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Review Article

Potential therapeutic applications of exosomes in different autoimmune diseases

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ABSTRACT

Autoimmune diseases are caused by self-immune responses to autoantigens, which damage body tissues and severely affect the patient's quality of life. Therapeutic drugs are associated with adverse side effects and their beneficial effects are limited to specific populations. Evidence indicates that exosomes which are small vesicles secreted by most cell types and body fluids, and may play roles in both immune stimulation and tolerance since they are involved in many processes such as immune signaling, inflammation and angiogenesis. Exosomes have also emerged as promising tools for therapeutic delivery, given their intrinsic features such as stability, biocompatibility and a capacity for stealth. In this review, we summarize existing literature regarding the production, efficacy, action mechanism, and potential therapeutic uses of exosomes in the contexts of autoimmune diseases such as type 1 diabetes mellitus, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome.

1. Introduction

Autoimmune diseases are among the leading causes of morbidity and mortality associated with chronic disease worldwide [1,2]. Interestingly, autoimmune diseases are predominant in females; for some diseases, more than 90% of affected patients are females [3]. Despite these known factors, the diseases' etiologies remain uncertain. Still, some patients harbor a genetic predisposition to developing autoimmune diseases, which other cases may be triggered by infections or other environmental factors [4]. Autoimmune diseases can be classified into two types. The first type is organ-specific, wherein the autoimmune process targets a single organ; this includes diseases such as type 1 diabetes mellitus (T1DM), multiple sclerosis (MS) and psoriasis [5]. The second type is systemic, wherein the immune response attacks different organs and tissues simultaneously; this type is exemplified by diseases such as systemic lupus erythematosus (SLE), Sjogren's syndrome (SS) and rheumatoid arthritis (RA) [6,7]. Regardless of type, damage to one or more body tissues or organs is a possible consequence of all autoimmune diseases.

Autoimmune diseases mainly develop due to a failure of the mechanisms of lymphocyte auto-tolerance, which causes an imbalance between the activation and regulation of these cells [8]. Dysregulated lymphocyte activation can lead to the production and targeting of autoantigens, and damage to different tissues on which these targets are expressed. Although nonsteroidal anti-inflammatory drugs (NSAIDs) and immunosuppressant drugs are often administered to patients to relieve immunological inflammation during progressive disease stages; these drugs are associated with serious side effects, such as increased risk of gastrointestinal ulcers bleeding, and myocardial infarction. Cell-based therapies, such as stem cell transplantation have also been used to treat some autoimmune diseases, but they are very costly. These drawbacks, together with the increasing number of newly diagnosed

Abbreviations: T1DM, type 1 diabetes mellitus; MS, multiple sclerosis; SLE, systemic lupus erythematosus; SS, Sjogren's syndrome; RA, rheumatoid arthritis; NSAIDs, nonsteroidal anti-inflammatory drugs; BBB, blood brain barrier; iMDEX, immature dendritic cell-derived exosomes; DCs, dendritic cells; SEC, size exclusion chromatography; ELISAs, enzyme-linked immunosorbent assays; RT-qPCR, real-time quantitative polymerase chain reaction; NTA, nanoparticle tracking analysis; DLS, dynamic light-scattering; AFM, atomic force microscopy; TEM, transmission electron microscopy; SEM, scanning electron microscopy; CNS, central nervous system; MSCs, mesenchymal stromal/stem cells; NK, natural killer; EAE, experimental autoimmune encephalomyelitis; GCs, glucocorticoids; TNF-α, tumour necrosis factor α; SGs, salivary glands; SSc, Systemic sclerosis; EAU, experimental autoimmune uveitis; MDSC, myeloid-derived suppressor cell; AA, Alopecia Areata; PM, plasma membrane; MVB, multivesicular compartments.

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autoimmune disease cases each year, underscore the urgent need to identify safe and effective therapies for prevention and treatment.

Exosomes have recently emerged as novel therapeutic effectors in immune therapy, regenerative medicine and drug delivery [9,10]. These entities possess several favorable features, including low immunogenicity, biodegradability, low toxicity, and the abilities to encapsulate endogenous bioactive molecules, provide strong protection for cargo and cross the blood brain barrier (BBB) [11–14]. These advantages of exosomes have attracted extensive attention of researchers. This review aims to summarize the most recent developments in exosome bioactivities and critically analyze exosomes' potential roles in autoimmune disease therapies.

