Tumor Accumulation and Penetration of Mesoporous Silica Nanoparticles and the Potential Role of Peritoneal Macrophages

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ABSTRACT SUMMARY
The accumulation and the penetration of mesoporous silica nanoparticles (MSNs) in peritoneal tumors were studied as a first approximation for the development of a $^{166}$Ho carrier for internal radiation therapy. High tumor accumulation and increasing tumor penetration were observed over time. The role of peritoneal macrophages as carrier cells was explored as a potential mechanism for tumor accumulation.

INTRODUCTION
Conventional intravenous delivery of chemotherapeutic agents limits their accessibility to peritoneal metastases. We previously described the intraperitoneal (i.p.) delivery of a high energy beta-emitting radionuclide, holmium-166 ($^{166}$Ho), using a versatile MSN platform, and were able to limit its distribution to the peritoneal cavity (1). Selective accumulation of $^{166}$Ho-MSN in tumors as well as penetration of these radiotherapeutic nanoparticles deep into tumor tissues would improve the safety of this brachytherapy approach and maximize its therapeutic efficacy. The aim of this work was to study the tissue distribution and tumor penetration of MSNs and explore the role of peritoneal macrophages on tumor selective accumulation as a first approach to the development of a MSN formulation to deliver $^{166}$Ho to metastatic peritoneal tumors.

EXPERIMENTAL METHODS
MSNs (120 nm) were synthesized as previously described (2) and their surfaces were aminated to allow labeling with fluorescein isothiocyanate (FITC) and Cy5.5 by a standard coupling reaction.

RESULTS AND DISCUSSION
After i.p injection, a significant tumor accumulation of the MSNs was observed. Ex vivo analysis of isolated tumors and abdominal organs showed high accumulation of MSNs in tumors and liver after 24 h. Over time, the fluorescent signal in tumors increased and was observed to decrease in liver, being undetectable at 144 h post injection (Figure 1).

To determine retention of the particles in tumors and abdominal organs after i.p administration, a tumor mouse model was used in which severe combined immunodeficiency (SCID) mice were injected intraperitoneally with $10^7$ MIA PaCa-2 human pancreatic tumor cells. The MSNs suspended in 0.5% hydroxypropyl methylcellulose in PBS were administered i.p. (500 µL) 4 weeks later. The distribution of the MSNs in various organs at 24 h, 96 h and 144 h post administration was determined by fluorescent imaging (IVIS Lumina Series III). Tumor slides (20 µm) were visualized by confocal microscopy (Leica TCS SP2) to evaluate the penetration of the MSNs. To assess the ability of peritoneal macrophages to take up MSNs, adherent cells were isolated from the ascites of tumor-bearing mice 96 h and 144 h after administration. Cells were fixed and observed under a confocal microscope. Anti-F4/80 mAb was used to confirm the presence of macrophages.

Tumor penetration of the MSNs also increased over time. At 24 h post injection, MSNs were observed within the initial 20 µm tumor section. After 96 h and 144 h, the MSNs had penetrated the tumors to a level of 100 µm and 150 µm, respectively (Figure 2).
Some authors have suggested that macrophages can deliver nanoparticles to tumors since they are found in high numbers within the tumor microenvironment (3). The results showed that MSNs were endocytosed by peritoneal macrophages in tumor bearing mice in vivo. This supports the plausibility of this mechanism for the high accumulation of nanoparticles in tumors (data not shown). However further confirmation is required.

CONCLUSION

In vivo and ex vivo images demonstrated that MSNs administered to tumor-bearing mice selectively accumulated in tumors and penetrated to deep tumor tissues over time. The delivery of nanoparticles by peritoneal macrophages appears to be a reasonable mechanism for this specific tumor accumulation and is currently under study.

REFERENCES


ACKNOWLEDGMENT

The authors are grateful for the financial support from the Connecticut Institute for Clinical and Translational Science.