Research & Reviews: Medical and Clinical Oncology

The Evolving Role of Eosinophils in Cancer Immunotherapy: Novel Insights and Therapeutic Potentials

Yong Chen, Yonggang Hu*

Department of Clinical Laboratory, People's Hospital, Luzhou, China

Review Article

Received: 04-May-2024, Manuscript No. MCO-24-134010; **Editor assigned:** 06-May-2024, Pre QC No. MCO-24-134010(PQ); **Reviewed:** 20-May-2024, QC No. MCO-24-134010; **Revised:** 27-May-2024, Manuscript No. MCO-24-134010(R); **Published:** 03-Jun-2024, DOI: 10.4172/medclinoncol.8.02.001.

***For Correspondence:**
Yonggang Hu, Department of Clinical Laboratory, People's Hospital, Luzhou, China

E-mail: maryam_inayat@live.com

Citation: Chen Y, et al. The Evolving Role of Eosinophils in Cancer Immunotherapy: Novel Insights and Therapeutic Potentials. 2024;08:001.

ABSTRACT

Recent research underscores the multifaceted roles of eosinophils in oncological contexts, highlighting their potential in cancer immunotherapy. This mini-review synthesizes findings from three pivotal studies, emphasizing eosinophils' dualistic nature in tumor suppression and immunological facilitation. By organizing immune responses and directly targeting tumor cells, eosinophils emerge as promising biomarkers and therapeutic targets in immuno-oncology.

Keywords: Eosinophils; Cancer immunotherapy; Tumor microenvironment; Immune modulation; Hematologic malignancies

INTRODUCTION

Eosinophils, traditionally viewed as key players in allergic reactions and parasitic infections, have recently garnered significant attention in the field of oncology [1, 2]. These immune cells, an integral part of the body's defense against diseases, are increasingly recognized not just for their roles in pathogen defense but also for their complex interactions within tumor microenvironments. Recent advancements in immunology and cancer biology have begun to unravel the dual roles of eosinophils as both promoters and inhibitors of tumor growth, underscoring their potential as targets in cancer therapy [3-6].

Historical perspective and biological function

Eosinophils are granulocytic cells that originate from the bone marrow and are primarily involved in the immune response against helminthic parasites and in the pathogenesis of allergic diseases [7].

They are equipped with granules containing potent cytotoxic proteins, such as Major Basic Protein (MBP) and Eosinophil Cationic Protein (ECP), which play critical roles in damaging parasitic worms and modulating inflammatory responses. Beyond these traditional roles, eosinophils are involved in a variety of biological functions including tissue remodeling, wound healing, and the modulation of immune responses.

Eosinophils in cancer research

The interest in eosinophils within cancer research has escalated due to their notable presence in various tumor types and their influence on tumor progression and immune surveillance. Eosinophils have been observed in the tumor microenvironments of cancers such as melanoma, colorectal, and breast cancers, where they appear to play complex and sometimes contradictory roles. In some contexts, they exhibit tumoricidal activities by directly inducing cancer cell apoptosis or by supporting the infiltration and activation of other immune cells, such as T-cells and Natural Killer (NK) cells, into the tumor mass [8,9].

Immunomodulatory roles

Eosinophils contribute to the shaping of the tumor microenvironment through the release of a variety of cytokines, chemokines, and growth factors. These mediators can recruit and activate other immune cells, enhance the antigen-presenting capabilities of dendritic cells, and influence the activation state of both innate and adaptive immune branches. This immunomodulatory capacity makes eosinophils significant players in the immune response against tumors and highlights their potential role in immunotherapy strategies.

Therapeutic implications

The potential therapeutic implications of modulating eosinophil activity in cancer are profound. Understanding how eosinophils can be manipulated to enhance their tumor-suppressive functions or to mitigate their tumor-promoting effects could open new avenues for cancer treatment. For instance, enhancing eosinophil recruitment and activation in tumors where they exert beneficial roles could improve the efficacy of existing therapies, including chemotherapy and immunotherapy.

