Pushing Back: Wound Mechanotransduction in Repair and Regeneration

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Human skin is a highly specialized mechanoresponsive interface separating our bodies from the external environment. It must constantly adapt to dynamic physical cues ranging from rapid expansion during embryonic and early postnatal development to ubiquitous external forces throughout life. Despite the suspected role of the physical environment in cutaneous processes, the fundamental molecular mechanisms responsible for how skin responds to force remain unclear. Intracellular pathways convert mechanical cues into biochemical responses (in a process known as mechanotransduction) via complex mechanoresponsive elements that often blur the distinction between physical and chemical signaling. For example, cellular focal adhesion components exhibit dual biochemical and scaffolding functions that are critically modulated by force. Moreover, the extracellular matrix itself is increasingly recognized to mechanically regulate the spatiotemporal distribution of soluble and matrix-bound ligands, underscoring the importance of bidirectional crosstalk between cells and their physical environment. It seems likely that a structural hierarchy exists to maintain both cells and matrix in mechanical homeostasis and that dysregulation of this architectural integrity may underlie or contribute to various skin disorders. An improved understanding of these interactions will facilitate the development of novel biophysical materials and mechanomodulatory approaches to augment wound repair and regeneration.

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INTRODUCTION

Human skin constantly senses and adapts to a wide range of mechanical cues that are ubiquitous throughout life. These physical interactions regulate key developmental and homeostatic mechanisms and underlie the tremendous functional plasticity of skin (Silver *et al.*, 2003; Blanpain and Fuchs, 2009). Although mechanical forces are implicated in the pathogenesis of numerous diseases (Ingber, 2003a), their role in cutaneous biology remains poorly understood. However, the fundamental mechanisms responsible for mechanotransduction (the conversion of physical stimuli into biochemical responses) are increasingly being elucidated on molecular and cellular levels (Ingber, 2006). The ongoing challenge for researchers and clinicians is to fully understand these mechanotransduction pathways in living organs so that they can be translated into clinical therapies.

In 1861, the German anatomist Karl Langer published the observation that skin exhibits intrinsic tension (Langer K, 1978), a finding he attributed to the French surgeon Baron Guillaume Dupuytren. Since then, surgeons have adhered to the concept of ''Langer's lines,'' which are topographical skin lines defined by the direction in which the circular wounds will elongate (becoming ellipsoid) in different anatomic regions of the body. Subsequent studies have defined numerous other topographical line maps throughout the body using different biomechanical methodologies (Wilhelmi *et al.*, 1999). Regardless, the common underlying theory is that incisions made across these imaginary lines are exposed to greater tension (from the orientation of collagen fibers or contraction of underlying muscles) and form quantitatively more scar tissue. This phenomenon is substantiated clinically as wounds in high-mechanical-stress regions (such as the sternum and shoulder) have been shown to be prone to exuberant fibrosis (Ogawa, 2008).

From the simplest single-celled organism to the most complex of mammals, all living systems are in constant interaction with the physical world. This ability to precisely sense and respond to mechanical cues has been retained throughout evolution and is embodied in humans as the integumentary system. As such, it is becoming increasingly clear that the mechanical environment has significant effects on cutaneous biology and may have wide pathogenic relevance. This review will focus in particular on the role of mechanical force in wound repair and explore previously unreported therapeutic approaches to mechanically control wound biology and phenotype.

INTRACELLULAR MECHANOTRANSDUCTION

There are several major interrelated pathways by which cells are mechanically stimulated, including integrin–matrix interactions, cytoskeletal strain, and stretch ion channels

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Abbreviations: ECM, extracellular matrix; NPWT, negative pressure wound therapy

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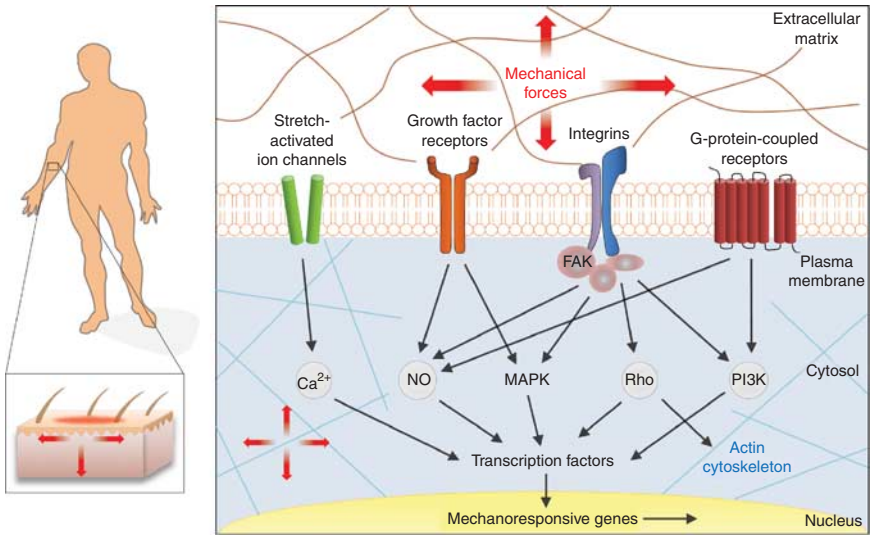

