Review

THE SMALLEST WORKERS IN REGENERATIVE MEDICINE: STEM CELL-DERIVED EXOSOMES

Ozer Oner[1,2,3], Suleyman Gokhan Kara[1,2,4], Ihsan Burak Karakaya[1,2], Ayla Eker Sariboyaci [1,2], Onur Uysal [1,2], Sibel Gunes [1,2,] Huseyin Avci[1,2,5,6]

[1]Cellular Therapy and Stem Cell Production Application and Research Centre, ESTEM, Eskisehir Osmangazi University, Eskisehir, Turkey

[2]Department of Stem Cell, Institute of Health Sciences, Eskisehir Osmangazi University, Eskisehir, Turkey

[3]Suhut Vocational School of Health Services, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey

[4]Department of Emergency Medicine, Eskisehir City Hospital, Eskisehir, Turkey

[5]Department of Metallurgical and Materials Engineering, Eskişehir Osmangazi University Eskişehir, Turkey

[6]Translational Medicine Research and Clinical Center, Eskisehir Osmangazi University, Eskisehir, Turkey

Abstract:

Extracellular vesicles (EVs) are secreted by cells into the extracellular space, which first discovered in 1967 as platelet dust. In recent years, the analysis of EVs treatment for various diseases has emerged in the studies to understand these vesicles' origin and biological functions. According to their size, biogenesis, content, release pathways and function, EVs have three main subtypes: microvesicle (MV), exosome (EX) and apoptotic body. EVs are found in all body fluids, including urine, plasma, and physiological fluids such as bronchial lavage. In addition, it is secreted by many cell types such as dendritic cells, B cells, T-cells, mast cells, tumour cells, and sperm. This review investigates the studies using stem cell-derived EVs in numerous clinical and preclinical research.

Keywords: Extracellular Vesicles, Stem Cell, Exosome, Regeneration, Regenerative Medicine.

Özet:

Ekstraselüler veziküller (EV), ilk olarak 1967'de trombosit tozu olarak keşfedilen, hücreler tarafından hücre dışı boşluğa salgılanan lipide bağlı veziküllerdir. Son yıllarda bu veziküllerin kökeninin ve biyolojik işlevlerinin anlaşılması için yapılan araştırmalarda EV'lerin çeşitli hastalıkların tedavilerinde kullanılabileceği fikri ortaya çıkmıştır. EV'lerin biyogenezlerine, salınım yollarına, boyutlarına, içeriğine ve işlevlerine göre farklılaşan, mikroveziküller (MV'ler), eksozomlar (EX) ve apoptotik cisimler olmak üzere üç ana alt tipi vardır. EV'ler; idrar, plazma ve bronşiyal lavaj gibi fizyolojik sıvılar dahil tüm vücut sıvılarında bulunurlar. Bunun yanında, B hücreleri, dendritik hücreler, mast hücreleri, T-hücreleri, tümör hücreleri, sperm gibi pek çok hücre tipi tarafından da salgılandığı gösterilmiştir. Bu derlemede çok sayıda klinik ve preklinik çalışmada kullanılan kök hücre kaynaklı EV'lerin terapötik etkinliğini gösteren çalışmaları derledik.

Anahtar Kelimeler: Ekstrasellüler veziküller, Kök Hücre, Eksozom, Rejenerasyon, Rejeneratif Tıp.

Correspondence Address : Ozer Oner Cellular Therapy and Stem Cell Production Application and Research Centre, ESTEM, Eskisehir Osmangazi University, Eskisehir, Turkey ozeroner@yandex.com

ORCID ID of the authors: O.O. 0000-0001-5352-7437, S.G. 0000-0002-7152-5643, İ.B.K. 0000-0001-7634-0771, A.E.S. 0000-0003-4536-9859, O.U. 0000-0001-6800-5607, S.G. 0000-0003-0846-1170, H.A. 0000-0002-2475-1963

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1.Introduction

Besides the hormones and neurotransmitters released from the secretory vesicles of specialized cells, all the cells can secrete various membrane vesicles known as the extracellular vesicle (EV). This process has been preserved in evolutionary processes from bacteria to humans (1).

