

Design of cell-penetrating peptides and study of their mechanism of cellular uptake

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Cell-penetrating peptides (CPPs) usually correspond to relatively short (8 to 30 residues) purely cationic or amphipathic sequences. They are currently considered as one of the most promising tools for the delivery of probes for studying intracellular processes or therapeutics. Using a method based on MALDI-TOF mass spectrometry to quantify internalisation, we have investigated the mechanism of entry inside cells of several CPPs and conjugates and determined the respective contribution of endocytosis and direct translocation across the plasma membrane. This study has highlighted the importance of cell surface glycosaminoglycans in the internalisation of CPPs by endocytosis. Studies on membrane models have also allowed a better understanding of the direct translocation mechanism.

Our research also involves the design of new CPPs. Several chemical modifications have been performed to increase the CPP efficiency of internalisation and metabolic stability including the incorporation in their sequence of α,α -disubstituted amino acids, their acylation with fatty acid chains and more recently, their head-to-tail cyclisation. This has led to the identification of minimalist CPPs entering cells more efficiently both by direct translocation and endocytosis.