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Original Article

Role of microRNAs in regulation of cutaneous wound healing

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Abstract: Chronic wounds are growing medical burdens to overall healthcare that cause high rates of morbidity and mortality. The development of clinical therapies should focus on the molecular biology of chronic wounds. As key post-transcriptional regulators of gene expression, miRNAs are verified involved in five vital phases of wound healing. This review reveals several miRNAs in different processes of wound healing including hemostasis, inflammation, cellular migration and proliferation, tissue formation and tissue remodeling and discusses the underlying modulatory mechanisms, Which may inspires the world on treatment of skin diseases and wound healing.

Keywords: microRNAs, cutaneous wound healing, hemostasis, inflammation, keratinocytes, fibroblasts, angiogenesis, epithelialization, scar

Introduction

Wound healing is a complex process that involves several physiological mechanisms being coordinated to tissue injury. Once the skin is wounded, the process of hemostasis begins, which leads to vasoconstriction and fibrin clot formation. Then, inflammatory mediators are produced in concert with the coagulation cascade, thereby a local concentration gradient is generated, which promotes fibrin matrix formation and neutrophil chemotaxis. Following inflammation, proliferation and migration of fibroblasts and keratinocytes are important to re-establish the cellular and extracellular matrix composition of the skin. Meanwhile, vascular endothelial cells (VECs) contribute to the formation of new blood vessels by supplying nutrients to skin cells [1]. Then, epithelialization and newly formed granulation tissue begin to cover and fill the wound area to re-establish tissue integrity. Finally, corrective tissue remodeling returns the skin section to its normal shape. Some chronic diseases, such as diabetic ulcers, are recalcitrant to all treatment approaches and eventually lead to chronic wounds. Drug treatment is the most effective therapy for chronic wounds, but the efficacy is typically unsatisfactory Thus, there is an important need to find better and more efficient treatment options.

MicroRNAs (miRNAs) are a group of naturally occurring, small, non-coding, single-strand RNAs of 20-22 nucleotides (nt). MiRNAs can interact with complementary sequences in the 3'UTR of the target mRNA to induce translational repression or target degradation. They have recently been shown to be involved in the regulation of many key biological functions in both physiological and pathophysiological states. MiRNAs are potentially involved in promoting or inhibiting wound healing. These molecules are promising therapeutic targets and have demonstrated great potential as diagnostic biomarkers for wound healing. However, the exact roles of miRNAs in wound healing are still unknown, and few studies are conducted on the way in which miRNAs regulate the sequential or overlapping phases of wound healing. This paper presents a review of the existing evidence on the roles of miRNAs in different physiological processes relevant to cutaneous wound healing.

Table 1. miRNAs in keratinocytes and fibroblasts

Keratinocytes		
miRNAs	Target	References
miR-21	TIMP3, TIAM1	[48]
miR-34a/34c	p63	[28]
miR-99 Family	AKT	[49]
miR-136	PPP2R2A	[30]
miR-197	IL22RA1	[50]
miR-205	ITGA5	[51]
miR-330-5p	Pdia3	[52]
miR-378b	NKX3.1	[53]
miR-483-3p	YAP1	[54]
miR-4516	STAT3	[55]
Fibroblasts		
miRNAs	Target	References
Let-7c	HSP70	[56]
miR-21	PTEN	[57]
miR-23b	Smad3	[58]
miR-29b	TGF-β1, Smad3	[59]
miR-143-3p	CTGF	[60]
miR-185, miR-203*, miR-690, miR-680, miR-434-3p	Versican, β-catenin	[61]
miR-191	CDK9, NOTCH2, RPS6KA3	[62]
miR-378a	vimentin, integrinβ-3	[63]
miR-5787	eIF5	[64]

miR-203*: miR-203-5p.

Hemostasis

Hemostasis enables a body to seal off injured blood vessels immediately, maintain blood flow under physiological and pathological states and form clots, which are necessary for the reconstruction of damaged vessels. Four principal actors in the hemostatic system are platelets, coagulation factors, anticoagulants, and fibrinolytic elements, all with the common objective of achieving a dynamic equilibrium that maintains adequate blood flow [2]. Several factors may disturb the fine regulations of the hemostatic system and lead to chronic wound. Growing evidence support the involvement of miRNAs in the regulation of many complex mechanisms, such as the hemostatic system. Indeed, the regulation of a physiological or pathological pathway by miRNAs may be extremely complex because such regulation may occur at different stages.

