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REVIEW

Beyond cancer: The potential application of CD47-based therapy in non-cancer diseases

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Future perspective

Abstract CD47 is an immune checkpoint widely regarded as a 'don't eat me' signal. CD47-based anti-cancer therapy has received considerable attention, with a significant number of clinical trials conducted. While anti-cancer therapies based on CD47 remain a focal point of interest among researchers, it is noteworthy that an increasing number of studies have found that CD47-based therapy ameliorated the pathological status of non-cancer diseases. This review aims to provide an overview of the recent progress in comprehending the role of CD47-based therapy in non-cancer diseases, including diseases of the circulatory system, nervous system, digestive system, and so on. Furthermore, we sought to delineate the promising mechanisms of CD47-based therapy in treating non-cancer diseases. Our findings suggest that CD47-based agents may exert their effect by regulating phagocytosis, regulating T cells, dendritic cells, and neutrophils, and regulating the secretion of cytokines and chemokines. Additionally, we put forward the orientation of further research to bring to light the potential of CD47 and its binding partners as a target in non-cancer diseases.

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1. Introduction

CD47, a 50-kDa protein, is a ubiquitously expressed transmembrane glycoprotein[1,2]. CD47 is originally termed an integrin-associated protein, owing to an interaction between integrin and CD47[3]. CD47 was reported to regulate phagocytosis, cell death, and cancer cell spreading when interacting with Integrin $\alpha_v\beta_3$[4,5]. Besides integrin, signal regulatory protein alpha (SIRPα) is another famous binding partner of CD47. Binding with CD47 stimulated aggregation of SIRPα at the phagocytotic synapse of macrophages, which phosphor-activate the immunoreceptor tyrosine-based inhibitory motif of SIRPα and later recruit tyrosine phosphatases, like Src homology region 2 domain-containing phosphatase 1 or 2 (SHP1/2), with subsequent downstream regulation, inhibits macrophage phagocytosis[6-9]. In addition to binding with SIRPα, CD47 is reported to interact with a typical member of the thrombospondin family of glycoprotein extracellular matrix protein thrombospondin 1 (TSP1), whilst taking part in regulating platelet aggregation, blood flow, angiogenesis, inflammation, and so on[10-13].

CD47 is well-known as a 'don't eat me' signal, especially in cancer. CD47 is highly expressed in extensive tumors, suggesting that a wide range of cancers adopt it to achieve immune escape[14-17]. Therefore, CD47-based agents were explored as anti-cancer modalities[18-21]. CD47-based therapies encompass a spectrum of agents targeting factors involved in the CD47−SIRPα axis, as well as CD47-decorated subjects. Concretely, targeting CD47 modalities includes anti-CD47 antibody (aCD47 Ab), SIRPα fusion protein[22], CD47 inhibitor[23], CD47-activating peptide[13], antisense oligonucleotide targeting CD47[24], and so on. Likewise, agents targeting other participants of the CD47−SIRPα axis, such as anti-SIRPα antibody (aSIRPα Ab)[25], agonistic aSIRPα Ab[26], and SHP1 inhibitor (SHP1i)[27], were also referred to as CD47-based therapies. Simultaneously, CD47-decorated nanoparticles[28], exosomes[29], extracellular vesicles[30], and cells[31] are implicated as a subtype of CD47-based agents. In addition to monotherapy, therapy combining CD47-based agents and other therapeutic modalities was incorporated into our discussion.

Despite growing interest in developing CD47-based therapy, clinical translation of aCD47 Ab remains hindered by side effects, especially hematotoxicity and limited efficacy of monotherapy[19,20,32-35]. Researchers have made extensive efforts to cope with this threat, albeit with a few twists and turns. To mitigate the adverse effect of aCD47 Ab, TJ011133 with negligible binding to red blood cells (RBCs) was screened out[36]. Besides, a SIRPα fusion protein IMM01 was developed with restricted erythrocyte conjugation[22]. Preliminary results showed that IMM01 led to a 65.6% objective response rate in classic Hodgkin lymphoma patients ($n = 32$)[37]. Phase IIII trials of IMM01 in classic Hodgkin lymphoma are ongoing (NCT06465446 and CTR20241938). IMM0306, a fusion protein of aCD20 Ab with CD47 binding domain, was also reported to rarely bind to RBCs[38]. As of November 21, 2023, the objective response rate was 30.3% ($n = 33$) in phase I study of IMM0306 in relapsed or refractory CD20-positive B-cell non-Hodgkin lymphoma patients (NCT05805943)[39]. Distinguishing from the conventional application, a recent study proposed that aCD47 Ab could be developed into a safety switch removing chimeric antigen receptor (CAR) T-cells when necessary, hinting that there is a lot of overlooked possibility in the era[40].

Recently, the therapeutic effects of CD47-based agents were highlighted in studies focusing on non-cancer diseases[13,41-43] (Fig. 1). The viewpoint from non-cancer diseases may pave a new way to optimally exploit the immune checkpoint CD47 as a target in human diseases. Apart from cancers, abnormalities of CD47 and its binding partners were commonly observed across non-tumor excrescence, inflamed tissue, dysfunctional organs, and other diseased regions[41,44]. High levels of CD47 were detected in benign lesions including atherosclerosis plaque and ectopic endometrium[41,45]. Inflamed tissue like human non-alcoholic steatohepatitis (NASH) liver also had abundant expression of CD47 on necrotic liver cells[25]. Variation of CD47 level between normal and diseased states highlights the probability for CD47-based therapy in treating non-cancer diseases. Indeed, there is an increasing number of studies probing the therapeutic effect of CD47-based therapy. There is a clinical trial exploring the application of the CD47/TNF-α antibody sB24M in purulent pyoderma patients (NCT04895566).

To comprehensively understand the feasible contributions of CD47-based therapy in human diseases, we summarize the promising applications of CD47-based agents in non-cancer diseases, especially the usage of targeting CD47 agents. Related papers published between 2013 and 2024 were screened through ($n = 2168$). Excluding cancer studies which took the highest proportion, there remained 544 papers of which only 50% focus on CD47-based therapy application. The studies ultimately involved in the discussion were screened based on eligibility, reliability, and representativeness of the literature. Referred to the International Classification of Diseases 11th revision, the main text was divided into 9 sections[46]. The sections and the content in each section were arranged in descending order of importance. Afterward, we conclude the major underlying mechanisms of CD47-based agents affecting non-cancerous disease progression. Perspectives were also presented here in terms of four aspects: agents' selection, drug administration, biological function, and indications.

2. Diseases of the circulatory system

2.1. *Atherosclerosis*

Atherosclerosis is a chronic inflammation, characterized by accumulated fatty and/or fibrous materials in the inner wall of arteries[47]. Once initiated, the atherosclerotic plaque develops with time[48]. In the early stage, foam-like cells containing cholesterol, lipids, and immunocytes deposit beneath the endothelia[49]. In the advancing stage, macrophages and smooth muscle cells (SMCs) proliferate and undergo programmed cell death[50,51]. When the clearance of dead cells is out of order, the fragments of cells will accumulate and contribute to form the necrotic core of atherosclerotic plaque together with foam-like cells and lipids[52,53].

CD47 may be useful in assisting the clinical diagnosis of atherosclerosis (Fig. 2 and Table 1[27,41,54-73]).

In early 2016, Kojima et al.[41] observed that upregulated CD47 in apoptotic tissue of atherosclerotic plaque, especially in the necrotic core. There has been extensive work examining the mechanisms. It was found that TNF-α bound with TNFR1, whilst increasing the transcription of *CD47* in SMCs[41]. And the elevation of *CD47* was found to be correlated to the combination of myocardial infarction-associated transcript and miR-149-5p in apoptotic macrophages[74]. Inspired by these evidences, researchers developed aggregation-induced emission luminogens nanoparticles decorated with aCD47 Ab to recognize atherosclerotic

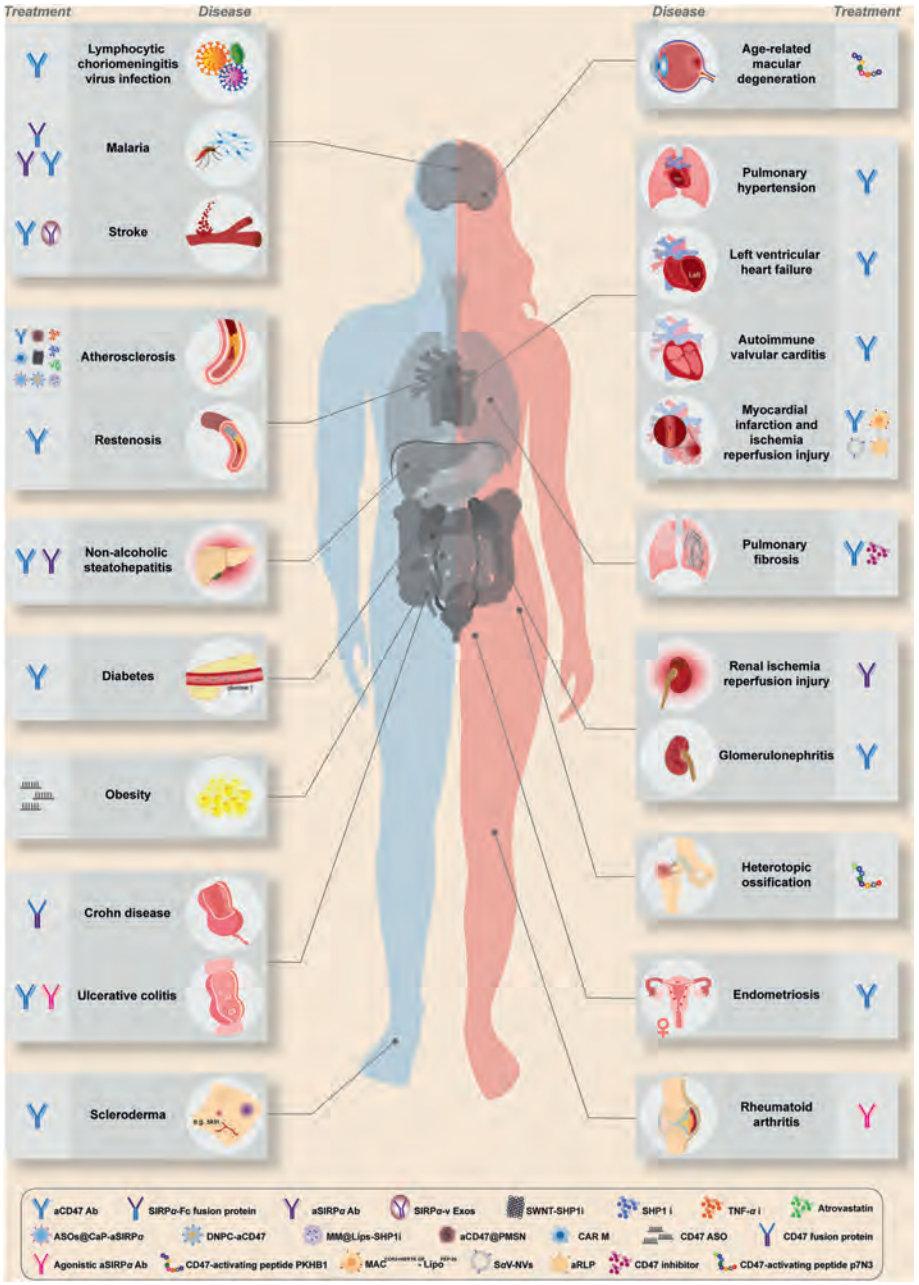

Figure 1 The potential applications of CD47-based therapy. The increasing number of pre-clinical studies highlight the effect of different CD47-based therapies in treating non-cancer diseases. aCD47 Ab, anti-CD47 antibody; SIRPα, signal regulatory protein alpha; aSIRPα Ab, anti-SIRPα antibody; ASOs@CaP-aSIRPα, anti-SIRPα antibody-modified, anti-sense oligonucleotides-loaded calcium phosphate nanoparticles; aCD47@PMSN, anti-CD47 antibody loaded platelet membrane coated mesoporous silicon nanoparticles; aRLP, senescent RBC-mimetic liposomes decorated with an anti-Ly6G antibody; CAR M, chimeric antigen receptor macrophage; CD47 ASO, antisense oligonucleotide targeting CD47; DNPC-aCD47, anti-CD47 antibody-conjugating polydopamine nanoparticles loaded with CY-09; SHP1i, a SHP1 inhibitor; MM@Lips-SHP1i, macrophage membrane-coated SHP1i-liposome nanoparticles; $MAC^{CCR2+MERTK\ CR}$-$Lipo^{PEP-20}$, C–C chemokine receptor type2 and cleavage-resistant MerTK overexpressed macrophages anchoring liposomes loaded with PEP-20; SIRPα-v Exos, modified exosomal SIRPα variants; SWNT-SHP1i, single-walled carbon nanotubes loaded with a SHP1 inhibitor; SαV-NVs, hybrid nanovesicles, which contain cell-derived nano vesicles overexpressing high-affinity SIRPα variants; TNF-α i, TNF-α inhibitor.

plaques[75]. It could effectively and specifically bind with CD47-high plaques, and achieve early detection. This kind of nanoparticles could identify 8 weeks high-fat diet (HFD)-induced atherosclerotic plaques in *Apoe*$^{-/-}$ mice, while MRI and CT only identified the presence of lesions after *Apoe*$^{-/-}$ mice were fed with HFD for at least 10 and 12 weeks, respectively[75].

Moreover, CD47 is considered a promising therapeutic target for atherosclerosis (Fig. 2 and Table 1). The rate of atherosclerotic lesion in CD47 deficient mice fed with a Western diet attenuated into 5.87 $\pm$ 0.68%, while that in wild-type (WT) mice was 11.84 $\pm$ 1.47%[76]. Blocking CD47 using aCD47 Ab could augment efferocytosis of diseased macrophages, apoptotic SMCs,