Focus of this review

This review aims to delve deeper into the recent discoveries regarding the role of eosinophils in cancer. By examining their interactions within the tumor microenvironment and the subsequent effects on tumor progression and treatment responses, we seek to highlight potential strategies that could control or modulate eosinophil functions for therapeutic benefit. The following sections will explore the mechanisms by which eosinophils influence cancer development, their potential as biomarkers for cancer prognosis and treatment outcomes, and the emerging therapeutic strategies aimed at exploiting their unique biology.

LITERATURE REVIEW

Eosinophils are multifunctional leukocytes that display significant cytotoxic capabilities and contribute to the modulation of immune responses within the Tumor Microenvironment (TIME) [10]. These cells are not only involved in combating pathogens but have also emerged as key players in oncological settings, particularly in hematological malignancies and solid tumors. Their activities can be broadly categorized into direct and indirect mechanisms that either suppress or promote tumor growth.

Direct cytotoxic activities

Eosinophils can directly inhibit tumor growth through the release of cytotoxic granules containing Major Basic Protein (MBP), Eosinophil Peroxidase (EPO), Eosinophil-Derived Neurotoxin (EDN), and Eosinophil Cationic Protein (ECP). These granules have been shown to induce tumor cell apoptosis and disrupt tumor cell proliferation [8,9,11,12]. For example, studies have demonstrated that eosinophils infiltrate various tumor tissues such as non-small cell lung cancer, breast cancer, and colorectal cancer, where they can exert direct cytotoxic effects by inducing apoptosis and inhibiting tumor cell migration and invasion.

Moreover, in hematological disorders characterized by eosinophilia, such as certain subtypes of Hodgkin's and non-Hodgkin's lymphoma [13], eosinophils contribute to the pathology by facilitating tumor cell survival through their inflammatory mediators, which can paradoxically promote tumor growth. This dual role highlights the complex nature of eosinophil involvement in cancer, necessitating an exact understanding of their function to control their therapeutic potential effectively.

Modulation of the immune landscape

Indirectly, eosinophils shape the immune landscape of tumors by releasing cytokines and chemokines that attract other immune cells [14-17], particularly T-cells, to the tumor site. This recruitment is critical for mounting an effective anti-tumor immune response. Eosinophils express T-cell-attracting chemokines such as CCL5, CXCL9, and CXCL10, which enhance the infiltration and activation of $CD8^+$ T-cells within the tumor microenvironment. This process is vital for the establishment of a cellular immune response capable of targeting and eliminating tumor cells.

Eosinophils also interact with other components of the immune system to enhance immune surveillance and response [18]. For instance, they can function as Antigen-Presenting Cells (APCs) to T-cells, thereby facilitating the adaptive immune response against tumors. In addition, eosinophils have been shown to promote the maturation and function of Dendritic Cells (DCs), further bridging innate and adaptive immunity.

Furthermore, the presence of eosinophils in tumor tissues has been correlated with improved outcomes in several types of cancer treatments, including checkpoint inhibitor therapies [19]. This correlation suggests that eosinophils could serve as predictive biomarkers for immunotherapy responsiveness.

Eosinophils as therapeutic targets

Given their potent immunomodulatory and cytotoxic activities, targeting eosinophilic pathways presents a promising therapeutic avenue in cancer treatment. Strategies to enhance their tumor-suppressive functions or inhibit their tumor-promoting effects could significantly impact the efficacy of existing cancer therapies, including chemotherapy, radiotherapy, and especially immunotherapy. Understanding the triggers and regulators of eosinophil activity within the tumor microenvironment could lead to novel approaches to manipulate these cells for therapeutic benefit.

In conclusion, the complex roles of eosinophils in cancer underscore their potential as targets for therapeutic intervention. By elucidating the mechanisms through which eosinophils influence cancer progression and immune responses, researchers can develop more effective strategies for cancer therapy that exploit the unique properties of these cells.

