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113. SICKLE CELL DISEASE, SICKLE CELL TRAIT AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: BASIC AND TRANSLATIONAL
IL-27 Promotes Neutrophil Extracellular Trap Generation in Sickle Cell Disease

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Introduction: Neutrophil Extracellular Traps (NETs) are neutrophil-derived damage-associated molecular patterns (DAMPs) composed of decondensed chromatin decorated with citrullinated histones and neutrophil proteases. Recently, we have shown that caspase-4-dependent activation (cleavage) of the pore-forming protein, Gasdermin-D (GSDMD) in neutrophils promotes NETs generation leading to lung injury in SCD. IL-27, an anti-inflammatory cytokine with some pro-inflammatory properties is significantly elevated in the plasma of SCD patients, however, it remains debatable whether IL-27 signaling in neutrophils serves to promote or inhibit NETs generation in SCD.

Methods: Citrated blood samples from SCD or race matched control humans were incubated with saline, hemin (20 mM), or hemin (20 mM) + recombinant human IL-27 (200 ng/mL) for 15 minutes at room temperature. Platelet-poor-plasma from the three treatment groups were incubated with sytox green and fluorescent Abs against neutrophil elastase (NE) and histones for *in situ* staining of extracellular DNA, NE and histones, respectively. Imaging flow cytometry was used to detect circulating NETs (cNETs) as 1-2 μm fragments triple-positive for extracellular DNA, NE, and histones.

Results: Incubation with hemin led to significant increase in cNETs concentration in SCD but not control human blood, which was further increased following incubation of SCD human blood with hemin in presence of IL-27.

Conclusion: Our current findings suggest that IL-27 signaling promotes NETs generation by neutrophils in SCD patient blood. Currently, studies are underway to identify the molecular mechanism underlying IL-27-dependent NETs generation in SCD.

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