Biomimetically Patterned Smart scaffolds for Tissue Engineering and Wound Healing

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Abstract

This thesis deals with critical and rudimentary issues in polymer material property stabilization, nature-inspired biophysical cue-mediated drug delivery and contact guidance in cell-matrix interaction, and the development of a cell-type independent diabetic wound healing scaffold. The prudent attributes of cutaneous wound healing scaffolds emerge to switch from a solitary cellular growth-supporting model to a comprehensive one that can promote quick healing with minimum scar formation. To fulfil this, a scaffold should always provide holistic support to the tissue microambience at the wound bed by starting the release of growth factors, initiating rapid cellular influx, setting angiogenesis in motion, augmenting granulation tissue formation, and maintaining an infection-free environment. To develop such a scaffold, the selection of appropriate biomaterials and fabrication techniques is important. In Chapter 2, optimization of the material properties of alginate has been reported. Dual cross-linking using calcium chloride and maleic anhydride is accomplished, which curbs the age-old problem of alginate's erratic degradation, and an optimized concentration of honey has been incorporated into the hydrogel, which becomes a healing substrate. *In vivo* experiments using a murine wound model prove this hydrogel to be an acute wound healing tool. However, to achieve diabetic wound healing, external guidance to the cells for proliferation and migration is needed, for which biomimetic biophysical cues have been introduced using soft lithography and freeze-drying on honey-embedded silk fibroin scaffolds in Chapter 3. We show that the rose petal-inspired hierarchical surface structures on the porous silk fibroin scaffolds can increase proliferation, mesenchymal to epithelial transition, and multilineage trans-differentiation of adipose-derived mesenchymal stem cells while restraining their senescence. In Chapter 4, we report the influence of these hierarchical structures on fibroblast behavior and model the cell-matrix cross-talk. The micro-nano features present on the ampicillin-loaded silk fibroin porous scaffold provide biophysical cues to the fibroblasts' sensors, which help the cells form a continuous monolayer. Topographic patterns also render the porous silk fibroin scaffold surface hydrophobic without any chemical functionalization, which in turn makes multiple-dose controlled drug release possible. In Chapter 5, *in vivo* studies have been conducted in a cutaneous excisional diabetic wound murine model to investigate the chronic wound healing efficacy of our developed scaffold. Upon treating full-thickness excisional diabetic wounds with the scaffolds, the wound closure kinetics, ultrastructural changes of the skin due to healing, and protein and gene expressions have been studied using different modalities, such as stereozoom microscopy, optical coherence tomography, scanning electron microscopy, histopathology, immunohistochemistry, immunofluorescence, and quantitative real-time polymerase chain reaction. Interestingly, the rose petal-patterned, replenishable, and controlled ampicillin-delivering porous silk fibroin scaffold has been able to achieve regenerative healing of a full-thickness cutaneous excisional diabetic wound in 20 days from the day of wound creation. Finally, Chapter 6 concludes with a summary of the whole doctoral work and the future scope of work for the present research.

Keywords: Dual-crosslinking, Honey-silk fibroin, Soft lithography, Biomimetic patterning, Biophysical cues, Cell-matrix cross-talk, Controlled and replenishable drug delivery, Diabetic wound healing