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Exosome-based therapies for inflammatory disorders: a review of recent advances

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Abstract

Exosomes, small extracellular vesicles secreted by cells, have emerged as focal mediators in intercellular communication and therapeutic interventions across diverse biomedical fields. Inflammatory disorders, including inflammatory bowel disease, acute liver injury, lung injury, neuroinflammation, and myocardial infarction, are complex conditions that require innovative therapeutic approaches. This review summarizes recent advances in exosome-based therapies for inflammatory disorders, highlighting their potential as diagnostic biomarkers and therapeutic agents. Exosomes have shown promise in reducing inflammation, promoting tissue repair, and improving functional outcomes in preclinical models of inflammatory disorders. However, further research is needed to overcome the challenges associated with exosome isolation, characterization, and delivery, as well as to fully understand their mechanisms of action. Current limitations and future directions in exosome research underscore the need for enhanced isolation techniques and deeper mechanistic insights to harness exosomes' full therapeutic potential in clinical applications. Despite these challenges, exosome-based therapies hold great potential for the treatment of inflammatory disorders and may offer a new paradigm for personalized medication.

Keywords Exosome, Inflammatory disorders, Delivery, Therapeutic potential, Personalized medication

Introduction

Inflammatory disorders impact a large number of people and are a major source of morbidity and death across the world. The overall number of patients on immunosuppressive medicines is continuously increasing. Long-term treatment of immunosuppressive drugs is associated with the possibility of infection and cancer due to the continuous suppression of antimicrobial and antitumor immunity [1, 2]. Exosomes with high biocompatibility, minimal immunogenicity, and toxicity provide insight into changed cellular or tissue states in a variety of diseases, and their detection in biological fluids has the potential to provide a multicomponent diagnostic readout [3, 4], and their lipid bilayer allows them to cross cellular barriers [5]. Exosomes can also be used with various biological activities and targeting capabilities via surface engineering technologies. Because of their versatility,

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they have considerable latent drug delivery systems for the treatment of chronic inflammatory disorders [6]. Furthermore, exosomes generated from mesenchymal stem cells (MSCs), astrocytes, and dendritic cells (DCs) from inflammatory sites with immunomodulatory capabilities are commonly employed as transport vehicles to deliver cargo to inflammatory areas for improved anti-inflammatory effects [7–9]. Exosomes released by inflammatory cells have strong inflammatory affinity and targeting, thus they can transport cargo to inflammatory cells via the interaction of surface-antibody and cell surface receptors, resulting in a more potent anti-inflammatory impact [9].

Exosome biogenesis, composition and target modification

Exosomes are double-membraned vesicles with diameters ranging from 30 to 200 nm that cells secrete into their environment. Exosomes transport lipids, proteins, messenger RNA (mRNA), microRNA (miRNA), long non-coding RNA (lncRNA), and DNA, allowing them to maintain cellular homeostasis, remove cellular trash, and facilitate intercellular and interorgan communication (Fig. 1). Exosomes circulate across all body fluids and carry molecular messages in an autocrine, paracrine, and endocrine way [10].

A variety of essential components for cell communication are included in exosomes, including about 4,563 proteins, particularly tetraspanins (Alix, TSG101, CD9,

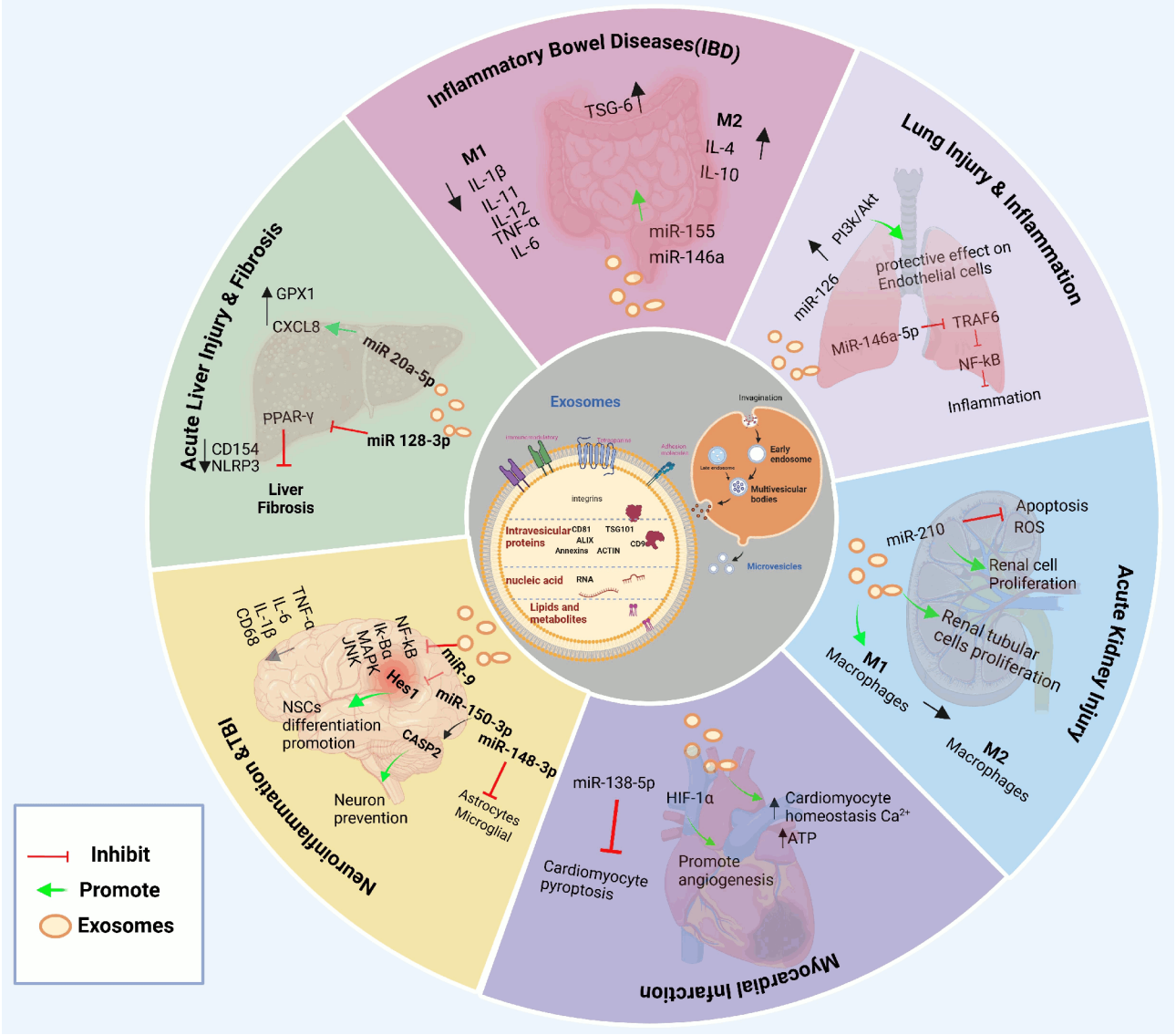

Fig. 1 Exosome biogenesis, their molecular composition, and protective effect on different inflammatory diseases. The figure is generated using Biorender scientific image and illustration software (https://www.biorender.com/)

CD63, CD81, and CD82), which control cell adhesion and fusion [11]. Additional proteins include different GTPases involved in intracellular transport and fusion, Rab proteins (Rab11, Rab27a, Rab27b), and heat shock proteins (HSP70, HSP90) [12]. Additionally, they have 194 known lipids that are essential to the exosomal structure, such as phosphatidylcholines, phosphatidylserines, and sphingolipids [13]. Exosomes contain DNA, including mitochondrial DNA, 1,639 mRNAs, and 764 miRNAs [14–16]. Certain miRNAs, such as miR-1 and miR-21, are associated with hematopoiesis and carcinogenesis [15]. Membrane proteins like CD55 and CD59 help to stabilize exosomes outside of cells by inhibiting the complement system [17]. There are two ways that exosomes are secreted: constitutive release through the Trans-Golgi network and pathogen-inducible release [18], which is controlled by Rab proteins (Rab27a, Rab27b, Rab35 & Rab11) [19] and impacted by variables like as pH and potassium levels [17, 20]. Through processes like phagocytosis and endocytosis, exosomes can fuse with destination cells after being released, delivering their cargo and producing biological consequences [21–23].

