The relationship between skin stretching/contraction and pathologic scarring: The important role of mechanical forces in keloid generation

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ABSTRACT

Keloids tend to occur on highly mobile sites with high tension. This study was designed to determine whether body surface areas exposed to large strain during normal activities correlate with areas that show high rates of keloid generation after wounding. Eight adult Japanese volunteers were enrolled to study the skin stretching/contraction rates of nine different body sites. Skin stretching/contraction was measured by marking eight points on each region and measuring the change in location of the marked points after typical movements. The distribution of 1,500 keloids on 483 Japanese patients was mapped. The parietal region and anterior lower leg were associated with the least stretching/contraction, while the suprapubic region had the highest stretching/contraction rate. With regard to keloid distribution, there were 733 on the anterior chest region (48.9%) and 403 on the scapular regions (26.9%). No keloids were reported on the scalp or anterior lower leg. Because these sites are rarely subjected to skin stretching/contraction, it appears that mechanical force is an important trigger that drives keloid generation even in patients who are genetically predisposed to keloids. Thus, mechanotransduction studies are useful for developing clinical approaches that reduce the skin tension around wounds or scars for the prevention and treatment of not only keloids but also hypertrophic scars.

A burn wound that heals in less than 10 days has a 4% risk of developing hypertrophic scars.[1] However, a burn wound that takes 21 days or more to heal has a 70% or greater risk of developing hypertrophic scars.[1] Thus, it has been suggested that nearly anyone can develop hypertrophic scars and that scars are largely a tributary of local wound conditions. On the other hand, keloids, but not hypertrophic scars, are subject to genetic influences; thus, keloids and hypertrophic scars seem to be different.[2] However, it is also true that they are both similar with respect to the fibroproliferative disorders they cause in skin.[3]

Keloids are subject to genetic influences; however, it is also known that keloids tend to occur on sites that are highly mobile and high tension, such as the anterior chest, suprapubic region, and upper arm.[4] Our studies on the relationship between skin tension and keloids have suggested that the characteristic butterfly, crab's claw, and dumbbell shapes associated with keloids are largely determined by the direction of mechanical forces at and around the wound site on skin.[5,6] Thus, it seems that mechanical force is a major factor involved in keloid production. However, extensive studies that map the mechanical force distribution on our body surface have not yet been performed. In the present study, we measured the skin stretching/contraction rates of various body sites. Moreover, we studied the distribution of keloid-affected sites to understand how skin mechanical properties relate to the generation of keloids.

We believe that these studies will develop clinical approaches that reduce skin tension around wounds or scars. Indeed, such approaches are likely to aid in the prevention and treatment of not only keloids but also other similar scars, including hypertrophic scars.

METHODS

Skin stretching/contraction rate by body sites

Eight adult Japanese volunteers (28–44 years old, all male) were enrolled in this study. The study was reviewed and approved by the institutional review board of Nippon Medical School in Tokyo. Because males with an average body type were selected, the average height was 172.6 cm, the average body weight was 69.5 kg, and the average body mass index was 23.2. The skin stretching rates of nine different sites on each volunteer were examined (Figure 1): (1) parietal region; (2) lower jaw/neck region; (3) anterior chest; (4) upper arm; (5) back; (6) scapular region; (7) suprapubic region; (8) lateral thigh; and (9) anterior lower leg.
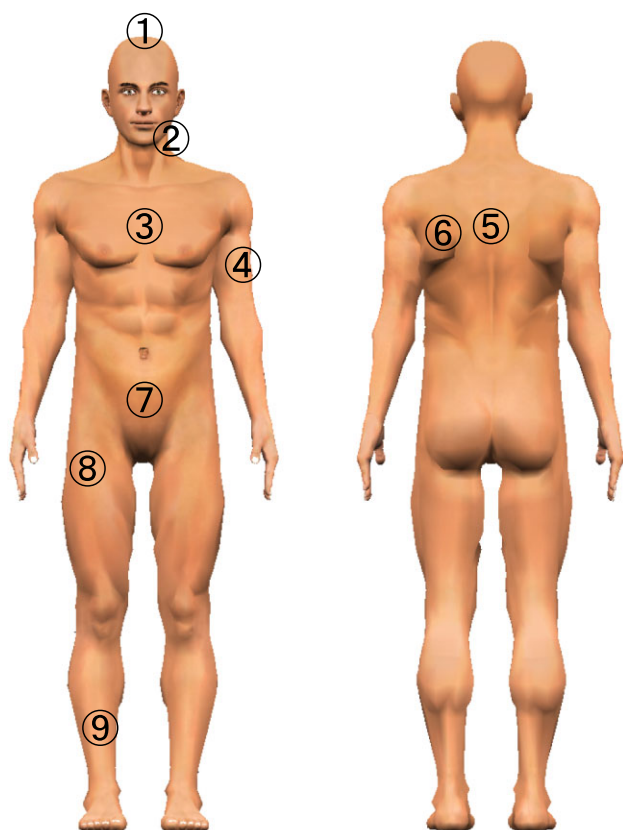
Figure 1. Body sites that were measured for skin stretching/contraction. (1) parietal region, (2) lower jaw/neck region, (3) anterior chest, (4) upper arm, (5) back, (6) scapular region, (7) suprapubic region, (8) lateral thigh, and (9) anterior lower leg. The skin stretching/contraction rates of these eight different regions were measured.

