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Cover Story

Effect of shape and size of polymer particles on cellular internalization

Macrophages specialize in the process of phagocytosis wherein foreign particles are internalized and then broken down. While phagocytosis evolved to counter infectious agents like viruses and bacteria, polymeric particles used for drug delivery are subject to the same process. The phagocytosis of polymeric particles by macrophages is of interest for two reasons. On one hand macrophages of the reticuloendothelial system (RES) enact rapid clearance of particles from the circulation, a process that limits the ability of the particles to extend the circulating half-life of an encapsulated drug. Knowledge on how to design particles to escape phagocytosis could help to overcome this limitation. On the other hand, macrophages are also key constituents in disease lesions, like tumors and atherosclerotic plaques. In this capacity, macrophages are actually viable drug targets, so knowing how to enhance phagocytosis of polymeric particles could be of benefit for targeted drug delivery. While most research on this topic has focused on altering the surface chemistry and receptor-binding properties of particles, recently there has been an increasing interest in manipulating particle size and shape for altering biodistribution [1,2].

In an article published in this issue of *Journal of Controlled Release* Professor Jeffrey Smith and his group report the results of a study where they quantified the effect of shape and size on phagocytosis of an ensemble of particles [3]. More significantly they show, for the first time, how shape can have contrasting effects on the sequential processes of attachment vs. internalization, which together define the phagocytic rate. The study focused on ellipsoidal particles, which can have a wide range of curvatures. The authors found that, in comparison to spheres and oblate ellipsoids, particles in the shape of prolate ellipsoids exhibit superior attachment to the macrophage membrane. Surprisingly though, the subsequent internalization of these particles was the slowest. They further noted that this contrasting effect holds for particles with volume less than 0.69 μm^3, whereas above this size no significant differences in phagocytosis were observed. Altogether their study underscores the fact that phagocytosis is a product of sequential processes, and that these steps can be influenced independently by altering the geometry of a particle.

Studies such as those reported by Professor Smith's group can guide the design of particles for distinct therapeutic applications. For example, particles with at least one extended axis, like prolate ellipsoids, are likely to be well suited for use as long circulating drug carriers because their phagocytosis by macrophages in the liver will be less efficient. In cases where the macrophage is to be targeted, e.g., cancer and atherosclerosis, oblate ellipsoids are likely to be more suitable because they are phagocytosed more rapidly. Altogether, this study provides mechanistic guidance and methodology for further exploration of how particle shape can be manipulated to achieve desired attachment and internalization. The concept of viewing attachment and internalization as separate steps is also of interest to virologists seeking to modulate the infectivity of viruses.

The current study by Professor Smith's group was done by making particles of different shapes through altering the shape of the spherical polystyrene particles (0.5–3.6 μm in diameter). The particles were loaded into a plasticized polyvinyl alcohol film which was subsequently stretched at 120 °C in oil either in one dimension or in two dimension to obtain particles of different aspect ratios. Since the current nanofabrication techniques allow fabrication of various sizes and shapes at will [4,5], the study by Professor Smith's group can be extended easily to a variety of shapes. To date, the true targeted delivery of drug delivery systems after intravenous administration has not been achieved, and only a small fraction of the administered particles reach the target site. Thus, a design of particle size and shape that can effectively phagocytosed or endocytosed will provide invaluable means of improving the drug delivery efficiency.

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