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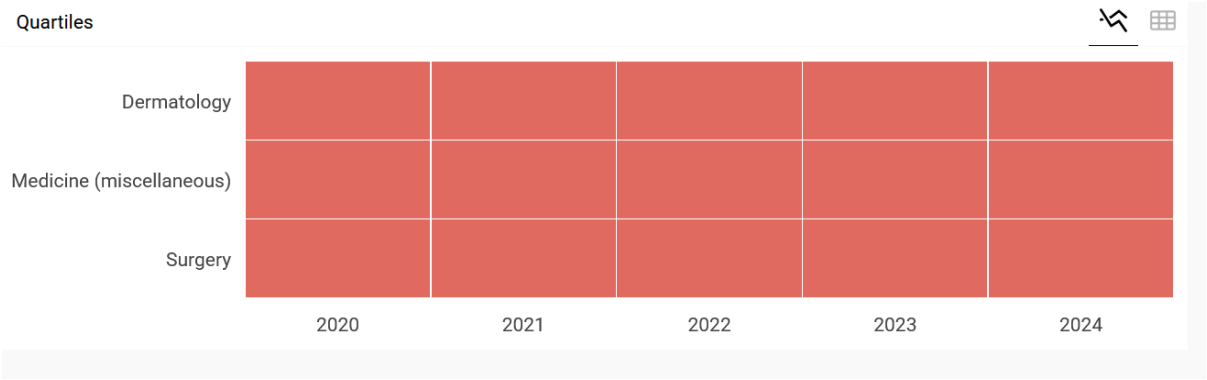
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Review

Exosome, a new interesting therapeutic to promote wound regeneration

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Abstract. *Introduction:* Exosomes are tiny extracellular vesicles secreted by mesenchymal cells. They are derived from a variety of sources, including human umbilical cord stem cells, epithelial cells, and fibroblasts. They have demonstrated therapeutic potential in wound healing, particularly for acute and chronic wounds, which are resistant to conventional treatments. *Aim:* This review summarizes the current understanding of exosome biogenesis, cargo composition, and their role in regulating inflammation, re-epithelialization, angiogenesis, and remodeling during wound healing. *Results:* Exosomes derived from MSCs promote wound healing by mitigating the inflammatory response, stimulating keratinocyte and fibroblast proliferation, enhancing angiogenesis, and regulating collagen deposition. *Conclusion:* The therapeutic effects of exosomes are attributed to their cargo of proteins, mRNAs, miRNAs, and lipids, which influence various cellular signaling pathways.

Key words: exosome, extracellular vesicle, wound regeneration

Introduction

Skin injuries can be classified into acute and chronic wounds. Acute wounds typically heal within a healing time of three to four weeks. Chronic wounds, on the other hand, are acute wounds that fail to heal normally and take longer to heal, often accompanied by excessive scarring and undesirable side effects. A disturbed inflammatory cascade is considered a key factor in the development of chronic wounds from acute injuries[1].

The healing process of wounds can be influenced by several elements. These can be broadly categorized into three groups: internal factors affecting the wound site itself, the body's overall health, and external conditions. Internal factors include infection, insufficient oxygen supply, problems with blood flow to the heart, and the presence of foreign objects. The body's overall health can also play a role, especially if someone is over 60 years old, obese, stressed, or has hormonal imbalances. Additionally, certain medical conditions, like diabetes, circulatory problems, and weakened immune systems, can hinder healing. External factors such as humidity, temperature, and pressure applied to the wound can also impact the healing process[2,3]. Several factors caused this slower healing. The body produces fewer substances (growth factors) needed for tissue repair. Blood vessel formation (angiogenesis) is reduced, limiting the supply of nutrients and oxygen to the wound. There is a decrease in mitogenic activity that stimulates cell division for healing. Additionally, the body's extracellular matrix which supports healing is broken down. Furthermore, there is an imbalance of molecules involved in healing, with excess production of certain reactive oxygen species (ROS), matrix metalloproteases and excessive activity of others like cytokines and proteases. This can lead to scar tissue formation or fibrosis[4].

