REVIEW

The Effects of Mesenchymal Stem Cells-Derived Exosomes on Metabolic Reprogramming in Scar Formation and Wound Healing

Xiangan Gong [ID][1,2], Qian Zhao[1,2], Huimin Zhang[1,2], Rui Liu[1,2], Jie Wu[1,2], Nanxin Zhang[3], Yuanxian Zou[1,2], Wen Zhao[1,2], Ran Huo [ID][1,2,4], Rongtao Cui[1-4]

[1]Department of Burn and Plastic Surgery, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, People's Republic of China; [2]Medical Science and Technology Innovation Center, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan, People's Republic of China; [3]School of Clinical Medicine, Shandong Second Medical University, Weifang, People's Republic of China; [4]Department of Burn and Plastic Surgery, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, People's Republic of China

Correspondence: Rongtao Cui, Department of Burn and Plastic Surgery, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, People's Republic of China, Tel +86 18653170822, Email cuirt1986@outlook.com

Abstract: Pathological scarring results from aberrant cutaneous wound healing due to the overactivation of biological behaviors of human skin fibroblasts, characterized by local inordinate inflammation, excessive extracellular matrix and collagen deposition. Yet, its underlying pathogenesis opinions vary, which could be caused by increased local mechanical tension, enhanced and continuous inflammation, gene mutation, as well as cellular metabolic disorder, etc. Metabolic reprogramming is the process by which the metabolic pattern of cells undergoes a systematic adjustment and transformation to adapt to the changes of the external environment and meet the needs of their growth and differentiation. Therefore, the abnormality of metabolic reprogramming in cells within wounds and scars attaches great importance to scar formation. Mesenchymal stem cells-derived exosomes (MSC-Exo) are the extracellular vesicles that play an important role in tissue repair, cancer treatment as well as immune and metabolic regulation. However, there is not a systematic work to detail the relevant studies. Herein, we gave a comprehensive summary of the existing research on three main metabolisms, including glycometabolism, lipid metabolism and amino acid metabolism, and MSC-Exo regulating metabolic reprogramming in wound healing and scar formation for further research reference.

Keywords: mesenchymal stem cells-derived exosomes, metabolic reprogramming, scar, wound healing, fibroblast

Background

Hypertrophic scar (HS) and keloids are the two most common pathological scars, causing both psychological burdens and physiological deformations for patients.[1,2] However, the pathogenesis and shortage of effective therapies hinder clinical treatment. Thus, it is urgent to explore the etiology and develop potential therapeutics.

The process of wound healing experiences hemostasis, inflammation, proliferation and remodeling stages.[3] Although the exact pathogenesis of pathological scars remains unclear, the excessive activities of local fibroblasts were the foundation during wound healing and scar formation.[4,5] However, the biological functions of fibroblasts are greatly decided by the metabolic status of fibroblasts.[6-8] Thus, further studying the mechanism of metabolic reprogramming of fibroblasts during wound healing and scar formation would provide theoretical references for other researchers and develop more effective therapeutics for pathological scars.

Exosomes are nano-sized extracellular vesicles (EVs) that serve as mediators between cell communication.[9] The origination of exosomes varies. However, mesenchymal stem cells-derived exosomes (MSC-Exo) have especially attracted much attention for their cell-free feature, immunomodulatory and regenerative functions in the treatment of HS and keloids by promoting wound healing and tissue repair through their cargo, including proteins, lipids and nucleic acids.[9-11] Our previous study demonstrated that the miRNA-138-5p loaded in MSC-Exo could attenuate pathological

scars by targeting silent information regulator 1 (SIRT1) and further inhibit the biological behaviors of human scar fibroblasts.[12] Recent studies suggest that exosomes play an important role in metabolic reprogramming.[13–15] The research in MSC-Exo-mediated metabolic reprogramming in wound healing and scar formation achieved great progress due to the importance of metabolic reprogramming of fibroblasts in wound healing and scar formation.[16–19] Yet, the clinical application of MSC-Exo still faces major challenges such as production and isolation methods, and ideal cell sources.[20,21]

Presently, the principal clinical strategies for preventing and treating pathological scars involve steroid injections and the external application of silicone gel adjuncts, other treatments like the localized injection of botulinum toxin and radiation therapy are utilized. However, these treatments lack adequate effectiveness and broad applicability. Considering that inflammation is a proven initiating factor in the formation of scars, and given the distinctive metabolic and immunoregulatory mechanisms of MSC-Exo, MSC-Exo is anticipated to be an effective therapeutic agent in the treatment of pathological scars.

However, the role of MSC-Exo regulates metabolic reprogramming in wound healing and scar formation lacks a systematic review. Therefore, the present study aims to provide an overview of how MSC-Exo promotes wound healing and tissue repair processes to attenuate the formation of pathological scars by regulating metabolic reprogramming and discuss current assessment challenges and fundamental insights leading to future clinically relevant exosome therapy directions.

