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Review paper

Therapeutic strategies targeting CD47-SIRPα signaling pathway in gastrointestinal cancers treatment

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ABSTRACT

Gastrointestinal (GI) cancers are prevalent globally, with leading incidence and mortality rates among malignant tumors. Despite notable advancements in surgical resection, radiotherapy, and chemotherapy, the overall survival rates remain low. Hence, it is imperative to explore alternative approaches that enhance patient outcomes. Cluster of differentiation 47 (CD47), serving as an early diagnostic marker, is predominantly overexpressed in GI cancers and associated with poor prognosis. Targeting the CD47-signal regulatory protein alpha (SIRPα) signaling pathway may provide a novel strategy for GI cancers treatment. This study summarizes current knowledge of the structure and function of CD47 and SIRPα, their roles in signaling pathways, the prognostic significance of CD47, therapeutic strategies targeting the CD47-SIRPα signaling pathway in GI cancer, and highlights key issues for future investigations.

1. Introduction

Gastrointestinal (GI) cancers, including esophageal, gastric, colorectal, pancreatic, and hepatocellular carcinoma (HCC), are prevalent worldwide, with the highest incidence and mortality rates [1]. Various treatment options, such as surgical resection, radiotherapy, and chemotherapy, have improved patient outcomes [2]. However, the prognosis for some GI cancers remains poor. Consequently, there is a critical need for innovative strategies to address GI cancers. Checkpoint inhibitor immunotherapy is a rapidly advancing field, showing promise in treating GI cancers.

The homeostatic balance of the immune system is crucial in the development of GI cancers. Research on immunotherapy targeting immune checkpoint blockade has made significant breakthroughs [3]. The development of immune checkpoint inhibitors (ICIs), such as programmed cell death protein-1 (PD-1) and programmed cell death-ligand 1 (PD-L1), as well as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), has enhanced the prognosis for patients [4]. However, a proportion of patients still progress to distant metastasis and treatment resistance, with an overall low response rate [5]. New immune checkpoint treatment strategies are therefore urgently needed to improve the prognosis of GI cancers [6]. One potential target is cluster of differentiation 47 (CD47), overexpressed in GI cancers and acting as a novel prognostic marker for early diagnosis [7].

CD47 binds to thrombospondin-1 (TSP1) and signal regulatory protein alpha (SIRPα), significantly affecting the homeostasis of the immune system [8]. TSP1 is an extracellular matrix protein that is widely present in various tissues and cell types [9]. The main effect of CD47-TSP1 interaction is to downregulate immune response by inhibiting inflammatory response and phagocytosis of immune cells [10]. This interaction is also involved in biological processes such as angiogenesis, tumor growth, and metastasis [11]. SIRPα is an immunoglobulin superfamily receptor mainly expressed in monocyte series and hematopoietic cells [12]. The interaction between CD47 and SIRPα can inhibit the phagocytosis function of macrophages and dendritic cells (DCs), thereby inhibiting inflammatory responses and immune cell activation [13]. Cancer cells avoid phagocytosis by macrophages through this interaction to evade immune surveillance and reduce the regulation of innate and adaptive immune responses [14]. Therefore, immunotherapy targeting the CD47-SIRPα signaling pathway has garnered increasing attention as a cancer treatment approach to stimulate the innate immune system [15]. However, the specificity of targeting the CD47-SIRPα signaling pathway in GI cancer treatment is poorly

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understood. This paper summarizes and discusses the prognosis of CD47 in GI cancers and the potential of therapeutic strategies targeting the CD47-SIRPα signaling pathway in GI cancers treatment.

2. CD47-SIRPα signaling pathway

CD47 is a 50 kDa transmembrane protein, also known as an integrin-associated protein due to its co-precipitation with platelet-derived β3 integrin and placental αvβ3 integrin [16]. As a member of the immunoglobulin superfamily, CD47's molecular structure includes an extracellular N-terminal IgV domain, five highly hydrophobic transmembrane segments, and a short hydrophilic cytoplasmic tail [17]. Different isoforms of CD47 have different structures and functions in tissues [18]. Past research indicates that human cell lines and tissues contain four established CD47 isoforms, each with various lengths of amino acids in the cytoplasmic tail [19]. The latest research reveals a fifth isoform of CD47 in humans, featuring a unique amino acid length and sequence in the cytoplasmic tail when compared to the traditional four isoforms [20]. CD47 is extensively expressed on the membrane of almost all of cell types, playing a crucial role in maintaining immune system homeostasis [17]. Under physiological conditions, it aids in maintaining immune tolerance toward the body's own cells, thereby preventing self-attacks by the immune system [21]. For example, CD47 is prominently displayed on the surface of young red blood cells, whereas its expression diminishes on aging red blood cells. This differential expression enables macrophages to perform phagocytosis, thereby renewing red blood cells efficiently [21]. Under pathological conditions, it can be highly expressed on a variety of hematological tumors and solid tumors including GI cancers [22] (Table 1). By binding to ligands on phagocytes, it initiates a series of inhibitory signal transductions, blocks the presentation of tumor antigens to phagocytes, thereby evades immune surveillance [22].

SIRPα, the most studied binding partner of CD47, is an inhibitory receptor and a transmembrane glycosylated protein [23]. Its structure comprises an extracellular domain containing three Ig-like domains, a single-span transmembrane region, and a cytoplasmic tail with two immunoreceptor tyrosine-based inhibitory motifs (ITIMs) [23]. Interaction occurs as the NH_2-terminal IgV domain of SIRPα binds to CD47's extracellular Ig-domain, activating the phosphorylation of the two ITIMs' tyrosine residues [24]. This phosphorylation of ITIM recruits and activates the phosphatases Src homology 2 domain-containing protein tyrosine phosphatase 1 and 2 (SHP1/2) leading to alterations in various substrates and downstream signaling pathways, including inhibition of non-muscle myosin IIA, which in turn prevents the cytoskeletal reorganization necessary for phagocytosis [25] (Fig. 1). Therefore, CD47 delivers an inhibitory “don't eat me” signal to macrophages via binding to SIRPα [26]. Furthermore, CD47 overexpression in cancer cells is often accompanied by decreased expression of calreticulin [27]. Calreticulin (CRT) is recognized as the main pro-phagocytic signal in cancer cells, interacting with its corresponding receptor, low-density lipoprotein (LDL)-receptor-related protein (LRP), on phagocytes and this interaction is counterbalanced by CD47 [27]. The overexpression of CD47 in cancer cells can trigger phagocytosis through fragment crystallizable receptor (FcR), thereby inhibiting and blocking calreticulin-mediated phagocytosis [28]. Consequently, the interplay between anti-phagocytic signal (such as CD47) and pro-phagocytic signal (such as CRT) is what ultimately dictates whether cancerous cells will undergo phagocytosis or not [28].

The widespread overexpression of CD47 in various cancers suggests its role in cancer immune evasion [29]. Therefore, inhibiting the CD47-SIRPα interaction can disrupt SHP1/2 recruitment and activation, improving phagocytosis and enhancing immune surveillance [30]. Current research indicates that blocking the CD47-SIRPα signaling pathway in GI cancers enhances immune cell phagocytosis and hampers malignant progression [24]. Therefore, the CD47-SIRPα signaling pathway is recognized as a promising target for GI cancer treatment.

3. Prognostic role of CD47 in GI cancers

Cancer cells often exhibit higher levels of surface CD47 than non-malignant cells, with its elevated expression being regarded as a poor prognostic factor [16] (Table 2 and Fig. 2). However, the prognostic role of CD47 in GI cancers remains ambiguous. This section aims to consolidate current research on CD47's prognostic role in GI cancers, thereby providing a foundation for preclinical diagnosis.

3.1. Esophageal cancer

Esophageal cancer ranks as the sixth leading cause of cancer-related mortality globally, with esophageal squamous cell cancer (ESCC) constituting approximately 90% of cases [31]. Characterized by its aggressive nature, ESCC is associated with a poor prognosis

Table 1
Expression levels of cluster of differentiation 47 (CD47) in gastrointestinal (GI) cancers using the Cancer Genome Atlas (TCGA) (https://tcga-data.nci.nih.gov), Gene Expression Omnibus (GEO) (http://www.ncbi.nlm.nih.gov/geo/), and International Cancer Genome Consortium (ICGC) (https://dcc.icgc.org) databases.

Cancer type	Dataset source	Sample size	CD47 expression level	
			Tumor	Normal
Esophageal cancer	TCGA	468	High	Low
GC	TCGA	618	High	Low
CRC	TCGA	624	High	Low
Pancreatic cancer	TCGA	644	High	Low
HCC	TCGA	529	High	Low
Esophageal Cancer	GEO (GSE23400)	208	High	Low
GC	GEO (GSE66229)	400	High	Low
CRC	GEO (GSE39582)	585	High	Low
Pancreatic cancer	GEO (GSE15471)	78	High	Low
HCC	GEO (GSE14520)	488	High	Low
Esophageal cancer	ICGC (ESCA-China)	2766	High	Low
GC	ICGC (STAD-United States)	200	High	Low
CRC	ICGC (COAD-United States)	90	High	Low
Pancreatic cancer	ICGC (pancreatic cancer-Australia)	144	High	Low
HCC	ICGC (liver cancer-Japan)	240	High	Low

GC: gastric cancer; CRC: colorectal cancer; HCC: hepatocellular carcinoma; ESCA: esophageal carcinoma; STAD: stomach adenocarcinoma; COAD: colon adenocarcinoma.