2. Exosomes

Exosomes are membrane-wrapped vesicles with a size of 30-150 nm. Early research of exosomes, based on electron micrographs, revealed cup-shaped vesicles with diameter of up to 100 nm, although recent work has widened this range from 50-180 nm [15]. Exosomes are released by most cells, including stem cells, T and B lymphocytes, macrophages, dendritic cells, neurons, endothelial cells, adipocytes and epithelial cells [16–18]. Notably, diseased/unhealthy cells secrete more exosomes than healthier cells. The density of exosomes ranges from 1.13 to 1.19 g/mL, and they have been found in many types of bodily fluids, including blood, urine, ascites, semen, breast milk, saliva, amniotic fluid, lymph fluid and cerebrospinal fluid, from both healthy and unhealthy individuals [19–25]. These vesicles are delivered throughout the body via circulatory system and are taken up by target cells. Where, depending on their origins, they can play different roles in physiological processes. For example, immature dendritic cell-derived exosomes (iMDEX) display a certain degree of immunosuppressive activity in autoimmune diseases. iMDEX are stable and can be easily stored in vitro; they may be a good substitute for iMDEX in inducing immune tolerance [26].

Previous studies have also demonstrated exosomes' involvement in immunoregulatory mechanisms, including the modulation of antigen presentation, immune activation, immune suppression, and immune surveillance [27]. Considerable interest in exosomes' clinical therapeutic applications has increased, given the relatively low cytotoxicity, biohazardous potential, and ability to transport proteins and nucleic acids without rapid degradation. In some cases, these vesicles may be more advantageous than parental cells [28]. For example, dendritic cell (DC)-derived exosomes modulate immune responses and prevent development of autoimmune diseases [27,29,30]. Several clinical trials (Table 1, data from http://clinicaltrials.gov) have been completed or are underway in order to evaluate this therapeutic potential in autoimmune diseases and other diseases. In the following, we discuss various strategies for isolating exosomes, as well as the characteristics, composition and functions of these vesicles.

2.1. Methods for isolating and characterizing exosomes

As noted above exosomes are secreted into cell culture supernatants or other biological fluids. However, these fluids many also contain several other types of vesicles (e.g. microvesicles, apoptotic bodies); therefore, it is critical to ensure there is no other contaminating material before performing any functional analyses. To date, multiple exosome isolation methods have been developed, including differential centrifugation, density gradient centrifugation, size exclusion chromatography (SEC), filtration, polymer-based precipitation, and immunological separation, as well as commercial exosome isolation kits [31]. Most commonly, exosomes are purified from cell-culture supernatants or biofluids through a series of centrifugation steps to remove dead cells and large debris, followed by a final high-speed ultracentrifugation step.

Exosomes are most commonly characterized via western blotting,

Table 1
The exosomes–based therapies in clinical trials.

Study title	Disease	Intervention/Treatment	Phase	NCT
Safety and Efficacy of Allogenic Mesenchymal Stem Cells Derived Exosome Enriched by miR-124 on Disability of Patients with Acute Ischemic Stroke	Cerebrovascular Disorders	Biological: exosome	Phase 1/2	NCT03384433
Effect of Plasma Derived Exosomes on Cutaneous Wound Healing	Ulcer	Other: plasma-derived exosomes	Early Phase 1	NCT02565264
Effect of Microvesicles and Exosomes Therapy on β-cell Mass in Type I Diabetes Mellitus (T1DM)	Diabetes Mellitus Type 1	Biological: MSC-exosomes	Phase 2/3	NCT02138331
Ability of Plant Exosomes to Deliver Curcumin to Normal and Malignant Colon Tissue	Colon Cancer	Dietary Supplement: Curcumin conjugated with plant exosomes	Phase 1	NCT01294072
Ability of Plant Exosomes to Mitigate Insulin Resistance and Chronic Inflammation in Patients Diagnosed with Polycystic Ovary Syndrome (PCOS)	Polycystic Ovary Syndrome	Other: Ginger exosomes and Aloe exosomes	Not Applicable	NCT03493984
Mesenchymal Stromal Cells Derived Exosomes with KrasG12D siRNA for Metastatic Pancreas Cancer Patients Harboring KrasG12D Mutation	Metastatic Pancreatic Adenocarcinoma	Drug: Mesenchymal Stromal Cells-derived Exosomes with KRAS G12D siRNA	Phase 1	NCT03608631
Major Activation of NCC in Graft Urinary Exosomes	Kidney Transplantation	Other: exosomes analysis	Complete	NCT03503461
MSC-Exos Promote Healing of MHs	Macular Holes	Biological: MSC-Exosomes	Early Phase 1	NCT03437759