The Effects of MSC-Exo on Scar Formation
Overview of MSC-Exo

Exosomes are one kind of extracellular vesicle (EV) with diameters ranging from 30 to 150 nm, secreted by nearly all cells and found in all body fluids including blood, urine, saliva, cerebrospinal fluid, and semen.[22] The lipid bilayer of the exosomes safeguards internal constituents like proteins, messenger RNA (mRNA), transfer RNA (tRNA), long non-coding RNA (lncRNA), mitochondrial DNA (mtDNA), microRNA (miRNA), and lipids, thus facilitating their biological roles.[23–25] Exosomes identify and attach to specific receptors on the cell surface and deliver their cargo into target cells either by fusing directly with the cell membrane or by endocytosis, thus orchestrating the regulation of intercellular signaling.[26–28] In addition to conveying specific signaling molecules and cytokines that impact the transcription and translation in target cells, exosomes also serve as biological vehicles for transporting a multitude of bioactive elements, contributing to signal transduction.[29]

Mesenchymal stem cells (MSCs), known for their strong exosome production and features such as widespread tissue presence, self-renewal, and multi-lineage differentiation potential, are applied in clinical studies across multiple areas including cancer, immune responses, neurological and cardiovascular diseases.[30] It is currently understood that MSCs mainly positively influence skin wound healing via paracrine mechanisms.[31] However, the use of MSCs in therapy poses issues such as tumorigenicity, immune rejection, and ethical concerns. More and more studies consider exosomes derived from MSCs (MSC-Exo) as potential substitutes for MSC-based therapies. MSC-EXO regulates local inflammation, oxidative stress, and metabolism by transferring cargoes such as proteins, lipids, and nucleic acids between cells. Compared to MSC therapy, MSC-Exo offers a cell-free treatment option with lower immunogenicity and a decreased risk of tumorigenesis.[32]

Function and Mechanism of MSC-Exo

MSC-Exo are primarily derived from adipose-derived stem cells (ADSC), bone marrow-derived stem cells (BMSC), human umbilical cord mesenchymal stem cells (hUC-MSC), and other stem cell types. Excessive inflammatory responses facilitate scar formation and fibrosis rather than tissue regeneration. Effectively managing the transition from the inflammatory phase to the proliferative phase may be key to minimizing scar formation and preventing pathological scars.[33,34] The inflammatory stage is characterized by dysregulation of immune cells, Research indicates that macro-phages, T lymphocytes, mast cells, and neutrophils each play a role in scar formation at varying degrees.[35] Studies have found that various MSC-Exo influence the activity of fibroblasts, immune cells, and endothelial cells in repairing inflammatory wounds and forming pathological scars. They work by modulating immune and inflammatory responses, promoting angiogenesis, inhibiting the proliferation and differentiation of fibroblasts, and reducing the secretion and

deposition of extracellular matrix (ECM) to facilitate wound repair and inhibit the formation of pathological scars.[17,36,37] The study by Blazquez et al demonstrated that ADSC-Exo significantly inhibited the proliferation and differentiation of CD 4 and CD 8 T cells and markedly reduced the production of γ interferon, affecting the γ interferon-mediated inflammatory response through immunoregulation, reducing the proportion of M1 macrophage polarization mediated by γ interferon, thus diminishing the release of inflammatory factors, thereby alleviating inflammation-induced impaired wound healing and scar fibrosis.[38] Li et al conducted immunohistochemical observations and qRT-PCR analyses to evaluate collagen I and III in wound areas in their research, discovering that ADSC-Exo promotes the expression of collagen I and III in the early stages of wound healing, enhancing the healing process, and suppresses collagen expression in the later stages, thereby lowering the levels of scarring, revealing that ADSC-Exo plays differing positive roles in the various stages of wound healing.[39]

In our previous research, we first demonstrated that exosomes derived from MSCs, serving as delivery vehicles for miR-138-5p, can downregulate SIRT1 to inhibit the growth and protein expression of hypertrophic scar fibroblasts (HSF) and mitigate pathological scarring.[12] Subsequently, we showed that MSC-exo alleviates HS by inhibiting fibroblasts via the TNFSF-13/HSPG 2 signaling pathway, which confirmed that TNFSF 13 is upregulated in HS tissues and HSF, TNFSF 13 activates the NF-κB pathway by interacting with HSPG 2, regulating the proliferation, migration, fibrosis, and inflammatory response of HSF, while MSC-Exo can reduce the expression of α-SMA and COL1A1, ultimately inhibiting the proliferation, migration, fibrosis, and inflammatory response of HSF.[40]

The transdifferentiation of fibroblasts into myofibroblasts is a crucial step in the pathogenesis of scar formation. In keloids, macrophages are primarily anti-inflammatory phenotype M2 macrophages responsible for tissue repair and remodeling, rather than the pro-inflammatory phenotype M1 macrophages that dominate the early stages of wound healing.[41] M2 macrophages can facilitate the transformation of fibroblasts into myofibroblasts by secreting transforming growth factor-beta (TGF-β). Li et al applied ADSC-Exo with high expression of miR-192-5p to HSFs, which significantly downregulating the level of the fibrogenic marker IL-17 RA, confirming that miR-192-5p in ADSC-Exo can mitigate fibrosis in HSFs and directly target IL-17 RA to regulate the role of the Smad pathway in the formation of hypertrophic scars, reducing collagen deposition and the transdifferentiation of myofibroblasts, ultimately inhibiting the formation of pathological scars.[42] Research by Jiang et al has shown that BMSC-Exo can suppress the TGF-β/Smad pathway, thereby inducing proliferation in HaCaT cells and human dermal fibroblasts, which in turn aids the process of wound healing.[43] Zhu et al demonstrated that hUC-MSC-Exo can promote wound healing by stimulating fibroblasts to secrete nerve growth factor (NGF), thus supporting the regeneration of skin nerves.[44]

Increasing evidence indicates that MSC-Exo have therapeutic effects on various types of ischemic diseases. Studies indicate that the deposition of ECM in pathological scars results from hypoxia, and hypoxia-inducible factor 1α (HIF-1α) is highly expressed in keloid tissues. HIF-1α influences the metabolism of nucleosides, amino acids, and sugars under hypoxic conditions, and also regulates the expression of immune cells and pro-inflammatory factors.[45,46] Bai and others injected ADSC-Exo pretreated with low doses of hydrogen peroxide into the abdominal transplant flaps of rats with ischemia/reperfusion injury, demonstrating that ADSC-Exo can improve the survival rate of the flaps, reduce ischemia/ reperfusion injury, promote neovascularization, and alleviate inflammation and apoptosis in the flaps, unveiling the crucial role of ADSC-Exo in facilitating angiogenesis.[47]

