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Review

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Review

Metabolic reprogramming in skin wound healing

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Abstract

Metabolic reprogramming refers to the ability of a cell to alter its metabolism in response to different stimuli and forms of pressure. It helps cells resist external stress and provides them with new functions. Skin wound healing involves the metabolic reprogramming of nutrients, such as glucose, lipids, and amino acids, which play vital roles in the proliferation, differentiation, and migration of multiple cell types. During the glucose metabolic process in wounds, glucose transporters and key enzymes cause elevated metabolite levels. Glucose-mediated oxidative stress drives the proinflammatory response and promotes wound healing. Reprogramming lipid metabolism increases the number of fibroblasts and decreases the number of macrophages. It enhances local neovascularization and improves fibrin stability to promote extracellular matrix remodelling, accelerates wound healing, and reduces scar formation. Reprogramming amino acid metabolism affects wound re-epithelialization, collagen deposition, and angiogenesis. However, comprehensive reviews on the role of metabolic reprogramming in skin wound healing are lacking. Therefore, we have systematically reviewed the metabolic reprogramming of glucose, lipids, and amino acids during skin wound healing. Notably, we identified their targets with potential therapeutic value and elucidated their mechanisms of action.

Key words: Metabolic reprogramming, Wound healing, Skin, Molecular mechanism, Therapeutic potential

Highlights

- Glucose, lipid, and amino acid metabolism are involved in skin wound healing and the inflammatory response.
- Reprogramming glucose, lipid, and amino acid metabolism can accelerate wound healing and reduce scar formation.
- Developing wound-healing drugs to target metabolic reprogramming may improve treatments for patients, such as those with diabetes.

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Background

Skin wound healing is a complicated, dynamic, multistep, and highly ordered biological process that mainly comprises three steps: the inflammatory response, cell proliferation, and tissue remodelling [1] (Figure. 1). The three phases are independent yet overlapping, and dysregulation during any phase can affect the wound-healing process [2]. Multiple cell types, including keratinocytes, fibroblasts, vascular endothelial cells, and immune cells, are required for wound repair. These cells work together to restore skin barrier function [3]. During the inflammatory phase, local vessel permeability increases, neutrophils are transported to the wound surface [4], and macrophages kill bacteria and engulf debris through phagocytosis and the release of their proteolytic enzymes. This process prevents infection, degrades necrotic tissues, and activates the signals required for wound healing [5]. The proliferative phase typically begins approximately 3 days after injury and includes endothelial cell-mediated angiogenesis, fibroblast-mediated granulation tissue formation, and keratinocyte-mediated re-epithelialization [6]. Fibroblasts produce large amounts of provisional extracellular matrix (ECM) to form granulation tissues that cover the wound bed [7], whereas keratinocytes advance, proliferate, differentiate, and reform a functional epidermis; these actions promote the closure and recovery of the vascular network and protect the tissue from further injury [8]. The remodelling phase rejuvenates the various cellular and non-cellular components of the tissue during the final stage of skin wound healing. Fibroblasts differentiate into myofibroblasts and control the fine balance between wound contraction and re-epithelialization [9], whereas the ECM components, such as collagen fibres, myofibres, and elastic fibers, proliferate and rapidly accumulate via the stimulation of cytokines [10]. These process help the tissue maintain its density and resistance to compression to protect it from exogenous pathogenic microorganisms [11].

Metabolism is a collective term referring to the chemical reactions that maintain life processes in organisms and is the basis for all life activities. Metabolism mainly comprises catabolism and anabolism and includes substantive and energy metabolism. A regular and ordered metabolic system is the biochemical basis that maintains normal physiological functions, such as growth, reproduction, the maintenance of structural stability, and responses to external stimuli. Aerobic glycolysis provides synthetic substance precursors and energy for nucleotides, amino acids, and lipids, which are essential for synthesizing macromolecules by cell division [12]. Lipid metabolism involves digestion, absorption, catabolism, and anabolism with the help of different related enzymes [13,14]. Lipid signal transduction can mediate parts of the cellular process and intercellular communication during skin wound healing and tissue regeneration [15]. Amino acids are substrates for protein synthesis and can be used during energy production to drive nucleoside synthesis and maintain cellular redox homeostasis [16].

Metabolic reprogramming refers to the process by which a cell alters its metabolism to cope with different stimuli and pressures. It helps cells resist external stress and perform various functions [17]. Metabolic reprogramming involves pathways regulating glucose, lipid, and amino acid metabolism and is closely associated with the occurrence and progression of multiple diseases [18,19]. Different stages of skin wound healing have different metabolic phenotypes [20]. This information suggests that the metabolic programming of glucose, lipids, and amino acids is closely related to the development of skin wound healing [21,22]. The key proteins in the metabolic reprogramming-related signalling cascades can become targets that ameliorate wound healing and require further investigation.

Eming *et al*. [23] summarized the metabolic reprogramming of macrophages and fibroblasts during distinct stages of normal healing and their metabolic interactions in the wound microenvironment. Manchanda *et al*. [24] used a combination of single-cell transcriptomics and metabolomics to study the major metabolic pathways in clinical human skin trauma samples. The researchers further conducted a preliminary validation of the sequencing results through human skin wound-healing tests and identified glycolysis and glutaminolysis as potential targets for therapeutic intervention. However, most applications that involve regulating metabolic reprogramming to improve skin wound healing are still in the research stage. In this review, we summarize the roles of the metabolic reprogramming of glucose, lipids, and amino acids in skin wound healing, as well as their targets and mechanisms of action. We also discuss new wound-healing drugs targeting metabolic reprogramming, emerging therapeutic opportunities, and associated challenges for the future.

Review

Glucose metabolic reprogramming in skin wound healing

Glucose provides energy for the body and plays an important role in metabolism. The decomposition and oxidation of glucose supply every cell and tissue in the body with energy so that they can grow normally. During the process of skin wound healing, glucose metabolism is enhanced, and the activities of key enzymes in the process are also changed (Figure. 2). Factors such as whole-body malnutrition, hyperglycaemia, and excessive inflammation can affect the skin wound-healing process and result in nonhealing chronic wounds [25,26]. Presently, among persons diagnosed with diabetes mellitus, the lifetime incidence of foot ulcers is as high as 25%, and they are at risk of needing amputation [27,28]. Therefore, improving the treatment of diabetic wounds by targeting glucose metabolism is an urgent clinical issue.