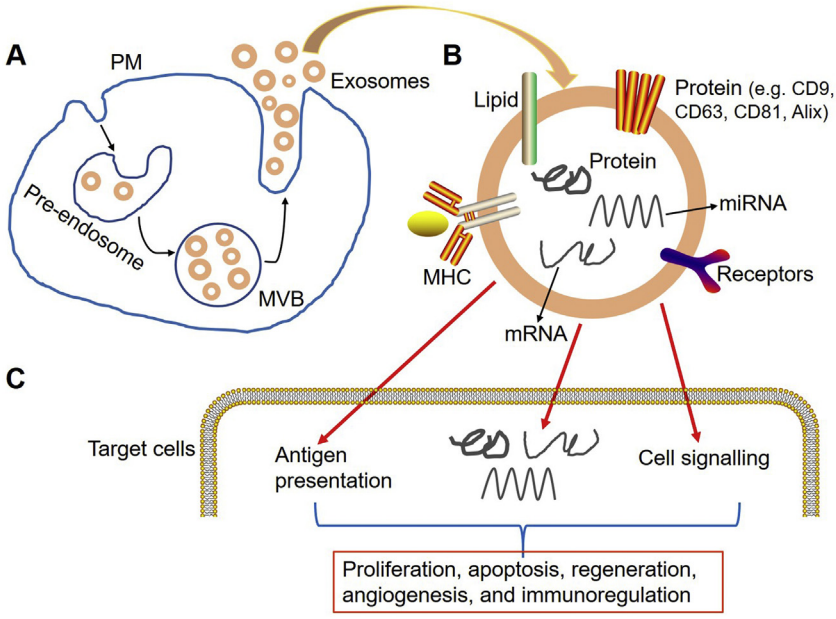

Fig. 1. The formation, composition and functions of exosomes. (A) Schematic representation of exosomes released by eukaryotic cells, either by direct budding from the plasma membrane (PM) or by fusion of internal multivesicular compartments (MVB) with the PM. (B) Schematic representation of the composition of exosomes. (C) Exosomes interact with target cells.

enzyme-linked immunosorbent assays (ELISAs), real-time quantitative polymerase chain reaction (RT-qPCR), fluorescence-based detection, nanoparticle tracking analysis (NTA), resistive pulse sensing, dynamic light-scattering (DLS), atomic force microscopy (AFM) and transmission and scanning electron microscopy (TEM, SEM) [32–36]. Western blotting and ELISAs are antibody-based methods that detect intravesicular or membrane protein markers [37], while RT-qPCR detects RNA molecules associated with exosomes [38]. NAT, AFM, and TEM are more recently developed methods that have become popular for determining exosomes' size, density, morphology, and composition [39,40].

2.2. Composition and function of exosomes

Extracellular vesicles, particularly exosomes, are important conveyers of information between cells. Accordingly, exosomes have been implicated in numerous biological and pathological processes, including antigen presentation and tissue repair [18,25,41,42]. Although these vesicles vary in composition according to their parental cells, all exosomes are formed from endosomes and contain abundant proteins, involved in membrane transport and fusion (e.g., GTPases, annexins and flotillins) and multivesicular body biogenesis (e.g., Alix, TSG101 and clathrin), as well as tetraspanins (e.g., CD9, CD63, CD81 and CD82) [43–45], heat shock proteins (e.g., HSC70 and HSP90), integrins, and RAB proteins, which regulate the docking and membrane fusion of exosomes with target cells [46]. Additionally, exosomes are enriched with various cytokines, lipid raft components (e.g., phosphoglycerides, cholesterol, ceramide and fatty-acyl chains), and nucleic acids (e.g., mRNAs, miRNAs, non-coding RNAs, tRNAs, rRNAs and DNA, although the latter is rare) [47–49]. A previous report suggested that exosomes not only help trigger downstream signaling but also target recipient cells to exchange certain proteins and nucleic acids [50]. Exosomes play a unique mediatory role in both proximal and distal intercellular communication within the body. These vesicles transduce information and affect the biology of target cells mainly through the following three mechanisms: (i) various endocytic pathways, including both clathrin-dependent endocytosis and clathrin-independent pathways (e.g., caveolin-mediated uptake, macropinocytosis, phagocytosis, and lipid raft-mediated internalization); (ii) direct fusion with the target cell membrane, to transmit mRNAs, miRNAs, proteins and signaling molecules; and (iii) activation of receptors and downstream signal transduction pathways in the target cell, via membrane proteins and surface adhesion molecules and receptors, activation of receptors, without entering the target cells [51,52].

