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Review Article

Exosomes: Pioneering the Future of Vitiligo Therapy

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Abstract

From disposal waste with no significant role in biology to a primary channel for long-distance communication between cells. Due to their precise function in microenvironments, exosomes are at the forefront of the future of regenerative therapy. Exosomes have a double-edged effect when it comes to regulating pathogenesis, whether in releasing inhibition or promotion factors, their effects influence the whole direction of the pathway. Exosomes are nanovesicles found in extracellular sites and body fluids. With their role in various pathological and physiological processes, studies have shown promising results, whether in a therapeutic or diagnostic approach. Vitiligo is an autoimmune disease with progressive loss of melanocytes and the formation of white patches on the skin epidermis. Due to its challenging nature, continuous studies are conducted to further understand the pathogenesis and newest approach to enhance pigmentation with no recurrence loss of melanin. A total of 27 studies have been collected from PubMed, ScienceDirect, and Google Scholar databases between the years 1974 and 2024. This review aims to deepen the understanding of vitiligo pathogenesis with the implication of exosomes from various sources of derivation that can be used in future approaches.

Keywords: exosome; vitiligo; melanogenesis; melanocyte; autoimmune disorder; stem cells

Introduction to Vitiligo and The Emergence of Exosomes:

Skin is the largest organ of the human body, making up 16% of the total body's weight [1]. Derived from ectoderm, the skin is composed of three layers: the outermost layer, called the epidermis, the middle layer, called the dermis, and the innermost layer, called the subcutaneous tissue. As a component of the integumentary system, the skin serves a variety of physiological functions, including controlling body temperature, forming a physical barrier to protect internal organs, and shielding the body from foreign objects. However, skin organs are exposed to various stressors internally and externally, where it challenges its epidermis to keep its integrity and normal function. Internal stressors such as genetics, hormones, stress, and external stressors such as medications, UV light, chemicals, environmental irritants, and infections can lead to skin disorders over time. One of the skin disorders is vitiligo, a depigmenting skin disease characterized by selective loss of melanocytes and the formation of white patches [2]. Since vitiligo can cause devastating psychological implications and is often dismissed as a cosmetic issue, rather than an autoimmune disorder, careful diagnostic and therapeutic approach should be followed.

Skin development is important in maintaining survival against stressors. Researchers have found exosomes to be involved in both physiological and pathological processes. Exosomes or extracellular vesicles (EV) are small natural nanoparticles with a diameter of 30 to 1000 nm that are found in most body fluids [3]. Exosomes originate from endosomes and function in delivering various bioactive products to target cells [4]. The recognition of exosomes follows specific steps: 1) Surface receptor recognition, 2) direct fusion of the exosome and the target cell membrane, 3) endocytosis ingestion by the target cell [4]. With the emergence of studies, the application of exosomes in various medical conditions has led to their gradual use in clinical practices.

Understanding Vitiligo

Epidemiology: Where it All Started and Daily Challenges

The journey of discovering vitiligo started thousands of years ago by the Egyptian and Indian civilizations, where it was described in ancient texts as a depigmenting disorder and often confused with leprosy, a chronic infectious disease [5,6].

Since the earliest global epidemiology survey was conducted in Denmark in 1977, the prevalence of vitiligo in the population was 0.38% [7]. The latest statistics show a global prevalence increase of 0.5%-1%, despite limited studies. The overall incidence was found to be 1.59 in every 10,000 patients per year, and the overall prevalence was 0.40% [8]. It was prevalent in West Asia and least prevalent in East Asia on a global scale. Both men and women are equally affected, and Jordan is considered the highest country in specific prevalence, while Sweden is considered the lowest [8][9]. Children's populations are less prevalent in comparison to the adult population [9]. Additional ethnic background surveys are required to predict the prevalence of vitiligo and to conduct genetic research on these populations.

Vitiligo patients face daily challenges, whether it's psychological or social, in their everyday lives. Due to its unpredictable chronic nature, well-being and quality of life are affected, whether because of the sun exposure or social acceptance [10]. Studies have found psychiatric disorders associated with vitiligo patients such as depression, anxiety, and maniac disorders [11]. In addition, hospitalization for mental disorders has increased among the adult population [12]. While in the children population, attention deficit and hyperactivity disorder are more prominent [13].

Results

Classification of Vitiligo

Clinical classification of vitiligo subtypes is based on the distribution and the shapes of the patches on the body. The following Table 1 demonstrates the subtypes of vitiligo.

Type of Vitiligo [2]	Subtype
Non-Segmental Vitiligo (NSV)	Focal Mucosal Universal Generalized Acrofacial Rare variants of vitiligo (follicular vitiligo, hypochromic vitiligo, (leukoderma punctata)
Segmental Vitiligo (SV)	Unisegmental Bi-segmental Multi-segmental Focal
Mixed Vitiligo (NSV + SV)	Coinciding occurrence of NSV and SV, depending on the severity of SV
Unclassified	Focal and mucosal onset, multifocal asymmetrical nonsegmental

Table 1: Classification of Vitiligo.

