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First-principle-based and data-driven design of therapeutic peptides

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To combat antibiotic resistance demands timely improvement of drug efficacy. Here we introduce a computational approach that systematically creates variants from known antimicrobial peptides (AMPs) and selects the ones with improved potency based on physical quantities computed from a short, so called "immerse and surface" (IAS), molecular dynamics (MD) simulation. The designed in-silico platform was used to evaluate the efficacy of a series of tryptophan-rich AMPs, targeting Gram-positive and negative lipid membranes without a mediating receptor. Structures of three AMPs were solved by nuclear magnetic resonance (NMR) spectroscopy revealing their formation of α-helices on membrane, supported by circular dichroism (CD) data. Insertion orientations of AMPs predicted by MD simulations were validated by Paramagnetic relaxation enhancement (PRE) experiments. It was found, from both NMR experiments and computation, that antimicrobial efficacy of AMPs increased with the characterized insertion depth. Simulations reveal atomistic details of the AMP insertion over time and the importance of spatial arrangement of key residues synergistically mediating the insertion. To preserve important insertion patterns, peptide X, an AMP with already characterized potency, has its sequence circularly shuffled to create 13 variants. Partition free energies of all these AMPs are calculated from the SAS simulations and found to highly correlate with their minimal inhibitory concentration (MIC) values. The resulting correlation coefficient (>0.84) is found much favorably compare to those obtained from data-driven (machine learning) algorithms implemented in published web servers. Our computational platform capable of predicting AMP potency for peptides with similar primary sequences lends itself well to the development of new AMP design as well as improving existing AMPs in our continuous battle against pathogenic microbes. If time allows, I will also mention how accumulated structural data could help the design of anti-cancer peptides.

Summary

A new computationl platform to design and screen therapeutic peptides will be reported

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