Past research has used stem cells to regenerate tissue, however they can unfortunately promote

cancer. Stem cells are capable of self-renewal, unlimited tissue migration and differentiation into a variety of adult cells. Cells with this plasticity then become increasingly aggressive and highly adaptive to certain conditions, including anticancer treatments. After undergoing a mutagenesis process, stem cells can become either origin or cancer cells[5]. CCS (Cancer Stem Cell) can be derived from normal stem cells (e.g. adult stem cells), progenitor cells, and differentiated cells. Adult stem cells are easily found in almost all tissues and have a long lifespan, making them more prone to mutation than other cells[6].

Meanwhile, exosomes derived from stem cells have the same properties but do not trigger cancer. A new discovery has recently been made on the subject of wound healing with a process that is safe, natural, and faster than any previous findings[7]. Exosomes transmit information between cells, produce many proteins related to the regeneration process of blood vessels, anti-inflammation, epithelial cell proliferation, and heal wounds effectively[7,8]. Exosomes are modified so that they have certain biological functions that enhance their ability as excellent drug delivery agents. In addition, exosomes can be combined with other ingredients, making it possible to create a single product with multiple benefits. These benefits make exosomes very promising in terms of wound healing[9].

Wound healing process

Normal wound healing has several stages that occur sequentially, namely haemostasis, inflammation, proliferation, and remodelling. In the haemostasis phase, vasoconstriction, platelet aggregation, and thrombus formation occur, which then release growth factors and pro-inflammatory cytokines (TGF-β, PDGF, FGF, and EGF). In the inflammatory phase, there is an infiltration of neutrophils, monocytes, lymphocytes, and macrophage differentiation. It starts with chemotaxis and haemostasis. Various mediators and cytokines are also released[2,10]. In the proliferation phase, re-epithelialization, collagen synthesis, angiogenesis, and extracellular matrix formation occur. Endothelial cells and fibroblasts are cells that have a major role in the formation of new capillaries, collagen, and granulation tissue. Fibroblasts also produce the main components of the extracellular matrix, namely glycosaminoglycans and proteoglycans. In the remodelling phase, there is remodelling of collagen, maturation, and regression of blood vessels[2].

In people without co-morbidities, wounds will heal faster than those with other diseases. Sometimes, to aid wound healing, apart from cell growth and regeneration itself, drugs containing growth factors are needed to accelerate the process and avoid any adverse outcomes[9].

Exosome biogenesis

Exosomes, also known as extracellular vesicles (EVs), were first discovered in 1980. Their role is to eliminate useless proteins from the cytoplasm. Exosomes have a spherical vesicle shape composed of a bilayer phospholipid membrane secreted by cells, measuring 40-160nm in diameter (usually 100nm)[11].

Over time, exosomes were found to have benefits in immune response and intercellular communication[12]. Exosomes are easy to find because they can be produced from a variety of prokaryotic (bacteria) and eukaryotic (animalia, fungi, plantae, and protists) organisms[13]. Exosomes are obtained by isolating the conditioned medium from mesenchymal stem cell (MSCs) cultures as well as from body fluids such as blood, amniotic fluid, plasma, breast milk, saliva, urine, semen, cerebrospinal fluid, and ascites[14–17].

Exosome is derived from endosome. In exosome formation, there are two invagination processes. The first invagination, namely, the early-stage endosome (ESE), is formed from the invagination of cell membrane plasma, which is semicircular and presents an accumulation of proteins on the cell surface and extracellular matrix. In the formation of ESE, the endoplasmic reticulum and Golgi apparatus also have a role[18]. The main function of ESE is to sort cargo for recycling and degradation[19]. The ESE then transforms into the late-stage endosome (LSE). The second invagination is the invagination of the late endosome membrane to form intraluminal vesicles (ILV) within the multivesicular body (MVB) in one second[11]. At this stage, there are two kinds of pathways, namely

