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Enzyme-instructed siRNA release and functional self-assembly of peptide-based delivery system

Cell penetrating peptide (CPP)-based small interfering RNA (siRNA) delivery is one of the approaches with great potential to achieve RNA interference (RNAi) applied in gene therapy. CPP-based siRNA carriers hold many merits, including bio-degradability, high transmembrane efficiency and capability of endosomal escape. Despite considerably high transfection efficiency achieved, there are still many challenges in further improving the CPP-based siRNA delivery systems. This work focuses on two of the challenges: (1) the dissociation of negatively charged siRNA from positively charged peptide; (2) minimization of cytotoxicity of CPPs while maintaining capacity in endosomal escape. Herein, we propose to utilize enzyme catalyzed phosphorylation to induce negatively charged phosphate groups onto the cationic CPPs presenting in CPP/siRNA complex; the emerged phosphate groups can facilitate the dissociation of CPPs and siRNAs due to electrostatic repulsion between the two negatively charged species. The presence of phosphate groups also alters the balance between repulsive and attractive forces that govern the self-assembly of the peptide. The transition from a non-toxic nanostructure to a membrane disruptive one after phosphorylation is achievable via rational peptide design. The physicochemical properties of peptide-siRNA will be visualized using gel electrophoresis; the cytotoxicity and the RNAi efficiency of the system will be tested against cancer cells