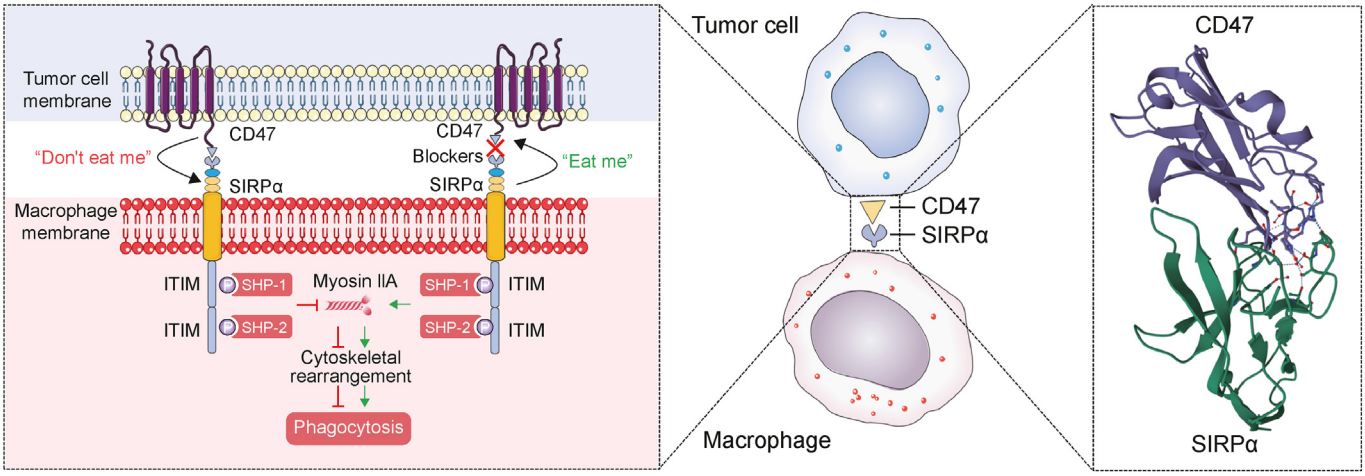

Fig. 1. Schematic representation of the cluster of differentiation 47 (CD47)-signal regulatory protein alpha (SIRPα) structures and interaction. CD47 consists of an extracellular N-terminal IgV domain, five transmembrane segments, and a short cytoplasmic tail, while SIRPα contains three Ig-like domains, a single-span transmembrane region, and a cytoplasmic tail with two immunoreceptor tyrosine-based inhibitory motifs (ITIMs). SHP-1: Src homology 2 domain-containing protein tyrosine phosphatase 1.

Table 2
The overall survival of cluster of differentiation 47 (CD47) in gastrointestinal (GI) cancers.

Cancer type	Cohorts	Median time (years)	Sample size	High groups	Log-rank *P*	95% confidence interval (CI)
Esophageal cancer	CD47 low	2.5	163	0.895	0.654	0.549
	CD47 high	2.1				1.457
GC	CD47 low	3.1	375	1.103	0.556	0.795
	CD47 high	2.2				1.532
CRC	CD47 low	7.6	455	0.786	0.226	0.532
	CD47 high	6.9				1.161
Pancreatic cancer	CD47 low	1.7	179	1.405	0.108	0.928
	CD47 high	1.6				2.125
HCC	CD47 low	4.7	371	1.322	0.116	0.933
	CD47 high	4.4				1.873

GC: gastric cancer; CRC: colorectal cancer; HCC: hepatocellular carcinoma.

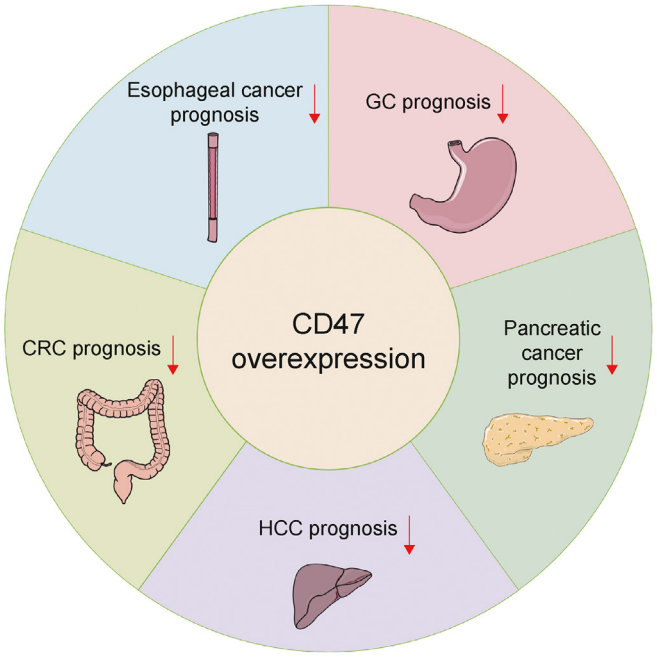

Fig. 2. Schematic representation of the relationship between cluster of differentiation 47 (CD47) expression and gastrointestinal (GI) cancer prognosis, where high levels correlate with poor outcomes. GC:gastric cancer; CRC:colorectal cancer; HCC: hepatocellular carcinoma.

[31]. Studies indicate that CD47 overexpression may correlate significantly with this dismal outcome in ESCC [32]. For instance, a study by Zhao et al. [32] demonstrated that ESCC cell lines express high levels of CD47, and human M2 macrophages can effectively phagocytose tumor cells in a dose-dependent manner following the blockade of the CD47-SIRPα pathway using anti-CD47 antibodies. Similarly, Suzuki et al. [33] reported a strong association between high CD47 messenger RNA (*CD47 mRNA*) levels and lymph node metastasis in 102 patients with curatively resected ESCC, suggesting a potential link between CD47 expression and ESCC metastasis. Furthermore, Wang et al. [34] found that CD47 is indicative of stemness in cancer cells, positing it as a promising prognostic marker and a target for stem cell-focused therapies in ESCC. Collectively, these findings underscore the potential of CD47 overexpression as a novel prognostic marker and a molecular target for early diagnosis in ESCC patients.

3.2. Gastric cancer (GC)

GC ranks the fifth in incidence and the fourth in mortality among cancer-related deaths worldwide [35]. Despite improvements in early diagnosis, identifying early diagnostic markers remains critically important. CD47 expression is considered as an independent negative prognostic factor for GC [36]. Specifically, Zhang et al. [37] demonstrated that CD47 is significantly upregulated in GC tissues and is strongly associated with a negative prognosis. Their study revealed that a synergistic anti-tumor effect can be achieved in GC treatment through combined antibody therapy targeting CD47 and vascular endothelial growth factor

(VEGF). In Epstein-Barr virus-associated gastric carcinoma (EBVaGC), overexpression of CD47 is noted and closely associated with immune cell infiltration [38]. Abe et al. [6] found that CD47 overexpression in EBVaGC diminishes anti-tumor immunity by impairing the function of infiltrating T lymphocytes. Additionally, research indicates that high CD47 expression in bone marrow correlates with increased lymphatic invasion and metastasis in GC. Contrarily, low peripheral blood CD47 levels are significantly associated with advanced tumor stages, deeper tumor invasion, and presence of lymphoid infiltration [39]. Studies also showed that the 5-year overall survival rates are significantly lower in patients with CD47-positive GCs compared to those with CD47-negative tumors [40]. Therefore, CD47 may serve as a valuable indicator for assessing lymphoid invasion in GC patients.

3.3. Colorectal cancer (CRC)

CRC is the third most common malignant tumor globally and the most prevalent in developed countries [41]. The expression level of CD47 is significantly linked to CRC prognosis, with intronic single nucleotide polymorphisms (SNPs) of CD47 being associated with patients' survival [42]. Specific associations have been identified between intron rs3804639 as well as 3′-untranslated region (UTR) SNPs rs9879947 and rs3206652 in CD47 and frequencies of tumor metastasis [43]. However, the precise impacts of these SNPs on CD47's transcriptional and post-translational modifications remain elusive [44]. Calreticulin, a chaperone protein that antagonizes CD47, is downregulated in CRC cells overexpressing CD47, suggesting a mechanism for immune evasion [45]. Schölch et al. [45] observed that this overexpression pattern is prevalent in circulating CRC tumor cells. This suggests that overexpression of CD47 downregulates calreticulin expression and may be a phenotype that facilitates CRC cells in evading the immune system [45]. Moreover, Zhang et al. [46] demonstrated an increase in $CD68^{+}$/$CD206^{+}$ M2 macrophages in human colon cancer cells, concurrent with increased CD47 and SIRPα expressions, indicating a potential for enhanced tumor cell migration and metastasis in CD47-influenced microenvironments. Additionally, Zhou et al. [47] suggested that the overexpression of CD47 driven by prolyl 4-hydroxylase subunit alpha 3 (P4HA3) might help colon cancer cells to evade phagocytosis by macrophages. Moreover, P4HA3 facilitates the secretion of cytokines interleukin (IL)-34 and macrophage-colony stimulating factor (M-CSF) in colon cancer cells, which further promotes the differentiation of macrophages into the M2 type, hence driving the progression of colon cancer [47]. Therefore, CD47 expression acts as a robust prognostic indicator in CRC.

3.4. Pancreatic cancer

Pancreatic cancer, a notably malignant GI cancer, is characterized by an extremely poor prognosis due to challenges in diagnosis and treatment [48]. While the clinical diagnostic markers for pancreatic cancer are well understood, current diagnostic methods remain limited [49]. Studies have indicated that CD47 expression correlates with a poor prognosis in pancreatic cancer [50]. Specifically, in pancreatic ductal adenocarcinoma (PDAC), Cioffi et al. [51] identified that PDAC cancer stem cells (CSCs) overexpress CD47 [51]. Blocking the CD47-SIRPα signaling pathway with anti-CD47 monoclonal antibodies enhances PDAC phagocytosis and induces apoptosis. Moreover, Xi et al. [52] reported that CD47 expression is significantly higher in primary PDAC tissues than in normal pancreatic tissues, with high expression levels associated with reduced survival rates in patients. In pancreatic neuroendocrine tumors (PanNETs), Krampitz et al. [53] showed that CD47 expression was higher in PanNETs tissues compared to adjacent normal pancreatic tissue. Blocking CD47-SIRPα interaction with monoclonal antibodies increased macrophage phagocytosis of tumor cells, thereby reducing tumor growth and metastasis, and positively impacting prognosis [53]. These findings collectively suggest that CD47 expression may be a marker of poor prognosis in pancreatic cancer.

3.5. HCC

HCC, a common type of GI cancer, is the sixth most common cancer and the third highest cause of cancer-related mortality worldwide [54]. In HCC patients, higher expression levels of CD47 in tumor cells correlate with decreased overall survival and lower recurrence-free survival rates [55]. Lee et al. [56] demonstrated that CD47 levels are higher in chemotherapy-resistant HCC patients compared to normal samples, correlating with reduced patient survival rates. This may be due to CD47 mediating HCC tumorigenicity, metastatic potential, and self-renewal through cathepsin S [56]. Additionally, CD47 expression levels are modulated by signal transducer and activator of transcription 3 (STAT3) [57]. Mechanistic studies revealed an abundance of macrophage infiltrates in HCC, with macrophage-derived IL-6 upregulating CD47 expression on HCC cells via the STAT3 signaling pathway [57]. MicroRNAs (miRNAs) regulation of CD47 expression at the post-transcriptional level via the 3′-UTR region of *CD47 mRNA* promotes HCC immune evasion [16]. However, CD47 expression in fibrolamellar HCC (FL-HCC) contradicts previous studies [58]. According to Cooney et al. [58], weak CD47 expression was observed in FL-HCC patient samples, with no significant difference compared to normal liver samples. Hence, further research is required to elucidate CD47's prognostic value in HCC through expanded clinical studies.