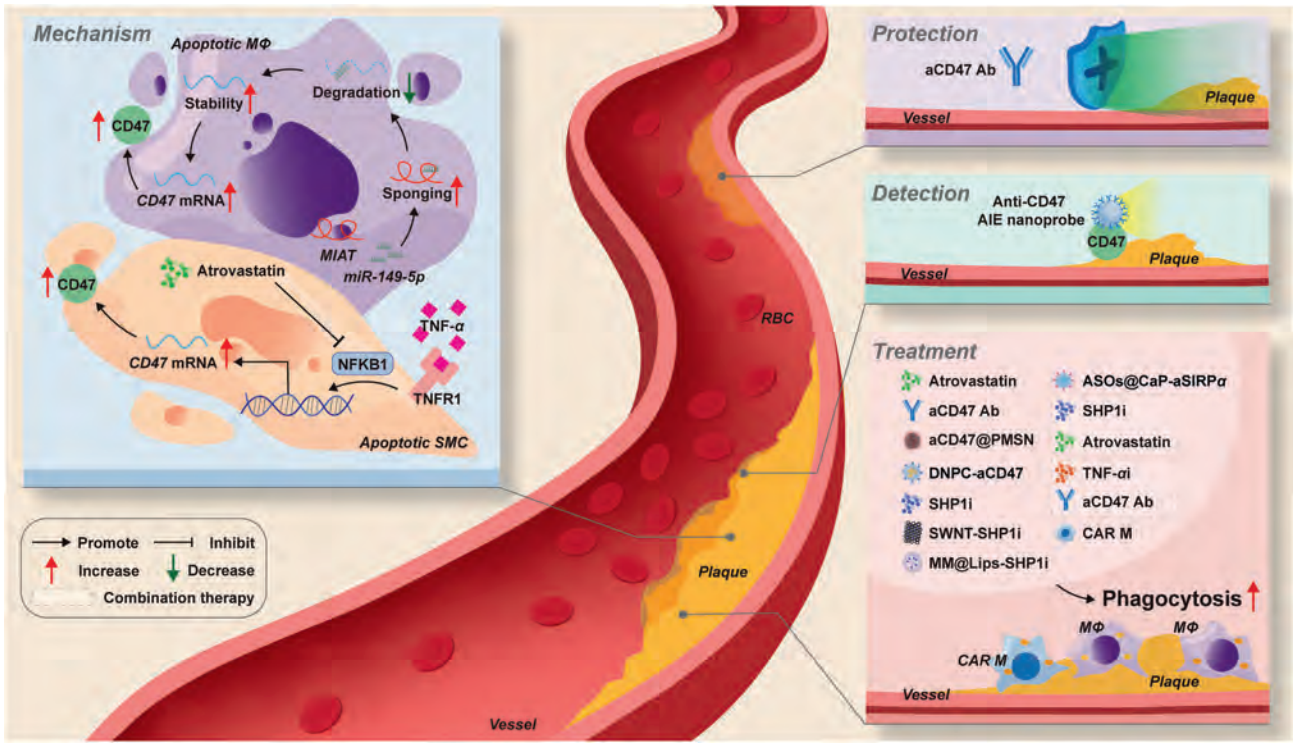

Figure 2 The effects of CD47-based therapies in atherosclerosis. CD47 was highly expressed in atherosclerotic plaques (Mechanism). LncRNA *MIAT* binds with miR-149-5p to prevent the degradation of *CD47* mRNA in apoptotic macrophages, whilst increasing CD47 expression in the cell membrane. In apoptotic SMCs, TNF-α increases translation of *CD47* mRNA *via* NFKB1, and then upregulates the level of CD47. Based on the high level of CD47, certain CD47-based therapies were designed to prevent, detect, or treat atherosclerosis (Prevention). The aCD47 Ab may prevent atherosclerosis (Detection). In addition, an anti-CD47 AIE nanoprobe was designed to bind with CD47-expressed plaques to achieve atherosclerosis detection (Treatment). Meanwhile, a series of CD47-based monotherapies or combination therapies were reported to ameliorate atherosclerosis by promoting phagocytosis. aCD47 Ab, anti-CD47 antibody; SIRPα, signal regulatory protein alpha; aSIRPα Ab, anti-SIRPα antibody; ASOs@CaP-aSIRPα, anti-SIRPα antibody-modified, anti-sense oligonucleotides-loaded calcium phosphate nanoparticles; AIE, aggregation-induced emission; aCD47@PMSN, anti-CD47 antibody loaded platelet membrane coated mesoporous silicon nanoparticles; aRLP, senescent RBC-mimetic liposomes decorated with an anti-Ly6G antibody; CAR M, chimeric antigen receptor macrophage; CD47 ASO, antisense oligonucleotide targeting CD47; DNPC-aCD47, anti-CD47 antibody-conjugating polydopamine nanoparticles loaded with CY-09; SHP1i, a SHP1 inhibitor; MIAT, myocardial infarction-associated transcript; MM@Lips-SHP1i, macrophage membrane-coated SHP1i-liposome nanoparticles; $MAC^{CCR2+MERTK\ CR}$-$Lipo^{PEP-20}$, C−C chemokine receptor type2 and cleavage-resistant MerTK overexpressed macrophages anchoring liposomes loaded with PEP-20; Mø, macrophage; RBC, red blood cell; SMC, smooth muscle cell; SIRPα-v Exos, modified exosomal SIRPα variants; SWNT-SHP1i, single-walled carbon nanotubes loaded with a SHP1 inhibitor; SαV-NVs, hybrid nanovesicles, which contain cell-derived nano vesicles overexpressing high-affinity SIRPα variants; TNF-α i, TNF-α inhibitor.

and cell debris *in vitro*, meanwhile, decreasing the area of atherosclerotic plaque with a smaller necrotic core in mice[41]. The necrotic core area in $Apoe^{-/-}$ mice treated with aCD47 Ab was 34.5% smaller[56]. To promote the ability of aCD47 Ab to target atherosclerotic plaques, researchers developed platelet membrane-coated mesoporous silicon nanoparticles loaded with aCD47 Ab (aCD47@PMSN). This aCD47@PMSN could selectively attach and enter the plaques[57]. Other than nanoparticles, cell therapy, one of the most sought-after treatments, was explored as an option to improve the efficacy of CD47 blockade. CAR Macrophage with anti-CD47 single chain antibody variable fragment could bind with apoptotic cells expressing CD47 and exert a better phagocytic effect than control CAR Macrophage[61].

In addition to debris accumulation, further work discovered another driving factor of atherosclerosis a cluster of evil SMCs. These SMCs which are Sac-positive in plaques, act as stem cells. Sac-positive SMCs seem to prefer clonally expanding and gathering around the necrotic core. Apart from narrowing the necrotic area, aCD47 Ab was found to suppress the cloning of SMCs in plaques but maintained the stability of plaques[58].

Moreover, aCD47 Ab in combination with other drugs may have a better therapeutic effect than monotherapy. Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are the first-line treatment of atherosclerotic cardiovascular disease[77]. Atorvastatin which could amplify efferocytosis enhanced the effect of aCD47 Ab on atherosclerosis. Atorvastatin in combination with aCD47 Ab decreased the plaque area to 17.52% of total vessel area, while the ratio of plaque area in the atorvastatin group was 23.36%[27]. In addition to statins, TNF-α inhibitor, etanercept, further enhanced the efficacy of aCD47 Ab in efferocytosis assays[41]. Different from previous studies in which drugs were given separately, researchers recently constructed a nanoparticle conjugating with aCD47 Ab and encapsulating NLRP3 inhibitor CY-09. This nanoparticle not only facilitated the clearance of diseased and apoptotic SMCs and macrophages, but also ameliorated inflammation *via* inhibiting NLRP3 activation[63].

Table 1 Pre-clinical studies of CD47-based therapy in diseases of the circulatory system.

Disease	Target	Experimental model	Administration design[a]	Main result	Ref.
Atherosclerosis	CD47	4-week-old *Apoe*$^{-/-}$ mice pre-fed with high-fat diet (HFD) for 8 weeks	i.p.; t.i.w.; BRB-002 (recombinant protein with CD47 binding and inactive Fc domain); N/A; 2.5 mg/kg; 6 weeks with HFD	Decreased plaque burden, size, and regions	54
		4-week-old *Apoe*$^{-/-}$ mice	s.q.; t.i.w.; BRB-002; N/A; 1/2.5/10/30 mg/kg; 12 weeks with HFD	Decreased plaque burden	
Atherosclerosis	CD47	8-week-old *Apoe*$^{-/-}$ mice implanted with subcutaneous Alzer minipumps containing Angiotensin II (1000 ng/kg/min) (Ang II pump)	i.p.; q.o.d.; anti-CD47 antibody; MIAP410; 200 μg; 4 weeks with HFD; initiated at the day before the pump implantation	Decreased atherosclerosis content, apoptotic debris, and necrotic cores; Increased efferocytosis; Decreased Src homology region 2 domain-containing phosphatase 1 (SHP1) phosphorylation; Induced self-limited anemia	41
		4-week-old *Apoe*$^{-/-}$ mice pre-fed with HFD	i.p.; q.o.d.; anti-CD47 antibody; MIAP410; 200 μg; 12 weeks with HFD	Decreased atherosclerosis content; No anemia	
		4-week-old *Apoe*$^{-/-}$ mice pre-fed with HFD for 8 weeks	i.p.; q.o.d.; anti-CD47 antibody; MIAP410; 200 μg; 6 weeks	Decreased atherosclerosis content	
		8-week-old *Apoe*$^{-/-}$ mice implanted with AngII pump	i.p.; q.o.d.; anti-CD47 antibody; MIAP410; 50 μg; 4 weeks with HFD; started the day before pump implantation	Decreased atherosclerosis content; No anemia	
		8-week-old *Apoe*$^{-/-}$ mice implanted with AngII pump and pre-fed with HFD for 23 days	s.q.; q.d.; anti-CD47 antibody; MIAP410; 200 μg; 5 days	Decreased atherosclerosis content; Decreased the number of apoptotic bodies that did not associate with macrophages	
		6-week-old *Apoe*$^{-/-}$ mice pre-fed with HFD for 6 weeks and later conducted "Tandem Stenosis"[55]	N/A; N/A; anti-CD47 antibody; MIAP410; 7 weeks; started the day before surgery	Decreased atherosclerosis content	
		8-week-old *Apoe*$^{-/-}$ mice implanted with AngII pump	i.p.; q.o.d.; anti-CD47 antibody; MIAP410; 50 μg; 4 weeks with HFD; started one day before the pump implantation s.q.; q.w.; Etanercept; 0.2 mg/kg; 4 weeks with HFD	Increased macrophages within the plaque; Decreased free apoptotic bodies; Decreased uncleared cells undergoing secondary necrosis	
		Primary smooth muscle cells (SMCs) from aortas; C57BL/Ka *Rosa26 mRFP1* transgenic mice-isolating bone marrow cells; RAW 264.7 cells	Anti-CD47 antibody; MIAP410; 10 μg/mL Infliximab; 100 μg/mL	Further increased the efferocytosis rate compared to the anti-CD47 antibody group	
Atherosclerosis	CD47	Apoptotic peritoneal macrophages from *Apoe*$^{-/-}$ and macrophage-specific low-density lipoprotein receptor-related protein 1 knockout (double knockout, DKO) mice	Anti-CD47 antibody; MIAP410; 10 μg/mL; 30 min	Increased efferocytosis rate by 30%; Not influence the efferocytosis rate of DKO phagocytes engulfing DKO apoptotic substrate	56

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Table 1 (*continued*)

Disease	Target	Experimental model	Administration design[a]	Main result	Ref.
		8-week-old *Apoe*$^{-/-}$ mice	i.p.; q.o.d.; anti-CD47 antibody; MIAP410; 200 μg/injection; 12 weeks with HFD	Decreased lesion area stained with oil red-O from 304,600 ± 77,390 μm^2 to 227,200 ± 69,310 μm^2; The necrotic core area was 34.5% smaller; Decreased the ratio of free apoptotic bodies: macrophage-associated apoptotic bodies	
		8-week-old DKO mice	i.p.; q.o.d.; anti-mouse CD47 antibody; MIAP410; 200 μg/injection; 12 weeks with HFD	Not significantly influence sectional lesion area, necrotic area, and phagocytic index	
Atherosclerosis	CD47	SMCs treated with 50 μg/mL of oxidized low-density lipoprotein (oxLDL); Mouse macrophages	Anti-CD47 antibody loaded platelet membrane coated mesoporous silicon nanoparticles (aCD47@PMSN); N/A	TNF-α-activating SMCs highly expressed CD47; Increased phagocytosis of SMCs to 43% and 79% in the group exposed to the oxLDL for 24 h and 72 h, respectively	57
		Apoe$^{-/-}$ mice pre-fed with HFD for 8 weeks	i.v.; q.3d.; aCD47@PMSN; 200 μg/injection; 42 days with HFD	Decreased the area of the atherosclerotic plaque from 46.7 ± 2% (control group) to 16.6 ± 1.7%; Decreased acellular lipid cores and cholesterol crystals; Increased the number of smooth muscle cells on the surface of the small plaques	
Atherosclerosis	CD47	8-week-old rainbow *Apoe*$^{-/-}$ mice initiated on HFD at the age of 9 weeks	i.p.; q.o.d.; anti-CD47 antibody; MIAP410; 200 μg/injection; 18 weeks with HFD	Decreased lesional level of complement component 3 (C3); Decreased the expansion of clonal SMCs in the atherosclerotic plaque; Decreased necrotic core size, but not increased the plaque vulnerability	58
		8-week-old mice implanted with the subcutaneous Ang II pump	i.p.; q.o.d.; anti-CD47 antibody; MIAP410; N/A; 4 weeks with HFD	Decreased circulating level of C3	
		Classical activated macrophages (M1)-state-THP-1 cells	si-CD47; 10 nmol/L	Increased the ability of THP-1 cells to sense and bind C3b	
		M1-state-THP-1 cells	Anti-CD47 antibody; MIAP410; 20 μg/mL	Increased the ability of THP-1 cells to sense and bind C3b	
Atherosclerosis	CD47	8-week-old male *Apoe*$^{-/-}$ mice pre-fed with HFD for 2 weeks	i.g.; q.d.; atorvastatin; 10 mg/kg; 9 weeks	Increased efferocytosis rate but not altered apoptosis; Decreased plague area (23.36% of total vessel area (TVA)), necrotic core (10.65% of TVA), and the number of apoptotic bodies in the lesion	27
		8-week-old male *Apoe*$^{-/-}$ mice pre-fed with HFD for 2 weeks	i.p.; q.o.d.; anti-CD47 antibody; MIAP410; 200 μg; 9 weeks i.g.; q.d.; atorvastatin;10 mg/kg; 9 weeks	Further decreased plague area (17.52% of TVA) and necrotic core (7.147% of TVA) than single therapies	

		8-week-old male *Apoe*$^{-/-}$ mice pre-fed with HFD for 2 weeks	i.v.; q.w.; SHP1 inhibitor; 200 μL of 400 nmol/L; 9 weeks i.g.; q.d.; atorvastatin; 10 mg/kg; 9 weeks	Further decreased plague area (16.28% of TVA) and necrotic core (6.789% of TVA) than single therapies; Further increased efferocytosis rate than single therapies	
		RAW 264.7 cells	Atorvastatin; 10 μmol/L	Increased efferocytosis rate but not altered apoptosis	
		RAW 264.7 cells	SHP1 inhibitor; 4 nmol/L Atorvastatin; 10 μmol/L	Further increased efferocytosis rate than single therapies	
		SMCs stimulated with TNF-α	Atorvastatin; 10 μmol/L	Decreased CD47 on both RNA and protein levels; Decreased the nuclear translocation of NF-κB1 p50	
Atherosclerosis	SHP1	RAW264.7 cells and primary vascular SMCs	Single-walled carbon nanotubes loaded with a SHP1 inhibitor (SWNT-SHP1i); 4 nmol/L	Increased the removal of apoptotic vascular cells by macrophages	59
		8−10 weeks old *Apoe*$^{-/-}$ mice implanted with subcutaneous osmotic minipumps containing Angiotensin II (AngII, 1000 ng/kg/min)	i.v.; q.w.; SWNT-SHP1i; 13.6 μg; 4 weeks with HFD; began one day before Ang II pump implantation	Decreased plaque area, necrotic area, and aortic ^{18}F-FDG uptake; Increased efferocytosis activity	
		8-week-old male pre-fed with HFD for 2 weeks	i.v.; q.w.; SWNT-SHP1i; 13.6 μg; 9 weeks with HFD	Decreased plaque area, necrotic area, and aortic ^{18}F-FDG uptake Increased efferocytosis activity	
Atherosclerosis	SHP1	RAW264.7 cells	Macrophage membrane-coated SHP1i-liposome nanoparticles; N/A	Decreased macrophage foaming; Decreased the production of TNF-α, IL-6, and IFN-γ, ROS, and iNO on LPS-induced-RAW264.7; Increased the phagocytosis index of macrophages treated with oxLDL from 20.43% (control group) to 62.51%	60
		8-week-old female *Apoe*$^{-/-}$ mice pre-fed with HFD for 12 weeks	i.v.; q.4d.; macrophage membrane-coated SHP1i-liposome nanoparticles; N/A; 4 weeks with HFD	Decreased area ratio of aortic plaque to vessel lumen from 94.71% (control group) to 27.22%; Decreased accumulation of collagen and necrotic area; Decreased the number of macrophages, monocytes, and SMCs in the plaque area; Decreased endothelial cell proliferation; Decreased the activity of phosphorylated SHP1; Decreased the ratio of free apoptotic cells to macrophages	

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Table 1 (*continued*)

