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Non-conding RNAs: Role in diabetic foot and wound healing

Tang YB *et al*. ncRNAs: Diabetic foot and wound healing

Abstract

Diabetic foot ulcer (DFU) and poor wound healing are chronic complications of patients with diabetes. The increasing incidence of DFU has a huge pressure worldwide. Diagnosing and treating this condition are therefore of great importance to control morbidity and improve prognosis. Finding new markers with potential diagnostic and therapeutic utility in DFU has gathered emerging interest. Wound healing is a process divided into three stages: Inflammation, proliferation, and regeneration. Non-coding RNAs (ncRNAs), which are small protected molecules transcribed from the genome without protein translation function, have emerged as important regulators of diabetes complications. Remarkably, ncRNA deregulation might be linked to accelerated DFU development and delayed wound healing. Moreover, ncRNAs can be used for therapeutic purposes in diabetic wound healing. Herein, we summarized the role of microRNAs, long ncRNAs, and circular RNAs in diverse stages of DFU wound healing and their potential use as novel therapeutic targets.

Core Tip: Non-coding RNAs (ncRNAs) have emerged as important regulators of diabetic foot and wound healing. NcRNAs can be used for therapeutic purposes in diabetic wound healing. In this study, we summarized the roles of microRNAs, long ncRNAs, and circular RNAs in diverse stages of diabetic foot ulcer wound healing and their potential use as novel therapeutic targets.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease that is increasing rapidly worldwide. DM is a global public health burden with a negative impact on global health and socioeconomic development. Chronic hyperglycemia causes blood vessel inflammation, which leads to macroangiopathy and microangiopathy, particularly diabetic foot ulcer (DFU) and delayed wound healing. Delayed healing of chronic ulcer wound in patients with diabetes is due to neuropathy, microangiopathy, and immune system dysfunction[1,2]. One of the leading causes of death in patients with diabetes is lower extremity amputation, which accounts for approximately 15% of DFU cases[3]. Different functional and structural microvascular changes in patients with diabetes increase the vulnerability of the skin and contribute to impaired wound healing[4]. DFU contributes to physical and psychological problems that hinder the health economy immensely. Conventional DFU treatments show inefficient impact on the reduction of amputation rate; thus, a more efficient treatment is needed. Therefore, a better understanding of the molecular mechanisms and biomolecules involved in DFU development is necessary to provide better therapeutic options for wound healing.

Non-coding RNAs (ncRNAs) are potential novel biomarkers transcribed from the genome without protein translation function but can still perform specific biological functions. NcRNAs can be divided into two categories depending on the length of nucleotides; short-stranded RNAs or microRNAs (miRNAs) are less than 200 nucleotides in length, and long ncRNAs (lncRNAs) are greater than 200 nucleotides in length. Emerging evidence suggests that ncRNAs have an important regulatory role in various metabolic diseases, such as DM, based on the development of microarray and high-throughput sequencing[5]. In addition, some lncRNAs are covalently bound to 3'-5' end, forming circular RNAs (circRNAs)[6]. NcRNAs can be protected from the effects of RNA enzyme activity, temperature changes, and extreme pH values by binding to proteins or being packaged into extracellular vesicles. In this way, ncRNAs can maintain a stable state in the extracellular environment and can be used as a potential biomarker for diagnosing and treating diseases[7-9]. NcRNAs regulate cellular chromatin rearrangements, histone modifications, variable splicing gene modifications, or gene

expression; mediate different biological processes; and ultimately influence the development of certain diseases[10]. Exosome-cargoed ncRNAs have been reported as pivotal regulators of angiogenesis during wound closure[11]. This background confers the treatment possibility of delayed wound healing using ncRNAs. In this study, we summarize the role and mechanism of miRNAs, lncRNAs, and circRNAs in the pathogenesis and process of wound healing in DFU and the research progress of ncRNAs in cell therapy.