Figure 1. Intracellular mechanisms of mechanotransduction. Mechanical force is sensed by the integumentary system and activates multiple intracellular signaling pathways. Several membrane-bound mechanosensory complexes have been described and include stretch-activated ion channels, growth factor receptors, integrins, and G-protein-coupled receptors. Of primary significance in fibroblasts and keratinocytes is matrix–integrin activation of focal adhesion complexes that contain focal adhesion kinase (FAK). Mechanical force is transmitted across the cell membrane to activate downstream biochemical pathways including but not limited to calcium-dependent targets, nitric oxide (NO) signaling, mitogen-associated protein kinases (MAPKs), Rho GTPases, and phosphoinositol-3-kinase (PI3K). The convergence of these signals results in the activation of transcription factors that translocate to the nucleus and activate mechanoresponsive genes (adapted from Jaalouk and Lammerding, 2009).

(Figure 1). Cells bind to the extracellular matrix (ECM) through transmembrane integrins that associate with various binding proteins and kinases (e.g., focal adhesion kinase) to trigger downstream targets such as the family of mitogen-activated protein kinases, GTPases, active oxygen species, and cytoskeletal elements (Katsumi *et al.*, 2004; Jaalouk and Lammerding, 2009). These integrin-associated proteins (known as focal adhesion complexes) also link to the actin cytoskeleton via adaptor proteins (e.g., talin, paxillin, vinculin) and directly modulate cell behavior such as motility and proliferation (Alenghat and Ingber, 2002). In addition, mechanosensitive stretch ion channels control calcium-dependent pathways that further regulate intracellular signaling and cytoskeletal remodeling (Silver *et al.*, 2003; Lumpkin and Caterina, 2007). It is important to note that many of these networks are also regulated by growth factor and G-protein-coupled receptor pathways (Jaalouk and Lammerding, 2009), which can potentially be transactivated by mechanical force in a ligand-independent manner (Knies *et al.*, 2006), further illustrating the complex intricacies of cellular mechanotransduction and intracellular signaling.

Despite this complexity, a unifying concept known as ''tensegrity'' has been proposed to describe how mechanical force regulates biological systems via perturbations in structural architecture (Figure 2) (Ingber, 2003b, c). Alterations in the physical microenvironment can disrupt this tensional integrity, thus triggering broad intra- and intercellular pathways to reestablish mechanical homeostasis (Eckes and Krieg, 2004). Structural components linking the ECM to nuclear chromatin have even been described, suggesting that mechanical force can directly modulate intranuclear programming (Gieni and Hendzel, 2008). Although the precise mechanisms are only beginning to be elucidated, it has been demonstrated that cells can distinguish subtle temporal differences in mechanical stimulation and adaptively strengthen their adhesion structures (Matthews *et al.*, 2006). Biosensor components implicated in this process include focal adhesion complexes, the Rho GTPase family of signaling molecules, and mechanosensitive ion channels. Rho signaling pathways, intimately involved in cytoskeletal dynamics, are also known to regulate fibroblast and keratinocyte responses to mechanical force (Harvey *et al.*, 2007; Reichelt, 2007), highlighting the important functional relationship between cell shape and behavior in skin cells.

Consistent with this paradigm, complex organs such as skin also exhibit tensegrity, and their response to physical stimuli may similarly function to restore biomechanical equilibrium (Silver *et al.*, 2003; Ingber, 2008). This hierarchical organization is likely to be of major relevance following cutaneous injury when skin architecture is extensively disrupted and the mechanical context of its constituent cells is dramatically altered. Current research supports the concept that these mechanotransduction events play a critical role in the response to injury and may underlie the etiology of fibroproliferative skin diseases (Aarabi *et al.*, 2007a; Gurtner *et al.*, 2011).

Another important concept is that cells not only passively respond to force but also actively generate intracellular tension as they probe their local environment, the so-called cell traction forces (Discher *et al.*, 2005; Wang and Lin, 2007). These key physical interactions regulate numerous cellular processes, including motility, adhesion, contraction, and cytoskeletal reorientation (Hersen and Ladoux, 2011).

