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REVIEW ARTICLE

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MiR equal than others: MicroRNA enhancement for cutaneous wound healing

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Abstract

Keratinocyte migration is vital in the re-epithelialisation of the skin during wound healing. Multiple factors conspire to impair closure of chronic wounds such as diabetic foot ulcers, venous leg ulcers and pressure wounds. Despite deep mechanistic understanding of microRNA (miRNA) biogenesis and function, the translational potential of these small genetic molecules has not been exploited to promote wound repair. In this review, I focus on miRNAs whose importance for wound healing stems from their impact on epidermal keratinocyte behaviour. These include miR-21-5p, miR-31-5p, miR-132-3p, miR-19b, miR-20a, miR-184, miR-129-5p and miR-335-5p which regulate diverse aspect of keratinocyte biology such as migration, proliferation, differentiation, inflammation and wound closure. A combinatorial approach where two or more miRNA mimics targeting distinct but complementary wound healing processes is proposed as this may enhance wound repair more effectively than any single miRNA mimic alone.

KEYWORDS
epidermis, keratinocytes, microRNA, skin, wound healing

1 | INTRODUCTION

Despite significant advances in understanding the multiple factors associated with chronic wounds, there remains a significant unmet need for therapeutic interventions to promote wound healing. With the ageing population and associated rise in the incidence of diabetes, pressure ulcers, venous leg ulcers and diabetic foot ulcers, the clinical and socioeconomic challenges presented by nonhealing wounds are likely to persist, exerting enormous pressure on health services in both industrialised and developing nations (Eming et al., 2014; Nunan et al., 2014; Whittam et al., 2016). Estimates put the costs of managing wounds and associated comorbidities at £5.3 billion annually in the United Kingdom and a staggering $25 billion in the United States (Guest et al., 2015; Sen et al., 2009). Four therapies have received been approved by the Food and Drug Administration for chronic cutaneous wounds: a bioengineered human skin equivalent, two dermal substitutes, and recombinant human platelet derived growth factor, this is despite healing rates of only 30% to 56% (Hamdan et al., 2017). Furthermore, the number of diabetics worldwide is projected to approach 630 million by 2045, hence the need for fundamental and translational research to drive the development of wound healing and wound care products in support of multi-disciplinary care pathways (Uckay et al., 2015).

The roles of microRNAs (miRNAs) in health and disease have been researched intensively for almost two decades. These small genetic molecules are ~22 nucleotides long and generally influence cell fate by reducing gene expression through mechanisms that converge on degradation of mRNA transcripts, thus lowering the

protein output (Bartel, 2018). A given miRNA can regulate numerous mRNAs, and consequently miRNAs function as master regulators of the molecular status of the cell. As a result, miRNAs represent attractive potential therapeutic targets for complex diseases with multiple pathological features, such as chronic wounds.

As the skin is constantly exposed to potential injury, wound healing is a fundamental physiological process required to maintain the integrity of the skin after trauma. It consists of a series of successive overlapping phases spanning haemostasis, inflammatory, proliferative and remodelling phases (Baltzis et al., 2014; Gonzalez et al., 2016). These stages are driven co-ordinated activity of diverse cell types including keratinocytes, fibroblasts, endothelial cells and infiltrating immune cells, of which keratinocyte replication and migration during the proliferative phase drive the re-formation of the epidermis to secure wound closure (Gonzalez et al., 2016; Martin & Nunan, 2015).

Recent years have seen significant growth in our understanding of miRNA function in keratinocyte migration and as candidate targets for the development of novel therapies for wound healing (Mulholland et al., 2017). In addition, long noncoding RNAs (lncRNA), which are broadly defined as >200 nucleotides, have recently been implicated in wound repair, wound and keratinocyte migration-associated long noncoding RNA 1 (WAKMAR1) and WAKMAR2 being notable examples (Herter et al., 2019; D. Li et al., 2019). Here, I introduce mechanisms of miRNA expression and function briefly, then focus on miRNAs that have translational promise for wound repair through elevated expression, for instance through miRNA mimics that stimulate keratinocyte migration and other aspects of wound healing.

