Nano Research
2023, 16(5): 6991–7006

ISSN 1998-0124 CN 11-5974/O4
https://doi.org/10.1007/s12274-022-5275-5

Review Article

Native and engineered exosomes for inflammatory disease

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Received: 15 September 2022 / **Revised:** 28 October 2022 / **Accepted:** 31 October 2022

ABSTRACT

Exosomes are extracellular vesicles which carry specific molecular information from donor cells and act as an intercellular communication vehicle, which have emerged as a novel cell-free strategy for the treatment of many diseases including inflammatory disease. Recently, rising studies have developed exosome-based strategies for novel inflammation therapy due to their biocompatibility and bioactivity. Researchers not only use native exosomes as therapeutic agents for inflammation, but also strive to make up for the natural defects of exosomes through engineering methods to improve and update the property of exosomes for enhanced therapeutic effects. The engineered exosomes can improve cargo-loading efficiency, targeting ability, stability, etc., to achieve combined and diverse treatment strategies in inflammation diseases. Herein, a comprehensive overview of the recent advances in application studies of native and engineered exosomes as well as the engineered methods is provided. Meanwhile, potential application prospects, possible challenges, and the development of clinical researches of exosome treatment strategy are concluded from plentiful examples, which may be able to provide guidance and suggestions for the future research and application of exosomes.

KEYWORDS

inflammation, exosome, engineered exosome, exosomes-based therapy

1 Introduction

An appropriate inflammatory response of the immune system provides a basic defense that protects human body from the attack of foreign antigens [1]. However, the overactivated inflammation can lead to various diseases such as tissue damage or autoimmune diseases [2], which can cause plenty of pathological organ damage and even be life-threatening (Fig. 1). And numerous chronic inflammatory diseases, such as chronic obstructive pulmonary disease (COPD) [3] and inflammatory bowel disease (IBD) [4], can be long-term and repeated due to the complex pathogenic factors and the lack of safe and effective clinical treatment strategies [5]. The current clinical treatment strategies including antibiotics, antivirals, glucocorticoids, and non-steroidal anti-inflammatory drugs (NSAIDs), still have side effects and bad medication adherence. For example, NSAIDs which inhibit prostaglandin production, are widely used, but they may cause gastrointestinal toxicity to patients and are always rapidly metabolized *in vivo* [6, 7]. Additionally, small molecule drugs and microRNAs have appeared as novel treatment strategies, but are difficult to achieve targeted and precise treatment and therefore have toxicity issues [8]. Moreover, antibiotics or antivirals can achieve targeting therapy, yet they only target extracellular antigens with single effect [9]. Researches of mesenchymal stem cells (MSCs) treatment are in progress due to their immunomodulatory functions, but also face challenges such as low cell viability and the immunogenicity of the cell itself [10]. Chimeric antigen receptor T cell (CAR-T) therapy is also used in the field of autoimmune diseases, but high price limits its clinical application. Hence, new treatment strategies for inflammation need to be developed to achieve low adverse reactions, high efficiency, sustained release, and targeted treatment.

Exosomes are membranous vesicles released by cells with a particle size of less than 200 nm, which can carry bioactive molecules (e.g., proteins, lipids, nucleic acids, and sugars) to transmit signals between cells [11]. Exosomes can regulate normal physiological functions and also produce positive or negative regulations during disease development [12]. Different from traditional drugs, exosomes have great biocompatibility, low cytotoxicity, and non-immunogenicity, and the membrane proteins have rich biological functions including recognition and immune escape, so they can achieve systemic microenvironmental regulation instead of one-factor treatment. Unlike cells, exosomes have no replicative or multidirectional differentiation potential, so they do not have the potential risk of tumor formation and thus have higher biosafety [13].

Exosomes from certain cell types inherit the surface proteins and contents of donor cells [14], which exhibit therapeutic properties, such as MSCs derived exosomes [15] and immune cells-derived exosomes [16]. Some researchers illustrated that the pro-inflammatory cytokines receptors in exosomes may act as a decoy for targeting inflammation therapy [17], others demonstrated that the secretion of exosomes will be increased during cellular inflammatory responses [18], which proved that exosomes can be used as therapeutic agents and the exosomal substances could also be used as markers for screening in inflammatory disease treatment [19]. In general (Fig. 2), exosomes as therapeutic agents can offer inflammation therapeutic effects including (1) increasing

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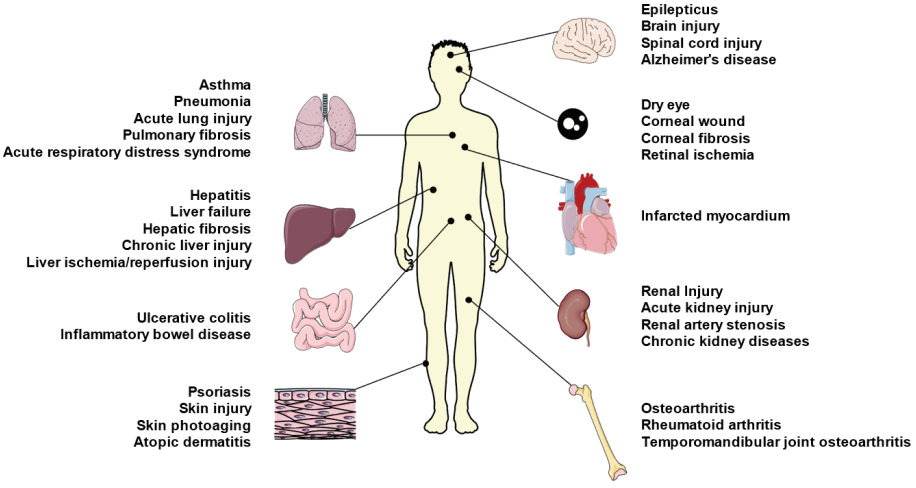


Figure 1 Inflammatory diseases of different organs.

the anti-inflammation cytokines such as interleukin (IL)-10 and transforming growth factor (TGF)-β; (2) decreasing the pro-inflammation cytokines such as IL-1β and interferon (IFN)-γ; (3) alleviating oxidative stress and reducing NO level; (4) alleviating excessive infiltration of immune cells and promoting polarization of M1 macrophages into M2, as well as proliferation and immune-suppression capacity of regulatory T cells (Tregs); (5) stimulating collagen regeneration, inhibiting fibrosis, and avoiding scarring; (6) regulating inflammatory associated signal pathways. Furthermore, as a cell-free therapy, exosomes can avoid the inflammatory response caused by unnecessary immunogenicity and are safer than traditional cell therapy [20].

What's more, except for the intrinsic anti-inflammation properties, exosomes could also be engineered by physical, chemical, or genetic methods for intensified therapeutic effects. For physical engineering or materials-engineering, anti-inflammatory drugs (including small therapeutic molecules, peptides, and proteins or artificial nanoparticles) are loaded with exosomes. Consequently, exosomes are also used as a vehicle for therapeutic cargo delivery. Exosomes, with diameters ranging from 30 to 200 nm and the capacity of plasma membrane fusion, exhibit great penetration ability and can even pass the blood–brain barrier (BBB), which does a favor for the delivery of drugs into deep tissues [21, 22]. Besides, the increased circulating half-life of exosomes enables prolonged travel distance within the body, which solves the problem of rapid metabolism and short effects of small molecule therapeutic drugs [23]. Moreover, exosomes packed with innate molecules can mediate targeted delivery for precise treatment. Additionally, exosomes with excellent biostability protect the contents from being phagocytosed by macrophages [24]. Overall, the above properties prove the potential of exosomes as a therapeutic agent and even a bioactive vehicle for drug delivery and thus-formed treatment strategy for inflammation (Scheme 1).

In this review, we will summarize the recent advances of the native and engineered exosomes as therapeutic agents in inflammation therapy (Table 1), and discuss the advantages and challenges of engineered exosomes, which will contribute to a better understanding of the current progress and future research directions in this field.

