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Review article

Mechanomodulatory biomaterials prospects in scar prevention and treatment

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ABSTRACT

Scarring is a major clinical issue that affects a considerable number of patients. The associated problems go beyond the loss of skin functionality, as scars bring aesthetic, psychological, and social difficulties. Therefore, new strategies are required to improve the process of healing and minimize scar formation. Research has highlighted the important role of mechanical forces in the process of skin tissue repair and scar formation, in addition to the chemical signalling. A more complete understanding of how engineered biomaterials can modulate these mechanical stimuli and modify the mechanotransduction signals in the wound microenvironment is expected to enable scar tissue reduction. The present review aims to provide an overview of our current understanding of skin biomechanics and mechanobiology underlying wound healing and scar formation, with an emphasis on the development of novel mechanomodulatory wound dressings with the capacity to offload mechanical tension in the wound environment. Furthermore, a broad overview of current challenges and future perspectives of promising mechanomodulatory biomaterials for this application are provided.

Statement of significance

Scarring still is one of the biggest challenges in cutaneous wound healing. Beyond the loss of skin functionality, pathological scars, like keloids and hypertrophic, are associated to aesthetic, psychological, and social distress. Nonetheless, the understanding of the pathophysiology behind the formation of those scars remains elusive, which has in fact hindered the development of effective therapeutics. Therefore, in this review we provide an overview of our current understanding of skin biomechanics and mechanobiology underlying wound healing and scar formation, with an emphasis on the development of novel mechanomodulatory wound dressings with the capacity to offload mechanical tension in the wound environment.

1. Introduction

Skin, as an organ belonging to the integumentary system, plays a pivotal role in maintaining a relative state of homeostasis and protecting our body from the external environment throughout life. However, it is highly susceptible to trauma that compromises not only its structure but importantly its function, even after healing. Wounds in mammalian adults are notoriously unable to regenerate and, instead, injured tissue is replaced by dysfunctional fibrotic tissue (scars) [1]. Scars are the end point of a fibrotic response that can be triggered by a variety of factors, led by a transition of fibroblasts into activated ECM-producing and ECM-remodeling cells - myofibroblasts. Although such phe-

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notype switch is required for tissue repair, when associated to other factors contribute to abnormal healing, leading to pathological scars formation (hypertrophic scars and keloids). Typically, this occurs in deep partial- or full-thickness excisional wounds or burns that have a prolonged acute inflammatory phase and consequently a longer healing time. Aberrant connective-tissue deposition and ECM accumulation occur (mainly excessive collagen content), altering ECM mechanics. Alteration of the overall mechanical behaviour of the tissue is a hallmark of this abnormal healing. Moreover, altered ECM mechanics caused by pathological matrix deposition and stiffening contributes to the maintenance of fibroblast activation, thereby amplifying the process [2–4]. These evidences have attracted scientific attention to the role of mechanical forces and tissue mechanics in regulating cell behaviour and tissue remodeling during cutaneous wound healing. Preventive therapeutic approaches, such as the use of silicone membranes, are effective in shielding tensile forces during the healing of surgical incisional wounds, resulting in diminished scar formation [5]. These approaches are equally successful in improving mature pathological scars after revision surgeries [6]. Nonetheless, therapeutic approaches that prevent the formation of pathological scars during wound healing are lacking. This is likely to be associated to the consistent absence of consensus regarding the mechanisms underlying the formation of pathological scars. In this review, we discuss the relevant mechanisms that link the mechanical macro- and micro-environment to cellular activation in the context of injury, repair, and fibrosis. Then, we review mechanomodulatory strategies with the capacity to offload mechanical tension in the wound environment discussing their potential for preventing progressive tissue scarring and possibly reversing established fibrosis.

2. Skin wound healing and abnormal scar tissue

The normal physiological response comprises four overlapping phases: (1) hemostasis, (2) inflammation, (3) proliferation and (4) remodeling [7]. Briefly, the first step involves the formation of a blood clot at the wound site mediated by platelets. After that, the inflammation stage begins with the initial recruitment of neutrophils, through cytokines released by the blood clot, which phagocyte bacteria and cellular debris [8]. These cells release several inflammatory factors, including interleukin (IL)-1, IL-6 and tumour necrosis factor-alpha (TNF-α) [9]. Neutrophils are then replaced by macrophages that are responsible for cleaning the remaining cell debris and bacteria and to recruit fibroblasts and vascular cells through the release of platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) [10]. The wound thus enters into the proliferative phase, where the well-coordinated interplay between fibroblasts, macrophages and vascular cells results in the formation of a temporary matrix filling the wound defect – the granulation tissue [11]. Angiogenesis provides new blood vessels to restore blood circulation while keratinocytes migrate from the wound edge over the granulation tissue and differentiate into a stratified epithelium to protect the exposed wound [12]. In the final remodeling phase, fibroblasts and myofibroblasts secrete matrix metalloproteinases (MMPs) to remodel the collagen-rich temporary matrix [13]. During this dynamic process that can last up to 2 years, scar tissue is formed - normotrophic scar - and most myofibroblasts progressively enter in apoptosis [14]. While scar tissue is meliorated overtime, it never equals native skin; neither morphologically - the composition, organization and structural orientation of the ECM proteins is different, the number of hair-follicles is sparse and the epidermis contains less rete-ridges [15], - nor physiologically - holding, for example, only 70% of its original tensile strength [16]. The only period that scarless wound healing occurs is restricted to early fetal stage (Fig. 1A) [17], where the ECM consists of fine a reticular collagen and abundant hyaluronic acid. In this unique setting of development, wound healing does not follow the classic four steps process as in adults, nonetheless the mechanisms behind fetal healing remain largely unknown. Normotrophic scar formation is therefore the natural consequence of human wound healing apart from this mentioned stage (Fig. 1B) [18].

