WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

NEUTROPHILS AND TUMOR ANGIOGENESIS IN CANCER: A DOUBLE-EDGED SWORD

Dr. MIYASA MOIDU C K[1], MARIYAM AZMEENA[2]

MALIK DEENAR COLLEGE OF PHARMACY, SEETHANGOLI, P/O BELA, 671321

ABSTRACT :

Angiogenesis, or the formation of new blood vessels, is a crucial biological process in tumor growth and metastasis. Historically, anti-angiogenic therapies have focused on the vascular endothelial growth factor (VEGF) pathway, but recently it has been established that tumor-associated neutrophils (TANs) are a key player in the regulation of angiogenesis in tumors. TANs positively regulate angiogenesis, which occurs via the release of pro-angiogenic factors and deposition of neutrophil extracellular traps (NETs), both directly support tumor vascularization and promote immune evasion. Regardless of having recently improved anti-VEGF therapies, resistance to anti-angiogenic therapies is common since these other mechanisms of vascularization and immune-vascular interactions always exist. This review will outline recent findings regarding the roles of neutrophils and NETs in angiogenesis, and implications for therapies and metastatic resistance mechanisms to anti- angiogenic treatment in cancer.

1. Introduction

Angiogenesis, or the formation of new blood vessels from the pre-existing vasculature, is an important process in various physiological functions such as wound healing. In pathological states like cancer, it assures the supply of oxygen and nutrients for an unchecked proliferation of cells. Plant metastasis involves the migration of cancer cells through the newly formed vasculature. Traditionally, the VEGF has always been considered the major player in tumor-induced angiogenesis; however, new evidence suggests that immune cells, mainly neutrophils, are vital for the initiation and the maintenance of angiogenesis in tumors [1,2]. This review, therefore, sheds light on how our understanding of neutrophil involvement in angiogenesis has progressed and the implications of therapeutic resistance to anti-angiogenic drugs.

2. Neutrophils as Key Modulators of Tumor Angiogenesis

2.1 Tumor-Associated Neutrophils (TANs)

Neutrophils, the most abundant type of circulating white blood cells, have traditionally been regarded as part of the body's innate immune defense. However, in cancer, they undergo functional reprogramming and become tumor-associated neutrophils (TANs), exhibiting pro-tumoral properties. TANs can promote tumor progression through multiple pathways, including immune suppression, matrix remodeling, and angiogenesis [3,4]. TANs secrete a variety of pro-angiogenic factors such as VEGF, MMP-9, and Bv8 (prokineticin 2), which enhance endothelial cell proliferation and vascular permeability. Moreover, these cells interact with other immune and stromal components to reinforce the "angiogenic switch"—a phase in tumor development where pro-angiogenic signals dominate [10].

2.2 Neutrophil-Derived Angiogenic Factors

Once activated, neutrophil granules secrete both the conventional and unconventional angiogenic mediators. Conventional angiogenic factors are VEGF-A, the fibroblast growth factors (FGFs), and angiopoietin-1 (ANGPT1), all of which are required for endothelial cell survival, proliferation, and permeability of the vessels. Non-conventional angiogenic mediators like elastase and cathepsin G degrade the extracellular matrix and thus help endothelial cells in migrating during vessel genesis [1,5].

Neutrophils may thus have an indirect influence on angiogenesis by attracting adjunct immune cells or activating the endothelial progenitor cells (EPCs) themselves in building the vascular network into tumors. These reports sustain that neutrophils exist not only as immune effectors but also as principal orchestrating elements of vascular dynamics within the tumor microenvironment [6,8].

3. Neutrophil Extracellular Traps (NETs) and Angiogenesis

Neutrophil extracellular traps (NETs) are web-like complexes of DNA and protein that can be released by neutrophils in response to stimuli such as inflammation, hypoxia, or signals derived from tumors. NETs were first noted as a mechanism for trapping pathogens, but they are now known to play a role in tumor growth and angiogenesis. NETs can aid in angiogenesis by acting as a scaffold for pro-angiogenic factors [2]. Additional, NETs contain many pro-angiogenic factors such as VEGF, MMP-9, and CXCL8 that enhance endothelial cell proliferation and migration. Interestingly, NETs can aid in tumor immunity by protecting cancer cells from cytotoxic T cells and NK cells [4].

4. Anti-Angiogenic Therapy: Focus on VEGF Inhibition

4.1 VEGF-Targeted Drugs

Bevacizumab, a monoclonal antibody directed against VEGF-A, was among the earliest antiangiogenic agents approved for clinical use. It binds and neutralizes VEGF inhibiting activation of endothelial cells to form new blood vessels. Other inhibitors of VEGF pathway signaling include TKIs such as sunitinib and sorafenib that prevent downstream actions of VEGF receptors. So far, these drugs have been used successfully in colorectal cancer, renal cell carcinoma, and glioblastoma treatments. The treatment results are often pleasing on the outset; however, the long-term control becomes challenging due to adaptive resistance mechanisms [5,7].