1.1 | MicroRNA biogenesis and function

The canonical pathway for miRNA biogenesis involves transcription from diverse genomic loci including introns, exons and intergenic regions to generate primary (pri-miRNA) (Finnegan & Pasquinelli, 2013). Subsequent processing of the pri-miRNA transcripts into ~70 nt precursor miRNA (pre-miRNA) hairpin loop structures appears to be almost completely dependent on DROSHA, a nuclear ribonuclease (RNAse) III enzyme that functions as a complex with the protein product of DiGeorge syndrome critical region gene 8 (DGCR8) (Denli et al., 2004; Gregory et al., 2004; Han et al., 2004; Landthaler et al., 2004; Lee et al., 2003). The pre-miRNAs are transferred from the nucleus into the cytoplasm via the Exportin 5 complex with RanGTP (Bohnsack et al., 2004; Lund et al., 2004; Yi et al., 2003). However, genetic ablation of the *XPO5* gene that encodes Exportin-5 only reduced miRNA maturation modestly, indicating the existence of alternative pathways for pre-miRNA translocation (Y. K. Kim et al., 2016). Once in the cytoplasm, each pre-miRNA is processed into a mature miRNA duplex by the RNAse III enzyme DICER, which contributes to the biogenesis of several small regulatory RNAs (Song & Rossi, 2017). One strand of the duplex is loaded into Argonaute (AGO) proteins to form the RNA-induced silencing complex (RISC), strand selection by AGO depending on 5′ nucleotide identity and the relative thermodynamic stabilities of the two ends of the miRNA duplex (Meijer et al., 2014; Sheu-Gruttadauria & MacRae, 2017). The guide stand is stabilised within AGO and targets the RISC to mRNA transcripts, while the other, minor species (the passenger strand, or miRNA*) is usually degraded (Bartel, 2018). However, both strands can accumulate

