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Exosomes As A Revolutionary Tool In Wound Healing And Skin Regeneration: Current Evidence And Therapeutic Potential

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ABSTRACT

Nano-sized extracellular vesicles, such as the exosomes, innovate wound healing and skin regeneration based on intercellular crosstalk via bioactive payloads (miRNA, proteins, lipids). This review outlines the ability of these compounds to accelerate wound healing, mitigate inflammation, and promote tissue remodeling, as well as recent findings from preclinical and clinical trials. Discoveries, such as exosome-derived biomaterials, including hydrogels, and targeted delivery systems, like CRISPR-engineered exosomes, enhance the efficacy of therapeutics. The existence of rare and exciting discoveries validates the future of transformative possibilities, including hypoxic-conditioned exosomes that stimulate HIF-1α and plant exosomes that enhance burn healing, such as those derived from ginger. Preliminary data indicate that mesenchymal stem cell-derived exosomes can improve healing rates by up to 30-50% in diabetic models, and early-phase clinical studies suggest a decrease in scarring and chronic wound inflammation in chronic wounds. Exosomes have significant clinical and translational potential in the treatment of chronic wounds, burns, and aesthetic dermatology, meeting the demand for biocompatible, low-immunogenicity products. These advances make exosomes a transformative type of regenerative medicine, marking a breakthrough in personalized and scalable applications of wound care and skin regeneration despite the challenges of scalability and standardization.

Keywords – Exosomes, wound healing, skin regeneration, nanoscale vesicles, intercellular communication, bioactive cargo, miRNAs, chronic wounds, burns, aesthetic dermatology, exosome-derived biomaterials, hydrogels, engineered exosomes, targeted delivery, plant-derived exosomes

1. INTRODUCTION

Healing of wounds is a highly choreographed, multi-stage physiological process that comprises four cumulative but distinct phases: hemostasis, inflammation, proliferation, and remodelling. Immediately following an injury, hemostasis occurs, characterized by the activation and degranulation of platelets and the formation of a fibrin clot, which serves as a provisional matrix to arrest the bleeding process and provide a scaffold on which the later stages of healing occur. This is followed by an inflammatory stage, during which neutrophils and macrophages infiltrate the area, phagocytose both pathogens and necrotic tissue and secrete cytokines that attract additional immune and repair cells (Gurtner et al., 2008). The proliferative stage involves the migration of keratinocytes to re-epithelialize and the deposition of the extracellular matrix (ECM) by the action of fibroblasts, as well as strong angiogenesis, which occurs mainly due to VEGF and FGF-2. The third phase of remodeling: In the final step of remodeling, the remodelling stage improves granulation tissue by replacing weaker type III collagen with stronger type I collagen, resulting in scar maturation and recovery of the tensile strength (Singer & Clark, 1999). Nevertheless, the process might be disrupted by pathological factors, such as diabetes, ischemia, or chronic infection, which most especially prolong the inflammatory phase. The chronic nature of the wound, resulting from hypoxia, high concentrations of matrix metalloproteinases (MMPs), and a residual microbial load, leads to the failure of fibroblast and keratinocyte function and an inability to efficiently close the wound completely (Falanga, 2005). On the same note, aberrant remodeling of the extracellular matrix (ECM), overactivation of fibroblasts, and dysregulated immune signaling are observable in severe burns and hypertrophic scars, resulting in poor tissue structure and chronic functional impairments (Tredget et al., 1997). Recent challenges have led to the discovery of a regenerative medicine therapy candidate, exosomes, which is transforming therapeutic interventions in the field. Such extracellular vesicles are nanosized (30 to 150 nm) and originate from multivesicular bodies; they are loaded with proteins (CD63, ALIX, and TSG101), lipids, as well as nucleic acids (miRNAs, circRNAs, and lncRNAs). They also remain intercellular messengers, controlling inflammation, angiogenesis, and cell proliferation on a spatiotemporally confined patrimony (Kalluri & LeBleu, 2020; Riazifar et al., 2017) Healing of wounds is a highly choreographed, multi-stage physiological process that comprises four cumulative but distinct phases: hemostasis, inflammation, proliferation, and remodelling. Immediately following an injury, hemostasis occurs, characterized by the activation and degranulation of platelets and the formation of a fibrin clot, which serves as a provisional.

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The use of conventional treatment options, which involve topical growth factor therapy using agents such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF), has been partially successful but is confronted with several drawbacks. These include a high degree of degradation, temporal bioactivity, costly production processes, a lack of donors, and a threat of immunologic complications or poor graft survival (Barrientos et al., 2008). Exosomes represent a desirable alternative because they are immune-modulatory, biocompatible, have low immunogenicity, are naturally targeted, and, to some extent, are resistant to enzymatic degradation. In terms of operation, mesenchymal stem cell (MSC)- derived exosomes or dermal fibroblast-derived exosomes have shown a pro-healing effect, including pro-angiogenesis (delivery of miR-126 and vascular endothelial growth factor, VEGF); anti-inflammatory effects (modulation of NF-κB transcription by miR-21); and re-epithelialisation (Thery et al., 2018). In recent years, such innovations have been proposed, including the development of exosome-laden biomaterials, such as hydrogels and electrospun scaffolds, which enable local and prolonged release. What has been discovered is that they can achieve wound closures more quickly in diabetic wounds. Moreover, gene editing strategies, such as CRISPR/Cas9, are applied to customize exosome cargo, thereby increasing specificity in miRNA delivery and enabling the tailoring of the vesicle to the wound phenotype (Li et al., 2025). The technologies are fast approaching translation to the clinic, and the safety and optimization of doses are constant questions in trials of exosome-based therapeutics (ClinicalTrials.gov, 2025). Exosome therapy is poised to move in future directions, including bio manufacturing at scale, developing cargo to target specific diseases or organelles, and integrating newer technologies such as 3D bioprinting into skin replacement, which can be tailored to individual patients. Providing promising remedies to address the current gaps in therapeutic interventions for wound treatment and cosmetic skin repair, exosomes could change the present paradigm and, in effect, usher in a new standard in regenerative dermatology and chronic wound care.

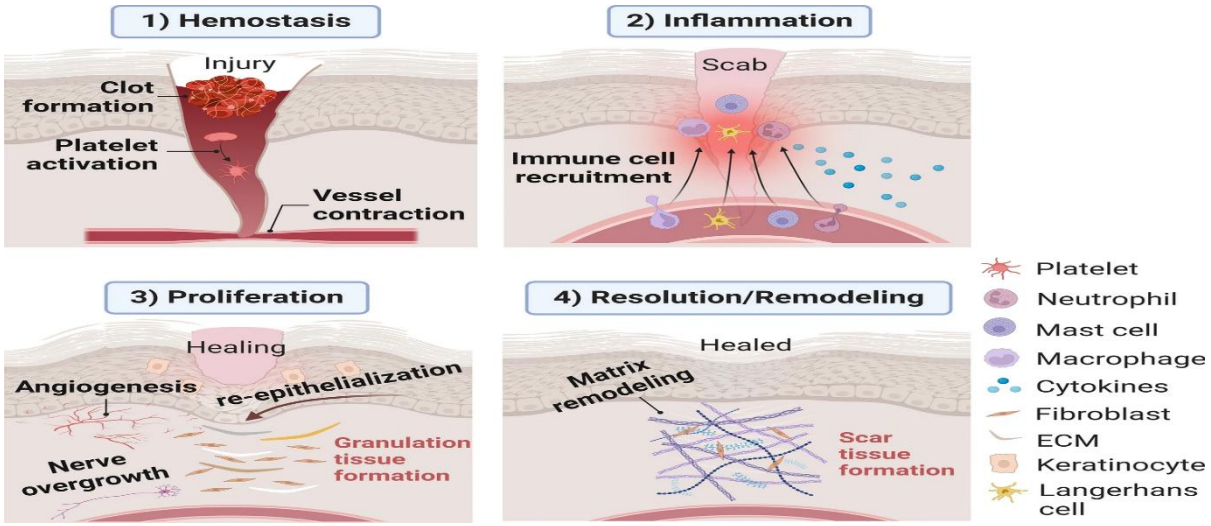

Figure 1: **Schematic overview of the four stages of wound healing: hemostasis, inflammation, proliferation, and remodeling. Each phase involves coordinated cellular and molecular activities essential for tissue repair and restoration of skin integrity. (Adapted from BioRender, 2024)**

