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The Role of Mesenchymal Stem Cell-Derived Exosomes in Skin Moisturization and Repair: A Review

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Abstract: Extracellular vesicles (EVs), especially exosomes derived from Mesenchymal Stem Cells (MSC-exosomes), are an innovative cell-free approach to improving skin health. The skin serves as the main barrier to the body and is compromised due to aging and environmental stressors. Topical therapies can be used; however, these therapies have minimal effects. This review provides an in-depth review on MSC-exosomes with respect to the role they may play in skin moisturization and repair. MSC-exosome biogenesis and their bioactive cargo are explained. MSC-exosomes contain a unique bioactivity such as a vast combination of growth factors, immunomodulatory cytokines, lipids (including ceramides), and microRNAs; collectively, these are able to induce skin rejuvenation. The complex mechanisms of action are detailed, focusing on ameliorating the epidermal barrier by synthesising Natural Moisturising Factors (NMF) and lipids, alongside remodeling the dermal extracellular matrix through the stimulation of collagen synthesis via pathways such as PI3K/Akt. The methodologies for isolating and characterising exosomes are also detailed, and the importance of standardization for clinical use is discussed. Preclinical studies have shown promise, but issues relating to GMP-produced exosomes and regulatory hurdles need to be addressed before full implementation in the healthcare setting. This review highlights the current state of the research pipeline and the next steps needed in order to realise the full therapeutic and cosmetic potential of MSC-exosomes to dermal health.

Keywords: Exosomes; Mesenchymal Stem Cells; Skin Repair; Moisturization; Collagen Synthesis.

1. Introduction

As the largest organ in the body, the skin provides an essential barrier to regulate hydration, protect against external influences, and maintain homeostasis [1]. When there are issues with the integrity of the skin (dryness, delayed repair, aging), one's quality of life can diminish significantly. Many of the traditional methods for repairing or restoring skin integrity (topical moisturizers, topical growth factor therapies) suffer from limited efficacy, poor penetration, or safety concerns, showing a need for a better alternative [2].

Exosomes are nanoscale extracellular vesicles that are naturally occurring cellular products that have become a focus of investigation relating to regenerative medicine [3]. Exosomes derived from stem cells are of interest because they share the regenerative potential of the stem cells they were produced from, along with the benefits of providing bioactive cargo (both protein and nucleic acid) that mediate communication between cells, without being immunogenic [4]. There is preliminary evidence supporting the use of stem cell-derived exosomes to improve skin hydration, promote repair, and support barrier function through the stimulation of fibroblast activity and collagen production. As observed in an industrial internship setting, where there was simultaneous research being conducted on MSCs and vesicles derived from them, stem-cell derived exosomes were successfully being incorporated into practical skin care research into usable by-products like facial masks. This process demonstrated the translational potential of MSC-derived exosomes into skin care applications and highlighted a clear need for systematic academic exploration to enhance understanding of their mechanisms and effectiveness.

This review, therefore, performs an assessment of the impact of stem cell-derived exosomes on skin health with an aim to clarify their impact on skin hydration and repair while connecting the laboratory to industry and developing a theoretical foundation for the maximizing value of exosomes in cosmetic or therapeutic products - addressing unmet needs in skin care and therapy.

2. MSC-Derived Exosomes: Biogenesis and Composition

Exosomes are a distinct subtype of EVs that have garnered immense scientific interest due to their role as natural nanocarriers [5].

2.1. Origin and Biogenesis

The therapeutic abilities of exosomes are directly connected to their unusual biogenesis, which is a highly regulated process that distinguishes them from other EVs [6]. The production of exosomes is mediated by cells in a regulated way, which is essentially a three-step process of "endocytosis, sorting and release."

It begins with the endocytosis of cells, forming a closed membrane structure—early endosomes. Early endosomes gradually mature and migrate towards the interior of cells, transforming into late endosomes. At this point, the membrane of the late endosome will sink inward and sprout, forming multiple small vesicles within its lumen. These small vesicles are suspended in the cavities of the late endosome and are called intraluminal vesicles (ILVs). When a late endosome contains a large number of ILVs, it is called a multivesicular body (MVB)—this is the core structure of exosome production [7]. At this stage, cells will perform precise sorting of "goods" through specific molecular mechanisms such as the ESCRT (Endosomal Sorting Complex Required for Transport) protein complexes and lipid rafts, selectively encapsulating bioactive substances (such as proteins, mRNA, miRNA, lipids, etc.) into the ILVs [8].