Exosomes' inherent characteristics offer them certain advantages in target cell absorption as compared to conventional nanomedicine delivery methods. However, additional changes are required to enhance exosomes' capacity to target disease sites [24]. It is commonly recognized that the most advanced targeted modification technique is genetic engineering, which aims to fuse ligands with distinctive functionalities to a wide variety of transmembrane proteins on the surface of exosomes, including CD9, CD63, and Lamp2b. Plasmids or viruses that encode fusion ligands for transmembrane proteins can be used to genetically modify parental cells [25]. HSTP1 and the membrane protein Lamp2b efficiently increased HSC-T6 cells' absorption of exosomes [26]. Exosome direct engineering provides a regulated and effective method of alteration [27]. Small peptides, proteins, and other specific molecules can be attached to the surface of exosomes via physical and chemical techniques, improving their usefulness without compromising their integrity [28]. By employing physical surface modification to momentarily break the lipid structure, physical alterations enable exosomes to subsequently revert to their original state [29]. Mild reactions are used in chemical modifications to bind suitable molecules covalently or non-covalently without changing size [25, 30]. Target cells absorb exosomes by membrane fusion, receptor-ligand interactions, and mostly endocytosis [31]. Fluorescent probes and laser confocal microscopy can be used to visualize exosome uptake and flow cytometry can be used to analyze the results [32]. Exosomes in living cells may be tracked in detail thanks to sophisticated methods like single-molecule localization microscopy (SMLM) [33]. Exosome distribution can also be tracked in vivo using other imaging techniques such as bioluminescence, nuclear imaging, CT, and MRI [34–36].

Exosome therapy has more benefits than stem cell-based therapy, such as preventing immunological reactions, preventing tumorigenicity, being stable and suited for long-term preservation, and promoting better signaling in intercellular communication, among other benefits [3, 37, 38].

Different cell-derived exosomes and their function

Several studies demonstrated that therapeutic agents known as mesenchymal stem cells (MSCs) are being used to target the pro-inflammatory cytokines [39, 40]. In any case, the utilization of MSCs as therapeutics has a few downsides including potential cancer development, non-specific differentiation, unwanted immune responses, difficulty of quality control, and short half-life before administration [41]. MSCs are intriguing alternative agents for the treatment of inflammatory diseases due to their immunomodulatory function. Several clinical trials on MSC-based products are currently being conducted [42]. Exosomes released by macrophages can transmit miRNA from the host cell to a particular target cell, facilitating tumor invasion [43] proving exosomes a promise nanocarriers for chemotherapeutic medicines, neuroprotective proteins, and imaging agents, efficiently delivering therapies for drug-resistant malignancies, Parkinson's disease, and gliomas [44].

Dendric cells-derived exosomes (Dex) are involved in antigen-specific immunity and tolerance [45]. Dex has demonstrated immunostimulatory properties and potential as a cancer immunotherapy vaccine, effectively eliciting antigen-specific immune responses, enhancing cytotoxic T lymphocyte activity, and inhibiting tumor growth, particularly in hepatocellular carcinoma (HCC) [46, 47]. Exosome-mediated signaling is a novel way for fetal and maternal communication. It can send birth signals by increasing maternal pregnancy cell inflammation. Amniotic epithelial-derived exosomes cause inflammation in uterine cells and restore ovarian function by delivering miRNAs that resist apoptosis [48, 49]. Exosomes derived from endothelial progenitor can inhibit microvascular dysfunction and sepsis by delivering miR-126 and inhibiting neointimal hyperplasia following carotid damage in rats [50, 51]. Exosomes from cardiac fibroblasts have a vital function in activating the renin-angiotensin system in cardiomyocytes [52]. Exosomes from nephron cell origin can transmit pro-inflammatory or pro-fibrotic signals from tubular epithelial and interstitial cells, including fibroblasts and immune cells. This can contribute to kidney fibrosis [53].

Anti-inflammatory medications, especially biologic disease-modifying antirheumatic drugs (bDMARDs),

which stop and slow the disease process in inflammatory diseases, such as TNF inhibitors and rituximab, raise the risk of severe infections including bacterial, mycobacterial, and HBV reactivation [54]. Non-steroidal anti-inflammatory drugs (NSAIDs) have significant concerns for individuals with treatment-resistant hypertension, high cardiovascular risk, and severe chronic kidney disease (CKD), and need rigorous pre-treatment evaluation and monitoring [55]. Furthermore, combination medications for inflammatory bowel disease (IBD) that include TNF antagonists and corticosteroids dramatically increase infection risks, although monotherapy with immunosuppressive drugs is rather safe [56]. Steroids used to treat IBD might worsen risk factors for atherosclerotic cardiovascular disease (ASCVD), increasing the chance of sudden myocardial infarction and stroke, especially in women and younger patients [57].

A recent study questions the effectiveness of using exosomes from adipose-derived stem cells (ADSC-Exos) in regenerative medicine. Exosome donors with metabolic problems had reduced adipose stem cell number and therapeutic potential [58]. Despite possible challenges, the utilization of exosomes derived from multiple cell types continues to show promise in the treatment of inflammatory diseases. Their distinct features and capacity to target specific cells make them a feasible alternative to existing immunosuppressive medicines, which are frequently associated with considerable risks and adverse effects. As research advances, better knowledge and development of exosome-derived therapies may lead to safer and more effective therapeutic choices for controlling chronic inflammatory disorders, ultimately enhancing patient outcomes and quality of life.

Characterization techniques for exosomes in biomedical therapies

Exosomes are characterized by their physical, chemical, functional, structural, and biological properties, for critical biomedical therapies such as enzyme replacement therapy (ERT). Robust characterization methods are essential to ensure consistency in composition, structure, and functionality (Fig. 2). Previously, the morphology of exosomes was often described as cup-shaped but now the gold standards for morphological characterization

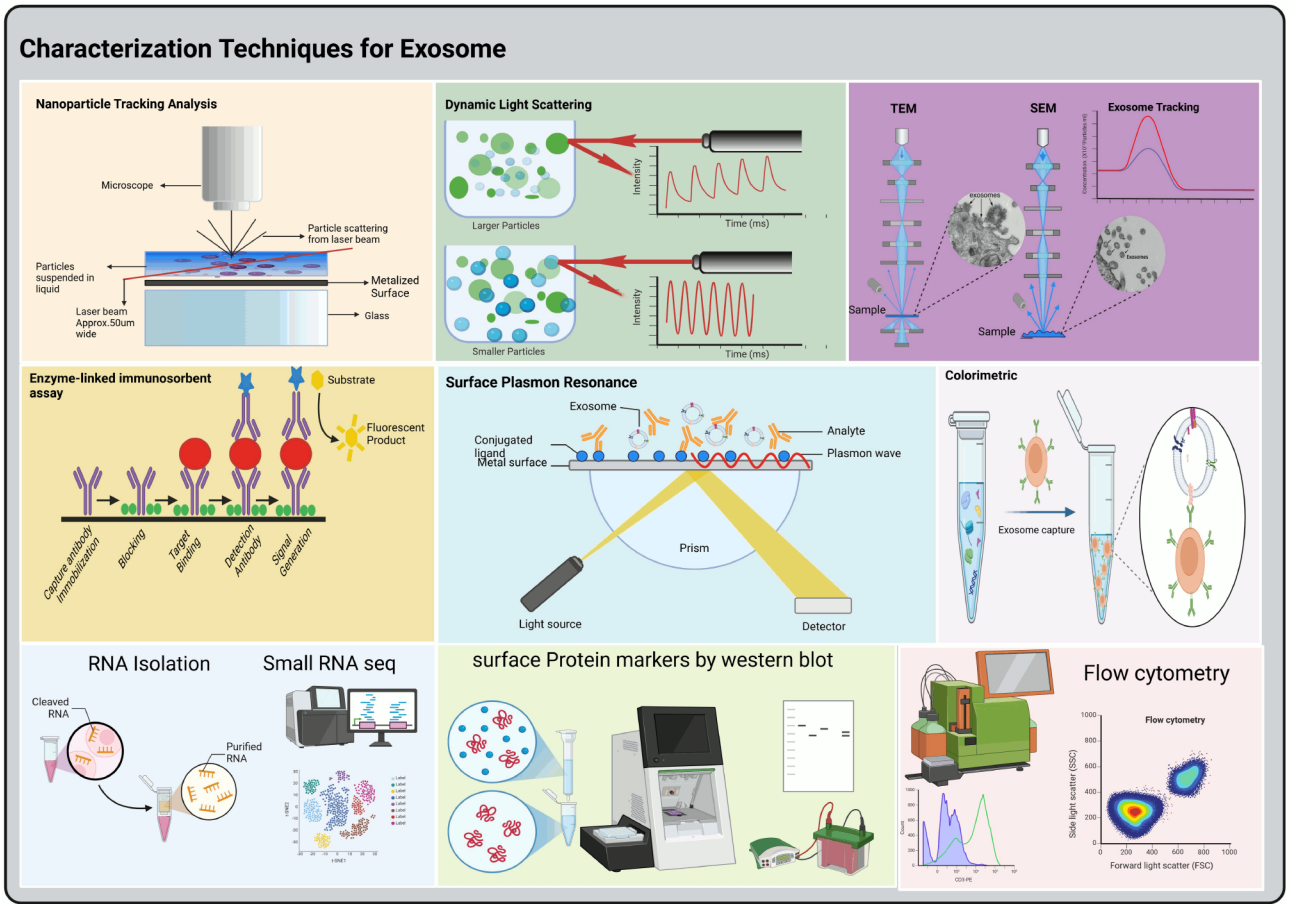

Fig. 2 Different techniques for characterization of exosomes before therapeutic applications. The figure was generated using Biorender scientific image and illustration software (https://www.biorender.com/)

