Current Trends in Biomedical Engineering & Biosciences
ISSN: 2572-1151

Juniper Publishers
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Mini Review
Volume 21 Issue 2 - February 2023
DOI: 10.19080/CTBEB.2023.21.556059

Curr Trends Biomedical Eng & Biosci

Tumor Associated Neutrophil Polarization and its Potential Effects in Cancer Therapy

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Submission: January 24, 2023; **Published:** February 13, 2023

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Abstract

Neutrophils are the first line of defense against pathogens in the immune system, and also has important implications for the tumor micro-environment. The effect of neutrophils on cancer is a double-edged sword in that they can both promote or inhibit tumor growth. When in different tumor environments or exposed to different stimulation, neutrophils would polarize toward anti-tumorigenic N1 or pro-tumorigenic N2 phenotype. The exact mechanism to polarize N1 and N2 are not yet well understood, but it is currently known that IFN-β or stimulation of the pathogen-associated molecular patterns (PAMPs) pathway can cause N1 polarization. On the contrary, in the presence of TGF-β or IL-10, N2 polarization occurs. When N1 population is dominant in the tumor micro-environment, they will inhibit tumor growth and enhance the effect of immunotherapy. But vice versa, dominance of pro-tumorigenic N2 phenotype within the tumor would enhance inflammation leading to more aggressive tumor growth and also hinders the effect of immunotherapy. Therefore, it is very important to understand the subtype of tumor associated neutrophils in the tumor when determining appropriate cancer therapy.

Keywords: TAN; Tumor Associated Neutrophil; Neutrophil; Cancer Therapy; Immune Checkpoint Inhibitor

Abbreviations: CXCR2: C-X-C Motif Chemokine Receptor 2; G-CSF: Granulocyte Colony Stimulating Factor; HVJ-E: Inactivated Hemagglutinating Virus of Japan Envelope; (IFN-β): Interferon- β; (IFN-γ): Interferon-γ; LPS: Lipopolysaccharide; IL-10: Interleukin 10; MMP-9: Matrix Metalloproteinase 9; OS: Median Overall Survival; PAMPs: Pathogen-associated Molecular Patterns; PGE2: Prostaglandin E2; RIG-I: Retinoic Acid-inducible Gene I; RFS: Recurrence-Free Survival; TANs: Tumor Associated Neutrophils; TGF-β: Transforming Growth Factor-β; VEGF: Vascular Endothelial Growth Factor

Introduction

In recent years, with the advancement of medical research, the importance of the tumor micro-environment is gaining much attention. The tumor environment is regulated by different immune cells, which commonly have dichotomic functions and evasive, thus making tumor treatment more complicated [1]. Neutrophils are one of the tumor associated immune cells, which are amongst the first lines of defense in immunity [2]. In order to target pathogens, neutrophils utilize cell surface C-X-C motif chemokine receptor 2 (CXCR2) to detect the C-X-C motif chemokines released from infected or inflamed sites and move into the affected site [3]. Tumors are often accompanied by an inflammatory response and release chemokines, following which neutrophils would be recruited to tumor site. These tumor infiltrated neutrophils are called tumor associated neutrophils (TANs). And depending on the inflammatory factors or external therapeutic factors in the tumor site, TAN will polarize into two different subtypes: 1) anti-tumor subtype N1 neutrophils or 2) pro-tumor N2 neutrophils [4]. These TANs often affect cancer treatment, recurrence, metastasis and immune therapy resistance in cancer patients. Therefore, it is very important to understand the TAN polarization mechanism and function. In this article, we will discuss TAN polarization, properties and the effect on cancer therapy.

Discussion

TAN polarization

Unfortunately, the detailed conditions to N1/N2 polarization within tumors remain largely unclear. However, neutrophils are highly plastic and can adapt their functionality to the environment or stimulation. In recent years, increasingly more studies have proposed that N1/N2 polarization can be mediated by immune-stimulatory molecules or inflammatory factors, both in vivo and in vitro. An in vivo mouse tumor model showed transforming growth factor-β (TGF-β) play an important role in N2 polarization [5]. In this work, TGF-β inhibition suppressed tumor growth and decreased N2 population. In contrast, N1 polarization can be