2 Native exosomes as therapeutic agents in inflammatory disease

2.1 Mesenchymal stem cells derived exosomes in inflammatory therapy

Mesenchymal stem/stromal cells are multipotent stem cells that have the ability to trilineage mesenchymal differentiation [25]. MSCs can not only self-renew, differentiate, and promote tissue repair, but also have immunomodulatory properties [26–28]. MSCs derived exosomes are enriched in various proteins and

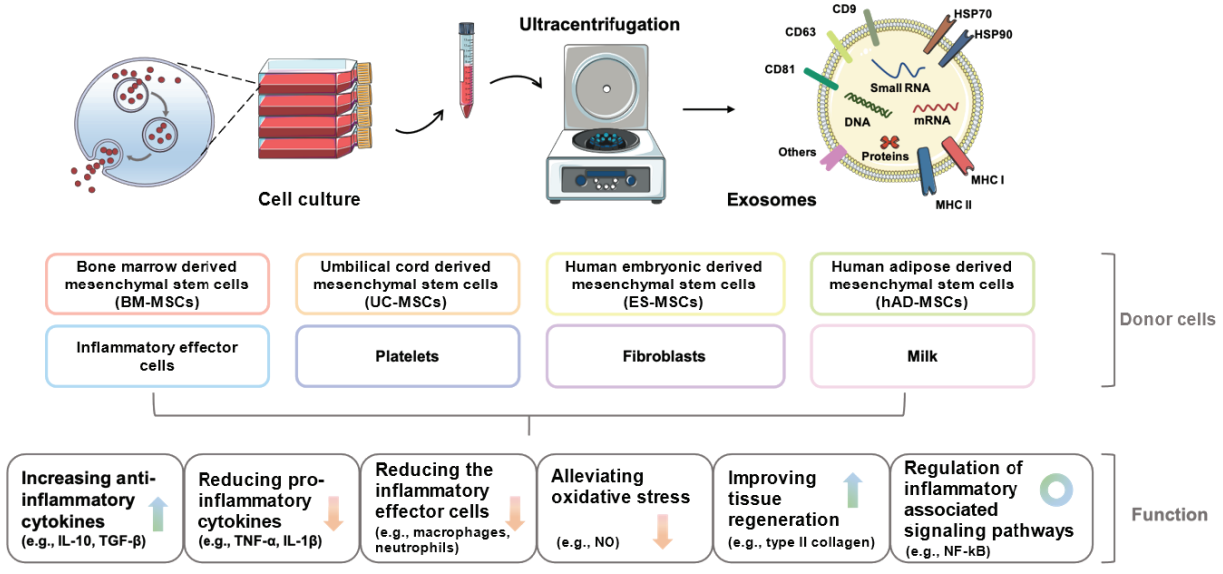
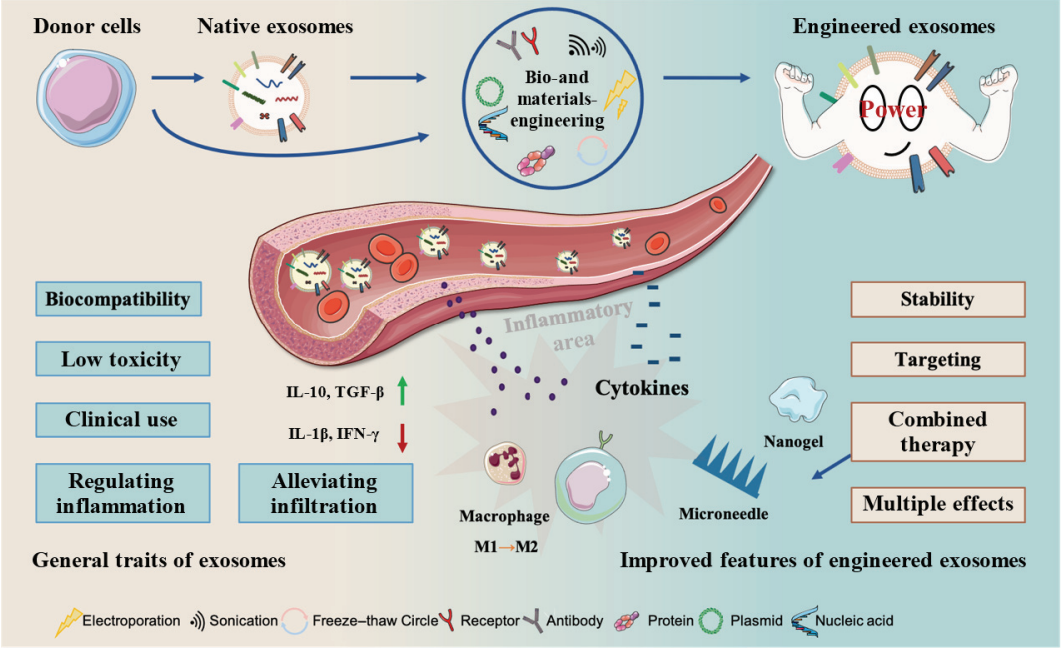


Figure 2 Different types of exosomes and their function in inflammatory diseases.



Scheme 1 Native and engineered exosomes as advanced nanomaterials for inflammation therapy. Bio- and materials-engineering techniques have been used to manipulate donor cells or their derived exosomes to generate engineered exosomes that deliver a variety of therapeutic molecules, drugs, and nanomaterials. Engineered exosomes have superior characteristics to their native counterparts, including high stability, targeting ability, efficient intracellular delivery, and combined therapy abilities, which remarkably improve the specificity, efficacy, and safety of exosome-based inflammation therapeutics.

factors by paracrine [29, 30]. Therefore, MSCs derived exosomes can participate in metabolism, microenvironment immunomodulation, and angiogenesis, thus being a new strategy in inflammatory diseases. Among multiple types of exosomes donor MSCs, bone marrow-derived mesenchymal stem cells (BM-MSCs), embryonic-derived mesenchymal stem cells (ES-MSCs), umbilical cord-derived mesenchymal stem cells (UC-MSCs), and adipose-derived mesenchymal stem cells (AD-MSCs) were highly applied.

2.1.1 *BM-MSCs*

As the first discovered MSCs, BM-MSCs have immunomodulatory function, may support angiogenesis [31], and are considered the main source of MSCs for clinical application [32]. The research of Lucienne A. Vonk et al. showed that BM-MSCs derived exosomes could be applicated in cartilage regeneration and osteoarthritis (OA) therapy, as they abrogated the tumor necrosis factor-α (TNF-α)-mediated upregulation of cyclooxygenase-2 (COX2) and pro-inflammatory interleukins, inhibited TNF-α induced collagenase activity, and stimulated the production of proteoglycans and type II collagen [33, 34, 35]. In addition, BM-MSCs derived exosomes may be promising candidates for IBD treatment as demonstrated by the increase in IL-10 and TGF-β levels and the decline in vascular endothelial growth factor (VEGF)-A, IFN-γ, IL-12, TNF-α, C–C motif chemokine ligand (CCL)-24, and CCL-17 levels, able to maintain intestinal barrier integrity, and polarize M2 macrophages but fight against intestinal fibrosis simultaneously [36, 37]. Similarly, BM-MSCs derived exosomes were found to promote cutaneous wound healing and contribute to heart injury repair [38, 39, 40]. Other researches demonstrated that BM-MSCs derived exosomes serve a neuroprotective function by inhibiting early neuroinflammation such as inhibiting the expression of proapoptotic protein Bcl-2-associated X protein (BAX) and proinflammation cytokines TNF-α and IL-1β, while enhancing the expression of the anti-apoptosis protein B-cell lymphoma 2 (BCL-2), which can be applied in several kinds of brain diseases [41–43]. The anti-inflammation cytokine IL-10 in BM-MSCs derived exosomes can mitigate liver inflammation and injury by regulating Kupffer cells and other signal pathways [44, 45, 46].

2.1.2 *ES-MSCs*

COVID-19 pneumonia threatened the whole world since 2019. Angiotensin-converting enzyme 2 (ACE2) receptor is a key component of the virus being able to enter host cells and replicate [47]. The use of MSCs has been suggested as a major anti-inflammation strategy, however, the transfused MSCs must be prevented from being a new target for the virus entry into patients [48]. ES-MSCs are pluripotent cells derived from the inner cell mass of the blastocyst, having been proved to express low levels of ACE2 receptors, thus were safe and effective for treatment in patients with COVID-19 pneumonia in clinical outcomes [49–51]. Similarly, ES-MSCs derived exosomes could offer a new therapeutic approach to treating COVID-19 pneumonia, due to their broad pharmacological characteristics including anti-inflammation, immunomodulation, regeneration, and so on [52]. More importantly, compared to BM-MSCs and AD-MSCs, ES-MSCs derived exosomes can significantly suppress the proliferation of peripheral blood mononuclear cells, increase the secretion of IL-10, TGF-β, and downregulate pro-inflammatory cytokines such as TNF-α, which may be suggested for therapy applications for liver injury, kidney injury, and even OA [53, 54–56].

