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Diabetic Mouse Delayed Wound Model Following Treatment with the NerveStim™ Neuropathy System

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Abstract

Delayed wound healing in diabetes is characterized by impaired angiogenesis, persistent inflammation, extracellular matrix dysregulation, and peripheral neuropathy. A preclinical study was conducted using a diabetic mouse delayed wound model to evaluate the surrounding tissue of a wound, (its periwound) and its tissue responses following treatment with the NerveStim™ Neuropathy System, a combination topical gel and neuromuscular electrical stimulation platform. Periwound tissue was harvested at Day 14 and analyzed using NanoString gene expression profiling. Treated animals demonstrated visibly increased periwound tissue thickness compared to untreated controls. Differential expression analysis identified 76 significantly upregulated and 17 downregulated genes. Upregulated pathways included angiogenesis (Vegfa, Fgf2, Pdgfb, Nos3), neurotrophic signaling (Ngf, Bdnf, Scn9a, Trpv1), macrophage polarization (Arg1, Mrc1, Il10), and extracellular matrix remodeling (Col1a1, Col3a1, Mmp9, Timp1). Downregulation of select pro-inflammatory mediators (Nos2, Mif) was observed. These coordinated transcriptional changes are consistent with activation of reparative immune, neurovascular, and matrix remodeling pathways in diabetic periwound tissue.

Introduction

Diabetic wounds exhibit impaired healing secondary to the underlying condition of the wound's surrounding tissue such as peripheral neuropathy, microvascular dysfunction, chronic inflammation, and extracellular matrix instability [1,2,3]. Animal models of diabetic delayed wound healing replicate key features of human disease, including reduced angiogenesis, altered inflammatory signaling, and impaired neurovascular repair [4,5].

Periwound tissue serves as a biologically active interface between viable tissue and the wound bed and plays a critical regulatory role in wound progression and closure [2,6]. Disruption of neurovascular signaling within this region contributes to chronicity and recurrence.

The NerveStim™ Neuropathy System combines a bioactive gel with a neuromuscular electrical stimulation device designed to target periwound tissue biology. This preclinical investigation evaluated morphological and transcriptional changes in periwound tissue in a diabetic mouse delayed wound model.

Methods

Study Design

A controlled preclinical study was conducted using a diabetic mouse delayed wound healing model to study the periwound and its release of biomarkers post treatment. Animals were assigned to:

- Treatment group: Hemastyl™ Gel + NeuroMuscular Electrical Stimulation Device
- Control group: Standard dressing alone

Periwound tissue was harvested at Day 14 following treatment initiation.

Morphological Assessment

Gross morphological images were obtained at Day 14 to assess periwound tissue characteristics.

Gene Expression Profiling

Periwound tissue underwent NanoString gene expression analysis using a custom wound healing and nerve repair codeset. Differential expression analysis was performed using predefined statistical thresholds. Genes were grouped into functional domains including inflammatory signaling, angiogenesis, neurotrophic signaling, macrophage polarization, and extracellular matrix remodeling.

Results

Periwound Tissue Morphology

By Day 14, treated animals demonstrated visibly increased periwound tissue thickness compared to untreated controls. Quantitative histomorphometry was not performed in this early-stage study.

Global Differential Gene Expression

NanoString analysis identified 76 significantly upregulated and 17 significantly downregulated genes (Figure 1). Pathway analysis demonstrated enrichment in cytokine–chemokine receptor interaction and TNF signaling pathways.

Angiogenesis and Endothelial Activation

Significant upregulation was observed in key angiogenic mediators including Vegfa, Fgf2, Pdgfb, Nos3, and Pecam1. VEGF and FGF2 are established regulators of endothelial proliferation and capillary formation during wound repair [7,8,9]. eNOS (Nos3) supports microvascular perfusion and nitric oxide–mediated vasodilation [10].

Neurotrophic and Neural Signaling

Upregulation of Ngf and Bdnf is consistent with known roles of these neurotrophins in peripheral nerve regeneration and axonal sprouting [11,12,13]. Increased Scn9a and Trpv1 expression has been associated with reactivation of regenerating sensory fibers [14].

Macrophage Polarization and Immune Regulation

Elevated Arg1, Mrc1, and Il10 with concurrent reduction of Nos2 suggests polarization toward a reparative M2 macrophage phenotype. Transition from M1 to M2 macrophages is critical for progression from inflammation to tissue repair [15,16,17].

Extracellular Matrix Remodeling

Increased Col1a1, Col3a1, Mmp9, and Timp1 expression indicates active matrix remodeling. Coordinated MMP and TIMP regulation is essential for balanced extracellular matrix turnover during wound healing [18,19].