Application of MSC-Exo

As a promising cell-free therapeutic strategy, MSC-Exo has garnered broad interest in recent clinical studies across multiple disciplines, showing significant therapeutic potential in various diseases. Previous studies have found that sepsis increases oxidative stress in the liver, thus promoting hepatocyte death and liver damage. Research by Cai et al has proven that MSC- Exos deliver miR-26a-5p which mediates the degradation of MALAT1.[48] The deficiency of MALAT1 significantly inhibits oxidative stress, and miR-26a-5p from MSC-Exo reduces liver damage in sepsis by silencing MALAT1. Cartilage damage resulting in osteochondral defects affects joint cartilage and subchondral bone tissue. The study by Zhang et al shows that MSC-Exo significantly increases the number of chondrocytes by enhancing proliferation, reducing apoptosis, and boosting recruitment, which simultaneously promotes matrix synthesis, thereby repairing and regenerating critical-sized osteochondral defects.[49] This study also observed an increase in exosome-mediated gene

expression related to proliferation (PCNA and FGF-2) and anti-apoptosis (Survivin and Bcl-2). In studies on muscle atrophy caused by diabetes, Song et al intravenously injected MSC-Exo into diabetic db/db mice models and found that MSC-Exo increased muscle strength and mass in db/db mice, activating autophagy mediated by AMPK/ULK1, thereby improving muscle atrophy in diabetes.[50] In studies on neurological diseases, Venkat et al found that exosomes from bone marrow mesenchymal stem cells of type 2 diabetic rats promote neural repair after stroke in type 2 diabetic rats, with the miR-9/ABCA1 pathway playing a significant role.[51]

With the progress in the study of MSC-Exo's mechanisms, there have been progress in the application of MSC-Exo in reducing scar formation and promoting wound healing in recent years. MSC-Exo preconditioned under specific conditions are often endowed with enhanced cytokine secretion and cell modulation capabilities. Yu et al found that atorvastatin-preconditioned BMSC-Exo promote angiogenesis and wound healing in a diabetic rat model.[52] Yang and others observed that exposure to 455 nm blue light significantly enhances the angiogenic capabilities of hUC-MSC-Exo.[53] Exosome-biomaterials demonstrate unique benefits in preserving exosome activity and improving delivery efficiency. Hu et al developed a GelMA hydrogel embedded with ADSC-Exo using non-covalent forces and physical encapsulation, and discovered that by modulating the mechanism of circ-Snhg 11 delivery of exosomes, diabetic wound healing is accelerated. Additionally, circ-Snhg 11-modified ADSC-Exos enhance the migration, proliferation, and angiogenic potential of endothelial cells.[54] This research investigates the function and downstream targets of hypoxia-engineered exosome hydrogels in diabetic wound management, presenting a new potential approach for clinical treatment.

Numerous studies have demonstrated the targeted therapeutic actions of MSC-Exo and its function as a therapeutic carrier, and have to some extent elucidated the mechanisms by which MSC-Exo inhibits pathological scarring. However, there is still a considerable gap in translating these experimental studies into applications, and many issues remain to be resolved, such as the need to improve the extraction and purification efficiency of MSC-Exo, as well as the need for extensive clinical studies to validate the safety and therapeutic efficacy of MSC-Exo targeted treatment and carrier functions. The clinical deployment of MSC-Exo encounters numerous challenges. Therefore, future research will focus on reducing the in vivo clearance rate of MSC-Exo, enhancing its targeting capabilities, and improving the safety and efficacy of MSC-Exo treatment.

Metabolic Reprogramming in Scar Formation
Glycometabolism
Overview of Glycometabolism

Glycometabolism, also known as carbohydrate metabolism, refers to the biochemical process responsible for the synthesis, breakdown, and conversion of carbohydrates within living organisms.[55,56] Carbohydrates are essential biomolecules that serve as a major energy source for the body, are involved in cellular structure, and play critical roles in various biological processes.[57,58] Glycometabolism primarily focuses on the transformation of sugars and starches into energy and other necessary metabolites.[58] This metabolic pathway is crucial for energy production, especially in organisms that rely heavily on glucose as their primary energy source.[59,60] The process includes several key phases, such as glycolysis, the Citric Acid Cycle, oxidative phosphorylation gluconeogenesis, glycogenesis and glycogenolysis, each integral to how cells and tissues manage energy resources.[61,62]

Glycolysis is the initial step in the breakdown of glucose and occurs in the cytoplasm of cells.[63,64] It converts glucose into pyruvate, producing a small amount of adenosine triphosphate (ATP, the energy currency of the cell) and nicotinamide adenine dinucleotide (NADH).[65,66] What should be noticed is that this process is anaerobic, meaning it does not require oxygen. Following glycolysis, pyruvate is transported into mitochondria and converted into acetyl-CoA, which enters the Citric Acid Cycle.[67,68] This cycle is a series of chemical reactions that generates ATP through the oxidation of acetyl-CoA derived from carbohydrates, fats, and proteins.[69,70] The electrons removed during glycolysis and the Citric Acid Cycle are transferred to oxygen in a series of steps in the mitochondria, a process known as oxidative phosphorylation, which produces a significant amount of ATP and is dependent on the presence of oxygen (aerobic).[71] Gluconeogenesis is essentially the reverse of glycolysis and involves the synthesis of glucose from non-carbohydrate

sources, such as lactate, glycerol, and amino acids.[64,72] This process primarily occurs in the liver and to a lesser extent in the kidneys, ensuring that glucose levels in the blood remain stable, especially during fasting or heavy exercise.[73] Glycogenesis is the process of glycogen synthesis, where excess glucose is stored as glycogen in liver and muscle tissues, which serves as a readily available storage form of glucose.[74,75] Glycogenolysis refers to the breakdown of glycogen back into glucose when energy is needed, ensuring a steady supply of glucose to body tissues, particularly the brain and muscles during fasting or vigorous activity.[76,77]