Glucose transporters (GLUTs) GLUTs are carrier proteins that transport glucose. They are embedded in the cell membrane and are widely distributed in various tissues in the

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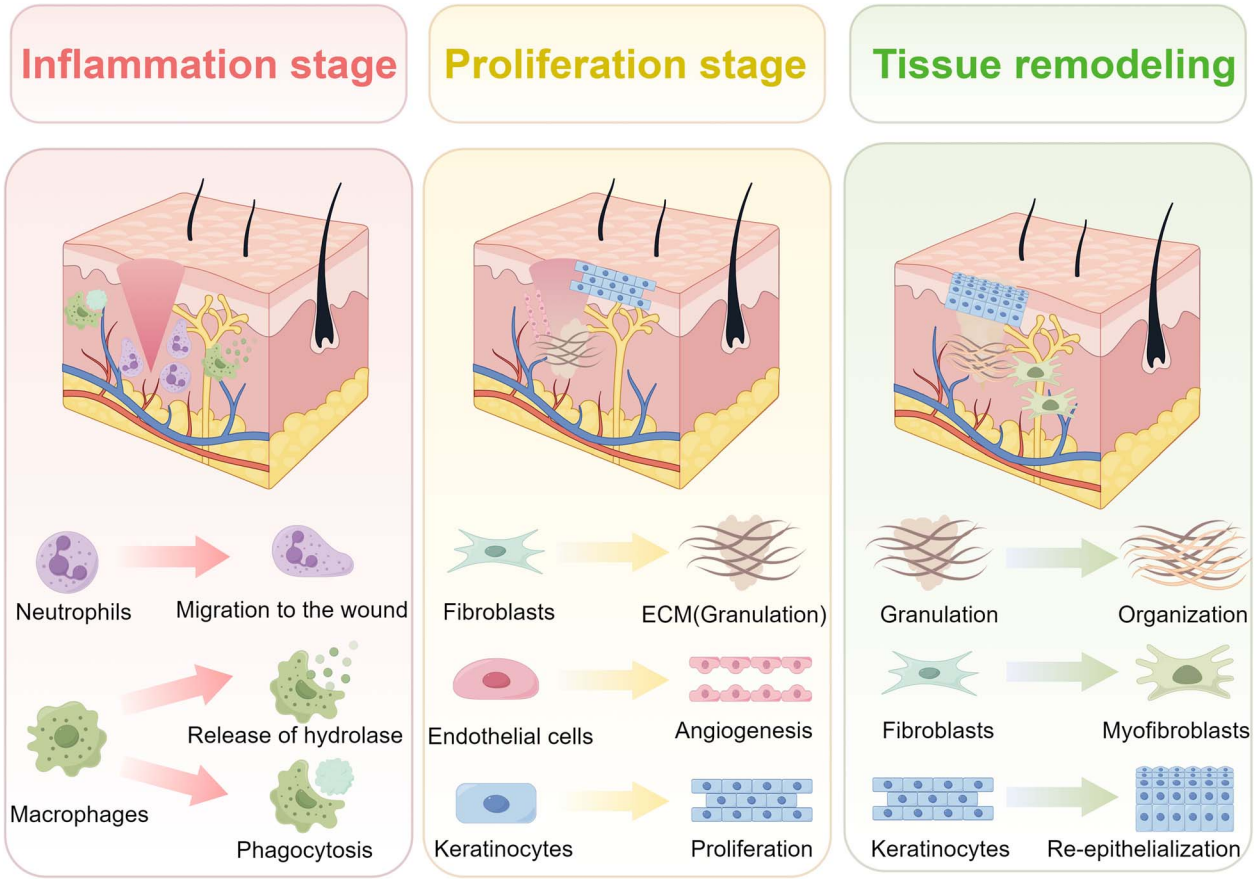

Figure 1. Three processes of wound healing (1) In the inflammatory stage, neutrophils migrate to the wound surface, and macrophages kill bacteria and ingest foreign debris through phagocytosis and hydrolase release. (2) In the proliferation stage, endothelial cells promote angiogenesis, fibroblasts produce a large amount of ECM to form granulation tissue to encapsulate damaged tissue, and keratinocytes mediate epithelialization. (3) At the stage of tissue remodeling, fibroblasts differentiate into muscle fibroblasts, and the ECM increases. *ECM* extracellular matrix

body. The uptake of glucose by cells needs to be completed by GLUTs on the cell membrane to maintain the balance of glucose metabolism in the body.

GLUT2 and GLUT4 regulate glucose transport during wound healing [29]. Placental mesenchymal stem cells modulate themselves under hypoxic conditions by secreting insulin and upregulating the expression of GLUT1/2/3 and adhesion molecules to eventually promote wound healing [30]. Hyperglycaemia-induced GLUT4 suppression in muscle and fibroblasts causes glucose intolerance in wound tissues and affects diabetic skin wound healing [31]. Freemerman *et al*. [32] demonstrated that GLUT1 overexpression in macrophages on the wound surface in high-fat diet-fed rodents increases glucose uptake and metabolism and the levels of intermediates in the pentose phosphate pathway, with a concomitant reduction in cellular oxygen consumption rates. Furthermore, GLUT1-overexpressing macrophages showed an increased secretion of inflammatory mediators, which is characteristic of the hyperinflammatory state, suggesting that the proinflammatory response is driven by glucose-mediated oxidative stress. GLUT1 levels are significantly higher in burn patients who develop keloids than in those without keloids, indicating that GLUT1 is a potential indicator of abnormal glucose metabolism and increased keloid risk [33].

Glucose phosphorylation The first step of glycolysis involving glucose phosphorylation at C6 to form glucose-6-phosphate is catalysed by hexokinase (HK). Nguyen *et al*. [34] detected the maximum HK activity in mice of all ages after skin injury and confirmed that glucose utilization and aerobic metabolic potential were increased after skin injury. Gupta *et al*. [35] monitored the activities of HK in the granulation tissue of normal and diabetic rats at different time points (2, 7, 14, and 21 days) post-injury. The researchers observed decreased HK activity in the wound tissue of the diabetic rats compared with that in the normal rats. The alterations in the energy-metabolizing enzymes in the wound tissue of the diabetic rats may have affected the energy levels required for cellular activity, thereby disrupting skin wound healing.