2.1.3 *UC-MSCs*

Low immunogenic UC-MSCs can secret multiple effective molecules regulating apoptosis, fibrosis, and neovascularization [57]. Tian Wang et al. demonstrated that UC-MSCs derived exosomes can reduce reactive oxygen species and DNA damage, and alleviate cellular and histological responses of inflammation and oxidation to improve antioxidant capacities in cells, which were applied to repair oxidative stress-induced skin injury [58]. In addition, for the amelioration of the inflammatory reaction in the brain such as perinatal brain injury, Alzheimer's Disease, and epilepsy, UC-MSCs derived exosomes can reduce the secretion of pro-inflammatory cytokines, and weaken the abnormal astrocytic

Table 1 Exosomes for inflammation therapy in different organs

Organs	Inflammation model	Source	Exosomes type	Outcomes	Ref.
Brain	Epilepticus	UC-MSCs	Native exosomes	Ameliorated inflammation-induced astrocyte alterations	[59]
	Alzheimer's disease	BM-MSCs	Native exosomes	Prevented cognitive and memory impairments	[60]
		UC-MSCs	Native exosomes	Modulated the activation of microglia in brains to alleviate neuroinflammation	[61]
		BM-MSCs	Native exosomes	Induced immunomodulatory and neuroprotective effects	[41]
	Brain injury	BM-MSCs	Native exosomes	Inhibited early neuro inflammation through modulating the polarization of microglia/macrophages	[42, 43]
	Spinal cord injury	hUC-MSCs	Native exosomes	Attenuated the inflammation of the injury region through down-regulation of the inflammatory cytokines	[62]
		BM-MSCs	Native exosomes	Promoted functional behavioral recovery	[63]
		AD-MSCs	Native exosomes	Improved neurological functional recovery, inhibited of NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome activation	[64]
		Neuron	Native exosomes	Promoted functional behavioral recovery	[65, 66]
		hMSCs	Exosomes in hydrogel	Mitigated inflammation and oxidation	[67]
	Parkinson's disease	Macrophage	Loaded catalase	Provided significant neuroprotective effects	[68]
Eye	Retinal ischemia	BM-MSCs	Native exosomes	Enhanced functional recovery and decreased neuroinflammation and apoptosis	[69]
	Corneal wound	ES-MSCs	Native exosomes	Enhancing proliferation, anti-inflammation, and suppressed apoptosis of corneal epithelial cells	[70]
	Dry eye	AD-MSCs	Native exosomes	Decreased corneal epithelial defects, decreased goblet cell loss, and reduced inflammatory cytokines production	[71]
	Corneal fibrosis	iPSC-MSCs	Exosomes in hydrogel	Promoted the repair of damaged corneal epithelium and reduced scar formation	[72]
Lung	Asthma	BM-MSCs	Native exosomes	Promoted proliferation and immune-suppression capacity of Tregs	[73]
	Lung injury	Neutrophil	Native exosomes	Targeting suppressor of cytokine signaling and induced M1 macrophage polarization	[74]
		BM-MSCs	Loaded microRNA (overexpression of miR-30b-3p)	Decrease the expression of serum amyloid A3 (SAA3) in recipient alveolar epithelial cells (AECs) and promote proliferation while inhibiting the apoptosis of AECs	[75]
	Pulmonary fibrosis	Lung Spheroid Cells	Native exosomes	Reestablished normal alveolar structure, decreased collagen accumulation, and myofibroblast proliferation	[76]
	Pneumonia	iPSC-MSCs	Native exosomes	Reduced infiltration of inflammatory cells and number of epithelial goblet cells	[77]
	COVID-19 pneumonia	H293T	Loaded polydopamines	Re-directed viral attack via S protein binding and control of the excessive immune response	[78]
Heart	Infarcted myocardium	BM-MSCs	Native exosomes	Stimulated neovascularization, restrained the inflammation response, and improved heart function	[38, 39]
Liver	Hepatic fibrosis	Liver stem cells	Native exosomes	Improved liver function and reduced signs of liver fibrosis and inflammation	[79, 80]
	Hepatitis	Macrophage	Native exosomes	Suppressed inflammatory cytokine production	[81]
	Liver failure	BM-MSCs	Native exosomes	Reduction of leukocytic infiltrates hepatocellular death and bile duct duplication	[44]
	Chronic liver injury	ES-MSCs	Native exosomes	Increased the secretion of anti-inflammatory cytokines, ameliorated cirrhosis	[53]
	Liver ischemia/reperfusion injury	UC-MSCs	Native exosomes	Downregulated CD154 expression on the intrahepatic $CD4^+$ T cells, reduced the infiltration of neutrophils, and alleviated oxidative stress	[82, 83]
Bowel	Inflammatory bowel disease	BM-MSCs	Native exosomes	Downregulated inflammatory responses, maintained intestinal barrier integrity	[36, 37]
Bone	Osteoarthritis	BM-MSCs	Native exosomes	Promote cartilage repair and extracellular matrix synthesis, as well as alleviate knee pain	[33, 34]
		AD-MSCs	Native exosomes	Promoted the proliferation and migration of osteoarthritis chondrocytes	[84, 85]
		AD-MSCs	Loaded curcumin	Alleviated oxidative stress and chondrocyte apoptosis	[86]
		$CD90^+$ MSCs	Loaded triamcinolone	Induced cartilage to restart the cell cycle and reduced cartilage apoptosis	[87]
	Achilles tendinopathy	Macrophage	Exosomes in microneedle	Suppressed of inflammation and the proliferation of tendon cells	[88]
Skin	Skin injury	UC-MSCs	Exosomes in hydrogel	Promoted wound healing, angiogenesis, and reduced inflammation cytokines	[89]
	Diabetic wound	HUVECs	Exosomes in microneedle	Accelerated collagen deposition, epithelial regeneration, and angiogenesis	[90]
	Atopic dermatitis	hAD-MSCs	Native exosomes	Reduced trans-epidermal water loss and decreased the levels of inflammatory cytokines	[91, 92]
	Psoriasis	ES-MSCs	Native exosomes	Inhibited complement activation and alleviated IL-17 release	[93]
	Skin photoaging	Fibroblast	Native exosomes	Increased dermal collagen deposition and have the potential to prevent and treat cutaneous aging	[94]

activation to alleviate neuroinflammation, meanwhile ameliorating LPS-induced aberrant calcium signaling and mitochondrial

dysfunction in culture [59, 61, 62, 95]. Intriguingly, UC-MSCs derived exosomes can modulate CD154 expression of intrahepatic $CD4^+$ T cells, reduce the infiltration of neutrophils, and alleviate the oxidative stress in hepatic tissue to protect the liver against ischemia/reperfusion injury [82, 83, 96]. Similarly, in another study by Wael Nassar et al., they proved that UC-MSCs derived exosomes can ameliorate the inflammatory immune reaction and improve the overall kidney function by down-regulating pro-inflammatory cytokines such as TNF-α and up-regulating anti-inflammatory cytokines such as TGF-β1 and IL-10 [97]. Moreover, miR-326 in UC-MSCs derived exosomes may inhibit neddylation and regulate macrophages thus relieving dextran sulfate sodium (DSS) induced IBD [98, 99].

2.1.4 AD-MSCs

With easier and safer isolating methods, larger amounts AD-MSCs are recognized to have the greatest clinical application value [100]. AD-MSCs derived exosomes share the same ability to inhibit the proliferation of allogeneic and activated immune cells [101]. For example, in OA disease, AD-MSCs derived exosomes can not only promote the proliferation and migration of chondrocytes, increasing type II collagen synthesis to protect cartilage from degeneration, but also can inhibit the infiltration of M1 macrophages [84, 85]. Current treatment options for atopic dermatitis (AD) are limited, therefore, convenient strategies need to be developed [102]. AD-MSCs derived exosomes were found to reduce pathological symptoms such as clinical score, the levels of serum IgE, the number of eosinophils in blood, and the infiltration of mast cells, $CD86^+$, and $CD206^+$ cells in skin lesions. AD-MSCs derived exosomes also significantly reduced mRNA expression of various inflammatory cytokines such as IL-4, IL-23, IL-31, and TNF-α, meanwhile reducing trans-epidermal water loss and enhancing stratum corneum hydration to restore epidermal barrier functions [91, 92]. In addition, miR-93-5p in AD-MSCs derived exosomes can prevent cardiac injury by inhibiting autophagy and the inflammatory responses [103]. Moreover, as a novel noncellular alternative therapy, AD-MSCs derived exosomes-based regenerative strategies might be useful for renal artery stenosis and liver failure through signaling regulation [104, 105].

