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Exploring the Therapeutic Potential of Exosomes in Pigmentation Disorders

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Abstract

Exosome therapy is a promising, non-invasive approach for treating pigmentation disorders such as vitiligo, melasma, and post-inflammatory hyperpigmentation. These small extracellular vesicles deliver bioactive compounds, including anti-inflammatory agents and skin-regenerative molecules, which target specific cells and processes to restore normal pigmentation. Current therapies for pigmentation disorders often have limited effectiveness and may result in side effects. Exosome-based therapy offers a novel solution by directly influencing melanogenesis and modulating the immune response to manage pigmentation abnormalities. Exosomes, with their biocompatibility and ability to cross biological barriers, function as natural drug delivery vehicles. They carry proteins, RNA, and lipids that can regulate pigmentation processes by transferring pigmentation-related factors such as melanin-regulating molecules from keratinocytes and melanocytes. This targeted approach allows exosome therapy to mitigate inflammation, oxidative stress, and cell damage in pigmentation disorders, which are central to their pathophysiology. This review explores the therapeutic potential of exosomes in pigmentation disorders, focusing on their unique biological properties, specific mechanisms of action, and potential advantages over traditional treatments. Although exosome therapy faces challenges in standardization, scalability, and delivery specificity, advancements in exosome engineering and increased clinical trials could optimize its efficacy. By addressing these issues, exosome therapy has the potential to redefine treatment options for pigmentation disorders, paving the way for personalized and minimally invasive dermatologic care.

Categories: *Dermatology, Immunology, Cosmetic Medicine*

Key words: *Pigmentation disorders, melanogenesis, exosome therapy, non-invasive*

1. INTRODUCTION

As the body's largest and most exposed organ, the skin is vulnerable to disorders like vitiligo, melasma, and post-inflammatory hyperpigmentation (PIH)—conditions that, though often benign, can cause significant psychological distress and reduce quality of life [1,2]. Despite their visibility, pigmentation disorders are frequently dismissed in primary care, leaving patients without adequate treatment or support [2,3]. Lesions on the face, hands, or genitals can lead to anxiety, depression, and low self-esteem [2].

Vitiligo affects ~2% of the global population and presents as hypopigmented patches due to autoimmune melanocyte destruction, often beginning in childhood or early adulthood [1,2]. The psychological impact is especially profound when lesions are visible or genital, leading to social withdrawal and diminished self-image [2].

Melasma and PIH, in contrast, are characterized by hyperpigmentation from increased melanin production. Melasma is strongly linked to hormonal changes, sun exposure, and genetics, while PIH commonly follows inflammation or injury and disproportionately affects individuals with darker skin tones [3,4,5]. Both can be persistent and cosmetically troubling, requiring sensitive and comprehensive care.

Conventional treatments for pigmentation disorders are limited by modest efficacy, long durations, and significant side effects. Vitiligo is managed with corticosteroids or topical immunomodulators like Ruxolitinib and Tacrolimus, though these therapies may cause skin atrophy, cancer risk, or relapse [2,6–8]. For melasma and PIH, Kligman's formula (hydroquinone, tretinoin, dexamethasone) remains standard but carries risks like dermatitis, ochronosis, and prolonged regimens [9]. Procedures like chemical peels and lasers may help, but results are inconsistent. These limitations underscore the need for safer, more effective alternatives—such as exosome-based therapies.

Exosomes are extracellular vesicles carrying nucleic acids, proteins, and signaling molecules involved in intercellular communication [10]. Derived from endosomal multivesicular bodies, exosomes can deliver therapeutic cargo—such as miRNAs or small compounds—into specific target cells, offering a natural, biocompatible drug delivery system [10]. In pigmentation disorders, keratinocyte-derived exosomes modulate melanocyte behavior by transferring miRNAs that influence melanin synthesis. For instance, they may suppress melanogenesis by downregulating MITF or enhance it via tyrosine kinase activation, especially under UVB exposure—contributing to conditions like melasma and PIH [10]. Targeting these pathways through engineered or selected exosome therapies could offer precision treatments with fewer side effects than current options.

