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Mesenchymal Stem Cells-Derived Exosomes for Wound Regeneration

Parisa Goodarzi, Bagher Larijani, Sepideh Alavi-Moghadam, Akram Tayanloo-Beik, Fereshteh Mohamadi-Jahani, Negar Ranjbaran, Moloud Payab, Khadijeh Falahzadeh, Maryamsadat Mousavi, and Babak Arjmand

P. Goodarzi and F. Mohamadi-Jahani
Brain and Spinal Cord Injury Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran

B. Larijani
Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

S. Alavi-Moghadam, A. Tayanloo-Beik, and N. Ranjbaran
Cell Therapy and Regenerative Medicine Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

M. Payab
Obesity and Eating Habits Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

K. Falahzadeh and M. Mousavi
Metabolomics and Genomics Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

B. Arjmand (✉)
Cell Therapy and Regenerative Medicine Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

Metabolomics and Genomics Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
e-mail: barjmand@sina.tums.ac.ir

Abstract

Wound healing is a complex process with the considerable burden on healthcare system. There are several cellular therapy methods that have been introduced to treat different types of wounds. Despite the advantages of cellular therapy, it is needed to overcome different limitations of this method such as; tumorigenicity and immune rejection. Accordingly, scientists have suggested cell-based vesicles and exosomes. Exosomes can promote proliferation, migration, and angiogenesis process in the wound environment. They have also some advantages such as the potential for drug and gene delivery, easy to storage, and stability in the body. These advantages make them as a novel approach in regenerative medicine without the limitations of cellular therapy. In this review, the authors emphasize on biological properties of MSC-exosomes and their therapeutic effects as a new strategy for wound regeneration.

Keywords

Exosomes · Mesenchymal stromal cells · Regenerative medicine · Transport vesicles · Wound healing

Abbreviations

ANGPT1	Angiopoietin 1
ASCs	Adipose-derived stem cells
BBB	Blood-Brain Barrier
BM-MSCs	Bone marrow-derived mesenchymal stem cells
CHA	Composite collagen–hydroxyapatite
ECM	Extra-cellular matrix
DFU	Diabetic foot ulcers
EGF	Epidermal growth factor
EVs	Extra-cellular vesicles
FDA	Food and Drug Administration
FGF 2	Fibroblast growth factor 2
IGF-1	Insulin growth factor 1
IL-1	Interlukin 1
IL-6	Interlukin 6
iPS	Induced pluripotent stem cells
MSCs	Mesenchymal stem cells
PDGF	Platelet-derived growth factor
STAT3	Signal transducer and activator of transcription 3
TGF-β1	Transforming growth factor beta 1
TNF-α	Tumor necrosis factor-alpha
UCB-MSCs	Umbilical cord blood mesenchymal stem cells
VEGF	Vascular endothelial growth factor
MSC Exo	Mesenchymal stem cells-derived exosomes
HGF	Hepatocyte growth factor
IGF-1	Insulin-like growth factor 1
SDF-1	Stromal cell-derived factor 1

1 Introduction

The skin is the outer soft tissue of the body which protects it against external agents such as infections. Damaging and loss of skin tissue integrity lead to wounds (Murphree 2017). There are several classification for wounds, including: acute or chronic wounds, penetrating or non-penetrating wounds, clean or contaminated wounds, and etc. (Percival 2002; Mohil 2012). Among different types of wounds, chronic ones as a considerable burden on healthcare system, affected ~6.7 million of people around the world and its healing costs ~$20 billion per year alone in the US (Järbrink et al. 2017). This type of wounds occurs when the natural wound healing process which includes three programmed stages (inflammatory phase, Proliferation phase, and Maturation phase) is impaired by several factors (Frykberg and Banks 2015). In this regard, investigators are looking for the safe and cost-effective approaches to wound management. Although various researches have concentrated on facilitating the wound healing process, currently definitive therapies are not available. In recent years progression in (stem) cell therapy have given the promise to improve the wound healing and the majority of studies have focused on the importance of applying mesenchymal stem cells (MSCs) in wound regeneration (Murphy and Evans 2012; You and Han 2014; Isakson et al. 2015; Zhang et al. 2015c). Despite the advantages of cell therapies, some limitations such as immunological rejection and genetic variation still exist (Herberts et al. 2011; Zhang et al. 2015c). More recent studies have revealed that the role of (stem) cells in wound healing and tissue regeneration have been mainly associated with their secretome and paracrine effects rather than their differentiation ability (Dittmer and Leyh 2014; Zhang et al. 2015c). Accordingly, many investigations have demonstrated that the exosomes which secreted by cells, strongly supports their paracrine effects (Rani et al. 2015; Zhang et al. 2015c). Exosomes are cell- secreted vesicles which can be applied as a biomarker of diseases and also can be potentially applied in the field of regenerative medicine including wound healing (De Jong et al. 2014; Edgar 2016; Bjørge et al. 2018; Jing et al. 2018). Under the scope of this review, we discuss the current state and feature perspective of MSC derived exosomes (MSC-EXO) for treatment of different types of wounds.

2 Current Treatment Strategies for Wound Regeneration

2.1 Wound Dressings

Generally, healing of wounds especially chronic wounds needs a long time and usually, if that possess the natural healing procedure, the severe scar will be induced (Kamoun et al. 2017). Therefore, the development of a method which provides acceleration of wound closure, reduction of scar formation, and promotion of wound repair, seems to play a crucial role in wound management. Accordingly, wound dressing is an almost old method which be used in different types of wounds. There are several types of wound dressing including rubber, foam, electro spun nanofiber, hydrogel, etc. that are usually composed of natural or synthetic biomaterial such as chitosan, hyaluronic acid, collagen, silicon based, cellulose, etc. (Tran et al. 2017; Zhao et al. 2017). Wound dressing can affect on wound management through various pathways. For instance, it can change wound environment, preserve the wound from bacterial infections, provide gas exchange, protect the wound from sever dryness, and maintain moist environment and consequently, it will be easy to remove without any pain (He et al. 2018; Zhou et al. 2018). It also can protect wound environment from infection during healing (Dreifke et al. 2015; Han and Ceilley 2017). However, despite several advantages, dressing cannot provide perfect peripheral circulation, fluid balance, sensation of environment and other desired conditions to promote complete regeneration. Therefore, developing new approaches to return natural skin construction and function seems to be critical (He et al. 2018).