III. Biogenesis and Characteristics of Exosomes

Biogenesis:

Nano-size extracellular vesicles (30-150 nm) play central roles in intercellular communication and exert their effects via a well-constrained biogenesis process in the endosomal pathway. It begins with the inward budding of the plasma membrane to form early endosomes, which are further invaginated to form late endosomes or multivesicular bodies, and this process will generate intraluminal vesicles (Kalluri & LeBleu, 2020). As multivesicular bodies fuse with the plasma membrane, these intraluminal vesicles become exosomes in response to the endosomal sorting complex required for transport machinery, consisting of such proteins as TSG101, ALIX, and VPS4 (Hessvik & Llorente, 2018). Moreover, exosomes are formed in part due to the endosomal sorting complex required for transport-independent pathways (which can involve lipid mediators such as ceramide or tetraspanins such as CD63) as a further indicator of the complexity of their biogenesis processes (Trajkovic et al., 2008). Among the most important molecular markers for identifying exosomes are tetraspanins CD63, CD81, and CD9, as well as TSG101, which enable the isolation of exosomes using methods such as ultracentrifugation and nanoparticle tracking analysis (Thery et al., 2018). Such markers not only help identify exosomes but also participate in cargo packaging and cellular delivery, which are critical considerations for their use in wound healing and tissue regeneration.

Its possible use in regenerative medicine is supported by the unique composition of exosomes (lipids, proteins, and nucleic acids). They have a lipid bilayer that is highly enriched in cholesterol, sphingomyelin, and ceramide and is essential for both structural stability and the ability to fuse with target cell membranes (Skotland et al., 2017). Damaged cells are transferred, and protein loads, as demonstrated by cytoskeletal proteins such as actin and heat shock proteins, including HSP70, as well as signalling proteins that activate fibroblasts and promote angiogenesis, which is essential for injury healing (Riazifar et al., 2017), regulate their functions. The nucleic acids, particularly microRNAs, such as miR-21, and long non-coding RNAs can regulate the expression of these genes in target cells, thereby affecting inflammation and extracellular remodelling (Valadi et al., 2007). In the example, exosomal miR-126 contributes to angiogenesis by repressing Sprouty-related protein 1 and enhancing repair processes in chronic wounds (Tao et al., 2018). One of the peculiarities of exosomes is their low immunogenicity and ability to cross biological barriers, which makes them distinct from other therapeutics, as recent studies have shown (Kalluri & LeBleu, 2020). Together with their biogenesis, these properties make exosomes a functional, bioactive cargo-delivery system. Research into the use of exosomes in clinical practice, analogous to their applications in skin regeneration and wound healing, is ongoing.

Composition:

Small extracellular vesicles, with diameters ranging from 30 to 150 nanometers, possess a lipid bilayer membrane and a wide variety of bioactive payloads and are classified as exosomes. Their complex interactions support intricate communication between cells. Their skeleton is not an inert coating but a biologically dynamic surface loaded with lipids, including cholesterol, sphingomyelin and ceramide. Such a lipid formulation provides membrane stiffness and resistance to enzymes, exhibiting characteristics that enable it to integrate with the host cell's membrane and deliver its payload to the cytosol (Skotland et al., 2017). An example of such a lipid is ceramide, which significantly contributes to vesicle integrity and endosomal sorting. Additionally, it enhances the efficiency of membrane fusion, resulting in increased cell uptake and higher therapeutic potential (Kalluri & LeBleu, 2020). Exosomal bioactive content comprises a complex mixture of multiple microRNAs (miRNAs), messenger RNAs (mRNAs), DNA fragments, proteins, and lipids, and all of these together coordinate cellular activity at the transcriptional, translational, and epigenetic levels. An important example, exosomal miR-21 alters inflammation by regulating the PDCD4 gene, and miR-126 plays a role in promoting angiogenesis by inhibiting negative regulators of the VEGF signaling pathway (Valadi et al., 2007). The exosome's mRNAs can be translated into functional proteins when exosomes enter the recipient cells, resulting in the production of essential growth factors and cytokines. Moreover, the HSP70 (heat shock protein 70), annexins, integrins, and cytoskeletal components, including actin, are key proteins that play a role in responses to stress, the immune system, and the activation of survival mechanisms (Riazifar et al., 2017). Such characteristics enable exosomes to become particular and low-immunogenic systems that can overcome biological barriers to payload delivery, creating a contrast with the lack of specificity and high immunogenicity of synthetic nanoparticles or bulk forms of protein therapeutics.

The role of exosomes in wound healing is grounded on their capability to modulate the cellular and molecular milieu in all steps of the tissue regeneration cascade. The role of exosomal content in the activation and perpetuation of angiogenesis, the stimulation of fibroblast activation, and the renovation of the extracellular matrix (ECM) is important. In particular, exosomal miR-126 suppresses the known inhibitor of the Ras/ERK signalling pathway, the Sprouty-related EVH1 domain-containing protein 1 (SPRED1) (Tao et al., 2018); consequently, it stimulates the proliferation of endothelial cells and neovascularization of ischemic and chronic wounds (Tao et al., 2018). Similarly, miR-21 regulates the inflammatory stage by inhibiting pro-apoptotic and pro-inflammatory mediators, thereby facilitating a transition into the proliferative stage. The vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF-beta) proteins contained in these exosomes actively promote angiogenesis and the growth of fibroblasts, the processes vital to the formation of the granulation tissue and wound contractions (Riazifar et al., 2017). The contribution of long non-coding RNAs to the process of ECM

remodelling, associated with fibroblast-to-myofibroblast differentiation and the overexpression of collagen I and III deposition, is a key feature in minimizing fibrosis and the formation of scars. It includes MALAT1 (metastasis-associated lung adenocarcinoma transcript 1; Liang et al., 2020). When these molecules synergise, they act synergistically to enable liver healing, with strict regulation of the wound microenvironment, thereby helping to heal them quickly and facilitating functional liver regeneration. Interestingly, exosome treatment has consistently yielded superior outcomes compared to conventional therapy in preclinical models of diabetic wounds, with improved re-epithelialization, increased vessel density, and enhanced anti-inflammatory activity. Recent molecular manipulation of exosomes enables the targeted control of exosome contents through genetic manipulations of donor cells or electroporation transfection, where engineering the exosome facilitates the development of a tailored therapeutic effect. Additionally, delivery vehicles (e.g., halo gels and nanofibers) could be wrapped around exosomes to enable slow, extended-release, optimize the bioavailability, and reduce the side effects of the system. These developments are pushing exosomes beyond their roots as simple vectors into the age of intelligent and programmable treatments. As the area matures toward clinical translation, exosomes play a functional role in the regenerative medicine field, providing a significant and flexible platform for targeting interventions in chronic wounds, burn wounds, and skin regeneration.