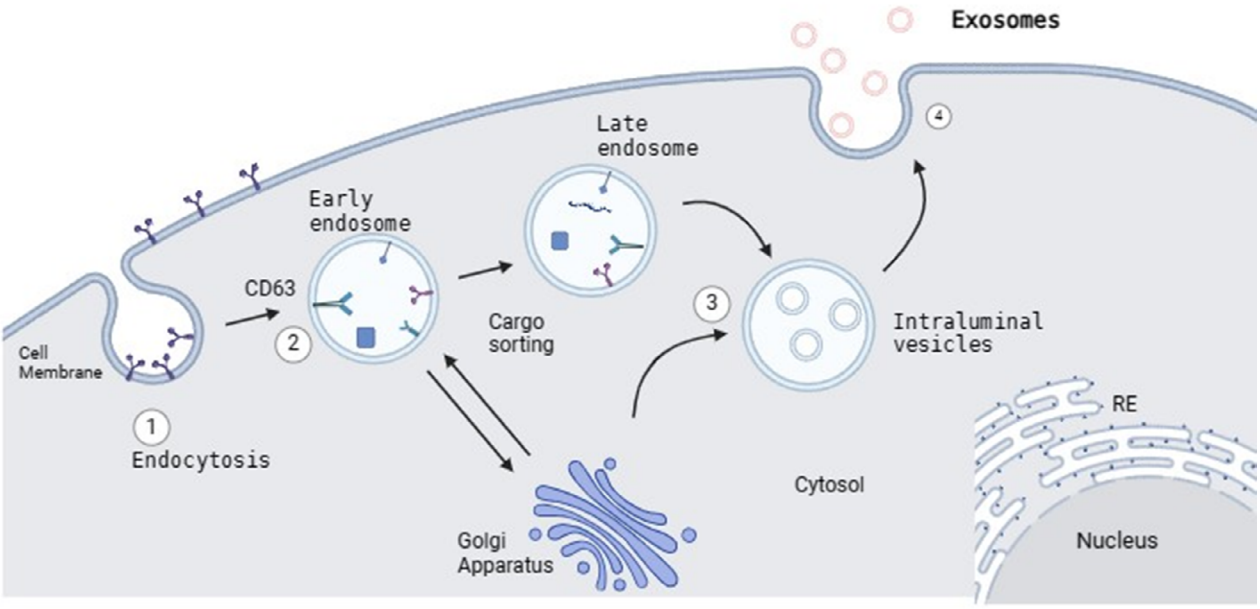

Figure 1. Exosome Production (Created with BioRender.com).

(1) fusion with lysosomes occurs leading to the degradation of the cargo contained in the ILVs and (2) the MVB fuses with the cell membrane, releasing the ILVs into the extracellular space in the form of vesicles (Figure 1). This is called the exosome[11,20].

Exosomes are composed of a lipid bilayer membrane, which has a composition consisting of DNA, mRNA, miRNA, enzymes (ADAMs, MMPs, ATPases, enolases), signal transduction (EGFR, EGFRvIII), cytoskeletal proteins (tubulin, actin, cofitin, vimentin), heat shock proteins (HSP70, HSP90, HSP60), MVB biogenesis (Alix, TSG101), membrane trafficking (Rabs, Annexins), which have roles in fusion and transport, antigen presentation (MHCI, MHCII), receptors, lipid rafts (Flotilins, Cholesterol), tetraspanins (CD9, CD63, CD81, CD82), adhesion & targeting molecules (CD31, Integrins)[14,21] (Figure 2).

Exosome on wound healing benefits

Exosomes are tiny extracellular vesicles released by Mesenchymal Stem Cells (MSCs). They share many characteristics with their parent cells but lack a nucleus[22,23]. Exosomes are considered a promising therapeutic alternative to MSCs due to their enhanced safety, stability, and ease of administration[23].