are Electron Microscopic Technologies [59]. Visualizing exosome structure is crucial using transmission electron microscopy (TEM) and Cryo-TEM, although sample preparation can influence results [60, 61]. Scanning electron microscopy (SEM) aided backscattered electron detection and revealed surface morphology and features [62]. Nanoparticle tracking analysis (NTA) and Flow Cytometry measure particle diameter through light scattering and Brownian motion, while dynamic light scattering (DLS) assesses particle size distribution, despite challenges with heterogeneous particle size [63–65]. Atomic force microscopy (AFM) provides high-resolution three-dimensional imaging and biophysical insight [66].

The characterization of exosomes using western blot and qPCR is critical for understanding their molecular composition and functional roles [67, 68]. Western blot provides insight into exosomal protein content, while qPCR allows for the sensitive and specific quantification of RNA species, especially miRNAs. A positive signal for tetraspanins (CD63, CD9, CD81) and ESCRT components (TSG101, Alix) confirms the presence of exosomes [69, 70]. The absence of negative markers such as calnexin indicates that the exosome preparation is free from cellular contaminants. Quantitative PCR (qPCR) is a pivotal method for characterizing exosomes, particularly in analyzing their RNA content, such as microRNAs (miRNAs) [71]. Analyzing the proteome content of exosomes is as challenging as determining RNA content. Exosomes have yielded a variety of RNA types, including mRNA, miRNA, and others. For RNA extraction, commercial kits are frequently utilized, and the main technique for profiling is reverse-transcription quantitative polymerase chain reaction (RT-qPCR) [16, 72]. In order to amplify DNA and analyze its length and nucleotide sequences, this procedure transforms extracted RNA into cDNA [73]. RNA sequencing (RNA-seq) is an effective tool for characterizing exosomes, providing insights into their RNA content, including mRNA, miRNA, and non-coding RNAs. This approach enhances our understanding of exosome biogenesis, their role in disease mechanisms, and their potential as diagnostic or therapeutic agents in various conditions [74].

The main methods for determining the protein composition of exosomes are two-dimensional gel electrophoresis (2DGE) and liquid chromatography combined with tandem mass spectrometry (LC-MS/MS) [75, 76]. Proteins are removed and produced as peptide fragments, which are more suited for LC-MS analysis, following the purification of extracellular vesicles (EVs). High-pressure liquid chromatography is then used to isolate these peptides before they are subjected to tandem mass spectrometry (MS/MS) [77]. Ions are created and segregated based on the mass-to-charge ratio in the first stage, and the chosen ions are broken up for additional examination in the second stage [77]. This allows the identification and quantification of thousands of proteins from complex samples by comparing the resultant data to a database.

Fluorescence correlation microscopy (FCM) and colorimetric enable specific identification and quantification of exosomes [78], while enzyme-linked immunosorbent assay (ELISA) measures exosomal proteins [79]. Surface plasmon resonance (SPR) and nuclear magnetic resonance (NMR) techniques further enhance characterization by analyzing biochemical and structural data [80, 81],. The SIMOA approach allows for the direct detection of plasma EVs [82], miR-141, cortisol, and IL-6, a 3-plex created by combining direct nucleic acid hybridization with competitive and sandwich immunoassays [83]. Using Glypican-1 (GPC-1) [84] for detection over a dynamic range of 5 orders of magnitude, with limits as low as 10 exosomes per microliter.

Therapeutic impacts of exosomes in inflammatory diseases and biomedical therapies

Exosome-based therapies in inflammatory bowel disease (IBD)

IBD, encompassing Crohn's disease (CD) and ulcerative colitis (UC), is a chronic immunological condition affecting the gastrointestinal tract caused by a dysregulated response to intestinal microbiota in genetically susceptible individuals [85]. The deregulation of mucosal immunity plays a pivotal role in the development and progression of IBD. Diagnosis is based on clinical symptoms, biochemical indicators, as well as imaging and histological investigations [86, 87]. This section examines the possibility of exosome-based therapeutics with an emphasis on therapeutic efficacy and biomarker identification in the management of IBD.

Biomarker identification using exosome

There is no specific biomarker that distinguishes between UC and CD individuals in IBD. Notable biomarkers such as ASCA, pANCA, CRP, lactoferrin, and calprotectin [88]. Alongside the saliva exosome biomarker PSMA7, the biomarkers α-amylase and calprotectin are also present in patients with IBD [89, 90]. Additionally, IBD patients exhibit elevated levels of endogenous ANXA1-containing EVs, which might act as a biomarker for intestinal mucosa inflammation [91]. Exosomes from intestinal luminal aspirates in IBD patients could also show promise as fecal biomarkers for detecting mucosal inflammation [92]. Exosomal RNA NEAT1 has been proposed as another potential biomarker for IBD pathogenesis [93]. Identifying precise and sensitive biomarkers for IBD could significantly enhance diagnosis, treatment, and prognosis, and pave the way for innovative medicines.

Therefore, continued research into these markers and their pathways is essential [94].

Therapeutic efficacy of exosome-derived treatments

Exosomes derived from murine colon cancer cells CT26 (CT26-Exos) were isolated by using ultracentrifugation, characterized via proteome analysis, and evaluated in DSS induced IBD mouse model. Compared to the control and 293 T exosome therapies, CT26-Exos treatment significantly reduced disease activity index (DAI) and colon shortening rate while histological examination showed decreased inflammatory infiltration and increased epithelial goblet cells. Mechanistically, CT26-Exos specifically suppressed Th17 cell differentiation in the colon and inhibited pro-inflammatory cytokine release by colonic DCs [95]. Intravenous administering human adipose mesenchymal stem cell-derived exosomes (hADSC-Exos) to DSS-induced IBD animals improves functional recovery, reduces inflammation, decreases intestinal cell apoptosis, promotes epithelial regeneration, and preserves intestinal barrier integrity. Furthermore, co-cultured injured colon organoids with hADSC-Exos and TNF-α demonstrate anti-inflammatory effects and enhanced proliferation of $Lgr5^+$ ISCs and epithelial cells. These findings suggested hADSC-Exos as a potential treatment for IBD and highlighted a cell-free therapeutic strategy for the disease [96].

Similar to human umbilical cord mesenchymal stem cells (hucMSCs), exosomes labeled with indocyanine green (ICG) were injected into IBD animals, and within 12 h, they targeted colon tissues. By upregulating IL-10 expression and downregulating TNF-α, IL-1β, IL-6, iNOS, and IL-7 gene expressions in spleen and colon tissues, the exosomes considerably reduced the severity of IBD. Exosome therapy also reduced macrophage infiltration in colon tissues of IBD animals. In vitro coculture of mouse enterocele macrophages with exosomes decreased iNOS and IL-7 expression, suggesting a potential mechanism for exosome-mediated inflammation control in IBD. Moreover, elevated IL-7 expression in colon tissues of colitis patients highlights a promising target for exosome-based IBD therapies [97]. Oral administration of colostrum-derived exosomes (Col-Exos) alleviates colitis symptoms such as weight loss, gastrointestinal bleeding, and persistent diarrhea by regulating intestinal inflammation. Bovine colostrum-derived exosomes exhibit exceptional stability and show significant potential as natural therapies for colitis recovery [98]. Exosomes derived from murine bone marrow-derived macrophages (BMDMs), cultured in the presence or absence of lipopolysaccharide (LPS) were analyzed via miRNA sequencing in a DSS-induced IBD animal model. MiR-223 emerged as a key miRNA deteriorating intestinal barrier dysfunction; target prediction and time-dependent mRNA analysis identified Tmigd1 as a critical barrier-related factor [99] (Fig. 3**).**

Current limitation and future direction

However, the use of exosomes in therapeutic applications has been limited due to the hazards of aggressive behavior and ambiguity regarding their biological function in other organs [100]. One notable limitation is the problem of purifying and characterizing exosomes, which is critical for their therapeutic value [101]. Infected cells can produce exosomes, which contain biomolecules that influence the innate immune responses of surrounding cells [102]. Overcoming these constraints necessitates a comprehensive research effort to develop reliable methods for isolating and characterizing exosomes, as well as a complete investigation of their biological activity and safety profile to ensure their safe and effective therapeutic application.