Disease	Target	Experimental model	Administration design[a]	Main result	Ref.
Atherosclerosis	CD47	Chimeric antigen receptor macrophage (CAR M) and irradiated cells	CAR M; N/A	Engulfed a greater number of CD47-coated beads compared to control macrophages; Engulfed whole-cell, multiple cell 'fragments', and apoptotic bodies; 69.8 ± 17.8% of CAR M engulfed apoptotic cells while only 34.9 ± 9.48% of control macrophages phagocytized after 2 h-co-culture	61
Atherosclerosis	Signal regulatory protein alpha α (SIRPα)	Mouse aortic endothelial cell line; RAW264.7 cells	Anti-SIRPα antibody-modified, anti-sense oligonucleotides-loaded calcium phosphate nanoparticles (ASOs@CaP-aSIRPα); 40 μg/mL	Stimulated macrophage clearance of apoptotic vascular cells	62
		Apoe$^{-/-}$ mice fed with HFD for 2 weeks	N/A; q.w.; ASOs@CaP-aSIRPα; 0.69 mg/kg; 11 weeks	Decreased plaque area from 19.5 ± 2.2% (ASOs@CaP group) to 10.3 ± 2.2%; Decreased the necrotic core area of the aortic root; Had the most SMCs on the surface of the plaque	
Atherosclerosis	CD47	RAW264.7 and MOVAS cells induced by oxidized phospholipids; Bone-marrow macrophages	Anti-CD47 antibody-conjugating polydopamine nanoparticles loaded with CY-09; 20 μg/mL	Induced the removal of diseased and apoptotic vascular SMCs and macrophages	63
	CD47	*Apoe*$^{-/-}$ mice fed with HFD for 11 weeks	N/A; q.3d.; anti-CD47 antibody-conjugating polydopamine nanoparticles loaded with CY-09; 1 month	Decreased the size of atherosclerotic plaques; Decreased the ratio of free apoptotic cells: macrophage-associated apoptotic cells	
Myocardial infarction	CD47	BMDM and dying adult mouse ventricular cardiomyocytes (CMs)	Anti-CD47 antibody; N/A	Increased CMs efferocytosis	64
	SIRPα	BMDM and dying adult mouse ventricular CMs	Anti-SIRPα antibody; N/A	Increased CMs efferocytosis	
	CD47	Mice transgenic for Mhc6-mCherry (CMs specific)	Intramyocardial; N/A; anti-CD47 antibody; MIAP301; 100 μg; during model construction	Increased CMs efferocytosis; Decreased infarct size and cardiac troponin release, increased left ventricular ejection fraction and led to a 2-fold reduction in collagen fraction	
Myocardial infarction	SIRPα	Mice received myocardial infarction injury-induced surgery	i.v.; once; senescent RBC-mimetic liposomes decorated with an anti-Ly6G antibody; N/A; 6 h after surgery	Increased apoptotic CMs efferocytosis; Decreased infarct size and fibrotic area; Decreased left ventricular end-diastolic and left ventricular (LV) end-systolic volume	65
Myocardial infarction	CD47	Hypoxia RCMs and H9C2 cells	Anti-CD47 antibody; 10 μmol/L SB216763; 10 μmol/L	Decreased the apoptosis of hypoxic cardiomyocytes; SB216763 further decreased the apoptosis of hypoxic cardiomyocytes	66

Myocardial ischemia/ reperfusion (I/R) injury	CD47	Mice myocardial ischemia-reperfusion injury model	i.v.; once; C−C chemokine receptor type2 and cleavage-resistant MerTK overexpressed macrophages anchoring liposomes loaded with PEP-20	Increased cardiac efferocytosis and affected resident macrophages; Preserved the left ventricular ejection fraction, the contraction efficiency of cardiomyocytes, the deterioration of cardiac function, myocardium, and reduced fibrosis; Decreased neutrophils and inflammatory monocyte infiltration, reduced the levels of IL-1 β, TNF-α, IL-8, and MCP-1, and increased the levels of IL-10 and TGF-β	67
Myocardial I/R injury	CD47	RAW264.7 cells; dead H9C2 cells	Hybrid nanovesicles, which contain cell-derived nanovesicles overexpressing high-affinity SIRPα variants (SαV-NVs); 0.1 μg/μL	The phagocytic activity exceeded 30% compared to 10% in the control group	68
		I/R model mice	i.m.; once; SαV-NVs; 20 μg; N/A	Decreased SHP1 phosphorylation; Increased prevalence of macrophages engulfing apoptotic bodies	
		I/R model mice	i.v.; q.d.; SαV-NVs; 200 μg; 3 days; a day after I/R surgery	Decreased myocardial apoptosis; Decreased IL-1β and TNF-α in serum; Decreased mRNA level of *IL1b* and *TNFa* in infarcted regions; Decreased scar size	
Pulmonary hypertension (PH)	CD47	Diseased pulmonary arteries from patients with end-stage PH	Anti-CD47 antibody; B6H12; 1 μg/mL	Improved both acetylcholine- and sodium nitroprusside-mediated vasodilation	69
		Human pulmonary arterial endothelial cells	Anti-CD47 antibody; B6H12; 1 μg/mL	Decreased *ET1* and *ETA* mRNA and soluble ET-1 protein	
		Mice treated with monocrotaline (50 mg/kg) to induce PH	N/A; N/A; anti-CD47 antibody; OX101; 0.4 μg/g; 2 weeks	Less increased in right ventricular-free wall weight; Not decreased the contractility index	
Sickle cell disease-associated pulmonary hypertension	CD47	Human pulmonary artery endothelial cells	Anti-CD47 antibody; B6H12.2; 2 μg/mL	Abrogated thrombospondin 1-stimulated reactive oxygen species production	70
Restenosis	CD47	Human aortic SMCs (HASMCs)	siCD47; N/A	Decreased thrombin-induced HASMCs migration and proliferation;	71
		HASMCs; Mouse aortic SMCs (MASMCs); THP-1 macrophage	Anti-CD47 antibody; 10 μg/mL	Decreased thrombin-induced HASMCs/ MASMCs migration and proliferation and promoted efferocytosis	
		C57BL/6J mice femoral artery guidewire injury model	i.p.; q.3d.; anti-CD47 antibody; MIAP301; 50 μg; 3 weeks	Decreased guidewire injury-induced SMC migration, SMC proliferation, and neointima formation and reduced apoptotic SMCs in the neointimal regions of arteries; Increased the number of apoptotic SMCs associated with macrophages in the neointimal regions of arteries	

(*continued on next page*)

Table 1 (*continued*)

Disease	Target	Experimental model	Administration design[a]	Main result	Ref.
Left ventricular (LV) heartfailure	CD47	Wild-type mice post transverse aortic constriction	i.p.; q.w.; anti-CD47 antibody; clone301; 0.4 μg/g body; 4 weeks; began 1 week after surgery	Decreased cardiac myocyte hypertrophy, LV fibrosis, ventricular stiffness, 7N3-stimulated cardiac myocyte hypertrophy, and apoptotic cells	72
		Cardiac myocytes	Peptide 7N3 (peptide derived from the C-terminal of thrombospondin 1); 10 μmol/L	Stimulated myocyte hypertrophy and increased HDAC3 level, nuclear HDAC3 and p-HDAC3, CaMKII protein, and p-CaMKII	
Autoimmune valvular carditis	CD47	K/B.g7 TCR transgenic mice (K/B.g7) mouse model	i.p.; b.i.w.; anti-CD47 antibody; MIAP410; 200 μg; 10 weeks; began at 4 weeks of age	Decreased mitral valve inflammation and fibro-inflammatory thickening, both qualitatively and quantitatively; Decreased active-caspase-3 staining relative to the control group; Decreased the overall apoptotic cell burden in the inflamed mitral valves; Decreased the serum level of IL-6 and CXCL1	73
		K/B.g7 mouse model	i.p.; b.i.w.; anti-CD47 antibody; miap410; 200 μg; 10 weeks; began at 6 weeks of age	Decreased mitral valve inflammation and fibro-inflammatory thickening, both qualitatively and quantitatively	
		K/B.g7 mouse model	i.p.; b.i.w.; anti-CD47 antibody; MIAP410; 200 μg; 2 weeks; began at 8 weeks of age	Decreased the number of leukocytes and $CX3CR1^{+}$ macrophages in the inflamed mitral valves; Increased the fraction of live macrophages containing active-caspase-3^{+} apoptotic cells; Decreased the level of mitral valve $SIRP\alpha^{+}$ macrophage-producing TNF and IL-6	
		Irradiated, CD47-expressing human Jurkat T cells; Mouse bone marrow-derived macrophages	Anti-CD47 antibody; MIAP410; 0.5 μg/mL Fc blocking antibody; clone 2.4G2; 10 μg/mL	Decreased the effect of anti-CD47 antibody on increasing uptake of the irradiated cells	

i.p., intraperitoneal; s.q., subcutaneous; i.v., intravenous; i.g., intragastric; i.m., intramuscular; t.i.w., three times a week; q.o.d., every other day; q.d., every day; q.3d., every three days; q.w., once a week; q.4d.; every four days; b.i.w., twice a week.

[a]*In vivo* assay: administration method; frequency; treatment; (clone of antibody) dosage; duration; others. *In vitro* assay: treatment; (clone of antibody) dosage; others.

Notably, aCD47 Ab was a potential agent that was not only a treatment for atherosclerosis but also a promising prevention strategy (Fig. 2). BRB-002 is an antibody constructed by a CD47 binding and an inactive Fc domain. BRB-002 dose-dependently reduced plaque burden in the descending aortas in *Apoe*$^{-/-}$ mice supplemented with HFD together with BRB-002[54]. It is worth mentioning that BRB-002 was one step ahead of other CD47-based therapies treating atherosclerosis to enter the clinical trial phase (ACTRN12624000405516). It did take a big step forward towards CD47-based agents' practical applications in atherosclerosis treatment.

Besides CD47, targeting the other two members in the CD47−SIRPα axis also ameliorates atherosclerosis (Fig. 2). ASOs @CaP-aSIRPα NPs are nano-bioconjugates modified with aSIRPα Ab. This nanoparticle accelerated the removal of apoptotic vascular cells to the greatest extent, whilst decreasing atherosclerosis plaque area from 19.5 $\pm$ 2.2% (ASOs@CaP NPs) to 10.3 $\pm$ 2.2% (ASOs@CaP-aSIRPα NPs)[62]. The other promising target is SHP1, a downstream factor of SIRPα. aCD47 Ab reduced SHP1 phosphorylation in the atherosclerosis model, hinting the critical role of SHP1. SHP1i was loaded into single-walled carbon nanotubes (SWNTs) and macrophage membrane-coated liposome nanoparticles, respectively[59,60]. SWNTs and macrophage membrane-coated liposome nanoparticles are not only low toxic but also capable of accumulating in plaques. Both these two nanoparticles may inhibit inflammation and necrosis in plaques probably by improving efferocytosis[59,60]. Combination therapy may further enhance the efficacy of SHP1 targeting agents. Atorvastatin amplified the effect of anti-SHP1 antibody on treating atherosclerosis, as demonstrated by about 7% smaller plaque area[27].

2.2. *Myocardial infarction and ischemic/reperfusion injury*

The incidence of myocardial infarction (MI) in young steadily increased. The high-level CD47 was observed in specimens from patients who suffered from MI, correspondingly, CD47 level was elevated in cardiomyocytes (CMs) of heart ischemic area in murine MI model[64,66]. The *in vivo* data demonstrated that aCD47 Ab improved systolic cardiac function and decreased infarct size. Besides, aCD47 Ab may suppress ventricular remodeling as the collagen content was halved[64]. Moreover, SB216763, a glycogen synthase kinase 3β, further enhanced the effect of aCD47 Ab on reducing the apoptosis of hypoxic cardiomyocytes[66]. The elimination of necrotic CMs tends to be vital for the prognosis of patients with MI, as the inefficient clearance of cell debris may cause secondary necrosis and further enlarge infarct area[78-80]. Both aCD47 Ab and aSIRPα Ab elevated efferocytosis towards apoptotic CMs. More recently, anti-Ly6G antibody-decorated senescent RBC-mimetic liposomes were reported to degrade SIRPα expressed on macrophage to enhance efferocytosis of apoptotic CMs, whilst decreased infarct area and improved cardiac function[65]. It is suggested that CD47-based therapies may alleviate MI by enhancing the phagocytosis of diseased CMs.

Myocardial ischemic/reperfusion injury (MIRI), which may happen in MI patients receiving reperfusion therapy, could also be ameliorated by CD47-based therapy[81,82]. MAC$^{\text{CCR2+MERTK CR}}$-Lipo$^{\text{PEP}-20}$ is C−C chemokine receptor type2 and cleavage-resistant MerTK overexpressed macrophages (MAC$^{\text{CCR2+MERTK CR}}$) anchoring with liposomes loaded with CD47 antagonist PEP-20[67]. SαV-NVs is a hybrid nanovesicle containing nanovesicles deriving from cells overexpressing high-affinity SIRPα variants[68]. Both MAC$^{\text{CCR2+MERTK CR}}$-Lipo$^{\text{PEP}-20}$ and SαV-NVs preserved cardiac function in mice suffering from MIRI[67,68]. The loaded-PEP-20 further increased the efferocytosis rate of adoptive and resident macrophages towards apoptotic CMs *in vivo*. In addition, MAC$^{\text{CCR2+MERTK CR}}$-Lipo$^{\text{PEP}-20}$ led to a lower level of IL-1β and TNF-α in the heart compared to macrophages without PEP-20[67]. Similar effects were observed in MIRI mice treated with SαV-NVs[68].

2.3. *Pulmonary hypertension*

Pulmonary hypertension (PH) refers to elevated pulmonary artery pressure, which may result in increased right cardiac load and right cardiac insufficiency[83]. Upregulation of CD47 was found throughout the SMC layer and adventitia of the vessel wall in PH patients[69,70]. CD47 deficiency improved endothelial function, which was marked by enhanced endothelial-dependent vasorelaxation in response to acetylcholine in sickle cell disease and pulmonary hypertension models[70]. In 24-month-old rats, aCD47 Ab upregulated coronary flow reserve in the left ventricle part 1 from 9.7 $\pm$ 9.3% in the IgG group to 84 $\pm$ 23.2% and part 2 from 7.3 $\pm$ 9.9% in the IgG group to 67.5 $\pm$ 15.7%[84]. Targeting CD47 may reverse the pathological state of PH to a certain extent. Indeed, it was reported that aCD47 Ab improved coronary and heart function[69,70,84]. Blocking CD47 by antibody improved TSP1-inhibited vasodilation[69]. Besides, aCD47 Ab relieved monocrotaline-induced RV-free wall weight increase and contractility index decrease in mice with PH[69]. Imbalanced reactive oxygen species (ROS) level may promote PH pathology *via* inducing dysregulated proliferation and migration of pulmonary artery SMCs[85−87]. One of the promising mechanisms by which CD47 blockade improved coronary arteriole function may be reducing oxidative stress. CD47 blockade inhibited ROS production in human pulmonary artery endothelial cells[70]. Meanwhile, aCD47 Ab alleviated superoxide production in arterioles from aging rats[84]. Apart from regulating oxidative stress, CD47 blockade may exert its therapeutic effect on PH by upregulating cMyc to inhibit ET-1/ETA as well[69].

2.4. *Restenosis*

One of the risk factors of restenosis is neointimal hyperplasia which frequently occurs after vascular interventions[88]. The aCD47 Ab not only suppressed thrombin-induced proliferation and migration of SMCs, but also enhanced the thrombin-inhibited efferocytosis *in vitro* phagocytosis assays. Simultaneously, it increased the number of apoptotic SMCs merging with macrophages *in vivo*[71]. Distinguishing from atherosclerosis, CD47-based therapy exhibits its role in relieving restenosis largely depending on the thrombin-associated physiological process on SMCs.

2.5. *Left ventricular heart failure*

Left ventricular heart failure (LVHF) is a common heart dysfunction disease. In *Cd47*$^{-/-}$ mice or WT mice treated with aCD47 Ab with transverse aortic constriction-induced-pressure overload LVHF, cardiac function was enhanced, and diastolic dysfunction was reduced. It was proposed that CD47 stimulated the increase of CaMKII *via* modulating cardiac myocyte Ca^{2+}, thereby upregulating the expression of HDAC3 which affects the output of the heart and the weight of LV[72].

2.6. Autoimmune valvular carditis

Autoimmune valvular carditis is an autoimmune disease characterized by inflammation, fibrosis, and remodeling of heart valves[89]. K/B.g7 TCR transgenic mice (K/B.g7) mice develop chronic systemic inflammation because of T cell- and B cell-driving-high levels of anti-glucose-6-phosphate isomerase antibodies. Fibro-inflammatory valvular carditis in K/B.g7 mice has many similarities with autoimmune valve diseases in human[90-92]. CD47 was overexpressed in inflamed mitral valves from K/B.g7 mice, especially on apoptotic cells. Likewise, high expression of CD47 was found in inflamed mitral valves of rheumatic heart disease patients[73].

Accordingly, interfering CD47−SIRPα interaction by aCD47 Ab was considered a candidate therapeutic strategy for autoimmune valvular carditis. On the one hand, aCD47 Ab may serve as a preventative strategy. Administrating aCD47 Ab to mice model at the onset of clinical disease, mitral valve inflammation and thickness were reduced, while serum levels of IL-6 and CXCL1 decreased. Additionally, preventative blockage of CD47 diminished apoptotic cells stained by active-caspase 3 and increased SIRPα^+ cells merging with active-caspase-3 positive cells[73].

On the other hand, the effects of aCD47 Ab when delivered therapeutically agreed with that of the protective blockade of CD47. Notably, therapeutically blocking CD47 did increase the number of cells co-staining with CD11b and active-caspase 3. Moreover, SIRPα^+ macrophages from the mitral valve of mice therapeutically treated with aCD47 Ab produced less TNF and IL-6 as well[73]. Taken together, CD47 blockade may play preventative and therapeutic roles in autoimmune valvular carditis *via* promoting phagocytosis and inhibiting cytokine production.