4.2 Resistance Mechanisms

There are multiple mechanisms through which tumors escape VEGF-targeted therapy:

- Epigenetic Adaptations: Cancer and endothelial cells go through an epigenetic change that renders them resistant to VEGF blockade [5].
- Alternative Pathways to Vascularization: Tumors may employ vasculogenic mimicry, vascular co-option, or intussusceptive microvascular growth (IMG) to remain independent of VEGF [7].
- Immune-Vascular Crosstalk: The dualism between angiogenesis and immune suppression, in particular involving TANs and NETs, may essentially negate VEGF inhibition therapy [2,10].

This highlights the need to consider the anti-angiogenic therapies aside from VEGF-targeting ones.

5. Therapeutic Implications and Future Directions

5.1 Targeting Neutrophils and NETs

To combat resistance, researchers are studying drugs that:

- Degrade NETs (i.e., DNase I)
- Inhibit NET formation (i.e., PAD4 inhibitors)
- Block neutrophil recruitment (i.e., CXCR2 antagonists) [4,9]

These might influence both angiogenesis and immunosuppression.

5.2 Personalized and Combination Therapies

Combating individual treatment in many patients has shifted advances in combination therapies. For instance, immune checkpoint inhibitors (ICIs) have combined with anti-angiogenic agents to have a synergistic effect, overcoming immune resistance and restoring vascular normalization. "Pan-omics" approaches (genomics, transcriptomics, proteomics) are also being explored to identify predictive biomarkers that tell us how patients will respond to therapy.

6. Conclusion

The pro-angiogenic mediators released from neutrophils along with the formation of NETs constitute processes critical to tumor angiogenesis. While VEGF inhibitors remain central in the anti-angiogenic arsenal, their limitations and resistance mechanisms warrant a wider set of options [1]. A thorough understanding of neutrophil biology, NETs, and the tumor microenvironment may eventually lead to the development of newer and more lasting cancer therapies. Angiogenesis blockade at the molecular, cellular, and immunological levels could prove a great boon to affected individuals [9].

REFERENCES

1. Allen E, Jabouille A, Rivera LB, Lodewijckx I, Missiaen R, Steri V, et al. Combined antiangiogenic and anti–PD-L1 therapy stimulates tumor immunity through HEV formation. Science translational medicine [Internet]. 2017 Apr 12 [cited 2021 Jan 13];9(385). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5554432/
2. Cools-Lartigue J, Spicer J, McDonald B, Gowing S, Chow S, Giannias B, et al. Neutrophil extracellular traps sequester circulating tumor cells and promote metastasis. Journal of Clinical Investigation. 2013 Jul 1;123(8):3446–58.
3. Fridlender ZG, Sun J, Kim S, Kapoor V, Cheng G, Ling L, et al. Polarization of tumor-associated neutrophil phenotype by TGF-beta: "N1" versus "N2" TAN. Cancer cell [Internet]. 2009 [cited 2019 Dec 6];16(3):183–94. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19732719/ 1.
4. Demers M, Krause DS, Schatzberg D, Martinod K, Voorhees JR, Fuchs TA, et al. Cancers predispose neutrophils to release extracellular DNA traps that contribute to cancer-associated thrombosis. Proceedings of the National Academy of Sciences. 2012 Jul 23;109(32):13076–81.
5. Ferrara N, Adamis AP. Ten years of anti-vascular endothelial growth factor therapy. Nature Reviews Drug Discovery. 2016 Jan 18;15(6):385–403.
6. Mantovani A, Cassatella MA, Costantini C, Jaillon S. Neutrophils in the activation and regulation of innate and adaptive immunity. Nature Reviews Immunology [Internet]. 2011 Aug 1;11(8):519–31. Available from: https://www.nature.com/articles/nri3024#ref-CR43
7. Kerbel RS. Reappraising antiangiogenic therapy for breast cancer. The Breast. 2011 Oct 1;20:S56–60.
8. Massena S, Christoffersson G, Vågesjö E, Seignez C, Gustafsson K, Binet F, et al. Identification and characterization of VEGF-A–responsive neutrophils expressing CD49d, VEGFR1, and CXCR4 in mice and humans. Blood. 2015 Oct 22;126(17):2016–26.
9. Carmeliet, P. and Jain, R.K., 2011. Molecular mechanisms and clinical applications of angiogenesis. *Nature*, 473(7347), pp.298–307.
10. Ozel, I., Duerig, I., Domnich, M., et al., 2022. The Good, the Bad, and the Ugly: Neutrophils, Angiogenesis, and Cancer. *Cancers*, 14(3), p.536.