

# A Piez-o the jigsaw: the Piezo1 channel in skin biology

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doi:10.1111/ced.15138

## Summary

The skin is the largest organ covering the entirety of the body. Its role as a physical barrier to the outside world as well as its endocrinological and immunological functions subject it to continuous internal and external mechanical forces. Thus, mechanotransduction is of the utmost importance for the skin in order to process and leverage mechanical input for its various functions. Piezo1 is a mechanosensitive ion channel that is a primary mediator of mechanotransduction and is highly expressed in the skin. The discovery of Piezo1 earned a Nobel Prize, and has had a profound impact on our understanding of physiology and pathology including paramount contributions in cutaneous biology. This review provides insight into the roles of Piezo1 in the development, physiology and pathology of the skin with a special emphasis on the molecular pathways through which it instigates these various roles. In epidermal homeostasis, Piezo1 mediates cell extrusion in conditions of overcrowding and division in conditions of low cellular density. Piezo1 also aids in orchestrating mechanosensation, DNA protection from mechanical stress and the various components of wound healing. Conversely, Piezo1 is pathologically implicated in melanoma progression, wound healing delay, cutaneous scarring and hair loss. By shedding light on these functions, we aim to unravel the potential diagnostic and therapeutic value Piezo1 might hold in the field of Dermatology.

## Introduction

From endosomes shuttling across cells to antlers clashing in stag confrontations, mechanical forces impact life at every scale. To process and respond to mechanical input, life has evolved mechanotransduction, the conversion of extracellular mechanical stimuli into intracellular biochemical signals. While mechanosensitive cells such as mammalian cochlear hairs and skin mechanoreceptors have been recognized and studied extensively, insight into the underlying molecular

mechanisms permitting mechanotransduction has only recently come to the fore. Central to this molecular elucidation is the discovery of the Piezo1 and Piezo2 channels, which culminated in the 2021 Nobel Prize in Physiology for Dr Ardem Patapoutian.<sup>1</sup> Using gene expression profiling and small interfering RNA silencing in the mechanosensitive neuroblastoma murine cell line, this group managed to isolate and categorize Piezo1 as a ubiquitous mechanically activated channel found in all organisms except for yeast and bacteria.<sup>1</sup> Subsequent research on Piezo1 has rationalized its evolutionary conservation throughout history as an indispensable orchestrator of mechanotransduction. As a barrier to the external world, the skin is subjected to frequent and variable degrees of mechanical forces. Beyond the physical protection it provides, the skin also serves multiple endocrinological and immunological functions that impose internal mechanical forces on its components, as dictated by the flux and activity

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Conflict of interest: the authors declare that they have no conflicts of interest.

Accepted for publication 9 February 2022

of different molecular and cellular players. This constant barrage of internal and external mechanical input on the skin coupled with the expression of Piezo1 in the skin<sup>1</sup> shows the major roles for Piezo1 in skin biology. In this paper, we shed light on the various functions Piezo1 plays in the development, physiology and pathology of the skin.

## Structure and properties

Piezo1 and Piezo2 are nonselective cationic mechanosensitive channels, which share a 42% sequence homology yet do not resemble any known ion channels or proteins.<sup>1,2</sup> The molecular structure of Piezo1 was elucidated by cryoelectron microscopy, which demonstrated a three-bladed, propeller-shaped homotrimeric architecture. Each of the 3 subunits is composed of 38 transmembrane helices with a central ion-conducting pore modulus and three peripheral mechanotransduction moduli.<sup>3–5</sup> Piezo channels are characterized by rapid activation and voltage-dependent inactivation, and their channel kinetics are congruent irrespective of cell type.<sup>6</sup> Human Piezo1 channels are permeable to monovalent ions (K<sup>+</sup>, Na<sup>+</sup>, alkali ions), divalent ions (Mg<sup>2+</sup>, Mn<sup>2+</sup>, Ba<sup>2+</sup>) with a preference for Ca<sup>2+</sup> and several organic cations (tetramethylammonium and tetraethylammonium).<sup>7</sup> The activation and regulation of Piezo1 can be instigated by mechanical or chemical stimulation. Among other types of mechanical stress, membrane stretch is an evolutionarily conserved mechanical input that directly gates Piezo1.<sup>8</sup> The synthetic small molecule Yoda1 has demonstrated a remarkable capacity to activate Piezo1 independent of mechanical stretch,<sup>9</sup> while the tarantula venom peptide GsMTx4 reversibly inhibits Piezo1-mediated currents.<sup>10</sup>

