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Advances in microRNA from adipose-derived mesenchymal stem cell-derived exosome: focusing on wound healing

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Skin wounds are a common condition causing economic burden and they represent an urgent clinical need, especially chronic wounds. Numerous studies have been conducted on the applications of stem cell therapy in wound healing, with adipose-derived mesenchymal stem cells (ADMSCs) playing a major role since they can be isolated easily, yielding a high number of cells, the less invasive harvesting required, the longer life span and no ethical issues. However, the lack of standardized doses and protocols, the heterogeneity of clinical trials, as well as the incompatibility of the immune system limit its application. Recent studies have demonstrated that specific stem cell functions depend on paracrine factors, including extracellular vesicles, in which microRNAs in exosomes (Exo-miRNAs) are essential in controlling their functions. This paper describes the application and mechanism whereby ADMSC-Exo-miRNA regulates wound healing. ADMSC-Exo-miRNA is involved in various stages in wounds, including modulating the immune response and inflammation, accelerating skin cell proliferation and epithelialization, promoting vascular repair, and regulating collagen remodeling thereby reducing scar formation. In summary, this acellular therapy based on ADMSC-Exo-miRNA has considerable clinical potential, and provides reference values for developing new treatment strategies for wound healing.

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1. Introduction

Skin injuries are one of the most common conditions that impose a financial burden. The National Health Service, for example, treats about 2.2 million wounds each year at a cost of £4.5–5.1 billion a year, almost as much as obesity.[2,3] Wound healing is a complex dynamic process involving multiple cytokines, accompanied by diverse biological effects. It is currently believed that it primarily undergoes four stages: hemostasis, inflammation, proliferation, and remodeling.[4–6] However, in the presence of factors such as age, metabolic disorders (*e.g.*, diabetes), mechanical stress, and vascular injury, the healing process may extend to more than 3 months, at which point the wound is considered a chronic wound.[7–9] The United States spends about $50 billion a year treating chronic wounds.[3,10] At present, the mainstream conventional clinical treatment methods, such as surgical debridement and negative pressure dressings, do not achieve optimal results in treating chronic wounds.[13,14] Hence, it is imperative to find cost-effective wound healing methods.

As mature stem cells have the ability to differentiate into multiple types of cells and are capable of self-renewal, stem cell therapy has a wide range of possibilities in the fields of tissue engineering and regenerative medicine,[15] of which mesenchymal stem cells (MSCs) are one of the most studied adult stem cells,[16] especially adipose-derived MSCs (ADMSCs) as they have many advantages (Fig. 1), including: (1) stromal vascular fraction (SVF) and mature adipocytes provide a rich source of ADMSCs, which could be readily obtained by liposuction from autologous subcutaneous adipose tissue with high cellular activity; (2) less invasive harvesting with a cellular yield of more than 1000-fold higher, and without decrease due to age increase compared with MSCs derived from bone marrow and umbilical cord. Thus, the challenges of extracting MSCs from elderly patients for therapeutic purposes can be overcome; (3) reducing some effects of continuous laboratory manipulation induced on genetic or epigenetic changes in regenerative function based on a longer life span, higher proliferative capacity, shorter doubling time, later *in vitro* senescence, and prolonged maintenance of phenotype; (4) no ethical issues compared with embryonic stem cells; (5) pain relieving properties.[17–23]

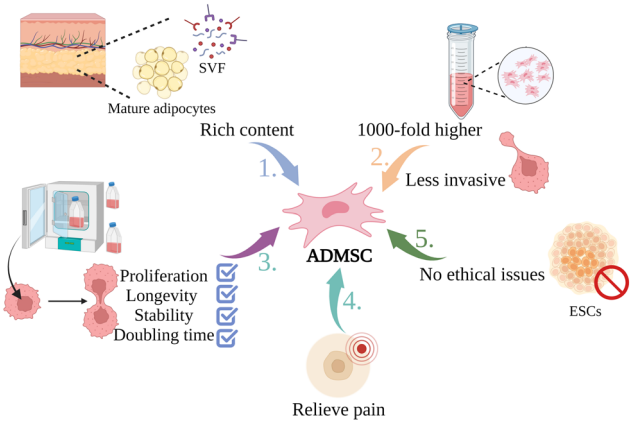

Fig. 1 The advantages of applying adipose stem cells. 1. Rich content; 2. high yield and less invasive harvesting; 3. longer life span, higher proliferative capacity, shorter doubling time, later *in vitro* senescence, and prolonged maintenance of phenotype; 4. no ethical issues; 5. pain relieving properties.

In wound healing management, ADMSC-based stem cell therapy has shown good results with regards to cell recruitment, angiogenesis, extracellular matrix remodeling and nerve regeneration,[24–27] especially autologous stem cell transplantation.[28–30] In spite of this, the lack of standardized doses or protocols, the heterogeneity of clinical trials, immune incompatibility, chromosome variation, and metabolic disorders, particularly metabolic disorders in diabetic patients can reduce the function of autologous cells and increase the risk of complications, thus limiting its application to a large extent.[13,15,24,31] In recent years, many studies have demonstrated that stem cell therapy relies on paracrine factor effects in wound healing therapy including secretome, whose exosome (Exo) is involved in a wide range of biological processes by affecting tissue response to injury, infection and disease,[30,32–37] in particular, microRNA (miRNA; miR) plays a precise regulatory role in intercellular communication.[1,38,39] miRNA is an endogenous, multifunctional, single-stranded small non-coding RNA that influences protein synthesis and participates in crucial steps of cell proliferation, differentiation, apoptosis, autophagy, mitochondrial function, immune response and other life activities.[40–43] Acellular therapy based on ADMSC-Exo-miRNA has the significant advantages of no immune rejection, easy dose control, reduced miRNA degradation, and easy storage.[44] Importantly, many studies have revealed that Exo-miRNA is involved in the wound healing process through the interaction with wound healing related genes and the regulation of signaling pathways.[45–49] Herein, we focus on the research progress of ADMSC-Exo-miRNA in wound healing, point out the challenges and possible solutions, and prospects for future clinical application.