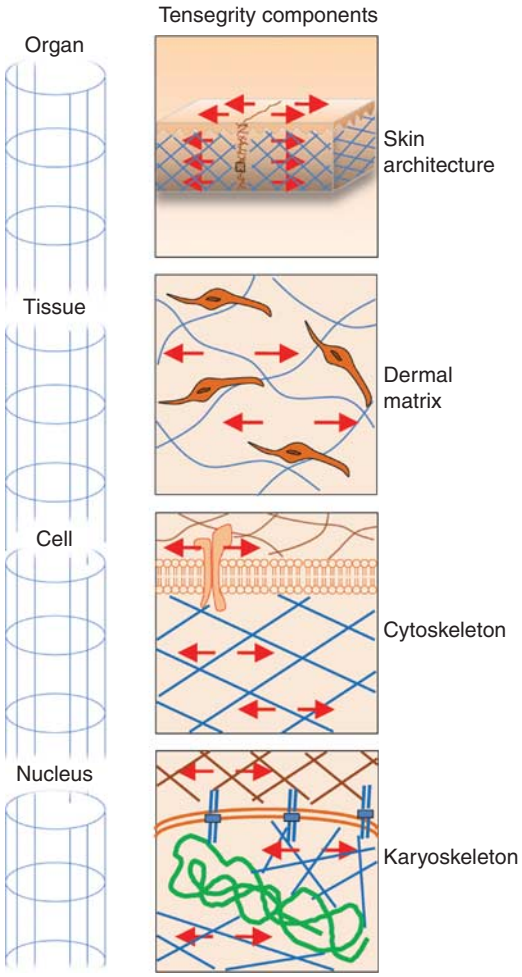

Figure 2. Hierarchical organization of skin tensegrity. The concept of tensional integrity, or ''tensegrity,'' first proposed by Donald Ingber, explains how the structural organization (blue) of cells and matrix is mechanically regulated and can be applied to all levels of the integumentary system. Skin is organized into discrete compartments (epidermis, dermis, hypodermis) with layer-specific structural properties. The dermis is arranged as a dense fibrillar network to provide strength and flexibility, while cell shape is largely maintained via its actin and microtubular cytoskeleton. Structural proteins have recently been described that link the cytoskeleton with intranuclear chromatin (e.g., nesprins, SUN proteins), thus establishing a direct physical connection between the extracellular matrix and the nucleus. This biomechanical equilibrium is disrupted following injury and may form the basis for pathogenic repair mechanisms such as scar formation.

Early studies in mechanobiology examined cell traction forces on deformable two-dimensional substrates (Harris *et al.*, 1980), and improvements in high-resolution microscopy, computer-based modeling, and molecular tools have increasingly allowed researchers to elucidate important subcellular mechanical events regulated by cell–substrate interactions (Wang and Lin, 2007). These *in vitro* systems substantiate the role of skin matrix elasticity in regulating cellular behaviors as diverse as locomotion, proliferation, contraction, and collagen production (Discher *et al.*, 2005; Karamichos *et al.*, 2007; Hadjipanayi *et al.*, 2009b).

EXTRACELLULAR MECHANISMS

The ECM is not only a static transducer of mechanical force but also plays a complex multifaceted role in mechanotransduction (Figure 3). The structural assembly of ECM during skin development and following cutaneous injury may determine a wide range of cell functions, as substrate stiffness and rigidity are known to critically regulate cell morphology, movement, differentiation, and function (Discher *et al.*, 2005). Both keratinocytes and fibroblasts reorganize their actin cytoskeletons depending on substrate stiffness (Hossain *et al.*, 2005), and scar hardness may result from a cycle of rigidity-induced collagen production and proliferation (Solon *et al.*, 2007; Hadjipanayi *et al.*, 2009a). Matrix stiffness is also thought to contribute to cancer growth and invasiveness (Paszek *et al.*, 2005; Jean *et al.*, 2011), and mechanical signaling has even been proposed to be as important as biochemical pathways in oncogenic transformation (Huang and Ingber, 2005).

Mechanical tension can also induce conformation changes in the ECM that subsequently modulate biological functions. For example, fibronectin unfolding can reveal cryptic binding sites that regulate cell activity (Krammer *et al.*, 1999; Baneyx *et al.*, 2002) and matrix components can potentially be deformed, which alters the spatial relationship of matrix-bound and biochemical cues (Hynes, 2009). Moreover, the ECM is increasingly recognized to specifically bind growth factors and cytokines such as transforming growth factor-β (Hynes, 2009). Load-induced exposure of basic fibroblast growth factor from hidden ECM sites has been proposed as a model for cartilage mechanotransduction (Vincent and Saklatvala, 2006), and chemokines such as monocyte chemoattractant protein-1 are bound by glycosaminoglycans (Distler *et al.*, 2006) and can potentially be released following mechanical deformation.

A new class of extracellular proteins has been recognized to modulate both cell and ECM function. These ''matricellular'' proteins are not directly utilized in building the physical matrix but play a crucial role in regulating numerous cell and matrix processes. Proteins such as thrombospondin, tenascin-C, tenascin-X, and the CCN family of proteins (including connective tissue growth factor) are increasingly implicated in wound repair and cutaneous disease (Bornstein and Sage, 2002; Leask and Abraham, 2006; Eckes *et al.*, 2010). In particular, the matricellular proteins tenascin-C and connective tissue growth factor are known to be mechanically regulated and may play an important role in scar formation (Matsui and Sadoshima, 2004; Chaqour and Goppelt-Struebe, 2006; Chiquet *et al.*, 2007). In support of these studies, we have found that skin-specific deletion of focal adhesion kinase markedly impairs load-induced matrix formation in a mouse model of hypertrophic scarring, in part through attenuated connective tissue growth factor signaling (Wong VW and Gurtner GC; unpublished data).

