

# The reciprocal interaction between neutrophil extracellular traps and cancer

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Sharma D. The reciprocal interaction between neutrophil extracellular traps and cancer. *J Cancer Metastasis Res.* 2023; 5(2):75-77.

## ABSTRACT

Major immune system regulators and effectors are neutrophils. They are crucial in the development and spread of cancer as well as the eradication of infections. On the other hand, neutrophil activity, development, and lifespan are impacted by the presence of cancer. Cancer cells take advantage of neutrophil biology by enhancing or suppressing vital neutrophil functions. One notable neutrophil pathogen defense mechanism that has been co-opted in this process is the creation of Neutrophil Extracellular Traps (NETs). NETs are filamentous extracellular web-like

structures made of DNA, histones, and proteins produced from cytotoxic granules. Here, we talk about the reciprocal interactions between cancer and NETs, which promote the development of the disease. We examine how an increased risk of cardiovascular death is induced by vascular dysfunction and thrombosis brought on by neutrophils and NETs. Heart problems in cancer patients. Finally, we suggest potential therapeutic approaches for fighting NETs in a clinical environment.

**Key Words:** *Cancer NETs; Neutrophils metastasis; Extracellular; Neutrophil tumor*

## INTRODUCTION

The mechanisms behind the multi-step carcinogenesis process can be reduced to a logical framework involving the acquisition of functional abilities, the so-called cancer hallmarks, which are collectively believed to be required for malignancy. These capacities are communicated by a few aberrant features of the malignant phenotype, which are present in both transformed cancer cells and the heterotypic accessory cells that collectively make up the Tumor Microenvironment (TME). This viewpoint examines the relationship between the nervous system and the induction of distinctive skills, exposing neurons and neuronal axons as distinctive ability-inducing components of the TME. We also go over the autocrine and paracrine neuronal regulatory pathways that may be a distinguishing "enabling" trait promoting the expression of signature functions and that are aberrantly activated in cancer cells cancer pathogenesis as a result [1-3].

The characteristics of cancer serve as a theoretical framework that has been consistently useful in explaining the enormous complexity of cancer and its underlying mechanisms. The eight acquired functional abilities that make up the hallmarks of the theory are combined with two "enabling characteristics," or neoplastic state anomalies, to form the heart of the idea. Maintaining proliferative signaling, dodging

growth inhibitors, resisting cell death, enabling replicative immortality, initiating or accessing vasculature, activating invasion and metastasis, deregulating cellular metabolism, and avoiding immune destruction are among the key hallmark skills. Instability and mutations in the cancer cells' genomes, as well as tumor-promoting inflammation, primarily by cells of the innate immune system, are the two well-validated aberrant aspects of the disease state that, in different ways, permit their acquisition. The bar for inclusion of these 10 factors was that each had broad applicability throughout the spectrum of human cancer types and subtypes rather than being selectively restricted to one or a few. While the basic idea still makes sense, there is mounting evidence that additional, possibly generalizable parameters are significant and difficult to classify within the confines of the 10 core signature parameters. Senescent cells in the tumor microenvironment, polymorphic microbiomes, non-mutational epigenetic reprogramming, and phenotypic plasticity have recently been raised as temporary criteria to encourage discussion, experimentation, and debate. The interaction between malignancies and the neurological system is a fascinating biomedical area that is not highlighted. This connection and its numerous dimensions are being supported by more and more experimental data, which ranges from, ranging from local remodeling of tissue innervation by tumors

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Received: 08-May-2023, Manuscript No. Pulcmr-23-6266; Editor assigned: 09-May-2023, PreQC No. Pulcmr-23-6266; Reviewed: 20-May-2023, QC No. Pulcmr-23-6266; Revised: 24-May-2023, Manuscript No. Pulcmr-23-6266; Published: 28-May-2023, DOI: 10.37532/pulcmr-2023.5(2).75-77



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to modulatory effects of the nervous system on tumor phenotypes, topics that have been extensively reviewed. These effects range from systemic effects of tumors on the functionality of the nervous system (e.g., cachexia, cognitive impairment, sleep disruptions) to local remodeling of tissue innervation by tumors. The growing understanding that connections between the nervous system and developing cancers at both the cellular and molecular levels can facilitate the acquisition of hallmark capabilities, which is the theme of this perspective, has not been a specific focus of such perspectives on cancer neuroscience[4].