Previously, Wang and colleagues have reviewed the function of exosomes in living organisms: (1) protecting against bacteria and viruses; (2) adjusting tumor immunity; (3) and mediating immune suppression of tumor host cells infection [53]. Exosomes' functions have been most intensively investigated in the following areas; the central nervous system (CNS), where they regulate the incorporation of neurons and glial cells [54,55]; the cardiovascular system, where they regulate coagulation, angiogenesis, and thrombosis [56–58] and both innate and adaptive immunity, including the regulation of antigen presentation, T-cell activation, and polarization into regulatory T cells, immune suppression and anti-inflammation [59]. Tan et al summarized antigen-presenting functions of exosomes derived from antigen-presenting cells (APCs) (e.g., B cell, DCs and macrophage) and the immunomodulatory functions of exosomes derived from T-cell [60]. Exosomes released from mesenchymal stromal cells (MSCs) can also induce immunosuppression, possibly by inducing myeloid immune suppressor cells [61] or regulatory T cells [62].

To date, overwhelming evidence indicates that exosomes from different cells can evoke totally different responses in recipient cells. When exosomes are engineered or loaded with specific therapeutic molecules, this phenomenon may yield therapeutically beneficial synergies between the cargo and exosomes. Accordingly, artificial exosomes containing both a clearly defined therapeutic active cargo and surface marker ensuring the specific targeting to the recipient cells have been proposed as a promising approach. As noted above, exosomes can serve as delivery vehicles [63] for various nucleic acids including siRNAs and miRNAs, proteins or even low-molecular-weight drugs [64–67]. For example, intravenously administered engineered c(RGDyK)-conjugated exosomes (cRGD-Exo) target the lesion region of the ischemic brain after intravenous administration. Furthermore, curcumin has been loaded onto the cRGD-Exo, and administration of these exosomes has resulted in a strong suppression of the inflammatory response and cellular apoptosis in the lesion region [68]. Exosomes were also found to efficiently deliver some encapsulated anticancer drugs, such as doxorubicin and paclitaxel, to treat brain tumors [69,70]. Overall, an exosome-based delivery system has several potential benefits, such as (i) specificity (i.e., delivery of cargo to a specific target); (ii) safety (i.e., as self-derived exosomes do not elicit undesired immunogenicity); and (iii) stability. Regarding the latter point, exosomes were found to be stable in blood circulation, and their contents were protected from RNases and proteases, thus ensuring the delivery of intact cargo to the

target cell [71,72]. Fig. 1 presents a general overview of the formation, composition and functions of exosomes.

3. The therapeutic effect of exosomes in different autoimmune diseases

The potential uses of exosomes have been intensively studied. Exosomes may be used for therapeutic applications by taking advantage of their unique endogenous characteristics (high biocompatibility and intrinsic targeting activity), and by adding modifications of choice (nano-phospholipid bilayer structure as natural nanocarriers). Given to their unique physical and biological properties, accumulating evidence indicates exosomes are associated with autoimmune diseases such as SLE [73,74], MS [75,76], Sjögren's syndrome SS [77] and so on. Excitedly, MSC-exosomes were treated on β-cell mass in Type I Diabetes Mellitus (T1DM) in clinical phase 2/3. Recent studies have found exosomes can stimulate immune responses both *in vitro* and *in vivo* and can confer immune suppression via several mechanisms. Specifically, exosomes can enhance regulatory T cell functions [78], suppress the activities of natural killer (NK) and $CD8^+$ T cells [79,80] and inhibit the differentiation of monocytes into DCs [81], as well as DCs maturation [82]. Moreover, exosome-like particles from thymic cells have been reported to induce the differentiation of $CD4^+CD25^-$T cells to $CD4^+CD25^+Foxp3^+$ T regulatory cells (Treg), which help maintain immune tolerance in peripheral tissues. This differentiation relies on TGF-β, a protein specific to these thymic exosome-like particles that induces T regulatory cells [83]. Several other investigations of exosomes derived from mesenchymal stem cells and APCs have demonstrated the potential uses of these vesicles as cell-free agents to treat autoimmune diseases [84–88]. In the following section we focus on exosomes' therapeutic applications in type 1 diabetes mellitus, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome and other autoimmune diseases.