Together, these studies demonstrate that a cell-centric view of mechanotransduction is incomplete and fails to account for the essential role of ECM and matricellular proteins in regulating fundamental biological processes. The physical properties of the ECM and the micromechanical

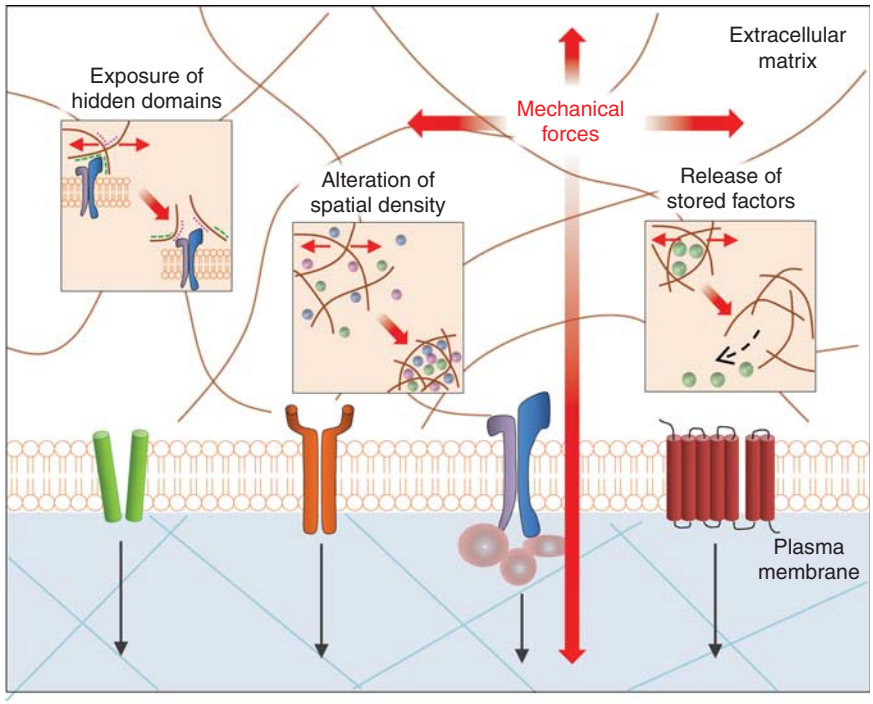

Figure 3. Extracellular mechanotransduction. The extracellular matrix is dynamically regulated by mechanical force. Although physical forces can be directly transmitted to the cellular cytoskeleton, additional matrix-specific mechanisms may also be important in wound mechanotransduction. Mechanical force can alter the folding and conformation of matrix elements to reveal hidden binding sites. The physical manipulation of extracellular space can modify the spatial density of both soluble and matrix-bound ligands. Furthermore, soluble growth factors and cytokines have been shown to specifically bind to matrix domains and may be sequestered or released in response to mechanical loading. Finally, matricellular proteins (not shown) are increasingly recognized to modulate both cell and matrix activity and likely play an important role in wound mechanotransduction.

signals it imposes on cells are undoubtedly altered by mechanical loading, which may trigger diverse cellular responses (such as matrix remodeling and cytokine secretion) to adapt to these changes (Ingber, 2003a, c). A mechanosensitive cycle of cell–matrix crosstalk is likely involved in balancing structure and function. These reciprocal interactions provide an important paradigm for understanding how intrinsic and extrinsic mechanical cues affect skin biology.

IN VITRO BIOMECHANICAL SYSTEMS

Much insight has been gained from utilizing biomechanical systems to study the effects of mechanical force *in vitro*. Strain systems are often composed of a deformable substrate for cell attachment and are controlled by automated servohydraulic or vacuum-type systems. Biomechanical parameters can be modified to simulate different mechanical conditions, including the magnitude of strain or compression, strain orientation, and strain kinetics. Automated compression systems are likewise available but have generally been used for bone and cartilage applications. Although these culture systems allow for detailed analyses of mechanotransduction pathways in specific cell types under controlled conditions, they fail to recapitulate the three-dimensional cues, matrix interactions, and biochemical crosstalk of *in vivo* environments.

In part to address this issue, models based on fibroblast-populated collagen lattices have been developed that allow researchers to study important three-dimensional cell–collagen interactions *in vitro* (Dallon and Ehrlich, 2008). Subsequent contraction of the cell-seeded lattice is thought to be due to combinations of cell contraction, locomotion, and elongation. Importantly, differences in how fibroblast-populated collagen lattices are cast determine the activation of particular physiologic mechanisms. For example, free-floating ''relaxed'' matrices involve minimal fibroblast contraction whereas fibroblast-populated collagen lattices cast onto a rigid surface and subsequently released contract rapidly via fibroblast contraction (Dallon and Ehrlich, 2008).

These *in vitro* systems have allowed the elucidation of key mechanotransduction pathways using standard molecular techniques (gene expression, immunoblot, immunofluoresence). However, recent advances in nanotechnology and high-resolution biomechanical systems have now enabled researchers to interrogate and measure mechanical interactions on a molecular scale in live cells (Hersen and Ladoux, 2011). Technologies such as atomic force microscopy, magnetic twisting cytometry, and traction force microscopy have permitted manipulations of mechanical force on the single-cell level (Sen and Kumar, 2009). Furthermore, advances in molecular imaging and fluorescence resonance energy transfer-based biosensors have provided unprecedented opportunities to detect subcellular mechanotransduction events across increasingly fine space and time scales (Wang and Wang, 2009; Delanoe-Ayari *et al.*, 2010; Liu *et al.*, 2010). These exciting technologies will undoubtedly provide greater insight into the mechanical regulation of

molecular interactions between cells and substrates in an *in vitro* environment.