2.2 Skin Substitutes

After sever disruptions such as burns and traumatic injuries, skin has a poor capacity to regenerate itself and needs to a suitable substitute for return its function (Jeschke et al. 2017). Skin substitutes have been largely used in various conditions such as grafts for surgical or burn defects. Based on the biological origin of skin substitutes they can be used as autografts, allografts, and xeno-grafts. Autografts are the most beneficial than others but requirement of adequate autologous skin is not possible in a single setting. Hence, allo and xeno-grafts are used as worthful alternatives because of their simple availability and ability to accelerate the healing process and help to reconstruct skin structure. In spite of the mentioned advantages of allo and xeno-grafts, immune rejection and also potential scar formation are serious disadvantages that need to be considered by investigators and clinicians (Yamamoto et al. 2018). Although, using of skin grafts and wound dressings are traditional methods, but their application would be more useful in combination with novel methods. Application of bioengineered skin substitute in skin grafts are examples of these new technologies (Yamamoto et al. 2018; Zeng et al. 2018). There are some serious limitations including: higher costs, risk of infection, antigenicity, time, and susceptibility to injury (Han and Ceilley 2017; Bhardwaj et al. 2018). Hence, scientists have focused on various novel strategies such as cell therapy and regenerative medicine. Accordingly, manufacturing bioengineered skin substitutes have been received considerable attention and investigated in recent years to replace the traditional healing methods.

2.3 Growth Factors and Cytokines

Wound healing consists of different overlapping phases including inflammatory, proliferative and remodeling (Cabral et al. 2018). Various of growth factors and cytokines are involved in controlling of these phases including: platelet-derived growth factors (PDGFs), granulocyte-macrophage colony stimulating factor (GM-CSF), and fibroblast growth factors (FGFs). It seems that PDGF as the most important factor is the first clinically approved growth factor for chronic non-healing ulcers. Several studies demonstrated the pivotal role of this factor in the

wound healing process (Embil and Nagai 2002; Werner and Grose 2003; Wang et al. 2018). In addition to PDGF, Platelets secrete other growth factors such as inflammatory cytokines (IL-1 and IL-6) to activate and recruit the neutrophils, macrophages, and fibroblasts. On the other hand, after initiating the clotting cascade and matrix formation, alpha granules are released by platelets secreting growth factors, including: epidermal growth factor (EGF), platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF- β) (Barrientos et al. 2008). They can be used in different forms such as topical gels for example, recombinant human PDGF-BB (Regranex®) is the only FDA approved growth factor (topical gel) over the past 20 years for chronic non-healing wounds especially diabetic foot ulcers (DFUs) (Han and Ceilley 2017; Laiva et al. 2018; Nakagami et al. 2018). However, there are some concerns about the excess usage of these products, such as its probable carcinogenic effects (Fürstenberger and Senn 2002). Therefore, in recent years, more novel promising methods have been introduced to provide a safe and effective strategy for wound management. In recent decade, cell therapy and regenerative medicine have opened a new horizon for investigators to develop efficient therapeutic methods for wound healing.

3 Stem Cells and Tissue Engineering Methods for Skin Repair

Stem cells have a unique capability to differentiate into various tissue specific cells. Several cells that can be derived from different tissues, such as bone marrow, peripheral blood; umbilical cord blood, and adipose tissue have been studied in preclinical and clinical wound healing studies. For instance, many clinical studies have demonstrated that autologous or allogeneic bone marrow and adipose tissue-derived MSCs can enhance the healing process of chronic wounds by inducing angiogenesis and tissue formation (Teng et al. 2014; Dreifke et al. 2015; Han and Ceilley 2017). Moreover, cell-based strategies can introduce various bio-products for clinical use in different diseases including wounds. Hence, cell therapy and regenerative medicine has progressed with developing several techniques in isolation, engraftment, and expansion of stem cells to provide safe and cost-effective products. In recent years, induced pluripotent stem cells (iPS) have been produced with reprogramming of somatic cells to provide patient or disease specific embryonic-like pluripotent stem cells and significantly reduce in rejection rate (Wilson and Wu 2015). Although, Stem cell therapy can improve chronic wound healing quality, some fundamental questions about the optimal cell population, suitable time of cell delivery, survival of transplanted cells, and the ability of cells to preserve their characterization in new conditions need to be answered (Eming et al. 2014). Additionally, such limitations in autologous skin grafting have been proposed. Accordingly, tissue engineering is a therapeutic method which creates bio-engineered tissues for regenerative medicine (Drury and Mooney 2003). Furthermore, various tissue engineering approaches were investigated by focusing on the various types of growth factors. However, the remarkable challenge in tissue engineering is providing an environment to promote pivotal mechanisms (Sorg et al. 2017). According to different stages and types of wounds, various methods have been used such as; cell delivery into the injured site, gene modification, and using scaffolds (Yu et al. 2014). There are several synthetic and natural scaffolds which can be used in tissue engineering such as: hydrogels, nano-fibrous scaffolds, composite collagen–hydroxyapatite scaffolds (CHA), etc. These scaffolds act as extra-cellular matrix (ECM) which organize cells and stimulate their growth processes to develop specific tissues. Type of scaffold strongly depends on the properties of specific application and cell types (Drury and Mooney 2003; Liu et al. 2017). One of the most common and promising types of stem cells which have been used in tissue engineering and regenerative medicine is MSCs. They can be isolated from various tissues and organs and differentiate into multiple cell lineages (Heo et al. 2018; Womack et al. 2018).

3.1 Mesenchymal Stem Cells in Wound Regeneration

3.1.1 Overview

Healing of wounds can be affected by several factors that can possess either positive or negative results. For instance, psychosocial issues (poor quality of life, low physical activity, etc.), obesity, and diseases like diabetes are influential factors. In this regard, researchers are always looking for a proper and cost-effective treatment to overcome the limitation of wound healing such as cost and effectiveness. MSCs due to their features such as differentiating potential, secreting paracrine factors, immunomodulatory effects, and self-renewal capacity are seriously considered by researchers for application in healing of wounds (Yu et al. 2014; Bai et al. 2017a, b; Wang et al. 2017).

