Host-defense peptide interaction with bacterial and host cells: An interplay of multiple equilibria regulating bactericidal activity and selectivity

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Host-defense peptides (HDPs) are natural molecules endowed with bactericidal and immunomodulating activity. Their mechanism of bacterial killing involves association to cell membranes and their perturbation. In vitro, they are selective for bacterial versus eukaryotic cells. For these reasons, HDPs are promising compounds to fight drug-resistant bacteria. However, rational design of new peptides or peptidomimetics with the same activity of HDPs, but with improved pharmacological properties, has proven difficult. In addition, several unanswered questions regarding the function of HDPs remain: is their main role related to the direct killing activity or to the immunomodulatory properties? What are the structural determinants of selectivity? Is cell selectivity real or an artifact of the assay conditions? Progress towards a better understanding of these molecules is hindered by the difficulties involved in the structural characterization of peptide-membrane systems, and by the fact that quantitative biophysical studies are usually performed on model systems, such as liposomes, and thus are difficult to compare and integrate with microbiological experiments on HDP activity and selectivity.
By combining spectroscopic experiments on liposomes and cells, molecular dynamics simulations and microbiological assays, we characterized how HDP activity and selectivity are regulated by multiple equilibria: membrane binding, aggregation, conformational transitions and orientation in the bilayer[1]. For instance, we showed that peptide folding or aggregation in solution are ways to increase peptide selectivity, by shielding the hydrophobic residues and reducing the hydrophobic-driving force for binding to the neutral surface of host cells. We determined the minimum number of peptide molecules that must bind to a single bacterial cell to kill it, and showed that a high coverage of the cell surface is needed to cause membrane lysis. We also studied how the activity depends on cell-density. Due to the peptide/cell binding equilibrium, the total peptide concentration in solution needed to reach the membrane coverage required for bacterial killing is always in the μM range, even at low cell densities. These data indicate that immunomodulation might prevail where these concentrations are not reached. Finally, selectivity depends on the relative densities of bacteria and human cells, but, at least under some conditions, specific killing of bacteria can take place also in the presence of a large excess of host cells. Overall, our studies indicate that characterization and modulation of the different phenomena involved in peptide behavior is a valuable approach to understand the function of HDPs and to improve their properties.

References:

The lecture is organized on behalf of the graduate programme in pharmaceutical sciences, Drug Research Academy, by Marco van de Weert, Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen.

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