Review Article

Optimizing Anti-CD47 Antibody Delivery toward More Effective Cancer Immunomodulation - A Scoping Review

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ABSTRACT

Cluster of Differentiation 47 (CD47), also known as integrin-associated protein (IAP), is a ubiquitously expressed transmembrane protein that functions as a key innate immune checkpoint by delivering a "don't-eat-me" signal to prevent macrophage-mediated phagocytosis of healthy cells. This inhibitory mechanism is mediated through the interaction of CD47 on target cells with signal regulatory protein-α (SIRPα) present on macrophages and dendritic cells. Tumor cells frequently exploit this pathway by overexpressing CD47, allowing them to evade immune surveillance, enhance survival, and promote malignant progression. Consequently, therapeutic targeting of the CD47/SIRPα axis has emerged as a promising strategy in cancer immunotherapy. Blocking CD47-SIRPα interactions using monoclonal antibodies, fusion proteins, or engineered SIRPα variants enhances macrophage-mediated phagocytosis, improves antigen presentation, and stimulates robust innate and adaptive antitumor immune responses. Preclinical and early clinical studies have demonstrated encouraging activity of these agents across various cancer types, either as monotherapy or in combination with immune checkpoint inhibitors, chemotherapy, or antibody-drug conjugates. However, clinical translation remains challenging because CD47 is broadly expressed on normal hematopoietic cells, leading to potential toxicities such as anemia, thrombocytopenia, and leukopenia. Thus, achieving tumor-selective targeting while minimizing off-target effects is critical for safe and effective therapy. Ongoing research focuses on improving antibody specificity, optimizing dosing regimens, and developing next-generation CD47/SIRPα-targeted agents with superior safety profiles. This review highlights the immunoregulatory role of CD47 in tumor immune escape, summarizes recent therapeutic advancements, and underscores the importance of refining CD47-based strategies to enhance clinical outcomes and support their integration into modern cancer immunotherapy.

Keywords: Immunotherapy, Cancer, Antibody, Phagocytosis.

1. INTRODUCTION

1.1 CD47-SIRP α Molecular biology and signaling

The CD47-SIRPα axis represents a crucial innate immune checkpoint regulating macrophage-mediated phagocytosis. CD47 is a ubiquitously expressed five-transmembrane immunoglobulin superfamily protein that binds to signal regulatory protein-α (SIRPα), an inhibitory receptor predominantly present on macrophages and dendritic cells. Upon ligand binding, the immunoreceptor tyrosine-based inhibitory motifs (ITIMs) located in the cytoplasmic domain of SIRPα become phosphorylated by Src family kinases, leading to the recruitment of SHP-1 and SHP-2 phosphatases. These phosphatases dephosphorylate downstream cytoskeletal and signaling proteins, generating an inhibitory

signal that suppresses myosin-II accumulation at the phagocytic synapse and ultimately blocks engulfment. Many tumor cells overexpress CD47 to evade immune surveillance by amplifying this "don't-eat-me" signal, making CD47–SIRPα a promising therapeutic target in cancer immunotherapy. Disruption of CD47–SIRPα signaling enhances macrophage phagocytosis, promotes antigen presentation, and stimulates adaptive anti-tumor immunity [1, 2, 3].