Etiopathogenesis of Vitiligo: A Glimpse of Possibilities

With the difficulty of biopsy being taken from patients to the complex theories of vitiligo pathogenesis, whether it was an autoimmune disease or a degenerative process of melanocytes [14]. Vitiligo is a multifactorial disorder, characterized by the loss of melanocyte function from the skin [2]. There have been theories upon discovering the precise pathophysiology and etiology of vitiligo, this includes genetics, autoimmunity disorder, oxidative stress, and inflammatory mediators' dysregulation [15]. Different mechanisms of vitiligo subtypes can result in the same outcome. Thus, convergence theory was proposed to combine all theories into one to help us understand the pathogenesis of vitiligo skin condition [16].

Genetics of Vitiligo

Genetic factors have been a contributing factor to the onset of the disease, accounting for 80% of the estimated risk, with environmental factors accounting for 20%. The frequency in first degree relatives, contributed to the occurrence of vitiligo by 7%-9% termed as "multiplex", 91% of vitiligo cases are from distant relatives, termed as "simplex", and in monozygotic twins' cases occurrence is at 23%. [17, 18]. In the family clustering phenomenon, polygenic inheritance can lead to partial vitiligo heritability [19]. Additional genetic risk factors for developing vitiligo is attributed to the presence of autoimmune diseases in family members or vitiligo patients such as, autoimmune thyroiditis, type 1 diabetes mellitus, Addison disease, alopecia areata, inflammatory bowel disease, pernicious anemia, rheumatoid arthritis, systemic lupus erythematous, and autoimmune gastritis [19].

To further understand the complex polygenic inheritance of vitiligo, DNA sequencing serves as a reliable source, such as genome-wide association studies (GWAS), which conducted large-scale analysis of European and Asian populations and discovered 50 different loci that contributed to the risk of vitiligo [19]. From the genome-wide linkage, five vitiligo loci have been alleged to be causal genes: XBP1, NLRP1, HLA, PDGFRA, and FOXD3. Whereas two other vitiligo loci are still unclear in their pathogenesis: Th17 and IL17. Table 2 below lists other genomes that correlate with the risk of vitiligo.

Genes Involved in Vitiligo [16][19]	Implicated Pathogenesis
HLA-DRB1, HLA-DQA1, CPVL	Antigen presentation risk gene.
GZMB, FASLG, RERE, NEK6	Implicate cell lysis and apoptosis.
TICAM1, IFIH1, CD80, NLRP1	Drive innate immunity.
TYR, PMEL, MC1R, OCA2-HERC2, IRF4	Affect melanocyte function.
CTLA4, FOXP3, PTPN22, IL2RA, BACH2	Drive adaptive immunity.
CDH1, DDR1	Polymorphism genes that promote cell adhesion.
ACE, CAT, MYG1, MIT, KIT, ESR1, AIRE, COMT, NALP1, FAS, EDN1, COX2, VIT1, IKZF4, DDR1.	Other genes involved in the pathogenesis of vitiligo.
FARP2-STK25, FBXO45-NRROS, SCAF1-IRF3-BCL2L12, ZC3H7B-TEF	Susceptible gene, unknown implication.

Table 2: Other Risk Genes Involved in Vitiligo.

Overview of Vitiligo Pathogenesis

Oxidative Stress and ROS Overproduction in Vitiligo

One of the initial events in melanocyte destruction is oxidative stress, which causes an imbalance in redox homeostasis and leads to the excessive production of ROS, a byproduct of melanin production. In contrast to healthy skin, vitiligo melanocytes proliferate slowly. A dysregulated redox balance leads to elevated hydrogen peroxide levels, increased ATP release from keratinocytes, and increased reactive oxygen species (ROS). Other prooxidants increase are xanthine oxidase, and malondialdehyde, and a decrease in antioxidants such as superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase, as noted in both blood and skin [20]. In 1989, a study demonstrated melanocytes are not the main cause of vitiligo; after grafting onto the nude mice, the skin repigmented rapidly [21]. Both endogenous and exogenous stressors can result in the apoptosis of melanocytes and excessive production of ROS. Exogenous stressors are environmental stimuli such as: UV light, monobenzone, medications, vaccinations, infections, natural disasters, etc which are also known to produce oxidative by-products [22]. ROS accumulation and cumulative damage, disrupts the function of DNA, proteins and lipids. The power horse for the energy supply, i.e., the mitochondria, is considered the key inducer of the ROS production after mitochondria damage [23].

The Bridge Between Oxidative Stress and Adaptive Immunity: Innate Immunity

After endogenous or exogenous stress exposure, innate immunity activation begins early with the genetic change in NALP1, a regulator of innate immunity. After melanocyte stress and an increase in innate immunity, as commonly seen in vitiligo cases, an increase in natural killer cells infiltrates, as they are early responders to stress [24]. Furthermore, it's normal to find type-1 innate lymphoid cells (ILC1) producing interferon-gamma (IFNγ) in blood and in vitiligo non-lesion skin [2].

Exosomes excretion is a way of communicating between innate system and stressed melanocytes. Nearby normal melanocytes secrete exosomes containing micro ribonucleic acid (miRNA), heat-shock proteins, melanocyte-specific antigens, and damage-associated molecular patterns (DAMPs). These exosomes deliver antigen specific to vitiligo cells and stimulate the maturation of dendritic cells into efficient antigen presenting cells [25]. One of the key roles of DAMPS, are heat-shock protein 70 (HSP70i) cells that act as cytoprotector preventing apoptosis [26]. A recent study has shown a mutation in Hsp70i that raises potential for discovering new treatments for vitiligo patients [27].

