Connecting the Dots: A Scoping Review on MicroRNA Expression and Angiogenesis Regulation in Chronic Wound Healing

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Introduction

What we know:

- MicroRNAs play a pivotal role in modulating gene expression during wound healing.
- In chronic wounds, such as Venous Leg Ulcers (VLUs) and Diabetic Foot Ulcers (DFUs), dysregulated microRNAs disrupt gene expression, contributing to delayed healing.
- About 24% of the Medicare beneficiaries >65 years old present with chronic VLUs or DFUs.

Areas to explore:

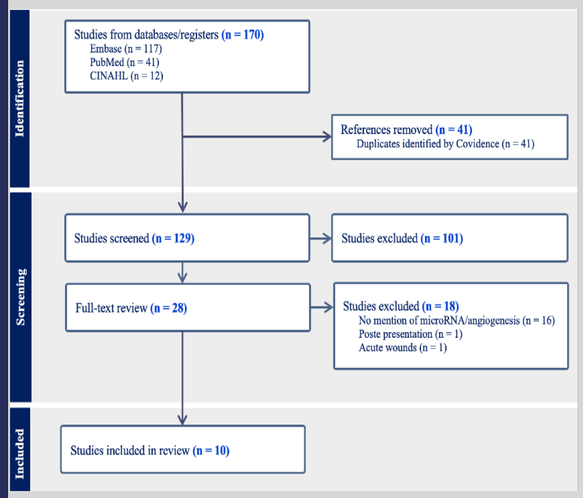
- Identifying microRNAs and their target pathways is essential for understanding the intricate mechanisms of wound healing. This knowledge can guide researchers towards potential therapeutic targets for effectively treating chronic wounds.

Aim

To identify microRNAs pathways associated with angiogenesis during wound healing process in DFUs and VLUs.

Methods

A literature review was conducted in October/2023 using keywords related to DFUs, VLUs, microRNAs, and wound healing. Studies published between 2020-2023 focusing on the role of microRNAs in angiogenesis regulation during the wound healing process were included. Studies were excluded if did not address microRNAs' involvement in angiogenesis.



Screening Process: PRISMA Flow diagram

Results

Table 1: MicroRNA profiling and effect on wound healing

miRNA profile	miRNA expression	Effect on angiogenesis and wound healing	miRNA target/signaling pathway
miR-21-5p	↑	Improve vascular function and endothelial tube formation	AKT, and MAKP
miR-23a-3p	↓	Endothelial dysfunction, impaired tube formation and angiogenesis	SDF-1α/3′-UTR
miR-23b-3p	↓	Endothelial dysfunction, impaired tube formation and angiogenesis	SDF-1α/ 3′-UTR
miR-23c	↑	Endothelial dysfunction, impaired tube formation and angiogenesis	eNOS, SDF-1α/3'-UTR, HIF-1α and VEGF
miR-27b	↑	Improve vascular function and endothelial tube formation	VEGF-A, Nrf2 & SDF-1α
miR-92a	↑	Impairment of angiogenesis	ITGA5, PTEN, SIRT1, KLF2, and KLF4
miR-204-3p	↑	Improve vascular function and endothelial tube formation	HIPK2
miR-205-5p	↑	Endothelial dysfunction, impaired tube formation and angiogenesis	VEGF-A
miR-144-3p	↑	Endothelial dysfunction, impaired tube formation and angiogenesis	NFE2L2/ HIF1
miR-181-5p	↑	Endothelial dysfunction, impaired tube formation and angiogenesis. increase senescence in endothelial cells.	Nrf2/3'UTR
miR-195-5p	↑	Endothelial dysfunction, impaired tube formation and angiogenesis	VEGF-A
miR-301a-3p	↑	Endothelial dysfunction, impaired tube formation and angiogenesis	IGF1, PI3κ/ AKT/PPARγ
miR-503	↑	Endothelial dysfunction, impaired tube formation and angiogenesis	IGF1

Legend: AKT: Serine – threonine kinase; MAKP: Mitogen-activated protein kinase; SDF-1α: Stromal cell-derived factor-1α; eNOS: Endothelial nitric oxide synthase; HIF-1α: Hypoxia-inducible factor 1α; VEGF: Vascular endothelial growth factor; Nrf2: Nuclear factor erythroid 2-related factor 2; HIPK2: Homeodomain-interacting protein kinase 2; ITGA5: Integrin subunit alpha-5; PTEN: Phosphatase and tensin homolog; SIRT1: Sirtuin 1; KLF: Krüppel-like factor; IGF1: Insulin-like growth factor 1

151 samples

- 84 DFUs
- 15 VLUs
- 52 other wounds

- The average age of the participants was 58 years old though demographic information was reported in only three studies.
- MicroRNAs were extracted from participants using different techniques from various sources across the studies, including blood serum, wound fluid, or biopsy.
- One study evaluated a wound care dressing coated with anti-miR-92a in an animal model of chronic diabetic foot ulcers (DFU) with promising results.
- Another study evaluated a hydrogel embedded with exosomes derived from adipose-derived stem cells (ADSCs) in a DFU model resulting in down-regulation of miR-144-3p and improvement of angiogenesis.
- Additionally, a study extracted miR-21-5p from mesenchymal stem cells and applied to in-vitro and in-vivo ischemic-induced DFU models with improvement of angiogenesis and wound healing.

Discussion

In a hyperglycemic wound microenvironment commonly seen in uncontrolled diabetes, the exacerbation of senescent cells leads to dysregulated microRNAs, resulting in impaired angiogenesis and delayed wound healing. MicroRNAs may exhibit opposing effects depending on the microenvironment. For instance, miR-21 may demonstrate either pro-angiogenic or anti-angiogenic properties depending on whether it is in a normoxic or hypoxic condition.

Several studies are exploring different delivery system technologies to effectively deliver microRNAs to the wound bed in clinical practice. These include hydrogel-based or nanofiber-based wound products, offering sustained release and demonstrating improved wound healing in animal models.

Hence, identifying the microRNAs implicated in wound healing must consider the diverse pathophysiological aspects of different wound etiologies, as well as their unique wound microenvironment.

Considering these factors is important for developing targeted therapeutic strategies that effectively modulate microRNA expression to enhance wound healing outcomes.

Conclusion and Implication for Practice

The wound healing process relies significantly on microRNA-mediated gene modulation.

While manipulating microRNA expression with miR-inducers/inhibitors holds promise for treating chronic wounds, further research is necessary to fully understand and optimize this therapeutic approach.

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References