3.1.2 Mesenchymal Stem Cells

MSCs are multipotent cells which were extracted from the bone marrow for the first time. Today, researchers have found that they can also be isolated from adipose tissue, nerve tissue, umbilical cord blood, dermis, dental pulp, placenta, synovial fluid, skeletal muscle, hair follicles and even from the circulatory system. MSCs have some properties including self-renewal differentiation potential into mesodermal, ectodermal and endodermal lineages. Based on scientific evidences, MSC is a stem cell which can express: CD29, CD44, CD73, CD90, CD105, while there is a lack of expression of CD14, CD34, CD45, CD19, CD11b, CD79α, and HLA-DR. Additionally, the other specifications of MSCs include the ability of sticking to the plastic surfaces, immunomodulatory features, homing and in vitro long-term banking and cryopreservation neuroprotection secretion of cytokines and growth factors proliferation (Dominici et al. 2006; Teng et al. 2014; Yu et al. 2014; Ullah et al. 2015; Lopez-Verrilli et al. 2016; Spees et al. 2016; Perez-Hernandez et al. 2017). Hence, according to these remarkable characteristics, MSCs can play a special role in cell therapy, treatment of various diseases, and tissue regeneration. For instance, in the wound regeneration processes, angiogenesis, immunomodulatory properties, and anti-inflammatory effects are resulted from their multi-lineage differential potential of MSCs (Lee et al. 2012; Scott Maxson et al. 2012; Yu et al. 2014; Lee et al. 2016). In addition, they can enhance angiogenesis and accelerate re-epithelialization by releasing vascular endothelial growth factor, pro-angiogenic factors, and angiopoietin-1 (ANGPT1) as their paracrine effect (Yu et al. 2014; Yáñez-Mó et al. 2015; Lee et al. 2016). On the other hand, MSCs can reduce inflammation, granulation tissue formation and scar formation. Reducing inflammation may have an effect on reduction of scar formation by decreasing fibrosis (Scott Maxson et al. 2012; Nuschke 2014). Furthermore, based on the antibacterial properties, they can also control bactericidal activities which are regulated by immune cells and decrease the rate of bacterial infection (Duscher et al. 2016). MSCs from different sources have different effects on wound regeneration. Therefore, various sources of MSCs were used for treatment of different types of wounds. Furthermore, several studies are trying to introduce MSC-derived exosomes (MSC-exosomes) as a safer alternative. Various secretory factors such as extra-cellular vesicles are released from MSCs. Nowadays, several studies revealed that exosomes as a type of these vesicles may have therapeutic potentials (Teng et al. 2014; Yu et al. 2014; Rani and Ritter 2016).

4 Stem Cell-Derived Exosomes

4.1 Overview

Cellular communication is essential for the proper coordination, normal function of living cells, and their acts against damages and traumas. This process occurs through transmitting different signals (such as cell-surface molecules and secreted molecules) which can come from the adjacent cells and also their environment. These signals can be transferred over the cell membrane and sometimes they can operate by communicating

with receptor proteins which are in close-contact with both the inside and outside of the cell (Rossello and Kohn 2010; Raposo and Stoorvogel 2013; Turturici et al. 2014). The releasing of extra-cellular vesicles (EVs) by cells is considered as the main mechanism which makes a communication between the cells. Any cell types can be able to produce various classes of EVs including exosomes and micro-vesicles (MVs) (De Jong et al. 2014; Keshtkar et al. 2018). In contrast to micro-vesicles (which are formed from the apoptotic bodies and plasma membrane), exosomes have an endocytic origin. Additionally, exosomes are carrying active signals which can influence the function of the target cells (Marote et al. 2016). According to the body of literature, use of exosomes in the field of regenerative medicine can put it forward as a cell-free therapy with promising curative outcomes (Marote et al. 2016; Cobelli et al. 2017).

4.2 Exosomes

Exosomes are extra-cellular nano-vesicles (30–150 nm) which transfer active cargoes between the cells (Zhang and Grizzle 2014; Marote et al. 2016). They have a particular compound of lipids, RNAs, and proteins which enveloped by a phospholipid layer. These type of EVs can be found in different body fluids such as plasma, cerebrospinal fluid, breast milk, urine, amniotic fluid, and saliva (Looze et al. 2009; Zhang and Grizzle 2014; Marote et al. 2016). Exosomes were discovered about 30 years ago (in the 1980s) by the Johnstone and their colleagues, for the first time (Théry 2011; Lin et al. 2015). There are some conventional methods of exosomes isolation including ultracentrifugation, immune-affinity capture techniques, density gradient separation, chromatography, and using commercial kits such as polymer-based precipitation. On the other hand, some proteins are known as particular exosomal markers such as CD9, CD63, and CD81 which can use for exosome identification (Zhang and Grizzle 2014; Marote et al. 2016). In recent years, the biomarker role of exosomes has attracted a great interest because of their considerable potential in the diagnosis of various diseases (De Jong et al. 2014; Hessvik and Llorente 2017). One of the most common approaches of regenerative medicine is cell-based therapy in which cells are applied for tissue repair either through direct manner or paracrine effects (Dittmer and Leyh 2014). There are several pathways of cell communication in the setting of paracrine functions. One of them is performed by their secreted factors and cytokines. Most of these factors are released as cargoes of exosomes, not essentially as soluble elements (Camussi et al. 2010; Dittmer and Leyh 2014; Vishnubhatla et al. 2014). In recent decades, regenerative medicine has focused on the development of MSC and their derived exosomes in treatment of various diseases and different damaged tissues such as wounds (Lou et al. 2017; Vizoso et al. 2017).

