Cutaneous Wound Healing

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Overall, burns are smaller than 20 years ago, but even small burns can leave patients with debilitating scars. The management of the burn wound and resultant scarring requires the integration of multiple disciplines. Despite our best efforts, the evaluation and treatment of burn wounds and burn scars has not been completely elucidated. The purpose of this work is to describe the state of knowledge regarding wound healing, both what is known and what is not known, and to recap the priorities set by the breakout sessions of the Burn State of the Science: Research meeting. Wound challenges in 2007 include wound coverage for patients with extensive full-thickness burns, management of donor sites and partial-thickness burns, and reduction of long-term morbidity from burn scars.

BACKGROUND

Early excision and grafting of the burn wound have indisputably impacted burn survival more than any other intervention during the past 30 years.[1] Removing the burn wound has been reported to decrease infection, shorten hospital length of stay, reduce the need for reconstructive surgery, and return patients to their premorbid level of function sooner.[2] These clinical advances have created a standard of care that emphasizes use of sheet skin grafts whenever possible with meshed grafts recommended for coverage of burns in patients with larger full-thickness wounds.[3,4] Larger wounds may benefit from coverage with skin substitutes. Existing skin substitutes include both dermal replacement templates and epidermal cultures.[5] Dermal substitutes, such as Integra (Integra Life Sciences Corp., Plainsboro, NJ), replace the cutaneous connective tissue and provide a template for ingrowth of indigenous cells from the wound bed.[6,7] Dermal substitutes have been reported to reduce scar formation and improve wound pliability. Keratinocyte grafts restore the epidermal layer and restore the cutaneous barrier to infection and fluid loss. Cultured epidermal allografts, which have gained popularity for treatment of nonhealing chronic wounds, have limited applicability in definitive burn treatment because of rejection. Reports of successful treatment of large burns with cultured dermal–epidermal autografts[8–12] have not yet progressed to multicenter trials because of their expense and complexity of fabrication.[13] Whereas development of these products has advanced the field, time of preparation and expense limit their availability for treatment of patients with extensive burn injuries.

Split-thickness skin grafting unavoidably creates donor sites, which share many problems of wound healing with partial-thickness burns, both of which heal spontaneously. The deeper the wound, the longer it takes to heal—increasing the risk of pain, infection and, ultimately, scar formation. Wound care has progressed significantly since fine mesh gauze was a standard donor site dressing. Now, there are many alternatives for antimicrobial-impregnated dressings, ranging from silver to beta-glucan. Nevertheless, our ability to modulate healing with topical growth factors or mediators has been limited despite of years of animal research in the field. Few dressings provide excellent antimicrobial coverage, pain relief, and rapid healing, in part because of the cytotoxicity of antimicrobial agents, which reduce wound contamination but may also delay cell migration and proliferation.

Deep partial-thickness wounds often lead to hypertrophic scar formation. Despite years of research and a moderate ability to predict which wounds are at risk for scar formation, our understanding of the pathophysiology of scar has not advanced. The same treatment alternatives of pressure garments, topical silicone, and steroid injection are used today as 30 years ago. With scar formation comes the other late se-

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quelae of hyperesthesia and itching. Our ability to treat these complications is limited to a few antihistamine agents and anecdotal experience with drugs such as topical doxepin hydrochloride (eg, Prudoxin; DPT Laboratories, Ltd. San Antonio, TX).

Many unanswered questions in burn wound healing center on development of improved skin substitutes. Better understanding of innate immune responses in the skin would facilitate development of cellular skin substitutes that are immunologically unreactive. Given the length of time for engraftment of currently available constructs, methods to increase vascular ingrowth will potentially improve their usefulness by increasing rates of engraftment, decreasing time to healing, and thereby shortening hospital length of stay and potentially cost. Likewise, improved microbial resistance would increase skin substitute efficacy.

Reduction of shearing of epidermal grafts may be best managed by ex vivo culture of dermal epidermal constructs as described by Boyce and colleagues.[11,12,14] Better understanding of keratinocyte adhesion, epithelial–mesenchymal interactions, and basement membrane biology will continue to contribute to more rapid and stable wound closure with engineered skin grafts.

The absence of important epidermal appendages, including hair follicles and sweat glands, in split thickness skin grafts and some healed burn wounds results in potentially embarrassing areas of alopecia and an inability to sweat. The role of somatic stem cells in wound healing and the ability to promote mobilization from the bone marrow represents one area of research that may promote regeneration of more complete cutaneous anatomy and physiology.

