

## Non-Coding RNAs: New Players in Skin Wound Healing

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**Significance:** Wound healing is a basic physiological process that is utilized to keep the integrity of the skin. Impaired wound repair, such as chronic wounds and pathological scars, presents a major health and economic burden worldwide. To date, efficient targeted treatment for these wound disorders is still lacking, which is largely due to our limited understanding of the biological mechanisms underlying these diseases. Research driven around discovering new therapies for these complications is, therefore, an urgent need.

**Recent Advances:** The vast majority of the human genome is transcribed to RNAs that lack protein-coding capacity. Intensive research in the recent decade has revealed that these non-coding RNAs (ncRNAs) function as important regulators of cellular physiology and pathology, which makes them promising therapeutic and diagnostic entities.

**Critical Issues:** A class of short ncRNAs, microRNAs, has been found to be indispensable for all the phases of skin wound healing and plays important roles in the pathogenesis of wound complications. The role of long ncRNAs (lncRNA) in skin wound healing remains largely unexplored. Recent studies revealed the essential role of lncRNAs in epidermal differentiation and stress response, indicating their potential importance for skin wound healing, which warrants future research.

**Future Directions:** An investigation of ncRNAs will add new layers of complexity to our understanding of normal skin wound healing as well as to the pathogenesis of wound disorders. Development of ncRNA-based biomarkers and treatments is an interesting and important avenue for future research on wound healing.

**Keywords:** wound healing, chronic wound, pathological scar, non-coding RNA, microRNA



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### SCOPE AND SIGNIFICANCE

IMPAIRED WOUND REPAIR, such as chronic wounds and pathological scars, is a major health and economic burden and efficient targeted treatment for these diseases is lacking, which is largely due to our limited understanding of their biological mechanisms. Non-coding RNAs

(ncRNAs) are recently identified gene regulators that are important for cellular physiology and pathology, which represent promising candidates for the development of new therapeutic and diagnostic approaches. In this review, we primarily focus on short ncRNAs, *i.e.*, microRNAs (miRNAs), and long ncRNAs (lncRNAs), and

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provide an overview about their roles in skin wound healing.

### TRANSLATIONAL RELEVANCE

Due to their specific expression, both miRNAs and lncRNAs hold great promises to serve as a novel class of biomarkers for diagnosis, prognosis, and monitoring of treatment effects. Development of ncRNA-based biomarkers would be an important avenue for future research on wound healing. Moreover, the modulation of miRNAs may be a more effective strategy than traditional drugs targeting single proteins, since a single miRNA has the capacity to regulate an entire functional network. Therefore, investigating the role of miRNAs in wound repair may lead to a novel therapeutic approach for those wound complications that are difficult to treat to date.

### CLINICAL RELEVANCE

Treatment of patients with complications in wound healing remains a major challenge. Understanding the molecular pathogenesis of chronic wounds and pathological scars will lead to development of more effective treatments, improving the life quality of patients and reducing the costs of wound care. An investigation of the role of ncRNAs represents an emerging concept, and it constitutes a promising area for pharmaceutical intervention. Moreover, ncRNAs are promising candidates for biomarkers to assess wounds to aid in timing of wound closure and to guide therapy.

### BACKGROUND

#### Skin wound healing

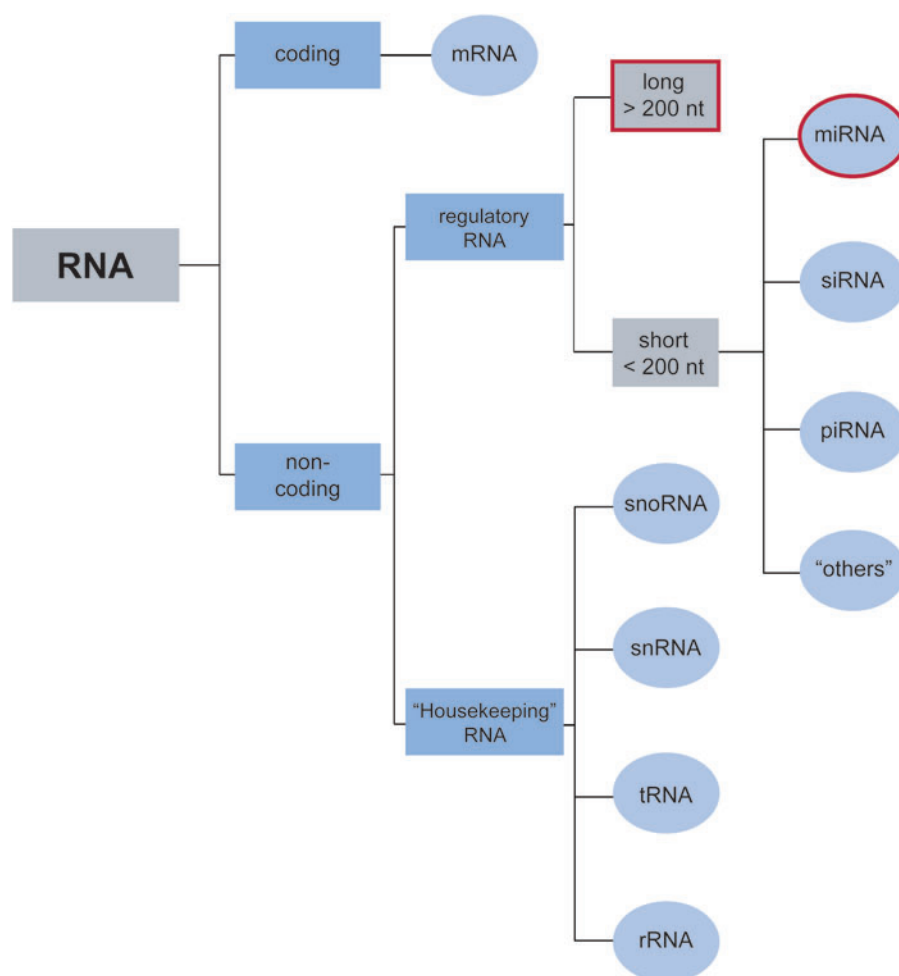
Wound healing is an essential physiological process that is utilized to keep the integrity of the skin. It is a complex and dynamic process, requiring a well-orchestrated cooperation of different cell types. Wound healing is often characterized as four sequential but overlapping phases: hemostasis (0–several hours after injury), inflammation (1–3 days), proliferation (4–21 days), and remodeling (21 days–1 year).<sup>1</sup> Various mechanical and pathological factors, *e.g.*, pressure, arterial or venous insufficiency, systemic inflammatory diseases, or diabetes mellitus, can impair the normal delicate healing response, resulting in chronic non-healing wounds, which present a major health and economic burden worldwide.<sup>2</sup> For instance, in Europe and Scandinavia, the associated costs for treating chronic wounds account for 2–4% of the total healthcare expenses.<sup>3</sup> This burden is continuously growing, resulting from increasing healthcare costs, population aging, and escalating prevalence

of diabetes.<sup>2</sup> Chronic wounds cause pain, disability, depression, and social isolation, severely affecting the life quality of patients.<sup>4</sup> Moreover, an increased risk for mortality has been shown in patients with chronic wounds.<sup>5,6</sup> The increased age of patients and the complex nature of wound environments make chronic wounds difficult to treat, and a high rate of recurrence has been observed.<sup>2</sup> Another burden of skin wound healing is excessive scarring, such as hypertrophic scars (HTS) and keloids, which can occur after burns, surgery, trauma, or spontaneously in predisposed patients, leading to profound functional and aesthetic consequences.<sup>2</sup> To date, there is still a lack of efficient targeted treatment approaches for these wound complications, which is largely due to our limited understanding of the biological mechanisms underlying these diseases.<sup>2,7</sup>