In summary, exosomes of different origins MSCs carry slightly different contents and therefore may have different applications, such as BM-MSCs derived exosomes are mostly used for orthopedic disease, and UC-MSCs derived exosomes are more commonly used in fibrosis and vascular diseases. However, the therapeutic functions or different characteristics of the exosomes harvested from different types MSCs are still unknown. But what is certain is that MSCs derived exosomes will become one of the key points of stem cell research.

2.2 Immune cells derived exosomes in inflammatory therapy

Exosomes can also be secreted via immune cells, such as dendritic cells (DCs) [106], mast cells (MCs) [107], macrophages [108, 109], B lymphocytes [110], and T lymphocytes [111, 112]. Immune cells derived exosomes could directly alter peripheral immune function as they carry cargoes that either promote a regulatory response or reduce inflammatory cytokines [113]. The heterogeneity of cargoes in immune cells-derived exosomes endows them with distinctive roles in immunity, serving as either immune activation or suppression mediators dependent on the donor cell. Dependent on the subtypes of immune cells, exosomes from same immune cells with different subtypes may display similar or opposite functions, in line with the biological effects of the parent cell. For example, exosomes derived from $CD4^+$ T cells and $CD8^+$ T cells share the same ability to cause the apoptosis of DCs, while exosomes secreted by regulatory T cells inhibit Th1 immune response and mediate immune suppression [114]. It has been reported that exosomes isolated from macrophages are capable of regulating concanavalin A-induced hepatitis by suppressing macrophage cytokine production [81]. Another study demonstrated that exosomal miR-30d-5p of neutrophils could promote lung inflammation by enhancing M1 macrophages polarization and priming macrophages proptosis [74]. Recent studies have also revealed that mast cell-derived exosomes mediated transfer of functional miRNAs from human mast cells-1 (HMCs-1) to intestinal epithelial cells contributes to inhibition of tight junction-related proteins expression, therefore disrupting intestinal barrier function and promoting the development of IBD [115]. Other than a disease treatment tool, exosomes are novel biomarkers in disease diagnosis. For instance, patients with chronic hepatitis C showed a higher level of circulating exosomes from $CD4^+$ and $CD8^+$ T cells, and patients with nonalcoholic fatty liver or nonalcoholic steatohepatitis also showed a higher level of circulating exosomes from iNKT cells and $CD14^+$ macrophages/monocytes. The number of immune cell exosomes in the sera indicates how severe the disease is, making it a feasible diagnostic approach for determining the degree of liver inflammatory conditions [116, 117]. Additionally, immature or suppressive DC derived exosomes contain anti-inflammatory properties, distinguishing themselves from mature DC derived exosomes, and can reduce T cell-dependent immune-activation in murine models of autoimmune diseases and transplantation [118, 119]. Notably, exosomes derived from DC could improve cardiac function via activation of $CD4^+$ T lymphocytes after myocardial infarction [120]. Meanwhile, exosomes from Tregs are widely recognized and prospectively applicable in organ transplantation due to their immunosuppression effects to inhibit the immune inflammation in the allografts [111, 121–123].

2.3 Tissue cells derived exosomes in inflammatory therapy

Exosomes inherit the biological properties of parental cells and act as messengers for intercellular signaling. Tumor derived exosomes that have tumor-associated antigens, may serve as a vaccine to stimulate the host immune system for tumor immunotherapy [124]. Normal tissue derived exosomes may be applied in tissue injury repair. Overexpression of collagen-degrading matrix-degrading metalloproteinases (MMPs) results in an excessive extracellular matrix (ECM) degradation that can lead to a variety of skin pathologies [125]. In the research of Shiqi Hu et, al., a needle-free injector was used to administer exosome treatments. Three-dimensional (3D) human dermal fibroblasts (HDFs) derived exosomes caused increased procollagen type I expression and a significant decrease in MMP-1 expression, mainly through the downregulation of TNF-α and the upregulation of TGF-β, manifesting their properties to prevent and repair skin aging (Fig. 3) [94, 126]. These cell-free and needle-free strategies may be beneficial for medical cosmetology.

In addition, human or mouse hepatocyte-derived exosomes downregulated fibrosis-associated genes expression and displayed anti-fibrotic and anti-inflammatory effects in chronic liver disease, repairing liver functions [79, 80]. Platelets play an important role in the healing of skin wounds, and the study of Ao Shi showed that platelets derived exosomes enriched with TGF-β promoted epithelial and vascular cell activity, enhancing angiogenesis to restore blood flow and mature skin function [127]. Moreover, the inflammatory response which protects against pathogens is essential in spinal cord injury (SCI) development [128]. Neuron-derived exosomes promoted functional behavioral recovery in SCI by suppressing the activation of M1 microglia and A1 astrocytes,

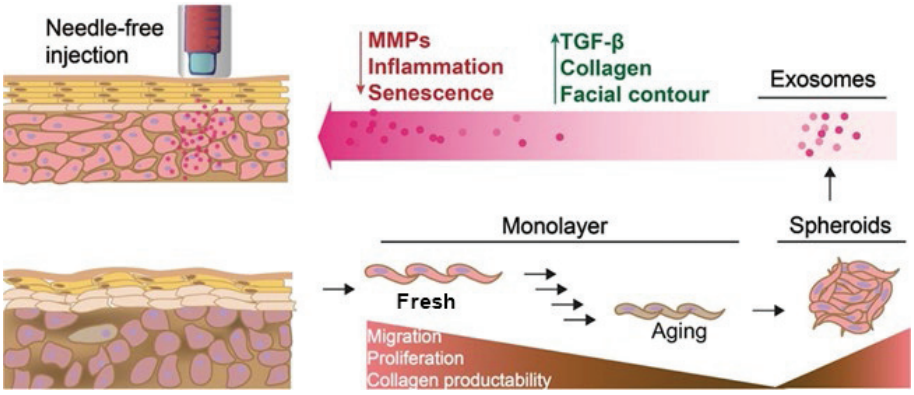


Figure 3 Schematic illustration of the needle-free injection and the anti-skin-aging properties of human dermal fibroblasts derived exosomes. Factors and exosomes derived from 3D spheroids (3D HDF-XOs) and the monolayer culture of HDFs (2D HDF-XOs) were collected and compared. Reproduced with permission from Ref. [94], © American Chemical Society 2019.

with the miR-124-3p playing a critical role in regulating associated pathways [65, 66].

2.4 Special exosomes in inflammatory therapy

2.4.1 Milk derived exosomes

Apart from the above-mentioned cells derived exosomes, multiple special exosomes are applied in inflammatory diseases. For example, milk-derived exosomes (MEs) as mixed exosomes may originate from different cell populations in the mammary, such as the gland-mammary epithelial cells, immune cells, and mammary stem cells [129, 130]. MEs carry a diverse cargo of proteins, lipids, RNA, and other bioactive compounds [131]. Recent researches have proved that MEs can regulate immunity, promote the proliferation of intestinal epithelial cells, etc. [132]. Furthermore, the integrity of the bilayer membrane can be maintained *in vitro* for a long time and remain intact even in alkaline environments [133]. Shimon Reif et al. demonstrated that MEs reduced the expression of IL-6 and TNF-α, and attenuated the severity of colitis induced by DSS [134]. The low immunogenicity, high stability, and the ability to cross the gastrointestinal barrier make MEs a promising oral delivery carrier [133, 135].

2.4.2 Probiotic, tea leaf, and honey derived exosomes

Probiotics offer various health benefits mainly aimed at gut function regulation upon administration [136]. Min-Hye Kim et al. revealed that *Lactobacillus plantarum*-derived exosomes (LEVs) can prevent skin inflammation in AD [137]. Besides, Wanil Kim et al. proved that LEVs which could induce secretion of the anti-inflammatory cytokine IL-10, along with immunomodulatory cytokines IL-1β and granulocyte macrophage colony stimulating factor (GM-CSF), can regulate the imbalance between M1 and M2 macrophages for skin inflammatory disease treatment [138]. Interestingly, researchers found another type of food-derived exosomes-like nanotherapeutics (NTs) which come from tea leaves. It was demonstrated that tea leaf-derived NTs can reduce the reactive oxygen species, inhibit the pro-inflammatory cytokines, and increase the IL-10 secreted by macrophages, which may benefit the prevention and treatment of IBD (Fig. 4) [139]. Moreover, honey as a daily nutrient is also being studied in exosome-related research. A recent research found that the vesicle-like nanoparticles derived from honey alleviated inflammation and liver damage in the experimentally induced acute liver injury, which may provide new insights for honey study [140].

