Burn wound and therapeutic challenge

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In the August issue of the *Journal of the Chinese Medical Association*, Dr. Feng and colleagues published an interesting research article entitled "Adipose-derived stem cells-induced burn wound healing and regeneration of skin appendages in a novel skin island rat model".[1] The authors tried to resolve one of the most troublesome problems—burn injury, which is the most traumatic, psychological, and physically debilitating injury, not only involving nearly every organ system, including the largest organ of the body-skin, but also leading to significant morbidity and mortality. Skin burn wound often contains the following characteristics, such as slow wound healing, infection, pain, contractures, and keloid formation.[2] Unfortunately, the real mechanisms of poor wound healing and occurrence of subsequent sequelae in burn injury are not well known. We congratulated Dr. Feng's success in their work.[1] Since existing burn wound therapies have been proved to be inadequate and far from satisfactory, the understanding of the precise roles of these stem cells (adipose-derived stem cells) and interplay of the associated regulatory pathway may lead to the much more effective therapy for this enigmatic and challenging condition.

First, the authors used the murine models (rat) for the current study, which are most commonly used to evaluate stem cells effects or stem cells delivery effects on various aspects of wound healing. The main advantages include high reproducibility in controlled conditions, the availability of wild-type, transgenic, and gene knock-in or knock-out animals to search for the potential target genes involving the wound healing process, and of most importance, their accessibility to lineage tracing, low cost, ease of access and handling, availability of inbred strains for transplant compatibility, and reduced donor and genetic variability.[3,4] Of course, there are not totally absence of limitation in murine models. Some limitations are often discussed, such as different architecture of human and mouse skin, difference of the hair follicle cycles, difference in biomarkers on skin stem cells, and difference in response to and in the influence of comorbidities on wound healing.[3,4] Other animal models are pig and sheep.

Second, the basic structure of skin was important for the study of wound healing. Skin is composed of two layers, an epidermis (a stratified epithelium and the basal-cell layer of keratinocytes with branched extensions) and a dermis (superficial papillary region and reticular dermis).[5] The former forms a protective barrier to the environment and the latter contains connective tissue (crosslinked elastic and well-organized collagen, elastic fibers-elasticity and flexibility, extracellular matrix-proteoglycans for hydration and viscosity, skin adnexa, such as hair follicles, oil glands, and sweat glands that are lined with keratinocytes, and a rich plexus of nerves and vessels), providing skin with its mechanical properties.[5]

Third, we should understand the progress of wound healing progress. Wound healing can be artificially separated into three phases, but we should know that these phases are continuous and overlapped.[6–8] The phase 1 (inflammatory phase) involves hemostasis, inflammation to restrict damage and cleanse wound (platelet activation and degranulation driving inflammation; clotting cascade generating fibrin clot to seal the wound; fibrin matrix forming a temporary scaffold for inflammatory cell; cytokines releasing to attract inflammatory, mesenchymal, and endothelial cells to the wound). The phase 2 (proliferative phase) restores skin architecture (switching M1 to M2 macrophage; producing and secreting extracellular matrix, including an increase in type III collagen and in type III to type I collagen ratio occurring as a result of the spur in collagen formation; forming granulation tissue; re-epithelizing; enhancing angiogenesis and fibrogenesis; and repairing adnexal structure). The phase 3 (remodeling phase) progresses scar formation, re-epithelizing wound bed, and closure wound (with the resultant extracellular and protease synthesis and secretion for matrix remodeling such as type III collagen being progressively replaced by type I collage and the normal predominance of type I over type III collagen being restored, optimizing vascular bed and dermal tensile strength and maturing scar formation as relevant to depth of injury).

Fourth, the outcome of wound healing depends on numerous factors, such as wound severity, extent and depth, anatomical site of the wound and skin thickness, the density of adnexal structures, the genetic and epigenetic background and age, the time to healing, comorbidities, microbial contamination, and

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the microenvironmental changes occurring in response to different types of tissue damage.[3] For example, burn wound can be classified into first-degree burn (intact barrier), which recovers within 2 weeks and causes minimal scarring; a second-degree (partial-thickness) burn, which penetrates into but not through the dermis; and a third-degree (full-thickness), which completely destroys the dermis and enters the fat. Furthermore, burns have systemic effects, influencing almost all body systems and causing changes in lung, kidney, heart, liver, gastrointestinal tract, bone marrow, and lymphoid organ function (significant immune imbalance, with resultant prolonged inflammatory phase) and multiple organ dysfunction syndrome, which are mainly mediated by inflammatory mediators, such as tumor necrosis factor alpha and interleukins 6, 8, and 1-β, and all of them are produced at the burn site.[9] Even at the early stage, overwhelming production of these toxic inflammatory cytokines results in the suppression of bone marrow leading to lymphoid and myeloid cell dysfunction, with a significantly increasing risk of infection and subsequently wound healing delay.[9]

Fifth, the application of stems cells, further separating into three main groups: autologous, allogeneic, or xenogeneic, in wound healing has been developed quickly in recent decades. Stem cells are classified by their origin as either embryonic or adult stem cells, which contain at least three different resources, including bone marrow-derived stem cells, adipose tissue-derived stem cells, and blastocyst/placenta/umbilical cord-derived stem cells; and three administration routes have been proposed, such as systemic treatment, topical application, and local injection.[10–14] Stem cells are of special interest in burn wound, as shown by Feng's study.[1] The authors used adipose-derived stem cells to promote angiogenesis, modulate inflammation, and enhance formation and maturation of well-organized wound tissue (hair follicles) in the setting of burn wound.[1] In fact, stem cells have multiple potential indications, including accelerating wound healing, improving skin regeneration to incorporate skin appendages, reducing fibrosis and improving scarring. Besides the use of stem cells, the following strategies are also reported to enhance the effectiveness of stem cell application, such as skin replacement with the use of growth factors, the cutting-edge nanotechnology (nanoscale delivery systems, nanofibers, scaffolds, polymeric, inorganic or lipid nanoparticles, nanoemulsions, nanohydrogel, and liposomes), cell-seeded scaffolds for skin tissue reconstruction, and acellular dermal matrix and/or expander/culture medium.[4,11,12] All of them offer an unprecedented opportunity to revolutionize and invent therapies or boost the effectiveness of current treatment. However, some challenges still exist, including that no ideal administration route to anchor bioactive molecules to applied area, sustain the drug release, and explicitly enhance the therapeutic effectiveness of drugs, no identified cell number for therapy, presence of legislation and concerns of biosafety. To overcome the above-mentioned limitations, induced pluripotent stem cells might be another choice, which can be done by somatic cell reprogramming process to develop patient-specific cells with a tailored phenotype and apply them in clinical practice. The most commonly used cells for reprogramming are obtained from the skin, such as dermal fibroblasts, melanocytes, and keratinocytes, because these are easily accessed and isolated and punch biopsies could provide a lot of cells for further use. Although they are convenient, some concerns about an increasing risk of tumor formation should be well informed.

Burns are the fourth most common type of trauma worldwide, and an estimating 11 million people worldwide sought medical care for burns in 2004.[15] Care of the burn wound is challenged, and there is a long way to go. The development of stem cell therapy, existing dressings, and tissue-engineered skin substitutes has provided an impressive insight for burn treatment. We are looking forward to seeing more studies to investigate this topic-burn wound.

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