A biophysical transport model to predict the enhanced permeability and retention effect for liposome accumulation in solid tumours.

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ABSTRACT SUMMARY

A novel biophysical transport model was developed to provide a theoretical framework for the EPR effect. The model was validated by comparing predictions with measurements of liposome accumulation and retention in two xenograft tumour models. Measurements consisted of using computed tomography (CT) to quantitatively image the pharmacokinetics and intra-tumoural accumulation of a liposomal contrast agent. The model produced predictions which agreed with the measured liposome accumulation in both tumor types. Furthermore, the model indicated that tumour size played an important role in the differential liposome accumulation observed between the two tumour types. Therefore, the transport model may be a useful theranostic tool to guide patient selection and predict therapeutic response.

INTRODUCTION

Passive targeting of macromolecular agents to solid tumours is known to rely on the enhanced permeability and retention (EPR) effect. The EPR effect is an empirical description of the increased extravasation and accumulation of macromolecular agents in solid tumours due to increased vascular permeability and impaired lymphatic drainage [1]. Indeed, passive targeting of drugs to solid tumours using nano-sized delivery systems has been reported to result in as much as a 10-20 fold increase in drug accumulation in tumours relative to normal tissues. However, the EPR effect does not fully describe the complex spatio-temporal retention and distribution of macromolecular agents, such as liposomes, that are commonly observed in tumours. The tumour accumulation profile and intra-tumoural distribution of each macromolecular agent are dependent on the physicochemical properties of the agent (i.e. size, morphology) and properties of the tumour microenvironment [2, 3, 4].

We have developed a biophysical transport model which describes the spatio-temporal accumulation and retention of liposomes in solid tumours. It is our hypothesis that the biophysical transport model provides a theoretical framework to describe the EPR effect. The goal of this work is to validate the transport model using an image based approach which allows for a direct comparison between the predicted and measured retention kinetics of a liposome contrast agent in a solid tumour.

EXPERIMENTAL METHODS

A CT-liposome contrast agent was prepared according to the methods described in [3]. The liposomes contain the CT contrast agent iohexol (Omnipaque, 300 mg/mL of iodine, GE Healthcare) in a lipid bilayer, which includes cholesterol for stability, and brushed with a polyethylene glycol (PEG) coating for immunogenicity. The native concentration of iohexol was 40 mg of iodine mL⁻¹ of solution. The liposomes had diameters between 75 and 80 nm.

Measurements of the tumour retention kinetics of the CT-liposomes were made in 5 mice bearing subcutaneous non-small lung cell (H520) tumours and 4 mice bearing orthotopic cervix tumours (ME180) for up to 6 days using micro-CT. The average concentration of CT-liposomes was quantitatively measured to generate time intensity curves which reflect the liposome retention as a function of time.

Validation of the transport model was performed by fitting the measured CT-liposome time intensity curves to the EPR transport model using least squares minimization and demonstrating a high coefficient of determination (R² > 0.9). Additionally, estimates of tumour transport properties (vascular-interstitial permeability, vascular pressure and interstitial volume fraction) obtained from fitting were compared with accepted values obtained from the literature.

RESULTS AND DISCUSSION

Figure 1 shows the spatial-temporal distribution of the liposomal agent in H520 and ME180 tumour bearing mice, respectively. Qualitatively, the spatial distribution of enhancement was primarily along the tumour periphery for ME180 mice. There was spatially heterogeneous enhancement throughout the tumour volume in the H520 tumours. Quantification of plasma PK and tumour accumulation for each of the H520 and ME180 tumour bearing mice is shown in figure 2. There were no statistical differences between the average peak plasma concentrations (t-test, p-value=0.09) and average half-lives (p-value=0.61) for the ME180 and H520 mice. On average the rate of liposome accumulation and wash-out was faster in H520 tumours compared to the ME180 tumours.

The EPR transport model fit the liposome retention curves in both tumour types with an R² > 0.90 (Figure 2 b,d). The EPR transport model identified that tumour size was an important factor which resulted in the different liposome retention kinetics observed between the two tumour types. The free parameters obtained from the fitting process had a large variability, but were within the range of previously published values [5].
Figure 1. Micro CT image series of the spatio-temporal distribution of CT-liposomes in (a) a subcutaneous H520 tumour bearing mice and (b) an orthotopic ME180 tumour bearing mouse. The tumour is indicated by the arrows.

The presented liposome transport model was based on biophysical transport equations which use tissue and liposome properties to describe the spatio-temporal distribution of liposomes in solid tumours. It was demonstrated that the transport model can predict the average time dependent accumulation of liposomes (a typical EPR metric) in two xenograft tumour models. The spatial distribution of liposomes was neglected in this study due to the difficulty in accurately measuring and modeling the tumour microvascular network. Additionally, cellular uptake of liposomes by the mononuclear phagocyte system was neglected in the transport model and could potentially play an important role in the retention kinetics of liposomes. Future iterations will incorporate these two key properties into the biophysical transport model.

CONCLUSION

This study demonstrated the ability of the proposed biophysical transport model to predict the EPR effect for liposomes in solid tumours. The long term goal is to use the transport model as a theranostic tool to guide patient selection and prediction of therapeutic response. Additionally, the transport model also offers a quantitative, image-based approach to non-invasively estimate microenvironment properties of solid tumours in the clinical environment.

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REFERENCES