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Researchers Take Another Step Toward Healing Chronic Venous Leg Ulcers

Building on their previous success, Marjana Tomic-Canic, Ph.D., and colleagues report molecular and genetic discoveries that could further the potential to transform chronic venous leg ulcers into normally healing wounds.

This could be good news for the 1% of people worldwide who live with the pain, risk of infection and physical disability associated with these chronic wounds.

In the 20 years since the Food and Drug Administration approved a bioengineered living cell construct, or BLCC (Apligraf, Organogenesis Inc.), to help transform acute wounds into acute, easier-to-heal forms, no one has discovered exactly how this product works.

Until now.

The University of Miami Miller School of Medicine investigators conducted a clinical trial to analyze biopsies from the center of fibrous venous leg ulcers before and after BLCC treatment to understand how it stimulates healing. The findings were highlighted on the cover of the March/April 2020 journal *Wound Repair and Regeneration*.

They found multiple molecular mechanisms at work, including remodeling of fibrotic material (excessive connective tissue) in the wound. They also uncovered changes to TGF-beta signaling that orchestrates fibrosis, enzyme changes that remodel the extracellular matrix (which provides structure and biochemical support to different components of the skin), and, surprisingly, the release of zinc.

“We performed genomic analyses to understand how this cell therapy changes patients’ own cells to become better at healing,” said senior study author Dr. Tomic-Canic, professor and vice chair of research and the William E. Eaglstein M.D. Chair in Wound Healing in the Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery at the Miller School.

“These findings provide a major advance in the clinical field of tissue repair,” added Dr. Tomic-Canic, who is also director of the Wound Healing and Regenerative Medicine Research Program at the Miller School.

Five novel findings emerged from this first-of-its-kind study:

- This is the first comprehensive genomic insight into a wound bed of any type of chronic wound. “This type of

in-depth analyses resulted in identification of major gene networks and functions that are contributing to pathophysiology," Dr. Tomic-Canic said.

- This paper is the first to demonstrate that specific inflammatory and pro-fibrotic characteristics of venous leg ulcers exhibit hallmarks of typical fibrotic disease.
- The study reveals two new factors associated with healing of chronic wounds: release of metallothioneins (metal-binding proteins) and zinc.
- The researchers discovered fibroblasts can serve as a source of the collagen cleaving enzyme, matrix metalloproteinase-8 (MMP8). MMP8 plays a role in dermal remodeling.
- The data introduce a novel concept that the center of a wound, also known as the wound bed, has distinct tissue properties compared with the wound edge and has unique response to therapy that complements the response from the wound edge.

The big-picture message from the study goes beyond Apligraf. The research "also provides new insights into potential mechanisms by which cell-based therapies may contribute to remodeling fibrotic tissue and promote healing in patients with chronic wounds and beyond," Dr. Tomic-Canic said. "And as such, the findings will have a very significant scientific and clinical impact."

In terms of next steps, the investigators plan to evaluate genes involved in "healing signatures" that boost the transition from non-healing to healing wounds. They are "clinically very relevant because they can be used as a

guiding tool, particularly in evaluating new therapies," she added.

Dr. Tomic-Canic's co-authors from the Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery include lead study author Rivka C. Stone, M.D., Ph.D., assistant professor, Irena Pastar, Ph.D., research associate professor, and Evangelos Badiavas, M.D., Ph.D., professor.

Dr. Stone received the Young Investigator Award when she presented this work at the Wound Healing Society Annual Meeting.

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