Pyruvate formation The phosphoenolpyruvate (PEP)-mediated transfer of high-energy phosphate groups to produce adenosine triphosphate (ATP) and pyruvate under the catalysis of pyruvate kinase (PK) is a crucial substrate-level

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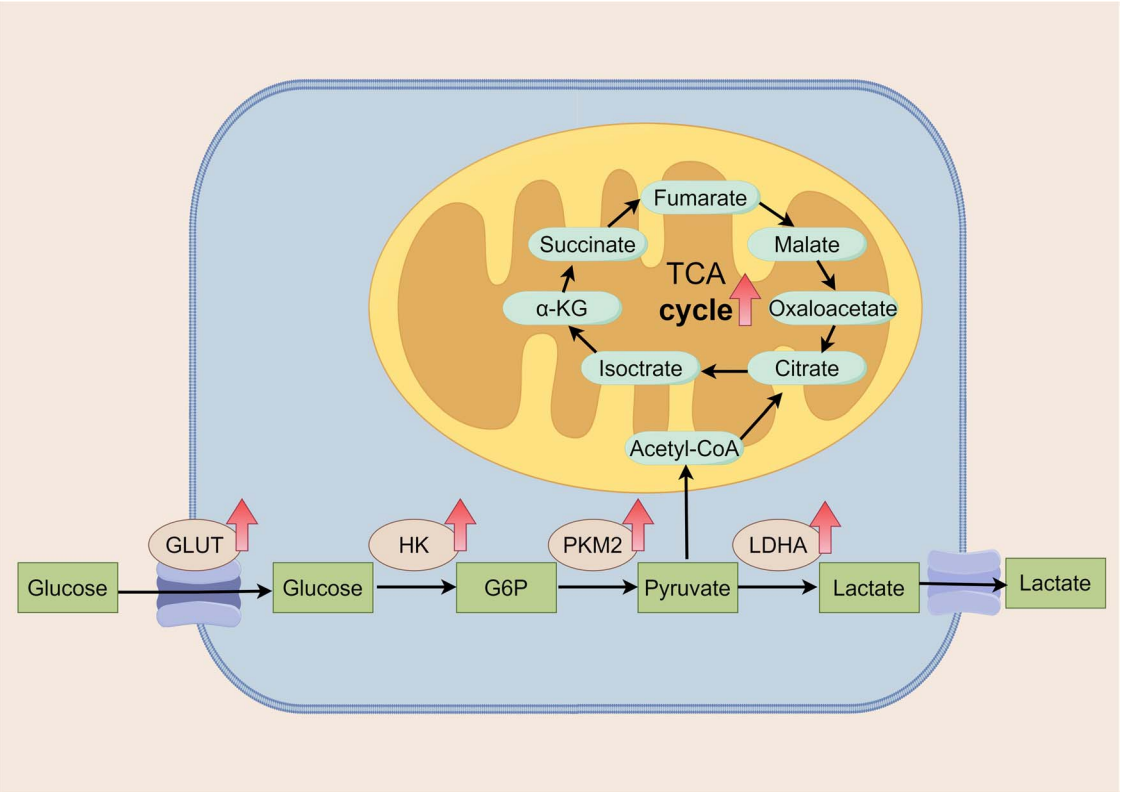

Figure 2. Reprogramming of glucose metabolism in wound healing. Glycolysis and the relative metabolic pathways are shown. Broad arrows (in red) indicate increased expression/activity of enzymes and the relative metabolic pathways. GLUT promotes glucose intake, supporting the glycolytic pathway. High expression of HK, PKM2, and LDHA activate glycolysis, promoting wound healing. *α-KG* α-ketoglutarate, *GLUT* glucose transporter, *G6P* glucose-6-phosphate, *HK* hexokinase, *LDHA* lactate dehydrogenase A, *PKM2* pyruvate kinase 2, *TCA* tricarboxylic acid

phosphorylation reaction in glycolysis. PK is a critical rate-limiting enzyme in glycolysis. There are two PK isoforms (PKM1 and PKM2) that catalyse the transfer of a phosphate group from PEP to adenosine diphosphate (ADP), yielding pyruvate and ATP [36]. Angiogenesis is a vital step in skin wound healing; vascular resident endothelial progenitor cells (VR-EPCs) can differentiate into epithelial cells (ECs) and can participate in angiogenesis to a certain extent [37]. The activation of PKM2 promotes VR-EPC angiogenesis by modulating glycolysis and mitochondrial fission and fusion [38]. Infiltrated/activated neutrophils at the wound site release PKM2 during the early stages of skin wound repair [39]. This process may increase angiogenesis to promote early skin wound healing. The glycolytic enzyme PKM2 regulates endothelial cell junction dynamics and angiogenesis through the regulation of ATP production [40]. In addition, PKM2 is upregulated in the inflammatory phase of skin healing and is coupled with angiogenesis during skin wound repair; this is required for the complete induction of vascular endothelial growth factor (VEGF) in keratinocytes [41].

Lactate formation The last step of glycolysis involves the conversion of lactate to pyruvate and the oxidation of NADH to NAD^+ by lactate dehydrogenase (LDH) [42]. Lactate mediates the production of angiogenesis-related factors and the recruitment of endothelial progenitor cells to the wound; this especially involves the signalling of collagen synthesis in fibroblasts and VEGF transcription in endothelial cells, which leads to the activation of procollagen and angiogenic factors [43]. Exogenous lactate reduces muscle atrophy and improves reperfusion in mice with ischaemic hindlimb wounds [44]. This findings suggest that the angiogenic potential of lactate accelerates angiogenesis and skin wound healing.

LDH is the key enzyme in lactate formation. A previously published proteomic analysis identified several proteins that may contribute to delayed wound healing, including LDH [45]. The knockdown of lactate dehydrogenase-A (LDHA) inhibits the proliferation and migration of vascular smooth muscle cells (VSMCs) [46]. This result suggests that LDHA prevents vessel lumen constriction and accelerates skin wound healing.

Lipid metabolic reprogramming in skin wound healing

Lipids are important substances for energy storage and supply, as well as important structural components of biofilms. Lipid metabolism involves the enzyme-mediated digestion, absorption, synthesis, and decomposition of lipids in the body. It is an important biochemical reaction comprising energy transformation in the body. The reprogramming of lipid metabolism in skin wound healing is shown in Figure. 3.