WOUND HEALING PROCESS

Wound healing is a complex and highly regulated process divided into three phases: Inflammation, proliferation, and regeneration[12]. Diabetic wound healing is widely associated with different cellular components and extracellular matrix (ECM) in different parts of the skin[13]. The main effector cells in the inflammatory phase are macrophages. When normal skin is damaged, macrophages polarize to M1 phenotype, producing pro-inflammatory cytokines and stimulating endothelial cells and fibroblasts to release reactive oxygen species (ROS) to remove bacteria and debris from wounds. The subsequent shift to the M2 phenotype is correlated with the remission of the inflammatory response and wound remodeling[14,15]. In diabetic wounds, the persistence of the M1 phenotype and the inability to subsequently polarize to the M2 phenotype are the key components delaying wound healing. Angiogenesis is the main basis of the proliferative phase of wound healing, cell proliferation, migration, and differentiation[14]. The integrity of the endothelial cell structure plays a very important role in maintaining normal blood circulation in the body. In healthy tissues, endothelial cells are in a quiescent phase. In diabetic patients, wound healing is slowed by decreased angiogenic growth factors, such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and hypoxia-inducible factor (HIF)-1α[16-18]. An unfavorable diabetic wound environment promotes the dysregulation of key signaling pathways, such as Notch and PI3K/AKT/eNOS[19,20]. The regenerative phase of wound healing includes re-epithelialization and ECM remodeling. Reduced blood flow restricts

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the migration of leukocytes, keratinocytes, fibroblasts, and endothelial cells to the wound, which is detrimental to wound healing[21]. Fibroblasts proliferate and secrete ECM components, such as collagen fibers, which provide supportive structures for cell proliferation and migration to restore skin tissue function and integrity to maintain tissue elasticity and strength[22]. DFUs have collagen degeneration and deformation and reduced fibroblasts in the proliferation and migration stages[23]. Keratinocytes are the main constituent cells of the epidermis involved in skin wound healing through migration, proliferation, and differentiation[24]. In addition, epithelial-to-mesenchymal transition (EMT) plays a crucial role in DFU regeneration and wound healing[25]. Many studies have shown that ncRNAs regulate EMT involved in DFU and wound healing[26,27].

MIRNAS

MiRNAs or DFU in multifactorial logistic regression analysis[28]. Furthermore, low miR-24 expression is negatively correlated with fasting blood glucose and glycated hemoglobin and positively correlated with inflammatory markers[28-30]. MiRNAs have been associated with DFU progression and severity; specific miRNAs, such as miR-26, increase DFU severity[31], whereas other miRNAs, such as miR-129 and miR-335, improve wound healing[26].

Inflammation

MiR-217 belongs to the group that increases DFU severity. A study showed that dual luciferase reporter gene assay confirmed HIF-1α as a direct target gene of miR-217. MiR-217 expression was upregulation whereas HIF-1α/VEGF expression was downregulated in patients with DFU and serum of rats with DFU compared with DM and healthy controls[32]. MiR-23c is upregulated in the peripheral blood and wound tissue in DFU, targeting stromal cell-derived factor-1α and inhibiting wound angiogenesis by recruiting inflammatory cells, such as macrophages[33]. In mouse DFU model, miR-497 expression was downregulated, which considerably increased the

expression of pro-inflammatory factors, such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β, resulting in a prolonged inflammatory phase of wound healing[34]. MiR-155 regulates insulin sensitivity and blood glucose levels in mice[35]. MiR-155 is remarkably upregulated in diabetic skin[36]. MiR-155 has pro-inflammatory effects; thus, miR-155 inhibition leads to reduced inflammation, increased macrophage M2 polarization, reduced IL-1β and TNF-α levels, more regular collagen fiber alignment, and faster diabetic wound healing[37-39]. MiR-217, miR-497, and miR-155 are effector molecules in the inflammatory phase of diabetic wound healing; however, a further exploration of their mechanisms might improve wound healing during the inflammatory phase.