Adaptive Immunity in Vitiligo: From Progression to Reactivation

In the pathogenesis of vitiligo, both humoral and cell-mediated immune dysregulations are involved, where destructive melanocyte antibodies and cytoplasmic melanocyte antigens are found [2]. However, the autoantibodies are not the main driver for the vitiligo pathogenesis and there is no activity correlation.

CD8+ T Cells and The Destruction of Melanocytes. One of the main melanocyte damage mediators for vitiligo patients is the melanocyte-specific CD8+ T, due to the release of antigen proteins to dendritic cells and identified by T cells. CD8+ T cells are present at higher levels in the serum of vitiligo patients when compared to healthy controls, as through this parameter, the severity of the disease can be measured [28]. Other cytokines involved are TNF-α as well as IFN-γ. After IFN-γ bind to their receptors, janus kinase (JAK) signal transduction and transcriptional activator stimulates and promotes chemokine ligands CXCL9 and CXCL10. CXCL10 represent as a biomarker in the serum of vitiligo patients to monitor their severity [29]. Regulatory T cells (Tregs) are relatively less in vitiligo skin, indicating a disadvantage in the ratio of Tregs/CD8+ T cells [30].

Resident memory T cells (TRM) and Reactivation. After the end of therapy, the possibility of depigmentation reappears at the same location due to the autoimmune memory, specifically Tissue-resident memory T (TRM) cells in chronic inflammatory skin conditions. Due to their long presence in the epithelial barrier tissues, this characteristic enables a swift immune response to the site [25].

Vitiligo Therapeutic Management

Vitiligo treatment is considered one of the most challenging to dermatologists due to its complex nature. Treatments range from systemic to topical applications based on the severity of the patient's disease,

patients' preference, disease activity, and evaluation. Target results are stabilizing depigmented lesions from the destruction of melanocytes and avoiding relapse after repigmentation [2]. Treatments range from phototherapy to systemic immunosuppressants, surgeries, and regenerative therapies. Clinical markers act as indicators such as the vitiligo signs of activity score (VSAS) is based on the presence of confetti-like depigmentation. Furthermore, the use of Koebner phenomenon in identifying hypochromic 15 body areas, is considered a reliable indicator to score visible clinical signs in segmental vitiligo. To determine efficiency, treatment should undergo 2-3 months to identify if any relapse occurs.

Management differs between phenotypes, for example SV is associated with poor responses to conventional treatments due to leukotrichia, while NSV responds. The earlier the diagnosis, the higher the success of treatment.

Medical Therapy

From topical immunosuppressant drugs (calcineurin inhibitors, corticosteroids, calcipotriol, cyclosporin) to UV lights whether the whole-body irradiation or targeted lesions. Topical corticosteroids are used for the treatment of localized vitiligo and systemic corticosteroids are given to stabilize the progression of the disease. When treating the lesions on the face or areas at high risk of atrophy, topical calcineurin inhibitors (tacrolimus and pimecrolimus) are used. Topical use of Pseudocatalase has been proven to stop the progression due to its mechanism in producing O2 and H2O from H2O2.

Phototherapy, including narrowband ultraviolet B (NBUVB) and psoralen plus ultraviolet A (PUVA) is considered one of the principal techniques in non-invasive treatments, because it stimulates resident melanocyte precursor and immunomodulates in generalized vitiligo [31]. The effectiveness of the treatment is noticed in early stages and used in medical and surgical treatment to accelerate repigmentation [32]. Other medications used in vitiligo treatment are mentioned in Table 3.

Other Medical Treatments	Use in Vitiligo
Medical Treatment [31]	
Janus Kinase Inhibitors	Downstream of proinflammatory pathways.
Cyclosporine	Inhibition of IL-2 production and the activation of the T-cell pathway.
Methotrexate	Antimetabolite drug used topically or systemically to decrease T cells.
Afamelanotide	Analogue of alpha melanocyte stimulating hormone binds to melanocortin-1 receptor (MC1R).
Minocycline	Anti-inflammatory free-radical destruction properties against ROS destruction.
Statins	Block cytokine expression, inhibit leucocyte chemotaxis, and scavenge free radicals.
Vitamin D3 analogues	Calcipotriol and tacalcitol inhibit antigen presentation.
5-Fluorouracil (5-FU)	Stimulating melanocyte pigmentation and increase the number melanosomes.
Levamisole	Anthelminthic agent, immunomodulatory property act on T lymphocytes and macrophages.
Antioxidant agents	Alpha-lipoic acid, ginkgo biloba, polypodium leucotomos, flavonoids, and green tea polyphenols decrease oxidative stress.
Prostaglandin F2 (PGF2α) analogues	Induce skin pigmentation and increase melanogenesis.

Table 3: Other Medical Treatments

Surgical Therapies in Vitiligo.

