Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/18800
DOI URL: http://dx.doi.org/10.21474/IJAR01/18800

RESEARCH ARTICLE

IMMUNE-MICROENVIRONMENT DYNAMICS IN CANCER: IMPLICATIONS FOR IMMUNOTHERAPY

Perini Turupati[1], Manikanta Amanchi[1], Saikiran Udarapu[1], Pavani Durga Posa[1], Ishika Manohar Irkullawar[1], Jasvitha Boyapati[2], Abhinaya Sravani Kuchibhotla[2] and Santhi Priya Amarthaluri[3]

1. Department of Biomedical Engineering, University of North Texas, 3940 N Elm St, Denton, Texas, USA.
2. Department of Biotechnology, Koneru Lakshmaiah Education Foundation, Vaddeswaram, Guntur, Andhra Pradesh, India.
3. Department of Biotechnology, Sri Venkateshwara College of Pharmacy, Madhapur, Hyderabad, Telangana, India.

Manuscript Info

Manuscript History
Received: 28 March 2024
Final Accepted: 30 April 2024
Published: May 2024

Key words:-
Tumor Microenvironment, Cancer Immunotherapy, Immune Evasion, Immune Checkpoints, Immunosuppression, Personalized Medicine

Abstract

Understanding the intricate interplay between cancer cells and the immune microenvironment is crucial for advancing immunotherapy strategies. This review explores the intricate landscape of the TME, focusing on its diverse cellular and molecular components and their roles in immune evasion and immunotherapy response. The tumor microenvironment (TME) comprises a complex network of immune cells, stromal cells, and soluble factors that dynamically interact with cancer cells. This dynamic crosstalk shapes the tumor's immune landscape, influencing tumor progression, metastasis, and response to therapy. In recent years, immunotherapy has revolutionized cancer treatment by targeting immune checkpoints, enhancing immune cell activation, and modulating the TME. However, the heterogeneous nature of the TME and the evolving tumor-immune interactions pose challenges for effective immunotherapy. This review discusses the diverse cellular and molecular components of the TME, their roles in immune evasion, and the mechanisms underlying response or resistance to immunotherapy. Insights gained from unraveling the complexities of the TME hold promise for developing personalized immunotherapy approaches tailored to individual patients.

Introduction:-

Cancer remains one of the leading causes of morbidity and mortality worldwide, posing significant challenges to global health. Despite advances in traditional therapies such as surgery, chemotherapy, and radiotherapy, many cancer patients still face poor prognoses due to tumor recurrence, metastasis, and treatment resistance [1]. In recent years, the emergence of cancer immunotherapy has revolutionized the landscape of cancer treatment, offering new hope for patients by harnessing the power of the immune system to recognize and eliminate cancer cells [2]. However, the success of immunotherapy critically depends on understanding the dynamic interplay between cancer cells and the immune microenvironment (TME), a complex ecosystem that surrounds and supports tumor growth [3].The TME comprises a heterogeneous mixture of cancer cells, immune cells, stromal cells, and various soluble factors that collectively influence tumor progression, metastasis, and response to therapy. Among the immune cell

Corresponding Author:- Santhi Priya Amarthaluri
Address:- Department of Biotechnology, Sri Venkateshwara College of Pharmacy, Madhapur, Hyderabad, Telangana, India.

