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Delivery of cd47-targeted drugs with precision and the invention of anti-phagocytic delivery systems: the cd47-sirp axis in cancer therapy

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ABSTRACT

Humans, mice, and other mammals express CD47 as a "marker of self" on the surface of every cell to prevent the phagocytic death of healthy cells by connecting with signal regulating protein on macrophages and dendritic cells and conveying a "don't eat me" signal. Unfortunately, a variety of cancer cells use this "don't eat me" signal to their advantage by overexpressing CD47 on their surface in order to circumvent immune surveillance and macrophage detection. As a result, blocking the CD47-SIRP axis may be a promising therapeutic target for the treatment of cancer. However, because to the broad expression of CD47 in normal tissues, CD47-targeted medicines can most likely result in major side effects including anaemia; hence, the precise administration of CD47-targeted therapeutics is essential. Contribute to enhancing clinical effectiveness and minimising negative effects. The "don't eat me" signal can also be used to create anti-phagocytic medication delivery systems that will lengthen blood circulation times and increase tumour site accumulation. The CD47-SIRP axis has two components that are the subject of this review: the precise delivery of CD47-targeted medicines by well-designed delivery systems, and the thoughtful design of CD47-based anti-phagocytic drug delivery systems.

Keywords: CD47-SIRPα axis; Drug delivery systems; Immunotherapy; Anti phagocytic

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INTRODUCTION

Several CD47-targeted treatments have entered clinical trials, and several biomedical businesses are placing their bets on CD47 blocking monotherapy or combined therapy by creating anti-CD47 antibodies, SIRP fusion proteins (targeting CD47), anti-SIRP antibodies, and bispecific antibodies. Although the early results were promising, Hu5F9G4 is the first CD47 to enter clinical development [1]. Due to the extensive expression of CD47, the increased adverse effects, particularly anaemia and thrombocytopenia, have drawn significant attention [2]. Patients typically receive modest doses of Hu5F9G4 to remove ageing red blood cells before receiving high doses of Hu5F9G4 for treatment to minimise adverse effects, however some patients continue to experience anaemia symptoms. Additionally, as SIRP blockage may have negative effects on the neurological system, it is important to take them into consideration [3]. Myeloid cells and cells of the central and peripheral nervous systems have significant levels of SIRP expression [4]. For CD47 targeted drug research and clinical use, striking a balance between improving antitumor activity and lowering possible toxicity of Hematology, particularly anemia, is one of the main concerns [5]. The accumulation and retention of payloads in tumour sites have been improved by drug delivery systems, leading to an improvement in the anti-tumor response and a decrease in off-target effects [6]. Varied kinds of smart DDSs have been developed to specifically deliver one or more payloads with varied features to targeted tissue or cells using passive or active techniques, and release payloads in a manner responsive to the tumour microenvironment to minimise drug exposure to healthy tissues [7]. Therefore, the conflict between the efficacies and potential toxicities of CD47-targeted medications may be resolved by appropriately designed DDSs [8]. Despite some significant advancement in DDS research, their potential immunogenicity as allogenic materials which causes rapid clearance by mononuclear phagocyte system remains a barrier to their clinical utilisation? Consequently, camouflage tactics are used [9]. To prolong the blood circulation half-life and boost the drug concentration at tumour locations by avoiding MPS detection and clearance of DDSs. By enhancing hydrophilicity and introducing steric hindrance, PEGylating is one of the most used techniques for lowering immunogenicity and speeding up systemic circulation [10]. Multiple injections, however, may cause allergies due to the development of anti-PEG

antibodies and a fast clearance of PEGylated DDSs. Because the PEG tether interferes sterically with the active site of the relevant binding partners, PEGylating may also lessen ligand-receptor interaction and cellular uptake by tumour cells. Additionally, after opsonisation, PEG's "stealth" trait can completely disappear. While opsonisation had no effect on CD47's capacity to inhibit phagocytic activity, a fresh method for creating "invisible" DDSs. With a focus on two areas, we will summarise the most recent developments in the use of the CD47/SIRP signalling pathway in cancer therapy.

