Design and In Vitro Characterization of Biodegradable, Drug Delivery Vehicle with the Adhesive Properties of Leukocytes

The site-specific expression of selectins (E- and P-selectin) on endothelial cells of blood vessels during inflammation provides an opportunity for the targeted delivery of anti-inflammatory drugs to the vascular endothelium for the purpose of reducing inflammation in chronic inflammatory diseases. Previous researches have shown that artificial capsules with the adhesive properties of leukocytes can be made by attaching leukocyte adhesive ligands to polystyrene microspheres. We adapted this technology to create a targeted delivery system using biodegradable, poly-lactic-co-glycolic-acid (PLGA) microspheres, where biotinylated-Sialyl Lewis X (sLex), a carbohydrate that serves as a ligand to selectins, was attached to the surface of avidin-linked PLGA microspheres. These carbohydrate-coated microspheres mimic the transient adhesive (rolling) behavior of leukocytes when interacting with selectin surfaces in flow chambers. Furthermore, we show that the time scale in which these sLeX-coated microspheres continued to recognize selectin in flow depended on the rate of microsphere degradation. Therefore, factors affecting degradation such as type of polymer, type of drug, extent of drug loading and microsphere size, provide an opportunity for engineering the time-scale of activity for the delivery system.

Since the selectin-ligand bond is weak, it cannot sufficiently maintain either firm leukocyte-endothelial interaction or cell transmigration. Firm arrest of leukocytes to the endothelium in vivo is mediated by endothelial intercellular adhesion molecules (ICAMs) binding to activated α2-integrin. Similarly, selectin-ligand interaction alone would not be sufficient for the firm binding of targeted, drug delivery vehicle to the endothelium. To this end, we explored the possibility of two-receptor, selectin and ICAM-1, targeting by functionalizing microspheres with both sLeX and anti-ICAM-1. We show that this two-receptor system is a more sophisticated leukocyte mimetic for targeting inflammation as selectin-ligand (sLeX) interaction is necessary for microspheres to firmly adhere via ICAM-antibody (anti-ICAM-1) interaction.