

CPP as Promising Delivery of Chemotherapeutic Agents: Review

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ABSTRACT

Side effects of the conventionally used chemotherapies and the limited cell-permeability of the drugs owe to find out the most efficient strategies for the cancer treatment. In the recent years combination of compounds with limited cell-permeability with efficient delivery systems to minimize side effects and enhance cell-permeability is the area of interest for the formulators. The major obstacle of the anticancer drug is having limited cell-permeability of the drugs which results into the low bioavailability which limits the biological application of the anticancer drugs. The ability of the CPPs to internalizing all the cell types' facilities the transport of cargos without any size restriction additionally they have high specificity and low toxicity profile. In this review we have discussed the challenges of the CPP as drug delivery and the applications of the CPP as compared to other conventionally used chemotherapies.

Keywords: Cell permeability; Size restriction; Chemotherapies

INTRODUCTION

Cell-Penetrating Peptides (CPPs) are typically consist of 5-30 amino acids with the ability to cross the cell membrane for this CPPs have been used for a variety of applications [1].

Cell-Penetrating Peptides (CPPs) correspond to short 30 residue synthetic peptides and are able to traverse biological membranes and to deliver numerous compounds including small molecules, nucleic acids, proteins, viruses, imaging agents and drugs inside the cells [2].

Major drawback of conventional chemotherapeutic agent is the low penetration of drugs into tumor tissues, dose dependent side effects and the resistant tumors to treatment [3].

LITERATURE REVIEW

The low penetration of drugs in the cancer tissues is due to a dense connective stroma that hinders the entry of molecules into tumoral tissue and the presence of high interstitial pressure caused by abnormal blood and lymphatic vessels [4]. CPPs can improve the drug delivery in tumor cells by facilitating extravasation and penetration of cancer cells while other tissues remain unaffected by the drug [5,6]. Therapeutic strategies that use antibodies or peptides recognizing target molecules specific to tumor cells allow concentrating into tumoral tissue an amount of drug able to inhibit cancer growth [7-10]. Thus, increased activity and reduced toxicity to healthy tissues are

expected when the drug is localized and accumulated preferentially in the tumor site [11].

Current challenges in peptide-based drug delivery

Typical short duration of action and lack of oral bioavailability limits the CPPs as pharmaceutical product [12]. One of the true drawbacks of peptide drugs is the increased proteolytic instability compared to not only small molecules but also monoclonal antibody therapeutics [13]. The modification of the peptide structure by acylation, PEGylation, unnatural amino acids or restricted conformation can largely remove this issue [14]. The introduction of D-amino acids instead of their L-amino acid configuration in CPP sequences represents a common strategy to protect peptides from degradation [15].

DISCUSSION

For peptide-based drug development, a compromise has to be found between the required peptide length and pharmacologically useful levels of receptor activation. The numerous variables include (i) the size and accessibility of ligand binding surfaces, (ii) possible induced fit; (iii) ligand stability and receptor residency time [16].

Peptides are rapidly excreted through the kidney; serum stability studies are not representative of true turnover [17].

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Cpps for delivery of chemotherapeutic agents

Development of a folate and tumor microenvironment-sensitive polypeptides dual-modified docetaxel-loaded nanostructured lipid carrier (F/TMSP-DTX-NLC) shows high encapsulation efficiency (>95%), sustainable release and targeted delivery manner. The enhancement in the cellular uptake and cytotoxic activity of F/TMSP-DTX-NLC in KB, HT-1080, MCF-7 and A549 cells proved the correlation with folate receptor expression and MMP-2/9 secretion. The F/TMSP-DTX-NLC significantly penetrates deeply into inner of multicellular tumor spheroids due to the function of cell-penetrating peptides. Finally, treatment with F/TMSP-DTX-NLC resulted in stronger antitumor efficacy and enhanced tumor cell apoptosis in KB tumor model in athymic nude mice [13,15,16].

In another study in which the constructed a photo-responsive CPP termed pCPP and conjugated it to the NLC aiming at enhanced targeted tumor therapy. The Cellular experiments showed that pCPP-NLC exhibited significantly elevated light-dependent

cellular accumulation in HT-1080 *via* clathrin mediated endocytosis and macropinocytosis, and improved the cytotoxicity of PTX. Furthermore, the pCPP-NLC significantly could penetrate deeply into inner of multicellular tumor spheroids due to the function of Pcpp [18], This study demonstrates the application of CPP for efficient delivery of therapeutic agents for oncotherapy [19,20].

CONCLUSION

TAT-based targeted nanoparticles encapsulating DOX and ICG for combined chemo/photothermal/photodynamic therapy significantly increased the cellular DOX accumulation due to the electrostatic interaction between TAT peptide and HSPGs on surface of cell membrane [21]. The released rate of loaded DOX could also be promoted after NIR irradiation. Meanwhile, the ICG efficiently converted NIR light into violent heat and plentiful ROS. *In vitro* study confirmed that the cRGD@TAT-DINPs showed higher cytotoxicity on both MDA-MB-231 and A549 cells. These presented results provide a promising approach for high-efficient combined anticancer treatment [18].

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