Sources

Exosomes, which play a crucial role in wound healing and skin regeneration, are extracted using various methods, ranging from conventional cell sources to novel techniques. Mesenchymal stem cells (MSCs) are the most commonly used MSCs and, in particular, bone marrow-derived cells and those that are cord umbilical are known to strongly produce exosomes that consist of miRNAs (e.g., miR-21) and proteins (e.g., VEGF) to enhance angiogenesis and fibre cell activation (Riazifar et al., 2017). Another common origin is adipose-derived stem cells (ADSCs), which can be utilized due to their ease of access and relatively large release of exosomes, carrying a cargo of miR-126, which can repair vascular networks in chronic wounds (Tao et al., 2018). A macrophage is an immune cell that releases exosomes, which are essential in balancing inflammation via M2 polarisation to aid in the resolution of chronic inflammatory wounds (Kalluri & LeBleu, 2020). In addition to this traditional source, new platforms are emerging, offering enticing therapeutic opportunities. Burn wounds affect vegetable-based exosomes, including ginger exosomes, which possess anti-inflammatory and antioxidant properties, thereby accelerating the wound healing rate by reducing oxidative stress (Zhang et al., 2016). Exosome-mimetic vesicles Liposomes that mimic the natural structure of exosomes have been synthesized. They may be designed to carry a particular cargo, allowing their dimensions to be scaled up and enabling the precise delivery of therapeutic miRNA or protein to wounds for repair (Jang et al., 2013). The range of possible exosome sources, including MSCs and ADSCs, plant-derived vesicles, and artificially derived vesicles, underscores the versatility of such a drug delivery system. Each of these sources has distinct advantages in the context of matching regenerative medicine with the wound-healing process.

Unique Properties:

Exosomes possess several distinctive features that make them a potential game-changer in wound healing and skin regeneration, particularly in terms of their stability in biofluids, permeability through biological barriers, and low immunogenicity compared to cell-based therapies. They have an enriched cholesterol and sphingomyelin lipid bilayer that guarantees their structural integrity, and bioactive cargos, such as miRNAs, mRNAs, and proteins, are supposed to be resistant to degradation in harsh physiological environments, including blood or wound exudates (Skotland et al., 2017). This stability allows exosomes to maintain their functionality upon administration, both systemically and topically, as evidenced during the preclinical model period, where the exosomes were observed to sustain activity within wound beds (Kalluri & LeBleu, 2020). They are also in the nanoscale (30150 nm), and surface proteins (e.g., tetraspanins: CD63, CD81) enable them to penetrate biological barriers (e.g., blood-brain barrier and skin extracellular matrix) in an efficient way, being able to target and deliver into specific ones such as fibroblasts or endothelial cells (Tao et al., 2018). In contrast to cell-based therapies (e.g., mesenchymal stem cell (MSC) transplants), exosomes exhibit minimal immunogenicity. They are less susceptible to immune rejection due to their acellular structure and the absence of major histocompatibility complex (MHC) molecules (Riazifar et al., 2017). This feature is vital in their application, particularly for allogeneic use, as chronic wound studies demonstrate that it induces a minimal immune response (Pittenger et al., 2019). With these properties, plus the options available to pack them with the bioactive molecules to stimulate angiogenesis through miR-126 or tissue repair through VEGF, exosomes are an up-and-coming, safe, and non-toxic platform of regenerative medicine with great potential in the clinical translation of its use in chronic wounds, burns, and aesthetic dermatology issues.

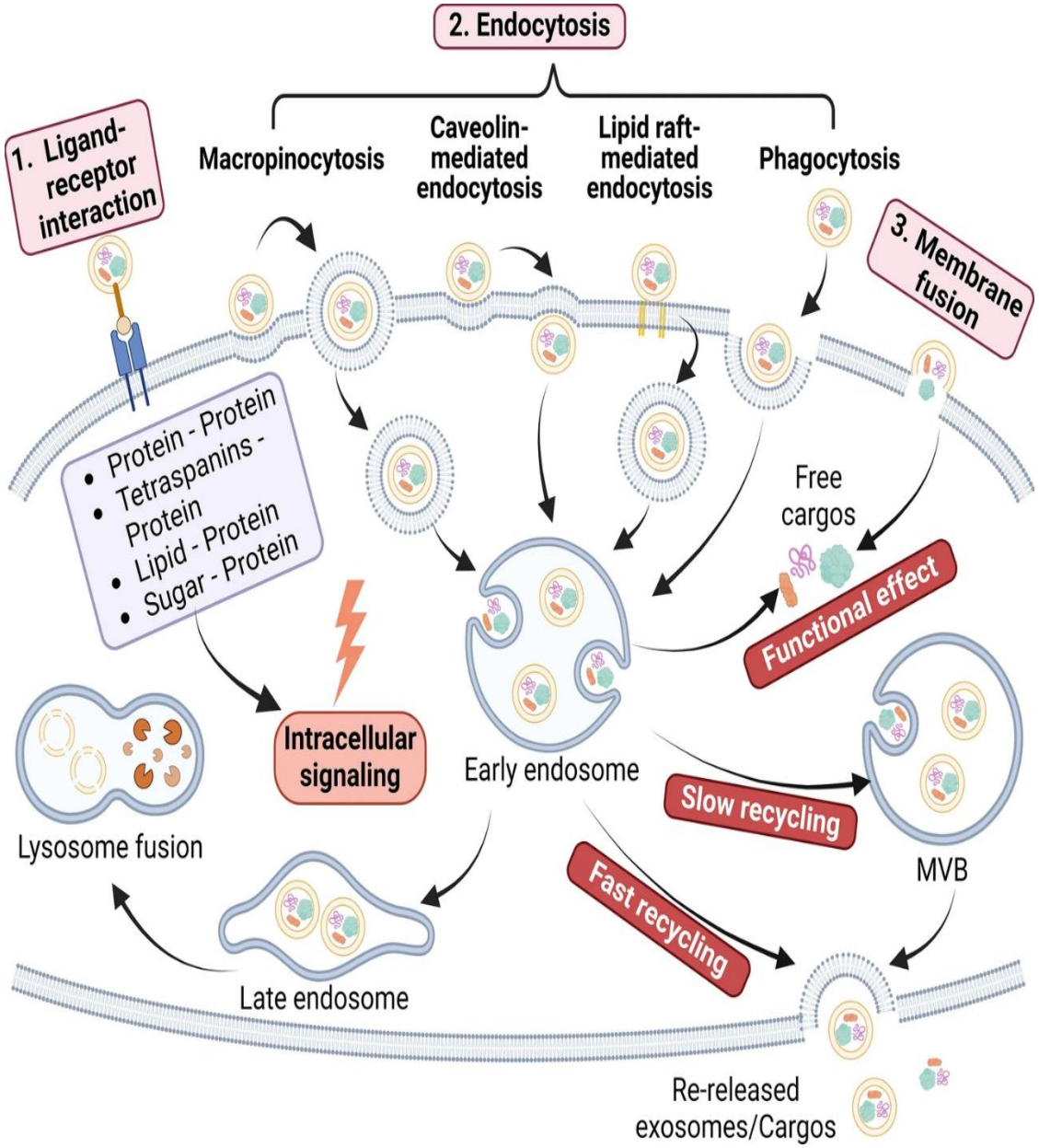

Fig. 2: **Exosome internalization mechanisms include ligand–receptor binding, various endocytosis pathways, and membrane fusion. Once internalized, exosomes influence cellular behavior through intracellular signaling or cargo release, contributing to wound healing via gene modulation, protein synthesis, and ECM remodeling. (Adapted from BioRender, 2024)**

IV. Mechanisms of Exosomes in Wound Healing

Exosomes play a pivotal role in wound healing by modulating key physiological processes across its phases: hemostasis, inflammation, proliferation, and remodeling.