4.3 MSCs-Derived Exosomes

Multiple studies have indicated the role of MSCs in regenerative medicine through the paracrine effects and producing different types of EVs including exosomes which carry as cargoes micro RNAs, mRNAs, and proteins (Phinney and Pittenger 2017). Although MSC-exosomes are same as other exosomes in morphology and also expression of the markers, but their RNA and protein composition are completely different. On the other hand, in contrast to other types of exosomes, MSC-exosomes play a fundamental role in altering the function of target cells through the horizontal transfer of their composition (Bai et al. 2017a, b; Phinney and Pittenger 2017). Additionally, according to several studies, MSC-exosomes from different sources are also different in function (Katsuda et al. 2013; Lopez-Verrilli et al. 2016; Bai et al. 2017a, b). In general, the composition of MSC-exosomes affects on differentiation and regenerative capacity of MSCs and give them a crucial therapeutic task (Nawaz et al. 2016).

5 Biological Properties of MSCs-Derived Exosomes

Recent investigations have indicated that MSC-exosomes due to their biological properties, are as potent as their sources (Batrakova and Kim 2015; Nooshabadi et al. 2018). These types of exosomes avoid degradation and phagocytosis by macrophages, circulate for prolonged periods of time within the body, and penetrate the blood-brain barrier (BBB). On the other hand, they attach to target cells by means of receptor ligands and cell surface proteins, and transfer their specific cargoes to target cells. Therefore, they can be suggested as appropriate vehicles for drug delivery (Lou et al. 2017). Additionally, MSC-exosomes can repress activation of T-cells and contribute to preserving immune homeostasis (Baquir and Hancock 2017; Casado et al. 2017). Hence, they can store safely and provide cell-free therapy without any risk of tumorigenicity and immunological rejection (Bai et al. 2017a, b). Moreover, they can support MSCs' functions within the preservation of homeostatic microenvironment (Lou et al. 2017). Finally, gathering all of biological properties in MSC-exosomes have changed them to a valuable cell-free therapy which can use in regenerative medicine.

6 Clinical Applications of MSCs-Derived Exosomes

As the mentioned, several studies have exhibited that the useful outcomes of MSC therapy are mainly resulted from their paracrine effects not trans-differentiation and engraftment. Accordingly, as MSC-exosomes contain of various secretory mediators derived from MSCs, they can use in cell-free therapeutic settings (Chen et al. 2017). Nowadays, scientists have paid a lot of attention to specific cargos of MSC-exosomes and their curative potential in different pathological conditions including immune disease, neurodegenerative disorders, cardiovascular and liver diseases, and also skin tissue damages. In addition, exososmes can be used as biomarkers for early diagnosis in different disease, especially cancers (Cheng et al. 2017). On the other hand, these vesicles have a low toxicity, and can tolerate the body environment –proved by ubiquitous presence in natural body fluids- compared with other curative tools such as transplanted (stem) cells. In summary, all of the mentioned properties of MSC-exosomes, have introduced them as a potential therapeutic techniques (Suntres et al. 2013).

7 Therapeutic Effect of MSCs-Derived Exosomes in Wound Regeneration

The wound healing cascade includes a series of molecular and cellular events such as angiogenesis, proliferation, cellular migration, tissue remodeling, and extra-cellular matrix deposition (Sinno and Prakash 2013). This cascade can be promoted by different types of biological molecules extracted from the exosomes (Than et al. 2017) through the various complex mechanisms (Table 1).

Composition of the exosomes can easily deliver the massage of signaling cells into target cells (e.g. endothelial, keratinocytes, and fibroblast) due to their lipid layer which can avoid proteolytic degradation (Schwab et al. 2015). Further, MSC-exosomes can activate some signaling pathways including STAT3, AKT, Wnt/β-catenin, and ERK in target cells which play an important role in wound healing process (Rani and Ritter 2016). Activation of these signaling pathways also can enhance the expression of several growth factors which involved in wound regeneration process by target cells, such as Interleukin-6 (IL-6), Signal Transducer and Activator of Transcription 3 (STAT3), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), and stromal cell-derived factor – 1 (SDF-1) (Hu et al. 2016; Rani and Ritter 2016). Accordingly, these growth factors can promote the angiogenesis, cell migration, cell proliferation, and re-epithelialization (Rani and Ritter 2016). On the other hand, it has been revealed that MSC-exosomes in wound environment can

Table 1 Sources and mechanisms of MSCs-derived exosomes in wound healing

References	Exosomes source	Model	Wound type	Effect
Zhang et al. (2015b)	Human umbilical cord mesenchymal stem cell (HUC-MSCs)	Rat	Second-degree burn	Promote angiogenesis
Zhang et al. (2015c)	Human induced pluripotent mesenchymal stem cell (hiPSC-MSCs)	Rat	Created wound on the dorsal skin	Promote collagen maturity angiogenesis
Shabbir et al. (2015)	Bone marrow mesenchymal stem cell (BM-MSCs)	Human	Diabetic wound	Promote angiogenesis
				Enhance fibroblast migration and proliferation
				Increase STAT3 genes
Liang et al. (2016)	Human adipose mesenchymal stem cell (adMSCs)	Mice	_	Promote angiogenesis
				Transfer miR125a to endothelial cell
Zhang et al. (2015a)	Human umbilical cord mesenchymal stem cell (HUC-MSCs)	Rat	Second-degree burn	Promote proliferation, migration, Re-epithelialization
				Inhibit apoptosis
Li et al. (2016)	Human umbilical cord mesenchymal stem cell (HUC-MSCs)	Rat	Third-degree burn	Decrease inflammation
Zhang et al. (2016)	Human umbilical cord mesenchymal stem cell (HUC-MSCs)	Rat	Deep second-degree burn	Promote self-regulation of Wnt/b-catenin signaling at the remodeling phase
Hu et al. (2016)	Human adipose mesenchymal stem cell (adMSCs)	Mice	Inguinal wound	promote migration, proliferation and collagen synthesis of fibroblasts.
Fang et al. (2016)	Umbilical cord mesenchymal stem cell (UC-MSCs)	Mice	Remove skin	Promote angiogenesis
				Reduce immune response
				Stimulate endogenous stem cell recruitment and proliferation

transfer Wnt4 to stimulate Wnt/β-catenin pathway in skin cells, and subsequently active AKT pathway to inhibit skin cell apoptosis. β-catenin signaling pathway also can stimulate pro-angiogenic effects in endothelial cells and enhance cutaneous wound healing (Zhang et al. 2015a; Rani and Ritter 2016). In general, several signaling pathways and biomolecules can be activated by MSC-exosomes to improve the wound healing outcomes (Fig. 1).

