Appropriate Timing in Responsive Anticoagulant Release Systems

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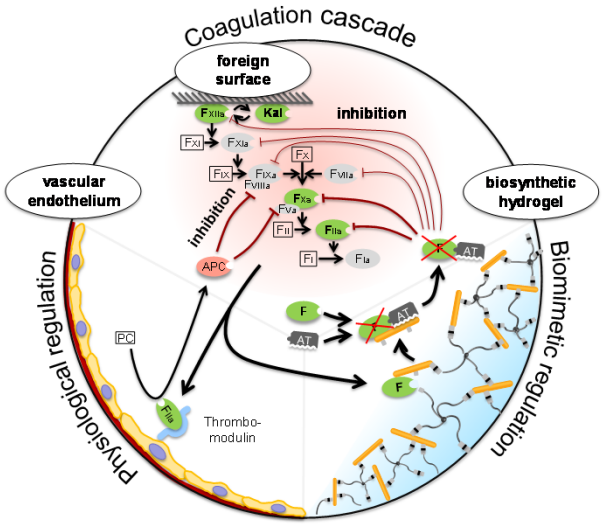
Background and Objectives

Background

A hydrogel system consisting of
- Heparin (anticoagulant)
- 4-armed PEG (bio-inert structure component)
- Thrombin-cleavable peptide as linker

… mimics the feedback controlled anticoagulant regulation of the vessel wall protein thrombomodulin:
- Anticoagulant effect only upon thrombin formation
- Anticoagulant activity shifts from surface to liquid phase



But:
- Thrombin is late activated in the coagulation process
- Earlier onset of anticoagulant release may be more effective

Objective

Improved anticoagulant profile by different timing of heparin release

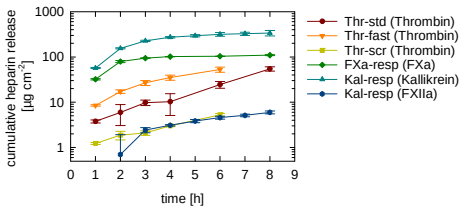
Study

Gel Properties

Method:

Hydrogels with linker peptides sensitive to
- FXIIa/kallikrein: onset of intrinsic coagulation surface dependent
- FXa: activation before thrombin low plasma concentration
- Thrombin late activation high plasma concentration

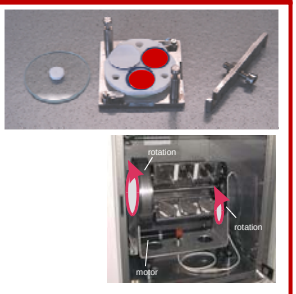
Hydrogel-degradation in isolated enzyme solutions:

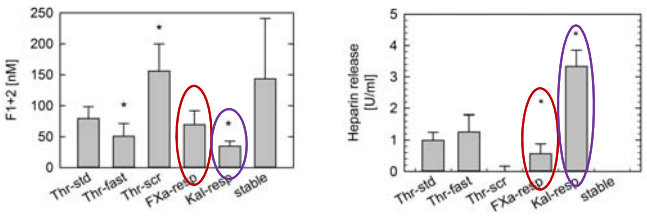


Degradation depends on turn-over rates and interaction with hydrogel matrix
Fast degradation by FXa may compensate for low plasma concentration

Blood Incubation

Whole blood incubation assay
- Freshly drawn whole blood
- Hydrogel coatings as top and bottom of incubation chambers
- 2h incubation at 37°C





FXa responsive: equal anticoagulation at lower heparin release compared to thrombin-responsive gel
FXIIa/Kal responsive: High anticoagulation by high heparin release

Conclusion

Early onset of anticoagulant release by upstream factors in the coagulation cascade improves the performance of coagulation-responsive anticoagulant release systems