2. Characterization, biological function, detection and preparation of Exo-miRNA

Exos contain abundant miRNAs that are involved in various biological and regulatory processes, and these short RNAs are capable of controlling the function of the entire regulatory protein cascade that contributes to the phenotype of a cell.[50] Researchers have recently made significant advances in understanding the precise mechanisms by which ADMSC-Exo-miRNA contribute to inflammation, fibrosis, tissue regeneration, and angiogenesis.[19,50,51]

2.1. Characterization and biological function of Exo-miRNA

MSC secrete a series of protective bioactive factors, namely the secretomes, which mainly contain growth factors, cytokines and extracellular vesicles (EVs) which includes Exo, microvesicle and apoptotic bodies.[52,53] Exos are membranous EVs with a diameter ranging from 30 to 200 nm, carries significant information and macromolecules from their source, including proteins, lipids,

mRNA, miRNA, *etc.* They are major contributors to the efficacy of stem cells and are considered to be the protagonists of tissue repair and regeneration through their paracrine role in mediating signal transduction between cells.[54–56] Exo, on the other hand, can minimize the risk of vascular obstruction, immune-mediated rejection, and malignant transformation compared to cell therapy.[57–59] miRNA is a group of small non-coding single-stranded RNA with an average of 19–24 nucleotides, which can regulate the expression of post-transcriptional genes and can be secreted into the extracellular fluid through EVs. It has been reported that Exo contain up to 764 kinds of miRNAs, which contribute to intercellular communication, surface modification and other functions. There is speculation that each functional miRNA can interact with up to 200 mRNAs, and this gene regulation is capable of resulting in translational repression, mRNA arrest, and general relaxation, which is more promising than conventional drug therapies that target only a single protein.[55,60] miRNAs regulate a series of biological processes involved in tumor progression, metabolic diseases, stem cell self-renewal, development, differentiation and growth.[61] At present, miRNA content in Exos can be regulated by cell modification or direct introduction.[55,62] Hearteningly, the following miRNAs have been found to be abundantly expressed in the skin: miR-152, miR-143, miR-126, miR-21, miR-27a, miR-214, miR-16, miR-203, miR-125b, miR-34a, miR-205, miR-27b, miR-30b, miR-125a, miR-191 and miR-200 family.[63] Accumulated studies have shown that the expression of many miRNAs is dysregulated in the process of wound healing, such as miR-146a, miR-155, *etc.*[48] Hence, it is urgent to develop miRNA-based wound repair treatment strategies. Upregulation of potentially beneficial miRNAs can be achieved through the use of synthetic double-stranded oligonucleotides known as miRNA mimics, whereas the downregulation of potentially harmful miRNAs can be achieved by complementary oligonucleotide enantiomers.[63,64] Li *et al.*[65] then found that miR-5591-5p inhibited reactive oxygen species (ROS) production and apoptosis in ADMSC mediated by advanced glycation end products/advanced glycation end products receptor/c-jun kinase (AGEs/AGER/JNK) signaling axis *in vitro*, in addition to promoting cell survival and enhancing the ability of ADMSC to repair diabetic wounds. One more study demonstrated that overexpression of miR-302b-3p accelerates skin fibroblast senescence *via* directly targeting and repressing the JNK2 gene while suppressing Sirtuin 1 (Sirt 1) expression to ultimately lead to skin senescence,[66] thus inhibition of miR-302b-3p may be a potential therapeutic strategy for maintaining fibroblast viability in wound healing. In conclusion, a better understanding of the specific molecular mechanisms of miRNAs in the process of wound healing will provide a more solid basis for future research and clinical transformation.

2.2. Detection for miRNA characterization

The detection of miRNAs is necessary for their practical applications. Northern Blotting was the earliest method for systematic analysis of miRNA expression, but it has disadvantages such as complicated operation, long analysis time, low detection sensitivity, radiolabeling requirement and large sample consumption.[67,68] However, the sensitivity of northern blotting can be greatly improved by using lock-in nucleic acid (LNA)-modified probes, 1-ethyl-3-(3-dimethylaminopropyl) carbon diimide hydrochloride (EDC) cross-linking probes, and dig-labeled oligonucleotide probes containing LNA and EDC.[69–71] Microarray analysis has been widely applied in miRNA expression profiling in recent years. LNA-modified capture probes can normalize the Tm of array capture probes, solve the limitation caused by miRNA length, increase probe specificity, and reduce the amount of miRNA purification and amplification. However, there are platform differences in the labeling process of commercial miRNA microarray probes. The introduction of label-free amplification reactions (such as "Stacking-Hybridized Universal Tag (SHUT)") can significantly simplify the process, achieving target binding and fluorescence signal generation in one step.[72] In addition, the miRNA detection method based on real-time PCR (RT-PCR) is highly sensitive, and the sample dosage is as low as the "ng" level. The signal is less noisy and more specific compared with microarray analysis. Quantitative PCR (qRT-PCR) using SYBR Green I and other dyes is considered to have high sensitivity, be simple to perform, require minimal equipment and reagents, and be appropriate for application in the laboratory.[73,74] Certainly, the solution of the limitation about only 21 to 23 base pairs of miRNA is to extend the length of miRNA during the reverse transcription step by either utilizing a miRNA specific stem loop primer for transcription or universal reverse transcription.[75] Microarrays and RT-PCR, however, are extremely expensive. To that end, various methods are currently being developed, such as nanoparticle-derived probes, isothermal amplification, electrochemical methods, and more.[76] Linkase chain reaction, rolling cycle amplification, hybrid chain reaction, loop-mediated amplification and chain substitution amplification have been applied to identify and detect target miRNAs.[77–79] Quite recently, the signal amplification technology based on nanomaterials (such as gold nanoparticles, silver nanoclusters, magnetic particles, quantum dots, graphene oxide, *etc.*) and their unique advantages of small size, low cost, low detection limit, and low cytotoxicity have also been applied in the detection of miRNA *in situ* or intracellularly.[76,80] A number of nanomaterial-based methods have now been developed, such as bio-barcode gels and gold nanoparticle-modified screen-printed carbon electrodes (GNPs-SPGEs). Through bioinformatics, high-throughput sequencing has been used to identify miRNA structures in recent years and a small RNA sequencing library has been constructed and sequenced to enable quantitative identification of all small RNA species in a particular sample, and to enable discovery of novel miRNAs and other small non-coding RNAs. For miRNA detection, paper-based miRNA sensors, photoelectrochemical biosensing platforms, nuclease-assisted signal amplification, and guanine-rich DNA-enhanced fluorescence of DNA-templated silver nanoclusters have all been developed in recent years.[81–83] They have the advantages of high sensitivity, high reproducibility, technical simplicity, and cost optimization, and future emerging technologies should also be developed in a manner that meets these advantages.