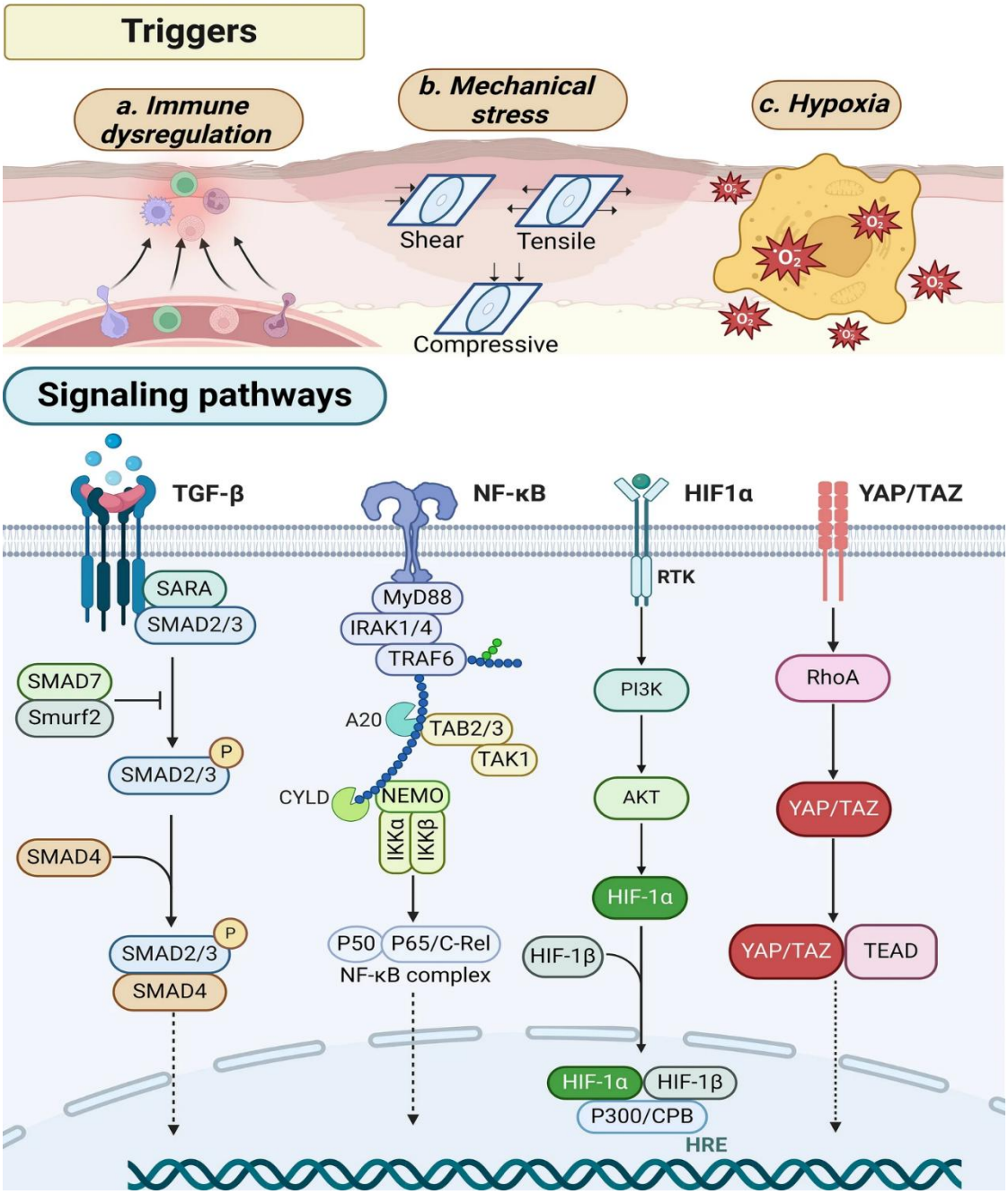

Fig.3: **Key pathophysiological triggers—immune dysregulation, mechanical stress, and hypoxia—activate signaling pathways (TGF-β, NF-κB, HIF-1α, YAP/TAZ), disrupting wound healing. These pathways are critical targets of exosome-mediated repair processes. (Adapted from BioRender, 2024)**

They are nanoscale vesicles (30-150 nm) that deliver bioactive cargos, such as microRNAs (miR-21, miR-146a), proteins (VEGF, TGF-beta), and lipids, to the recipient cell, thereby promoting intercellular communication (Kalluri & LeBleu, 2020). The delivery of exosomal miR-146a causes the pro-inflammatory M1 macrophage polarisation to the pro-regenerative M2 macrophage, which restricts inadequate inflammatory responses in cases of chronic wounds by limiting the number of pro-inflammatory macrophages (Riazifar et al., 2017). During a proliferation period, exosomes enhance angiogenesis through miR-126, which promotes cell division in endothelial cells, and VEGF, which repairs vascular damage (Tao et al., 2018). TGF-b released in exosomes activates fibroblasts to produce more collagen and heal a wound. Long non-coding RNAs, such as MALAT1, regulate the level of collagen during remodeling to reduce scarring (Liang et al., 2020). More importantly, HIF-1 signaling is increased by the secretion of exosomes of hypoxic-conditioned mesenchymal stem cells, which close wounds 30 to 50 per cent faster in diabetic models (Shabbir et al., 2015). These processes highlight the multitasking roles of exosomes in wound healing with therapeutic potential in chronic wounds, burns, and skin regenerations.