4. The rationale of targeting CD47-SIRPα signaling pathway in the GI cancer

The tumor microenvironment (TME) of GI cancer is a complex and dynamic system comprising immune cells, blood vessels, fibroblasts, stromal cells, and various cytokines [59]. The activity and quantity of immune cells, such as antigen-presenting cells, T cells, B lymphocyte (B cells), macrophages, and natural killer (NK) cells, are critical in influencing the progression and prognosis of GI cancer [59]. Blood vessels and fibroblasts contribute to tumor growth and metastasis, while stromal cells influence tumor invasion and spread by regulating extracellular matrix components like collagen and fibronectin [60]. Additionally, a series of cytokines, such as angiogenic factors, inflammatory factors, and growth factors, are also closely related to the proliferation, metastasis, and prognosis of GI cancer [61]. CD47 is expressed not only on cancer cells, but also on stromal cells such as endothelial cells, fibroblasts, and immune cells within TME [62]. The expression of CD47 on stromal cells plays a role in angiogenesis, cancer progression, and immune escape [63]. Therefore, targeting CD47 boosts macrophage-induced clearance of cancer cells and has a direct impact on stromal cell activity in the GI TME. In this section, we summarize how blocking the CD47-SIRPα signaling pathway in the TME promotes tumor cell elimination through four distinct pathways [64] (Fig. 3).

In the first pathway, blocking the anti-phagocytic signal is mediated by the CD47-SIRPα interaction with CD47 or SIRPα antibody [65] (Fig. 3A). This process shifts the immunosuppressive phenotype of tumor-associated macrophages (TAMs) towards an anti-tumor M1 subtype and promotes M1 macrophage-mediated antibody dependent cellular phagocytosis (ADCP) activity [66]. Duan et al. [67] reported that Epstein-Barr virus (EBV)-induced CD47 upregulation in EBVaGC via the cyclic gaunosine monophosphate (cGMP)-adenosine monophosphate (AMP) synthase

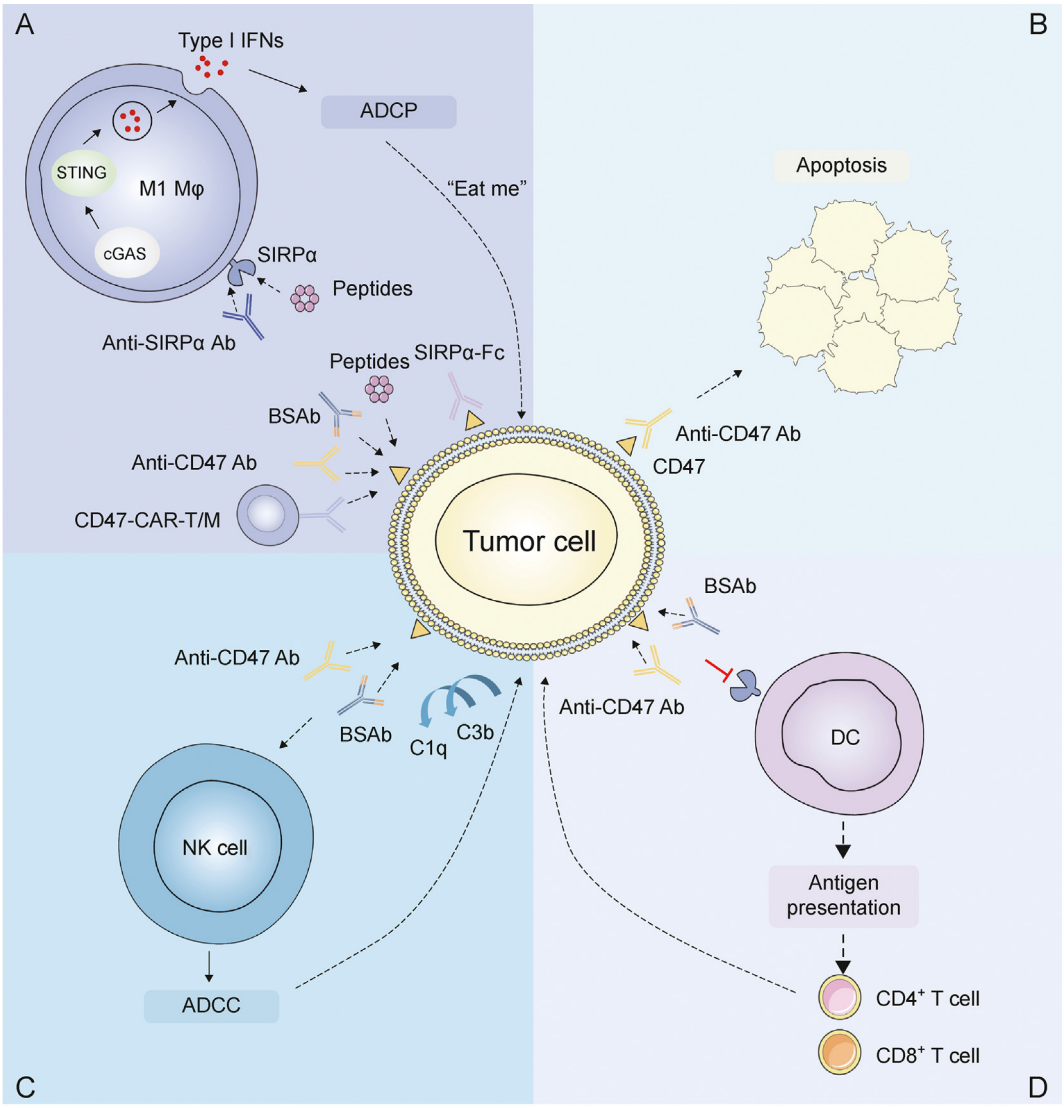

Fig. 3. Rationale for targeting the cluster of differentiation 47 (CD47)-signal regulatory protein alpha (SIRPα) signal pathway in gastrointestinal (GI) cancer. (A) First, blocking the anti-phagocytic signal is mediated by CD47 or SIRPα antibody. (B) Second, anti-CD47 antibodies induce tumor cell apoptosis. (C) Third, anti-CD47 antibodies activate the innate immune response, mediated by natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC). (D) Fourth, blocking the CD47-SIRPα signaling pathway enhances the antigen presentation ability of dendritic cell (DC), subsequently presenting antigens to $CD4^+$ and $CD8^+$ T lymphocytes (T cells). cGAS: GMP-AMP synthase; STING: stimulator of interferon genes; M1 Mϕ: M1 macrophages; IFN: interferon; Anti-CD47 Ab: monoclonal antibodies (mAbs) targeting CD47; SIRPα-Fc: the extracellular domain of SIRPα with the IgG1 Fc fragment of an antibody; BSAbs: bispecific antibodies; CD47-CAR-T/M: CD47 antigen-binding chimeric antigen receptor (CAR)-T cells/macrophages; C1q: complement C1q protein; C3b: complement C3b protein; ADCP: antibody-dependent cellular phagocytosis.

(cGAS)-stimulator of interferon genes (STING) pathway can be counteracted by anti-CD47 antibody blockade, thereby enhancing interferon (IFN)-β-mediated macrophage infiltration and ADCP in EBVaGC. Kosaka et al. [68] demonstrated that combined anti-CD47 and cyclic GMP-AMP (cGAMP) monoclonal antibody (mAb) treatment induces robust anti-tumor immune responses through the activation of the STING and type I IFNs signaling pathways.

In the second pathway, anti-CD47 antibody induces tumor cell apoptosis primarily through direct CD47 ligation, independent of the caspase pathway [69] (Fig. 3B). Trabulo et al. [70] demonstrated that anti-CD47 treatment not only promotes macrophage-mediated phagocytosis of pancreatic cancer cells but also directly induces apoptosis of these cells without affecting normal cells.

In the third pathway, anti-CD47 antibody activates the innate immune responses through antibody-dependent cytotoxicity, inducing NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC) in an Fc receptor-dependent manner [24] (Fig. 3C). Chao et al. [71] demonstrated that magrolimab (Hu5F9-G4) mAb treatment enhanced Fc receptor-mediated effector functions, primarily through ADCC, to inhibit CRC cell growth. Du et al. [72] reported that glypican-3 (GPC3)/CD47 bispecific antibody (BSAb) treatment impedes HCC cell growth via NK cell-mediated ADCC.

In the fourth pathway, blocking the CD47-SIRPα signaling pathway enhances the antigen presentation capacity of DCs, activating $CD4^+$ and $CD8^+$ T cells and the adaptive immune response [73] (Fig. 3D). Zhang et al. [46] observed that an antibody blocking SIRPα enhanced DC antigen presentation capabilities, inhibiting the malignant progression and metastasis of colon cancer cells in a TAM-rich TME. Tao et al. [74] showed that CD47 mAb treatment significantly increased the number of intratumoral $CD8^+$ T cells, enhancing adaptive immune responses and inhibiting ESCC cell

proliferation. While therapeutic strategies targeting the CD47-SIRPα pathway have been primarily studied in hematological malignancies, limited research demonstrated the underlying mechanisms for treating GI cancers with this approach [73]. Thus, a more detailed understanding of targeting the CD47-SIRPα signaling pathway in GI cancer is necessary.

5. Therapeutic strategies targeting the CD47-SIRPα signal pathway in GI cancers

Immune checkpoint inhibition therapies for tumors have achieved breakthrough progress in recent years, significantly improving patient prognosis [75]. Currently, extensive research focuses on lymphocyte checkpoint regulators modulating adaptive T cell responses, such as PD-1, PD-L1, and CTLA-4 [76]. Beyond lymphoid immune checkpoints, CD47 acts as an immune checkpoint for myeloid cells, part of the innate immune system, and presents as a potential target for cancer immunotherapy [18]. The overexpression of CD47 in various cancers has directed increased research to evaluate its therapeutic potential [77]. Basic and clinical trials of CD47-targeted therapies have shown encouraging results in hematological malignancies [78]. However, the development of blockers targeting the innate immune checkpoint CD47-SIRPα signaling pathway in GI cancers remains nascent in cancer treatment [78]. We next summarize blockers targeting the CD47-SIRPα signaling pathway for treating GI cancer, including 1) monoclonal antibodies, 2) recombinant fusion proteins, 3) BsAb, 4) miRNA, 5) small molecules inhibitors, 6) peptides, and 7) CD47-chimeric antigen receptor (CAR)-T cell/macrophages (Table S1).