According to their size, release pathways, biogenesis, and function, EVs have three main subtypes: microvesicle (MV), exosome (EX) and apoptotic body. MVs are large vesicles formed by membrane budding, apoptotic bodies occur by bubbling into senescent or dying cells, and EXs are the smallest vesicles released from cells by the multivesicular endosomal route. EXs are, in general, 40-100 nm in diameter, contain 1.13-1.19 g/ml sucrose, and sedimenting at 100,000xg. Its membranes are rich in cholesterol, ceramide, sphingomyelin and lipid. EXs contain protein and RNA. Most EXs have protein sets such as tetraspanins (CD81, CD63 and CD9), TSG101 and Alix, and also contain tissue/cell type-specific proteins that indicate their cellular origin. Removal of unwanted proteins, protein-protein interaction, and intercellular communication in line with the exchange of proteins and genetic materials are among the critical functions of EXs. EXs also play an essential role in the transfer of proteomic and genomic materials between the cells.

EVs carry components of the cells from which they are produced. In animal models and clinical studies, it has been reported that tissue and cellular functions show similar regenerative effects with the cells from which they are produced. The molecular mechanisms of the contents, secretion, uptake and function of EXs form the basis of preclinical studies. This intercellular communication of EVs has brought the view that the desired therapeutic molecule can be loaded and used as a natural drug deliverer (Table 1) (2–4). Stem cells can transform into different cell types, replace injured tissues, and repair at the injury site with a paracrine mechanism of action. Stem cell in vivo studies has been used successfully to treat graft-versus-host disease (GvHD), haematological malignancies, autoimmune diseases, and acute thrombocytopenia (5–7).

Table 1. Properties of exosomes [2].

Size (nm)	40-100
Biogenesis	Exocytosis of multivesicular bodies
Markers	CD63, CD81, CD9, Tsg101, Alix, Hsc70.
Contents	Proteins, lipids, mRNA and microRNA and rarely DNA.

Whether EXs will be superior to angiogenic drugs, recombinant growth factors, other peptides, and stem cell-based therapies is unclear and is a crucial issue to be investigated. As a result of in vitro and in vivo characterization analyses performed till now, EXs are emerging as a popular cell-free candidate that can be used to overcome many of the challenges posed by using cells as therapeutic agents. It has been used as a source of cell-free therapy in animal models of many tissues damage and diseases (8,9).

2. Mechanism of Action and Biologıcal Effects of Exosomes

The genetic material of EXs and MVs is transferred locally and systematically. EV-mediated therapeutic effects are thought to be due to two different mechanisms: First; EVs released from damaged tissues can act on local stem cells and regulate the release of regenerative microvesicles for tissue repair (10). Latter; local stem cells around damaged or degenerated tissues can produce microvesicles to stimulate regeneration, re-enter the cell cycle near damaged tissues and enable dedifferentiation.

Investigating the relationship between wound repair and SC-EV in preclinical studies contributes to paving the way for SC-EVs in clinical studies (11–13). Preclinical studies have demonstrated that SC-EVs may repair tissue damage by maintaining stemness, induction of regeneration, inhibition of apoptosis, and immunoregulation (Table 2).

SC-EVs can protect against cell apoptosis and reduce tissue damage. Human umbilical cord-derived mesenchymal stem cell extracellular vesicles (hUC-MSC-EVs) can carry antioxidant enzymes, and manganese superoxide dismutase in mitochondria inhibit oxidative stress-induced hepatocyte apoptosis and protect against hepatic Ischaemia-Reperfusion injury (IRI) in rats (14–17).

3. Stem Cell Culture for Extracellular Vesicle Production

3.1. Stem Cell Selection

The secretion of EVs is also affected by the senescence of MSCs (18–21). Abello et al. (2019), hUC-MSC-EXs gadolinium lipid (GdL-EXs) or infrared dye in tumour-bearing mice, 1,1'-dioctadecyl-3,3,3',3'-tetramethylindotricarbocyanine iodide (DiR-EXs), analyzed the biodistribution of EXs by labelling them (22). Intravenous infusion of lower doses of EV showed relatively higher hepatic accumulation compared to higher doses (22,23) (Fig. 1).

Table 2. Experimental model diseases treated with different stem cell-derived EVs.