3.1. Type 1 diabetes mellitus (T1DM)

T1DM is caused by the infiltration of islet antigen-specific autoreactive T cells into pancreatic islets and, consequently, by the autoimmune-mediated destruction of insulin-producing β-cells [89]. T1DM accounts for approximately 5%~10% of all diabetes cases (11~22 million) worldwide [90]. The incidence of type 1 diabetes has been increasing by approximately 3% per year and, in 2006, this disease affected 440,000 children younger than 14 years of age and was the primary cause of diabetes in children younger than 10 years [91]. Compared to their male counterparts, women with T1DM have a 40% higher risk of death [92]. Although pancreatic islet transplantation is one of the most promising treatments for T1DM, many challenges must be overcome before this option is suitable for widespread use. Meanwhile, reports have indicated that plasma exosomes from patients with T1DM carry upregulated or downregulated miRNAs levels, and most of which are associated with disease progression [93,94].

Research suggests that stem cell-derived exosomes might protect the pancreatic islets of patients with T1DM from autoimmune targeting, thus slowing disease progression [26]. Moreover, exosomes might also enhance the survival of transplanted pancreatic islets and enhancing the efficiency and success rate of the treatment [95,96]. Additionally, Jiang et al. found that intravenous administration of USCs-Exo, which contain anti-apoptotic, regenerative, angiogenic, and immunomodulatory factors, might reduce the urine volume and urinary microalbumin excretion, prevent podocyte and tubular epithelial cell apoptosis, suppress caspase-3 overexpression, and increase glomerular endothelial cell proliferation in a rat model of diabetes. USCs-Exo might prevent diabetes-related renal injury by inhibiting podocyte apoptosis and promoting vascular regeneration and cell survival [97]. These findings strongly suggest that exosomes released by stem cells are at least partially responsible for the supportive effects of whole stem cells on islet β-cells. Therapies incorporating these exosomes could improve the appeal and practicality of islet transplantation for patients suffering from T1DM and extend the functional lives of islet grafts while reducing the need for immunosuppressive treatments.

3.2. Multiple sclerosis (MS)

Multiple sclerosis (MS) typically affects young adults at approximately 30 years of age. In this demyelinating disease of the CNS, autoreactive T and B cells that specifically target myelin antigens are thought to initiate and perpetuate a devastating pathologic process [98–100]. MS is characterized by the accumulation of neurologic deficits, which impairs the patient's daily living activities during later disease stages [101]. Current treatment options include immunosuppressive and immunomodulatory therapies that limit lymphocyte infiltration into the affected brain. Unfortunately, however, these options are rather ineffective [102]. In addition, some researchers have emphasized remyelination as a therapeutic target and suggest MS patients would benefit from the use of exosomes to stimulate this process [103]. Pusic et al. demonstrated that exosomes isolated from interferon γ-stimulated rat bone marrow derived DCs containded miRNA-219, which stimulates myelination in vivo in Wistar rats [104]. Similarly, another team found that exosomes derived from MS patients (MS-exosome) could selectively target IFN-γ^-IL-17A$^-$Foxp3$^+$CD4$^+$ Treg cells *in vitro*, and exosomal let-7i regulates MS pathogenesis by blocking the IGF1R/TGFBR1 pathway [75]. Additionally, Yu and colleagues isolated exosomes from DCs expressing membrane-associated TGF-β and observed more potent immunosuppressive activity with mTGF-β-EXOs *vs* sTGF-β-EXOs *in vitro*. In that study, mTGF-β-EXOs inhibited development and progression of experimental autoimmune encephalomyelitis (EAE), an animal model of MS [105]. In another MS model study, MSC-microvesicles inhibited auto-reactive lymphocyte proliferation and stimulated secretion of the anti-inflammatory cytokines IL-10 and TGF-β [106]. Other researchers investigated whether exosomes could deliver anti-inflammatory drugs to treat MS. Specifically, they encapsulated curcumin or the Stat3 inhibitor JSI124 in exosomes (Exo-cru and Exo-JSI124, respectively). When administered intranasally, both Exo-cur or Exo-JSI124 rapidly delivered the encapsulated cargo to the brain, where the drugs were selectively taken up by microglial cells; consequently, the target cells were induced to undergo apoptosis [107]. In this study, EAE mice treated intranasally with Exo-cru or Exo-JSI124 exhibited significantly delayed EAE progression, demonstrating that exosomes might represent a novel therapeutic approach to MS treatment.