Proliferation

Angiogenesis is an essential step in the proliferative phase associated with DFU prognosis and wound healing. Recent studies have focused on the mechanisms and applications of miRNAs in regulating angiogenesis during the proliferative phase[40-42]. A maggot therapeutic approach study found that miR-18a/19a is remarkably upregulated and thrombospondin-1 (TSP-1) expression is downregulated in DFU wounds as a result of impaired angiogenesis. The target activation of miR-18a/19a transcript levels and the regulation of TSP-1 expression may be a novel strategy for DFU treatment[40]. MiR-15a-3p is upregulated in the blood exosomes of patients with diabetes[41]. *In vivo* and *in vitro* experiments showed that exosomes with low miR-15a-3p expression inhibited diabetic wound healing. By contrast, knockdown of circulating exosomal miR-15a-3p expression may accelerate wound healing through the activation of NADPH oxidase (NOX) 5 and increase ROS release[41]. NOX activates redox signaling pathways and promotes angiogenesis[43]. Phosphatase and tensin homolog (PTEN) expression is regulated by blood glucose concentrations, is mainly in epithelial cells, and activates signaling cascades that affect angiogenesis[44]. MiR-152-3p is an upstream negative regulator of PTEN upregulated in diabetic wounds; hence, inhibiting the angiogenic function of PTEN leads to delayed wound healing[45]. MiR-195-5p and miR-

205-5p carried by extracellular vesicles in DFU wound fluid negatively regulate angiogenesis and wound healing in DFU[42]. Increased miR-133b expression induces downregulation of EGF receptor (EGFR), affecting endothelial cell proliferation and angiogenesis in all diabetic wounds. *In vitro* experiments showed that miR-133b downregulation in human umbilical vein endothelial cells partially reverses impaired angiogenesis[46]. These findings imply that miR-133b negatively regulates angiogenesis during the proliferative phase of wound healing. Huang *et al*[47] found that miR-489-3p downregulation increases sirtuin (SIRT) 1 expression, promotes the PI3K/AKT/eNOS signaling pathway, improves cellular antioxidant capacity, and alleviates DFU. MiR-199a-5p has an important role in the development of diabetes and its complications[48,49]. Moreover, miR-199a-5p promotes apoptosis and ROS production within pancreatic β-cells in type 2 DM (T2DM)[50]. MiR-199a-5p sponge-adsorbed to hsa-circ-006040 inhibits macrophage-mediated inflammatory responses in T1DM[48]. Wang *et al*[49] found that downregulating miR-199a-3p in endothelial cells alleviates the inhibition of the target VEGFA and Rho-related kinase 1, rescuing the cellular damage induced by high glucose and restoring angiogenic function. Therefore, these findings suggest that regulating miRNA expression during the proliferative phase of wound healing has great potential in DFU treatment and wound repair.

Regeneration
Recently, Moura *et al*[36] also found that the local inhibition of miR-155 in diabetic wounds increased the expression of its target, fibroblast growth factor (FGF) 7, which sequentially increased re-epithelialization and accelerated wound healing[36,51]. Yuan *et al*[52] found that miR-203 upregulation in DFU tissues may inhibit the EMT process and delay wound healing in rat DFU model. On the contrary, miR-203 knockdown promoted wound healing by activating the target gene, IL-*8*, and IL-8/AKT downstream pathways. High miR-203 expression reduces keratinocyte proliferation and migration, partially explaining the development of DFU into chronic refractory wounds[52]. On the contrary, recent studies have found that negative pressure wound