5.1. mAb targeting CD47

GI cancer cells commonly display an overexpression of CD47 on their surface, acting as a defense mechanism against phagocytosis [79]. Monoclonal antibodies targeting CD47 disrupt the CD47-SIRPα interaction, thereby blocking anti-phagocytic signal transmission and significantly enhancing macrophage phagocytosis of GI cancer cells [79]. The use of CD47 monoclonal antibodies has provided new insights into the immunotherapy for GI cancer [50]. Here, we present reliable evidence for the use of monoclonal antibodies in GI cancer treatment, including Hu5F9-G4, B6H12, and MIAP410.

Hu5F9-G4, a humanized IgG4 mAb, specifically targets human CD47 [78]. It has shown notable anti-tumor effects in GI cancers and is currently in phase III clinical trials [71]. Chao et al. [71] demonstrated that Hu5F9-G4 treatment inhibits CRC development by promoting a strong pro-phagocytic signal through Fc receptor-mediated ADCC. Additionally, Barkal et al. [80] observed that Hu5F9-G4 significantly increases macrophage phagocytosis of PanNET by blocking the CD47-SIRPα interaction and opsonizing cells through its functional IgG4 crystallizable fragment, which serves as an “eat me” signal to activate macrophage Fc receptors.

B6H12, an IgG1-type anti-CD47 mAb, is widely used in preclinical studies [53]. It enhances macrophage phagocytosis of cancer cells in GI cancer treatment by targeting CD47 to disrupt its interaction with SIRPα [81]. In recent years, the use of B6H12 in GI cancer treatment has increased, showing promising therapeutic effects [51]. Yoshida et al. [40] found that B6H12, targeting CD47, inhibits GC cell dissemination and prolongs survival by enhancing macrophage-mediated ADCP against GC cells (Fig. 4A). Cioffi et al. [51] showed that B6H12 enables macrophage phagocytosis of PDAC cells and directly induces PDAC cell apoptosis, without affecting normal cells (Fig. 4B). By targeting CD47 on PDAC cells, it alters TAM infiltration behavior, thereby inhibiting tumor proliferation [51]. Additionally, the use of B6H12 in HCC treatment strategies significantly enhances tumor inhibition [82]. Lo et al. [82] demonstrated that B6H12 suppresses tumor-initiating, migration, and invasion abilities, and mediates macrophage phagocytosis of HCC cells.

MIAP410, a mouse mAb under preclinical studies, specifically binds to human CD47 [83]. While it shows a weaker ability to disrupt the SIRPα-CD47 interaction, it possesses a higher affinity for mouse-derived FcR compared with other anti-CD47 monoclonal antibodies [83]. MIAP410 has been demonstrated to target CD47 in GI cancers [74]. Tao et al. [74] found that MIAP410 treatment in ESCC enhances both macrophage phagocytosis and DC antigen presentation, thus triggering a robust anti-tumor immune response (Fig. 4C). This suggests its potential as a novel target for enhancing the efficacy of PD-1 and CTLA-4 antibodies in ESCC.

In recent years, significant progress has been made in clinical studies involving CD47 monoclonal antibodies, including ligufalimab (AK117), lemzoparlimab (TJC4), AO-176, and CC-9000245 [84]. These antibodies are widely applied in treating both hematological malignancies and solid tumors [85]. However, research into their use in GI cancers is lacking. Hence, further exploration and expansion of their clinical use in treating GI cancers are essential.

5.2. mAb targeting SIRPα

SIRPα, predominantly found on myeloid cells, presents a therapeutic opportunity [86]. Using monoclonal antibodies to target SIRPα offers advantages over anti-CD47 antibodies, notably by avoiding adverse effects caused by non-specific binding to non-tumor cells [69]. Anti-SIRPα mAb can block the CD47-SIRPα interaction, inhibit anti-phagocytic signal transmission, and enhance macrophage-mediated ADCP, thus improving anti-tumor efficacy in GI cancers [7]. Abe et al. [87] showed that anti-SIRPα mAb increases macrophage phagocytosis of CRC cells, consequently inhibiting CRC progression and significantly boosting overall survival rates (Fig. 5A). Furthermore, anti-SIRPα mAb has been applied in HCC treatment and thoroughly evaluated in clinical trials, specifically in a trial (NCT02868255) focusing on the expression of CD47 and SIRPα on HCC cells and the therapeutic impact of anti-SIRPα mAb on HCC patients [22] (Fig. 5B). Additionally, anti-SIRPα mAbs like OSE-172 (BI 765063), FSI-189, and CC-95251 have shown progress in tumor treatments [84,88,89]. However, research on using anti-SIRPα mAb to disrupt the CD47-SIRPα signaling pathway in GI cancers is still nascent, necessitating further exploration of anti-SIRPα antibody applications in GI diseases.

5.3. The recombinant fusion protein targeting CD47

Recombinant fusion proteins, binding to CD47 on tumor cells, disrupt phagocytic inhibitory signals and facilitate macrophage-mediated phagocytosis [84]. This is achieved by fusing the extracellular domain of SIRPα with the IgG1 Fc fragment of an antibody, similar to dual-arm monoclonal antibodies blocking CD47 [90,91]. These recombinant fusion proteins offer the advantages of high affinity and a lower molecular weight compared to monoclonal antibodies, enabling easier penetration into solid tumors through leaky capillaries by simple diffusion [92]. Notably, ALX148, IMM01, and TTI-621 emerge as novel strategies in GI cancer treatment [18,92,93].

ALX148 combines a mutated SIRPα domain with an inactive immunoglobulin Fc region, forming a decoy receptor fusion protein [94]. It enhances the innate immune system's anti-tumor response by boosting DC antigen presentation and macrophage phagocytosis, and by transforming TAMs into an inflammatory phenotype [92]. It also augments the adaptive immune system's anti-tumor response, increasing T cell effector function, inflammatory factor production, and inhibiting tumor cell proliferation

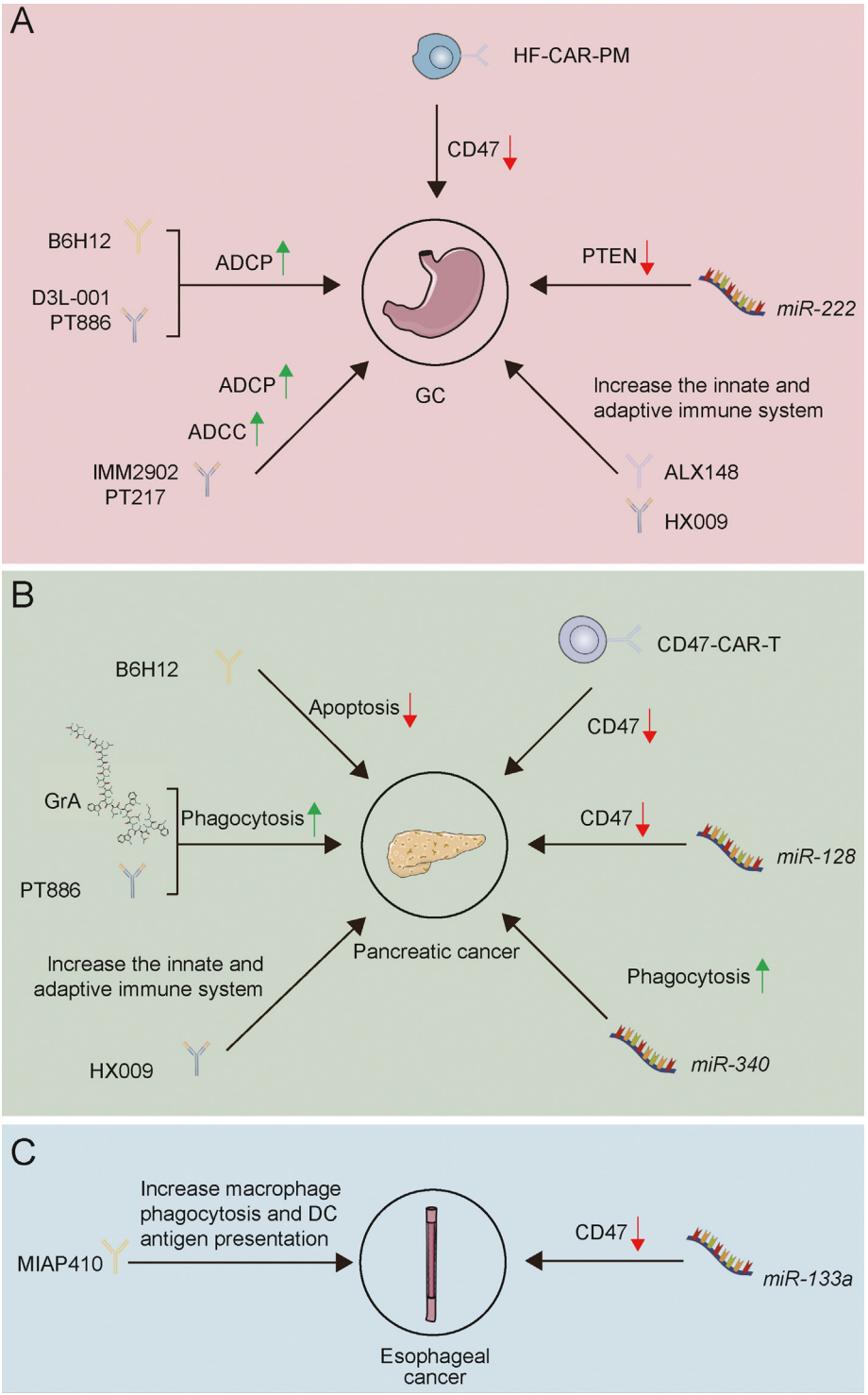

Fig. 4. Schematic representation of the mechanisms of action of different strategies for treating esophageal cancer, gastric cancer (GC), and pancreatic cancer. (A) Therapeutic strategies targeting the cluster of differentiation 47 (CD47)-signal regulatory protein alpha (SIRPα) signal pathway in GC. (B) Therapeutic strategies targeting the CD47-SIRPα signal pathway in pancreatic cancer. (C) Therapeutic strategies targeting the CD47-SIRPα signal pathway in esophageal cancers. HF-CAR-PM: human epidermal growth factor receptor 2-Fc epsilon receptor Ig-chimeric antigen receptor-peritoneal macrophages; ADCP: antibody-dependent cellular phagocytosis; ADCC: antibody-dependent cellular cytotoxicity; PTEN: phosphatase and tensin homologue; CD47-CAR-T: CD47 antigen-binding chimeric antigen receptor (CAR)-T cells; GrA: gramicidin A; DC: dendritic cell.