Donor sites, regardless of size, are consistently recognized as a potential source of concern even in patients with small burns. Cost-effective interventions with novel agents that accelerate healing, decrease pain, minimize infection, and reduce scar formation would improve postoperative management of donor sites. Despite the common use of topical antimicrobials, burn wounds often are contaminated and are at risk for burn wound infection or sepsis. Recent insights into the natural behavior of bacteria raise the possibility that current topical and systemic antimicrobial agents inadequately disrupt biofilms, the protective extracellular environments created by bacteria. Currently, elimination of these networks requires excision of the nonhealing wound. Pharmacologic or enzymatic destruction of biofilms may provide an important advance in treatment of burn and donor site infections by increasing the availability of topical or systemic agents, which can be used concurrently.

Pain associated with healing wounds can be directly related to the dressing itself or may be limited to dressing changes. In either case, minimizing wound pain by developing pain-free topical agents or long-acting dressings that allow regular examination of the wound would improve patient comfort when nonoperative wound care is appropriate.

Altered or deficient wound innervation is a major concern to burn patients. Pruritis and hyperesthesia can be intolerable for many patients with hypertrophic scars. Conversely, even successful skin grafts are relatively numb, limiting tactile sensation and potentially manual labor. Ability to modulate reinnervation of healing wounds could significantly affect quality of life and return to function.

DISCUSSION

Areas for future research were identified during the sessions (Table 1). First, development of standardized tools to assess wound healing need to be developed so that wound healing research, both clinical and basic science, will have common endpoints. Questions such as "When is a wound healed?" have implications for the determination of treatment efficacy and the diagnosis of late complications of wound healing. The development of these tools is an essential first priority in the evaluation of wound healing.

The second priority for wound healing research centers on later sequelae of burn injury. Hypertrophic scars and intractable itching are the most significant long-term problems for burn survivors. These late outcomes transcend all areas of cutaneous wound healing research because scars and pruritis develop in healed partial-thickness burns, donor sites, and in the interstices of meshed grafts. A unified definition and grading system for pruritis and hypertrophic scars will enable researchers to have a common frame of reference when conducting clinical studies. Understanding the pathophysiology behind these processes will enable us to develop new treatment regimens.

The third priority for cutaneous wound healing research continues to be the development of innova-

Table 1. Priorities in wound healing research

Development and validation of standardized tools to assess wound healing.
Defining, grading, and understanding the pathophysiology of hypertrophic scarring and pruritis.
Development of innovative treatment modalities for wound healing and scarring.
Optimization of wound healing.

tive treatment modalities for wound and scar management. The continued need for an immunologically neutral engineered skin substitute for major wounds that may eventually be applicable to burns smaller than 5% TBSA would be a major advancement in burn care. This would greatly decrease donor site complications, which can actually cause more morbidity than the initial burn injury.

The final priority in wound healing and repair is the optimization of wound healing. Methods to augment keratinocyte migration and proliferation to accelerate healing of partial-thickness burns and donor sites and development of novel delivery systems for growth factors, antimicrobial agents, and/or morphogens would improve patient outcomes. To achieve these goals, as mentioned above, standardized tools to quantify healing and scar formation need to be developed and validated. Ideally, advances in wound healing will benefit from multicenter trials that are either investigator or industry initiated.

The primary obstacle to achieving these research goals will be establishing sources of funding. Clearly, industry has the necessary research and development resources (both money and management) to bring novel wound healing modalities to market. However, the limited magnitude of the burn market has discouraged development of several promising therapies. Nonetheless, collaboration between burn research teams and researchers in the healthcare industry will be essential for advances in this field. Early consultation by industry with burn experts will maximize likely successes of industry-sponsored clinical trials by outlining clinically relevant sources of morbidity and mortality.

A larger challenge will be identification of funding for an infrastructure that facilitates clinician-initiated clinical trials. The National Institutes of Health (NIH) has recognized this need and addressed it in the NIH Roadmap with establishment institutional awards for clinical and translational research (http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-06-002.html). These mechanisms of funding are crucial to the continued reduction of morbidity and mortality in patient populations at high risk. Coordination of activities among burn researchers, NIH and industry holds the greatest potential to study and intervene in the biologic and medical mechanisms that contribute to morbidity and mortality in victims of burn injuries.

CONCLUSIONS

Research in cutaneous wound healing after burn injury has resulted in the adoption of several clinical practices, such as early excision and grafting, which have impacted patient outcomes. However, the future progress of cutaneous wound healing research will rely on the development of consistent definitions of wound healing and pruritis as well as the development of an understanding of the pathophysiology underlying these processes. Development of cutting edge wound healing technologies, such as skin substitutes, and methodologies for accelerating wound healing form the framework for future studies. Interdisciplinary translational research has the potential to further advances in this area, but funding mechanisms need to be developed to support these types of research and improve patient outcomes.

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