3.3. Systemic lupus erythematosus (SLE)

SLE is a chronic autoimmune disease that affects multiple organs and presents with a variety of clinical manifestations [108,109]. This disease is characterized by the presence of autoreactive T cells and hyperactive B cells that produce autoantibodies, which later form immune complex deposits [110,111]. SLE's prevalence varies from 20 to 150 cases per 100,000 people and has a strong female predominance (female:male patient ratio = 9:1) [112]. Currently, glucocorticoids (GCs) are the most effective anti-inflammatory drugs available for SLE [113]. Nevertheless, a few patients respond poorly or not at all, a condition known as GC resistance [114]. Recently reported novel immunotherapies for SLE were developed to target biological pathways that overlap with oncology, transplantation and other autoimmune diseases such as RA [115]. These targeted immunotherapies involve different approaches, such as B-cell depletion/survival (e.g., Rituximab, Bortezomib), cytokine therapies (e.g., Tocilizimab, secukinumab), peptide-based immune modulation (e.g., Forigerimod) and JAK kinase inhibitors (e.g., Tofacitinib) [116]. Although these therapies improved patients' survival rates and durations, they are associated with adverse side effects and maybe effective in only specific subgroups of patients,

such as those with low interferon signatures or active SLE without nephritis [117,118]. In addition, these new drugs are also expensive and, thus, affect the long-term medical costs associated with the disease [119,120]. Therefore, new approaches to improve the clinical efficacy and safety of SLE treatment are urgently needed.

Existing evidence suggests that circulating exosomes are immunologically active and their levels correlate with disease activity in SLE patients. These circulating exosomes might, therefore, serve as novel biomarkers of SLE disease activity [73]. Many studies of autoimmunity and SLE assessed transplantation of MSCs in murine models and human patients [121]. However, no published reports describe the investigation of exosomes from MSCs in SLE animal models or human patients.

3.4. Rheumatoid arthritis (RA)

RA is a chronic and systemic autoimmune disorder in which persistent synovial inflammation causes joint destruction. Research has extensively demonstrated that RA patients' fibroblast-like synoviocytes and T lymphocytes exhibit altered sensitivity to apoptosis, which leads to both synovial hyperplasia and chronic inflammation [122]. Several pharmaceutical agents have been developed for RA, including nonsteroidal anti-inflammatory drugs, corticosteroids, and disease-modifying anti-rheumatic drugs [123]. However, none of these therapies are curative, and many have serious side effects or lose effectiveness over time [124]. Although medical treatments for RA have improved dramatically in recent years, most notably with the development of tumour necrosis factor α (TNF-α) targeting agents for use in combination with methotrexate, the outcomes for a substantial number of RA patients remain suboptimal. Specifically, most patients fail to respond completely to these new treatments, and many other patients will experience reduced the beneficial effects over time. Given the extremely high costs of RA for patients, their families, and society [125,126], new and more effective treatments are clearly warranted.

Recent studies have revealed that exosomes play important roles in RA therapy. For example, the administration of DC/IL-4 or exosomes derived from DC/IL-4 can modulate the activities of APCs and T cells in vivo through a MHC class II and partly Fas ligand/Fas-dependent mechanism, and can effectively treat established collagen-induced arthritis and suppress the DTH inflammatory response [127]. Kim et al. demonstrated that periarticular administration of exosomes purified from bone marrow-derived DCs either transduced ex vivo with an IL-10-expressing adenovirus or treated with recombinant murine IL-10 could suppress delayed-type hypersensitivity responses within both injected and untreated contralateral joints. Furthermore, the systemic injection of IL-10-treated DC-derived exosomes suppressed the onset of murine collagen-induced arthritis and reduced the severity of established arthritis [128]. In other studies, both indoleamine-expressing DCs and exosomes derived from these cells had immunosuppressive and anti-inflammatory effects and could reverse established arthritis [129]. In addition, Martinez-Lostao and colleagues have recently demonstrated that the bioactivity of Apo2 ligand or tumor necrosis factor (TNF)-related apoptosis-inducing ligand (APO2L/TRAIL) increased upon tethering to a liposome membrane (a surrogate of naturally occurring exosomes), which led to the more effective treatment of experimental arthritis in rabbit knee joints relative to soluble; unconjugated APO2L/TRAIL; with substantially reduced synovial hyperplasia and inflammation in rabbit knee joints [130]. All the evidence suggests that exosomes could be used to treat and prevent flares in patients with RA. However, further investigation is needed to elucidate the precise effects of with immunomodulatory exosomes treatment.

