Stem Cell Research & Therapy

REVIEW Open Access

Stem cell derived exosome trilogy: an epic comparison of human MSCs, ESCs and iPSCs

Siti Zawiah Abdul Malik[1†], Yugashini Muhilan[1†], Fazlina Nordin[1*], Min Hwei Ng[1], Jia Xian Law[1], Siti A. M. Imran[2], Izyan Mohd Idris[3] and Gee Jun Tye[4,5]

Abstract

Exosomes, containing molecular constituents of their cell of origin, including proteins and nucleic acids, were first discovered in immature red blood cells in 1983. Excellent intercell communication can be achieved by shuttling these various molecules between cells. Stem cell-derived exosomes (SC-Exos) contain paracrine-soluble factors that play important roles in tissue development, homeostasis, and regeneration. This paracrine activity of SC-Exos has been found to be a predominant mechanism by which stem cell-based therapies mediate their effects on degenerative, autoimmune and/or inflammatory diseases. Compared to other types of stem cells, human embryonic stem cells (hESCs), human induced pluripotent stem cells (hiPSCs), human mesenchymal stem cells (hMSCs) are the most popular because of their efficient immunomodulatory effects. The advantages and disadvantages of using exosomes isolated from the stem cell trio for therapeutic applications are further discussed in this review.

Keywords Exosomes, Stem cells, SC-Exos, hMSCs, hESCs, HiPSCs

Introduction

In recent years, exosomes derived from stem cells have shown great promise in regenerative medicine, offering an alternative to traditional cell-based therapies. Exosomes are nanosized extracellular vesicles (EVs) originating from the endosomal pathway. These particles serve as messengers between cells, transporting bioactive molecules such as ribonucleic acid (RNA), messenger ribonucleic acid (mRNA) and other functional cargos that can mimic the therapeutic functions of their parent cells [1]. In addition to their small nanoparticle size, which allows easy transport and delivery, their unique biocompatibility also presents a low risk of immune rejection and tumor formation, which is desirable in generative treatments [2]. Therefore, exosomes have emerged as attractive candidates for targeted drug delivery and tissue engineering strategies because they can transfer bioactive molecules to targeted cells [3, 4].

†Siti Zawiah Abdul Malik and Yugashini Muhilan have contributed equally to this work.

*Correspondence:
Fazlina Nordin
nordinf@hctm.ukm.edu.my
[1]Department of Tissue Engineering and Regenerative Medicine (DTERM), Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latiff, Bandar Tun Razak, Cheras, Kuala Lumpur 56000, Malaysia
[2]Ming Medical Sdn. Bhd., Dana 1 Commercial Centre, Jalan PJU 1a/46, Petaling Jaya 47301, Selangor, Malaysia
[3]Institute for Medical Research (IMR), National Institutes of Health (NIH), Ministry of Health Malaysia, Shah Alam, Selangor, Malaysia
[4]Malaysian Institute of Pharmaceuticals and Nutraceuticals, National Institutes of Biotechnology Malaysia, Halaman Bukit Gambir, 11700 Gelugor, Pulau Pinang, Malaysia
[5]Institute for Research in Molecular Medicine (INFORMM), Universiti Sains Malaysia, Gelugor, Malaysia

SC-Exos have shown great efficacy in increasing the rate of proliferation, reducing apoptosis, and promoting cell cycle [5]. Moreover, SC-Exos also harbor antimicrobial properties by directly transferring cargo proteins to targeted cells and indirectly stimulating immune responses [6]. Each type of SC-Exos has a different molecular composition, functional property, and cargo content, which contributes to their distinct therapeutic potential for various applications. Therefore, it is imperative to understand these variations to allow specific tailoring for specific treatment needs.

This review comprehensively compares exosomes derived from hiPSCs, hMSCs, and hESCs, focusing on their molecular characteristics, therapeutic potential, cargo composition, pathways, and mechanisms underlying their actions. Figure 1 shows a graphical summary of the topics discussed on the three types of SC-Exos. By examining these aspects, we aim to shed light on the advantages and limitations of each exosome type, providing a foundation for selecting the most effective exosome sources for therapeutic applications.

Stem cells: hiPSCs, hMSCs and hESCs as exosome sources

The use of hiPSCs, hMSCs, and hESCs as sources for exosome isolation and production offers different advantages and limitations based on their biological properties. hiPSCs are adult somatic cells reprogrammed to mirror an embryonic stem cell state [7]. Due to their unlimited expansion potential and low risk of tumorigenicity, hiPSCs are an interesting source for exosome production [8]. They can also be modified to create standardized off-the-shelf products and offer immense potential for autologous treatments tailored to patients' needs [9]. This presents a significant opportunity for precision and personalized treatment. Moreover, hiPSCs are also free of any ethical dilemmas, as they are easily reprogrammed from existing somatic cells.

hMSCs are multipotent stem cells that are typically isolated from various adult tissues, including bone marrow

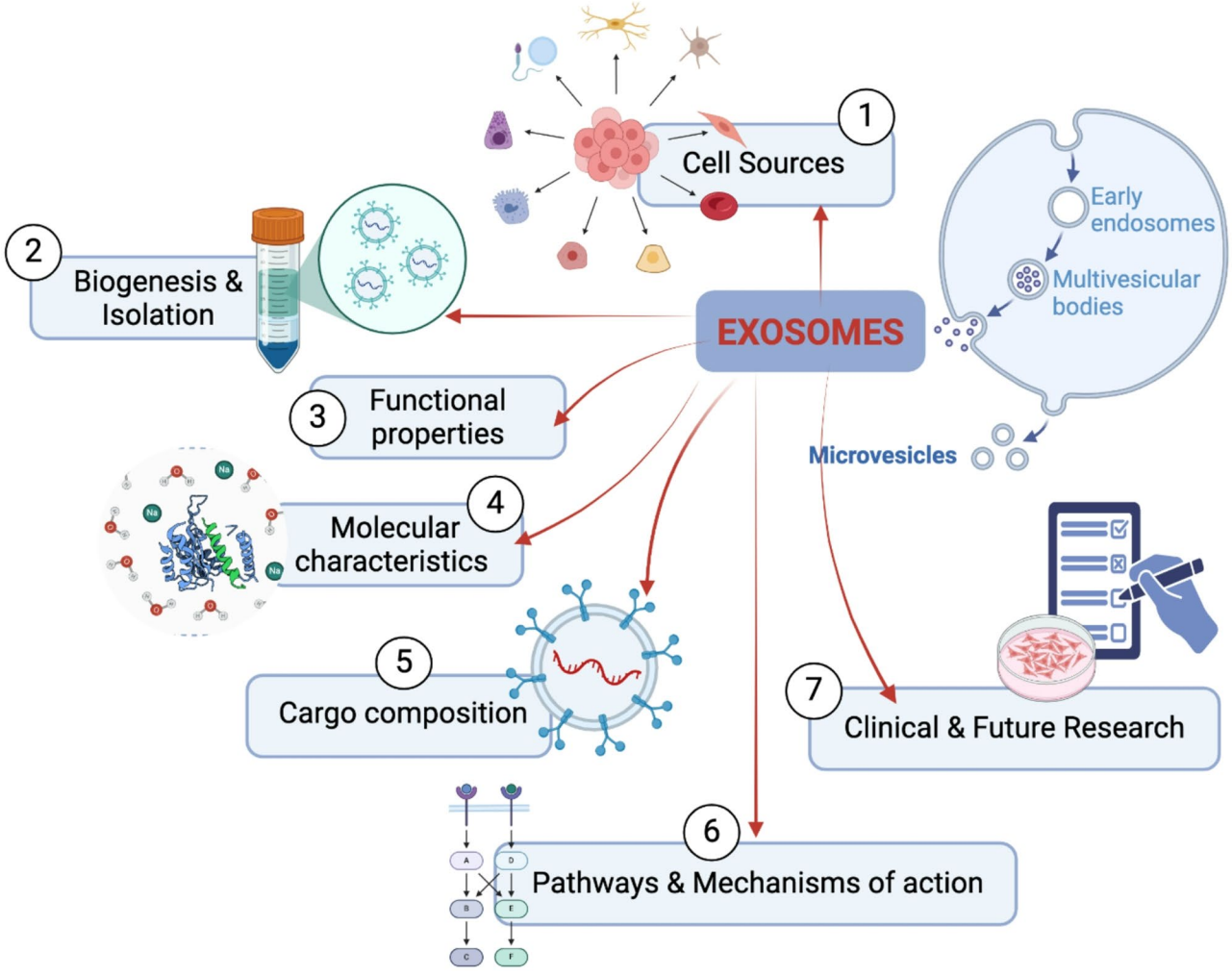

Fig. 1 Graphical summary of SC-Exos trilogy review

(BM), adipose tissue (AT), and umbilical cord (UC) [10]. hMSCs are considered an ideal source for exosome production, given that these cells are readily available, free of ethical issues, and can be isolated from diverse origins. Additionally, hMSCs not only possess the ability to secrete large amounts of exosomes and low immunogenicity but also exhibit the ability to transport cargo molecules across biological barriers, further enhancing their appeal as drug carriers [11]. hMSC-derived exosomes (hMSC-Exos) display tissue repair capabilities and homing ability and can effectively act as substitutes for hMSC transplantation, highlighting their therapeutic potential in treating cardiovascular diseases such as ischemic stroke [12] and other treatments such as wound healing [13]. These exosomes can be modified to increase their targeting ability, delivering therapeutic molecules such as microRNAs (miRNAs) to specific sites in the brain, ultimately improving post-stroke symptoms and outcomes [12].

hESCs share similar advantages with hiPSCs due to their pluripotent nature [14]. hESCs are obtained from the inner cell mass of a blastocyst [15]. Their ability to differentiate into all three germ layers makes them attractive candidates for exosome isolation. However, challenges exist in terms of the ethical concerns that surround ESCs as a source of treatment, as this dampens the enthusiasm for their use in research and studies [16]. This ethical dilemma has led to restrictions and regulations in many countries, limiting the availability of hESCs for research purposes [17, 18].