1.2 CD47 expression patterns and Role in immune evasion

CD47, a ubiquitously expressed five-transmembrane immunoglobulin superfamily protein, is present across a wide array of normal tissues, including hematopoietic lineages, endothelial cells, smooth muscle cells, fibroblasts, neurons, and various stem and progenitor cell populations, where it plays essential roles in self-recognition, cell adhesion, and migration [4]. Physiologically, basal CD47 expression prevents unwarranted phagocytosis by engaging SIRPα on myeloid cells; this interaction recruits SHP-1 and SHP-2 phosphatases to the SIRPα cytoplasmic ITIM motifs, resulting in downstream inhibition of cytoskeletal rearrangements required for phagocytic synapse formation [5, 1]. Tumor cells exploit this regulatory pathway by **markedly upregulating CD47**, a phenomenon documented in acute myeloid leukemia, non-Hodgkin lymphoma, glioblastoma, melanoma, hepatocellular carcinoma, and breast, ovarian, and colorectal cancers [6, 7]. This pathological overexpression of CD47 not only suppresses macrophage-mediated engulfment but also inhibits dendritic-cell cross-presentation, thereby weakening T-cell priming and diminishing adaptive antitumor immunity [8]. Increased CD47 levels correlate strongly with tumor invasiveness, metastatic potential, chemoresistance, and reduced overall survival, underscoring its function as a dominant innate immune checkpoint molecule utilized by cancer cells to evade immunosurveillance [2, 9]. In addition, stromal and cancer stem cell compartments within the tumor microenvironment also express high CD47, fortifying a multilayered shield against immune clearance and contributing to relapse and minimal residual disease [10]. Collectively, dysregulated CD47 expression disrupts host immune equilibrium and constitutes a central mechanism by which tumors achieve immune evasion, making the CD47–SIRPα axis a compelling target for next-generation immunotherapies.

1.3 Therapeutic agents targeting the CD47 axis

Therapeutic agents targeting the CD47 axis constitute a rapidly expanding class of Immunotherapeutics designed to overcome tumor-mediated innate immune evasion by disrupting the interaction between CD47, a ubiquitously expressed "don't-eat-me" signal, and signal regulatory protein-α (SIRPα) on macrophages and dendritic cells. Among the leading approaches, anti-CD47 monoclonal antibodies such as magrolimab (Hu5F9-G4) operate by directly blocking CD47–SIRPα engagement and inducing macrophage-mediated phagocytosis through Fc-dependent mechanisms, with demonstrated clinical efficacy in hematologic malignancies, particularly in combination with hypomethylating agents like azacitidine. However, because CD47 is expressed on erythrocytes, first-generation antibodies often exhibit "antigen sink" effects and on-target anemia, necessitating priming-dose strategies to mitigate hemagglutination and haemolysis. To overcome these limitations, engineered SIRPα-Fc fusion proteins such as TTI-621 (SIRPα-IgG1 Fc) and ALX148 (SIRPα-IgG1 Fc with attenuated effector function) have been developed as high-affinity decoy receptors that selectively bind tumor-overexpressed CD47 while minimizing erythrocyte-associated toxicity. Additionally, bispecific antibodies that co-target CD47 and tumor-associated antigens such as CD20, CD19, EGFR, or mesothelin provide enhanced specificity and reduce off-tumor binding to normal tissues, thereby improving therapeutic windows.

Emerging modalities include small-molecule inhibitors, peptidomimetics, and high-affinity SIRPα mutants, which display improved tissue penetration and customizable pharmacokinetic profiles [9]. Furthermore, nanoparticle-based

CD47 blockade using biomimetic vesicles, polymeric nanoparticles, or exosome-coated delivery systems offers controlled release, immune-cell activation, and potential synergy with chemotherapy and radiotherapy. Beyond direct CD47 inhibition, several agents are being developed to modulate downstream signaling pathways, including SHP-1/SHP-2 phosphatases and cytoskeletal rearrangement mechanisms that regulate phagocytic synapse formation. Importantly, combination strategies have shown powerful synergistic effects: pairing CD47 inhibitors with rituximab enhances antibody-dependent cellular phagocytosis in lymphoma, while combinations with PD-1/PD-L1 inhibitors, TLR agonists, or STING activators stimulate both innate and adaptive immune responses, resulting in durable antitumor immunity [6]. Despite significant progress, challenges such as systemic toxicity, the necessity for optimized dosing regimens, and the complexity of macrophage functional states remain active areas of investigation. Nonetheless, the CD47 axis represents one of the most promising frontiers in next-generation immuno-oncology, with the potential to revolutionize treatments across leukemias, lymphomas, and solid tumours.