Adults abnormal healing may occur due to a wide range of possible causes, such as predisposition in certain anatomical location, persistent inflammation, among others, leading to fibrotic/pathological scars of two kinds: hypertrophic scars or keloids [19]. The understanding of the pathophysiology behind the formation of these scar types remains elusive [20], making the correlation between the wound healing hallmarks/stages and the type of generated scar difficult to establish. These two scar types can be easily distinguished by their growth pattern, progression overtime and association to contractures (Fig. 1C). Macroscopically, hypertrophic scars do not extend beyond the initial site of the injury and, like normotrophic scars, they can experience spontaneous regression overtime. Hypertrophic scars are linked to excess tissue tension or other extensive traumatic injuries such as burns. In turn, keloids extend beyond the borders of the original wound, do not regress spontaneously and do not have associated contractures. This type of scars can be formed after minor injuries or even without antecedent wound, being more common among Asians and dark skinned individuals [20]. There are also several histopathological markers that allow, although from highly observer-dependent perspective, distinguishing hypertrophic scars and keloids, as recently extensively reviewed [21]. In both cases, stromal cells are known to produce abnormal amounts of collagen, 7-fold higher in hypertrophic scars and 20-fold higher in keloids than in normal skin. Ultimately, the ratio between collagen I/III also differs among them, being lower in hypertrophic scars (6:1) than in keloids (17:1), in opposition to the 5:1 ratio in native skin. Moreover, hypertrophic scars present larger collagen nodules than keloids [21]. The latter are also characterized by thick hyaline collagen bundles due to exuberant crosslinking, which are also found in hypertrophic scars, but in smaller amounts and less frequently [22]. The presence of alpha smooth muscle actin (α-SMA) positive myofibroblasts is also long gone to be exclusive in identifying the type of scar [23]. Both pathological scars contain α-SMA+ cells, nonetheless these cells are found in higher number in hypertrophic scars than in keloids. Moreover, human dermal fibroblasts isolated from the two scar types display distinct expression levels of the most relevant isoforms of growth factors from the TGF-β family, known to be critical for the fibrotic phenotype. TGF-β1 and TGF-β2 expression is lower in hypertrophic scars than in keloids. The latter on its turn, features higher expression of TGF-β3, not only when compared to hypertrophic scars but also to native skin tissue [24]. Other markers, such as higher inflammatory infiltrate and unbalanced ratio of some MMPs and TIMPs during healing, as well as, increased epidermal thickness and diminished rete-ridges, have been used to distinguish these pathological scars from normal skin. However, the great variance on the biopsied sites, the scar maturity and even the anatomic location [25] that can be determinant for the histopathological heterogenicity, have been impairing a consensus.

3. From biomechanics to mechanobiology: the role on cell behaviour and fate

It is well recognized that the wound mechanical environment has an effect on wound healing and scar formation by regulating cell behaviour [26]. Importantly, the mechanical environment comprises not only the mechanical forces of the tissue provided for example by the ECM, but also external forces or displacements to which the tissue is subjected to - biomechanics. There-

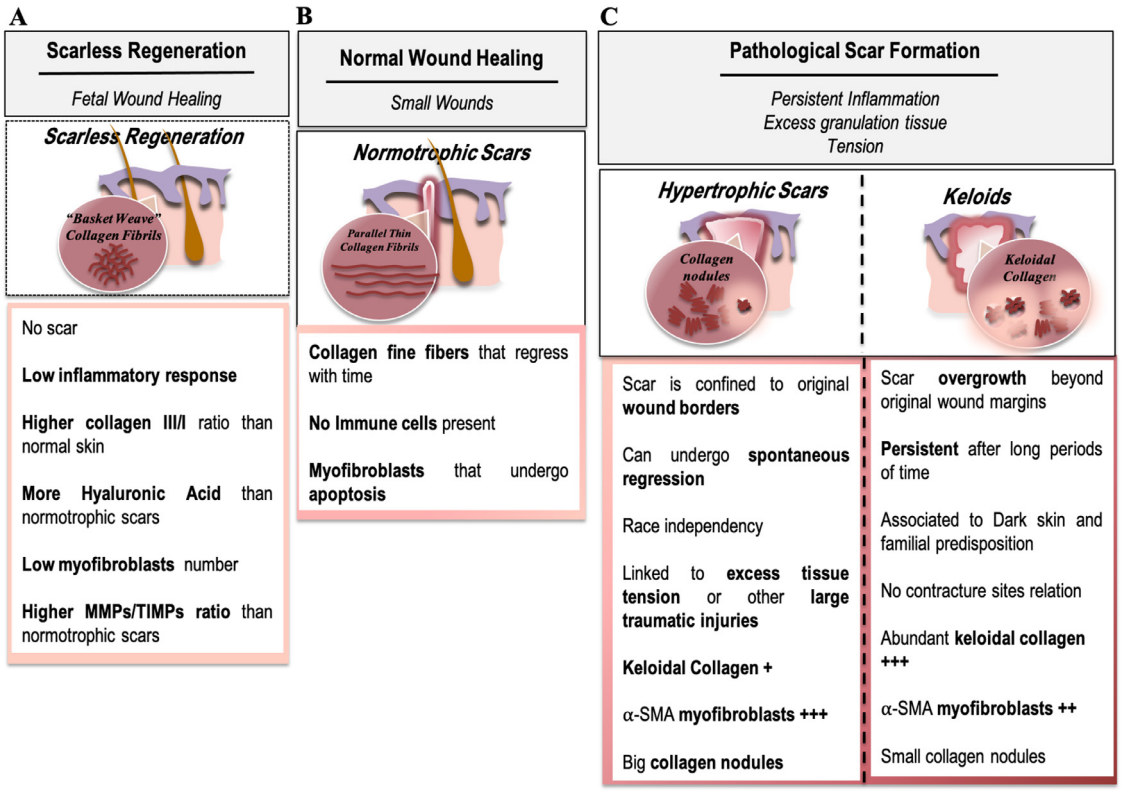

Fig. 1. Schematic overview of the different endpoints of wound healing process in humans. (A) The scarless regeneration that occurs just in a short period of fetal development, (B) the normotrophic scar as a natural restorative outcome of cutaneous wound healing, and (C) the pathological scar formation that leads to hypertrophic scars and keloids. The different scenarios and main characteristics of the distinct ECM formed are highlighted in the correspondent schemes.

fore, when discussing wound healing and scar formation, an holistic perspective is required to provide an integrated picture of how cells behave in response to the mechanical forces, from the nano to the macroscale. Moreover, this is also valid while developing innovative biomaterials for scar treatment or prevention (either in space or in time). Elastomeric materials possess a stress relaxation capacity, i.e. the material either stiffens or relaxes in response to skin biomechanics, particularly to a continued duration or increased level of strain, respectively. The way cells specifically respond to those changes over time remains elusive but understanding the elusive associated mechanosensing and mechanotransduction mechanisms will be critical not only to better understand the mode of action of elastomers but also to advance biomaterial's design capable of to counteract scarring. In the following sections, we thoroughly review the mechanical properties of healthy, injured and scar tissue, and how those correlate with tissue/ECM composition and organization. Moreover, we describe what is known about the effect of specific mechanical stimulus in individual skin cells and what are the mechanobiological signalling pathways involved.