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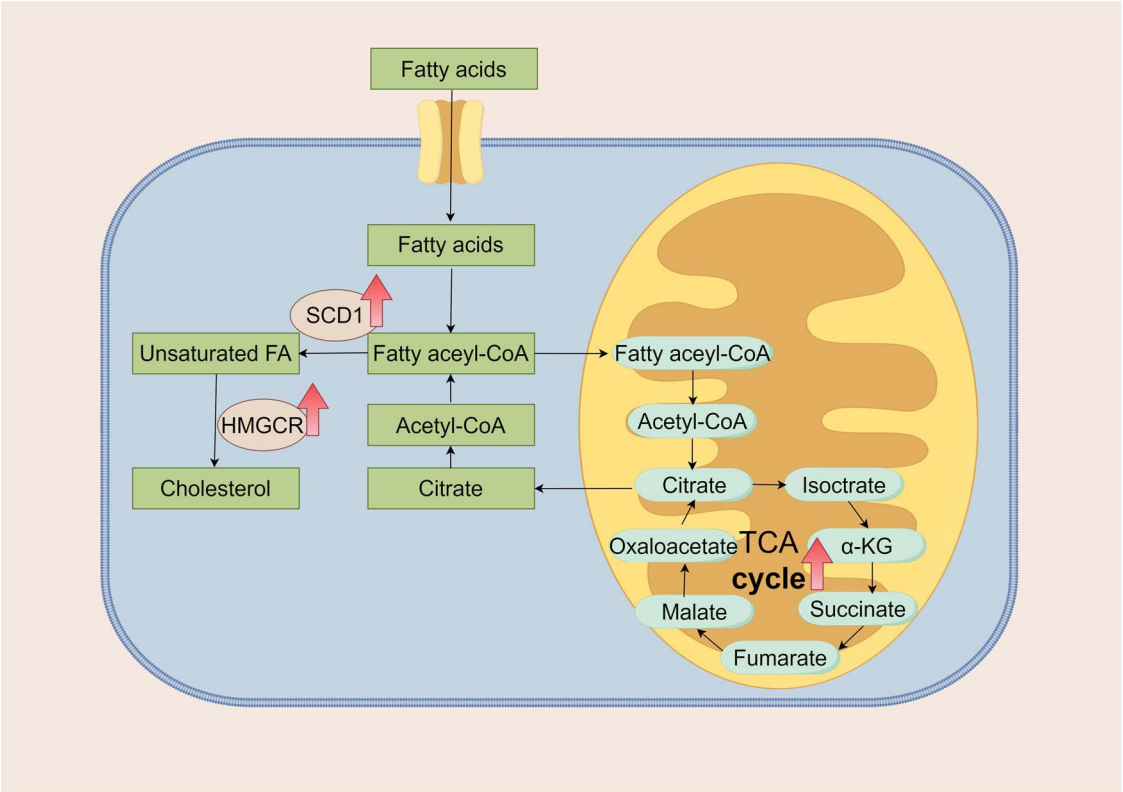

Figure 3. Reprogramming of lipids metabolism in wound healing. Lipid synthesis, β-oxidation, and the relative metabolic pathways are shown. Broad arrows (in red) indicate increased expression/activity of enzymes and the relative metabolic pathways. The consequent raise of exogenous fatty acids up-take sustains increased lipid synthesis and β-oxidation. Fatty aceyl-CoA stimulates citrate, which acts as positive feedback, driving the progression of wound healing. α-*KG* α-ketoglutarate, *FA* fatty acid, *HMGCR* 3-hydroxy-3-methyl glutaryl coenzyme A reductase, *SCD1* stearoyl-CoA desaturase-1, *TCA* tricarboxylic acid

De novo fatty acid synthesis *De novo* fatty acid synthesis takes place in the cytoplasm. It requires acetyl coenzyme A, which is produced by various metabolic processes utilizing ATP. Platelets mainly transfer mitochondria to mesenchymal stem cells through endocytosis to enhance their wound-healing ability by activating the *de novo* fatty acid synthesis pathway and enhancing their angiogenic activity [47].

Sterol regulatory element-binding proteins (SREBPs) are a vital regulatory transcription factors for *de novo* fatty acid synthesis and govern cellular lipid homeostasis. They also play crucial roles in regulating angiogenesis in response to VEGF [48]. SREBP1 is responsible for the biosynthesis of cholesterol and fatty acids, and SREBP2 mainly mediates cholesterol biosynthesis [49,50]. Interleukin-8 (IL-8) is a chemokine involved in inflammation. The activation of SREBP1 and SREBP2 has been found to stimulate IL-8 in human microvascular endothelial cells and rabbit skin wound-healing models [51]. SREBP1 also contributes to promoting anti-inflammatory Toll-like receptor 4 signalling by reprogramming macrophage lipid metabolism [52]. Mitochondrial autophagy regulatory factor (BNIP3) is regulated by the SREBP1/FASN pathway and promotes free fatty acid (FFA) synthesis, which reduces the wound-healing capacity of mouse skin [53].

Fatty acid oxidation (FAO) FAO refers to the oxidation and decomposition of glycerol and fatty acids produced by fatty hydrolysis to generate carbon dioxide and water. This process provides the body with a large amount of energy and plays a vital role in skin wound healing. Increased FAO is essential for the remodelling and tissue repair function of M2 macrophages [54,55]. LncFAO is a long noncoding RNA that directly interacts with the HADHB subunits of mitochondrial trifunctional proteins and activates FAO [56]. It promotes the resolution of inflammation and tissue repair by activating FAO. Macrophages engulf apoptotic cells via efferocytosis [57]. This leads to elevated levels of cellular fatty acids, which promote mitochondrial respiration and activate NAD-dependent signal transduction. This metabolic signalling pathway promotes anti-inflammation and skin wound healing.

Fatty acid desaturation Polyunsaturated fatty acids (PUFAs), which mainly comprise omega-3 and omega-6 fatty acids, can regulate the immune response and participate in skin wound healing, repair, and tissue remodelling [58–60]. In diabetic rat skin wound healing models, omega-3 PUFAs have been found to alter proinflammatory cytokine production, which substantially decreased the number of grade three mast cells on

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days 3 and 5 and the wound area by day 7 [61]. The number of fibroblasts capable of repair was significantly increased in the wound areas of omega-3 PUFA-treated rats, whereas that of macrophages was decreased, thereby accelerating healing [62].