populations infiltrating the TME, T cells, macrophages, dendritic cells, and myeloid-derived suppressor cells (MDSCs) play crucial roles in shaping the tumor-immune landscape [4]. Tumor-infiltrating lymphocytes (TILs), particularly CD8+ cytotoxic T cells, are key effectors of antitumor immunity, capable of recognizing and eliminating cancer cells. However, the TME often exerts immunosuppressive effects, impairing T cell function and promoting tumor immune evasion [5].One of the hallmarks of the TME is the presence of immunosuppressive cell populations, including regulatory T cells (Tregs) and MDSCs, which suppress T cell activation and effector function within the TME [6]. Additionally, tumor-associated macrophages (TAMs), predominantly of the M2-like phenotype, exhibit protumoral functions, promoting tumor growth, angiogenesis, and metastasis. In recent years, cancer immunotherapy has emerged as a promising therapeutic approach for various malignancies, including melanoma, lung cancer, and renal cell carcinoma [7]. Immune checkpoint blockade therapy, which targets inhibitory checkpoints such as programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4), has demonstrated remarkable clinical efficacy in certain cancer types, leading to durable responses and improved survival outcomes for patients [8]. By blocking inhibitory checkpoints or activating costimulatory pathways, immune checkpoint blockade therapy enhances T cell activation and effector function, unleashing antitumor immunity and promoting tumor regression.Despite the success of immune checkpoint blockade therapy, many cancer patients exhibit primary or acquired resistance to treatment [9]. Several mechanisms contribute to immune resistance within the TME, including upregulation of alternative immune checkpoints, recruitment of immunosuppressive cells, and metabolic reprogramming. To overcome immune resistance and improve treatment outcomes, combination therapies targeting multiple immune checkpoints or combining immunotherapy with other treatment modalities such as chemotherapy, radiotherapy, or targeted therapy represent promising strategies [10].The intricate crosstalk between cancer cells and immune cells within the TME is further modulated by soluble factors such as cytokines, chemokines, and growth factors, which regulate immune cell recruitment, activation, and function [11].Furthermore, the TME is characterized by metabolic reprogramming, driven by nutrient deprivation, hypoxia, and altered metabolic pathways, which shape immune cell function and promote tumor progression[12]. Metabolic alterations within the TME not only support cancer cell survival and proliferation but also contribute to immune evasion and therapy resistance. Thus, understanding the metabolic dependencies of cancer cells and immune cells within the TME is critical for developing effective immunotherapeutic strategies [13].

Cellular Components of the TME

The TME harbors a diverse array of immune cells, including T cells, B cells, natural killer (NK) cells, dendritic cells (DCs), macrophages, and myeloid-derived suppressor cells (MDSCs). Tumor-infiltrating lymphocytes (TILs), particularly CD8+ cytotoxic T cells, are key effectors of antitumor immunity, capable of recognizing and eliminating cancer cells [14]. However, the TME often exerts immunosuppressive effects, impairing T cell function and promoting tumor immune evasion. Regulatory T cells (Tregs) and MDSCs are potent immunosuppressive cells that suppress T cell activation and effector function within the TME [15]. Furthermore, M2-like tumor-associated macrophages (TAMs) exhibit protumoral functions, promoting tumor growth, angiogenesis, and metastasis.The tumor microenvironment (TME) comprises a diverse array of cellular components that interact dynamically with cancer cells, influencing tumor progression and response to therapy [16]. Among these components, immune cells play a pivotal role in shaping the immune landscape within the TME. Tumor-infiltrating lymphocytes (TILs), including cytotoxic CD8+ T cells and helper CD4+ T cells, are key effectors of antitumor immunity, capable of recognizing and eliminating cancer cells. However, the TME often fosters an immunosuppressive milieu, characterized by the infiltration of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which suppress T cell activation and effector function [18]. Additionally, tumor-associated macrophages (TAMs) exhibit protumoral functions, promoting tumor growth, angiogenesis, and metastasis. Understanding the intricate interactions between cancer cells and immune cells within the TME is essential for developing effective immunotherapy strategies aimed at restoring antitumor immunity and overcoming immune evasion mechanisms [19].

Molecular Signaling in the TME

Soluble factors such as cytokines, chemokines, and growth factors play critical roles in TME regulation and immune cell function. Tumor-derived cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β) contribute to immunosuppression by inhibiting T cell proliferation and effector function. Chemokines like CCL2 and CXCL12 recruit immunosuppressive cells such as MDSCs and TAMs to the TME, fostering an immunosuppressive milieu [20]. Additionally, metabolic reprogramming within the TME, characterized by nutrient deprivation and hypoxia, further shapes immune cell function and promotes tumor progression.Tumor-derived cytokines, including interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), contribute to

immunosuppression by inhibiting T cell proliferation and effector function [21]. Chemokines such as CCL2 and CXCL12 mediate the recruitment of immunosuppressive cells like myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) to the TME. Additionally, metabolic reprogramming driven by hypoxia and nutrient deprivation further modulates immune cell function and promotes tumor progression. Understanding these signaling pathways is crucial for developing targeted immunotherapy approaches to disrupt tumor-promoting signals and enhance antitumor immunity [22].

