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BIODISTRIBUTION OF siRNA DELIVERED WITH CHITOSAN-DECORATED POLY(ISOBUTYLCYANOACRYLATE) NANOPARTICLES

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INTRODUCTION

In previous works, we showed that chitosan-decorated poly(isobutylcyanoacrylate) (PIBCA) nanoparticles were suitable carriers for intravenous delivery of active siRNA to xenografted model tumors implanted in mice. A spectacular reduction of the tumor volume accompanied by a reduction of the amount of the target mRNA acknowledged the specific effect of the siRNA delivered with the nanoparticles in a model of the papilloma thyroid carcinoma⁽¹⁾. A similar result was reported on a model of Ewing sarcoma, another cancer caused by the expression of a junction oncogene. Although tumor volume reduction was less spectacular, the activity of the siRNA was highlighted by the reduction of the amount of the target mRNA in the tumor⁽²⁾. To elucidate the delivery of the siRNA to the tumor using these nanoparticles, the present work was aimed to investigate the biodistribution of the siRNA and that of the nanoparticles after an intravenous administration to mice xenografted with a model tumor of Ewing sarcoma.

MATERIALS AND METHODS

Preparation and characterization of the fluorescent labeled nanoparticles

Fluorescent nanoparticles were synthesized by radical emulsion polymerization (40°C, 1h) of isobutylcyanoacrylate and polyfluor[®] 570 in 200 mM nitric acid containing 16 mM cerium ammonium nitrate and 3% pluronic F68. Nanoparticles were dialysed. Targeted nanoparticles were obtained by grafting an anti-CD99 biotinylated antibody⁽³⁾. Characterization included measurements of size and zeta potential, evaluation of the activation of the C3 component of the complement system and study of the association of the siRNA (adsorption adsorption, isothermal titration calorimetry). All characteristics were compared with those of unlabelled nanoparticles.

siRNA-nanoparticle association and biodistribution studies

siRNA was labeled on the 5' end with T4 polynucleotide kinase and [³²P] ATP. For the *adsorption isotherm*, siRNA was incubated with nanoparticles (10 min, NP/siRNA mass ratio = 0 to 300). The radioactivity was measured in the supernatant obtained after centrifugation (45000 rpm, 1h, 4°C). For *biodistribution studies*, the siRNA was associated with the nanoparticles to a NP/siRNA mass ratio of 50.

All animal experiments were approved by the ethic committee on animal experimentation of the Institute Gustave Roussy (Villejuif, France). siRNA-loaded nanoparticles (non targeted nanoparticles) were injected in the tale vein of mice (24µg/kg siRNA, 547300 cpm). Mice were sacrificed after 24 h using a CO₂ chamber. Tumors and organs were retrieved, grounded and centrifuged. The radioactivity of the supernatant was measured using a Wallac 1409, Pegasus Scientific Inc., USA). The biodistribution of the fluorescent nanoparticles (non-targeted and targeted nanoparticles) was determined using a live animal imaging system (IVIS 50, Caliper).

RESULTS

All characteristics of the fluorescent-labeled nanoparticles were identical to those of the non labeled nanoparticles ⁽⁴⁾. The biodistribution study of the siRNA revealed that the amount of radioactivity reaching the tumor was at the same level than that found in the liver and in the spleen (Figure 1). Quite large amounts of radioactivity were also found in other organs. This indicated that the nanoparticles were stealth and could deliver siRNA to the tumor.

After intravenous administration, the nanoparticles accumulated importantly in the tumor (Figure 2). As expected, the targeted nanoparticles accumulated more in the tumor than the non targeted nanoparticles (Figure 3).

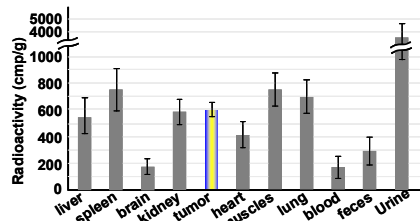


Figure 1: Distribution of the siRNA after iv injection of siRNA-nanoparticles in mice bearing a xenografted model tumor of the Ewing sarcoma.

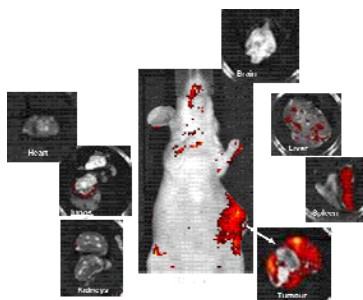


Figure 2: Imaging of the mice and isolated organs 24h after iv injection of the fluorescent nanoparticles.

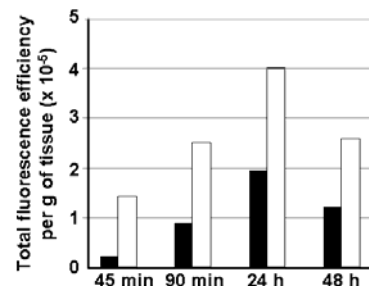


Figure 3: Fluorescence in tumor after iv injection of siRNA-loaded targeted (white) and non-targeted (black) nanoparticles.

CONCLUSION

Fluorescent labeled nanoparticles displayed same properties than unlabelled nanoparticles.

After intravenous administration, the chitosan-decorated nanoparticles could deliver the siRNA in the tumor in agreement with their own distribution in the tumor xenografted in mice. Addition of a targeting ligand to the nanoparticles increased further the accumulation of the delivery platform in the tumor.

These nanoparticles are a suitable delivery platform for siRNA delivery to tumor after intravenous administration.

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