The more detailed information about the therapeutic effects and mechanisms of CD47-based agents in diseases of the circulatory system is listed in Table 1.

3. Diseases of the nervous system

3.1. Stroke

3.1.1. Intracerebral hemorrhage

Intracerebral hemorrhage (ICH) is one of the most dangerous strokes with a poor prognosis. The survival rate and prognosis of ICH patients largely depend on the site, size, and the mass effect of the hematoma[93]. Hematoma may result in unreversible damages, such as neurological and physical disorders, because it not only induces high intracranial pressure but also leads to neurotoxicity and inflammation[94-97]. There are two main ways for hematoma self-clearing, microglia (MG) and macrophage (Mϕ) phagocyte RBCs and erythrocyte lysis[98,99]. Changes in membrane permeability and complement activation may lead to erythrocyte lysis, followed by neurotoxicity caused by hemoglobin, heme, and iron release[100,101]. Improving the phagocytosis rate to remove erythrocytes in an early stage may help to eliminate hematoma and prevent the second injury caused by autolysis of RBCs.

Early in 2016, it was reported that mice whose brain was injected with the blood of CD47 knockout mice had better outcomes, evidenced by smaller T2* lesion volume, less brain swelling, and fewer neurological deficits compared to mice injected with WT blood[102]. To further explore the potential therapeutic effect of targeting CD47 therapy, they preadded aCD47 Ab into the autologous blood, then, constructed an ICH model by injecting experimental animal autologous blood into mice's brains[103]. Similarly, aCD47 Ab promoted hematoma clearance which probably resulted from higher infiltration of MG and Mϕ, whilst relieving ICH mice from brain swelling, neuronal loss, and neurological deficits[103-106]. The aCD47 Ab decreased the residual hematoma from 72.6 ± 5.3% (IgG group) to 50.4 ± 4.6% (aCD47 Ab group) on Day 7, and reduced neuronal loss induced by ICH from 25.1 ± 4.1% (IgG group) to 10.5 ± 4.6% (aCD47 Ab group)[103]. MG and Mϕ are responsible for swallowing RBCs and their fragments. Moreover, clodronate liposomes counteracted the potential therapeutical effect of aCD47 Ab towards ICH[103]. These evidences suggest that aCD47 Ab contributed to hematoma clearance *via* promoting the phagocytosis effect of MG and Mϕ (Fig. 3).

As ICH occurs in elders more frequently, and macrophages in the aged tend to be less active, researchers evaluated the efficiency of aCD47 Ab in aged rats[104]. Likewise, aCD47 Ab protected elder rats from brain injuries after ICH, as demonstrated by T2* lesion volume decreased from 13.0 ± 14.6% in IgG groups to −2.6 ± 16.4% in aCD47 Ab group on Day 3. And neurological deficits which were assessed by the corner turn test, decreased from 74 ± 16% in the IgG group to 57 ± 11% in the aCD47 Ab group. Notably, the used dosage of antibody was lower compared with their former studies[104].

To better trace the location of MG and Mϕ that contribute to hematoma clearance, an enhanced green fluorescent protein gene was inserted into a microglia-specific gene to visualize microglia in mice[107]. Three days after ICH, the number of macrophages and microglia located in the core of hematoma was almost the same between the aCD47 Ab groups and IgG groups. Even so, macrophages and microglia were further recruited in both the periphery and core of hematoma in mice treated with aCD47 Ab seven days after ICH, suggesting macrophages and microglia might play a more prominent role seven days after ICH[107].

In a more recent study, collagenase IV, instead of using autologous blood, was used to form ICH models[105]. They administrated aCD47 Ab through cisterna magna after ICH, it is quite different from the above studies but facilitates the translation to clinical practice. The results of this murine study showed that 0.9 μg/mice may be the most suitable dosage, as improved recruitment of MG and Mϕ together with a decreased number of apoptotic cells were found in the brain slices from ICH mice treated with 0.9 μg of aCD47 Ab[105].

SIRPα-v Exo is a kind of exosome extracted from mesenchymal stem cells transfected with lentivirus containing SIRPα variant sequence. SIRPα-v Exo could release variant SIRPα and bind with CD47-expressed RBCs *in vitro*[108]. The results from *in vivo* assays showed that SIRPα-v Exo reduced the volume of hematoma and relieved ICH mice from motor and cognitive dysfunction. Moreover, SIRPα-v Exo promoted M2 polarization which could be further facilitated by Treg cells. Likewise, SIRPα-v Exo combined with Treg cells engulfed larger and more particles than SIRPα-v Exo did *in vitro* microglia phagocytosis assays[108]. It demonstrated that Tregs promoted the pro-phagocytosis effect of SIRPα-v Exo towards RBCs. However, the underlying mechanism is still unclear.

3.1.2. Intraventricular hemorrhage

Intraventricular hemorrhage (IVH) frequently occurs after ICH, predicting a poor prognosis[109-112]. The aCD47 Ab decreased hematoma volume from 41.2 ± 13.6 mm^3 (IgG group) to 17.4 ± 18 mm^3 (aCD47 Ab group) within three days, while attenuating hydrocephalus[109]. The efficacy of aCD47 Ab in IVH

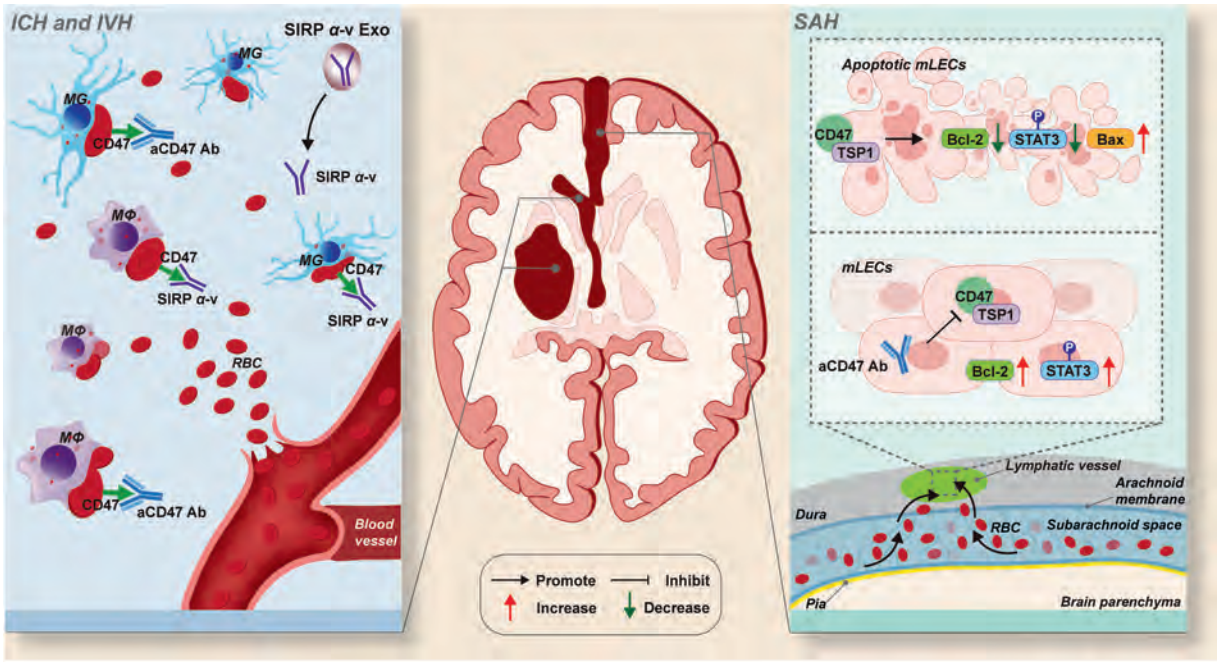

Figure 3 The effects of CD47-based therapies in stroke. In ICH and IVH, aCD47 Ab and SIRPα-v Exo reduced the size of hematoma by increasing the phagocytosis of RBC. In SAH, aCD47 Ab may disrupt TSP1 and CD47 interaction to protect mLECs *via* inhibiting apoptosis. aCD47 Ab, anti-CD47 antibody; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; mLECs, meningeal lymphatic endothelial cells; MG, microglia; Mϕ, macrophage; RBC, red blood cell; SIRPα, signal regulatory protein alpha; SAH, subarachnoid hemorrhage; SIRPα-v Exos, modified exosomal SIRPα variants; TSP1, thrombospondin 1.

may depend on phagocytosis as in ICH. The intra-hematoma ferritin/Iba1 double-positive cells were 382 $\pm$ 136 cells/mm^2 in the aCD47 Ab group, compared to that in the control group was 209 $\pm$ 83 cells/mm^2, revealing that aCD47 Ab enhanced the engulfment of hematoma. Consistently, the effect of aCD47 Ab in attenuating hematoma was reversed by clodronate[109]. CD47 blocking antibody may promote hematoma removal after IVH depending on macrophages and macrophage-like cells (Fig. 3).

3.1.3. Subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH) is another kind of hemorrhagic stroke, and is responsible for approximately 373,000 deaths annually[113]. According to results from single-cell RNA sequencing and spatial transcriptomics, the TSP1−CD47 axis was remarkably activated 24 h after SAH. Meningeal lymphatic vessels (mLVs) could transport intracranial fluid including extravasated RBCs from cerebrospinal fluid to deep cervical lymph nodes[114,115]. In addition to regulating phagocytosis, aCD47 Ab alleviated mLVs disorders and improved neural function in SAH model[43]. The property of aCD47 Ab was associated with its capacity to protect meningeal lymphatic endothelial cells from apoptosis to maintain the function of mLVs (Fig. 3).

3.2. Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, characterized by demyelination and neurodegeneration[116]. Experimental autoimmune encephalomyelitis (EAE) induced by myelin oligodendrocyte glycoprotein peptide amino acid 35 to 55 is a widely used MS animal models[117-119]. In the early stage of EAE, monocytes, and macrophages infiltration-induced T cell recruitment, especially that of CD4$^+$ T cell, causes neuronal demyelination. But in later stage, also termed as recovery phase, remyelination and recovery were promoted by the clearance of myelin debris[120,121]. Early observations demonstrated that *Cd47*$^{-/-}$, and SIRPα mutant mice were resistant to EAE induction[122,123]. CD47 fusion protein may suppress the macrophage-derived-IL-1β production *via* Src/iNOS axis, whilst impairing Th17 infiltrating into the central nervous system to protect mice from EAE[124]. Similar results were observed in another study that aCD47 Ab inhibited pro-inflammatory cell infiltration, including Th17, into the central nervous system[121]. However, the effects of CD47-based therapy on MS were controversial. Though administrating aCD47 Ab in the initial immunization delayed EAE onset by 2 days and ameliorated disease in the beginning 13 days[121]. Different from CD47 fusion protein, aCD47 Ab worsened disease in EAE mice model[121,124,125]. CD47 was found to be expressed in some myelin-containing fractions. The aCD47 Ab promoted the phagocytosis of purified human myelin fraction[125]. In addition, there were fewer myelinated neurons found in spinal cords from mice treated with aCD47 Ab during the recovery stage of EAE[121]. The reverse effect of aCD47 Ab may be caused by impaired remyelination in the recovery phase of EAE.

The more detailed information about the therapeutic effects and mechanisms of CD47-based agents in diseases of the nervous system is listed in Table 2[43,103-109].

4. Diseases of the digestive system

4.1. Non-alcoholic steatohepatitis

NASH is a widespread disease caused by multiple factors, like liver steatosis, liver cell death, and inflammation[126]. A certain

Table 2 Pre-clinical studies of CD47-based therapy in diseases of the nervous system.

Disease	Target	Experimental model	Administration design[a]	Main result	Ref.
Intracerebral hemorrhage (ICH)	CD47	2- to 4-month-old-C57BL/6 mice injected by 30 μL autologous arterial blood through the right basal ganglia	Once; anti-CD47 antibody; B6H12; 10 μg/mL; mixed with 30 μL autologous blood	Decreased the residual hematoma on Day 7 from 72.6 ± 5.3% (IgG group) to 50.4 ± 4.6%, reduced brain swelling on Day 1 from 4.8 ± 1.7% (IgG group) to 2.5 ± 1.6%, and reduced ICH-induced neuronal loss on Day 28 from 25.1 ± 4.1% (IgG group) to 10.5 ± 4.6%; Decreased behavior deficits; Reversed by clodronate	103
Intracerebral hemorrhage	CD47	Piglet received an injection with total 2.5 mL autologous arterial blood	Once; anti-CD47 antibody; B6H12; 10 μg/mL; mixed with 2.5 mL autologous blood	Increased HO-1 positive cells infiltrated into the hematoma areas with white matter fibers; 5.4-Fold and 14-fold increased the infiltration of MSR1 positive cells into the hematoma with white matter fibers on Days 3 and 7, respectively	106
Intracerebral hemorrhage	CD47	18-month-old-rats received an intracaudate injection by 50 μL autologous arterial blood	Once; anti-CD47 antibody; N/A; 1 μg/mL; mixed with autologous blood	Decreased T2* lesion volume on Day 3 from 13.0 ± 14.6% (IgG group) to −2.6 ± 16.4%; Decreased brain swelling (ipsilateral ventricle/ contralateral) on Day 3 from 48.3 ± 17.3% (IgG group) to 70.6 ± 13.7%; Decreased brain atrophy on Day 28 from 160 ± 34% (IgG group) to 127 ± 28%; Increased neurological function and decreased early hemolysis; Decreased neuronal loss on Day 28 from 19.4 ± 6.5% (IgG group) to 10.9 ± 5.9%; Increased CD68 positive cells in perihematomal region on Day 3 from 687 ± 154 cells/ mm^2 (IgG group) to 1021 ± 313 cells/mm^2	104
Intracerebral hemorrhage	CD47	Mice injected by 30 μL autologous arterial blood into the right basal ganglia	Once; anti-CD47 antibody; B6H12; 10 μg/mL; mixed with 30 μL autologous blood	Increased the number of monocyte-derived macrophages in the hematoma core from 28 cells/mm^2 (IgG	107

				group) to 90 cells/mm^2 and in the peri-hematomal area from 71 ± 25 cells/mm^2 (IgG group) to 194 ± 87 cells/mm^2 7 days after ICH; Increased the number of microglia in the hematoma core from 122 ± 46 cells/mm^2 (IgG group) to 309 ± 193 cells/mm^2 and in the peri-hematomal area from 1009 ± 153 cells/mm^2 (IgG group) to 1349 ± 162 cells/mm^2 7 days after ICH	
Intracerebral hemorrhage	CD47	14- to 16- week-old-rats injected 1 μL saline containing 0.23 U bacterial collagenase type IV over a 5-min period through the right striatum stereotaxically	Administrated into the cisterna magna; once; anti-CD47 antibody; N/A; 0.3 μg/0.9 μg/1.8 μg; 10 min after ICH model construction	Increased the number of CD68-positive cells accumulating around the hematoma in rats treated with 0.9 μg and 1.8 μg anti-CD47 antibody; Decreased the expression of Caspase-3 in ICH models treated with 0.9 μg and 1.8 μg anti-CD47 antibody; Decreased the number of TUNEL-positive cells in ICH models treated with 0.9 μg anti-CD47 antibody	105
Intracerebral hemorrhage	CD47	Mice injected by 30 μL autologous arterial blood through the right basal ganglia	i.v.; q.d.; modified exosomal SIRPα variants; 6 mg/kg; 14 days	No hematologic toxicity; Decreased the volume of intracerebral hematoma; Decreased the error ratio in paw placement on grid-walking; Decreased the time to touch the paw and remove the sticker; Ameliorated depressive symptoms and protected against axonal injury; Preserved the structural integrity of white matter and the myelin sheaths of axons	108
Intraventricular hemorrhage	CD47	Rats injected by 200 μL autologous arterial blood through the right ventricle	Once; anti-CD47 antibody; clone OX101; 10 μg/mL; mixed with 200 μL autologous blood	Decreased hydrocephalus development from Day 1 to Day 3 from 27.5 ± 10.5% (IgG group) to −14.5 ± 10.2%; Decreased intraventricular hematomas from	109

(*continued on next page*)

Table 2 (*continued*)

Disease	Target	Experimental model	Administration design[a]	Main result	Ref.
				41.2 ± 13.6 mm^3 (IgG group) to 17.4 ± 18 mm^3 at 72 h post-hemorrhage; Increased number of intra-hematoma ferritin/Iba1 double-positive cells from 209 ± 83 cells/mm^2 to 382 ± 136 cells/mm^2 and reversed by clodronate	
Subarachnoid hemorrhage	CD47	Mice received an intra-prechiasmatic cisternal injection by 60 μL autologous blood	Once; anti-CD47 antibody; B6H12; (or anti-thrombospondin 1 antibody; clone A6-1); 10 μg/mL; mixed with autologous blood	Decreased meningeal lymphatic dysfunction at 24 h post-subarachnoid hemorrhage; Increased neurological function; Increased pSTAT3 and Bcl-2 expression in meninges	43
		Primary meningeal lymphatic endothelial cells	Anti- thrombospondin 1 antibody; clone A6-2; 5 μg/mL	Decreased the apoptosis of lymphatic endothelial cells	
Multiple sclerosis	CD47	C57BL/6 mice immunized by myelin oligodendrocyte glycoprotein peptide amino acid 35 to 55 (MOG_{35-55})	i.p.; q.o.d.; CD47-Fc fusion protein (purified from MCD47-Fc CHO cells); 200 μg/mouse; from Day 3 to Day 9; after MOG_{35-55} immunization	Decreased clinical scores before Day 21	124
		C57BL/6 mice immunized by MOG_{35-55}	i.p.; q.o.d.; CD47-Fc fusion protein; 200 μg/mouse; from Day 10 to Day 24; after MOG_{35-55} immunization	Decreased clinical scores; Decreased infiltrated lymphocyte and demyelination in the mice on Day 18 compared to the isotype control group; Decreased the frequency of Th17 cells and the $CD4^+$ T cell numbers in the central nervous system sections, spleen, draining lymph node, and peripheral blood	
		C57BL/6 mice immunized by MOG_{35-55}	i.p.; q.o.d.; CD47-Fc fusion protein; 200 μg/mouse; from Day 10 to Day 24; after MOG_{35-55} immunization i.v.; q.3d.; recombinant murine IL-1β; 10 ng/mouse; from Day 1 to Day 22; after MOG_{35-55} immunization	Reversed the effect of CD47-Fc fusion protein	

i.v., intravenous; i.p., intraperitoneal; q.d., every day; q.o.d., every other day; q.3d., every three days.