To measure skin stretching/contraction, eight points in a 50 mm × 50 mm square were marked by a black marker on each region, as shown in Figure 2, while the volunteer stood straight. The volunteers were then asked to perform a typical movement of the region that occurs regularly during daily life, as shown in Figure S1. The change in the lengths of the horizontal (H), vertical (V), oblique-left (OL), and oblique-right (OR) lines were measured for each region (Figure 2). The ratios of the lengths before and after the movement were calculated. For example, if the 50-mm long horizontal line was changed by the movement to measure 60 mm, it was denoted as +20% (stretch). However, if it changed to 40 mm, it was denoted as −20% (contraction). Statistical analysis of the data of the eight volunteers was performed by using paired t test.

Distribution of keloids

The keloid distribution on 483 Japanese patients (301 males, 182 females, average age 37.6 years) was mapped. The location of the 1,500 keloids of the 483 patients was determined, and their distribution on each of the eight regions described

earlier was analyzed. In 362, 878, and 260 cases, the causes were idiopathic, acne vulgaris, and minor traumas (such as insect bites and bra hook trauma), respectively. Keloids caused by deliberate wounding, such as by a Caesarean section or earlobe piercing, were excluded to reduce bias because these wounds are intentional. The frequencies with which keloids occurred on various regions of the human body were mapped and counted.

RESULTS

Skin stretching/contraction rates of nine body regions

Parietal region

When the volunteers wrinkled their forehead, the area marked on the parietal region barely moved (Table 1 and Figure 3). Consequently, the average stretching/contraction ratios in the horizontal, vertical, oblique-left, and oblique-right directions were −1%, −1%, 0%, and −1%, respectively. This region was the most motionless of the eight regions that were studied.

Lower jaw/neck region

When the volunteers opened their mouths horizontally, horizontal stretching/contraction rates were greater than vertical rates (18% vs. 0%, $p < 0.05$). Moreover, when the volunteers inflated their mouths, horizontal stretching/contraction rates were greater than vertical rates (5% vs. 1%, $p < 0.05$).

Anterior chest

When the volunteers pulled their chest in, the horizontal stretching/contraction rates were greater than the vertical
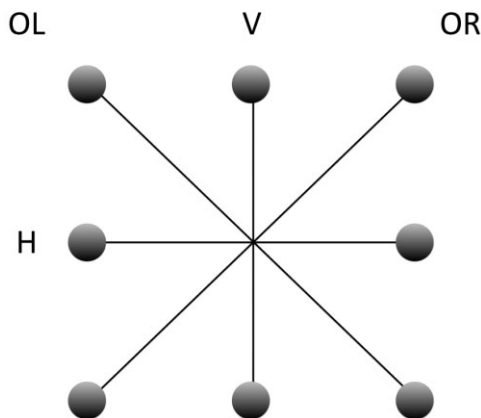

Figure 2. Marking of the skin to measure skin stretching/contraction. To measure the degree to which skin is stretched/contracted by typical daily movements, eight points on a 50 mm × 50 mm square were marked on the skin by a black marker on the eight regions indicated in Figure 1 while the volunteer was in a straight position. The volunteer was then asked to perform a typical daily movement, and the changes in the length of the horizontal (H), vertical (V), oblique-left (OL), and oblique-right (OR) lines were measured.

