DOI 10.18699/SBB-2022-162

Statistical approach to regulation of membrane-permeabilizing activity of antimicrobial peptides

Kondrashov O.V., Akimov S.A.*
A.N. Frumkin Institute of Physical Chemistry and Electrochemistry, RAS, Moscow, Russia
* *akimov_sergey@mail.ru*

Key words: lipid membrane, theory of elasticity, antimicrobial peptide, partition function, Mayer cluster expansion

Motivation and Aim: Antimicrobial peptides (AMP) are considered promising antibiotics with an extremely low predicted probability of drug resistance appearance. The development of new antimicrobial drugs is currently especially urgent: the problem of antibiotic resistance, according to the World Health Organization, is one of the most serious threats to human health, food security and development of the entire world. Purposeful rational development of antimicrobial drugs is impossible without a detailed understanding of the fundamental molecular mechanisms of their action. The action of some types of AMP is based on an increase in the permeability of the membranes of pathogenic cells, leading to their death. The formation of a through pore in the membrane is a cooperative process that requires the participation of several peptides. Permeabilization of membranes by AMPs at a certain surface concentration is a stochastic process, for understanding and adequate description of the mechanisms of which it is necessary to use statistical approaches.
Methods and Algorithms: We developed the statistical model that allows describing the effect of membrane-deforming inclusions on the equilibrium between AMP monomers and their cooperative membrane-permeabilizing structures. Permeabilization of the membrane via formation of pores or ion channels is accompanied by elastic deformations of the membrane, and these deformations contribute to characteristics of the membrane-permeabilizing structures. Thus, the average conductivity of the membrane should depend on the spatial structure of its deformations. Rigid membrane inclusions that purposefully modify the deformation fields of the membrane can potentially regulate the activity of AMPs. The pairwise interaction potentials of peptide molecules, membrane-permeabilizing structures, peptides in transient configurations, and rigid membrane inclusions regulating the deformation fields were calculated in the framework of theory of elasticity of lipid membranes. The obtained energies were then used to obtain the partition function of the system in the framework of the Mayer cluster expansion.
Results: Short transmembrane peptides were shown to strongly favor the membrane-permeabilizing states of channel-forming antimicrobial peptides (CFAP). Small amphipathic peptides were also shown to increase the average conductivity of the membrane due to CFAP, although their working concentrations should be about two orders of magnitude higher as compared to short transmembrane peptides. Helical amphipathic peptides favored formation of hydrophobic defects in the membrane, but they hindered formation of small hydrophilic pores.
Conclusion: The results obtained may be utilized for analysis of amplifying or weakening the effect of various membrane-deforming inclusions with respect to different types of AMPs. The only requirement is that at the sequential stages of the

action, the AMP should induce different deformations of the membrane. In multiple systems, where membrane-deforming particles (monomers) can form higher-order aggregates (dimers, trimers, etc.) an addition of deformation-inducing inclusions can change the equilibrium distribution of the aggregates. In such reactions, the inclusions can strongly favor or stabilize a particular state or aggregate thus shifting the equilibrium towards that state. The model predicts that amphipathic peptides and short transmembrane peptides playing the role of the membrane-deforming inclusions, even in low concentration can substantially increase the average conductivity of membranes.
Acknowledgements: The study was supported by the Russian Science Foundation (grant No. 22-24-00834).