Glycometabolism is the fundamental process for providing the energy for all cellular functions, which is intricately linked to other metabolic pathways, including lipid and protein metabolism, and is critical for brain function, muscle activity, and overall energy management.[78,79] Disruptions in carbohydrate metabolism can lead to various metabolic disorders, such as diabetes mellitus, hypoglycemia, and metabolic syndrome.[57,80] Therefore, Glycometabolism is a complex and essential set of processes that manage how the body utilizes, stores, and generates energy from carbohydrates. Proper regulation of these metabolic pathways is vital for maintaining health and supporting the body's diverse physiological functions.

Glycometabolism in Scar Formation

Glycometabolism plays a critical role in wound healing and the formation of scars by providing the necessary energy and biosynthetic precursors required for cell proliferation, migration, and extracellular matrix synthesis.[81] Carbohydrates, being a primary energy source, are crucial during the increased metabolic demands of tissue repair.

Rapidly dividing cells, such as fibroblasts and keratinocytes in the wound bed, require significant amounts of ATP, which is generated through glycolysis and the Citric Acid Cycle.[82] Efficient energy production is essential for all phases of wound healing and scar formation, including inflammation, proliferation, and remodeling.[83,84] In addition, The pentose phosphate pathway, which branches from glycolysis, generates ribose-5-phosphate for nucleotide synthesis and NADPH for fatty acid synthesis and maintaining cellular redox status.[85] Both are crucial for cell division and for managing oxidative stress during wound healing. Moreover, Glucose, as a precursor, can be converted into several intermediates that serve as precursors for collagen synthesis, which is the essential component of the extracellular matrix in scar formation.[86]

The previous studies investigated how the upregulation of glycolytic enzymes affects the rate of wound healing, and found that enhancing glycolysis can speed up the healing process by providing more energy and biosynthetic substrates to wound sites, but excessive glycolysis might lead to fibrosis or excessive scarring.[87] Numerous studies have explored how impaired glycometabolism in diabetic patients affects wound healing. These studies generally show that hyperglycemia impairs various aspects of cellular function and immune response, leading to slower wound healing rates and increased risk of infection.[88] Additionally, research into how dietary modifications, such as carbohydrate intake, influence wound healing outcomes demonstrated that a balanced diet with adequate carbohydrates can improve wound healing, whereas others highlight the benefits of specific diets, like ketogenic diets, in reducing inflammation and oxidative stress.[89,90]

However, to thoroughly understand the impact of glycometabolism on scar formation, a multidisciplinary approach involving biochemistry, cellular biology, and clinical research is necessary. Future studies might focus on more nuanced aspects of carbohydrate metabolism to scar formation processes would provide more definitive insights, such as the role of specific glycolytic intermediates in cell signaling during wound repair and scar formation, genetic variations in glycometabolism enzymes and their impact on wound healing and scar formation, the development of therapeutic strategies that target glycometabolic pathways to enhance wound healing and reduce scarring.

Lipid Metabolism
Overview of Lipid Metabolism

Lipid metabolism is the process involved in the synthesis, breakdown, and utilization of lipids in the body, which plays a critical role in energy storage, cellular signaling, and the formation of cell membranes.[91] Lipid metabolism can be broadly divided into two main categories: catabolism (breakdown of lipids) and anabolism (synthesis of lipids).[92] Each of these processes involves a series of biochemical reactions that are essential for maintaining overall energy balance and health.

Lipid catabolism is subdivided into lipolysis and fatty acid oxidation. Lipolysis is the process where triglycerides (the main form of stored fat in the body) are broken down into glycerol and free fatty acids, which primarily occurs in adipose tissue and is regulated by hormones such as adrenaline, noradrenaline, glucagon, and insulin.[93,94] After being released from adipose tissue, free fatty acids travel through the bloodstream to other tissues where they can be oxidized to produce energy.[93] In the mitochondria of cells, fatty acids undergo fatty acid oxidation (beta-oxidation), a cycle of reactions that systematically breaks down the carbon chains of fatty acids into acetyl-CoA units, which then enter the Citric Acid Cycle to produce ATP.[95,96]

Whereas, lipid anabolism mainly includes fatty acid synthesis, triglyceride synthesis. Fatty acid synthesis primarily occurs in the liver and to a lesser extent in adipose tissue, involving the conversion of acetyl-CoA and malonyl-CoA (derived from carbohydrates and proteins) into fatty acids, which requires acetyl-CoA carboxylase and fatty acid synthase.[97,98] Once fatty acids are synthesized, they are often esterified with glycerol to form triglycerides, which can be stored in adipose tissue or secreted into the blood as very low-density lipoproteins (VLDL).[98]

Additionally, cholesterol is an essential lipid that serves as a structural component of cell membranes and a precursor for the synthesis of steroid hormones, bile acids, and vitamin D.[99] Cholesterol can be ingested from dietary sources or synthesized de novo in the liver.[100] The regulation of cholesterol levels involves complex feedback mechanisms and is tightly regulated by the enzyme HMG-CoA reductase.[99]