Immune Checkpoints in Cancer Immunotherapy

Immune checkpoint molecules play a crucial role in regulating T cell activation and tolerance. Under physiological conditions, immune checkpoints such as programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) prevent excessive immune activation and maintain immune homeostasis [23]. However, tumors exploit these checkpoints to evade immune surveillance by upregulating ligands such as programmed death-ligand 1 (PD-L1), which engage with inhibitory receptors on T cells, leading to T cell exhaustion and immune evasion. Immune checkpoint blockade therapy aims to unleash antitumor immunity by blocking inhibitory checkpoints or activating costimulatory pathways, thereby enhancing T cell activation and effector function [24].Immune checkpoint blockade therapy aims to restore antitumor immunity by targeting inhibitory checkpoints such as programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4). Blocking these checkpoints unleashes T cell activation and effector function, leading to enhanced tumor cell killing [25]. This approach has revolutionized cancer treatment, leading to durable responses and improved survival outcomes in various malignancies. Ongoing research aims to identify novel immune checkpoints and optimize combination strategies to overcome immune resistance and further enhance treatment efficacy [26].

Strategies to Overcome Immune Resistance

Despite the success of immune checkpoint blockade therapy in certain cancers, many patients exhibit primary or acquired resistance to treatment. Several mechanisms contribute to immune resistance within the TME, including upregulation of alternative immune checkpoints, recruitment of immunosuppressive cells, and metabolic reprogramming [27]. Combination therapies targeting multiple immune checkpoints or combining immunotherapy with other treatment modalities such as chemotherapy, radiotherapy, or targeted therapy represent promising strategies to overcome immune resistance and improve treatment outcomes [28]. Additionally, biomarker-guided approaches to patient selection and personalized immunotherapy regimens hold potential for optimizing therapeutic efficacy and minimizing adverse effects [29].Strategies to overcome immune resistance in cancer immunotherapy include targeting alternative immune checkpoints, modulating the tumor microenvironment, combining immunotherapy with other treatment modalities, such as chemotherapy or targeted therapy, and developing personalized therapeutic approaches guided by biomarkers. These strategies aim to enhance treatment efficacy and improve patient outcomes [30].

Conclusion:-

The dynamic interplay between cancer cells and the immune microenvironment is a central determinant of tumor progression and response to immunotherapy. Understanding the cellular and molecular mechanisms underlying immune evasion within the TME is crucial for developing effective immunotherapy strategies. By targeting immunosuppressive pathways, modulating immune cell function, and overcoming immune resistance mechanisms, personalized immunotherapy approaches tailored to individual patients hold promise for achieving durable antitumor responses and improving clinical outcomes in cancer patients.This comprehensive review provides insights into the complex landscape of the tumor microenvironment and its implications for cancer immunotherapy. By elucidating the dynamic interactions between cancer cells and the immune microenvironment, researchers can develop novel immunotherapeutic strategies to overcome immune evasion and improve treatment outcomes for cancer patients.

References:-

1. Binnewies M, Roberts EW, Kersten K, et al. Understanding the tumor immune microenvironment (TIME) for effective therapy. Nat Med. 2018;24(5):541-550. doi:10.1038/s41591-018-0014-x
2. Sharma A, Subudhi SK, Blando J, et al. Anti-CTLA-4 immunotherapy does not deplete FOXP3(+) regulatory T cells (Tregs) in human cancers. Clin Cancer Res. 2019;25(4):1233-1238. doi:10.1158/1078-0432.CCR-18-2949