Tissue factor

TF is a primary initiator of blood coagulation. When it is exposed to blood, the coagulation cascade is activated, resulting in the transformation of prothrombin to thrombin, the appearance of fibrin, platelet activation and thrombus formation [3, 4]. Further, TF can trigger coagulation and may support thrombosis, which is also a key receptor in angiogenesis [5]. Different research groups have shown that miRNAs are involved in the regulation of TF during hemostasis. For example, miR-19a and miR-126, are verified to regulate TF-mediated cellular thrombogenicity by adjusting the protein expression of TF in both normal and inflammatory states of endothelial cells [6]. In addition, miR-19 controls TF expression by binding to the 3'UTR of the TF gene directly and provids a molecular basis for the selective expression of the TF gene [7]. Conversely, the inhibition of miR-19 increased the expression of TF. Indirectly, miRNAs can also impact the expression of TF via the tissue factor pathway inhibitor (TFPI) [8]. According to Eisenreich. A, the activities of TF and the TF-regulated procoagulant are directly inhibited by TFPI [9]. What's more, miRNAs, especially miR-616, plays a key role in regulating the expression of TFPI [10].

Table 2. miRNAs in angiogenesis

Pro-angiogenesis			
miRNAs	Target	Signaling pathways	References
miR-15b	BCL-2		[65]
miR-17-92 cluster	TSP-1, CTGF, TIMP-1, HIF-1α	TGFβ	[66, 67]
miR-29a	PTEN	AKT	[68]
miR-101	Cul3		[69]
miR-126	Spred-1, PI3R2/P85-b		[70-72]
miR-130a	GAX, HOXA5		[73]
miR-146a	CREB3L1		[74]
Anti-angiogenesis			
miRNAs	Target	Signaling pathways	References
miR-23a	MET		[75]
miR-24	GATA-2, PAK4		[76]
miR-26a	SMAD1		[77]
miR-29a	COL1A2, VEGF-A	Notch2/jagged2	[78]
miR-191	ZO-1		[17]
miR-199a-5p	Ets-1		[79]
miR-200b	GATA2, VEGFR2, Ets-1		[80, 81]
miR-203	VEGFA		[82]
miR-223-3p	Rps6kb		[83]
miR-320	IGF-1	RPS6KB1/hif-1a	[84]
miR-329	VEGF, TNF-α		[85]
miR-378a	ITGB3		[63]
miR-492	eNOS		[86]

Thrombin

In general, thrombin, which is a natural coagulant factor, has a stabilized expression in coagulation [2]. In mammals, thrombin remains at a stable concentration, even in a fast-moving blood [11]. A recent study shows human aortic endothelial cells transfected with miR-146a mimics decrease the HG/thrombin-induced up-regulation of NAPDH oxidase 4, ROS generation and inflammatory phenotypes in diabetic patients with high blood glucose and thrombin production [12]. Moreover, miR-146 was uncovered as an inhibitor of inflammation by the thrombin-GPCR-NF-κB pathway in retinal endothelial cells [13].

Fibrinogen

As a final part of hemostasis, fibrin, which is composed of fibrinogen and other factors, is deemed to enhance wound repair by supporting inflammatory and mesenchymal progenitor egress into the zone of injury [14]. Once the fibrinogen converts into fibrin, it provides the necessary structural conditions, including strength and adhesive surfaces, to grow clots [15]. The fine-tuning of miRNAs is a key event in platelet pathophysiology [16]. As an important component in serum, platelet fibrinogen consists of three protein chains (Aα, Bβ, and γ), which are encoded by FGA, FGB, and FGG, respectively. Recently, it was found that overexpression of miR-29 members (a, b, c) reduced the transcription of these three genes [15]. In addition, miR-29a and miR-29b have an indirect impact on gene expression by targeting upstream factors. miR-409-3p has been shown to suppress the expression of FGB. Additionally, another study discovers differential protein profiles: the expression of fibrinogenα polypeptide isoform 2 precursor is approximately 2-fold higher in the absence of miR-451, which demonstrates that miR-451 influences the expression of fibrinogen α chain mRNA and protein [16]. Furthermore, altered miR-191 expression influences the angiogenesis and migratory capacities of diabetic dermal endothelial cells or fibroblasts partly via its target zonula occludens-1 [17]. In short, these results point

toward a potential cause of variable circulating fibrinogen levels and demonstrate that a screening approach can identify miRNAs that regulate clinically important proteins.

