Exploring MicroRNA-Mediated Pathways in Wound Healing in Patients with Chronic Venous Leg Ulcers

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Significance

What we know:

The incidence of Chronic Venous Leg Ulcers (CVLU) is escalating among the adult and elderly population.

About 24% of the Medicare beneficiaries >65 years old present with CVLUs or Diabetic Foot Ulcers (DFU).

The pathophysiology of wound healing is not yet clearly understood, with multiple factors contributing to the healing process

Purpose

To explore the influence of microRNAs associated with wound healing in CVLU patients.

Methods

Literature search:
Medline/PubMed
EMBASE
96

Inclusion Criteria:
Published in English from 2013-2023. Analyzing miRNA expression in CVLU

Exclusion Criteria:
Studies with focus on diabetic ulcers

13 selected for full text review

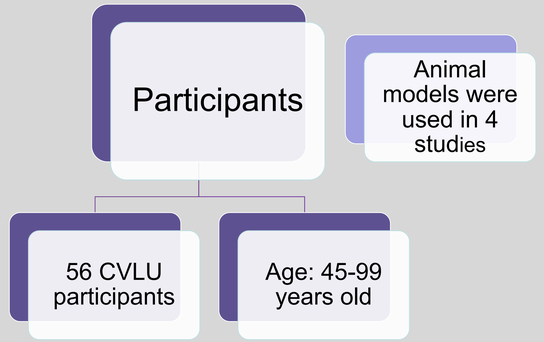
5 included

Findings

Table 1:MicroRNA Regulation of Wound Healing

MicroRNA Profile	Effect on Wound Healing	Cellular Response	Target/Signaling Pathway	Expression in CVLU
miR-17~92	+	Enhances angiogenesis	VEGF	Downregulated
miR-19a/b	+	Restores wound healing by downregulating keratinocytes' inflammatory response	NF-kB	Downregulated
miR-20a	+	Restores wound healing by downregulating keratinocytes' inflammatory response	NF-kB	Downregulated
miR-34a	-	Impairs wound healing by enhancing keratinocytes' inflammatory response	miR-34-LGR4 axis	Overexpressed
miR-34c	-	Impairs wound healing by enhancing keratinocytes' inflammatory response	miR-34-LGR4 axis	Overexpressed
miR-92a	-	Hinders angiogenesis	ITGA5, PTEN, SIRT1, KLF2, and KLF4	Overexpressed
miR-96-5p	+	May enhances cellular growth	TP53INP1, LAMC1, EDNRA, GJC1, and FN1	Downregulated
miR-126	+	Enhances angiogenesis	?	Downregulated
miR-205	-	Impairment of keratinocytes migration and epithelialization	ITGA5	Overexpressed
miR-210	+	Enhances angiogenesis	?	Downregulated
miR-218-5p	+	May enhances cellular growth;	?	Downregulated
miR-221	-	Hinders angiogenesis	?	Overexpressed
miR-222	-	Hinders angiogenesis	?	Overexpressed
miR-296	+	Enhances angiogenesis; Upregulates VEGFR2 expression	VEGFR2	Downregulated
miR-301a-3p	-	Impairs angiogenesis; Exacerbates vascular endothelial cell damage, Mediates inflammatory responses, Increases HUVEC apoptosis, Elevates oxidative stress, Impairing wound healing	IGF1/PI3K/Akt/PPARγ/NF-κB/MMPs	Overexpressed
miR-378	+	Enhances angiogenesis	?	Downregulated
miR-424-5p	-	Increases inflammatory response; inhibits keratinocyte proliferation	E2F	Overexpressed
miR-450-5p	-	Increases inflammatory response and inhibits keratinocyte proliferation	?	Overexpressed
miR-516-5p	-	Increases inflammatory response and inhibits keratinocyte proliferation	E2F	Overexpressed
miR-7704	-	Increases inflammatory response and inhibits keratinocyte proliferation; Downregulate insulin	ERBB, and small GTPase-mediated signaling pathway	Overexpressed

Legend: VEGF: Vascular endothelial growth factor; NF-kB: Nuclear Factor kappa-light-chain-enhancer of activated B cells; TP53INP1: Tumor protein 53-induced nuclear protein 1; LAMC1: Laminin subunit gamma-1; EDNRA: Endothelin receptor type A; GJC1: Gap junction alpha-1 protein; FN1: Fibronectin 1; ITGA5: Integrin subunit alpha 5; VEGFR2: Vascular endothelial growth factor receptor 2; IGF1: Insulin-like growth factor 1; PI3K: Phosphoinositide 3-kinase; Akt: Protein kinase B; PPARγ: Peroxisome proliferator-activated receptor gamma; MMPs: Matrix metalloproteinases; E2F: E2F transcription factor; ERBB: Erb-B2 receptor tyrosine kinase.



miR-301a-3p was overexpressed in both chronic vascular insufficiency (CVI) and CVLU groups, showing a negative correlation with the levels of MMP1, MMP3, MMP9, IL-1β, and TNFα. This suggests a potential role of miR-301a-3p in the pathogenesis of CVI and its associated complications.

Discussion and Implication for Practice

MicroRNAs play a pivotal role in regulating angiogenesis, inflammatory responses, cell migration, and remodeling during the wound healing process.

Given the likelihood of differential microRNA expression patterns between diabetic foot ulcers (DFUs) and chronic venous leg ulcers (CVLUs), identifying the microRNAs involved in wound healing requires careful consideration of the pathophysiological aspects inherent in each wound etiology, as well as their unique wound microenvironments.

The dentification of specific microRNAs and their target-gene pathways offers valuable insights, guiding researchers towards potential therapeutic targets for treating chronic venous leg ulcers.

Acknowledgment

University of Florida Graduate School and College of Nursing for funding and support.

References