Omega-6 PUFAs include linoleic, conjugated linolenic, gamma-linolenic, and arachidonic acids. Linoleic acid and its products act as inflammatory mediators in skin wound healing. They enhance local neovascularization, fibroblastic protein stability, ECM remodelling [63], and fibroblast proliferation [64]. They eventually increase the rate of wound closure and decrease the bleeding time to accelerate dynamic skin wound healing. The wound closure rate has been found to substantially improve in mice fed a 1% conjugated linoleic acid-supplemented diet during the early stages of skin wound healing (inflammatory stage), which increased the wound closure rate by modulating oxidative stress and the inflammatory response [65]. Gamma-linolenic acid inhibits inflammatory responses by inactivating NF-κB and AP-1 by suppressing oxidative stress and the ERK and JNK signal transduction pathways in lipopolysaccharide-induced macrophages [66]. Arachidonic acid stimulates endothelial cell adhesion *in vivo* [67]. Its metabolites have anti-inflammatory capabilities, including stimulating inflammatory cell chemotaxis and increasing elastin activity to degrade extracellular proteins; this affects the formation and remodelling of tissue healing [68]. Arachidonic acid levels decrease when fatty acid levels decrease at the local wound site, which primarily occurs when the body has an essential fatty acid deficiency that may cause excessive keloid formation.

Cholesterol synthesis The skin barrier comprises keratinocytes buried in extracellular lipids [69], which mainly consist of cholesterol, fatty acids, and ceramides [70]. The critical enzyme regulating cholesterol synthesis is3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase. The angiogenic and proliferative responses of keratinocytes are biphasically regulated through HMG-CoA reductase expression and activity during skin wound healing [71]. HMG-CoA reductase inhibitors have been found to reduce granulation tissue formation in mouse wound chambers by 64.7%, accompanied by associated ultrastructural evidence of apoptosis in fibroblasts, which demonstrates the capability of HMG-CoA reductase inhibitors to induce fibroblast apoptosis [72]. An HMG-CoA reductase inhibitor was also found to inhibit smooth muscle cell (SMC) proliferation *in vitro* and to reduce neointimal formation caused by vascular injury [73]. HMG-CoA reductase inhibitors further reduced hypertrophic scar formation by inhibiting connective tissue growth factor in rabbit ear models [74], blocked endothelial cell migration [75], inhibited angiogenic factor-induced endothelial cell proliferation *in vivo* [76], and increased intraperitoneal fibrinolysis to decrease postoperative adhesions [77].

Hypercholesterolaemia is also closely related to the state of skin wound healing. High-density lipoproteins (HDLs) play functional roles in anti-inflammation and angiogenesis [78]. In endothelial cells, HDLs interact with scavenger receptor class B type I to activate the PI3K/Akt signalling pathway; activation of this pathway leads to a decrease in inflammatory protein production and an increase in angiogenic growth factors [79]. HDLs inhibit inflammation by deactivating the NF-κB pathway in macrophages [80]. Additionally, reconstituted HDLs (rHDLs) reduce CCL2, CCL5, and CX (3) CL1 expression in monocytes and human coronary artery endothelial cells and chemokine receptor CCR2 and CX (3) CR1 expression, demonstrating their anti-inflammatory properties [81].

Amino acid metabolic reprogramming in skin wound healing

Amino acids are among the many bioactive macromolecules involved in the construction of biological organisms. They are also the basic materials for the construction of cells and tissue repair. The balance of amino acids is a basic prerequisite for human health. The metabolic reprogramming of amino acids helps in tissue repair during skin trauma (Figure. 4).

Arginine metabolism Arginine, a versatile amino acid used to synthesize various bioactive molecules by arginase, plays a crucial regulatory role during skin wound healing. There are two isoforms of arginase: Arg-I and Arg-II. Arg-I is highly expressed in the liver; it catalyses the conversion of arginine to ornithine and urea, participates in the urea cycle, and plays a vital role in ammonia detoxification. Arg-II is a mitochondrial enzyme that hydrolyses arginine to ornithine, which is further metabolized into polyamine and proline. Polyamine is an essential medium for cell proliferation and differentiation, and proline is a vital component of collagen, constituting approximately one-third of the amino acid residues of collagen. Therefore, amino acid metabolism is vital for collagen synthesis, ECM production, wound healing, and tissue remodelling [82,83].

Arginase competes with nitric oxide synthase (NOS) for the substrate, L-arginine. This competitions inhibits NO synthesis in vascular endothelia, SMCs, and other diseased tissues and causes dysfunction; the deactivation of arginase or a reduction in its expression can restore NO synthesis [84,85]. NO activates guanylyl cyclase-C to produce cGMP in vascular endothelial cells, leading to SMC relaxation and vasodilation [86,87]. An increase in arginase activity leads to the uncoupling of endothelial NOS, and the chronic inhibition of arginase *in vivo* can restore the nitroso-redox balance and improve endothelial function [88,89].

Glutamine metabolism Glutamine is the most abundant free amino acid in the human body. It regulates the expression of multiple genes related to metabolism, signal transduction, cell defence, and repair and activates signalling pathways in cells [90–92]. Glutamine is rapidly metabolized in macrophages [93], and human monocytes subsequently convert citrulline to arginine to promote skin wound healing. A glutamine-containing supplement can shorten the time needed for

