UKE Paper of the Month September 2016

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Neutralizing Blood-Borne Polyphosphate In Vivo Provides Safe Thromboprotection

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ABSTRACT:

Polyphosphate is an inorganic procoagulant polymer. Here, we develop specific inhibitors of poly-phosphate and show that this strategy confers thromboprotection in a factor XII-dependent manner. Recombinant E. coli exopolyphosphatase (PPX) specifically degrades polyphosphate while a PPX variant, lacking domains 1 and 2 (PPX_Δ12) binds to the polymer without degrading it. Both PPX and PPX_Δ12 interfere with polyphosphate- but not tissue factor- or nucleic acid-driven thrombin formation. Targeting polyphosphate abolishes procoagulant platelet activity in a factor XII-dependent manner, reduces fibrin accumulation and impedes thrombus formation in blood under flow. PPX and PPX_Δ12 infusions in wild-type mice interfere with arterial thrombosis and protect animals from acti-vated platelet-induced venous thromboembolism without increasing bleeding from injury sites. In contrast, targeting polyphosphate does not provide additional protection from thrombosis in factor XII-deficient animals. Our data provide a proof-of-concept approach for combating thrombotic diseases without increased bleeding risk, indicating that polyphosphate drives thrombosis via factor XII.

STATEMENT:

The study identifies the first specific inhibitors for the procoagulant mediator polyphosphate and shows that targeting polyphosphate provides thromboprotection without therapy associated increased bleeding with broad implications for treatment of thromboembolic diseases.

BACKGROUND:

The translational project was performed at the Institute for Clinical Chemistry and Laboratory Medicine in collaboration with leading medical universities in Europe and the USA including Mayo Clinic, Karolinska Institute, Case Western Reserve University, Oregon University and University of Utrecht. The first and senior authors have a strong research interest in exploring the crosstalk of coagulation and inflammation to develop novel therapies for interference with both thromboembolic and inflammatory disease states. The study comprises inorganic chemistry, pharmacology, cardiovascular research and biochemistry and is parts of the PhD thesis of Linda Labberton. Support by the SFB841 and SFB877 is greatly acknowledged.