Furthermore, lipoproteins are complexes of lipids and proteins that transport lipids through the bloodstream.[101] There are several classes of lipoproteins, including chylomicrons, VLDL, low-density lipoproteins (LDL), and high-density lipoproteins (HDL). Each of them plays a specific role in lipid transport and metabolism. For example, LDL is often referred to as "bad cholesterol" because high levels can lead to plaque formation in arteries, while HDL is known as "good cholesterol" because it helps transport cholesterol away from artery walls.[102]

However, lipid metabolism is crucial for providing energy, especially during prolonged exercise and periods of fasting. The dysregulation of lipid metabolism is associated with various health disorders, including obesity, type 2 diabetes, cardiovascular diseases, and metabolic syndrome.[103–105] Understanding and managing lipid metabolism through diet, exercise, and medication can significantly impact an individual's health and quality of life. Therefore, lipid metabolism encompasses a complex set of processes that are vital for energy production, cellular structure, and numerous biological functions, which are essential for maintaining health and preventing disease.

Lipid Metabolism in Scar Formation

Lipid metabolism plays a crucial role in various physiological processes, including inflammation, cell signaling, and tissue repair, which are all integral to wound healing and scar formation.[106–108] In the context of wound healing and scar formation, lipid metabolism impacts several key processes.

First, fatty acids are fundamental components of cellular membranes. Rapidly proliferating cells in a healing wound require new membranes, which necessitates an increase in lipid synthesis.[109] Second, carbohydrates are the primary energy source, while lipids provide a substantial secondary energy reserve, which can be particularly important in prolonged phases of wound healing.[110] Third, many lipids, such as phospholipids, steroids, and eicosanoids, function as signaling molecules that regulate inflammation, cell proliferation, and other critical aspects of the healing process.[108,111,112] Fourth, Lipid mediators like prostaglandins and leukotrienes, derived from arachidonic acid, are crucial in the inflammatory phase of wound healing, influencing vasodilation, vascular permeability, and leukocyte recruitment.[113,114]

A previous study from various clinical and experimental studies focusing on the dietary intake of omega-3 fatty acids and their metabolic effects related to wound healing showed that omega-3 fatty acids can enhance wound healing by reducing inflammation and potentially improving collagen deposition, leading to less scarring.[115,116] There are studies focused on enzymes involved in lipid metabolism, such as fatty acid synthase (FAS) or lipoprotein lipase (LPL), and their roles in the wound healing process, their results illustrated that upregulation of these enzymes in wound sites correlates with improved healing rates, possibly through increased availability of lipid-based energy and structural components.[117] In addition, some other studies explored the lipidomic profiles associated with different types of scarring, such as hypertrophic scars or keloids, they identified specific lipid signatures that predict scar formation or severity, offering targets for therapeutic intervention to minimize scarring.[118]

Therefore, future investigation into the specific pathways by which lipid metabolites affect fibroblast and keratinocyte function in wound healing as well as advanced lipidomic techniques could develop lipid-based therapies or dietary interventions that modulate the wound healing process or improve skin scarring.

Amino Acid Metabolism
Overview of Amino Acid Metabolism

Amino acid metabolism is a set of biochemical processes that govern the synthesis, breakdown, and conversion of amino acids, which are the building blocks of proteins.[119] It is crucial for protein synthesis, energy production, and the generation of other important molecules such as neurotransmitters, hormones, and nucleotides.[120,121] Amino acids are central to many metabolic processes and can be categorized as essential and non-essential.[79]

Non-essential amino acids are synthesized from intermediates of major metabolic pathways. For example, glutamate can be synthesized from α-ketoglutarate, a component of the citric acid cycle.[122] While other amino acids, like serine, glycine and cysteine, are derived from compounds like 3-phosphoglycerate (a glycolytic intermediate) and methionine.[123] Essential acids are primarily obtained through dietary proteins, which are broken down into their constituent amino acids during digestion and absorbed into the bloodstream.[124] Interestingly, essential amino acids cannot be synthesized by the body and must be obtained from the diet, while non-essential amino acids can be synthesized internally from other metabolic intermediates.[125,126]

Once amino acids are available in the cell, they can be used to synthesize new proteins according to the genetic instructions encoded in DNA, which is known as translation, occurs in the ribosomes and involves the assembly of amino acids into specific sequences forming proteins, which are crucial for countless cellular functions.[127,128] On the contrary, the breakdown of amino acids typically begins with the removal of the amino group through a process called deamination. The amino group is usually converted into ammonia, which is subsequently transformed into urea in the liver and excreted in the urine.[129] While the remaining part of the amino acid, often referred to as the carbon skeleton, enters various metabolic pathways, primarily for energy production.[130] Depending on their structure, these skeletons can be converted into pyruvate, acetyl-CoA, or one of the intermediates of the Citric Acid Cycle.[130]

The urea cycle is a vital process that occurs in the liver and is responsible for converting potentially toxic ammonia into urea, which is less harmful and can be excreted in the urine.[131] This cycle is crucial for detoxifying ammonia produced during amino acid catabolism. Besides, amino acids are also precursors for many biologically important molecules. For instance, tryptophan is a precursor for serotonin (a neurotransmitter) and niacin (vitamin B3); tyrosine is a precursor for dopamine, norepinephrine and thyroid hormones; arginine is a precursor for nitric oxide.[132–134]

Anyway, amino acid metabolism is essential for maintaining protein turnover, supporting growth and repair, producing energy and synthesizing critical molecules that regulate many aspects of physiology and metabolism.[135] Disorders of amino acid metabolism can lead to serious conditions, such as phenylketonuria, maple syrup urine disease, and homocystinuria, which can affect growth, development, and overall health.[135,136] Thus, amino acid metabolism encompasses a complex network of processes that are fundamental to supporting life, as they contribute to the structural components of cells, the production of energy, and the synthesis of numerous vital biomolecules.

