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Biodistribution of polymer hydrogel capsules for the delivery of therapeutics

Tracey M. Hinton [a,*], Paul Monaghan [a], Diane Green [a], Sander A.A. Kooijmans [b], Shuning Shi [a], Kerry Breheney [c], Mark Tizard [a], Joseph A. Nicolazzo [b], Alexander N. Zelikin [d], Kim Wark [e]

[a] CSIRO Livestock Industries, Australian Animal Health Laboratory, 5 Portarlington Road, East Geelong, Victoria 3219, Australia
[b] Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville Campus), 381 Royal Parade, Parkville, Victoria 3052, Australia
[c] CSIRO Materials Science and Engineering, 343 Royal Parade, Parkville, Victoria 3220, Australia
[d] Department of Chemistry and iNANO Interdisciplinary Nanoscience Centre, Aarhus University, Denmark
[e] Victorian Cancer Agency, 12 Victoria Street, Carlton, Victoria 3053, Australia

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ABSTRACT

A key phase in the development of intelligently designed nanoparticle delivery vehicles for new therapeutic agents is to gain an understanding of their interaction with tissues and cells. We report a series of in vitro and in vivo experiments aimed at tracking a potential delivery vehicle for therapeutic agents, including vaccine peptides and drugs derived from poly(methacrylic acid) hydrogel capsules in certain organs and cell types. For the in vitro studies, two immortal liver-derived cell lines (Huh7 and Hepa1-6) and primary cultures of mouse hepatocytes were incubated with Alexa 647 labelled fluorescent capsules to track their internalization and intracellular distribution by confocal microscopy. Capsules, 500 nm in diameter, were taken up into the cells in a time-dependent manner in all three cell lines. Capsules were observed in plasma membrane-derived vesicles within the cells. After 24 h a significant proportion of the capsules was observed in lysosomes. To understand the behaviour of the capsules in vivo, Alexa 488 labelled fluorescent capsules were intravenously injected into Sprague–Dawley rats and after 24 h the fate of the capsules in a number of organs was determined by flow cytometry and confocal microscopy. By flow cytometry, the majority of the capsules were detected in the spleen whilst similar numbers were found in the lung and liver. By confocal microscopy, the majority of the capsules were found in the liver and spleen with significantly less capsules in the lung, heart and kidney. Colocalization of capsules with cell-type specific markers indicated that in lung, heart and kidney, the majority of the capsules were located in endothelial cells. In the spleen ~50% of the capsules were found in CD163-positive cells, whereas in the liver, almost all capsules were located in CD163-positive cells, indicating uptake by Kupffer cells. Electron microscopy confirmed the presence of capsules within Kupffer cells.

1. Introduction

The requirement for improved tissue and cell targeting of new therapeutics to minimize toxic side effects as seen with many anti-cancer agents has triggered an interest in the development of "smart" vehicles for targeted delivery of these next generation drugs [1]. Improving access to poorly accessible tissues such as the brain and targeting not just organs, but specific cell types within organs, has wide-reaching implications for the treatment of cancer, genetic diseases and viral infections.

At present, many novel delivery systems for cancer treatment rely on a combination of targeted delivery to cancerous cells using ligands for receptors that are upregulated in these cells and the leaky vasculature resulting from the enhanced permeability and retention (EPR) effect to deliver the vehicles to the tumour site [2–5]. Whilst this can be successful, a large proportion of the nanoparticles are rapidly cleared from the circulation by phagocytic cells in the organs of the reticuloendothelial system (RES), particularly the liver and spleen. This is thought to occur through opsonization as a result of serum proteins (especially albumin) adhering to the surface of the particle [6,7]. There have been several methods reported to overcome this, such as coating nanoparticles with polyethylene glycol (PEG) [8], to alter the fate of the nanoparticles [9].

The path to successful development of novel drug delivery systems requires a number of steps which include toxicity studies to determine the safety of the vehicle [10], in vitro modelling and proof of efficacy followed by in vivo trials. In vitro and in vivo studies in a number of systems have confirmed delivery of drug [2,11–13] or RNA interference payloads [14–16] into cells and a number of studies have used whole animal imaging such as PET or quantitative PCR from tissue lysate to determine the location of the delivery vehicle in the animal or the effect of delivery [17–19]. PET imaging is non-invasive and gives important information about

* Corresponding author. Tel.: +61 3 5227 5746; fax: +61 3 5227 5555.
E-mail address: Tracey.Hinton@csiro.au (T.M. Hinton).

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