Membrane Translocation of Arginine-rich Peptides

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Arginine-rich peptides including HIV-1 Tat peptide are regarded as one representative class of cell-penetrating peptides (CPPs) as intracellular delivery vectors. It has been suggested that macropinocytosis plays a crucial role in cellular uptake of these peptides. We have recently shown that treatment of cells with arginine-rich peptides induces activation of Rac protein leading to F-actin organization and macropinocytosis. We have also shown that depletion of membrane-associated proteoglycans results in the failure of this signaling pathway, suggesting the possibility that membrane-associated proteoglycans may act as a potential receptor for the induction of macropinocytic uptake of arginine-rich peptides. However, when the macropinocytic pathway is inhibited at a low temperature or cholesterol depletion, these peptides can be internalized by a non-endocytic mechanism. Studies using R12 (arginine 12-mer) peptide suggest the initiation of non-endocytic uptake and cytosolic labeling is also dependent on serum concentration and extracelluar peptide concentration. At relatively low concentrations the peptide labels endocytic structures, but upon raising the peptide concentration the fraction labeling the cytosol increases dramatically, which results in a non-linear increase in total cellular fluorescence. Membrane-associated proteoglycans also contribute to increase the peptide concentration at the cell surface by enhancing their recruitment via electrostatic interactions. These results demonstrate that uptake mechanisms of these compounds are highly dependent on both the presence of serum and the effective extracellular peptide concentration.