## Functions

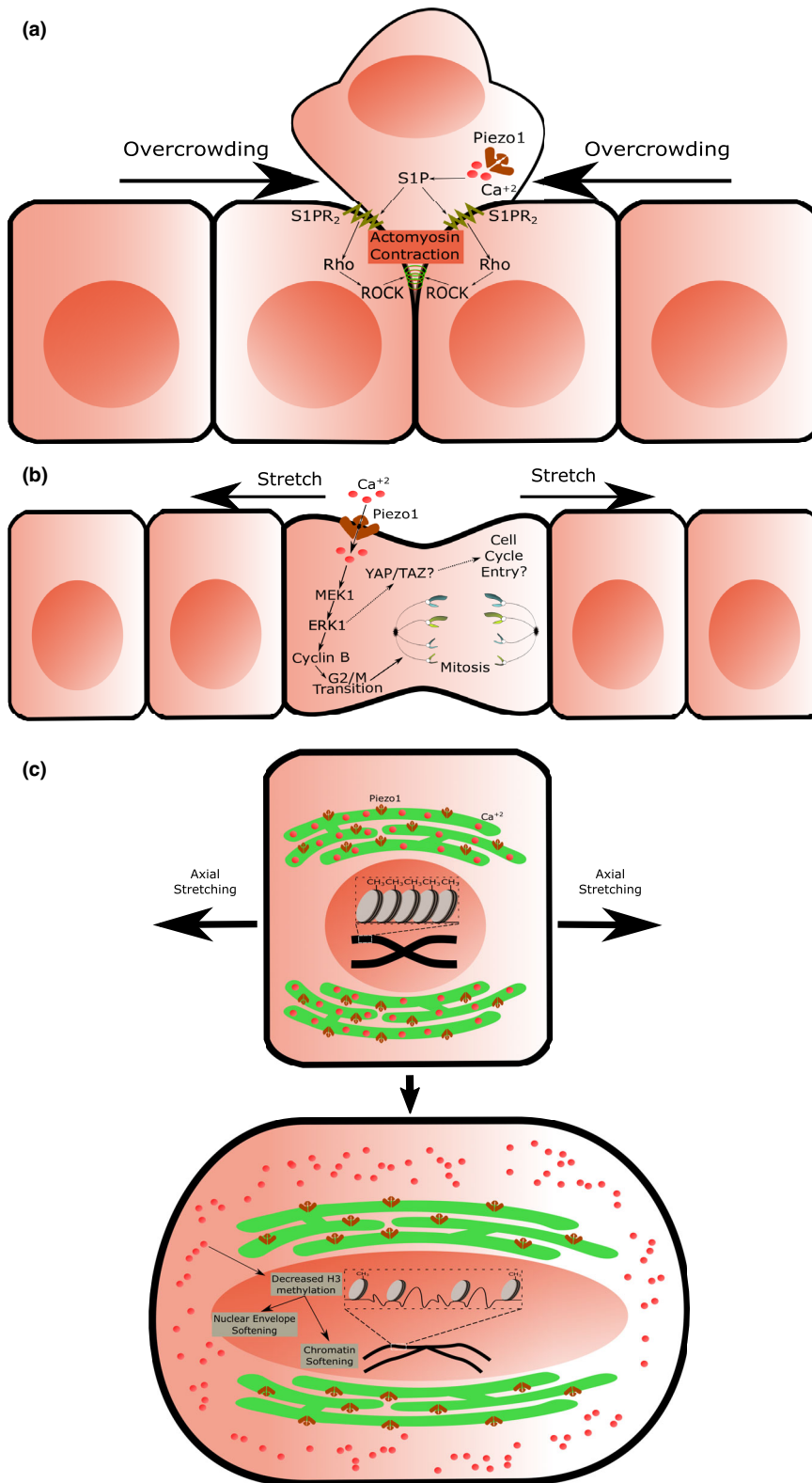
### Epidermal homeostasis

All epithelia, including the epidermis, maintain homeostasis by ensuring that the delicate balance between cell loss and cell regeneration is upheld. This fine equilibrium presupposes the existence of mechanisms that seek to simultaneously sustain epithelial integrity in the face of a decrease in epidermal cell density while also preventing a tentatively tumourigenic overcrowding of cells. The chief operator in orchestrating these paradoxical processes is Piezo1.<sup>11,12</sup>

Cell extrusion is the main mechanism by which simple epithelia such as zebrafish epidermis rid themselves

of apoptotic and live cells.<sup>11,13</sup> In their seminal work on epithelial homeostasis, Eisenhoffer *et al.*<sup>11</sup> cultured Madin–Darby canine kidney (MDCK) cells on a stretched silicone membrane until confluence was attained. Membrane release induced overcrowding of the cultured cells, which reverted to their prerelease levels over time; however, the stretch-activated ion channel blocker gadolinium prevented live, but not apoptotic, cell extrusion. The nature of the implicated ion channel was elucidated when *in vivo* Piezo1 knockdown recapitulated the latter finding in the highly cellular dense epidermis of the zebrafish fin edges by inciting epidermal masses. Furthermore, inhibition of sphingosine-1-phosphate (S1P) signalling and Rho kinase, both previously shown to be mediators of apoptotic cell extrusion,<sup>14</sup> prevented MDCK extrusion under overcrowding conditions.<sup>11</sup> Piezo1 seems to signal overcrowding upstream of S1P to subsequently recruit and incite the circumferential and downward contraction of the actin/myosin ring to squeeze the extruding cell apically (Fig. 1a).<sup>15</sup>