Exosomes serve as crucial mediators of intercellular communication and material exchange. Their advantage lies in their cargo of active substances that are readily degraded, resulting in a short retention time when administered individually. Additionally, exosomes exhibit remarkable safety in targeting specific cells, making them suitable for immune regulation, cancer diagnosis and therapy, and tissue repair[11]. MSCs can be derived from various sources, including the Bone Marrow (BM), Adipose Tissue (AT), and the Umbilical Cord (UC)[23].

Umbilical cord mesenchymal stem cell (UC-MSC) exosomes are especially rich in TGF-β, a protein crucial for tissue repair and regrowth. Interestingly, these UC-MSC exosomes also contain microRNAs that can dampen the TGF-β2/SMAD2 pathway, which helps prevent excessive scar formation. In contrast, bone marrow mesenchymal stem cell (BM-MSC) exosomes excel at stimulating fibroblast growth. Fibroblasts are essential to produce new tissue. Additionally, these BM-MSC exosomes contain Wnt4 protein, which promotes skin cell movement and multiplication. Overall, mesenchymal stem cell

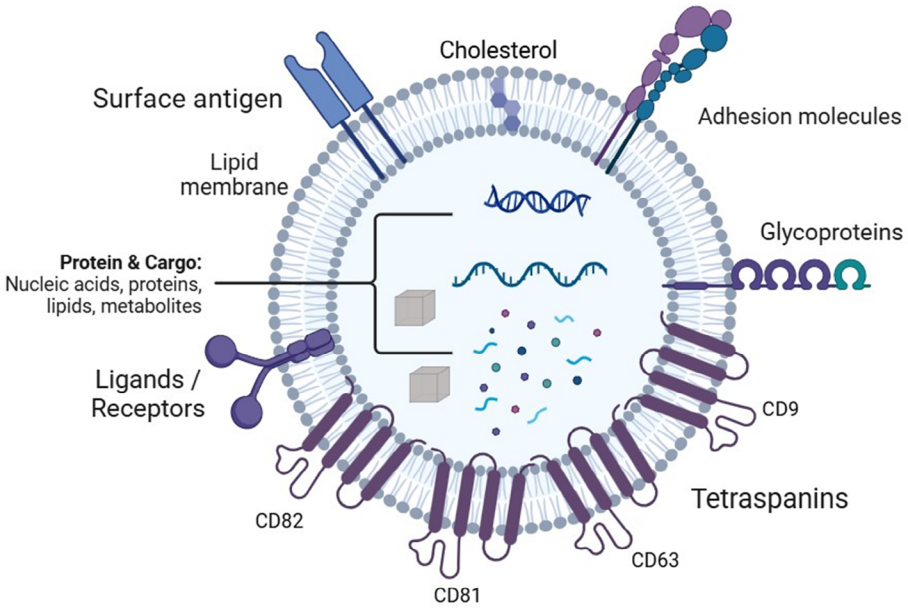

Figure 2. Exosome Structure (Created with BioRender.com).

exosomes from various sources hold promise for accelerating wound healing and minimizing scar tissue. Their effectiveness stems from a combination of factors, including their protein composition, microRNAs, and their influence on cellular signaling pathways[23].

Exosomes secreted by mesenchymal stem cells have emerged as key players in wound healing facilitated by mesenchymal stem cells[24].

Inflammation

Exosomes inhibit the inflammatory process in several ways, namely blocking neutrophil infiltration and reducing neutrophil numbers, reducing pro-inflammatory factors (IL-1, IL-6, TNF-α, IFN-γ, IL-1β) and increasing anti-inflammatory factors (IL-10, TGF-β) in the wound to accelerate the inflammatory process[25]. At a later stage, pro-inflammatory M1 macrophages are converted into anti-inflammatory M2 macrophages through transactivation of arginase-1 by the active signal transducer and activator of transcription 3 (STAT-3) carried by exosomes, which are capable of stimulating fibroblasts, keratinocytes, and endothelial cells to accelerate re-epithelialization and angiogenesis. In addition, there is a reduction of the proliferation and activation of B cells, a suppression of inflammatory T cell proliferation, an increase in T cells to become regulatory cells, an increase in the number and proliferation of Treg, and an inhibition of dendritic cells that can promote T cell proliferation[25,26].

