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Review

Cancer immunotherapy targeting the CD47/SIRPα axis

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Abstract The success of cancer immunotherapy has generated tremendous interest in identifying new immunotherapeutic targets. To date, the majority of therapies have focussed on stimulating the adaptive immune system to attack cancer, including agents targeting CTLA-4 and the PD-1/PD-L1 axis. However, macrophages and other myeloid immune cells offer much promise as effectors of cancer immunotherapy. The CD47/signal regulatory protein alpha (SIRPα) axis is a critical regulator of myeloid cell activation and serves a broader role as a myeloid-specific immune checkpoint. CD47 is highly expressed on many different types of cancer, and it transduces inhibitory signals through SIRPα on macrophages and other myeloid cells. In a diverse range of preclinical models, therapies that block the CD47/SIRPα axis stimulate phagocytosis of cancer cells *in vitro* and anti-tumour immune responses *in vivo*.

A number of therapeutics that target the CD47/SIRPα axis are under preclinical and clinical investigation. These include anti-CD47 antibodies, engineered receptor decoys, anti-SIRPα antibodies and bispecific agents. These therapeutics differ in their pharmacodynamic, pharmacokinetic and toxicological properties. Clinical trials are underway for both solid and haematologic malignancies using anti-CD47 antibodies and recombinant SIRPα proteins. Since the CD47/SIRPα axis also limits the efficacy of tumour-opsonising antibodies, additional trials will examine their potential synergy with agents such as rituximab, cetuximab and trastuzumab. Phagocytosis in response to CD47/SIRPα-blocking agents results in antigen uptake and presentation, thereby linking the innate and adaptive immune systems. CD47/SIRPα blocking therapies may therefore synergise with immune checkpoint inhibitors that target the adaptive immune system. As a critical regulator of macrophage phagocytosis and activation, the potential applications of CD47/SIRPα blocking therapies extend beyond human cancer. They may be useful for the treatment of infectious disease, conditioning for stem cell transplant, and many other clinical indications.

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1. Introduction

The field of immuno-oncology has rapidly translated hypothetical concepts into clinical strategies, yielding a new era of cancer investigation and treatment. A large emphasis has been placed on therapies that stimulate the adaptive immune system to attack cancer, in particular T cells. This is rightfully due to the success of immune checkpoint inhibitors targeting CTLA-4 and the PD-1/PD-L1 axis, which disable inhibitory signals to T cells and generate anti-tumour responses. However, both adaptive and innate immune cells are endowed with specialised functions to eliminate pathogens, and many of these functions can be redirected against tumours. Cells of the myeloid lineage are the most abundant immune cells in the body, yet few immunotherapeutic approaches have been aimed at stimulating them to attack cancer. Macrophages in particular have remarkable potential as mediators of anti-cancer therapies based on their robust ability to perform phagocytosis. However, macrophages have a complex relationship with tumours, and in many cases they may promote tumour growth or metastasis. The CD47/signal regulatory protein alpha (SIRPα) axis is a critical molecular interaction that inhibits the activation of macrophages and other myeloid cells against tumours and thereby acts as a myeloid-specific immune checkpoint (Fig. 1). Therapies targeting the CD47/SIRPα axis have demonstrated success in a wide range of preclinical models and are now under investigation in clinical trials for both solid and haematologic malignancies. The CD47/SIRPα axis has emerged as one of the most promising new targets for immuno-oncology.

2. Discovery of CD47 as a 'marker of self'

CD47 is a 50 kDa multipass transmembrane protein with an extracellular region composed of a single immunoglobulin superfamily (IgSF) domain. Early studies described CD47 as a molecule expressed by a variety of ovarian cancers [1], a cell-surface protein that interacted with integrins on haematopoietic cells [2] and a glycoprotein on the surface of red blood cells [3]. A unifying theme to these studies and subsequent investigations was widespread expression of CD47 on both normal and malignant tissues.

The development of $CD47^{-/-}$ knockout mice permitted further functional evaluation of CD47, thereby establishing its role as an immunoregulatory molecule. Oldenborg et al. found that upon transfusing $CD47^{-/-}$ red blood cells into wild-type mice, the mutant red blood cells were rapidly eliminated from circulation [4]. Removal of $CD47^{-/-}$ cells was impaired in splenectomised mice and those treated with liposomal clodronate, indicating a requirement for macrophages of the reticuloendothelial system for the removal process.

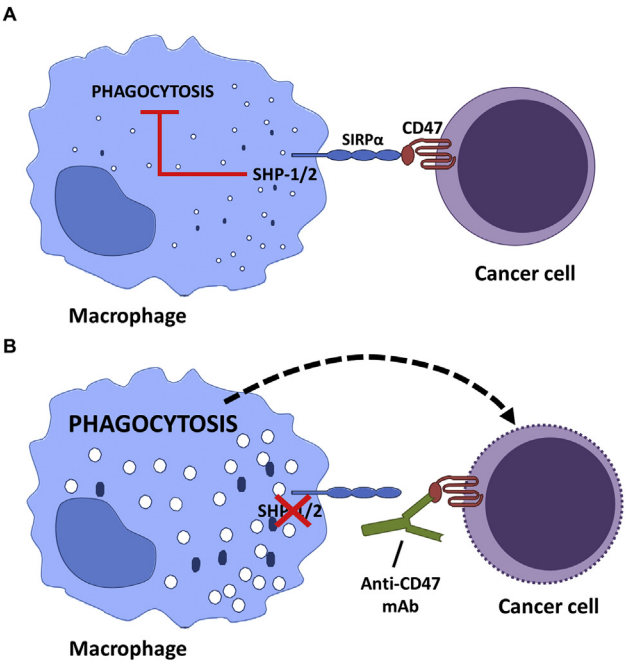

Fig. 1. **The CD47/SIRPα myeloid-specific immune checkpoint**. CD47 is highly expressed on many different types of cancers. SIRPα is an inhibitory receptor expressed on macrophages and other myeloid immune cells. (A) When CD47 binds to SIRPα, it causes activation of the SHP-1 and SHP-2 phosphatases that inhibit phagocytosis via downstream mediators. (B) Disruption of the CD47/SIRPα axis using antibodies or recombinant proteins disables inhibitory signalling by SIRPα, thereby stimulating phagocytosis of cancer cells.

Histological analysis confirmed the mutant red blood cells were engulfed by macrophages in the spleen, and *in vitro* phagocytosis assays identified SIRPα as the inhibitory receptor that mediated this process [4]. Further studies using cells from $CD47^{-/-}$ mice revealed a similar effect on platelet removal [5]. Moreover, transplanted bone marrow cells from $CD47^{-/-}$ mice failed to engraft when transplanted into wild-type mice, suggesting a role for CD47 in protecting stem and progenitor cells from removal by macrophages [6]. A number of studies have now demonstrated CD47 acts as a 'marker of self,' and it plays particular importance in permitting solid and haematologic transplant across xenogeneic barriers [7–9].

3. Molecular characterisation of the CD47/SIRPα interaction

Extensive biophysical characterisation of the CD47/SIRPα interaction has been performed, including crystallographic analysis of the extracellular domain of SIRPα alone an in complex with CD47 [10,11]. These studies have demonstrated that the distal, N-terminal domain of SIRPα is responsible for contacting CD47 [11,12]. SIRPα was first characterised as a receptor tyrosine kinase that associates with the inhibitory phosphatases SHP-1 and