Consequently, studies related to the isolation of exosomes derived from hESCs remain relatively scarce in the current scientific literature. This trend is largely attributable to predominant research focusing on alternative cell sources, notably hiPSCs and hMSCs, which are free of consequential ethical issues. The source of stem cells plays a crucial role in determining the content and biological activity of the exosomes they produce, and understanding these differences is important for evaluating their therapeutic use.

While there are numerous studies exploring the therapeutic potential of stem cell-derived exosomes, direct comparative studies between different stem cell sources at the basic level remain limited. Exosomes from hMSCs, hiPSCs, and hESCs differ in how they are formed, what molecular cargo they carry, and how they affect target cells. hMSCs are multipotent stem cells that contain anti-inflammatory and pro-angiogenic molecules such as TGF-β, IL-10, and VEGF [19]. These factors contribute to their potential in immune modulation and tissue repair, making them particularly attractive for therapeutic applications [19]. In contrast, both hESCs and hiPSCs are pluripotent stem cells that carry common pluripotent factors like OCT4, SOX2, and NANOG [20]. These factors make them a promising cell source for regenerative medicine, promoting cell proliferation and tissue regeneration [20]. The diversity of exosomes from hMSCs is also shaped by their tissue source, such as bone marrow, adipose tissue, and umbilical cord, which affects their cargo and function. In comparison, exosomes derived from PSCs may be more consistent, as they originate from clonal populations. These differences between multipotent and pluripotent exosomes are important when deciding which cell source is more suitable for specific therapeutic applications. To better appreciate how these vesicles can be therapeutically utilized, it is essential to understand their origin, biogenesis, and isolation.

Exosomes: biogenesis and isolation techniques

Exosomes, or also commonly known as small vesicles is a subtype of extracellular vesicles (EV). Over the years, the term 'exosome' is commonly used in scientific literature to refer to small, membrane-bound extracellular vesicles, originally thought to be homogenous in origin and function [21]. However, it has become increasingly clear that the isolation of exosomes often co-purify with other types of EV, including macrovesicles and apoptotic bodies. As a result, the definition of exosomes has gradually broadened in practice. The International Society for Extracellular Vesicles (ISEV) 2018 guidelines consensus recommended EV as a more inclusive term for all membrane-bound vesicles secreted by cells [22]. In this review, the term 'exosome' is used for consistency with the original studies cited, many of which refer to small EVs characterized by their size (30–150 nm) and common markers such as CD9, CD81 and CD63.

The biogenesis of exosomes, shown in Fig. 2, began with the maturation of early endosomes into late endosomes, leading to the formation of multivesicular bodies (MVBs). During this process, inward budding of the endosomal membrane generates intraluminal vesicles (ILVs) within the MVBs. When MVBs fuse with the plasma membrane, ILVs are released into the extracellular space as exosomes. Once secreted, these exosomes move through biological fluids carrying various proteins, lipids, nucleic acids, and signalling molecules to target cells. This cargo transfer facilitates diverse cellular functions, including immune regulation, tissue repair, and cell proliferation [1].

The most common methods for isolating and purifying exosomes include ultracentrifugation, size exclusion chromatography (SEC), and immunoaffinity capture, as shown in Fig. 3. Ultracentrifugation is a widely used technique that involves a series of centrifugation steps to remove debris, organelles, and other large vesicles [24]. Initially, low-speed ultracentrifugation (300–2000 g) removes cells and debris, followed by medium-speed ultracentrifugation (10,000–20,000 g) to pellet larger

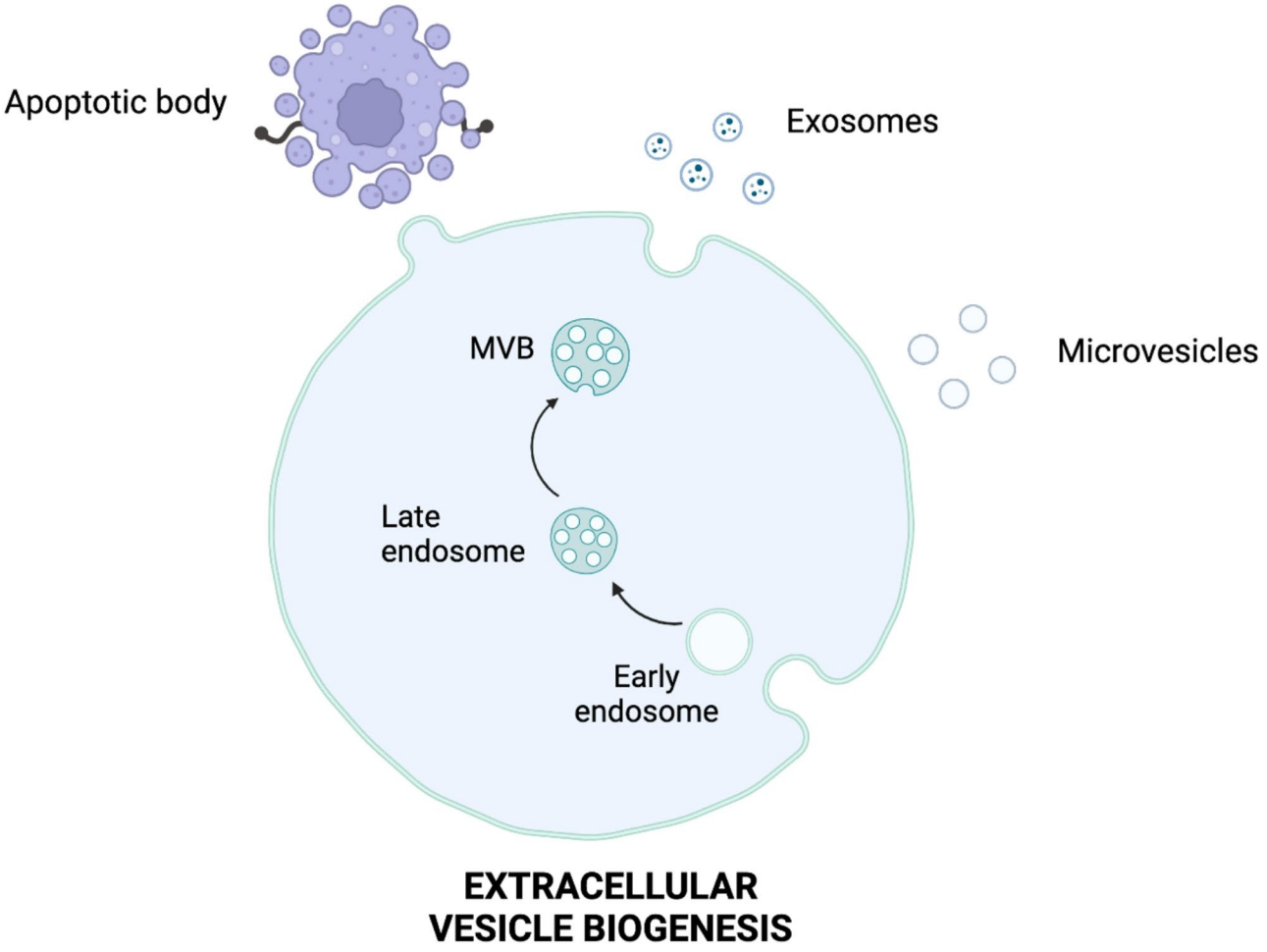

Fig. 2 Biogenesis of EVs such as exosomes, microvesicles (MVs), and apoptotic bodies. Figure adapted from [23] with modifications

EVs. Finally, high-speed ultracentrifugation (100,000 g or higher) is used to sediment exosomes while soluble proteins and smaller contaminants remain in the supernatant. However, this method may lead to exosome aggregation and may cause protein contamination. Similarly, SEC involves size-based isolation to separate exosomes from other EVs and contaminants. SEC separates exosomes based on their size rather than density. This technique is carried out by filtering fluids through a filter with a column packed with porous beads, retaining larger molecules while allowing smaller exosome particles to elute earlier [25]. Compared to ultracentrifugation, SEC maintains exosome integrity and reduces protein contamination. However, it may not completely discard co-eluting proteins and lipoproteins. Another common technique is immunoaffinity capture, where exosomes are isolated by using specific antibodies to target specific exosome markers [26]. For example, exosomal surface markers CD9, CD63, and CD81. This method allows high specificity but may result in a lower yield due to the selective capture of only marker-positive exosomes. Table 1 below outlines the advantages and disadvantages of the common isolation techniques discussed above.

While the traditional isolation and purifying methods such as ultracentrifugation and SEC are suitable and commonly used in a laboratory-scale exosome production, clinical translation requires strategies that would enable consistent exosome qualities, high yield and scalable production.

