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PH-responsive and macrophage evading low molecular weight chitosan coated nanoparticles for tumor-specific drug delivery

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Background and Aims: We aimed to engineer NPs coated with Low molecular weight chitosan (LMWC) as an alternative to polyethylene glycol to remain stealth in neutral pH, blood, and interact with cancer cells in slight acidic pH of tumor microenvironment.
Methods: PLGA was conjugated to LMWCs via amide bond formation. The resulting polymer and/or polymer-drug (paclitaxel, PTX) were made into NPs by single emulsion technique. NPs pH-responsive interaction with ovarian cancer cells (SKOV3) at pH 7.4 and 6.2 and macrophages uptake at neutral pH were investigated via confocal microscopy. The pH-responsive PTX release and cell viability of SKOV3 against drug-laden NPs were tested.
Results: PLGA-LMWC NPs of LMWC sizes (2-4 kDa and 4-6.5 kDa) were of sizes (< 250 nm) amenable for systemic drug delivery. The NPs surface charge remained slightly negative at pH 7.4 (~ -6 mV) and was positive (~ +4 mV) at pH 6.2 compared to pH-irresponsive PLGA NPs (~ -10 mV), control. While PLGA NPs did not interact with SKOV3 cells at either pH, PLGA-LMWC NPs associated with SKOV-3 at pH 6.2. PTX was encapsulated in PLGA-LMWC NPs without loss, and only ~10% of PTX was released in the first 3h. SKOV3 cells exposed to 1000nM of PTX/ PLGA-LMWC at pH 6.2 for 3h had 40% viability compare to 85% at pH 7.4 or the cells incubated with PTX/PLGA NPs at either pH. PLGA-LMWC showed less protein adsorption (18.8±2.2µg/mL) and macrophage uptake than PLGA NPs (42.6±3.8µg/mL) at pH 7.4, indicating the potential of LMWC as a stealth coat.
Conclusions: PLGA-LMWC NPs showed reduced interaction with cells at pH 7.4 and enhanced interaction at pH 6.2. This property may allow the PLGA-LMWC NPs to achieve both long-term circulation and tumor-specific drug delivery, which are difficult to achieve simultaneously with the conventional NP systems.

Keywords: Tumor targeting; Stealth coating; Nanoparticle