Conversely, epithelia, including epidermis, can experience a sudden decline in cell number during injury. Under these circumstances, neighbouring cells undergo modifications by which they flatten and stretch to cover a wider area. Cell stretching has long been known to augment survival and proliferative capacities,<sup>16</sup> but the mechanotransductive mechanisms at play have only recently emerged. Using experimentally stretched MDCK cells, Gudipaty *et al.* demonstrated a five-fold increase in mitotic figures 1 h post-stretching, which was abolished by siRNA Piezo1 knockdown.<sup>12</sup> Piezo1 knockdown also inhibited stretch-mediated proliferation using zebrafish epidermis.<sup>12</sup> Additionally, Piezo1 acts directly at the G<sub>2</sub>/M transition via the stretch-induced accumulation of cyclin B, a major player in G<sub>2</sub>/M progression.<sup>17</sup> Moreover, extracellular signal-regulated kinase (ERK)1, a calcium-activated kinase involved in regulating the G<sub>2</sub>/M transition,<sup>18</sup> was detected minutes after stretching and its inhibition abrogated the rapid proliferative response. Therefore, Piezo1 appears to mediate a rapid proliferative response in G<sub>2</sub> cells by stretch-induced calcium influx, which activates ERK1/2, and this in turn triggers the transcription of cyclin B (Fig. 1b).<sup>12</sup> Interestingly, Piezo1 silencing also significantly diminished proliferation in confluent steady-state epithelia, raising the possibility of a role for Piezo1 in cell cycle entry. Such a role would involve an interaction between Piezo1 and YAP/TAZ, the mechanosensitive transcription factors that drive cell cycle entry,<sup>19</sup> similar to their interaction in lineage choice determination in neuronal stem cells.<sup>20</sup>



**Figure 1** (a–c) Piezo1 is instrumental in epithelial and epidermal homeostasis. (a) Under overcrowding conditions, Piezo1 effectuates cellular extrusion through S1P-rho signalling while (b) stretching of epidermal cells due to low cellular density induces transition from the G<sub>2</sub> phase of the cell cycle to mitosis via the accumulation of cyclin B. (c) Under extreme mechanical stress, Piezo1 mediates DNA protection by reducing H3 methylation, which in turn softens chromatin and the nuclear envelope to subvert DNA-damaging mechanical energy. ERK1, extracellular signal-regulated kinase 1; H3; histone 3; MEK1, mitogen-activated protein kinase kinase 1; ROCK, rho kinase; S1P, sphingosine-1-phosphate; S1PR2, sphingosine-1-phosphate receptor 2.

The ability of Piezo1 to control cell extrusion and stretch-induced cell proliferation, two opposing homeostatic processes, is rationalized by its dynamic pattern of expression and localization. Under low cellular density conditions, low levels of Piezo1 localize to the nucleus but accumulate over time.<sup>12</sup> In confluent but sparse locales, Piezo1 localizes to the plasma membrane and the endoplasmic reticulum (ER); however, Piezo1 levels substantially drop as translocation to the nucleus occurs upon cell stretching.<sup>12</sup> Alternatively, in overcrowded cultures where cells are prone to extrude, Piezo1 accumulates in large cytoplasmic aggregates. Therefore, shifts in degree of expression and/or intracellular localization may modulate Piezo1 function.<sup>12</sup>

Unlike zebrafish epidermis, mammalian epidermis is a stratified squamous epithelium with keratinocytes making up > 90% of its composition. Keratinocytes express high levels of Piezo1 and demonstrate mechanosensitivity via the production of mechanically evoked currents.<sup>21</sup> The abrogation of these currents in 65% of keratinocytes from Piezo1 conditional knockout mice suggests that Piezo1 is the primary, but not exclusive, keratinocytic mechanotransducer.<sup>22</sup> The homeostatic ability of keratinocyte stem cells to withstand mechanical strain involves Piezo1.<sup>23</sup> In contrast to cancer cells, in which mechanical deformations lead to nuclear rupture and DNA damage,<sup>24</sup> epithelial sheets such as mammalian epidermis can weather extreme mechanical deformation without incurring damage.<sup>25</sup> By subjecting epidermis progenitor cells (EPCs) to distinct amplitudes of uniaxial mechanical stretch, Nava *et al.*<sup>23</sup> unravelled the molecular mechanisms underlying protection from mechanical strain. It was shown that stretch-induced nuclear envelope and ER deformation triggers Piezo1-mediated calcium release from the ER.<sup>23</sup> This calcium influx causes perinuclear filamentous actin to reorient to the direction of stretch and induces the downregulation of histone H3 lysine 9 trimethylation (H3K9me3) given the reduction in the expression of H3K9me3 methyltransferase, Suv39H1. The latter heterochromatin modification promotes heterochromatin softening, leading to mechanical energy dissipation to subvert direct force propagation

