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REVIEW

# An updated review of mechanotransduction in skin disorders: transcriptional regulators, ion channels, and microRNAs

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**Abstract**
*Introduction* The skin is constantly exposed and responds to a wide range of biomechanical cues. The mechanobiology of skin has already been known and applied by clinicians long before the fundamental molecular mechanisms of mechanotransduction are elucidated.
*Materials and methods* Despite increasing knowledge on the mediators of biomechanical signaling such as mitogen-associated protein kinases, Rho GTPases or FAK-ERK pathways, the key elements of mechano-responses transcription factors, and mechano-sensors remain unclear. Recently, canonical biochemical components of Hippo and Wnt signaling pathway YAP and β-catenin were found to exhibit undefined mechanical sensitivity. Mechanical forces were identified to be the dominant regulators of YAP/TAZ activity in a multicellular context. Furthermore, different voltage or ligand sensitive ion channels in the cell membrane exhibited their mechanical sensitivity as mechano-sensors. Additionally, a large number of microRNAs have been confirmed to regulate cellular behavior and contribute to various skin disorders under mechanical stimuli. Mechanosensitive (MS) microRNAs could not only be activated by distinct mechanical force pattern, but also responsively target MS sensors such as e-cadherin and cytoskeleton constituent RhoA.
*Conclusion* Thus, a comprehensive understanding of this regulatory network of cutaneous mechanotransduction will facilitate the development of novel approaches to wound healing, hypertrophic scar formation, skin regeneration, and the progression or initiation of skin diseases.

**Keywords** TRP · Piezo · Wound healing · Hypertrophic scar · Fibrosis · Scleroderma

**Abbreviations**

| | |
|---|---|
| YAP | Yes-associated protein |
| AP-1 | Activator protein 1 |
| ECM | Extracellular matrix |
| MS | Mechanosensitive |
| MAPKs | Mitogen-associated protein kinases |
| FAK | Focal adhesion kinase |
| ERK | Extracellular regulated protein kinases |
| PI3K | Phosphoinositol-3-kinase |
| HF | Hair follicles |
| IFE | Interfollicular epidermal |

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| | |
|---|---|
| MSCs | Mesenchymal stem cells |
| GPCRs | G-Protein-coupled receptors |
| CaSR | Calcium-sensing receptor |
| TRP | Transient receptor potential |
| ECs | Endothelial cells |
| Cx | Connexin |

## Introduction

The skin is exposed to mechanical cues throughout life. As the outermost layer of human, it is an easily accessible tissue layer to investigate how mechanical force regulates adult stem cell renewal, lineage selection, and tissue assembly. Although fundamental mechanisms of mechanotransduction (the process of sensing mechanical cues and the subsequent biochemical response) [1] are still mostly unknown, the concept of Langer's lines, topographical skin lines defined by skin mechanobiology, high mechanical stress regions for hypertrophic scar formation, has been widely used in clinical therapies. Decreasing mechanical force on the skin is the core principle for plastic surgeons to reduce pathologic scarring. Another example, skin expansion is a procedure that stimulates and promotes skin regeneration through continuous mechanical stretching provided by an underlying silicone expander. It has been used for a variety of plastic and reconstructive procedures due to its ability to regenerate additional normal skin [2].

It is becoming well known that the mechanical environment has significant effects on cutaneous biology. As such, researchers and clinicians are pursuing the underlying molecular mechanisms of mechanotransduction pathway. Researches have demonstrated that mechanical force is transmitted across the cell membrane to activate downstream biochemical pathways including, but not limited to calcium-dependent pathways, nitric oxide (NO) signaling, MAPKs, Rho GTPases, and phosphoinositol-3-kinase (PI3K) [3]. A convincing study confirmed the association between mechanical force and pathologic scar through inflammatory FAK-ERK-MCP-1 pathways and that molecular strategies targeting FAK can effectively uncouple mechanical force from pathologic scar formation [4]. Besides, tissue architecture of cell–extracellular matrix (ECM), such as matrix stiffness and rigidity, cell–cell adhesions and the organization of cytoskeleton, controls the proliferation, migration, self-renewal, differentiation and cell death of stem cells (for more details seen in the excellent review of Wong et al. [5]). Notably, the process of epidermal stratification can be interpreted as a differentiation process induced by loss of cell-ECM contacts. However, except from the above signaling pathways, the role of most recent research revealed that mechano-related transcription factors and co-regulators, mechano-sensor ion channels, and a number of mechanosensitive microRNAs are not reviewed yet. Therefore, this review will focus on these molecular components of mechanotransduction in skin: mechanosensitive transcription regulators, ion channels, and microRNAs, which may provide basis for clinical therapies, rather than universal signaling passengers (Fig. 1).