Surgical therapies are considered the last step when repigmentation has been assessed poorly. This can range from tissue grafts transplant to the whole epidermis or dermis such as epidermal sheet transplantation. Other graft techniques are mini punch graft, suction blistering, split-thickness skin graft, hair follicle graft, and cultured melanocytes graft. Cellular graft is the transplant of cell such as non-cultured epidermal cell and microneedling. Other non-grafting surgery techniques are tattoo pen for micropigmentation [32].

Regenerative Medicine in Vitiligo.

Various cell-based therapies in regenerative medicine focus on intrinsic regenerative capacity of the pathologic tissue or the replacement by a pluripotent stem precursor cells graft. Through melanocyte transplantation, melanocyte– keratinocyte cell transplantation (MKCT). It has been reported that 90% of cases have been repigmented [33]. In contrast, cell free approaches have been seen in treating vitiligo lesions such as Platelet-rich plasma (PRP), stem cell secretome, and adipose tissue secretome [32].

Exosomes: A New Breakthrough in Medicine?

In 1983, Pan and Johnstone were the first to discover exosomes in mammalian reticulocytes maturation and were thought to be an excess waste product of cellular components with no biologic activity [34]. Exosomes are characterized by their cup-shaped, phospholipid bilayer membrane morphology with a diameter of 30-150 nm and originate from multivesicular bodies (MVBs). Exosomes are formed through a process of early sorting endosomes where dual invagination of plasma membrane contain genetic material, phagocytic proteins, cytosolic proteins, and

cytoplasm protein. When exosomes are finally formed into a disc shape, they are either degraded by phagocytes or released into extracellular space to be fused with the recipient cell [35].

Exosomes are composed of lipids such as: cholesterol, ceramide, glucosylceramides, glycerophospholipids, sphingolipids, and diglycerides, and by bioactive lipids such as leukotrienes and prostaglandins. Exosome composition is based on the origin of the cell type, and they typically carry nucleic acid including mRNAs, miRNA, lipids, cytokines (Figure.1). Transcription factors, and proteins. Two types of proteins are contained inside the exosome: exosome-specific proteins and conserved proteins. Conserved proteins serve as a marker for exosome detection, these are heat shock protein (Hsp)60, Hsp70, Hsp90, ALIX, cluster of differentiation (CD)63, CD9, CD81, CD82, and tumour susceptibility gene 101 (TSG101). However, exosome-antigen specific proteins appear on antigen-presenting cells and can be altered based on the cellular origin, physiological changes, and exposure to stimuli [36]. For example, major histocompatibility complex (MHC) class I and II proteins appear on exosomes, which are secreted by antigen presenting cells (APCs).

Figure 1.

Exosome Diagram.

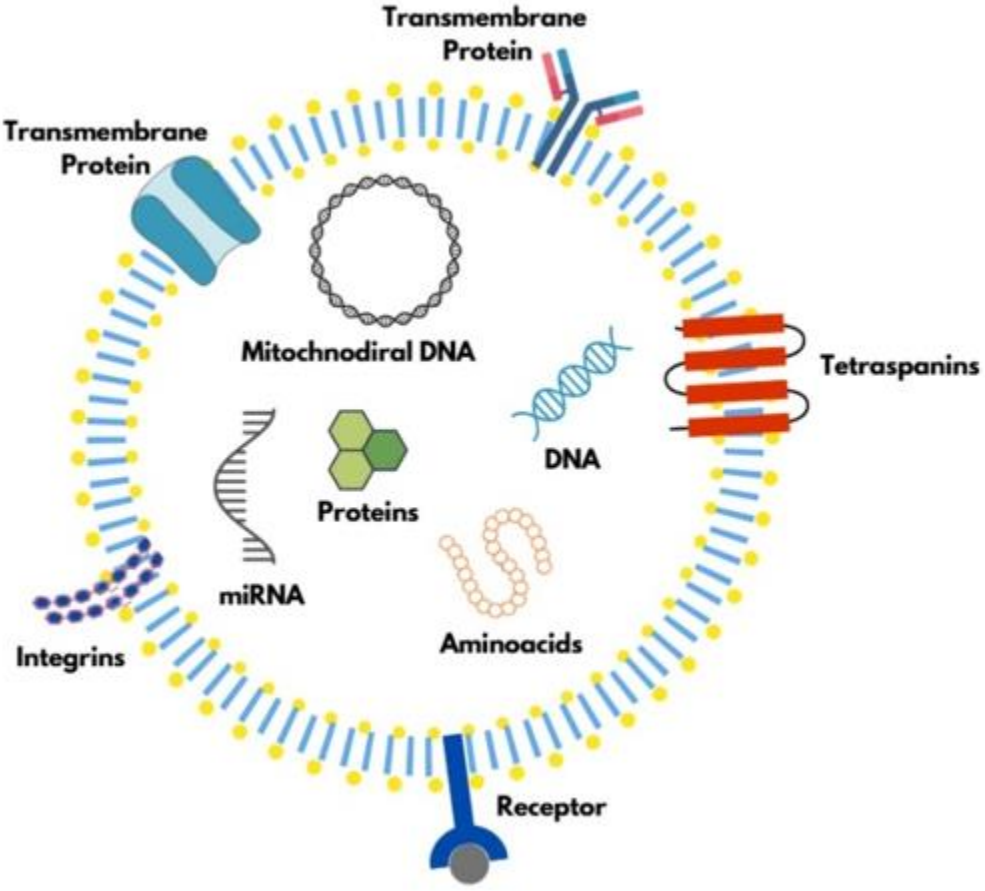

Figure 1: Exosome are composed of phospholipid protein cell membrane with transmembrane proteins, integrins, receptors, and tetraspanins, and they contain genetic material such as miRNA, deoxyribonucleic acid DNA, mitochondrial DNA, amino acids and other proteins.