DISCUSSION

Accurate CD47-targeted therapeutic delivery through a properly designed DDS for effective tumour immunotherapy and functionalization of DDSs with CD47 protein, self-peptide CD47-rich cell membrane, and CD47-expressing exosomes for reasonable design of anti-phagocytic DDSs are the two areas we will cover in this review. The most recent developments in this rapidly expanding field are highlighted, along with the challenges and aspirations for the future. Originally known as integrin-associated protein (IAP), CD47 is a ubiquitous 50 kDa multichannel transmembrane protein that is a member of the immunoglobulin superfamily. It was first discovered on ovarian carcinomas as a protein that promoted the interaction between integrin's and adhesion molecules involved in cellular adhesion. The N-terminal extracellular variable region, the transmembrane region made up of five extremely hydrophobic membrane-spanning segments, and the short hydrophilic carboxyl terminus cytoplasmic tail were all verified by later investigations to make up the structure of CD47. Cell proliferation, migration, phagocytosis, apoptosis, and immunological homeostasis are just a few of the physiological processes that were mediated by CD47's interactions with its related ligands. Oldenburg et al. achieved a significant advancement in 2000 by pinpointing the crucial functions of CD47. When RBCs missing CD47 were injected into normal mice, macrophages quickly consumed and removed them, but RBCs expressing CD47 were not phagocyte, showing that CD47 functions as a "marker of self" to prevent phagocytosis. As was previously noted, CD47 was initially identified as being linked to integrin v3 to mediate a number of tasks. Humans, mice, and other mammals express CD47 as a "marker of self" on the surface of every cell to prevent the phagocytic death of healthy cells by connecting with signal regulating protein on macrophages and dendritic cells and conveying a "don't eat me" signal. Unfortunately, a variety of cancer cells use this "don't eat me" signal to their advantage by overexpressing CD47 on their surface in order to circumvent immune surveillance and macrophage detection. Therefore, inhibiting the CD47-SIRP axis may be a promising therapeutic target for the treatment of cancer. However, because to the broad expression of CD47 in normal tissues, CD47-targeted medicines can most likely result in major side effects including anaemia; hence, the precise administration of CD47-targeted therapeutics is essential.

CONCLUSION

The "don't eat me" signal can also be used to create anti-phagocytic medication delivery systems that lengthen blood circulation times and increase tumour site accumulation. In this study, we concentrate on the two components of the CD47-SIRP axis involved in the treatment of tumours: the precise administration of CD47-targeted therapies by well-designed delivery systems, and the thoughtful design of CD47-based anti-phagocytic drug delivery systems. Since myeloid cells, central nervous system cells, and peripheral nervous system cells all express SIRP to a considerable degree, potential adverse effects of SIRP blocking on the nervous system should also be taken into account. For CD47 targeted drug research and clinical use, striking a balance between improving antitumor activity and lowering possible toxicity of haematology, particularly anaemia, is one of the main issues. Humans, mice, and other mammals have widespread expression of CD47 on the surface of all cells as a defence mechanism to prevent macrophages from phagocytizing and destroying healthy cells. However, it has been shown that a number of tumours overexpress CD47 in an effort to evade phagocytic removal and immune monitoring. Higher levels of CD47 expression in cancer cells are linked to poor prognosis and poor treatment response. The inhibition of CD47/SIRP axis monotherapy is typically insufficient to produce a significant immune response against tumours because of the immunosuppressive TME. Therefore, the majority of preclinical research is concentrated on using CD47/SIRP inhibition in conjunction with drugs that can reverse the immunosuppressive TME to increase immune response. A long-lasting inhibitory effect on tumour development and recurrence was produced by the prolonged release of CD47 from gels, which persistently improved phagocytic clearance of residual or relapsing tumours by blocking the "don't eat me" signal.

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