3.1. Skin biomechanics

Healthy skin and scar tissue mechanics differ significantly. Undamaged skin is naturally viscoelastic, while scar tissue is stiff and inelastic [27–30]. It is common knowledge that skin mechanical properties are determined by the composition and organization of the dermal fibrous ECM proteins, mainly, but not limited to, fibrillar collagen such as type I and III, and elastin [31–33]. Collagen I (~75–80% by dry weight) and collagen III (~15% by dry weight) are distributed in a disorderly "basket-weave" pattern that lends skin tensile strength, enabling resistance to plastic deformation and rupture [28,34]. Cross-linked elastin fibers (~2–5% by dry weight) provide skin recoil, allowing the tissue to repeatedly extend and return to its original dimensions after removal of the force [35]. Both collagen and elastin form fibrous networks that are intimately interwoven, contributing to the "J-shaped" stress-strain behaviour of skin tissue under uniaxial tensile loading [36]. This type of stress-strain response display three distinct stages, beginning with a linear elastic extension due to the alignment of elastin's disordered structure (low-stiffness region). As extension progresses, the crimped collagen fibers gradually elongate and tend to align in the direction of the applied force with a linear behaviour at increased deformations (high-stiffness region), and up to plastic deformation and rupture (Fig. 2A) [37].

Dysregulation of ECM composition, abundance and organization alters not only the matrix mechanical properties but also the overall tissue mechanics, which in turn influence the cellular signalling [38,39]. Matrix deposition by fibroblasts is an important aspect of scar formation, but the (re)-organization of the ECM and how this affects the mechanical properties of the developing scar is equally important. Thus, there is no denying that skin mechanic is altered in the fibrotic state. However, there is no clear and straightforward mechanical profiling according to the type of scars (normotrophic or pathological scars). Despite the characterization of skin mechanical behaviour in normal and pathological conditions, reproducible and reliable data are still scarce (Fig. 2B, Table 1), owing primarily to the adopted testing method, sample type (e.g. tissue source, harvesting site, pathophysiological condition) and tissue condition (e.g. *in-vivo, ex-vivo*, preservation type). Most data come from *ex-vivo* uniaxial tensile tests, which demonstrate that scar tissue has a greater elastic modulus and a lower stress and failure strain than healthy skin [28,40]. Other studies, focusing on creep or stress relaxation tests and atomic force microscopy (AFM) nanoindentation, showed that scar tissue have a higher degree of orientation of its collagen fibrils and stiffer be-

Table 1
Mechanical properties of skin: from healthy tissue to scar.

Skin origin	Tissue condition	Testing Method	Main Findings	Refs.
Human				
Full-thickness *(In-vivo)*	Unwounded HS (Scar grading from 1 to 5)	Uniaxial loading device	k (Unwounded, at 0.2 N) = 0.42 N/mm k (Unwounded, at 0.4 N) = 0.75 N/mm ε (Unwounded, at 0.4 N) = 10.2 ε (Unwounded, at 1 N) = 15.0 k (HS, Grade 4-5 at 0.2 N) = 2.3 N/mm k (HS, Grade 4-5 at 0.4 N) = 3.0 N/mm ε (HS, Grade 4-5 at 0.4 N) = 2.1 ε (HS, Grade 4-5 at 1 N) = 3.6	[27]
Full-thickness *(Ex-vivo)*	Unwounded HS	Uniaxial tensile test: - constant stress-strain rate test - Incremental relaxation test	Constant stress-strain rate test: -σ_{ult} (Unwounded) = 697 g/mm^2 -E (Unwounded) = 1586 g/mm^2 -$\varepsilon_{at\ failure}$ (Unwounded) = 1.08 -σ_{ult} (HS) = 446 g/mm^2 -E (HS) = 2011 g/mm^2 -$\varepsilon_{at\ failure}$ (HS) = 0.47 Incremental relaxation test: -σ_{ult} (Unwounded) = 646 g/mm^2 -E (Unwounded) = 3164 g/mm^2 -$\varepsilon_{at\ failure}$ (Unwounded) = 0.80 -σ_{ult} (HS) = 351 g/mm^2 -E (HS) = 2994 g/mm^2 -$\varepsilon_{at\ failure}$ (HS) = 0.43	[28]
Full-thickness *(Ex-vivo)*	Unwounded Normotrophic Scar	Cyclic uniaxial tensile test	σ_{max} (Unwounded) > σ_{max} (Scar) ε (Unwounded) > ε (Scar)	[40]
Papillary dermis *(Ex-vivo)*	Unwounded Normotrophic Scar	AFM: - Static indentation test (Young's modulus) - Indentation creep (viscoelastic creep behaviour)	E (Scar) > E (Unwounded) Viscoelasticity (Scar) < Viscoelasticity (Unwounded)	[29]
Dermis *(Ex-vivo)*	Unwounded: -dermal tissue -normal fibroblasts (NFs) Keloid: -dermal tissue -keloid fibroblasts (KFs)	AFM: - Static indentation test (Young's modulus)	E (Unwounded: dermal tissue) = 2406 Pa E (Unwounded: NFs) = 1539 Pa E (Keloid: dermal tissue) = 14213 Pa E (Keloid: KFs) = 1133 Pa	[41]
Animals				
Murine, full-thickness *(In-vivo; Ex-vivo)*: -Act mice: transgenic mice expressing activin βA -WT: Wild-type littermates	Unwounded *In-vivo* (excisional wound, 3-21d post-excision) *Ex-vivo* excisional wound (21d post-excision)	Uniaxial tensile test Non-invasive optical strain analysis [49]	- σ_{ult} (Unwounded) > σ_{ult} (Excisional wound Act mice/WT) - ε (nearby-unwounded region) > $\varepsilon_{at\ 10\%\ in\ the\ nearby\text{-}unwounded\ region}$ (Excisional wound WT) > $\varepsilon_{at\ 10\%\ in\ the\ nearby\text{-}unwounded\ region}$ (Excisional wound Act mice)	[46]
Murine, full-thickness *(Ex-vivo)*	Unwounded Excisional wound (7 and 14d post-excision)	Uniaxial tensile test; Lucas-Kanade optical flow tracker for local strain analysis [50]	Uniaxial tensile tests to failure: - σ_{ult} (Unwounded) > σ_{ult} (Excisional wound 14d) > σ_{ult} (Excisional wound 7d) - Global strain: ε (Unwounded) > ε (Excisional wound 14d) > ε (Excisional wound 7d) - Local strain: ε (wound periphery 7d) > ε (wound periphery 14d) > ε (Unwounded) Deformation behavior at physiological load levels (0.025 N/mm): - Local strain: ε (wound periphery 7d) > ε (wound periphery 14d) > ε (wound core 14 d)) > ε (wound core 7 d)	[42]
Murine, full-thickness *(Ex-vivo)*	Unwounded Incisonal wound (20days post-incision)	Uniaxial tensile test	F_{max} (Unwounded)- 2.3 N F_{max} (Incisional wound)- 1.4 N	[43]
Porcine, full-thickness *(Ex-vivo)*	Unwounded Excisional wound (70days post-excision)	Uniaxial tensile test	Axial direction (cranial–caudal): - F_{max} (Unwounded)- 203.9 N - F_{max} (Excisional wound)- 82.2 N - $\mu_{failure}$ (Unwounded)- 13.9 mm - $\mu_{failure}$ (Excisional wound)- 4.75 mm - Energy to failure (Unwounded)- 1394 mJ - Energy to failure (Excisional wound)- 225 mJ Transverse direction (dorsal–ventral): - F_{max} (Unwounded)- 178.9 N - F_{max} (Excisional wound)- 61.5 N - $\mu_{failure}$ (Unwounded)- 11.96 mm - $\mu_{failure}$ (Excisional wound)- 5.39 mm - Energy to failure (Unwounded)- 1222 mJ - Energy to failure (Excisional wound)- 230 mJ	[45]