Exosome-based therapies in acute liver injury and fibrosis

Hepatic fibrosis, caused by chronic liver damage, results in excessive collagen and extracellular matrix (ECM) buildup. Hepatitis B and C, alcoholic liver disease, and nonalcoholic steatohepatitis (NASH) all contribute to fibrosis [103]. Hepatic fibrosis was once believed to be irreversible [104]. TGF-β has a crucial role in chronic liver disease, influencing its development from injury to fibrosis [105]. TGF-β activates growth factors and cytokines implicated in fibrogenesis, including PDGF, CCN2, ILs (IL-1α, IL-β, IL-6), and TNF-α [106, 107]. The activation of myofibroblasts from fibroblasts, which include hepatic stellate cells (HSCs), portal fibroblasts (PFs), and fibrocytes, is an important event in liver fibrosis. Fibroblasts either stay dormant or activate into myofibroblasts depending on the ECM composition [108].

Biomarker identification by using exosome

Accurately determining the degree and progression of liver fibrosis is critical for guiding clinical decisions on patient care. The "gold standard" in liver biopsy though effective, is expensive, invasive, and carries risk. Exosome components offer a promising alternative novel biomarker for the identification and evaluation of molecular markers associated with liver fibrosis, acting as a dynamic reflection of the core pathologic disease in patients. Moreover, exosomal components can be detected in circulating plasma and serum with stability owing to their resistance to proteinase-dependent degradation, which makes them ideal biomarkers for various therapeutic applications [109, 110]. Studies have linked elevated amounts of CD10 protein in the urine exosomes of glycine N-methyltransferase mutant mice to steatosis, fibrosis, and hepatocellular injury [111]. Furthermore, the degree of fibrosis and inflammation has been correlated

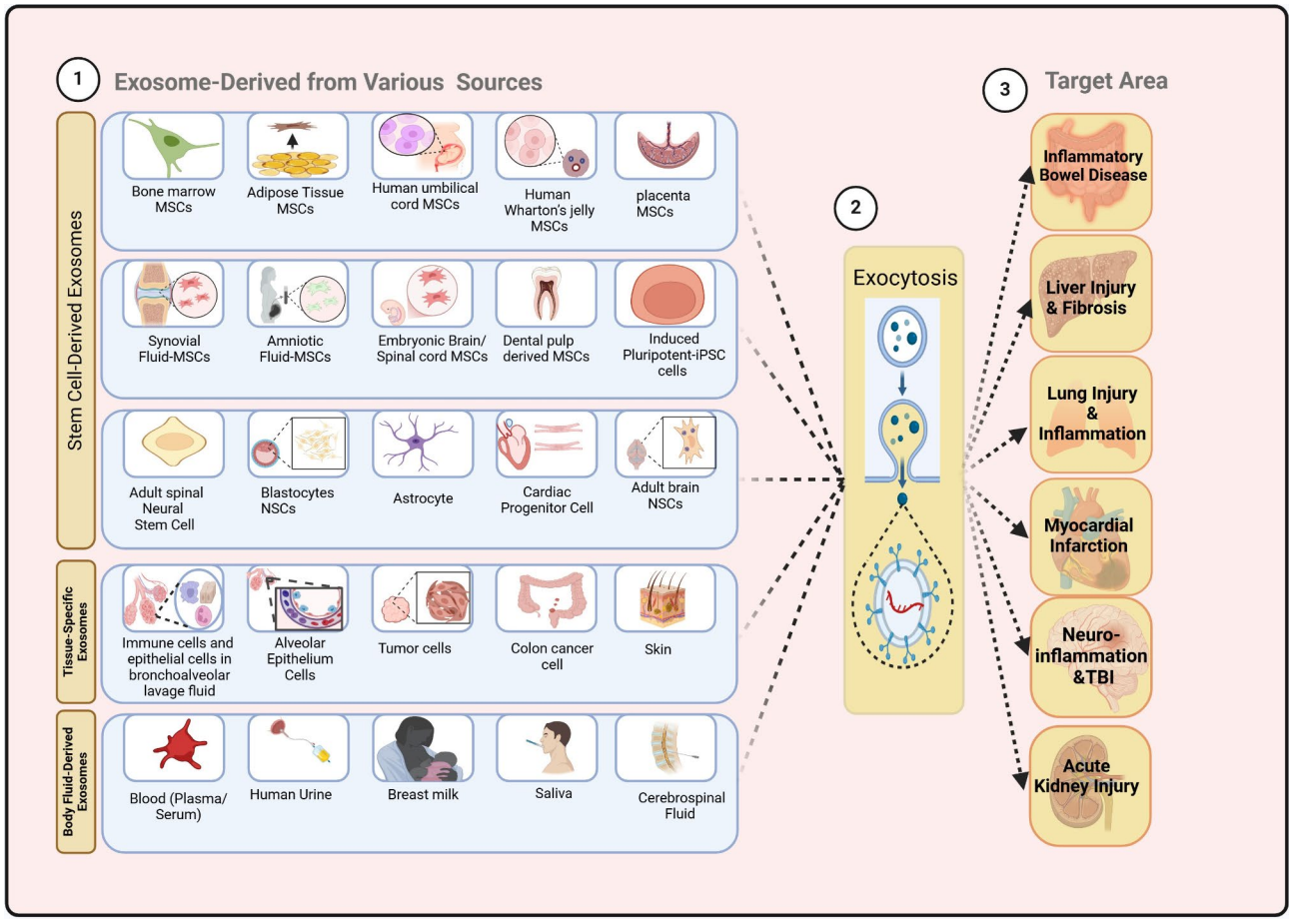

Fig. 3 (**1**) Therapeutic efficacy of exosomes derived from different cells. (**2**) Exosome biogenesis extracted from donor cells (**3**) Delivery of exosomes to the diseased area according to their therapeutic efficacy. The figure was generated using Biorender scientific image and illustration software (https://www.biorender.com/)

with CD81-enriched serum exosomes in patients with chronic HCV infection [112]. Decreased levels of miRNAs (miR-34c, miR-151-3p, miR-483-5p, or miR-532-5p) in serum exosomes from CCl4-induced mice or human patients with F3/4 fibrosis suggest their potential as an indicator of disease severity [113].

Therapeutic efficacy of exosome-derived treatments

Human umbilical cord-derived MSC-Exos have been shown to modify macrophage phenotypes, regulating the inflammatory milieu in the liver and facilitating tissue repair. Delivery of miR-148a, which inhibits the STAT3 pathway and targets Kruppel-like factor 6 (KLF6), resulted in this modulation, which suppresses pro-inflammatory macrophages and promotes anti-inflammatory macrophages. These effects demonstrate the potential of MSC-Exos in treating liver fibrosis by controlling inflammatory responses within the liver and orchestrating macrophage functions [114]. Adipose tissue stem cells (ADSCs) derived exosomes inhibited pro-fibrogenic indicators and the activation of hepatic stellate cells (HSCs). Glutamine synthetase (Glul) was upregulated in hepatocytes during ADSC-Exos therapy, and the metabolic pathways for glutamine and ammonia were altered, according to an RNA-seq study. Glul inhibition reduced the therapeutic effects of ADSC-Exos, emphasizing the function of this compound in metabolic reprogramming to relieve hepatic fibrosis. According to Wu et al. results, targeting HSC activation and metabolic pathways with ADSC-Exos is a potentially effective therapeutic approach for treating hepatic fibrosis [115].

