Hypertrophic scar treatment by using nanofibers releasing anti-fibrogenic factors

[1+] Poormasjedi-Meibod, M; [1] Hartwell, R; [2] Leung, V; [1] Salimi, S; [2] Ko, F; [1] Ghahary, A

[1] Department of Surgery, University of British Columbia, Vancouver, Canada
[2] Advanced Fibrous Materials Laboratory, University of British Columbia, Vancouver, Canada

Introduction:

Wound healing is a dynamic process that strikes a fine balance between synthesis and degradation of extracellular matrix (ECM). Non-healing and over-healing are two extreme cases in which the bio-mechanical processes of normal tissue are disturbed due to either deficiencies or alterations in ECM composition and organization. Although the promotion of healing in patients is clearly desirable, its cessation is equally important. Over healing processes in skin such as post-burn hypertrophic scarring are disfiguring and devastating results in bulky, itchy and inelastic scars that are detrimental to millions of burn and trauma patients [1,2]. Unfortunately current treatment modalities for dermal fibrosis still remain unsatisfactory. Moving toward novel approaches to rapidly repair burn wounds, our research group identified a small molecule, Fibrosis Stop 1 (FS1), having anti fibrotic properties. Our in vivo studies demonstrate that daily application of a cream containing FS1 effectively eliminates evidence of scarring in a rabbit ear fiber-optic model. In extensive burns, where the daily application of the cream is not possible, an effective wound dressing, releasing controlled doses of FS1, will be beneficial.
This study aims to determine the cellular and molecular mechanisms responsible for the anti scarring effects of FS1 and developing a new generation of wound dressing, having anti scaring properties, via incorporation of FS1 in nanofibers by using electrospinning process.

Method and materials:

In order to determine the effects of FS1 on dermal cells viability and proliferation dermal fibroblasts and keratinocytes were treated with increasing concentrations of FS1 (6.25, 12.5, 25, 50, 100 and 150 μg/ml). Cell proliferation and viability were evaluated by using MTT and FACS analysis, respectively. Effects of FS1 treatment on the expression of different ECM components, collagen type-I, fibronectin and matrix metalloproteinase-1 (MMP1), were evaluated by Western blotting. Wound dressings containing FS1 were fabricated by electrospinning process. The FS1 was dissolved in an aqueous solution, and polyvinyl alcohol (PVA) was used as the carrier for its water solubility. The drug and polymer mixture was fabricated into nanofibers by electrospinning at a voltage of 17 – 20kV. In order to control and prolong the FS1 release from nanofibers the drug-loaded PVA was enveloped by polycaprolactone (PCL). Also, the enveloped drug-loaded PVA was co-electrospun with polylactic-glycolic acid (PLGA) to form a two-phased center layer. Drug release was measured by incubating nanofibre dressings in a phosphate buffered saline (PBS) solution for predetermined durations. The amount of released drug was determined by spectrometric assays.The biological activity of released FS1 from nanofibers was evaluated by measuring its stimulatory effect on MMP1 expression by dermal fibroblasts.

Results:

Our in vitro experiments revealed that while FS1 doesn't have any adverse effect on dermal cells viability or proliferation, it modulates the expression of ECM components by these cells. Subsequent studies demonstrated that fibroblast treatment with increasing concentrations of FS1 leads to a significant decrease in the expression of collagen type-I and fibronectin while it increases the expression of MMP1, which is a collagenase. Decreasing the ECM deposition and increasing the rate of ECM degradation resulted in improving the quality of wound healing outcome and prevention of hypertrophic scar emergence. The FS1 loaded PVA demonstrated immediate and complete drug release, due to its water solubility. The addition of PCL envelop and co-spinning with PLGA leads to a significant reduction in the burst release, as a result of the added tortuosity and increasing the hydrophobicity of the nanofiber shell. Incubation of fibroblast with nanofibers containing FS1 leads to a significant increase in the expression of MMP1 by these cells, in comparison to untreated cells or cells incubated with nanofibers alone. This increase in the expression of MMP1 revealed that incorporation of FS1 in nanofibers doesn't have any adverse effect on drug activity while prolonging and controlling the drug release profile.

Conclusion:

This study revealed that FS1 mediates its anti-fibrotic properties through increasing the expression of matrix metalloproteinases (MMPs) and reducing the production of ECM components, collagen type I and fibronectin, by dermal fibroblasts. Also the current study sets the stage for development of a new generation of wound dressings that can facilitate the controlled and prolonged release of this hydrophilic anti scarring drug while maintaining the biological activity of it. This study showed that using a hydrophobic polymer (PCL) as a scaffold envelop or co-spinning the drug carrier with other hydrophobic polymer (PLGA) is effective in reducing burst release by increasing tortuosity for penetrating fluid.

We anticipate that this research project provides new therapeutic options that will improve healing outcome and quality of life for millions of patients who suffer from devastating fibroproliferative disorders, such as hypertrophic scarring and keloid worldwide including Canada.

References:

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