(*continued on next page*)

Table 1 (*continued*)

Skin origin	Tissue condition	Testing Method	Main Findings	Refs.
Porcine, full-thickness *(Ex vivo)*	Unwounded Burned tissue (deep dermal partial thickness burn, 42days post-burn)	Uniaxial tensile test	F_{max} (Unwounded)- 450–500 N F_{max} (Burned tissue)- 45–50 N $\mu_{failure}$ (Unwounded)- 48–50 mm $\mu_{failure}$ (Burned tissue)- 14–15 mm	[44]

k- Stiffness (k = F (force)/δL (change in length)); ε- Strain ($\varepsilon = \delta L/L_0$ (original length)); σ_{ult}- Ultimate tensile strength ($\sigma_{ult} = F_{max}$ (maximum load or load at failure)/A (cross-sectional area)); E- Young's modulus (E = σ (stress)/ε (strain)); $\mu_{failure}$- Displacement at failure; HS- Hypertrophic Scar.

haviour than unwounded skin, as well as weaker viscoelastic creep and ability to dissipate energy at physiologically relevant frequencies [29,41]. Consistent with *ex-vivo* findings, an *in-vivo* study on human post-burn hypertrophic scar during pressure therapy treatment, revealed that a higher scar grading resulted in an increase in linear stiffness and it was also associated with a decrease in extensibility [27]. Due to the difficulty of access to human tissue, studies have also been conducted in murine and porcine scars and skin tissue at the different post-injury times [42–46]. *Ex-vivo* testing of scar and unwounded porcine skin samples, revealed that in comparison to unwounded skin, the parallel organization of collagen fibers on scar tissue (70 days after wounding) results in a stiffer response at low-loads, comparable stiffness at high-loads, and significantly reduced failure properties (ultimate tensile strength, failure strain, and toughness) [45]. Tensile strength measurements made with incisional wounded murine skin, revealed a nearly 40% lower strength 20 days post-incision (1.4 ± 0.2 N) in comparison to unwounded skin (2.3 ± 0.1 N) [43]. Others employed imaging-based techniques to investigate global and local *ex-vivo* murine tissue deformation at a nearly physiological level of tension (0.025 N/mm) [42]. Local strain analysis of excisional murine wounds (7 and 14-day post-excision) revealed two distinct regions within the wound. Lower strains were measured at the wound core, in contrast to the extremely large elongation of a surrounding cushion, which appears mechanically very different from the core as well as from the unwounded tissue. It is presumed that the wound periphery appears to protect the newly-formed tissue from excessive deformation during the phase of new tissue formation [42]. More recently, a non-invasive *in-vivo* method for biomechanical analysis of wounds in mice showed evidences that wounds/scars were consistently stiffer than the surrounding non-wounded skin [46]. Moreover, this allowed to attain mechanistic insight into the roles of activin in wound repair and fibrosis confirming that wounds in wild-type mice were at least 80% more deformable than those from transgenic mice at 3-5d post-injury. This difference increased between d10 and d21 as transgenic mice developed stiffer scars. Interestingly, recovery of tissue deformability was slower in wounds of transgenic mice at 3–5d and 14–21d, but faster at 7–10d post-injury.

These recent insights, together with the evidences, long provided that extrinsic forces also impact scarring [47,48]. This demonstrates the need to go beyond the current mechanical testing approaches and focus on biomechanics and on understanding wound cellular signalling as the basis for improved therapies.

3.2. Mechanobiological signalling in skin cells

Cells are continuously exposed to forces of different types (compression, tensile, and shear) and of varying magnitude, direction, and frequency, affecting their behaviour. These forces can be experienced at a macro and micro level – mechanosensing – and then converted into a biological response – mechanotransduction [26,37]. A number of cell types that are found in the skin, including neurons, endothelial cells, adipocytes, stem cells, langerhans cells and melanocytes, contain mechanoreceptors such as integrins, G-protein coupled receptors (GPCR), ion channels or growth factor receptors, that mediate these mechanisms via specific signaling pathways [37].