TNF-α pretreatment of umbilical cord mesenchymal stem cell-derived exosomes showed strong anti-inflammatory effects in an acute liver failure (ALF) animal model brought on by LPS and D-GalN after it was enriched and examined for size and surface markers. Inhibiting the activation of NLRP3 and other inflammation-associated proteins, T-Exos therapy substantially decreased serum levels of ALT, AST, and pro-inflammatory cytokines [116]. Through the reduction of collagen buildup, enhancement of liver function, suppression of inflammation, and promotion of hepatocyte

regeneration, hBM-MSCs-Exos therapy considerably reduced hepatic fibrosis. Mechanistically, in both hepatic stellate cells (HSCs) and liver fibrosis tissue, hBM-MSCs-Exos suppressed the production of important elements of the Wnt/β-catenin signaling pathway (PPARγ, Wnt3a, Wnt10b, β-catenin, WISP1, Cyclin D1), as well as α-SMA and Collagen I [117]. Exosomes derived from NK-92MI cells (NK-Exo) were extracted and identified using transmission electron microscopy, nanoparticle tracking analysis, and western blotting. After that, mice with liver fibrosis produced by CCl4 and LX-2 cells treated with TGF-β1 were given NK-Exo. NK-Exo reduced CCl4-induced liver fibrosis and decreased TGF-β1-induced HSC activation and proliferation. The exosome inhibitor GW4869 reversed this HSC-inhibitory action. Consequently, NK-Exo efficiently prevents liver fibrosis brought on by CCl4 and HSC activation produced by TGF-β1 [118] (Fig. 3).Rat bone-marrow-derived.

Current limitation and future direction

Many studies on chronic liver illnesses have made progress, but exosomes continue to present significant obstacles. The majority of present research on exosome-based therapeutics is focused on cell and animal models, with clinical trials yet to be completed. Exosomes and microvesicles in human fluids are difficult to distinguish due to their similar sizes, necessitating the development of particular biomarkers. Further investigation into the molecular processes of exosome synthesis, release, and interaction with target cells is required for therapeutic use. As more researchers enter the field, the practical use of exosomes may soon benefit patients [119].

Exosome-based therapies in lung injury and inflammation

Acute lung inflammation is caused by an innate immune defense against invading microorganisms; chronic inflammation occurs when the response fails to eliminate the inflammatory trigger [120]. Acute lung injury (ALI) is a common clinical lung condition that can be fatal. In survivors, fibrotic lung healing may result in acute respiratory distress syndrome (ARDS). Respiratory distress, hypoxemia, and non-cardiogenic pulmonary edema are the hallmarks of the debilitating clinical condition known as ARDS [121].

Therapeutic efficacy of exosome-derived treatments

Exosomes derived from macrophages, neutrophils, and epithelial cells in bronchoalveolar lavage fluid (BALF) throughout time after ALI was induced in mice using LPS. The main early secretors of pro-inflammatory cytokines in BALF-exosomes stimulated neutrophils to generate cytokines and IL-10. Post-ALI fibrosis may have been exacerbated by neutrophil-derived IL-10 in BALF-exosomes, which polarized macrophages to M2c [122]. Alveolar epithelial cells (AECs)-derived Exosome play a role in alveolar macrophage (AM) activation and sepsis-induced ALI. By using a rat model of septic lung injury, Liu et al. discovered that GW4869 inhibited exosomes, which decreased lung harm. LPS-treated cells produced AEC-derived exosomes (LPS-Exos), which activated AMs and increased alveolar permeability and pulmonary inflammation. By inducing the NF-κB pathway and downregulating PTEN, miR-92a-3p, which is abundant in LPS-Exos, stimulated AMs. These proinflammatory effects were lessened by inhibiting miR-92a-3p. Thus, exosomes produced from AECs activate AMs and cause inflammation through miR-92a-3p, indicating an ALI therapeutic target [123].

Rat bone-marrow-derived MSC exosomes outperformed the phosgene group in terms of respiratory performance, wet-to-dry lung weight ratio, and total protein content in BALF. They reduced inflammatory markers TNF-α, IL-1β, and IL-6 while boosting IL-10. Furthermore, exosomes reduced MMP-9 and increased SP-C levels. Thus, MSC-derived exosomes reduce phosgene-induced ALI by regulating inflammation, decreasing MMP-9, and increasing SP-C levels [124]. BMSC-derived exosomes suppress glycolysis in macrophages, making them effective in treating sepsis-induced lung damage. They decreased M1 polarization while promoting M2 polarization in MH-S cells (murine alveolar macrophages) by reducing cellular glycolysis. Inhibiting hypoxia-inducible factor 1 (HIF-1) α resulted in the down-regulation of critical glycolysis proteins. In an LPS-induced ARDS mouse model, BMSC-derived exosomes decreased inflammation and lung damage while inhibiting LPS-induced glycolysis in lung tissue [125]. Macrophages absorbed ADMSC-derived exosomes, which reduced IL-27 release in vitro. In vivo, IL-27 deletion reduced CLP-induced ALI, while ADMSC-derived exosomes blocked macrophage aggregation in lung tissues, decreased IL-27 secretion, and decreased levels of IL-6, TNF-α, and IL-1β. Furthermore, ADMSC-exosomes reduced pulmonary edema, tissue damage, and vascular leakage, hence increasing survival rates. Injecting recombinant IL-27 abolished the protective benefits of ADMSC-derived exosomes. Thus, ADMSC-derived exosomes reduce sepsis-induced ALI by reducing IL-27 secretion in macrophages [126] (Fig. 3).

Current limitations and future direction

Cell-free treatment, notably with exosomes, has received a lot of attention for treating lung diseases. Despite advances, the actual mechanism of action of exosomes is still unknown, with recent studies focused on their RNA cargos but not fully comprehending other components. Limitations include the high costs and technical problems of isolating and purifying exosomes, as well as

the requirement to immortalize stem cells for large-scale production, which entails hazards and complications [127].

Exosome-based therapies in neuroinflammation and traumatic brain injury

Therapies for neuroinflammatory diseases like multiple sclerosis, acute disseminated encephalomyelitis, viral encephalitis, and bacterial meningitis, as well as other conditions of the central nervous system that have an inflammatory component (such as schizophrenia, migraine headaches, and neurodegenerative disorders like Parkinson's and Alzheimer's disease), are being developed through extensive translational research [128]. Exosomes released by several neural cell types perform crucial roles in both CNS development and adult brain maintenance, such as synaptic activity control and regeneration after damage [129].

Exosomal biomarker in neuroinflammatory disorders

Neuroinflammatory disorders are frequently misdiagnosed due to unknown pathophysiology and a lack of early diagnostic markers [38, 130]. Exosome identification in Parkinson's and Alzheimer's disorders can help with early diagnosis and tracking [131]. Exosomes from cerebrospinal fluid (CSF) can be analyzed to help researchers understand illness development [132, 133].

Exosomes from neuroinflammatory disease samples are analyzed for protein markers α-syn and tau via mass spectrometry and immunoassay, as well as dysregulated exosomal RNAs such as miR-132 using RT-PCR. MiR-132, miR-125b-5p and miR-132-3p were increased and downregulated in AD brain tissues and EVs, respectively, which delivers neuroprotection in tauopathies (disorders characterized by deposition of abnormal tau protein in the brain) [134–136], is downregulated in plasma-derived exosomes from Alzheimer's patients [137] CSF volume has limitations, and nanoparticles identical to exosomes contaminate samples and are unrecognizable by nanoparticle tracking analysis (NTA) [138, 139]. A study published in the European Journal of Neurology suggests that the proportion of α-synuclein in brain-derived exosomes in the blood can serve as a biomarker for early-stage Parkinson's disease (PD) [140].

Stuendl et al. created a high-sensitivity ELISA utilizing 0.5 mL of CSF to detect exosomal α-syn via electrochemiluminescence [141]. Vandendriessche et al. employed the ExoView R100 platform to discriminate exosomes from other CSF particles in an Alzheimer's animal model, detecting CD9+/CD81+extracellular vesicles and choroid plexus-specific CSF EVs using an anti-transthyretin antibody [142]. ExoView syndicates immunodetection and imaging in a small sample volume, and it shows potential for characterizing CSF-derived exosomes [139].