8 Conclusion

Nowadays, many therapeutic methods have been developed for different types of wounds. Cell-based therapy is one of the promising methods which have been widely used in recent years. Variety of stem cells can be used in this era specifically for reducing scars following wound healing (Han and Ceilley 2017). Beside tremendous advantages of cell therapy, it has some serious limitations such as: tumorigenicity and immune rejection. To overcome these limitations more novel cell-free therapies have been developed by scientists which demonstrated interesting therapeutic effects. One of the considerable cell-free methods is using exosomes which can be extracted from different sources. Exosomes that contain siRNA, DNA, protein, miRNA, and peptides can moderate and regulate gene expression in target cells (Fang et al. 2016; Pham 2017). According to the capacities of exosomes especially MSC-derived exosomes in regulation and carrying signal and various pathways (inflammation, apoptosis, immune response, migration and proliferation), they can play an important role in promoting the wound healing cascade and worthful therapeutic effects. Additionaly, using of exosomes have been proposed for different applications such as: apoptosis, inflammation, cardiac remodeling, and

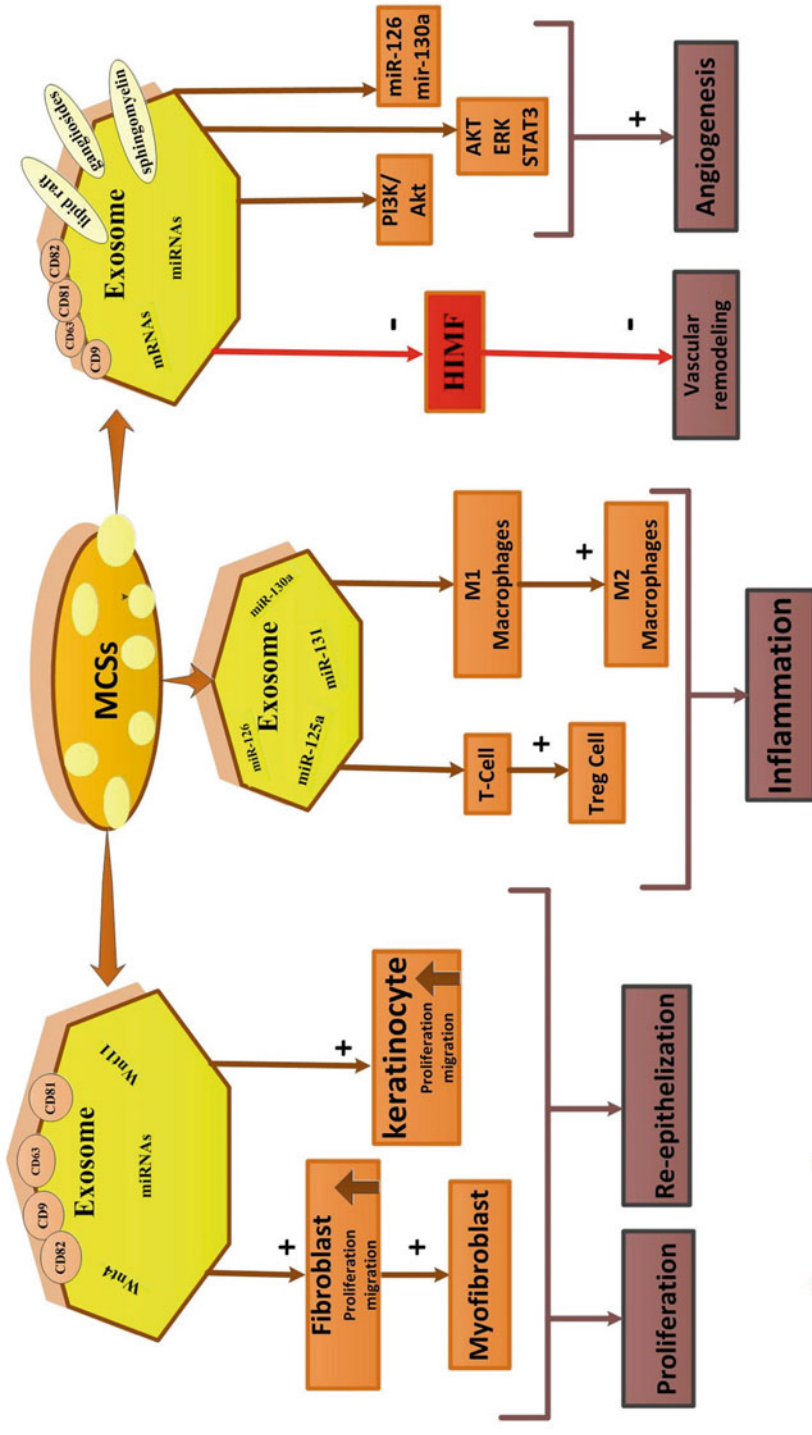

Fig. 1 MSCs-derived exosomes mediate different phases of wound healing. MSC-exosomes lead to proliferation and re-epithalization by enhancing proliferation and migration of fibroblasts and keratinocytes through mediating activation of several factors. MSC-exosomes enhance wound healing by delivering Wnt4 (Zhang et al. 2015a). MSC-exosomes can exhibit immunosuppressive effects by regulating proliferation and differentiation of lymphocytes, MSC-exosomes can repress T-lymphocyte proliferation and they exchange T lymphocytes into the T-regulatory phenotype. MSC-exosomes also enhance converting of macrophages toward the anti-inflammatory M2 phenotype in the inflammation phase (Silva et al. 2017). MSC-exosomes exhibit angiogenic effects through several mechanism (Wu et al. 2018), they cause anti-vascular remodeling by suppress HIMF (Huang et al. 2015)

cardiac regeneration in cardiovascular system, myocardial ischemia/reperfusion (MI/R) injury, and cancers (Raposo and Stoorvogel 2013; Zhang et al. 2015a, b; Rager et al. 2016; Pham 2017). Also, they are widely used in cutaneous wound healing (Monsel et al. 2016; Pashoutan Sarvar et al. 2016; Sun et al. 2016). Hence, MSC-exosomes could be candidate as the alternative of cell therapy methods (Herberts et al. 2011; Wu et al. 2018). On the other hand, many researchers drew attention to special features of exosomes on drug (Lou, Chen et al. 2017) and gene delivery (Samanta et al. 2017). Despite the several clinical trials, their safety and potency and also their task in drug/gene delivery are still unanswered (Cheng et al. 2017). In this regard, the International Society for Extracellular Vesicles was established in 2011, to develop this knowledge around the world (Raposo and Stoorvogel 2013). Nevertheless, more preclinical and clinical studies are needed to reveal unknown aspects of exosomes and their therapeutic effects.

