ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

International Journal of Dental Science and Innovative Research (IJDSIR)
IJDSIR : Dental Publication Service
Available Online at: www.ijdsir.com
Volume – 5, Issue – 2, April - 2022, Page No. : 582 - 586

Neutrophil Extracellular Traps and their title role in Tumourogenesis

[1]Dr. Jayanta Chattopadhyay, Kusum Devi Sunderlal Dugar Jain Dental College& Hospital, Kolkata, India.
[2]Dr. Surajit Bose, Kusum Devi Sunderlal Dugar Jain Dental College& Hospital, Kolkata, India.
[3]Dr. Rakhshith Shetty, Kusum Devi Sunderlal Dugar Jain Dental College& Hospital, Kolkata, India.
[4]Dr. Subhalaxmi Sen, Kusum Devi Sunderlal Dugar Jain Dental College& Hospital, Kolkata, India.
[5]Dr. Moumita Bhattacharya, Kusum Devi Sunderlal Dugar Jain Dental College& Hospital, Kolkata, India.
[6]Ishita Basu, Department of Allied Health Science, Brain ware University, Barasat, India.
Corresponding Author: Ishita Basu, Department of Allied Health Science, Brain ware University, Barasat, India.

Citation of this Article: Dr. Jayanta Chattopadhyay, Dr. Surajit Bose, Dr. Rakhshith Shetty, Dr. Subhalaxmi Sen, Dr. Moumita Bhattacharya, Ishita Basu, "Neutrophil Extracellular Traps and their title role in Tumourogenesis", IJDSIR- April - 2022, Vol. – 5, Issue - 2, P. No. 582 – 586.

Type of Publication: Original Research Article
Conflicts of Interest: Nil

Abstract

Neutrophil extracellular traps (NETs) are released by neutrophils to capture and eliminate pathogens during the programmed death of neutrophils by DNA expulsion. Numerous factors are involved in this process of cancer metastasis that include NETs as well as the importance of Tumor Associated Macrophages (TAMs) in development of Tumor Microenvironment (TME). Thus, various biomarkers have been studied to monitor and predict the growth of cancer cells, their response to medicines, and prognosis of tumourogenesis due to NETs. This article describes the involvement of neutrophil and the direct and indirect interactions of NETs with cancer cells.

Keywords: Intravasation, Extravasation, Angiogenesis, Immunosuppression, Neutrophil-Lymphocyte Ratio, Invasion, Colonization, Macrophages

Introduction

Cancer is causing many deaths every year throughout the world. The main reason behind the low mortality rate in cancer is because of its property of metastasis i.e., spread from their site of origin to different parts of the body. The process of cancer invasion is unclear till date, but it is well-known that it has multiple steps including- local tumor cell invasion followed by intravasation (entry into the vasculature), colonization at distal sites and extravasation (exit from circulation). For all these steps to be accomplished, cancer cells must evade immune surveillance in which the role of T-cells and macrophages are identified. In some recent studies, there are many instances where role of neutrophils can't be overlooked (1).

Nowadays, neutrophils are being studied with for its role in cancer progression specially in its early stage when

the tumor is still developing (2). The most abundant type of WBC in blood are neutrophils that have different subpopulations like- low density neutrophils (LDNs), normal density neutrophils (NDNs), high density neutrophils (HDN). All these types have a unique function of releasing cytokines and generating inflammatory responses during pro-metastatic stages of malignancy (3).

Materials and methods

An elaborate search was done on the relevant search engines like Google Scholar, PubMed and Springer for the data published within 2007-2020

Neutrophil Extracellular Traps (nets)

Neutrophil extracellular traps (NETs) are extracellular neutrophil-derived DNA webs released in response to inflammatory cues that trap and kill invading pathogens (4). After the death of the neutrophil, the residual DNA structure forms NET and contribute to chronic inflammatory conditions (5-7). Production and activation of NETs are primarily for the immune defense mechanisms that help in the development of inflammation, hemodynamics alterations, immune hyper responsiveness, endothelial barrier function, and induction of tumor microenvironment (TME) heterogeneity. The production of NETs and NET osis formations are evolutionary process, in which defects and dysregulation can result into many disorders (8). NETs can directly lead to the development of brain parenchyma pathology, as they are observed in patients with thrombosis-associated ischemic stroke, especially higher in older thrombi and characterized by citrullinated histone H3. NETs appeared in the cerebrospinal fluid of patients, in forms of meningitis like pneumococcal meningitis caused by viruses (9). NETs were observed in the outer layers of thrombi in patients with acute ischemic stroke and was associated with endovascular therapy (10).