MECHANOSENSING CELLS OF THE SKIN

The integumentary system is the largest mechanoreceptor system in the body (Lumpkin and Caterina, 2007). Accordingly, every major cell type found in skin has been shown to be mechanoresponsive (Figure 4) (Reichelt, 2007; Wang and Thampatty, 2008). However, to understand wound mechanotransduction, the individual cell response to physical force needs to be integrated across local and systemic-derived populations in the wound. One of the most well-studied mechanoresponsive skin populations is the fibroblast. We and others have shown that tension can markedly alter fibroblast expression of matrix remodeling and inflammatory genes (Kessler-Becker *et al.*, 2004; Derderian *et al.*, 2005). Moreover, mechanical forces can induce fibroblast collagen production, α-smooth muscle actin expression, cytokine expression, and proliferation *in vitro* (Yang *et al.*, 2004; Webb *et al.*, 2006; Hinz *et al.*, 2007; Lu *et al.*, 2011), suggesting that mechanical tension is largely driven by fibroblast-mediated mechanisms.

Keratinocytes, which form the initial barrier to the external world, are also mechanically responsive and are important regulators of skin activity. They are potentially regulated by many of the same mechanotransduction pathways found in fibroblasts, but the polarity of keratinocytes requires that signals from at least two unique mechanical environments must be simultaneously integrated (Reichelt, 2007). Although the precise mechanisms are still unclear, the predominant *in vitro* response to strain involves proliferation via matrix–integrin and mitogen-activated protein kinase-associated pathways (Takei *et al.*, 1998; Tamaki *et al.*, 2004; Reichelt, 2007). Keratinocytes also regulate other aspects of wound repair via important epithelial–mesenchymal interactions (Werner *et al.*, 2007), and it is possible that mechanically disrupted crosstalk may contribute to pathologic healing and scar formation (Ghahary and Ghaffari, 2007).

Skin nociceptors are a diverse family of peripheral sensory neurons that include mechanoresponsive unmyelinated C fibers or thinly myelinated Aδ fibers that secrete inflammatory neuropeptides upon mechanical stimulation (Yagmur *et al.*, 2010; Dubin and Patapoutian, 2011). Cyclical stretching of murine skin can induce neuropeptide secretion (Chin *et al.*, 2009), and the mechanical activation of neurogenic inflammation has been proposed to underlie fibroproliferative diseases such as hypertrophic scar and keloid formation (Ogawa, 2008; Akaishi *et al.*, 2008a, b). Other mechanoresponsive skin components include D-hair mechanoreceptors, Merkel cell–neurite complexes, Pacinian corpuscles, and

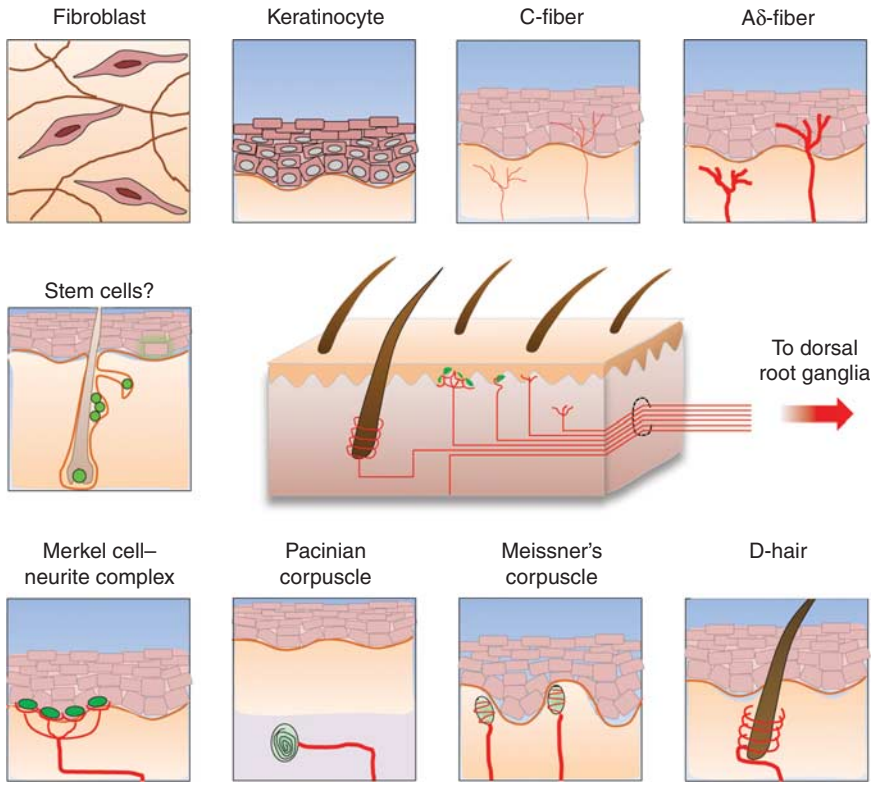

Figure 4. Mechanosensing components of skin. The mechanosensing abilities of fibroblasts, keratinocytes, and nociceptors have been well established in normal skin development and homeostasis. However, their integrated roles in mechanosensing during wound repair remain unclear. Furthermore, physical cues (such as force and matrix interactions) are suspected to direct skin stem cell fate but the molecular mechanisms remain undefined. Injury and trauma significantly disrupt cell–matrix interactions, and in the setting of mechanical force normal repair mechanisms are further disturbed. An improved understanding of mechanoregulated crosstalk between these adult and progenitor skin populations may reveal previously unreported mechanisms in cutaneous disease.