Indication	Species	EV Sources	Main outcome	Mechanism	Reference
Traumatic brain injury (TBI)	Rat	Human AdMSC-EXs	Improvement of motor behavior function and cortical brain injury	Delivering MALAT1	[24]
Stroke	Rat	Rat BMSC-EXs	Neurite remodeling	Neurogenesis	[25]
Alzheimer's disease	Mouse	EXs from hypoxia-stimulated BMSCs	Learning and memory abilities	Restoration of synaptic dysfunction and regulation of inflammatory responses through miR-21	[26]
Spinal cord injury (SCI)	Rat	BMSC-EXs	Improvement of functional behavioral recovery effects	Activation of A1 neurotoxic reactive astrocytes	[27]
Spinal cord injury	Rat	Human BMSC-EVs	Inflammatory response, improved motor function, enhanced mechanical sensitivity threshold	uncertain	[28]
Spinal cord injury	Mouse	hucMSC-EXs	Improving functional recovery	Decreases inflammation	[29]
Myocardial infarction	Mouse	iPSC-EVs	Preservation of viable myocardium	Delivery of ESC specific miR-294	[30]
Myocardial infarction	Mouse	Mouse ESC-EXs	Resurgence of cardiac proliferative response	Delivering miR-294	[31]
Myocardial infarction	Mouse	Mouse BMSC-EVs	Improving cardiac function	Delivering miR-210	[32]
Myocardial infarction	Mouse	EXs derived from hypoxia-stimulated BMSC	Better cardiac functions recovery	Delivering miR-210	[33]
Lung injury	Mouse	Human BMSC-EVs	Reduces pulmonary vascular permeability	Modulating cytoskeletal signaling	[34]
Acute lung injury	Mouse	Human BMSC-MVs	Reduces pulmonary capillary permeability	Delivering Angiopoietin-1 mRNA and immune regulation	[35]
Neonatal hyperoxic lung injury	Rat	hUCB-MSC-EVs	Reduces impaired alveolarization and angiogenesis	Transfer of VEGF protein	[36]
Liver injury	Mouse	Mouse BMSC-EVs	Increase the mRNA expression of anti-inflammatory cytokines	Immunosuppression and immune protection	[37]

Renal ischemia/reperfusion injury	Rat	hiPSC-MSC-EVs	Decrease serum levels of creatinine and urea nitrogen	Exosomal SP1 activating the expression of SK1 and the generation of S1P	[42]
Rejuvenation of skin	Human skin tissues	hUCB-MSC-EXs	Increase expressions of Collagen I and Elastin	Uncertain	[44]
Wound healing	Mouse	hucMSC-EXs	Decrease scar formation and myofibroblast accumulation	Transfer of specific microRNAs and suppression of TGF-β /Smad2 pathway	[45]
Osteoporosis	Rat	hiPSC-MSC-EXs	Preventing bone loss	Activation of the PI3K/Akt signaling pathway	[41]
Stabilized fracture	Rat	hucMSC-EXs	Increase angiogenesis and bone healing	HIF-1alpha mediated promotion of angiogenesis	[47]
Osteogenesis imperfecta	Mouse	Murine BMSC-EVs	Facilitating bone growth	Delivery of miRNAs	[48]

4. Use of Stem Cell-Derived Exosomes in Treatment

4.1. Exosomes in Neurological Diseases

In recent years, it has been reported that EXs are effective in the pathogenesis of neural diseases. E.g., EXs are released from neurons, astrocytes and glial cells to facilitate different functions such as removing unwanted stress proteins and amyloid fibril formation. EXs containing α-synuclein have been shown to induce cell death in neuronal cells, suggesting that EXs potentiate and increase Parkinson's disease pathology. Again, in Alzheimer's disease, β-amyloid is released in association with EXs (24).

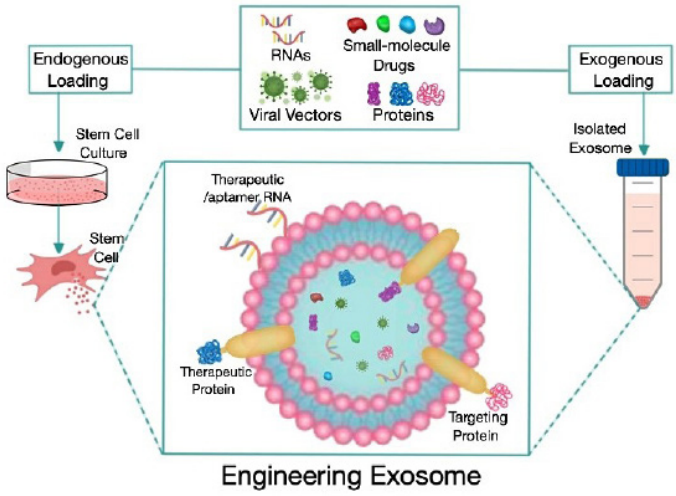

Figure 1. Engineering EVs. Extracellular vesicles (EVs) can provide therapeutic assets, including proteins, RNAs, oncolytic viruses, and small molecule drugs by endogenous loading during EV biogenesis or by exogenous loading after EV isolation. Engineered EVs can express targeted peptides or therapeutic proteins on their surface and bind aptamers or therapeutic RNAs via RNA-binding proteins.