Table 1. Skin stretching/contraction rates of nine body regions

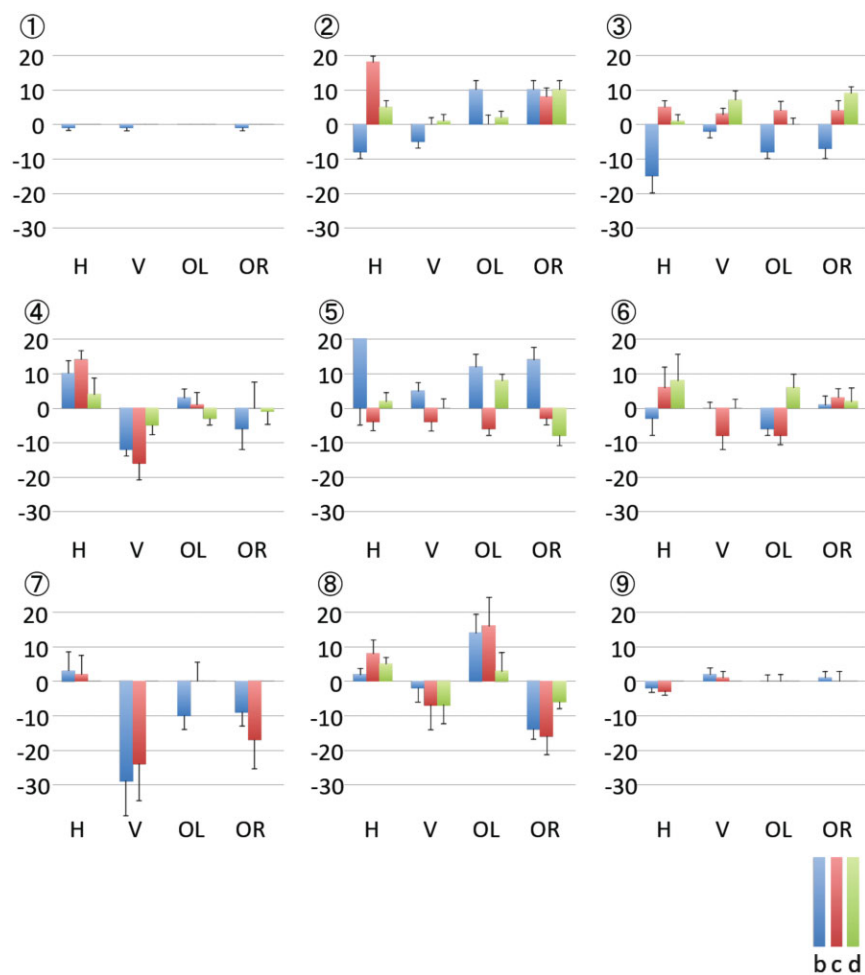| Region	Movement	Stat	Horizontal (H) Actual measured value (mm)	Horizontal (H) Ratio of stretching or contraction	Vertical (V) Actual measured value (mm)	Vertical (V) Ratio of stretching or contraction	Oblique-left (OL) Actual measured value (mm)	Oblique-left (OL) Ratio of stretching or contraction	Oblique-right (OR) Actual measured value (mm)	Oblique-right (OR) Ratio of stretching or contraction
(1) Parietal region	b Wrinkle forehead	Average	49.5	−1%	49.5	−1%	70.8	0%	70.2	−1%
		SD	1.2	2%	1.0	2%	0.8	1%	0.8	1%
(2) Lower jaw/neck region	b Open mouth vertically	Average	46.2	−8%	47.4	−5%	78.1	10%	78.3	10%
		SD	1.2	2%	1.1	2%	1.8	3%	1.7	3%
	c Open mouth horizontally	Average	41.2	18%	50.2	0%	71.3	3%	76.7	8%
		SD	1.5	2%	1.6	2%	1.9	3%	1.8	3%
	d Inflate mouse	Average	52.3	5%	50.4	1%	72.6	2%	78.4	10%
		SD	1.3	2%	1.4	2%	1.6	2%	1.8	3%
(3) Anterior chest	b Pull chest in	Average	42.4	−15%	49.0	−2%	64.9	−8%	65.9	−7%
		SD	2.7	5%	1.2	2%	1.1	2%	2.4	3%
	c Throw out chest	Average	52.4	5%	51.4	3%	73.8	4%	73.5	4%
		SD	0.9	2%	1.2	2%	2.0	3%	1.8	3%
	d Raise left hand	Average	50.5	1%	53.6	7%	70.5	0%	77.1	9%
		SD	0.8	2%	1.3	3%	1.6	2%	1.7	2%
(4) Upper arm	b 90-degree abduction of shoulder	Average	55.0	10%	43.9	−12%	73.1	3%	66.1	−6%
		SD	2.0	4%	1.1	2%	2.4	3%	4.5	6%
	c 180-degree abduction of shoulder	Average	56.9	14%	42.1	−16%	71.1	1%	70.6	0%
		SD	1.5	3%	2.7	5%	3.1	4%	4.8	7%
	d 90-degree abduction of shoulder and 90-degree flexion of elbow	Average	51.9	4%	47.5	−5%	68.6	−3%	69.8	−1%
		SD	2.7	5%	1.4	3%	1.4	2%	2.5	4%
(5) Dorsal region	b Anteflexion	Average	60.3	21%	52.5	5%	79.3	12%	80.9	14%
		SD	2.5	5%	1.6	3%	2.7	4%	3.2	4%
	c Extension	Average	48.3	−4%	48.0	−4%	66.8	−6%	68.9	−3%
		SD	1.5	3%	1.7	3%	1.4	2%	1.6	2%
	d Twist 30 degrees to the right	Average	50.9	2%	50.0	0%	76.6	8%	64.8	−8%
		SD	1.5	3%	1.5	3%	1.7	2%	1.9	3%
(6) Scapular region	b 90-degree abduction of shoulder	Average	48.5	−3%	50.0	0%	66.5	−6%	71.8	1%
		SD	2.6	5%	0.9	2%	1.2	2%	2.4	3%
	c 180-degree abduction of shoulder	Average	53.0	6%	46.3	−8%	65.0	−8%	72.6	3%
		SD	2.8	6%	1.9	4%	2.2	3%	1.9	3%
	d 90-degree medial rotation of shoulder	Average	54.0	8%	50.1	0%	74.9	6%	72.4	2%
		SD	4.1	8%	1.5	3%	2.6	4%	2.7	4%
(7) Suprapubic region	b Sitting on a chair	Average	51.3	3%	35.6	−29%	63.6	−10%	64.6	−9%
		SD	3.0	6%	5.2	10%	3.1	4%	3.0	4%
	c Twist 30 degrees to the right in a seated position	Average	50.9	2%	38.0	−24%	70.6	0%	58.6	−17%
		SD	2.8	6%	5.3	11%	4.3	6%	5.4	8%
(8) Lateral thigh	b 90-degree flexion of hip joint	Average	51.0	2%	49.3	−2%	80.8	14%	61.1	−14%
		SD	1.1	2%	2.1	4%	3.9	5%	2.4	3%
	c 120-degree flexion of hip joint	Average	53.9	8%	46.6	−7%	82.1	16%	59.8	−16%
		SD	1.8	4%	3.4	7%	5.9	8%	3.7	5%
	d 50-degree abduction of hip joint	Average	52.3	5%	46.4	−7%	73.1	3%	66.4	−6%
		SD	0.9	2%	2.7	5%	3.7	5%	1.4	2%
(9) Anterior lower leg	b Dorsal flexion of ankle joint	Average	49.1	−2%	51.1	2%	71.0	0%	71.1	1%
		SD	0.4	1%	1.0	2%	1.1	2%	1.4	2%
	c Planter flexion of ankle joint	Average	48.6	−3%	50.4	1%	70.5	0%	70.6	0%
		SD	0.7	1%	1.1	2%	1.7	2%	1.8	3%

