Development of a dual-receptor targeted drug delivery system for treating vascular disease

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Introduction. Drug delivery systems targeted to the vasculature provide an effective mean for increasing the therapeutic efficiency of various drugs and reducing the side effects as well as the frequency of the dosages taken by the patient. Studies have shown that two-receptor targeted drug carriers have higher efficiency in binding and delivery of therapeutic agents to the targeted tissue in comparison with single-receptor targeting approaches. In the past, antibody coated fluorescent microspheres have been widely used as a model leukocyte to mimic leukocytes adhesion cascade. In this study we present a novel dual-receptor (selectins and ICAMs) targeting approach to enhance the drug carrier's binding efficiency to the inflamed tissue in endothelial wall.

Methods. Dual-receptor targeted model drug carriers (florescent microspheres) were prepared by coating the microspheres with different ratios of antibodies against ICAM-1 (αICAM-1) and E-selectin (αE-selectin). The ratio of antibodies attached on the microspheres was quantified by fluorescence intensities using the Nikon Software and a Nikon Eclipse TE200 inverted microscope equipped with a fluorescence illumination system. The level of adhesion of the microspheres on HUVEC was quantified by counting the number of adherent microspheres on HUVEC using a fluorescent light microscope. Differences in the level of firm adhesion of microspheres with different ratios of αICAM-1/αE-selectin were examined under different flow condition.

Results. Microspheres coated with different ratios of antibodies (αICAM/αE-selectin = 30/70, 50/50 or 70/30) were prepared and tested under flow. Our findings indicate that microspheres coated with 50/50 ratio of αICAM-1 and αE-selectin have the highest binding efficiency compared to the single antibody coated microspheres. The number of αICAM-1+αE-selectin microspheres bound to HUVECs appeared to decrease with increase in wall shear stress in the flow chamber. Moreover, the number of adherent αICAM-1+αE-selectin microspheres was significantly higher than the adherent αE-selectin microspheres under different flow conditions. In particular, the level of firm adhesion of the dual-receptor targeting microspheres was 1.1 times than αE-selectin microspheres at wall shear stress of 0.5 dynes/cm^2; 2.3 times at 2 dynes/cm^2; and 3.4 times at 4 dynes/cm^2.

Conclusions. We have designed a two-receptor targeted drug delivery carrier that recognize endothelial expressed inflammation markers, selectin and ICAM, for the purpose of targeting inflammation in vivo. We conclude that the adhesion efficiency of the two-receptor targeting microspheres is significantly higher than the single-ligand microspheres under various flow conditions and that the drug carrier adhesion ability can be optimized by optimizing the ratio of the two ligands on the surface of the microsphere. Therefore a novel dual-receptor targeted drug delivery system may be developed to achieve higher targeting efficiency and effectiveness in therapeutic treatment of vascular diseases.