Amino Acid Metabolism in Scar Formation

Amino acid metabolism is crucial in wound healing and scar formation, primarily because amino acids are the building blocks for protein synthesis, including the production of collagen, which is essential for tissue repair and scar formation.[137,138] Amino acid metabolism is also connected to various metabolic pathways that contribute to cell proliferation, immune response, and tissue remodeling.

It has been confirmed that amino acids are essential for repairing damaged tissues and regenerating new tissues. For example, Certain amino acids, like arginine and glutamine, play roles in immune function, influencing both the inflammatory response and the activity of immune cells.[139] Moreover, amino acids like glycine, proline, and lysine are direct precursors to collagen, a major component of the extracellular matrix in the skin.[140] Importantly, amino acids can act as signals themselves or be involved in the synthesis of signaling molecules that regulate the process of wound healing and scar formation.[137]

The previous study showed that the supplementation of amino acids like arginine or leucine can enhance wound healing. Thereinto, arginine supplementation enhances collagen synthesis and increases the strength of the healed wound tissue, and ornithine, derived from arginine, plays a role in the synthesis of proline, which is crucial for collagen stabilization in the extracellular matrix, indicating that dietary supplementation with arginine and ornithine might improve wound healing and reduce the risk of abnormal scar formation.[141] Identically, leucine supplementation significantly accelerated wound closure rates in diabetic rats compared to controls with improved collagen deposition and reduced inflammation observed in the wounds of leucine-supplemented rats, suggesting that leucine may have therapeutic potential in enhancing wound healing and improving scar attenuation, especially in populations with impaired healing capacities such as diabetic patients.[142–144] These studies highlighted potential therapeutic strategies that involve the manipulation of amino acid levels to enhance tissue repair and reduce the risk of pathological scarring.

Therefore, the precise mechanisms by which specific amino acids influence the healing process at the molecular and cellular levels could provide us with target therapeutics. Additionally, genetic studies to understand variations in amino acid metabolism among individuals and how these affect wound healing and scar outcomes are promising future research directions (Figure 1).

MSC-Exo Regulates Metabolic Reprogramming in Scar Formation

MSC-Exo Regulates Glycometabolism in Scar Formation

The content and function of MSC-Exo can be influenced by the metabolic state of their cells of origin, which in turn can affect the metabolic status of recipient cells.[13] This makes them significant in the context of metabolic diseases such as
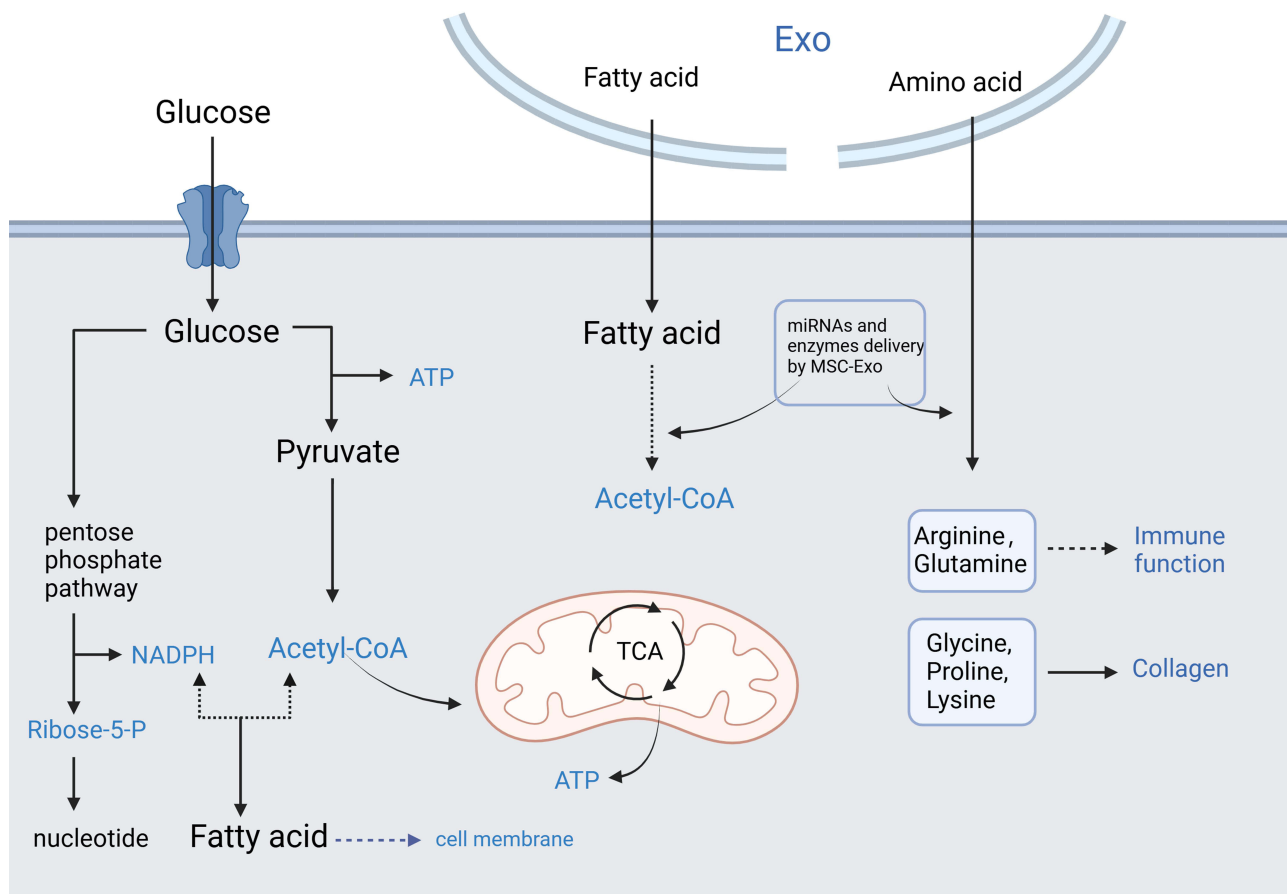