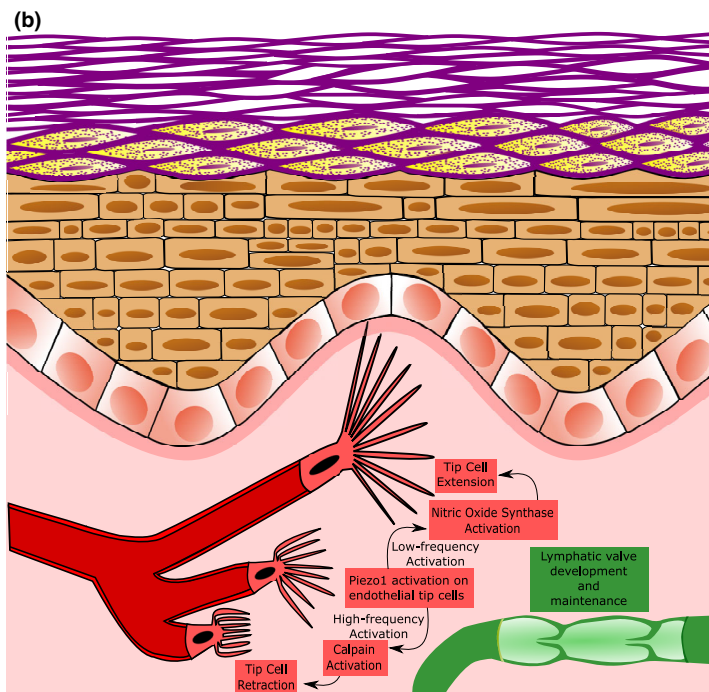
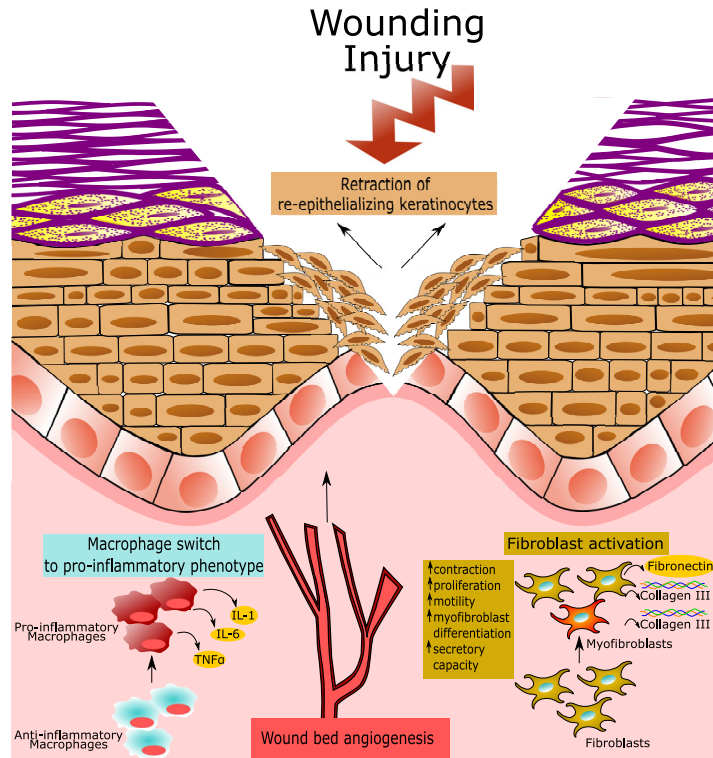
and damage to DNA.<sup>26</sup> Moreover, H3K9me3 reduction results in nuclear envelope softening,<sup>27</sup> which allows the nucleus to withstand mechanical stretch (Fig. 1c). The role of Piezo1 in these protective responses was corroborated by the lack of H3K9me3 reduction, the absence of nuclear softening and substantially enhanced stretch-induced DNA damage in Piezo1-depleted EPCs.<sup>23</sup>

### Wound healing

Cutaneous wounding compromises skin homeostasis and predisposes to an increased risk of infection and scar formation. In response, coordinated cellular and molecular responses are evoked in order to restore skin integrity. Immune cells are recruited to clear invading pathogens and orchestrate reparative processes, while keratinocytes migrate across the wound edges to start re-epithelialization.<sup>28</sup> Meanwhile, local and blood-borne fibroblast migration and proliferation leads to granulation tissue formation that subsequently allows extracellular matrix (ECM) formation and wound bed perfusion via angiogenesis.<sup>28</sup> Piezo1 has demonstrated a role in each of these wound-healing processes (Fig. 2a).

Re-epithelialization during wound closure has been shown to respond to mechanical cues and cell-generated traction forces.<sup>29,30</sup> The underlying mechanistic pathways rely on Piezo1 expression and activity.<sup>31</sup> By imaging the spatiotemporal localization of Piezo1 channels, Holt *et al.*<sup>31</sup> revealed Piezo1 enrichment at the wound edge and at the rear of migrating keratinocytes, where it triggers localized cellular retraction during single and collective migration in a wounded monolayer of keratinocytes.<sup>31</sup> *In vivo* confirmation of Piezo1-mediated wound-edge retraction and wound-closure impairment was demonstrated in wounded epidermal-specific Piezo1 gain-of-function mice, which exhibited slower wound closure rates than controls. Conversely, epidermal-specific Piezo1 knockout mice demonstrated faster wound closure than controls.<sup>31</sup> Localized cellular retraction is accounted for by local myosin II force generation through phosphorylation by myosin light chain kinase