[a]*In vivo* assay: administration method; frequency; treatment; (clone of antibody) dosage; duration; others. *In vitro* assay: treatment; (clone of antibody) dosage; others.

amount of NASH patients will develop liver injury, necroinflammation, and even fibrosis[127-129]. Liver sinusoidal endothelial cells were characterized by fenestrated phenotype. Abnormalities in the liver, like necrosis and fibrosis, may induce defenestrated[130-132]. CD47 blockade tended to protect liver sinusoidal endothelial cells from defenestrated phenotype through Rho−ROCK−myosin signaling[133]. CD47-related agents may have important applications for NASH treatment. CD47 overexpressed in NASH liver tissues in comparison with normal liver tissue[25]. Besides, CD47 is highly expressed in liver cells which were specifically induced necrosis. aCD47 Ab facilitated necrotic liver cell internalization by macrophages *in vitro* and *in vivo*, leading to downregulated plasm ALT level and fibrosis[25]. However, aCD47 Ab was unable to alleviate steatosis in the liver, revealing that aCD47 Ab may relieve NASH by promoting phagocytosis. It was also observed that the number of hepatic-infiltrated neutrophils was reduced by aCD47 Ab treatment[134].

Together with upregulated CD47 level in necrotic liver cells, high expression of SIRPα was found in liver macrophages in human NASH liver. The aSIRPα Ab treatment elevated the number of necrotic hepatic cells internalized by macrophages *in vitro* and *in vivo*. Likewise, aSIRPα Ab attenuated hepatic fibrosis with evidence that less hepatic stellate cells activation and lower the levels of mRNAs associated with liver fibrosis[25].

Whether aCD47 Ab or aSIRPα Ab exerts a liver protection role relying on promoting the phagocytosis effect of macrophages, highlighting the promising therapeutic efficacy of blocking the CD47−SIRPα axis in NASH.

4.2. *Ulcerative colitis*

Ulcerative colitis (UC) with unknown etiology is a kind of inflammatory bowel disease. Neutrophil infiltration has been observed across tissues from patients with active UC[135,136]. The blockade of CD47 suppressed CD11b/CD18-dependent neutrophil chemotaxis and migration[137]. Likewise, other CD47-based therapies CD47 Fc fusion protein and agonistic aSIRPα Ab exerted effects on inhibiting TNF-α and G-CSF secretion and reducing CXCL1-mediated neutrophil and monocyte migration[26]. Correspondingly, the numbers of neutrophils and monocytes infiltrating into the mucosa and lamina propria were downregulated in T cell transfer colitis mice model treated with agonistic aSIRPα Ab[26,138-140]. Agonistic aSIRPα Ab was further found to ameliorate colon edema and thickness in the T cell transfer colitis model. Besides, agonistic aSIRPα Ab reduced foci of epithelial inflammation, crypt loss, and reactive epithelial hyperplasia, while protecting animal from severe weight loss[26].

4.3. *Crohn disease*

Besides ulcerative colitis, Crohn disease (CD) is the other inflammatory bowel disease[141,142]. Compared to healthy colon tissues, inflamed colon tissues of CD patients have a higher transcription level of *SIRP*α. In addition, a cohort of SIRPα^+ monocytes accumulated in mesenteric lymph nodes and inflamed mucosa of CD patients[143]. CD47 fusion protein, termed CD47-Var1, could specifically identify SIRPα^+ cells and alleviate chronic colitis development[144]. Without affecting uninflamed tissues from CD patients, CD47-Var1 attenuated the secretion of a series of cytokines, including IL-1β, IL-6, IL-8, TNF, and IFN-γ, in inflamed tissue. In this case, CD47 fusion protein potentially ameliorated colon inflammation *via* inhibiting inflammatory factors secretion[143]. However, *in vivo* data are warranted to confirm the anti-inflammation ability of CD47-based therapies, especially CD47 fusion protein, in CD.

5. Endocrine, nutritional or metabolic diseases

5.1. *Diabetes*

Diabetes is characterized by insulin absolute lack caused by islet β cell injury or inadequate insulin of dysfunctional β cell[145]. Streptozotocin-induced diabetic mice have less CD47 in their islets[146]. However, emerging evidence suggested that CD47 was downregulated in islets of patients with type 1 diabetes endotypes 2, and reversely upregulated in β cells of patients with type 1 diabetes endotypes 1[147]. Though the level of CD47 in diabetic islets is still uncertain, it was observed that CD47 had a bias in expression against β cells. It was further reported that the islet's CD47 level increased during the transition from nondiabetic to diabetic in nonobese diabetic mice[42].

CD47 signaling may be responsible for insulin secretion. si-CD47 and morpholino targeting CD47 effectively induced the secretion of insulin in murine islets and human islets stimulated by glucose, respectively. Granules docking and exocytosis were enhanced in CD47-deficient β cells. It was proposed that CD47 may modulate insulin secretion *via* regulating the docking and exostosis of granules in a Cdc42-dependent pathway[42].

CD47 targeting agents may delay the onset of diabetes by elevating insulin secretion. The aCD47 Ab delayed the initiation of hyperglycemia in mice for 3−5 weeks, and may further postpone when tripled the dosage[42]. Moreover, 80% of euglycemic nonobese diabetic mice in the isotype group were diagnosed with diabetes after 4 weeks, while only half of the mice in the aCD47 Ab group developed into diabetes[42]. The therapeutic efficacy of aCD47 Ab in diagnosed type 1/2 diabetes patients is still largely unknown. According to the regulatory role of CD47 in insulin secretion, aCD47 Ab or other CD47-based therapy may be beneficial to type 2 diabetes patients.

After conventional therapeutic approaches fail, transplantation of allogeneic islets will be the ultimate therapeutic modality for patients with diabetes[148,149]. However immunological rejection restricts its broad applicability. Nevertheless, CD47 overexpression-endowed hypoimmune HLA class I- and class II-deficient pseudoislets have the capability of escaping innate and adaptive immune attack[31,150,151]. These transgenetic pseudoislets successfully survived in humanized mice for 30 days and in rhesus monkeys for 40 weeks[31,150]. In addition to controlling glucose levels in humanized mice with diabetes within 2 weeks, a most recent study demonstrated that this transgenetic psedoislet achieved curative diabetic treatment in cynomolgus monkeys without immunosuppression medication[151]. Concomitantly, aCD47 Ab could accelerate the clearance of pseudoislets when necessary, suggesting the safety of transplantation[31].

5.2. *Obesity*

Obesity is a multi-caused disease, which leads to a series of comorbidity, like cardiovascular disease, diabetes, and heart failure[152,153]. Early observations in *Cd47*$^{-/-}$ mice demonstrated that

CD47 deletion protected mice from HFD-induced-obesity by decreasing inflammation and enhancing fat utilization[154]. Not only did CD47 regulate the progression of obesity, but also CD47 was recently considered to be a potential target for obesity. An antisense oligonucleotide targeting CD47 (CD47 ASO) was proven to effectively knock down CD47 in metabolic tissues, including liver, muscle, and fat tissue. CD47 ASO inhibited body weight increase both in HFD-induced obesity mice and genetically-engineered obesity mice[24]. In epididymal white fat tissue of HFD-induced-obesity mice, CD47 ASO decreased the size of lipid cells and increased fat degradation-related genes, suggesting that CD47 ASO enhanced lipid degradation. In addition, CD47 ASO seems to boost the exercise motivation of mice[24].

6. Diseases of the genitourinary system

6.1. Renal ischemia reperfusion injury

Renal ischemia−reperfusion injury (RIRI) is the result of sudden and temporary obstruction followed by restoration of blood flow to the kidney. The aSIRPα Ab restored blood flow in the kidney as well as relieved the kidney from serious renal tubular injury in IRI animal model[155]. TSP1 may be one of the driving factors of RIRI, as TSP1 stimulates the production of $O_2^{\cdot -}$ and limits vasodilation[155-157]. aSIRPα Ab inhibited the inhibitory effect of TSP1 on NO-stimulated vasodilation[155]. Concomitantly, CD47 blocking antibody downregulated the level of TSP1 and limited the injury and fibrosis of the kidney as aSIRPα Ab did in RIRI model[156]. Besides, aCD47 Ab alleviated RIRI following kidney transplantation[158,159]. The histological scores of acute tubular injury and necrosis were lower in aCD47 Ab group[158,159]. The aCD47 Ab may increase the survival rate for kidney transplantation[158].

6.2. Glomerulonephritis

Glomerulonephritis includes a series of immune-mediated-disorder mediating renal inflammation[160]. The aCD47 Ab demonstrated significant improvements in spontaneous crescentic glomerulonephritis-forming/Kinjoh mice suffered from systemic necrotizing glomerulonephritis. The aCD47 Ab relieved the kidney injury to a certain degree, as the serum creatine decreased, and decreased the glomerular score from 2.8 ± 0.41 (IgG group) to 2.0 ± 0.63 (aCD47 Ab group)[161].

6.3. Endometriosis

Endometrial-like tissue growing at extrauterine sites was considered endometriosis, an estrogen-dependent disorder[162]. Abnormally higher expression of CD47 in ectopic endometrial stromal cells (ESCs) may result from estrogen receptor β which could directly bind with CD47 promoter[45]. Recent studies showed that targeting CD47 agents ameliorated endometriosis by enhancing phagocytosis and inducing apoptosis towards ESCs. Blocking CD47 by antibody or downregulating CD47 by si-RNA elevated the phagocytotic rate of human ESCs[163,164]. Besides, the silence of CD47 seems to induce apoptosis in ESCs co-incubated with macrophages. In agreement with *in vitro* assays, more phagocytosis and apoptosis of ectopic ESCs were observed across *in vivo* assay[164].

7. Diseases of the musculoskeletal system or connective tissue

7.1. Heterotopic ossification

Abnormal formation of bone in soft tissue is regarded as heterotopic ossification (HO)[165]. The ectopic bone formation could be stimulated by macrophages-secreting TGF-β1[166]. The suppressive role of CD47 in TGF-β1 expression has been reported[167,168]. It makes sense that peptide-activating CD47 rather than antibody-blocking CD47 suppressed chondrogenesis and HO. However, the therapeutic effect of CD47-activating peptide p7N3 was independent of CD47−SIRPα interaction. Instead of, p7N3 decreased the expression of TGF-β1 in macrophages[169].

7.2. Rheumatoid arthritis

Rheumatoid arthritis (RA) is considered a chronic inflammatory disease mainly involving joints[170]. Both CD47 Fc fusion protein and agonistic aSIRPα Ab inhibited neutrophils and monocytes infiltration[26]. In joint synovial fluids from arthritis mice treated with agonistic aSIRPα Ab, the numbers of neutrophils and monocytes were reduced by more than 80%. Even more, the enrichment of pro-inflammation cytokines was downregulated in joint tissue. Agonistic aSIRPα Ab alleviated arthritis, characterized by reduced paw and joint erythema, reduced synovial inflammation, and diminished articular cartilage erosion. In addition, the therapeutic effect of agonistic aSIRPα Ab was further confirmed in collagen-induced arthritis model[26].

K/B.g7 mice also develop arthritis due to chronic systemic inflammation. However, there was no significant difference in ankle width between the control and aCD47 Ab group, suggesting aCD47 Ab had little effect on the progression of arthritis that occurred in K/B.g7 mice[73].

8. Diseases of the immune system

8.1. Systemic lupus erythematosus

Lupus nephritis is a common complication of systemic lupus erythematosus (SLE), characterized by immune complex depositing in kidney tissues[171]. *Fas*^{lpr} mice, cell-surface *Fas* receptor-deficient mice, all developed pathological proteinuria at the age of 8 months, while only about 25% of *Cd47*$^{-/-}$*Fas*^{lpr} mice did[172]. IgG reduction caused by impaired germinal center development may result in better outcomes for *Cd47*$^{-/-}$ mice after immunization. Indeed, aCD47 Ab lowered IgG levels in WT mice. But 24-week-old *Fas*^{lpr} mice with lupus symptoms developed significantly worse proteinuria with a higher level of IgG after aCD47 Ab treatment[172]. It suggested that aCD47 Ab had an inverse effect on lupus nephritis *via* an unknow mechanism, though CD47 deficiency alleviated it. Whereas, it was announced that IMC-002 (CD47 $\times$ CD20 mAb-Trap) targeting CD47 and CD20 induced peripheral blood CD19$^+$ B cell exhaustion in SLE patients. Additionally, a clinical trial of IMC-002 (CTR20242914) was approved for SLE by the National Medical Products Administration[173]. Considering aCD47 Ab-associated proteinuria deteriorated with disease progression in *Fas*^{lpr} mice[172], therapeutic potency and side-effects of this bispecific fusion protein in

volunteers with different SLE stages warrant attention in clinical trials.

8.2. Scleroderma

Vascular obliteration and fibrosis in the skin and diverse organs are hallmarks of scleroderma[174]. Antibody blocking CD47 could relieve scleroderma as a monotherapy. When supplementing aCD47 Ab, the uptake of *Jun*-inducible fibroblasts by mouse macrophages was enhanced. Moreover, aCD47 Ab eliminated dermal fibroblasts that were transplanted under mice's kidney capsule[175].

In addition to being monotherapy, aCD47 Ab could combine with an IL-6 inhibitor to elicit a better efficacy. No matter in the *Jun*-induced mice model or the doxycycline-induced mice model, combination therapy of aCD47 Ab and IL-6 inhibitor increased dermal fat tissue and the fatty area. aCD47 Ab combined with IL-6 inhibitor may suppress T cell infiltration and cell proliferation in dermal lesions, as the numbers of $CD3^+$ cells and $KI67^+$ cells decreased[175]. In sum, aCD47 Ab may ameliorate scleroderma by facilitating phagocytosis, regulating T-cell infiltration, and decreasing cell proliferation, while having a combined effect with IL-6 inhibitor.

9. Diseases of the respiratory system

9.1. Pulmonary fibrosis

Pulmonary fibrosis is a lung ailment characterized by lung destruction and scarring[176]. From the data obtained from clinical samples, over 20% of pulmonary fibrosis cells expressed CD47[44]. More importantly, CD47 inhibitor, RRx-001, preserved pulmonary architecture and reduced collagen deposition in bleomycin-induced pulmonary fibrosis mice model[23].