Reepithelialization

Exosomes in this phase work by enhancing the function of keratinocytes and fibroblasts. Keratinocyte function is enhanced by, among others: (1) activating the Wnt/β-catenin signaling pathway, AKT/HIF-1alpha, or AKT pathway; (2) exosomes rich in microRNA-21, increasing the expression of MMP-9 through the PI3K/AKT pathway. The function of fibroblasts is enhanced by (1) inhibiting miR-19b expression through lncRNA H19 (H19) and activating the Wnt/β-catenin pathway by increasing SOX9; and (2) containing lncRNA MALAT1, which can enhance fibroblast migration. Exosomes transport Wnt3a signals to target cells to improve fibroblast and

endothelial cell functions and contain microRNAs that can suppress fibroblast differentiation into myofibroblasts by inhibiting collagen formation so that re-epithelialization is accelerated[25].

Angiogenesis is the formation of new blood vessels, which is a major factor in the proliferative phase of wound healing. These new blood vessels supply oxygen, blood, and metabolic pathways necessary for the wound healing process[25]. Following injury, the oxygen-deprived (hypoxic) environment triggers the release of FGF-2, VEGF, and EGF[25,26]. This stimulates the proliferation of vascular endothelial cells to build new blood vessels. Exosomes also contain molecules that can trigger angiogenesis, such as angiopoietin-2 (Ang-2) and endothelin (ET-1). Exosomes are reported to activate Nrf2 to repair aged endothelial cells. Another study found that exosomes from stem cells can transfer RNA or protein molecules, such as miR-125a, miR-31, and miR-21, to promote angiogenesis in wound healing. Exosomes activate the PI3K/AKT signaling pathway and other similarly effective signaling pathways, including the AKT/eNOS pathway and the Wnt4/β-Catenin pathway[25].

Remodelling

The remodelling stage focuses on reducing scar formation. Scars occur due to excessive amounts of type III collagen and an uncontrolled buildup of myofibroblasts and cells that play a role in wound tightening. In the granulation tissue, type I collagen gradually replaces type III collagen to promote reparation without scarring[25]. Exosomes can promote extracellular matrix reconstruction in skin wound regeneration by regulating the proportion of type III:type I collagen, TGF-β3:TGF-β1, and MMP3:TIMP1[26]. Exosomes expressing miR-192-5p can reduce hypertrophic scar fibrosis by modulating the smad pathway. The effects on wound healing are decreased collagen formation, transdifferentiation of fibroblasts into myofibroblasts, and hypertrophic scar formation. Specific microRNAs from EPSC-exos, such as miR-425-5p and miR-142-3p, can decrease TGF-β1 expression in dermal fibroblasts to inhibit myofibroblast differentiation[25,26] (Table 1).

How to store and administer exosomes

Exosomes are highly recommended to be stored at -80°C, although they can be stored at 4°C but for a short time because it will potentially reduce the effectiveness of the exosome[31]. The most common methods of exosome administration are intravenous (IV), intramuscular (IM), and subcutaneous (SC). IV administration has the disadvantage of being easily eliminated through the kidneys and liver. The half-life is 10-60 minutes. Often used in the fields of cancer, cardiovascular, and orthopedics. IM administration is often used in the neuromuscular field, such as in cases of muscular dystrophy[32,33]. SC administration is often used in the aesthetic field and is very beneficial in aging and age-related diseases[33], which improve antioxidant defense and protect cells from free radical damage, enhancing cellular repair, which promotes wound healing and stimulates tissue regeneration, and have anti-inflammatory functions[24,34].