regulated by interferon-β (IFN-β). Another research showed that IFN-β treatment altered TAN polarization towards anti-tumor N1 in the mouse model, as well as in clinically in type-I IFN therapy treated melanoma patients [6]. Our previous study has showed that inactive virus therapy(inactivated Hemagglutinating virus of japan envelope (HVJ-E)) treatment can cause N1 population to be dominant in the tumor site, and can also directly stimulate neutrophils to become N1 in an in vitro model [7]. Viral nucleic acid stimulated retinoic acid-inducible gene I (RIG-I) after fusion between virus and neutrophil cell and induced N1 polarization. In addition to this, another previous study proposed that a cocktail of immune-stimulatory molecules or inflammatory factors could artificially polarize neutrophils. They showed that lipopolysaccharide (LPS), IFN-α and IFN-β in combination can induce N1 polarization, while a cocktail of TGF-β, Interleukin 10 (IL-10), Prostaglandin E2 (PGE2), granulocyte colony stimulating factor (G-CSF), L-lactate and adenosine could induce N2 polarization [8]. Hence, although N1/N2 polarization is still not well understood, the above-mentioned studies showed the possible applications of artificial methods to polarize N1/N2 in vivo and in vitro.

Properties of TANs

Like other tumor associated immune cells, N1/N2 neutrophils have their own characteristics. The neutrophil nucleus plays a key role in differentiation processes and the nuclei shape showed different morphology with varying stages of neutrophil activation. In addition, N1 and N2 neutrophils possess different cell surface receptors and produce different secreted factors [9]. The N1 neutrophil nucleus is segmented shape, and has increased expression of intercellular adhesion molecule 1 (ICAM-1). In addition, in order to facilitate anti-tumor effect, death receptor Fas expression would increase, along with secretion of inflammatory factors such as TNF-β and IFN-β. In contrast, N2 neutrophils have ring-shaped nuclei, increased CXCR4 expression to increase neutrophil life span, secretes vascular endothelial growth factor (VEGF) to promote angiogenesis, and matrix metalloproteinase 9 (MMP-9) to breakdown the extracellular matrix, all of which contributes to enhance tumor invasion and metastasis.

Effects on cancer therapy

Recent research indicates that the TAN ratio is very important in cancer treatment. The N1/N2 ratio can be used as a predictive indicator for median overall survival (OS) and recurrence-free survival (RFS) of cancer patients. Pancreatic ductal adenocarcinoma patients with high N1 neutrophils had significantly longer OS and RFS than those with low N1 [10]. Besides expected patient survival, TANs also play a very important part in cancer immunotherapy. A previous study had pointed out that tumor angiogenesis causes TAN infiltration which led to increase in immune checkpoint inhibitor (ICI) resistance of tumor [11]. TAN infiltration into the tumor will be polarized into N2 neutrophils due to the tumor environment, N2 neutrophils would release the CC chemokine ligand 17 (CCL17) which increases the presence of regulatory T cells in the tumor. Eventually, the tumor would attract and accumulate increasingly more immune-suppressive cells into the tumor and weakens the effectiveness of ICI therapy. Therefore, when ICI therapy is combined with angiogenesis inhibitory drugs, this reduces the infiltration of TAN into the tumor by inhibiting angiogenesis and can potentially improve the effect of ICI therapy. In other studies, similar findings have also been mentioned [12]. Such as the use of neutrophil depletion to remove neutrophils in tumors could improve the effect of anti-PD-1 antibody therapy. In addition to reducing TAN in the tumor site, our previous work demonstrated that increasing intra-tumoral N1 TANs could relieve ICI resistance [13]. When inactivated virus particles HVJ-E were treated to 4T1 tumor, inactivated virus particles will fuse with neutrophils to stimulate N1 polarization. Our results showed that the usually anti-PD-1 antibody therapy resistant 4T1 mouse mammary cancer cell line transplanted model can be made to be receptible to ICI therapy after neutrophil depletion. Our research also showed the possibility that administration of nucleic acid drugs by intracellular drug delivery methods such as electroporation or needle-free injectors [14] may improve the therapeutic effect by stimulating the RIG-I immune pathway in cells and influencing the ratio of TANs.