This review explores the role of exosomes in regulating pigmentation and their emerging potential in treating vitiligo, melasma, and PIH.

2. Mechanisms of Pigmentation and Pathogenesis of Disorders

2.1. Physiologic Pigmentation Process

Skin pigmentation is primarily determined by melanin synthesis, or melanogenesis, within melanocytes. Melanocytes are specialized pigment-producing cells located in the basal layer of the epidermis. They synthesize two primary types of melanin: eumelanin, which is black or brown and pheomelanin which is yellow or red. These pigments determine skin, hair, and eye color while also protecting against UV radiation [11]. The production of melanin occurs in organelles called melanosomes that undergo maturation and are later transported to neighboring keratinocytes, where melanin accumulates to protect DNA from UV-induced damage [12]. Melanogenesis begins with the enzymatic conversion of L-tyrosine into L-dihydroxyphenylalanine (L-DOPA), followed by rapid oxidation to dopaquinone (DQ). This reaction is catalyzed by tyrosinase (TYR) which serves as the rate-limiting enzyme. In the presence of cysteine or glutathione, DQ undergoes a series of redox reactions to form pheomelanin. In contrast, when there is limited availability of these compounds, eumelanin is predominantly synthesized [13]. This pathway is tightly regulated to ensure that pigmentation stays balanced.

The regulation of melanogenesis is dependent on complex signaling pathways with α-melanocyte stimulating hormone (α-MSH) and its interaction with G protein-coupled receptor melanocortin 1 receptor (MC1R) serving as principal modulators. In response to UV radiation, keratinocytes and melanocytes produce α-MSH, which binds to MC1R on melanocytes [14]. This interaction activates the cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA) signaling cascade. This activation leads to phosphorylation of cAMP-response element binding protein (CREB) which subsequently enhances the transcription of MITF [15]. MITF is the dominant transcription factor in melanocyte function by regulating the expression of fundamental melanogenic enzymes, including TYR, tyrosinase-related protein 1 (TYRP1), and tyrosinase-related protein 2 (TYRP2) [16]. Dysfunction in this pathway is implicated in both hypopigmentation and hyperpigmentation disorders discussed in later sections of this review.

Once melanin is synthesized in melanocytes, it must be distributed to keratinocytes. Although multiple methods have been proposed, recent studies support the coupled exocytosis and phagocytosis model. This model details the release of melanin cores (melanocores) into the extracellular space that are phagocytosed by keratinocytes [17]. High resolution electron microscopy studies have provided strong evidence for this by showing extracellular

melanocores being internalized by keratinocytes rather than direct organelle transfer via fusion of cytophagocytosis [17,18]. Recent findings highlight key regulators of melanin transfer, including Ras-related protein 11b (Rab11b), which facilitates melanocore secretion, and protease-activated receptor (PAR-2), which enhances keratinocyte uptake [19]. This evidence points toward coupled exocytosis and phagocytosis as the primary mechanism of melanosome transfer.

2.2. Pathophysiology of Vitiligo

The pathophysiology of vitiligo is a complex interplay of immune, genetic, and environmental factors that ultimately result in the destruction of melanocytes [20]. A central mechanism in vitiligo pathophysiology is the cell-mediated destruction of melanocytes by CD8+ T cells confirmed by skin biopsies of the highly active margins of lesional vitiligo [21]. These T cells recognize melanocyte specific antigens such as TYR, gp100, melanoma antigen recognized by T cells (MART-1/Melan-A) [22]. Upon activation, T cells release interferon-γ (IFN-γ), which stimulates keratinocytes to produce chemokines CXCL 9, CXCL 10, and CXCL 11. These chemokines are highly expressed in the serum and lesional skin of vitiligo patients, and they act to recruit additional T cells to the epidermis [23,24]. In addition, IFN-γ upregulates CXCR3, a key chemokine receptor that responds to CXCL10 in both keratinocytes and T cells. Importantly, the CXCR3B isoform in melanocytes plays a critical role in driving apoptosis when stimulated by CXCL10 [25]. Oxidative stress also contributes to the initiation and perpetuation of melanocyte damage in vitiligo. Excessive production of reactive oxygen species (ROS) in melanocytes, driven by environmental stressors or inherent metabolic dysfunction, can lead to cellular damage and exposure of melanocyte specific antigens [26]. In this context, IFN-γ-induced chemokine production and CXCR3-mediated apoptosis synergize with oxidative stress, creating a destructive feedback loop that drives melanocyte loss.

