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| Title: | Development of nano-magnetic transducers for travelling the blood-brain barrier and elucidation of their thermal response for globalastoma tyherapy |
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| Abstract: | Glioblastoma multiforme (GBM) is the most aggressive form of brain tumour that accounts for nearly 15% of all brain cancers. Despite the advances, the standard care of treatment for patients with GBM remains surgical resection followed by combinatorial therapy with either radiotherapy or chemotherapy. However, recurrence of tumours persists as the infiltrating tumour cells reside away from the bulk tumour mass leading to resistance from the present therapies. Moreover, the presence of blood-brain barrier further possesses as a major challenge for GBM therapy as it limits passage of majority of therapeutic agents into the brain region. Hence, new therapeutic approaches are urgently required. In this regard, magnetic hyperthermia-based cancer therapy (MHCT) has surfaced as a promising therapy regime for treatment of such inaccessible solid tumours. MHCT is based on generation of localized heat specifically at the tumour site on subjection of magnetic nanoparticles (MNPs) to an alternating magnetic field (AMF). The heating efficiency of these MNPs depends mainly upon the magnetic properties of the nanomaterials and the AMF parameters. Hence, recent advances in MHCT are focussed on generation of efficient nano-heaters capable of generating maximum heat at the lowest concentration, and lowest magnetic field frequency and field values. In this regard, the work in this thesis focusses on tuning the magnetic properties of the MNPs by varying their size, composition and shape in order to optimize their heating efficiencies. The particles synthesized were further evaluated for in vitro hyperthermia potential against glioma cell lines in terms of tumour inhibition, generation of intracellular oxidative stress, morphological and cytoskeletal alterations, and most importantly for the capability of the nano-system to be retained inside glioma cells for re-exposure of AMF treatment. This would greatly limit the amount of MNP dosage required to be administered to achieve the desired therapeutic heating response. Further, to validate the use of optimized nano-system for GBM therapy, the capability of the selected MNP to traverse the blood-brain barrier was also evaluated under in vitro and in vivo conditions. The transport across the barrier was facilitated by dual magnetic targeting using external magnetic field and heat generated by AMF exposure to transiently disrupt the tight junctions. After successful delivery into the brain region, the synthesized nano-transducer was investigated for in vivo hyperthermia experiments in the xenograft models developed in Wistar rats in an effort to test the efficacy of MHCT to cause regression of not only primary tumours but also to study its effect on secondary untreated tumours. The effect of inhibiting cellular defence mechanism by downregulating heat shock proteins was further assessed to enhance the efficiency of MHCT for improved glioma therapy. |
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