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Arg/Trp cell-penetrating peptides incorporating Trp analogues: internalisation properties and interactions with cell membrane components

Cell Penetrating Peptides (CPPs) are small peptides able to cross cell membranes in a receptor-independent way. They are generally cationic and often amphipathic, which leads them to interact favourably with membrane lipids and glycosaminoglycans (GAGs) of the cell surface. Their internalisation can occur according to two pathways: endocytosis which is energy-dependent and translocation which does not require energy. In both mechanisms, the first step involves interactions between the peptide, GAGs and/or lipids. Most of CPPs contain arginine or lysine residues able to create electrostatic interactions with the negatively charged membrane components. Some sequences also contain Trp residues, which are essential for penetration properties. Trp may be implicated in various interactions with both lipids and GAGs, including hydrophobic contacts, hydrogen bonds (1), and recently, ionpair- π interactions involving tryptophan have been identified (2).

The aim of this study is to decipher the role of Trp in the internalisation mechanisms by modulating its physico-chemical properties in Arg/Trp peptide sequences, using RW9 (RRWRRRWR) as a model sequence. For this purpose, a small peptide library, where Trp has been substituted by other natural amino acids or by non-natural Trp analogs was designed and synthesized, in order to better understand the type of interaction in which it is involved.

The quantification of the internalisation of these peptides in cell lines more or less enriched in GAGs has been performed by MALDI-TOF mass spectrometry. Isothermal calorimetry and differential scanning calorimetry have been used to characterize their binding with GAGs and lipids but also the bilayer perturbation caused by these peptides.

All these results provide precious information on the role of Trp in the internalisation mechanisms and lead us to design new peptides comprising unusual amino acids with improved cell penetration properties.

References:

- 1) Khemaissa, S., Sagan, S., & Walrant, A. (2021). Tryptophan, an Amino-Acid Endowed with Unique Properties and Its Many Roles in Membrane Proteins. *Crystals*, 11(9), 1032.
- 2) Walrant, A., Bauzá, A., Girardet, C., Alves, I. D., Lecomte, S., Illien, F., ... & Sagan, S. (2020). Ionpair- π interactions favor cell penetration of arginine/tryptophan-rich cell-penetrating peptides. *Biochimica et Biophysica Acta (BBA)-Biomembranes*, 1862(2), 183098.

Session

Molecular interactions at the membrane surface

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