Molecular dynamics simulation of keratin-derived antimicrobial peptides (KAMPs) in solution and of their interaction with bacterial membranes

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Abstract

Antimicrobial resistance (AMR) is one of the biggest threats of modern medicine, as pathogens become more resistant to available antibiotics. Overuse and misuse of antibiotics in humans and animals seem to be the main drivers of AMR, thus rendering necessary the search for alternative antimicrobial agents. A promising such class of agents is antimicrobial peptides (AMPs) characterized by selective cytotoxicity against microorganisms and slower development of AMR compared to conventional antibiotics. The structure, size and charge of AMPs directly influence their mechanism of action against cell membranes or intracellular targets.

AMPs derived from keratin (KAMPs) have been considered as a new, promising class of antimicrobial and antifungal agents as experimental studies have shown that they can be effective against a range of bacteria, including both Gram-positive and Gram-negative species. Unlike most antimicrobial peptide candidates, their biological activity is independent of the presence of an α-helix. It has also been established that some KAMPs form pores in the bacterial membrane.

In the present work, we employ molecular simulations to examine the structure of seven KAMPs derived from human cytokeratin 6A (KAMP-10/10G2A/18C/18N/19/19scrumbled/36) and one from poultry feather keratin (Pw-Antibac12$_3$), both in dilute and in semi-dilute aqueous solutions, and their interactions against model bacterial membranes. The predictions of detailed molecular dynamics (MD) simulations confirm the experimentally determined structure of KAMPs in dilute solutions, namely a dominant non-canonical secondary structure with a very low helical content (< 10%). The helical content is somewhat promoted by peptide aggregation in semi-dilute conditions, with the formed clusters being stabilized by β-bridges. Enhanced aggregation propensity was observed for KAMP-36 and Pw-Antibac12$_3$, while the substitution of glycine by alanine in KAMP-10 was found to hinder the tendency of KAMPs for self-association into a single big cluster.

As no spontaneous pore formation in both Gram-positive and Gram-negative membranes was observed when these were brought into contact with KAMP-10 and KAMP-18C even after about 2 μs of simulation time, systems with pre-assembled pores or with KAMPs embedded into the bilayer membrane were designed and studied in terms of their stability over time or in terms of KAMPs' ability to diffuse through the membrane, self-assemble into larger structures and create defects. Pore stability, in particular, was assessed by computing the time evolution of the volume of the initially formed pore in the presence of different KAMP structures using a geometric algorithm. Results from these calculations will be presented and discussed in due detail.