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Comparison of cell-penetrating ability of polymer carrier decorated with various cell penetrating peptides

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Cell-penetrating peptides (CPPs) are commonly used substances that enhance the cellular uptake of various cargoes that don't easily cross the cellular membrane. CPPs can be either covalently bound directly to the cargo, or they can be attached to the transporting system such as a polymer carrier together with the cargo. The main aim of this work was to compare the biological efficacy of fluorescently labeled polymer carriers decorated with various cell-penetrating peptides. This work was focused on preparation of polymer conjugates based on copolymers of N-(2-hydroxypropyl)methacrylamide (pHPMA) bearing various cell-penetrating peptides, e.g. GRKKRRQRRR (TAT), RRMKWKK (PEN), PFVYLI, VPMLK, YARAAARQARA, RYIRS and a fluorescent dye Dyomics 633 attached along the main polymer chain. First, copolymers containing reactive thiazolidine-2-thione (TT) groups with narrow distribution of molecular weights were prepared by reversible addition-fragmentation chain transfer (RAFT) polymerization. Selected cell-penetrating peptide sequences were prepared by Fmoc solid phase peptide synthesis using TentaGel rink amide resin. 15-Azido-4,7,10,13-tetraoxapentadecanoic acid (N3-PEG(4)-COOH) was used as a linker between the peptide and the polymer chain. Coupling of the copolymer with an amino derivative of the dye was performed in N,N-dimethylacetamide, as well as coupling with an amino derivative of dibenzocyclooctyne group (DBCO). Subsequently, DBCO reacted with the azide groups of the peptides via a strain-promoted azide-alkyne cycloaddition (metal-free click chemistry). The course of all reactions was monitored by HPLC. Cell-penetrating ability of the polymer conjugates was evaluated *in vitro* on HeLa cells using flow cytometry and confocal microscopy. A labeled polymer without the peptide was used as a control. Incubation with polymer-peptide conjugates was performed at 4°C for one hour with various concentrations of peptides. In this experiment setting only TAT peptide and minimal sequence of penetratin (PEN) (RRMKWKK) showed significant cell penetration ability. Moreover dependency of cell-penetrating ability on the length of linker between the polymer chain and peptide sequence was studied and will be presented. After attachment of a suitable cytostatic drug, these polymer-peptide conjugates might serve as targeted polymer cancerostatics with enhanced penetration to tumor cells.

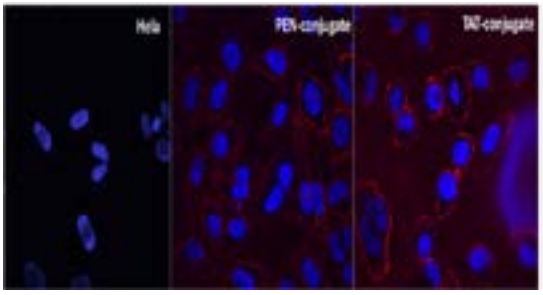

Figure 1: Fluorescence images of HeLa cells (nuclei: Hoechst 33342- blue color) incubated for 1 h with polymer bearing cell-penetrating peptides TAT and PEN (10 μM, Dyomics 633 – red color)

Biography

Eliska Bohmova finished her Master's degree in 2016 at the University of Chemistry and Technology in Prague, Czech Republic. At present time, she is a PhD student at the Department of Biomedical polymer of the Institute of Macromolecular Chemistry CAS in Prague. The topic of her dissertation thesis is "Targeted polymeric drugs with enhanced penetration into tumor cells". Her scientific interests are polymer chemistry, solid phase peptide synthesis, design and synthesis of polymer drug delivery systems for treatment of cancer.

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