After the formation of MVBs, a portion of them will fuse with lysosomes and be degraded. The other part will move

towards the cell membrane and eventually fuse with it. This fusion event releases the ILVs into the extracellular space, where they are now termed exosomes [7].

2.2. Structure and Composition

The structure and composition of exosomes depend on several factors including the donor cell, microenvironment, and physiological conditions [4]. As freight transporters, exosomes can carry proteins, peptides, nucleic acids, and lipids.

2.2.1. Proteomic and Lipidomic Cargo

Exosomal proteins perform a wide range of functions including adhesion/targeting, anti-apoptosis, membrane fusion, signal transduction, metabolism, and structural dynamics [9], [10]. MSC-exosomes contain a potent combination of growth factors vital for skin repair, including Vascular Endothelial Growth Factor (VEGF), a key mediator of angiogenesis, and Fibroblast Growth Factor (FGF), which promotes keratinocyte and fibroblast proliferation [11]. The cytokine profile is mostly anti-inflammatory; large concentrations of Interleukin-10 (IL-10) and Transforming Growth Factor-beta (TGF-β), which suppress inflammatory responses, are contained in the exosomes [12].

The lipids are of functional importance as well. The exosomal membrane is enriched in specific lipids, including cholesterol, sphingomyelin, and particularly ceramides [13]. Ceramides are waxy lipids and an important species for the formation of the skin barrier to prevent water loss [14].

2.2.2. Nucleic Acid Cargo and Regulatory MicroRNAs

Another equally important cargo is RNAs, which explains exosomes acting as intermediaries of internal cellular communication [15]. The most powerful units are non-coding RNAs, and in particular microRNAs. miRNAs are small RNA molecules that function as master coordinators of gene expression in its recipient cell [16]. MSC-exosomes have a defined signature of miRNAs that act in concert in the skin repair process. Of the many miRNAs, two have undergone extensive study. The first, miR-21, is an important pro-regenerative signal because it stimulates fibroblast and keratinocyte proliferation and migration as well as angiogenesis by targeting the PTEN/PI3K/Akt signalling pathway [17]. The second important miRNA, miR-146a, is a master regulator of anti-inflammation that targets key adapter proteins (IRAK1 and TRAF6) to dampen the production of inflammatory cytokines in the TLR (Toll-like receptor) signalling pathway [18].

2.3. Advantages of Mesenchymal Stem Cell (MSC) Exosomes

Selecting exosomes from MSCs rather than exosomes from other cell types offers many benefits. MSCs are multipotent, non-hematopoietic, adult stem cells that can be isolated from a variety of biological sources, including adipose tissue, umbilical cord, and bone marrow [4].

MSCs have a high secretion capacity and a good ability to repair tissue. MSC extracellular vesicles are plentiful in numerous cytokines and growth factors that can more effectively induce cell proliferation, stimulate angiogenesis, and inhibit cell apoptosis [19]. The most notable advantage is the low immunogenicity. MSCs and exosomes from MSCs have virtually low or undetectable expressions of Major Histocompatibility Complex class II (MHC-II) and other important co-stimulatory molecules (e.g., CD86 and CD80). The absence of these signals prevents the activation of an adaptive immune response, which effectively hides the exosomes from the immune system of the recipient and makes off-the-shelf allogeneic therapies possible [20].

3. Mechanisms of MSC-Exosomes in Skin Moisturization and Repair

The therapeutic efficacy of MSC-exosomes in dermatology is not attributable to a single mechanism but rather to a synergistic interplay of their bioactive cargo with multiple cell types and signaling pathways in the skin.

3.1. Epidermal Barrier Restoration and Hydration

A healthy epidermal barrier is fundamental to skin health. It prevents water loss and protects against environmental aggressors. MSC-exosomes directly target and reinforce this barrier through several key mechanisms.

3.1.1. Replenishing Natural Moisturizing Factor (NMF) Components

Natural Moisturizing Factor (NMF) is a group of water-soluble small molecules in the stratum corneum, one of the core components that maintain the skin's moisture balance. For exosomes, they contain many NMF components. For example, they can encapsulate and transport various free amino acids, carbohydrates, and peptides. The moisturizing principle of NMF is mainly based on the hydrophilicity of its components, which bind water molecules from the environment and lock them into the stratum corneum to prevent rapid evaporation [21]. The specific composition of NMF is detailed in Table 1.