Moreover, it is possible to identify the target genes of miRNA by fluorescence quantitative PCR and western blot in order to

detect changes in mRNA and protein levels in cells after transfection or knockdown of miRNA, and then to determine the corresponding relationship between miRNA and target genes. The luciferase reporter gene method is commonly used.[84] Furthermore, a number of computational methods have been applied to predict miRNA targets, including miRanda, mirSVR, PicTar, TargetScan, TargetScanS, RNA22, PITA, RNAhybird, and Diana-Microt, although these methods have a high rate of false-positives and false-negatives. In addition, different miRNA-target prediction algorithms predict targets with different techniques and criteria including base pairing, target accessibility and evolutionary conservation of the target site.[75,85,86]

2.3. Extraction and preparation of Exo

Exo is a nanoscale EV that has remarkable physiological properties. Exos are released into the extracellular environment after the multivesicular body fuses with the plasma membrane and can be taken up by target cells residing in the microenvironment or carried away by biological fluids.[87,88] Since miRNAs are highly vulnerable to nucleases, there are already nanoparticle platforms that allow for intracellular delivery and protection with minimal toxicity, such as liposomes, polyethylamine particles, adenoviruses, gold nanoparticle nuclear conjugations, and so on.[89,90] As ''naturally acclimated'' endogenous nanocarriers, Exos have low immunogenicity and high safety characteristics, enabling them to maintain the biological activity of their inclusions *in vivo*. Hence, cell-to-cell communication may be more effective with Exo-based miRNA delivery than with plasma-based miRNA delivery. Additionally, Exos are cell-derived particles, therefore, they exhibit more safe and stable properties than other delivery compounds such as liposomes.[91] Moreover, Exos carry many proteins on their surface, which enter cells in various ways upon contact with them because of their heterogeneous nature. CD9, CD63, as well as tumor susceptibility gene (TSG) 101 are considered to make ADMSC-Exo characteristic exosomal markers.[19,92] Due to its ability to be stored for at least 90 days at −80 °C, Exo is an advantageous product for clinical application and basic research, as ADMSC infused systemically will die after two days.[93] Due to its ability to penetrate physiological tissue barriers, deliver genetic material over long distances, and prevent miRNA degradation, Exo will become a mainstream alternative to traditional ADMSC therapies in the near future.[19,94] The methods of Exo isolation include: (1) differential centrifugation coupled with ultracentrifugation (UC); (2) precipitation methods; (3) using anti-EpCAM (epithelial cell adhesion molecule) coated magnetic bead immunoaffinity pull-down; (4) density gradient separation; (5) sequential centrifugal ultrafiltration by tangential flow filtration; (6) using ExoQuick-TC; (7) rapid isolation of Exo by an alternating current electrokinetic microarray chip device; (8) using a commercially available size exclusion chromatography column (SEC) for rapid vesicle purification.[93] The ultracentrifugation samples had an average concentration of 16×10^9 particles per 250 μL starting plasma, while the PRE Exos sample generated by the precipitation method has about 2.5 fold higher Exo (41.7×10^9 particles per 250 μL starting plasma)[95] and the ExoQuick is about 150 fold as much.[96] According to the quantitative analysis of the protein, the abundance of the density-gradient separations and the immunoaffinity capture methods can reach about 2–3 times and 3–5 folds of UC, respectively.[97] Meanwhile, the method based on scalable microcarrier-based three-dimensional (3D) cultures further improves the yield of Exos (tangential flow filtratio) 7-fold over UC.[98] On the other hand, the technology of the alternating current electrokinetic microarray chip device significantly reduces the number of processing steps and time required compared with UC.[99] The advantages of SEC mainly focus on low levels of contingents and co-recipients, leading to a relatively domestic final Exo isolation, while the efficiency does not seem to be significantly improved.[100,101] Although UC is still considered the gold standard for Exo separation methods, more rapid and efficient methods are needed due to the drawbacks of co-purification of protein aggregates, morphological changes (such as agglomeration, membrane rupture), and cumbersome processing times.[93,102] SEC ultrafiltration has a better purification efficiency and can produce a high yield of pure and intact Exos when combined with SEC.[103] Nevertheless, some protein loss occurs during the concentration step, resulting in low recovery.[104] It is therefore necessary to develop separation methods that are more effective in the future in order to meet the dosage requirements of mass clinical transformation. In other words, future research should focus on the development of research directions that prevent miRNA loss, simplify operations, and maximize the extraction rate.

The enrichment of therapeutic miRNA in Exo can be achieved by either cell modification or by directly loading. For cell modification, miRNA mimics can be loaded into cells by transfection (viral, hybrid, and non-viral approaches through either physical or chemical methods). In addition, miRNA content in Exo can also be regulated by enrichment or silencing of RNA binding proteins in stem cells and cell priming (hypoxia, inflammatory cytokines). On the other hand, direct loading includes strategies such as sonication, electroporation, and $CaCl_2$-heat shock.[105–107]

2.4. Administration of Exo

In the field of wound healing, Exos can be administered by intravenous injection or direct injection into wound target sites, but there is a limitation of rapid clearance, which is extremely unfavorable for chronic wounds.[108] In recent years, Exo paired with biological materials have become a main focus for research, particularly those using chitosan, alginate, pH-responsive peptides and water gels. They typically possess adjustable physical properties, possess excellent ductility and other characteristics of the natural extracellular matrix, resulting in improved durability and stability of delivery, slow release, and good biocompatibility.[108–110]