Review of literature

Neutrophils in tumor development

Tumor Associated Neutrophils (TANs) with the help of chemokines and cytokines and depending on their activation status are engaged into the tumor microenvironment resulting in effects on tumorogenic in N1 and N2 TANs. N1 TANs, by direct or indirect cytotoxicity exhibit antitumor property. N2 TANs play an important role in developing new blood vessels (angiogenesis), tumorigenesis, metastasis (due to DNA instability), release of cytokines and chemokines and all these results in weakened immune system (immunosuppression) (11). In tumor patients, Neutrophil-to-Lymphocyte Ratio (NLR) and large number of TANs do correlate with poor prognosis, as TAN counts and NLR are considered as biomarkers. Minding the crucial role of TANs in inducing tumorigenesis, many therapeutic strategies have been suggested to target TANs. The proposals that are addressed in this case are primarily two types: (a) CXCL-8/CXCR-1/CXCR-2 axis are targeted, for inhibiting TANs, (b) Inducing tumor growth which are manufactured by polymorpho-nuclear cells (12). Many studies are being conducted either in vitro or in vivo, i.e., on animal body by restraining the clinical studies as it is associated with the risk of immunosuppression (13).

Role of Neutrophils in Immunity

Neutrophils constitute an important portion of the immune cells penetrating the tumor microenvironment. Well-known for the first line of defense against infections, it is now accepted that neutrophils also have an important role in numerous aspects of cancer biology (14). Many heterogeneous subsets of neutrophils are identified in tumors and in circulation. Evidence

obtained from various studies in recent years pointed the fact that tumor-associated neutrophils (TANs) present in the tumor microenvironment exhibit notable adaptive changes that are driven by various factors (15). However, the role of neutrophils in the tumor microenvironment with evidence for having both pro- and anti-tumor roles, remains controversial (16).

Neutrophils causing Cancer Metastasis

Neutrophils are the first to respond to any kind of infection and inflammation. Neutrophils by physically interacting with circulating tumor cells (CTCs) facilitates their binding to the endothelium (17). Nowadays, an elevated neutrophil-to-lymphocyte ratio is studied as a prognostic indicator of poor overall survival in cancer. NETs produced during inflammation may induce the awakening of dormant tumor cells (18). Cancer metastasis as studied in recent years have pointed the fact that in mouse models, metastasis is associated with the DNA component of NETs (NET-DNA) (19, 20, 21). Instead of all the interventions, the functional role and clinical importance of NET-DNA in metastasis in patients with cancer remain unclear. NETs are abundantly metastasised in the liver of patients with breast and colon cancers, and that serum NETs can predict breast cancer in early stages. (22). NET-DNA acts as a chemotactic factor that attract cancer cells. It is identified that the transmembrane protein CCDC25 as a NET-DNA receptor on cancer cells senses extracellular DNA and subsequently activates the ILK–β-parvin pathway to enhance cell motility. NET-mediated metastasis is abrogated in CCDC25-knockout cells (23).

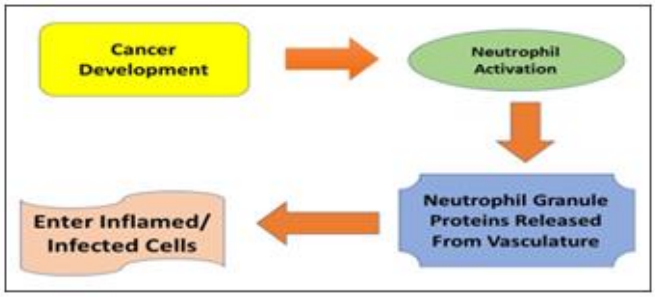

Figure 1

Role of TMEs

Tumor microenvironment (TME) is a complex system where myeloid cells play important roles in developing cancer from tumor initiation to metastasis. Immune cells are prime factors of the formation of tumor microenvironment where they promote and inhibit cancer formation and development. Plasticity is a widely accepted hallmark of myeloid cells and of the monocyte–macrophage lineage. It displays a wide range of activation states in response to distinct signals as well as classical M1 or alternative M2 macrophages represent this feature. Neutrophils are considered as terminally differentiated effector cells for many years, as they play a major role during the acute phase of inflammation and resistance against microbes (24). In many solid tumor types, tumor-associated macrophages (TAMs) are important components of the tumor microenvironment (TME) (25). TAMs by producing cytokines and growth factors create an immunosuppressive microenvironment that inhibit proteins in immune checkpoints facilitating the cascade of metastasis. Thus, TAMs crosstalk with other factors producing TME to develop multiple steps of metastasis like- (a) Invasion in primary site (b) Intravasation in vasculature (c) Extravasation outside the vasculature (d) Adaptation and growth of the metastatic sites etc. (26).

