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Red blood cell-like particles with the ability to avoid lung and spleen accumulation for the treatment of liver fibrosis

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ABSTRACT

Micro-sized drug-carrier particles accumulate mainly in the lungs and nano-sized particles tend to accumulate in the liver and spleen. Here, we show that micro-particles designed to mimic red blood cells (RBCs) can overcome these limitations. The RBC-MPs created in this study have a unique intra-particle elasticity distribution (IED), enabling them to bend around the central axis of the RBC-like dent, enabling them to pass through pores smaller than their diameter, mechanically behaving as authentic RBCs. In contrast, spherical MPs (SPH-MPs) and RBC-MPs hardened by incorporating a siloxane network (SiO_2-RBC-MPs), could not. In addition to the IED, we discovered that the deformability also depends on the shape and average particle elasticity. RBC-MPs did not accumulate in the lungs and the spleen, but were targeted specifically to the liver instead. In contrast, non-RBC-MPs such as SPH-MPs and SiO_2-RBC-MPs showed heavy accumulation in the lungs and/or spleen, and were dispersed non-specifically in various organs. Thus, controlling the shape and mechanical properties of RBC-MPs is important for achieving the desired biodistribution. When RBC-MPs were loaded with a (TGF)-β receptor inhibitor, RBC-MPs could treat liver fibrosis without pneumotoxicity.

1. Introduction

Medical techniques that utilize nanoparticles (NPs) or micro-particles (MPs), such as drug-delivery systems (DDSs), have become mainstream over the past 50 years [1]. However, these techniques are limited owing to the observation that large particles, although capable of delivering multiple functional materials in abundant amounts, are also more likely to lodge in the pulmonary capillaries compared to small particles [1–6]. Compared with NPs, MPs can deliver large quantities of various functional NPs, drugs, and dyes simultaneously; therefore, MPs may act as a platform for theranostics and multiple therapies. However, because of the very small diameters of pulmonary capillaries (approximately 2 μm in mice), particles with diameters over 100 nm can easily become lodged [1–9], potentially causing pulmonary thromboembolism [10,11]. In addition, the blood vessel walls of splenic sinuses, which are formed from rod cells that have fusiform-shaped or orbicular-ovate hollows, also result in a significant physical barrier to the passage of MPs [12]. Furthermore, most particles larger than 10 nm are trapped in the pores less than 10 nm in glomeruli, regardless of their composition or their surface chemistry. Hence, novel methods for avoiding the accumulation of MPs in the lungs and spleen are required in order to exploit the superior delivery capacity of MPs (compared with that of NPs), so that the full therapeutic potential of MPs can be realized.

Many studies have been conducted to evaluate the effects of particle size and surface charge on biodistribution [3–7]. Recent findings have shown that the elasticity of particles affects their biodistribution [13–16]. However, conflicting findings regarding the accumulation of particles with different elasticities in the lungs have been reported. For example, Anselmo et al. reported that soft particles accumulate at higher rates in the lungs than do hard particles [15], whereas Müllner et al. reported the opposite [16]. Furthermore, although the specific effects of the particle shape on biodistribution are not yet known, some reports have described the effects of particle shape on biodistribution and interactions with cells [1,13,14,17]. For example, in one analysis using a laminar flow that mimicked the hydrodynamic conditions encountered during microcirculation, discoidal particles were subjected to different torque forces compared to spherical particles, resulting in tumbling and rotation that increased their lateral drift towards the blood vessel walls [18]. An *in vitro* study revealed that particle shape, not

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