Meissner's corpuscles (Tsunozaki and Bautista, 2009). The specific role of nociceptive mechanoreceptors in wound healing and cutaneous disease remains unclear, but current research is exploring the potential crosstalk with keratinocytes and/or fibroblasts, given their close spatial relationship. Interestingly, the chemokine monocyte chemoattractant protein-1 is linked to numerous wound cells (including nociceptors, fibroblasts, keratinocytes, and inflammatory cells), highly mechanoresponsive, and strongly associated with fibrogenesis, suggesting that chemokine signaling may be a central mediator of scar mechanotransduction (Sun *et al.*, 2006; Wynn, 2007; Shynlova *et al.*, 2008; Distler *et al.*, 2009). Recruited fibroblasts and immune cells may further contribute to the inflammatory milieu, potentially setting up a ''vicious cycle'' of cytokine/chemokine signaling that is both initiated and sustained by mechanical loading.

Finally, the influence of physical force and cell–matrix interactions on stem cell fate is increasingly being proposed (Blanpain and Fuchs, 2009; Guilak *et al.*, 2009). Mechanical cues are an important component of the stem cell niche (Jones and Wagers, 2008), and tension has been shown to regulate key mechanisms in epithelial morphogenesis in nematodes (Zhang *et al.*, 2011). Mechanotransduction signaling has also been shown to direct mesenchymal stem cell fate (Guilak *et al.*, 2009), but similar mechanisms in epithelial stem cells have not yet been reported. Progenitor cells in the hair follicle bulge, interfollicular epidermis, and sebaceous gland continuously restore epithelium throughout life (Fuchs and Horsley, 2008) and are constantly being bombarded by mechanical signals that may influence their activity. Potential mechanisms by which mechanical forces regulate stem cell function include induction of chromatin remodeling, nuclear translocation of transcription factors, and modulation of intracellular targets (including RhoA and mitogen-activated protein kinases) linked to both mechanical and biochemical signaling (Estes *et al.*, 2004; Jakkaraju *et al.*, 2005; Cohen and Chen, 2008; Wolf and Mofrad, 2009). Moreover, it has been shown that substrate rigidity itself can direct stem cell fate (Engler *et al.*, 2006), demonstrating the feasibility of biomaterial approaches to engineer and control stemness for wound applications. Thus, it appears likely that the therapeutic success of stem cell-based strategies will depend on our ability to control the physical contexts of the wound environment.

IN VIVO BIOMECHANICAL SYSTEMS

Biomechanical studies of skin explants and noninvasive studies in living patients indicate that human skin behaves as a viscoelastic and anisotropic material with properties that change throughout life (Agache *et al.*, 1980; Escoffier *et al.*, 1989; Khatyr *et al.*, 2004). Mechanical studies have been performed on pathologic specimens (hypertrophic scars, keloids, sclerodermatous skin) and have provided important insight into potential disease mechanisms (Dunn *et al.*, 1985; Clark *et al.*, 1996; Dobrev, 1999a, b). However, detailed molecular studies are difficult or impractical in these systems and have prompted the development of mechanically based animal models of cutaneous disease.

The scarless healing of early gestation mammalian fetal skin may be related to the mechanical properties of its ECM (Lorenz *et al.*, 1993; Aarabi *et al.*, 2007a; Gurtner *et al.*, 2008; Satish and Kathju, 2010). We and others have shown that fetal and adult mouse skin have low levels of resting stress (and do not form significant scar), but when exposed to elevated mechanical loads (within the range experienced by human skin), it will heal with hypertrophic scar-like fibrosis (Aarabi *et al.*, 2007a) (Figure 5a, left). Other small animal models have been recently developed to study the effects of mechanical stress on skin. For example, cyclical stretching of unwounded murine skin with a servo-stretch device was shown to increase the expression of inflammatory genes and promote epidermal proliferation and angiogenesis (Chin *et al.*, 2009). Further, a mouse model of rapid tissue expansion has been shown to induce the expression of genes related to cell growth and proliferation (Zhu *et al.*, 2002). Finally, acute cyclic stretching of mouse skin flaps has been demonstrated to augment mitogenic and neovascular pathways in the skin (Shrader *et al.*, 2008).

Small animal models have also been developed to study the molecular mechanisms underlying negative pressure wound therapy (NPWT), a mechanotransduction-based application that has revolutionized reconstructive surgery and wound care (Orgill *et al.*, 2009). A vacuum-assisted closure model was developed to study the effect of different mechanical regimens for wound closure in diabetic mice (Scherer *et al.*, 2009), and a rat model of NPWT demonstrated increased angiogenic growth factor production and matrix deposition (Jacobs *et al.*, 2009). Future studies combining these biomechanical systems with transgenic mouse models and live-imaging biosensor technologies will enable greater understanding of how clinical therapies modulate wound biomechanics on a molecular level. Although much insight has been gained from the use of small animal models to understand wound repair processes, the anatomy and physiology of rodent skin is dramatically different from that of human skin and thus limits the translational relevance of these studies (Wong *et al.*, 2011).

