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Battle Between MicroRNAs and Scar Formation During Wound Healing

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Abstract

Wound healing is defined as a regular step by step process leading to full recovery of a wound. However, in many cases, scar formation influences the full repair of the wound area. When healing is completed, there is no foot print in the wound area, but in some cases a scar can be formed and affect full recovery. A molecular view of scar formation specifies that there is an unbalanced expression of some genes, which leads to incomplete healing and the formation of scars in the wound location. During the past decade, similar to many regulators, microRNAs (miRNAs) have been found to play an effective role in this process; in particular, their effect on the TGF-β family has been heavily studied and is now well understood. The purpose of this article is to review recent research on the interaction between miRNAs and scar formation during wound healing.

Keywords: Wound Healing, Regenerative Medicine, Scare Formation, Micro RNAs, TGFβ family

1. Context

Skin is the largest organ in the body and plays an important protective role against the entry of pathogens (1). The skin is the body's first line of defense against external agents, which can destroy the skin, causing destruction of the barrier and creating a wound. The wound healing process is a strong mechanism to repair and regenerate injured tissues (2). In the popular view, a wound is usually defined as a cut or damage to the skin; however, the true definition of a wound is an injury or disruption in the normal skin structure and function. Therefore, the term wound encompasses a wide range of lesions and traumas, including simple epithelium injuries and deeper damage. In histological studies, a wound can include muscle, tissues below the skin, nerves, tendon, vessels, and, in some cases, bones (3). Thus, skin lesions can be very simple to treat or indeed very dangerous, and therefore, skin wound treatment is a vital part of the health care system. Presently, heft of hospital services for skin wounds are focused on the treatment of burns, pressure ulcers, diabetic chronic wounds, venous ulcers, and accidental lacerations (4).

2. Evidence Acquisition

In recent years, there has been an increasing amount of literature on the wound healing process, and it is now well understood that when an injury takes place, our body performs a scheduled repair process known as wound healing. Healing is multistage and during this complex process, the damaged part of the skin is slowly repaired (3).

3. Results

3.1. Wound Healing

The wound healing process can be divided into four main phases: hemostasis, inflammation, proliferation, and remodeling (5). During tissue injury, blood vessels are damaged, and a continuation of this situation may lead to bleeding. If this is not stopped, the body can lose a large amount of blood. To control this condition, a process called hemostasis starts (6). Factors such as histamine, kinases, prostaglandins, leukotrienes, hyaluronic acid, and ROS affect vessel contraction and permeability in the inflammation phase (7). During wound healing, angiogenesis, collagen deposition, granulation tissue formation, and epithelialization occur (8). Several hours after injury, growth factors, including EGF and TGF-α, induce the final stage of epithelialization (9).

3.2. MicroRNAs

Recent studies indicate that microRNAs (miRNAs) participate broadly in dermal repair during healing of skin legions (10, 11). Generally, miRNAs are defined as small noncoding RNA molecules about 22 nucleotides in length (12). A eukaryotic cell uses these small RNA molecules to inhibit translation or degradation of mRNA, which can encode

proteins; this process is called post-transcriptional regulation of gene expression. A number of studies have found that miRNAs are not specific for animals because they are found in plants and some viruses as well (13, 14). Using complementary hydrogen bonds between nucleotides, these small regulators attach to their target mRNAs. Release of induced silencing complex, which is a main enzymatic complex for RNA silencing, is triggered when a miRNA attaches to its target mRNA, and, at this time, the cleavage and degradation of mRNA commences and therefore, protein production is inhibited (15). Degradation is not the only pathway for post transcriptional gene regulation; in another strategy, pairing of mRNA and miRNA causes less translation of mRNA by ribosomes. Although these two mechanisms are functionally different, both lead to a reduction in protein production. First, Lin-4 miRNA was discovered and reported in the 1990s (16). During the past couple of decades, many members of this family have been discovered, and it is now well understood that they play important roles in different cellular process including skin wound healing (10, 17, 18), as a cutaneous neovascularization (19), and subsequently in tissue regeneration (20). The fine tuning and regulation of miRNAs, which play a role in wound healing along with their target genes, are listed in Table 1.

