UKE Paper of the Month November 2015

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The polyphosphate-factor XII pathway drives coagulation in prostate cancer-associated thrombosis

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ABSTRACT:
Cancer is a leading cause of thrombosis. We identify a new procoagulant mechanism that contributes to thromboembolism in prostate cancer and allows for safe anticoagulation therapy development. Prostate cancer-mediated procoagulant activity was reduced in plasma in the absence of factor XII or its substrate of the intrinsic coagulation pathway factor XI. Prostate cancer cells and secreted prostasomes expose long chain polyphosphate on their surface that colocalized with active factor XII and initiated coagulation in a factor XII-dependent manner. Polyphosphate content correlated with the procoagulant activity of prostasomes. Inherited deficiency in factor XI or XII or high-molecular-weight kininogen, but not plasma kallikrein, protected mice from prostasome-induced lethal pulmonary embolism. Targeting polyphosphate or factor XII conferred resistance to prostate cancer-driven thrombosis in mice, without increasing bleeding. Inhibition of factor XII with recombinant 3F7 antibody reduced the increased prostasome-mediated procoagulant activity in patient plasma. The data illustrate a critical role for polyphosphate/factor XII-triggered coagulation in prostate cancer-associated thrombosis with implications for anticoagulation without therapy-associated bleeding in malignancies.

STATEMENT:
Thromboembolism is a significant cause of morbidity and mortality in patients with cancer. Our translational study identifies a new mechanism by which cancer drives venous thrombosis. Inhibition of this novel pathway could present an opportunity for the first safe anticoagulation therapy that is not associated with excess bleeding.

BACKGROUND:
The study results from collaboration between the Institute of Clinical Chemistry and Laboratory Medicine, the Clinical Department of Hematology and Oncology, the Institute for Pathology and Martini-Clinic at the UKE, encompassing both experimental and clinical expertise in coagulation and cancer. The work was supported in part by DFG grants within SFB877 and SFB841. The project received support from collaborative partners from Sweden (Karolinska Institute and Uppsala University) and USA (University of Chapel Hill and Case Western Reserve University). All authors have an interest in the crosstalk between coagulation and cancer, with the aim of improving outcome for patients with malignancies.