Figure 3. Typical movements used to measure the skin stretching/contraction of eight body regions. (1) Parietal region: a. normal position; b. wrinkling of the forehead, (2) lower jaw/neck region: a. normal position; b. open mouth vertically; c. open mouth horizontally; d. inflate mouth, (3) anterior chest: a. normal position; b. pull chest in; c. throw chest out; d. raise left hand, (4) upper arm: a. normal position; b. 90-degree abduction of the shoulder; c. 180-degree abduction of the shoulder; d. 90-degree abduction of the shoulder and 90-degree flexion of the elbow, (5) dorsal region: a. normal position; b. anteflexion; c. extension; d. twist 30 degrees to the right, (6) scapular region: a. normal position; b. 90-degree abduction of the shoulder; c. 180-degree abduction of the shoulder; d. 90-degree medial rotation of the shoulder, (7) suprapubic region: a. normal position; b. seated on a chair; c. twist 30 degrees to the right while seated, (8) lateral thigh: a. normal position; b. 90-degree flexion of the hip joint; c. 120-degree flexion of the hip joint; d. 50-degree abduction of the hip joint, (9) anterior lower leg: a. normal position; b. dorsal flexion of the ankle joint; c. planter flexion of the ankle joint.

rates (-15% vs. -2%, $p < 0.05$). However, when the volunteers raised their hands, the vertical and oblique stretching rates were greater than the horizontal rates (7% and 9% vs. 1%, $p < 0.05$).

