Functions and inhibitors of SecA, an essential protein in bacterial Sec protein secretion

**Abstract**

SecA is an essential component in the bacterial Sec-dependent protein translocation across cytoplasmic membranes. In addition to the high-affinity SecA-SecYEG-SecDF•YajC protein-conducting channels, we have found that there are low-affinity SecA-only channels that elicit ion channel activity and promote protein translocation. These pore channels are less efficient, and like Prl suppressors, lack signal peptide specificity; they function in the absence of functional signal peptides. The addition of SecYEG-SecDF•YajC coverts the low affinity SecA-only channels to the high-affinity channels to restore efficiency and specificity. The 901 aminoacyl residues *E. coli* SecA forms multi-functional domains that interact with many ligands for functions. We identify the N-terminal domains that interact with lipids for ATPase activity, pore structure, ion channel activity, and protein translocation for SecA-only channels. We further determine the SecA domains that interact with SecYEG-SecDF•YajC to form more efficient channels. Since SecA is unique in bacteria and not present in mammalian cell, we develop inhibitors to target SecA as antimicrobial agents that are active against Gram-positive and Gram-negative pathogens. The presence of SecYEG-SecDF•YajC alters the sensitivity of the inhibitors. The suppressor membranes are much more resistant to SecA inhibitors than wild-type and reveal biphasic responses. The inhibitions of ion current and protein translocation activities show a low IC50 similar to SecA-only channels and a very high IC50. However, the suppressor strains are as sensitive to the inhibitor as the parental strain. Moreover, during stationary phase of bacterial growth, SecY decreases and SecA increases, and some cytoplasmic proteins without signal peptides are secreted. We propose that SecA-only channels inhibited by the SecA inhibitor have some essential physiological functions in the cells.