COMMENTARY

Targeting Neutrophils in Pancreatic Cancer

Yi Jin, Keyu Li*

Department of Pancreatic Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China

DESCRIPTION

We recently published a review paper that comprehensively examines the critical role of neutrophils in the tumorigenesis and progression of Pancreatic Ductal Adenocarcinoma (PDAC) and their potential as novel therapeutic targets [1]. PDAC is characterized by four primary types of immune deficiencies: A paucity of high-quality T cells, such as CD8+ T cells; a formidable stromal barrier that impedes the infiltration of effector cells and therapeutic agents into the Tumor Microenvironment (TME); an immunosuppressive TME comprising suppressive cells and matrix; and the limited efficacy of immune checkpoint inhibition. Additionally, a single PDAC patient often exhibits multiple types of immune deficiencies, which may evolve during treatment [2]. Consequently, immunotherapy for PDAC patients necessitates a combined and individualized approach. In the context of neutrophils, immunotherapeutic strategies aim to enhance their activation, recruitment, and polarization to effectively reprogram the TME.

The article also highlights pancreatitis as a significant risk factor for PDAC. Neutrophils, as key effector cells in inflammation, are activated as part of the body's defense against inflammatory responses. However, excessive activation of neutrophils can inflict damage and increase cancer risk. For instance, targeting CCR2+ Tumor Associated Macrophages (TAMs) induces a compensatory influx of Tumor Associated Neutrophils (TANs), potentially undermining the intended therapeutic effect. In animal models, concurrent targeting of CXCR2+ TANs and CCR2+ TAMs has been shown to inhibit compensatory intramedullary flow, thereby inducing a more robust anti-tumor immune response.

The article summarizes critical factors for Tumor Associated Neutrophil (TAN) recruitment and corresponding targeted studies. For instance, prior research has indicated a correlation between elevated plasma levels of IL-8 and poorer prognosis (NCT02451982, unpublished data). The author's team demonstrated, for the first time, the efficacy of IL-8 targeted antibodies in enhancing the effectiveness of PD-1 checkpoint blockade in tumor treatment. Additionally, the CXCR1 and CXCR2 signaling pathways are major mechanisms for recruiting neutrophils and Myeloid Derived Suppressor Cells (MDSCs) into the TME, where they differentiate into TANs or Polymorphonuclear MDSCs (PMN-MDSCs). Consequently, CXCR1 and CXCR2 antagonists, such as ladarixin, have been evaluated as strategies to deplete the TME of immunosuppressive N2 TANs and PMN-MDSCs [3].

As noted in the article, TANs exhibit different polarization states, and specific factors can induce their transition from one state to another. Recent research demonstrated that localized release of SB52533, a TGF-β1 inhibitor, *via* nanoparticles could modulate TANs from a pro-tumor to an anti-tumor state, thereby enhancing the treatment response to combined irreversible electroporation and anti-PD-1 immunotherapy [4]. Furthermore, other therapies targeting TAN polarization, proven effective in other tumors, are also considered worthy of investigation in PDAC.

Extensive research has been conducted on the role and mechanisms of neutrophils in PDAC, encompassing numerous preclinical trials. In the article, the author also summarized clinical trials associated with TAN-targeted immunotherapy. It is evident that, compared to preclinical trials, the number of clinical trials is significantly lower, highlighting a substantial gap between preclinical and clinical research. Many studies struggle to transition seamlessly from animal experiments to clinical applications.

Several important clinical trials warrant attention. For instance, SX-682, an inhibitor of CXCR1 and CXCR2, has been shown to inhibit the transport of tumor MDSCs and enhance natural killer cell immunotherapy in head and neck cancer. Currently, it is being evaluated in combination with immune checkpoint inhibitors such as nivolumab

Received 07-Jun-2024 Manuscript No. IPP-24-20405 **Editor assigned** 11-Jun-2024 PreQC No. IPP-24-20405 (PQ) **Reviewed** 25-Jun-2024 QC No IPP-24-20405 **Revised** 02-Jul-2024 Manuscript No. IPP-24-20405 (R) **Published** 09-Jul-2024 DOI: 10.51268/1590-8577-24.S10.005

Correspondence Keyu Li

Department of Pancreatic Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China

E-mail colinlikeyu@qq.com

Citation: Jin Y, Li K. Targeting Neutrophils in Pancreatic Cancer. JOP. J Pancreas. (2024) 24:17- 18.

