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Co-delivery of a growth factor and a tissue-protective molecule using elastin biopolymers accelerates wound healing in diabetic mice

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ABSTRACT

Growth factor therapy is a promising approach for chronic diabetic wounds, but strategies to efficiently and cost-effectively deliver active molecules to the highly proteolytic wound environment remain as major obstacles. Here, we re-engineered keratinocyte growth factor (KGF) and the cellular protective peptide ARA290 into a protein polymer suspension with the purpose of increasing their proteolytic resistance, thus their activity *in vivo*. KGF and ARA290 were fused with elastin-like peptide (ELP), a protein polymer derived from tropoelastin, that confers the ability to separate into a colloidal suspension of liquid-like coacervates. ELP fusion did not diminish peptides activities as demonstrated by ability of KGF-ELP to accelerate keratinocyte proliferation and migration, and ARA290-ELP to protect cells from apoptosis. We examined the healing effect of ARA290-ELP and KGF-ELP alone or in combination, in a full-thickness diabetic wound model. In this model, ARA290-ELP was found to accelerate healing, notably by increasing angiogenesis in the wound bed. We further showed that co-delivery of ARA290 and KGF, with the 1:4 KGF-ELP to ARA290-ELP ratio, was the most effective wound treatment with the fastest healing rate, the thicker granulation tissue and regenerated epidermis after 28 days. Overall, this study shows that ARA290-ELP and KGF-ELP constitute promising new therapeutics for treatment of chronic wounds.

1. Introduction

The number of patients with diabetes is rapidly increasing around the world with an estimated 439 million adults affected by 2030 [1]. Around 25% of this population can be expected to develop diabetic ulcers, which could lead to amputation due to progression of the disease for more than 14% of these patients. Annual chronic wound management costs exceed $20 billion in the United States alone [2] and already severely burden the US healthcare system [3]. Clinical practice guidelines recommend the treatment of diabetic foot ulcers with surgical debridement, infection control, redistribution of pressure off the wound, and a selection of dressings that allow for a moist wound environment and control excess exudation [4]. Despite good wound care, non-healing ulcers remain a leading cause of non-traumatic amputation in the US [5] with an increased incidence of death among these patients [6], highlighting the need for new viable treatments.

The wound healing response is a complex and dynamic process that relies on a coordinated effort from different cell types along with protein and chemical mediators to restore skin function. The healing process is divided into several overlapping, interdependent phases: hemostasis, inflammation, cell proliferation, migration, angiogenesis, reepithelialization and remodeling of the extracellular matrix [7]. Hyperglycemia caused by diabetes often interferes with the initiation, regulation, and/or termination of the healing stages leading to an impaired wound healing response. Diabetic ulcers are non-healing wounds characterized by a chronically inflamed wound bed due to numerous factors including neuropathy, improper oxygenation, insufficient vascular supply to the extremities, and bacterial infection [4].

Growth factors and cytokines are essential in the organization of the molecular processes involved in making cutaneous wound healing efficient [8]. Specifically, growth factors have been shown

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