As exosome-based therapies progress towards clinical and industrial applications, the scalability of production remains a significant challenge. Ahn et al. discuss the challenges in large-scale manufacturing and quality control, particularly in cell line development, upstream processing for increased exosome yield and downstream purification methods, where the definition of 'pure' exosome fractions remains debated [29]. Traditionally, flask-based static cell culture systems are commonly used in laboratory settings for exosome production, where large number of cells are cultured in a flask with multiple wells. However, bioreactor systems such as stirred-tank reactors and hollow-fiber membranes are increasingly

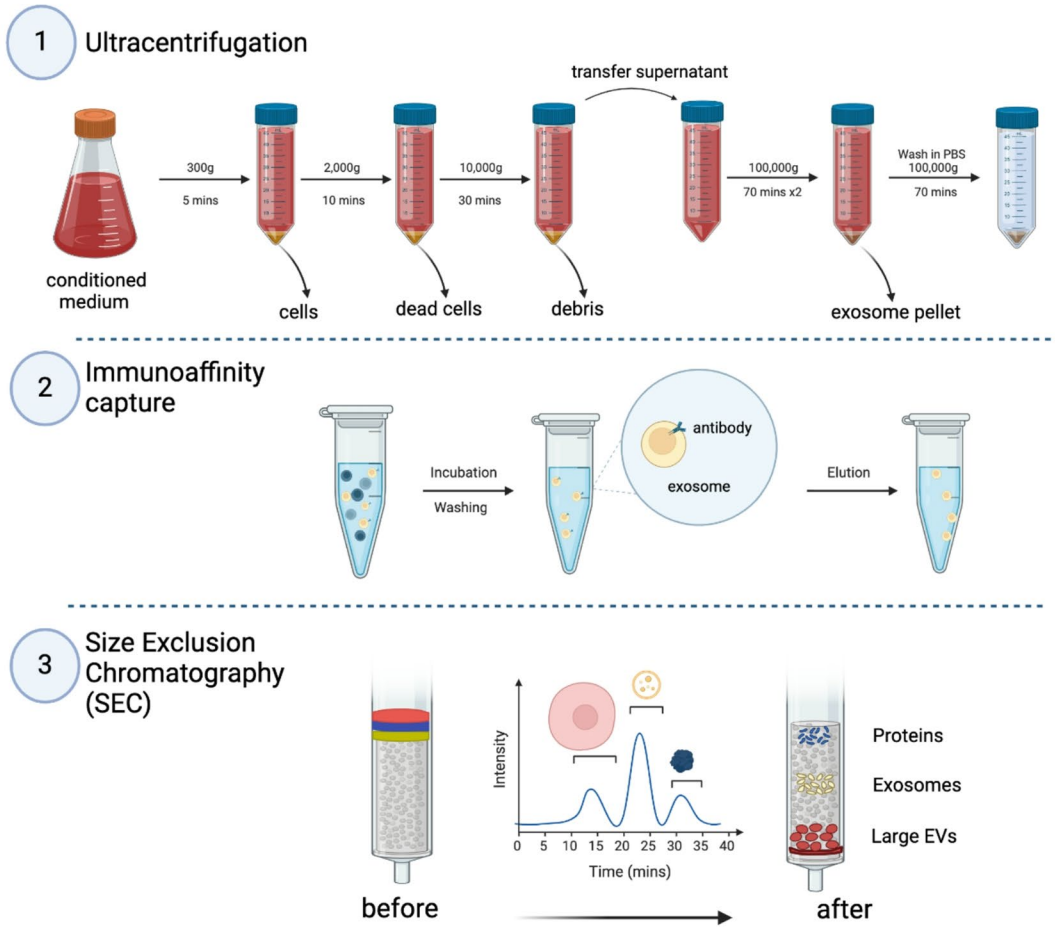

Fig. 3 Common exosome characterization techniques. (**1**) Ultracentrifugation, (**2**) immunoaffinity capture, and (**3**) SEC. Figure adapted from [27] with modifications

Table 1 Advantages and disadvantages of common exosome isolation techniques

Isolation method	Advantages	Disadvantages
Ultracentrifugation [24]	• 'Gold Standard' method • Produces highly enriched EVs fractions	• Time-consuming • Require expensive specialized equipment • Low isolation yield
Section [28]	• The biological function of exosomes is maintained (minimal sample manipulation) • Time efficient • Cost-effective	• Requires a large volume of biofluids/ supernatant • Cannot distinguish exosomes and other MVs of the same size
Immunoaffinity capture [27]	• High specificity (Targets specific markers) • High exosome purity	• Time-consuming • High cost • Strict requirements for reagent quality and storage specifications

adopted for large-scale culture. In terms of isolation, Visan et al. have shown that the combination of tangential flow filtration (TFF) and SEC is now widely used in industrial settings due to its scalability, higher purity and ability to preserve exosome integrity [30]. Despite the growing enthusiasm for exosome-based therapies, major regulatory hurdle remains: the lack of standardized guidelines or protocol for exosome manufacturing and clinical translation.

Molecular characteristics

Before investigating the efficacy of exosomes in any study, it is crucial to characterize them thoroughly. Given that exosomes are isolated from stem cell sources, other components and contaminants could be present.

Table 2 summarizes key findings on the surface markers, morphology, size range, and isolation methods of exosomes derived from hiPSCs, hMSCs, and hESCs, providing a comprehensive comparison of their molecular characteristics.

Doyle and Wang [31] reported that exosomes typically fall within the size range of 30–150 nm and are characterized by the presence of endosomal sorting complex required for transport-associated proteins such as ALG-2-interacting Protein X (Alix), tumor susceptibility gene 101 protein (TSG101), heat shock cognate 71 kDa protein, and heat shock protein 90β, along with tetraspanins CD63, CD9, and CD81. These proteins are crucial for exosome formation and are commonly enriched in exosomes, serving as key markers that facilitate their identification and confirm their purity across different stem cell sources. Furthermore, according to Lässer et al. [32], to ensure that exosome preparations are pure and free from contamination by other cellular components, it is advisable to verify the absence of specific proteins from these compartments. For example, proteins from the endoplasmic reticulum, such as calnexin and 78-kDa glucose-regulated protein, as well as Golgi apparatus proteins, such as130 kDa cis-Golgi matrix protein 1 (GM130), should not be detected in purified exosome samples. Their absence confirms that the samples are minimally

Table 2 Comparison of surface markers, morphology, and size ranges of exosomes derived from different stem cell sources

Stem cell source	Isolation method	Morphology (Technique)	Size range (Technique)	Surface markers (Technique)	References
hiPSCs	MagCapture Exosome Isolation Kit PS	spheroidal morphology Transmission electron microscope (TEM)	~100-nm diameter (TEM)	Presence: CD9, CD63, and CD81 Absence: HLA-ABC and HLA-DR (flow cytometry)	[33]
	Ultracentrifugation	Round-shaped (TEM)	~30 to 120 nm Nanoparticle Tracking Analysis (NTA)	Presence: CD9 and CD63 Absence: Calnexin (Western blot)	[5]
	Ultracentrifugation	Cup-shaped (TEM)	143.5 nm diameter (NTA)	Presence: CD9 and TSG101 Absence: Calnexin (Western blot) Presence: IgG, CD63, CD81 (Flow NanoAnalyzer)	[34]
	Ultracentrifugation	Cup-shaped (TEM)	83.83 ± 4.63 nm	Presence: Alix, heat shock protein (HSP70), CD63, CD81, and (TSG101) Absence: calnexin (western blot)	[35]
hMSC	Isolated from BM-, AT-, and UC -MSCs by ultracentrifugation	cup-shaped vesicles (TEM)	Range: 30–200 nm Mean = 150-nm diameter (NTA)	Presence: CD105, CD29, CD73, and CD44 Absence: IgG1, IgG2b, CD11b, CD34, and CD45 (flow cytometry)	[36]
	Isolated from human bone marrow mesenchymal stem cells (hBM-MSCs) by ultracentrifugation	vesicular structure (TEM)	~ 30–150 nm diameter (Scanning Electron Microscopy)	Presence: CD81 Absence: calnexin (western blot)	[37]
	Isolated from Human UC (hUC) -MSCs by sequential centrifugation	Cup-shaped (TEM)	~69.88 nm (nano flow cytometry)	Presence: Alix, CD9, CD81, and Tsg101 (western blot)	[38]
	Isolated from hUC-MSCs by ultracentrifugation	double-layered vesicles (TEM)	~30 to 120 nm (NTA)	Presence: TSG101, CD9, and CD63 Absence: Calnexin (western blot)	[39]
hESCs	ultracentrifugation	round-shaped morphology (TEM)	~75 nm (flow nano analyzer)	Presence: CD63, Alix, and TSG101 Absence: Golgi membrane bound protein GM130 (western blot)	[40]
	ultracentrifugation	cup-shaped morphology (TEM)	50–150 nm (qNano analysis)	Presence: CD9, CD63, and TSG101 Absence: cis-Golgi matrix protein GM130, Actin, and Lamin A/C	[41]
	ultracentrifugation	ball-shaped morphology (TEM)	50–125 nm (qNano analysis)	Presence: CD9 and Alix (western blot)	[42]
	ultracentrifugation	cup-like morphology (TEM)	146.3 ± 61.9 nm (NTA)	Presence: Alix, CD81, and β-actin (western blot)	[43]

contaminated by vesicles from other parts of the cell. As shown in Table 2, exosomes from hiPSCs, hMSCs, and hESCs consistently express common exosomal markers, such as CD9, CD63, CD81, and TSG101, and share similar morphological characteristics and size ranges (30–150 nm), highlighting their uniformity despite originating from different stem cell sources.