In animal models of brain injury, systemic administration of SC-EXs has been shown to reduce neuroinflammation. (25–27). Traumatic spinal cord injuries can cause clinical conditions up to complete loss of motor and sensation in the lower extremities (28,29). Sun et al. (2018), in a study on rats, showed that UC-MSC-EXs support functional recovery in spinal cord injuries by reducing inflammation (30). Liu et al. (2021) reported that MSC-EVs pretreated with melatonin recovered the traumatic spinal cord injury with NRF2 stabilization (19).

4.2. Exosomes in Cardiovascular Diseases

The proliferation abilities of cardiomyocytes usually are pretty poor (31–33). Sun et al. (2018), in a study, conducted, in an animal model of dilated cardiomyopathy induced by doxorubicin: They have resulted that BM-MSC-EXs improved cardiac function, inhibited cardiac dilation, attenuated cardiomyocyte apoptosis, decreased the number of pro-inflammatory macrophages in the infiltration zone and the expression of inflammatory factors (34).

4.3. Exosomes in Lung Diseases

Potter et al. (2018) showed that BM-MSC-EVs could significantly reduce pulmonary vascular permeability induced by hemorrhagic shock in mice through regulation of cytoskeletal signalling (35). In another study, Tang et al. (2017) showed that BM-MSC-MVs, administering angiopoietin-1 (Ang-1) mRNAs to mice, can support the stability of the pulmonary vasculature and reduce inflammation in the lungs (36).

On the other hand, Sengupta et al. (2020) conducted a phase I clinical study showing that BM-MSC-EXs can be used safely in lung damage due to COVID-19 (37). With the increase in clinical studies, it is predicted that SC-EXs will enter our daily routine in respiratory system diseases.

4.4. Exosomes in Gastrointestinal Diseases

4.4.1. Intestines

Inflammatory bowel diseases (IBD) are considered chronic, recurrent inflammatory diseases that can affect any part of the gastrointestinal tract. IBD includes two diseases, Crohn's disease and ulcerative colitis. Although both diseases usually have similar clinical manifestations, they affect different parts of the gastrointestinal tract, and the degree of intestinal wall inflammation may differ (38).

There is evidence that EXs play a role in the pathogenesis of IBD. Macrophage pyroptosis, a cell death process after inflammatory activation of NOD-like receptor family pyrin domain-containing 3 (NLRP3), is thought to be part of the cause of an abnormal immune response in IBD pathogenesis. Macrophage pyroptosis plays an essential regulatory role in reducing colitis by hUC-MSC-EXs. Cai et al. (2021), in their in vivo experiments, showed that hUC-MSC-EXs inhibited the activation of NLRP3 inflammations in the mouse colon and inhibited the secretion of IL-1β, IL-18 and Caspase-1 cleavage, resulting in a decrease in cell pyroptosis (39). Barnhoorn et al. (2020) demonstrated that local application of BM-MSC-EX as a cell-free substitute for MSC therapy in an animal model of IBD reduces intestinal epithelial damage by stimulating epithelial regeneration (40).

4.4.2. Liver

Studies have shown that SC-EVs can treat liver diseases by the administration of various active molecules. In animal models of liver injury, the use of SC-EXs has been found to reduce injury and increase regeneration (41–43). In addition, studies have revealed that hUC-MSC-EXs can alleviate liver fibrosis in mice by inactivating TGF-β/Smad signalling, reducing collagen deposition and inflammation (44). hUC-MSC-EXs carrying glutathione peroxidase-1 have been shown to protect against liver failure in mice by reducing inflammation and oxidative stress (45).