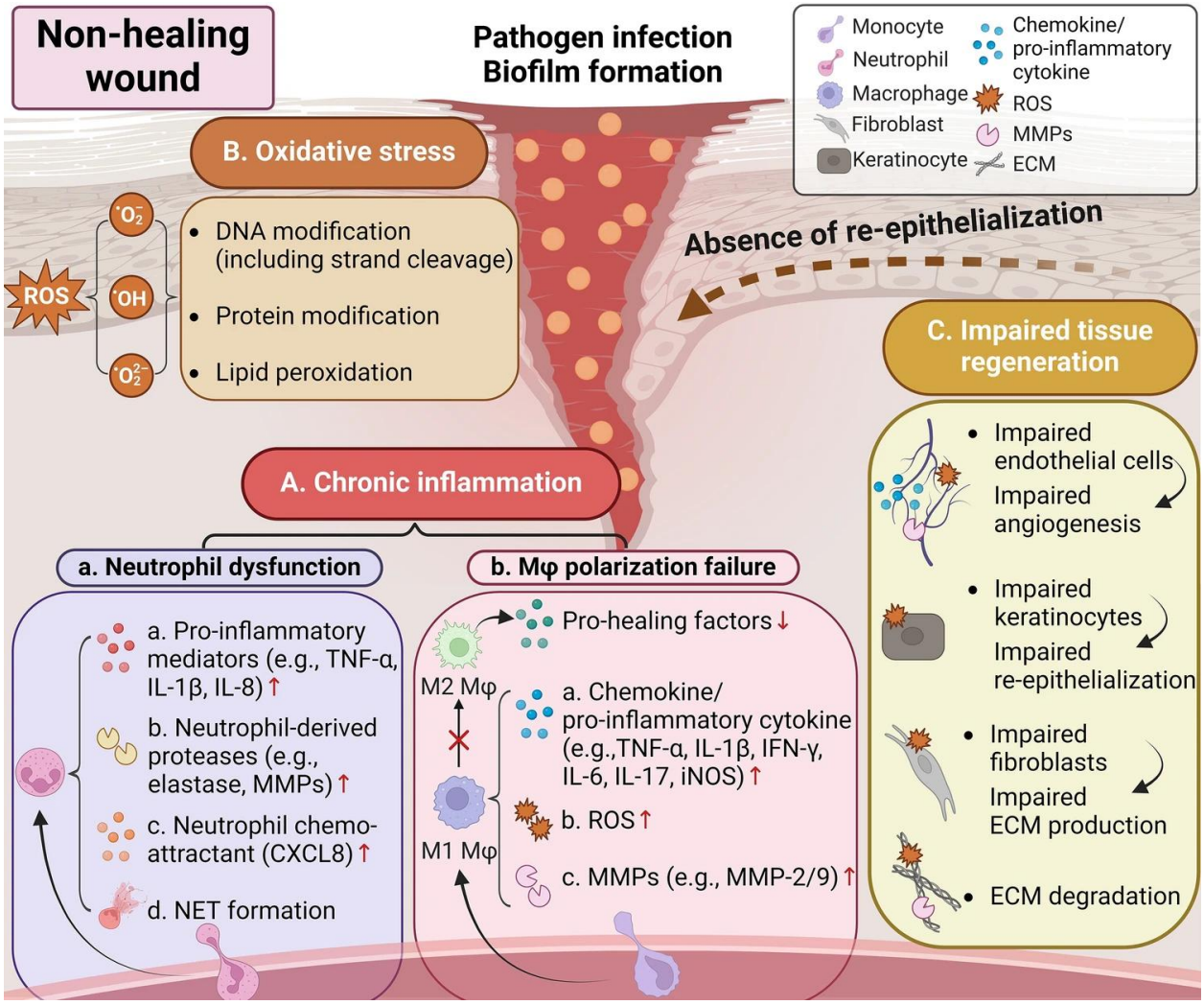

Fig.4: *:* **Pathophysiological mechanisms underlying non-healing wounds, including chronic inflammation, oxidative stress, and impaired tissue regeneration due to neutrophil dysfunction and macrophage polarization failure. These processes obstruct re-epithelialization, angiogenesis, and ECM remodeling, creating a hostile wound microenvironment. (Adapted from BioRender, 2024)**

Hemostasis and Inflammation:

Exosomes play a significant role in the minute regulation of immune responses during the hemostasis and inflammation phases of wound healing by transferring miRNAs, such as miR-21 and miR-146a, which decrease excessive inflammation. Such nano-vesicles (30 nm 150 nm) deliver bioactive cargos to immune cells and modulate gene expression and cellular functions (Kalluri & LeBleu, 2020). In particular, miR-146a downregulates pro-inflammatory pathways, including the NF-κB signalling pathway, to reduce cytokine formation, such as TNF-α and IL-6, in wounds with chronic inflammation (Riazifar et al., 2017). This protection is crucial in preventing tissue destruction, especially in diabetic wounds. Additionally, miR-21 stimulates the production of anti-inflammatory genes, thereby creating a well-balanced immune response (Dang et al., 2016). Exosomes derived from mesenchymal stem cells (MSCs) are especially useful, as they deliver these miRNAs to macrophages and other immune cells, thereby establishing a healing-favorable environment. Targeting the inflammatory cascade, exosomal miRNAs can also lead to a shift from destructive inflammatory processes to repair mechanisms, with therapeutic potential in wound healing, as chronic inflammatory processes are currently managed.

An essential effect of wound healing by exosomes is to favor the polarization of macrophages from the pro-inflammatory M1 to pro-regenerative M2 phenotypes, which are necessary to resolve excess inflammation and initiate tissue regeneration. Such emission involves exosomal miR-146a, together with miR-21, in conjunction with proteins such as IL-10, to evoke this turnover by up-regulating M2-specific markers, namely arginase-1 and CD206, and down-regulating M1 markers, such as iNOS (Ti et al., 2016). This pro-inflammatory polarizations further augments the secretion of anti-inflammatory cytokines (e.g., IL-10) and growth factors (e.g., TGF-B) to promote angiogenesis and fibroblast activation during later stages of healing (Riazifar et al., 2017). Exosomes generated by MSCs have shown anti-inflammatory effects in diabetic wound models

preclinically with a 30-40% reduction in inflammation rates by speeding polarization towards the M2 phenotype (Shabbir et al., 2015). This transition is not only able to reduce excessive inflammation but also create a regenerative microenvironment, making exosomes an interesting approach to chronic wound healing, as well as in patients with burns and other inflammatory skin diseases, where the impaired resolution of the macrophage response delays healing.

Proliferation:

Exosomes play a very important role in the proliferation stage of wound repair process by inducing angiogenesis through the transportation of vascular endothelial growth factor (VEGF) and miR-126. These nanoscale vesicles (30 -150 nm) deliver and carry bioactive loads to endothelial cells to facilitate the growth of blood vessels and tissue regeneration (Kalluri & LeBleu, 2020). In preclinical studies, the proliferation and migration of dermal endothelial cells were actively stimulated by exosomal VEGF in exosomes derived from mesenchymal stem cells (MSCs), resulting in a 40% increase in angiogenesis in diabetic wound models (Shabbir et al., 2015). Simultaneously, miR-126 targets Sprouty-related protein 1 (SPRED1) and the adverse effects of this protein on angiogenic pathways are prevented by miR-126, consequently increasing the growth and tube formation of endothelial cells (Tao et al., 2018). This mutual activation of VEGF and miR-126 is crucial in establishing neovascularisation, ensuring that wounded tissues can access oxygen and vital minerals. It also improves the ability of exosomes to deliver these cargos through their survival within biological fluids, and it can become a useful technology that advances angiogenesis at a faster rate in chronic wounds and burns, whose vascularisation tends to be impaired (Riazifar et al., 2017).

A second proliferation-stage activity of exosomes is the stimulation of fibroblast proliferation and collagen production, a key part of the proliferation stage, by delivering growth factors such as transforming growth factor-beta (TGF-beta). Exosomal TGF5 activates fibroblasts by promoting the signaling pathways, including SMAD, which increases the production of collagen and myofibroblast differentiation, which is necessary to close the wound (Fang et al., 2016). Upon preclinical analysis, exosomes derived from MSCs are reported to enhance fibroblast growth by 30-50% in wound models, thereby augmenting the development of granulation tissue (Shabbir et al., 2015). This concerted effort enhances tissue reconstruction and strength, which is crucial in wound healing. Exosomes provide a cell-specific means to promote fibroblast activity by delivering these growth factors; thus, exosomes represent a potential therapeutic in the management of chronic wounds.