1.4 Clinical Development status of major anti-CD47 antibodies

The clinical development of major anti-CD47 antibodies has advanced rapidly over the past decade, with several agents progressing from early-phase trials toward late-stage evaluation. Hu5F9-G4 (Magrolimab), a humanized IgG4 monoclonal antibody developed by Advani et al. (2018), was the first anti-CD47 therapy to demonstrate meaningful clinical activity by blocking the CD47–SIRPα axis and promoting macrophage-mediated phagocytosis. Magrolimab, in combination with azacitidine, showed promising efficacy in high-risk myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML), resulting in its advancement into multiple Phase II/III trials; however, [11] reported dose-limiting anemia as a major on-target toxicity due to CD47 expression on erythrocytes, necessitating priming-dose strategies. Another leading agent, Lemzoparlimab (TJC4), developed by [9]., is an engineered IgG4 antibody designed to minimize erythrocyte binding and reduce hemolytic risk. Early-phase trials have shown favorable safety with reduced anemia, enabling its evaluation in combination regimens for hematologic malignancies. AO-176, a humanized IgG2 antibody characterized by [12]. Zhang *et al.*, exhibits preferential binding to tumor cells over normal cells and demonstrates enhanced phagocytosis at acidic tumor microenvironment pH, a property that supports its ongoing testing in solid tumors. Additional molecules, including SRF231 and bispecific constructs such as IBI322, are in Phase I/II development, reflecting a broader shift toward engineering safer and more selective CD47-targeting therapeutics. Collectively, current clinical evidence underscores both the therapeutic potential and challenges of CD47 blockade, particularly regarding hematologic toxicity management, while ongoing trials aim to optimize combination strategies and identify patient populations most likely to benefit.

1.5 Safety concerns and toxicity management

Targeting the CD47–SIRPα innate-immune checkpoint represents a promising immunotherapy strategy blockade of the CD47–SIRPα interaction disrupts the "don't-eat-me" signal, thereby allowing macrophage-mediated phagocytosis of tumor cells and enhancing anti-tumor immune responses [13]. However, because CD47 is ubiquitously expressed on healthy cells, especially on erythrocytes (red blood cells, RBCs), systemic administration of anti-CD47 antibodies or other CD47-targeting agents can lead to significant "on-target, off-tumor" toxicity: notably, hematological adverse effects such as anemia (due to phagocytosis of RBCs), thrombocytopenia, and leukopenia This hematotoxicity constitutes one of the major barriers to clinical translation of CD47 blockade. Moreover, inhibition of CD47 may perturb immune homeostasis more broadly, since CD47 is expressed not only on RBCs but also on various immune cells; blocking CD47–SIRPα may interfere with normal immune cell functions for instance, certain CD47 antagonists have been linked to T-cell apoptosis and depletion when epitopes within the

immunoglobulin variable region are engaged. There is also concern that chronic or systemic blockade of CD47/SIRPα could have unintended consequences in other tissues: for example, in the nervous system, where SIRPα is expressed on cells including microglia, disturbed signaling might affect neural homeostasis or lead to aberrant synaptic pruning. To overcome these limitations and manage toxicity while preserving therapeutic efficacy, several strategies have been proposed and are under active development. These include: (1) engineering of CD47-targeting agents with reduced binding affinity to RBCs (or modified Fc domains) to spare normal erythrocytes and minimize phagocytosis of healthy cells; (2) development of bispecific antibodies that simultaneously target CD47 and a tumor-associated antigen (TAA), thereby increasing tumor-selectivity while reducing off-tumor binding; (3) use of SIRPα-Fc fusion proteins or other alternative scaffolds with negligible RBC binding; and (4) optimizing dosing regimens, for example through initial low "priming" doses followed by maintenance doses to allow compensatory hematopoiesis, thereby reducing the severity of anemia and other hematotoxic effects. Recent advances illustrate the feasibility of such approaches: for instance, a newly developed anti-CD47 antibody with minimized erythrocyte and thrombocyte toxicities has been reported in 2025, suggesting that structural modifications (e.g., altered glycosylation) could significantly improve the therapeutic index of CD47-targeted therapy [14]. In addition, combination strategies such as pairing CD47 blockade with established therapies (e.g., anti-angiogenic agents, checkpoint inhibitors, or chemotherapy) may not only enhance antitumor efficacy but also allow lower, safer dosing of the CD47-targeting agent, thus mitigating toxicities