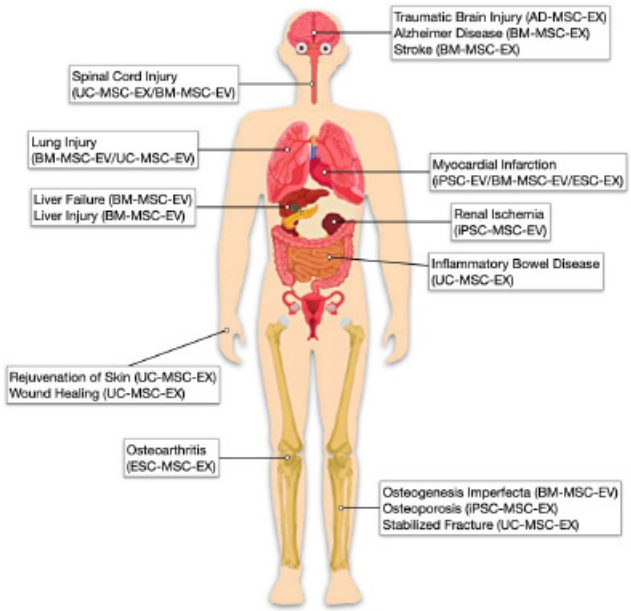

Figure 2. Schematic representation of diseases treatment with exosomes isolated from stem cells through different sources.

4.5. Exosomes in Ocular Disease

Preclinical studies have shown that the administration of MSC-EXs can protect against retinal ischemia (46). Shen et al. showed that AD-MSC-EX treatment regulates CSC proliferation, inhibits apoptosis, triggers higher collagen and fibronectin expression, and causes lower expression of matrix metalloproteinases in vitro (47).

4.6. Exosomes in Renal Diseases

Preclinical studies have shown that SC-EVs have a positive effect on kidney disease. EVs from human iPSC-derived MSCs (hiPSC-MSC-EVs) transport the specificity protein (SP1) to renal tubular epithelial cells, increasing the expression of sphingosine kinase 1 and inhibiting necroptosis, thus, showed that it prevents renal IRI in rats (48).

Tomasoni et al. (2013) revealed that BMSC-EXs transport insulin-like growth factor 1 (IGF-1) receptor mRNAs to renal tubular epithelial cells in vitro; these mRNAs are then translated into IGF-1 receptor proteins, which can be used to increase the sensitivity of the IGF-1 receptor to local IGF-1 and to treat cisplatin-induced renal tubule injury (49).

5. Conclusion and Future Perspectives

SC-EV therapy has made significant progress in regenerative medicine and numerous preclinical trials, laying a solid foundation for clinical transformation practice. It is important to note that selecting an early passage of EV-producing cells, optimizing techniques of cell culture conditions, and using EVs for delivery of genomic materials, proteins, or small-molecule drugs can increase their efficacy against many diseases.

However, we still have a long way to go before the clinical application of EVs. Current research mainly focuses on treating a limited number of diseases in regenerative medicine and oncology using SC-EVs. The functions of SC-EVs should be tested for many other diseases.

High-quality EVs are needed for successful results in studies. To obtain higher quality EVs, it is necessary to select the appropriate culture medium, optimize cell density, cell phenotype, culture time, collection time and other parameters. Furthermore, pre-condition EVs are similarly crucial.

On the other hand, the drug loading potential of SC-EVs should be further investigated. Genome editing techniques currently facilitate EV engineering with different contents and functions but can cause indeterminate mutations in EV-producing cells, affecting the contents and functions of related EVs. Therefore, it is necessary to improve the safety and operability of genome editing techniques, reduce off-target efficiency, and

ultimately accurately produce EVs with specific functions and components.

It is imperative to improve the drug loading efficiency of EV by novel methods. Exogenous drugs are currently loaded into EVs mainly by electroporation, but the efficacy of this technique is insufficient. Although drug loading efficacy is not proportional to therapeutic efficacy, balancing these two types of efficacies is recommended. Therefore, optimum drug concentrations with the lowest side effects may be preferred to achieve the highest therapeutic efficacy. For this, we still need to increase drug loading efficiency.

The advantages and excellent application potential of SC-EVs are driving the advancement of regenerative medicine. The future development goal should be to optimize EV production conditions, improve production technology, improve yield and quality, measure their therapeutic efficacy, design operations to give EVs more therapeutic functions, and ultimately drive their clinical transformation to benefit people more broadly. On the other hand, it is considered to have potential limitations. For example, EXs are a mixture of biologically active molecules. Some of these molecules may have beneficial effects under certain conditions, while others may have a detrimental effect (e.g., pro-inflammatory). Whether exosomes will be superior to angiogenic drugs or purified recombinant growth factors and other peptides in the context of cell-free approaches for tissue regeneration is unclear and remains an important issue to be explored.

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