therapy can reverse the inhibition of keratinocytes as a result of high levels of miR-203 by reducing miR-203 in the peripheral blood and wound tissue and upregulating p63 expression[53]. Sprouty homolog (SPRY) 1, an antagonist of the FGF pathway, is expressed in fibroblasts, and its downregulation plays an important role in wound healing[54,55]. MiR-21-3p is downregulated in diabetic patients compared with healthy control and in fibroblasts stimulated with D-glucose compared with control fibroblast[56]. Enhanced miR-21-3p expression may inhibit SPRY1, stimulate fibroblast proliferation and migration, and accelerate wound healing[42]. MiR-146a is downregulated in DFU wound tissue. Bioinformatics analysis revealed that A-kinase-anchoring protein 12 (AKAP12) and Toll-like receptor 4 (TLR4) are the target genes of miR-146a. Peng *et al*[57] showed that miR-146a activates in the inflammatory phase of diabetic wound healing by inhibiting the TLR4/nuclear factor-kappaB axis involved in macrophage M2 polarization. In addition, Zhang *et al*[58] constructed an *in vitro* DFU model using human keratinocyte-derived HaCaT cells and demonstrated that miR-146a is activated during the tissue regeneration phase. *In vivo* and *ex vivo* results showed that miR-146a overexpression inhibited the angiogenic regulator AKAP12, activated the HIF-1α/Wnt3α/β-catenin signaling pathway, and promoted cell proliferation and migration[57]. MiRNAs have regulatory effects on a wide range of cells involved in tissue remodeling during the regeneration phase. MiRNAs are the most studied ncRNAs and act in various periods of DFU and wound healing, respectively or continuously. We summarized some of the considerably altered miRNAs in diabetic patients as shown in Table 1. Notably, most of these pooled miRNAs have not been reported to have a clear therapeutic role in DFU and should therefore be evaluated in future studies.

LNCRNAS

LncRNAs are located in highly conserved genomic regions with spatially and temporally tightly regulated expressions and dysregulated expression profiles as important markers of altered disease or developmental status. The main mechanism

and function of lncRNAs are to act as competing endogenous RNAs (ceRNAs) for miRNAs, which interact with mRNA target base pairs to control various signaling pathways[59]. Another mechanism is by interacting with RNA-binding proteins[60]. Increasing evidence shows that lncRNAs play an important role in diabetic complications. LncRNA 3632454L22RiK can promote corneal epithelial wound healing in diabetic mice by sponging miR-181a-5p[61]. The regulatory role of lncRNA MIAT in diabetic cardiomyopathy has also been demonstrated[62]. These findings indicate an increased awareness of lncRNAs in diabetic complications.

Inflammation

The mechanism of lncRNAs in the inflammatory phase lacks enough evidence. LncRNA growth arrest specific 5 (GAS5) has been identified as a tumor suppressor that inhibits cell proliferation and promotes apoptosis[63]. GAS5 expression was remarkably elevated in DFU wounds[64]. GAS5 promotes the M1 phenotypic polarization of macrophages through the upregulation of signal transducer and activator of transcription 1 (STAT1), leading to prolonged inflammatory phase and delayed wound remodeling and closure[64]. STAT1 signaling is exactly the central pathway that controls M1-M2 polarization in macrophages. Reduced GAS5 levels in wounds appear to promote healing by facilitating the conversion of M1 macrophages to M2 macrophages. Thus, targeting lncRNA GAS5 may contribute to efficient therapeutic intervention for impaired wound healing in diabetes.

Proliferation

GAS5 regulates the inflammatory process of wound healing and plays a part in the proliferative phase. During the proliferative phase, GAS5 activates the HIF-1α/VEGF pathway by binding to TATA box-binding protein associated factor 15, stimulating endothelial cell proliferation and angiogenesis and leading to accelerated DFU wound healing[65]. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is a relatively well-studied transcript among lncRNAs. The role of MALAT1 has been

reported in a variety of diseases, including renal tumors, osteosarcoma, and gestational diabetes[66-68]. MALAT1 protects endothelial cells from oxidative stress injury by activating the nuclear factor erythroid-2-related factor 2 (Nrf2) pathway. MALAT1 is remarkably reduced in DFU-infected tissues, leading to insufficient HIF-1α/VEGF activation and impeding angiogenesis[69]. The exogenous uptake of exosome lnc01435 by vascular endothelial cells alters the subcellular localization of transcription factor yin yang 1 (YY1) and synergistically upregulates histone deacetylase (HDAC) 8 expression with YY1. HDACs are important components of the NOTCH signaling pathway with negatively regulated expression levels and thus affect endothelial cell function and angiogenesis[70,71]. In summary, targeting GAS5, MALAT1, and lnc01435 may help develop new therapeutic strategies to treat DFUs.