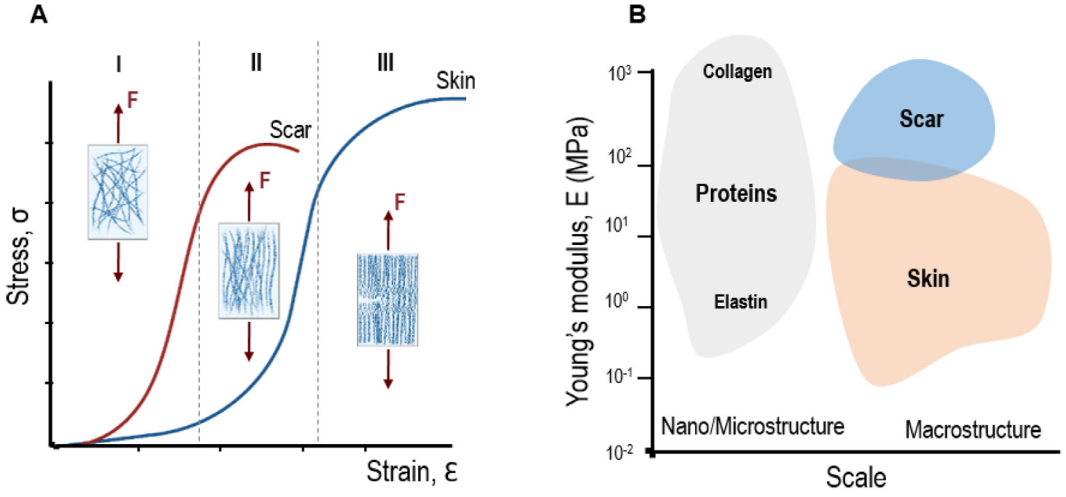

Fig. 2. Schematic illustration of the differences between the mechanical properties of healthy and scarred skin tissue. (A) J-shaped stress–strain curves of healthy and scarred skin with a schematic representation of the collagen fibers organization. In the healthy tissue, three distinct stages can be identified: I- the crimped collagen fibers begin to be oriented along the tensile axis but its contribution can be neglected; II- collagen fibers are straightening, larger and larger amount of the fibrils re-orient near to the tensile axis; III- collagen fibers are fractured and curled back. These stages are followed by: 1- toe-region (initial strain-stiffening phase); 2-linear/elastic region (high-stiffness region); 3- non-linear/plastic region and failure. In scar tissue, as the collagen fibers are not curly, only two stages can be identified. Scar tissue exhibit stiffer response at low loads and reduced failure properties ((ultimate tensile strength, failure strain). (B) Chart illustrating the elastic modulus range of the ECM components, healthy and scarred skin tissue at different length scales.

Table 2
Elastomers for mechanomodulation in scar prevention and treatment.

Elastomeric Material		Model	Experimental Conditions	Study Period	Main Findings	Refs.
Silicone-based dressings	Embrace device (Neodyne Biosciences, Inc.)	Human	Incisional wound Scar revision surgery	12-moths 6-months	- Improved scar appearance	[80–82]
	Microporous silicone rubber membrane bilayer	Murine	Full-thickness excisional wound	1, 3 and 7d post-wounding	- Accelerated wound closure, angiogenesis and increased granulation tissue, in relation the control (without treatment). - Scarring markers were not studied/evidenced.	[84]
Polyurethane (PU)- based dressings	Cutinova Thin Hydrocolloid Dressing	Human	Hypertrophic Scar (at least 5mm in width)	8-weeks of treatment: 12h (overnight) vs. 24 hours per day	- Improved colour (redness), elevation, hardness and elasticity	[90,91]
	PU-urea dressing	Murine	Full-thickness excisional wound TegadermTM was used as control	3, 7, 14d post-wounding	- Enhanced collagen deposition with a weave-like organization in relation to control - Higher contraction of the wound at earlier time points	[92]
	PU	Murine	Third-degree burn	30d post-injury	- *In-vivo* reduced scar contraction and stiffness	[102]
Poly(L-lactide-co-ε-caprolactone) (PLCL)- based dressings	PLCL randomly-oriented electrospun micro-fibrous scaffold	Murine Porcine	Third-degree burn Integra® was used as control	30d post-injury 45d post-wounding	- ECM alignment more prevalent in the control wounds	[93] [94]
	3D printed PLCL scaffold	Murine	Full-thickness excisional wound	2 months	- enhanced wound contraction and low quality healing - presence of engrailied-1-negative and neurofibromin-positive fibroblasts, indicative of a non-fibrotic environment.	[95]
Poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV)-based dressings	PHBV nanofiber mesh and film	Murine	Third-degree burn TegadermTM was used as control	14d post-wounding	Mesh-treated wounds characterized by: - Collagen fibers more organized - Softer and more elastic new tissue - Downregulation of α-SMA and TGF-β1, and upregulation of TGF-β3	[97]
	Freeze-dried 3D porous scaffold	Rat	Full-thickness wound	28 days post-treatment	- Lower levels of TGF- β1 - Higher expression of TGF-β3 - Reduced number of α -SMA positive cells	[98]
Hybrid-based dressings	Liquid crystal elastomers (LCEs)	Murine	Full-thickness excisional wound Dressing and suturing were used as controls	14d post-wounding	- LCEs-treated wounds without signs of scarring	[99]

LAP- latency-associated peptide.

The difficulty of understanding the molecular mechanisms in the wound that are activated by mechanical stress has derived towards studying the effect of specific mechanical stimulus in individual skin cells. Tensile forces have shown to drive keratinocytes towards a more proliferative/immature profile, and fibroblasts to a more "synthetic" phenotype that coincides with the one of myofibroblast [37]. On the other side, compression forces have shown to induce opposite responses promoting the differentiation of keratinocytes [51] and increasing the production of MMPs by fibroblasts [52]. These findings indicate that mechanobiological signalling is key in the scarring process. Recently, injection of a FAK inhibitor has shown to be sufficient to revert hypertrophic scar formation in mechanical loaded wounds in mice [53]. Hypertrophic scar formation was also abolished in fibroblast-specific FAK knockout mice lacking the activation of the inflammatory FAK–ERK–MCP-1 pathway [47]. These few findings indicate that treatments directing the mechanobiological processes are of great interest to reduce scar formation during wound healing. Other signalling pathways, including integrin β1-P130Cas [54], Transient Receptor Potential (TRP)C3-nuclear factor-kappa B (NFκB) [55], and p38MAPK [56], are known to be involved in mechanical stress-related pathological scarring, indicating a myriad of therapeutic targets that can be further explored as anti-scarring approaches.

