Austin Biochemistry

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Editorial

Cationic Cell Penetrating Peptides

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Received: October 28, 2016; **Accepted:** November 10, 2016; **Published:** November 14, 2016

Editorial

Cell Penetrating Peptides (CPPs) or membrane transduction peptides are named for their ability to penetrate various types of cells [1,2]. They are synthetic peptides typically less than 30 amino acids in length. Their primary sequences come either from a parent protein expressed in cells or are derived from natural peptides [3-11]. CPPs can carry cargos ranging from small molecules to macro molecules such as proteins and nucleic acids [12,13], which are otherwise difficult to translocate into cells. For this reason, they were quickly earmarked as potential cellular delivery tools. Understanding the mechanism of CPP cell entry is of great significance in both cell biology and targeted drug delivery.

The mechanisms, through which the CPPs translocated into cells, have been studied but are inconclusive. Some evidence indicates receptor independent endocytosis as the CPP cell entry mechanism [14-18]. The CPP endosomal release is considered as the main obstacle for the application of CPPs in drug delivery. Other evidence supports direct translocation through the cell membranes or non-endocytic pathways [19-22]. Still other studies have suggested that both endocytosis and direct translocation coexist for the CPPs' cell entry [23-25]. The relative importance of the endocytosis and non-endocytosis mechanisms seems to depend on the extracellular concentration, the peptide sequence, and the cell types. The increasing concentration of the peptides increases the likely importance of non-endocytic translocation mechanisms.

CPPs could be hydrophobic, amphipathic, or hydrophilic. Although they lack a definite pattern for their primary sequences, the majority of CPPs are cationic being rich in basic amino acids such as arginine and lysine. They are, therefore, attracted to the partially negatively charged cell membranes [26] and proteoglycans on cell surfaces [27]. Cationic polypeptides, such as poly-lysine, Kn, and poly-arginine, Rn, were found to increase the serum albumin uptake in cells [28]. The fact that Rn has been shown to be more efficient at translocating into cells than Kn led to the belief that the guanidino group in arginine is crucial for cellular uptake of CPPs [26-30]. On the other hand, peptides such as Transportan, Hel 11-7, MAP, and MPG-α contain only lysine as their basic amino acids [31-34]. Therefore, it appears that the guanidino group though beneficial, is not required for CPP penetration. It is necessary to investigate the roles of the secondary structures of CPPs in their translocation across the cell membrane. For example, Penetratin and Transportan have adopted more α-helix in the presence of 2,2,2-trifluoroethanol (TFE) than in aqueous solutions [22]. TFE which provides a low dielectric constant similar to that of the cell membrane, favours the formation of intra-peptide hydrogen bonds [35]. My previous study of Penetratin in live melanoma cells revealed that the peptide contained both random coil and β-strand in the cytoplasm, and possibly assembled as β-sheets in the nucleus. Furthermore, evaluation of Rn, where n is between 6 to 30, for their cellular uptake showed the cell penetrating capacity peaked at R15 [29]. With the high structural flexibility and the short length, lysine and arginine rich CPPs have demonstrated the potential to adjust their conformation that may assist them with the translocation into the cell [34]. Further research needs to focus on the secondary structure of the CPPs in various conditions, and how they interact with cell membranes with the hope of revealing the connection between the structure and the peptide cell entry.

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Citation: Ye J. Cationic Cell Penetrating Peptides. Austin Biochem. 2016; 1(1): 1004.

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Austin Biochem - Volume 1 Issue 1 - 2016
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Citation: Ye J. Cationic Cell Penetrating Peptides. Austin Biochem. 2016; 1(1): 1004.