PreSens
PRECISION SENSING

Scientific Paper:

Int. J. Mol. Sci. (2022) 23, 3195

Formation of Neutrophil Extracellular Traps by Reduction of Cellular Cholesterol Is Independent of Oxygen and HIF-1α

Timo Henneck[1,2], Ahmed Elmontaser Mergani[1,2], Sabrina Clever[1,2], Anna E. Seidler[1,2], Graham Brogden[1], Sandra Runft[3], Wolfgang Baumgärtner[3], Katja Branitzki-Heinemann[1,2] and Maren von Köckritz-Blickwede[1,2]
[1]Department of Biochemistry, University of Veterinary Medicine Hannover, Hannover, Germany
[2]Research Center for Emerging Infections and Zoonoses (RIZ), University of Veterinary Medicine Hannover, Hannover, Germany
[3]Department of Pathology, University of Veterinary Medicine Hannover, Hannover, Germany

Abstract:

Formation of neutrophil extracellular traps (NETs) is a two-faced innate host defense mechanism, which, on the one hand, can counteract microbial infections, but on the other hand, can contribute to massive detrimental effects on the host. Cholesterol depletion from the cellular membrane by Methyl-_-cyclodextrin (M_CD) is known as one of the processes initiating NET formation. Since neutrophils mainly act in an inflammatory environment with decreased, so-called hypoxic, oxygen conditions, we aimed to study the effect of oxygen and the oxygen stress regulator hypoxia-inducible factor (HIF)-1_ on cholesterol-dependent NET formation. Thus, murine bone marrow-derived neutrophils from wild-type and HIF-knockout mice or human neutrophils were stimulated with M_CD under normoxic (21% 02) compared to hypoxic (1% 02) conditions, and the formation of NETs were studied by immunofluorescence microscopy. We found significantly induced NET formation after treatment with M_CD in murine neutrophils derived from wild-type as well as HIF-1_ KO mice at both hypoxic (1% 02) as well as normoxic (21% 02) conditions. Similar observations were made in freshly isolated human neutrophils after stimulation with M_CD or statins, which block the HMG-CoA reductase as the key enzyme in the cholesterol metabolism. HPLC was used to confirm the reduction of cholesterol in treated neutrophils. In summary, we were able to show that NET formation via M_CD or statin-treatment is oxygen and HIF-1_ independent.

Keywords: neutrophil extracellular traps, hypoxia, statin, HIF-knock-out mice