The participation of exosomes in physiological or pathological processes, gained them function of predicting treatment and diagnostic approach. Some of the physiological involvement is angiogenesis, cutaneous wound healing, inflammatory response, coagulation, immune response, tissue homeostasis, bone fracture healing, transneuronal transport, skin immunity, melanogenesis. Exosomes are also involved in the pathogenesis of several diseases such as cancer, Parkinson disease, Alzheimer disease, multiple sclerosis, autoimmune disorders, atherosclerosis, and skin diseases [36].

Exosomes Uses in Skin Disorders

Exosomes use has been an eye-opening to various medical specialties in its applications, whether used as diagnostic tool such as biomarker, drug delivery, therapeutic managements such as tissue repairing agent, as well as in the developing of vaccinations. In dermatology, exosomes gained attention in various applications whether cosmetically e.g., antiaging care or in skin disorders, i.e., vitiligo, psoriasis, atopic dermatitis, etc. Exosomes are extracted from extracellular spaces such as fluids, stem cells tissues, umbilical cord, blood, saliva, urine, breast milk from both animal and human sources [37]. The following sections will discuss the common use of exosomes in the skin.

Development of Skin through Exosomes.

The development of skin epidermis cells is crucial for the organism's survival. An imbalance between self-renewal and differentiation can lead to skin disorders. Through progenitor stem cells, exosomes (EXOSC7, EXOSC9 and EXOSC10) are abundant in epidermal layer which helps in avoiding premature differentiation of progenitor cells. Homeostasis is also regulated through exosomes, as the hair is a predominant function for warmth in mammals. Androgenetic alopecia is a chronic skin condition

that causes hair loss. A recent study has shown exosomes derived from mesenchymal stem cells promote hair growth into thicker and longer [38].

Wound Healing and Regeneration in Exosomes.

Studies have shown exosomes promote wound healing based on the source of the exosomes through paracrine mechanisms. For example, adipose tissue exosome derivative and amniotic human epithelial cells share common characteristics with MSCs. Exosomes can promote collagen synthesis and angiogenesis. Adipose stem cells derived exosomes (ASC-Exo) are found in fibroblasts that affect proliferation, cell migration of collagen, as well as enhancing fibroblasts properties. Further studies are needed to prolong the wound healing period in cases like diabetic patients or post-operatives for wound repair [4].

Inflammatory Skin Diseases and Exosomes

From psoriasis to atopic dermatitis (AD), studies have found that the use of exosomes derived from stem cells alleviate diseases through immune regulation and promotes the skin barrier, respectively. A study has shown that, topical application of epidermal stem cells derived exosomes (ESC-Exo) relieved pathogenesis of psoriasis through relieving imiquimod IMQ-induced psoriasis in mice [39]. While in atopic dermatitis, a study reported a subcutaneous injection of ADSC-Exo could decrease AD symptoms in mice by decreasing IgE levels, IL-4, IL-23, IL31, immune cell infiltration, and TNF-α expression [40].

Autoimmune Skin Disorders and Exosomes

Both systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) have their own distinct autoimmune nature despite their similarity in their pathophysiology, clinical features, and complications. Exosomes study has been found in SLE applications, where clinical symptoms are alleviated using bone marrow mesenchymal stem cells (BMSCs)-exos to promote M2 macrophages and decrease T cell infiltration [39]. Whereas in SSc, reduction of fibroblasts reduces dermal thickness through various uses of derived exosomes from mesenchymal stem cells [39,41]. Other use of exosomes includes immune response regulation, presenting antigen specific cells, induce innate immunity, regulation of redox balance from oxidative stress, present immunoregulatory molecules [42].

Exosome in Skin Pigmentation: Vitiligo

Pigmentation is the core process of the skin disorder vitiligo and is regulated by α-melanocyte-stimulating hormone/melanocortin 1 receptor, Wnt signaling pathway, and eosinophil-derived neurotoxin [4]. For skin pigmentation, communication between cells is vital for melanin production. For example, UVB light induces melanin production in melanoma cells. Abnormal skin pigmentation can either cause hyperpigmentation or hypopigmentation through keratinocyte-derived exosome carry specific miRNA (miRNA-3196 and miRNA-203) to regulate pigmentation [43]. For example, circulating exosomal miR-493-3p are increased in segmental vitiligo (SV) [44].

