The CD47-SIRPα Axis in Cancer: Mechanisms of Immune Evasion and Innovative Therapeutic Approaches

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The CD47-SIRPα axis plays a crucial role in tumor immune evasion by transmitting a "don't eat me" signal from cancer cells to macrophages, thereby inhibiting phagocytosis and facilitating tumor progression. CD47, a transmembrane protein overexpressed in a wide range of hematological and solid tumors, binds to signal regulatory protein alpha (SIRPα) on myeloid cells to suppress innate immune responses. This interaction has emerged as a promising therapeutic target, leading to the development of various strategies including monoclonal antibodies, fusion proteins, bispecific antibodies, and nanoparticle-based delivery systems aimed at disrupting CD47-SIRPα signaling. While promising, challenges such as off-tumor toxicity, immune-related adverse effects, and tumor heterogeneity remain. This review discusses the molecular biology of the CD47-SIRPα axis, its role in cancer immune evasion, current therapeutic developments, and emerging combination strategies, highlighting its potential as a next-generation target in cancer immunotherapy.

1. INTRODUCTION

The CD47-SIRPα axis is critically implicated in the process of immune evasion by cancer cells, primarily by functioning as a "don't eat me" signal. CD47, a five-transmembrane protein ubiquitously expressed on cell surfaces, interacts with signal regulatory protein alpha (SIRPα) on myeloid cells to inhibit phagocytosis, thereby allowing cancer cells to evade immune destruction. This mechanism of immune evasion has been observed in various cancers, including acute myeloid leukemia and non-Hodgkin lymphoma, contributing significantly to the poor prognosis associated with these malignancies. As such, the CD47-SIRPα axis has become a focal point for developing novel therapeutic strategies aimed at blocking this interaction to enhance immune-mediated clearance of cancer cells. Targeted interventions such as monoclonal antibodies and bispecific antibodies are currently being investigated to disrupt this axis, thereby offering new prospects for cancer immunotherapy.

A. Biology of the CD47-SIRPα Axis

CD47 is characterized as a five-transmembrane protein that is broadly expressed across various cell types. It serves a fundamental role in evading immune surveillance by interacting with signal regulatory protein alpha (SIRPα), primarily expressed on myeloid cells. This binding inhibits phagocytosis, facilitating the survival of cancer cells within the host's immune environment. Moreover, CD47 can interact with thrombospondin-1 (TSP-1), although this interaction's relevance in cancer immune evasion warrants further investigation. According to research, the inhibition of phagocytosis mediated by the CD47-SIRPα interaction represents a critical mechanism whereby tumor cells escape immune-mediated destruction, underscoring the importance of this axis in oncogenesis [1].

B. CD47 in Cancer

Overexpression of CD47 is commonly observed in various malignancies, including acute myeloid leukemia (AML), non-Hodgkin lymphoma, and breast cancer, and is intricately linked with adverse clinical outcomes. Notably, CD47 serves as a potent marker of poor prognosis due to its role in aiding cancer cells to circumvent phagocytic elimination by macrophages [2]. This immune evasion mechanism significantly contributes to the aggressive nature and persistence of these malignancies, highlighting the axis as a critical target for therapeutic intervention [3]. Research indicates that targeting CD47 not only impedes tumor growth but also enhances the efficacy of existing treatments, making it a promising candidate in the development of combinatorial therapeutic strategies [4]. Consequently, understanding the expression patterns and multifaceted roles of CD47 across diverse cancer types remains a pivotal aspect of current oncological research.

C. Therapeutic Targeting of the CD47-SIRPα Axis

The therapeutic targeting of the CD47-SIRPα axis has garnered significant attention due to its central role in cancer immune evasion. Monoclonal antibodies such as Magrolimab, SRF231,