Functional properties

In a comprehensive exploration of hiPSC-derived exosomes (hiPSC-Exos), several studies have elucidated their significant roles in various cellular processes. Kobayashi et al. [33] revealed their ability to increase fibroblast migration and proliferation, thereby accelerating wound healing in diabetic mouse skin fibroblasts. Similarly, Oh et al. [44], reported that hiPSC-Exos significantly increased human dermal fibroblast proliferation without inducing cytotoxicity, indicating their potential in tissue repair. In addition to their role in wound healing, hiPSC-Exos have shown significant potential in nerve regeneration. Pan et al. [45] reported improved peripheral nerve regeneration and functional recovery in Sprague-Dawley rats with long-distance peripheral nerve defects. Intriguingly, Lu et al. [46] reported that both autologous and allogeneic hiPSC-Exos promoted wound healing and improved cell viability in skin wounds, with no significant immune rejection in rhesus macaques. These findings highlight the profound role of hiPSC-Exos in driving regeneration across diverse tissues, paving the way for their application in advanced therapeutic strategies.

Studies on the functional properties of hMSC-Exos have highlighted their significant biological activities. Wang et al. [47] reported that exosomes isolated from hMSCs have the capacity to increase endothelial cell proliferation, migration, and angiogenesis while concurrently protecting against rapamycin-induced apoptosis. In a rabbit cartilage regeneration model, Jiang et al. [48]. demonstrated that Wharton Jelly-derived hMSC-Exos combined with an acellular cartilage extracellular matrix scaffold successfully reduced joint inflammation, facilitated cartilage repair, and stimulated stem cell migration. Furthermore, Yang et al. [49] revealed the efficacy of adipose-derived hMSC-Exos in diabetic wound healing, which significantly improved angiogenesis, collagen deposition, and extracellular matrix formation, while reversing glucose-induced fibroblast dysfunction. Gao et al. [50] expanded on these findings, showing that exosomes derived from hBM-MSCs cultured on hydroxyapatite scaffolds significantly enhanced endothelial cell proliferation, migration, and angiogenesis both in vitro and in vivo. Collectively, these findings highlight the versatility of hMSC-Exos in addressing a broad range of regenerative challenges across various tissue types and conditions.

hESC-derived exosomes (hESC-Exos) exhibit diverse biological activities that significantly contribute to tissue regeneration and repair. Zhang et al. [51] demonstrated that hESC-Exos enhance cartilage repair in adult rats by stimulating chondrocyte migration, proliferation, and matrix synthesis while simultaneously reducing apoptosis and inflammation. Consistent with these findings, Chen et al. [41] reported that hESC-Exos accelerated pressure ulcer healing in aged mice by rejuvenating senescent endothelial cells and enhancing angiogenesis through the miR-200a/Nuclear Factor Erythroid 2-related Factor 2 (Nrf2) signaling pathway. The potential of hESC-Exos in combating cellular stress was further established by Hu et al. [43], who observed that hESC-Exos reduce chemotherapy-induced deoxyribonucleic acid damage in cells by reducing reactive oxygen species production. Moreover, Zhang et al. [52] showed that hESC-Exos facilitated the regeneration of cartilage and subchondral bone in a rat osteochondral defect model, with no adverse inflammatory responses. Together, these findings position hESC-Exos as transformative tools for regenerative therapies that are capable of addressing complex pathological conditions with precision.

In summary, exosomes derived from hiPSCs, hMSCs, and hESCs all exhibit significant potential in promoting cell proliferation, migration, differentiation, and tissue regeneration. The roles of hiPSC-Exos are particularly noted for their roles in wound healing and nerve regeneration, hMSC-Exos for their angiogenic and anti-inflammatory properties, and hESC-Exos for their comprehensive regenerative capabilities and immunomodulatory effects. These findings demonstrate the versatility of SC-Exos and their promising role in advancing regenerative medicine.

While the above studies offer valuable insights into the functional properties of exosomes derived from specific stem cell types, it is essential to note that they represent individual investigations focusing on a single cell type. However, to gain a comprehensive understanding and enable a direct comparison, it is imperative to conduct studies that perform side-by-side comparisons of exosomes derived from different stem cell sources within the same study, utilizing consistent parameters.

In a study conducted by Wang et al. [5], hiPSC-Exos and hMSC-Exos were compared to assess their therapeutic potential for treating corneal epithelial defects. In vitro investigations demonstrated that both hiPSC-Exos and hMSC-Exos enhanced human corneal epithelial cell proliferation and migration, as well as having antiapoptotic effects. Notably, hiPSC-Exos displayed a stronger influence on these cellular activities compared to hMSC-Exos. Subsequent in vivo evaluation using a rat epithelial mechanical injury model corroborated these findings, showing accelerated corneal epithelial defect healing with

both types of exosomes, with hiPSC-Exos demonstrating superior performance.

In conclusion, despite the wealth of research elucidating the diverse biological activities of exosomes derived from hiPSCs, hMSCs, and hESCs, there is a notable absence of direct comparative studies systematically evaluating their functional properties within the same experimental setting. This gap highlights the need for comprehensive investigations to discern the relative efficacy and therapeutic potential of exosomes derived from different stem cell sources in regenerative medicine and tissue repair applications.

Cargo composition

Exosomes, small vesicles secreted by various cell types, are pivotal in cell-to-cell communication due to their bioactive molecule content, which reflects the characteristics of their cell of origin [53]. These vesicles facilitate the transfer of vital biological information between cells [54]. The mechanisms by which exosomes are taken up by recipient or target cells, as shown in Fig. 4, include endocytosis followed by the release of their contents into the cytoplasm, receptor-ligand interactions leading to their internalization, and direct fusion with the plasma membrane [54].

Research conducted by Bobis-Wozowicz et al. [56] and Vallabhaneni et al. [57] shed light on the intricate molecular composition of EVs. These findings highlight the distinct cargo content of EVs, which encompasses a spectrum of mRNAs, miRNAs, long non-coding RNA (lncRNAs), and proteins. According to their study, some of these molecular constituents, such as specific mRNAs, miRNAs, and selective proteins in EVs, are less abundant than their levels in parent cells. This finding suggests a selective sorting mechanism into EVs that may not entirely mirror the molecular profile of the cell of origin. These studies underscore the critical notion that the cargo contents of EVs can markedly differ from those of their cell of origin, emphasizing a complex and highly regulated mechanism of EV formation and cargo selection that reflects their diverse functional roles. Thus, understanding the differences in exosomal contents among various stem cell sources, such as hiPSCs, hMSCs, and hESCs, is crucial for advancing their therapeutic potential in regenerative medicine. Table 3 compares the exosomal contents from hiPSCs, hMSCs, and hESCs.

While the cargo content of exosomes is often extensively characterized, it does not guarantee that all bioactive molecules are effectively transferred to target cells, highlighting the necessity of studies specifically designed to confirm this critical transfer. In a study by

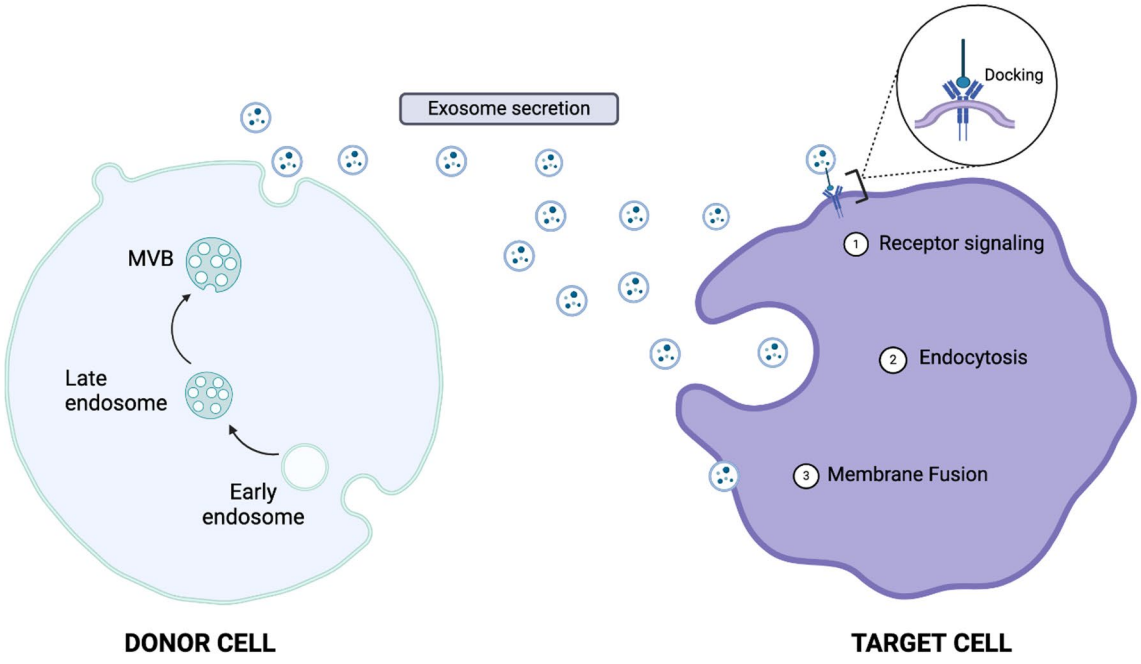

Fig. 4 Mechanisms of Exosome Uptake by Recipient Cells. Following release, exosomes aretaken up by target cells via the following steps: (**1**) Receptor-ligand interaction, (**2**) Endocytosis, and (**3**) Membrane fusion. Figure adapted from [55] with modifications