(a) The different roles of Piezo1 in Wound Healing



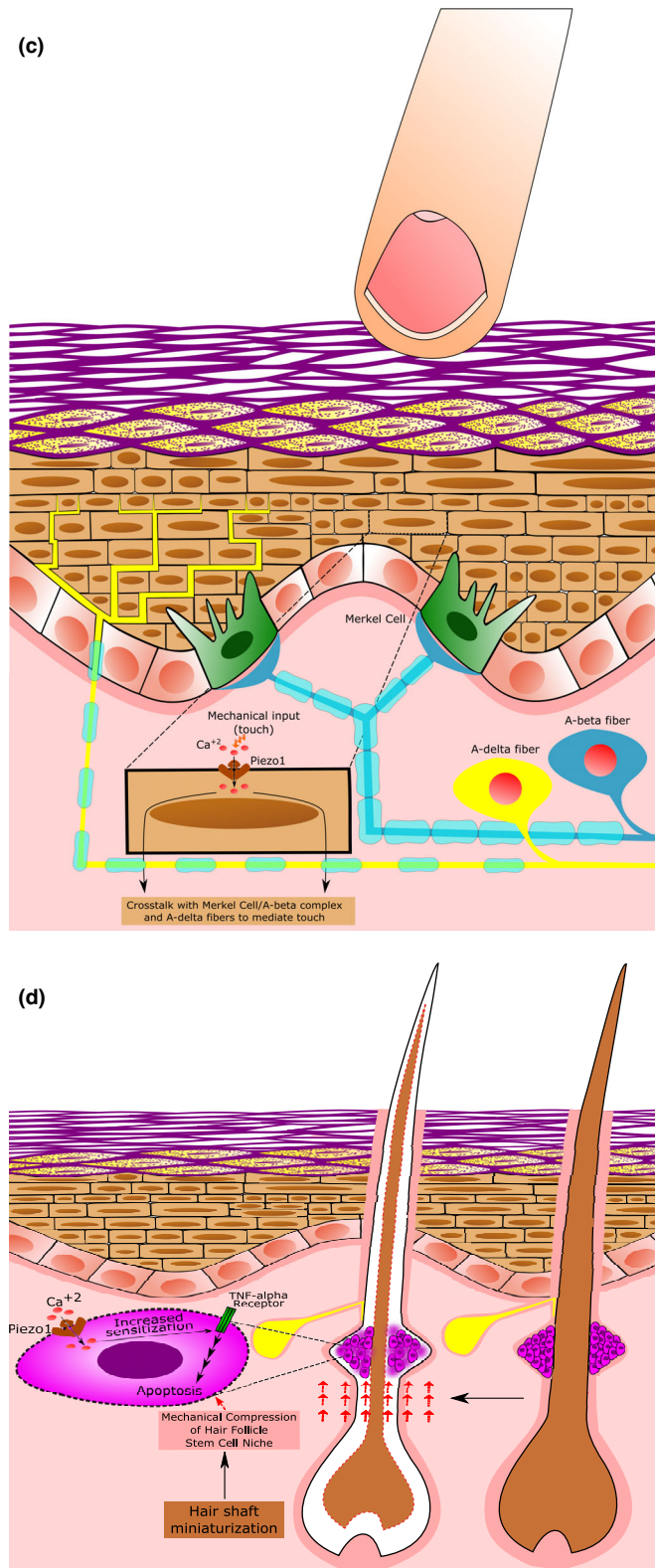


Figure 2 Continued.

**Figure 2** (a–c) Piezo1 plays major cutaneous physiological and pathological roles. (a) During wound healing, Piezo1 expression can trigger cellular retraction in re-epithelializing keratinocytes. On the other hand, Piezo1 promotes fibroblast proliferation, secretory capacity and fibroblast-to-myofibroblast differentiation. Piezo1 can also promote wound bed angiogenesis and phenotype switching in macrophages to a proinflammatory phenotype in the context of increased stiffness. (b) Angiogenesis and lymphangiogenesis both rely on Piezo1. The frequency of Piezo1 affects endothelial tip cell activity: high-frequency activation leads to endothelial tip cell retraction via calpain signalling while low-frequency activation leads to extension through the nitric oxide synthase pathway. Lymphatic valve leaflet formation is also reliant on Piezo1 activation as is the maintenance of lymphatics. (c) Piezo1 on keratinocytes also works in tandem with Piezo2 on Merkel cells, A-beta and A-delta fibres to mediate the sensation of touch. (d) Hair shaft miniaturization exerts undue mechanical pressure on hair follicle stem cells in the bulge region. This mechanical stress is sensed by Piezo1, which increases tumour necrosis factor (TNF)- $\alpha$  sensitivity, leading to apoptosis of these stem cells and eventual hair follicle stem cell niche loss.

(MLCK), which triggers Piezo1-mediated  $\text{Ca}^{2+}$  flickers.<sup>32</sup> This then increases local myosin II phosphorylation via  $\text{Ca}^{2+}$ -regulated MLCK and force generation in a feedforward loop, leading to cellular retraction and delayed wound closure.<sup>31</sup>

Another component of wound healing is ECM deposition and wound contraction by fibroblasts and myofibroblasts.<sup>33</sup> However, extreme fibroblastic responses during wound repair can lead to exaggerated scarring in the form of a hypertrophic scar (HS). In stark contrast to the impaired wound healing mediated by Piezo1 in keratinocytes, Piezo1 expression in dermal fibroblasts promotes scarring. Human dermal fibroblasts demonstrated baseline high levels of Piezo1 with increased expression and activity on cyclic mechanical stretching, a major risk factor for HS formation.<sup>34</sup> Moreover, Piezo1 was shown to ameliorate human dermal fibroblast proliferation, motility, differentiation to myofibroblast and secretory capacity.<sup>34</sup> *In vivo*, daily intradermal injections of the Piezo1 inhibitor GsMTx4 decreased hyperaemia and scar elevation, and histologically attenuated collagen density and  $\alpha$ -smooth muscle actin expression relative to control in a rat-tail model of induced HS.<sup>34</sup> As HS is characterized by stiff scar tissue, a feedforward loop hypothetically ensues, whereby the increased stiffness triggers overexpression in Piezo1, which causes fibroblasts to increase secretion of ECM components and exacerbate contraction. Additionally, mechanosensitive molecules identified as regulators of scar formation, including ERK and YAP,<sup>35</sup> have been shown to act downstream of Piezo1 in other cellular contexts.<sup>12,20</sup>