#### Non-coding RNAs

For decades, the focus of research has been centered on protein-coding genes, even though they constitute less than 2% of the human genome. However, in 2012, the ENCODE project stated that around 80% of the genome is transcribed.<sup>8</sup> Therefore, the majority of the transcriptional output of the human genome is constituted by the RNAs that lack protein-coding capacity (Fig. 1).<sup>9,10</sup> Among the ncRNAs, only a few classes have been characterized for their functional roles. For instance, transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs) are indispensable for translation of messenger RNAs (mRNAs) into proteins.<sup>11</sup> Small nucleolar RNAs (snoRNAs) are responsible for the modifications of rRNAs and tRNAs.<sup>12</sup> Small nuclear RNAs (snRNAs) play an important role in the process of RNA splicing.<sup>13</sup> Besides these housekeeping ncRNAs, most of the other ncRNAs have been considered “side-products” of gene transcription and without any functional importance. This view was changed with the discovery of miRNAs in the 1990s.<sup>14</sup> Intensive research in the past two decades has revealed that many ncRNAs actually function as important regulators of cellular physiology and pathology, which makes them promising therapeutic and diagnostic entities. In this review, we primarily focus on short ncRNAs, *i.e.*, miRNAs, and lncRNAs (Table 1), and provide an overview about their roles in skin wound healing.

**MicroRNAs.** miRNAs are short ncRNAs with an average length of 22 nucleotides. Their primary precursors (pri-miRNAs) are mainly transcribed by RNA Polymerase II.<sup>15</sup> The pri-miRNAs are cleaved by the nuclear RNase III Drosha to form a shorter RNA with a hairpin structure, *i.e.*, pre-miRNAs,



**Figure 1.** Classification of RNAs. mRNA, messenger RNA; miRNA, microRNA; piRNA, piwi-interacting RNA; rRNA, ribosomal RNA; siRNA, short-interfering RNA; snRNA, small nuclear RNA; snoRNA, small nucleolar RNA; tRNA, transfer RNA. To see this illustration in color, the reader is referred to the web version of this article at [www.liebertpub.com/wound](http://www.liebertpub.com/wound)

and then transported into the cytoplasm.<sup>15</sup> After subsequent cleavage by the cytoplasmic RNase III DICER, the mature miRNAs incorporate into the RNA-induced silencing complex and bind to the 3' untranslated region (UTR) of the target mRNA,

which results in translational repression or degradation of the target mRNA.<sup>15</sup> It has been proposed that the majority of protein-coding genes in humans are regulated by miRNAs.<sup>16</sup> Recent clinical trials have demonstrated that the modulation of

**Table 1.** Comparison of miRNAs and lncRNAs

	<i>microRNA</i>	<i>Long Non-Coding RNA</i>
Coding potential	Non-protein coding, regulatory functions	
Functions	Important roles in both physiological and pathological conditions	
Length	~ 22 nt	>200 nt
Conservation	Highly conserved between species	Poorly conserved between species
Expression pattern	Not specific	Often highly tissue/cell type specific
Number in human	2,588	~ 60,000
Biogenesis	Majority transcribed by RNA Pol II as primary transcripts (pri-miRNAs) Drosha- and Dicer-dependent cleavage Mostly intronic and intergenic	Majority transcribed by RNA Pol II orientated sense, antisense, bidirectional, intronic, or intergenic to protein coding genes
Action modes	Post-transcriptional gene silencing	Regulation of gene transcription Post-transcriptional regulation Epigenetic regulation Regulation of chromatin structure Other mechanisms of action

miRNA expression by the administration of specific miRNA mimics or inhibitors has beneficial effects on several diseases.<sup>17</sup> Importantly, the modulation of miRNAs may be a more effective strategy than traditional drugs targeting single proteins, since a single miRNA may regulate multiple targets within a functional network. Here, we focus on the recent research progress on the roles of miRNAs in skin wound healing, the knowledge of which is a prerequisite for the development of an miRNA-based treatment to improve wound repair.

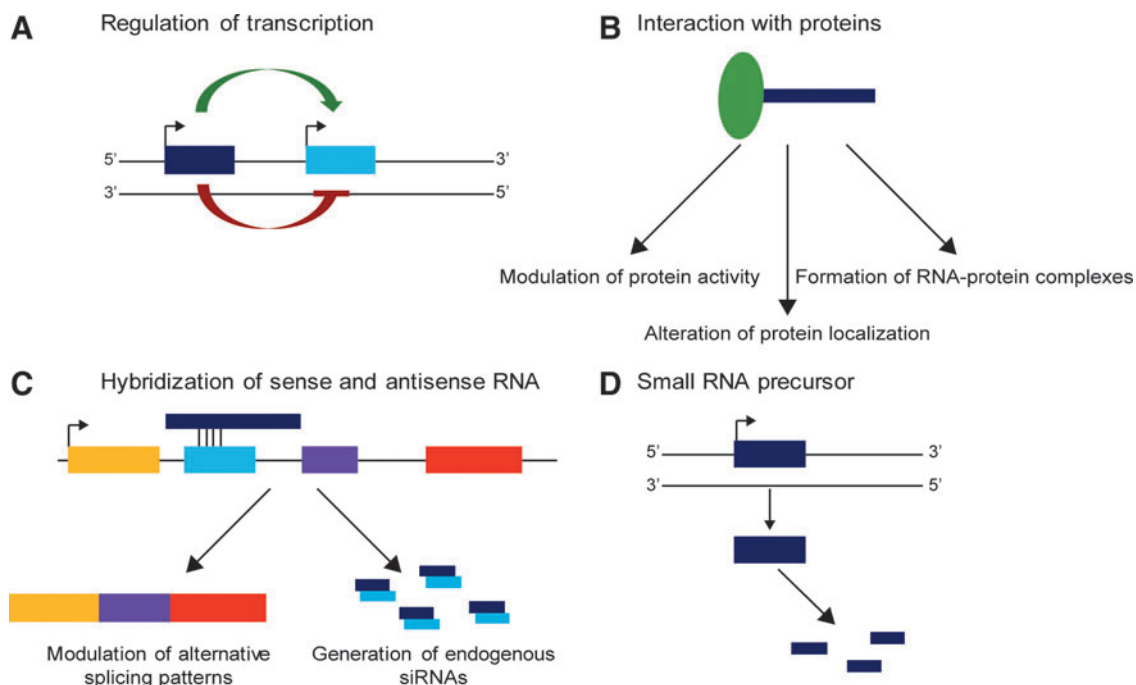
**Long ncRNAs.** lncRNAs are defined as the ncRNAs that are more than 200 nucleotides long and that represent a large and diverse class of ncRNA molecules.<sup>10</sup> Although 60,000 lncRNAs have been discovered in humans, only a small portion has been characterized in detail.<sup>18</sup> Some of them are transcribed as natural antisense transcripts to coding genes, located between genes or within introns. Some of them are derived from pseudogenes.<sup>19</sup> According to their localization and direction of transcription in relation to protein coding genes, lncRNAs are categorized into different sub-groups, *i.e.*, antisense, intergenic, overlapping, intronic, bidirectional, and processed.<sup>20</sup> In general, compared with mRNAs, lncRNAs are less

abundant in the cell and are expressed in a more tissue- and cell-type specific fashion.<sup>21</sup> lncRNAs can inhibit or activate gene expression through a variety of mechanisms (Fig. 2). For instance, they can act in transcriptional regulation or in chromatin modification both in *cis* and in *trans*; they can serve as precursors for smaller regulatory RNAs, *e.g.*, miRNAs or piRNAs; they can bind to complementary RNA and affect RNA processing, turnover, or localization; and they can interact with proteins, forming riboprotein complexes and affecting protein function and localization (Fig. 2).<sup>22</sup> The important regulatory roles of lncRNAs have been recently revealed in the skin, such as in epidermal development, keratinocyte differentiation, and melanocyte functions.<sup>23</sup> However, their function in skin wound healing remains largely unexplored. A comparison between lncRNAs and miRNAs can be found in Table 1.

## DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

### miRNAs in skin wound healing

Extensive studies over the past two decades have provided important insights into the function of miRNAs in a wide range of physiological and pathological conditions. The essential role of



**Figure 2.** Overview of some action modes of lncRNAs. **(A)** lncRNAs can regulate downstream gene transcription by inhibiting RNA polymerase II recruitment or by inducing chromatin remodeling and histone modifications. **(B)** lncRNAs can bind to protein partners to modulate protein activity, alter protein localization in the cell, or serve as structural components for larger RNA-protein complexes. **(C)** By hybridizing to the complementary transcript, antisense lncRNA can modulate alternative splicing patterns or allow Dicer to generate endogenous siRNAs. **(D)** lncRNAs can be further processed to generate small RNAs such as miRNAs or piRNAs. To see this illustration in color, the reader is referred to the web version of this article at [www.liebertpub.com/wound](http://www.liebertpub.com/wound)

miRNAs in skin wound healing has been recently revealed. Ghatak *et al.* showed that the expression of Dicer, an enzyme essential for miRNA biogenesis, was increased during wound healing; depletion of Dicer in keratinocytes in mice before wounding impaired wound closure.<sup>24</sup> In this review, we summarized the function of individual miRNAs in the various phases of skin wound healing (Table 2).

**Hemostasis and inflammation.** When skin gets injured, clotting factors are released immediately and activate the extrinsic clotting cascade.<sup>1</sup> The thrombocytes are activated and aggregate, which leads to formation of a blood clot containing fibrin, vitronectin, fibronectin, and thrombospondin.<sup>25</sup> This provisional wound matrix provides a scaffold for the migration of fibroblasts, keratinocytes, and leukocytes.<sup>1</sup> The activated platelets release large amounts of cytokines and growth factors that are critical for wound repair, such as epidermal growth factor (EGF), transforming growth factor (TGF), and the platelet-derived growth factor (PDGF). Degranulation of platelets also activates the complement cascade.<sup>26</sup> In response to chemokines, complements, and invading bacteria, neutrophils

are recruited from the circulation to the wound site, which perform phagocytosis and are important for cleaning the pathogens and cell debris from the wound.<sup>27</sup> Approximately 3 days after injury, a large amount of monocytes enter the wound site, are activated by local signals, and differentiate into macrophages with various functional phenotypes.<sup>28</sup> On exposure to pro-inflammatory cytokines, interferons (IFNs), microbes, or stressed cells, macrophages with a pro-inflammatory phenotype (M1 subset) predominate the early phase of wound repair; perform phagocytosis of microbes; scavenge cellular debris; and produce pro-inflammatory mediators.<sup>29</sup> Later during the healing process, interleukin (IL)-4, IL-10, glucocorticoids, prostaglandins, and modulators of glucose and lipid metabolism induce macrophages to switch to a reparative phenotype (M2 subset), which secretes anti-inflammatory mediators and growth factors, promoting fibroblast proliferation, angiogenesis, and extracellular matrix (ECM) synthesis.<sup>30</sup> Moreover, macrophages play a central role in removing neutrophils from the wounds by phagocytosis, which, in turn, induces the M1-M2 phenotype switch of macrophages.<sup>31</sup> The transition from M1 to

**Table 2.** *MicroRNAs in normal skin wound healing*

	<i>miRNA</i>	<i>Function</i>	<i>Target</i>	<i>References</i>
Inflammation	miR-21	Inhibits LPS-induced inflammatory response and increases IL-10 production in macrophages	PTEN, GSK3B, PDCD4	48
	miR-146a	Suppresses excessive inflammatory response in keratinocytes and macrophages	TRAF6, IRAK1, IRAK2, CCL5, IL-8	23,34,37,39
	miR-155	Regulates development and functions of immune cells	BCL6, RHOA, SHIP1	38,41,42
	miR-132	Decreases chemokine production by keratinocytes	HBEGF	38
		Restricts overproduction of pro-inflammatory cytokines by monocytes and macrophages; induces M2 polarization in macrophages	IRAK4, ACHE	33,43,44
		Suppresses the IL-12 signal in natural killer cells	STAT4, IFNG	46
Proliferation		Increases anti-inflammatory transmitter acetylcholine level	ACHE	47
	miR-21	Promotes migration of keratinocytes and fibroblasts; overexpression of miR-21 inhibits re-epithelialization and granulation tissue formation	TIMP3, TIAM1 LEPR	57–60
	miR-132	Promotes keratinocyte growth and angiogenesis	HBEGF, RASA1	38,71
	miR-31	Promotes proliferation and migration of keratinocytes	EMP1	61
	miR-198	Suppresses keratinocyte migration and proliferation	DIAPH1, PLAU, LAMC2, CCND2	62,63
	miR-99 family	Suppresses keratinocyte migration and proliferation	IGF1R, AKT1, mTOR	38,64
	miR-210	Suppresses keratinocyte proliferation, promotes angiogenesis	E2F3, EFNA3	38,65–67
	miR-199a-5p	Inhibits angiogenesis	ETS1	68
	miR-130a	Inhibits re-epithelialization and granulation tissue formation, promotes angiogenesis	LEPR, MEOX2, HOXA5	60,72
	miR-200b	Inhibits angiogenesis	ETS1, GATA2, VEGFR2	69,70
Remodelling	miR-1908	Increases proliferation and production of TGF- $\beta$ 1, IL-1 $\alpha$ , TNF- $\alpha$ , and collagen I by scar-derived fibroblasts	SKI	78
	miR-29b	Improves ECM remodeling	COL3A1, COL4A1, COL4A2, COL5A1, COL1, COL2, FN	79–82

ACHE, acetylcholinesterase; AKT1, V-Akt murine thymoma viral oncogene homolog 1; BCL6, B cell CLL/lymphoma 6; CCL5, chemokine (C-C motif) ligand 5; CCND2, cyclin D2; COL, collagen; DIAPH1, diaphanous-related formin 1; EMP1, epithelial membrane protein 1; E2F3, E2F transcription factor 3; ETS1, erythroblastosis virus 26 oncogene homolog 1; ECM, extracellular matrix; EFNA3, ephrin-A3; FN, fibronectin; GSK3B, glycogen synthase kinase 3B; GATA2, globin transcription factor binding protein 2; HBEGF, heparin-binding EGF-like growth factor; IL, interleukin; IRAK, interleukin 1 receptor-associated kinases; IFNG, interferon gamma; IGF1R, insulin-like growth factor 1 receptor; LPS, lipopolysaccharide; LEPR, leptin receptor; LAMC2, laminin subunit gamma 2; mTOR, mechanistic target of rapamycin; PTEN, phosphatase and tensin homolog; PDCD4, programmed cell death protein 4; PLAU, plasminogen activator urokinase; RHOA, Ras homolog family member A; RASA1, Ras P21 protein activator 1; SHIP1, inositol polyphosphate-5-phosphatase D; STAT4, signal transducer and activator of transcription 4; TRAF6, TNF receptor-associated factor 6; TIMP3, TIMP Metalloproteinase Inhibitor 3; TIAM1, T cell lymphoma invasion and metastasis 1; VEGFR2, vascular endothelial growth factor receptor 2.