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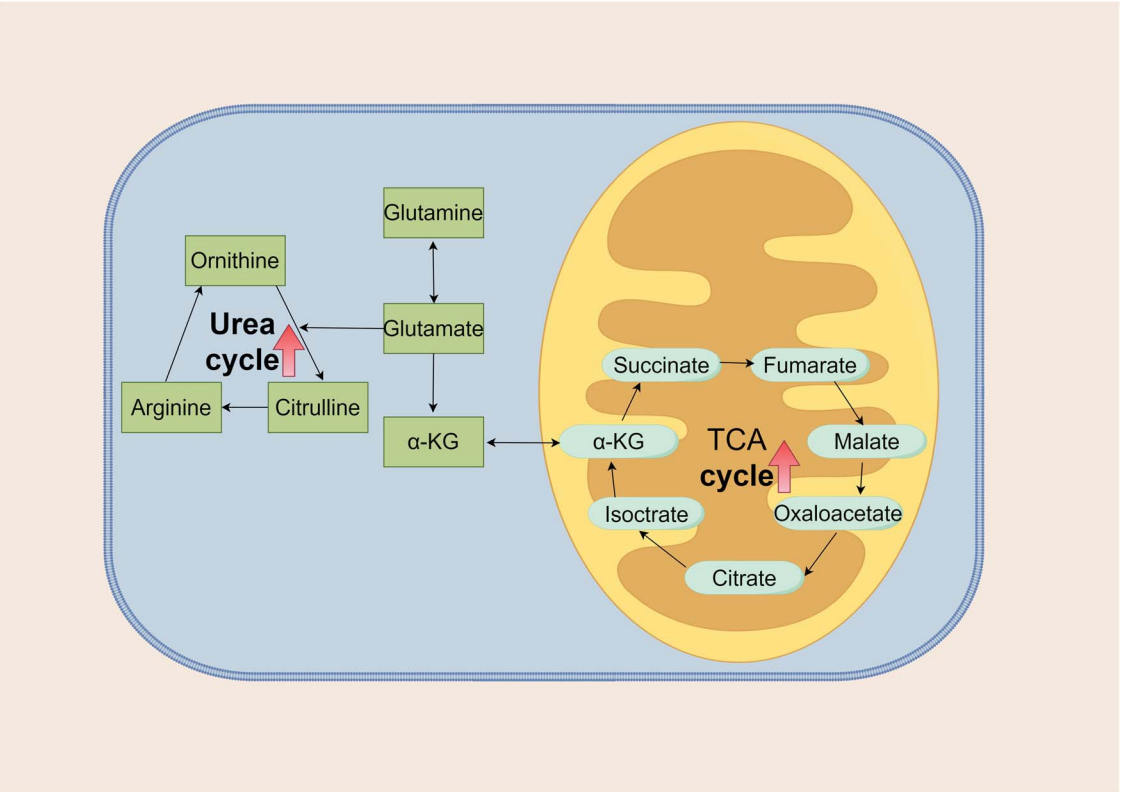

Figure 4. Reprogramming of amino acids metabolism in wound healing. Metabolism of amino acids in wound healing are shown. Broad arrows (in red) indicate activity of the relative metabolic pathways. Amino acids are crucial for collagen synthesis, ECM production, wound healing, and tissue remodeling, all of which are achieved through the metabolism of amino acids. *α-KG* α-ketoglutarate, *TCA* tricarboxylic acid

wound closure in patients with trauma and wound-healing disorders [94].

Glutamine also reduces C-reactive proteins (CRPs), which play vital roles in the inflammatory process, including NO release, cell apoptosis, and the production of IL-6 and tumour necrosis factor-α [95]. IL-6 is crucial in mediating wound healing by regulating the differentiation, activation, and proliferation of keratinocyte fibroblasts and endothelial cells [96]. The PI (3) K-PKB-FOXO network regulates autophagy via the modulation of glutamine metabolism [97], and the importance of autophagy in skin wound healing has been demonstrated in numerous other studies [98–102].

Tryptophan metabolism Many studies have shown that tryptophan metabolism is altered in skin wound healing. Tryptophan catabolism induces an increase in FAO by destabilizing hypoxia inducible factor 1 to impair endothelial glucose metabolism [103]. These metabolic changes diminish basal intracellular cGMP levels, impair endothelial migration, and produce a proinflammatory response. Tryptophan is also a precursor for 6-formylindolo [3,2-b] carbazole, which has been found to enhance keratinocyte migration and promote wound healing in a MAPK/ERK-dependent manner in multiple mouse models [104].

Indoleamine 2,3-dioxygenase 1 (IDO1) is a key enzyme in tryptophan metabolism. Ito *et al*. [105] found that skin wound healing in IDO1-knockout (IDO-KO) mice was substantially better than that in wild-type (WT) mice, and the inhibition of IDO1 activity could accelerate wound healing. Another study by Bandeira *et al*. demonstrated that IDO1 expression increased 5 days after wounding. The numbers of neutrophils, macrophages, and T cells increased and were reversed by tryptophan. The administration of tryptophan further decreased myofibroblast density, collagen deposition, re-epithelialization, and wound contraction. These findings indicate that the tryptophan-induced reduction in the inflammatory response and IDO1 expression may have accelerated cutaneous wound healing in chronically stressed mice.

Therapeutic potential of targeted metabolic reprogramming in skin wound healing The key proteins in the abovementioned metabolic pathways may be therapeutic targets to improve skin wound healing and are worth investigating (Figure. 5). In terms of glucose metabolism, Apolinário *et al*. [106] revealed that the topical use of insulin may improve skin wound healing in hyperglycaemic mice by modulating the expression of inflammatory factors, growth factors, and proteins in the insulin signalling pathway. Yang *et al*. [107] proved that the exogenous application of insulin could promote the apoptosis of neutrophils and subsequently trigger the polarization of macrophages and improve diabetic