Upper arm

Upon 90- to 180-degree abduction of the shoulder, the horizontal and vertical stretching/contraction rates were 10% or more. However, 90-degree abduction of the shoulder with 90-degree flexion of the elbow resulted in stretching/contraction rates of 5% or less for all directions.

Dorsal region

When the volunteers performed anteflexion of the back, the skin was stretched into every direction by 5% or more. Extension of the back and twisting did not have greater effects than anteflexion.

Scapular region

The 180-degree abduction or 90-degree medial rotation of the shoulder induced up to 8% skin stretching/contraction.

Suprapubic region

When the volunteer was seated, the contraction rate in the vertical direction was 29%. This was the biggest stretching/contraction rate observed in this study.

Lateral thigh

Flexion of the hip joint generated stretching rates in the oblique directions of around 15%. This was larger than the stretching rates in the horizontal and vertical directions ($p < 0.05$).

Anterior lower leg

Dorsal or planter flexion of the ankle joint did not induce skin stretching/contraction rates that exceeded 3%. This was the second lowest rate observed in this study (the first was observed in the parietal region).

Distribution of keloids

There were 182 keloids (12.1%) on the lower jaw/neck region, 733 (48.9%) on the anterior chest region, three (0.2%)
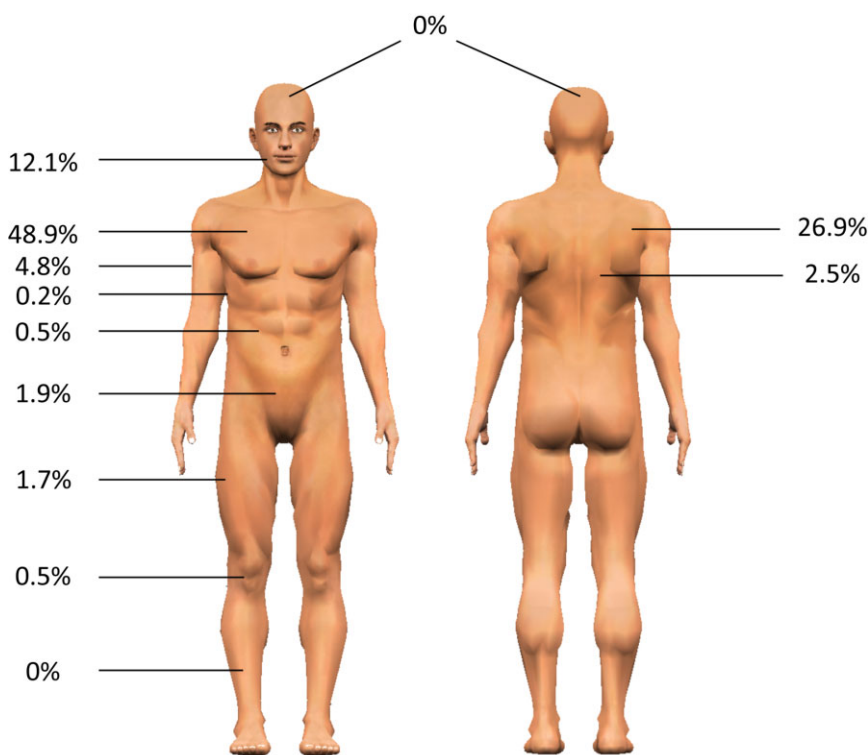
Figure 4. Distribution of keloids on various regions of the body. There were 182 keloids (12.1%) on the lower jaw-anterior neck region, 733 (48.9%) on the anterior chest region, 3 (0.2%) on the lateral chest, 403 (26.9%) on the scapular regions, 38 (2.5%) on the dorsal regions, 72 (4.8%) on the upper arm, 8 (0.5%) on the upper abdomen, 28 (1.9%) on the lower abdomen, 26 (1.7%) on the femoral regions, and 7 (0.5%) on the knee. There were no keloids on the scalp or anterior lower leg.

on the lateral chest, 403 (26.9%) on the scapular regions, 38 (2.5%) on the dorsal regions, 72 (4.8%) on the upper arm, 8 (0.5%) on the upper abdomen, 28 (1.9%) on the lower abdomen, 26 (1.7%) on the femoral regions, and 7 (0.5%) on the knee (Figure 4). There were no keloids on the scalp or anterior lower leg.