M2 macrophages is an essential step in wound healing, and impairment of the transition has been implicated in the pathogenesis of chronic wounds.<sup>32</sup> Interestingly, miRNAs have been involved in regulating the polarization of macrophages. For instance, miR-9, miR-127, miR-155, and miR-125b promote M1 polarization; whereas miR-124, miR-223, miR-34a, let-7c, miR-132, miR-146a, and miR-125a-5p induce M2 polarization.<sup>33</sup>

At the early stage of wound healing, several miRNAs have been revealed to play critical roles. miR-146a, miR-155, miR-125b, and miR-132 were the first miRNAs linked to inflammatory response, which expression was induced in a monocytic cell line treated with lipopolysaccharide (LPS), a ligand to Toll-like receptor 4 (TLR4).<sup>34,35</sup> The increased expression of miR-146a was also observed in epidermal keratinocytes stimulated with the ligands to TLR2, TLR3, or TLR5.<sup>36</sup> miR-146a was found to negatively regulate inflammatory response in monocytes, macrophages, and keratinocytes by targeting the IL-1 receptor-associated kinases 1 (IRAK1), IRAK2, and tumor necrosis factor receptor-associated factor 6 (TRAF6), several key factors within the NF- $\kappa$ B signaling pathway.<sup>23,34,37</sup> These evidences suggest that miR-146a may function as a brake of inflammatory response and facilitate inflammation resolution. We have found that at the inflammatory phase of human skin wound healing, miR-146a was downregulated compared with the intact skin, reflecting the need of an efficient immune response at this stage of wound repair.<sup>38</sup> Interestingly, decreased miR-146a expression was observed in the wounds of a diabetic mouse model, which correlates with the enhanced expression of its targets, *i.e.*, IRAK1, TRAF6, and increased NF- $\kappa$ B signaling in the same model.<sup>39</sup>

miR-155 is a multifunctional miRNA that is important for the development and functioning of immune cells.<sup>40</sup> It has been shown that miR-155 is upregulated at the inflammatory phase in skin wounds of both humans and mice.<sup>38,41</sup> Treatment of the wounds in mice with miR-155-specific inhibitors reduced the recruitment of inflammatory cells into the wound site and improved the architecture of the regenerated tissues.<sup>42</sup> In line with this, miR-155 mutant mice exhibited quicker wound closure accompanied by an increased type-1 collagen deposition, in comparison to wild-type mice.<sup>41</sup>

The anti-inflammatory role of miR-132 has been revealed in several cell types that are critical for skin wound healing. For example, in monocytes and macrophages, miR-132 is induced by TLR ligands and restricts the overproduction of pro-inflammatory cytokines.<sup>43,44</sup> Moreover, miR-132

also induces M2 polarization in macrophages that are involved in immunosuppression and tissue repair.<sup>33</sup> In neutrophils, the level of miR-132 is upregulated after extravasation and migration into the skin, indicating a potential functional role.<sup>45</sup> In natural killer cells, IL-12 treatment upregulates the expression of miR-132, which, in turn, suppresses the IL-12 signal, such as by decreasing the expression of the signal transducer and activator of transcription 4 (STAT4) and IFN $\gamma$ .<sup>46</sup> In addition, Shaked *et al.* found that inflammation induced the expression of miR-132 in leukocytes, which increased the level of anti-inflammatory transmitter acetylcholine by targeting acetylcholinesterase.<sup>47</sup> Our recent study showed that miR-132 decreased the production of chemokines and the capability of keratinocytes to attract leukocytes by targeting heparin-binding EGF-like growth factor.<sup>38</sup> In line with the anti-inflammatory functions of miR-132, we found that its expression was upregulated during the transition from the inflammatory to the proliferative phases of skin wound healing.<sup>38</sup>

miR-21 has been shown to be important for resolving inflammation.<sup>48,49</sup> Its expression is induced in macrophages by resolving D1, an endogenous lipid mediator produced during inflammation resolution.<sup>49</sup> Also, the level of miR-21 is increased in macrophages after engulfment of apoptotic neutrophils, which is a key process to shift inflammation toward tissue repair.<sup>48</sup> In macrophages, miR-21 inhibits the LPS-induced inflammatory response by silencing its targets, phosphatase and tensin homolog (PTEN) and glycogen synthase kinase (GSK) 3 $\beta$ . Moreover, by targeting programmed cell death protein 4 (PDCD4), miR-21 promotes the activity of c-Jun-AP-1, which leads to increased production of IL-10, an anti-inflammatory cytokine, by macrophages.<sup>48</sup>

Several miRNAs have been involved in regulating polarization and the inflammatory response of macrophages, indicating that they may play a role in wound healing. For instance, miR-125b has been shown to be downregulated in LPS-treated macrophages.<sup>35,50,51</sup> Overexpression of miR-125b enhances responses of macrophages to the M1 inducer IFN $\gamma$ , thus potentiating the role of macrophages in inducing immune responses.<sup>52</sup> miR-223 induces M2 polarization in macrophages.<sup>53</sup> Its overexpression in macrophages inhibits LPS-stimulated release of IL-6 and IL-1 $\beta$  by targeting STAT3.<sup>53</sup> Interestingly, miR-223 expression has been found to be upregulated in human wounds at the inflammatory phase compared with the intact skin.<sup>38</sup>

**Proliferation.** The proliferative phase typically occurs 1–3 weeks after injury and is dedicated to

covering the wound surface (re-epithelialization), restoring the vascular network (angiogenesis/neovascularization), and forming granulation tissue.<sup>25</sup> Re-epithelialization starts with local keratinocyte migration across the wound bed, which happens in a few hours to 1 day after injury.<sup>54,55</sup> Approximately 2–3 days later, basal layer keratinocytes and epithelial stem cells from nearby hair follicles and sweat glands start to proliferate to generate more keratinocytes for wound repair. Re-epithelialization is stimulated by various growth factors and cytokines, such as EGF, keratinocyte growth factor, nerve growth factor, and insulin growth factor-1 (IGF-1).<sup>56</sup> To supply the new forming tissue with nutrients, it is essential to restore the vascular network. Angiogenesis is initiated by different growth factors, *e.g.*, PDGF, vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2), and the serine protease thrombin.<sup>1</sup> During the proliferative phase, the provisional wound matrix formed earlier is replaced by the granulation tissue, which contains a high density of fibroblasts, granulocytes, macrophages, capillaries, and collagen bundles, forming a scaffold for cell adhesion, migration, and growth in the wound.<sup>1</sup>

miR-21 has been found to play an important role not only in the inflammatory phase but also in the proliferative phase. On wounding, the expression of miR-21 was upregulated in wound-edge keratinocytes and dermal mesenchymal cells.<sup>57,58</sup> miR-21 has been shown to promote migration of both keratinocytes and fibroblasts.<sup>58,59</sup> Inhibition of miR-21 in the wound delays re-epithelialization and impairs wound contraction and collagen deposition.<sup>57,58</sup> Conversely, Pastar *et al.* showed that local overexpression of miR-21 delayed re-epithelialization in an acute human skin *ex vivo* wound model, as well as inhibited re-epithelialization and granulation tissue formation in a rat wound model.<sup>60</sup> These seemingly contradictory results indicate the importance of tight control of miR-21 level during wound healing.