Inflammation

Pro-inflammation

The early stage of inflammation serves as a critical period of the wound healing process. It is essential for clearing contaminating bacteria and creating an environment that is conducive to the succeeding events of tissue repair and regeneration. Pro-inflammatory miRNAs are therefore important in the early stages of injury. One study shows an interesting example of how miR-511 transforms the expression of gene products and activates macrophage functions [18]. miR-155 decreases suppressor of cytokine signaling 1 (SOCS1) expression. Furthermore, miR-155 limits the amount of interleukin-2 by inhibiting activation of signal transducer and activator of transcription 5 (STAT5) transcription factor, which enhances the inflammatory response [19].

Anti-inflammation

An excessive influx or infiltrating leukocytes into the damaged tissue may have negative effects on downstream cell migration, proliferation, differentiation and, ultimately, the quality of the healing response. Therefore, the timely activation of an anti-inflammatory signal is crucial. There are some miRNAs that can reduce the inflammatory response by controlling signaling pathways and mediators. In keratinocytes, miR-132 decreases the production of chemokines and the capability to attract leukocytes by suppressing the NF-κB pathway. Conversely, miR-132 increased the activity of the STAT3 and ERK pathways, thereby promoting the growth of keratinocyte [20]. miR-146, a NF-κB-target gene, modulates the inflammatory response by down-regulating IRAK1 (IL-1 receptor-associated kinase 1) and TRAF6 (TNF receptor-associated factor 6), which are involved in the Toll-like receptor (TLR) and cytokine signaling pathway. Meanwhile, an increase of miR-146 results in the down-regulation of TNF-α and IL-6 [21]. A recent study demonstrats that miR-124a and miR-125b have a big effect on cytokines and chemokines such as TNF-α macrophage chemoattractant protein-1, acting as anti-inflammation markers [22]. Additionally, miR-124a directly binds to the 3'UTR region of ccl2, exclusively controlling the expression of ccl2, which is a type of pro-inflammatory chemokine [23]. Dangwal finds that miR-191 and miR-200b significantly suppress higher circulating C-reactive protein and pro-inflammatory cytokine levels in patients with diabetes mellitus [17]. As described above, several alternative miRNAs are critical regulators of skin wound healing that accelerate the transition from the inflammatory phase to the proliferative phase.

Cellular migration and proliferation

Following the inflammation phase, infiltrating leukocytes play a major role in the secretion of inflammatory cytokines, growth factors, and chemokines, which can stimulate the migration and proliferation of progenitor cells and the recruitment of keratinocytes, endothelial cells, and fibroblasts during the proliferative phase of wound healing [24, 25]. It is well recognized that a coordinated cellular response of keratinocytes, vascular endothelial cells (VECs) and fibroblasts is absolutely necessary for rapid and effective wound healing [26]. Cellular migration and proliferation are very significant for the formation of cutaneous appendages and re-epithelialization after wounding [27].

Vascular endothelial cells (VECs)

With the proliferation of VECs, new blood vessels begin to form to readily supply the healing area with plentiful oxygen and nutrients via angiogenesis/neovascularization [1]. This process is vital to fueling the activity of keratinocytes and fibroblasts. Multiple miRNAs are involved in proangiogenic and antiangiogenic regulation, including miR-15b, -16, -17, -92a, -126, and -503.

Keratinocytes

In addition, keratinocytes migrate from the wound edge to the wound site and begin to proliferate and differentiate to restore skin integrity (**Table 1**). The process can be inhibited by various miRNAs, including miR-34, -210, -198, -203, and -483-3p. In particular, miR-34 family members, including miR-34a and miR-34c, have the ability to arrest the cell G1-phase, decrease cell cycle regulators (cycle regulators cyclin D1 and cyclin-dependent kinase 4) and

target the downstream of p63 to retard the proliferation of keratinocytes [28, 29]. Inversely, some miRNAs, including miR-136, -21, and -31, have the ability to accelerate the process. miR-136 can enhance proliferation and play an important function in TGF-1-induced proliferation arrest by targeting PPP2R2A [30]. In fact, PPP2R2A, which is known as one of the four major serine/threonine (Ser/Thr) phosphatases, is a regulatory subunit of the protein phosphatase 2A (PP2A) and is implicated in negative control of cell growth in mammalian cells [31, 32].

