Enhancing the Oncotoxic Effects of Mitochondrial-Targeting D-(KLAKLAK)2 Peptide by Improving Cell Membrane Permeability via Chemical Conjugation With Imidazopyridinium (IP+)

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Prior research has indicated that the synthetic peptide D-(KLAKLAK)2 and its analogues exhibit potent cancer toxicity (oncotoxicity) and pro-apoptotic activity when internalized within mammalian cancer cells. The limitations of these peptides as therapeutic agents, however, are cancer specificity and membrane permeability. Research on tumor-homing domains to attach to these kinds of peptides has had relative success in conferring specificity, but they remain inefficient in promoting membrane permeability. Therefore, the only remaining obstacle is membrane permeability. The research conducted investigates chemical grafting of Imidazopyridinium (IP+) onto D-(KLAKLAK)2 and its analogues and its effect on their cellular permeability. IP+ is a heterocyclic compound designed to facilitate the diffusion of large peptides across the cell membrane. This research tested if grafting IP+ onto D-(KLAKLAK)2 and its analogues would improve their ability to diffuse across the cell membrane, which could aid in the development of a cancer therapeutic based on this peptide or others like it. Experimental methods included first preparing D-(KLAKLAK)2, its analogues, and subsequently grafting IP+ and a chloroalkane tag onto them. Then, the effects of IP+ were evaluated by running Chloroalkane Penetration Assays (CAPA) on HEK293 cells to assess to what degree the peptides with or without IP+ could access the cytosol of the cells. Results indicated that IP+ significantly enhanced the intracellular localization of D-(KLAKLAK)2 and D-KLAK compared to controls lacking IP+. These results support the hypothesis and suggest that combining D-(KLAKLAK)2, a tumor-targeting domain, and IP+ may provide a promising approach for developing broad-spectrum cancer therapeutics in the future.

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