2.3. Pathophysiology of Melasma

Melasma is a hyperpigmentation disorder usually affecting the face that is characterized by excess melanin deposition. Hormonal factors and UV exposure are the fundamental contributors to its development [27]. Estrogen and progesterone increase melanin synthesis by upregulating MITF, TYR, and other melanogenic enzymes which explains the higher prevalence of the condition in pregnant women [28].

UV radiation exacerbates melanocyte hyperactivity by stimulating α-MSH, endothelin-1 (ET-1), and fibroblast growth factor-2 (FGF-2). It also causes solar elastosis, basement membrane distribution, and increased vascularity which can all contribute to persistent hyperpigmentation [29]. Lesional skin of melasma has shown that fibroblasts produce increased levels of stem cell factor (SCF), hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF). These factors cause vascular abnormalities that further increase pigment deposition [29]. The combination of hormonal, UV radiation, and vascular changes make persistent hyperpigmentation that is often not responsive to current therapeutic interventions.

2.4. Pathophysiology of Post-Inflammatory Hyperpigmentation

Post-inflammatory hyperpigmentation occurs after cutaneous insult or inflammation. It is driven primarily by an inflammatory cascade that drives melanocyte hyperactivity and excessive melanin production [30]. Inflammatory mediators such as tumor necrosis factor-alpha (TNF- α), interleukin-1 (IL-1), and interleukin-6 (IL-6) are released by immune cells and keratinocytes in response to cutaneous trauma. Through paracrine signaling, these cytokines act on melanocytes by upregulating pro-melanogenic enzymes, such as TYR, TYRP1 and MITF [31]. Inflammation also exacerbates oxidative stress, which further stimulates melanogenesis through the enhanced expression of ET-1 and α-MSH. The accumulation of ROS causes DNA damage, lipid peroxidation, and mitochondrial dysfunction in melanocytes. With chronic oxidative stress, epidermal homeostasis is impaired and there are delays in normal melanin clearance. This results in retention of melanin and prolonged hyperpigmentation [32]. Interestingly, the disruption due to oxidative stress is more persistent in darker skin tones due to their higher baseline melanocyte density [33]. The dysregulated inflammatory and oxidative processes in PIH lead to sustained hyperpigmentation even after the initial insult has resolved.

3. Exosome Biology and Therapeutic Potential

3.1. Exosome Formation and Composition

Exosome formation begins with the inward budding of plasma membranes to create early

endosomes. Early endosomes are single lipid bilayer vesicles that require maturation to become late endosomes. During this process, the endosomes move closer to the nucleus, their internal pH decreases, and their membrane composition changes [34]. The essential event in this maturation is the inward budding of the endosomal membrane to form intraluminal vesicles (ILVs), leading to the formation of a multivesicular body (MVB). MVBs are subsequently moved to and fuse with the cell membrane where they release their ILVs into the extracellular space as exosomes [34]. Exosome biogenesis is regulated by two mechanisms, the Endosomal Sorting Complex Required for Transport (ESCRT)-dependent and ESCRT-independent pathways. The ESCRT-dependent complex uses protein complexes to mediate cargo sorting and form ILVs while the independent pathway uses lipids such as ceramide [35]. Once MVBs are formed, their release as exosomes is initially mediated by Rab GTPases. Specifically, Rab27a and Rab27b were found to function in movement of MVBs along the cytoskeleton and fusion with the plasma membrane [36]. Soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs) then form complexes that bring the MVB membrane and the plasma membrane together allowing for fusion and release of exosomes into the extracellular space [37]. This process enables exosomes to deliver a diverse array of proteins, lipids, and nucleic acids. By facilitating the transfer of this cargo, they influence gene expression, immune responses, and cellular behavior [38]. This ability makes exosomes critical vehicles for intracellular communication.

