

ABSTRACT

**A Modified Collagen Gel Resolves Wound Inflammation via Microrna-21-**

**dependent Pro-healing Macrophage Polarization**

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**Background**: Collagen based dressings are widely used in wound care yet their

modified collagen gel (MCG) dressing demonstrated robust vascularization of

ischemic wounds and improved healing outcomes. Wound macrophages play a

critical role in enabling wound angiogenesis and timely healing. Thus, in this

work, we sought to investigate the direct action of MCG dressing on wound

macrophage phenotype and function.

**Methods:** Wound cells were isolated from

MCG treated PVA sponges implanted subcutaneously on the back of mice.

**Results:** MCG increased macrophage recruitment to the wound site and promoted

polarization to pro-healing (m/heal) phenotype indicative of robust

inflammation followed by timely resolution (p < 0.05; n54). Increased m/heal

phenotype polarization was associated with copious production of anti-inflammatory

cytokine IL-10 and proangiogenic VEGF suggesting a direct action of MCG on wound macrophages in supporting resolution of inflammation and improving angiogenesis

(p < 0.05; n54). Impaired clearance of apoptotic cell bioburden at wound-site feeds chronic inflammation. Previous studies in our laboratory reported that engulfment of apoptotic cells by macrophages (efferocytosis) drives polarization of pro-inflammatory macrophages (m/inf) to m/heal via a miR-21-PDCD4-IL-10 pathway. Significantly increased (p < 0.05;

n54) efferocytosis index was noted in macrophage from MCG treated wounds.

Such favorable outcome resulted in a significant induction (p < 0.05; n54) of

miR-21 expression. Implicating miR-21 as a causative factor, MCG mediated

induction of IL-10 in wound macrophages was blunted under conditions of

miR-21 knockdown by miR-21-zip. Pharmacological inhibition of JNK in macrophages

resulted in attenuated IL-10 production by MCG, indicating a role of

miR-21-JNK pathway in MCG-mediated IL-10 release in macrophages.

**Conclusion:**

The findings of this work provide a novel paradigm in macrophage-ECM

interactions as well as reshape the understanding of the mechanisms of action

of collagen based dressings in the treatment of chronic wounds.

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