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Targeting the Tumor Microenvironment in Prostate Cancer: New Frontiers in Anti-Stromal Therapies

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ABSTRACT

Prostate cancer is a prevalent malignancy affecting men worldwide, contributing significantly to morbidity and mortality rates. Despite advances in treatment, many patients experience disease progression, treatment resistance, and metastasis due to the complex interplay within the tumor microenvironment (TME). The TME consists of various cellular and non-cellular components, including cancer-associated fibroblasts (CAFs), immune cells, endothelial cells, and the extracellular matrix (ECM). CAFs play a crucial role in reshaping the TME by secreting growth factors, cytokines, and remodeling enzymes that enhance tumor proliferation and survival. Immune cells contribute to immune evasion and create an immunosuppressive environment, limiting the effectiveness of conventional therapies. Angiogenesis, facilitated by endothelial cells within the TME, supports tumor vascularization and provides a constant supply of nutrients and oxygen. The ECM undergoes continuous remodeling, further facilitating cancer progression. This review explores emerging anti-stromal therapeutic strategies aimed at disrupting these critical stromal components within the TME of prostate cancer. It highlights the promise of targeting CAFs, modulating the immune landscape, inhibiting angiogenesis, and remodeling the ECM to prevent metastasis. Future research should focus on innovative combination therapies that integrate anti-stromal strategies with conventional treatments to improve patient outcomes and develop more effective interventions.

Keywords: Prostate cancer, tumor microenvironment, anti-stromal therapies, cancer-associated fibroblasts, angiogenesis, immune modulation

INTRODUCTION

Prostate cancer (PCa) remains a significant health concern, especially in men over 50 years old, with more aggressive forms often leading to poor clinical outcomes [1–3]. While traditional treatments such as surgery, radiation, and androgen deprivation therapy (ADT) have been the cornerstones of PCa management, treatment resistance and disease recurrence remain substantial challenges. A growing body of evidence suggests that targeting the tumor microenvironment (TME) holds promise for overcoming resistance to therapy and improving patient outcomes. The TME, comprising a complex network of cancer-associated fibroblasts (CAFs), immune cells, blood vessels, and the extracellular matrix (ECM), plays an integral role in the progression of prostate cancer[4–6]. Stromal components interact with cancer cells through signaling pathways, cytokine secretion, and the formation of a pro-tumorigenic niche, facilitating tumor growth and metastasis. Consequently, the TME has emerged as a potential therapeutic target. This review focuses on the new frontiers in anti-stromal therapies, discussing key therapeutic targets within the TME and the potential for novel treatment strategies in prostate cancer.

THE TUMOR MICROENVIRONMENT IN PROSTATE CANCER

Cancer-Associated Fibroblasts (CAFs)

Cancer-associated fibroblasts (CAFs) are a significant component of the tumor microenvironment (TME) in prostate cancer, often linked to poor clinical outcomes and increased tumor aggressiveness. CAFs interact with cancer cells and other elements of the TME to create a supportive niche for tumor growth through several key mechanisms[7]. These include the suppression of growth factors, matrix remodeling, securitization of pro-inflammatory cytokines, enhancement of angiogenesis, and immunosuppression. CAFs secrete various growth factors that promote cancer cell proliferation, invasion, and metastasis. Notable examples include Transforming Growth Factor-β (TGF-β), Fibroblast Growth Factor (FGF), Hepatocyte Growth Factor (HGF), matrix remodeling enzymes, securitization of pro-inflammatory cytokines, and enhancement of angiogenesis[8]. They also contribute to the suppression of anti-tumor immune responses by secreting factors that attract regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) into the TME, which inhibit the activity of cytotoxic T lymphocytes and natural killer (NK) cells.

