Smart Heparin Transcutaneous Patch

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Statement of Purpose:

Thrombosis, a pathological hemostatic condition, has become one of the leading causes of cardiovascular mortalities and morbidities worldwide.[1] Conventioal adminstration of anticoagulants remains difficult for precise anticoagulant regulation. Under- or over-dosage may lead to dangerous consequences due to either rapid clearance in the body or bleeding complications that may lead to spontaneous hemorrhages.[2] Herein, we design an engineered feedback-controlled anticoagulant system based on thrombin-responsive polymer-drug conjugates.

Methods:

We present here a thrombin-responsive heparin microneedle (MN) patch (Figure 1). A thrombin-cleavable peptide is introduced as a linker during the conjugation of heparin (HP) to the main chain of hyaluronic acid (HA). The peptide can be cleaved when thrombin is activated, triggering the release of anticoagulant drug from the backbone in a thrombin-responsive fashion. The thrombin-responsive HP conjugated HA (TR-HAHP) matrix can be obtained via polymerization under UV light treatment. And this TR-HAHP matrix was loaded into the tips of MNs for painless transdermal delivery.[3] We studied the anticoagulant capability of heparin patch both *in vitro* in human plasma and *in vivo* in a thrombotic challenge mouse model.

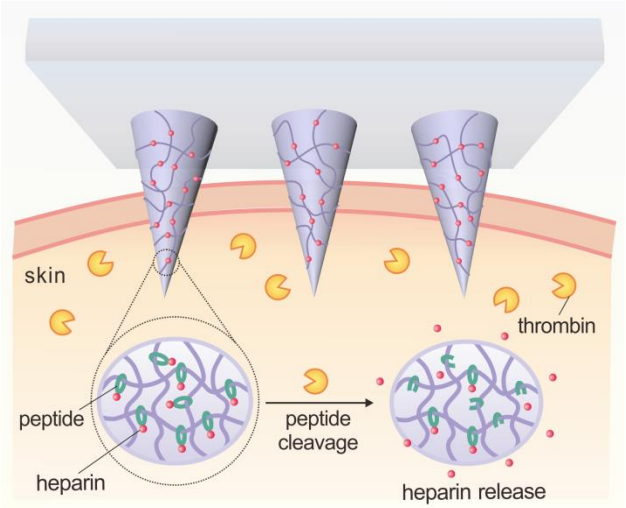

Figure 1. Schematic of TR-HAHP MN-array patch in response to thrombin. Peptide that links HP and HA is cleaved by thrombin and releases anticoagulant drug.

Results:

The TR-HAHP matrix released loaded heparin in response to difference thrombin level and stayed stable without significant drug leaking in 24 hrs. *In vitro* studies with human plasma indicated efficient anticoagulant capacity of TR-HAHP gel. Moreover, the TR-HAHP gel maintained its anticoagulant function when incubated with fresh plasma in the second period. Whereas HP gel only prevent coagulation in the first incubation period due to its burst release of heparin. In addition, thrombin-responsive MN patch exhibited effective protection of mice from death in an acute thromboembolism mice model without causing any inflammatory response (Figure 2). The TR-HAHP MN still maintained its anticoagulant capacity even 6 h-post administration.

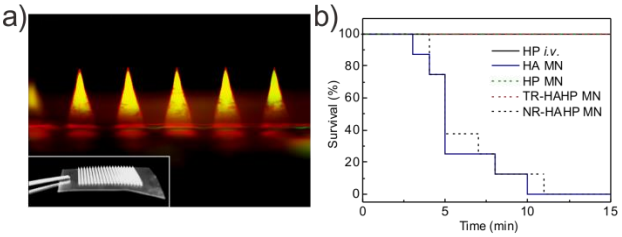

Figure 2. (a) A fluorescent image inserted with a photograph of thrombin-responsive heparin microneedle array patch. (b) Kaplan−Meier survival curves for the mice challenged with thrombin injection (1000 U/kg). Each group was pre-treated with HP i.v. injection or different types of MN patch: empty HA MN, HP MN, TR-HAHP MN and NR (non-responsive)-HAHP MN (HP: 200 U/kg). Shown are eight mice per treatment group.

Conclusions:

In conclusion, we developed a thrombin-responsive patch for auto-regulation of blood coagulation by integrating TR-HAHP matrix with MN-array. The thrombin-cleavable peptide unit enabled thrombin-specific activation of drug release from the system with a rate highly dependent on the thrombin concentration. More importantly, it enabled feedback-controlled anticoagulation therapy with minimized risk of over- or under-dosage. The in vivo studies in a thrombolytic challenge model demonstrated effective protection from acute pulmonary thromboembolism in a long-lasting fashion.

References:

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