Exosome Preparation: From Extraction to Packaging for Use

To use exosomes, controlled steps from extracting to purifying, as well as quality control to ensure its safety in clinical practice [45]. There are various techniques used to extract exosomes from fluids, such as differential ultracentrifugation (DC), which is a common method to separate samples, yet when exosomes were isolated, the purity and yield is relatively medium to low respectively [46]. Other techniques used are Density gradient centrifugation (DGC), which is used to isolate components in various sizes and molecular weight. The purity is highly yet the yield is low in terms of intensive preparation before operation [47]. In addition to various sizes isolation, ultrafiltration has a similar concept with no special equipment's needed and high purity results yet clogging onto filters have been seen [48]. Size-Exclusion Chromatography (SEC) method is used on various particles sizes and molecular weight, its economical with high purity but special columns are used for lipoproteins [49]. Finally, Immunoaffinity method is used based on the interaction between specific membrane proteins of exosomes and antibodies, with high purity results yet yield is medium due the high expenses of the method [50].

The Role of Exosome in the Pathogenesis of Vitiligo

Exosomes have various roles in the pathogenesis of vitiligo, from regulating immune responses to influencing melanocytes apoptosis or synthesis. With the difference expression of exosomal-miRNA between vitiligo patients and healthy individuals, studies have found miRNA's influence different steps in the pathogenic pathway, from immune responses, oxidative stress, to abnormal melanin production. For example, in CD8+ T cells in vitiligo are overexpressed in miR-370-3p, and miR-143-5p, and down regulated by miR-885-5p, miR-16-5p, miR-92a-3p, and miR-92b-3p [51]. Following details will demonstrate the roles of exosome-miRNA based on the source of origination.

Mesenchymal Stem Cells Derived Exosomes: Vitiligo's Cutting-edge Therapy

Since its discovery 150 years ago, mesenchymal stem cells (MSCs) were identified in the bone marrow stromal stem cells (BMSCs) by Friedenstein in the 1970s. Ever since, MSCs have gained attention in the research world with their ability to self-renewal and differentiate from stromal cells in a variety of populations, including adults, fetal, and perinatal tissues [52]. This milestone laid the foundation of regenerative medicine and its future potential therapeutics, from bone marrow support to tissue repair. Mesenchymal stem cell-derived exosomes were identified 30 years ago, and they have been new in research trials in the last 14 years. Studies have proved its efficacy from preclinical models to clinical trials, such as in cerebrovascular disease treatment in cardiac repair against myocardial infarction to skin regeneration in alopecia. Its potent regulatory effects in various types of cells, whether its anti-inflammatory effects or survival effects in promoting and regenerative potentials [52]. Studies have shown the effect of mesenchymal stem cells-derived exosomes on vitiligo condition with its promotion of melanogenesis to its downregulation of PTEN pathway as future therapy with promising results for patients [52]. Mesenchymal cells derived exosome can improve keratinocyte antioxidant capacity against H2O2 damage and reduce oxidative stress [53].

Human Umbilical Cord Derived Exosomes (hUMSC-Exo)

Therapeutic efficacy has been proven of deriving mesenchymal stem cells from the human umbilical cord, as it's been associated with the paracrine secretion of extracellular vesicles [54]. In a study conducted at Sun Yat-sen University, it was claimed that melanocyte treated with hUMSC-Exo at a lower dose of (1 μg/mL) than a higher dose before H2O2-induction, enhanced proliferation of melanocytes and the reduction of p21, p53 IL-1β, IL-8, and IL-6 expressions, as well as MITF and TRP1 expression, that were caused by H2O2 damage [55].

A preclinical study used a 3D hUMSC-Exo results showed efficacy against skin depigmentation with the expansion of Treg cells and less CD8+T cells infiltration that was caused by H2O2-induced melanocyte apoptosis. Targeting Sirt1 and Bak1 in vitiligo through the aggregation of miR-132-3p and miR-125b-5p helped in the suppression of oxidative stress [56]. It has been shown that mesenchymal stem cells in 3D biomaterial scaffolds have gained recognition as it is a cell free platform that serves to augment therapeutic potentials [57]. In contrast, a study has shown hUMSC-Exo of miR181a-5p and miR-199a inhibit melanogenesis and promote melanosome degradation in excessive skin pigmentation [58]. Future clinical studies are needed for vitiligo melanocytes from donors to understand the therapeutic management of the above studies.

Adipose Stem Cell Derived Exosome (ACS-Exo)

One of the main sources where mesenchymal stem cells can be obtained is adipose tissue. It has gained interest in various fields, from regenerative plastic surgeries to dermatological skin conditions. With its unique quality of sharing the same origin as the mesenchymal stem cell from mesoderm, it can replenish damaged skin tissues. In the purpose of regeneration, stromal vascular fraction (SVH) is obtained after the breakdown of adipose tissue, where adipose-derived stem cells carry multilineage [59]. New studies have favoured adipocytes among the other MSC derivatives with their complex molecules that can be beneficial in regeneration. For example, in fat grafting, adipocyte derivatives have biophysical integrity that support stem cells in accordance with the volume used in a specific area of the body [59].

Adipose stem cells have been proven to produce many exosomes compared to other cells, with their cutaneous regeneration and immune tolerance [60]. In terms of exosome derivatives from adipose stem cells, studies have shown ASC-Exo results have the same therapeutic effect compared to ASC.

