LH Peptides, a Histidine-Based Peptide With pH-Specific Cell Penetrating Abilities: From Tumors and Beyond The Brain

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Cell-penetrating peptides (CPPs) are amino-acid sequences that could facilitate the uptake mechanisms of cells. Due to its biocompatibility and synthetic simplicity, CPPs have been popularly investigated as drug delivery carriers. However, due to major drawbacks regarding poor biostability, lack of specificity, and low efficacy, no CPPs were issued as FDA-approved systemic drugs until the present day. To overcome the limitations of CPPs, our research group reported LH peptide, a novel histidine-based CPP. Dimeric LH peptide (LH2) displayed cell penetration activity in weak acidic pH conditions, even in nanomolar conditions. Biodistribution analysis uncovered the tumor-specific targeting abilities of LH2 peptides. The drug loading scheme of dimeric LH peptide (LH2-PTX) displayed a substantial anti-tumor effect on triple-negative breast cancer cells in mouse xenograft models. These results reflect the notable biostability, efficacy, and tumor-targeting ability of LH peptides.

Due to its notable biostability and tumor-targeting abilities in vivo, our research group is currently focusing on the delivery of LH peptides to the brain. The presence of the Blood-Brain Barrier (BBB) blocks the penetration of harmful exogenous antigens. However, it also functions as a barrier to the delivery of potent drug molecules. Previous studies reported that BBB endothelial cells are enriched with various membrane transporters[i], and conjugation of these molecular transporter ligands facilitates the delivery of exogenous materials. Thus, a combinatorial strategy of cancer-targeting LH peptide and BBB-crossing small molecule is proposed. Such ligands are covalently conjugated to LH peptide, and tested for BBB-crossing ability and antitumor effect.

References

[i] Huttunen. J.; Adla K. S.; Markowicz-Piasecka. M.; Huttunen M. K.; Increased/Targeted Brain (Pro)Drug Delivery via Utilization of Solute Carriers (SLCs) *Pharmaceutics.* **2022,** *14(6)*, 1234