Conclusive remarks

Pathogenic microorganisms are developing resistance to conventional antibiotics at an alarming rate. The threat posed by these microorganisms urgently demands a new class of antibiotics which can evade their mechanism of resistance. Naturally occurring antimicrobial peptides are widely recognized as a potent weapon to combat pathogenic microorganisms. However, prospect of systemic application of antimicrobial peptide based therapeutics is shattered by their poor cell selectivity, instability in physiological condition and cost aspect. This study was focused towards identification of structural elements which can play crucial role in toxicity of membrane active antimicrobial peptides. Towards this end the role of leucine zipper sequence in controlling toxicity of naturally occurring antimicrobial peptides, melittin, bombolitin V and magainin 2 has been extensively studied here. Leucine(s)/isoleucine(s) at the ‘a’ and ‘d’ position(s) of this motif were found to be key regulators of toxic activity. Substitution of these crucial amino acids by alanine residues significantly reduced cytotoxicity of melittin and bombolitin V. Moreover, introduction of this motif in magainin 2 induced toxicity towards hRBCs and other mammalian cells. Interestingly, antibacterial activity of these peptides were unaffected by 1-2 leucine to alanine residue(s) substitution(s) in this structural element. The presence of sufficient number of cationic residues in an antimicrobial peptide (bombolitin V) is essential for its activity against microorganisms has been demonstrated in the present investigation. Compiling all the results presented in this work together recognizes leucine zipper motif as a signature of toxicity, its presence always accompanied toxic activity towards mammalian cells. This information augments the strategies to design cell selective analogs of potent antimicrobial peptides which can open the doors for new generation of peptide antibiotics. Detailed structural and functional studies by several biophysical and cell biological approaches showed the molecular basis of mode of action of several different native peptides and their analogs investigated here.