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References

Bai L, Shao H et al (2017a) Effects of mesenchymal stem cell-derived exosomes on experimental autoimmune uveitis. Sci Rep 7(1):4323

Bai L, Shao H et al (2017b) Effects of mesenchymal stem cell-derived exosomes on experimental autoimmune uveitis. Sci Rep 7(1):017–04559

Baquir B, Hancock RE (2017) Exosomes, your body's answer to immune health. Ann Transl Med 5(4):81

Barrientos S, Stojadinovic O et al (2008) Growth factors and cytokines in wound healing. Wound Repair Regen 16(5):585–601

Batrakova EV, Kim MS (2015) Using exosomes, naturally-equipped nanocarriers, for drug delivery. J Control Release 219:396–405

Bhardwaj N, Chouhan D et al (2018) 3D functional scaffolds for skin tissue engineering. Functional 3D Tissue Engineering Scaffolds, Elsevier, pp 345–365

Bjørge IM, Kim SY et al (2018) Extracellular vesicles, exosomes and shedding vesicles in regenerative medicine–a new paradigm for tissue repair. Biomater Sci 6(1):60–78

Cabral J, Ryan AE et al (2018) Extracellular vesicles as modulators of wound healing. Adv Drug Deliv Rev 129:394–406

Camussi G, Deregibus MC et al (2010) Exosomes/microvesicles as a mechanism of cell-to-cell communication. Kidney Int 78(9):838–848

Casado JG, Blázquez R et al (2017) Mesenchymal stem cell-derived exosomes: immunomodulatory evaluation in an antigen-induced synovitis Porcine Model. Front Vet Sci 4:39

Chen B, Li Q et al (2017) Stem cell-derived extracellular vesicles as a novel potential therapeutic tool for tissue repair. Stem Cells Transl Med 6(9):1753–1758

Cheng L, Zhang K et al (2017) Focus on mesenchymal stem cell-derived exosomes: opportunities and challenges in cell-free therapy. Stem Cells Int 2017:6305295

Cobelli NJ, Leong DJ et al (2017) Exosomes: biology, therapeutic potential, and emerging role in musculoskeletal repair and regeneration. Ann N Y Acad Sci 1410:57–67

De Jong OG, Van Balkom BW et al (2014) Extracellular vesicles: potential roles in regenerative medicine. Front Immunol 5:608

Dittmer J, Leyh B (2014) Paracrine effects of stem cells in wound healing and cancer progression. Int J Oncol 44 (6):1789–1798

Dominici M, Le Blanc K et al (2006) Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 8(4):315–317

Dreifke MB, Jayasuriya AA et al (2015) Current wound healing procedures and potential care. Mater Sci Eng C Mater Biol Appl 48:651–662

Drury JL, Mooney DJ (2003) Hydrogels for tissue engineering: scaffold design variables and applications. Biomaterials 24(24):4337–4351

Duscher D, Barrera J et al (2016) Stem cells in wound healing: the future of regenerative medicine? A mini-review. Gerontology 62(2):216–225

Edgar JR (2016) Q&A: What are exosomes, exactly? BMC Biol 14(1):46

Embil JM, Nagai MK (2002) Becaplermin: recombinant platelet derived growth factor, a new treatment for healing diabetic foot ulcers. Expert Opin Biol Ther 2 (2):211–218

Eming SA, Martin P et al (2014) Wound repair and regeneration: mechanisms, signaling, and translation. Sci Transl Med 6(265):3009337

Fang S, Xu C, Zhang Y, Xue C, Yang C, Bi H, Qian X, Wu M, Ji K, Zhao Y, Wang Y, Liu H, Xing X (2016) Umbilical cord-derived mesenchymal stem cell-derived exosomal micrornas suppress myofibroblast differentiation by inhibiting the transforming growth factor-beta/SMAD2 pathway during wound healing. Stem Cells Transl Med 5(10):1425–1439

Frykberg RG, Banks J (2015) Challenges in the treatment of chronic wounds. Adv Wound Care 4(9):560–582

Fürstenberger G, Senn H-J (2002) Insulin-like growth factors and cancer. Lancet Oncol 3(5):298–302

Han G, Ceilley R (2017) Chronic wound healing: a review of current management and treatments. Adv Ther 34 (3):599–610

He P, Zhao J et al (2018) Bioprinting of skin constructs for wound healing. Burns & Trauma 6(1):5

Heo SJ, Szczesny SE et al (2018) Expansion of mesenchymal stem cells on electrospun scaffolds maintains stemness, mechano-responsivity, and differentiation potential. J Orthop Res 36(2):808–815

Herberts CA, Kwa MS et al (2011) Risk factors in the development of stem cell therapy. J Transl Med 9 (1):29

Hessvik NP, Llorente A (2017) Current knowledge on exosome biogenesis and release. Cell Mol Life Sci:1–16

Hu L, Wang J, Zhou X, Xiong Z, Zhao J, Yu R, Huang F, Zhang H, Chen L (2016) Exosomes derived from human adipose mensenchymal stem cells accelerates cutaneous wound healing via optimizing the characteristics of fibroblasts. Sci Rep 6:32993

Huang L, Ma W et al (2015) Exosomes in mesenchymal stem cells, a new therapeutic strategy for cardiovascular diseases? Int J Biol Sci 11(2):238–245

Isakson M, De Blacam C et al (2015) Mesenchymal stem cells and cutaneous wound healing: current evidence and future potential. Stem Cells Int 2015:1–12

Järbrink K, Ni G et al (2017) The humanistic and economic burden of chronic wounds: a protocol for a systematic review. System Rev 6(1):15