3.5. Sjögren's syndrome (SS)

Sjögren's syndrome (SS) is a chronic inflammatory autoimmune disease that mainly targets the salivary glands (SGs) and lacrimal glands. The disease has an incidence of approximately 1% in the general population and up to 3% of people older than 50 years; more than 90% of all diagnosed cases are in women [131]. SS is characterized mainly by hypofunction SGs or xerostomia, which exacerbates dental caries and periodontal disease and causes problems with mastication, swallowing, speech, sleep and the taste. Accordingly, this disease severely impairs patients' quality of life and no effective treatment is currently available. A recent study demonstrated that the intracellular autoantigenic Ro/SSA, La/SSB, and Sm RNPs are present in vesicles that are constitutively released by resting and viable cells, and that significant expression of these RNPs was invariably observed in exosomes derived from both SS patients and non-SS disease controls [132]. In another report, intravenous infusion of allogeneic mesenchymal stem cells or MSCs isolated from the bone marrow or umbilical cord alleviated both experimental and clinical SS [133], so exosomes derived from MSCs maybe as a way to treat SS substituting cell therapy. Relatively few studies, however, have investigated exosomal microRNAs as potential diagnostic biomarkers. Michael et al. reported the first successful isolation and initial characterization of miRNA-carrying exosomes from saliva, finding that the salivary exosome protein and miRNA levels might be useful detecting SS [134–137]. However, more studies are needed to elucidate these factors and better assess the value of salivary exosomal microRNAs in the diagnosis and prognosis of SS. This will also lead to new biomarkers for selection of the appropriate exosomes related therapy on SS.

3.6. Other autoimmune diseases

Systemic sclerosis (SSc) is a rare systemic autoimmune disorder characterized by vascular damage, immune activation and fibrosis of the skin and/or internal organs [138]. In a previous study of a mouse model of SSc/scleraderma, donor MSCs were found to transfer miR-151-5p to recipient bone marrow MSCs and, thus, inhibit IL4Rα expression, which downregulated activation of the mTOR pathway to enhance osteogenic differentiation and reduce adipogenic differentiation. Moreover, the systemic delivery of miR-151-5p could rescue osteopenia, bone marrow MSC impairment, skin-stiffenin and disordered immune responses in SSc mice, suggesting that miR-151-5p may be a specific target for SSc treatment [139]. Most recently, Bai and colleagues demonstrated that MSC-derived exosomes efficiently attenuated experimental autoimmune uveitis (EAU), a well established murine model of autoimmune uveitis. Both clinical and histological analyses revealed that periocular injection of MSC-derived exosomes significantly ameliorated EAU [140]. Moreover, bone marrow stem cell derived exosomes protected against liver injury in an experimental model of autoimmune hepatitis through a mechanism associated with the regulation of NLRP3 and caspase-1 by exosomal miR-223 [87]. In another study, proteomics analysis yielded important insights into the potential activities of myeloid-derived suppressor cell exosomes (MDSC-Exo), which preferentially homed into Alopecia Areata AA-affected organs. Most importantly, the observed changes in leukocyte mRNA in AA mice treated with MDSC-Exo indicates that these vesicles have a strong impact on both the adaptive and innate immune systems, and particularly on Treg expansion [141]. We summary the exosomes related therapeutic applications on different autoimmune diseases in Table 2. Taken together, these findings suggest that exosomes are attractive candidates for clinical treatment of autoimmune diseases.

From the above, exosomes (especially exosomes derived from mesenchymal stem cells) have shown a great potential therapy in autoimmune diseases; and MSC-Exos play therapeutic roles in many autoimmune diseases [97,106,133,139,140,142,143]. MSCs are a type of multipotent cell (deriving from many tissues such as adipose tissue, bone marrow, fetal tissues, umbilical cord and so on), have many properties that enable their therapeutic use. MSC-Exos exhibited commendably beneficial functions similar to the MSCs, suppressing both adaptive and innate immunity by inducing polarization of macrophages

Table 2
The exosomes related therapeutic applications on different autoimmune diseases.