Therapeutic efficacy of exosome-derived treatments

hWJ-MSC (Human Wharton's jelly mesenchymal stem cells)-derived Exosome inhibited LPS-induced inflammation-related gene expression and pro-inflammatory cytokine production in BV-2 microglia and primary mixed glial cells. They influenced Toll-like receptor 4 signaling in BV-2 microglia, preventing NFκB inhibitor degradation and mitogen-activated protein kinase activation after LPS stimulation. hWJ-MSC-derived exosome delivered intranasal stretch to the brain and concentrated microglia-mediated neuroinflammation in rat pups which caused brain damage, indicating their promise as a treatment for perinatal brain injury [143, 144]. Astrocyte-derived exosomes isolated from cultured astrocytes after exposure to brain extracts, facilitated the transition of microglia from the M1 to M2 phenotype, with miR-148a-3p playing critical role. Exosomes containing miR-873a-5p reduced LPS-induced microglial M1 transition and inflammation by lowering ERK and NF-κB p65 activation, as confirmed in *vitro* and in vivo studies [145]. Similarly, miR-148a-3p controlled the phenotypic shift and suppressed the inflammatory response in microglia. In animal models of TBI, both miRNAs inhibited the nuclear factor κB pathway, improving neurological results and reducing brain injury [146]. In summary, these findings highlight the therapeutic potential of astrocyte-derived exosomal miR-873a-5p and miR-148a-3p in modulating the microglial phenotype and treating traumatic brain injury (TBI). Both miRNAs have been shown to reduce inflammation and improve neurological outcomes by inhibiting key pathways involved in microglial activation and brain injury.

Bone marrow MSCs-derived exosomes (BMSC-Exos) decrease proinflammatory cytokines and enhance anti-inflammatory cytokines while also promoting the polarization of activated BV2 microglia to an anti-inflammatory phenotype. In mice models of traumatic brain injury (TBI), BMSC-Exos reduced cell death in cortical tissue, suppressed neuroinflammation, and induced microglial anti-inflammatory phenotypes. MicroRNA sequencing identified miR-181b as an important role in this process. Overexpression of miR-181b in TBI mice models through lentiviral transfection reduced apoptosis and neuroinflammation while fostering an anti-inflammatory microglial phenotype through the interleukin 10/STAT3 pathway [147]. The hADSC-Exos had similar effects to hADSC treatment in terms of functional recovery, neuroinflammation suppression, neuronal apoptosis reduction, and neurogenesis enhancement. In vivo, imaging revealed the accumulation of DiR-labeled hADSC-Exos in the lesion area, and immunofluorescent staining confirmed microglia/macrophage uptake in brain slices and primary mixed neural cell cultures. In a lipopolysaccharide-induced inflammatory model, hADSC-Exos

suppressed microglia/macrophage activation by regulating P38 MAPK and NF-κB signaling pathways. hADSC-Exo's ability to target and enter microglia/macrophages, decreases their activity, thereby reducing inflammation and enhancing neurological recovery [148].

Neural stem cell- and mesenchymal stem cell-derived exosomes can promote axonal outgrowth and neural repair in PC12 cells, influence inflammatory responses, and cause microglial polarization towards the M2 phenotype. Furthermore, a nanofibrous scaffold loaded with these dual stem cell-derived exosomes (Duo-Exo@NF) enhanced functional recovery in a mouse traumatic brain injury model by lowering microglia and reactive astrocytes and increasing levels of growth-related protein-43 and doublecortin [149] (Fig. 3).

Current limitation and future direction

More study is needed to improve their separation and characterization procedures, as well as to clarify their mechanisms of action, although exosomes have great promise as a novel therapy option for TBI and PCS [150]. Until now, Exosomal miRNA delivery has received minimal attention for its therapeutic potential in neurological illnesses [151, 152]. However, before conducting large-scale clinical research, isolation techniques must be developed and enhanced, along with a complete understanding of the extracellular vesicle biology aspects linked with the neurological system, to improve their sensitivity and specificity in the field of TBI application [153].

Exosome-based therapies in myocardial infarction

Myocardial infarction (MI), one of the major causes of death globally, occurs when the coronary artery is stopped by rupture or erosion of an atherosclerotic plaque, resulting in cell death in the ischemia and hypoxic region [154]. Even though prompt interventions improve MI patients' survival rates, permanent cardiomyocyte loss and unfavorable left ventricular remodeling continue to cause heart failure or sudden cardiac death in many survivors [155, 156]. Therefore, additional effective therapeutic strategies are needed to improve the prognosis of patients with MI.

Exosomal biomarkers

Researchers have discovered particular exosomal proteins and miRNAs linked to particular acute myocardial Infection (AMI) by examining the molecular pathways of MI progression [157]. For instance, patients with AMI had greater plasma levels of miRNA-1, miRNA-133a, miRNA-208a and miRNA-499 than do people without AMI demonstrated to be a more accurate and precise biomarker for AMI than traditional cardiac troponin test (cTn) [158]. Exosomes generated from platelets that carry miRNA-21, miRNA-191, miRNA-223, miRNA-320, and miRNA-339 have been connected to platelet aggregation, which results in the development of atherosclerosis [159]. Cheng et al. created a microfluidic device that detects proangiogenic and cardioprotective miR-21 and miR-126 from serum samples. This system combines exosome isolation and microRNA extraction, with antibody-coated magnetic beads and field effect transistors (FETs) for detection. By targeting PTEN and FoxO1 and activating the AKT/mTOR pathway, miR-486 protects against cardiac I/R injury and myocardial apoptosis and mediates the positive effect of exercise on myocardial protection [160]. The FET sensors are highly sensitive, detecting miRNAs at femtomolar concentrations using a 5-hour procedure. Although still in development, these devices have potential for exosomal investigations and CVD diagnosis [158, 161].

Therapeutic efficacy of exosome-derived treatments

M2 macrophage-derived exosomes (M2-Exos) dramatically improved heart function, increased angiogenesis, and decreased infarct size both in vivo and in vitro. The increased abundance of miR-132-3p in M2-Exos was critical to these effects, as it reduced THBS1 expression by binding to its 3'UTR. M2-exos' proangiogenic and cardioprotective activities were dependent on miR-132-3p regulation. M2-Exos promotes heart healing by delivering miR-132-3p to endothelial cells, offering fresh insights into the mechanics of intercellular communication in post-infarction angiogenesis [162] ADSC-Exos dramatically increased left ventricular ejection fraction while decreasing MI-induced cardiac fibrosis and it reduced cardiomyocyte apoptosis while increasing angiogenesis. ADSC-Exos stimulates microvascular endothelial cell proliferation and migration via miRNA-205, which enhances angiogenesis and decreases cardiomyocyte death. These findings indicate that ADSC-Exos can reduce cardiac injury and improve cardiac function recovery [163].

Induced pluripotent stem cell-derived cardiomyocytes-derived Exosome (iCM-Exos), like cell transplantation, enhances cardiomyocyte survival under hypoxia as well as cardiac function in a mouse myocardial infarction model. They cause transcriptional alterations in the peri-infarct area, namely altering mTOR signaling, and increasing autophagy and autophagic flux. Thus, iCM-Ex might be a viable bioactive alternative to live cell injections for ischemic myocardial healing [164]. Mouse embryonic stem cell-derived exosomes (mES Ex) improved the survival, proliferation, and cardiac differentiation of cardiac progenitor cells (CPCs), resulting in an increase in c-kit+CPCs and the production of new cardiomyocytes in the infarcted heart. Analysis of miRNA content in these exosomes indicated a considerable presence of the miR-290-295 cluster, particularly

miR-294, which was associated with CPC survival, cell cycle progression, and proliferation [165]. BMSC-Exos under hypoxia-reoxygenation (H/R) conditions reduced apoptosis while increasing H9c2 cell proliferation, myocardial damage, and motility. Molecular investigations revealed that apoptotic protease activating factor-1 expression dropped whereas autophagy-related protein 13 expression increased. The use of an autophagy inhibitor reduced the positive effects of exosomes, implying that MSC exosomes prevent myocardial infarction development by controlling autophagy [166].

Hybridization with platelet membranes increases exosome absorption by endothelial cells and cardiomyocytes by macropinocytosis. In vivo investigations showed that hybrid exosomes can target the heart in a mouse myocardial infarction mode, and demonstrated more therapeutic efficacy than non-modified exosomes, offering proof-of-concept evidence for improving exosome binding and accumulation in wounded tissues [167] (Fig. 3).

Current limitation and future direction

However, there are significant limits and hurdles to using exosomes in the setting of myocardial infarction. Despite their numerous benefits, exosomes' biological activities, safety, and therapeutic specificity remain unknown [168]. Furthermore, the variability of exosome populations and the complexity of their cargo, which can comprise proteins, lipids, and nucleic acids, make developing exosome-based therapeutics difficult [169]. Another restriction is the ability to efficiently transfer exosomes to the target tissue because their tiny size and fragile nature might make it difficult to transport and keep at the site of damage [169].