3. ADMSC-Exo-miRNA in wound healing

A method known as Coleman's suction is the most commonly used technique for collecting adipose tissue, with higher yields in the thighs than in areas such as the abdomen. Collagenase

digestion is the gold standard for the isolation of ADMSCs. Typical culture conditions include culture with 10% fetal bovine serum and 1% antibiotics at 37 °C and 5% CO_2, and simultaneously autogenous non-activated PRP has been shown to promote proliferation. The analysis of ADMSCs is usually conducted by flow cytometry and the international society of cell therapy has outlined the minimum criteria for ADMSC status: (1) cells must be plastic adherent; (2) CD73, CD90, and CD105 must be expressed, but CD14, CD11b, CD45, CD19, CD79 and human leukocyte antigen DR are absent; (3) they must have the potential to differentiate into preadipocytes, chondrocytes and osteoblasts.[22] In addition, ADMSC has better differentiation, migration, proliferation and autocrine activities in comparison to bone marrow MSC (BMSC), as well as excellent paracrine potential, which makes ADMSC-Exo a hot topic in the field of skin wound repair and treatment.[111] In recent years, miRNA related studies have provided new treatment methods and research directions for skin wound healing. The study of Zhu *et al.* showed that AMDSC-Exo reduces inflammatory infiltration and increases collagen deposition in wound skin tissue *via* lncRNA-XIST↑/miR-96-5p↓/discoidin domain receptor 2 (DDR2)↑ axis.[112] miRNA can play a role in promoting healing in each stage of wound healing through different mechanisms which have been summarized in Table 1, including regulating the inflammatory response, regulating fibroblast function, promoting angiogenesis and inhibiting scar formation.[44,48,55]

3.1. Regulation of immunity and inflammation

The inflammatory phase determines the healing process of either normal or damaged wounds and involves the removal of bacteria, tissue debris, apoptotic cells, and clots from the wound.[113] After skin injury, the coagulation cascade is activated, when platelets aggregate, forming a blood clot, releasing multiple factors (platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), epidermal growth factor (EGF), *etc.*) and successfully stopping bleeding with the combined action of serotonin, arachidonic acid metabolites, and other substances, followed by a phase of humoral and cellular inflammation.[6,7,114,115] Neutrophils, macrophages, B lymphocytes and T lymphocytes are active in the wound to establish an immune barrier against microbial invasion during this period.[116,117] However, the prolonged presence of neutrophils with excessive infiltration and inappropriate termination ways and the production of inflammatory mediators.[118] miRNA-126 and miRNA-23 overexpression, and miRNA-21 and miRNA-155 downregulation are involved in inflammatory mechanisms through phosphatidylinositide 3-kinases (PI3K)/protein kinase B (AKT)1/nuclear factor kappa-B (NF-κB) gene expression. Phagocytic activity of macrophages replaced by persistent inflammation can prevent the transformation of damaged tissue into a proliferative and remodeling phase of wound healing, inducing chronic inflammation.[119–121] Upon upregulation of tumor factor-inducible gene 6 (TSG-6) expression, ADMSC-Exo (5 μg mL^{-1}) induced polarization of M2 macrophages by expressing miR-34a-5p, miR-124-3p, and miR-146a-5p which attenuated immune responses and inflammation.[122] Therefore controlling the inflammation appropriately can ensure wound healing. Indeed, miRNAs have great potential in regulating the induction and regression of inflammatory responses by

Table 1 Regulation mechanism of miRNA in different stages of wound healing

Action stage	miRNA type	Mechanism	Ref.
Regulations of immune response and inflammation	miR-34a-5p, miR-124-3p, miR-146a-5p	IL-6↓, TNF-α↓, IL-8↓, IL-10↑, TSG-6↑, TGF-β1↑	122
	miR-132, miR-146a	ROCK1/PTEN↓	150
	miR-21-3p/miR-126-5p/miR-31-5p↑, miR-99b/miR-146a↓	PI3K/AKT↑	58
	miR-21-5p	—	1
	miR-4484, miR-619-5p, miR-8679-5p	NPM1, PDCD4, CCL5, NUP62↓	130
Promotion of cell proliferation and migration	miR-378	Caspase-3↓, lncRNA-MALAT1/miR-378a↓/FGF2↑	120 and 131
	miR-21	PI3K/AKT↑/MMP-9↑/TIMP-1↓, CCL1↓/TGF-β↑	132 and 133
	miR-19b	lncRNA-H19↑/miR-19b/ SOX9↑/Wnt/β-catenin↑	119
	miR-124	lncRNA-MALAT1↑/Wnt/β-catenin↑	136
	miR-21-5p	Wnt/β-catenin↑, MMP-7↑	1
	miR-132, miR-21, miR-29a	Fibronectin, collagen, VEGF proteins↑	122
	miR-21-3p/miR-126-5p/miR-31-5p↑, miR-99b/miR-146a↓	PI3K/AKT↑	58
	miR-146a	SERPINH1↑/p-ERK↑	160
	miR-128-3p	mmu_circ_0000250↑/miR-128-3p/Sirt1↑	144
	miR-590-3p	VEGFA↓	146
Acceleration of angiogenesis	miR-125a-3p	PTEN↓/PI3K/AKT↑	147
	miR-126-3p	PIK3R2↓	148
	miR-125a	DLL4↓	149
	miR-132, miR-146a	ANGPT1↑, KDR↑, VASH1↓, THBS1↓	150
	miR-21	PTEN↓/AKT/ERK1/2↑/HIF-1α, VEGF↑	145
	miR-486-5p	Sp5/CCND2↓	161
	miR-21-5p	—	1
Reduction of scar formation	miR-29a	TGF-β2/Smad3↓	157
	miR-192-5p	IL-17RA↓/Smad2, Smad3↓	49
	miR-449	PLOD1, ROS, TGF-β1, collagen I, α-SMA, fibronectin, M2-like macrophage↓	158
	miR-486-5p	Sp5/CCND2↓	161

regulating the differentiation and development of immune cells, controlling the activation of inflammatory signaling paths.[64,123] Wang *et al.*[58] demonstrated that ADMSC-Exo (100 μg mL^{-1}) obtained from hypoxia treatment promoted fibroblast proliferation and migration and inhibited inflammation through activation of the PI3K/AKT pathway, and notably, miR-21-3p, miR-126-5p, and miR-31-5p expressions related to wound healing were upregulated, and miR-99b and miR-146a gene expressions were downregulated, and whether this is related to the effects produced by Exo needs further validation.