3.2. Relevance to Pigmentation Disorders

Skin pigmentation relies heavily on the transfer of exosomes between melanocytes and keratinocytes. The impact of exosomes on pigmentation was demonstrated in a study of melanocytes treated with exosomes derived from UVB-exposed and non-exposed keratinocytes. The findings showed that melanocytes treated with exosomes from UVB-exposed keratinocytes had significantly greater melanin production. Interestingly, the number of MVBs was not increased, suggesting the change in pigmentation was due to alternations in melanogenesis pathways rather than an increase in the number of exosomes [38]. Exosomal microRNAs (miRNAs) derived from keratinocytes can both promote and inhibit the expression of melanogenic genes. For example, an overexpression of miR-330-5p found in exosomes derived from keratinocytes induced downregulation of TYR expression and melanin production in melanocytes [39]. Exosomes derived from immune cells cause modulation of immune response and oxidative stress associated with pigment disorders like vitiligo and melasma. In vitiligo, exosomes promote the activation of CD8+ T cells and downregulate regulatory T cells causing melanocyte destruction [40].

Under oxidative stress, exosomes respond by increasing the release of antioxidant enzymes like glutathione peroxidase and superoxide dismutase to mitigate cellular damage from ROS [41]. These findings highlight the effect exosomes have on pigmentation disorders.

3.3. Advantages of Exosome-Based Therapy

Therapies involving the use of exosomes offer several advantages over current treatment options. One of the most important reasons for this is biocompatibility. Since exosomes are naturally occurring vesicles, they are extremely well tolerated by the body. Their low immunogenicity greatly reduces the risk of immune rejection and adverse reactions compared to synthetic carriers [42]. Exosome therapy also offers very targeted treatment by delivering cargo only to cells of interest. This not only increases the precision of treatment but also decreases the likelihood of side effects [43].

Traditional therapy options for pigmentation disorders include topical agents like hydroquinone that offer poor penetration and limited efficacy. A randomized placebo controlled-study evaluated the skin brightening efficacy of exosomes derived from human adipose tissue-derived mesenchymal stem/stromal cells (ASC-exosomes). The results were visible improvement in hyperpigmentation and significantly reduced melanin in treatment vs placebo after only four weeks [44]. ACS-exosomes demonstrate the potential of a new therapeutic option that could alter the future of cosmetic therapy.

3.4. Exosome Engineering

Engineering exosomes for precise therapy involves various cargo loading techniques and targeted modifications. Incorporating cargo into exosomes is achieved through either an endogenous or exogenous approach. The endogenous approach genetically modified parent cells to produce exosomes that carry desired molecules. The exogenous approach incorporates cargo into exosomes after they are

isolated through methods such as electroporation, sonication, and freeze-thaw cycles [45].

Both approaches have their advantages and disadvantages based on different drug types and therapeutic applications. The benefit of multiple approaches has allowed exosomes to be used to deliver chemotherapy agents, RNA, and immune modulators. Due to exosomes being cell-derived, they are ideal candidates for patient-specific treatments. They can avoid host immunity while reaching desired target cells [46]. With continued advancement in engineering strategies, exosome therapy holds the potential to revolutionize personalized medicine.

4. Exosomes in the Regulation of Melanogenesis

4.1. Melanocyte Derived Exosomes

Exosome therapy offers a novel approach for treating dermatologic conditions linked to melanogenesis dysregulation. Among various exosome sources, melanocyte-derived exosomes are particularly notable for their role in regulating pigmentation through intercellular transfer of miRNAs, proteins, and lipids. Exosomes from B16F10 melanoma cells contain miRNAs that upregulate melanin synthesis genes, including tyrosinase, thereby enhancing pigmentation in neighboring melanocytes [47]. UVB exposure further stimulates human melanocytes to secrete exosomes enriched with pigmentation-related miRNAs, which amplify melanin production in recipient cells, illustrating an adaptive response to environmental stress [48]. In pathological contexts, melanoma-derived exosomes promote epithelial-mesenchymal transition (EMT) in melanocytes via paracrine and autocrine signaling, contributing to tumor progression [49]. These findings underscore the dual role of melanocyte-derived exosomes in both normal pigmentation and melanoma pathogenesis.

