Scientific Foundation SPIROSKI, Skopje, Republic of North Macedonia
South East European Journal of Immunology. 2025 Mar 31; 8(CITIM):036
https://doi.org/10.3889/seejim.2025.6097
eISSN: 1857-9388
Category: *CITIM - Cancer Immunotherapy & Immunomonitoring (CITIM2025)*
Section: *Invited Lectures*

Neutrophil Extracellular Traps (NETs) in cancer and beyond

Nuha Al-Sharif, Mohamad Qaisi, Naomi Kaisar, Dan Padawer, Osnath Bohana, Yael Volman, Zvi G. Fridlender*

Hadassah-Hebrew University Medical Center, Jerusalem, Israel

Citation: Al-Sharif N, Qaisi M, Kaisar N, Padawer D, Bohana O, Volman Y, Fridlender ZG. Neutrophil Extracellular Traps (NETs) in cancer and beyond. SEE J Immunol. 2025 Mar 27;8(CITIM):036. https://doi.org/10.3889/seejim.2025.6097
Keywords: Neutrophil Extracellular Traps (NETs); Cancer progression; Tumor immunity; NETosis; T-cell activation
***Correspondence:** Zvi G. Fridlender Hadassah-Hebrew University Medical Center, Jerusalem, Israel
E-mail: Fridlender@hadassah.org.il
Received: 26-Fev-2025
Accepted: 25-Mar-2025
Copyright: © 2025 Nuha Al-Sharif, Mohamad Qaisi, Naomi Kaisar, Dan Padawer, Osnath Bohana, Yael Volman, Zvi G. Fridlender. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0)
Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

Neutrophils play a major role in tumor biology. The main effects described by us and others of neutrophils in cancer are directly on tumor cells, or indirectly by affecting the stromal immune system. An exciting relatively novel phenomenon described is the neutrophils' ability to release webs of fibrous decondensed chromatin named neutrophil-extracellular traps (NETs). Originally characterized as a novel antimicrobial mechanism, NETs were later described also in the context of cancer, but the exact effects of NETs on tumor and immune cells, and the importance of NETs production (NETosis) in cancer progression is still not clear.

In the current work we characterize the release of NETs from neutrophils during cancer progression, and the effect that NETs confer on tumor and immune cells, comparing the effects of NETs from healthy donors and from lung cancer patients.

We isolated NETs from blood samples of lung cancer patients and healthy donors. Combining multiple approaches such as confocal microscopy, ELISA and flow cytometry and more we tested the impact of human NETs on tumor cell viability and migration ("wound repair"), and tumor-related T-cell proliferation, and activation.

We found that neutrophils from lung cancer patients (LC) produce smaller amounts of NETs Compared to healthy donors (HD) were found to be cytotoxic to A549 lung cancer tumor cells, though NETs from both HD and LC are capable of killing tumor cells and inhibit their motility. NETs were able to show increased activation of T-cells. Activation of CD8 T-cells was at least partly dependent on the presence of DNA, whereas activation of both CD4 and CD8 continued at least to some extent after prolonged heat and use of DNase, suggesting a metabolic mechanism. Furthermore, NETs increased proliferation of CD8 T-cells, somewhat more when originated from HD compared to LC. The mechanism of this effect was also suggested to be through a metabolite.

We next assessed different inhibitors of NETosis in vitro and investigated their efficacy in vivo models of cancer. Interestingly we found that inhibition of ROS production didn't lead directly to reduction of NETosis as it's generally accepted, suggesting an alternative pathway for NETosis. Using a physiologic activator of NETosis that acts through the TLR4 receptor and ROS production we noted in a mouse model of lung cancer that primary tumor growth was inhibited, while the metastatic process was increased.

Our continuous studies on the mechanisms of production of NETs in cancer and beyond as well as the understanding of their effects on both tumor and immune cells shed a light on the role of this exciting, relatively recently described phenomenon in cancer, and could aid in the development of new strategies to direct the immune system against the tumor.