## Mechanosensitive (MS) transcription factors and co-regulators in skin

### β-Catenin

The Wnt pathway is of central importance in regulating the development of skin and its appendages, hair follicles (HFs), interfollicular epidermal (IFE) stem cells renewal, and melanocytes [6]. Different members of the Wnt family are expressed in specific subsets of cells in developing and adult epidermis. Although loss of epidermal β-catenin resulted in loss of hair follicle specification, its role in IFE remains elusive [7]. Genetic evidence suggests that β-catenin is dispensable for interfollicular epidermal function [8], but a recent study of Lim et al. [9] showed that self-renewal of interfollicular epidermal stem cells is regulated via autocrine Wnt signaling. While conflicting evidences exist as to whether Wnt/β-catenin signaling is involved in IFE development and adult IFE maintenance, many Wnt signaling mutations do result in IFE phenotypes. In addition to its role as the key cytoplasmic effector of the Wnt pathway, β-catenin is also a component of intercellular adhesive junctions, binding to the cytoplasmic domain of E-cadherin. β-catenin then in turn binds to α-catenin, resulting in the formation of the cadherin–catenin complex [10]. Besides, α-catenin can bind to a variety of actin-binding proteins, indicating that the cadherin–catenin contact is essential to be subjected to mechanical stress, and β-catenin may function as mechano-mediator.

Direct regulation of Wnt signaling by biophysical signals has been demonstrated [11]. In osteoblasts, mechanical strain caused a rapid, transient accumulation of active β-catenin in the cytoplasm and its translocation into the nucleus in osteoblasts. Mechanical stimulation (3,600 cycles/day, 2 % strain) also can prevent adipogenic and improve osteogenic lineage differentiation of mesenchymal stem cells (MSCs) [12] by inactivating GSK3β and therefore inducing activation of both β-catenin and NFATc1 signaling. It has been found that mechanotransduction often caused conformational changes in the protein domains of β-catenin when β-catenin was subjected to tension. Using single-molecule force spectroscopy and molecular dynamics, armadillo repeat region (ARM) of β-catenin was found to be very sensitive to small changes in

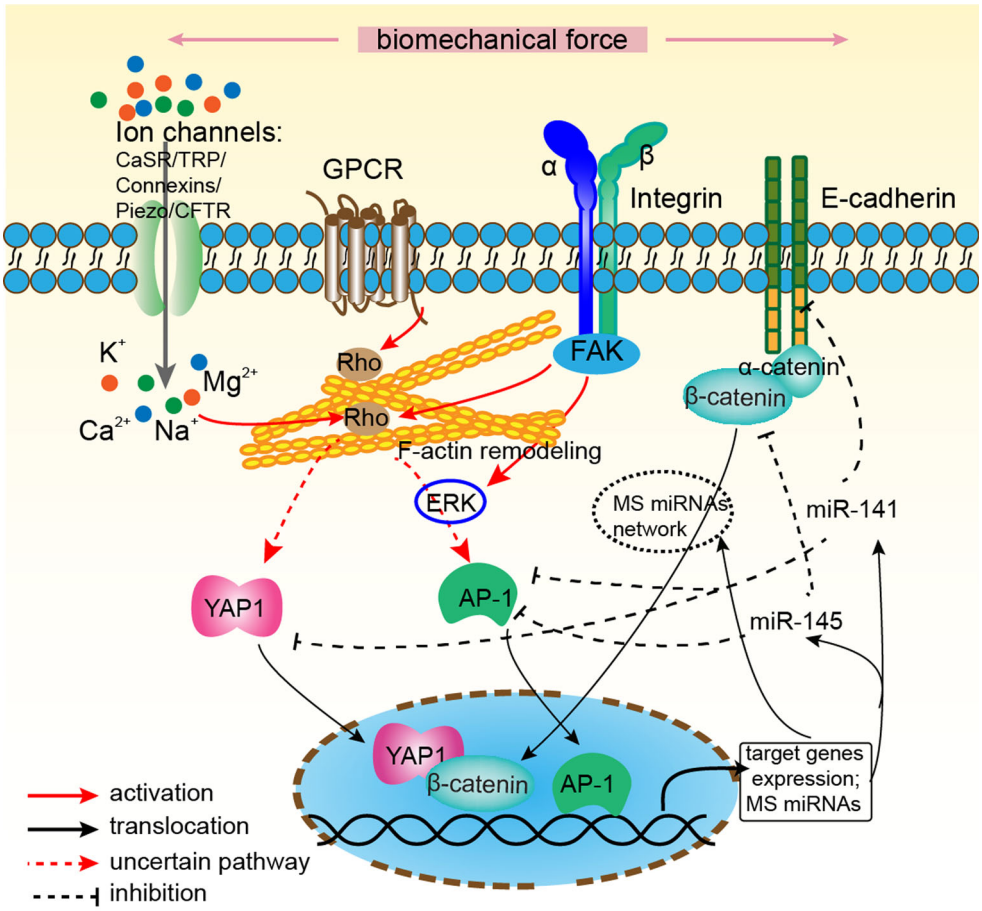


**Fig. 1** Novel intracellular components of mechanotransduction in skin. Mechanical force activated multiple mechano-sensors have been described and include stretch-activated ion channels (Calcium-sensing receptor (CaSR), Transient receptor potential (TRP), Connexins and Piezos), integrins-focal adhesion kinase (FAK) complex, G-Protein-coupled receptors (GPCR) and cell-cell adhesion structure e-cadherin/α-catenin. Mechanical signal is transmitted across the cell membrane to activate multiple downstream biochemical pathways, Rho GTPases and F-actin remodeling of cytoskeleton. The convergence of these signals are mediated by three critical mechanosensitive (MS) transcription factors β-catenin, YAP and AP-1. While YAP could be activated by conformational change of GPCR directly or intermediate Rho GTPases, β-catenin could directly be regulated by the destruction of cell-cell adhesion structure. These transcription factors translocate into the nucleus and activate mechanoresponsive genes. Furthermore, plenty of MS microRNAs such as miR-141, miR-145 are expressed and target mechanosensitive elements, which may form a positive or negative feedback