4.2. Keratinocyte-Derived Exosomes

Exosomes from UVB-irradiated keratinocytes enhance melanogenesis by upregulating key melanogenic proteins, including MITF, TYR, TRP1, and TRP2, with MITF acting as a central regulator [50]. Their miRNA cargo further modulates pigmentation, as miRNAs like hsa-miR-644a, hsa-miR-365b-5p, and hsa-miR-29c-3p promote melanin production, while others such as hsa-miR-18a-5p, hsa-miR-197-5p, and hsa-miR-4281 inhibit it [50]. Beyond melanogenesis, these exosomes influence melanosome maturation, melanocyte dendricity, and pigment transfer to keratinocytes, all which shape pigmentation patterns [51]. Their secretion and effects are UVB-responsive and phototype-dependent, indicating an adaptive mechanism that modulates pigmentation based on skin type and UV exposure [38]. This adaptation likely evolved to optimize the skin's response to UV radiation, balancing protective pigmentation with potential risks of photodamage.

4.3. Immune Cell-Derived Exosomes

Immune cell-derived exosomes critically modulate inflammatory pathways that influence pigmentation, particularly in disorders such as vitiligo. These exosomes, secreted by CD8+ T cells, Tregs, and Th17 cells, contribute to melanocyte apoptosis and immune dysregulation. CD8+ T cell-derived exosomes carry cytotoxic molecules like perforin and granzyme B, along with pro-inflammatory cytokines such as IFN-γ, which create a hostile microenvironment that accelerates melanocyte destruction [52]. In contrast, Treg-derived exosomes promote immune tolerance by delivering immunosuppressive mediators including TGF-β and IL-10, thereby protecting melanocytes and offering therapeutic promise in autoimmune pigmentary disorders [53]. Conversely, Th17 cell-derived exosomes, rich in IL-17A, IL-1β, IL-6, and TNF-α, downregulate melanogenesis genes (MITF, TYR, TYRP1, TYRP2) and induce melanocyte apoptosis, further driving depigmentation [54]. More broadly, the balance between pro- and anti-inflammatory exosomal signaling shapes melanocyte survival and activity, with chronic inflammation tipping the scale toward pigmentary disruption.

4.4. Stem Cell-Derived Exosomes

Stem cell-derived exosomes, particularly those from mesenchymal stem cells (MSCs), play a vital role in melanocyte regeneration and offer promising therapeutic potential in pigmentation disorders. MSC-derived exosomes exert anti-inflammatory, pro-proliferative, and anti-apoptotic effects that enhance skin repair [55]. Their cargo—rich in miRNAs, proteins, and lipids—regulates gene expression and activates pathways critical for melanocyte survival and pigmentation homeostasis [56]. In vitiligo, human umbilical MSC-derived exosomes (hUMSCs-Exos) improve outcomes by enhancing Treg-mediated immunosuppression and reducing oxidative stress-induced melanocyte damage [53]. Notably, exosomes from 3D spheroid-cultured hUMSCs (3D-Exos) demonstrate superior efficacy over 2D-derived

exosomes, further expanding Tregs and protecting melanocytes from H_2O_2-induced apoptosis [53]. These properties position stem cell-derived exosomes as a multifaceted therapeutic strategy for restoring pigmentation through immunomodulation, oxidative stress reduction, and melanocyte repair.

5. Therapeutic Applications of Exosomes in Pigmentation Disorders

5.1. Exosome Application in Vitiligo

Exosomes hold therapeutic potential in vitiligo by modulating immune responses and reducing oxidative stress, both central to disease pathogenesis. Human umbilical MSC-derived exosomes (hUMSCs-Exos) enhance Treg-mediated immunosuppression and protect melanocytes from oxidative damage [53].

