

Synthesis and Evaluation of Dual-action Anticancer Agents: Targeting Tumor Cells and the Tumor Microenvironment

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Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide and despite significant advances in the development of therapeutic strategies, current treatments often fall short of offering long-term solutions. Conventional cancer therapies, including chemotherapy, radiation and targeted therapies, primarily focus on eradicating tumor cells. However, the effectiveness of these treatments is frequently limited by factors such as drug resistance, tumor heterogeneity and the complex nature of the Tumor Microenvironment (TME). The TME, composed of stromal cells, immune cells, extracellular matrix components and blood vessels, plays a critical role in tumor progression, metastasis and resistance to therapy. As a result, strategies that target both tumor cells and the TME are gaining increasing attention as potential avenues for improving cancer treatment outcomes. Recent advances in cancer research have highlighted the importance of the TME in facilitating tumor survival and progression. Therefore, targeting the TME alongside tumor cells represents a promising strategy to overcome therapeutic resistance and improve clinical outcomes. By targeting key components of the TME, such as stromal cells, immune modulators and angiogenesis, dual-action agents seek to create a more favorable environment for the immune system to recognize and attack cancer cells. Moreover, these agents can potentially reduce the adverse effects of traditional therapies by minimizing off-target toxicity and improving the specificity of treatment [1].

Description

Cancer remains one of the most pervasive and lethal diseases worldwide, with millions of new cases diagnosed each year. Despite significant progress in our understanding of cancer biology and the advent of novel therapeutic modalities, the treatment of cancer remains a significant challenge. The majority of conventional cancer therapies, such as chemotherapy, radiation and targeted therapies, primarily focus on targeting the tumor cells themselves. However, these approaches often face limitations due to the complexity and heterogeneity of tumors. Moreover, even with advances in targeted therapies, these treatments do not account for the Tumor Microenvironment (TME), which plays a crucial role in tumor growth, metastasis and therapeutic resistance. The TME is composed of a variety of cellular and non-cellular components, including cancer-associated fibroblasts, immune cells (e.g., tumor-associated macrophages, T cells and neutrophils), endothelial cells and extracellular matrix components. Similarly, regulatory T cells (Tregs) are often recruited to the TME, further contributing to immune evasion. These immunosuppressive mechanisms are a significant challenge in cancer therapy, especially with the emergence of immune checkpoint inhibitors, which have shown promising results in some cancers but remain ineffective in others due to the complex interplay between tumor cells and the TME [2].

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In addition to immune evasion, the TME also promotes tumor growth by facilitating angiogenesis, the process by which new blood vessels are formed to supply nutrients and oxygen to the growing tumor. Angiogenesis is primarily driven by pro-angiogenic factors such as Vascular Endothelial Growth Factor (VEGF), which is secreted by both tumor cells and the stromal cells within the TME. The development of tumor vasculature not only supports tumor growth but also enables metastasis by providing a route for cancer cells to invade the bloodstream and spread to distant sites. Moreover, the TME often contains regions of hypoxia, which can further exacerbate the aggressiveness of tumors by promoting genetic instability and resistance to conventional therapies. These factors collectively contribute to the difficulty of eradicating tumors using traditional therapies, as they allow tumors to survive and evolve in response to treatment. Recognizing the crucial role of the TME in cancer progression, researchers have begun to explore strategies that target not only the tumor cells themselves but also the TME. These strategies aim to disrupt the interactions between tumor cells and the supportive stroma, thereby enhancing the efficacy of cancer treatment. By targeting both aspects of cancer biology, dual-action agents have the potential to enhance treatment efficacy, reduce the likelihood of resistance and improve patient outcomes [3].

One of the key strategies in designing dual-action anticancer agents is the identification of molecular targets that are shared between tumor cells and the TME. These targets include receptor molecules, enzymes and signaling pathways that are dysregulated in cancer and the TME. Several anti-VEGF therapies have been developed, such as bevacizumab, which has shown efficacy in various cancers. However, the inhibition of VEGF alone does not necessarily eliminate the tumor, as tumors can adapt to this inhibition by using alternative mechanisms to maintain blood flow. Therefore, combining anti-VEGF therapies with agents that target tumor cells directly, such as chemotherapy or immune modulators, may provide a more effective therapeutic strategy. Another promising approach for dual-action therapy is the targeting of immune checkpoint pathways, which are crucial for the regulation of immune responses within the TME. Immune checkpoint inhibitors, such as anti-PD-1 and anti-CTLA-4 antibodies, have revolutionized cancer therapy by reactivating the immune system to attack tumor cells. However, not all patients respond to these treatments and the presence of an immunosuppressive TME can limit their effectiveness. Dual-action agents that combine immune checkpoint inhibition with targeting components of the TME, such as TAMs or MDSCs, are being explored to enhance the immune response against tumors. Similarly, targeting MDSCs or Tregs could help restore the body's natural immune surveillance, further boosting the anti-cancer immune response [4].

In addition to immune modulation, another approach for dual-action therapy involves targeting stromal cells within the TME. Cancer-Associated Fibroblasts (CAFs) are a major component of the stroma and play an essential role in tumor progression by secreting growth factors, cytokines and extracellular matrix proteins. These factors contribute to tumor growth, metastasis and resistance to therapy. Nanotechnology has also emerged as a powerful tool for developing dual-action anticancer agents. Nanoparticles can be engineered to carry multiple therapeutic agents, allowing for the simultaneous delivery of tumor-targeting drugs and agents that modulate the TME. One of the major challenges is the heterogeneity of the TME. The composition of the TME varies significantly between different tumors and even within different regions of the same tumor. This variability can complicate the design of universal dual-action agents that are effective across a broad range of tumor types. Additionally, the

complexity of the interactions between tumor cells and the TME means that targeting a single component of the TME may not be sufficient to achieve therapeutic success. A comprehensive understanding of the molecular mechanisms governing the TME is essential for the rational design of dual-action therapies [5].

Conclusion

In conclusion, dual-action anticancer agents represent a promising strategy to overcome the limitations of conventional cancer therapies by targeting both tumor cells and the Tumor Microenvironment (TME). By simultaneously disrupting tumor growth and modulating the supportive stroma, immune cells and angiogenesis within the TME, these agents have the potential to enhance treatment efficacy, reduce resistance and improve patient outcomes. While challenges remain in optimizing drug delivery and addressing the heterogeneity of the TME, the continued development of these innovative therapies holds great promise for advancing cancer treatment and providing more effective, personalized options for patients. As research progresses, dual-action agents are poised to play a transformative role in the future of cancer therapy.

Acknowledgment

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Conflict of Interest

None.

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