within the TME [92]. CD47 is a known prognostic biomarker linked to immune infiltration in CRC [95]. It has been found that ALX148 targets CD47, enhancing DC antigen presentation, macrophage phagocytosis, and T cell proliferation, thereby amplifying the immune response to CRC [95] (Fig. 5A). ALX148 was previously under evaluation in phase I clinical trials [96]. In one trial (NCT03013218), ALX148 combined with standard anti-cancer therapies showed promising anti-tumor activity in advanced GC treatment [96]. Another ongoing randomized phase 2/3 study (NCT05002127) is investigating ALX148 in combination

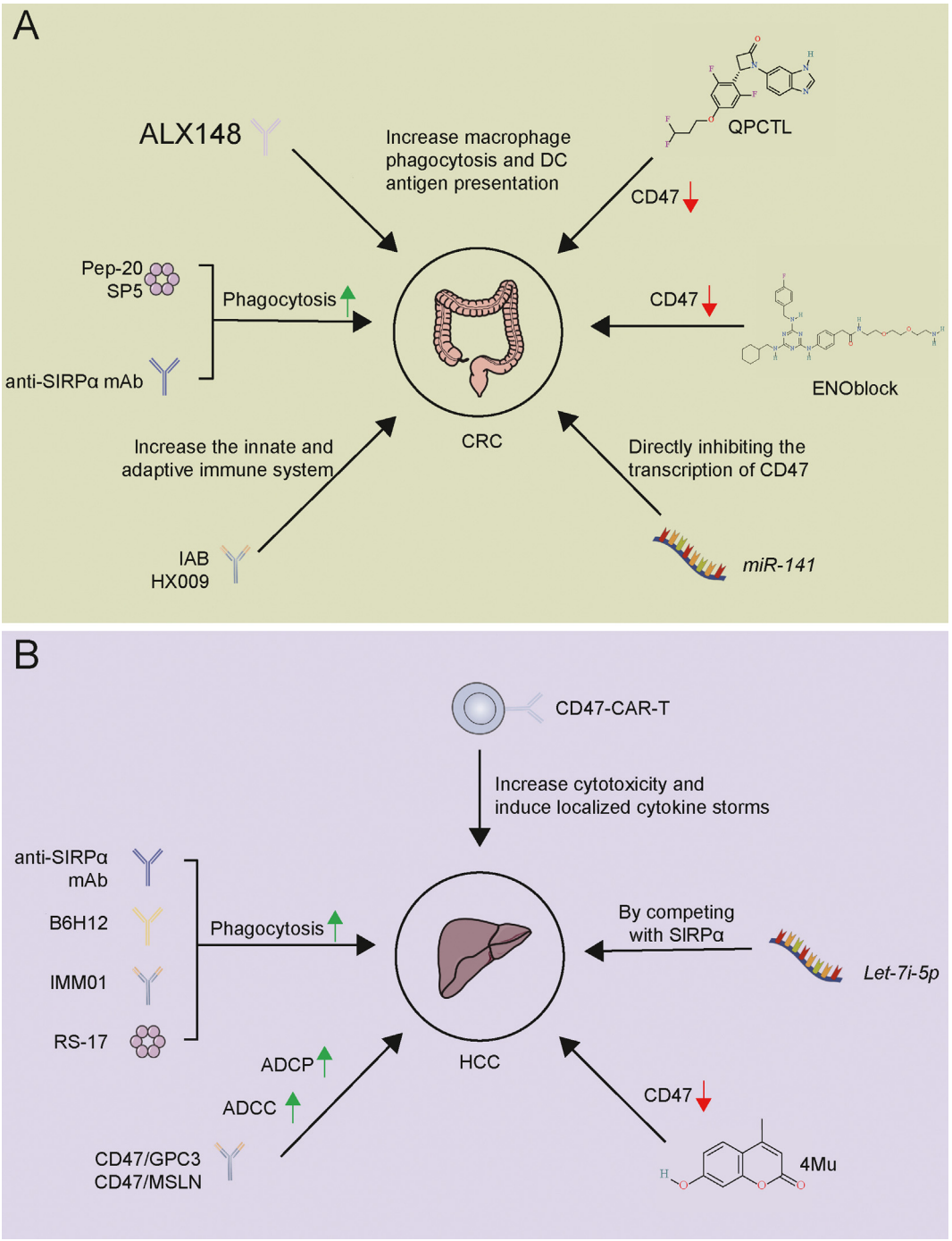

Fig. 5. Schematic representation of the mechanisms of action of different strategies for treating colorectal cancer (CRC) and hepatocellular carcinoma (HCC). (A) Therapeutic strategies targeting the cluster of differentiation 47 (CD47)-signal regulatory protein alpha (SIRPα) signal pathway in CRC. (B) Therapeutic strategies targeting the CD47-SIRPα signal pathway in HCC. DC :dentric cell; QPCTL: glutaminyl-peptide cyclotransferase-like; ENOblock: AP-III-a4; mAb:monoclonal antibody; 4Mu: 4-methylumbelliferone; CD47-CAR-T: CD47 antigen-binding chimeric antigen receptor (CAR)-T-cell; 4Mu: 4-methylumbelliferone; ADCP: antibody-dependent cellular phagocytosis; ADCC: antibody-dependent cellular cytotoxicity.

with trastuzumab, ramucirumab, and paclitaxel in treating advanced positive human epidermal growth factor receptor 2 ($HER2^+$) GC [97]. These studies are expected to provide a substantial theoretical basis for ALX148's targeted therapy in GI cancer clinical research.

IMM01, derived from V2D1 with an N80A mutation in the context of wild-type IgG1-Fc, notably does not bind to human erythrocytes, thus avoiding the "antigenic sink" phenomenon [98]. As a single-agent therapy, IMM01 exhibits potent anti-tumor activity through a dual mechanism: it effectively blocks the CD47-SIRPα signaling pathway and activates the "eat me" signal via Fc-FcγR interactions [99]. By targeting CD47, IMM01 stimulates macrophages to efficiently eliminate tumor cells and enhances tumor antigen presentation to T cells, demonstrating robust anti-tumor efficacy as a monotherapy [99]. A recent clinical trial (NCT05833984) by ImmuneOnco Biopharmaceuticals (Shanghai) Inc. (Shanghai, China) aims to assess IMM01's effectiveness in advanced solid tumors, including HCC [24] (Fig. 5B). However,

research into IMM01's application in GI cancer treatment remains limited, necessitating further clinical trials and in-depth studies to ascertain its effectiveness and potential in this area.

TTI-621, a SIRPα-IgG1 Fc fusion protein, functions as a decoy receptor that binds to CD47 on tumor cells to block the "don't eat me" signal [100]. This recombinant protein comprises the N-terminal V domain of a human SIRPα allelic variant V2 fused to the human IgG1 Fc region [100]. The interaction between TTI-621's IgG1 Fc region and Fcγ receptors on macrophages enhances phagocytosis and augments anti-tumor activity [101]. Studies have shown TTI-621 targeting CD47 boosts macrophage phagocytosis of tumor cells in acute myeloid leukemia (AML) and B cell lymphoma xenografts [102]. Previously, TTI-621 was in phase I clinical trials (NCT02663518 and NCT02890368, conducted by Trillium Therapeutics Inc. (Toronto, Canada)), showing promising results in patients with relapsed or refractory hematological cancers and several solid tumors [22,101]. However, specific data on TTI-621's efficacy in GI cancer treatment was not mentioned in these reports. These clinical studies imply TTI-621's potential in GI cancer treatment, but further research and clinical trials are essential to determine its efficacy.

5.4. BSAb targeting CD47

BSAbs targeting CD47 can be developed using CD47 or SIRPα targeting antibodies and other antigen targeting molecules [102]. These antibodies possess the ability to simultaneously bind to either two different epitopes of one target or two separate targets [103]. The antigen-binding sites of BSAbs can consist of either two antibodies or proteins (ligand or receptor), or a combination of one antibody and one protein [103]. Rational design of BSAbs, based on biological activity, can lead to distinct or enhanced efficacy in tumor treatment compared to mAb therapies [85]. Currently, there are seven BSAbs, IMM2902, D3L-001, IAB, CD47/GPC3, CD47/MSLN, PT217, and HX009, that have shown potential in the treatment of GI cancer.

IMM2902, a BSAb targeting CD47 and HER2, is utilized in treating gastric and breast cancers [104]. IMM2902's mechanism involves enhancing ADCP and ADCC activities and accelerating HER2 degradation when the targets are crosslinked by IMM2902 [18]. Tian et al.'s [105] preclinical studies showed that IMM2902 exhibits strong anti-tumor activity, capable of completely eradicating established tumors in GC and breast models (Fig. 4A). Additionally, other clinical trials (NCT05805956 and NCT05076591) are evaluating IMM2902's therapeutic efficacy in advanced GC [106]. These results indicate IMM2902's potential as an effective treatment for $HER2^+$ cancers, particularly in patients unresponsive to trastuzumab therapy.

D3L-001, another BSAb targeting CD47 and HER2, exhibits higher affinity for HER2 over CD47 [107]. Its unique design results in a preference for binding to HER2/CD47 double-positive tumor cells over CD47 single-positive cells [107]. Studies have demonstrated D3L-001's significant anti-tumor effects in solid tumor models, including gastric and breast cancers [108]. Rui et al. [108] used immunohistochemistry to analyze formalin fixed paraffin embedded (FFPE) tumor sections, assessing HER2 and CD47 expressions in their tested models, and found D3L-001 capable of effectively inhibiting tumor growth in HER2 and CD47 double-positive GC and breast cancer (Fig. 4A). Hence, D3L-001's potential in $HER2^+$ GC and breast cancers implies its applicability in GI cancers, though further studies are needed to specifically ascertain its efficacy in GI cancers.

IAB is an innovative dual-target fusion protein engineered to concurrently target CD47 and PD-L1. It stimulates T cell activation, induces tumor cell phagocytosis, and enhances ADCC, playing a significant anti-tumor role in colon cancer treatment (Fig. 5A). Experimental studies in colon cancer animal models have demonstrated that IAB augments the synergistic effect of both innate and adaptive immunity. This occurs through the blockade of CD47 and PD-L1, enhancing macrophage and T cell mediated tumor cell destruction, and preventing immune escape of circulating tumor cells. Additionally, IAB displays high safety but no hematological toxicity in GI cancer treatment. Therefore, IAB is a promising candidate for therapeutic strategies in GI cancers.