Autoimmune disease	Source of exosomes	Effects	References
Type 1 diabetes mellitus (T1DM)	endothelial progenitor cells	enhance neoangiogenesis	[96, 97]
	human urine-derived stem cells	inhibit podocyte apoptosis and promote vascular regeneration and cell survival	
Multiple sclerosis (MS)	DCs	though containing miRNA-219, which stimulates myelination	[104, 75, 106-107]
	plasma	exosomal let-7i regulates MS pathogenesis by blocking the IGF1R/TGFBR1 pathway	
	MSCs	inhibit auto-reactive lymphocyte proliferation and stimulated secretion of the anti-inflammatory cytokines IL-10 and TGF-β	
	microglial cells	induce microglial cells to undergo apoptosis	
Systemic lupus erythematosus (SLE)	serum	inflammatory response and immunoregulation	[73]
Rheumatoid arthritis (RA)	DCs	modulate the activities of APCs and T cells in vivo through a MHC class II and partly Fas ligand/Fas-dependent mechanism	[127-130]
	DCs	suppress delayed-type hypersensitivity responses	
	DCs	immunosuppressive and anti-inflammatory effects	
	synovial fluid	reduce synovial hyperplasia and inflammation	
Systemic sclerosis (SSc)	MSCs	exosomal miR-151-5p could rescue osteopenia, bone marrow MSC impairment, skin-stiffenin and disordered immune responses	[139]
Experimental autoimmune uveitis (EUA)	MSCs	inflammatory response and immunoregulation	[140]
Autoimmune hepatitis	MSCs	regulation of NLRP3 and caspase-1 by exosomal miR-223	[87]
Alopecia Areata AA	myeloid-derived suppressor cell	strong impact on both the adaptive and innate immune systems, and particularly on Treg expansion	[141]

towards alternative phenotype, by attenuating maturation and capacity for antigen presentation of dendritic cells, by inhibiting activation and proliferation of T and B lymphocytes, by promoting the generation of Treg cells and enhancing the function of regulatory T cells. At the same time because exosomes contain peculiar protein, DNA and RNA (especially miRNA). Therefore, exosomes may carry out therapeutic effect in many autoimmune diseases through these immunoregulatory effect.

4. Conclusion and perspectives

Currently, we lack a full understanding of autoimmune disease causes and the effective means of diagnosis, treatment, and prevention. Therefore, it is unlikely that the urgent need for better treatment would be satisfied by a single biomarker or drug. For decades, researchers and doctors worldwide have been struggling for decades to seek better diagnosis, treatment, and prevention methods for autoimmune disease patients. By studying exosomes in different autoimmune disease states we may find inspiration for how to optimize them both for preventive and therapeutic applications in human diseases. This will also lead to new biomarkers for disease and for selection of the appropriate treatment. As recently as a few decades ago, exosomes were identified as potent immune response stimulators, potential biomarkers, and therapeutic agents for autoimmune disorders. A rapidly expanding body of evidence now indicates that exosomes play important physiological and pathological roles in autoimmune diseases. These exosomes possess several features that suggest potential success for the treatment of diseases. Firstly, exosomes can be isolated from various body fluids and are stable under long-term storage at $-80\,^{\circ}C$. Secondly, exosome have a relatively long half-life in the body. Thirdly, exosomes can encompass bioactive substances and protect them from enzymatic degradation. Fourthly, exosomes can be further modified to meet the needs of specific treatment scenarios. In this review, we have provided evidence of the direct and indirect immunomodulatory effects mediated by exosomes in the contexts of several autoimmune diseases particularly the modulation of immune responses and interference with multiple cellular and molecular processes. However, the underlying mechanisms by which exosomes can serve as both therapeutic vehicles and targets in autoimmune diseases are not fully understood. Both basic and applied research for exosomes is still in the early stages. In the future, many aspects of exosomal treatment for autoimmune diseases will require further detailed exploration, including: (i) the separation and purification of exosomes, (ii) a precise understanding of exosome biogenesis and targeting, (iii) evaluation of the effects of exosomal treatment *in vivo*, (iv) clarification of the mechanisms underlying the effects of exosomes both *in vitro* and *in vivo*, and (v) clinical applications. Briefly, despite the great challenges and difficulties in practically using exosomes, this endogenous vesicle has shown a great potential in the biomedical field and would be the next generation of advanced drug therapy. In summary, continued research into the biology and functions of exosomes should lead to more extensive clinical applications and the designation of these vesicles as alternatives to cell therapies for the treatment of autoimmune diseases.

Authors' contributions

Each author substantially contributed to the review. HX: conception and design, drafting the review; HX, SCJ and HMX: revising it critically for important intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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Disclosures

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