Kinetic Analysis of Cellular Internalization and Expulsion of Unstructured D-chirality Cell Penetrating Peptides

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Abstract

Most cell penetrating peptides (CPPs) are unstructured and susceptible to proteolytic degradation. One alternative is to incorporate D-chirality amino acids into unstructured CPPs to allow for enhanced uptake and intracellular stability. This work investigates CPP internalization using a series of time, concentration, temperature, and energy dependent studies, resulting in a three-fold increase in uptake and 50-fold increase in stability of D-chirality peptides over L-chirality counterparts. CPP internalization occurred via a combination of direct penetration and endocytosis, with a percentage of internalized CPP expelling from cells in a time-dependent manner. Mechanistic studies identified that cells exported the intact internalized D-chirality CPPs via an exocytosis independent pathway, analogous to a direct penetration method out of the cells. These findings highlight the potential of D-chirality CPPs as bio-vectors in therapeutic and biosensing applications, but also identify a new expulsion method suggesting a relationship between uptake kinetics, intracellular stability, and export kinetics

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