PT886, a native IgG-like BSAb, targets claudin-18 isoform 2 (CLDN18.2) and CD47 [109]. It shows a strong affinity for cell surface CLDN18.2 and a weaker affinity for CD47 [109]. This unique attribute allows PT886 to selectively bind to tumor cells overexpressing both CLDN18.2 and CD47, while minimizing binding to normal cells expressing CD47 alone [110]. PT886's therapeutic approach, targeting both CLDN18.2 and CD47, combats cancer progression via two mechanisms: 1) blocking the CD47-SIRPα interaction and stimulating macrophage-mediated tumor cell phagocytosis and 2) leveraging the functional Fc of the BSAb for effects like ADCC and ADCP [111]. In a pancreatic cancer xenograft model, Li et al. [111] showed that PT886 prompts macrophages to enhance phagocytosis of pancreatic cancer cells, leading to complete tumor eradication (Fig. 4B). Furthermore, MD Anderson Cancer Center (Houston, TX, USA) is conducting a phase I interventional clinical trial (NCT05482893) to evaluate PT886's therapeutic efficacy in patients with advanced gastric and gastroesophageal junction adenocarcinomas [112]. Preliminary results suggest PT886's effectiveness in treating advanced GC by intensifying TAMs' killing activity [60]. These findings highlight PT886's potential as a viable treatment option for GI cancers characterized by overexpression of CLDN18.2 and CD47.

CD47/GPC3, a BSAb targeting both CD47 and GPC3, effectively inhibits tumor growth by recognizing these two antigens [113]. GPC3 is a distinctive cell surface-associated antigen in HCC. Like CD47, it is overexpressed in liver cells and may be used as an early diagnostic marker [72]. Compared to anti-CD47 antibodies alone, CD47/GPC3 BSAbs exhibit greater specificity, stability, and a lack of adverse systemic effects in HCC treatment [114]. In a xenotransplantation HCC model, Du et al. [72] found that CD47/GPC3 BsAb effectively activates Fc-mediated effector functions in double-positive liver cancer cells *in vitro*, leading to macrophage and neutrophil stimulation and consequent suppression of xenografted HCC (Fig. 5B). Significantly, CD47/GPC3 BsAb demonstrates enhanced efficacy compared to separate treatments with CD47 or GPC3 mAb [72]. Thus, the CD47/GPC3 strategy appears promising for improving HCC treatment by augmenting the innate immune response.

CD47/MSLN is a BSAb that specifically binds to the proximal membrane epitope of MSLN and disrupts the CD47-SIRPα signaling cascade to enhance ADCP and ADCC functions through preferentially activating the FcγR-IIIA pathway [114]. In a hepatic xenograft tumor model, Hatterer et al. [115] showed that CD47/MSLN exhibits significant anti-tumor activity by enhancing both ADCC and ADCP. Additionally, Ferlin et al. [116] observed that CD47/MSLN effectively eliminates HCC cells by boosting ADCP through macrophage recruitment (Fig. 5B). These studies underscore CD47/MSLN's role in facilitating immune-mediated tumor cell eradication, highlighting its potential as an effective cancer therapy.

PT217, a novel native IgG-like BSAb, targets DLL3 and CD47 to treat refractory tumors [117]. It is designed to eradicate tumor cells through both macrophage-mediated ADCP and NK cell-mediated ADCC [118,119]. PT217 also aids in presenting tumor neoantigens by directing tumor cells to antigen-presenting cells, indirectly activating T cell responses against DLL3-expressing tumor cells through recognition of tumor neoantigens, thereby stimulating the adaptive immune system [102]. A clinical trial (NCT05652686) at

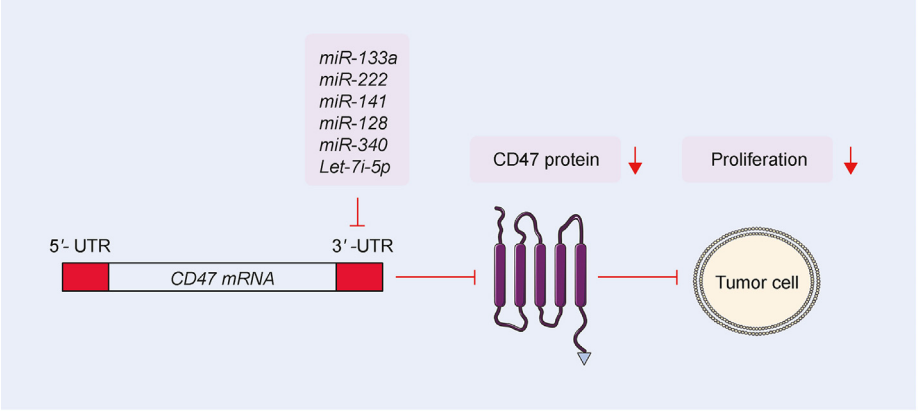

Fig. 6. Schematic representation of microRNAs (miRNA) regulating tumor cell proliferation by directly binding to the 3′-untranslated region (UTR) of cluster of differentiation 47 messenger RNA (*CD47 mRNA*).

the Dana-Farber Cancer Institute (Boston, MA, USA) is currently evaluating PT217's therapeutic efficacy in treating advanced gastroenteropancreatic neuroendocrine tumors expressing DLL3 [120] (Fig. 4A). Consequently, PT217 exhibits considerable potential in GI cancer treatment.

HX009 is a BSAb targeting the extracellular domain of SIRPα and the human IgG4-Fc region of anti-PD-1 mAb [121]. It achieves synergistic anti-tumor effects by concurrently activating both innate and adaptive immune responses, thus preventing tumor immune escape [85]. HX009 was undergoing a phase I clinical trial (NCT04097769), designed to assess its therapeutic effect in patients with advanced solid tumors, including CRC, pancreatic cancer, gastroesophageal junction adenocarcinoma, and others [122]. Consequently, developing HX009 as a targeted treatment for GI cancers represents a promising approach.

5.5. miRNA targeting CD47

MiRNAs are small non-coding RNA molecules that profoundly influence gene expression at the post-transcriptional level [123]. By binding to the 3′-UTR of target mRNAs, they can inhibit translation or promote degradation [124] (Fig. 6). miRNAs play a crucial role in cellular processes such as cell proliferation, differentiation, and apoptosis by downregulating their target genes [124]. Thus, miRNAs have garnered significant interest as potential therapeutic tools for treating GI cancers in humans [125]. Currently, identified miRNAs targeting CD47 in GI cancer treatment include *miR-133a*, *miR-222*, *miR-141*, *miR-128*, *miR-340*, and *Let-7i-5* [119,126].

miR-133a, a direct regulator of CD47, has shown a notable inhibitory effect on tumor occurrence and metastasis *in vivo* [126]. Extensive research into *miR-133a* across different cancer types has identified variations in its expression levels and regulatory functions [127]. These findings have prompted exploration of *miR-133a* as a potential therapeutic target or biomarker for cancer [127]. Suzuki et al. [33] found that *miR-133a* expression was significantly reduced in ESCC compared to adjacent normal tissues [33]. There was a negative correlation between *miR-133a* transfected cells and CD47 expression (Fig. 4C). Additionally, *in vivo* studies revealed *miR-133a*'s tumor growth inhibitory effects, acting as a tumor suppressor in ESCC and impacting CD47's role in tumorigenesis [33]. Thus, CD47 expression is identified as a novel prognostic marker in ESCC, directly suppressed by the tumor suppressor *miR-133a*, offering new insights into cancer progression mechanisms and a promising target for ESCC therapy.

miR-222 is a significant miRNA located on the Xp11.3 region of the human chromosome, displaying high sequence similarity [128]. It suppresses CD47 expression by directly binding to the 3′-UTR of *CD47 mRNA* at the transcriptional level [126,129]. Zhang et al. [130] showed that elevated levels of *miR-222* lead to a marked reduction in the sensitivity of GC cells to radiation by repressing phosphatase and tensin homolog (PTEN) (Fig. 4A). Conversely, Shi et al. [129] found that CD47 is a target of *miR-222*, and its overexpression increases the radiosensitivity of cervical and lung cancer cells by inhibiting CD47 at both the transcriptional and protein levels. Thus, *miR-222* may enhance the radiosensitivity of GC cells by targeting CD47, offering new avenues for therapeutic intervention and radio sensitization in GC.

miR-141, part of the *miR-200* family, negatively regulates CD47 by binding to its 3′-UTR, impacting cancer progression [131]. Numerous studies have identified *miR-141*'s significant role in colon cancer treatment [132]. Tang et al. [132] demonstrated decreased *miR-141* expression and increased CD47 and cullin 3 (CUL3) expressions in colon tissue of Hirschsprung disease patients compared to controls (Fig. 5A). *In vitro* experiments indicated that *miR-141* reduces tumor cell proliferation and migration by directly inhibiting the transcription of CD47 and CUL3 [132]. These findings suggest that targeting CD47 with *miR-141* could be a novel therapeutic approach for CRC.

miR-128, an intronic miRNA, is produced by two separate genes, *miR-128-1* and *miR-128-2*, located in the introns of R3H domain containing 1 (*R3HDM1)* and cyclic AMP (cAMP)-regulated phosphoprotein (ARPP-21) genes, respectively [133]. It acts as a key regulatory factor in tumor immunity, influencing the E-box binding homeobox 1 (ZEB1)-CD47 signaling pathway and epithelial-mesenchymal transition (EMT) in PDAC treatment [134]. Xi et al. [134] demonstrated that *miR-128* effectively inhibits the growth and metastasis of pancreatic cancer cells by regulating ZEB1, which in turn affects CD47 expression in pancreatic cancer cells, enhancing macrophage phagocytosis and DC activity for anti-tumor effects (Fig. 4B). This study unveils a new mechanism where *miR-128* enhances anti-tumor immunity via modulation of the ZEB1-CD47 signaling pathway, linking EMT regulation to anti-tumor immunity in PDAC.

miR-340, an intragenic miRNA located within the intronic region of the *RNF130* host gene on chromosome 5q35.3, regulates tumor cell progression as a tumor suppressor by binding directly to the 3′-UTR of *CD47 mRNA* [135]. It exerts a direct regulatory effect on CD47 and is inversely correlated with CD47 levels, serving as a potential prognostic indicator for tumor patient survival rates [136]. Xi et al. [52] identified *miR-340* as a novel predictor of survival in pancreatic cancer patients and found that it enhances macrophage-mediated phagocytosis by binding directly to the 3′-UTR of *CD47 mRNA* on

pancreatic cancer cells (Fig. 4B). Therefore, *miR-340*'s role in regulating CD47 underscores its potential for immunotherapy in pancreatic cancer.

