UKE Paper of the Month (UKE-Webpage: Wissenschaftler > Aktuelles aus der Forschung)

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Myeloperoxidase attracts neutrophils by physical forces

*Klinke A, *Nussbaum C, Kubal L, Friedrichs K, Rudolph TK, Rudolph V, Paust H-J, Schröder C, Benten D, Lau D, Szocs K, Furtmüller PG, Heeringa P, Sydow K, Duchstein H-J, Ehmke H, Schumacher U, Meinertz T, Sperandio M , Baldus S
*contributed equally

Abstract: Recruitment of polymorphonuclear neutrophils (PMN) remains a paramount prerequisite in innate immune defense and a critical cofounder in inflammatory vascular disease. Neutrophil recruitment comprises a cascade of concerted events allowing for capture, adhesion and extravasation of the leukocyte. Whereas PMN rolling, binding and diapedesis are well-characterized, receptor-mediated processes, mechanisms attenuating the electrostatic repulsion between the negatively charged glycocalyx of leukocyte and endothelium remain poorly understood. Here, we provide evidence for myeloperoxidase (MPO), an abundant PMN-derived heme protein, facilitating PMN recruitment by its positive surface charge: *In-vitro,* MPO evoked highly directed PMN motility, which was solely dependent on electrostatic interactions with the leukocyte's surface. *In-vivo,* PMN recruitment demonstrated to be MPO-dependent in a model of hepatic ischemia / reperfusion, upon intraportal delivery of MPO and in the cremaster muscle exposed to local inflammation and following intraarterial MPO application. Given MPO's affinity to both the endothelial and the leukocyte´s surface, MPO evolves as a mediator of PMN recruitment due to its positive surface charge. This electrostatic effect of MPO not only displays a so far unrecognized, catalysis-independent function of the enzyme, but also highlights a principal mechanism, which yields PMN attraction driven by physical forces.

Statement: "Recruitment of polymorphonuclear neutrophils displays a hallmark in innate immune defense and stands out as a principal prerequisite in vascular inflammatory disease. In the current work we demonstrate in a series of translational studies that the neutrophil-derived enzyme myeloperoxidase (MPO) is a powerful attractant of PMN. Myeloperoxidase provoked PMN locomotion irrespectively of its catalytic activity, independently of cytoskeletal rearrangements but based on electrostatic interactions between the cationic peroxidase and the negatively charged surface of the leukocyte. Thus, our work describes not only a so far unrecognized concept of cell motility relying on physical forces but also an unknown biological function of MPO. Given the significance of PMN motility in health and disease, we believe that these findings are of principal interest to a broad readership and of high impact to the field.
The current project is based on close collaboration between several UKE research groups, involving different members of the Cardiovascular Research Center CVRC (Baldus; Rudolph; Sydow; Ehmke) and members of the departments of Nephrology, Anatomy II and Gastroenterology. It represents interdisciplinary work among UKE institutes with special regard to the contribution of young scientists (Klinke, Friedrichs, Rudolph, Rudolph, Schröder, Szocs, Sydow)."

The work was performed at the CVRC, Department of Cardiology in the group of Stephan Baldus. It was part of the PhD thesis of Anna Klinke and funded by the DFG (BA 1870/7-1). The group focuses on vascular inflammatory processes with special interest on the leukocyte peroxidase myeloperoxidase. The group includes T.K. Rudolph and K. Sydow, also belonging to the Department of Cardiology, who both share the interest in leukocyte activation in vascular inflammatory processes and focus on effects of nitrated fatty acids and the NO-synthase inhibitor ADMA, respectively. Dr. Paust contributed by leukocyte analysis as assessed by flow cytometry, the group of Prof. Schumacher provided techniques of leukocyte analysis under flow conditions and Dr. Benten and Prof. Ehmke provided expertise in mouse models of inflammation.