Precision Targeting Of Solid Tumors Using Smart Magnetic Theranostic Nanocomposites: A Targetless Strategy

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The specificity of cancer treatment is one of the most important parameters that dictate patient outcome. In breast cancer for example, while targeted therapies have been developed for all other subtypes, no specific treatment is available for triple-negative-breast-cancer (TNBC), and survival rates are much worse.[1,2]. Here we present a novel concept to target solid tumors by the combination of magnetic nanocomposites (NCs) [3], cell penetrating peptides (CPPs) and magnetic actuation. Upon local external magnetic stimulation, smart magnetic NCs expose CPPs that promote their internalization in tumor tissues. A simple melt-emulsification protocol was used to prepare in one step smart drug-loaded hybrid magnetic NCs (< 200 nm) displaying two types of ligands on their surface: long PEGylated units and CPPs. The PEG molecules were anchored to the NCs through thermosensitive Diels-Alder (D-A) bonds. Once in the tumor, magnetic hyperthermia (MH) can be locally applied to generate heat, break the D-A bonds and expose the CPPs, which will promote the specific accumulation of the NCs in the tumor. The incorporation of chemotherapeutic drugs in the NCs and their subsequent enhanced release via MH will treat the tumor reducing off-target effects. In addition, the magnetic nature of the NCs enables their tracking non-invasively *in vivo* through MRI. This system was validated *in vitro* (2 and 3D), *ex vivo* (CAM model) and *in vivo* (mice). *In vitro*, the IC50 of the NCs was superior to that of the free drug (55%) and was further improved upon MH application (86%). In 3D spheroids, the NCs could effectively revert their growth (-2%/day). The same was observed *ex vivo* in the CAM model (-45% growth) where angiogenesis was also inhibited compared to saline or free DOX treatment. *In vivo* the vehicle was well tolerated without significant organ damage and in terms of treatment, animals treated with the NCs+MH presented tumors in average ~30% smaller than the saline group and ~15% smaller than the free DOX group. In terms of imaging, T_2 times of the tumor area of animals injected with NCs+MH were in average 24 and 22% shorter than saline or NCs only animals, respectively. The NCs presented here combine imaging and therapeutic capabilities with external actuation (through magnetic fields) to display high specificity. This new concept represents a promising strategy for the treatment and monitoring of tumors for which a targeted therapy has not been developed yet, increasing the efficacy and decreasing off-target side effects.

References

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Figures

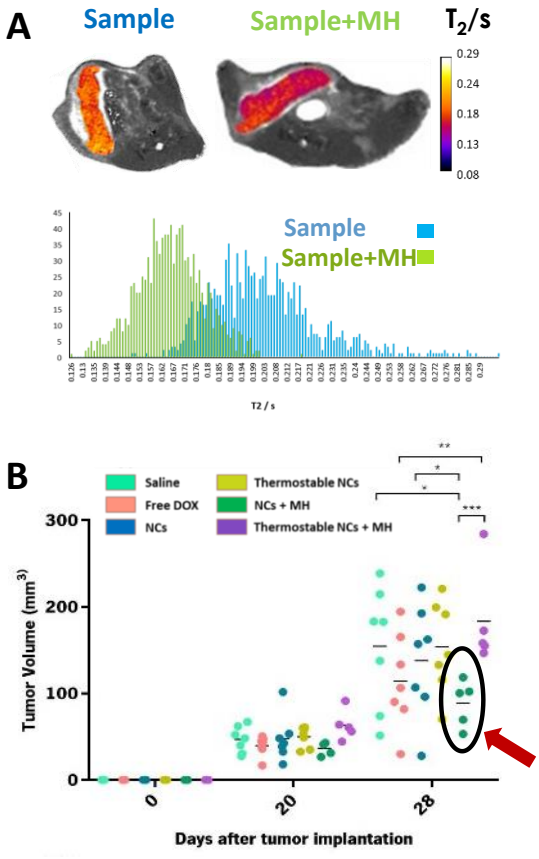

Figure 1. (**A**) T_2 maps of tumor slices of animals injected with NCs and subjected (left) or not (right) to MH. (**B**) Tumor volume evolution for animals under the different treatment schemes and controls.