Table 3 Comparative analysis of Exosomal contents from hipscs, hMSCs, and hESCs

Stem Cell source	Cargo Type	Profiling method	Content details	Key Findings/ Significance	References
hiPSCs	RNA content	RNA content: Selective identification via real-time Polymerase Chain Reaction (PCR) for specific transcripts.	mRNA: OCT4, NANOG, SOX2, and REX1 (pluripotency); GATA4, NKX2.5, TRP63 (cardiac differentiation); TIE2, FLK1, ENDOGLIN, vWF, and VE-Cadherin (endothelial differentiation).	Present in both vesicles and hiPSCs, albeit less abundantly in vesicles Reflects potential for pluripotency and differentiation.	[56]
		miRNA content: miRNA panel analysis using a predefined panel of 720 known human miRNAs.	miRNA: 235 significantly present, abundant miRNAs include hsa-miR-423-3p, hsa-miR-1260a, hsa-miR-320a, miR-302 family.	The majority expressed at lower levels than in hiPSCs; 29 miRNAs are enriched in vesicles. Enriched miRNAs might play key roles in specific regulatory pathways.	
	Protein Content	A combination of pluripotent stem cell array kit for specific pluripotency-associated proteins and Liquid chromatography–mass spectrometry for global protein profiling	Pluripotency proteins: Lower levels of OCT4, high levels of E-Cadherin, GATA4 Global Protein Composition: 221 unique to vesicles; 637 common; 461 more abundant in cells	hiPSC vesicles enriched in receptor binding, and signal transduction proteins; hiPSCshave more gene regulation and metabolic proteins	
hMSC	RNA content	Small RNA-seq for miRNA/lncRNA profile, focusing on miRNAs and lncRNAs with known roles in cell cycle regulations; Selective Quantitative PCR (qPCR) for target RNAs	lncRNA: 7SK, Y1 miRNA: miR-21, miR-34a	Both lncRNAs enriched twofold in EVs compared to hMSCs. miR-21 is 2–3 folds higher in EVs. miR-34a follows a similar pattern, with a 3-fold increase.	[57]
	Protein content	Liquid Chromatography with tandem mass spectrometry (LC-MS/MS) for proteomics identified 156 proteins; Selective Western Blot for specific proteins in EVs versus whole cells.	PDGFR-β, LAMP2, TIMP-1, TIMP-2, CD90, CD9, CD81	Selective sorting of proteins; LAMP2, CD90, CD9, and CD81 serve as significant markers. Over 30% of proteins in EVs promote tumor growth and cell proliferation.	
hESC	RNA content	Heatmap for miRNA expression; qPCR for validation of top miRNAs	miRNA: miR-92a-3p, miR-302d-3p, miR-302b-3p, miR-222-3p, miR-17-5p, and miR-21-5p	These miRNAs are believed to play roles in intercellular communication and maintaining pluripotency.	[58]
	Protein content	Proteomics (LC-MS/MS) for untargeted protein analysis, identifying high-abundance proteins such as FGF2	Proteomic analysis of hESC-Exos identified numerous proteins, with FGF2 notably in abundance.	FGF2 stimulates mesenchymal cell proliferation (fibroblasts, endothelial, smooth muscle) and offers cardioprotection against ischaemia–reperfusion injury	[42]

Bobis-Wozowicz et al. [56], hiPSC-MVs were shown to rapidly transfer critical cytoplasmic contents, including mRNAs and miRNAs, to recipient cardio-sphere-derived mesenchymal stem cells (cMSCs) within mere hours of co-culture. This resulted in notably high expression levels of pluripotency- and differentiation-associated mRNAs, such as hSOX2 and hNKX2.5, in the cMSCs. Furthermore, this efficient transfer was further evidenced by the elevated levels of specific miRNAs, such as miR-92b-3p and miR-302b-3p, in recipient cMSCs after co-culture. Additionally, the present study revealed time-dependent upregulation of proteins involved in vital cellular functions post hiPSC-MVs treatment, revealing the depth of influence these exosomes exert on recipient cell behaviour and signalling processes.

Furthermore, Q. Liu et al. [58] highlighted the remarkable uptake of miRNAs such as miR-221-3p and miR-17-5p, which are associated with regeneration. The increased expression levels of these miRNAs in recipient cells reinforce the idea that SC-Exos play a crucial role in delivering key signals that promote a cellular environment conducive to healing and regeneration.

These observations support the hypothesis that stem cell exosomes serve as highly effective vehicles for delivering bioactive molecules, altering the transcriptomic landscape and protein expression patterns of target cells. To harness the full therapeutic potential of exosomes, particularly those derived from stem cells, it is crucial to verify the transfer of bioactive molecules to recipient cells. This step elucidates the functional pathways influenced by exosomes, revealing how they modulate cell behaviour and fate. By understanding which specific mRNAs, miRNAs, and proteins are successfully transferred and their subsequent impact on cellular processes,

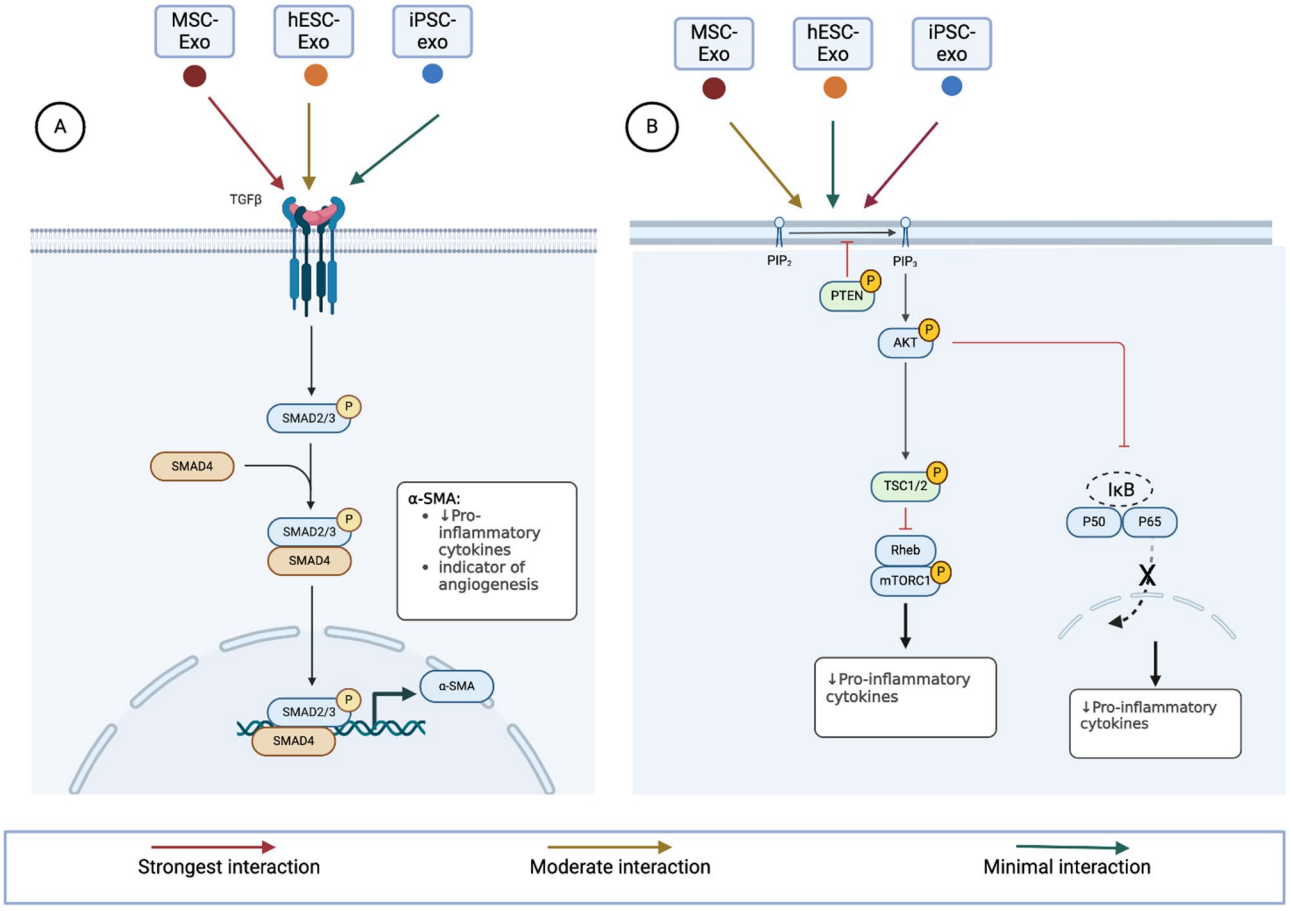

Fig. 5 MOAs of different types of SC-Exos. MOA shows distinct molecular pathways modulated by exosomes derived from hMSCs, hESCs, and hiPSCs. (**A**) TGF-β pathway (**B**) AKT pathway

researchers can better tailor exosome-based therapies for more effective disease treatment and tissue regeneration strategies.