ASC-Exo demonstrates an anti-inflammatory effect in suppression of the catabolic environment, such as NF-κB-dependent inflammation [60]. In addition to anti-inflammatory effects, ACS-Exo contains Arg-1 that inhibits T cell proliferation while promoting macrophage polarization. With its original function, ACS-Exo transfers mitochondrial components by enhancing its integrity and oxidative phosphorylation [60]. ACS-Exo proves to have an advantage ahead of ACS due to its precise and simple structure that can facilitate its transportation. The size of the adipose tissue depends on the patient characteristics that can be chosen for selective treatment and desired effects. Studies have also shown that ACS-Exo modulates tumor progression and promotes wound repair [61]. However, there aren't studies that focus on ACS-Exo effects on vitiligo condition, although the current information we have does prove its efficacy.

Keratinocyte Stem Cells Derived Exosomes: Next Generation Therapy

Keratinocytes, the primary cells of the skin's outermost layer, make up approximately 90% of the epidermis. They contain direct progeny cells as they are located in the basal layer and can resist light due to their strong DNA single-strand break and thymine dimer repair ability [62]. With their critical role in the body, keratinocyte stem cells can provide support in different fields, from regenerative medicine to wound healing up to diagnostic uses for skin conditions like vitiligo. The use of keratinocytes has captured researchers' attention ever since the mid-20th century due to their functionality and abundance in the human body. A recent study showed the use of dermal MSCs (DMSCs) in 23 vitiligo patients by the process of transplantation of autologous melanocytes. The results showed promising results for vitiligo patients by inhibiting CD8+ T lymphocyte activity that could improve therapeutic efficacy [63]. No studies have been found regarding Keratinocyte Stem Cells Derived Exosomes (KSC-Exo) when treating vitiligo. However, there are studies that spark interest in the use of KSC-Exo. In the following sections, various studies are presented that can help in developing KSC-Exo applications in vitiligo which will be discussed under therapeutics and diagnostics headlines.

Therapeutic Approach of Keratinocytes Stem Cell Derived Exosome (KSC-Exo) in Vitiligo

Keratinocytes Stem Cell Derived Exosome has a significant impact on the proliferation of melanogenesis by influencing melanocytes of the skin tissue with its abundance and speed of regeneration. A study was conducted by irradiating keratinocytes with UVB light to derive exosomes and discover the potential regulators of melanogenesis by the upregulation of TRP1, TRP2, TYR expression, and MITF as well as inhibitory effects. The microRNAs (miRNAs) that upregulated melanogenesis are hsa-miR-365b-5p, hsa-miR-29c-3p, and hsa-miR-644a, while the ones that downregulated melanogenesis are hsa-miR-4281, hsa-miR-18a-5p, and hsa-miR-197-5p [64]. A study has shown that exosomal miR-675 inhibits melanin synthesis through the phosphorylation of CREB, AKT, and ERK as well as suppressing the expression of TYR, TYRP1, and TYRP2 [65]. Figure 2 reviews two examples of melanogenesis regulation.

One of the regulation factors that are elevated in vitiligo disorder is PTEN expression as well as, decrease in AKT phosphorylation in vitiligo skin compared to normal skin. However, there is no difference between vitiligo and normal skin in AKT expression. An encouraging study showed cocultured melanocytes target regulation of cell proliferation and apoptosis through PI3K/AKT/PTEN pathway. It was also found in wound repairing by promoting axonal growth in targeting PTEN/mTOR pathway in vitiligo melanocytes [66].

Figure 2.

Keratinocyte Derived Exosome and Vitiligo Pathogenesis in Melanin Synthesis.

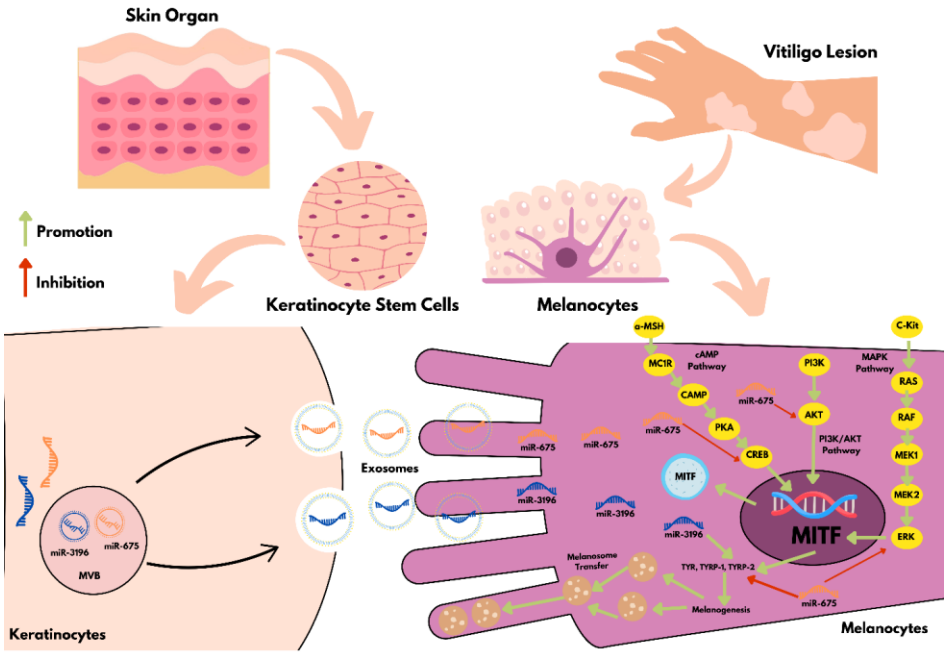

Figure 2: Keratinocyte derived exosomes contribute to the regulation of melanogenesis.