miR-132 is another miRNA that is critical for both inflammatory and proliferative phases. We have recently found that miR-132 promoted keratinocyte growth by increasing the activity of the STAT3 and the mitogen-activated protein kinase (MAPK) signaling pathways.<sup>38</sup> Moreover, using the mouse *in vivo* and human *ex vivo* wound model, we showed that blockage of miR-132 led to severe inflammation, decreased keratinocyte growth, and delayed wound closure.<sup>38</sup>

miR-31 was found to be highly upregulated in human wound-edge keratinocytes in the proliferative phase compared with the inflammatory phase or

the intact skin.<sup>61</sup> In line with this, miR-31 promotes proliferation and migration of keratinocytes by targeting the epithelial membrane protein 1 (EMP-1), contributing to wound re-epithelialization.<sup>61</sup>

miRNA-198 is a miRNA, inhibiting keratinocyte migration and proliferation.<sup>62,63</sup> Interestingly, miR-198 is derived from the 3'-UTR of follistatin-like 1 (FSTL1) mRNA, which codes a protein promoting keratinocyte migration.<sup>62</sup> During wound healing, TGF- $\beta$  decreases the expression of KH-type splicing regulatory protein (KSRP), which is essential for miR-198 processing. Consequently, the expression of miR-198 is turned off, whereas the expression of FSTL1 is switched on, allowing keratinocyte migration.<sup>62</sup> Impairment of this switch, as shown in chronic diabetic ulcers, results in deficiency in keratinocyte migration, re-epithelialization, and wound closure.<sup>62</sup>

Several members of the miR-99 family, including miR-99a, miR-99b, and miR-100, have been found to be downregulated at the inflammatory phase in both human and mouse wound models.<sup>38,64</sup> Downregulation of the miR-99 family members results in increased expression of their targets, *i.e.*, IGF-1 receptor (IGF1R), mechanistic target of rapamycin, and V-Akt murine thymoma viral oncogene homolog 1 (AKT1), which, in turn, increase keratinocyte proliferation and migration, facilitating wound closure.<sup>64</sup>

A high level of hypoxia in ischemic chronic wounds induces the expression of miR-210, which inhibits keratinocyte proliferation and wound re-epithelialization by targeting cell-cycle regulatory protein E2F transcription factor 3 (E2F3).<sup>65</sup> Moreover, miR-210 has been shown to repress mitochondrial metabolism and decrease oxygen cost of survival.<sup>66</sup> In endothelial cells, hypoxia-induced miR-210 promotes angiogenesis by targeting Ephrin-A3 (EFNA3).<sup>66</sup> In normal human skin wounds, miR-210 has been found to be downregulated at the inflammatory phase compared with the intact skin.<sup>38</sup> Recently, Ghatak *et al.* delivered the miR-210 inhibitor encapsulated in lipid nanoparticles into murine ischemic skin wounds, which effectively accelerated wound closure, demonstrating miR-210 as a promising therapeutic target to improve wound healing.<sup>67</sup>

Several miRNAs have been identified as important regulators of angiogenesis during skin wound healing. For instance, miR-199a-5p is downregulated in dermis and endothelial tissue during skin wound healing.<sup>68</sup> Chan *et al.* found that miR-199a-5p negatively regulated angiogenic responses of human dermal microvascular endothelial cells by targeting a crucial angiogenesis-related transcription factor,

*i.e.*, avian erythroblastosis virus 26 oncogene homolog 1 (ETS1), and its downstream mediator, matrix metalloproteinase 1.<sup>68</sup> Accordingly, mice with homozygous deletions in the ETS1 gene exhibit impaired angiogenesis, insufficient granulation tissue formation, and compromised wound closure.<sup>68</sup> Similarly, miR-200b, which is downregulated by hypoxia in endothelial cells, also suppresses angiogenesis by targeting ETS1, globin transcription factor binding protein 2 (GATA2), and VEGF receptor 2 (VEGFR2) expression.<sup>69,70</sup> On the other hand, both VEGFA and FGF2 enhance the expression of miR-130a and miR-132 in endothelial cells.<sup>71,72</sup> miR-130a promotes angiogenesis by targeting mesenchyme homeobox2 (MEOX2) and homeobox A5 (HOXA5).<sup>72</sup> miR-132 increases endothelial cell proliferation and vascularization by targeting RAS p21 protein activator 1 (RASA1).<sup>71</sup>

**Remodeling.** The final stage of wound healing is the remodeling phase. Due to stimulation of mechanical tension and cytokines, such as TGF- $\beta$ , fibroblasts differentiate into myofibroblasts, which attach to collagen and induce wound contraction.<sup>73</sup> Granulation tissue stops growing, whereas cells undergo apoptosis.<sup>74</sup> In the ECM, type I collagen, which has a higher tensile strength, replaces the quickly produced type III collagen.<sup>74</sup> The wound-healing cascade ends with scar formation, and the healed skin can achieve maximally  $\sim 80\%$  of the original tensile strength.<sup>75</sup> Interestingly, it is known that human fetuses have the ability to heal without scarring until the 24th week of gestation, although the underlying mechanism remains unclear.<sup>76</sup>

miR-1908 has recently been demonstrated to target SKI, a protein that reduces scar formation in rats by decreasing collagen production and relieving inflammation.<sup>77</sup> The expression levels of miR-1908 and SKI are inversely correlated in the intact and wounded skin as well as in the scar tissues of humans.<sup>78</sup> miR-1908 increases cell proliferation and production of TGF- $\beta$ 1, IL-1 $\alpha$ , tumor necrosis factor (TNF- $\alpha$ ), and type I collagen by fibroblasts derived from human scars.<sup>78</sup> An injection of miR-1908 inhibitors into the burn-wounded scars of rats reduced the area, volume, and fibrosis of scars.<sup>78</sup>

miR-29b has been associated with TGF- $\beta$ 1-directed fibrogenesis, and it targets multiple ECM genes, such as COL3A1, COL4A1, COL4A2, and COL5A1.<sup>79–81</sup> Importantly, local delivery of miR-29b using a collagen scaffold has been shown to significantly reduce wound contraction and increase collagen type III/I ratios, improving ECM remodeling in a rat wound model.<sup>82</sup>

### miRNAs in wound complications

As discussed earlier, miRNAs are indispensable for all the steps of skin wound healing. It is not surprising that accumulating evidences demonstrate that aberrant expression of miRNAs contributes to the pathogenesis of major wound complications, such as pathological scars and chronic non-healing wounds (Table 3). The findings about the miRNA-mediated regulation, from a new angle, add to our understanding about molecular mechanisms of these diseases, which may also lead to the development of novel therapeutic approaches to improve wound healing.