Angiogenesis, the process of forming new capillaries from pre-existing vessels, is an integral part of wound healing. At the onset of angiogenesis, endothelial cells (ECs) are activated and secrete metalloproteinases required for the sprouting of new vessels.<sup>36</sup> The role of Piezo1 in vascular structure and development is supported by the embryonic lethality secondary to vascular defects seen in mice with global and EC-specific

knockout of Piezo1.<sup>37,38</sup> Predictably, mice with EC-specific deletion of Piezo1 demonstrate significant wound healing delay compared with control mice.<sup>39</sup> In response to wall shear stress, a known mechanical inducer of sprouting vessels in angiogenesis,<sup>40</sup> murine ECs with conditional knockout of Piezo1 demonstrate a reduction in invading ECs, thickness, invasion distance and lumen formation in sprouting vessels relative to control ECs.<sup>39</sup> S1P, released by activated ECs and platelets in response to ischaemia, acts synergistically with shear stress to modulate Piezo1  $\text{Ca}^{2+}$  gating function via the activation of c-Src. In turn, Piezo1-mediated  $\text{Ca}^{2+}$  influx allows matrix metalloproteinase (MMP)-2 and membrane type 1 MMP activation to pave the way for angiogenesis.<sup>39</sup> Changes in the frequency of Piezo1-induced  $\text{Ca}^{2+}$  influx also aid endothelial tip cells at the forefront of growing vasculatures to steer their angiogenic sprouts into the appropriate microlocales (Fig. 2b).<sup>41</sup>

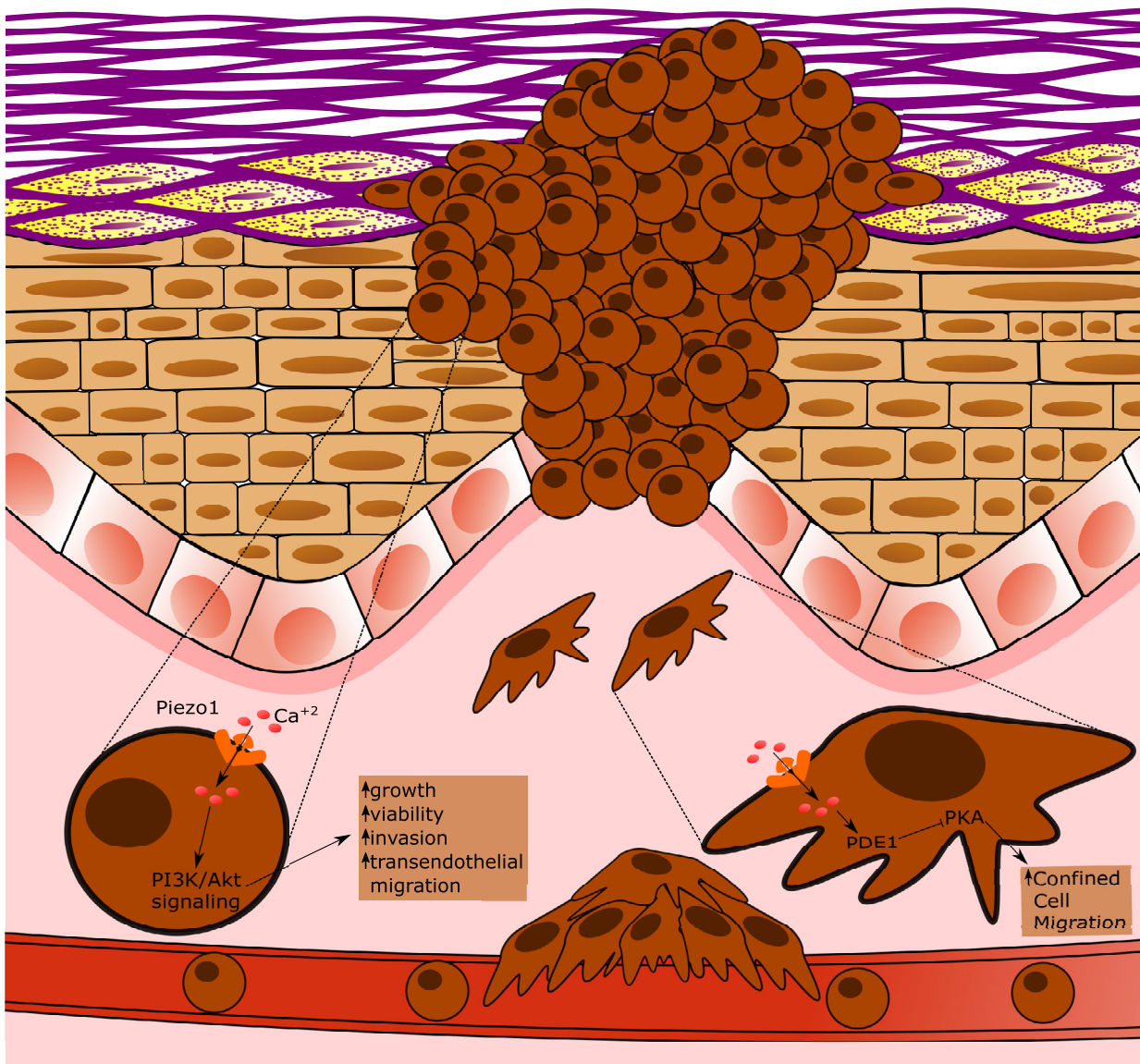
Chief among the cellular players in wound healing are the macrophages, whose phenotype changes from proinflammatory 'M1' macrophages that purge wounds of bacteria to anti-inflammatory 'M2' macrophages that mediate the reparative and fibrotic processes required for wound closure.<sup>42</sup> Macrophage polarization relies on Piezo1 activation in the context of differing substrate stiffness.<sup>43</sup> On stiff substrates such as cutaneous foreign bodies, Piezo1-induced  $\text{Ca}^{2+}$  influx is positively regulated by actin polymerization, itself enhanced by interferon  $\gamma$ -lipopolysaccharide signalling; this favours a proinflammatory phenotype through activation of the transcription factor nuclear factor  $\kappa\text{B}$ , upregulation of inflammatory markers including tumour necrosis factor (TNF)- $\alpha$  and interleukin-6, inhibition of the transcription factor signal transducer and activator of transcription-6, and decrease in expression of healing markers.<sup>43</sup> This Piezo1-driven mechanism provides a theoretical basis for the change in macrophage phenotype seen during wound healing as the surrounding wound microenvironment changes over time.