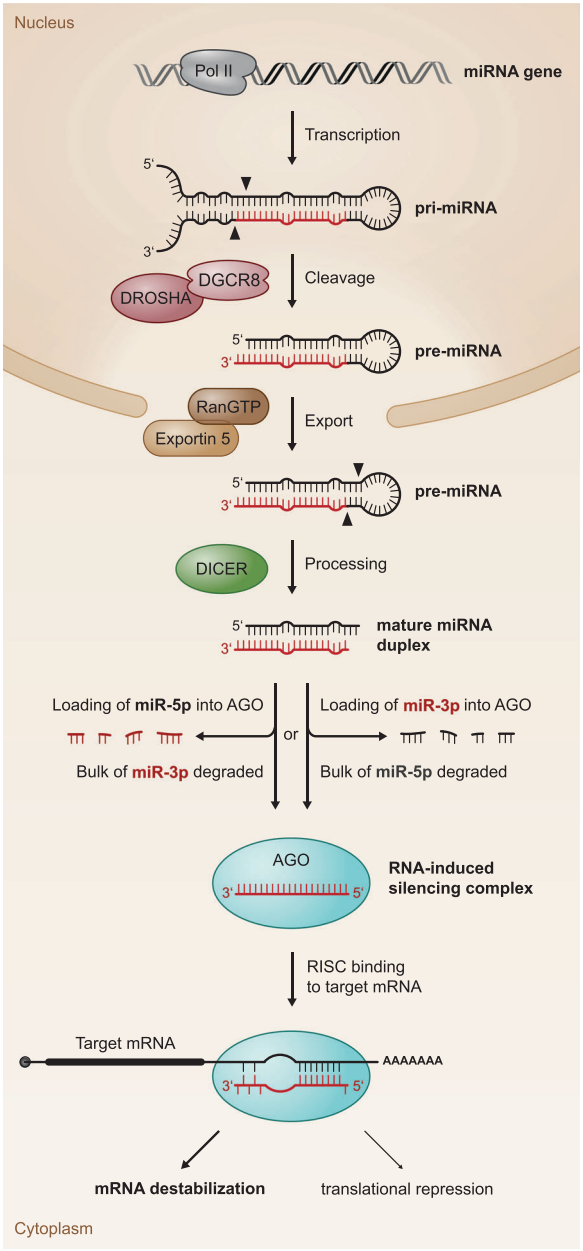

FIGURE 1 Schematic depiction of the canonical pathway of miRNA biogenesis. After transcription from diverse genomic loci, the primary miRNA transcript (pri-miRNA) is cleaved by the DROSHA/DGCR8 microprocessor complex, yielding pre-miRNA which is exported from the nucleus to the cytoplasm predominantly by the Exportin-5 Ran-GTP complex. After processing by DICER to form a mature miRNA duplex one strand from the duplex is loaded onto the AGO family of proteins to form the RISC, while the other strand is largely degraded. The RISC can repress translation but the dominant mechanism of silencing involves mRNA destabilization. AGO, Argonaute; mRNA, messenger RNA; miRNA, microRNA; RISC, RNA-induced silencing complex

to detectable levels and mediate RISC function, hence mature miRNAs are designated miR-#−5p or miR-#−3p according to the precursor hairpin arm from which they arise (Guo & Lu, 2010; Marco et al., 2012; Okamura et al., 2008; J. S. Yang, Phillips, et al., 2011). Such unambiguous nomenclature is also pertinent given that the choice of guide or passenger strand can vary with cell type or under pathological conditions, with very recent work indicating that the uridylation status of the miRNA strands is a key factor driving this choice (H. Kim et al., 2020). In any case, the RISC binds to the 3′ untranslated region (3′ UTR) of target mRNA transcripts and, in animals, results in abrogation of protein expression through complex mechanisms dominated by mRNA destabilization rather than translational repression (whose overall impact is modest) or mRNA cleavage, which dominates RISC function in plants (Eichhorn et al., 2014; Fang & Qi, 2016; Iwakawa & Tomari, 2015). Key elements of the canonical pathway of miRNA biogenesis are summarised in Figure 1, but it should be noted that several pathways of miRNA biogenesis are known to bypass Drosha or Dicer processing, and these noncanonical mechanisms have been reviewed critically elsewhere (Bartel, 2018; Treiber et al., 2019).

1.2 | Enhancing miRNA levels for wound healing: A focus on keratinocytes

The formation of new epidermal tissue over the denuded wound surface is fundamental to the completion of wound healing. Keratinocytes migrate from the wound edge to repopulate the exposed extracellular matrix but in chronic wounds, such keratinocyte migration is impaired (Usui et al., 2008). Diverse cytokines and growth factors promote keratinocyte migration, and early work by Woodley and colleagues found transforming growth factor α (TGFα) was the most potent stimulator of keratinocyte migration among a panel of 11 cytokines and growth factors, while transforming growth factor β (TGFβ) was the weakest (Y. Li et al., 2006). Nonetheless, several TGFβ-induced miRNAs, including miR-21-5p, miR-31-5p and miR-132-3p that have emerged as key miRNAs whose elevation drives keratinocyte migration, re-epithelialisation and other elements of wound healing (Table 1), while the impact of TGFα on miRNA expression and function in keratinocytes remains obscure.

1.3 | MicroRNA-21-5p in keratinocytes

Early studies demonstrated miR-21-5p induction by TGFβ in HaCaT keratinocytes (X. Yang, Wang, et al., 2011). Antisense inhibition of miR-21-5p slowed TGFβ-dependent migration of these cells in scratch assays, while a miR-21 mimic significantly enhanced HaCaT keratinocyte migration (Ahmed et al., 2011; X. Yang, Wang, et al., 2011). In mouse wounds, miR-21-5p appears as one of the most elevated miRNAs during the proliferative granulation formation stage, and antisense inhibition of miR-21-5p impaired re-epithelialisation of murine skin wounds while a pre-miR-21 plasmid enhanced granulation tissue formation and wound contraction (T. Wang, Feng, et al., 2012). A miR-21 mimic was also recently shown to accelerate wound closure (Simões et al., 2019). Interestingly, down-regulation of miR-21-5p in cutaneous diabetic mouse wounds was associated with delayed wound healing, although a causal relationship was not established (Madhyastha et al., 2012). Together, these rodent studies suggest abrogation of miR-21-5p activity impairs wound healing while enhancement of pre-miR-21 accelerates wound repair. On the other hand, topical application of a miR-21-5p mimic inhibited re-epithelialisation in ex vivo human skin wounds and reduced granulation tissue formation and re-epithelialisation in a rat model (Pastar et al., 2012). Thus, while a very recent study showed that keratinocyte-derived microvesicles carrying miR-21-5p potentiate fibroblast and endothelial cell wound healing functions in diabetic rats (Q. Li et al., 2019), the translational potential of miR-21-5p in wound healing remains an open question. The ability of miR-21-5p to enhance dynamic inflammatory processes such as infiltration of immune cells (Pastar et al., 2012) or the secretion of cytokines and chemokines (Guinea-Viniegra et al., 2014; Q. Li et al., 2019) also needs further investigation to establish their roles in wound repair. Furthermore, unlike miR-31-5p and miR-132-3p (see below), miR-21-5p does not appear to stimulate keratinocyte proliferation, at least as measured in HaCaT cells (Ahmed et al., 2011; X. Yang, Wang, et al., 2011), although a recent study suggests otherwise (Simões et al., 2019).