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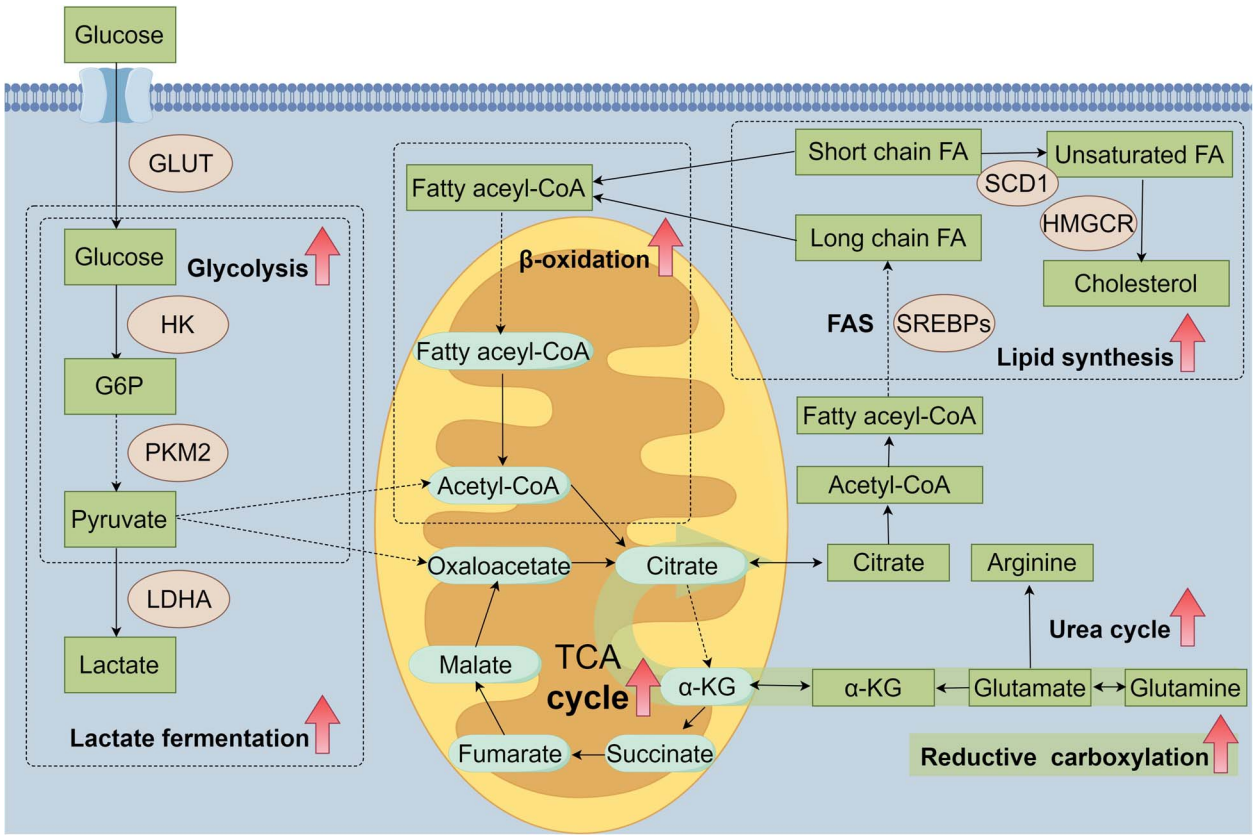

Figure 5. Landscape of metabolic reprogramming and related pathways in wound healing. The metabolism of glucose, lipids, and amino acids is reprogrammed owing to changes in key enzymes and transporters. These altered metabolic pathways provide opportunities for therapy. Long solid and dotted arrows represent direct and indirect shifts or bioconversions, respectively. Square symbols (in blue) represent metabolic materials and products in metabolic reprogramming in wound healing, whereas yellow oval symbols represent enzymes and transporters. *α-KG* α-ketoglutarate, *FA* fatty acid, *GLUT* glucose transporter, *G6P* glucose-6-phosphate, *HK* hexokinase, *HMGCR* 3-hydroxy-3-methyl glutaryl coenzyme A reductase, *LDHA* lactate dehydrogenase A, *PKM2* pyruvate kinase 2, *SCD1* stearoyl-CoA desaturase-1, *SREBPs* sterol-regulatory element binding proteins, *TCA* tricarboxylic acid

wound healing in Wistar rats. Liang *et al*. [108] designed a metformin-releasing hydrogel with pH/glucose dual sensitivity, adhesion, and self-healing properties, which helped heal athletic diabetic foot. A glucose-responsive multifunctional metal–organic drug-loaded hydrogel was further found to decompose excess glucose into hydrogen peroxide and glucuronic acid [109] and to change the hyperglycaemic wound microenvironment. This approach may be helpful for diabetic wound repair with synergistic antibacterial and angiogenic activity. Peroxisome proliferator-activated receptor-delta ligand-coated stents have been found to induce the expression of pyruvate dehydrogenase kinase isozyme 4, downregulate GLUT1 expression, prevent thrombocyte activation, and support vessel re-endothelialization in VSMCs [110] to prevent in-stent restenosis and stent thrombosis.

Targeting aberrant glucose metabolism with shikonin, a PKM2 inhibitor, improves healing *in vivo*. This finding indicates a potential clinical application for shikonin in preventing abnormal scarring [33]. Lactic acid released from a Matrigel matrix was found to induce repair angiogenesis, improve reperfusion, and prevent muscle atrophy in ischaemic hindlimb wounds in mice [44]. Poly lactate-glycolic acid (PLGA) is biodegradable and biocompatible and has received regulatory approval for clinical use [111].

A subcutaneous implant of PLGA was found to enable sustained local and systemic lactate release. This promoted fibroblast proliferation [112], granulation tissue formation [113], collagen deposition [114], and re-epithelization [115], thus contributing to skin wound healing.

In terms of lipid metabolism, clinical studies have shown that HMG-CoA reductase inhibitors accelerate the skin wound-healing process [116–118] and reduce scar formation [119]. HMG-CoA reductase inhibitors, such as statins, are cholesterol-reducing agents that block the synthesis of wound-healing inhibitors by targeting the cholesterol pathway [120]. Kerecis® is derived from the skin of wild Atlantic cod, which contains a complete epidermis and dermis and comprises a substrate that retains natural omega-3 fatty acids. Kerecis® has gained popularity as a dermal substitute for skin wound healing owing to its high PUFA content [121]. Fatty acid extracts from *Lucilia sericata* larvae promote angiogenic activity and wound healing in the murine cutaneous layer [122]. The topical application of omega-3, omega-6, and omega-9 fatty acid emulsions in rats with excision wounds has been found to accelerate wound closure compared to untreated wounds [123,124]. Additionally, oral PUFAs have been found to accelerate the inflammatory stages of mouse wound healing [125,126].