**Pathological scars.** Excessive scarring leads to profound functional and aesthetic consequences and lacks effective treatment to date.<sup>2</sup> It is classified into HTS and keloids, which are different in clinical appearance, histology, and epidemiology.<sup>83</sup> In general, both scar types are characterized by an increased number of myofibroblasts and excessive ECM deposition.<sup>83</sup> TGF- $\beta$  signaling has been shown to play a central role in the pathogenesis of excessive scarring.<sup>83</sup>

Recent findings about miRNA-mediated regulation in excessive scarring significantly enhance our understanding about this disease (Table 3). For instance, miR-145 has been found to be upregulated in HTS compared with healthy skin, the expression of which is induced by TGF- $\beta$ 1 in fibroblasts.<sup>84</sup> miR-145 increases the level of  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA), an important contributor to contractile force generation in myofibroblasts, by directly targeting a known inhibitor of  $\alpha$ -SMA, Kruppel-like factor 4 (KLF4).<sup>84</sup> Treatment of myofibroblasts with miR-145 inhibitors strongly reduced the expression of collagen I and TGF- $\beta$ 1, as well as decreased contractile force generation and migration.<sup>84</sup> On the contrary, miR-143-3p expression has been found to be decreased in fibroblasts derived from human HTS.<sup>85</sup> Mu *et al.* showed that miR-143-3p inhibited proliferation but promoted apoptosis of HTS fibroblasts, and it suppressed expression of collagen I, collagen III, and  $\alpha$ -SMA, thus inhibiting HTS formation.<sup>85</sup> Decorin (DCN) is a proteoglycan that reduces fibrosis and induces regeneration in many tissues; however, it is significantly downregulated in HTS.<sup>86</sup> Kwan *et al.* found that DCN was targeted by miR-181b, which is an miRNA that is increased in HTS.<sup>86</sup> Inhibition of miR-181b in HTS fibroblasts reversed TGF- $\beta$ 1-induced DCN downregulation and myofibroblast differentiation, suggesting its therapeutic potential for HTS.<sup>86</sup> In 2012, Kashiyama *et al.* identified a unique miRNA signature in keloid-derived



**Table 3.** *MicroRNAs in wound complications*

	<i>miRNA</i>	<i>Function</i>	<i>Target</i>	<i>References</i>
Hypertrophic scar	miR-145	Promotes myofibroblast differentiation	KLF4	84
	miR-143-3p	Inhibits HTS formation by regulating proliferation and apoptosis of fibroblasts	CTGF	85
	miR-181b	Decreases DCN levels and promotes fibrosis	DCN	86
	miR-21	Promotes fibroblast proliferation	SMAD7, PTEN	90,94,95
	miR-200b	Inhibits proliferation and promotes apoptosis of HTS fibroblasts	ZEB1	91,94
	miR-10a	Regulates collagen I generation	PAI1	89
	miR-181c		PLAU	
Keloid	miR-196a	Decreases type I and type III collagen levels	COL1A1, COL3A1	87
	miR-29a	Decreases collagen expression in fibroblasts	COL3A1	88
	miR-21	Increases fibroblast proliferation	PTEN	92
	miR-199a-5p	Inhibits fibroblast proliferation	DDR1, PODXL	93
Chronic wound	miR-26a	Inhibits angiogenesis, granulation tissue formation and impairs wound closure	SMAD1	101
	miR-155	Suppresses proliferation and migration of endothelial cells	SIRT1	102
	miR-200b	Inhibits angiogenesis	GATA2, VEGFR2	70
	miR-15b	Suppresses angiogenesis	BCL2, HIF1A, VEGFA	103
	miR-27b	Improves the function of impaired bone marrow-derived angiogenic cells and accelerates wound healing	TSP1, TSP2, SHC1, SEMA6A	104
	miR-191	Suppresses angiogenesis and fibroblast migration	ZO1	107
	miR-146a	Is induced in wounds infected with biofilms and leads to impaired	ZO1, ZO2	109
	miR-106b	epidermal barrier function		

CTGF, connective tissue growth factor; DCN, decorin; DDR1, discodin domain receptor tyrosine kinase-1; HTS, hypertrophic scar; HIF1A, hypoxia-inducible factor 1 alpha; KLF4, Kruppel-like factor 4; PAI1, plasminogen activator inhibitor-1; PODXL, podocalyxin-like; SMAD, SMAD family member; SIRT1, sirtuin-1; SHC1, Src homology 2 domain containing transforming protein 1; SEMA6A, semaphoring 6A; TSP, thrombospondin; VEGFA, vascular endothelial growth factor A; ZEB1, zinc finger E-box binding homeobox 1; ZO, zona occludens.

fibroblasts compared with normal fibroblasts.<sup>87</sup> Among the differentially expressed miRNAs, they focused on miR-196a, which was strongly down-regulated in keloid fibroblasts, and demonstrated that it targeted and downregulated the expression of type I and type III collagens in keloid fibroblasts.<sup>87</sup> Recently, miR-29a, another miRNA with decreased expression in keloid fibroblasts, was also shown to negatively regulate type I/III collagen expression.<sup>88</sup> Further miRNAs involved in pathological scar formation include miR-21, which promotes fibroblast proliferation in HTS formation and in keloids; miR-200b and miR-199a-5p, which inhibit fibroblast proliferation; and miR-10a and -181c, which regulate collagen I generation (Table 3).<sup>89–95</sup>

**Chronic wounds.** Chronic non-healing wounds are a major and rising health and economic burden worldwide. It is known that chronic wounds are trapped in a persistent inflammatory state and fail to progress through the normal wound-healing process.<sup>32</sup> In chronic wounds, a large amount of inflammatory cells are present at the wound site, which produce proteolytic enzymes, cytokines, and reactive oxygen species, destroying growth factors and ECM.<sup>32</sup> Keratinocytes are hyperproliferative, but they lack migration and differentiation.<sup>96</sup> Fibroblasts exhibit decreased growth and motility as well as impaired ECM deposition.<sup>96</sup> Angiogenesis is also reduced in chronic ulcers.<sup>97</sup>

Accumulating evidences have demonstrated that miRNAs play a major role in the pathogenesis of chronic wounds (Table 3). In this field, a large part of studies focuses on the chronic diabetic wound, since it is one of the most difficult wounds to heal and to treat, leading to high mortality and amputation rate.<sup>98,99</sup> A unique miRNA signature has been identified in the cutaneous wounds of a rat diabetic model compared with that in normal rats.<sup>100</sup> Bioinformatic analysis suggests that these differentially expressed miRNAs may regulate the signaling pathways that are important for wound healing, *e.g.*, MAPK, TGF- $\beta$ , and Wnt signals.<sup>100</sup> Several miRNAs have been demonstrated to be responsible for the abnormal cellular behavior in chronic wounds. For instance, miR-26a, which is upregulated in the wounds of a mouse diabetic model compared with normal mice, directly targets SMAD1 and increases expression of the cell cycle inhibitor p27.<sup>101</sup> Inhibition of miR-26a induced angiogenesis, increased granulation tissue formation, and advanced wound closure.<sup>101</sup> miR-155 was shown to suppress proliferation and migration of human endothelial cells by targeting Sirtuin-1 (Sirt-1).<sup>102</sup> In line with this, the treatment of wounds in diabetic mice with bone marrow mesenchymal stem cells inhibited miR-155 expression and accelerated wound healing.<sup>102</sup> As aforementioned, injury decreases miR-200b expression, which switches on angiogenesis.<sup>69,70</sup> In diabetic

mice, excessive TNF- $\alpha$  induces the expression of miR-200b, which inhibits angiogenesis by targeting GATA2 and VEGFR2.<sup>70</sup> In addition, miR-15b and miR-27b have been shown to play a role in angiogenesis in diabetic wounds. Increased expression of miR-15b leads to impaired angiogenesis, whereas miR-27b rescues the function of impaired bone marrow-derived angiogenic cells and accelerates wound healing.<sup>103,104</sup> Of note, the animal models of diabetes used in these studies only exhibit a delayed healing response, but they do not entirely mimic the chronic wound situation. Recently, Dhall *et al.* successfully induced non-healing chronic wounds in mice under diabetic condition by inhibiting two key antioxidant enzymes, catalase and glutathione peroxidase.<sup>105</sup> This model would be helpful in understanding the pathophysiology and in developing new diagnostic and therapeutic approaches for human chronic wounds.