3 Engineered exosomes' application in inflammatory disease and their engineering strategies

Exosomes have been widely used in therapeutic and detection studies and have shown brilliant prospects [141]. The biological properties of exosomes have been elucidated [142], however, their clinical applications are still insufficient. On the one hand, clinical trials showed that the therapeutic effects of exosomes alone are limited [143]. On the other hand, native exosomes have some tropism depending on the epitopes expressed by the donor cell but the process is limited. Moreover, native exosomes exhibit poor endolysosomal escape thus limiting the capacity to release their contents into the cell cytoplasm [144]. Engineering of exosomes could enhance their stability, targeting ability, and therapeutic efficiency, which allows exosomes to be more versatile for the therapy of inflammatory disease [78, 145]. In this review, the engineering of exosomes is divided into two parts, which are materials-engineering and bio-engineering.

3.1 Materials-engineering of exosomes

Materials-engineering of exosomes means loading drugs (including small therapeutic molecules, nucleic acid, peptides, and proteins) or artificial nanoparticles into exosomes as a delivery platform for combining treatment. Besides, the application of exosomes with new dosage forms, such as nano-gel or microneedle, is also new strategy in recent years. The loading methods or engineering methods include two major aspects, which are passive and active encapsulation [146].

3.1.1 Active encapsulation methods

The fluidity of the lipid bilayer membrane is beneficial for passive exogenous loading methods [147]. One of the passive encapsulation methods is co-incubate the cargoes with exosomes under suitable temperature and pH so that the cargoes could diffuse into exosomes through the membrane. Another choice is to pre-treat the cargoes with the donor cells and then purify the exosomes released by exocytosis [148]. For instance, Xiaoyi Ma et al. engineered HACE2-293T cells loading with polydopamine (PDA) nanoparticles for COVID-19 pneumonia treatment, in which PDA was endocytosed by cells and later exocytosed along with exosomes. The results showed that PDA enhanced the anti-inflammation ability of exosomes. What's more, PDA@Exosome has higher stability and competitive binding ability to fight against S protein invasion [78]. Similarly, by labeling UC-MSCs with Fe_3O_4 nanoparticles (NPs) and then isolating MSC-derived exosomes, the exosome (EXO) + NPs upregulated the expression of injured skin repair-related proteins and enhanced the targeting efficacy, which suggests that the application of EXO + NPs with magnetic guidance may be a promising therapeutic strategy for

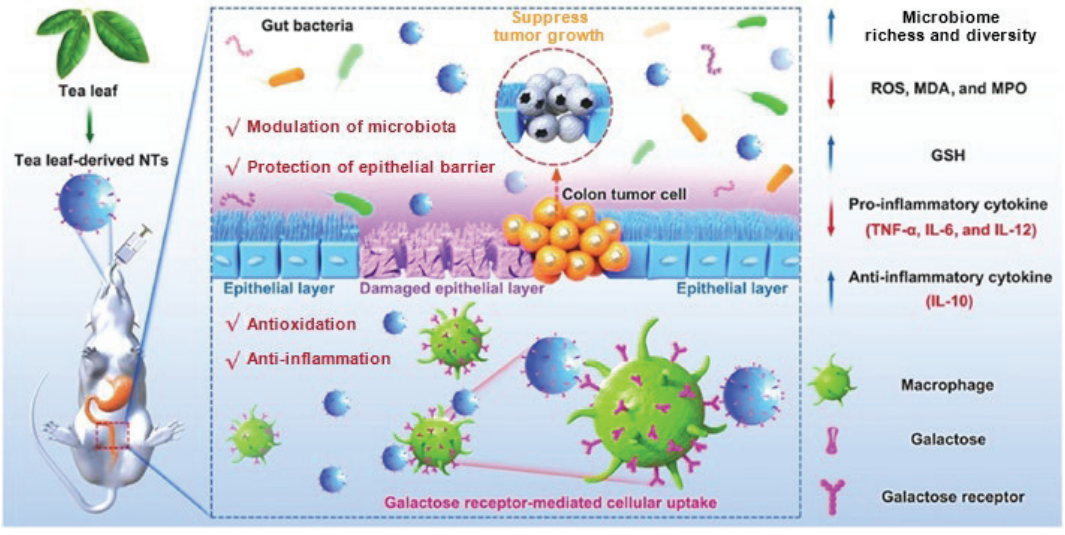


Figure 4 Schematic illustration of the preventive and therapeutic effects of oral tea leaf-derived natural exosomes like NTs on IBD. These NTs which were found to contain large amounts of lipids, some functional proteins, and many bioactive small molecules, can prevent or alleviate inflammatory bowel disease. Reproduced with permission from Ref. [139], © Elsevier Ltd. 2021.

cutaneous wound healing [149]. In addition, Dongfen Yuan et al. loaded a model cargo protein brain derived neurotrophic factor (BDNF) into macrophage-derived exosomes by co-incubation and showed that BDNF successfully penetrated BBB and got delivered to the inflammatory area in the brain, which enhanced the neural repair capacity of exosomes [150]. Chen Xu et al. loaded curcumin into AD-MSCs derived exosomes by co-incubation, and the results showed improved synergism exerts chondro protective effects and more efficaciously alleviated oxidative stress and chondrocyte apoptosis in OA cartilage, which demonstrates the enormous potential for the recovery of articular cartilage loss in OA therapy [86].

These findings suggest that compared to native exosomes alone, the engineering of exosomes can improve their therapeutic efficiency and even their stability and targeting ability, which represents a novel approach for exosome-involved inflammation therapy. However, the reliable and convenient passive encapsulation method is more suitable for hydrophobic and small molecule cargoes. While for hydrophilic and macromolecule cargoes, stronger stimulations are needed to load the cargoes into exosomes. So, in the following, we will illustrate different types of active encapsulation strategies and their application in inflammatory diseases (shown in Fig. 5).

3.1.2 Passive encapsulation methods

The principles of sonication, electroporation freeze–thaw cycles, and co-extrusion are similar, which all involve using mechanical techniques to transiently and reversibly open the exosome membrane to allow diffusion of compounds into the vesicle [151].

(1) Sonication

Myung Soo Kim et al. have compared different methods of engineering exosomes released by macrophages with paclitaxel (PTX) through basic morphology characterization and efficacy [152, 153]. The results proved the convenience and high loading efficiency of sonication, thus sonication is regarded as a widely used method in membranes coating, such as red blood cells [154]. The sonication loading strategy is recently used in OA and rheumatoid arthritis (RA) therapy and delivered satisfying results [87, 155]. Sonication is efficient, and the ultrasound instruments are commonly used in laboratories, but this method is still unstable and uncontrollable, which may lead to unsuccessful loading of drugs into exosomes, but adhering to the surface of exosomes, resulting in reduced stability, and limited therapeutic effects.

(2) Electroporation

Gregor Fuhrmann et al. proved that the loading efficiency into exosomes is mainly influenced by the hydrophobicity of the cargo but can be substantially improved by electroporation, and the encapsulation into exosomes significantly improved cellular uptake and the effect of cargoes [156]. Similarly, the published results have shown that RNA-associated cargoes may be suitable for electroporation encapsulation and delivery into exosomes [157, 158]. The electroporation method is simple and fast, but it requires related equipment and daily maintenance cost. Besides, improper operation may also cause damage to the exosome structure and loss of surface protein activity, etc.

(3) Freeze–thaw circles

The cell cryopreservation follows the principle of slow freezing and quick thawing to avoid the damage to cell structure caused by rapid freezing, and the freeze–thaw circles method takes advantage of this to load cargoes into the exosome membrane to not damage bio-characteristics of the exosome [159]. Matthew J. Haney et al. loaded catalase into macrophage-derived exosomes by freeze–thaw circles method to cure inflammation and neurodegeneration in Parkinson's disease [68]. The freeze–thaw cycle does not require a machine, but it requires repeated temperature changes, which may take a long time and may lead to incomplete exosome structure.