Figure 1 MSC-Exo Regulate Metabolic Reprogramming in Scar Formation.(The blue font indicates that the item directly affects scar formation and wound healing).
Abbreviations: ATP, adenosine triphosphate; NADPH, nicotinamide adenine dinucleotide phosphate; TCA, tricarboxylic acid cycle; EXO, exosomes.

diabetes, obesity, and metabolic syndrome. In the context of glycometabolism, MSC-Exo can modulate insulin signaling, affect the expression of glucose transporters, and interact with metabolic enzymes and pathways, thereby impacting overall metabolic homeostasis.[145–147]

Importance of MSC-Exo in Glycometabolism

First of all, MSC-Exo can carry insulin receptors and other key molecules that influence insulin signaling pathways, potentially affecting insulin sensitivity in peripheral tissues.[146,148] Furthermore, MSC-Exo can directly influence glucose metabolism pathways in recipient cells by transferring enzymes and regulatory proteins.[149] In addition, since metabolic diseases are often associated with chronic inflammation, exosomes can modulate inflammatory responses, which are crucial in the development and progression of metabolic disorders.[29,150]

MSC-Exo Regulates Glycometabolism in Scar Formation

MSCs are multipotent stromal cells that can differentiate into a variety of cell types. MSC-Exo have been shown to have regenerative properties, including promoting wound healing and alleviating scar formation.[150] Their role in glycometabolism during these processes is increasingly recognized as significant.

The improved wound healing and scarring mediated by MSC-Exo is mainly due to its effects on inhibiting the biological behaviors of human skin fibroblasts and promoting new blood vessel formation, which is essential for delivering nutrients and oxygen necessary for tissue repair.[12,151] MSC-Exo could also modulate the inflammatory milieu of a wound site, promoting a switch from a pro-inflammatory environment to an anti-inflammatory or pro-healing environment.[16,29] Specifically in the context of glycometabolism, MSC-Exo can enhance glucose utilization in wound tissues, potentially accelerating the healing process and improving the quality of the healed tissue.[152]

While the exact mechanisms through which MSC-Exo regulates glycometabolism in wound healing and scar formation are still under investigation, their ability to modulate glucose and energy metabolism at wound sites presents a promising therapeutic avenue. Future research should focus on elucidating these mechanisms in detail, which could lead to innovative treatments for wound management, particularly in metabolic disorders where wound healing is compromised.

MSC-Exo Regulates Lipid Metabolism in Scar Formation

As cellular communication vehicles, MSC-Exos carry a variety of molecular cargoes including lipids, proteins, and nucleic acids.[24,28] They are instrumental in regulating lipid metabolism, which involves the synthesis, transport, storage, and breakdown of lipids.[153] MSC-Exo influences these processes by transferring enzymes involved in lipid metabolism, signaling molecules that regulate these enzymes, and RNAs that modulate gene expression related to lipid pathways.[145,153]

Importance of MSC-Exo in Lipid Metabolism

MSC-Exo directly transports cholesterol, fatty acids, and other lipids between cells, influencing lipid levels and metabolism in recipient cells.[154] MSC-Exo can also impact lipid profiles by transferring cholesterol, fatty acids, and enzymes involved in lipid metabolism, thus changing the storage and breakdown of lipids.[155,156] Moreover, MSC-Exo carries proteins and miRNAs that can modulate the activity of enzymes involved in lipid synthesis and breakdown, such as lipases and fatty acid synthase.[153] Additionally, by affecting signaling pathways, MSC-Exo attaches great importance to the formation and turnover of lipid droplets, which are key cell storage structures.[157] Most importantly, MSC-Exo could communicate metabolic states between different tissues, such as adipose tissue, liver, and muscle, thus coordinating systemic lipid metabolism.[158,159]

MSC-Exo Regulates Lipid Metabolism in Scar Formation

Mesenchymal stem cells (MSCs) are known for their ability to differentiate into various cell types and MSC-Exo plays a pivotal role in promoting tissue repair and modulating immune responses.[29,160] MSC-Exo also plays an important role in regulating lipid metabolism in wound healing and scar formation, which is crucial for energy supply and cellular functions during the repair process.

MSC-Exo enhances the utilization of lipids as an energy source in wound healing.[161] This is crucial in energy-demanding processes such as cell proliferation and migration. The delivery of specific miRNAs or proteins by MSC-Exo

that upregulate or downregulate enzymes involved in lipid metabolism, affecting the local availability of lipids necessary for membrane biosynthesis and signaling during tissue repair.[36,162] Furthermore, MSC-Exo modulates the production of lipid mediators such as prostaglandins and leukotrienes that are involved in the inflammatory response during wound healing, regulating the subsequent healing and scarring process.[163] In addition, the impact of MSC-Exo on lipid metabolic pathways related to fibroblast proliferation and synthesis of the extracellular matrix could potentially reduce abnormal scar formation.[164]

Therefore, MSC-Exo plays a multifaceted role in regulating lipid metabolism during wound healing and scar formation. Their ability to transport lipids and lipid-regulating molecules makes them a promising tool in regenerative medicine. Understanding and harnessing these functions could lead to novel therapeutic strategies for improving wound healing and scar attenuation, particularly in metabolic conditions characterized by impaired lipid metabolism. However, further research is still needed to fully elucidate the mechanisms through which MSC-Exo influences lipid metabolism in tissue repair processes.