Recently, Wang and colleagues also observed that miR-21-5p was reduced in aged mouse skin compared to their younger counterparts, and this was associated with impaired wound healing in the aged mice (Long et al., 2018). The delayed wound closure was reversed in aged miR-21 knock-in mice or by intradermal injection of a pre-miR-21 plasmid. However, although miR-21 was depleted in aged mouse skin (12-month vs. 2-month-old mice) in the Wang study, Botchkarev and co-workers found miR-21-5p was elevated in aged mice (2-year vs. 8-week-old mice) (Ahmed et al., 2019). Hence, the dynamics of miR-21 expression in aged murine skin require further clarification, as do the mechanisms underpinning alterations in miR-21 levels in aging skin.

Some aspects of keratinocyte migration during wound healing, such as the reduction of cell–cell and cell–matrix adhesion overlap with features of epithelial mesenchymal transition (EMT) (Haensel & Dai, 2018). Conflicting observations have been reported in relation to the impact of miR-21-5p on EMT in HaCaT keratinocytes: work by Su and colleagues suggest modulation of miR-21-5p had limited impact on EMT whereas recent studies by Qian and co-workers found miR-21 mediates TGF-β1-dependent mesenchymal transition (J. Wang et al., 2016; T. Wang, Zhang, et al., 2012). In any case, it will be important to establish the impact of miR-21-5p on EMT in primary keratinocytes and ex vivo human skin to verify the physiological significance of these observations.

1.4 | MicroRNA-31-5p in keratinocytes

Studies in both human and mouse skin have implicated miR-31-5p in re-epithelialisation (D. Li et al., 2015; Shi et al., 2018). The expression

TABLE 1 Candidate microRNA mimics for wound healing in the skin

MicroRNA	Inducer(s)	Validated targets	Process	Model	Refs.
miR-21-5p	TGFβ	*PTEN*, *PDCD4*, *TIMP3*, *TPM1*	Migration	HaCaT keratinocytes	Ahmed et al. (2011); J. S. Yang, Phillips, et al. (2011)
			Re-epithelialisation Wound closure	Wounded mouse skin	Simões et al. (2019); T. Wang, Zhang, et al. (2012)
miR-19b + miR-20a	Cocktail of TNF-α, IFNγ, IL-17, IL-22	*SHCBP1* and *SEMA7A*, respectively	Inhibition of inflammation Wound closure	Primary human keratinocytes, wounded db/db diabetic mouse skin	D. Li et al. (2020), Zhang et al. (2018)
miR-31-5p	TGFβ, IL-6	*EMP-1*, *RASA1*, *SPRED1*, *SPRED2* and *SPRY4*	Proliferation Migration	Primary human keratinocytes	D. Li et al. (2015)
				HaCaT keratinocytes	Shi et al. (2018)
			Proliferation Wound closure	Wounded mouse skin	Chen et al. (2019), Shi et al. (2018)
miR-132-3p	TGFβ	*HB-EGF*	Re-epithelialisation	Ex vivo human skin	D. Li et al. (2015), X. Li, D. Li, Wikstrom, et al. (2017)
			Proliferation Wound closure	Primary human keratinocytes, ex vivo human epidermis, wounded db/db diabetic mouse skin	D. Li et al. (2015), X. Li, D. Li, Wikstrom, et al. (2017)
			Inhibition of inflammation pathways	Primary human keratinocytes, wounded db/db diabetic mouse skin	D. Li et al. (2015), X. Li, D. Li, Wikstrom, et al. (2017)
miR-184	Ca^{2+}	*K15*, *FIH1*	Migration	Primary human keratinocytes	Richardson et al. (2020)
			Differentiation	Primary human keratinocytes, miR-184 knockout and miR-184 transgenic mice	Nagosa et al. (2017), Richardson et al. (2020)
					Nagosa et al. (2017)
miR-129-5p miR-335-5p	Unknown	*Sp1*	Reduction of MMP-9 expression Wound closure	HaCaT keratinocytes, streptozotocin-induced diabetic rats	W. Wang et al. (2018)