Fibroblasts

A natural and correct fibroblast proliferation is considered as the precondition for optimal wound closure. Fibroblasts are responsible for attracting new cells by secreting growth factors and extra-cellular proteins. But aberrant fibroblast dynamics will lead to the generation of keloids, which will invade adjacent healthy tissue (**Table 1**). Thus, fibroblasts become the main cell type in the wound. miRNAs have variable effects on fibroblasts, such as miR-21, which increases the rate of fibroblast migration towards the wound [33]. The over-expression of miR-200b has been verified as contributing to the aberrant proliferation of fibroblasts. In various fibrogenic diseases, including hypertrophic scarring and liver fibrotic progression, the expression of miR-200b is deregulated [34]. Previous studies have reported that the up-regulation of miR-200b represses proliferation and induces apoptosis of hypertrophic scar fibroblasts, vice versa [35]. miR-24, -181b, -421, -526b, and -543 can decrease decorin in deep dermal fibroblasts [36].

Tissue formation

Proper cellular migration and proliferation contributes to the proper occurrence of tissue formation, including epithelialization and new granulation tissue formation. Likewise, the sprouting of capillaries from existing blood vessels is indispensable by nourishing the tissue to expedite wound healing. Indeed, complex interactions between the epidermal and dermal compartment are essential. Over the past decade, numerous factors have been distinguished that are engaged in a complex reciprocal dialogue between epidermal and dermal cells to facilitate wound repair [37].

Angiogenesis

Angiogenesis is the process by which new blood vessels develop from a pre-existing vascular system. Angiogenesis plays a substantial role in the physiological course of wound healing. Dysregulation of angiogenesis leads to pathological conditions [38]. A group of miRNAs has been reported to regulate angiogenesis as activators or inhibitors (**Table 2**).

Epithelialization

The epidermis is considered the skin's gatekeeper and is necessary for avoiding harm from external factors. Complex interactions of keratinocytes, fibroblasts, endothelial, immune cells and other cell types result in re-epithelialization. E-cadherin reinforces the stabilization of epithelial cell-cell junctions and epithelial barrier function. miR-192/215 increases the expression of E-cadherin by repressing translation of ZEB2 [39]. miR-203 controls the target proteins of RAN and RAPH1 to inhibit the re-epithelialization and re-establishment of epidermal homeostasis in injured skin [40].

Tissue remodeling

When the wound is closed, the remodeling phase begins. Tissue remodeling is defined as the ultimate phase of wound healing, which involves shaping the physiological skin section, adjustments of ECM, collagen deposition, and scar formation. In most favorable cases, the injury is resolved and the fibrogenic response is then limited. Furthermore, the temporary scar tissue is repopulated by fully differentiated functional cells, and the repair reaches a functional and morphological unification [41, 42]. However, in some cases, chronic or reiterative ulcers drive a pathogenic fibrogenic response. This response causes tissues to lose the normal regenerative process, resulting in permanent scarring and substantial tissue remodeling.

Collagen deposition

In intact skin, the ratio of collagen type III to collagen type I is significantly lower than that in wounded skin. A higher ratio of collagen type III to collagen type I contributes to a more compliant, ductile granulation tissue, which makes for extracellular matrix remodeling [43]. In par-

ticular, miR-29b increases the ratio of collagen type III to collagen type I. miR-29a regulates the contractility of dermal fibroblasts by targeting TABL1 [44]. Moreover, miR-29b and miR-29c modulate the ECM remodeling response and reduce maladaptive remodeling such as aggressive deposition of collagen type I after injury [43, 45].

Scar

Scar is widely believed to be the excessive and persistent accumulation of extracellular matrix components in response to chronic tissue injury. As a crucial component of cell production, TGF-β plays a role in fibroblast proliferation, collagen synthesis regeneration and excessive deposition of ECM, which leads to the final formation of hypertrophic scar tissue [46]. The role of TGF-β in scar formation is increasingly attracting researchers' attention. As of 2015, 106 miRNAs have been detected to contribute to scarless wound healing by targeting the TGF-β pathway in fetal keratinocytes of different gestational ages [47].

Conclusion

miRNAs play significant roles in initiating repair and progression of wound healing by regulating the processes mentioned above. In addition, there could be many undiscovered miRNAs that are involved in wound repair. Because few treatment options are effective in wound healing, miRNA modulation might be a novel therapeutic approach. Some miRNAs may contribute substantially to wound healing and could thus potentially be used therapeutically. Despite these encouraging findings, before miRNA-targeted wound therapies can become a reality, large clinical trials are needed.

Disclosure of conflict of interest

None.

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