Regeneration

LncRNA H19, located on chromosome 11, exhibits negative regulation of diabetic wound healing. LncRNA H19 acts as a sponge for miR-29b and competitively represses miR-29b expression; therefore, it upregulates fibrillin 1 (FBN1), activates the TGFβ/Smad signaling pathway, and promotes ECM accumulation[72]. Connective tissue growth factor (CTGF) is a matricellular protein from the Cyr61/CTGF/Nov protein family, which interacts with ECM protein to mediate external signal transduction into cells through many subtypes of integrin receptors[73]. During the proliferative phase of diabetic wound healing, lncRNA H19 recruits the transcription factor SRF to the CTGF promoter region, activating CTGF and its downstream MAPK signaling pathway to accelerate fibroblast proliferation and wound healing[74]. These findings elaborate lncRNA H19 as a regulator in the regenerative phase of wound healing. A novel lncRNA MRAK052872, named lnc-upregulated in diabetic skin (URIDS), is involved in the mechanism of DFU wound healing. Lnc-URIDS is highly expressed in diabetic skin and dermal fibroblasts treated with advanced glycosylation end products. Lnc-URIDS binds to procollagen-lysine and 2-oxoglutarate 5-dioxygenase 1 (plod1), decreases plod1 protein stability, and leads to dysregulated collagen deposition and delayed

wound healing[27]. LncRNA cancer susceptibility candidate 2 (CASC2) was originally discovered in an endometrial cancer study and is located on human chromosome 10q26[75]. Furthermore, CASC2 overexpression inhibited fibroblast migration and proliferation, suppressed apoptosis, and facilitated wound healing, especially in DFU mice. By contrast, miR-155 overexpression inhibited the function of CASC2[75]. Another study showed that HIF-1α inhibition reversed the effects of miR-155 downregulation on fibroblasts[76]. Evidently, lncRNAs have a considerable regulatory role in cellular functions during re-epithelialization and remodeling.

The mechanisms by which lncRNAs cause DFU and delayed wound healing are atypical inflammatory responses, impaired angiogenesis, impaired and abnormal ECM accumulation, and epithelial processes that regulate wound healing. The lncRNAs in DFU and delayed wound healing are listed in Table 2. These findings provide new information for the clinical treatment of diabetic chronic non-healing wounds.

CIRCRNAS

CircRNAs are a unique type of ncRNA derived from exons, introns, or intergenic regions that are covalently linked to produce a closed loop structure in the absence of 50 caps and 30 tails. CircRNAs are conserved among species owing to their resistance properties to RNase R. CircRNAs are involved in a wide range of biological processes, such as transcription and mRNA splicing, RNA decay, and RNA translation; the dysregulation of circRNAs leads to abnormal cellular functions and human diseases[77,78]. CircRNAs can also act as a miRNA sponge to inhibit miRNA function, which plays a crucial role in the pathogenesis of diabetes and its vascular complications[79]. Circ-PNPT1 and has_circ_0046060 promote the development of gestational DM by regulating trophoblast cell function or causing insulin resistance[80,81]. Circ-ITCH improved renal inflammation and fibrosis in diabetic mice by regulating the miR-33a-5p/SIRT6 axis[82]. CircRNAs are closely related to the development of diabetes and its complications. Studies on the role and mechanism of circRNAs in DFU and

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delayed wound healing are relatively few. Existing studies evaluated the regulatory role of circRNAs on angiogenesis and re-epithelialization.