Abbreviations: *EMP-1*, epithelial membrane protein 1; *FIH1*, factor inhibiting hypoxia-inducible factor-1; *HB-EGF*, heparin-binding EGF-like growth factor; *K15*, cytokeratin 15; MMP-9, matrix metalloproteinase-9; *PDCD4*, programmed cell death 4; *PTEN*, phosphatase and tensin homolog; *RASA1*, RAS P21 protein activator 1; SEMA7A, semaphorin 7A; *SHCBP1*, SHC binding and spindle associated 1; *Sp1*, specificity factor 1; *SPRED*, Sprouty-related, EVH1 domain-containing protein; *SPRY4*, Sprouty RTK signalling antagonist 4; *TIMP3*, tissue inhibitor of metalloproteinase 3; *TPM1*, tropomyosin 1.

of miR-31-5p was strongly induced in skin at the wound edge and was predominantly expressed in keratinocytes (D. Li et al., 2015; Shi et al., 2018). In early work from the Sonkoly group, TGFβ1 and TFGβ2 induced miR-31-5p modestly in primary human keratinocytes, whereas tumour necrosis factor α (TNF-α), interleukin (IL)−22, IL-6, interferon γ (IFNγ), and other agents had little effect (D. Li et al., 2015; Xu et al., 2013). In contrast, later work from Wang and colleagues found IL-6 evoked a fourfold increase of miR-31-5p in primary human keratinocytes, as well as modest induction by IL-22, IFNγ and TNF-α (Yan et al., 2015). More notably, IL-6-dependent elevation of miR-31-5p was mediated by the transcription factor NF-κB, and similar observations have been made recently in murine keratinocytes and HaCaT keratinocytes (Shi et al., 2018). Whether signal transducer and activator of transcription 3 (STAT3), a primary mediator of IL-6 signalling, drives miR-31-5p expression is less clear: at least in HaCaT keratinocytes, a STAT3 inhibitor did not impair IL-6-dependent miR-31-5p expression (Yan et al., 2015) whereas silencing of STAT3 with short-interfering RNA (siRNA) abrogated both TNF-α- and IL-6-mediated miR-31 induction (Shi et al., 2018).

Conditional deletion of miR-31 from murine epidermis impaired keratinocyte proliferation and delayed wound closure (Shi et al., 2018). Conversely, a miR-31 mimic increased the rate of wound closure in a mouse skin wound-healing model (Chen et al., 2019). Further, exogenous miR-31-5p mimics enhanced proliferation and migration of human keratinocytes by silencing epithelial membrane protein 1 (EMP-1) and negative regulators of the RAS/MAPK pathway, including RASA1, SPRED1, SPRED2 and SPRY4 (D. Li et al., 2015; Shi et al., 2018). Of these targets, RASA1 (also known as p120RasGAP) is particularly interesting because it was also downregulated in keratinocytes loaded with pre-miRNA-132 (see supplementary tab. 1 in D. Li et al., 2015) and has been confirmed as a miR-132-5p target in fibroblasts (X. Li, D. Li, Wikstrom, et al., 2017) and endothelial cells (Anand et al., 2010). Studies in the context of psoriasis, an immune-driven epidermal disorder have revealed repression of protein phosphatase 6 (ppp6c) as a further mechanism through which miR-31-5p promotes keratinocyte proliferation (Yan et al., 2015).