3.2. Promotion of cell proliferation

Acute wounds undergo tissue repair following hemostasis and the completion of the immune and inflammatory responses. This process is referred to as proliferation.[124] The condition is characterized by an accumulation of many cells and a great deal of connective tissue. Meanwhile, this phase could be seen as a process of granulation tissue formation and replaces the clots formed during the hemostatic phase from a macroscopic point of view.[6] The wound mainly contains fibroblasts, keratinocytes and endothelial cells at this time.[125] Fibroblasts produce large amounts of the matrix proteins hyaluronic acid, fibronectin, and type 1 and type 3 procollagen, which are the basis for extracellular matrix (ECM) formation, and they differentiate into myofibroblasts, driving muscle contraction. The type III procollagen in a scar gradually replaces the type I procollagen as healing proceeds and the tensile strength of the scar increases, but only about 80% is eventually restored.[126,127] Keratinocytes at the wound edge are activated by mechanical tension, hydrogen peroxide, and other factors to undergo partial epithelial-mesenchymal transition and become more invasive and migratory, proliferating or migrating from the wound edge or skin attachment structures. Keratinocytes interact with structural proteins of the initial matrix *via* integrin receptors to cross debris and necrotic tissue of the wound bed, while their migration is mainly regulated by matrix metalloproteinases (MMP), as MMP contribute to the dissociation of integrin receptors, and concurrently lateral migration of leading edge keratinocytes across the wound changes the epidermal layer, *i.e.* re-epithelialization.[7,128] However, marginal keratin-forming cells show abnormal presence of β-catenin nuclei and elevated c-myc in chronic wounds, which directly delays *in vitro* migration, in addition to ulcerated wound marginal epidermis showing misexpression of multiple cell cycle, differentiation and bridging granule markers, impaired growth factor receptor signaling pathways, the absence of hair follicles, high trabecular protease levels significantly inhibiting dermal reconstitution, not only destroying extra-dermal matrix components but also degrading growth factors (*e.g.* vascular endothelial growth factor (VEGF), TGF-β) and cytokines (*e.g.* tumor necrosis factor-α (TNF-α)).[9] In parallel, fibroblasts are highly senescent, further impairing ECM deposition and insensitive to ECM-stimulating factors such as TGF-β,[7] for example, unhealed diabetic foot ulcers are typically characterized by hyperkeratosis and hyperkeratosis of the epidermal wound edges.[129] Thus, it is urgent to find efficient cell proliferation therapies.

According to the summary, miR-152, -29, -424, -92a, -181a, -30a, -15b, -125a-3p, -219a-3p, and 302b-3p are associated with skin aging and fibroblast senescence.[64] Fibroblast proliferation and migration, as well as the production of ECM were stimulated by up-regulating miR-132, miR-21, and miR-29a, thereby enhancing the expression of fibronectin, collagen, and VEGF proteins.[122] Furthermore, it has been indicated that ADMSC-Exo (10 μg mL^{-1}) contains miRNAs (such as hsa-miR-4484, -619-5p, -6879-5p) that inhibit the expression of nucleophosmin 1 (NPM1), programmed cell death 4 (PDCD4), C–C motif chemokine ligand 5 (CCL5), and nucleoporin 62 kDa (NUP62) genes and promote the regeneration of skin fibroblasts by stimulating the proliferation of dermal fibroblasts.[130] ADMSC-Exo-miR-378 protects HaCaT cells from oxidative damage by targeting caspase-3, including promoting proliferation and migration and reducing apoptosis.[131] At the same time, ADMSC-Exo-miR-21 (Exo: 2 mL) increases MMP-9 expression and decreases TIMP-1 expression to promote migration and proliferation of HaCaT cells *via* the PI3K/AKT pathway.[132] In the meantime, miR-19b expression in HaCaT cells was significantly increased by co-culture with ADMSCs or their derived Exo (2 μg Exo/1 × 10^5 recipient cells), followed by regulation of the TGF-β pathway by targeting CCL1, which significantly ameliorated the H_2O_2-induced decrease in cell viability and apoptosis, and subsequent improvement in wound healing in skin-injured mice further confirmed the critical regulatory role of the miR-19b/CCL1↓/TGF-β1↑ pathway.[133] Moreover, ADMSC-Exo (50 μg mL^{-1}) promotes wound healing by suppressing miR-19b expression *via* lncRNA-H19, upregulating SRY-related high-mobility-group box 9 (SOX9) to activate the Wnt/β-catenin pathway, and *via* acting on the lncRNA-MALAT1/miR-378a↓/FGF2↑ axis to promote proliferation, migration and invasion of human skin fibroblasts.[134,135] In addition, AMDSC-Exo-lncRNA-MALAT1 binds to miR-124 and also activates the Wnt/β-catenin pathway to promote cell proliferation, migration and inhibit apoptosis in HaCaT and human dermal fibroblast (HDF) cells damaged by H_2O_2.[136] The above findings provide evidence for the feasibility of ADMSC-Exo-miRNA-based therapeutic regimens for the proliferation, migration and invasion of cells during the proliferative phase of wound healing.

3.3. Promoting neovascularization

Wound healing relies heavily on angiogenesis, regenerating blood vessels and providing the necessary oxygen supply to stimulate repair and neovascularization.[137] During this period the endothelium is mainly responsible for the construction of blood vessels, and in excellent wound healing the granulation tissue shows intense angiogenesis, giving it a characteristic pink swelling.[138] However, microvascular damage can occur as a result of uncontrolled diabetes, continuous stress, and other factors, leading to local tissue hypoxia, arterial vascular disease, and/or lower extremity neuropathy.[7] Impaired angiogenesis due to microangiopathy may reduce the blood flow and oxygenation necessary for normal wound healing.[139] Hypoxia in wounds not only enhances the inflammatory state, but also affects various metabolic processes, including fibroblast activity (synthesis of collagen, *etc.*).[140,141] In addition, persistent

hyperglycemia in diabetic patients directly contributes to healing defects, impairs leukocyte function, causes cellular senescence, and induces non-enzymatic glycosylation of the extracellular matrix and the formation of AGEs, which not only alter skin structure but also trigger inflammation and ROS through AGER, actions that directly damage neovascularization.[142,143]

