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The role of NETs and their aggregates in disease.

Christine Schauer[1], Maximilian Dölling[1], Martin Herrmann*[2]

[1] Internal Medicine, University Clinic, Erlangen, Germany.
[2] Department of General-, Visceral-, Vascular- and Transplant Surgery, University Hospital Magdeburg, Magdeburg, Germany

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***Correspondence:** Martin Herrmann Department of General-, Visceral-, Vascular- and Transplant Surgery, University Hospital Magdeburg, Magdeburg, Germany
E-mail: martin.herrmann@medma.uni-heidelberg.de
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Abstract

Neutrophil extracellular traps (NETs) are structures released by neutrophils in response to infections or tissue damage. They are made of decondensed chromatin, histones, various antimicrobial proteins, and a plethora of enzymes, growth factors, chemokines, and cytokines. Importantly, NETs generated in high neutrophil densities tend to form aggregates that often reach large sizes (1). Whereas solitaire NETs are rapidly degraded, these NET aggregated can persist for many months and even years. In this time NETs accumulate further compounds like complement and fibrin. In certain locations aggregated NETs calcify. Recent research has linked NETs to various diseases, including cancer.
NETs display various tumor modifying features and can (I) create a "sticky" scaffold in the bloodstream that promotes the growth of metastatic cells (II) degrade the extracellular matrix and release factors for tumor cell growth and invasion. (III) stimulate neo-angiogenesis (IV) shield (cancer) cells from immune attack (V) promote an immunosuppressive environment (VI) form immune thrombi as well as fibrin and platelet aggregates.
In formalin-fixed paraffin-embedded tissues the decondensed, extracellular DNA of NETs can reliably be differentiated from condensed nuclear DNA by immunodetection with anti-DNA IgM. Using high-resolution stimulated emission depletion (STED) microscopy, we showed that citrullinated histone H3 (H3cit) closely associated with the de-condensed extracellular DNA of NETs.
In patients with colon cancer we detected NETs preferentially only in the tumour centres or both in the centre and the invasive front. Citrullinated NETs were associated with high histopathological tumour grades and lymph node metastasis.
In vitro, NETs increased mRNAs of mesenchymal markers vimentin and fibronectin and epithelial-mesenchymal transition promoting transcription factors ZEB1 and Slug (SNAI2); the epithelial markers E-cadherin (CDH1) and epithelial cell adhesion molecule (EPCAM) were downregulated. This indicates that NETs have activated an epithetlial-mesenchymal transition-like process in these cells and may contribute to the metastatic progression of CRC.
(1) Aggregated neutrophil extracellular traps limit inflammation by degrading cytokines and chemokines. Schauer C, ….. Bilyy R, ….., & Herrmann M.; Nat Med. 2014 May;20(5):511-7. doi: 10.1038/nm.3547. cited 977 times.