As there is a subset of pulmonary fibrosis cells co-expressed CD47 and PD-L1, it is conceivable that treatment containing aCD47 Ab, aPD-L1 antibody, and anti-IL-6 antibody displayed the most superior effect on pulmonary fibrosis compared to other combinations. The therapeutic effect of aCD47 Ab was supported by CT scan results and other indexes like decreased $PD\text{-}L1^+CD47^+$ fibroblasts and a lower level of collagen[44]. These observations are in agreement with a study focusing on coronavirus disease 2019 (COVID-19) lung fibrosis. The aCD47 Ab in combination with anti-IL-6 antibody ameliorated the severe immune infiltration and fibrotic expansion in humanized mice with COVID lung fibrosis, suggesting the promising applicability of CD47-based therapies in pulmonary fibrosis including that in response to COVID-19 infection[177].

10. Other diseases

10.1. Age-related macular degeneration

The accumulation of mononuclear phagocytes (MP) is one of the hallmarks of age-related macular degeneration (AMD)[178,179]. As a pathogenic factor, complement factor H binding with CD11b inhibits TSP1 activation of CD47, whilst inhibiting CD47-mediated MP removal. Naturally, pharmacological activation of CD47 by CD47-activating peptide PKHB1 reversed this effect and exerted an inverse effect that promoted the clearance of MP[13].

10.2. Malaria

Malaria is one of the most prevalent infectious diseases, especially in Africa. Different from virus infection, CD47-based therapies may have distinct contributions to malaria infection. CD47 deletion mice infected by *Plasmodium berghei* ANKA (*Pb*-A) exhibited a more preserved epithelium and better blood−brain barrier (BBB) integrity compared to infected WT mice[180]. In the murine *Plasmodium yoelii* 17XNL model, CD47 deletion mice had a higher level of $CD8^+$ T cells and macrophages in the spleen, while had a lower serum level of IL-10 of which deletion seems to lead to resistance towards *P. yoelii* 17XNL[181].

Corresponding with the results from CD47 deletion mice, aCD47 Ab decreased malaria burden from $0.39 \pm 0.05\%$ to $0.026 \pm 0.008\%$[181]. And 80% of mice in the aCD47 Ab group did not grow into malaria and survived *Pb*-A infection[182]. The aCD47 Ab also facilitated the phagocytotic rate of RBCs infected by malaria[182]. Simultaneously, SIRPα fusion protein promoted macrophages to engulf RBCs infected by ring-stage malaria, and LPS and IFN-γ further enhanced engulfment[180].

However, the anti-malaria capacity of aCD47 Ab may not rely on the macrophage, as the survival rate of mice had no change after macrophage and monocyte cleavage in the *Pb*-A model[182]. As mice treated with aCD47 Ab exhibited more integrated BBB, researchers speculated that aCD47 Ab may contribute to malaria *via* exerting other biological functions, like protecting BBB, rather than facilitating phagocytosis[182].

10.3. Virus infection

The transcription of CD47 was enhanced in cells infected by human respiratory syncytial virus or human parainfluenza virus 3[183]. CD47 seems a negative factor towards the influenza virus as well. CD47 was induced and exposed on the apical surface of nasal and bronchial epithelial cells infected by virus pH1N1 in an NF-κB/IFN-dependent manner[184]. CD47 deleted mice were better protected from influenza by vaccination, as less weight loss and virus titer in lung[185]. In addition, aCD47 Ab decreased the susceptibility of pH1N1-infected mice to secondary *S. aureus* infection[184].

In mice infected by lymphocytic choriomeningitis virus (LCMV), aCD47 Ab cleared viremia below the level of detection, while the titer of control groups was $2.8\log_{10}$ by eight days post-infection. In addition, kidney virus showed a 27-fold reduction in the aCD47 Ab group in comparison to control group after ten days of infection. Further, aCD47 Ab activated dendritic cells, whilst regulating the activation and proliferation of $CD8^+$ T cells rather than macrophages in LCMV infection[186]. Meanwhile, CD47 neutralizing antibody alleviated clinical scores and calcified myofibers in mice with Theiler's murine encephalomyelitis virus infection[187].

The peripheral monocytes collected from human immunodeficiency virus (HIV) patients also had a higher level of CD47, and CD47 binding partner SIRPα. However, aCD47 Ab only relieved HIV syndromes in one cohort rather than in both two cohorts[186]. The efficacy of aCD47 Ab in HIV infection remains largely obscure but is worthwhile exploring.

The more detailed information about the therapeutic effects and mechanisms of CD47-based agents in non-cancer diseases except for that of the circulatory and nervous system is shown in Table 3[13,23-26,42,44,134,143,155,156,161,163,164,169,175,177,180−182,184,186,187] and Fig. 4.

11. Discussion

11.1. The potential indications of CD47-based therapy in non-cancer diseases

More and more studies have emphasized the property of CD47 and its binding partners in non-cancer disease progression. For instance, the plaque area and neointima area were smaller in *Cd47*$^{-/-}$ mice induced by western diet[76]. CD47 deficiency seems to protect mice from EAU[188]. Mice injected by blood from *Cd47*$^{-/-}$ mice rather than WT mice tended to have slighter brain swelling and less neurological deficits[102]. Inhibition of CD47 and/or its binding partners may therefore be beneficial in non-cancer diseases.

To uncover the wider applicability of CD47-based therapy, we summarized the applications of CD47-related agents in non-cancer diseases in this decade (Fig. 1). In addition to conventional agents like anti-CD47 antibody and anti-SIRPα antibody, some novel agents like CD47 fusion protein, ASO targeting CD47, SIRPα-activating peptide, were utilized in these studies as well. The beneficial effects of aCD47 Ab on cardiovascular diseases were widely reported. aCD47 Ab was found to accelerate the clearance of atherosclerosis plaque and brain hematoma[41,43,102]. The property of CD47-related agents in treating metabolic disorder diseases was also mentioned. The secretion of insulin was induced by aCD47 Ab in islet β cells. The aCD47 Ab decreased the incidence of diabetes in nonobese diabetic mice[42]. Conversely, HO and AMD were alleviated by CD47-activating peptide[13,169]. Similarly, the SIRPα-activating peptide mitigated the symptoms in mice with UC and RA[26]. More detailed information about the applications of CD47-related agents has been summarized in Figs. 1−4 and Tables 1−3.

Among non-cancer diseases, atherosclerosis is one of the most high-profile diseases with the most pre-clinical studies and clinical trials (Fig. 2 and Table 1). CD47-based agents may have broad applicability to different stages of atherosclerosis. BRB-002, a kind of aCD47 Ab, was reported to exert a preventative role towards atherosclerosis in mice with HFD induction[54]. After the formation of plaques, CD47 was served as a biomarker and target[41]. A CD47-targeting nanoparticle identified the plaque in a very early stage[75]. aCD47 Ab, aSIRPα Ab, and SHP1i reduced the plaque area by stimulating the process of efferocytosis[59,62,63]. And combination therapy could further enhance their therapeutic efficacy.

Apart from enhancing dying cells removal, CD47-based therapy may also reduce vessel inflammation to achieve preventative and curative effects on atherosclerosis. SWNT-SHP1i reduced aortic ^{18}F-FDG uptake in mice[59]. In a phase Ib/II clinical trial, it was found that patients treated with aCD47 Ab magrolimab had lower arterial uptake of ^{18}F-FDG, as maximum standardized uptake values decreased from 2.68 $\pm$ 0.59 to 2.06 $\pm$ 0.52, suggesting inflammation in arteria was ameliorated[189]. It was proposed that magrolimab or SWNT-SHP1i may relieve vascular inflammation which is a core risk factor towards atherosclerosis to narrow plaques.

Even though, aCD47 Ab may have inverse effects on atherosclerosis with *JAK2*^{V617F} (*JAK2*^{VF}) mutation[190]. RBCs from *Jak2*^{VF} mice had a lower CD47 level, while RBCs from humans with *JAK2*^{VF} mutation had a higher level of calreticulin[190,191]. Macrophages preferred to swallow mutant RBCs rather than apoptotic cells within plaques in *Jak2*^{VF} mice with atherosclerosis[191]. aCD47 Ab may further enhance the clearance of RBCs rather than plaques in *Jak2*^{VF} mice[190].

Stroke is another promising indication of CD47-related agents (Fig. 3 and Table 1). The investigations on the role of CD47 in stroke date back to ten years ago. Researchers have estimated the benefits of targeting CD47 therapy in treating stroke by different animal models, including mice, rats, and piglets[103,104,107-109]. Three subtypes of stroke, ICH, IVH, and SAH could all be alleviated by CD47-related therapy. No matter aCD47 Ab or exosomal SIRPα variant exerted potential clinical efficacy towards ICH[103,104,107-109]. In a more recent study, researchers further confirmed the association between the TSP1−CD47 axis and SAH by single-cell RNA sequencing and spatial transcriptomics[43]. Targeting CD47 therapy, especially aCD47 Ab, is believed to lead stroke-induced hematoma to fade *via* regulating the capacity of macrophages and microglia or protecting the function of mLVs in the present studies[43,103,105,107]. Generally, exogenous macromolecules including antibodies rarely penetrate BBB[192,193]. It may be a potential explanation as to why aCD47 Ab was delivered across BBB by invasive technology in preclinical studies. Researchers will premix blood with aCD47 Ab to inject into animals' brains to construct a model together with drug administration[103,104,106,107,109]. In addition, aCD47 Ab could be invasively administrated by direct cisterna magna injection[105]. However, it is reported that the integrity of BBB is impaired following stroke[194], making it possible to deliver antibodies by systemic administration. Then, it may raise concern that aCD47 Ab leakage caused by systematic administration or impaired BBB may facilitate the removal of RBCs around the body rather than only enhancing the clearage of brain hematoma. Additionally, considering the upregulation of CD47 on neurons, oligodendrocytes, microglia, and macrophages, one would imagine potent side effects of antibody blocking CD47[195]. Fortunately, aCD47 Ab is generally given once a time when treating stroke in studies[104,105].

Apart from the two potential indications mentioned above, fibrotic disease is another promising candidate. aCD47 Ab was able to ameliorate pulmonary fibrosis and scleroderma[23,44,175]. Moreover, both aCD47 Ab and aSIRPα Ab decreased liver fibrosis in mice with NASH[25].

It is worth mentioning that potent non-cancer indications in recent clinical trials partially matched with pre-clinical studies. By far, there have been three CD47-based therapy are approved for clinical trials of non-cancer diseases. The first one is sB24M, a CD47/TNF-α antibody. Researchers speculated that sB24M may facilitate impaired tissue epithelialization *via* the CD47/TNF-α axis. A clinical trial of sB24M for purulent pyoderma has been completed (NCT04895566). Secondly, it is BRB-002, an aCD47 Ab comprising of CD47 binding region and inactive Fc domain. BRB-002 presented both preventative and therapeutic efficacy in animal atherosclerosis model[54]. It is undergoing phase I clinal trial being in charge by Bitterroot Bio (ACTRN12624000405516). The last one is IMC-002 (CD47 $\times$ CD20 mAb-Trap). IMC-002 was designed to target both CD47 and CD20. IMC-002 was pronounced to exert a great effect on inducing B cell exhaustion without inducing severe side effects in a phase I clinical trial for lymphoma[196]. B cell elimination therapy was reported to achieve durable autoimmune disease remission[197]. The applications of

Table 3 Pre-clinical studies of CD47-based therapy in diseases other than those of the circulatory and nervous system.

Disease	Target	Experimental model	Administration design[a]	Main results	Ref.
Non-alcoholic steatohepatitis (NASH)	CD47	Mice fed with diet enriched with fat, fructose, and cholesterol for 20 −30 weeks	i.p.; q.o.d.; anti-CD47 antibody; MIAP410; 200 μg/mouse; 4 weeks	Did not affect hepatic steatosis development; Decreased plasm ALT level; Decreased histology scores of liver inflammation and fibrosis; Decreased hepatic neutrophils infiltration and liver NF-κB levels; Decreased the level of α-SMA and collagen I; Decreased both trichrome and Sirius red positive staining areas; Decreased the number of neutrophils in the blood	134
		Hepatic stellate cell	Anti-CD47 antibody; N/A; N/A	Decreased hepatic stellate cell activation	
		3D spheroid microtissue (containing human hepatocytes, macrophages, and stellate cells) treated with NASH-inducing media for 5−10 days	Anti-CD47 antibody; MIAP410; 20 μg/mL; 5 days	Decreased α-SMA and collagen I positive staining	
Non-alcoholic steatohepatitis	CD47	necHCs (primary hepatocytes isolated from AAV8-TBG-mRIP3-2xFV mice or hRIP3-2xFV-transduced human hepatocytes to AP20187); Mouse/human macrophages	Anti-CD47 antibody; MIAP410; 20 μg/mL	Increased necHC uptake; This co-culture medium induced HSC activation genes	25
		AAV8-TBG-mRIP3-2xFV transduced mice administrated with AP20187	i.p.; once; anti-CD47 antibody; MIAP410; 200 μg per mouse; N/A	Increased the engulfment of $RIP3^{+}$ necHCs by liver macrophages	
		Fructose-palmitate-cholesterol (FPC) diet-induced NASH for 8 weeks before treatment	i.p.; q.3w.; anti-CD47 antibody; MIAP410; 200 μg per mouse; 8 weeks with FPC diet	Not altered body weight or liver weight; Increased the engulfment of necHCs by macrophages; Decreased plasm ALT levels and fibrosis	
		High-fat choline-deficient L-amino-defined diet (HF-CDAA)-induced NASH for 2 weeks before treatment	i.p.; q.3w.; anti-CD47 antibody; MIAP410; 200 μg per mouse; 6 weeks with HF-CDAA diet	Did not alter body weight; Increased the engulfment of necHCs by macrophages; Decreased plasm ALT levels; Did not increase apoptotic cell clearance; Decreased fibrosis; Not changed the number of red blood cells	
		Mice fed with FPC diet for 8 weeks before treatment and a total 16 weeks	AAV8-H1-shCD47; N/A	Increased the engulfment of necHCs by macrophages; Decreased plasm ALT levels	
	SIRPα	necHCs (primary hepatocytes isolated from AAV8-TBG-mRIP3-2xFV mice); Mouse macrophages	Anti-SIRPα antibody; cloneP84; 20 μg/mL	Increased the engulfment of necHCs by macrophages;	
		FPC diet-inducing NASH for 8 weeks before treatment	i.p.; q.3w.; anti-SIRPα antibody; cloneP84; 100 μg per mouse; 8	Did not alter body weight; Increased the engulfment of necHCs by	

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Table 3 (*continued*)

Disease	Target	Experimental model	Administration design[a]	Main results	Ref.
			weeks with FPC diet	macrophages; Decreased hepatic fibrosis; Decreased plasm ALT levels; Not changed the number of red blood cells	
		HF-CDAA diet-induced NASH for 2 weeks before treatment	i.p.; q.3w.; anti-SIRPα antibody; cloneP84; 100 μg per mouse; 6 weeks with HF-CDAA diet	Increased the uptake of necHCs by macrophages; Did not alter body weight, liver weight, liver steatosis, and plasm ALT; Decreased hepatic fibrosis and collagen deposition	
Ulcerative colitis	SIRPα	$CD45RB^{high}CD4^{+}$T cell transfer colitis model	s.q.; t.i.w.; agonistic anti-SIRPα antibody; clone 6F2; 250 μg/mice; 12 weeks; initiated right after T cell transfer	Decreased body weight loss; Decreased visual colon and histopathology score	26
		$CD45RB^{high}$ $CD4^{+}$T cell transfer colitis model	s.q.; b.i.w.; agonistic anti-SIRPα antibody; 250 μg/mice; 6 weeks; initiated 6 weeks after T cell transfer	Increased body weight; Increased visual colon score which reflects colon edema and thickness; Decreased foci of epithelial inflammation, crypt loss, and reactive epithelial hyperplasia; Decreased the ratio of GR1 expressing neutrophil: monocytes in the mucosa and lamina propria regions	
Crohn disease (CD)	SIRPα	Mesenteric lymph nodes and intestinal mucosa of CD patients	Avidity-improved human CD47 fusion protein (CD47-Var1); 10 μg/mL	Selectively identifies CD172a on $HLA\text{-}DR^{+}$ cells in intestinal mucosa and mLNs of CD patients	143
		T Cells isolated from mesenteric lymph nodes of surgical specimens	Avidity-improved human CD47 fusion protein (CD47-Var1); 10 μg/mL	Decreased the ability of HLA-DR-$CD172a^{+}$ cells to stimulate memory Th17 responses	
		Inflamed CD tissues	Avidity-improved human CD47 fusion protein (CD47-Var1); 10 μg/mL	Decreased the production of IL-1β, IL-6, IL-8, IL-10, TNF, IFN-γ, IL-23, MIP-1α, and MIP-1β in the inflamed tissue without significantly affecting the secretion of cytokines by the noninflamed tissues in CD patients	
Type I diabetes	CD47	Human islet	Anti-CD47 antibody; B6H12; N/A	Increased insulin expression	42
		Primary murine β cells isolated from mice	CD47 siRNA; N/A	Increased insulin secretion	
		MIN6 cell	A morpholino targeting human CD47; N/A	Increased insulin secretion	
		MIN6 cell	CD47 siRNA; N/A	Increased phosphorylation of Lyn kinase	
		Isolated human islet	Anti-CD47 antibody; MIAP301; N/A	Increased phosphorylation of Lyn kinase	
		Primary murine β cells isolated from mice	CD47 siRNA; N/A	Decreased Cdc42 phosphorylation at serine-71	
		6-week-old nonobese diabetic mice	i.p.; N/A; anti-CD47 antibody; MIAP301; 0.4 μg/g; N/A	Delayed the onset of hyperglycemia for 3–5 weeks compared to the IgG group;	