Conclusion

The therapeutic potential of exhosomes in wound healing has gained significant attention due to their ability to modulate inflammation, angiogenesis, cell proliferation, and the remodeling of the extracellular matrix (ECM). Despite promising preclinical results, challenges such as standardized isolation and purification methods, optimized delivery strategies, and large-scale clinical trials need to be overcome before exosome-based wound healing therapies can be widely adopted in the clinical practice. Nevertheless, exosomes hold great promise for revolutionizing wound healing therapy, especially for acute and chronic wounds that are resistant to conventional treatments. Extensive investigations are required to fully elucidate the mechanisms underlying exosome-mediated wound healing and to develop effective and safe exosome-based therapies for clinical use.

Table 1. Comparison of Normal Wound Healing Factors and Exosomes Ingredients Role.

Wound Phase	Normal Wound Healing Important Factors	Exosomes Role
Haemostasis	• Platelet • glycoprotein VI • extracellular matrix (ECM) proteins (fibronectin, kolagen, von Willebrand)[27]	Exosomes derived from BM-MSCs, HDCs, and UC-MSCs contain 757 miRNAs and 400 proteins that support and trigger platelet aggregation[28].
Inflammation	• neutrofil • monosit • SASP (cytokines, chemokines, growth factors, and matrix proteases) • ROS • IL-6[27,29]	• Exosomes mediating transfer of SASP factors to recipient cells[29]. • Exosomes facilitate wound closure by suppressing MMP-1/MMP-3 expression. • M2-derived exosomes are cytokines (CCL27, CCL11, CCL22, CCL24, IL4, CXCL12, bFGF, and MFG-E8) that convert M1 to M2 to reduce inflammation, induce re-epithelialization, and angiogenesis. • ADSC-derived exosomal miR-21 downregulates TGF-β1, thereby modulating MMP-2 and TIMP-1 expression through the PI3K/AKT pathway. • Exosome cargo (miR-223) from BM-MSCs regulates M2 polarization for anti-inflammatory purposes. • Exosome-mediated IL-6 upregulation promotes angiogenesis and enhances wound healing in burn injuries. • MiR-181c-enriched exosomes mitigate LPS-induced TLR4 expression in macrophages, thereby reducing wound inflammation. • Inhibiting miR-15a-containing exosomes accelerates wound healing by promoting NOX5-mediated ROS generation and endothelial cell activation[30].
Proliferation	• activation of keratinocytes • fibroblasts • macrophages • endothelial cells[27]	• hucMSC-derived exosomes increase wound epithelization via increased CK10, angiogenesis via increased CD31, inhibits fibrogenesis by downregulating αSMA. • Exosomal PD-L1 attenuates inflammation by directly inhibiting T cell activation and promotes wound closure by enhancing epidermal cell and dermal fibroblast migration. • Exosome cargo (miRNA-221-3p) increases wound vascularity. • miR-135a-enriched exosomes promote cellular migration and facilitate wound healing. • miR-126-3p-containing exosomes enhance angiogenesis and wound healing by activating MAP/ERK and PI3K/AKT signaling pathways. • Exosome cargo (miR-21) can increase wound closure, re-epithelialization, angiogenesis, and collagen deposition. • miRNAs (miR-126, -130a, and -132) that act to induce angiogenesis • Exosome cargo (miR-128-3p) can increase autophagy of damaged endothelial cells, re-epitelialization, and angiogenesis[30].
Remodelling	• fibroblast • proteoglycans • collagen[27]	• miR-106b-containing exosomes induce autophagy and collagen downregulation in dermal fibroblasts via direct ERK1/2 activation. • Exosome cargo (miR-21) can increase collagen maturation[30].

BM-MSCs - bone marrow-derived mesenchymal stromal cells; HDCs – heart-derived cells; UC-MSCs – umbilical cord derived MSCs; hucMSC – human umbilival cord mesenchymal stem cells; ADSCs – adipose derived stem cell; miRNA – microRNA; SASP - senescence-associated secretory phenotype; ROS – reactive oxygen species; IL-6 – interleukin-6; TGF – transforming growth factor; MMP – matrix metalloproteinase; TIMP – tissue inhibitor of metalloproteinases; LPS - lipopolysaccharide ; TLR – toll-like receptor ; PD-L1 – programmed death-ligand 1

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