Remodeling

Exosomes are also vital during wound healing, as they play a crucial role in the remodeling of the wound. This process involves maintaining an effective extracellular matrix (ECM) remodeling to alleviate scarring and facilitate the recovery of deformed tissue, ultimately forming a healthy structure. At this stage, exosomes fulfil their role by transferring bioactive materials, including proteins and nucleic acids, to fibroblasts, thereby coordinating collagen deposition and breakdown in the tissue and inhibiting the excessive formation of scarring (Kalluri & LeBleu, 2020). The TGF-β and exosomal growth factors could be used to modulate the behaviour of fibroblasts to synthesize a patterned structure of collagen. Meanwhile, MMPs expressing exosomes increase the degradation of the ECM, providing appropriate tissue remodeling (Riazifar et al., 2017). In preclinical studies, MSC-enriched exosomes successfully limited scar thickness in a stringent model of burn injuries by reducing excess collagen I and promoting collagen III, thereby enhancing tissue elasticity (Shabbir et al., 2015). In chronic wounds, exosomes have the effect of reducing fibrosis, resulting in more aesthetically and practically satisfactory outcomes as the skin regenerates due to the decreased synthesis and catabolism of the extracellular matrix (ECM). A recent exciting finding revealed that exosomal long non-coding RNAs (lncRNAs), including MALAT1, play a crucial role in maintaining harmonious collagen deposition and tissue morphology during remodeling. Exosomal MALAT1 regulates the dynamic balance of miR-141-3p and ZNF217, increasing VEGF levels and rebalancing fibroblast activity to prevent excessive collagen deposition (Liang et al., 2020). The lncRNA-mediated process ensures a balanced production and degradation of collagen, resulting in a tissue architecture that resembles native skin. The present finding demonstrates the promising therapeutic benefit of exosomal lncRNAs as a scar-minimizing therapy, providing a paradigm shift in wound healing for both chronic wounds and aesthetic dermatology.

Rare Discovery:

Even though exosomes of hypoxic-conditioned mesenchymal stem cells (MSCs) are an infrequent occurrence in wound care, it is a promising element in chronic wound healing since this exosome has been found to assist in raising closure rates through the amplification of the hypoxia-inducible factor-1 (HIF-1alpha) signal. Exposure of human MSCs to low oxygen (hypoxic preconditioning) increases the production and enrichment of exosomes, which contain exosomes different pro-angiogenic and regenerative molecules, such as miR-210 or VEGF (Shabbir et al., 2015). Exosomes respond to hypoxic conditions by activating an essential signaling pathway, namely HIF-1, which utilizes exosomes in chronic open wounds to mediate angiogenesis, cell survival, and tissue repair in recipient cells (Kalluri & LeBleu, 2020). In vitro studies have shown that cell-culture studies demonstrate that hypoxia-derived MSC-exosomes significantly stimulate wound healing, and the rate of wound healing is increased by 30-50% compared to normoxic cells in diabetic mouse models. It is primarily associated with the increase in HIF-1-induced VEGF production, as well as endothelial cell renewal (Zhang et al., 2016). The new route increases vascularisation and peripheral delivery of oxygen to the hypoxic microenvironment that impedes chronic wound

healing. Furthermore, it enhances the therapeutic potential of these exosomes by reducing their immunogenicity and increasing their stability, making them a promising novel mode of chronic wound treatment and skin regeneration. Their clinical translation is currently under active investigation.

V. Novel Discoveries in Exosome Applications

New technologies utilizing exosomes are revolutionizing wound healing and incorporating higher-tech spinoffs in the areas of biomaterials, engineered tissue, and fluid delivery systems. Chitosan-based scaffolds, when loaded with exosomes, can deliver bioactive products over an extended period in the wound bed and provide significantly stronger tissue regeneration in diabetic counterparts (Hu et al., 2018). These scaffolds have produced a biocompatible gel that forms the extracellular environment, facilitating cell migration and angiogenesis through the release of exosomal miRNA (such as miR-126) and proteins (such as VEGF). According to researchers, the use of chitosan-exosome constructs reduces the time required for wound healing by 25-35% in diabetic mice compared to controls (Tao et al., 2018). CRISPR/Cas9-engineered exosomes can facilitate the specific delivery of therapeutic miRNAs, such as miR-29, which exerts an anti-fibrotic effect by inhibiting excessive collagen synthesis and consequent suppression of hypertrophic scarring (Li et al., 2025). Concerning chronic wounds, surface-modified exosomes, which are grafted onto cell-targeting peptides, including RGD, will increase skin penetration and improve cell targeting of fibroblasts, making them helpful to researchers studying chronic wounds (Riazifar et al., 2017). They overcome the disadvantages of natural exosomes, which include low yield and non-specific targeting, and bring us to a new chapter in personalised regenerative medicine that is clinically promising.