Comparison of pathways and mechanisms of exosomal action

Exosomes derived from various stem cell sources exhibit unique pathways and mechanisms that mediate their therapeutic effects. Figure 5 shows an overview of the mechanism of action (MOA) of different types of SC-Exos. By comparing these pathways, we can better understand the specific roles of exosomes and their potential in regenerative medicine.

hMSC-Exos are known for their broad therapeutic potential, primarily through the modulation of several key signalling pathways. Gao et al. [50] identified the High Mobility Group Box 1/Protein Kinase B (HMGB1/AKT) pathway as a significant mediator of angiogenesis. This pathway is crucial for enhancing endothelial cell proliferation, migration, and tube formation, which are all vital for new blood vessel formation. Additionally, hMSC-Exos have shown anti-cancer properties, as shown in the study by Jahangiri et al. [37], where they suppress tumour growth and metastasis in colorectal cancer by modulating the miR-100/mammalian target of rapamycin (mTOR)/miR-143 axis.

Moreover, hMSC-Exos have been shown to possess strong anti-inflammatory properties. Gao et al. [38] demonstrated that these exosomes inhibit neuroinflammation by targeting the Toll-Like Receptor 2/Myeloid Differentiation Primary Response 88/Nuclear Factor kappa-light-chain-enhancer of Activated B cells (TLR2/MyD88/NF-κB) signalling pathway, effectively reducing cytokine production and microglial activation. This pathway is significant for neuroinflammation, particularly in conditions such as neuropathic pain. hESC-Exos, on the other hand, exhibit therapeutic effects across various contexts, including neuroprotective, rejuvenative, and antifibrotic effects. Gao et al. [59] identified their ability to promote Müller cell proliferation and differentiation by upregulating Brain-Derived Neurotrophic Factor (BDNF), a critical factor for neuronal survival and repair, highlighting their neuroprotective potential. Similarly, Chen et al. [41] observed that hESC-Exos rejuvenate senescent

endothelial cells by transferring miR-200a, which activates the Nrf2 pathway to reduce oxidative stress and improve cellular function.

In the context of antifibrotic effects, hESC-Exos have shown promise through the downregulation of profibrotic proteins such as Thrombospondin-2via miR-17-5p [58]. This highlights their potential in treating fibrotic diseases. Furthermore, hESC-Exos have been shown to suppress inflammation through the miR-302c/NOD-Like Receptor Family Pyrin Domain Containing 3 (NLRP3) inflammasome axis, particularly in neural progenitor cells [60], emphasizing their role in managing neurological inflammatory conditions.

hiPSC-Exos demonstrate significant regenerative capabilities, although the exact pathways involved are still being elucidated. Ye et al. [61] showed that iPSC-derived endothelial cell exosomes (hiPSC-EC-Exos) promote angiogenesis via the Notch signalling pathway, regulating Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) expression to increase vascular regeneration in ischemic tissues. This pathway is essential for the formation of new blood vessels, similar to the role of hMSC-Exos, but through a different signaling mechanism.

In liver regeneration, exosomes from hiPSC-derived-MSC-Exos (hiPSC-hMSC-Exos) have been shown to protect against hepatic ischemic/reperfusion injury by activating the sphingosine-1-phosphate (S1P) and sphingosine kinase (SK) pathways [62]. This pathway promotes hepatocyte proliferation and reduces liver damage by mitigating inflammation and oxidative stress [63]. The dual role of hiPSC-hMSC-Exos in reducing damage and promoting cell proliferation highlights their comprehensive approach to tissue regeneration.

The therapeutic potential of hMSC-Exos, hESC-Exos, and hiPSC-Exos is rooted in their ability to activate distinct molecular pathways (Fig. 4), making them uniquely suited for specific applications in regenerative medicine. hMSC-Exos and hiPSC-EC-Exos both promote angiogenesis through distinct molecular mechanisms. hMSC-Exos enhance blood vessel formation via the HMGB1/AKT (Fig. 4A) signalling pathway, as demonstrated by Gao et al. [50], whereas hiPSC-EC-Exos utilize the Notch/VEGFR2 pathway, according to Ye et al. [61]. This finding indicates that while both exosome types can support vascular growth, their distinct pathways may make them better suited for different therapeutic applications, depending on the targeted mechanism. On the other hand, the anti-inflammatory effects of hMSC-Exos and hESC-Exos also differ. hMSC-Exos act through the TLR2/MyD88/NF-κB pathway [38] (Fig. 4B), effectively moderating inflammation, whereas hESC-Exos impact the NLRP3 inflammasome [60]. This difference in pathways suggests that each type of exosome might be more effective for specific inflammatory conditions on the basis of the signaling pathway involved.

In terms of cell proliferation and rejuvenation, hESC-Exos are particularly effective due to their activation of the BDNF and Nrf2 pathways, which promote cell growth and reduce oxidative stress [41, 59], hiPSC-hMSC-Exos primarily support tissue regeneration, such as hepatocyte proliferation, through the S1P-SK signalling pathway [62, 63]. This distinction implies that hESC-Exos are better suited for therapies aimed at cellular rejuvenation and combating aging, whereas hiPSCs and hMSC-Exos are more appropriate for organ regeneration and repair.

While all these exosomes share the common feature of promoting therapeutic effects through various signalling pathways, the specific mechanisms differ depending on the stem cell source. Understanding these differences is crucial for developing targeted exosome-based therapies, as each type may be more effective in certain contexts on the basis of the pathways they influence. Despite the valuable insights provided, comparing findings from different studies on hMSC-Exos, hESC-Exos, and hiPSC-Exos can be challenging owing to variations in experimental conditions, cell types used, and other parameters. These differences may affect the outcomes and make direct comparisons less straightforward. Therefore, while the current findings are informative, more standardized and comparative studies are needed to accurately evaluate the relative effectiveness of these exosome types and refine their therapeutic applications.

Clinical and future research

The exploration of exosomes is expanding rapidly, driven by a growing number of clinical trials studying their therapeutic use. In recent years, over 100 clinical trials on exosome therapy have been registered globally, with 31 focusing on exosomes derived from stem cells [2]. To date, a database search at the Clinical Trials website (ClinicalTrials.gov, accessed in December 2024) has shown 53 searches using the keyword "stem cell exosomes". This finding shows that exosome-based therapies are actively being evaluated, reflecting the significant interest in translating these findings to clinical settings.

Among these, 6 (11.3%) studies investigated the efficacy and applications of MSC-derived exosomes, such as ointments, nebulizers, and intravenous infusions. For example, one study using nebulized exosomes derived from allogenic adipose hMSCs from patients with severe pneumonia caused by COVID-19 reported improved pulmonary lesions on computerized tomography scans, with no instability during or immediately after treatment [64]. Currently, 18 (34%) studies are actively recruiting, 13 of which focus on hMSC-Exos and three of which focus on hiPSC-Exos. Moreover, 8 studies are not yet recruiting, and the rest are withdrawn, suspended, or

have unknown statuses. Among the different stem cell sources, hMSC-Exos have become the focus of research for treatments. However, as the field progresses, the focus must be broadened beyond hMSC-Exos to include other stem cell sources, such as hiPSCs and hESCs. This broader perspective will enable the full potential of SC-Exos to be harnessed.

Conclusion

This review thoroughly discusses the comparisons between exosomes derived from various stem cell sources, mainly hiPSCs, hMSCs, and hESCs, emphasizing their comparative molecular compositions, mechanisms of action, and cargo contents. While all three exosome types have shown promising potential as therapeutic agents in regenerative medicine, their specific properties make them uniquely suited to therapeutic contexts.

hiPSC-Exos are highly effective at promoting wound healing and nerve regeneration due to their ability to differentiate and low immunogenicity. hMSC-Exos demonstrate significant anti-inflammatory and angiogenic properties, making them effective in tissue repair and cancer suppression. hESC-Exos, despite their ethical challenges, offer comprehensive regenerative capabilities and significant potential for anti-fibrotic therapies. Future research should focus on optimizing the isolation and purification processes of these exosomes, establishing standardized protocols, and exploring the therapeutic potential of exosomes derived from various stem cell sources other than hMSCs. More importantly, investigating the mechanisms of action of these exosomes will allow direct comparisons across different exosome sources, further advancing their clinical applications.

