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The preferential targeting of the diseased microvasculature by disk-like particles

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ABSTRACT

Different classes of nanoparticles (NPs) have been developed for controlling and improving the systemic administration of therapeutic and contrast agents. Particle shape has been shown to be crucial in the vascular transport and adhesion of NPs. Here, we use mesoporous silicon non-spherical particles, of disk and rod shapes, ranging in size from 200 nm to 1800 nm. The fabrication process of the mesoporous particles is described in detail, and their transport and adhesion properties under flow are studied using a parallel plate flow chamber. Numerical simulations predict the hydrodynamic forces on the particles and help in interpreting their distinctive behaviors. Under microvascular flow conditions, for disk-like shape, 1000×400 nm particles show maximum adhesion, whereas smaller (600×200 nm) and larger (1800×600 nm) particles adhere less by a factor of about two. Larger rods (1800×400 nm) are observed to adhere at least 3 times more than smaller ones (1500×200 nm). For particles of equal volumes, disks adhere about 2 times more than rods. Maximum adhesion for intermediate sized disks reflects the balance between adhesive interfacial interactions and hydrodynamic dislodging forces. In view of the growing evidence on vascular molecular heterogeneity, the present data suggests that thin disk-like particles could more effectively target the diseased microvasculature as compared to spheres and slender rods.

1. Introduction

Since the first liposomal formulations in the 70s [1,2], several different classes of nanoparticles (NPs) have been developed for controlling and improving the systemic administration of therapeutic and contrast agents [2–5]. NPs offer distinctive advantages over systemically administered individual therapeutic and imaging agents. First, NPs can simultaneously carry multiple molecules to the diseased site in a controlled manner. Second, different agents can be simultaneously loaded into NPs and co-delivered, for multimodal imaging and poly-pharmacy. Finally, NPs can be engineered to enhance accumulation at biological targets and change the biodistribution of the active agents [6–10].

Most NPs were developed for the treatment and imaging of tumors. In this context, the commonly used strategy to maximize accumulation at the biological target (tumor mass) relies on the enhanced permeation and retention (EPR) effect [11,12]. The tumor vasculature is discontinuous with fenestrations of a few hundreds of nanometers in size. Therefore, sufficiently small NPs could passively cross the fenestrations and eventually accumulate in the tumor interstitium. Curiously enough, this same mechanism is used by organs of the mononuclear phagocyte system (MPS), such as the liver and the spleen, to sequester circulating foreign objects, including pathogens, macromolecules and NPs. Not surprisingly, then, a large portion of systemically injected NPs end up in the MPS. Also, it should be emphasized that the EPR effect strongly depends on the tumor type, stage and location [13].

The notion that endothelial cells (ECs) are inhomogenous and may express organ-specific receptor molecules appeared in the early 90s [14]. Since then, several studies have focused on identifying vascular molecules, and the corresponding ligands, expressed specifically on the diseased vascular districts and with a low, or even null, expression on normal ECs [15]. These specific receptors can be used as vascular docking sites for systemically injected NPs, whose surface has been decorated with ligand molecules. Indeed, exploiting the biochemical affinity of the ligands for the corresponding receptors, circulating NPs would recognize and firmly adhere to the diseased ECs. Thence, NPs can preferentially release their cargo toward the extravascular matrix or enhance the local tissue contrast for imaging. Note that whilst EPR is specific to

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