DISCUSSION

Possible mechanisms that generate pathologic scars

A recent study on single nucleotide polymorphisms (SNPs)[7] has suggested that keloid generation involves a genetic predisposition. If this is true, then it is possible that while keloids are strongly influenced by genetics, the genetic predisposition of hypertrophic scars may be weaker. However, our previous[8] and present studies revealed the interesting observation that keloids were never found on the parietal region or the anterior lower leg even in patients who had many keloids on their body. As shown in Table 1 and Figure 3, these sites are also rarely subjected to skin stretching/contraction. This suggests that even in patients who are genetically predisposed to develop keloids, skin tension/external mechanical force is needed to drive the development of keloids. Keloids can be considered as a multifactorial disorder with a genetic disposition that has a tendency to be affected by local factors, such as mechanical force. Thus, future elucidation of the functional relevance of SNPs and their possible relation to mechanotransduction would be a significant step in validating the mechanical hypothesis of keloid pathogenesis.

Another interesting observation was that keloids were never generated on the earlobe by idiopathic causes, acne

vulgaris, or minor traumas. This means that almost all earlobe keloids are caused by piercing. Significantly, many patients with earlobe keloids noted that they repeatedly felt pain or had discharge when they removed or replaced the earring. Thus, it may be that the inflammation caused by small but repeated injuries to the pierced skin strongly influences the generation of keloids in this site. If these were true, keloids would not only be caused by mechanical force but also by cyclical or prolonged inflammation. However, it remains possible that the earlobe is also affected by friction produced by the pillow during sleep or by the weight of the earring.

An additional interesting finding was that the most highly mobile regions did not correlate completely with the keloid distribution results. For example, while the anterior chest (Figure 5A) was the most frequent keloid-bearing site (Figure 4), the anterior chest was not the site with the most frequent stretching/contraction (Figure 3). Moreover, comparison of the dorsal and scapular regions (Figure 5B) reveals that although the dorsal region had higher stretching/contraction rates than the scapular region (Figure 3), the scapular region bore keloids more frequently (Figure 4). This suggests that not only skin mobility but also the dermal structure influences the development of pathologic scars. Because the stiffness/thickness of skin differs markedly depending on the site of the body, precise analysis of this factor in the future is warranted. Moreover, it is suggested that high tension with cyclical stretching rather than static forces or cyclical mobility without tension is important for generating keloids, although these issues need to be studied in the future.

For these reasons, it is reasonable to propose that: (1) mechanical forces may influence not only the ingravescence of pathologic scars but also their generation; (2) one of the
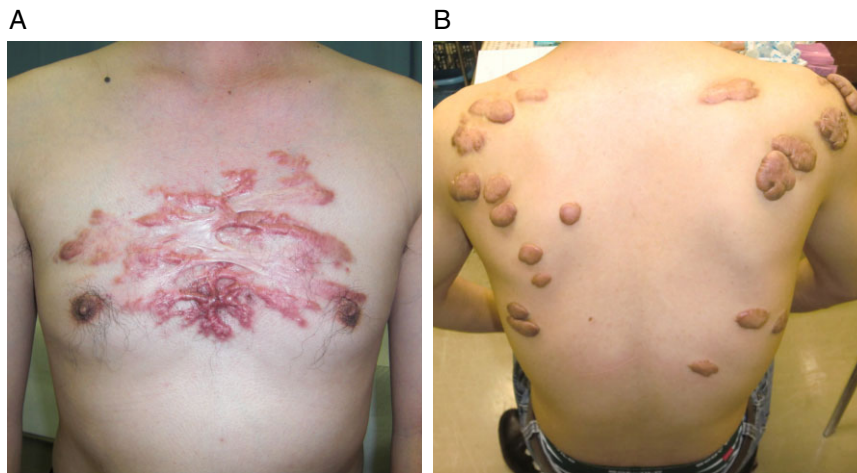
A   B

Figure 5. Typical keloids. (A) anterior chest keloids; (B) scapular-back keloids. Keloids occur more frequently on the scapular regions than on the dorsal region.

mechanisms that generate pathologic scarring is cyclical/prolonged inflammation because of repeated skin stretching or minor injury (an example may be the keloids that develop on pierced earlobes); (3) not only mechanical force distribution but also structural differences in the skin at various sites may influence pathologic scar generation/ingravescence; and (4) if the patient has a genetic disposition, the risk of developing a pathologic scar increases.

These observations suggest that we should focus on reducing the mechanical forces on and the inflammation of wounds/pathologic scars in the clinical setting.

Reduction of mechanical forces and inflammation

As indicated earlier, both mechanical force reduction and antiinflammatory treatments play important roles in the current pathologic scar-treatment strategy.

