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Effect of orientation and density of nanotopography in dermal wound healing

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ABSTRACT

We report on the effect of synthetic extracellular matrix (ECM) scaffold in the form of uniformly-spaced nanogrooved surfaces in dermal wound healing. The rate of wound coverage was measured on various nanotopographical densities with vertical or parallel orientation using nanogrooves of 550 nm width with three different gaps of 550, 1100, and 2750 nm (spacing ratio: 1:1, 1:2 and 1:5). Guided by the nanotopographical cues in the absence of growth factors in wound healing process, the cultured NIH-3T3 cells demonstrated distinctly different migration speed, cell division, and ECM production as dictated by the topographical density and orientation, whereas the proliferation rate turned out to be nearly the same. Based on our experimental results, the nanopattern of 1:2 spacing ratio yielded the best wound healing performance in terms of migration speed, which seems similar to the natural organization of collagen fibers.

1. Introduction

The skin is a representative protective tissue and acts as a barrier, preventing invasion of various pathogens or as a mechanical damper, absorbing mechanical impact. In the multiple layers of skin, the dermis presents distinctive regenerative functions upon trauma through hemostasis, inflammation, deposition of connective tissues, neovascularization, wound contraction and scar maturation [1]. For dermal wound healing, two factors are mainly involved for the guidance of fibroblasts: growth factors and extracellular matrix (ECM). When a deep scratch such as incisional wound is generated, platelets, neutrophils and macrophages release growth factors and form a concentration gradient of growth factors around the wound site, leading to the recruitment of neighboring fibroblasts. As the fibroblasts migrate across the concentration gradient of growth factors, their migration pathways are guided by the topography of ECM, which is composed of various fibers such as multiple collagens and fibronectin. Here, the recruitment of fibroblasts by the concentration gradient of growth factors is termed 'chemotaxis' [2], while the guided migration following the topographical cue 'contact guidance' [3].

The ultimate goal of dermal wound healing is to cure the damaged skin tissue effectively without scar formation. In dermal wound healing, various growth factors participate including platelet-derived growth factors (PDGF), transforming growth factors-β (TGF-β) and basic fibroblast growth factor (bFGF) [1]. These growth factors play crucial roles in wound healing by rapidly recruiting fibroblasts to the wound site as well as stimulating the fibroblasts to secret neoconnective tissues such as collagen and fibronectin. During the wound healing, an unavoidable problem is 'scar formation'. Except one isoform of TGF-βs (TGF-β_3), it is known that other growth factors such as PDGF, bFGF, TGF-β2 and TGF-β3 induce scar since they stimulate fibroblasts to excessively produce ECMs [4]. Interestingly, unlike neonatal and adult wound healing, it has been revealed that fetal wound healing has amazing characteristics of no scar formation due to the absence or very small amount of growth factors in the initial wound healing stage [5]. Inspired from such scar-free nature of fetal wound healing, Ferguson and coworkers have neutralized growth factors immunologically, demonstrating scarless dermal wound healing [4]. This work suggests that the utilization of growth factors may not be desirable in preserving the esthetic nature of the regenerated skin tissue.

Although the immunological neutralization of growth factors may present minimized scar formation, the absence of growth factors, in turn, would retard the rate of wound healing due to delayed infiltration of the fibroblasts in the wound bed. Instead of the growth factors, the topography of ECM can also promote dermal wound healing via guided cell migration and proliferation at the wound site. For many decades, in an effort to engineer dermal wound dressing scaffolds, the basket-weave structure of ECM toward the depth direction in dermis has particularly drawn much interest. For example, transplantation of randomly electrospun

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