Wound healing models in pigs have proven useful to study human-like cutaneous repair physiology. Porcine skin resembles human skin in numerous ways, including epithelial rete peg architecture, microvasculature, and the ability to form robust scar (Cuttle *et al.*, 2006; Harunari *et al.*, 2006; Xie *et al.*, 2007). Pig models have been developed to study the effects of negative pressure on wound microvascular flow (Morykwas *et al.*, 1997; Malmsjo *et al.*, 2009a, b; Borgquist *et al.*, 2010) and neuropeptide release (Torbrand *et al.*, 2008). Pigs have also been described as an ideal large animal to study human hypertrophic scarring (Ramos *et al.*, 2008). The application of mechanical stress to pig skin explants in a bioreactor setup has been shown to modulate collagen fibril thickness (Sanders *et al.*, 2002), as demonstrated with mechanical compression of human scar (Costa *et al.*, 1999). Shear stresses have also been applied to pigs to study pressure ulcer pathophysiology, but mechanotransduction mechanisms were not examined (Goldstein and Sanders, 1998).

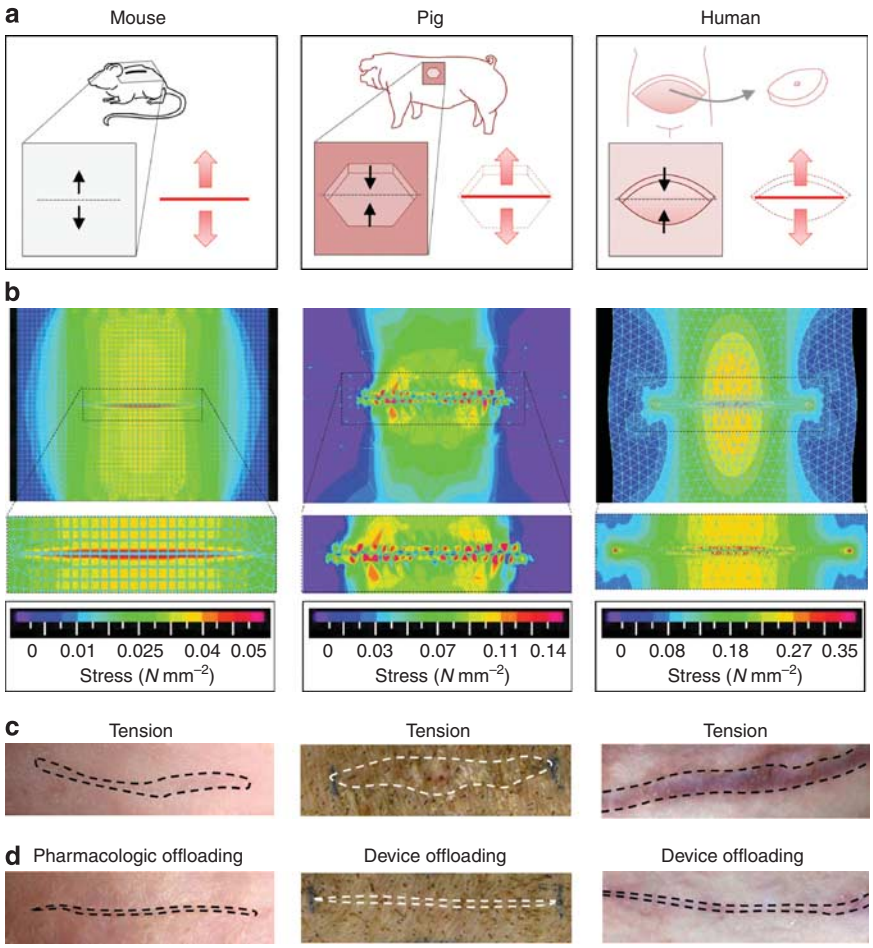

Figure 5. Scar mechanotransduction in animal models and humans. (**a**) Schematics of mouse and pig models of overscarring based on mechanical forces. An analogous situation occurs following closure of abdominoplasty wounds in humans. (**b**) Linear elastic finite element analysis predicts that linear incisions experience increased tension in these models. Refer to Supplementary Methods online for details. (**c**) Photographs of incisions exposed to high tension in mouse (21 days postinjury), pig (8 weeks postinjury), and human (8 months postinjury). (**d**) Photographs of loaded incisions treated with either pharmacologic (small-molecule focal adhesion kinase (FAK) inhibitor PF573228) or device (stress-shielding polymer) approaches to offload wound tension and attenuate fibrosis.

Our group has recently shown that postinjury fibrosis in the red Duroc pig can be controlled by manipulating mechanical forces across closed incisions (Figure 5a, middle) (Gurtner *et al.*, 2011). Specifically, incisions closed under higher tension exhibited greater scar formation compared with those closed under minimal tension, replicating the outcomes observed in human scarring (Wray, 1983). Region-specific differences in the mechanical properties of pig skin were also observed to correlate with suspected regional differences in the propensity to form scar in humans (Wong *et al.*, manuscript in preparation), further substantiating the red Duroc as a robust model to study fibrotic skin disease. Future focus on the molecular pathways driving scar mechanotransduction in red Duroc pigs may validate established pathways in rodent models and will likely be of greater relevance to human pathology. Taken together, these preclinical studies clearly demonstrate that mechanical forces play an important role in wound repair and suggest that many of these pathogenic mechanisms are pertinent to human disease.