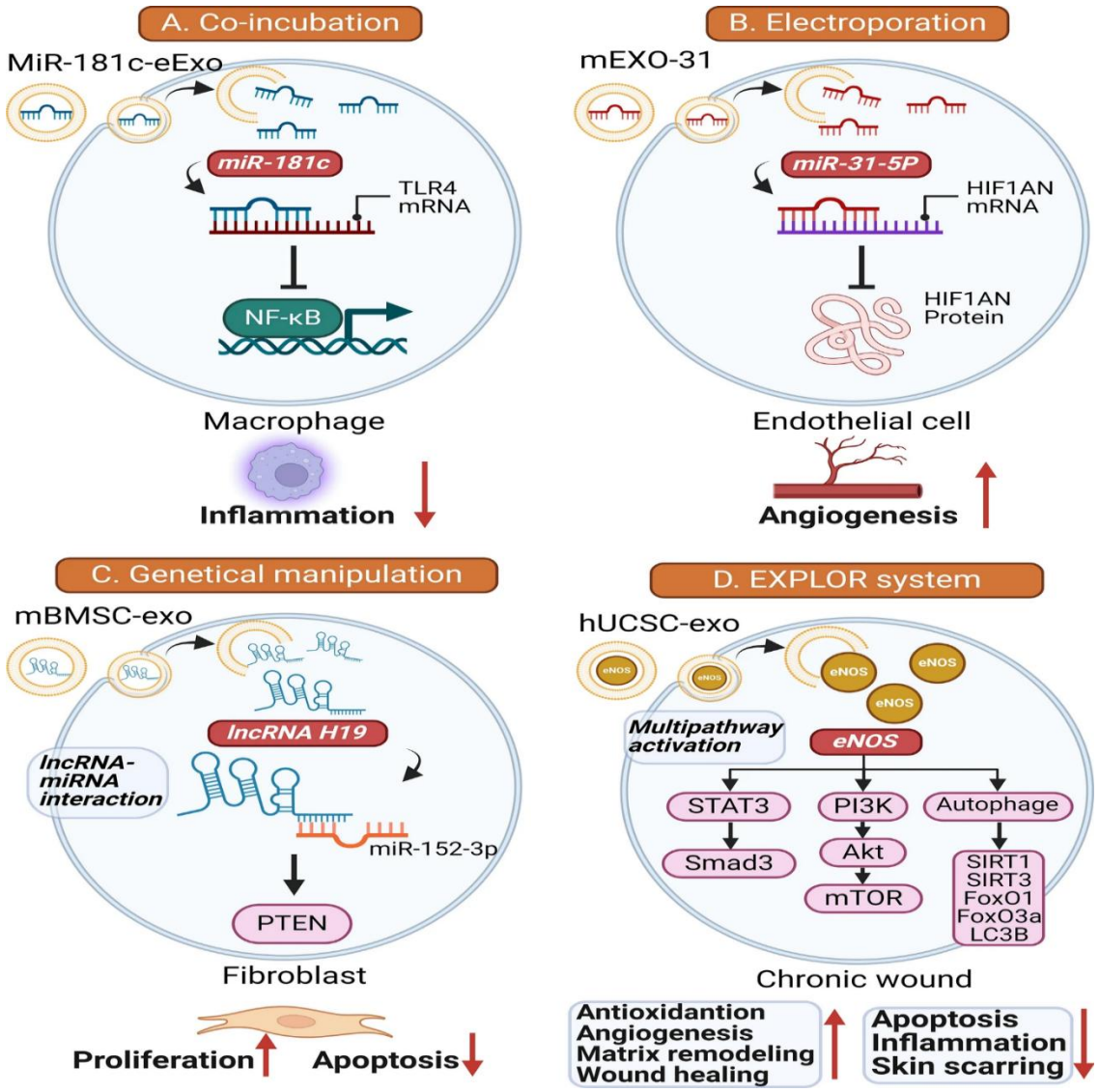

Figure 5: **Engineered exosomes (eExo) deliver bioactive RNAs to target cells using co-incubation, electroporation, genetic modification, and EXPLOR systems. These strategies reduce inflammation, promote angiogenesis, enhance fibroblast proliferation, and activate antioxidant pathways to support chronic wound healing. (Adapted from BioRender, 2024)**

Exosomes and exosome-mimetic nanovesicles of plant origin additionally expand the treatment horizon. This little-known exosome type has potent anti-inflammatory and regenerative effects, reducing burn-induced inflammation by modulating oxidative pathways (Zhang et al., 2016). The plant-based vesicles offer an advantageous, commercially feasible alternative to cell-based exosomes, with preclinical studies demonstrating improved burn closure rates. The customizable production of synthetic exosome-mimetics enables the loading of specific cargo, such as miR-146a, to confer anti-inflammatory activity and facilitate targeted drug delivery (Jang et al., 2013). These vesicles address scalability limitations associated with conventional isolation methods and can reduce production costs by up to 50% compared to traditional exosome isolation techniques (Kalluri & LeBleu, 2020). All these developments have the potential to make biomaterials-engineered exosomes and vesicles prepared via plants and mimetic nanovesicles scalable and cost-effective, thereby increasing the clinical landscape of exosome therapies for chronic wounds, burns, and aesthetic dermatology. Their translational potential is supported by ongoing efforts that continue to undergo clinical trials (ClinicalTrials.gov, 2025).

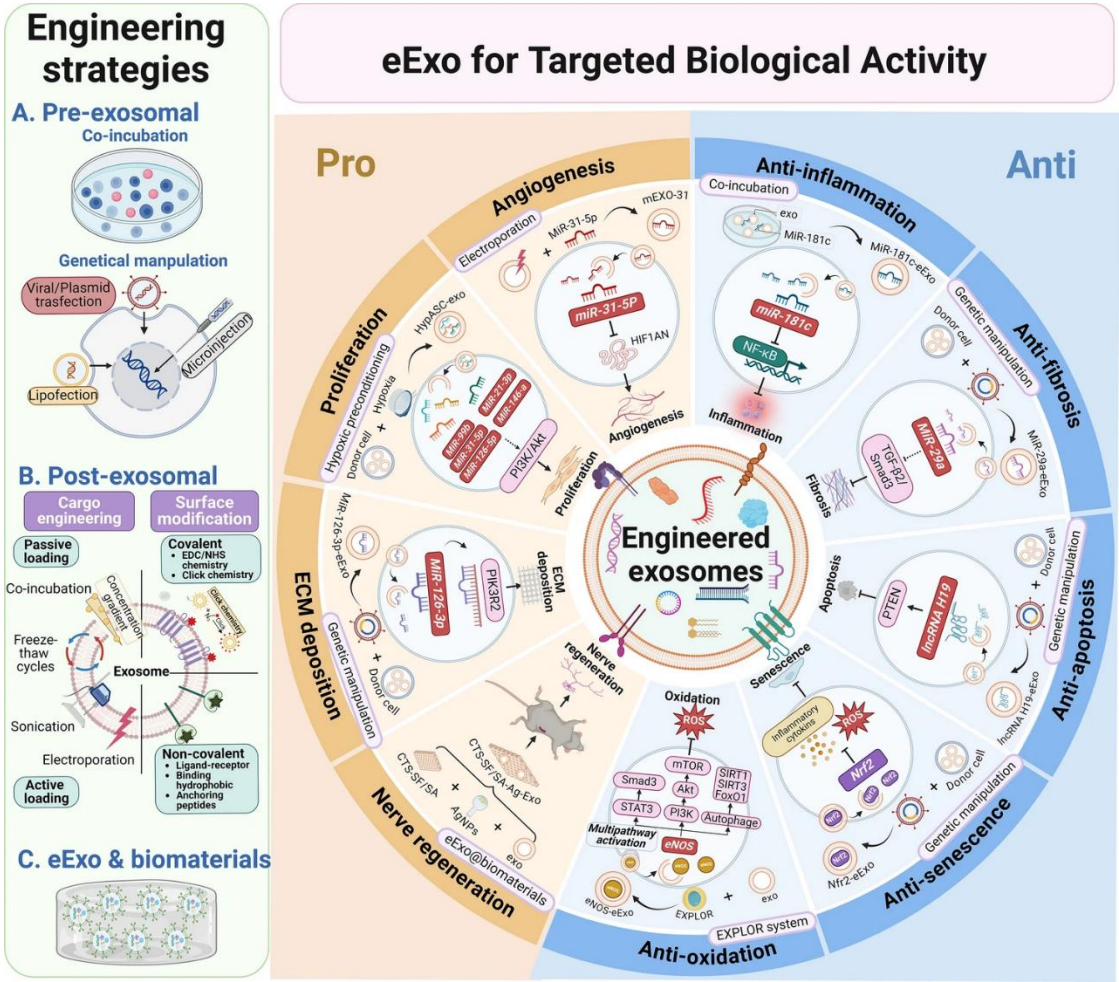

Fig. 6: Engineered exosomes (eExo) enhance targeted biological activities through diverse pre- and post-exosomal engineering strategies and biomaterial integration, enabling multifunctional therapeutic effects including angiogenesis, anti-inflammation, and nerve regeneration. (Adapted from Liu, C., et al., 2025)

VI. Current Evidence from Preclinical and Clinical Studies

The effectiveness of mesenchymal stem cell (MSC)-derived exosomes in accelerating wound healing is well supported by preclinical studies, which have shown that exosomes can reduce wound closure time by 30-50% in diabetic mouse models compared to controls (Shabbir et al., 2015). The cargo carried by these exosomes, including miR-126 and VEGF, stimulates angiogenesis and the proliferation of fibroblasts, thereby improving vascularisation, which is typically poor and slow in healing diabetic wounds. Combinations of exosomes with hydrogels, such as chitosan-based scaffolds, also enhance the therapeutic effect in burn injury models by improving cargo release and, thereby, accelerating wound healing by 2,535% and reducing scar formation (Hu et al., 2018). The constructs develop a biocompatible microenvironment that promotes cell migration and tissue regeneration. Preclinical evidence indicates that they enhance collagen alignment and reduce fibrosis. Due to the relatively low immunogenicity of exosomes in biological fluids and their variant instability, the potential of their use increases, which is an advantage of this method as an alternative to cell-based therapies. Outcomes precondition the

application of cell-free exosomes across various wound types with promising clinical applications. Currently, the clinical trials are not at a distant enough phase. However, the thus-processed data suggest that the potential of any exosome-based treatment may be substantial, as such treatments can accelerate the wound healing process, specifically those targeting adipose-derived stem cell (ADSC) exosomes. In this regard, ADSC-secreted exosomes have produced significant effects when used in the management of chronic diabetic ulcers, particularly in improving the rate of ulcer healing and reducing the magnitude of the inflammatory process when combined with other standard treatment regimens (Tao et al., 2018). Much of this credit can be attributed to exosomal microRNAs, such as miR-146a, which negatively regulate pro-inflammatory cytokines, including TNF-alpha, and modulate the immune response to promote rapid tissue repair.