3.1.2. Restoring the Skin's Lipid Matrix

Similarly, exosomes also contain important moisturizing ingredients for the skin, such as ceramides. Ceramides belong to the lipid class substances and are an important component of the skin barrier structure. They reduce the transdermal water loss by forming an ordered lipid bilayer structure between keratinocytes [14]. In inflammatory conditions like atopic dermatitis, which are characterized by a defective barrier and ceramide deficiency, exosomes from adipose-derived MSCs have been shown to induce the de novo synthesis of ceramides in keratinocytes, significantly reducing transepidermal water loss (TEWL) [22].

3.2. Dermal Matrix Remodeling and Collagen Synthesis

The skin is divided into the epidermis and the dermis. Dermal tissue cells are found in the meshes at the junctions of the dermal fibrous network. The main cell type here is fibroblasts. Motivated fibrocytes are called fibroblasts. They produce collagen, elastin, and matrix proteins.

Collagen forms an "elastic net" that "supports" the skin, making it moist, plump, and firm. Its synthesis primarily occurs in the dermis. In the skin, fibroblasts are the primary producers of collagen, regulating collagen synthesis through the PI3K-AKT-mTOR pathway. The PI3K-AKT pathway is an intracellular signaling pathway that responds to extracellular signals and promotes metabolism, proliferation, cell growth, and survival. When growth factors bind to receptors on the cell membrane, they stimulate PI3K isozymes. Activated PI3Ks catalyze the phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP2) to produce the

second messenger molecule, phosphatidylinositol-3,4,5-trisphosphate (PIP3). PIP3 then acts as a key molecule to help activate Akt (protein kinase B) [23].

Table 1. Composition of NMF.

constituents	mass number%
Free amino acids	40
Pyroalkane carboxylic acids	12
Lactic acids	12
Carbohydrates, organic acids, polypeptides, and unconfirmed substances	8.5
Urea	7
Chlorides	6
Sodium	5
Potassium	4
Ammonia, uric acid, glucosamine and creatine	1.5
Calcium	1.5
Magnesium	1.5
phosphate	0.5
Citrate, formate	0.5

Activated Akt promotes collagen synthesis from two core aspects: gene transcription and protein translation. It can synergize with TGF-β (a key cytokine that promotes collagen synthesis) to promote gene transcription of collagen (e.g., COL1A1) [24]. After mRNA transcription of collagen, its translation process is regulated by mTORC1 (mammalian target of rapamycin complex 1), a core regulatory molecule of the PI3K-Akt pathway. Activated mTORC1 promotes ribosome assembly and the translation process of collagen mRNA by phosphorylating downstream molecules S6K1 and 4E-BP1 [25].

The activation of the PI3K-Akt signaling pathway is associated with numerous factors. Exosomes contain multiple cytokines that can promote this pathway by attaching to receptors on the target cell's surface. For instance, one common cytokine is Vascular Endothelial Growth Factor (VEGF), which attaches to its receptor (VEGFR), a type of receptor tyrosine kinase (RTK). Similarly, exosomes can transport Epidermal Growth Factor (EGF) and Fibroblast Growth Factor (FGF); when bound to their respective receptors (EGFR, FGFR), these factors will activate the cascade [26].

4. Methodology For Exosome Isolation and Characterization

4.1. Isolation of Exosomes by Ultracentrifugation

The exosomes involved in this study are mainly separated by ultracentrifugation. This is the core separation technology used to produce the facial mask products in this research. The method separates particles according to their sedimentation coefficients (size, density, and shape) by using centrifugation. Although using ultracentrifugation has some weaknesses, such as contaminants, long duration, and the need for expensive equipment, it also has many advantages. Its high level of reproducibility makes it a classic and commonly used method [27]. It remains a gold standard for research purposes due to its feasibility for isolating EVs from large volumes. It also causes minimal interference with the biological activity of the EVs.

The specific ultracentrifugation method used is differential ultracentrifugation (DUC). DUC is a method that utilizes the differences in sedimentation rates of different particles. It gradually increases the magnitude of centrifugal force and performs multiple centrifugations. This is done to sequentially remove particles of different sizes. The process begins with a low-speed centrifugation step to remove cells and dead cells. This is followed by a high-speed centrifugation to pellet cell debris. Subsequently, an ultracentrifugation step is performed to remove larger vesicles like apoptotic bodies and microvesicles. Finally, the exosomes are pelleted via a final, higher-speed ultracentrifugation, typically at over 100,000 x g.