WOUND HEALING AND MECHANOMODULATORY THERAPIES

It is clear that exuberant scarring following injury can lead to severe functional and esthetic complications for which current therapies are largely ineffective (Mustoe *et al.*, 2002; Wynn, 2007). The role of mechanical tension in cutaneous fibrosis has been suspected for centuries, but only recently have the underlying mechanisms become more apparent. One particular type of pathologic scarring following injury is hypertrophic scar formation, a significant global health burden that can produce severe disfigurement and functionally disabling contracture formation (Aarabi *et al.*, 2007b). Despite the use of multimodality regimens including corticosteroid injections, laser and radiation therapies, and scar revision surgeries, outcomes remain poor (Mustoe *et al.*, 2002; Aarabi *et al.*, 2007b). Interestingly, among several therapies that have shown some success are silicone sheeting and compression bandages, both of which may work through mechanical offloading of the wound environment (Ward, 1991; Costa *et al.*, 1999; Akaishi *et al.*, 2010). Even paper

tape application has been shown to mitigate scar formation, the effects being attributed to passive mechanical stabilization of wounds (Atkinson *et al.*, 2005; Daya, 2011).

Based on these preclinical studies and anecdotal clinical reports implicating the profibrotic effects of mechanical tension, it seems likely that scar formation would be blocked if mechanical forces were actively offset by stress-shielding to reestablish mechanical homeostasis across the wound. Our group has recently completed a phase I clinical trial using a dynamic polymer device to actively offload high-tension abdominoplasty incisions that are prone to excess scarring (Figure 5a, right) (Gurtner *et al.*, 2011). Stress-shielding of the treatment side for 8 weeks produced a significant improvement in scar appearance for up to 1 year compared with contralateral within-patient control incisions. These early clinical studies suggest that mechanical tension upregulates fibrotic pathways in humans and that device approaches to actively offload these wounds may be an effective physical approach to prevent scar formation.

Keloidal disease is another form of pathologic scarring that remains poorly understood (Alster and Tanzi, 2003; Kose and Waseem, 2008). It is mainly distinguished from hypertrophic scarring in that keloid growth extends beyond the original wound margins. The etiology remains obscure but proposed pathogenic factors include genetics, impaired apoptosis, dysregulated epithelial–mesenchymal signaling, and mechanical tension (Butler *et al.*, 2008). Recent research suggests that keloid fibroblasts exhibit augmented expression of profibrotic cytokines and collagen in response to mechanical strain, an effect associated with activation of focal adhesion kinase (Wang *et al.*, 2006). Moreover, physical tension has been proposed to dictate the pattern of keloid growth as areas of maximal mechanical stimulation have an increased incidence of keloid formation (Akaishi *et al.*, 2008a). These studies suggest that keloid pathogenesis may in part be related to mechanical forces and that disease progression might be controlled with mechanomodulatory therapies.

Another line of evidence for the importance of mechanical signaling in scar formation is related to the use of botulinum toxin. Botulinum toxin type A is primarily used in facial esthetic surgery to decrease wrinkles through temporarily paralysis of underlying facial muscles (Carruthers *et al.*, 2004). However, it has also been reported to reduce scar formation following surgical revision of facial scars (Wilson, 2006). These effects were attributed to reduced wound tension during early remodeling (from impaired contraction of underlying muscle). Intralesional injections of botulinum type A have even been shown to improve hypertrophic scarring in a small prospective clinical trial (Xiao *et al.*, 2009). However, larger controlled trials are needed to substantiate the benefits of this therapy for hypertrophic scarring.

The treatment of acute and chronic wounds has been revolutionized by negative pressure vacuum-assisted closure technology (Orgill and Bayer, 2011). Preclinical studies suggest that the primary mechanisms of action include apposition of wound edges, stabilization of the wound environment, reduction in wound edema and exudates, and microdeformational forces (Orgill *et al.*, 2009). NPWT is increasingly utilized for cutaneous wound applications ranging from the treatment of diabetic foot ulcers to improving skin graft survival (Venturi *et al.*, 2005). Although randomized controlled trials have advocated the use of vacuum-assisted closure therapies for certain wounds (Expert Working Group, 2008), serious complications such as bleeding have also been reported in a few patients (Orgill and Bayer, 2011). An international expert panel recently proposed evidence-based guidelines for the use of NPWT, with the strongest support for its use on skin grafts (Runkel *et al.*, 2011). Mechanotransduction mechanisms are undoubtedly important in understanding its therapeutic benefits, and future research should aim to clarify the optimal pressure waveforms, treatment duration, and wound interface materials for NPWT. Collectively, these studies illustrate the ubiquitous nature of mechanotransduction pathways in cutaneous disease and indicate that mechanobiology concepts should be increasingly recognized in the development of new medical and surgical therapies.

CONCLUSION AND FUTURE DIRECTIONS

The increasing abundance of basic science and preclinical studies corroborate widely recognized clinical observations that mechanical forces modulate skin and wound behavior. The convergence of mechanobiology with materials science and nanotechnology will allow researchers to precisely manipulate subcellular mechanical events and nanotopographical cues that ultimately determine cell function and fate. The discovery of new mechanotransduction targets will guide the development of novel molecular and pharmacologic-based therapies. Additionally, devices that control wound mechanics will be increasingly customized to the type, anatomic location, and dimension of patient-specific wounds. Finally, the exploitation of micromechanical cues to direct stem cell fate will facilitate strategies for skin regeneration. The future is exciting for this expanding field as we learn to ''push back'' on mechanical force and exploit its influence on all aspects of repair and regeneration.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

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