Following the degradation and biological fate of polymeric poly (lactic-co-glycolic acid) nanoparticles

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Abstract

Due to their small size and unique physic-chemical properties, nanoparticles (NPs) have been proposed as diagnostic, therapeutic or even theragnostic tools. By appropriate multi-functionalization, NPs can be administered systemically and directed towards specific organs or tissues, providing thus enhanced therapeutic/diagnostic efficacy while reducing significantly undesired side- or toxicological effects [1].

When moving to *in vivo* applications, the determination of the pharmacokinetic properties and biological fate of NPs is of paramount importance, both to assess potential toxicological effects and to anticipate therapeutic efficacy. However, NPs are extremely difficult to detect and quantify once distributed in a biological system. One alternative to overcome this problem consists of labeling the NPs with radionuclides that can lead to their detection with ultra-high sensitivity using *in vivo* imaging techniques such as Positron Emission Tomography (PET) or Single Photon Emission Computerized Tomography (SPECT) [2,3]. Of note, radiolabelling and subsequent imaging studies provide information about the loci of the radionuclide, but no information about the radiochemical integrity or the chemical stability of the NPs is obtained.

Here, we present an unprecedented dual-labeling strategy to assess simultaneously the pharmacokinetic properties and biological fate of core-shell NPs after intravenous administration in rodents. Fe_3O_4/poly(lactic-co-glycolic acid) (PLGA)/Bovine serum albumin (BSA) NPs (Figure 1) were simultaneously labelled with ^{111}In, which was entrapped into the Fe_3O_4 crystal lattice, and ^{125}I, which was covalently attached to the tyrosine residues of BSA. Both isotopes emit gamma rays with different energies (171 and 245 keV for ^{111}In, 35.5 keV for ^{125}I).

In a first step, biodistribution studies were performed in mice using dissection/gamma counting. With that aim, dual-labelled NPs (containing c.a. 111 kBq of ^{125}I and 370 kBq of ^{111}In) were administered to animals, which were sacrificed at different time points (5 min-48h), the organs were harvested and the gamma emission spectra for each organ and blood were analyzed using a multichannel analyzer. Progressive accumulation of ^{125}I in the thyroid glands, the intestine and the bladder, together with preferential accumulation of ^{111}In in other major organs such as the lungs and the liver, suggest a fast degradation of the NPs after administration.

The results were confirmed by *in vivo* SPECT studies, using a microSPECZT-Visio SPECT-CT system. Labelled NPs (containing c.a. 7.4 MBq of each radionuclide) were administered via the tail vein and static images were acquired at 1, 24 and 48 hours after administration. Reconstruction of the images in different energy windows was performed, and energy-resolved images to determine the loci of both isotopes over time were obtained. As for dissection/counting studies, images showed progressive accumulation of ^{125}I in the thyroid gland, and elimination of this isotope mainly via urine and intestine. This pattern is compatible with a progressive dissociation of the protein (BSA) from the NPs and subsequent detachment of ^{125}I.

The strategy reported here, based on incorporation of two different gamma emitters (with different emission energies) followed by imaging studies with energy discrimination, might be applied to the determination of the biodistribution pattern and biological fate of a wide range of core-shell NPs.

References

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[3] Frigell J, Garcia I, Gómez-Vallejo V, Llop J, Penades S. J Am Chem Soc **136(1)** (2014) 449-457.

Figures

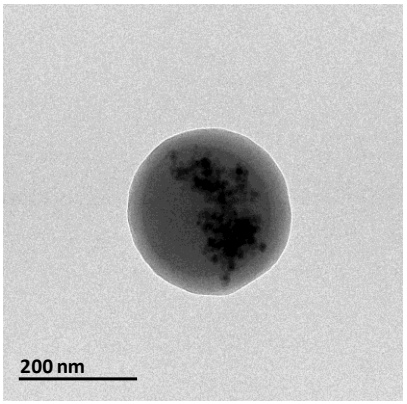

Figure 1: TEM image of Oleic acid-coated iron oxide nanoparticles encapsulated with PLGA and stabilized with BSA