UKE Paper of the Month Januar 2018

Host DNases prevent vascular occlusion by neutrophil extracellular traps

Miguel Jiménez-Alcázar, Chandini Rangaswamy, Rachita Panda, Josephine Bitterling, Yashin J. Simsek, Andy T. Long, Rostyslav Bilyy, Veit Krenn, Christoph Renné, Thomas Renné, Stefan Kluge, Ulf Panzer, Ryushin Mizuta, Hans Georg Mannherz, Daisuke Kitamura, Martin Herrmann, Markus Napirei, Tobias A. Fuchs

Science. 2017; 358(6367):1202-1206;

ABSTRACT: Platelet and fibrin clots occlude blood vessels in hemostasis and thrombosis. Here we report a noncanonical mechanism for vascular occlusion based on neutrophil extracellular traps (NETs), DNA fibers released by neutrophils during inflammation. We investigated which host factors control NETs in vivo and found that two deoxyribonucleases (DNases), DNase1 and DNase1-like 3, degraded NETs in circulation during sterile neutrophilia and septicemia. In the absence of both DNases, intravascular NETs formed clots that obstructed blood vessels and caused organ damage. Vascular occlusions in patients with severe bacterial infections were associated with a defect to degrade NETs ex vivo and the formation of intravascular NET clots. DNase1 and DNase1-like 3 are independently expressed and thus provide dual host protection against deleterious effects of intravascular NETs.

STATEMENT: *Our study identifies a novel mechanism for vascular occlusion at inflammatory states, which utilizes the physical properties of DNA. In brief, we show that extracellular DNA filaments, known as Neutrophil Extracellular Traps (NETs), can form aggregates that occlude blood vessels independently of fibrin and platelets. Two DNA-degrading enzymes (DNase1 and DNase1-like 3) in blood circulation degrade NETs in healthy individuals, but can be absent in severe inflammatory conditions e.g. sepsis. Such patients may profit from supplementation therapy with recombinant DNases in future.*

BACKGROUND: The work was part of the PhD theses of Miguel Jiménez-Alcázar, MSc. and Chandini Rangaswamy, MSc. at the Institute of Clinical Chemistry and Laboratory Medicine in the group of Dr. Tobias Fuchs, which focuses on the role of neutrophils in inflammation, infection, and immunity. Several UKE investigators contributed to the study, including Prof. Dr. Dr. Thomas Renné (Institute of Clinical Chemistry and Laboratory Medicine), Prof. Dr. Stefan Kluge (Department of Intensive Care), and Prof. Dr. Ulf Panzer (III. Medical Clinic). The project received funding from the SFB841, SFB1192, KFO306, DGKL, and DAAD.