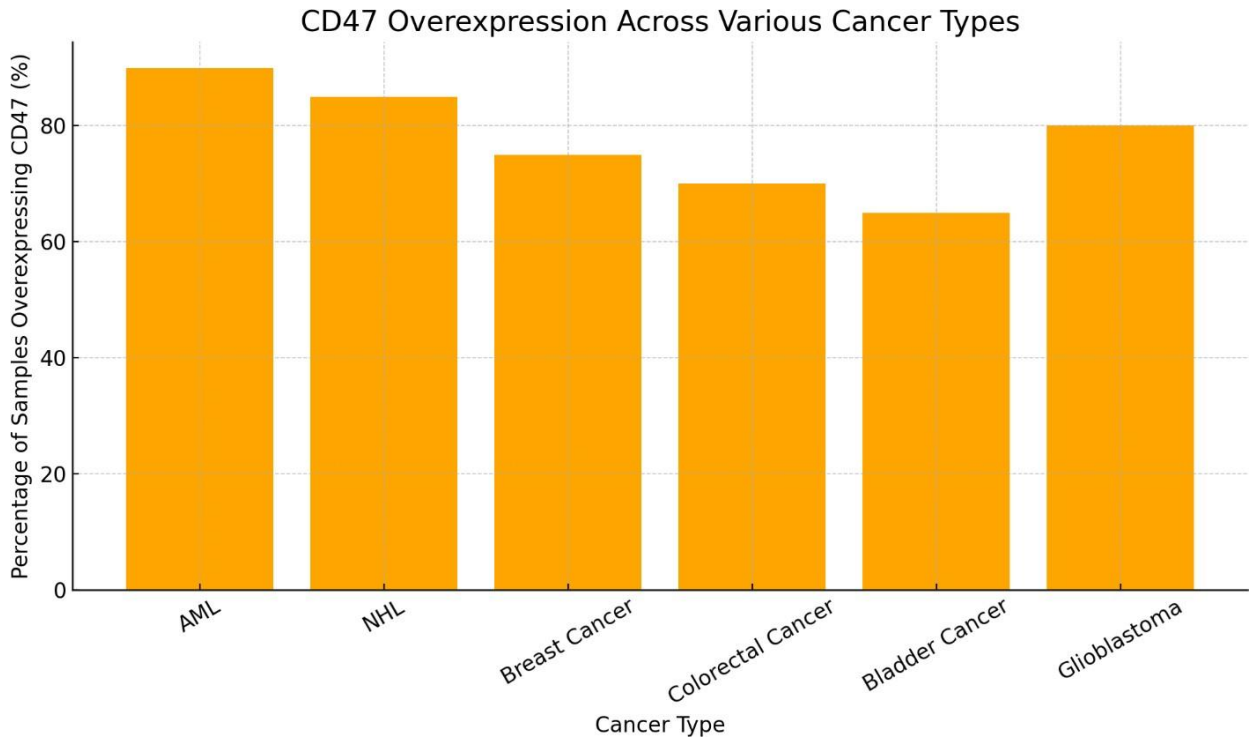

Fig. 1. Elevated CD47 expression is observed in a range of cancers including acute myeloid leukemia (AML), non-Hodgkin lymphoma (NHL), breast cancer, colorectal cancer, bladder cancer, and glioblastoma. This overexpression facilitates immune evasion by delivering inhibitory signals to macrophages via the SIRPα receptor, thereby preventing phagocytosis.

and AO-176 have been developed to specifically block the interaction between CD47 and SIRPα, thereby promoting phagocytosis of cancer cells [5]. In addition, SIRPα-Fc fusion proteins like TTI-621 and TTI-622 have shown promise by sequestering CD47, effectively disrupting its signaling pathway [6]. Bispecific antibodies hold unique potential by targeting CD47 while simultaneously binding to tumor-specific antigens, thus enhancing selectivity and reducing off-target effects [7]. Furthermore, nanoparticle-based strategies offer innovative approaches for the targeted delivery of CD47 inhibitors, contributing to a growing arsenal of tools aimed at overcoming the challenges associated with immune evasion in cancer.

D. Challenges and Considerations

Addressing the challenges associated with targeting the CD47-SIRPα axis is crucial for the successful development of these therapies. One prominent issue is hematologic toxicity, as CD47 is also expressed on red blood cells, leading to potent off-target effects during treatment [2]. Additionally, treatment with CD47-targeting agents may result in immune-related adverse events, such as autoimmunity and inflammation, which necessitate careful monitoring and management [6]. Another factor that complicates therapeutic efficacy is tumor heterogeneity; the variable expression of CD47 among and within cancer types can affect how tumors respond to therapeutic interventions [8]. Therefore, overcoming these challenges requires a multifaceted approach, including the development of more refined targeting mechanisms and combinatory treatment strategies that could mitigate these adverse effects while enhancing therapeutic impact.

E. Future Directions and Combination Therapies

Advancing the efficacy of CD47-targeted therapies necessitates innovative combination strategies, integrating PD-1/PD-L1 inhibitors, radiation, chemotherapy, and gene editing technologies. Notably, combining CD47 blockade with immune checkpoint inhibitors is under investigation for enhanced anti-tumor responses [6]. Furthermore, the incorporation of radiation and chemotherapy aims to augment immune system activation while directly targeting cancer cells, potentially leading to synergistic effects. Additionally, gene editing technologies offer promising avenues to modify tumor cells or immune cells, enhancing their susceptibility to CD47-targeted therapies [4]. Through these multifaceted approaches, the potential of CD47-targeted treatments could be significantly amplified, offering a paradigm shift in immunotherapy for diverse cancer types.

2. CONCLUSION

The CD47-SIRPα axis plays a pivotal role in cancer treatment due to its significant involvement in immune evasion mechanisms. As the "don't eat me" signal, CD47 allows cancer cells to circumvent destruction by the immune system, underscoring its value as a therapeutic target. Current therapeutic strategies, including monoclonal antibodies, SIRPα-Fc fusion proteins, and bispecific antibodies, show potential in disrupting this axis and enhancing tumor cell clearance. Additionally, innovative approaches such as nanoparticle-based delivery systems are expanding the possibilities of CD47 targeting. Future research directions focus on combination therapies that integrate CD47 blockade with other treatments, aiming to improve efficacy and address challenges like tumor heterogeneity and immune-related adverse effects.

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