Conclusion

Neutrophils, which are the first line of defense of the immune system and are present in large numbers in the peripheral blood. Hence, they are easily recruited to the tumors and become TANs. Depending on the specific stimulation and the tumor micro-environment, TANs would polarize into N1 anti-tumor or N2 pro-tumor neutrophils. The resultant N1/N2 ratio in the tumor will affect the OS and RFS of cancer patients and would also correlate with resistance to ICI. Therefore, increasing the proportion of N1 or reducing the proportion of N2 would increase the ratio of N1/N2 in the tumor site which could potentially relieve ICI therapy resistance. The intra-tumoral N2 population can be decreased by angiogenesis suppression drugs, while immune-stimulatory molecules such as inactivated viral molecules could increase N1 population in tumor sites. Although the differentiation of N1/N2 is still not well understood, it has been possible to artificially differentiate N1 or N2 cells in vivo and in vitro.

Acknowledgement

The funding was supported by Osaka University Collaborative Research Funding (J200701803).

References

1. Baghban R, Roshangar L, Esfahlan JR, Seidi K, Kalan EA, et al. (2020) Tumor microenvironment complexity and therapeutic implications at a glance. Cell Communication and Signaling 18: 59.

How to cite this article: Chin Yang Chang and Jiayu A Tai. Tumor Associated Neutrophil Polarization and its Potential Effects in Cancer Therapy. Curr Trends Biomedical Eng & Biosci. 2023; 21(2): 556059. DOI: 10.19080/CTBEB.2023.21.556059

2. Kraus RF, Gruber MA (2021) Neutrophils-From Bone Marrow to First-Line Defense of the Innate Immune System, Frontiers in immunology 12: 767175

3. Masucci MT, Minopoli M, Carriero MV (2019) Tumor Associated Neutrophils. Their Role in Tumorigenesis, Metastasis, Prognosis and Therapy. Frontiers in oncology 9: 1146.

4. Fridlender ZG, Albelda SM (2012) Tumor-associated neutrophils: friend or foe. Carcinogenesis 33(5): 949-55.

5. Fridlender ZG, Sun J, Kim S, Kapoor V, Cheng G, et al. (2009) Polarization of tumor-associated neutrophil phenotype by TGF-beta: "N1" versus "N2" TAN. Cancer cell 16: 183-94.

6. Andzinski L, Kasnitz N, Stahnke S, Wu CF, Gereke M et al. (2016) I IFNs induce anti-tumor polarization of tumor associated neutrophils in mice and human. International journal of cancer 138(8): 1982-1993.

7. Chang CY, Tai JA, Li S, Nishikawa T, Kaneda Y (2016) Virus-stimulated neutrophils in the tumor microenvironment enhance T cell-mediated anti-tumor immunity 7(27): 42195-42207.

8. Ohms M, Moller S, Laskay T (2020) An Attempt to Polarize Human Neutrophils Toward N1 and N2 Phenotypes in vitro. Frontiers in immunology 11: 532.

9. Piccard H, Muschel RJ, Opdenakker G (2012) On the dual roles and polarized phenotypes of neutrophils in tumor development and progression.Critical Reviews in Oncology/Hematology 82: 296-309.

10. Chen Q, Yin H, Liu S, Shoucair S, Ding N, et al. (2022) Prognostic value of tumor-associated N1/N2 neutrophil plasticity in patients following radical resection of pancreas ductal adenocarcinoma. Journal for ImmunoTherapy of Cancer 10(12): e005798.

11. Faget J, Peters S, Quantin X, Meylan E, Bonnefoy N (2021) Neutrophils in the era of immune checkpoint blockade 9(7): e002242.

12. Wang PF, Zhang YX, Su J, Yao K, Li (2020) Neutrophil depletion enhances the therapeutic effect of PD-1 antibody on glioma 12(15): 15290-15301.

13. Pan YC, Nishikawa T, Chang CY, Tai JA, Kaneda Y (2021) CXCL2 combined with HVJ-E suppresses tumor growth and lung metastasis in breast cancer and enhances anti-PD-1 antibody therapy 20: 175-186.

14. Chang C, Sun J, Hayashi H, Suzuki A, Sakaguchi Y, et al. (2019) Stable Immune Response Induced by Intradermal DNA Vaccination by a Novel Needleless Pyro-Drive Jet Injector 21(1): 19.

DOI: 10.19080/CTBEB.2023.21.556059

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