ADMSC-Exo containing mmu_circ_0000250-modified has been shown to promote Sirt 1 expression *via* miR-128-3p adsorption, increase angiogenesis, and inhibit apoptosis through autophagy activation, as well as promotes wound healing in diabetic rats.[144] In addition, while ADMSC-Exo-miR-21 promoted endothelial cell angiogenesis through targeting phosphatase and tensin homologs deleted on chromosome ten (PTEN), leading to AKT activation and extracellular regulated protein kinase (ERK)1/2 signaling pathways, and thereby enhancing HIF-1α and VEGF expression.[145] Sun *et al.*[146] confirmed that miR-590-3p could impede the angiogenesis of human dermal microvascular endothelial cells by binding and inhibiting VEGFA. As well as increasing the viability, migration and angiogenesis of HUVECs, ADMSC-Exo-miR-125a-3p (Exo: 25 μg mL^{-1}) inhibited PTEN in mouse wound granulation tissue, activating PI3K/AKT pathway promoted wound healing and angiogenesis.[147] The co-incubation of HUVECs with ADMSC or ADMSC-Exo enhanced fibroblast proliferation and migration, as well as angiogenesis and further enhancement was achieved by overexpression of miR-126-3p. Furthermore, ADMSC-Exo-miR-126-3p increased wound healing, collagen deposition, and new blood vessel formation in rats with full-thickness skin defects by downregulating phosphoinositide-3-kinase regulatory subunit 2 (PIK3R2).[148] miR-125a may be transferred to endothelial cells by ADMSC-Exo (100 μg mL^{-1}) and may contribute to angiogenesis *in vitro* and through inhibiting the expression of delta-like 4 (DLL4).[149] Through the delivery of miR-132 and miR-146a, ADMSC-Exo (5 μg mL^{-1}) exhibit anti-inflammatory effects by targeting the Rho kinase 1 (ROCK1)/PTEN pathway. These miRs markedly increased the expression levels of angiopoietin1 (ANGPT1) and flk1 (KDR) (the pro-angiogenic genes) and reduced the expression of vasohibin-1 (VASH1) and thrombospondin-1 (THBS1) thereby increasing angiogenesis.[150] In conclusion, ADMSC-Exo-miRNA has a positive impact on angiogenesis in wound healing. Additionally, miR-18a-5p↓/hypoxia inducible factor-1 (HIF-1)↑/VEGF↑, a new miRNA regulatory pathway, has been shown to influence diabetic wound healing in hypoxia-treated ADMSC-circ-Gcap14.[151]

3.4. Reduction of scar formation

A wound remodel is the final stage of the healing process, during which the degree of scarring is determined by the amount of ECM synthesized and degraded.[152] As scar formation is characterized by excessive collagen deposition, factors that negatively affect collagen structure and function, such as diabetes, may contribute to scar development, thus inhibiting collagen formation at a later stage may reduce scarring.[153,154]

In terms of pathological scarring, hypertrophic scarring and keloid formation are the most common types, with a high incidence. Furthermore, these scars are associated with significant pain and severely affect the appearance of the patient.[155] Previous studies have demonstrated that miR-495 is a therapeutic target for hypertrophic scars.[156] ADMSC-Exo (20 μg miR-29a transfection, Exo: 1.43E + 10 mL^{-1}) overexpressing miR-29a reduces scar formation by inhibiting the TGF-β2/Smad3 signaling pathway.[157] At the same time, miR-192-5p is highly expressed in ADMSC-Exo (20 μg mL^{-1}) and suppressed Samd2/Smad3 expression *via* down-regulating interleukin-17RA (IL-17RA) expression, reducing the levels of profibrotic protein, collagen deposition and fibroblast-to-myofibroblast transdifferentiation to decrease hypertrophic scarring.[51] In addition, miR-449 inhibits protein translation in ADMSCs by targeting the 3′-UTR of PLOD1 mRNA (procollagen lysine 1, 2-oxoglutarate 5-dioxygenase 1, a powerful fibrosis stimulant). PLOD1 protein levels were reduced in mice following transplantation of ADMSC-Exo-miR-449, wound fibrosis was decreased, macrophage polarization was shifted from M2-like to M1-like, and ROS were lower in fibroblasts, as well as TGF-β1, collagen I, alpha-smooth muscle actin (α-SMA) and fibronectin levels were lessened at the site of the skin injury and the activation of myofibroblasts was inhibited.[158] As a result of these studies, a novel ADMSC-Exo-miRNA therapy for reducing the scarring associated with wound healing has been developed.

3.5. Multi-process interventions for wound healing

Considering that skin wound healing is a dynamic and interactive process,[4] treatment strategies that include multiple wound healing processes can result in a more optimal healing outcome. HDFs co-cultured with ADMSC express significantly higher levels of miR-29b and miR-21 associated with wound healing, resulting in significantly higher wound closure rates *via* the AKT signaling pathway in a rodent skin excision wound model.[159] Modified ADMSC-Exo transfected with miR-146a was capable of upregulating Serpin family H member 1 (SERPINH1), phosphorylated extracellular regulated protein kinase (P-ERK), migration, proliferation of fibroblasts, neovascularization, and wound healing in rats.[160] The survival and proliferation of ADMSCs were significantly increased by hypoxia induction, as found by Wang *et al.*[58] It is possible that up-regulated miR-21-3p/miR-126-5p/miR-31-5p and down-regulated miR-99b/miR-146-a promote the proliferation and migration of fibroblasts by ADMSC-Exo (100 μg mL^{-1}) as well as regulate immune responses by activating PI3K/AKT pathways, thus markedly promoting wound healing. As can be seen, ADMSC-Exo-miRNA possesses good therapeutic potential for promoting cell proliferation, vascular repair, or inhibition of inflammatory processes. ADMSC-Exo-miR-486-5p (Exo: 200 μg/100 μL) demonstrates increased viability and mobility of HSF and HMECs *via* reducing the Sp5/cyclin D 2 (CCND2) pathway as well as an increase in HMEC angiogenic activity. Furthermore, it accelerates the healing of whole skin wounds, increases epithelial regeneration, reduces scar thickness, and enhances collagen synthesis and angiogenesis.[161] A lack of targeting and rapid clearance in the body may make natural Exos less effective as therapeutic agents. In this case, studies have also been conducted on the enhancement of miRNA activity in Exo by stimulation or engineering.[102] Lv *et al.*[1] activated the

Wnt/β-catenin signaling pathway by engineering Exos (E-Exos) obtained from naive hADMSC-Exo carrying exogenous miR-21-5p. MMP-7 expression upregulation promotes keratinocyte proliferation and migration, as well as accelerating wound healing in diabetic rats through presenting better inflammatory control, re-epithelialization, tissue matrix remodeling, and vessel growth and maturation. Clearly, these studies have confirmed that ADMSC-Exo-miRNAs could contribute to wound healing in a broader sense, opening up a new avenue for future therapeutic strategies.