CircRNAs protein kinase, DNA-activated, catalytic subunit (circ_PRKDC, has-circ-0084443) is involved in the promotion of keratinocyte proliferation and the suppression of keratinocyte migration during wound healing[83]. Circ_PRKDC negatively regulates keratinocyte migration *via* the EGFR pathway, impeding re-epithelialization and angiogenesis[84]. However, circ_PRKDC knockdown promotes epidermal keratinocyte migration *via* the miR-31/FBN1 axis[83]. This finding shows that circ_PRKDC has therapeutic potential for skin wound healing. Shang *et al*[85] evaluated the effect of circ-Klhl8 in epithelial progenitor cells (EPCs) on diabetic wound closure by establishing an *in vivo* mouse model of total skin defect and found that circ-Klhl8 overexpression increases the therapeutic effect of EPCs to promote diabetic wound healing by targeting the miR-212-3p/SIRT5 axis. Altered circRNA expression (Table 3) can affect disease progression and wound healing in DFU. Studies on circRNAs in various stages of DFU and wound healing are few and prompted the need of further research on functional circRNAs in the future to identify limitations in DFU treatment.

NCRNAS IN CELL THERAPY

The standard treatment for DFUs includes optimizing blood flow, debridement, infection control, and offloading. In standard treatment, only 50% of patients heal within 20 wk and 50% relapse within 18 mo; thus, efficient treatment for DFUs are urgently needed[86]. Cell-based DFU therapy is a new treatment intervention therapy studied in the last few years. Stem cells can affect ulcer healing through various pathophysiological processes, such as stimulating tissue repair, increasing ECM synthesis, and promoting angiogenesis in ischemic tissues[87]. Soluble factors and extracellular vesicles secreted by stem cells are active factors in diabetic wound healing. Extracellular vesicles from mesenchymal stem cells (MSCs) are considered an alternative treatment for immune disorders, including diabetes. Emerging evidence suggests that MSC-derived exosomes applied to the wound surface can promote

angiogenesis and tissue repair[88]. MSC regenerative therapy is a novel tissue regeneration modality that accelerates wound healing in DFU and identifies patients at high risk of amputation[89]. Adipose-derived stem cells (ADSCs) have become an alternative to cell therapy owing to their abundancy, subcutaneous location, easy accessibility, and longer culture time than bone marrow mesenchymal cells (BMSCs) and thus exert greater proliferation and differentiation capacity. Previous studies found that ADSC transplantation can promote foot wound healing in diabetic rats whereas stem cell transplantation may have clinical application in DFU treatment[90]. EPCs are the precursor cells of vascular endothelial cells that can be directed to the site of ischemic injury and form new vessels through proliferation and differentiation to promote wound healing[91]. Cell-derived exosomes loaded with ncRNAs have a therapeutic effect on refractory DFUs.

Gondaliya *et al*[51] revealed the therapeutic potential of miR-155 inhibitor-loaded MSC-derived exosomes in diabetic wound healing and demonstrated that wrapping miRNA and antibiotics in MSC-derived exosomes improved the management of chronic, non-healing diabetic wounds. Studies found that miR-129 may promote diabetic wound healing by balancing ECM synthesis and degradation through the inhibition of Sp1-mediated MMP-9 expression[26]. A recent study also showed that miR-129 loaded in MSC-derived extracellular vesicles promoted wound healing *via* the downregulation of tumor necrosis factor receptor-associated factor 6[92]. Evidently, miR-129 is an important regulator of proliferative and regenerative phases of wound healing and may be a biologically active molecule in MSC for DFU treatment. Xu *et al*[93] showed that miR-221-3p in EPC-derived exosomes accelerated skin wound healing in normal and diabetic mouse models. The latest study further demonstrated the mechanism of miR-221-3p in diabetic wound treatment[94]. MiR-221-3p overexpression may inhibit the anti-angiogenic function of its direct targeted homeodomain-interacting protein kinase 2 (HIPK2) and promote endothelial cell proliferation[94].