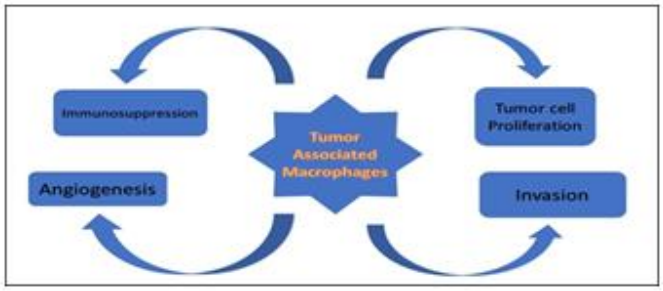

Figure 2

Conclusion

Obtained results suggests that neutrophils, that act as the primary defense during infections, promote cancer metastasis.

References

1. Wu M. et.al., Neutrophil: A New Player in Metastatic Cancers: Front Immunol. 2020 11; 565165.

2. Wang et.al, The role of neutrophil extracellular traps in cancer metastasis: Clin Transl Med. 2020: 10(6); e126

3. Sagiv JY et al., Phenotypic diversity and plasticity in circulating neutrophil sub populations in cancer: Cell Rep. 2015: 10 (5); 62–73.

4. Lartigue J.C et.al., Neutrophil extracellular traps in cancer progression: Cellular and Molecular Life Sciences. 2014: (71); 4179–4194

5. Kessenbrock K et al., Proteinase 3 and neutrophil elastase enhance inflammation in mice by inactivating anti-inflammatory progranulin:
J Clin Invest. 2008: 118; (24) 38–47

6. Zhang D, et al., Neutrophil ageing is regulated by the microbiome: Nature. 2015: (32); 525-528.

7. Nywening TM, et al., Targeting both tumours associated CXCR2(+) neutrophils and CCR2(+) macro phages disrupts myeloid recruitment and improves chemotherapeutic responses in pancreatic ductal adeno carcinoma. Gut. 2018 :(67); 1112–23.

8. Snoderly et.al., Neutrophil extracellular traps in breast cancer and beyond: current perspectives on NET stimuli, thrombosis and metastasis, and clinical utility for diagnosis and treatment. Breast Cancer Res. 2019; 21(1):145

9. Mohanty T et al., Neutrophil extracellular traps in the central nervous system hinder bacterial clearance during pneumococcal meningitis. Nat Common. 2019:10 (1);1667.

10. Duc roux C et al., Thrombus neutrophil extracellular traps content impair tpa-induced thrombolysis in acute ischemic stroke. Stroke. 2018: 49 (3); 754-757.

11. Masucci M.T et.al., Tumor Associated Neutrophils. Their Role in Tumorigenesis, Metastasis, Prognosis and Therapy. Front. Oncol: 2019

12. Gregory AD et.al., Tumor-associated neutrophils: new targets for cancer therapy. Cancer Res. 2011: 71(2411–6).

13. Eruslanov EB et.al., Mouse versus human neutrophils in cancer: a major knowledge gap. Trends Cancer. 2017: 3; 149–160.

14. Retamozo V.C et.al., Origins of tumor-associated macrophages and neutrophils. PNAS. 2012: 109 (7); 2491-2496.

15. Gregory D.A et.al., Tumor-Associated Neutrophils: New Targets for Cancer Therapy. Cancer Res. 2011: 71(7); 2411–6.

16. Powell D.R et.al., Neutrophils in the Tumor Micro environment. Trends in Immunology. 2016: 3 (1); 41-52.

17. Faustino Mollinedo, Neutrophil Degranulation, Plasticity, and Cancer Metastasis. Trends in Immunology. 2019: 40 (3); 228-242.

18. Brinkmann, V. et al. Neutrophil extracellular traps kill bacteria. Science. 2004: 303, 1532–1535.

19. McDonald B. et.al., Intravascular neutrophil extracellular traps capture bacteria from the bloodstream during sepsis. Cell Host Microbe. 2012: 12; 324–333.

20. Fuchs T. A. et al., Novel cell death program leads to neutrophil extracellular traps. J. Cell Biol. 2007: 176; 231–241.

21. Cools-Lartigue, J. et al. Neutrophil extracellular traps sequester circulating tumor cells and promote metastasis. J. Clin. Invest. 2013: 123; 3446–3458.

22. Cedervall, J., Zhang, Y. & Olsson, A. K. Tumor-induced NETosis as a risk factor for metastasis and organ failure. Cancer Res. 2016: 76; 4311–4315.

23. Park, J. et al. Cancer cells induce metastasis-supporting neutrophil extracellular DNA traps. Sci. Transl. Med. 2016: 8; 31-36.

24. Galdiero M.R. et.al., Tumor associated macrophages and neutrophils in cancer. Immunobiology. 2013: 218(11); 1402-1410.

25. Chen, Y., Song, Y., Du, W. et al. Tumor-associated macrophages: an accomplice in solid tumor progression. J Biomed Sci 26. 2019: 78.

26. Lin, Y., Xu, J. & Lan, H. Tumor-associated macrophages in tumor metastasis: biological roles and clinical therapeutic applications. J Hematol Oncol 12. 2019:76.