Jeschke MG, Sadri A-R et al (2017) A surgical device to study the efficacy of bioengineered skin substitutes in mice wound healing models. Tissue Eng Part C: Methods 23(4):237–242

Jing H, He X et al (2018) Exosomes and regenerative medicine: state of the art and perspectives. Transl Res 196:1–16

Kamoun EA, Kenawy E-RS et al (2017) A review on polymeric hydrogel membranes for wound dressing applications: PVA-based hydrogel dressings. J Adv Res 8(3):217–233

Katsuda T, Tsuchiya R et al (2013) Human adipose tissue-derived mesenchymal stem cells secrete functional neprilysin-bound exosomes. Sci Rep 3:1197

Keshtkar S, Azarpira N et al (2018) Mesenchymal stem cell-derived extracellular vesicles: novel frontiers in regenerative medicine. Stem Cell Res Ther 9:63

Laiva AL, O'Brien FJ et al (2018) Innovations in gene and growth factor delivery systems for diabetic wound healing. J Tissue Eng Regen Med 12(1):e296–e312

Lee Y, El Andaloussi S et al (2012) Exosomes and microvesicles: extracellular vesicles for genetic information transfer and gene therapy. Hum Mol Genet 21 (R1):R125–R134

Lee DE, Ayoub N et al (2016) Mesenchymal stem cells and cutaneous wound healing: novel methods to increase cell delivery and therapeutic efficacy. Stem Cell Res Ther 7(1):37

Li X, Liu L, Yang J, Yu Y, Chai J, Wang L, Ma L, Yin H (2016) Exosome derived from human umbilical cord mesenchymal stem cell mediates mir-181c attenuating burn-induced excessive inflammation. EBioMedicine 8:72–82

Liang X, Zhang L, Wang S, Han Q, Zhao RC (2016) Exosomes secreted by mesenchymal stem cells promote endothelial cell angiogenesis by transferring miR-125a. J Cell Sci 129(11):2182–2189

Lin J, Li J et al (2015) Exosomes: novel biomarkers for clinical diagnosis. Sci World J 2015:657086

Liu L, Jin X et al (2017) Exosomes derived from mesenchymal stem cells rescue myocardial ischaemia/reperfusion injury by inducing cardiomyocyte autophagy via AMPK and Akt pathways. Cell Physiol Biochem 43(1):52–68

Looze C, Yui D et al (2009) Proteomic profiling of human plasma exosomes identifies PPARγ as an exosome-associated protein. Biochem Biophys Res Commun 378(3):433–438

Lopez-Verrilli M, Caviedes A et al (2016) Mesenchymal stem cell-derived exosomes from different sources selectively promote neuritic outgrowth. Neuroscience 320:129–139

Lou G, Chen Z et al (2017) Mesenchymal stem cell-derived exosomes as a new therapeutic strategy for liver diseases. Exp Mol Med 49(6):e346

Marote A, Teixeira FG et al (2016) MSCs-derived exosomes: cell-secreted nanovesicles with regenerative potential. Front Pharmacol 7:231

Mohil R (2012) Classification of wounds. Principles and practice of wound care 1:42–52

Monsel A, Zhu YG et al (2016) Mesenchymal stem cell derived secretome and extracellular vesicles for acute lung injury and other inflammatory lung diseases. Expert Opin Biol Ther 16(7):859–871

Murphree RW (2017) Impairments in Skin Integrity. Nurs Clin 52(3):405–417

Murphy PS, Evans GR (2012) Advances in wound healing: a review of current wound healing products. Plastic Surg Int 2012:1–8

Nakagami H, Sugimoto K et al (2018) Physician-initiated clinical study of limb ulcers treated with a functional peptide, SR-0379: from discovery to a randomized, double-blind, placebo-controlled trial. NPJ Aging Mech Dis 4(1):2

Nawaz M, Fatima F et al (2016) Extracellular vesicles: evolving factors in stem cell biology. Stem Cells Int 2016:1–17

Nooshabadi VT, Mardpour S et al (2018) The extracellular vesicles-derived from mesenchymal stromal cells: a new therapeutic option in regenerative medicine. J Cell Biochem

Nuschke A (2014) Activity of mesenchymal stem cells in therapies for chronic skin wound healing. Organogenesis 10(1):29–37

Pashoutan Sarvar D, Shamsasenjan K et al (2016) Mesenchymal Stem Cell-Derived Exosomes: New

