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Effect of skin graft thickness on scar development in a porcine burn model

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ABSTRACT

Animal models provide a way to investigate scar therapies in a controlled environment. It is necessary to produce uniform, reproducible scars with high anatomic and biologic similarity to human scars to better evaluate the efficacy of treatment strategies and to develop new treatments. In this study, scar development and maturation were assessed in a porcine full-thickness burn model with immediate excision and split-thickness autograft coverage. Red Duroc pigs were treated with split-thickness autografts of varying thickness: 0.026 in. ("thin") or 0.058 in. ("thick"). Additionally, the thin skin grafts were meshed and expanded at 1:1.5 or 1:4 to evaluate the role of skin expansion in scar formation. Overall, the burn-excise-autograft model resulted in thick, raised scars. Treatment with thick split-thickness skin grafts resulted in less contraction and reduced scarring as well as improved biomechanics. Thin skin autograft expansion at a 1:4 ratio tended to result in scars that contracted more with increased scar height compared to the 1:1.5 expansion ratio. All treatment groups showed Matrix Metalloproteinase 2 (*MMP2*) and Transforming Growth Factor β1 (*TGF-β1*) expression that increased over time and peaked 4 weeks after grafting. Burns treated with thick split-thickness grafts showed decreased expression of pro-inflammatory genes 1 week after grafting, including insulin-like growth factor 1 (*IGF-1*) and *TGF-β1*, compared to wounds treated with thin split-thickness grafts. Overall, the burn-excise-autograft model using split-thickness autograft meshed and expanded to 1:1.5 or 1:4, resulted in thick, raised scars similar in appearance and structure to human hypertrophic scars. This model can be used in future studies to study burn treatment outcomes and new therapies.

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1. Introduction

Hypertrophic scarring is a common complication following burn injury, with reported incidence rates ranging from 30–75% [1]. The scars are associated with pain, pruritus, erythema, and stiffness [2]. In addition, contractures due to hypertrophic scarring can lead to significant deformities and result in loss of function of the affected limb or joint [3]. Although there is a range of treatment options available including pressure garments [4,5], silicone gels [6,7], corticosteroid injections [8], and laser treatment [9,10], none of these therapies has been able to completely prevent or cure hypertrophic scarring. To develop more efficacious therapies, further research is necessary; however identifying the ideal environment for these studies remains challenging. Clinical studies are limited by wide variability in factors including burn depth and location, patient compliance, and genetics in the patient population. Animal studies provide the ability to control the initial injury, resulting in uniform scars that can be used to investigate novel treatments and systematically assess treatment outcomes.

There have been a limited number of animal models that can simulate hypertrophic scarring due to the tendency of animals to heal without scarring [11]. Excessive scarring has been shown to occur after excisional wounds created in rabbit ears [12], and human hypertrophic scars can be transplanted onto athymic mice [13]. The rabbit ear model has several significant anatomical differences versus human skin including thickness and cartilaginous base limiting its use as an analog to human hypertrophic scar [13]. Both of these models are also limited by the size of the defect that can be created, and therefore have limited applicability to studying large full-thickness burns [11]. Studies involving transplanted human scars are also limited by the availability of explanted human tissues and the scar-to-scar and person-to-person variability commonly observed among human scars. Furthermore, neither of these models involves a burn, which can impose physiological changes that significantly impact wound healing compared with excisional or surgical wounds. Due to these limitations, there has been interest in the use of porcine models. In addition to the increased ability to create larger defects, porcine skin closely resembles human skin, with a sparse hair coat, similar thickness of epidermis, similar elastic content, and abundant subdermal adipose tissue [14]. While loose skinned animals, such as mice, heal predominantly by contraction, pig skin heals similarly to humans by a combination of contraction and re-epithelialization [15].

A range of porcine wound models have been employed in the study of hypertrophic scarring, including excisional [11,16–18], burn only [15,19–21], and burn-excise-autograft models [22–25]. Excisional injuries produced on red Duroc pigs using a dermatome have been shown by others to create scars that are thick, raised and contracted, similar to human hypertrophic scars [11,26–28]. In addition, similarities in the expression of several genes related to scarring, including *Decorin (DCN)*, *Versican (VCAN)*, *Insulin-like Growth Factor-1* (*IGF-1*) and *Transforming Growth Factor* β1 (*TGF-*β1) have been observed between human hypertrophic scars and scars in the porcine excision model [16].

Although excisional wounds on red Duroc pigs have shown promising results related to simulating the production of hypertrophic scars, this wound model lacks the ability to simulate the pathophysiology of burn wounds. Burns can result in blisters, formation of eschar, and increased capillary permeability and fluid loss that do not occur in excisional wounds [29]. In addition, there is propagation of tissue damage into the region surrounding the initial burn wound that occurs due to lipid peroxidation chain reactions [30]. Burn only models, in which a burn injury is created and allowed to heal through sloughing of the necrotic tissue, have been used in both Yorkshire [15,20] and Duroc pigs [31]. These wounds have been shown to create purple, contracted raised scars in Yorkshire pigs [15,32], as well as contracted, hypopigmented, raised scars in Duroc pigs [31]. In a recent study comparing the scar formation of burn only and excisional wound models, we found that burn wounds produced scars that were thicker, more contracted, and had reduced biomechanics compared to scars formed using the dermatome excisional model [21].

Burn only models are an improvement over excisional models due to the ability to simulate the physiological environment of burn wounds, but the models do not replicate the standard of care for human patients. Full thickness burns in human patients are excised and autografted as early as possible to quickly close the wounds and reduce infection and mortality rates [33]. Recently, burn, excision, autograft models have been used in Yorkshire pigs to investigate the effect of topical treatments on re-epithelialization [23,34]. A recent study compared the resultant scarring from autografted excisional wounds to autografted, excised burn wounds on Yorkshire pigs. In that report, creation of an initial burn injury prior to grafting resulted in greater contraction, increased scar height, and decreased scar pliability compared with grafted excisional wounds [22]. Therefore, to effectively study treatment outcomes, it is necessary to use a model that more precisely reproduces the initial injury and treatment that occurs in the human population.

The goal of this study was to examine scar formation in a burn-excise-autograft model using female red Duroc pigs and investigate the effect of autograft thickness and mesh ratio on the resulting scars. Full-thickness burn wounds were created on red Duroc pigs, excised, and autografted with split-thickness skin of varying thickness and mesh ratio. Scar characteristics were monitored over time, including scar contraction, depth, biomechanics, and erythema as well as the expression of multiple genes related to scar formation and remodeling.

2. Materials and methods

2.1. *Animal care and wound creation*

All experiments were completed following a protocol approved by The Ohio State University Institutional Animal Care and Use Committee. Anesthesia was initiated with Telazol (Zoetis, Florham Park, NJ) and maintained via inhaled isoflurane (2–5%). The dorsal trunk was prepared for wounding by shaving and sterilizing with two alternating 2% chlorohexidine and 70% ethanol scrubs (Butler Schein, Columbus OH).

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