				Showed better glucose tolerance over the time course of treatment at 16 and 20 weeks of age	
		11-week-old nonobese diabetic mice	N/A; q.2w.; anti-CD47 antibody; MIAP301; 0.8 μg/g; 5 weeks	50% of the MIAP301-treated mice turned into diabetics while 80% of IgG-treated mice turned into diabetics by 28 weeks	
Obesity	CD47	Mice fed with a high-fat diet for 6 weeks	i.p.; q.2w.; antisense oligonucleotide targeting CD47 (CD47 ASO); 25 mg/kg; 8 weeks with HFD	Knockdown CD47 in the liver, skeletal muscle, or fat tissues; Decreased high-fat diet-induced weight gain; Decreased fat mass, plasma triglyceride and cholesterol, hepatic steatosis, plasma ALT and AST levels, and Nos2; Decreased the size of adipocytes of epididymal white fat tissue; Increased glucose tolerance, lipolysis genes in epididymal white fat tissue, Arg1 expression, oxygen consumption, energy expenditure, and voluntary wheel running distance	24
		Genetic obese mice	i.p.; q.2w.; CD47 ASO; 25 mg/kg; 8−9 weeks	Induced weight loss after 5 weeks of CD47 ASO; Decreased adiposity; Increased glucose tolerance	
Renal ischemia reperfusion injury (RIRI)	SIRPα	Vascular smooth muscle cells	Anti-SIRPα antibody; N/A; 1 μg/mL	Blocked TSP1-mediated phosphorylation of both SIRPα and the downstream signal transducer SHP1; Decreased TSP1-stimulated $O_2^{\cdot -}$ generation	155
		Vascular smooth muscle cells	SIRPα siRNA; N/A	Decreased TSP1-stimulated $O_2^{\cdot -}$ generation	
		Endothelial-free arteries	Anti-SIRPα antibody; clone C20; 1 μg/mL	Decreased TSP1-mediated inhibition of NO-stimulated vasodilation	
		Human renal tubular endothelial cell	Anti-SIRPα antibody; clone C20; 1 μg/mL	Blocked TSP1-mediated phosphorylation of SIRPα and SHP1	
		Mice with renal IRI	i.p.; N/A; anti-SIRPα antibody; clone C20; 0.4 μg/g; 90 min before surgery	Decreased subsequent $O_2^{\cdot -}$ production; Restored kidney blood flow to near preischemic level after 24 h; Decreased oxidative stress and proinflammation cytokines and chemokines transcript expression (*CCL2*, *CXCL2*, *IL1b*, and *TNFa*); Decreased renal tubular injury, neutrophil infiltration, and serum urea and creatinine levels	
Renal interstitial fibrosis	CD47	Mice suffered from unilateral ischemia reperfusion injury followed by contralateral nephrectomy	i.p.; q.w.; anti-CD47 antibody; MIAP301; 0.8 μg/g; 3 weeks; a week following injury at the time of nephrectomy	Improved histology and fibrosis; Downregulated the expression of TSP1, TGF-β, CTGF, α-SMA, and vimentin	156
Glomerulonephritis	CD47	Anti-neutrophil cytoplasmic antibody-induced neutrophil extracellular trap (NET) neutrophils; Macrophages	Anti-CD47 antibody; B6H12; 10 μg/mL; pretreated NET	Increased the efferocytosis rate of NETs but not altered NET formation	161

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Table 3 (*continued*)

Disease	Target	Experimental model	Administration design[a]	Main results	Ref.
		Human umbilical vein endothelial cells (HUEhT); Macrophages	Anti-CD47 antibody; B6H12; 10 μg/mL; pretreated HUEhT	Promoted macrophages to engulf HUEhT	
		SCG/Kj mice developed systemic necrotizing glomerulonephritis with anti-neutrophil cytoplasmic antibody production	i.p.; q.5d.; anti-CD47 antibody; MIAP301; 200 μg; 2 weeks	Decreased serum creatinine; Decreased kidney injury as glomerular score decreased from 2.8 ± 0.41 (IgG group) to 2.0 ± 0.63; Decreased the area of myeloperoxidase and citH3 double positive NETs in glomeruli; Bound to injured glomerular and not altered the infiltration of neutrophils, macrophages, and lymphocytes in the kidney	
Endometriosis	CD47	Macrophages; ectopic endometrial stromal cells (ESCs)	Anti-CD47 antibody; N/A; 2.5 μg/mL	Increased engulfment by macrophages	163
Endometriosis	CD47	The abdominal endometriosis model was established by injecting ESCs into the abdominal cavity	Anti-CD47 antibody; N/A; 4 μg/mL; used to treat ESCs	Increased the phagocytosis rate to ectopic ESCs and ectopic ESCs apoptosis	164
		Ectopic ESCs; macrophage	Anti-CD47 antibody; N/A; 4 μg/mL	Increased phagocytosis rate to ectopic ESCs	
Heterotopic ossification	CD47	Mice that underwent burn/tenotomy	CD47-activating peptide (p7N3); N/A; 3 weeks	Decreased cartilage formation and mature heterotopic ossification formation; Decreased levels of Tgfb1 in macrophages; Decreased the level of Arg1 and Mrc1; Increased iNos expression	169
Rheumatoid arthritis	SIRPα	K/BxN serum-induced arthritis model	N/A; q.o.d.; agonistic anti-SIRPα antibody; clone 6F2; 250 μg/mice; 8 days; start one day before serum transfer	Decreased clinical arthritis scores; Decreased synovial and intra-articular inflammation; Decreased articular cartilage erosion and bone remodeling; Decreased the number of neutrophils and inflammatory monocytes from joint synovial fluids; Increased the number of neutrophils and monocytes in the spleen	26
		Collagen-induced arthritis model	N/A; q.o.d.; agonistic anti-SIRPα antibody; clone 6F2; 250 μg/mice; 18 days; Day 21 post the first immunization	Decreased joint swelling, edema, and erythema; Decreased in arthritis severity on histopathology	
Scleroderma	CD47	Peritoneal macrophages from B6 mice; JUN inducible fibroblasts	Anti-CD47 antibody; N/A; N/A	Increased phagocytosis	175
		Immunocompromised mice transplanted with primary mouse dermal fibroblasts under their kidney capsule	Anti-CD47 antibody; N/A; N/A	Decreased dermal fibroblasts	
		Skins fibrosis induction mice model (i.d.; q.o.d.; doxycycline for 2	N/A; q.o.d.; anti-IL-6 antibody; 20 μg/kg; 2 weeks	Decreased the skin hydroxyproline content; Increased the fat area and reversed the skin to	

		weeks)	N/A; q.o.d.; anti-CD47 antibody; 500 μg/injection; 2 weeks	an almost normal state; Induced an only side-effect that anemic change in bone marrow	
		Jun-induced mice	N/A; q.o.d.; anti-CD47 antibody; first dosage was 100 μg, the other is 500 μg; 2 weeks i.p.; b.i.d.; Vismodegib (PD-L1 inhibitor); 30 mg/kg; 2 weeks	Decreased the dermal number of $CD3^+$ cells and $Ki67^+$ cells; Decreased the agglomeration of macrophages	
		Jun-induced mice	N/A; q.o.d.; anti-CD47 antibody; first dosage was 100 μg, the other is 500 μg; 2 weeks N/A; q.o.d.; anti-IL-6 antibody; 20 μg/kg; 2 weeks	Increased dermal fat tissue and fatty area; Decreased the dermal number of $CD3^+$ cells and $Ki67^+$ cells; Decreased the agglomeration of macrophages	
Pulmonary fibrosis	CD47	Mice induced by bleomycin	i.p.; q.o.d.; anti-CD47 antibody; MIAP410; 500 μg; 2 weeks i.p.; b.i.w.; anti-IL-6 antibody; clone MP5-20F3; 20 mg/kg; 2 weeks i.p.; q.d.; HAC protein; 250 μg; 2 weeks	Decreased fibrosis in the lung	44
		Mice induced by bleomycin	i.p.; q.o.d.; anti-CD47 antibody; MIAP410; 500 μg; 2 weeks i.p.; q.d.; HAC protein; 250 μg; 2 weeks	Decreased fibrosis in the lung	
Pulmonary fibrosis	CD47	Mouse lung fibroblast Mlg cells	CD47 inhibitor (RRx-001)	Decreased TSP1 overexpression-induced upregulation of α-SMA and fibronectin protein expression; Decreased TSP1 overexpression-induced ROS and ER stress	23
		Bleomycin-induced lung fibrosis	i.p.; q.d.; RRx-001; 10 mg/kg; 2 weeks	Decreased ROS production; Decreased bleomycin-induced upregulation of Grp78 and CHOP; Decreased collagen deposition and preserved pulmonary architecture; Decreased pulmonary levels of hydroxyproline, fibronectin, and α-SMA	
COVID pulmonary fibrosis	CD47	IsI-rtTA *Jun* mice co-transduced with human ACE2 lentivirus and a SARS-CoV-2 pseudovirus (huACE2/S-protein) in the lung and induced JUN with doxycycline	i.p.; b.i.w.; anti IL-6 antibody; clone MP5-20F3; 20 mg/kg; 4 weeks; after 13 days of huACE2/S-protein transduction i.p.; q.o.d.; anti-CD47 antibody; MIAP410; 500 μg; 4 weeks; after 13 days of huACE2/S-protein transduction	Restored normal lung morphology; Decreased extracellular matrix/collagen deposition, fibrosis, activated fibroblasts	177
		Humanized NOD-SCID-*IL2Rg*$^{-/-}$ mouse implanted with human lung	i.p.; b.i.w.; anti-IL-6 antibody; clone MP5-20F3; 20 mg/kg; 4	Decreased neutrophils and macrophage infiltration, fibrosis-mediated interstitial	

(*continued on next page*)

Table 3 (*continued*)

Disease	Target	Experimental model	Administration design[a]	Main results	Ref.
		and transduced with huACE2/S-protein	weeks; after 13 days of huACE2/S-protein transduction i.p.; q.o.d.; anti-CD47 antibody; MIAP410; 500 μg; 4 weeks; after 13 days of huACE2/S-protein transduction	expansion, and bronchiolization of alveoli	
Age-related macular degeneration	CD47	Mice with laser injury	Intravitreally; CD47-activating peptide PKHB1; 200 μmol/L; on Days 4 and 7	Accelerated subretinal mononuclear phagocyte elimination	13
		Acute thioglycolate-induced peritonitis	i.p.; CD47-activating peptide PKHB1; 500 μmol/L; on Day 1	Increased the elimination of recruited monocyte-derived inflammatory macrophages	
Malaria	CD47	Human MDMs; RBCs infected by *P. falciparum* (Pf RBCs)	SIRPα Fc; 10 μg/mL	Increased uptake of ring-stage Pf RBCs	180
	SIRPα	Human MDMs; Pf RBCs	Anti-SIRPα antibody; N/A; 20 μg/mL	Increased uptake of ring-stage Pf RBCs	
Malaria	CD47	RBCs from *P.berghei* ANKA (*Pb*-A)-infected mice; Mouse macrophages	Anti-CD47 antibody; MIAP410; N/A	4.7-Fold increased parasitized RBCs (pRBCs) phagocytosis;	182
		P. falciparum-infected human RBCs; human macrophages	Anti-CD47 antibody; Hu5F9G4; N/A	2.3-Fold increased pRBCs phagocytosis	
		Mice infected by *Pb*-A develop symptoms that resemble the clinical features of human cerebral malaria (CM)	i.p.; N/A; anti-CD47 antibody; MIAP410; 100 μg; N/A; initiated on 3 days post injection (dpi)	80% of mice did not develop experimental CM and survived from cerebral phase of infection while all mice in the control group developed experimental CM and succumbed on 6 to 9 dpi; Had intact meningeal architecture; Protected the blood−brain barrier from vascular leakage; Decreased $CD8^+$ T cell migrating into brain tissue; $CD8^+$ T cells in the brain produced less Granzyme B and IFN-γ	
Malaria	CD47	Mice infected by *Plasdmodium yoelii*	i.p.; N/A; anti-CD47 antibody; MIAP301; 100 μg/dose; on the day of GFP-*Py*NL infection	Decreased parasite burden from 0.39 ± 0.05% (isotype) to 0.026 ± 0.008 on Day 3 postinfection	181
Influenza virus-mediated bacterial super-infection	CD47	Influenza virus-infected human nasal epithelial cells and human bronchial epithelial cells infected by *S. aureus*	Anti-CD47 antibody; B6H12.2; N/A	Decreased paracellular permeability disruption and trans-epithelial electrical resistance; Decreased cytopathogenic effects of super-infection	184
		Influenza virus-infected mice infected with *S. aureus*	i.n.; twice in total; anti CD47 antibody; MIAP301; N/A; day 5 and 7 after viral infection (mice were infected by	Decreased body weight loss and increased survival rates; Decreased signs of pneumonia and histological lung injury score;	

			bacteria on Day 7)	Decreased bacterial adherence and invasion in the lung; Decreased the level of TNF-α and IL-6 in bronchoalveolar lavage fluids	
Lymphocytic choriomeningitis virus infection	CD47	Mice infected with lymphocytic choriomeningitis virus	i.p.; q.d.; anti-CD47 antibody; MIAP410; 100 μg; 5 days; initiated at 2 dpi	27-fold reduction in kidney virus compared to mice in the control group at 10 dpi; Increased macrophage activation by 5 dpi and dendritic cell activation by 3 dpi; Increased the number of $CD4^+$ and $CD8^+$ T cells in the spleen by 3 dpi; Increased functional $CD8^+$ T cells	186
Virus-induced myositis	CD47	Mice inoculated i.p. with Theiler's murine encephalomyelitis virus	i.p.; q.o.d.; anti-CD47 antibody; 100 μg; 9 days; initiated at 5 dpi	Decreased clinical disease scores; Decreased calcification of skeletal muscle compared with controls	187

i.p., intraperitoneal; s.q., subcutaneous; i.n., intranasal; q.o.d., every other day; q.3d., every three weeks; t.i.w., three times a week; b.i.w., twice a week; q.2w., every 2 weeks; q.w., once a week; q.5d., every 5 days; q.d., every day.
[a]*In vivo* assay: administration method; frequency; treatment; (clone of antibody) dosage; duration; others. *In vitro* assay: treatment; (clone of antibody) dosage; others.

IMC-002 clinical trials for B cell-associated autoimmune diseases including systemic lupus erythematosus (CTR20242914) and neuromyelitis optica spectrum disorders (CTR20243045) were therefore applied and have been approved by the National Medical Products Administration this year[173,196]. At this point, despite extensive effort, we do not have access to study the unpublic results of these clinical trials. But it is certain that preclinical studies did encourage the researchers to be confident about launching clinical trials and contribute to the evaluation of CD47-based therapeutic strategies for non-cancer diseases. Simultaneously, new clinical studies in more non-cancer diseases are needed to be done to confirm the action of CD47-based treatments.

Meanwhile, understanding the potential side effects of CD47-based therapies in non-cancer diseases is an essential step. Drawing lessons from clinical trials of cancer, drug-induced anemia probably retarded the development of CD47-based agents[34]. CD47 on healthy RBCs functions as a "bell" to remind macrophages not to engulf. Once CD47 is blocked, RBCs will be rapidly eliminated by macrophages and natural killer cells, due to CD47−SIRPα axis blockage and Fc/FcγR interaction[32,198]. In recent years, investigations of reducing the toxicity of CD47-based agents have increased tremendously. These studies have shown that therapeutic modalities, such as selective antibody[36], SIRPα fusion protein[22], and bispecific fusion protein[39] are reasonable to reduce side effects in clinical trials. Concomitantly, strategies used in preclinical studies may be beneficial for reducing the rate of side effects. For example, BRB-002, aCD47 Ab used in atherosclerosis studies, was endowed with inactive Fc fragment which restricts Fc/FcγR interaction[54]. Besides, low-dose aCD47 Ab was used in diabetes studies[42]. Orthotopic drug delivery and nanomaterial targeting drugs may also contribute to the increased safety of CD47-based therapies[63,105].