Abbreviations

SC-Exos	Stem cell-derived exosomes
hESCs	Human embryonic stem cells
hiPSCs	Human induced pluripotent stem cells
hMSCs	Human mesenchymal stem cells
EVs	Extracellular vesicles
RNA	Ribonucleic acid
mRNA	Messenger RNA
BM	Bone marrow
AT	Adipose tissue
UC	Umbilical cord
hMSC-Exos	hMSC-derived exosomes
miRNA	MicroRNA
ILVs	Intraluminal vesicles
MVBs	Multivesicular bodies
MVs	Microvesicles
SEC	Size exclusion chromatography
Alix	ALG-2-interacting Protein X
TSG101	Tumor susceptibility gene 101 protein
GM130	130 kDa cis-Golgi matrix protein 1
TEM	Transmission electron microscope
NTA	Nanoparticle tracking analysis
hBM-MSCs	Human bone marrow mesenchymal stem cells
hUC-MSCs	Human umbilical cord mesenchymal stem cells
hiPSC-Exos	HiPSC-derived exosomes
hESC-Exos	HESC-derived exosomes
Nrf2	Nuclear factor erythroid 2-related factor 2
lncRNAs	Long non-coding RNA
PCR	Polymerase chain reaction
qPCR	Quantitative PCR
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
cMSCs	Cardio-sphere-derived mesenchymal stem cell
MOA	Mechanism of action
HMGB1/AKT	High mobility group box 1/protein kinase B
mTOR	Mammalian target of rapamycin
TLR2/MyD88/NF-κB	Toll-like receptor 2/myeloid differentiation primary response 88/Nuclear Factor kappa-light-chain-enhancer of activated B cells
BDNF	Brain-derived neurotrophic factor
NLRP3	NOD-Like receptor family pyrin domain containing 3
hiPSC-EC-Exos	iPSC- derived endothelial cells exosomes
VEGFR2	Vascular Endothelial Growth Factor Receptor 2
hiPSC-hMSC-Exos	hiPSC–Derived MSC - Exos
S1P	sphingosine-1-phosphate
SK	sphingosine kinase

Acknowledgements

We would like to thank the members of the Department of Tissue Engineering and Regenerative Medicine (DTERM), Ming Medical Sdn. Bhd, and the UKM Medical Centre (UKMMC) for their support and assistance. We also thank Universiti Kebangsaan Malaysia (UKM) for the support and approval to conduct this study (Ethics approval code CTERM/FP/2024/FAZLINA NORDIN/17-JAN/1400-JAN-2024-DIS-2026).

Author contributions

Siti Zawiah Abdul Malik and Yugashini Muhilan contributed equally to this work.

Funding

This study is supported by grant FF-2024-092 provided by Ming Medical Sdn. Bhd to Universiti Kebangsaan Malaysia (UKM).

Data availability

The basic data used to support the findings of this study are included in the article. Access to the raw data could be obtained upon request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Artificial intelligence (AI)

AI tools were used solely to improve the style and readability of the human generated texts and were not employed for content creation.

Received: 24 March 2025 / Accepted: 10 June 2025
Published online: 23 June 2025

References

1. Zhang Y, Liu Y, Liu H, Tang WH. Exosomes: biogenesis, biologic function and clinical potential. Cell Bioscience. 2019;9(1):19.
2. Zhang K, Cheng K. Stem cell-derived exosome versus stem cell therapy. Nat Rev Bioeng. 2023;1(9):608–9.
3. Sharma V, Mukhopadhyay CD. Exosome as drug delivery system: current advancements. Extracell Vesicle. 2024;3:100032.
4. Xiong M, Chen Z, Tian J, Peng Y, Song D, Zhang L, et al. Exosomes derived from programmed cell death: mechanism and biological significance. Cell Communication Signal. 2024;22(1):156.

5. Wang S, Hou Y, Li X, Song Z, Sun B, Li X, et al. Comparison of exosomes derived from induced pluripotent stem cells and mesenchymal stem cells as therapeutic nanoparticles for treatment of corneal epithelial defects. Aging. 2020;12(19):19546–62.
6. Keshtkar S, Kaviani M, Soleimanian S, Azarpira N, Asvar Z, Pakbaz S. Stem Cell-Derived Exosome as Potential Therapeutics for Microbial Diseases. Front Microbiol. 2022 Feb 14 [cited 2024 Nov 15];12. Available from: https://www.frontiersin.org/journals/microbiology/articles/https://doi.org/10.3389/fmicb.2021.786111/full
7. Marei HE, Althani A, Lashen S, Cenciarelli C, Hasan A. Genetically unmatched human iPSC and ESC exhibit equivalent gene expression and neuronal differentiation potential. Sci Rep. 2017;7(1):17504.
8. Tsai ET, Peng SY, Wu YR, Lin TC, Chen CY, Liu YH, et al. HLA-Homozygous iPSC-Derived mesenchymal stem cells rescue Rotenone-Induced experimental leber's hereditary optic Neuropathy-like models in vitro and in vivo. Cells. 2023;12(22):2617.
9. Flippe L, Gaignerie A, Sérazin C, Baron O, Saulquin X, Anegon I, et al. Generation of CD34 + CD43 + Hematopoietic progenitors to induce thymocytes from human pluripotent stem cells. Cells. 2022;11(24):4046.
10. Stanko P, Kaiserova K, Altanerova V, Altaner C. Comparison of human mesenchymal stem cells derived from dental pulp, bone marrow, adipose tissue, and umbilical cord tissue by gene expression. Biomedical Papers. 2014;158(3):373–7.
11. Rao D, Huang D, Sang C, Zhong T, Zhang Z, Tang Z. Advances in mesenchymal stem Cell-Derived exosomes as drug delivery vehicles. Front Bioeng Biotechnol. 2022;9:797359.
12. Shan XQ, Luo YY, Chang J, Song JJ, Hao N, Zhao L, Immunomodulation. The next target of mesenchymal stem cell-derived exosomes in the context of ischemic stroke. World J Stem Cells. 2023;15(3):52.
13. Zakeri A, Khaseb S, Akhavan Rahnama M, Hajaliaskari A, Soufi Zomorrod M. Exosomes derived from mesenchymal stem cells: A promising cell-free therapeutic tool for cutaneous wound healing. Biochimie. 2023;209:73–84.
14. Narsinh KH, Plews J, Wu JC. Comparison of human induced pluripotent and embryonic stem cells: fraternal or identical twins?? Mol Ther. 2011;19(4):635–8.
15. Lee JE, Lee DR. Human embryonic stem cells: derivation, maintenance and cryopreservation. Int J Stem Cells. 2011;4(1):9–17.
16. Volarevic V, Bs M. M G, A V, N J, N A, Ethical and Safety Issues of Stem Cell-Based Therapy. International journal of medical sciences. 2018 Jan 1 [cited 2024 Nov 15];15(1). Available from: https://pubmed.ncbi.nlm.nih.gov/29333086/
17. Matthews KR, Moralí D. National human embryo and embryoid research policies: a survey of 22 top research-intensive countries. Regen Med. 2020;15(7):1905–17.
18. Verginer L, Riccaboni M. Stem cell legislation and its impact on the geographic preferences of stem cell researchers. Eurasian Bus Rev. 2021;11:1–27.
19. Liang W, Chen X, Zhang S, Fang J, Chen M, Xu Y, et al. Mesenchymal stem cells as a double-edged sword in tumor growth: focusing on MSC-derived cytokines. Cell Mol Biol Lett. 2021;26(1):3.
20. Swain N, Thakur M, Pathak J, Swain B. SOX2, OCT4 and NANOG: the core embryonic stem cell pluripotency regulators in oral carcinogenesis. J Oral Maxillofac Pathol. 2020;24(2):368–73.
21. Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol. 2013;200(4):373–83.
22. Théry C, Witwer,Kenneth W et al. Aikawa, Elena, Alcaraz, Maria Jose, Anderson, Johnathon D, Andriantsitohaina, Ramaroson,. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines. Journal of Extracellular Vesicles. 2018;7(1):1535750.
23. Di Bella MA. Overview and update on extracellular vesicles: considerations on exosomes and their application in modern medicine. Biology (Basel). 2022;11(6):804.
24. Coughlan C, Bruce KD, Burgy O, Boyd TD, Michel CR, Garcia-Perez JE, et al. Exosome isolation by ultracentrifugation and precipitation and techniques for downstream analyses. Curr Protoc Cell Biol. 2020;88(1):e110.
25. Yakubovich EI, Polischouk AG, Evtushenko VI. Principles and problems of exosome isolation from biological fluids. Biochem (Mosc) Suppl Ser Membr Cell Biol. 2022;16(2):115–26.
26. Filipović L, Spasojević M, Prodanović R, Korać A, Matijaševic S, Brajušković G, et al. Affinity-based isolation of extracellular vesicles by means of single-domain antibodies bound to macroporous methacrylate-based copolymer. N Biotechnol. 2022;69:36–48.
27. Chen J, Li P, Zhang T, Xu Z, Huang X, Wang R et al. Review on Strategies and Technologies for Exosome Isolation and Purification. Front Bioeng Biotechnol. 2022 Jan 5 [cited 2024 Nov 15];9. Available from: https://www.frontiersin.org/journals/bioengineering-and-biotechnology/articles/https://doi.org/10.3389/fbioe.2021.811971/full
28. Sidhom K, Obi PO, Saleem A. A review of Exosomal isolation methods: is size exclusion chromatography the best option?? Int J Mol Sci. 2020;21(18):6466.
29. Ahn SH, Ryu SW, Choi H, You S, Park J, Choi C. Manufacturing therapeutic exosomes: from bench to industry. Mol Cells. 2022;45(5):284–90.
30. Visan KS, Lobb RJ, Ham S, Lima LG, Palma C, Edna CPZ, et al. Comparative analysis of tangential flow filtration and ultracentrifugation, both combined with subsequent size exclusion chromatography, for the isolation of small extracellular vesicles. J Extracell Vesicles. 2022;11(9):12266.
31. Doyle LM, Wang MZ. Overview of extracellular vesicles, their origin, composition, purpose, and methods for exosome isolation and analysis. Cells. 2019;8(7):727.
32. Lässer C, Eldh M, Lötvall J. Isolation and characterization of RNA-Containing exosomes. J Vis Exp. 2012;(59):3037. https://doi.org/10.3791/3037
33. Kobayashi H, Ebisawa K, Kambe M, Kasai T, Suga H, Nakamura K, et al. Effects of exosomes derived from the induced pluripotent stem cells on skin wound healing. Nagoya J Med Sci. 2018;80(2):141–53.
34. Gu Z, Yin Z, Song P, Wu Y, He Y, Zhu M et al. Safety and biodistribution of exosomes derived from human induced pluripotent stem cells. Front Bioeng Biotechnol. 2022 Aug 26 [cited 2024 May 16];10. Available from: https://www.frontiersin.org/articles/https://doi.org/10.3389/fbioe.2022.949724
35. Lee CH, Hunt D, Roth JG, Chiu CC, Suhar RA, LeSavage BL, et al. Tuning pro-survival effects of human induced pluripotent stem cell-derived exosomes using elastin-like polypeptides. Biomaterials. 2022;291:121864.
36. Wang Zgang, He Z yi, Liang S, Yang Q, Cheng P, Chen A. min. Comprehensive proteomic analysis of exosomes derived from human bone marrow, adipose tissue, and umbilical cord mesenchymal stem cells. Stem Cell Research & Therapy. 2020;11(1):511.
37. Jahangiri B, Khalaj-Kondori M, Asadollahi E, Purrafee Dizaj L, Sadeghizadeh M. MSC-Derived exosomes suppress colorectal cancer cell proliferation and metastasis via miR-100/mTOR/miR-143 pathway. Int J Pharm. 2022;627:122214.
38. Gao X, Gao L, fei, Zhang Y nan, Kong X, qing, Jia S, Meng C. yang. Huc-MSCs-derived exosomes attenuate neuropathic pain by inhibiting activation of the TLR2/MyD88/NF-κB signaling pathway in the spinal microglia by targeting Rsad2. International Immunopharmacology. 2023;114:109505.
39. He L, Zhang H, Zhao N, Liao L. A novel approach in biomedical engineering: the use of Polyvinyl alcohol hydrogel encapsulating human umbilical cord mesenchymal stem cell-derived exosomes for enhanced osteogenic differentiation and angiogenesis in bone regeneration. Int J Biol Macromol. 2024;270:132116.
40. Zhu Q, Ling X, Yang Y, Zhang J, Li Q, Niu X, et al. Embryonic stem Cells-Derived exosomes endowed with targeting properties as chemotherapeutics delivery vehicles for glioblastoma therapy. Adv Sci (Weinh). 2019;6(6):1801899.
41. Chen B, Sun Y, Zhang J, Zhu Q, Yang Y, Niu X, et al. Human embryonic stem cell-derived exosomes promote pressure ulcer healing in aged mice by rejuvenating senescent endothelial cells. Stem Cell Res Ther. 2019;10:142.
42. Pang Y, Ma M, Wang D, Xia J, Wang X, Hou L, et al. Embryonic stem Cell-Derived exosomes attenuate transverse aortic constriction induced heart failure by increasing angiogenesis. Front Cardiovasc Med. 2021;8:638771.
43. Hu X, He C, Zhang L, Zhang Y, Chen L, Sun C, et al. Mesenchymal stem cell-derived exosomes attenuate DNA damage response induced by cisplatin and bleomycin. Mutat Research/Genetic Toxicol Environ Mutagen. 2023;889:503651.
44. Oh M, Lee J, Kim YJ, Rhee WJ, Park JH. Exosomes derived from human induced pluripotent stem cells ameliorate the aging of skin fibroblasts. Int J Mol Sci. 2018;19(6):1715.
45. Pan J, Zhao M, Yi X, Tao J, Li S, Jiang Z, et al. Acellular nerve grafts supplemented with induced pluripotent stem cell-derived exosomes promote peripheral nerve reconstruction and motor function recovery. Bioactive Mater. 2022;15:272–87.
46. Lu M, Peng L, Ming X, Wang X, Cui A, Li Y, et al. Enhanced wound healing promotion by immune response-free monkey autologous iPSCs and exosomes vs. their allogeneic counterparts. EBioMedicine. 2019;42:443–57.
47. Wang W, Zhao Y, Li H, Zhang Y, Jia X, Wang C, et al. Exosomes secreted from mesenchymal stem cells mediate the regeneration of endothelial cells treated with Rapamycin by delivering pro-angiogenic MicroRNAs. Exp Cell Res. 2021;399(1):112449.

