PARAMAGNETIC DY(III)-LOADED LIPOSOMES AS T2 SUSCEPTIBILITY MRI AGENTS

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Purpose

To assess the potential of paramagnetic Lanthanide-loaded liposomes as T_2-susceptibility MRI agents.

Introduction

Paramagnetic low molecular weight Dy(III)-based complexes have been investigated in the late 80s as T_2-susceptibility MRI agents in virtue of their heterogeneous tissue distribution.[1] In spite of the promising results obtained (also in humans) in several diagnostic applications, the interest for these agents has slowly diminished, mainly for the advent of the much more sensitive iron oxide particles, which affect the images on the basis of analogous relaxation processes.[2] Recently, the challenge brought about by Molecular Imaging applications prompted the design of highly-sensitive nano-sized systems aimed at lowering the contrast agent concentration threshold for MRI detection. Among the available nano-sized platforms, liposomes have received much attention, primarily for their high chemical versatility, high biocompatibility and for the peculiar pharmacokinetic properties.[3] As T_2-susceptibility effects arise from the compartmentalization of a paramagnetic compound, it is expected that the encapsulation of an hydrophilic Dy(III) complex in the intraliposomal cavity leads to a significant T_2-shortening.

In this contribution, the relaxometric properties of a series of Dy(III)-loaded liposomes are discussed and compared with those ones of the reference iron oxide particles. In addition, the potential of these agents has been tested in MRI targeting experiments *in cellulo* and *in vivo* on mice models.

Results and Discussion

The large T_2-sensitivity enhancement determined by the encapsulation of a Dy(III) complex (Dy-HPDO3A) in a liposome is shown in Figure 1 where the T_2-contrast of a liposome filled with the paramagnetic complex is compared with an aqueous solution of Dy-HPDO3A at the same concentration (7 T, 25°C). In these experimental conditions, a 10-fold increase of R_{2p} was observed when the relaxation data are normalised to the metal content, but this difference increases enormously (*ca.* 10^7) if the transverse relaxivity is normalised to the concentration of the paramagnetic nanoparticle. The efficiency of the Dy(III)-loaded liposomes is affected by the concentration of the entrapped compound, the liposome size, and, of course, the magnetic field strength. In addition, a further enhancement in the T_2-effects can be gained by increasing the amount of encapsulated complex (e.g. by using neutral multimers) or by incorporating amphiphilic Dy(III) complexes in the liposome membrane. The latter strategy have two advantages: i) to enhance the magnetic susceptibility of the liposome by increasing the concentration of the paramagnetic ion in the intraliposomal cavity (contribution of the amphiphilic Dy(III) units pointing inwards), and ii) to exploit the Curie relaxation mechanism which is expected to be relevant at high fields for such slowly-rotating systems.

The transverse relaxivities of the different Dy(III)-loaded liposomes investigated in this work are comparable, and often even higher than the values reported for iron oxide particles of similar size and measured at the same experimental conditions.

The promising T_2-properties found for the aqueous suspensions of Dy(III)-loaded liposomes have been confirmed in some MRI targeting experiments *in vitro* (targeting fibrin on human clots), *in cellulo* (targeting glutamine transporters on Neuro 2A cell line), and *in vivo* on mice models (targeting xenografted neuroblastoma).

In conclusion, Dy(III)-loaded liposomes may be considered as an interesting alternative to the use of iron oxide particles as T_2-susceptibility MRI agents. In addition to their high sensitivity, these systems can also be potentially used as dual, T_2 and CEST, agents.

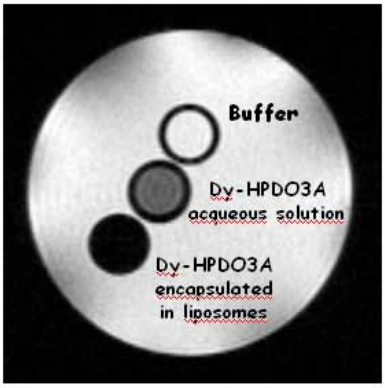

Figure 1: RARE-T_{2w}-MR image at 7 T and 39°C.
Liposome size: 170 nm, liposome membrane: POPC/Chol/DSPE-PEG (55:40:5 in moles), estimated concentration of the encapsulated agent: 0.2 M

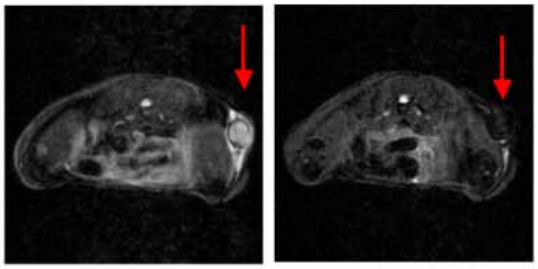

Figure 2: Axial RARE-T_{2w}-MR images (7 T) of a mouse bearing a xenografted neuroblastoma (red arrow). Left: pre-contrast. Right: 24 h post-injection of Dy(III)-loaded liposomes

References

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