Delicate clinical genomics tests and case reports also sustain these pieces of evidence. For example, diabetic wounds treated with exosomes recover more quickly than those without exosomes, exhibiting a greater level of re-epithelialization and angiogenesis. This is attributed to the anti-fibrotic miRNAs (miR-29), which regulate the remodeling of the extracellular matrix and collagen deposition (Riazifar et al., 2017). Although these results are encouraging, several challenges still hinder the clinical translation of exosome therapies. Such discrepancies in performance by exosomes as therapeutics occur because of the variable contents of exosomes, which are highly dependent on the type of donor cells, culture conditions, and methods of isolation. Additionally, the lack of uniform manufacturing guidelines and robust large-scale clinical trial studies, combined with legal uncertainties and the high cost of production processes, hinders outreach in the clinical market. To overcome these barriers, it is essential to have harmonized quality control actions, scalable bioprocessing technologies, and collaboration between researchers, regulatory bodies, and biotech industries. It is only through such strategic moves that the complete regenerative capacity of exosomes in chronic wound healing and aesthetic dermatology can be effectively harnessed and successfully integrated into mainstream therapeutic benefits.

VII. Therapeutic Potential and Clinical Applications

Exosomes hold revolutionary therapeutic possibilities for chronic wounds and burns, given their ability to carry therapeutic bioactive cargos, such as miRNAs (e.g., miR-126) and proteins (e.g., VEGF), to facilitate healing. Exosomes derived with mesenchymal stem cells (MSCs) repair chronic wounds (i.e., diabetic foot ulcers, venous ulcers, and pressure sores) faster than untreated wounds by assisting in the growth of new blood vessels (angiogenesis) and decreasing inflammation preclinically, exosome-derived MSCs closed wounds 30 to 50 percent faster in diabetic models (Shabbir et al., 2015). The integration of exosomes with the most recent wound dressings, including chitosan hydrogels, can enhance functionality by providing extended cargo release, boosting fibroblast migration and collagen deposition within wound beds by 25–35% (Hu et al., 2018). In cases of burn and trauma, exosomes facilitate quicker re-epithelialization due to an increase in keratinocyte proliferation and a decrease in scar formation, attributed to the anti-fibrotic miRNAs such as miR-29 (Riazifar et al., 2017). A novel application is exosome sprays as a non-invasive treatment for superficial burns, filled with anti-inflammatory cargos, such as miR-146a, to counter tissue damage and accelerate the repair process. Initial experiments have demonstrated a reduction in recovery time (Tao et al., 2018). These techniques demonstrate the versatility of exosomes in treating various complex wound types.

Exosomes are becoming new solutions in aesthetic dermatology and precision medicine. Antioxidants, such as superoxide dismutase, when delivered in exosomes, enhance the skin rejuvenation process and prevent aging by detoxifying oxidative stress, thereby increasing skin elasticity by up to 20 percent in small studies (Kalluri & LeBleu, 2020). A novel approach based on exosome-mediated micro needling, which utilizes miR-29 to regulate the collagen remodeling algorithm, reduces scar thickness and provides SCs with a minimally invasive scar-minimizing procedure (Riazifar et al., 2017). Personalized medicine can be utilized by using autologous stem cell-derived exosomes that are tailored to accommodate the unique cargo needs of the patient, such as wound healing. A notable example is the maximization of exosome cargo to apply the concept of adversarial imbalanced learning, aiming to identify the optimal miRNA/protein content within exosomes and create a personalized treatment plan that increases therapeutics by 40 percent in animal models (Li et al., 2025). It can result in the scalability of exosomes as a specialized solution for chronic wounds, burns, and aesthetic applications, and clinical trials are already being conducted to corroborate their clinical importance.

VIII. Challenges and Future Directions

Exosome-based therapies suffer significant limitations to clinical application. The major obstacles are scalability and cost, as exosomes for clinical use are challenging to produce and purify due to the resource-intensive technique required for ultracentrifugation, which yields low outputs at high costs, thereby limiting their application to a smaller audience. Regulatory approval is complicated by the necessity to adhere to Good Manufacturing Practice standards and thoroughly perform safety profiling, as the heterogeneity of exosomes is a source of concern regarding the potential for inconsistent efficacy and minimizing off-target effects. Additionally, the standardization of isolation and characterization methods is challenging due to the variability in exosome compositions between exosomes derived from different cell sources, which affects reproducibility and reliability during therapeutic use. Such challenges require the development of new measures to facilitate production and ensure its safety for introduction into broad-scale clinical practice. The innovation trends in exosome research focus on addressing these challenges with the aid of innovative technologies and new methods. The creation of off-

the-shelf products using exosomes with a consistent therapeutic effect is a priority, and synthesizable exosome-mimetic vesicles offer one potential solution. 3D bioprinting, in combination with exosome-incorporated skin grafts, enhances the benefits of these grafts, facilitating the recovery of more complex tissue in wounds. Combining exosomes with immunotherapy and/or gene therapy may exhibit synergistic activity in the healing of chronic wounds. Among the areas they provide that have the potential to transform personalized regenerative medicine is the regulation of the skin microbiome, promoting the expansion of desirable microbes to reduce infection and inflammation.

IX. Conclusion

Exosomes are emerging as a transformative tool in wound healing and skin regeneration due to their ability to deliver bioactive cargos such as microRNAs (miRNAs), vascular endothelial growth factor (VEGF), and long non-coding RNAs directly to target cells. These nanoscale vesicles facilitate precise modulation of key processes like angiogenesis, inflammation resolution, and extracellular matrix remodeling, making them particularly effective in treating chronic wounds and burns. Breakthrough innovations include CRISPR/Cas9-engineered exosomes that deliver miR-29 to suppress fibrosis, and plant-derived vesicles, such as those from ginger, which exhibit potent anti-inflammatory effects with minimal immunogenicity. Additionally, integrating exosomes into smart biomaterials like hydrogel scaffolds allows for sustained and localized therapeutic release. Artificial intelligence is also being leveraged to optimize exosomal cargo selection and predict patient-specific responses, paving the way for personalized regenerative medicine. However, translating these advances into clinical practice requires rigorous, large-scale clinical trials to ensure safety, efficacy, and reproducibility. Standardization of isolation, characterization, and delivery methods is also crucial. Cross-disciplinary collaboration between biomedical researchers, clinicians, and biotech industries will be essential to build regulatory frameworks and manufacturing scalability. With continued innovation and strategic investment, exosomes have the potential to redefine the future of wound care and aesthetic dermatology as precise, cell-free therapeutics.

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