(4) Co-extrusion method

By packaging the purified exosomes together with cargoes in a syringe-based lipid extruder with a porous membrane, the exosome membrane is ruptured by mechanical force and mixed with cargoes. This method may be more suitable for artificial nanoparticle cargoes which have basic particle morphology, similar to red blood cell membrane coating [160], and sheltering with membranes can produce a potent effect increasing cargoes' circulation time in the blood [161]. The research illustrated that the loading efficiency of extrusion is comparable to that of sonication and is higher than that of co-incubation or freeze–thaw circles [68]. Moreover, extrusion can also be used in the engineering of exosome mimetics [162]. Although the co-extrusion operation is convenient, it may cause multiple coating on the surface of the particles, resulting in excessive particle size and difficulty in delivery, etc.

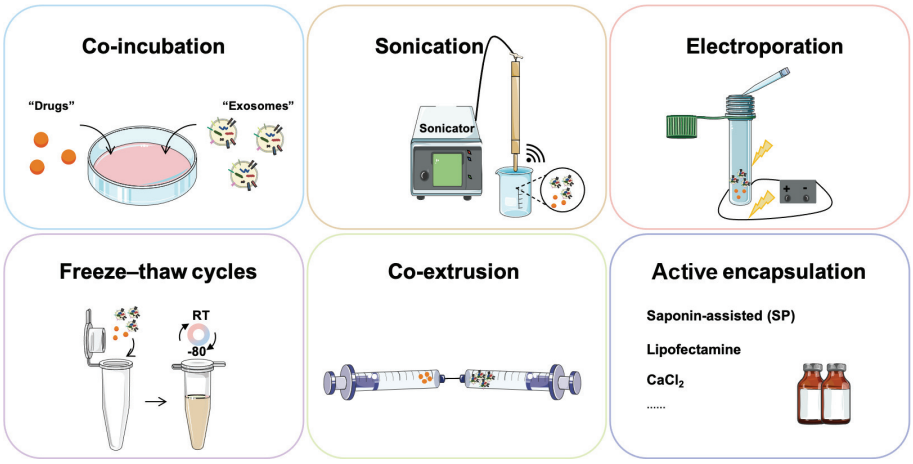


Figure 5 The main materials-engineering strategies of exosomes.

(5) Saponin method

Saponin as detergent can interact with membrane cholesterol, selectively removing it and leaving holes in the membrane [163]. Beneficial from the permeabilization of saponin, the saponin method is developed as another encapsulation method that has high loading efficiency and exosomes produced by this method have superior therapeutic effects compared to those obtained by sonication [68]. Especially, this method allows a mild encapsulation of cargoes without compromising the structural integrity of the exosomes [164]. Besides, Hyoeun Kim et al. suggested that the use of $CaCl_2$ treatment may enhance the delivery of exosomes without causing toxicity [165]. However, if there are residual reagents after loading, it may have a certain impact on the results.

Overall, the above five active encapsulation methods are faster and more efficient than the passive engineered method but have limitations such as damage to membranes, instability, or toxicity. Therefore, further research and improvement are needed. A standardized active encapsulation method is conducive to in-depth study on the engineering of exosomes to further improve the therapeutic effects and efficiency of exosomes, and is also conducive to scale-up production and clinical promotion.

3.1.3 Exosomes with new dosage form

(1) Nanogel

Except for loading cargoes into exosomes, using exosomes with new dosage forms is also developing rapidly. Different gels as new dosage forms loading with exosomes have been widely used in inflammatory treatments [166]. In the research of Liming Li et al., the MSCs derived exosomes were immobilized in a peptide-modified adhesive hydrogel, which provided an exosome-encapsulated extracellular matrix to the injured nerve tissue, thus exhibiting efficient retention and sustained release of exosomes, which is good for SCI. The EXO-pGel elicits significant nerve recovery and urinary tissue preservation by effectively mitigating inflammation and oxidation (Fig. 6) [67]. Similarly, Chaoshan Han et al. delivered UC-MSCs derived exosomes with the composite hydrogel formed by silk fibroin and silk sericin, which can promote wound healing, angiogenesis, and reduce inflammation cytokines for tissue repair, enhancing the effect of exosomes [89].

(2) Microneedle

The microneedle (MN) array provides a painless, invasive, and controlled drug delivery system [167]. A recent study designed a detachable MN array to deliver tendon stem cells derived exosomes for Achilles tendinopathy (AT) healing. As exosomes can only partially reach the injury site by passive diffusion, which greatly reduced the therapeutic effects, the MN patch provides a promising strategy for transdermal delivery of exosomes, achieves effective penetration of exosomes, and enhances the concentration of exosomes at the injury site. Besides, 2-methacryloyloxyethyl phosphorylcholine (MPC), N,N'-bis(acryloyl) cystamine (BAC), and L-arginine are enriched around EXOs to form EXO/MBA particles. The results proved notably suppressed inflammation in AT, the proliferation of tendon cells, and prevented extracellular matrix degradation (Fig. 7) [88]. Additionally, MN patch promoted cell migration and angiogenesis by slowly releasing MSCs derived exosomes and penetrating into the deep layer of the skin, presenting a potentially valuable method for repairing diabetic wound in clinical applications [90].

In summary, on the one hand, the materials-engineering of exosomes keeps the native characteristics of exosomes and another functional "drug" was added to enhance therapeutic ability. On the other hand, new dosage forms provide exosomes with better retention, stability, and permeability, which makes way for the upgraded applications of exosomes. Different materials-engineering methods have different loading efficiencies and their respective advantages and disadvantages, but all of them can enhance the function of exosomes. The nature of the loaded drugs, the characteristics of the disease model, and the treatment cycle can be used as criteria for screening suitable engineering methods.

3.2 Bio-engineering of exosomes

Exosomes can be conveniently surface modified through bio-engineering methods, including genetic engineering and chemical engineering (Fig. 8) [168]. In the genetic engineering method, donor cells were transfected with plasmids encoding fusion proteins, which impart exosomes with new properties or overexpression of proteins for targeting therapeutic effects [169]. For instance, the N-terminus of lysosome-associated membrane glycoprotein 2b (Lamp2b) is displayed on the surface of exosomes which can be appended with targeting sequences for surface modification [158]. Wu et al. developed a therapeutic strategy by using exosomes with decoy receptor ACE2 for neutralization of SARS-CoV-2, which successfully inhibited the infection of S-pseudo virus in various cells [170]. Similarly, Yujie Liang et al. fused a chondrocyte-affinity peptide (CAP) with the lysosome-associated membrane glycoprotein 2b protein on the surface of dendritic cells derived exosomes, the CAP-exosomes that can efficiently encapsulate microRNA-140, specifically enter, and deliver the cargo into chondrocytes, which can be retained in the joints and penetrate to deep cartilage regions to alleviate OA progression (Fig. 9) [171].

Moreover, the overexpressing transmembrane protein CD47

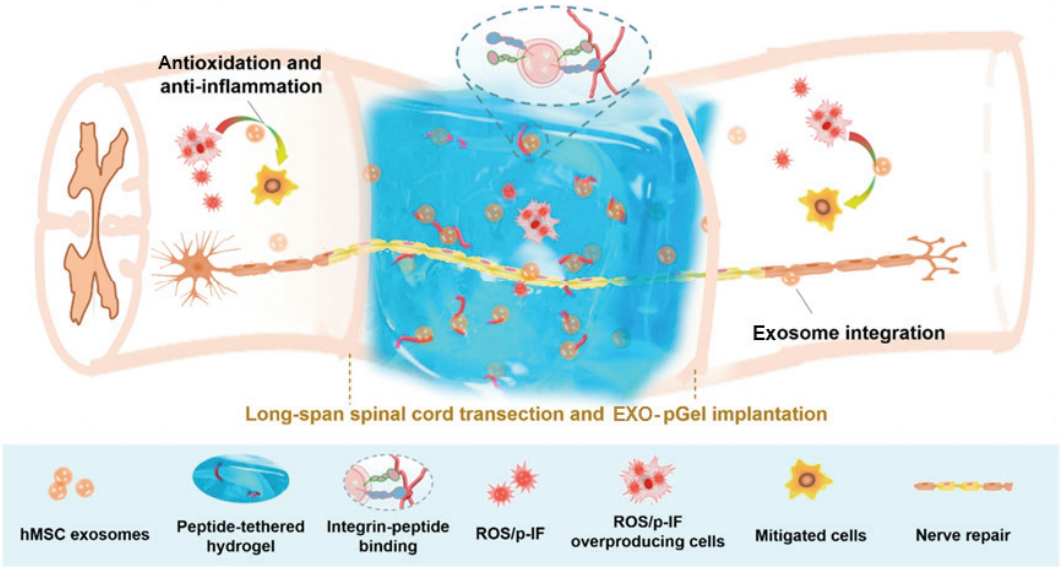


Figure 6 Schematic illustrations of the exosomes derived from hMSCs were implanted with a peptide-modified adhesive hyaluronic acid (HA) hydrogel and the Exo-pGel therapy of SCI. The implanted exosomes exhibit efficient retention and sustained release in the host nerve tissues. Reproduced with permission from Ref. [67], © American Chemical Society 2020.