4. Challenges and improving strategies

As shown in Fig. 2A, notably, (I) Exo isolation is a vital step for the accurate detection of exosomal miRNAs.[162] It is imperative that Exo isolation methods be standardized due to significant differences in the acquired protein and RNA content caused by cell lysis or miRNA degradation from age, sample collection, preparation or storage.[163–165] Some of the miRNAs have yet to be clarified which poses challenges in terms of safety and efficacy, such as miR-495 and miR-126; (II) the efficacy may be affected by non-specified miRNAs, impurities, cell debris, and Exo-miRNA derived from parental cells.[93,166] Moreover, in order to determine the efficacy and long-term safety in large-scale clinical diabetic patients, further study of the dose response, treatment window, and method of administration needs to be conducted;[167] (III) local injections, intravenous injections, and local dressings are all possible methods of administering Exos. Despite the fact that intravenous injections of Exo stimulate hADMSC *in vivo* to release more Exo for wound repair, conventional injections can easily interfere with this function since they are quickly cleared by the body. The high concentration of Exos in large doses of injection will result in waste, and the operation will become more complicated in low doses of multiple injections.[21,59]

Certainly, in response to the above challenges, the corresponding improvement strategies are as follows (Fig. 2B): (I) the organic combination of separation methods is an effective method and future trend to improve the purity of Exo. According to some studies, after Exos are extracted by UC and ultrafiltration, magnetic beads can be used to adsorb affinity bodies that contain the colonic epithelial cell-specific A33 antibody by immunoaffinity capture technology to significantly improve the efficiency of isolation and purification.[102] At the same time, Exo can also be purified by lyophilization, which allows it to be manufactured in large quantities for clinical application;[168] (II) delineation of all mechanisms of miRNA action can minimize the risk of off-target effects and maintain therapeutic effectiveness within the optimal range. Specific miRNAs will be significantly upregulated with hypoxia and growth factor stimulation,[166] which reduces the overall amount of Exos for treatment, thereby decreasing the side effects of other substances present in the Exos; (III) the combination of Exo with biomaterials has become a major focus of research on Exo-based therapies due to defects in Exo delivery.[169] As shown in Fig. 3, in addition to the E-Exos carrying exogenous miR-21-5p that can increase the natural availability and biocompatibility of extracellular miRNAs and carry mentioned above, a

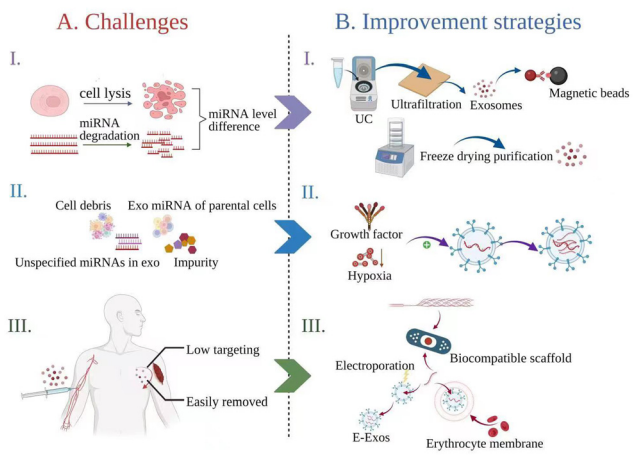

Fig. 2 Challenges in the wound healing treatments with ADMSC-Exo-miRNA and the corresponding improvement strategies.

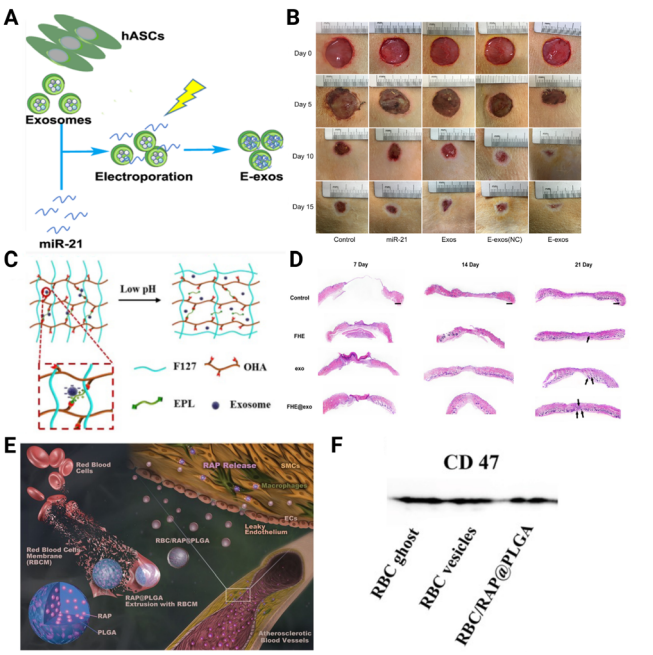

Fig. 3 Referenceable strategies for Exo-miRNA delivery systems. (A) miR-21-enriched E-Exos obtained by electroporation of ADMSC-Exo; (B) representative images of wound closure in a diabetic rat model at days 0, 5, 10, and 15 post-operation. Adapted with permission.[1] Copyright 2020, American Chemical Society; (C) scheme of pH-responsive exosomes release in FHE hydrogel; (D) H&E staining images of full-thickness wounds on days 7, 14 and 21; the arrows indicate newly formed dermal appendages, scale bar: 1000 μm. Adapted under the terms of the CC BY-NC 4.0 license.[11] Copyright 2019, Ivyspring International Publisher; (E) illustrations displaying the preparation of rapamycin (RAP)-loaded poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles are cloaked with the cell membrane of red blood cells (RBCs) (RBC/RAP@PLGA) for the treatment of atherosclerosis; (F) western blot analysis of CD47 in RBC ghost, RBC vesicles, and RBC/RAP@PLGA. Adapted under the terms of the CC BY-NC 4.0 license.[12] Copyright 2019, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