Exosome-based therapies in acute kidney injury

Acute kidney injury (AKI) is caused by numerous factors such as hypoxia, mechanical trauma, surgery, drugs, and inflammation [170]. AKI also lowers the glomerular filtration rate and causes blood creatinine, urea nitrogen, and other metabolites to accumulate, which is indicative of a rapid decline in renal function [171, 172]. The syndrome's corresponding clinical manifestations, which constitute a common clinical emergency [173, 174], are also caused by AKI. In the majority of instances, complete recovery is not attained, despite the renal tissue's inherent capacity to heal following damage [175]. As a result, several treatment modalities for renal regeneration are under consideration.

Exosomal biomarkers

miRNAs have recently shown promise as biomarker candidates in AKI. In intercellular communication, miRNAs have a function in controlling gene expression. Because they bind to certain proteins like Ago2 or are carried by exosomes [176, 177], these molecules can act in organs that are far from their place of origin. This allows for the stable maintenance of miRNAs in bodily fluids. In the field of oncology, miRNAs are already regarded as promising biomarkers for diagnostic and therapeutic targets due to their stability and accessibility [178]. Detection on clinical serum samples showed that blood urea nitrogen (BUN), serum creatinine (SCr), and TLR9 were elevated and miR-342-5p level was suppressed in the serum of patients with S-AKI [179]. According to Saikumar et al., miRNA-21 and −155 may be translational biomarkers for the identification of AKI and may be essential for the pathophysiology of kidney damage and the process of tissue repair [180]. Additionally, miR-29c is known to decrease renal interstitial fibrosis by activating HIF-α and the PI3K-PKB pathway [181, 182], while miR-205 and miR-19 affect renal damage by controlling PTEN (Phosphatase and TENsin homolog deleted on chromosome 10) [183–185].

Therapeutic efficacy of exosome-derived treatments

Mesenchymal stem cells (MSCs) were extracted from a fresh human umbilical cord and characterized using 2D (2D-Exos) and 3D culture. 3D-Exos outperformed 2D-Exos in terms of renoprotective efficacy in treating cisplatin-induced AKI, and they provide an efficient method for the continuous generation of MSC-Exos, which has greater therapeutic potential for cisplatin-induced AKI [186]. Sepsis-induced acute kidney injury (S-AKI) is attenuated by exosomes released by fibroblastic reticular cells (FRCs), among which CD5L is the most prevalent protein. Through the selective binding of kidney tubular cells by modified CD5L-enriched FRC-Exos, NLRP3 (nucleotide-binding oligomerization domain, Leucine-rich Repeat, and Pyrin domain 3) inflammasome activation was inhibited by PINK-Parkin-mediated mitophagy, increasing kidney function and survival. FRC-Exos shows significant promise as a drug delivery vehicle with highly targeted therapeutic potential for S-AKI [187].

Human Amnion Epithelial Cells (hAECs)-derived exosomes showed kidney protective properties that were comparable to those of their parent cells. In vivo, exosomes prevented endothelial cell hyperactivation while in vitro, they preserved the adhesion connection between endothelial cells. The mechanism by which exosomes inhibited the activation of the proinflammatory nuclear factor kappa B (NF-κB) pathway in the kidneys of CLP mice and Primary Human Umbilical Vein Endothelial Cells (HUVECs) treated with LPS [188]. In the S-AKI model, exosomes derived from bone marrow mesenchymal stem cells (BMSCs-Exos) reduce inflammatory responses and apoptosis while also altering proteins linked to autophagy and the autophagic pathway. This

suggests that BMSCs-Exos reduces S-AKI by regulating autophagy through the AMPK(adenosine monophosphate-activated protein kinase) /mTOR (mechanistic target of rapamycin) pathway [189]. During ischemia-reperfusion and hypoxia-reoxygenation injuries in rats, Human urine stem cells-derived exosomes (USC-Exos) can complement circ DENND4C, which is deficient in HK-2 cells (An immortalized proximal tubule epithelial cell line from normal adult human kidney). Through the DENND4C/miR 138-5p/FOXO3a pathway, it promotes cell proliferation and prevents NLRP3 activation to lessen pyroptosis and lower AKI, perhaps offering a new target for the clinical therapy of AKI [190].

Current limitation and future direction

Large-scale production, clinical application safety and efficacy study, and BMSCs-Exo designed to optimize cellular absorption and the biological information they provide are the specifics [189]. For the best therapeutic outcomes, it is still need to create and implement customized protocols about the ideal stimulation parameters. Second, it would be very beneficial for future research to determine the main sources of releasing plasma exosomes with nephroprotective effects generated by mVNS, given the variety of exosome sources in circulation [191].

In this review, we discussed the results of studies about different cell-derived exosomes used for the therapy of inflammatory diseases (Table 1)**.**

Limitation and future prospective

Despite exosomes' potential as a therapeutic alternative, there are substantial obstacles and limitations to their usage, including the need for dependable methods for collecting and characterizing exosomes, as well as a lack of understanding of their biological activity and risk profile. Further study is required to fully explore exosomes' promise as a therapeutic therapy for inflammatory diseases. In quantitative terms, batch-to-batch manufacturing, coupled with detection accuracy, the functional research of the engineered delivery system might be quite complex. Additionally, before clinical trials, the donor of MSCs should be investigated for infectious or genetic diseases. Further studies are needed to explore the exact signaling pathways and exact dosage of exosomes for clinical use.

Size and density are used in a variety of microfluidics devices (filtration, on-chip centrifugation). Antibodies are not required for these devices; yet, their primary challenges are clogging and size overlap. Purchasable exosome specimens might not match the precise exosome kinds that were requested, leading to inaccurate categorization. Understanding the characteristics and functions of exosomes may be hampered by a lack of thorough analytical characterization [192].

Proteomics and live-cell imaging have demonstrated that exosome membrane proteins are essential for information transfer via exosomes. Identifying disease-specific exosome membrane proteins and learning more about their physiological and pathological roles in various conditions has significant implications for future clinical applications, particularly in diagnostics and treatments [193].

However, present exosome-cargo-loading techniques are insufficient to provide the loading efficiency needed for clinical applications. Transfection methods should help to simplify the procedure and lower the cost of mass production. The present physical therapy, such as electroporation, is the most effective way for loading nucleic acids like siRNA or miRNA into exosomes. However, because this process can cause the aggregation and destruction of charged nucleic acids, as well as alter the characteristics of exosomes, novel techniques are required [194]. Poor yields Exosomes are another significant barrier to therapeutic implementation. The majority of preclinical experimental research uses cell culture to obtain exosomes. Exosomal protein production is limited to less than 1 μg per ml of culture, necessitating large-scale cell culture for clinical studies [195, 196].

Exosomes have emerged as an appealing alternative to cell treatment because of their flexibility, which allows scientists to change their composition to produce the desired exosomes containing specific medicines, RNA, or proteins. Recently, DNA-containing exosomes have been shown to increase T cell priming and infiltration, resulting in a tumor-specific immunological response [197, 198]. Advances in nanomaterials technology have worked with the improvement of nanocomposite biomimetic frameworks and nano hydrogel scaffolds that coordinate the positive properties of natural and synthetic materials, possibly opening up another road for future research on bio-scaffold-loaded exosomes, especially when combined with 3D printing technology [199].

Furthermore, chronic disease, drug use, and immunological conditions can all influence a patient's reaction to exosome therapy. These characteristics may influence cell sensitivity or resistance to treatment. Patients may develop an immunological reaction to treatment, which causes exosomes to be eliminated or lose function. More research is needed to determine how these characteristics influence the efficacy of exosome therapy [200]. Hence, while exosomes are regarded as a promising platform for targeted cargo delivery, major efforts are critically required to move exosome-based cargo delivery from scientific theory to practical application.

Tetraspanin proteins are not ubiquitously and uniformly present on the exosomal surface [201].