### **Influence of neurons and innervation on the development of distinctive skills**

In addition to supporting bodily activities like movement and sensation, the nervous system also heavily arborizes throughout the body, innervating niches for tissue stem cells that control the growth, homeostasis, and regeneration of many organs and tissues. Therefore, it is not surprising that the neurological system influences cancer phenotypes in a similar manner, frequently by co-opting neural systems that play similar roles in healthy tissues. Here, we'll look at a few instances that show how innervation affects the development of several trademark skills. The three main categories of peripheral innervation are the motor, sensory, and autonomic (including sympathetic and parasympathetic) nerves. Multiple hallmarks of cancer are enabled by signaling between innervation (distant neurons' axonal projections, orange/yellow) and cancer cells, and the reciprocal effects of cancer cells on the nervous system lead to the remodeling of neural form and function, which increases the effects of neurons on cancer pathophysiology. Glutamatergic neuronal activity stimulates proliferative signaling through paracrine mitogens secreted both from neurons and from other stromal cells in a neuronal activity-dependent manner in various CNS cancers, including glioblastoma, diffuse intrinsic pontine glioma, and optic pathway glioma. Neuronal activity has been shown to strongly promote cancer cell proliferation and tumor growth using optogenetic stimulation of neuronal activity in patient-derived high-grade glioma models<sup>10</sup> or Genetically Engineered Mouse Models (GEMMs) of Neurofibromatosis type 1 (NF1)-associated low-grade optic pathway glioma. Cancer cell proliferation is markedly increased when neurons and glioma cells are co-cultured, which can be largely attributed to the actions of paracrine secreted factors: Glioma cell proliferation is accelerated when cultivated glioma cells are exposed to conditioned media made from either cortical explants or retinal + optic nerve explants. through activity-regulated, mitogenic paracrine substances such the postsynaptic adhesion protein neuroligin-3 and neurotrophin Brain-Derived Neurotrophic Factor (BDNF) (NLGN3). In a manner controlled by activity, NLGN3 is secreted from the cell surfaces of neurons and oligodendrocyte precursor cells (brain stromal cells), which induces PI3K-mTOR and other oncogenic signaling pathways in glioma cells <sup>10</sup>. Exposure to NLGN3 in the TME also increases NLGN3 expression and excretion by the glioma cells, which promotes oncogenic signaling via both autocrine and paracrine processes. In addition to gliomas, NLGN3 has also been connected to the autocrine promotion of neuroblastoma growth, which is also aided by activating the PI3K-mTOR pathway[3-7].

Searches for mechanisms other than neuronal activity-regulated paracrine mitogens, which revealed functional relationships, were sparked by the dramatic effects of neuronal activity on glioma proliferation and growth. It was discovered that functional synaptic signaling between glutamatergic neurons and glioma cells via calcium-permeable AMPA receptors in both pediatric and adult forms of glioma caused depolarizing currents in the cancer cells. These findings were the result of a search for additional mechanisms beyond neuronal activity-regulated paracrine mitogens. Genetic blockade (glioma cell expression of a dominant-negative version of the GluA2 subunit of AMPA receptors) or by pharmacological blockade of AMPA receptors in neuron-glioma co-culture and in vivo, this genuine synaptic communication regulates glioma cell proliferation and growth. A second kind of neuron-to-glioma synapse has been discovered in the aforementioned pontine glioma, involving GABAergic interneurons and diffuse midline glioma cells expressing GABAA receptors. GABAergic synapses in diffuse midline gliomas resulted in membrane depolarization rather than hyper-polarization due to the elevated intracellular chloride concentration in cancer cells.<sup>16</sup> Membrane depolarization alone was adequate to enhance glioma growth, but the electrochemical current resulting from synaptic transmission was crucial to the proliferation-promoting mechanism.

This method exemplifies a fundamentally neurological type of communication that encourages the development of proliferative signaling, a crucial cancer characteristic. Both BDNF and NLGN3, in addition to serving as mitogens, enhance neuron-to-glioma synaptogenesis, demonstrating a relationship between the paracrine and synaptic mechanisms of neuronal activity-regulated glioma formation. Furthermore, primary brain tumors are not the only places where such electrochemical signaling occurs. In order to activate glutamatergic NMDA receptors, breast cancer metastases to the brain imitate astrocytes in pseudo-tripartite synapses.

### **CONCLUSION**

Brain activity involving neurons TME thus encourages the characteristic of maintaining proliferative signaling via neuron-to-cancer synaptic communication, a classically neuronal method, as well as paracrine signaling mechanisms that activate oncogenic pathways like PI3K-mTOR.

### **DATA SHARING AGREEMENT**

The data presented in this study are available on request.

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