Recently, miRNAs have been shown to be also present in the circulation in a stable form, functioning as messengers mediating cell communication.<sup>106</sup> Dangwal *et al.* compared the plasma miRNA profile in type 2 diabetic patients with and without chronic wounds and identified 41 miRNA to be differentially expressed. Furthermore, they showed that proinflammatory stress increased endothelial- or platelet-derived secretion of miR-191, which was taken up by dermal endothelial cells or fibroblasts. By targeting zonula occludens-1 (ZO-1), miR-191 suppresses angiogenesis and fibroblast migration, and it, therefore, delays skin repair.<sup>107</sup>

Biofilms, which are communities of aggregated bacteria embedded in a self-secreted extracellular polysaccharide matrix, are often present in chronic wounds. Biofilms protect bacteria from host defenses and antibiotic treatment, impairing wound repair.<sup>108</sup> Roy *et al.* found miR-146a and miR-106b to be induced on wound infection with biofilms in a porcine burn wound model. Increased expression of these miRNAs leads to compromised tight junction function by targeting ZO-1 and ZO-2 in keratinocytes, and therefore to impaired epidermal barrier function.<sup>109</sup>

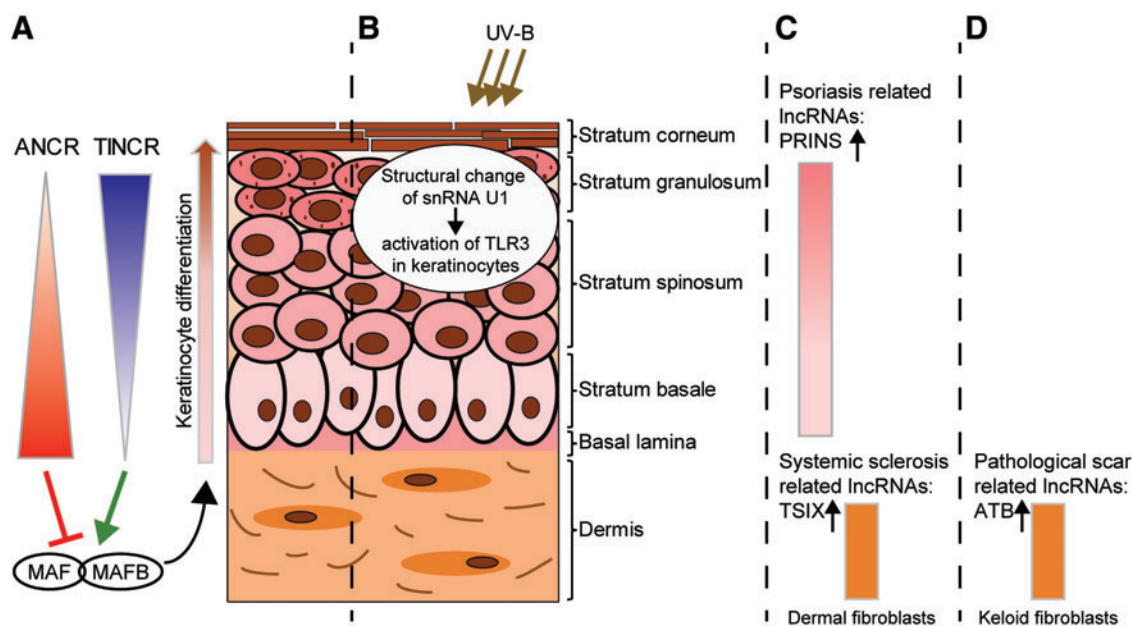
### Other types of ncRNAs in the skin

The knowledge about miRNAs involved in wound healing is constantly growing, whereas the expression and function of lncRNAs in this process remains largely unexplored. Intensive studies in recent years have revealed that many lncRNAs play important roles in various cell/tissue types under both physiological and pathological conditions.<sup>110</sup> Notably, an increasing number of lncRNAs have been linked to the biological pro-

cesses in the skin, *e.g.*, tissue differentiation-inducing ncRNA (TINCR) and anti-differentiation ncRNA (ANCR) (Fig. 3).<sup>111,112</sup> TINCR is a 3.7 kb lncRNA that is mainly present in the cytoplasm of differentiated keratinocytes.<sup>111</sup> It associates with mRNAs that are important for differentiation through a 25-nucleotide motif, while binding to the Staufen1 (STAU1) protein, which leads to increased stability of these differentiation-related mRNAs by STAU1.<sup>111</sup> Therefore, TINCR is indispensable for keratinocyte differentiation.<sup>111</sup> In contrast, ANCR has been shown to be strongly downregulated during differentiation of keratinocytes, adipocytes, and osteoblasts.<sup>112</sup> It is important to repress the epidermal differentiation program and to maintain the undifferentiated state in the epidermal progenitor compartment.<sup>112</sup> Interestingly, a recent study reveals that both ANCR and TINCR act upstream of MAF and MAFB, which are transcription factors that are both sufficient and essential for epidermal differentiation (Fig. 3).<sup>113</sup> Since keratinocyte differentiation is a key step of skin wound healing, which is impaired in chronic wounds,<sup>96</sup> we propose that these lncRNAs may also play a regulatory role during skin wound repair, which warrants future investigation.

It has been known that keratinocytes require TLR3 to respond to RNA from damaged cells due to skin injury or prolonged exposure of ultraviolet (UV) B-radiation, with the release of inflammatory cytokines, *e.g.*, TNF- $\alpha$  and IL-6, and increased expression of the genes involved in repair and maintenance of the epidermal permeability barrier.<sup>114–116</sup> Bernard *et al.* found that UV-B induced structure alterations of an ncRNA, *i.e.*, snRNA U1, which activated TLR3 in keratinocytes and contributed to inflammatory response and wound repair<sup>114</sup> (Fig. 3). It is not clear whether this TLR3 activation during wound repair is unique to snRNAs, or may involve other ncRNAs, which is an interesting question that is needed to be answered by further research.

The expression and function of lncRNAs have also been characterized in various skin diseases, such as psoriasis, which is a chronic inflammatory skin disease sharing many common properties with wound healing<sup>117</sup> (Fig. 3). Using differential display, an lncRNA, psoriasis susceptibility-related RNA gene induced by stress (PRINS), was found to be increased in the epidermis of psoriasis patients.<sup>118</sup> Later studies showed that PRINS contributes to cellular stress response and apoptosis in keratinocytes.<sup>119</sup> With the advancement of gene profiling technologies, more detailed pictures of lncRNA expression in



