Strategies for Optimizing Wound Healing and Reducing Scarring

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The repairing of injured skin tissue is a fundamental biological process essential to the continuity of life. Wound repair is a complex and dynamic process which consists of inflammation, angiogenesis, and tissue formation and remodeling [1,2]. The wound site is deposited with fibrin clots to prevent hemorrhage upon injury. Neutrophils and macrophages infiltrate the wounds and keratinocytes migrate to the wound to recover the barrier function of skin. Granulation tissues are built up by endothelial cells and fibroblasts which migrate to the wounds and deposit extracellular matrices such as collagen. Fibroblasts produce matrix metalloproteinases which remodel the matrices over several months during the final stages of repair.

Restoration of the anatomy and function of normal skin as well as underlying tissues is an ideal wound healing. Though regeneration and repair are closely related, there are subtle differences in the inflammatory responses. Reconstruction of the damaged organs and tissues by developmental process, not repair process, is a key concept in regenerative wound healing [3,4]. Recently multipotent stem cells or progenitor cells have been suggested for tissue repair in regenerative medicine. Mesenchymal stem cells (MSCs), which are found from various tissues, form fibroblast-like colonies and proliferate extensively in vitro [5]. MSCs secrete growth factors and cytokines, which activate the wound repair process, and recruit progenitor cells or endogenous stem cells to the wound. In addition, MSCs have the potential to be differentiated into the required cells in wounds because they have multipotency; for example, they can be differentiated into adipocytes, endothelial cells, osteoblasts, and chondrocytes [3]. Our recent report showed that that topically delivered adipose derived stem cells (ASCs) exhibit an activated fibroblast phenotype, enhance macrophage recruitment, and increase granulation tissue formation in the rabbit ear wounds [6]. Our data supports ASCs as a promising cell therapy candidate for the repairing of wounds.

Wound repair is an organized sequential process where signals from one cell type regulate other cell types in a cascade. Derangement of the wound healing process can lead to excessive (hypertrophic) scar formation for which therapeutic options are limited. Scares without skin appendages can cause loss of thermal regulation, less resistance to UV light, abnormal skin hydration, and restricted joint motion. Regeneration of lost tissue and restoration of the function of injured tissues by reducing scar formation are the ultimate goals of wound repair. Use of MSCs for the reduction of scar formation and optimal restoration of tissue in skin is promising because recent reports showed that injected MSCs can attenuate scarring after myocardial infarction [7,8]. MSCs in vivo are surrounded by extracellular matrix (ECM) which consists of collagen and hyaluronic acid. Delivery of MSCs in the presence of matrices will augment the function of MSCs for the reduction of scar and enhancement of wound repair because matrices provide a suitable microenvironment for MSCs.

It has been observed that mucosal wounds heal with minimal scarring, undergo faster healing and exhibit less inflammation than equivalent cutaneous wounds. Compared to skin wounds, mucosal wounds demonstrate a more highly regulated angiogenic response, have a differential expression of key profibrotic growth factors, and result in less scarring. Of note, mucosal epithelium lacks a stratum corneum, but water loss is prevented by its fully hydrated environment. It is shown that the difference in scar formation between mucosal and cutaneous wounds is attributable to differences in their ability to maintain hydration [9]. In addition, microarray analyses identified many genes that were differentially expressed in the epithelium of skin compared to mucosa following injury.

Applying multiple layers of a semiocclusive polyurethane dressing on cutaneous wounds, which mimics a mucosal environment, enhanced healing of rabbit partial-thickness incisional wounds [10]. Microarray analysis showed that increased expression of proinflammatory genes - such as IL-1β, IL-8, COX-2 (cyclooxygenase 2), and TNF-α (tumor necrosis factor-α) - in non-occluded wounds compared with occluded wounds. Both molecular and pharmacological analyses showed that TNF-α and IL-1β independently regulate IL-8 expression in response to reduced hydration. We showed that hydration status directly regulates expression of genes involved in the inflammation in the epidermis. Identification of pathway involved in the epithelial hydration signaling will contribute for the development of novel strategies to optimize wound healing and reduce scarring in clinics.
REFERENCES