Let-7i-5p, part of the *Lethal-7 miRNA* family, is widely conserved across species, from reptiles to mammals [137]. Unlike miRNAs like *miR-21*, *miR-221*, and *miR-222*, which are often overexpressed in HCC, *Let-7i-5p* is frequently downregulated in HCC [123]. Research has shown that *Let-7i-5p* impacts liver cancer progression by disrupting the CD47-SIRPα interaction [138]. Yang et al. [138] found that the downregulation of *Let-7i-5p* increases the expression of TSP1, competing with SIRPα for binding to the CD47 receptor. This prevents anti-phagocytic and angiogenic signaling between macrophages and HCC cells, reducing HCC growth, proliferation, angiogenesis, and metastases by blocking the CD47-SIRPα signaling pathway [138] (Fig. 5B). Consequently, the downregulation of *Let-7i-5p* offers a new perspective for HCC treatment and highlights miRNA's potential as a therapeutic target.

miRNA-targeted CD47-SIRPα signaling pathway therapy is showing promise as a novel therapeutic approach in GI cancer treatment, however, there are several limitations that need to be addressed [123]. Firstly, miRNA-targeted therapy typically affects the regulation of multiple genes or signaling pathways beyond just CD47-SIRPα, potentially leading to unintended side effects [139]. Secondly, the specificity of miRNA molecules used in targeted therapy is crucial to ensure precise regulation of the target gene, presenting a challenge in achieving molecular specificity [140]. Thirdly, the delivery of miRNAs to target cells can be hindered by instability and background degradation, which may result in suboptimal therapeutic dosages or toxic effects [139]. Finally, the current research on miRNA-targeted treatment of the GI tract mainly focuses on targeting CD47 through affecting the CD47-SIRPα interaction via regulating CD47 expression [123]. Directly targeting the CD47-SIRPα signaling pathway remains an unexplored area, and further studies are needed to verify the therapeutic efficacy of miRNAs in this pathway.

5.6. Small-molecule inhibitors targeting CD47

Small-molecule inhibitors targeting the CD47-SIRPα signaling pathway represent a promising therapeutic strategy for GI cancers [5]. These inhibitors are categorized into two types based on their action mechanisms: the first type interferes with the CD47-SIRPα binding without cellular entry, while the second type penetrates cells and diminishes protein synthesis linked to the CD47-SIRPα signaling through regulation of transcription, translation, or post-translational modification [136]. Advantages of small-molecule compounds include easy tumor cell penetration, a short metabolic half-life, and manageable side effects [141]. Gramicidin A (GrA), AP-III-a4 (ENOblock), 4-methylumbelliferone (4Mu), and glutaminyl-peptide cyclotransferase-like (QPCTL) are four small-molecule inhibitors with potential in GI cancer therapy.

GrA, an ionophore antibiotic derived from microorganisms, forms channels across cell membranes, disrupting cellular ionic homeostasis and leading to cell dysfunction and death [142]. GrA modifies the distribution of CD47 protein on the cell membrane by inducing ultrastructural changes in the cancer cell membrane, thus regulating CD47 protein expression [143]. Wang et al. [144] found that GrA is particularly effective in targeting pancreatic CSCs. Mechanistically, GrA induces an immunosuppressive effect by downregulating CD47 protein levels on pancreatic CSCs and enhancing macrophage phagocytosis in these cells [144] (Fig. 4B). Therefore, GrA's targeted regulation of CD47 could positively impact pancreatic cancer treatment.

ENOblock, a newly identified small-molecule inhibitor, hampers ENO activity in tumors and disrupts the CD47-enolase 1 (ENO1) signaling pathway, thus inhibiting tumor proliferation [145]. Hu et al.'s [146] study revealed that ENOblock's inhibition of ENO1 activity reduces CD47-mediated colon cancer cell proliferation and metastasis (Fig. 5A). Clinically, the concurrent expressions of CD47 and ENO1 serve as a reliable prognostic biomarker in CRC patients. Given the significance of the CD47-ENO1 signaling pathway, ENOblock's indirect regulation of CD47 expression levels presents a viable approach for CRC treatment.

4Mu, a hyaluronic acid synthesis and angiogenesis inhibitor, targets CD47 to reduce CD47-related mRNA and protein production in cells, thus enhancing macrophage phagocytosis of cancer cells [147]. Rodríguez et al. [148] showed that 4Mu significantly reduces tumor volume and improves overall survival rates in an orthotopic HCC mouse model by downregulating CD47 at both transcriptional and protein levels in HCC cells (Fig. 5B). Furthermore, when combined with IL-12, 4Mu modulates CD47 expression, induces a potent cytotoxic T cell response, and extends survival in an HCC model developed in fibrotic liver [148]. Consequently, 4Mu's targeted regulation of CD47 at transcriptional and protein levels is a new promising therapeutic approach for GI cancers.

QPCTL, an enzyme catalyzing the cyclization of N-terminal glutamine and glutamic acid residues into the N-terminal pyroglutamate residue (pGlu), is targeted by inhibitors that disrupt CD47's N-terminal pGlu formation [149]. These inhibitors block the post-translational modification of CD47 protein, significantly reducing its binding to SIRPα and enhancing neutrophil-mediated cancer cell killing *in vivo* [126]. Wu et al. [150] demonstrated that QPCTL inhibitors downregulate CD47 expression by inhibiting its post-translational modification, thereby curbing the growth of colon cancer cells through macrophage-mediated phagocytosis (Fig. 5A). Therefore, targeting QPCTL represents a promising strategy for inhibiting CD47 expression in GI cancer treatment.

5.7. Peptides targeting CD47 or SIRPα

Bioactive peptide inhibitors effectively disrupt the CD47-SIRPα signaling pathway by binding to either CD47 or SIRPα, thereby achieving optimal anti-tumor effects [136]. Compared to monoclonal antibodies and recombinant proteins, peptides offer substantial advantages in terms of low immunogenicity, toxicity, cost, and ease of production and storage [151]. Recent reports on the use of peptides in GI cancer treatment include Pep-20, RS-17, D4-2, and SP5 and their derivatives [152]. Among these, RS-17 and Pep-20 inhibit the CD47-SIRPα signaling pathway by binding to CD47, while D4-2 and SP5 target SIRPα to disrupt this pathway [153].

5.7.1. Peptides targeting CD47

Pep-20, a 12-amino acid peptide, demonstrates high affinity for CD47, enhancing macrophage-mediated phagocytosis and the immune response in cancer immunotherapy [136]. Wang et al. [154] found that Pep-20 D12, a Pep-20 derivative, effectively suppresses colon cancer cell proliferation by promoting macrophage recognition and phagocytosis (Fig. 5A). Further studies, including docking models and alanine substitution experiments with Pep-20/CD47, identified phenylalanine 4, glutamic acid 104, and glutamic acid 106 on CD47 as critical sites for targeting by peptides [154]. These insights into Pep-20 D12's inhibitory role and the identification of key CD47 sites open new avenues for targeted GI cancer therapy. RS-17, a 17-amino acid peptide, directly targets human CD47 [154]. Xu and Wang [155] observed that RS-17 significantly reduces tumor growth in HCC xenotransplantation models by binding to CD47 on HCC cells, thereby enhancing macrophage phagocytosis efficiency (Fig. 5B). These findings provide valuable information about CD47 binding sites and the structural importance of peptides in GI cancer treatment.

5.7.2. Peptides targeting SIRPα

SP5 exhibits a strong affinity for SIRPα, blocking the SIRPα-CD47 signaling pathway in a dose-dependent manner [156]. Gao et al. [157] determined that SP5 effectively enhances macrophage phagocytosis of human colon tumor cells by binding to SIRPα and disrupting the CD47-SIRPα signaling pathway. Furthermore, SP5 has shown promising efficacy *in vivo* in colon tumor mouse models [157] (Fig. 5A). This suggests that SP5 could be a novel therapeutic strategy for colon cancer treatment. D4-2, a macrocyclic peptide binding to the extracellular domain of SIRPα, effectively inhibits the SIRPα-CD47 interaction through allosteric blocking [136]. Hazama et al.'s [151] research revealed that combining D4-2 with additional antibodies, such as CD20 or GP75, significantly enhances macrophage phagocytosis and effectively halts the growth and spread of solid tumors *in vivo*. However, D4-2's application in GI cancer research has yet to be reported, suggesting potential for its use in peptide-targeted GI cancer therapies.

5.8. Engineered T cells and macrophages

Immunotherapy has shown promise in treating various tumors using T cells engineered with a CAR [158]. CD47 antigen-binding CAR-T cells, termed CD47-CAR-T, are specifically designed to target the CD47 antigen [159]. By inhibiting CD47 and inducing localized cytokine storms, CD47-CAR-T cells significantly enhance cytotoxicity against cancer cells, including those in pancreatic cancer and HCC cell lines [159] (Figs. 4B and 5B). Golubovskaya et al. [160] employed the single-chain fragment variable (ScFv) of mouse CD47 antibody to generate CD47-CAR-T cells targeting diverse cancer cell lines, demonstrating their cytotoxic effects on HCC and pancreatic cancer cells, as well as cytokine production correlated with CD47 expression levels. Thus, CD47-CAR-T represents a novel immunotherapeutic avenue for GI cancer treatment.

Macrophages, the most prevalent tumor-infiltrating cells in various solid tumors, have garnered attention for their tumor-infiltrating capability, phagocytic activity, and antigen presentation role, particularly in the form of CAR-macrophage (CAR-M) [161,162]. In research by Dong et al. [163], a novel CAR-M was developed by genetically modifying human peritoneal macrophages (PMs) to express a HER2-FcεR1γ-CAR (HF-CAR). Their findings highlight HF-CAR-PM's potential as a promising therapeutic for $HER2^+$ GC [163] (Fig. 4A). Furthermore, other molecules like Megf10, FcgR, CD147, and CD3ζ have been investigated in the context of CAR-M [161,164]. This research suggests that employing CAR-M to block the CD47-SIRPα signaling pathway, either by targeting CD47, delivering CD47 blockers, or silencing SIRPα, could be effective in treating GI cancers.