(NCT04477343) and tislelizumab (NCT05604560) in patients with metastatic and resectable PDAC. Additionally, AZD5069, a highly selective CXCR2 receptor small molecule antagonist, has been demonstrated to reduce TAN density in patients with metastatic castration-resistant prostate cancer. This compound is currently being tested in combination with durvalumab, an anti-PD-L1 monoclonal antibody, in patients with metastatic PDAC, although no results have been reported yet (NCT02583477). Plerixafor (AMD3100), the only FDA-approved CXCL12/CXCR4 antagonist, is undergoing a Phase 2 clinical trial to evaluate its safety and clinical activity in combination with cemiplimab (a PD-1 blocker) for the treatment of metastatic pancreatic cancer (NCT04177810). Although these studies have not yet produced definitive clinical outcomes, they provide a foundational basis for exploring neutrophil-targeted and combined immunotherapy in PDAC.

As previously mentioned, PDAC patients exhibit various types of immune deficiencies. The same type of immune deficiency may have different underlying causes in different patients, and most patients present with multiple types of deficiencies. Furthermore, the types of immune deficiencies can evolve during treatment. Consequently, treatment for PDAC patients is dynamic and complex, necessitating further investigation to develop effective, individualized therapeutic strategies [5].

In recent years, an increasing number of studies have revealed the significant role of neutrophils in the tumorigenesis, progression, and metastasis of PDAC, drawing considerable attention to the research on neutrophils in PDAC. Neutrophils exhibit unique plasticity and heterogeneity, enabling them to exert both anti-tumor and pro-tumor effects within tumors. Immunotherapy targeting neutrophils in PDAC represents a promising emerging field with substantial potential. It is important to note, however, that targeting neutrophils alone is unlikely to achieve sufficient anti-tumor activity. Therefore, combination immunotherapy should be the strategic approach for developing neutrophil-targeted therapies.

FUNDING

This manuscript was funded by a National Natural Science Foundation of China 82303740, a Key Research and Development Project of Science and Technology Department of Sichuan Province 2023YFS0167, and the Postdoctor Research Fund of West China Hospital Sichuan University 2023HXBH053.

REFERENCES

1. Jin Y, Christenson ES, Zheng L, Li K. Neutrophils in pancreatic ductal adenocarcinoma: Bridging preclinical insights to clinical prospects for improved therapeutic strategies. Expert Rev Clin Immunol. 2024. [PMID: 38690749]
2. Zheng L. Immune defects in pancreatic cancer. Ann Pancreat Cancer. 2018;1:33. [PMID: 30613834]
3. Piro G, Carbone C, Agostini A, Esposito A, De Pizzol M, Novelli R, et al. CXCR1/2 dual-inhibitor ladarixin reduces tumour burden and promotes immunotherapy response in pancreatic cancer. Br J Cancer. 2023;128(2):331-341. [PMID: 36385556]
4. Peng H, Shen J, Long X. Local release of TGF-β inhibitor modulates tumor associated neutrophils and enhances pancreatic cancer response to combined irreversible electroporation and immunotherapy. Adv Sci. 2022;9(10):2105240. [PMID: 35128843]
5. Hu ZI, O'Reilly EM. Therapeutic developments in pancreatic cancer. Nat Rev Gastroenterol Hepatol. 2023:1-8. [PMID: 37798442]

Citation: Jin Y, Li K. Targeting Neutrophils in Pancreatic Cancer. JOP. J Pancreas. (2024) 24:17-18.