**Figure 3.** lncRNAs in epidermal homeostasis and skin diseases. **(A)** Schematic of human skin. ANCR is the most highly expressed in the basal layer keratinocytes, which is important to maintain the undifferentiated state in the epidermal progenitor compartment. TINCR is the most abundant in the differentiated layers and regulates the differentiation of keratinocytes. Both act upstream of MAF and MAFB, which are transcription factors that are both sufficient and essential for epidermal differentiation. **(B)** On injury with UV-B, snRNA U1 undergoes a structural change and activates TLR3 in keratinocytes. **(C)** A set of lncRNAs has been identified to be differentially expressed in psoriasis skin, compared with healthy skin. PRINS is one of the lncRNAs upregulated in psoriasis skin. TSIX regulates the stability of collagen I mRNA and is overexpressed in dermal fibroblasts from patients with systemic sclerosis. **(D)** The lncRNA ATB, which regulates TGF- $\beta$  signaling, is strongly expressed in keloid fibroblasts. ANCR, anti-differentiation ncRNA; PRINS, psoriasis susceptibility-related RNA gene induced by stress; TGF, transforming growth factor; TINCR, tissue differentiation-inducing non-coding RNA; TLR, toll-like receptor; UV, ultraviolet. To see this illustration in color, the reader is referred to the web version of this article at [www.liebertpub.com/wound](http://www.liebertpub.com/wound)

healthy and diseased skin have been generated. For example, using RNA deep sequencing, a unique lncRNA expression profile has been recently identified in the psoriasis skin compared with the healthy skin.<sup>120,121</sup> The abnormal expression of lncRNAs in psoriasis was reverted after successful treatment with adalimumab, a humanized antibody against TNF- $\alpha$ .<sup>121</sup> Interestingly, bioinformatics analysis revealed that many of these psoriasis-related lncRNAs were co-expressed with genes with immune functions, suggesting that these lncRNAs may function as immune regulators, contributing to the pathogenesis of psoriasis.<sup>120</sup> Recently, in dermal fibroblasts from patients with systemic sclerosis, an lncRNA, the reverse of X-inactive specific transcript (TSIX), was found to be overexpressed, which was induced by TGF- $\beta$  signaling<sup>122</sup> (Fig. 3). Depletion of TSIX strongly reduced the stability of collagen I mRNA, indicating that TSIX overexpression contributes to the constitutive upregulation of collagen in systemic sclerosis dermal fibroblasts.<sup>122</sup>

Although the role of lncRNAs in normal skin wound healing remains unexplored, emerging evidences have linked lncRNAs to pathological scars (Fig. 3). By microarray analysis, Liang *et al.* iden-

tified more than 2,500 lncRNAs to be differentially expressed in keloid tissue compared with the normal human skin.<sup>123</sup> In keloids, TGF- $\beta$  signaling has been demonstrated to be highly activated.<sup>124</sup> In line with this, in keloid fibroblasts a TGF- $\beta$ -induced lncRNA, lncRNA-ATB, was shown to sequester miR-200c away from its target mRNA, ZNF217, which is a transcriptional activator of TGF- $\beta$ . This leads to increased ZNF217 expression and autocrine secretion of TGF- $\beta$ .<sup>125</sup> In addition, Li *et al.* identified almost 1,900 lncRNAs and 900 mRNAs to be differentially expressed in regressive scars compared with mature scars.<sup>126</sup> Gene ontology and pathway analysis showed that many processes over-represented in regressive scars were related to immune response.<sup>126</sup>

The published research data regarding the role of lncRNAs in skin biology and diseases strongly support the potential role of lncRNAs in wound repair, although the experimental evidence is still scant. Investigating the expression and function of lncRNAs will open a new avenue for understanding the molecular mechanisms of wound healing and may identify novel therapeutic targets for wound complications.

## SUMMARY

The vast majority of the human genome consists of ncRNAs; however, the knowledge about their expression and function is meager compared with what we know about protein-coding genes. Intensive studies in the past decades have revealed that different species of ncRNAs play important roles in both physiological and pathological conditions. In this review, we summarized the recent research progress about the role of ncRNAs, especially miRNAs and lncRNAs, in skin wound repair, which adds new layers of complexity to our understanding of normal skin wound healing as well as to the pathogenesis of wound disorders, *e.g.*, chronic wounds and pathological scars. Because their expression is subjected to extremely precise regulation, which is dependent on cell/tissue type or disease,<sup>120,127</sup> both miRNAs and lncRNAs have a high potential to serve as a novel class of biomarkers for risk assessment, diagnosis, prognosis, and monitoring of treatment effects. Notably, miRNAs have been found to exist in biofluids, *e.g.*, blood, in very stable forms, and reflecting various physiological and pathological status, which increase the likelihood of the development of miRNA-based biomarkers.<sup>128</sup> To date, there are no specific and sensitive biomarkers to assess wounds to guide therapy and to aid in the timing of wound closure.<sup>129</sup> Development of ncRNA-based biomarkers would be an interesting and important avenue for wound-healing research. For instance, a clinical trial is currently ongoing to test whether miR-210 may serve as a molecular marker in chronic wounds to predict healing outcomes.<sup>130</sup>

miRNAs are powerful gene regulators that often target several genes within the same gene network. Modulation of a single miRNA may result in a strong effect due to multiple gene expression changes in the same pathway. Therefore, miRNA-based treatment may be more effective compared with traditional drugs targeting single proteins.<sup>17</sup> With the identification of miRNAs that are important for diseases and the development of methods modulating miRNA function *in vivo*, several miRNA-based treatments have entered clinical trials and exhibit very promising therapeutic effects.<sup>17</sup> To date, increasing numbers of miRNAs have been identified that are critical for skin wound repair, and it is important to evaluate their therapeutic potentials for skin wounds. If successful, this will lead to a novel therapeutic approach for those wound complications, which are difficult to treat to date. In comparison to

## TAKE-HOME MESSAGES

- The vast majority of the human genome consists of ncRNAs; however, their importance in cellular physiology and pathology has not been recognized until recent decades.
- miRNAs are short ncRNAs with a powerful gene-regulating capacity, and they have been found to be indispensable for all the phases of skin wound healing.
- Deregulated miRNA expression has been shown in wound complications, *e.g.*, chronic wounds and pathological scars. Multiple miRNAs play important roles in the pathogenesis of wound disorders, and they may serve as therapeutic targets for these diseases.
- The role of lncRNAs in skin wound healing remains largely unexplored. Recent studies revealed the essential role of lncRNAs in epidermal differentiation and stress response, indicating that they may be also key regulators during skin wound healing, which warrants future research.
- Investigation of ncRNAs adds new layers of complexity to our understanding of normal skin wound healing as well as to the pathogenesis of wound disorders, which may open up a broad new field of potential biomarkers and therapeutic targets.

miRNAs, we know even less about the role of lncRNAs in skin wound healing. Investigation of lncRNAs will increase our understanding about skin wound repair, which may open up a broad new field of potential biomarkers and therapeutic targets.

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### Abbreviations and Acronyms

ANCR = anti-differentiation ncRNA
ECM = extracellular matrix
EGF = epidermal growth factor
FGF = fibroblast growth factor
FSTL1 = follistatin-like 1
GATA2: globin transcription factor binding protein 2
HOXA5 = homeobox A5
HTS = hypertrophic scar
IFN = interferon
IGF1R = insulin-like growth factor 1 receptor
IL = interleukin
IRAK = interleukin 1 receptor-associated kinases
KSRP = KH-type splicing regulatory protein
lncRNA = long non-coding RNA
LPS = lipopolysaccharide
MAPK = mitogen-activated protein kinase
MEOX2 = mesenchyme homeobox2
miR = mature form of microRNA
miRNA = microRNA
mRNA = messenger RNA
ncRNA = non-coding RNA
PDGF = platelet-derived growth factor
PRINS = psoriasis susceptibility-related RNA gene induced by stress
PTEN = phosphatase and tensin homolog
RASA1 = Ras P21 protein activator 1
rRNA = ribosomal RNA
snRNA = small nuclear RNA
snoRNAs = small nucleolar RNAs
STAT4 = signal transducer and activator of transcription 4
TGF- $\beta$ = transforming growth factor beta
TINCR = tissue differentiation-inducing non-coding RNA
TLR = toll-like receptor
TNF = tumor necrosis factor
TRAF6 = TNF receptor-associated factor 6
TSIX = the reverse of X-inactive specific transcript
UTR = untranslated region
UV = ultraviolet
VEGF = vascular endothelial growth factor
VEGFR2 = vascular endothelial growth factor receptor 2
$\alpha$ -SMA = $\alpha$ -smooth muscle actin