Remote Targeting of Etoposide-bound Magnetic Nanoparticles for Treating Cancer Cells Disseminated within Cerebrospinal Fluid Pathways

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Introduction

- Medulloblastoma cells notoriously disseminate through CSF pathways. Magnetic nanoparticles (MNPs) have potential for enhancing delivery of chemotherapy to these and other leptomeningeal cancer cells. To date, successful clinical use of MNPs has been hampered due to 1) the limited capacity for targeting at human-sized distances, and 2) choice of the therapeutic component. Here, we present data related to the

In vitro testing of a hybrid MNP containing: 1) AuFe base particles having streptavidin binding sites, and 2) biotinylated etoposide. Etoposide was chosen due to its previous use within CSF and ease of biotinylation. Nanoparticle clusters were moved by a rotating magnet, which causes them to “surface walk” within fluid conduits, even at physiologic distances.

Methodology

- Base MNPs were manufactured by IMRA America, Inc., using a pulsed laser ablation fabrication technique. These particles contain streptavidin binding sites, to which biotinylated drugs may be attached. Here, biotinylated etoposide was used, in order to create the novel AuFe-etoposide nanoparticles (“Etop-MNPs”). Etop-MNPs were characterized by methods including scanning transmission electron microscopy (STEM), size determination via Nanosight, and energy dispersive spectroscopy (EDS). Videography was used to determine MNP velocity in response to a rotating permanent magnet (3 Hz). Etop-MNP treatments of D283 and Daoy (human medulloblastoma), and H2122 (human lung cancer) cells were studied using light microscopy, SEM, MTT (cellular viability) assays, and flow cytometry.

Results

- Biotinylated etoposide was successfully bound to the IMRA base particles, as confirmed by STEM, Nanosight, and EDS. Etop-MNP clusters could be moved remotely, with a maximum velocity of 0.13±0.010 cm/sec. With 24 hours of treatment, Etop-MNPs caused morphologic changes, and decreased D283 viability to 43.6±5 % that of controls. This chemotherapeutic effect was retained, even after remote movement (10 cm) of the Etop-MNP clusters by the rotating magnet.

Conclusion

- Etop-MNPs have a cytotoxic effect on cancer cells, and can be targeted at clinically-relevant distances. While further studies are underway, Etop-MNPs, may prove useful for magnetic targeting of cancer cells within CSF pathways, after introduction via lumbar puncture or Ommaya reservoir. An improved ability to eradicate malignant cells within CSF would be a major step forward in the treatment of patients with disseminated medulloblastoma, and leptomeningeal metastases.