Interestingly, mechanobiology also plays a key role after scar formation, as demonstrated by the response of fibroblasts isolated from keloids and hypertrophic scars to mechanical stimulation. Keloid-derived fibroblasts exposed to stretch at 10% strain showed an ERK-mediated increased (exaggerated) production of TGF-β1, TGF-β2, and collagen I in comparison to the non-stimulated cells [57]. The same mechanical stimulus applied to hypertrophic scars-

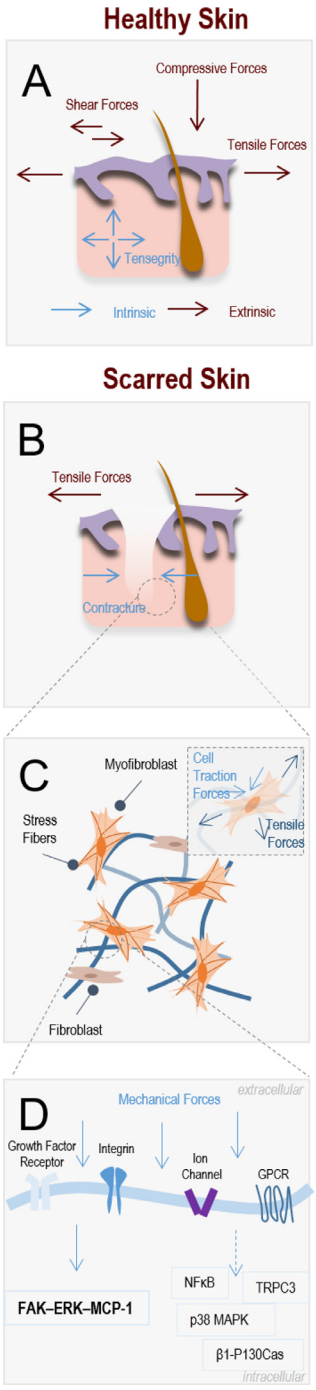

Fig. 3. Schematic representation of the mechanical forces existing in healthy and wounded skin and the associated mechanobiological processes. (A) The skin is in tensional integrity – tensegrity – resulting from opposite intrinsic forces and can be exposed to extrinsic forces, such as compressive, tensile and shear forces [37]. (B) The skin loses tensegrity after wounding, experiencing extrinsic tensile forces resulting from the wound opening and the contracture at the wound site. (C) Myofibroblasts, differentiated from fibroblasts, are the key cells in the contracture due to their ability to contract and pull the ECM through cell traction forces. During this process, the ECM is shortened and myofibroblasts synthesise new ECM to occupy the left open space [61]. (D) This process is mediated by signalling pathways activated by the mechanical forces that act on mechanoreceptors, such as integrins, G-protein coupled receptors (GPCR), ion channels or growth factor receptors. Several evidences have shown the involvement of FAK-ERK-MCP-1 signalling pathway in hypertrophic scarring [47,53]. Other data also suggest the involvement of other signalling pathways, including integrin β1-P130Cas [54], Transient Receptor Potential (TRP)C3-nuclear factor-kappa B (NFκB) [55], and p38MAPK [56], in mechanical stress-related pathological scarring.

derived fibroblasts lead to a switch towards a "synthetic" phenotype characterized by an increase on the expression of α-SMA and TGF-β1 involving p38 MAPK signalling pathway [56]. On the other hand, compression forces promoted upregulation of MMPs, and downregulation of the collagens mRNA levels, respectively mediated by the SMAD3 and SMAD2 in fibroblasts isolated from hypertrophic scars [58]. Thus, a deeper understanding of these signalling pathways instigated by mechanical stress may also contribute to find new approaches for scar management/treatment or prevention.

Other skin cells are also responsive to mechanical stress and may have an impact on scar formation. Dermal microvascular endothelial cells subjected to cyclic stretch at 15% strain showed increased levels of endothelin-1 (ET-1), a molecule that was found to be significantly increased in hypertrophic and keloid scars [59]. Considering that ET-1 has shown to induce myofibroblast differentiation and collagen synthesis in cultured dermal fibroblasts through the RhoA/Rho-kinase pathway [59], mechanical stress-mediated ET-1 production by endothelial cells may also contribute to abnormal scar formation. In addition, although not explored in the context of scaring, application of mechanical stress onto skin neurons may lead to the release neuropeptides and other biochemical mediators [60] that may also contribute to abnormal scarring.

4. Elastomeric materials for mechanomodulation in scar prevention and treatment

Scar prevention, i.e. procedures that reduce the likelihood of wounds to heal with aberrant scars, should always be prioritized over scar treatment due to greater effectiveness. An example of scar prevention refers to surgical procedures where incisions are planned parallel to relaxed skin tension lines, avoiding excessive tension at the wound borders. Nonetheless, traumatic wounds are unpredictable, and scar prevention begins after the injury. The transition from prevention to treatment occurs when a pathological scar already formed and matured. At present, pathological scar treatments remain without effective nonsurgical options. The positive clinical results that currently exist typically yield modest improvements. As mentioned before, mechanical forces are key in modulating biological processes associated to pathological scar formation [47,62], which lead the use of tension-relieving strategies such as paper tape, pressure garments and stress-shielding devices including those based on elastomeric materials [62–65]. Elastomers have been used to treat wound scarring since the year 1980 [63,64]; these undergo deformation under stress without rupture, recovering to their original state when the stress is removed (viscoelasticity). This stress relaxation behavior is fundamental to relieve the tension field that exist around the wound or mature scar and contribute to trigger apoptosis in scar-forming cells (myofibroblasts) (Fig. 4). Although the molecular pathways that link stress release to myofibroblast apoptosis are still unclear, growing findings from *in vitro* and *in vivo* studies suggest the inhibition of pro-survival mechanotransduction pathways [65–69].

4.1. Silicone

Silicone elastomers can be classified as soft, stretchy materials, with a tensile strength of 2.4–7 MPa, elastic moduli around 1.5 MPa and elongation at break in the range of 100–700% (i.e., the maximal strain at rupture), being then able to undergo varying degrees of deformation under stress without rupture [70–72]. These mechanical properties of silicone derive from the three-dimensional structure comprising a network of long and flexible polymer chains. Polysiloxane, also called siloxane, was one of the first silicone elastomers used to prevent or improve the appearance