11.2. The mechanisms of CD47-based therapy in non-cancer diseases

After clarifying promising non-cancer indications of CD47-based therapy, a deeper comprehension of the mechanisms of CD47-related agents on non-cancer diseases is worthwhile. Increasing evidence in pre-clinical studies brings it to light. There are three major mechanisms.

Firstly, CD47-based therapy promotes the phagocytotic capacity of macrophages and other phagocytes. Phagocytosis of apoptotic cells was amplified. Both aCD47 Ab and SHP1i promoted efferocytosis of apoptotic cells containing atherosclerotic plaques, and that decreased the volume of plaques and the necrotic area[41,59]. Concomitantly, the uptake of necrotic hepatocytes was enhanced by blockade of CD47 or SIRPα[25]. In addition to dying cells, CD47-related agents drove phagocytic cells to internalize oligodendrocyte progenitor cells and neural progenitor cells with *16p11.2* deletion, fibroblasts, and RBCs in brain hematoma, and so on[103,175,199]. Notably, aCD47 Ab may not elicit its role in malaria depending on enhancing phagocytosis as usual[182]. It was speculated that CD47 blockade may promote the engulfment of myelin fraction, and that disturbs the recovery of MS[121]. By contrast, nanoparticles, extracellular vesicles, and exosomes will be modified with CD47 to achieve immune evasion as cancer cells did[28-30]. CD47 overexpression pseudoislets failed to elicit an innate and adaptive immune response, ultimately surviving in recipient[31,150,151]. Moreover, mutant CD47 expressed on cells may

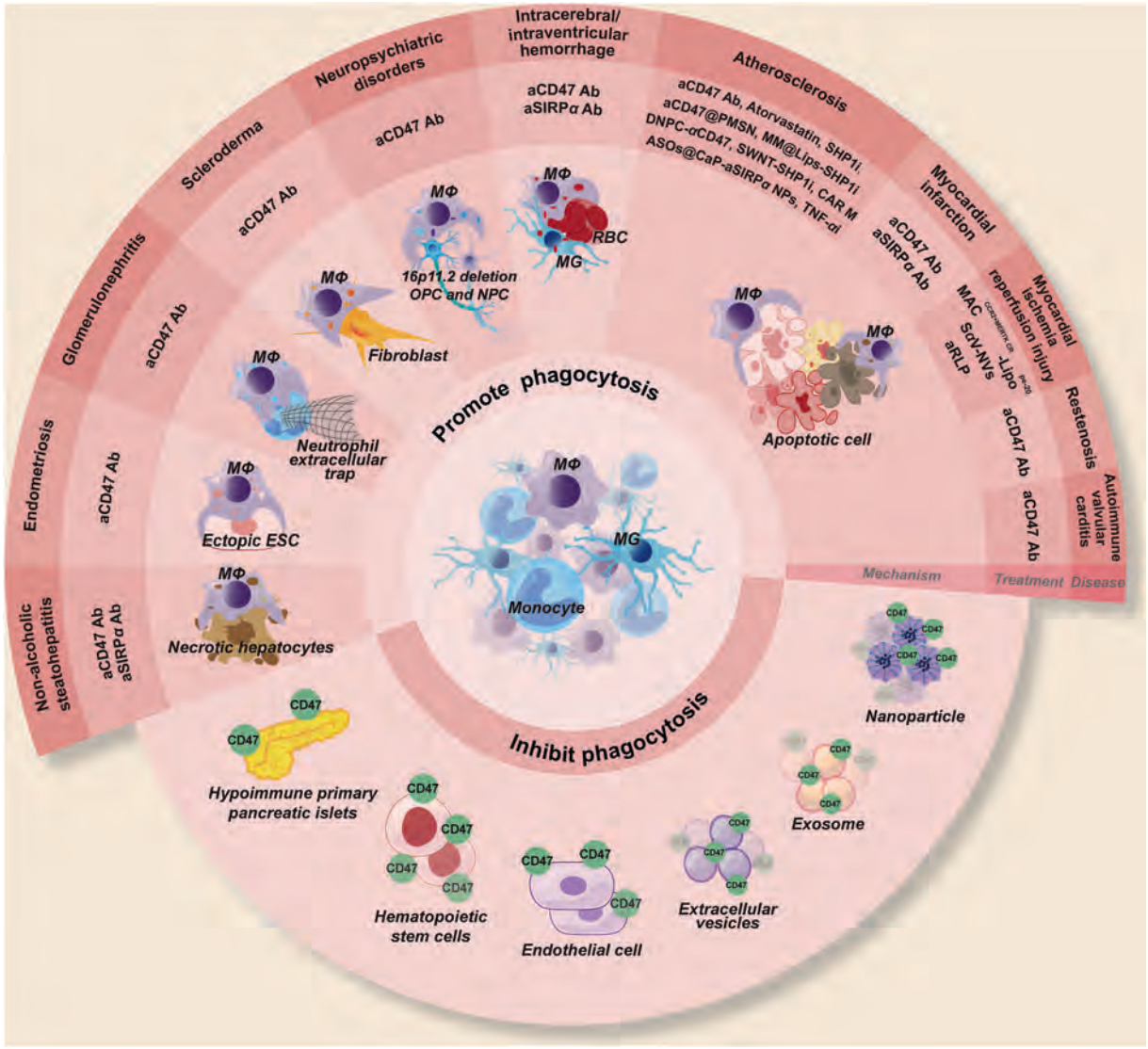

Figure 4 The effects of CD47-based therapies on regulating phagocytosis. CD47-based therapies enhanced the ability of macrophages to remove diseased or redundant cells in pathological tissues. On the contrary, CD47 decorated on cells, nanoparticles, extracellular vesicles, and exosomes was beneficial for evading phagocytosis to achieve better therapeutic efficacy. aCD47 Ab, anti-CD47 antibody; SIRPα, signal regulatory protein alpha; aSIRPα Ab, anti-SIRPα antibody; ASOs@CaP-aSIRPα, anti-SIRPα antibody-modified, anti-sense oligonucleotides-loaded calcium phosphate nanoparticles; aCD47@PMSN, anti-CD47 antibody loaded platelet membrane coated mesoporous silicon nanoparticles; aRLP, senescent RBC-mimetic liposomes decorated with an anti-Ly6G antibody; CAR M, chimeric antigen receptor macrophage; CD47 ASO, antisense oligonucleotide targeting CD47; DNPC-aCD47, anti-CD47 antibody-conjugating polydopamine nanoparticles loaded with CY-09; ESC, endometrial stromal cell; MG, microglia; Mø, macrophage; NPC, neural progenitor cell; OPC, oligodendrocyte progenitor cell; RBC, red blood cell; SHP1i, a SHP1 inhibitor; MM@Lips-SHP1i, macrophage membrane-coated SHP1i-liposome nanoparticles; $MAC^{CCR2+MERTK\ CR}$-$Lipo^{PEP-20}$, C−C chemokine receptor type2 and cleavage-resistant MerTK overexpressed macrophages anchoring liposomes loaded with PEP-20; SIRPα-v Exos, modified exosomal SIRPα variants; SWNT-SHP1i, single-walled carbon nanotubes loaded with a SHP1 inhibitor; SαV-NVs, hybrid nanovesicles, which contain cell-derived nano vesicles overexpressing high-affinity SIRPα variants; TNF-α i, TNF-α inhibitor.

present fewer adverse effects than wild-type ones, as evidenced by hematopoietic stem cell function and endothelial cell angiogenesis were reported to not be affected by membrane-expressed mutant CD47[200] (Fig. 4).

Secondly, CD47-based therapy influenced other immune cells besides macrophages. CD47-based therapy decreased the infiltration of neutrophils in focus of non-cancer diseases, like RA and NASH[25,26]. In LCMV infecting mice, it was observed that aCD47 Ab activated dendritic cells and $CD8^+$ T cells[186].

Thirdly, the secretion of cytokines and chemokines was also influenced by CD47-related agents. For instance, CD47 fusion protein and aCD47 Ab downregulated the level of inflammatory cytokines in Crohn disease and autoimmune valvular carditis, respectively[73,143]. Similarly, CD47-activating peptide p7N3 may relieve HO *via* inhibiting macrophage-secreting TGF-β1[169]. However, whether the effects of CD47-based therapy on other immune cells and the regulation of cytokines are residue effects of phagocytosis is uncertain.

Notably, the property of CD47-based therapy on regulating the CD47−TSP1 axis may be associated with its capacity in some non-cancer diseases as well. TSP1 was reported to increase the level of ROS and superoxide production in arterioles, subsequently promoting PH[70,84]. Moreover, overexpression of TSP1 may lead to pulmonary fibrosis through increasing ROS production and inducing endoplasmic reticulum stress[23]. Blocking CD47 by antibody improved TSP1-inhibited vasodilation in PH[69]. TSP1-induced HDAC3 upregulation was correlated with LVHF. Profoundly, aCD47 Ab abrogated the effect of TSP1 in LVHF[72]. There may be direct interaction between CD47 and TSP1. CD47-activating peptide was used to rectify TSP1−CD47 interaction to relieve AMD[13]. Disrupting TSP1−CD47 interaction may be meaningful during SAH[43]. TSP1 which is highly expressed in platelet α-granules also plays an important role in thrombus formation[201]. TAX2 is a peptide targeting TSP1. Moreover, the peptide binds TSP1 at CD47-binding site[202]. TAX2 peptide suppressed human blood platelet aggregation induced by ADP and collagen by 28 $\pm$ 8.7% and 36.8 $\pm$ 6.9% compared to scrambled peptide, respectively. The process of vascular occlusion was delayed in arterioles from $FeCl_3$-induced mice treated with TAX2 peptide, meanwhile, this peptide did not influence tail bleeding time[203].

11.3. The perspectives of future development of CD47-based therapy in non-cancer diseases

Recent advances have shown that CD47-based agents ameliorated defective phagocytosis to remove diseased cells and cell debris, regulating T cells, dendritic cells, and neutrophils, and regulating the secretion of cytokines and chemokines, whilst preventing and/or treating non-cancer diseases. Yet there are some lurking suspicions. For example, the residual effects of phagocytosis could be harmful. Toxic products would be released during polymorphonuclear leukocyte and eosinophils degranulating after phagocytic contact and uptake[204]. Besides, overactivated macrophages may engulf illegitimate targets, whilst causing excessive injuries on the surrounding healthy but fragile cells and reversely deteriorating diseases[205-207]. Moreover, epithelial CD47 may facilitate rather than suppress intestine mucosal repair[208]. Whereas, more basic research on the underlying mechanisms and more clinical trials on the therapeutic efficacy regarding to CD47-related agents are pivotal. The gap could be filled in the following four aspects: agents' selection, drug administration, biological function, and indication.

First, select the right agents. Most studies emphasized the therapeutic effect of aCD47 Ab, while CD47-activating peptide may have more important applications for age-related macular degeneration and heterotopic ossification[13,169]. Besides, agonistic aSIRPα Ab had a plethora of beneficial and irreplaceable effects as a treatment in autoimmune diseases[26]. Nonetheless, most of the studies paid attention to one or two CD47-related agents. The differences in therapeutic efficacy, side-effects, and detailed mechanisms among different CD47-related modalities remain largely obscure.

In terms of the structure of antibodies, the role of the Fc domain of antibodies won considerable attention. Emerging data from the study on cancer demonstrated that aCD47 Ab elicits anticancer activities relying on its Fc part, through interacting with Fc receptors on macrophages[209]. Concomitantly, an active Fc domain is required in aSIRPα Ab-driving immune migration. Further study to clarify the role of the Fc domain of antibodies in treating non-cancer diseases is also needed[26].

It is also necessary to select CD47-based agents according to the different binding modes of CD47 in diverse pathological situations. In most instances, *trans* interaction between CD47 (on diseased cells) and SIRPα (on macrophage) is implicated as a major mechanism that suppresses phagocytosis. However, *cis* interaction between CD47 (on macrophage) and SIRPα (on macrophage) was reported[210]. And most recent study provided evidence that CD47 is capable of inhibiting phagocytosis in a SIRPα-independent manner. CD47 (on tumor cell) *cis* interacts with SLAMF7 (on tumor cell) to interrupt the *trans* interaction between SLAMF7 on tumor cell and SLAMF7 on the macrophage, thereby instigating the inhibition of phagocytosis[211].

Second, adjust drug administration. CD47-based agents were intraperitoneally administrated in most studies. Complicate approaches of administration, like orthotopic injection and target-specific drug delivery systems, were also utilized. It may be necessary to consider efficacy, convenience, and clinical transformation difficulty when selecting a drug delivery method.

The dosage of agents is another significant factor. In a murine ICH study, they identified that a medium dosage of aCD47 Ab exerted the best effect, while a low dosage had limited effect and a high dosage may induce cell apoptosis[105]. In addition, researchers constructed the ICH model together with antibody treatment in an overwhelming majority of studies[103]. And the expression of CD47 in hematoma decreased with time. These evidenced suggested the necessity of selecting the optional time for treatment[98].

Besides, it is worth mentioning that combination therapy enhanced the therapeutic efficacy of aCD47 Ab in atherosclerosis, scleroderma, and myocardial infarction, as in cancer. For instance, TNF-α inhibitors and NLRP3 inhibitors enhanced the therapeutic effectiveness of aCD47 Ab in atherosclerosis[41,63].

Third, investigate the role of CD47 and its binding partners in other normal cells, except for diseased cells. CD47 also expresses on macrophages. It was found that expression of CD47 in M1-like macrophages may be a potential explanation as to why some macrophages in atherosclerosis plaques lost their opsonin-sensing ability. CD47-deficient BMDMs polarized into the M1-state may have a higher phagocytic rate of latex beads than the control. It hints the critical role of CD47 in macrophages[58].

Besides, recent studies have implicated the roles of CD47 blockade in suppressing T cell transmigration and LTB4-induedbone marrow-derived neutrophils migration[137]. And TSP1−CD47 axis was reported to suppress IFN-γ production in NK cells by activating the JAK−STAT pathway[212]. Further studies are needed to answer the question of whether CD47 has a direct role in other cells, especially immune cells.

Fourth, further enrich the applicability of CD47-based therapy. CD47-based agents may have important applications for postponing cell senescence. Emerging data from studies highlighted the critical effect of the CD47/TSP1 axis on senescence. TSP1 was reported to mediate senescence in endothelial cells by regulating CD47[213]. Meanwhile, senescent cells are likely to evade removal *via* CD47−QPCT/L axis[214]. Accordingly, it was demonstrated that TSP1 blockade activated aged muscle cells and restored muscle strength *in vivo*[215].

Along with cell senescence, the effect of CD47-based therapy on neural diseases cannot be underestimated. In the hippocampus of Alzheimer's disease patients, upregulated CD47 protein was found to co-localize with PHF-tau protein[216]. Similarly, *CD47* mRNA was elevated in the hippocampus in mice with schizophrenia[217]. Based on the aberrantly higher level of CD47 and its

binding partners, attenuating CD47 expression may be a potential therapeutic strategy for cell senescence-associated diseases and various nervous system disorders.

Some immune diseases, like lethal inflammation that occurred in *Ptpn6*^{spin} mice and autoimmune uveitis, were mild in the corresponding animal model with CD47 deficiency[218]. The therapeutic effect of CD47-related agents on these immune diseases warrants further investigation.

Nevertheless, CD47 was downregulated in focal cortical dysplasia type IIb tissue, hippocampus of patients with perioperative neurocognitive disorders, and tuberous sclerosis complex tissue[219,220]. Activating agents rather than inhibitors may reversely relieve these illnesses.

12. Conclusions

In this review, we summed up CD47-based therapies in treating non-cancer diseases and highlighted atherosclerosis and stroke as two remarkable candidate indications. The efficacy of CD47-based therapy in relieving these non-neoplastic diseases may be attributed to regulating the immune system and adjusting the biological roles of CD47. However, further work will now be necessary to compare the therapeutic efficacy among different CD47-based therapies and to figure out suitable drug administration. It is also worthwhile devoting much effort to exploring the role of CD47 and its binding partners in cells except for diseased cells and more potent indications of CD47-based therapy.

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Author contributions

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Conflicts of interest

The authors declare no conflicts of interest.

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