Notably, exosomes from 3D-cultured MSCs (3D-Exos) demonstrate superior efficacy by expanding Treg cells and suppressing H_2O_2-induced melanocyte apoptosis. These exosomes are enriched with miR-132-3p and miR-125b-5p, targeting Sirt1 and Bak1, which are key to oxidative stress reduction and melanocyte survival [53]. Exosomes also regulate CD8+ T cells, Tregs, and Th17 cells, maintaining immune tolerance and supporting melanocyte function through intercellular communication, particularly between keratinocytes and melanocytes [57].

Exosomal miRNAs are emerging as pivotal regulators in vitiligo. Circulating miR-493-3p influences epidermal dopamine levels, increasing ROS and promoting melanocyte apoptosis in segmental vitiligo, while downregulation of miR-200c in keratinocyte-derived exosomes suppresses melanogenesis via reduced MITF and TYR expression [58]. Additionally, MSC-derived exosomes bolster skin defenses against oxidative stress, promoting melanocyte resilience [57].

5.2. Exosome Application in Melasma

Exosomes regulate hyperactive melanogenesis in melasma by modulating melanin production and inflammatory pathways. Human amniotic stem cell-derived exosomes enriched with miR-181a-5p and miR-199a suppress melanogenesis by inhibiting MITF and activating autophagy, promoting melanosome degradation [59]. Keratinocyte-derived exosomes also influence melanogenesis; UVB-exposed keratinocytes release exosomes that upregulate MITF, TYR, TRP1, and TRP2. Some miRNAs (e.g., hsa-miR-644a, hsa-miR-365b-5p) enhance melanogenesis, while others (e.g., hsa-miR-18a-5p, hsa-miR-197-5p) inhibit it, illustrating their dual regulatory roles [50].

Fibroblast-derived exosomes carrying miR-25-5p can reduce melanin synthesis by targeting TSC2 and disrupting organelle function [60]. Anti-inflammatory compounds also target melanogenesis and may be delivered via exosomes for enhanced efficacy. For instance, 3,6’-dimethoxychalcone (3,6’-DMC) reduces melanin and tyrosinase activity by downregulating MITF through ERK, PI3K/Akt, and GSK-3β/catenin activation while suppressing inflammatory mediators [61]. Other agents such as Bay 11-7082 [62], solamargine (SM) [63], and dimethyl itaconate (DMI) [64] inhibit pro-inflammatory cytokines and melanogenesis via MAPK, NF-κB, and AKT pathways. Incorporating these agents into exosome therapies may offer a multifaceted approach to treating melasma by targeting both pigmentation and inflammation.

5.3. Exosome Application in Post-Inflammatory Hyperpigmentation

Mesenchymal stem cell-derived exosomes, including those from adipose-derived stem cells (ADSCs) and umbilical cord MSCs (UCMSCs), offer promising therapy for post-inflammatory hyperpigmentation (PIH) by targeting inflammation and oxidative stress. ADSC-derived exosomes modulate macrophage polarization via the Nrf2/HO-1 pathway, reducing pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) and ROS accumulation [65]. Similarly, UCMSC-derived exosomes enhance skin cell viability, decrease intracellular ROS, stabilize mitochondrial function, and suppress inflammatory cytokines [66]. Hypoxia-pretreated ADSC exosomes further protect against UV-induced skin injury by inhibiting ROS and inflammatory signaling [67]. Exosomes from hUMSCs and human amniotic stem cells (hASCs) also support melanocyte recovery post-injury through immunosuppressive and antioxidant actions, preventing melanin overproduction and promoting pigment balance [53]. Collectively, these exosomes restore skin homeostasis in PIH by reducing its key drivers—oxidative stress and inflammation.