48. Jiang S, Tian G, Yang Z, Gao X, Wang F, Li J, et al. Enhancement of acellular cartilage matrix scaffold by wharton's jelly mesenchymal stem cell-derived exosomes to promote osteochondral regeneration. Bioactive Mater. 2021;6(9):2711–28.
49. Yang C, Zhang H, Zeng C, Tian C, Liu W, Chen Y, et al. Exosomes from adipose-derived stem cells restore fibroblast function and accelerate diabetic wound healing. Heliyon. 2024;10(1):e22802.
50. Gao W, Liang T, He R, Ren J, Yao H, Wang K, et al. Exosomes from 3D culture of marrow stem cells enhances endothelial cell proliferation, migration, and angiogenesis via activation of the HMGB1/AKT pathway. Stem Cell Res. 2021;50:102122.
51. Zhang S, Chuah SJ, Lai RC, Hui JHP, Lim SK, Toh WS. MSC exosomes mediate cartilage repair by enhancing proliferation, attenuating apoptosis and modulating immune reactivity. Biomaterials. 2018;156:16–27.
52. Zhang S, Chu WC, Lai RC, Lim SK, Hui JHP, Toh WS. Exosomes derived from human embryonic mesenchymal stem cells promote osteochondral regeneration. Osteoarthr Cartil. 2016;24(12):2135–40.
53. Foo JB, Looi QH, How CW, Lee SH, Al-Masawa ME, Chong PP, et al. Mesenchymal stem Cell-Derived exosomes and MicroRNAs in cartilage regeneration: biogenesis, efficacy, MiRNA enrichment and delivery. Pharmaceuticals (Basel). 2021;14(11):1093.
54. Jung JH, Fu X, Yang P. Exosomes generated from iPSC-Derivatives: new direction for stem cell therapy in human heart diseases. Circul Res. 2017;120:407–17.
55. Gurung S, Perocheau D, Touramanidou L, Baruteau J. The exosome journey: from biogenesis to uptake and intracellular signalling. Cell Communication Signal. 2021;19(1):47.
56. Bobis-Wozowicz S, Kmiotek K, Sekula M, Kedracka-Krok S, Kamycka E, Adamiak M, et al. Human induced pluripotent stem cell-Derived microvesicles transmit RNAs and proteins to recipient mature heart cells modulating cell fate and behavior. Stem Cells. 2015;33(9):2748–61.
57. Vallabhaneni KC, Penfornis P, Dhule S, Guillonneau F, Adams KV, Mo YY, et al. Extracellular vesicles from bone marrow mesenchymal stem/stromal cells transport tumor regulatory microrna, proteins, and metabolites. Oncotarget. 2014;6(7):4953–67.
58. Liu Q, Bi Y, Song S, Zhu K, Qiao X, Wang H, et al. Exosomal miR-17-5p from human embryonic stem cells prevents pulmonary fibrosis by targeting thrombospondin-2. Stem Cell Res Ther. 2023;14:234.
59. Gao Y, Li H, Qin C, Yang B, Ke Y. Embryonic stem cells-derived exosomes enhance retrodifferentiation of retinal Müller cells by delivering BDNF protein to activate Wnt pathway. Immunobiology. 2022;227(3):152211.
60. Yu Y, Li W, Xian T, Tu M, Wu H, Zhang J. Human embryonic Stem-Cell-Derived exosomes repress NLRP3 inflammasome to alleviate pyroptosis in nucleus pulposus cells by transmitting miR-302c. Int J Mol Sci. 2023;24(8):7664.
61. Ye M, Ni Q, Qi H, Qian X, Chen J, Guo X, et al. Exosomes derived from human induced pluripotent stem cells-Endothelia cells promotes postnatal angiogenesis in mice bearing ischemic limbs. Int J Biol Sci. 2019;15(1):158–68.
62. Du Y, Li D, Han C, Wu H, Xu L, Zhang M, et al. Exosomes from Human-Induced pluripotent stem Cell–Derived mesenchymal stromal cells (hiPSC-MSCs) protect liver against hepatic ischemia/ reperfusion injury via activating sphingosine kinase and sphingosine-1-Phosphate signaling pathway. Cell Physiol Biochem. 2017;43(2):611–25.
63. Nong K, Wang W, Niu X, Hu B, Ma C, Bai Y, et al. Hepatoprotective effect of exosomes from human-induced pluripotent stem cell–derived mesenchymal stromal cells against hepatic ischemia-reperfusion injury in rats. Cytotherapy. 2016;18(12):1548–59.
64. Zhu YG, Shi MM, Monsel A, Dai CX, Dong X, Shen H, et al. Nebulized exosomes derived from allogenic adipose tissue mesenchymal stromal cells in patients with severe COVID-19: a pilot study. Stem Cell Res Ther. 2022;13(1):220.

Publisher's note