DISCUSSION

The role of eosinophils in cancer therapy is increasingly recognized as significant, not only for their direct cytotoxicity against tumor cells but also for their ability to modulate the immune microenvironment. This dual role facilitates a

more robust and targeted immune response against cancer cells, enhancing the overall efficacy of various cancer therapies, particularly immunotherapies.

Eosinophils exert direct cytotoxic effects through the release of granule proteins such as Eosinophil-Derived Neurotoxin (EDN), Eosinophil Cationic Protein (ECP), Major Basic Protein (MBP), and Eosinophil Peroxidase (EPO). These proteins can induce apoptosis or necrosis in tumor cells, disrupting their growth and proliferation. For instance, studies have shown that eosinophils can directly interact with tumor cells to induce cytotoxic effects that lead to tumor cell death [20, 21]. This direct interaction is facilitated by the eosinophils' ability to recognize tumor-specific antigens and respond by releasing their cytotoxic granule contents.

Indirectly, eosinophils contribute to shaping the tumor microenvironment by secreting a range of cytokines and chemokines that recruit and activate other immune cells [14,15,18], including T-cells, dendritic cells, and macrophages. This recruitment enhances the anti-tumor immune response and can significantly improve the effectiveness of immunotherapies. For example, the presence of eosinophils in tumor tissues has been correlated with increased infiltration of $CD8^+$ T-cells, which are critical for effective anti-tumor responses. Eosinophils also play a role in enhancing the antigen-presenting capabilities of dendritic cells, thus boosting the adaptive immune response.

The association of eosinophil presence with improved prognosis in various cancers such as melanoma, non-small cell lung cancer, and gastrointestinal cancers suggests their potential utility as biomarkers for predicting immunotherapeutic outcomes [5,6]. This correlation implies that higher levels of eosinophils in the tumor microenvironment could indicate a more active and potentially effective immune response against the tumor. Therefore, monitoring eosinophil levels could help in predicting patient responses to immunotherapy and potentially guide the customization of treatment plans.

The potential for targeting eosinophilic pathways to enhance cancer immunotherapy outcomes is a promising area of research. Strategies that could increase the recruitment and activation of eosinophils in the tumor microenvironment might amplify the immune system's natural anti-tumor response. Furthermore, understanding the regulatory mechanisms that control eosinophil activity could lead to novel therapeutic interventions. For instance, enhancing eosinophil survival in the tumor microenvironment or boosting their cytotoxic capacity could be beneficial for patients undergoing cancer treatment.

Future research should focus on delineating the specific conditions under which eosinophils exert beneficial versus detrimental effects on the tumor microenvironment. Additionally, exploring how eosinophils interact with other components of the immune system in the context of cancer can uncover new ways to manipulate these interactions for therapeutic benefit. Clinical trials specifically designed to assess the impact of enhancing eosinophil functions in cancer therapy could provide valuable insights and potentially open new avenues for the treatment of various cancers.

CONCLUSION

In conclusion, eosinophils hold significant potential in the domain of cancer therapy, both as direct effectors of tumor cell destruction and as modulators of the immune response. Controlling their capabilities could lead to more effective and targeted therapeutic strategies, ultimately improving patient outcomes in cancer treatment. Eosinophils are pivotal in the intersection of tumor biology and immunotherapy. Their ability to influence the tumor microenvironment and facilitate robust anti-tumor immune responses positions them as potential dual-function agents in cancer

therapy. Further exploration of eosinophilic functions could lead to novel therapeutic strategies that strengthen their unique capabilities to improve patient outcomes in cancer treatment.

AUTHOR CONTRIBUTIONS

Yong Chen and Yonggang Hu have jointly completed the initial draft and both approve the submission of the paper.

COMPETING INTERESTS

The authors state no conflict of interest.

RESEARCH FUNDING

None declared.

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