6. Combination therapeutic strategy targeting the CD47-SIRPα signaling pathway

In the realm of GI cancer treatment, there is growing interest in employing combination therapeutic strategies targeting the CD47-SIRPα signaling pathway, in addition to developing new immunotherapies targeting CD47 or SIRPα [7]. These combination treatments primarily involve anti-CD47/anti-SIRPα therapies coupled with chemotherapy and ICIs, laying a foundation for clinical research in this area [69].

6.1. CD47-SIRPα blockers combined with chemotherapy

Chemotherapy drugs are widely used in managing GI cancer, yet patients exhibit varying response rates, and long-term use may lead to tumor resistance and additional side effects [165]. Consequently, identifying new combination strategies that enhance the efficacy of GI cancer treatment and mitigate the side effects of chemotherapy drugs is essential [166].

Anti-SIRPα antibodies, such as ALX148 and KWAR23, when combined with chemotherapy regimens, have shown excellent tolerability in GI cancers [18]. ALX148, in conjunction with standard doses of trastuzumab, ramucirumab, and paclitaxel, has yielded promising results [167]. This combination has proven effective in treating patients with advanced $HER2^+$ gastric or gastroesophageal junction cancer following HER2-targeted therapy [167]. Similarly, a recent clinical trial (NCT03013218) revealed that ALX148 combined with trastuzumab, ramucirumab, and paclitaxel in advanced head and neck squamous cell carcinoma (HNSC) and GC patients demonstrated a higher clinical remission rate compared to historical controls [18]. Moreover, Ring et al. [81] discovered that combining KWAR23 with cetuximab or panitumumab inhibited the growth of colorectal adenocarcinoma cells by promoting macrophage-mediated phagocytosis. Additionally, in a phase II clinical trial (NCT05167409), the efficacy of ALX148 combined with cetuximab and pembrolizumab is being evaluated in metastatic microsatellite-stable CRC [168].

Anti-CD47 antibodies, such as AK117 and B6H12, when combined with chemotherapy regimens, have shown significant progress in GI cancers [169]. AK117, a novel humanized IgG4 anti-CD47 antibody that disrupts the CD47-SIRPα signaling pathway, has been proven effective and safe, receiving U.S. Food and Drug Administration (FDA) approval for treating GC and gastroesophageal junction adenocarcinoma [170]. In a clinical study (NCT05235542), Xia et al. [170] found that AK117 combined with cadonilimab and chemotherapy was well-tolerated and exhibited strong anti-tumor activity in patients with unresectable locally advanced gastric or gastroesophageal junction cancer. In another study (NCT05960955), Akeso [171] is exploring the use of AK117 in combination with cadonilimab and chemotherapy for treating resectable gastroesophageal junction adenocarcinoma. Furthermore, the effectiveness of B6H12 combined with standard chemotherapy drugs like 5-fluorouracil (5-FU), gemcitabine, abraxane, and doxorubicin has been extensively proven [169]. Liu et al. [169] demonstrated that targeting CD47 with B6H12, in conjunction with 5-FU, significantly reduced tumor size in GC liver metastasis by enhancing Kupffer cells' phagocytic activity. Similarly, Cioffi et al. [51] found that B6H12 combined with gemcitabine or abraxane substantially reduced the growth of primary PDAC tumors through macrophage-mediated phagocytosis and induced cancer cell apoptosis. Additionally, Lo et al. [82] showed that B6H12, when used with doxorubicin, suppressed HCC's self-renewal, tumorigenesis, and migration by inducing macrophage-mediated phagocytosis. Moreover, combining anti-CD47 therapy with established treatments like sorafenib or doxorubicin has demonstrated synergistic inhibition in HCC [74]. Based on these findings, CD47-SIRPα blockade combined with chemotherapy is a promising strategy for GI cancer treatment.

6.2. CD47-SIRPα blockers combined with ICIs

ICIs, including antibodies against CTLA-4, epidermal growth factor receptor (EGFR), PD-1, and PD-L1, are primary treatments for GI cancer immunotherapy [29]. Therefore, investigating the combined targeting of CD47 and ICIs for GI cancer treatment is imperative [172]. Recent research on the combination of anti-CD47 with anti-CTLA-4, EGFR, PD-1, and PD-L1 has shown considerable progress [172]. Tao et al. [74] discovered that combining anti-CD47 antibodies with anti-PD-1 and CTLA-4 treatments maximized anti-tumor efficacy in ESCC patients by enhancing anti-tumor inflammation and T cell recruitment through a DC-dependent mechanism. This suggests that a combination of CD47 with PD-1 and CTLA-4 could be a potential target for ESCC treatment.

Recent reports indicate that radiation may increase the expressions of CD47 and PD-L1 in CRC cells by activating the Janus tyrosine kinase (JAK) 2/STAT3 or ataxia-telangiectasia-mutated and Rad3-related (ATR)-mediated DNA repair signaling pathways [173]. Hsieh et al. [173] demonstrated that combining anti-SIRPα antibody with radiotherapy and anti-PD-1 in CRC led to potent adaptive anti-tumor immune responses. This was achieved by promoting efficient tumor-associated antigen cross-presentation, triggering specific $CD8^+$ T cell expansion and activation, and increasing granzyme B expression [173]. Furthermore, Shi et al. [174] investigated the anti-tumor effects of combining B6H12 with anti-human VEGF-A mAbs in treating GC. They found that B6H12 and anti-VEGF-A together enhanced anti-tumor efficacy by reversing macrophage migration and phagocytosis [174]. Additionally, the combined treatment of Hu5F9-G4 with ICIs has shown significant anti-tumor synergy [175]. In preclinical models, Huang et al. [176] reported that Hu5F9-G4 combined with anti-EGFR (cetuximab) mAbs synergistically inhibited CRC growth and metastasis, attributed to the cancer-targeting mAb, providing a strong prophagocytic signal through Fc receptor-mediated ADCP. Moreover, a phase Ib/II clinical trial (NCT02953509) led by Dana-Farber Cancer Institute (Boston, MA, USA) demonstrated that the combination of Hu5F9-G4 and cetuximab exhibited promising efficacy in B-cell non-Hodgkin's lymphoma [177]. The potential of anti-CD47 or anti-SIRPα combined with other ICIs has been recognized in preclinical research and early clinical trials for GI cancer [178]. However, due to limited sample sizes, the effectiveness of these combination strategies must be confirmed through larger, randomized controlled clinical trials before clinical implementation [179]. In the future, targeting CD47-SIRPα in conjunction with other ICIs presents a promising direction for GI cancer immunotherapy.

7. Targeting the CD47-SIRPα signaling pathway in the clinical treatment of GI cancers

The importance of targeting the CD47-SIRPα signaling pathway in GI immunotherapy has been established and achieved rapid advancements in clinical studies. This review summarizes the latest developments in targeting the CD47-SIRPα signaling pathway for GI cancer treatment, using data from the PubMed database and clinical trial registration information from the U.S. National Clinical Trials Registry (NCT) system (www.clinicaltrials.gov) (Table S2).

8. Future perspective

The targeting of the CD47-SIRPα signaling pathway has achieved significant achievements in treating GI cancers. However, the development of new targeted therapeutic strategies continues to face substantial challenges [24]. CD47 is expressed not only on cancer cells but also on healthy cells, potentially leading to treatment side effects like anemia and other hematological toxicities due to the phagocytosis of healthy red blood cells [180]. Prolonged use of CD47-targeted drugs could prompt cancer cells to upregulate alternative phagocytic checkpoints or increase CD47 expression, resulting in drug resistance [181]. Tumors consist of diverse cancer cells with varying CD47 expression levels, leading to varied responses to CD47-targeted therapy [77]. However, immunosuppressive cells and factors in the TME, such as TAMs, DCs, neutrophils, regulatory T (Treg) cells, and cytokines like IL-2, IL-10, transforming growth factor-β (TGF-β), and VEGF, may diminish the effectiveness of CD47-targeted therapy [182]. While CD47-SIRPα targeted therapies have shown promise in preclinical and early clinical studies, more extensive clinical data is required to assess their long-term safety, efficacy, and optimal use across different cancer types [18]. Additionally, CD47 monotherapy may not be adequate for generating lasting anti-tumor responses and should be combined with other treatment modalities to enhance tumor suppression [7].

Combination treatment approaches can improve overall treatment response [169]. However, they have certain limitations that need to be understood [183]. CD47 combination therapy may lead to drug interactions, affect efficacy, or increase toxic and side effects [84]. Notably, the combination of CD47 and chemotherapy has recently been partially placed on hold by the U.S. FDA in clinical trials (NCT04313881, NCT04778397, and NCT03248479) due to an apparent imbalance in suspected unexpected serious adverse reactions [184]. Furthermore, when CD47 is combined with immunotherapy, another ICI may non-selectively eliminate peripheral Treg cells, potentially leading to immune-related adverse reactions [184]. Therefore, for some patients who are prone to serious adverse reactions, the risks of combination therapy may be higher than the benefits, so a more complex treatment plan needs to be designed, including medication order, dosage, and treatment duration [7]. This places higher requirements on the management and compliance of doctors and patients [185]. The cost of treatment with combination drugs is usually higher than that of a single drug, putting greater financial pressure on patients [186]. Additionally, when selecting CD47 combination therapy, it is necessary to balance the efficacy advantages and safety risks, pay attention to factors such as patient accessibility and affordability, and develop a more reasonable and feasible treatment plan [187]. Consequently, addressing these challenges will be pivotal in guiding future research. With the advancement of new inhibitors and evolving technologies, the CD47-SIRPα signaling pathway is poised to become a rapidly developing and significant focus in GI cancer immunotherapy.

9. Conclusions

The ubiquitous “don't eat me” signal, CD47, is upregulated in nearly all GI cancers and its overexpression correlates with a negative prognosis. This suggests that CD47 could serve as a novel diagnostic marker in early GI cancers. Consequently, blocking the CD47-SIRPα signaling axis offers a new direction in current GI cancer treatment. This review encapsulates CD47's role as a prognostic indicator and examines both foundational and immunotherapeutic strategies targeting the CD47-SIRPα signaling pathway in GI cancers. Currently, the development of targeted CD47-SIRPα blockers for GI cancer immunotherapy is still in its infancy. Therefore, developing precise, stable, and minimally side-effect-laden targeted therapeutic strategies remains a crucial objective in integrating checkpoint inhibitors into precision medicine.

CRediT authorship contribution statement

Zhengping Che: Writing – original draft, Visualization, Validation, Investigation, Formal analysis, Data curation, Conceptualization. **Wei Wang:** Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Lin Zhang:** Writing – review & editing, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Zhenghong Lin:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpha.2024.101099.

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