Table 1 Therapeutic effects of exosome-derived from different cells in attenuation of inflammatory diseases

Diseases	Exosome sources for therapeutic effect	Model	Target	References
Inflammatory bowel disease	Murine Colon Cancer cell CT26-Exos	In vivo Mouse Model	Pro-inflammatory cytokine secretion by colonic DCs and selective suppression of Th17 cell	[95]
	Human ADSC-Exos	In vivo C57BL/6 (6–8 weeks) mice; In vitro Cell line Hcoepic, MSCs, and Human adipose tissues;	Increased the growth and empower colon organoids	[96]
	hucMSCs-Exos	In vitro human umbilical cord MSCs, In vivo Male KM mice (6-week)	Inhibit the expression of IL-7 in macrophages and reduce inflammatory responses	[97]
	Bovine colostrum-derived Exosomes	In vivo Murine Model	Alleviate colitis Symptoms by modulating intestinal inflammatory immune responses.	[98]
	Macrophage-derived exosomes	In vivo C57BL/6 mice aged 7 weeks	Colitis induced by inducing intestinal barrier Dysfunction through the inhibition of *TMIGD1*.	[99]
Liver Injury and Fibrosis	hucMSCs-Exos	In vivo C57BL/6 J mice (6–8 weeks)	Induce proinflammatory macrophages into an anti-inflammatory phenotype	[114]
	ADSC-Exos	In vivo C57/BL6 mice; In vitro Immortalized human hepatic stellate cell line LX-2 & Mouse hepatocyte cell line AML12	Suppress HSCs activation and modify hepatocellular glutamine synthetase-mediated glutamine and ammonia metabolism.	[115]
	TNF-α pretreatment of hucMSCs-Exos	In vivo C57BL/6 male mice (6 week); In vitro RAW264.7 mouse celiac monocytes	Inhibiting the activation of the NLRP3-related inflammatory pathway and increasing the expression of microRNA 299 3p in T-Exo.	[116]
	Human BMSCs-Exos	In vivo Sprague Dawley (SD) rats (8-week old)	Improve CCl4-induced liver fibrosis by inhibiting Wnt/β-catenin signaling, preventing HSC activation.	[117]
	Exosomes derived from natural killer cells	In vivo BALB/c mice (6–8 weeks); In vitro LX-2 cells (human HSC line)	Inhibited TGF-β1-induced HSC proliferation and alleviated CCl4-induced liver fibrosis	[118]
Lung Inflammation and Injury	Alveolar Epithelial Cells-derived Exosome	In vivo SD rats (4–5 weeks old); In vitro alveolar epithelial cell line RLE-6TN	Activate AMs, which cause pulmonary inflammation and constitute a potential diagnostic biomarker for ALI.	[122]
	Alveolar macrophage-derived exosomes	In vivo (SPF) Balb/c mice (10 weeks); In vitro rat alveolar macrophage cell line NR8383	BALF-exosomes as a modulator of the inflammatory response and cell communication during ALI	[123]
	BMSCs-Exos	In vivo SD rats (4–6 weeks old)	Effects on phosgene-induced ALI by regulating inflammation, decreasing MMP-9 production, and increasing SP-C levels.	[124]
	BMSCs-Exos	In vivo Adult male C57BL/6 mice; In vitro murine alveolar macrophage cell line MH-S	Inhibited endotoxin-induced glycolysis and alleviated LPS-induced inflammation and lung pathological damage.	[125]
	ADSC-Exos	In vivo C57BL/6 mice aged 6–8 weeks and IL27r−/−C57BL/6 mice	Inhibited IL-27 production in macrophages alleviated sepsis-induced ALI	[126]
Neuroinflammation and Traumatic Brain Injury	hucMSCs-Exos	In vivo Wistar rat pups(2 days old); In vitro human Wharton's jelly-derived mesenchymal stem cells	Suppressing pro-inflammatory cytokine transcription and production, as well as reducing microglial accumulation.	[143]
	Astrocyte-derived exosomes	In vivo mice (C57BL/10ScNJ (10–12 weeks); In vitro damaged brain tissue	Reduces neuroinflammation by inhibiting the NF-κB signaling pathway and microglia-mediated inflammation.	[145, 146]
	BMSCs-Exos	In vivo C57BL/6J male mice (6–8 week); In vitro BV2 cells (RRID: CVCL_0182)	Polarization of microglia to the anti-inflammatory phenotype, inhibiting neuroinflammatory response	[147]
	hADSC- Exos	In vivo Sprague-Dawley rats (6–8 weeks); In vitro Mixed neural cell culture	Improving the injury microenvironment, reducing exacerbated neuronal injury, and preventing proinflammatory activation.	[148]
	Dual mesenchymal stem cells and neural stem cells derived exosome	In vivo Murine Model	Modulate microglial polarization toward the M2 phenotype, enhance axonal outgrowth, and neural repair in PC12 cells.	[149]

Table 1 (continued)

Diseases	Exosome sources for therapeutic effect	Model	Target	References
Myocardial infarction	M2 macrophage-derived exosome	In vivo C57BL/6 male mice (8–10 weeks*);* In vitro Human endothelial cells	Enhanced the angiogenic ability of Ecs, promoting angiogenesis after myocardial infarction	[162]
	Embryonic Stem Cell-Derived exosomes	In vivo male C57BL/6, 8–12 weeks old; In vitro MEFs, H9c2 myoblasts, and human umbilical vein endothelial cells	Has cardiac regeneration capabilities and affects both cardiomyocytes and CPC-based repair mechanisms in the heart.	[165]
	ADSC-Exos	In vivo male C57BL/6 wild-type mice; In vitro human microvascular endothelial cells (HMEC-1)	Alleviate cardiac injury and promote cardiac function recovery	[163]
	BMSCs-Exos	In vivo male Sprague Dawley rats (3 weeks); In vitro cardiac H9c2 cells	Inhibitory effects on myocardiocyte apoptosis associated with MI,	[166]
	Induced cardiomyocytes-derived exosome	In vivo Female beige mice (10–14 weeks*); In vitro* included induced pluripotent stem cell-derived cardiomyocytes (is	Regulating autophagy in hypoxic cardiomyocytes, enabling a cell-free, patient-specific therapy.	[164]
Acute Kidney Injury	hucMSCs-Exos	In vivo Adult male; *In vitro Mouse tubular epithelial cells*	The cell viability of cisplatin-injured TECs was significantly improved by treatment with 3D-Exos	[186]
	FRCs -derived Exosome	In Vivo 25–30-gram C57/BL6 mice	CD5L-enriched FRC-Exos, inhibits NLRP3 inflammasome by PINK-Parkin-mediated mitophagy, increasing kidney function and survival rate.	[187]
	hAECs-derived Exosomes	In vivo (8–12 weeks)Male C57BL6/J mice In vitro Human umbilical vein endothelial cells	Exosomes prevented sepsis-induced NF-κB pathway activation and endothelial hyperactivation, preserved the endothelial cell adhesion junction, and inhibited LPS-induced	[188]
	BMSCs-Exos	In vivo Adult male Sprague-Dawley *rat*; In vitro human renal tubular epithelial cell line HK-2	BMSCs-Exos mitigate inflammation and apoptosis through autophagy in S-AKI.	[189]
	USC-Exos	In vivo Adult Sprague Dawley rats; In vitro HK-2 H/R model	Exosomes reduce pyroptosis and AKI by promoting cell proliferation and blocking the activation of the NLR family pyrin domain containing 3 via the circ DENND4C/miR 138-5p/FOXO3a pathway.	[190]

Note: (ADSC-Exos) adipose-derived stem cells derived exosomes, (hucMSCs-Exos) human umbilical cord mesenchymal stem cells derived exosomes, (BMSCs-Exos) Bone marrow mesenchymal stem cells derived exosomes, (USC-Exos) Human urine stem cells-derived exosomes, (FRCs) fibroblastic reticular cells

Customized Simoa assays (use antibodies against particular exosomal transmembrane markers) were used to capture all subpopulations of vesicles detected in each sample. To address this issue, membrane-sensing peptides [202] that recognize common properties of all tiny EVs membranes have been created and are being used in Simoa technology. This innovative technique could be fine-tuned for exosomal use, allowing extraction and analysis straight from any biofluid, without a pre-isolation process. Additionally, peptides are versatile; they can be used on a variety of platforms. Taken together, these advancements provide a promising outlook for the future of exosome research and therapeutic use [203].

Conclusion

To summarize, exosomes have demonstrated significant potential as a novel therapy option for wide-ranging inflammatory diseases, including inflammatory bowel disease, liver injury and fibrosis, lung injury and inflammation, neuroinflammation and traumatic brain injury, and myocardial infarction. Their distinctive characteristics, including excellent biocompatibility, low immunogenicity and toxicity, and capacity to overcome cellular barriers, make them ideal candidates for drug delivery. Exosomes can be changed and manufactured to have varied biological functions and targeting capabilities, and have been demonstrated to successfully transport proteins, nucleic acids, tiny chemicals, and nanoparticles into inflammatory microenvironments. Furthermore, exosomes generated by inflammatory cells and MSCs have been shown to have a high inflammatory affinity and targeting, making them effective for delivering cargo to inflammatory cells and influencing immune responses.

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Author contributions
M.S, K.A.S, and M.M: Conception and design. M.S, S.S, and Q.Z: data collection and writing. M.S, S.D, K.A.S, and S.W administrative support, figures drawing. S.W and I.I.S financial support and final approval of the article.

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Data availability
Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

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