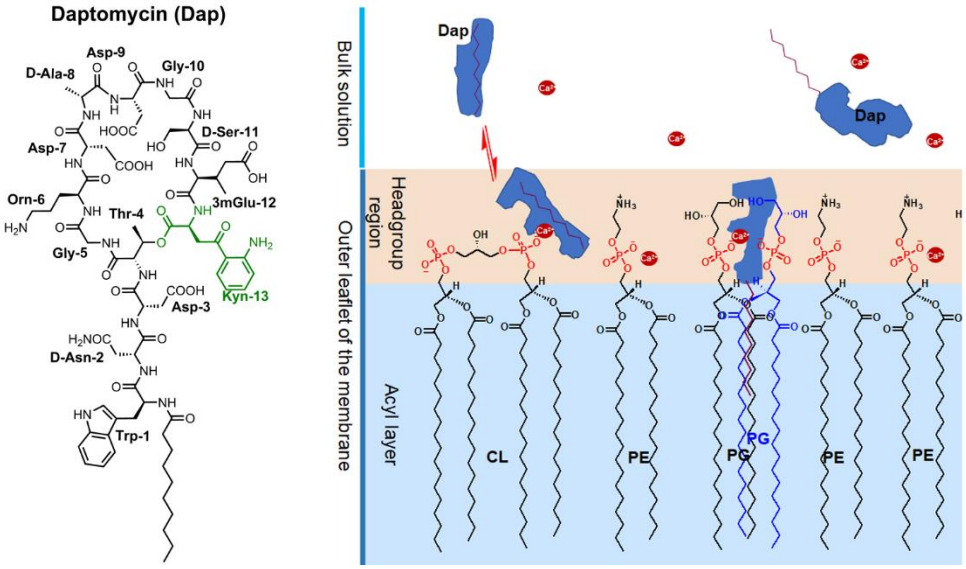
Daptomycin is a potent lipopeptide antibiotic used in the treatment of live-threatening Gram-positive infections, but its clinical efficacy is eroding due to resistance. Interestingly, its antibacterial potency and resistance are both reliant on phosphatidylglycerol, a phospholipid specific for bacteria, without a known molecular mechanism. We find that the phospholipid allows the antibiotic to insert irreversibly into membrane in minutes. In absence of this phospholipid, membrane reversibly binds the antibiotic on its surface in a millisecond process. Steady-state binding assays indicate that the antibiotic simultaneously binds two molecules of phosphatidylglycerol with a nanomolar binding affinity in the presence of calcium ion, strongly supporting a unique mechanism for the uptake of daptomycin in which the antibiotic forms a multi-component complex with calcium and phosphatidylglycerol. This stable complex has been successfully captured in vitro for structural studies and investigation of its disruption of the cell membrane is in progress. Results from these studies have provided fresh insights into the mode of action of daptomycin, which may lead to new strategies to attenuate the resistance to the drug.



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