5.4. Combination Therapies with Exosomes

Combining exosome therapy with lasers and topical agents enhances the treatment of pigmentation disorders by improving efficacy,

safety, and recovery. Exosomes' anti-inflammatory, immunomodulatory, and targeted delivery properties make them ideal adjuncts. In a double-blind split-face study, human adipose stem cell-derived exosomes combined with fractional CO_2 laser significantly improved acne scars (32.5% vs. 19.9%, $p < 0.01$) while reducing erythema and downtime [68]. Similarly, hUCMSC exosomes paired with nonablative fractional laser or microneedling yielded superior outcomes and higher patient satisfaction in melasma treatment, likely due to enhanced skin penetration through microchannels [69]. Plant-derived extracellular vesicles (EVs), such as those from Ecklonia cava, combined with antioxidants like phlorotannin, inhibited UV-induced melanogenesis by reducing oxidative stress and suppressing the TXNIP/NLRP3/IL-18 pathway [70]. These integrated therapies not only improve pigmentation but also promote skin repair and minimize systemic exposure, offering a safe and patient-friendly approach to managing hyperpigmentation.

6. Challenges and Limitations in Exosome-Based Therapies

6.1. Technical Challenges

While exosome-based therapy emerges with potential due to its diagnostic potential, the presence of technical, biological, and regulatory challenges highlights facets encouraging further development. Primarily, technical challenges surrounding therapy involve structure, efficiency, and consistency. Protocols involving the isolation of exosomes remain without standardization, as the more conventional methods involve a tedious process of multi-step ultra-centrifugation that serves the risk of contamination [71]. This would limit abilities in the diagnostic potential of pigmentation disorders through the difficulties of conducting protocol and the nuances created from variations in experimental technique. Another factor to consider is scalability as it is essential to incorporating exosome-based therapy as a clinical application. This challenge could potentially be met by the numerous sources which exosomes may arise from; however, homogeneity is found in select quantities—limiting clinical application [72]. While certain production methods are in progress to target this limitation, another challenge involves ensuring cargo stability and delivery.

There are a variety of methods of loading cargo, however, limitations arise as there are only two that provide stability: exogenous and fusion [72]. On the other hand, biological limitations of exosome-based therapy involve specificity and potential adverse effects. The clinical application of exosomes requires a higher specificity in targeting tissue, as failure to do so consists of a waste of resources as well as implications of risks. Addressing this limitation is met by the obstacle of EVs with a half-life of approximately 70-80 minutes decreasing the probability of success [73]. Without the assurance of clearance, the risk of adverse effects increases. Exosomes can accumulate and implicate immune responses in alternate sites including the liver, spleen, and bone marrow, specifically with some forms of delivery like injection [73]. Thus, developing a sustainable method to increase the half-life of exosomes will not only assist in its development as a clinical tool but also ensure the safety of use.

6.2. Regulatory Challenges

To consider exosomes as a tool for clinical application, regulation is essential, however, limitations surrounding standardized guidelines and approval indicate further development is needed. The Pharmaceutical Inspection Convention and Current Good Manufacturing Practices and Co-Operation Scheme Good Manufacturing Practices both provide regulation on quality, but the focus set by each country is an avenue for complications since countries such as the USA prefer the former organization as the entire production process is strictly observed [74]. This division in regulation between countries thus potentiates the problem of utilizing exosomes as a clinical tool. It is important to note that, while countries differ in their regulatory specifications, there are still obstacles to clinical approval and commercialization. Although many questions remain unclear, some include frequency of treatment for homeostasis, the endurance of benefits, and side effects [75]. Clinical approval is essential to providing information on the composition of exosomes, however, demonstrating pharmacokinetics remains a challenge for agencies [74]. Without this detail, utilizing exosomes as a clinical tool remains uncertain. Another challenge to approval involves the changes that arise from variations within preparations, which could be targeted by conducting more trials to demarcate their mechanism of action since this can vary based on size and active drug substance contained within the exosome [74]. Thus, the regulatory challenges surrounding exosomes require further development with a focus on clarifications of their constituents. As the diagnostic and therapeutic potential for exosomes increases,

another avenue that requires the development of regulation involves genetic engineering to improve precision as a potential treatment option for more than pigmentation disorders including Parkinson's Disease [76]. Once again, regulation poses a challenge for this opportunity which is being targeted by ongoing research studies in the field of cellular engineering. Regulation of exosome-based therapies thus remains unclear with complexities from agencies, countries, and protocols.