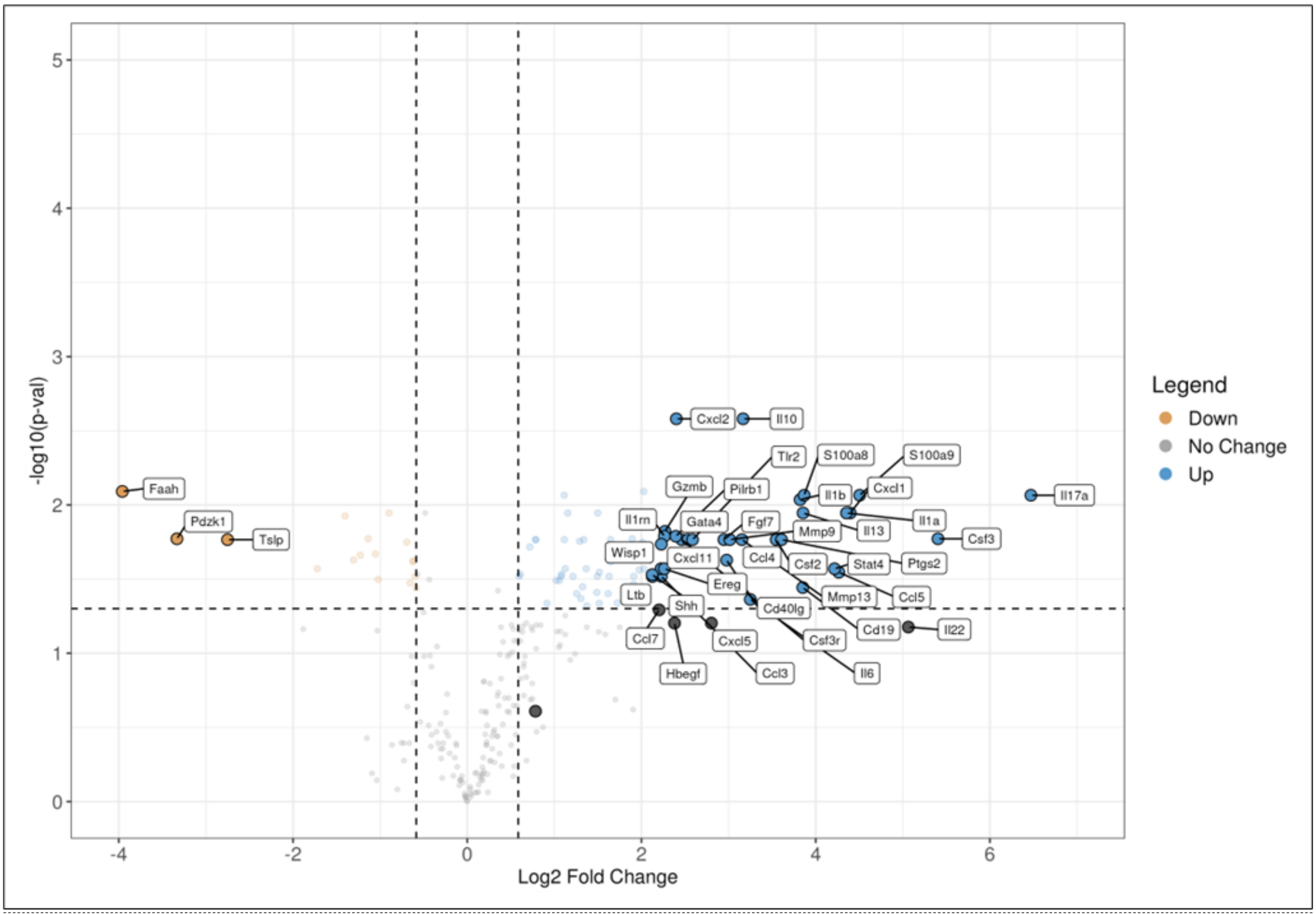

Figure 1. Volcano plot demonstrating statistically significant upregulation and downregulation of genes in periwound tissue at Day 14 following treatment with the NerveStim™ Neuropathy System, as assessed by NanoString gene expression profiling.

Discussion

Treatment of the periwound with the NerveStim™ Neuropathy System in a diabetic mouse delayed wound model was associated with coordinated transcriptional modulation across angiogenic, neurotrophic, immune, and extracellular matrix pathways.

Hemastyl™ induces a coordinated molecular response characterized by controlled early inflammation followed by transition to a reparative phenotype. Downregulation of chronic inflammatory mediators (IL17A, MIF, NOS2), alongside increased anti-inflammatory signaling and M2 macrophage markers, supports resolution of inflammation. Concurrent upregulation of angiogenic, extracellular matrix, and neurotrophic factors is consistent with enhanced tissue repair, neovascularization, and structural remodeling, indicating effective progression through key phases of wound healing.

Upregulation of Vegfa, Fgf2, Nos3, and Pecam1 supports activation of angiogenic programs.

Concurrent elevation of Ngf and Bdnf indicates engagement of neurotrophic signaling.

Increased Arg1, Mrc1, and Il10 with reduced Nos2 expression suggests macrophage polarization toward a reparative phenotype.

Because functional nerve conduction testing, capillary density quantification, and histomorphometric analysis were not performed, conclusions are limited to gene expression and gross morphological observations.

Conclusion

In a diabetic mouse delayed wound model, treatment of the periwound with the NerveStim™ Neuropathy System was associated with transcriptional activation of angiogenic, neurotrophic, immune-regulatory, and extracellular matrix remodeling pathways within periwound tissue. These findings provide mechanistic insight into biological processes involved in healing diabetic tissue surrounding a wound that may support enhanced wound repair in diabetic environments.

Ethics Statement

All animal procedures were conducted in accordance with institutional preclinical research standards.

Conflict of Interest

The author declares no conflict of interest.

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