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The secrets and potential of a novel cyclic antimicrobial and cell penetrating peptide

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The development of antimicrobial peptides as antibiotic agents requires structural characterization and understanding of their diverse mechanisms of action. We investigated small cyclic anginine (R)- and tryptophan (W)-rich peptides characterised by variations in the amino acid position, exchange of R and W by other charged or aromatic residues, introduction of D-amino acid residues and reduction and enlargement of the ring size. The cyclic hexapeptide cycloRRRWFW (cWFW) revealed high antimicrobial activity and proved to be not toxic against eukaryotic cells. Its amphipathic structure and arginine content provide the prerequisites for membrane permeabilisation and translocation as modes of action. Using a number of techniques to study peptide interaction with bacterial and eukaryotic cells and model membranes, we could show that the activity of cWFW is based on a novel antimicrobial mechanism. Strong interactions with the bacterial membrane lead to reduction in membrane fluidity and disturbance of the native lipid matrix. The formation of distinct lipid domains is related to a severe disturbance in the positioning of functional proteins. Chemical modifications such as enhancement of the peptide hydrophobicity or enlargement of the cycle eliminated the bacterial selectivity and induced a membrane permeabilising mode of action. Although cWFW does not enter the cytoplasm of bacteria, it is rapidly internalized into human cells. The combination of cell penetrating properties with high antimicrobial activity and the novel mechanism of action render the cyclic hexapeptide an eligible compound with regard to the treatment of intracellular bacterial infections.

Biography

Margitta Dathe studied Physics at the Humboldt University of Berlin and completed her PhD in 1978 from the Academy of Sciences of the GDR. Since 1999 she has been working as Head of the Peptide-Lipid Interaction research group of the Leibniz Researchinstitute of Molecular Pharmacology. Her research interest is focused on targeting, cellular uptake promoting and antimicrobial peptides. She has published more than 100 papers in reputed journals.

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