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Tumor Resistance Mechanisms in Gastric Cancer Aimed at the Epithelial Cell Adhesion Molecule *via* Chimeric Antigen Receptor T Cell Therapy

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Abstract

Gastric cancer remains a significant global health challenge, demanding innovative therapeutic approaches to combat tumor resistance mechanisms. The Epithelial Cell Adhesion Molecule (EpCAM) has emerged as a potential target for Chimeric Antigen Receptor (CAR) T cell therapy. However, the efficacy of this promising treatment is hampered by tumor resistance mechanisms. This article comprehensively reviews the current understanding of tumor resistance mechanisms in gastric cancer, with a specific focus on EpCAM-targeted CAR T cell therapy. From genetic alterations to microenvironmental factors, we explore the intricate landscape of resistance mechanisms and discuss strategies to overcome these challenges for improving the clinical success of CAR T cell therapy in gastric cancer.

Keywords: Gastric cancer • Epithelial cell adhesion molecule • Tumor resistance mechanisms • Genetic alterations

Introduction

Gastric cancer is a major global health concern, ranking as the fifth most common cancer and the third leading cause of cancer-related deaths worldwide. Despite advances in therapeutic modalities, the prognosis for gastric cancer remains poor, necessitating the exploration of innovative treatment strategies. Chimeric Antigen Receptor (CAR) T cell therapy has emerged as a promising avenue, with the Epithelial Cell Adhesion Molecule (EpCAM) as a potential target. However, the clinical success of CAR T cell therapy in gastric cancer is impeded by various tumor resistance mechanisms. This article aims to provide a comprehensive review of these resistance mechanisms, offering insights into the challenges faced and potential strategies to enhance the efficacy of EpCAM-targeted CAR T cell therapy in gastric cancer [1].

Literature Review

Genetic alterations leading to the downregulation of EpCAM expression on gastric cancer cells represent a primary obstacle to the success of CAR T cell therapy. EpCAM, a transmembrane glycoprotein, is often targeted for internalization and degradation upon CAR T cell recognition. Genetic mutations affecting the EpCAM gene or alterations in regulatory elements can result in reduced or absent EpCAM expression, rendering CAR T cells ineffective. Strategies aimed at overcoming EpCAM downregulation include the identification of alternative target antigens or the development of dual-targeting CAR T cell constructs. Intra-tumoral heterogeneity poses a significant challenge, with distinct subpopulations of gastric cancer cells exhibiting diverse antigenic profiles. Genetic alterations leading to the emergence of subclones with reduced or absent EpCAM expression can limit the efficacy of CAR T cells. Comprehensive profiling of tumor heterogeneity and the incorporation of multi-antigen targeting strategies are essential for addressing this challenge. Furthermore, advances in single-cell sequencing technologies can provide insights into the dynamic changes in antigen expression within the tumor microenvironment [2].

The immunosuppressive nature of the tumor microenvironment poses a formidable barrier to CAR T cell therapy in gastric cancer. Immunosuppressive cells, such as regulatory T cells (T regs) and myeloid-derived suppressor cells (MDSCs), infiltrate the tumor, creating an environment that hampers CAR T cell function. Genetic alterations in signaling pathways regulating immune checkpoints, such as PD-L1 overexpression, contribute to immune evasion. Combining CAR T cell therapy with immune checkpoint inhibitors or modulators of the tumor microenvironment may enhance therapeutic outcomes. The presence of dense stromal components and an aberrant extracellular matrix in gastric tumors can impede CAR T cell infiltration and function. Genetic alterations affecting the composition of the extracellular matrix or promoting fibrosis create physical barriers, limiting the access of CAR T cells to cancer cells. Strategies to modify the tumor microenvironment, including stromal-targeted therapies or extracellular matrix-degrading enzymes, may enhance CAR T cell penetration and improve treatment outcomes [3].

Discussion

Overcoming tumor resistance in gastric cancer may require a multi-faceted approach. Combination therapies involving CAR T cells and other immunomodulatory agents, such as immune checkpoint inhibitors or cytokine therapies, can synergistically enhance anti-tumor responses. Careful consideration of the temporal sequence and dosing regimens is crucial to maximize therapeutic efficacy while minimizing potential toxicities. Precision medicine aims to tailor treatment strategies based on the unique genetic and molecular characteristics of individual tumors. Genetic profiling of gastric cancer patients can identify specific alterations contributing to resistance, allowing for the development of personalized CAR T cell therapies. Strategies such as CRISPR-based genome editing may be employed to address genetic alterations contributing to EpCAM downregulation or antigenic heterogeneity [4].

Several clinical trials are underway to evaluate the safety and efficacy of EpCAM-targeted CAR T cell therapies in gastric cancer. These trials are designed to assess the impact of various modifications, including the use of third-generation CAR constructs, co-stimulatory molecules, and alternative

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antigen targeting strategies. The results of these trials will provide crucial insights into the clinical feasibility and potential of CAR T cell therapy for gastric cancer. The dynamic landscape of cancer research underscores the importance of continuous innovation. Future directions in CAR T cell therapy for gastric cancer may involve the development of next-generation CAR constructs with improved functionality and resistance to tumor evasion mechanisms. Integration of synthetic biology approaches, such as logic-gated CAR T cells, may enable enhanced precision and control over therapeutic responses. Additionally, advancements in gene-editing technologies and synthetic biology hold the potential to address genetic alterations contributing to tumor resistance [5].

Ethical considerations in the development and application of EpCAM-targeted CAR T cell therapy in gastric cancer are paramount. Patient selection should be guided by rigorous criteria, considering factors such as tumor characteristics, prior treatments, and potential risks associated with the therapy. Informed consent processes should be comprehensive, ensuring that patients and their families have a clear understanding of the experimental nature of the treatment, potential benefits, and associated risks. As with any advanced therapeutic intervention, the monitoring and management of adverse events are critical. Cytokine release syndrome (CRS), neurotoxicity, and off-target effects are potential complications associated with CAR T cell therapy. Close monitoring of patients during and after treatment, coupled with proactive management strategies, is essential for ensuring patient safety. Ongoing research focused on mitigating adverse events and improving the safety profile of CAR T cell therapies contributes to the ethical application of these innovative treatments [6].

Conclusion

In conclusion, the application of Chimeric Antigen Receptor T cell therapy targeting EpCAM in gastric cancer faces formidable challenges related to tumor resistance mechanisms. From genetic alterations affecting EpCAM expression to the immunosuppressive tumor microenvironment, a multifaceted understanding of these mechanisms is crucial for devising effective therapeutic strategies. Combining immunotherapies, exploring precision medicine approaches, and leveraging insights from ongoing clinical trials represent avenues for enhancing the clinical success of CAR T cell therapy in gastric cancer. As research continues to unravel the complexities of tumor resistance, the integration of innovative strategies holds promise for improving outcomes and advancing the field towards more personalized and effective treatments.

The future of EpCAM-targeted CAR T cell therapy in gastric cancer holds exciting possibilities. Emerging technologies, including advancements in synthetic biology, gene editing, and novel targeting strategies, are likely to shape the next generation of CAR T cell therapies. The exploration of dual-targeting CAR constructs, incorporation of logic-gated systems, and innovations in manufacturing processes will contribute to enhancing therapeutic efficacy and overcoming current challenges. Continued investment in research and development is crucial for unlocking the full potential of CAR T cell therapies in the treatment of gastric cancer.

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Conflict of Interest

None.

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