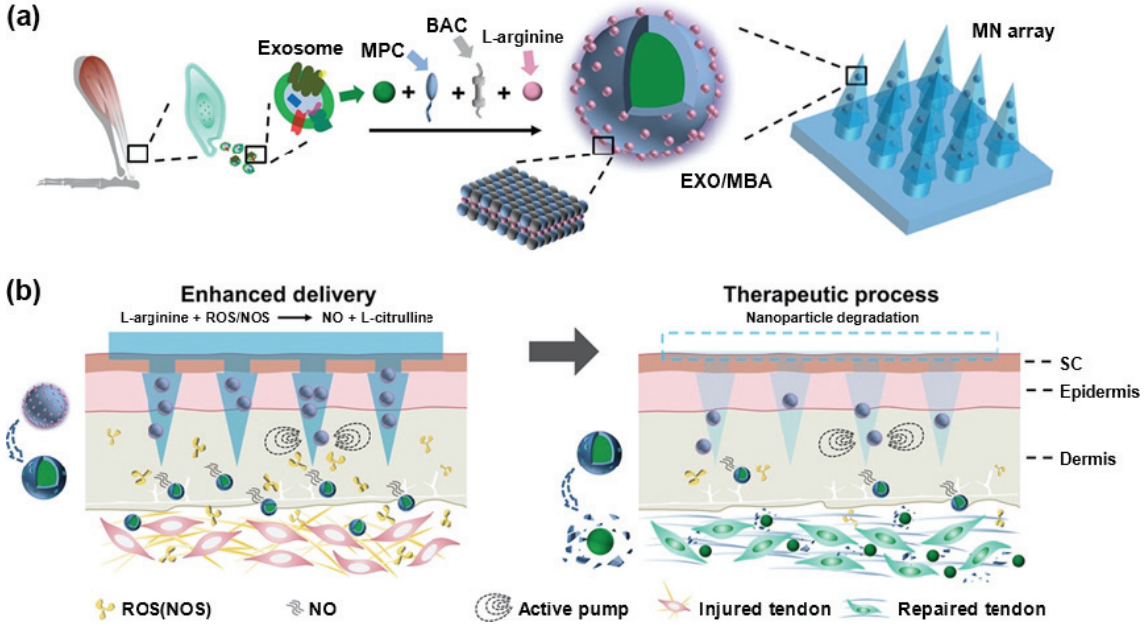


Figure 7 Schematic illustrations. (a) Manufacturing procedure of EXO/MBA-loaded MN array. (b) Healing process of AT after application of EXO/MBA-loaded MN array. L-arginine was converted to nitric oxide by nitric oxide synthase (NOS) or reactive oxygen species (ROS) as the driving force, forming an active pump to enhance the movement of EXOs to inner tissues. With the degradation of the high-molecular polymer formed by MPC and BAC, EXOs will be exposed and released to repair the injured tendons. Reproduced with permission from Ref. [88], © American Chemical Society 2021.

MSCs derived exosomes can evade clearance by macrophages and preferentially accumulate in the heart, with prolonged retention in circulation, which sheds new light on myocardial infraction reperfusion injury treatment [172]. Analogously, overexpressing programmed death ligand 1 (PD-L1) exosomes derived from UC-MSCs can specifically bind to PD-1 on the T cell surface, thus suppressing local over-active immune cells in the fracture site for adequate fracture healing [173].

In the chemical engineering method, ligands can be displayed through conjugation reactions or lipid assembly for more precise receptor targeting or multi-function. In the research of Dong Gil You et al., AD-MSCs derived exosomes were modified by metabolic glycoengineering mediated bio-orthogonal copper-free click chemistry for the targeted reprogramming of macrophages. The therapeutic efficacy obtained from the engineered exosomes was 10 times better than pure exosomes in RA treatment [174]. Besides, Hojun Choi et al. loaded the super repressor IκB (srIκB) into exosomes by reversible protein–protein interactions controlled by optogenetics, which can attenuate the inflammatory responses in various disease models. The results showed that EXO-srIκB acting as an inhibitor of nuclear factor (NF)-κB can directly control the inflammatory response in sepsis treatment [175].

Overall, bio-engineering of exosomes can regulate corresponding signaling pathways through ligand-receptor binding, achieve regulatory treatment, and enhance the targeting efficiency of exosome delivery, providing better therapeutic effects for exosomes in inflammatory treatment. The engineering of exosomes shows a better combination treatment effect, more accurate targeted regulation, and longer-lasting sustained release and residence. It further enriches the function of the exosome delivery platform in inflammatory treatment.

4 Development status of new drugs based on

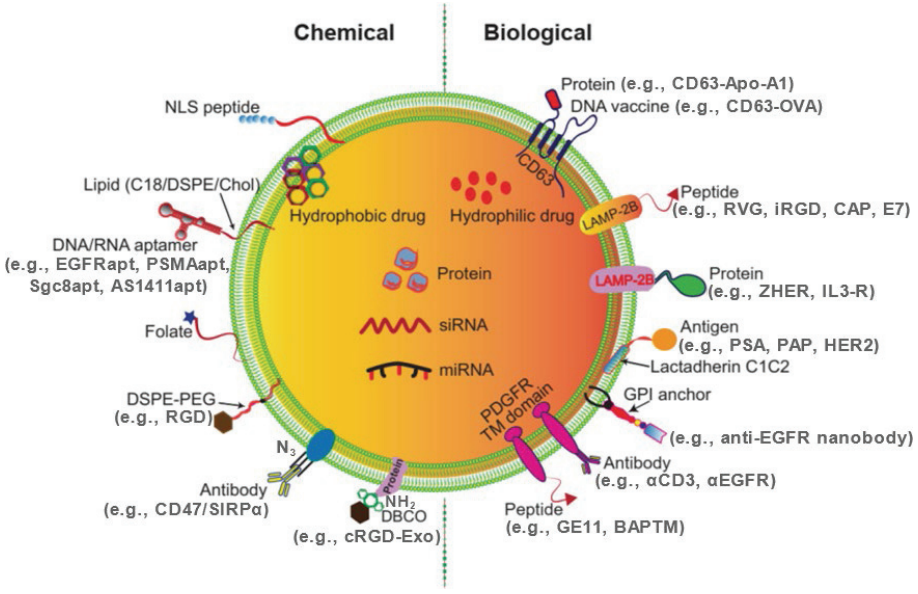


Figure 8 Schematic illustration of the surface engineering of exosomes via genetic/biological manipulation or chemical modification. Reproduced with permission from Ref. [168], © Liang, Y. J. et al. 2021.