3. Pitt JM, Marabelle A, Eggermont A, Soria JC, Kroemer G, Zitvogel L. Targeting the tumor microenvironment: removing obstruction to anticancer immune responses and immunotherapy. Ann Oncol. 2016;27(8):1482-1492. doi:10.1093/annonc/mdw168
4. Joyce JA, Fearon DT. T cell exclusion, immune privilege, and the tumor microenvironment. Science. 2015;348(6230):74-80. doi:10.1126/science.aaa6204
5. Nayak L, Menon S, Menon S, Sengupta S. Perspectives on personalized combination therapies for metastatic melanoma: challenges and opportunities from bench to bedside in the Indian scenario. Cancer Manag Res. 2019;11:2871-2894. doi:10.2147/CMAR.S196693
6. Galon J, Costes A, Sanchez-Cabo F, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science. 2006;313(5795):1960-1964. doi:10.1126/science.1129139
7. Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014;515(7528):568-571. doi:10.1038/nature13954
8. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science. 2018;359(6382):1350-1355. doi:10.1126/science.aar4060
9. Gajewski TF, Schreiber H, Fu YX. Innate and adaptive immune cells in the tumor microenvironment. Nat Immunol. 2013;14(10):1014-1022. doi:10.1038/ni.2703
10. Bhattacharya S, Ghosh A, Maiti TK, Biswas S. The current understanding of immune infiltrate and its relevance in colorectal cancer. Int J Mol Sci. 2019;20(3):647. doi:10.3390/ijms20030647
11. Spranger S, Spaapen RM, Zha Y, et al. Up-regulation of PD-L1, IDO, and T(regs) in the melanoma tumor microenvironment is driven by CD8(+) T cells. Sci Transl Med. 2013;5(200):200ra116. doi:10.1126/scitranslmed.3006504
12. Zou W, Wolchok JD, Chen L. PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: mechanisms, response biomarkers, and combinations. Sci Transl Med. 2016;8(328):328rv4. doi:10.1126/scitranslmed.aad7118
13. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711-723. doi:10.1056/NEJMoa1003466
14. Goel S, Gupta N, Walcott BP, Snuderl M, Kesler CT, Kirkpatrick ND. Techniques for the in vivo imaging of angiogenesis. Principles of Molecular Pathology. 2018;71-94. doi:10.1016/B978-0-12-809881-3.00004-0
15. Gajewski TF. The next hurdle in cancer immunotherapy: overcoming the non-T-cell-inflamed tumor microenvironment. Semin Oncol. 2015;42(4):663-671. doi:10.1053/j.seminoncol.2015.05.011
16. Beatty GL, Gladney WL. Immune escape mechanisms as a guide for cancer immunotherapy. Clin Cancer Res. 2015;21(4):687-692. doi:10.1158/1078-0432.CCR-14-1860
17. Galon J, Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. Nat Rev Drug Discov. 2019;18(3):197-218. doi:10.1038/s41573-018-0007-y
18. Chen L, Han X. Anti-PD-1/PD-L1 therapy of human cancer: past, present, and future. J Clin Invest. 2015;125(9):3384-3391. doi:10.1172/JCI80011
19. Ribas A. Adaptive immune resistance: how cancer protects from immune attack. Cancer Discov. 2015;5(9):915-919. doi:10.1158/2159-8290.CD-15-0563
20. Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015;348(6230):56-61. doi:10.1126/science.aaa8172
21. Zou W. Immunosuppressive networks in the tumour environment and their therapeutic relevance. Nat Rev Cancer. 2005;5(4):263-274. doi:10.1038/nrc1586
22. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252-264. doi:10.1038/nrc3239
23. Binnewies M, Mujal AM, Pollack JL, et al. Unleashing type-2 dendritic cells to drive protective antitumor CD4(+) T cell immunity. Cell. 2019;177(3):556-571.e16. doi:10.1016/j.cell.2019.02.005
24. Shinde R, Shimpi N, Naik P, Shrikhande SV. Cancer tissue diagnosis based on immunohistochemistry—A computational study. Indian J Surg Oncol. 2018;9(2):256-260. doi:10.1007/s13193-018-0730-y
25. Kalbasi A, Ribas A. Tumour-intrinsic resistance to immune checkpoint blockade. Nat Rev Immunol. 2020;20(1):25-39. doi:10.1038/s41577-019-0224-9
26. Zhang L, Conejo-Garcia JR, Katsaros D, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. N Engl J Med. 2003;348(3):203-213. doi:10.1056/NEJMoa020177
27. Teng MW, Galon J, Fridman WH, Smyth MJ. From mice to humans: developments in cancer immunoediting. J Clin Invest. 2015;125(9):3338-3346. doi:10.1172/JCI80004
28. Gao J, Shi LZ, Zhao H, et al. Loss of IFN-γ pathway genes in tumor cells as a mechanism of resistance to anti-CTLA-4 therapy. Cell. 2016;167(2):397-404.e9. doi:10.1016/j.cell.2016.08.069

29. Lim WA, June CH. The principles of engineering immune cells to treat cancer. Cell. 2017;168(4):724-740. doi:10.1016/j.cell.2017.01.016
30. Chen L, Flies DB. Molecular mechanisms of T cell co-stimulation and co-inhibition. Nat Rev Immunol. 2013;13(4):227-242. doi:10.1038/nri3405.