The deeper understanding of the role of Piezo1 in the different facets of wound healing provides a prospective novel therapeutic target in the acceleration of wound healing and prevention of HS formation. Inhibition of Piezo1 in keratinocytes can theoretically hasten wound healing but can alternatively prevent HS formation in fibroblasts. These insights provided the theoretical framework for an experimental electricity auto-generating, glucose-responsive enzymatic-biofuel cell skin patch that successfully stimulated wound healing in a rat wounded-skin model; this

enhanced healing effect was achieved by electrically activating Piezo1 in ECs and fibroblasts to enhance angiogenesis, fibroblast activity and matrix synthesis.<sup>44</sup>

### Lymphatic valve development and maintenance

The role of Piezo1 in the development of lymphatic structures was first suggested when individuals manifesting generalized lymphatic dysplasia, a primary lymphoedema characterized by generalized cutaneous



**Figure 3** Piezo1 can act as an oncogene in the tumorigenicity of cutaneous malignant melanoma. Piezo1 promotes melanoma progression through the phosphoinositide-3-kinase (PI3K/Akt) signalling pathway while it promotes migration in confined spaces through the PDE1/PKA pathway. AKT, AKT serine/threonine kinase 1; PDE1, phosphodiesterase type 1; PI3K, PKA, protein kinase A.

lymphoedema and systemic manifestations including chylothorax and intestinal/pulmonary lymphangiectasia, were found to have homozygous and compound heterozygous Piezo1 mutations.<sup>45</sup> It was later shown that Piezo1 is responsible for lymphatic valve development, as mice lacking Piezo1 in ECs demonstrated reduced numbers of lymphatic valves and died postnatally due to pleural effusion.<sup>46</sup> Mechanistically, Piezo1 regulates the process of lymphatic valvular leaflet protrusion, which is associated with collective cell migration, actin polymerization and remodelling of cell–cell junctions during lymphatic development.<sup>46</sup> Moreover, adult mice demonstrated lymphatic valve degeneration in the lymphatic vessels of tail skin following Piezo1 deletion in lymphatic ECs, which occurred at Day 21 of the mouse lifecycle.<sup>47</sup> Piezo1 effectively senses the oscillating shear stress afforded by lymphatic fluid flow to induce the upregulation of lymphatic valve signature genes, including *FOXC2* and *GATA2*, which control lymphatic valve development and maintenance.<sup>47</sup> Thus, Piezo1 regulation could be leveraged as a potentially novel therapeutic strategy for the treatment of congenital and acquired lymphoedema (Fig. 2b).

### Mechanosensation

The mammalian sense of touch is mediated by the Merkel cell–neurite complex consisting of A-beta sensory neurons and epidermal cells known as Merkel cells. Piezo2 has been shown to be responsible for the mechanosensitivity of both components of the Merkel cell–neurite complex and is thus the major mechanotransducer in touch sensation.<sup>48,49</sup> Conversely, keratinocytes have demonstrated an ability to modulate mechanosensory afferent firing<sup>50</sup> and are necessary for normal touch sensation.<sup>21</sup> As Piezo1 is the primary mechanotransducer in keratinocytes, it should also be ascribed a role in touch sensation (Fig. 2c). As confirmation, Piezo1-knockout mice fail to exhibit behavioural responses to innocuous punctate and dynamic stimulation, and their slow-adapting A-beta and A-delta fibres demonstrate decreased action potentials in the sustained phase of the response to receptive field stimulation.<sup>22</sup> Therefore, touch sensation is a complex phenomenon that requires tandem Piezo1 and Piezo2 activity in keratinocytes and Merkel cells, respectively.

