Tilted peptides: from viral lipid fusion to amyloidosis.

Lins, L., Thomas, A, Brasseur, R

CBMN

Many important biological processes involve the partitioning of peptides into lipid bilayer membranes. Such peptides are typically quite hydrophobic. A few years ago, we discovered a peculiar property of hydrophobic fragments in viral fusion proteins. When we modeled those short peptides (10 to 20 residues) as α-helices, we found that they had a gradient of hydrophobic amino acids along their axis (1,3). They are not only amphipathic (hydrophobic on one side, less hydrophobic on the other side), but also their net hydrophobicity increases from one end of the helix to the other. Because of this `top-to-bottom' hydrophobic asymmetry, we predicted that such peptides would have an equilibrium tilt when they are at a hydrophobic/hydrophilic interface, such as the lipid/water interface (1). We call them « tilted » or oblique peptides. Recent neutron diffraction experiments have now confirmed the existence of tilted peptides in bilayers (2).
The tilted orientation allows them to destabilize organized molecular systems and to induce processes such as lipid fusion.
The asymmetric hydrophobic gradient appears to be crucial for the destabilizing activity of tilted peptides. In order to assess the importance of this gradient, mutants of different tilted peptides were calculated by molecular modelling. Those mutants are designed to be parallel- or perpendicular-oriented towards the hydrophobic/hydrophilic interface. It was shown that those mutants are unable to experimentally induce fusion processes, either with the isolated peptide or with the entire viral fusion protein, while mutants where the gradient is restored retrieve their fusogenic activities.

Tilted peptides are also present in various proteins such as membrane proteins, proteins involved in lipid metabolism, toxins,... In a more surprising fashion, they were detected in proteins involved in neurodegenerative diseases, for instance in Aβ protein and PrP protein responsible for respectively Alzheimer's and prion diseases (4,5). The role of those tilted peptides in neurotoxicity could be either a direct effect of the peptide on the neuronal membrane, leading to cell death or in protein transconformation, leading to neurotoxic protein aggregation.

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