To target CAFs, strategies aimed at disrupting their pro-tumorigenic functions include inhibiting CAF activation, reprogramming CAFs to revert their tumor-promoting phenotype into a more normal, tumor-suppressing state, and targeting the Hedgehog (Hh) signaling pathway. Inhibiting TGF-β signaling has shown promise in preclinical studies by reducing CAF activation and impairing their ability to support tumor progression[9]. Blocking PDGF signaling can also inhibit CAF activation, as PDGF is involved in fibroblast recruitment and differentiation into CAFs.[10] In summary, CAFs play a critical role in prostate cancer progression through their ability to support tumor growth, promote metastasis, suppress immune responses, and contribute to therapeutic resistance. Targeting CAFs through inhibition of their activation or reprogramming their function represents a promising avenue for therapeutic intervention in prostate cancer. Further research into the complex interactions between CAFs and cancer cells in the TME will be crucial for developing more effective and targeted therapies.

Immune Cells in the TME

The immune landscape within the TME is complex, involving tumor-promoting immune cells such as tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), which suppress anti-tumor immunity. On the other hand, T cells, particularly cytotoxic CD8+ T cells, have the potential to eradicate cancer cells, though they are often rendered ineffective due to the immunosuppressive TME. Anti-stromal therapeutic approaches that modulate immune responses according to [11–13] include:

Immune checkpoint inhibitors (ICIs) ICIs, such as anti-PD-1/PD-L1 and anti-CTLA-4 antibodies, have shown success in other cancers but have limited efficacy in prostate cancer. However, combining ICIs with stromal targeting agents, such as CAF inhibitors or angiogenesis blockers, may enhance immune responses.

Macrophage reprogramming: Targeting TAMs to shift their phenotype from tumor-promoting M2 macrophages to anti-tumor M1 macrophages has shown potential in preclinical models of prostate cancer.

Angiogenesis in the Tumor Microenvironment

Tumor angiogenesis is a hallmark of cancer progression, providing the necessary nutrients and oxygen for tumor growth. Endothelial cells in the prostate cancer TME are key players in forming new blood vessels through angiogenic factors such as vascular endothelial growth factor (VEGF).[14–17] Anti-angiogenic therapies have been explored to inhibit tumor vascularization, with some showing promising results:

VEGF inhibitors: VEGF-targeting agents, including bevacizumab, have been tested in clinical trials for prostate cancer. While early results were not promising, ongoing studies are investigating VEGF inhibition in combination with other therapies, such as chemotherapy and immune modulators.

Endothelial cell targeting: Novel strategies aim to selectively target endothelial cells in the TME, preventing them from contributing to tumor growth and metastasis. Inhibiting key pathways, such as the angiopoietin-TIE2 axis, is currently under investigation.

Extracellular Matrix Remodeling and Therapeutic Targeting

The ECM provides structural support for the tumor and facilitates interactions between stromal and cancer cells. In prostate cancer, ECM components such as collagen, fibronectin, and proteoglycans are remodeled by enzymes like matrix metalloproteinases (MMPs), leading to tumor invasion and metastasis. Targeting ECM remodeling in prostate cancer has emerged as a potential therapeutic approach[18, 19]:

MMP inhibitors: Despite the early promise of MMP inhibitors in clinical trials, their application in cancer therapy has faced challenges due to toxicity and limited efficacy. However, recent advances in drug design and combination therapies are reigniting interest in this approach[20, 21].

ECM-integrin interactions: Integrins, which mediate cell-ECM interactions, have also emerged as potential targets. Inhibiting integrin signaling, particularly through αvβ3 integrin antagonists, has shown anti-tumor effects in preclinical studies of prostate cancer[22, 23].

Combination Therapies

Targeting multiple components of the TME simultaneously offers a promising approach to overcome the challenges of therapeutic resistance in prostate cancer. Combining anti-stromal therapies with androgen deprivation therapy, chemotherapy, or immunotherapy may enhance overall efficacy and prevent tumor escape mechanisms. Current clinical trials are exploring various combination strategies, with early results showing improved outcomes.

Precision Medicine and Biomarker Development

The heterogeneity of the TME in prostate cancer necessitates a precision medicine approach. Identifying specific biomarkers for TME components, such as CAFs or TAMs, can help tailor anti-stromal therapies to individual patients[24]. Liquid biopsy techniques, such as circulating tumor DNA (ctDNA) and exosome analysis, offer non-invasive methods to monitor TME dynamics and predict treatment responses[4, 25].