Extensive reviews[9,10] of the literature regarding keloids have revealed that many treatment methods are effective. These include surgery, the application of corticosteroid ointment or injection,[11,12] radiation,[4,13,14] dye or Nd:YAG laser therapy,[15] the administration of 5-fluorouracil,[16,17] cryotherapy,[18,19] gel sheeting,[20,21] and taping fixation. These treatments can be classified roughly into three types on the basis of their purpose. One purpose is to reduce mechanical forces by using gel sheeting and taping fixation. The second is to reduce inflammation using radiation, corticosteroids, or laser treatment. The third is to reduce the amount of accumulated collagen and the number of proliferating cells/vessels. Thus, the concept of reducing both mechanical force and inflammation is already incorporated in the current algorithms of pathologic scar treatments.

However, it may be useful to focus on this concept even more acutely in future pathologic scar management. For example, because keloids and hypertrophic scars arise from the dermis, we have speculated that eliminating mechanical forces on the dermis may reduce the risk of pathologic scar formation after surgery. For this reason, we have started to use subcutaneous/fascial tension reduction sutures where the tension is placed on the layer of deep fascia and superficial fascia.[22,23] This minimizes the use of dermal sutures; indeed, dermal sutures can be avoided altogether if the wound edges

can be joined naturally under very small tension. Moreover, because skin grafting tends to generate secondary contractures, it may be better to perform flap surgery to reconstruct keloids because it is associated with superior tension reduction.[24]

Basic research on the mechanical forces in scarring

Supporting this study are studies that used a sophisticated servo-controlled device to stretch murine dorsal skin.[25,26] These studies showed that the stretched samples exhibited up-regulated epidermal proliferation and angiogenesis, which are also features of keloids and hypertrophic scars.[25,26] Moreover, real-time reverse transcription polymerase chain reaction (RT-PCR) analyses revealed that cyclically stretched skin expresses growth factors and neuropeptides more strongly than statically stretched skin.[25,26] In addition, in a study[27] with a hypertrophic scar mouse model where healing scars were exposed to mechanical force loading, it was shown that scars subjected to tension exhibit less apoptosis and that inflammatory cells and mechanical forces promote fibrosis. Moreover, a study using red Duroc swine indicates that mechanical manipulation of the wound environment using a dynamic stress-shielding polymer device can significantly reduce scar formation.[28] These findings support the now well-established notion that mechanical forces strongly modulate the cellular behavior that leads to abnormal scarring.[29]