Opportunity in Cell-Free Therapy. Adv Pharm Bull 6 (3):293–299
Percival NJ (2002) Classification of wounds and their management. Surgery-Oxford Int Edition 20 (5):114–117
Perez-Hernandez J, Redon J et al (2017) Extracellular vesicles as therapeutic agents in systemic lupus erythematosus. Int J Mol Sci 18(4):717
Pham PV (2017) Concise review: extracellular vesicles from mesenchymal stem cells as cellular therapy. BioMed Press:2198–4093
Phinney DG, Pittenger MF (2017) Concise review: MSC-derived exosomes for cell-free therapy. Stem Cells 35(4):851–858
Rager TM, Olson JK et al (2016) Exosomes secreted from bone marrow-derived mesenchymal stem cells protect the intestines from experimental necrotizing enterocolitis. J Pediatr Surg 51(6):942–947
Rani S, Ritter T (2016) The exosome-a naturally secreted nanoparticle and its application to wound healing. Adv Mater 28(27):5542–5552
Rani S, Ryan AE et al (2015) Mesenchymal stem cell-derived extracellular vesicles: toward cell-free therapeutic applications. Mol Ther 23(5):812–823
Raposo G, Stoorvogel W (2013) Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol 200 (4):373–383
Rossello RA, Kohn DH (2010) Cell communication and tissue engineering. Commun Integr Biol 3(1):53–56
Samanta S, Rajasingh S et al (2017) Exosomes: new molecular targets of diseases. Acta Pharmacol Sin
Schwab A, Meyering SS et al (2015) Extracellular vesicles from infected cells: potential for direct pathogenesis. Front Microbiol 6:1132
SCOTT MAXSON EAL, Yoo D, Danilkovitch-Miagkova A, Leroux MA (2012) Concise review: role of mesenchymal stem cells in wound repair. Stem Cell Transl Med 1:142–149
Shabbir A, Cox A, Rodriguez-Menocal L, Salgado M, Van Badiavas E (2015) Mesenchymal stem cell exosomes induce proliferation and migration of normal and chronic wound fibroblasts, and enhance angiogenesis in vitro. Stem Cells Dev 24(14):1635–1647
Silva AM, Teixeira JH et al (2017) Extracellular vesicles: immunomodulatory messengers in the context of tissue repair/regeneration. Eur J Pharm Sci 98:86–95
Sinno H, Prakash S (2013) Complements and the wound healing cascade: an updated review. Plastic Surg Int 2013:146764
Sorg H, Tilkorn DJ et al (2017) Skin wound healing: an update on the current knowledge and concepts. Eur Surg Res 58(1-2):81–94
Spees JL, Lee RH et al (2016) Mechanisms of mesenchymal stem/stromal cell function. Stem Cell Res Ther 7 (1):125
Sun L, Xu R et al (2016) Safety evaluation of exosomes derived from human umbilical cord mesenchymal stromal cell. Cytotherapy 18(3):413–422
Suntres ZE, Smith MG et al (2013) Therapeutic uses of exosomes. Exosomes Microvesicles 1:5
Teng M, Huang Y et al (2014) Application of stems cells in wound healing–an update. Wound Repair Regen 22 (2):151–160
Than UTT, Guanzon D et al (2017) Association of extracellular membrane vesicles with cutaneous wound healing. Int J Mol Sci 18(5):956
Théry C (2011) Exosomes: secreted vesicles and intercellular communications. F1000 Biol Rep 3:15
Tran P, Huynh E et al (2017) The ability of a colloidal silver gel wound dressing to kill bacteria in vitro and in vivo. J Wound Care 26(Suppl 4):S16–S24
Turturici G, Tinnirello R et al (2014) Extracellular membrane vesicles as a mechanism of cell-to-cell communication: advantages and disadvantages. Am J Physiol Cell Physiol 306(7):C621–C633
Ullah I, Subbarao RB et al (2015) Human mesenchymal stem cells-current trends and future prospective. Biosci Rep 35(2):e00191
Vishnubhatla I, Corteling R et al (2014) The development of stem cell-derived exosomes as a cell-free regenerative medicine. J Circ Biomark 3:2
Vizoso FJ, Eiro N et al (2017) Mesenchymal stem cell secretome: toward cell-free therapeutic strategies in regenerative medicine. Int J Mol Sci 18(9):1852
Wang L, Hu L et al (2017) Exosomes secreted by human adipose mesenchymal stem cells promote scarless cutaneous repair by regulating extracellular matrix remodelling. Sci Rep 7(1):13321
Wang S, Mo M et al (2018) Platelet-derived growth factor receptor beta identifies mesenchymal stem cells with enhanced engraftment to tissue injury and pro-angiogenic property. Cell Mol Life Sci 75 (3):547–561
Werner S, Grose R (2003) Regulation of wound healing by growth factors and cytokines. Physiol Rev 83 (3):835–870
Wilson KD, Wu JC (2015) Induced pluripotent stem cells. JAMA 313(16):1613–1614
Womack S, Milner D et al (2018) 178 differential behavior of porcine mesenchymal stem cells from bone marrow and adipose during osteogenic differentiation on a glycosaminoglycan hydrogel scaffold for bone and cartilage tissue engineering. Reprod Fertil Dev 30 (1):229–229
Wu P, Zhang B et al (2018) MSC-exosome: a novel cell-free therapy for cutaneous regeneration. Cytotherapy 9 (17):002
Yamamoto T, Iwase H et al (2018) Skin xenotransplantation: Historical review and clinical potential. Burns
Yáñez-Mó M, Siljander PR-M et al (2015) Biological properties of extracellular vesicles and their physiological functions. J Extracellular Vesicles 4(1):27066
You H-J, Han S-K (2014) Cell therapy for wound healing. J Korean Med Sci 29(3):311–319
Yu B, Zhang X et al (2014) Exosomes derived from mesenchymal stem cells. Int J Mol Sci 15 (3):4142–4157

Zeng R, Lin C et al (2018) Approaches to cutaneous wound healing: basics and future directions. Cell Tissue Res 2018:1–16

Zhang H-G, Grizzle WE (2014) Exosomes: a novel pathway of local and distant intercellular communication that facilitates the growth and metastasis of neoplastic lesions. Am J Pathol 184(1):28–41

Zhang B, Wang M, Gong A, Zhang X, Wu X, Zhu Y, Shi H, Wu L, Zhu W, Qian H, Xu W (2015a) HucMSC-exosome mediated-Wnt4 signaling is required for cutaneous wound healing. Stem Cells 33 (7):2158–2168

Zhang B, Wu X, Zhang X, Sun Y, Yan Y, Shi H, Zhu Y, Wu L, Pan Z, Zhu W, Qian H, Xu W (2015b) Human umbilical cord mesenchymal stem cell exosomes enhance angiogenesis through the Wnt4/beta-catenin pathway. Stem Cells Transl Med 4(5):513–522

Zhang J, Guan J, Niu X, Hu G, Guo S, Li Q, Xie Z, Zhang C, Wang Y (2015c) Exosomes released from human induced pluripotent stem cells-derived MSCs facilitate cutaneous wound healing by promoting collagen synthesis and angiogenesis. J Transl Med 13 (1):49

Zhang B, Shi Y, Gong A, Pan Z, Shi H, Yang H, Fu H, Yan Y, Zhang X, Wang M (2016) HucMSC exosome-delivered 14-3-3ζ orchestrates self-control of the Wnt response via modulation of YAP during cutaneous regeneration. Stem Cells 34(10):2485–2500

Zhao X, Wu H et al (2017) Antibacterial anti-oxidant electroactive injectable hydrogel as self-healing wound dressing with hemostasis and adhesiveness for cutaneous wound healing. Biomaterials 122:34–47

Zhou J, Yao D et al (2018) Bacteria-responsive intelligent wound dressing: simultaneous In situ detection and inhibition of bacterial infection for accelerated wound healing. Biomaterials 161:11–23