Thrombus-Responsive Drug Delivery Systems for Targeted Fibrynolisis

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The blockage of blood vessels by clots is the primary cause of vascular diseases, like myocardial infarction and ischemic stroke. Current treatment of this involves intravascular administration of fibrinolytic agents, like tissue plasminogen activator (tPA), to rapidly remove the clot and restore blood flow. However, such systemic administration results in rapid drug clearance and also poses risks of side-effects like hemorrhage due to off-target drug action. Such effects can be avoided by utilizing drug delivery systems (DDS) that can anchor specifically to the clot site and release the encapsulated drug via clot site-specific triggers for localized action. To this end, a liposome-templated DDS was developed that can specifically bind to clots via ligand-mediated anchorage to activated platelets and fibrin, the two major components of blood clot. The DDS design was further refined to enable destabilization of the liposomes via the action of thrombin, an enzyme upregulated at the clot site, to release the payload. For this, a thrombin-cleavable lipopeptide, Stearyl-TCP, was incorporated within the liposomal membrane, and a model fluorescent payload carboxyfluorescein (CF) was encapsulated in the liposome core. Thrombin-responsive CF release from these engineered DDS was monitored by UV-Vis spectrometry and the amount of Stearyl-TCP content in the membrane was optimized to maximize thrombin-triggered CF-release. Subsequently the optimized clot-targeted thrombin-triggerable liposomal DDS was loaded with Streptokinase (SK) as a model fibrinolytic agent, and its clot-responsive targeted fibrinolytic action was studied using microfluidic set-up. Future studies will be directed at evaluating this DDS in appropriate in vivo models of thrombosis.