Future Perspectives

While anti-stromal therapies have shown promise in preclinical and early clinical studies, several challenges remain, including treatment resistance, off-target effects, and the complexity of the TME. Future research should focus on improving the specificity of stromal targeting agents, exploring novel therapeutic targets, and developing personalized treatment strategies based on TME characteristics.

CONCLUSION

Targeting the tumor microenvironment represents a new frontier in the treatment of prostate cancer. By focusing on stromal components such as CAFs, immune cells, and the ECM, researchers and clinicians aim to disrupt the supportive niche that facilitates tumor growth and metastasis. While challenges remain in the development of effective anti-stromal therapies, ongoing research holds great potential for improving clinical outcomes in prostate cancer patients. As we continue to unravel the complexities of the TME, anti-stromal therapies may offer new hope for patients with advanced or resistant prostate cancer.

REFERENCES

1. Antonarakis, E.S., Armstrong, A.J., Dehm, S.M., Luo, J.: Androgen receptor variant-driven prostate cancer: clinical implications and therapeutic targeting. Prostate Cancer Prostatic Dis. 19, 231–241 (2016). https://doi.org/10.1038/pcan.2016.17
2. Alum, E.U., Tufail, T., Uti, D.E., Aja, P.M., Offor, C.E., Ibiam, U.A., Ukaidi, C.U.A., Alum, B.N. Utilizing Indigenous Flora in East Africa for Breast Cancer Treatment: An Overview. Anticancer Agents Med Chem. 2024 Sep 18. doi: 10.2174/0118715206338557240909081833.
3. Ibiam, U.A., Uti, D.E., Ejeogo, C.C., Orji, O.U., Aja, P.M., Nwamaka, E.N., Alum, E.U., Chukwu, C., Aloke, C., Chinedum, K.E., Agu, P., Nwobodo, V.: In Vivo and in Silico Assessment of Ameliorative Effects of Xylopia aethiopica on Testosterone Propionate-Induced Benign Prostatic Hyperplasia. Pharmaceutical Fronts. 05, e64–e76(2023). https://doi.org/10.1055/s-0043-1768477
4. Babar, Q., Saeed, A., Tabish, T.A., Sarwar, M., Thorat, N.D.: Targeting the tumor microenvironment: Potential strategy for cancer therapeutics. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 1869, 166746 (2023). https://doi.org/10.1016/j.bbadis.2023.166746
5. Domínguez-Cejudo, M.A., Gil-Torralvo, A., Cejuela, M., Molina-Pinelo, S., Bofill, J.S.: Targeting the Tumor Microenvironment in Breast Cancer: Prognostic and Predictive Significance and Therapeutic Opportunities. International Journal of Molecular Sciences. 24, 16771 (2023). https://doi.org/10.3390/ijms242316771
6. Wang, Q., Shao, X., Zhang, Y., Zhu, M., Wang, F.X.C., Mu, J., Li, J., Yao, H., Chen, K.: Role of tumor microenvironment in cancer progression and therapeutic strategy. Cancer Medicine. 12, 11149 (2023). https://doi.org/10.1002/cam4.5698
7. Wright, K., Ly, T., Kriet, M., Czirok, A., Thomas, S.M.: Cancer-Associated Fibroblasts: Master Tumor Microenvironment Modifiers. Cancers. 15, 1899(2023). https://doi.org/10.3390/cancers15061899
8. Xing, F.: Cancer associated fibroblasts (CAFs) in tumor microenvironment. Front