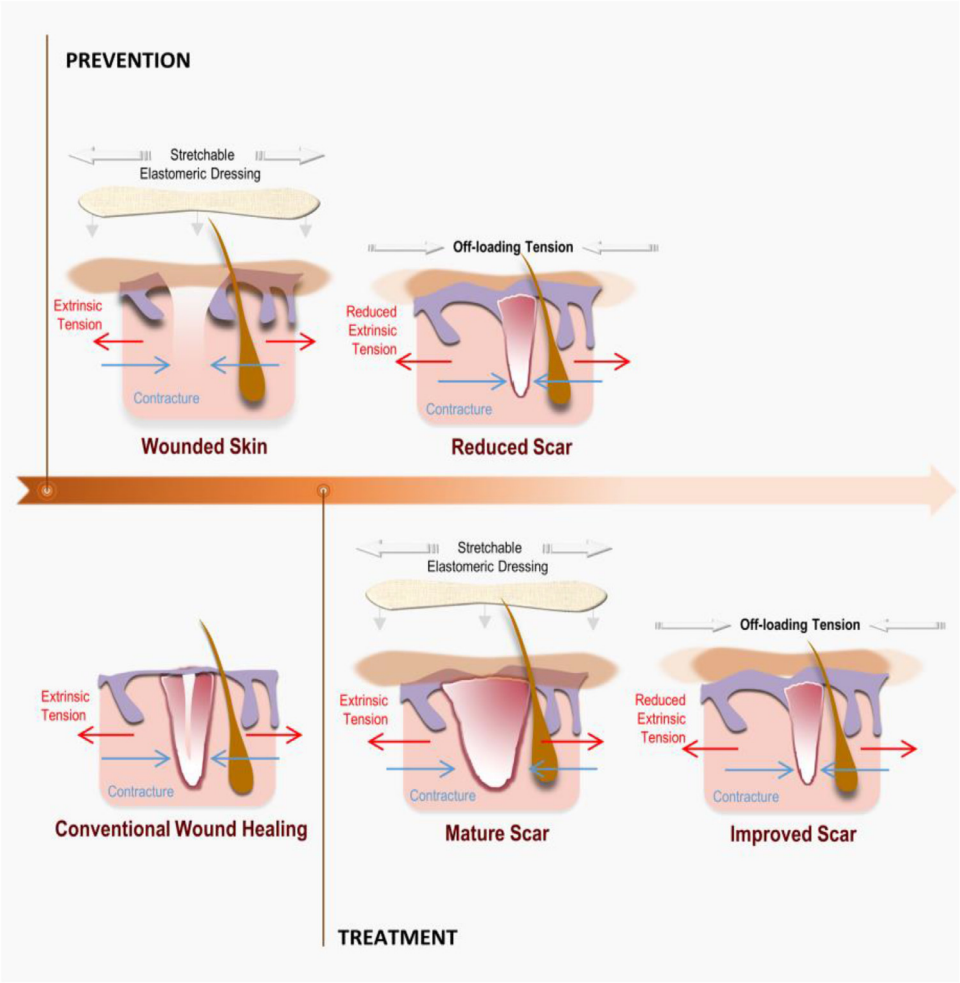

Fig. 4. Schematic representation of the application of elastomeric dressings in wounds, to prevent or treat scarring. Wounded skin is subjected to extrinsic (red arrows) and intrinsic (blue arrows) mechanical stimuli, which are known to have a significant role in the pathogenesis of pathological scars. The use of a pre-stretched elastomer allows reducing the excessive tension in the tissue surrounding the wound or the mature scar due to the viscoelastic recovery of the elastomer (tension-relieving), respectively preventing scar formation or treating mature scars improving their appearance.

of hypertrophic and keloid scars [73]. The first application was reported in 1982 as silicone gel sheeting to treat post-burn hypertrophic scars and contractures [64]. Since then, it became widely used and accepted as an effective dressing to prevent and treat scars. However, the associated mechanism of action is still unprecise, and several hypotheses have been posed along the years. There are some indications that silicone gel sheeting work by hydrating the stratum corneum acting as an occlusive barrier, and by reducing fibroblasts activity and collagen synthesis [74,75]. Moreover, it has been suggested that the increased temperature caused by the silicone induce the breakdown of collagen by collagenases in hypertrophic and keloid scars [76]. Others postulate that the release of silicone-related compounds (from a commercial silicone gel sheet Cica-Care) may have pharmacological effects on the tissue [77]. The induction of a static-electric field by a silicone cushion (silicone occlusive sheeting envelope partially filled with high viscosity silicone oil) was also suggested to contribute to the involution of hypertrophic and keloid scars [78]. Among the hypotheses attempting to explain silicone's mechanism of action in scar prevention and treatment, one that drew the scientific community's attention was its ability to mitigate scar formation by mechanical offloading the wound [79]. The Embrace Advanced Scar Therapy, in which a silicone-based sheet relieves the natural tension that exists during the skin's healing process, was one of the earliest demonstrations of that mechanism [80–82]. This therapy was tested in incisional and excisional wounds and post-operative scars in humans showing an improvement in overall scar appearance [81,82]. A mechanomodulatory mechanism resulting from the interaction of the scar-forming cell type (myofibroblasts) with silicone through their integrin receptors has been also proposed by Noskovicova et al. [83]. While the way that myofibroblasts behave in the context of cutaneous wounds could be different, such findings are of relevance in regenerative approaches that envisage the downregulation of pro-scarring signaling from the early onset of the healing cascade. Interestingly, other silicone-based dressings were shown to accelerate wound closure and promote angiogenesis but whether these co-exist with an anti-scarring effect is yet to be demonstrated [84].

4.2. Polyurethane

Like silicone elastomers, polyurethane (PU) presents high elongation at break (280–778%), elastic recovery and high mechanical strength (ranging from 11 to 65.5 MPa). The microphase-separated structure of PUs resulting from the hard and soft segments of linear PU [85] is responsible for the high elasticity of PUs and their ability to gain the original recovery when the stress is removed [86–89]. In line with silicone, PU dressings have also been used

for scar treatment. The application of a polyurethane self-adhesive dressing for 12–24 h per day for 8 weeks revealed positive results in hypertrophic scars [90]. The colour (redness), elevation, hardness and elasticity were improved after treatment. This result was similar to the one obtained with silicone, nevertheless, the PU dressing caused less skin irritation [91]. Other innovative PU-based dressings have been developed along the years to further enhance this outcome. A PU-urea dressing was developed by combining polycaprolactone (PCL), owed to its mechanical properties, polyethylene glycol (PEG), due to its wettability, and the electroactive aniline trimer (AT). While the healing of full-thickness mice wounds treated with the PU-urea dressing were characterized by lower inflammatory cell infiltrate, and enhanced collagen deposition in relation to Tegaderm™, higher contraction of the wound was also observed at earlier time points [92]. Additional histological analysis would allow confirming the organization of the new tissue to conclude about a potential anti-scarring effect of the proposed dressings.

