Enhanced MRI Relaxivity in Surface-Modified Morphology-Tunable Iron Oxide Based Building Blocks: Towards High Performance Targeted Cancer Imaging

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Introduction

Superparamagnetic iron oxides nanoparticles (SPIONs) used as effective contrast agents (CAs) provide improved visibility of internal body structures in MRI scans. To further enhance the MRI relaxivity and blood circulation half-lives, our research group is developing polymeric-coated iron oxide nanostructures with active surface areas in a such a way they are more exposed to receptors on cell surfaces and targeting ligands, thus favoring multivalent interactions and homing to tumors. Our findings indicate that spherical SPIONs (~11 nm cores) PEGylated without anchoring groups exhibit a spin-spin relaxivity of 123 $mM^{-1}s^{-1}$, while nitrodopamine (ND)-PEG grafted cubic SPIONs produce marked dual contrasts in MRI with enhanced transverse relaxivity of 791 $mM^{-1}s^{-1}$. Such SPIONs have also the ability to endow graphene oxide (GO) with magnetism when integrated within the GO layers yielding a spin-spin relaxivity of 162 $mM^{-1}s^{-1}$, which is related to the static dephasing regime. Our observations indicate that surface-treated SPIONs are strong candidates for next-generation MRI CAs, which is vital for noninvasive real-time detection of nascent cancer cells in vivo and for monitoring stem cells transplants.

Experimental

PEG and nitrodopamine-PEG SPIONs were synthesized via hydrothermal and thermal decomposition methods, and physico-chemically (TEM, FTIR, XRD, DLS & SQUID) and biologically characterized. The relaxivity measurements were performed using an NMReady-60e benchtop relaxometer (60 MHz at 1.40 T), whereas the T_2-weighted MR phantom images were acquired using an Agilent 4.7 T/200 MHz MRI scanning system (AMRIS).

Results and Discussion

Figure 1 shows the contrast mechanism of spherical PEG-SPIONs, and T_2-weighted MR phantom images of spherical PEG-SPIONs and cubic ND-PEG-SPIONs at different iron concentrations (up to 1.0 mM). The images obtained from different slices of single aliquots show contrast enhancement as the iron concentration increases. This enhancement is ascribed to the great number of iron ions with unpaired electrons on the NPs surface, and to the strong susceptibility effect and large surface area of the spherical polymer-coated SPIONs. Similarly, the observed saturation magnetization is large enough to create strong local magnetic susceptibility gradients or field inhomogeneity, and the large effective radius of cubic nanoparticles can perturb a larger number of water molecules effectively distorting the protons' spin coherence and accelerating the T_2 relaxation.

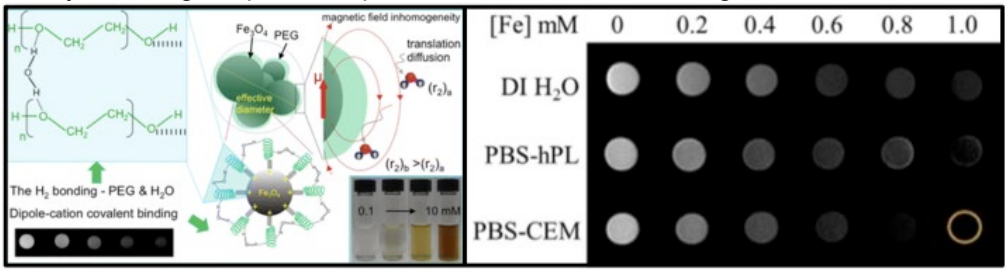

Fig. 1. Enhanced contrast mechanism (left) and T_2-weighted MR phantom images (right) of PEGylated SPIONs.

Conclusions

Surface-modified morphology-tunable SPIONs generate MRI contrast enhancement (r_2 ~800 $mM^{-1}s^{-1}$) on T_2-weighted sequences, and hence can be considered as highly sensitive spin-spin CA. This is in part correlated to the increased effective radii due to nanoparticle clustering, and the local field inhomogeneity of the magnetic cores, which is critical to the pursuit of alternative nanoformulations that replace discontinued commercial CAs.

Acknowledgements

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References

[1] Thapa B., et al., ACS Applied Bio Materials **1**, 79-89 (2018).
[2] Thapa B., et al., Nanoscale Research Letters **12**, 312 (2017).