Biosci. 15, 166 (2010). https://doi.org/10.2741/3613
9. Monteran, L., Erez, N.: The Dark Side of Fibroblasts: Cancer-Associated Fibroblasts as Mediators of Immunosuppression in the Tumor Microenvironment. Front. Immunol. 10, 1835 (2019). https://doi.org/10.3389/fimmu.2019.01835
10. Xiang, X., Niu, Y.-R., Wang, Z.-H., Ye, L.-L., Peng, W.-B., Zhou, Q.: Cancer-associated fibroblasts: Vital suppressors of the immune response in the tumor microenvironment. Cytokine & Growth Factor Reviews. 67, 35–48 (2022). https://doi.org/10.1016/j.cytogfr.2022.07.006
11. Clappaert, E.J., Murgaski, A., Van Damme, H., Kiss, M., Laoui, D.: Diamonds in the Rough: Harnessing Tumor-Associated Myeloid Cells for Cancer Therapy. Front. Immunol. 9, 2250 (2018). https://doi.org/10.3389/fimmu.2018.02250
12. Chaib, M., Chauhan, S.C., Makowski, L.: Friend or Foe? Recent Strategies to Target Myeloid Cells in Cancer. Front. Cell Dev. Biol. 8, 351 (2020). https://doi.org/10.3389/fcell.2020.00351
13. Fleming, V., Hu, X., Weber, R., Nagibin, V., Groth, C., Altevogt, P., Utikal, J., Umansky, V.: Targeting Myeloid-Derived Suppressor Cells to Bypass Tumor-Induced Immunosuppression. Front. Immunol. 9, 398 (2018). https://doi.org/10.3389/fimmu.2018.00398
14. Lugano, R., Ramachandran, M., Dimberg, A.: Tumor angiogenesis: causes, consequences, challenges and opportunities. Cellular and Molecular Life Sciences: CMLS. 77, 1745 (2019). https://doi.org/10.1007/s00018-019-03351-7
15. Ziyad, S., Iruela-Arispe, M.L.: Molecular Mechanisms of Tumor Angiogenesis. Genes & Cancer. 2, 1085 (2011). https://doi.org/10.1177/1947601911432334
16. Liu, Z.-L., Chen, H.-H., Zheng, L.-L., Sun, L.-P., Shi, L.: Angiogenic signaling pathways and anti-angiogenic therapy for cancer. Sig Transduct Target Ther. 8, 1–39(2023). https://doi.org/10.1038/s41392-023-01460-1
17. Li, X., Zhou, J., Wang, X., Li, C., Ma, Z., Wan, Q., Peng, F.: New advances in the research of clinical treatment and novel anticancer agents in tumor angiogenesis. Biomedicine & Pharmacotherapy. 163, 114806 (2023). https://doi.org/10.1016/j.biopha.2023.114806
18. Prakash, J., Shaked, Y.: The Interplay between Extracellular Matrix Remodeling and Cancer Therapeutics. Cancer Discovery. 14, 1375 (2024). https://doi.org/10.1158/2159-8290.CD-24-0002
19. Popova, N.V., Jücker, M.: The Functional Role of Extracellular Matrix Proteins in Cancer. Cancers. 14, 238 (2022). https://doi.org/10.3390/cancers14010238
20. Winer, A., Adams, S., Mignatti, P.: Matrix Metalloproteinase Inhibitors in Cancer Therapy: Turning Past Failures into Future Successes. Molecular cancer therapeutics. 17, 1147 (2018). https://doi.org/10.1158/1535-7163.MCT-17-0646
21. Almutairi, S., Kalloush, H.M., Manoon, N.A., Bardaweel, S.K.: Matrix Metalloproteinases Inhibitors in Cancer Treatment: An Updated Review (2013–2023). Molecules. 28, 5567 (2023). https://doi.org/10.3390/molecules28145567
22. Liu, F., Wu, Q., Dong, Z., Liu, K.: Integrins in cancer: Emerging mechanisms and therapeutic opportunities. Pharmacology & Therapeutics. 247, 108458 (2023). https://doi.org/10.1016/j.pharmthera.2023.108458
23. Pang, X., He, X., Qiu, Z., Zhang, H., Xie, R., Liu, Z., Gu, Y., Zhao, N., Xiang, Q., Cui, Y.: Targeting integrin pathways: mechanisms and advances in therapy. Sig Transduct Target Ther. 8, 1–42 (2023). https://doi.org/10.1038/s41392-022-01259-6
24. Zhang, A., Miao, K., Sun, H., Deng, C.-X.: Tumor heterogeneity reshapes the tumor microenvironment to influence drug resistance. International Journal of Biological Sciences. 18, 3019 (2022). https://doi.org/10.7150/ijbs.72534
25. Xiao, Y., Yu, D.: Tumor microenvironment as a therapeutic target in cancer. Pharmacology & therapeutics. 221, 107753 (2020). https://doi.org/10.1016/j.pharmthera.2020.107753

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