1.5 | MicroRNA-132-3p in keratinocytes

Inflammation is an essential early stage of wound healing that supports the generation of a provisional extracellular matrix for subsequent phases and helps neutralise infectious agents and remove debris (Zhao et al., 2016). However, prolonged inflammation is detrimental to wound healing, which is where the translational utility of miR-21-5p and miR-31-5p becomes equivocal as they direct axes of epidermal inflammation associated with psoriasis, through tissue inhibitor of metalloproteinase 3 (TIMP3) and serine/threonine kinase 40 (STK40), respectively (Guinea-Viniegra et al., 2014; Xu et al., 2013).

In contrast, miR-132-3p is distinguished by the ability to decrease inflammation while concomitantly stimulating keratinocyte proliferation and re-epithelisation during wound healing (D. Li et al., 2015; X. Li, D. Li, Wang, et al., 2017). Using surgical abdominal wounds, Landén and colleagues identified miR-132-3p as a dynamically regulated miRNA in human skin (D. Li et al., 2015). Among multiple stimuli, only TGF-β1, and TGF-β2 induced miR-132-3p in primary keratinocytes. Transcriptomic profiling and gene ontology analysis of pre-miR-132 loaded keratinocytes found high enrichment of downregulated immune response genes (D. Li et al., 2015). Crucially, pre-miR-132 expression in keratinocytes reduced transcription of chemokines (IL-8, CXCL5, CXCL1, CCL20) and cytokines (IL-1α, IL1βb, TNF-α) and decreased chemokine secretion into culture medium, which impaired induction of adhesion molecules E-selectin and vascular cell adhesion protein 1 (VCAM1) on human endothelial vein endothelial cells (HUVEC). This in turn blunted the ability of conditioned supernatant to recruit neutrophils and mononuclear cells. Mechanistically, the attenuation of chemokine production by pre-miR-132 was associated with impaired activation of the transcription factor NF-κB pathway in keratinocytes.

The other key finding from the gene ontology analysis was that genes whose expression was elevated in the pre-miR-132 transfected cells were enriched for processes associated with the cell cycle (D. Li et al., 2015). Indeed, pre-miR-132 enhanced keratinocyte proliferation by increasing the activation of EGFR and its downstream targets STAT3 and ERK.

The anti-inflammatory and proliferative impacts of miR-132 were attribute to the ability of miR-132-3p to repress heparin-binding epidermal growth factor (HB-EGF). Reporter assays along with analysis of HB-EGF levels upon modulation of miR-132 expression all confirmed regulation of HB-EGF by miR-132 (D. Li et al., 2015). Further, silencing of HB-EGF with siRNA phenocopied the effects of pre-miR-132 on keratinocytes, including inhibition of NF-κB and accentuation of EGFR signalling. However, studies with target site blockers to specifically block miR-132-3p binding to the 3′ UTR of HB-EGF are needed to clarify the relative contribution of HB-EGF to pre-miR-132 effects on inflammation and proliferation as other pathways may be involved. For instance, miR-132-3p potentiates cholinergic anti-inflammatory responses in macrophages and other cell types by targeting acetylcholinesterase (AChE), leading to impaired NF-κB activation (Liu et al., 2015; Shaked et al., 2009) and epidermal keratinocytes have long been known to express AChE (Grando et al., 1993).

More importantly, depletion of miR-132 delayed wound closure in mouse skin while a miR-132-3p mimic promoted wound healing in leptin receptor-deficient diabetic (db/db) mice (D. Li et al., 2015; X. Li, D. Li, Wang, et al., 2017). Similarly, in human ex vivo skin wounds, inhibition of miR-132 abrogated re-epithelialisation, while a miR-132-3p mimic enhanced this process (D. Li et al., 2015; X. Li, D. Li, Wang, et al., 2017). Because miR-132 was under-expressed in diabetic foot ulcers compared with wounded healthy skin, these findings together suggest elevation of miR-132 holds strong translational potential for treatment of chronic wounds.