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Table 1. Clinical application of targeted metabolism reprogramming to improve skin wound healing

Targets	Name	Roles in wound healing	References
Glucose	Insulin	Modulating inflammatory factors and growth factors	[106]
Glucose	Insulin	Promoting anti-inflammatory macrophage polarization	[107]
pH/Glucose	pH/glucose dual-responsive hydrogel	Reducing inflammation and enhancing angiogenesis	[108]
Glucose	Glucose-responsive multifunctional hydrogel	Changing the hyperglycemic wound microenvironment	[109]
Pyruvate dehydrogenase kinase isozyme4 and glucose transporter 1	PPARδ ligand-coated	Preventing thrombocyte activation and supporting vessel re-endothelialization	[110]
PKM2	Shikonin	Abnormal scar prevention	[33]
Lactate	L-lactide-co-glycolide (PLGA)	Pro-angiogenic	[44]
Lactate	PLGA-curcumin nanoparticles	Re-epithelialization, granulation tissue formation, and anti-inflammatory	[111]
HMG-CoA reductase	Statins	Managing wound infections, reducing scar elevation index, decreasing type I/III collagen content, and myofibroblast persistence	[113] [114] [115] [116] [117]
PUFAs	Acellular fish skin	Decreasing scar formation and providing pain relief	[118]
PUFAs	Omega fatty acids	Inducing early deposition of collagen, promoting new microvasculature, moderating pro-inflammatory cytokines and growth factors, and restoring impaired plasticity of macrophage progenitor cells	[119] [120] [121] [122] [123]
Arginase	2(S)-amino-6-boronohexanoic acid NH4 (ABH)	Promoting re-epithelialization and localization of myofibroblasts beneath the wound epithelium	[124]
Arginine	Arg-Lig-NF gel	Increasing re-epithelialization, collagen deposition, and angiogenesis	[125]
Arginine	PVA/HA/CNCs/L-arginine	Promoting proliferative and adhesive potential on cells	[126]
Glutamine	L-glutamine	Acting on collagen synthesis, wound contraction, and epithelialization	[127]
Tryptophan	ALA/PCL-based ENMs	Enhancing type I collagen synthesis and reducing smooth muscle actin expression	[128]

PUFAs polyunsaturated fatty acids, *HA* hyaluronic acid, *ALA* α-Lactalbumin, *PCL* polycaprolactone, *ENMs* electrospun nanofibrous mats, *HMG-CoA* 3-hydroxy-3-methyl glutaryl coenzyme A, *PVA* polyvinyl alcohol, *PPAR* peroxisome proliferator-activated receptors

In terms of amino acid metabolism, drug discovery has mostly focused on inhibitors with arginase as a target. For example, 2(S)-amino-6-boronohexanoic acid NH_4 (ABH) is an active arginase inhibitor with high efficiency and specificity. Animals treated with ABH have exhibited increased amounts of granulation tissue and improved re-epithelialization and localization [127]. An *in vivo*, full-thickness wound-healing assay of a gel containing nanofibres that were surface-modified by arginine molecules (Arg-Lig-NF gel) increased re-epithelialization, collagen deposition, and angiogenesis and ultimately accelerated wound closure in rats [128]. Similarly, researchers incorporated CNCs as nanofillers and loaded L-arginine into citric acid-crosslinked poly (vinyl alcohol)-hyaluronic acid (HA)-based nanofibres (NFs) (PVA-HA NFs) to develop a new bioactive wound dressing (PVA/HA/CNC/L-arginine). This nanofibre had substantial potential for proliferation and adhesion, excellent haemocompatibility, high protein adsorption, and antibacterial activity [129]. The oral administration of L-glutamine (1 g/kg) further induced complete epithelialization with new blood vessel formation and increased amounts of fibrous tissue [130]. The wound area substantially decreased, and the rate of wound contraction increased to promote wound healing compared with that in control rats.

α-Lactalbumin (ALA) is a dietary protein rich in tryptophan. As a precursor of the neurotransmitter serotonin, ALA can promote burn wound healing and reduce scar formation. Guo *et al*. [131] designed electrospun nanofibrous mats (ENMs) based on ALA and polycaprolactone. These ENMs adhered to fibroblasts, resulting in increased fibroblast proliferation, type I collagen synthesis, decreased smooth muscle α-actin expression, and reduced scar formation. A summary of the clinical use of targeted metabolic reprogramming to improve skin wound healing, as well as its action targets and roles in wound healing, is presented in Table 1.

Conclusions

Metabolic reprogramming plays a vital role in skin wound healing by providing multiple repair cells with energy and substrates. Reprogramming glucose, lipid, and amino acid metabolism can accelerate wound healing and reduce scar formation. Glucose-mediated oxidative stress drives the proinflammatory response and promotes wound healing.

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Reprogramming lipid metabolism enhances local neovascularization and improves fibrin stability to promote extracellular matrix remodelling. Reprogramming amino acid metabolism affects wound re-epithelialization, collagen deposition, and angiogenesis. Therefore, developing wound-healing drugs to target metabolic reprogramming may improve treatments for patients, such as those with diabetes. It is believed that a comprehensive understanding of metabolic reprogramming in skin wound healing will potentially provide theoretical references for promoting the development of new wound-healing drugs.

Abbreviations

ABH, 2(S)-amino-6-boronohexanoic acid NH_4; ALA, α-lactalbumin; α-KG, α-ketoglutarate; ATP, adenosine triphosphate; CLA, conjugated linoleic acid; CRP, C-reactive protein; EC, epithelial cell; ECM, extracellular matrix; ENM, electrospun nanofibrous mat; FAO, fatty acid oxidation; FFA, free fatty acid; GLUT, glucose transporter; GS, glutamine synthetase; HDL, high density lipoprotein; HK, hexokinase; HMGCR, 3-hydroxy-3-methyl glutaryl coenzyme A reductase; IDO1, indoleamine 2,3-dioxygenase 1; LDHA, lactate dehydrogenase A; LPS, lipopolysaccharide; NOS, nitric oxide synthase; PCL, polycaprolactone; PEP, phosphoenolpyruvate; PK, pyruvate kinase; PKM2, pyruvate kinase 2; PLGA, poly lactate-glycolic acid; PUFA, polyunsaturated fatty acid; SMC, smooth muscle cell; SREBP, sterol-regulatory element-binding protein; VEGF; vascular endothelial growth factor; VR-EPC, vascular resident endothelial progenitor cell; VSMC, vascular smooth muscle cell.

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors agree to publish this review.

Data Availability

Not applicable.

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Competing interests

All authors declare no conflicts of interest.

Authors' contributions

All authors contributed to the writing of this manuscript. All authors have read and approved the final version of the manuscript.

ZW, ZTW: Conceptualization; ZW: Funding acquisition; ZTW, CCX, QQZ, HYR, XH, CH, JJM: Writing—original draft preparation; FZ: Project administration; ZW: Supervision.

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