Engineering Nanomaterial Morphology for Targeting Immune Cells Within Atherosclerotic Lesions

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Atherosclerosis is a chronic vascular inflammatory disease, in which several types of immune cells have been identified as playing important roles. Nanomaterials can function as powerful theranostic platforms for diagnostic imaging and controlled delivery of therapeutics in atherosclerosis. Here, we present a detailed investigation into the effects of morphology on the *in vivo* biodistribution of nanomaterials in naïve mice following intravenous injection. We applied these findings towards the targeting of diverse immune cells within the lesions of atherosclerotic mice. Three different nanostructures of the same surface chemistry were assembled from poly(ethylene glycol)-*bl*-poly(propylene sulfide) (PEG-*bl*-PPS) block copolymers: micelles (30 nm), vesicles (120 nm) and filomicelles (50 nm diameter by micron length). To assess the effects of the different morphologies, a multimodal approach was utilized that included 1) near infrared fluorescence (NIRF) imaging to quantify organ targeting, and 2) fluorescent polymer conjugation for subsequent flow cytometric analysis of uptake by immune cells. Of note, vesicles were exceptionally efficient at targeting the spleen and were associated with up to 85% of plasmacytoid dendritic cells. Micelles were associated with up to 90% of macrophages in the liver, and filomicelles were most effective at avoiding uptake by the cells of the mononuclear phagocyte system. Due to their enhanced uptake by dendritic cell subsets relative to other nanostructures, vesicles were selected for targeting cells within aortic lesions of atherosclerotic $LDL^{-/-}$ mice. In addition to associating with macrophages and eosinophils, vesicles were found to target significantly higher percentages of atheroma-resident dendritic cells (25%). In conclusion, differences in morphology can drastically change the biodistribution of nanomaterials at both the organ and cellular level. The ability to target or avoid phagocytic cell subsets will enhance current and future theranostic strategies. Furthermore, the targeting of dendritic cells by vesicular nanostructures within atherosclerotic lesions opens new avenues for immunotherapies in cardiovascular disease.

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