Design of polyamines-grafted starches for nucleotide analogues delivery: in vitro evaluation of the anticancer activity

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Résumé en anglais	Nucleotide analogues are a therapeutic class really promising and currently used in clinic notably against viral infectious diseases and cancer. However, their therapeutic potential is often restricted by a poor stability in vivo, the induction of severe side effects and a limited passive intracellular diffusion due to their hydrophilicity. Polysaccharide-based polymers (e. g. starch) have considerable advantages including a lack of toxicity and absence of antigenicity. The aim of this study was to develop new cationic starches able to form complexes with nucleotide analogues: to protect them and increase their cell uptake. The material should demonstrate good biocompatibility and low cytotoxicity. Different oligoamines, (TREN, TEPA and spermine) were covalently grafted to starch: the resulting cationic starch derivatives were characterized (e.g. degree of modification) and compared in their properties to form polyplexes with ATP as a model nucleotide. Among the tested candidates, the formulation of starch-TEPA and ATP with a N/P ratio = 2 led to nanoparticles with a size of 429 nm, a PdI of 0.054 and a zeta potential of -9 mV. MTT and LDH assays on A549 cell line showed a low toxicity of this cationic starch. Confocal microscopy studies proved that the cell internalization was an incubation time and energy dependent process. Most important, starch-TEPA complexes with ddGTP (0.3 mg/mL) showed a significant biological activity on A549 cancer cells (> 90 %) compared to plain ddGTP (~ 21 %) at the same concentration, revealing a real promising system to deliver intracellularly nucleotide analogues.
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