### Hair follicle stem cell apoptosis

In humans, hair growth relies on hair follicle stem cells (HFSCs), which undergo cycles of proliferation and quiescence. The dysregulation of HFSC

differentiation and survival is at the core of the hair findings associated with ageing and androgenetic alopecia,<sup>51,52</sup> but the underlying molecular mechanisms governing HFSC survival are not yet fully elucidated. Piezo1 is attributed a major role in inciting HFSC apoptosis in relation to hair shaft miniaturization. Using aged mice and mouse models of hypotrichosis, Xie *et al.*<sup>53</sup> demonstrated that HFSC niche compression secondary to hair shaft miniaturization leads to Piezo1- and Ca<sup>2+</sup>-dependent apoptosis by conferring increased TNF- $\alpha$  sensitivity in a hair cycle-dependent manner. TNF- $\alpha$  signalling in HFSC leads to caspase-3 activation and HFSC apoptosis (Fig. 2d). Notably, long-term monitoring of the effects of hair-follicle miniaturization in the hypotrichosis mouse model demonstrates a progressive decrease in hair shaft diameter and persistent HFSC apoptosis, culminating in near-complete loss of HFSCs.<sup>53</sup> Consequently, the Piezo1-mediated regulation of HFSC niche maintenance could be therapeutically leveraged to prevent and potentially reverse hair loss in humans.

### Melanoma progression

Tumour cells are subjected to mechanical stimuli from the extracellular environment in the form of tissue stiffness and ECM components. The tumour microenvironment is characterized by matrix stiffening, which promotes tumour growth and metastasis through mechanotransduction.<sup>54,55</sup> Piezo1 is involved in promoting tumour proliferation and metastasis in multiple cancers.<sup>56–60</sup> Increased Piezo1 levels were found in primary and metastatic melanoma, and Piezo1 expression was associated with overall shorter survival.<sup>6</sup> Piezo1 inhibition in mouse and human melanoma cell lines and in a mouse metastasis tumour model led to the suppression of melanoma cell viability, invasion, transendothelial migration and expression of mesenchymal-related genes (N-cadherin and E-cadherin) and invasion/metastasis-related genes (*MMP2* and *MMP9*).<sup>61</sup> Mechanistically, Piezo1 seems to activate phosphoinositide-3-kinase-AKT signalling to promote the tumorigenicity of melanoma.<sup>61</sup> Moreover, Piezo1 appears to act as a mechanosensor for regulating melanoma migration during confinement: elongation of the migrating melanoma cell in a confined space induces Piezo1 activity to promote confined cell migration (Fig. 3).<sup>62</sup> Therefore, Piezo1 acts as an oncogene that promotes melanoma progression and metastasis through multiple signalling pathways, yet provides a novel prognostic and therapeutic candidate for melanoma management.

## Conclusion

Ever since its discovery 10 years ago, Piezo1 has proven to be an indispensable component in the physiology and pathology of the skin. Various cutaneous roles in epidermal homeostasis, wound healing, mechanosensation, hair physiology and melanoma biology have made Piezo1 an enticing prospective therapeutic target. However, several questions of paramount importance remain unanswered. Mechanical forces are ascribed a role in the pathogenesis of many dermatoses.<sup>63</sup> Does Piezo1 play a role in koebnerization, the trauma-induced appearance of new skin lesions in previously unaffected sites in dermatoses such as psoriasis, lichen planus and vitiligo? Is Piezo1 involved in the predilection of acral melanomas to the weight-bearing area of the foot? Furthermore, dermatoses such as psoriasis and atopic dermatitis demonstrate altered cholesterol and sphingolipid amount and composition.<sup>64</sup> As Piezo1 function is directly dependent on membrane composition for coordination of activity,<sup>65</sup> could dysregulated Piezo1-mediated mechanotransduction be contributing to the pathogenesis of the dermatoses in question via membrane lipid distortion? Moreover, Piezo1 is of oncological relevance in the tumorigenicity of melanoma as highlighted above; does Piezo1 also factor into other skin cancers such as basal cell carcinoma and squamous cell carcinoma, and if so, is it oncogenic or tumour suppressive? Future studies will hopefully provide insights to these tantalizing questions before Piezo1 can be thrust into the clinical and therapeutic realm of dermatology.

### Learning points

- Piezo1 is a mechanosensitive ion channel that orchestrates mechanotransduction.
- Piezo1 has high expression in the skin and plays major roles in the development, physiology and pathology of the skin.
- Piezo1 mediates key aspects of epidermal homeostasis including the paradoxical processes of cell extrusion and cell division.
- Further pathological roles in skin biology include vital contributions to DNA protection from mechanical stress, wound healing and mechanosensation.
- Conversely, Piezo1 is involved in hair loss, delayed wound healing, cutaneous scarring and melanoma tumorigenesis.

• These diverse functions make Piezo1 an enticing prospective diagnostic and therapeutic target in the field of dermatology.

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