4.3. Poly(lactide-co-ε-caprolactone)

Co-polymers composed of non-elastomeric materials can also present elastomeric properties due to specific organizational structure of the different components. This is the case of poly(lactide-co-ε-caprolactone) (PLCL) due to the phase separation of the crystalline PLA and the amorphous PCL segments, creating hard and soft domains somewhat akin to that observed in elastomeric PU. Despite this, the potential of PLCL for scar prevention/treatment has only been studied in animals. A PLCL randomly-oriented electrospun scaffold coated with collagen delayed the closure of a third degree burn when compared to the standard of care Integra® [93]. Interestingly, ECM alignment appeared more prevalent in Integra treated wounds indicating the presence of scar tissue. Authors claim that this might be associated to the loss of integrity of Integra before completion of the remodeling phase and that the maintenance of the structure of the PLCL is likely to be related to reduced HS formation by mitigating wound contraction. Less contraction and delayed closure were also observed in full-thickness pig wounds treated with other PLCL scaffolds, also in relation to Integra [94]. Despite these promising results, it is also important to highlight that an assessment at longer implantation times with a deeper understanding of the scarring process is necessary to fully validate these approaches. In fact, rat full-thickness wounds treated with 3D printed PLCL structures showed enhanced contraction and lower quality healing that was significantly improved when these structures are combined with punched skin grafts [95]. However, both conditions showed comparable levels of engrailied-1-negative and neurofibromin-positive fibroblasts, indicative of a non-fibrotic environment.

4.4. Poly(3-hydroxybutyrate-co-3-hydroxyvalerate)

PHBV is a copolymer of poly (3-hydroxybutyrate) P(3HB) with a different percentage of 3-hydroxyvalerate (3HV). Incorporating 3 HV into the P(3HB) structure results in a polymer with lower melting point and crystallinity, tougher and better flexibility [96]. The higher the 3HV content, the greater the polymer's elasticity. Interestingly, PHBV solution-cast films depicting higher yield strength and elastic modulus but lower elongation at break than corresponding electrospun nanofibrous meshes, were shown to impact differently the healing of full-thickness mouse wounds from third-degree burns due to distinct withstanding of physiological strains. Wounds treated with PHBV meshes showed an ordered arrangement of collagen fibers, whereas in the PHBV films- and Tegaderm-treated wounds were disorganized. Importantly, softer and more elastic new tissue characterized by a downregulation of α-SMA and TGF-β1, and upregulation of TGF-β3, was formed indicating that electrospun PHBV meshes mitigate scar formation by regulating myofibroblast differentiation [97]. In another work, a PHBV 3D porous scaffold produced by freeze-drying has also shown an anti-scarring effect in full-thickness rat wounds, although this effect was significantly potentiated when in combination with adipose derived stem cells. Both conditions showed lower levels of TGF-β1 than in the control group and a higher expression of TGF-β3, with a remarkable reduction of the number of α-SMA positive cells [98].

4.5. Hybrid dressings

Recently, elastomers have also been combined with other materials with the rational to tailor the desired tension-relieving effect on scar tissue [99–101]. An example is the class of liquid crystal elastomers (LCEs), which are soft materials capable of large, reversible shape changes in response to thermal and/or optical stimuli. Recently, LCE metamaterials with unprecedented biaxial actuation strain (−53%) and biaxial coefficient of thermal expansion (−33 125 ppm K−1), were integrated into a dressing which was capable of biaxial contraction upon heating to 46 °C (dropping a saline solution), counter-acting the forces of rat full-thickness excisional wounds [99]. In contrast to the conventional strategies (e.g., medical dressing and suturing), LCEs-treated wounds were closed and without signs of scarring 14 days post-treatment. Others have reported a method to assemble hydrogels and elastomers into hybrid structures with extremely robust interfaces (interfacial toughness over 1000 Jm^{-2}) [100]. While the proposed method was demonstrated to be applicable to various types of tough hydrogels (hyaluronic acid, alginate or chitosan based) and diverse commonly used elastomers (polydimethylsiloxane, polyurethane, latex) to fabricate stretchable structures, its efficacy in scar prevention or treatment is yet to be demonstrated.

5. Emerging challenges and future prospects

Pathological scars such as hypertrophic and keloids are associated with pain and mental distress due to cosmetic and esthetic reasons. To tackle this problematic, a wide range of therapeutic procedures are currently available, however, none of them is ideal to treat or prevent scar formation.

So far, the understanding of the molecular mechanisms that are activated by mechanical stress is limited to cell-based studies. Insights of these factors in a wound environment can grasp the primary mechanisms of scar formation and the associated dynamics. Altogether, the unravelling of the molecular pathways of mechanical transduction with optimal profiling of scar/wound type can contribute to better scar prevention/treatment and ultimately to the identification of potential therapeutic targets. Emerging high-throughput omics technologies, such as genomics, transcriptomics, and proteomics, can be a breakthrough to dismantle the main signalling pathways and molecules underlying the scarring process. This knowledge will potentiate the discovery of new therapeutic targets and the development of more directed therapies.

The use of tension-shielding elastomeric biomaterials for scar prevention and reduction have gained attention, as mechanical offloading treatments showed to reduce scars in specific situations. Nonetheless, the success of current anti-scarring treatments seems to be weakened not only by the lack of knowledge in healing mechanics, but also on the mechanical profiling of the wound healing process along the time and according to each scar type. New and more uniformed testing methods are urgently needed to improve the current data and achieve more reproducible and reliable data. Such knowledge on the dynamics of pathological scarring

process would be of great importance as it would allow the development of biomaterials, potentially elastomeric-based ones but not limited to, with properties specifically tailored to counter-act the scar-driving mechanical forces at the different healing. The ideal biomaterial would either be specifically designed for neutralize those forces or to respond to them leading a site- and time-specific mechanoresponse. While myofibroblasts are critical, together with fibroblasts to remodel the collagen-rich temporary matrix, during the remodeling phase of the healing, strategies that reduce their number at this stage are expected to diminish scarring. Thus, biomaterials that mechanically perform towards an environment less prone to myofibroblasts differentiation and activation prior the remodeling phase are likely to prevent scarring or help reducing it. This is also important if biodegradable biomaterials are considered since their mechanical features will change along time and with the healing. This is the case for example of hybrid elastomer-based dressing, in which the elastomeric layer is combined with a hydrogel layer, known to benefit re-epithelialization but which degradation rate (as then mechanical stability) is highly dependent on the wound microenvironment. While the definite demonstration of these concepts has not been possible biomaterials capable of mechanically modulating the cutaneous wound healing response are emerging anticipating great progress for the prevention and treatment of pathological scars.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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