Mechanotransduction is the process by which physical forces are converted into biochemical signals that then result in cellular responses.[29] In this study, we used the term "stretch" and "contraction" on a macro level. On the other hand, in vitro studies have clearly shown that cellular "stretch" and "contraction" can produce dramatically different biologic effects, e.g., proliferation vs. apoptosis on a micro level.[30] Macro and micro "stretch" and "contraction" forces should be considered as different because macro "stretch" and "contraction" forces may be categorized as matrix distortion forces that are recognized as the same signal at the cellular level. In future studies, it would be informative to determine what kinds of force, e.g., stretch, contraction, compression, shear, hydrostatic pressure, or osmotic pressure, lead to collagen production.
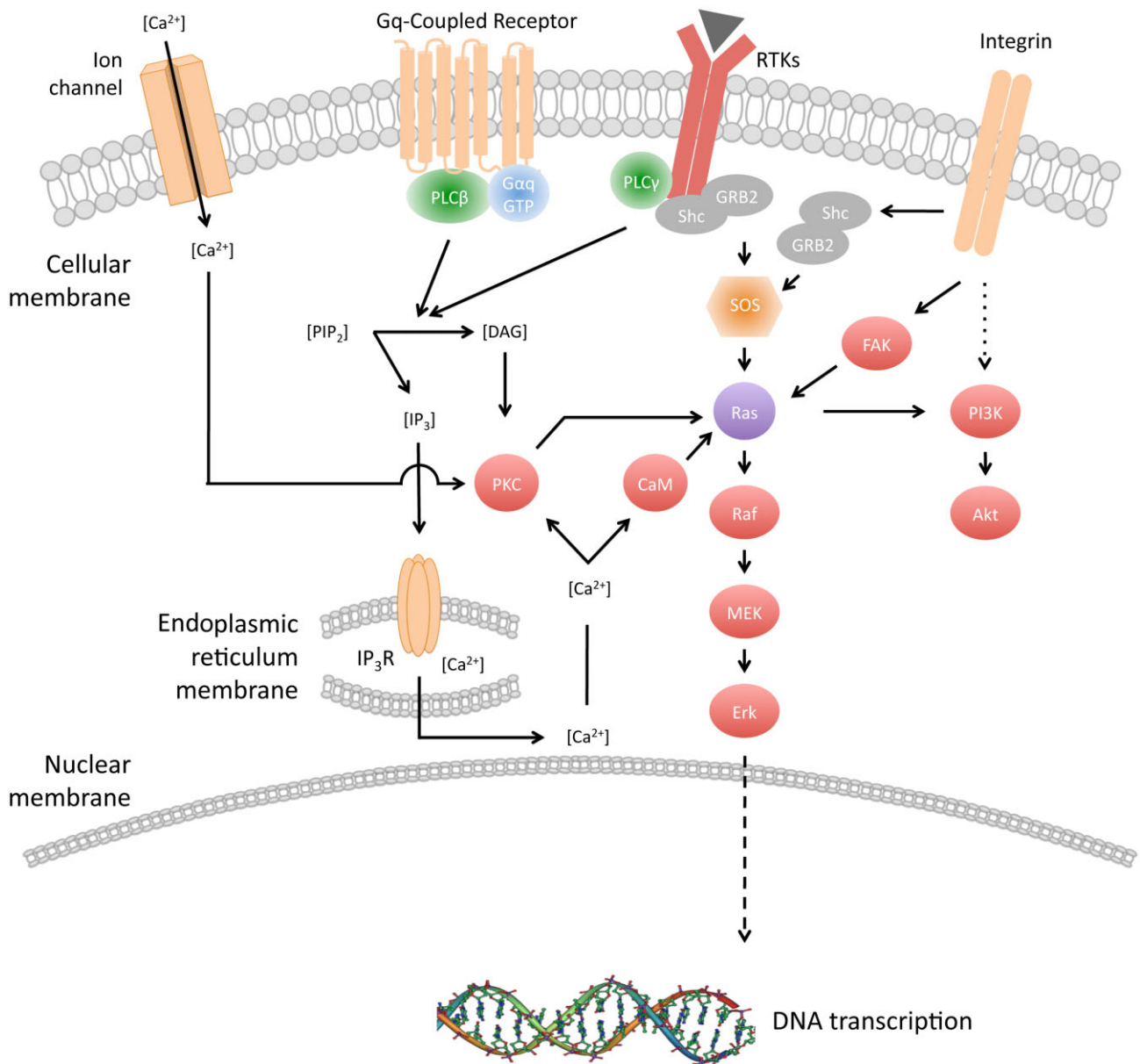
Figure 6. An example of the mechanosignaling pathways that participate in scarring. The mechanosignaling pathways that participate in the formation and growth of cutaneous scars mainly include the transforming growth factor β/Smad, integrin, mitogen-activated protein kinase and G protein, tumor necrosis factor α/nuclear factor-κB, Wnt/β-catenin, interleukin, and calcium ion pathways. The cellular mechanosignaling pathways also interact actively with the extracellular matrix during scar development.

The discovery and development of various molecular pathways have revolutionized the fundamental and clinical views of the formation and progression of cutaneous scars.[31,32] The mechanosignaling pathways (Figure 6) that participate in the formation and growth of cutaneous scars mainly include the transforming growth factor β/Smad, integrin, mitogen-activated protein kinase and G protein, tumor necrosis factor α/nuclear factor-κB, Wnt/β-catenin, interleukin, and calcium ion pathways.[33] The cellular mechanosignaling pathways also interact actively with the extracellular matrix during scar development. Moreover, there is extensive crosstalk between these scar mechanosignaling pathways and the pathways of hypoxia, inflammation, and angiogenesis. The elucidation of scar mechanosignaling pathways provides a new platform for understanding scar development, although it will be necessary to pursue the identification of novel targets that are specific to pathologic scars. This better understanding will facilitate research into this promising field and may help to promote the

development of pharmacologic interventions that could ultimately prevent, reduce, or even reverse scar formation or progression.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Skin stretching/contraction rates of the nine body sites. The stretching/contraction rates of the marked points in four directions (horizontal [H], vertical [V], oblique-left [OL], and oblique-right [OR], as shown in Figure 2) were measured for the nine body sites (shown as 1–9 in Figure 3) after specific movements (shown in b, c, and d of Figure 3) were performed. The colored bars indicate the degree of skin stretching (positive % on the vertical axis) or contraction (negative % on the vertical axis) when the specific movements denoted as b (blue), c (red), or d (green) were performed. These data show that the parietal region (1) and the anterior lower leg (9) are the least mobile sites.

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