Table 1. Some miRNAs Involved in the Skin Wound Healing Process; the miRNA Names, Related Genes, and Evaluated Organisms are Listed

miRNA	Related Gene	Organism	Reference
miR-21	TP53	Rat	(21)
miR-222-3p	DDK2, AXIN2, FRAT2	Rat	(21)
miR-31	TGF-β2	Rat	(22)
miR-196a	Collagen	Human skin fibroblasts	(23)
miR-29b	Type I collagen	Human	(24)
miR-31	STK40, Ki67	Human	(24)
miR-34c-5p	TGF-β3, TGF-βRII, SMAD4, SAR1A	Human	(25)
novel miRNA (seq-915_x4024)	SAR1A, SMAD2, SMAD3, SMAD4, TGF-β2, TGF-β3	Human	(25)
miR-34a-5p	TGF-β3, TGF-βRII, SMAD4, SAR1A	Human	(25)
miR-34b-3p	TGF-βRI, SMAD4, SAR1A. TGF-βRII, SMAD3	Human	(25)
miR-181b	TGF-β1	Human	(26)
miR-132	TGF-β, HB-EGF	Human	(22)

3.3. TGFβ Family

This protein is a multi-functional cytokine belonging to the transforming growth factor beta (TGF-β) superfamily and consists of some isoforms, including TGF-β 1-3. TGFβ plays an important role in cell function and the wound healing process. In recent years, there has been an increasing interest in its regulation. Intermediacy of TGFβ is very well understood in many functions and signaling pathways in the cell. In the wound healing process, TGFβ is impressionable by thrombospondin-1 (TSP-1). TSP-1 is up-regulated at the site of the injury and induces a conformational rearrangement, which prevents it from binding to the matured TGF-β (27).

3.4. MiRNAs and TGFβ Proteins Family Interaction

Gras et al. showed that miRNA gene therapies using miR-145 strongly reduce skin myofibroblast activity that is triggered by TGF-β 1, and that the use of this technique significantly inhibited scar formation (23). In addition, researchers have suggested that miR-145 is a valuable gene therapy target for the treatment of visual loss caused by corneal fibrosis in the eye injuries (28). However, miR-145 is not the only target for treating wounds. For example, in another study it was demonstrated that overexpression of miR-200b inhibits cell proliferation and induces programmed cell death of hypertrophic scar fibroblasts in vitro by affecting collagen I and III synthesis (29). In 2015, Zhao et al. showed that MiRNA-34 family members contribute to scarless wound healing by targeting the TGF-β pathway (25). Kwan et al. showed that miRNA-181b regulates production of decorin, reduces fibrosis, and induces regeneration in many tissues by dermal fibroblasts; thus, it may be a potential therapy for hypertrophic scars (26).

4. Conclusions

Faster and better wound healing with decreased scar formation can be performed on patients if we can obtain a better understanding of cell functions, their interactions, and the subcellular processes that occur in the wound area. Recent studies have shown that in regeneration pathways, a number of miRNAs play a regulatory role and control gene expression in the wound healing process (30-33). Recent developments in the field of miRNAs have led to renewed interest in their use as therapeutic agents. Based on the literature cited in this review, miRNAs have great potential for use as therapeutic reagents for wound healing, in particular in the prevention of scar formation. Primary studies confirm this hypothesis, but further research is required to bring such treatments to the clinic.

Footnotes

Authors' Contribution: Study concept and design, Madjid Momeni-Moghaddam; drafting of the manuscript, Zahra Kardoost; critical revision of the manuscript, Jalal Omrani Bidi; study supervision, Madjid Momeni-Moghaddam.

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