Hemodynamic Targeting Stimuli Responsive Therapeutic Delivery to Atheroprone Vasculature

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Cardiovascular disease is the leading cause of death in the developed world. Current therapeutics, such as statins, reduce adverse vascular events by only 40% due to residual risk after cholesterol lowering. Importantly, atherosclerosis occurs at areas of disturbed flow where production of reactive oxygen species (ROS) increases, and there is no treatment that is programmed to target and releases molecules to these specific areas. Therefore, we are developing a new drug delivery system that can target sites of disturbed blood flow and release therapeutics locally in response to ROS overproduction. The following two parts of the project have been done so far. First, the area of disturbed flow was successfully targeted by in vivo phage display in a mouse model partial carotid artery. Two 12 amino acid linear peptide sequences and two 7 amino acid cyclic sequences were also identified to target the endothelium of atheroprone vasculature under disturbed flow. One of phage displayed peptides ("PREY") was then used to form targeted liposomes as a test vehicle. This peptide-liposome nanocarrier was observed to accumulate in areas of disturbed shear *in vivo*. Second, a combination of bio-conjugation methods and controlled RAFT polymerization was utilized to synthesize a new ROS-cleavable nano micelle as a potential nanocarrier for plasmid DNA delivery. The nano micelleplexes were physiochemically characterized for their ability to form stable polyplexes with pDNA, size, morphology, ROS responsiveness, serum stability and blood compatibility. The novel polyplex nanocarrier developed in this study exhibited enhanced cellular uptake and transfection when vascular cells were activated to overproduce ROS, suggesting that it is a promising delivery platform for vascular gene delivery. Developing a nanoscale agent that can target regions of "atheroprone" flow, before the development of atherosclerotic lesions, and deliver therapeutics in a site-specific fashion could revolutionize treatment of atherosclerosis.