6.3. Ethical Challenges

Ethical concerns also play an important role in the challenges facing exosome therapy, specifically concerning sourcing. The avenues of cultivating exosomes remain broad, ranging from animal to botanical cells, they can be derived from stem cells that derive from mesenchyme, umbilical cord, and even induced pluripotency [77]. The use of stem cells remains a controversial topic, which provides another challenge for the application of exosome-based therapy. One study highlights utilizing umbilical cord mesenchymal stem cells as a source in the repair of pancreatic tissue and showcased inhibition of cellular death and inflammation within the pancreas [78]. However, the wide range of sources still includes bovine colostrum and plant sources such as Phellinus, which might serve as sustainable and more ethical sources [77]. The use of various sources in the implementation of exosomes as a clinical tool not only targets the issue of ethical concern but also displays its versatility. For instance, exosomes arising from bovine milk display integrity within extreme environments of the gastrointestinal tract and even in transit in a study highlighting a nano-oral delivery system of paclitaxel [72]. Thus, targeting concerns on sourcing of exosomes regarding stem cells can be addressed by exploring a variety of options with unique and potentially advantageous characteristics.

7. Future Directions and Research Opportunities

Advancements in exosome engineering are underway with the goal of continuous improvements in the techniques for optimizing cargo loading, targeting, and delivery [79]. The past use of synthetic drug administration which included the use of micelles and liposomes were limited due to stability, long-term safety, and possible activation of an acute hypersensitivity reaction. Exosome engineering is more attractive due to its inherent biological advantages that minimize some of the limitations in other carriers such as their lower immune response and bilayer vesicles which can withstand extremes and lyophilization. The focus of modern engineering is on regenerative medicine to ensure that the limitations for the novel uses of exosomes can be targeted and improved to specifically treat dermatological disorders, such as in the role of skin hyperpigmentation. However, there is still scarce data, with the need for more dermatology clinical trials to assess safety, efficacy, and long-term outcomes [80].

In current literature there is progress with exosome-based therapy for many systemic conditions but dermatology use is still underway. Examples of novel use of exosomes therapy in clinical trials can be traced back to 2014 for the use of β-cell mass in Type I Diabetes Mellitus (T1DM) and other conditions such as severe novel coronavirus pneumonia [81]. Exosome therapy for treating dermatological conditions has clinical trials for conditions such as Dystrophic Epidermolysis Bullosa and preclinical trials are underway for skin pigmentation therapy in countries such as Brazil [82]. Yet, the exploration of exosome therapy in dermatological conditions is missing regulatory data information and not proper understanding of side effects and risks in clinical use due to lack of knowledge [81].

With an understanding of the biological mechanisms of exosomes to repair, regenerate, and rejuvenate skin tissues, this can hopefully be tailored for individual pigmentation disorder profiles and into precise dermatology frameworks in the future [46] Using exosome therapy based on Fitzgerald Skin Type will be needed to ensure that proper melanin resolution is achieved as desired by individual patient desires [83]. Further broader applications of exosomes into treatment such as the exploration for hair pigmentation changes and treating pigmentation changes due to systemic conditions still requires attention [84].

8. Conclusion

Exosomes play multiple roles in the regulation of pigmentation with melanocyte, UVB-irradiated keratinocyte, immune cell, and stem cell derived exosomes influencing melanogenesis in pigmentation disorders. This review highlights the therapeutic potential of exosomes through their ability to affect T-cell immune responses, regulate melanin transport and gene expression, and reduce H2O2-induced keratinocyte damage. Current therapies for pigmentation disorders often lack targeted delivery to melanocytes—a

gap that exosomal therapy could effectively bridge due to its role in cellular communication. Compared to traditional treatments, exosomal therapy demonstrates fewer side effects owing to its direct biological activity and minimal invasiveness, thus presenting promising clinical implications. However, significant challenges remain, including issues related to scalability, efficient delivery, and consistent therapeutic outcomes, as few clinical trials have been conducted. Addressing these challenges could not only optimize exosomal therapy for pigmentation disorders but also pave the way for its application in other inflammatory dermatological conditions.

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