1.6 | MicroRNA-19a/b and microRNA-20a in keratinocytes

Very recently, the Landén group has also identified a further set of miRNAs that dampen inflammation in wound healing. The six

miRNAs encoded by the miR-17~92 cluster (miR-17, miR-18a, miR-19a, and miR-19b, miR-20a, miR-92) were depleted in chronic wounds compared to wounded healthy skin, with miR-19a, miR-19b and miR-20a specifically downregulated in the epidermis (D. Li et al., 2020). Wound closure was delayed in mice with keratinocyte-specific miR-17~92 conditional knockout mice, especially when diabetes was induced experimentally by streptozocin injection. Conversely, wound repair was accelerated in diabetic mice with KC-specific conditional knock-in (cKI) of the miR-17~92 cluster or miR-19b alone (D. Li et al., 2020). Based on observations that damaged cells release endogenous RNAs that activate Toll-like receptor (TLR3), the authors tested the impact of miR-19a, miR-19b and miR-20a on cytokine and chemokine expression in keratinocytes challenged with a TLR3 agonist. Each miR-19a, miR-19b and miR-20a mimic inhibited the TLR3-dependent induction of cytokines and chemokines in keratinocytes and reduced neutrophil recruitment by the keratinocyte-conditioned media (D. Li et al., 2020). Likewise, chemokine expression and neutrophil infiltration were dampened in the wound edges of miR-19b cKI mice. Interestingly, a combination of miR-19a, miR-19b and miR-20a mimics did not alter keratinocyte proliferation, even though other investigators have shown that the miR-17~92 cluster promotes keratinocyte proliferation and cell cycle progression, apparently by the co-ordinated activity of miR-17, miR-18a, miR-19a, and miR-19b (Zhang et al., 2018). Thus, elevation of miR-19a and miR-19b alone appears insufficient to phenocopy the effects of the larger cluster on keratinocyte proliferation. More importantly, although a mixture of miR-19b and miR-20 accelerated wound closure in db/db mice, it may be necessary to combine miR-19b/miR-20 with miRNAs that enhance other aspects of wound healing such as neoangiogenesis or re-epithelialisation to maximise their translational potential.

1.7 | MicroRNA-184 in keratinocytes

While miR-31-5p and miR-132-3p drive keratinocyte migration and proliferation, miR-184 is distinguished by its ability to stimulate keratinocyte migration and differentiation (Nagosa et al., 2017; Richardson et al., 2019, 2020). Mature miR-184 arises from the 3p arm of the pre-miR-184 duplex and there is no evidence for a minor miRNA from the 5p arm (see http://www.mirbase.org/). Although early studies did not detect miR-184 in proliferating epidermal keratinocytes maintained in monolayer culture, we observed miR-184 expression in reconstituted human epidermis, which comprises proliferating keratinocytes and differentiating suprabasal cells (Roberts et al., 2013). This led us to suspect that miR-184 may play a role in keratinocyte differentiation. Consistent with this, we and others recently showed that elevation of extracellular Ca^{2+}, a major inducer of keratinocyte differentiation, induces miR-184 in these cells (Nagosa et al., 2017; Richardson et al., 2020). In addition, we found that the induction of miR-184 required Ca^{2+} entry through the store-operated Ca^{2+} entry (SOCE) channel ORAI1 though strict dependence on the SOCE trigger STIM1 (stromal interaction molecule 1) has not been verified. Elevation of miR-184 was associated with a reduction in keratinocyte proliferation and enhancement of keratinocyte differentiation through the cyclin E:DNA damage and NOTCH pathways (Nagosa et al., 2017; Richardson et al., 2020). Given that migration through the suprabasal layers is inherent to epidermal differentiation, we examined the impact of miR-184 on keratinocyte migration (Richardson et al., 2019, 2020). High-density scratch wounding of keratinocyte monolayers led to a 50-fold induction of miR-184 after 5 days, suggesting miR-184 may function critically during the latter phases of re-epithelialisation. Exogenous miR-184 accelerated keratinocyte migration threefold, while a miR-184 inhibitor dampened keratinocyte migration threefold (Richardson et al., 2019, 2020). However, the targets of miR-184 required for epidermal keratinocyte migration have not been defined and the impact of miR-184 on cutaneous wound healing in vivo is not known. Hence, studies of re-epithelialisation in miR-184-deficient and miR-184 transgenic mice, such as those generated by Shalom-Feuerstein and colleagues (Nagosa et al., 2017), will be crucial to deepen our understanding of miR-184 function in re-epithelialisation, along with studies in diabetic mouse models. Further studies are also required to establish whether miR-184 can promote tissue regeneration in normal human or diabetic wounds through its effects on keratinocyte differentiation and migration. This is important because it is keratinocyte differentiation rather than proliferation that appears to be impaired at the edges of chronic ulcers (Stojadinovic et al., 2008; Usui et al., 2008; Wikramanayake et al., 2014). Given that terminal differentiation is the ultimate destiny of epidermal keratinocytes, the ability of miR-184 to mobilise differentiation pathways in conjunction with migration may underpin its translational potential.