1.6 Future perspectives and emerging delivery platforms

The future of CD47-mediated immunomodulation in cancer therapy lies in the development of innovative delivery platforms that can maximize therapeutic efficacy while minimizing systemic toxicity. Traditional administration of anti-CD47 antibodies is often limited by widespread expression of CD47 on normal cells, particularly erythrocytes, leading to dose-limiting hematologic toxicities. To address these challenges, emerging strategies are focusing on targeted and controlled delivery systems, such as nanoparticle-based carriers, bispecific antibodies, and antibody-drug conjugates, which can preferentially direct anti-CD47 agents to tumor tissues while sparing healthy cells [15, 2]. Lipid-based nanoparticles and polymeric nanocarriers offer the advantage of improved pharmacokinetics and enhanced tumor penetration through the enhanced permeability and retention (EPR) effect. Additionally, engineering of pH- or enzyme-responsive delivery systems enables site-specific release within the tumor microenvironment, thereby amplifying local immunomodulatory effects. Bispecific formats targeting both CD47 and tumor-specific antigens are also under investigation, as they can increase selectivity and reduce off-target interactions. Looking forward, integration of these advanced delivery platforms with combination immunotherapies, including checkpoint inhibitors and macrophage-activating agents, holds significant potential to overcome current therapeutic limitations and improve clinical outcomes in various malignancies [16]. Overall, the convergence of antibody engineering and precision delivery technologies represents a promising frontier in harnessing CD47 blockade for effective and safe cancer immunotherapy.

2. DISCUSSION

The CD47-SIRPα axis has emerged as a critical immune checkpoint in cancer, with CD47 functioning as a "don't-eat-me" signal that enables tumor cells to evade macrophage-mediated phagocytosis The therapeutic blockade of CD47 using monoclonal antibodies has shown promising preclinical and early clinical efficacy, enhancing phagocytosis, stimulating antitumor immune responses, and synergizing with other immunotherapies such as checkpoint inhibitors and chemotherapy Notably, anti-CD47 therapies demonstrate broad applicability across hematological malignancies and solid tumors, suggesting their potential as a versatile

immunotherapeutic approach. However, despite these advances, significant challenges remain. First, systemic administration of anti-CD47 antibodies can lead to on-target toxicity, particularly anemia and thrombocytopenia, due to the ubiquitous expression of CD47 on normal hematopoietic cells Second, the optimal dosing regimen and combination strategies to maximize efficacy while minimizing adverse effects are not yet fully defined. Third, tumor heterogeneity and the differential expression of CD47 in various cancer types raise questions regarding patient stratification and predictive biomarkers for therapy response. Importantly, the long-term immune consequences of CD47 blockade, including the risk of autoimmunity or immune exhaustion, remain poorly understood. Therefore, while anti-CD47 antibody administration represents a promising immunotherapeutic avenue, further studies are urgently required to optimize delivery platforms, refine dosing strategies, identify reliable biomarkers, and assess long-term safety in diverse patient populations. Addressing these gaps will be critical to translating preclinical successes into durable clinical outcomes.

3. CONCLUSION

CD47-mediated immunomodulation represents a pivotal mechanism by which tumor cells evade innate immune surveillance, primarily through the "don't-eat-me" signal that inhibits macrophage-mediated phagocytosis. The therapeutic targeting of CD47 with monoclonal antibodies has emerged as a promising strategy to restore antitumor immunity, enhance phagocytosis, and potentiate the effects of existing immunotherapies, including checkpoint inhibitors and conventional chemotherapy. Current preclinical and early clinical studies indicate that anti-CD47 therapies can selectively disrupt tumor immune evasion while demonstrating manageable safety profiles when appropriately engineered to minimize hematologic toxicity. Despite these encouraging advances, challenges such as on-target off-tumor effects, optimal dosing regimens, and combinatorial strategies remain critical areas for further investigation. Future research should focus on the development of innovative delivery platforms, combination therapies, and predictive biomarkers to maximize the therapeutic potential of anti-CD47 antibodies. Collectively, targeting the CD47-SIRPα axis holds significant promise in reshaping the landscape of cancer immunotherapy and offers a compelling avenue for the design of next-generation anticancer strategies.

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