Biological Principles of Scar and Contracture

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KEYWORDS

• Burns • Hypertrophic scar • Wound healing • Contracture • Cicatrix

KEY POINTS

- Burn hypertrophic scars result from deep burns that take longer to heal and may be related to activation of deep dermal fibroblasts.
- The extracellular matrix of a hypertrophic scar is significantly different from that of normal skin and normotrophic scar, and influences dermal fibroblast behavior.
- Multiple interconnected pathways contribute to hypertrophic scar formation after a burn injury.
- Various treatments for hypertrophic scar can be demonstrated to affect known pathways in hypertrophic scar formation.

INTRODUCTION

As the primary means of physical interaction with the environment, our hands often bear the brunt of burn injury, and therefore hand burns are quite common.[1] In children and toddlers, scald burns frequently occur as they explore the environment,[2] whereas adults tend to suffer flame and flash burns during occupational and recreational activities.[3] Unfortunately, hypertrophic scarring (HSc) and contractions in the hands result in thick, rigid scars that impair function,[4] and can be very disfiguring[5] (**Fig. 1**). This potential for significant morbidity makes hand burns one of the American Burn Association criteria for mandatory burn center referral.[6] This article aims to improve understanding of the underlying pathophysiology of HSc and contracture after a burn injury of the hand, with the hope that this will lead to new treatments and research that improve patient outcomes.

The factors leading to HSc formation are components of an integrated and complex wound healing process that has become dysregulated or dysfunctional. The net result is a pathologic profibrotic environment that produces excessive scar and contracture. To better understand the processes leading to HSc and contracture, we first examine the factors leading to scarring or regeneration, the underlying signaling molecules involved, the local cell populations involved, and the systemic immune response. Finally, we discuss some of the therapies available and their mechanisms of action.

CRITICAL INJURIES PRODUCE SCARS AND CONTRACTURES

The formation of scar and HSc after a burn injury is tied intimately to the depth of injury, and the time it takes for healing and reepithelialization to occur. It is well-established that superficial burn wounds healing within 2 weeks regenerate and reepithelialize with minimal deformity[7]; deeper burn wounds taking longer than 3 weeks to heal will form a scar, often require excision and skin grafting, and are prone to HSc and contractures.[8] The key difference between superficial and deep

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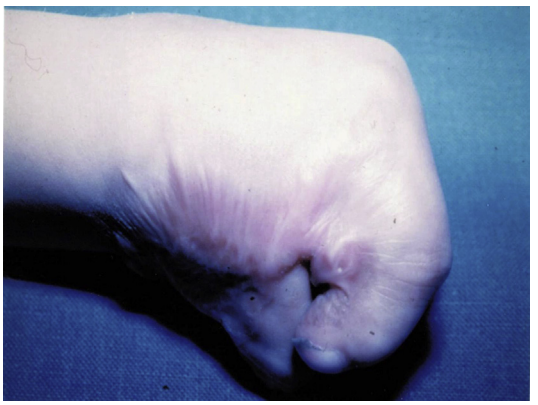

Fig. 1. Hypertrophic scarring and scar contractures of the hand impair function and appearance. (*From* Kwan P, Hori K, Ding J, et al. Scar and contracture: biological principles. Hand Clin 2009;25(4):512; with permission.)

burn wounds relates to the degree of damage, and the predominant fibroblast subpopulation present. This concept of a critical depth of injury is best demonstrated by the linear scratch model of Dunkin and colleagues,[9] where a wound of increasing depth was made through the skin, and the superficial portion regenerated, whereas those areas deeper than 0.56 mm produced scar. This idea of a critical depth for scarring correlates with multiple studies demonstrating that dermal fibroblasts can be divided into superficial (papillary) and deep (reticular) based on their location within the dermis, and that these subpopulations have very different responses to injury[10,11] (**Fig. 2**).

A number of studies have demonstrated that the fibroblasts in HSc most closely match those of the deep dermis in behavior, appearance, and extracellular matrix (ECM) production,[12] and this suggests 2 major hypotheses of HSc formation:

1. Selective proliferation of profibrotic deep dermal fibroblasts in response to fibrogenic cytokines, and
2. Destruction of regenerative superficial dermal fibroblast by deep burn injuries, leaving deeper dermal fibroblasts to repopulate the wound and form HSc.[13]

EXTRACELLULAR MATRIX PROPERTIES INFLUENCE PHYSICAL SCAR AND CELLULAR BEHAVIOR

The ECM formed during the wound closure and the proliferation phase is remodeled over time as wound healing and scarring occur. However, the local wound environment and ECM persist in a significantly altered fashion in HSc as compared with normal skin. Conceptually, the dermal ECM contains 2 main constituents: fibrillar collagen, which provides mechanical strength, and glycosaminoglycans and proteoglycans, which contribute to hydration.[13] On a clinical level, HSc is raised, erythematous, and firm.[14] Histologically, HSc ECM is also thicker, hyperhydrated, and has a thicker epidermis, as compared with normal skin[13] (**Fig. 3**). Morphologically, this is reflected by a change from the basket weave pattern of thick collagen bundles seen in normal skin, to dense nodules or whorls of poorly organized and thin collagen fibrils in HSc[15] (see **Fig. 3**). This is a result of alterations in both collagen and glycosaminoglycan content.

In normal skin, the ECM is composed primarily of type I collagen (80%), type III collagen (10%–15%), and minimal type V collagens, whereas HSc is quite different with more type III (33%) and type V (10%) collagens.[16,17] Because type III and type V collagens alter the fibrillar diameter of type I collagen bundles, these different ratios in HSc likely account for some of the morphologic changes seen.[18,19]

In addition to these major changes in collagen composition, the glycosaminoglycan content of HSc is significantly different from that of normal skin.[20] There is a 2-fold increase in glycosaminoglycan content, which leads to HSc hyperhydration and is clinically manifested as firmness.[13] In normal skin, decorin (DCN), a small leucine-rich proteoglycan, is the predominant proteoglycan, whereas in HSc DCN levels are markedly and significantly reduced.[20] This finding is significant because DCN is not only an ECM structural component that modulates collagen fibril formation,[21] but it also regulates transforming growth factor-β (TGF-β),[22] reduces fibrosis,[23] and reduces contraction.[24] In contrast, 2 other

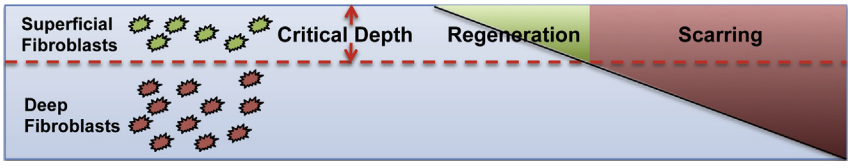

Fig. 2. Superficial skin injuries regenerate, whereas deeper injuries scar. (*From* Kwan P, Hori K, Ding J, et al. Scar and contracture: biological principles. Hand Clin 2009;25(4):513; with permission.)