Effect of the electrostatic potential on the internalization mechanism of cell penetrating peptides derived from TIRAP

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In order to develop future therapeutic applications for cell penetrating peptides (CPPs), it is essential to characterize their internalization mechanisms, as they might affect the stability and the accessibility of the carried drug. Several internalization mechanisms have been described in literature, such as endocytosis and transduction. In this work we study the internalization mechanism in HeLa cells of two TIRAP derived peptides: pepTIRAP and pepTIRAPALA, where some of the cationic amino acids were replaced with alanines. Detailed analysis of inter-nalization and the peptides electrostatic potential was carried out, to shed light on the internalization mechanism involved. Molecular modeling studies showed that the main difference identified between pepTIRAP and pepTIRAPALA is the distribution of their electrostatic potential field. The structure of pepTIRAP displays a predominantly positive potential when compared to pepTIRAPALA, which has a more balanced potential distribution. I