new sustained-release biocompatible scaffold (F127/OHA-EPL) carrying Exo has been developed by Wang *et al.*[11] which has shown significant effects in promoting angiogenesis, reepithelialization, collagen deposition, and the formation of new appendages on the skin as well as resulting in fewer scars. Meanwhile, this material is shown to provide a greater wound closure rate than Exo alone due to a fast self-healing process, shear-thinning injectable ability, efficient antibacterial activity, and long term pH-responsive bioactive Exos release behavior. Moreover, an increasingly sophisticated nanomedicine targeted delivery system based on erythrocyte membranes has attracted significant attention in recent years,[170,171] which brings excellent targeting and immune escape capabilities, providing a solution to the shortage of intravenous injection. In light of the negative regulatory role of many miRNAs, therapeutic strategies using anti-miR, endothelial microparticle delivery systems have been applied in clinical practice.[172,173] To conclude, combining conventional intravenous Exo-miRNA with nanodelivery systems based on erythrocyte membrane in the future will be a high-potential strategy for improving its poor targeting and easy removal. On the other hand, the combination of Exos engineered to carry biological functional miRNA and gels with protective, sustained release, high biocompatibility, shear-protection injectable ability, pH response, and thermal response will be the future trend of Exo-miRNA in promoting wound healing. In the treated Exos, the relative level of specific miRNA required can be several folds or even tens of folds that of the control group. However, it is worth mentioning that most miRNA quantification methods are relative quantification rather than absolute quantification, as described in these studies.[1,159,161,174] This is a limitation to achieving safer and more effective clinical translation of miRNAs, which will require significant efforts by researchers in the future to overcome, and requires further quantification of its detection methods.

Up to now, direct application of ADMSC-Exo-miRNA in burn wound models is still rarely reported. However, it has been studied that the Integral 3D-ADMSCs/NO hydrogel scaffolds prepared by 3D bioprinting can easily increase neovascularization by up-regulating the VEGF signaling pathway.[175] This indicates that ADMSC-Exo-miRNA has great research value and prospects in burn models. It is worth mentioning that the already mentioned Exo-related advantages create the possibility for its manufacturing of clinical-grade products on a commercial scale, and the US miRNA market is reported to have exceeded US $98.6 million in revenue in 2015.[160] These data all demonstrate that miRNA therapy has clinical value and great potential in the field of wound healing.

5. Conclusions

It is evident that the therapeutic strategy of ADMSC-Exo-miRNA has great potential for wound healing and regeneration in clinical practice. They are capable of modulating an immune response and wound inflammation, stimulating the proliferation of fibroblasts and keratinocytes, reducing cell apoptosis, and promoting angiogenesis. In the meantime, they prevent scar hyperplasia by reducing fibrosis, collagen deposition, and trans-differentiation from fibroblasts to myofibroblasts, especially in chronic wounds (such as diabetic wounds). The properties of ADMSC-Exo-miRNA make them excellent tools for developing cell-free therapies for wound healing, while providing new ideas for promoting wound healing and scarless skin repair in diabetics. The applications of ADMSC-Exo-miRNAs for wound repair have raised excellent anticipations and are involved in various biological processes, as well as new targets for medical treatment, promoting the development of "cell-free therapy". Pretreatment or engineering editing of stem cell cultures is capable of smoothly tuning the function of miRNAs. The development of criteria for therapeutic efficacy and safety concerns will facilitate the implementation of ADMSC-Exo-miRNA as a therapeutic strategy for the healing of wounds.

Author contributions

D. Sun, X. Zhang and L. Jin contributed to the conception of this review. W. Wu, J. Ma, L. Yong, P. Lei, H. Li and Y. Fang analyzed the literature and wrote the manuscript. L. Wang, H. Chen and Q. Zhou completed the figure drawing. D. Sun and L. Jin revised the manuscript. All authors read and approved the final manuscript.

Abbreviation

ADMSCs	Adipose-derived MSCs
AGEs	Advanced glycation end products
AGER	Advanced glycation end products receptor
α-SMA	Alpha-smooth muscle actin
ANGPT1	Angiopoietin1
BMSC	Bone marrow MSC
CCL5	C–C motif chemokine ligand 5
JNK	C-jun kinase
CCND2	Cyclin D 2
DLL4	Delta-like 4
DDR2	Discoidin domain receptor 2
EGF	Epidermal growth factor
Exo	Exosome
ECM	Extracellular matrix
EVs	Extracellular vesicles
HDFs	Human dermal fibroblasts
HIF-1	Hypoxia inducible factor-1
IL-17RA	Interleukin-17RA
LNA	Lock-in nucleic acid
MMP	Matrix metalloproteinases
MSCs	Mesenchymal stem cells
miRNA	MicroRNA
nPRP	Non-activated PRP
NF-κB	Nuclear factor kappa-B
NPM1	Nucleophosmin 1
NUP62	Nucleoporin 62 kDa
PTEN	Phosphatase and tensin homologs deleted on chromosome ten
PI3K	Phosphatidylinositide 3-kinases

PIK3R2	Phosphoinositide-3-kinase regulatory subunit 2
P-ERK	PPhosphorylated extracellular regulated protein kinase
PDGF	Platelet-derived growth factor
PLGA	Poly(lactic-*co*-glycolic acid)
PLOD1	Procollagen lysine 1, 2-oxoglutarate 5-dioxygenase 1
PDCD4	Programmed cell death 4
AKT	Protein kinase B
qRT-PCR	Quantitative real-time PCR
RAP	Rapamycin
RBCs	Red blood cells
ROCK1	Rho kinase 1
SERPINH1	Serpin family H member 1
Sirt 1	Sirtuin 1
SEC	Size exclusion chromatography column
SVF	Stromal vascular fraction
THBS1	Thrombospondin-1
TGF-β	Transforming growth factor-β
TSG	Tumor susceptibility gene
UC	Ultracentrifugation
VEGF	Vascular endothelial growth factor
VASH1	Vasohibin-1

Conflicts of interest

There are no conflicts to declare.

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