1.8 | MicroRNA-129-5p and microRNA-335-5p in keratinocytes

The diabetic wound is a highly proteolytic environment where sustained elevation of matrix metalloproteinases (MMPs) contributes to extracellular matrix degradation, dysregulated inflammation and impaired wound closure (Ayuk et al., 2016). Increasing evidence points to MMP-9 in particular as a key driver of non-healing wound pathology (Gao et al., 2015; Gooyit et al., 2014; C. Yang et al., 2009). Ren and colleagues found that the specificity protein 1 (Sp1) regulates MMP-9 expression in HaCaT keratinocytes, and that exposure to glycated albumin to reproduce the advanced glycation end product (AGE)-enriched microenvironment of diabetic wounds raised expression of both Sp1 and MMP-9 in HaCaT and primary keratinocytes (W. Wang et al., 2018). Profiling diabetic patient serum revealed 58 downregulated miRNAs, among which miR-129-5p and miR-335-5p stood out as predicted regulators of Sp1, which was confirmed by luciferase reporter assays and western blot analysis. More importantly, both miR-129-5p and miR-335 were underexpressed in diabetic skin wounds from patients and rats, and decreased in HaCaT keratinocytes treated with glycated serum

albumin, establishing a link between miR-129-5p and miR-335-5p depletion and elevation of their target Sp1 (W. Wang et al., 2018). Indeed, AGE-dependent elevation of Sp1 and MMP-9 in HaCaT keratinocytes was completely abrogated by miR-129-5p and miR-335-5p mimics. Consistent with this, repeated intradermal injection of miR-129-5p and miR-335-5p mimics into diabetic rat wounds accelerated wound repair, and this was associated with down-regulation of SP1 and MMP-9 (W. Wang et al., 2018).

2 | CONCLUSION

It is tempting to speculate that a concomitant or sequential combinatorial approach in which miRNA mimics targeting different aspects of wound repair may yield the best patient outcomes for miRNA-directed wound healing. For instance miR-132-3p and miR-184 to target proliferation, inflammation and differentiation, with the addition of miR-129-5p to target MMP-9. Given the recent clinical evaluation of a miR-29b mimic (remlarsen) for the prevention of keloids and hypertrophic scars following intradermal injection (Gallant-Behm et al., 2019), there appears to be a strong appetite for exploitation of miRNAs in the context of skin disorders. It will be crucial to determine the safety of combinatorial miRNA approaches and to establish which delivery vehicles prove most suitable for clinical deployment of miRNA mimics (Mandal et al., 2020; Ross, 2018).

The growing number of miRNAs implicated in keratinocyte migration and cutaneous wound healing also provide ample opportunity for further curiosity-driven investigations. For example, what are the relative levels of these miRNAs in keratinocytes under resting and migrating conditions? Is there a relationship between the amount of exogenous mimic loaded per cell and migration rates, and is this relationship constant for diverse miRNA mimics? The impact of exogenous miRNA mimics on the morphological heterogeneity of cultured keratinocytes from healthy and diabetic skin would also be of interest given recent advances in image processing tools (Driscoll et al., 2019; Wu et al., 2020). Finally, given the asymmetric distribution of mRNA and proteins in polarised migrating cells (Liao et al., 2015), it would be interesting to assess the subcellular localisation of miRNAs during keratinocyte migration.

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CONFLICT OF INTERESTS

The author has filed a patent application relating to the use of microRNA-184 for regulating keratinocyte migration.

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