Discussion

Exosomal miR-3196 promotes melanin production through the upregulation of TYR expression, while exosomal miR-675 inhibits melanin synthesis through phosphorylation of CREB, AKT, and ERK pathways and suppression of the TRY, TYRP1, and TYRP2 expression.

Diagnostic Approach of Keratinocytes Stem Cell Derived Exosome (KSC-Exo) in Vitiligo

The use of diagnostics can be as a mediator to treat autoimmune skin disorders, whether in its ability to reflect upon the pathological and physiological form of keratinocyte stem cells or KSC-Exo. One of the studies used circulating exosomes as a potential biomarker to identify the pathogenesis of segmental vitiligo. In terms of melanocyte survival and its function, the circulating exosomal miR-493-3p regulates epidermal dopamine concentration in SV. When miR-493-3p is over expressed in keratinocytes along with an increase dopamine concentration in vivo, it led to increased reactive oxygen species (ROS). Therefore, melanocyte apoptosis increases and a decrease in melanin synthesis by targeting HNRNPU gene, which binds to the main degradative enzymes of dopamine [43,44].

A similar study was conducted, where two miRNAs were found to contribute to melanocyte apoptosis, and four miRNAs enhanced proliferation through the MITF axis [67]. Finally, another keratinocyte derived exosome (miR-200c) can be a future target for vitiligo treatment management and pathogenesis. KSC- miR-200c exosome suppresses melanogenesis-related genes such as SOX1 that activate β-catenin and downregulate melanogenesis [42]. In contrast, a study has shown the inhibition of the MITF axis through miR-330-5p extracted from keratinocytes and inhibition of melanin production, as well as the presence of protein biomarkers such as CD63, Alix, and TSG101 [68,43]. It was also shown that miR-3196 exosomes regulated melanin synthesis through regulating TYR expression [68]. Exosome miR-211 from keratinocytes promotes melanin production by altering the p53 and MMP9 axis, as well as acting as an oxidative stress relief after UVB induction [69]. Finally, miRNA-141-3p and miRNA-200a-3p stimulate amelanocyte-stimulating hormone to regulate melanogenesis [70].

Other Sources for Exosome Derivation in Vitiligo Treatment and Diagnosis

Various sources are still under study, from plant-based exosome derivation to drug-induced exosomes, such as chemotherapy drugs. One of the current sources that raises interest in stem cell exosome derivation is from plasma cells. Plasma exosomal microRNAs (miRNAs) are emerging as a biomarker that can help in tracking the pathogenesis stage of vitiligo. The study investigated miRNA exosomes from the plasma of a patient with non-segmental vitiligo (NSV). The miR-1469 exosome is delivered to natural killer cells (NKC) to enhance proliferation in the IFN-γ pathway and downregulate CD122. The targeted therapy is to upregulate CD122 in NSV cases [71]. Further clinical trials are needed to target CD122 to understand further therapeutics management in NSV patients. Recently, a study has found that circulating miR-21-5p, melanogenesis inhibition from vitiligo patients that target SATB1 [72]. Another study has found that vitiligo accelerates catabolism and hsa-miR-487 b-3p exosome in the serum of vitiligo patients serve as a biomarker for the progression of vitiligo [73]. A further insight into the proteomic profile for vitiligo patients by detecting ALDH1A1 and EEF1G exosomes as a potential biomarker for the vitiligo pathogenesis and process [74]. In contrast, milk derived exosome regulates melanogenesis by inhibiting melanogenesis through the Akt-GSK3b pathway [75].

Conclusions

Knowledge of disease pathophysiology is a topic of interest for researchers to unlock key information in improving patient's quality of life, whether in diagnostics or therapeutics. One of the main challenging skin disorders is vitiligo, which was discovered thousands of years ago. With its complex autoimmune nature, vitiligo is characterized as a selective loss of melanocytes and the formation of white patches on the surface of the skin. To this day, vitiligo patients face daily challenges psychologically and mentally when not kept aware or controlled. Recent

studies have shown the possible use of exosomes, which are nanosized vehicles found in extracellular spaces and body fluids. They are paracrine mediators found in various tissues and help in communicating between cells in microenvironmental sites. Exosomes in clinical practice have been used gradually in the past 10 years. Further studies are needed to ensure safety and bring out the potential uses of exosomes. Limited studies are available on the usage of exosomes in skin disorder diseases, whether in their pathogenesis level or applied therapeutics results. Innovation in regenerative medicine is on the rise when using pluripotent immature stem cells such as mesenchymal cells, adipose tissues, umbilical cord, and blood due to their pure properties and successful results in treatment. Exosome therapy can be a breakthrough in regenerative medicine as they contribute to regulating and promoting different pathways in immune modulations. However, further studies are needed, from the selection of donors for stem cells to the frequency of treatment to obtain the desired results and the best delivery. The production of large-scale exosome therapy should be carefully monitored as current methods produce low yields in high-purity exosomes as well as quality control. Furthermore, stability, standardized production, and safe and effective preparation are needed for treating vitiligo patients.

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