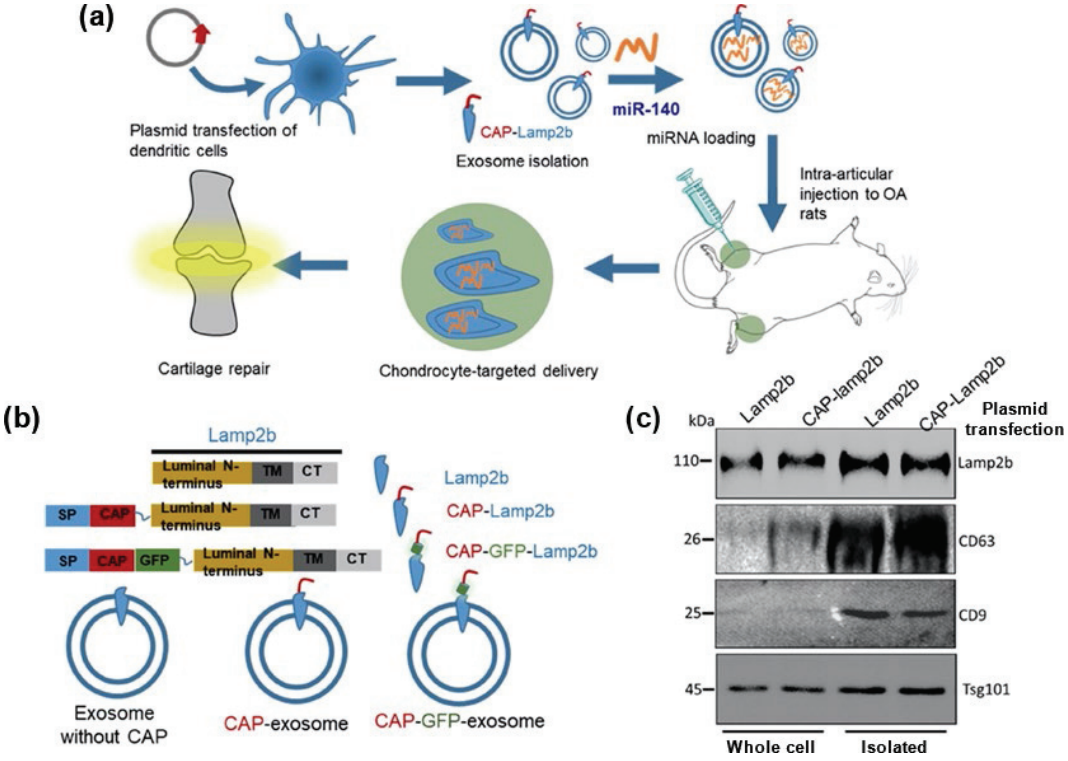


Figure 9 Schematic illustration of the surface engineering of exosomes via genetic/biological manipulation or chemical modification for cartilage repair. (A) Schematic illustration of surface engineering of exosomes for targeted delivery of miR-140 to chondrocytes for OA treatment. (B) Schematic representation of the plasmid constructs containing Lamp2b, CAP-Lamp2b, and CAP-GFP-Lamp2b. (GFP: green fluorescent protein; SP: signal peptide; TM: transmembrane domain; CT: C terminus). (C) Expression of marker proteins in whole cell lysates and lysates of purified exosomes examined by western blotting. Reproduced with permission from Ref. [171], © American Chemical Society 2020.

exosomes

We have illustrated the application of native and engineered exosomes in inflammation treatment and summarized the engineering strategies as well as their pros and cons. Finally, we will discuss the current status of new drugs based on exosomes and analyze the prospects and challenges of the clinical application.

Exosomes play an important role in the molecular mechanism of disease occurrence as well as in the diagnosis and treatment of disease, and as a possible new drug, the application of exosomes is divided into three aspects: (1) alleviate or treat diseases by intervening in the production, release, and uptake of functional contents in disease-related exosomes [176]; (2) native exosomes that are rich in bioactive substances act as therapeutic agents themselves; (3) engineering exosomes that are physically loaded with anti-inflammatory drugs or bio-decorated with regulating molecules for improved therapeutic effects. The advantages of exosome-based drugs illustrated above can be concluded as lower immunogenicity, higher biocompatibility, better deep tissue permeability, and diversified modes of action.

At present, most exosome products are in the preclinical stage, among which the exosomes are almost all directly used as therapeutic agents or carriers, while intervention in disease-related

exosomes production has not been considered as a possible clinical strategy which may be due to the complex mechanism of exosome regulation of diseases, and the specific target is still not clear. Only a few have entered the phase I clinical study stage such as the exosome for bronchopulmonary dysplasia treatment from United Therapeutics Corporation. For instance, the AVA203 from Avalon GloboCare and the exoASO from Codiak BioSciences both utilize exosomes for direct treatment of fibrosis. The exosomes from NeurEXO Sciences and CellTex Theraputics are both used for neurological disorders treatment such as Alzheimer diseases. Besides, the exosomes from Codiak BioSciences are used as a delivery vehicle for autoimmune disorders treatment. In conclusion, the exosome products of the above companies are still in the preclinical research stage, of which the majority of products are applied to neurological diseases, which may be related to the good deep tissue penetration of exosomes and the ability to pass the BBB.

The new carrier technology in the field of nucleic acid drugs is the direction that major pharmaceutical companies pay close attention to. Exosomes are considered to have the potential to solve the *in vivo* drug delivery bottleneck of small RNA. MDimune extrusion cell culture media with proprietary device and yielded nearly 100 times as more cell-derived vesicles (CDVs) as natural exosomes. Recently, Reyon Pharmaceuticals and MDimune company have reached an agreement to jointly develop exosome-delivered viral vaccines and mRNA for rare genetic diseases treatment.

As mentioned before, one of the obstacles to the widespread use of exosomes in the treatment of diseases is their production and purification. Codiak BioSciences holds core patents for exosome design and production and can produce exosomes of industrial grade and scale, which lays the foundation for exosome products to be clinically applied. However, the technology of production and standardization of engineered exosomes for precise treatment strategy is limited, even the patent from Evox Therapeutics is not so mature.

On the one hand, solving the problem from the source of exosomes which is how to efficiently cell culture; on the other hand, overcoming the difficulty of how to amplify the extraction of exosomes. These are two important key points to cross the barrier of exosomes to clinical practice. Therefore, exosome technology needs more in-depth research, and exosome technology needs to be better combined with existing therapeutic technologies. However, what is certain is that exosomes will definitely find their irreplaceable position in future drug treatment.

5 Conclusions and prospects

Inflammation is the root cause of multiple diseases, acute or chronic inflammatory responses induce various organ dysfunction, and the key treatment strategies for inflammation are not just downregulating the immune responses but maintaining the immune homeostasis. Traditional therapeutic drugs have shortcomings such as poor targeting, single effect, short half-life, or high cell cytotoxicity, so it is difficult to penetrate or accumulate in the inflammatory area for lasting and precision regulation treatment.

Exosomes as novel bioactive therapy platform have been increasingly studied in recent years. Researchers study exosomes from many aspects such as properties, contents, and functions, gradually turn to take advantage of their unique characteristics, and study how to enhance the ability of exosomes, and realize combination therapy. Exosomes that have excellent biocompatibility are known to be an ideal vehicle to transfer information between cells, but have low therapy efficiency, thus researchers combined exosomes with anti-inflammatory "drugs" or engineered them for improved therapeutic effects. On the one hand, the loaded therapeutic agents can enhance the efficacy of exosomes and diversify treatment, and engineering them can also improve the targeting ability of exosomes and prolong blood circulation time; on the other hand, exosomes serving as delivery vehicles can also improve the stability of the overall therapeutic platforms and enhance the sustained release effect.

Researchers have used many advanced methods to carry out exosome engineering and shown desirable results. However, there are still numerous questions that need to be explored in the future, which including but not limited to:

(1) Loading efficiency and stability. Which of the different types of material engineering and bio-engineering exosomes is more convenient and efficient, has a higher loading rate, and forms a more stable combination therapy platform, or how can we improve existing methods, or find innovative methods?

(2) The activity of the cargoes and the influence of exosome biofilm composition. Engineered exosomes have been proved to have higher therapeutic efficiency than native exosomes, but in the combined therapeutic platform, whether the properties of the loaded drugs have changed, and whether the composition and content of the modified exosomes have changed, remain unknown.

(3) Intracellular release mechanism. After the combination therapy platform is delivered to the targeting site, what is the release mechanism of the loaded therapeutic agents inside exosomes, and what is the release efficiency.

What's more, the quality of each batch of engineered exosomes needs to be uniform. In the long run, the engineering of exosomes needs to be standardized and scaled up just like the separation and purification of exosomes to achieve real clinical application.

In conclusion, the recent studies of using native exosomes and engineered exosomes by different methods to treat plentiful kinds of inflammation diseases in preclinical studies are summarized in this review. Besides, parts of new exosome drugs that have entered phase I clinical trials or are proposed to be marketed are also listed. Although research challenges and blanks remain and more in-depth research and exploration are needed, engineered exosomes are novelty and have a good application prospect in the treatment of inflammation, which may become a safe and efficient brand-new strategy for clinical inflammation therapy in the near future.

Acknowledgements

This work was financially supported through grants from the National Natural Science Foundation of China (Nos. 51773154, 31771090, 31971323, and 81871315), Shanghai Science and Technology Innovation (No. 18JC1414500), and Young Hundred-Talent Program of Tongji University.

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