4.2. Extraction of Exosomes' Contents by Repeated Freeze-Thaw

The main principle in extracting exosomal contents is the repeated freeze-thaw method. It exploits the aggressive nature of temperature variation on the exosomal membrane. The method can be summarized as follows. First, purified exosomes are resuspended in an appropriate buffer, like PBS. The resuspended exosomes are then frozen at -80°C and thawed at 37 °C for 3-5 cycles, which ruptures the exosome membrane. After this treatment, the mixture undergoes high-speed centrifugation (e.g., 12,000-16,000 x g). This pellets any remaining un-ruptured exosomes and other debris. The

supernatant, which has the exosomal contents (proteins and RNA), remains in the solution and is collected for downstream analysis.

4.3. Modern Isolation Techniques and Characterization Standards

Although ultracentrifugation is a common technique, the field is transitioning to preferable techniques. They are preferred because they yield higher yield and purity that preserve bioactivity. This is particularly important for clinical-grade production. A notable alternative is Size Exclusion Chromatography (SEC). It is a gentle, chromatography-based technique that separates exosomes from smaller soluble proteins based on size, yielding a product with high purity [28]. Another popular technique is Tangential Flow Filtration (TFF). This is a filtration-based technique used for processing high volumes. It also scales easily for industrial-level manufacturing [29]. A combined TFF-SEC workflow is now considered the gold standard for manufacturing clinical grade exosomes [30].

To ensure rigor and reproducibility, studies in this area must follow the "Minimal Information for Studies of Extracellular Vesicles 2018" (MISEV2018) from the International Society for Extracellular Vesicles (ISEV) [31]. This includes a multifactorial approach for characterizing exosomes as prescribed in MISEV2018. This requires providing a visual image of the vesicle morphology by Transmission Electron Microscopy (TEM). It also requires the determination of the size distribution (30-150 nm) using Nanoparticle Tracking Analysis (NTA). Furthermore, it requires performing protein analysis using methods such as Western blotting. This analysis must identify positive markers to verify the product is exosome-based (CD9, CD63, TSG101). It must also confirm the absence of negative markers from other cellular compartments (Calnexin).

5. Discussion and Future Perspectives

In summary, the evidence collectively demonstrates that MSC-derived exosomes are powerful tools for skin hydration and repair. The mechanism of action is multi-factorial. It is not a single molecule but rather a synergistic mixture of bioactive cargo. By delivering bioactive components that resemble NMF and ceramides, MSC-derived exosomes have the potential to improve epidermal hydration. They also have the potential to improve barrier function. In sending growth factors and miRNAs, the MSC-derived exosomes can stimulate fibroblasts to regenerate the dermal collagen matrix and repair the structural loss associated with aging skin, through pathways including, but not limited to, PI3K/Akt.

That said, significant challenges remain between the bench and the bottom shelf. The first challenge is manufacture. Industry will require a robust, scalable, GMP compliant process that can standardize for a safe, effective, and consistent therapeutic or cosmetic product [32]. This will require standardizing and control for the MSC source, culture system, the isolation method, and the purification process from start to finish.

Another limitation is the optimization of topical delivery. Although exosomes are nanoscale in size, there is no guarantee that they will efficiently overcome the significant challenge of the stratum corneum to deliver exosomes to target cells in the dermis. Future studies will most likely seek out more sophisticated delivery systems, such as exosomes being mixed or incorporated into microneedle patches or biocompatible hydrogels, to facilitate delivery and improve exosome penetration and bioavailability [33].

In terms of what might come next, it's possible the next wave of innovation in exosome delivery will come in the form of bio-engineered "designer" exosomes, which could either be vesicles actively loaded with specific therapeutic molecules (such as more miRNAs or small-molecule drugs), or surface-modified exosomes to contain targeting ligands to facilitate delivery to specific skin cells (for example, inflamed keratinocytes or senescent fibroblasts). With precision engineering, exosomes could be considered less a regenerative agent and more a specific and well-engineered drug delivery platform in dermatology [34].

6. Conclusion

In conclusion, exosomes derived from mesenchymal stem cells constitute a promising new development in dermatology. They act as natural nanocarrier vehicles for a multi-faceted regenerative cargo. Exosomes represent a cell-free, low-immunogenicity platform that is capable of coordinating a comprehensive repair process within the skin. Their restorative and regenerative properties address the fundamental traits of skin aging and dehydration. They achieve this by restoring barrier function and dermal matrix remodeling. Although there are barriers related to standardized manufacturing and delivery, ongoing research efforts and strict characterization standards will be essential for translating the tremendous scientific potential of MSC-exosomes to new therapies in skin rejuvenation and the treatment of dermatological disorders.

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