MSC-Exo Regulates Amino Acid Metabolism in Scar Formation

MSC-Exo is involved in the regulation, distribution, and utilization of amino acids within and between tissues by transporting various biomolecules during the process of amino acid metabolism, including the transport of enzymes, regulatory proteins, and RNAs that are involved in the synthesis, breakdown, and conversion of protein.[165]

Importance of Exosomes in Amino Acid Metabolism

MSC-Exo helps coordinate metabolic activities between different cells, tissues and organs through the transfer of metabolic information, ensuring a systemic metabolic balance. By delivering microRNAs and other non-coding RNAs, MSC-Exo can influence the expression of genes involved in amino acid metabolism, thereby altering the metabolic profile of target cells.[166] Additionally, the enzymes that directly participate in amino acid metabolism or proteins could be carried by MSC-Exo, allowing for the fine-tuning of metabolic pathways in recipient cells.[13] Furthermore, MSC-Exo is also involved in nutrient signaling mechanisms, relaying information about nutrient availability and requirements between cells and tissues, which is crucial during physiological processes like growth, immune responses, and tissue repair.[167,168]

MSC-Exo Regulates Amino Acid Metabolism in Scar Formation

Protein synthesis is necessary for the repair and regeneration of damaged tissues. And the role of MSC-Exo in modulating amino acid metabolism is crucial for protein synthesis, cellular function, and energy production during wound healing and scar formation.[169] Whereas the tRNAs, aminoacyl-tRNA synthetases, and mRNAs delivered by MSC-Exo play a key role in it.[170,171]

Amino acid metabolism is critical for the function of fibroblasts, which play a key role in wound healing and scar formation. The previous study showed that the proliferation, differentiation, and collagen synthesis of fibroblasts is greatly inhibited by MSC-Exo through the modulation of amino acid metabolism.[172] As is known that autophagy is a process that recycles cellular components, including proteins, during stress and starvation.[173,174] Interestingly, MSC-derived exosomes could modulate such pathways, thereby affecting amino acid recycling and availability during the healing process.[175]

The role of MSC-Exo in regulating amino acid metabolism during wound healing and scar formation is a promising area of research, which not only supports the structural rebuilding of tissues but also ensures the proper metabolic environment for healing processes. Therefore, it is necessary to fully understand the mechanisms by which MSC-Exo influences amino acid metabolism and how this can be harnessed in therapeutic contexts, particularly in chronic wounds or in conditions with impaired healing and scar formation.

Discussion

Pathological scars are the excessive repair of local tissues when the injury is up to the reticular dermis.[2] In particular, the overactivation of local human skin fibroblasts, resulting in excessive extracellular matrix and collagen deposition, is deemed to be the main pathogenesis of aberrant scar proliferation.[176,177] However, the molecular mechanisms of functional change of fibroblasts remain unclear.

Metabolic reprogramming refers to a process that the cells undergo a systematic adjustment and transformation to adapt to the changes of the external environment and meet the needs of their growth and differentiation.[178,179] Thus, the metabolic reprogramming of fibroblasts, including three main metabolic processes such as glycometabolism, lipid metabolism and amino acid metabolism, could greatly affect the function status of fibroblasts.[7,180] Previous studies demonstrated that metabolic reprogramming is a driver of fibroblast activation, resulting in pulmonary, renal, and liver fibrosis.[7,181,182] However, few studies were reported to elucidate the metabolic reprogramming of fibroblasts in cutaneous scarring. In 2018, Qi Li et al confirmed that keloids underwent a reprogrammed metabolic phenotype of aerobic glycolysis, which was essential for keloid hyperplasia, and glycolytic inhibitors might provide a potential treatment for keloids.[183] Later, Rong Huang et al showed that polypyrimidine tract binding regulates aerobic glycolysis and the cell functions of keloid fibroblasts via alternative splicing of pyruvate kinase muscle.[184] Therefore, further exploration of metabolic mechanisms within wound healing and scarring is extremely needed to understand etiology and develop effective therapeutics.

MSC-Exo was proven to improve wound healing and attenuate scar formation, resting with its modulatory functions in local inflammation, oxidative stress, and metabolism by transferring cargo like protein, lipid and nucleic acid between cells.[161,168,185] Our previous study proved that MSC-Exo-loaded miR-138-5p may significantly alleviate pathological scarring by inhibiting biological behaviors of human skin fibroblasts via targeting silent information regulator 1 (SIRT1).[12] Additionally, recent studies illustrated that MSC-Exo plays a pivotal role in tumor progression and tumor microenvironment by rewriting the metabolic processes in tumor cells and environmental stromal cells.[13,186] Moreover, the previous study by Shihao Xu et al demonstrated that MSC-Exo significantly ameliorated unilateral ureter obstruction-induced renal fibrosis by inhibiting glycolysis in tubular epithelial cells via delivery miR-21a-5p.[187] Therefore, MSC-Exo may improve wound healing and scarring by mediating metabolic reprogramming of microenvironmental fibroblasts, either key enzymes or pathways, which require further study.

In conclusion, MSC-Exo regulates the metabolic status of fibroblasts is crucial to accelerated wound healing and scar alleviation. We are determined to explore the molecular mechanisms of metabolic reprogramming in wound and scar microenvironments, and then further develop MSC-Exo-related treatments, aiming to reveal the pathogenesis and therapeutics of pathological scars.

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