Li *et al*[95] showed that the MSC-derived exosomal lncRNA, lncRNA H19, causes fibroblast inflammation and apoptosis by disrupting miR-152-3p-mediated PTEN

inhibition, leading to stimulated wound-healing process in DFU. MSCs have demonstrated a therapeutic effect in DFU by generating pro-angiogenesis factors, such as VEGF. Recent research shows that genetically modified MSCs have been used in therapy, and the depletion of miR-205-5p in human MSCs promotes VEGF-mediated therapeutic effects in DFU[96,97]. LncRNA MALAT1 is a ceRNA for miR205-5p but has a low expression in human MSCs. Ectopic MALAT1 expression in human MSCs considerably decreased miR-205-5p levels, resulting in the upregulation of VEGF production and improved *in vitro* endothelial cell tube formation. In a diabetic foot model of immunodeficient NOD/SCID mice, the transplantation of human miR-205p-depleted MSCs resulted in better therapeutic effects on DF recovery than control MSCs. Moreover, MALAT1-expressing MSCs showed even better therapeutic effects on DF recovery than miR-205-5p-depleted MSCs. This difference in DF recovery was associated with the levels of on-site vascularization. Overall, MALAT1 functions as a sponge RNA for miR-205-5p to increase the therapeutic effects of MSCs on diabetic foot[97]. As mentioned above, miR-205-5p is an anti-angiogenic factor that inhibits VEGFA expression at the post-transcriptional level in MSCs, and the inhibition of its expression leads to angiogenesis and considerably improves the therapeutic effect of MSCs on diabetic wounds[97,98]. BMSC-derived exosome can encapsulate lncRNA Kruppel-like factor 3 antisense RNA 1 (KLF3-AS1); adequately promote vascular endothelial cell proliferation, migration, and tube formation; and inhibit high glucose-induced apoptosis[99]. Diabetic wound healing by lncRNA KLF3-AS1 encapsulated by MSC-derived exosomes was achieved by downregulating miR-383 and upregulating its target, VEGFA[99].

High-throughput sequencing revealed an abnormally reduced expression of mmu_circ_0000250 in diabetic mice[100]. Exosomes from mmu_circ_0000250-modified ADSCs promote wound healing in diabetic mice through the induction of miR-128-3p/SIRT1-mediated autophagy[100]. In Shi *et al*[100]'s study, the exosomes of ADSCs exerted therapeutic effects by restoring vascular endothelial cell function under high-glucose conditions. Circ-0000250 expression may increase the effectiveness of exosome

therapy. Circ_ARHGAP12 is a cyclic molecule that inhibits high glucose-induced cell apoptosis by enhancing cellular autophagy[101]. Circ_ARHGAP12 was able to directly interact with miR-301b-3p and subsequently stimulate miRNAs to regulate the expression of ATG16L1 and ULK2, the target genes of miR-301b-3p, as well as downstream signaling pathways[101]. These findings propose a prospective therapeutic strategy of targeting circ_ARHGAP12 in MSCs to promote diabetic wound healing. Recent studies have found that circRNAs HIPK three (circHIPK3)-rich exosomes derived from human umbilical cord-derived MSCs have promising therapeutic effects in DFU. Exosomal circHIPK3 significantly promotes revascularization and wound healing by sponging to miR-20b-5p and upregulating the Nrf2/VEGFA axis[102]. Some ncRNAs for the cell therapy of DFU are shown in Table 4. NcRNAs and vector exosomes are effector molecules with great potential among the cellular therapeutic approaches for DFU and are expected to be of clinical use in the near future.

CONCLUSION

This study summarized the role and intrinsic mechanisms of ncRNAs in diabetic wound healing and provided more potential targets for future studies on wound healing in patients with diabetes. NcRNAs are regulatory molecules that modify many physiological processes and aspects of human diseases. The inflammation, proliferation, and regeneration phases of diabetic wound healing overlap, and ncRNAs are biologically active during all three phases. NcRNAs have a crucial role in the pathogenesis and impairment of wound healing in patients with diabetes. NcRNAs activate certain signaling pathways by downregulating or upregulating certain genes. Some of these molecules may provide valuable information in the clinical setting and serve as diagnostic or screening tools to predict high-risk DFU and provide basis for early prevention. These findings suggest that cell therapy using ncRNAs for DFU has great potential in the field of regenerative medicine.

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