its structure and followed multiple unfolding pathways upon stretching. Simulations of the ARM/E-cadherin cytosolic tail complex emulated the most probable stress geometry occurring in vivo [13]. In skin, β-catenin was demonstrated to protect the epidermis of mice from mechanical stresses; while loss of β-catenin did not result in defects of epidermal differentiation and cell–cell contacts, tight junction protein localization was diminished in β-catenin knockout epidermis [14]. Another direct evidence of β-catenin in mechanotransduction in skin was that ROCK activation in mouse skin elevated tissue stiffness via increasing collagen production. β-catenin was stabilized by ROCK activation, leading to its nuclear accumulation, transcriptional activation, and consequent keratinocytes' hyperproliferation and skin thickening [15]. So, β-catenin is indispensable to maintain tight junctions and mechanotransduction of skin under mechanical stretch.

## Yes-associated protein (YAP)

The Hippo pathway has been demonstrated its function in precise skin size control [16, 17], with two key downstream effectors: YAP and its homolog transcriptional co-activator with PDZ-binding motif (TAZ). Transient overexpression of YAP resulted in enlarged liver and epidermis. However, sustained YAP overexpression eventually led to the development of liver and skin tumors. Clinical samples showed elevated expression and nuclear localization of YAP in various human cancers. Furthermore, YAP was inhibited by junctional proteins, such as angiomotin

(AMOT) family proteins [18, 19], ZO-2, and alpha-catenin [20]. Besides, as the downstream components of canonical Hippo pathway, YAP/TAZ was also regulated by several extracellular signals including the G-protein-coupled receptors (GPCRs) signaling, the Wnt signaling, and mechanical stimulation. Rho GTPase and remodeling of F-actin, known effectors of GPCR signaling, were found to be required for YAP/TAZ regulation [21, 22]. Interestingly, GPCRs were also found to be mechano-sensor (discussed in section of Calcium channels).

Recently, mechanical signals were found to be transduced by two related transcriptional coactivators, YAP and TAZ [23]. To classify the complex crosstalk between these different inputs feeding on YAP/TAZ (mechanical stimulation, Hippo, Wnt, or GPCR signaling), Aragona et al. [24] demonstrated that mechanical forces were overarching regulators of YAP/TAZ in multicellular contexts, setting responsiveness to Hippo, WNT, and GPCR signaling. Another fascinating research found that YAP/TAZ could act as an intracellular mechanical rheostat that stored information from past physical environments and influenced the cells' fate [25]. In fibroblasts, YAP function was required for cancer-associated fibroblasts to promote matrix stiffening, cancer cell invasion, and angiogenesis. Responsively, matrix stiffening further enhanced YAP activation, thus establishing a feed-forward self-reinforcing loop [26] during oncogenesis. So, YAP/TAZ was now widely recognized as mechano-sensors and mechanotransducers in regulating organ size and tumor growth (for more details seen in the excellent review of Low et al. [27]).

As the mechanical control checkpoint of multicellular growth, YAP controls epidermal growth and is involved in various skin diseases. YAP, through its interaction with α-catenin, acts as a critical mediator of crowd control in the epidermis of mice [20]. So, whether α-catenin could form a general mechano-sensor complex with β-catenin and YAP1, which orchestrates cellular responses to divergent mechanical stimuli, deserves more well-designed research. Increased cellular density limits stem cells expansion by inactivating YAP. Low basal cell density, as in a growing embryo or after wounding, would translate into nuclear YAP and proliferation. YAP/TAZ localization to the nucleus is required in skin wound healing [28], activation of stem/progenitor cell in the epidermis [29], promoting epidermal proliferation and inhibiting terminal differentiation [30]. During these pro-proliferation capacity, YAP also functioned in basal cell carcinoma [31] and contributed to the invasive and metastatic capacity of melanoma cells, with increased expression of TAZ and its downstream targets genes connective-tissue growth factor (CTGF) [32]. Collectively, YAP is the governor of epidermal proliferation and may act as a mechanical sensor in skin.

### Activator protein 1 (AP-1)

The transcription factor AP-1 mediates gene expression in response to a variety of extracellular stimuli including growth factors, cytokines, and mechanical stress [33]. AP-1, a heterogeneous set of dimeric proteins, consists of members of the Jun, Fos, and ATF families. AP-1 proteins are now being recognized as critical regulators of oncogenesis, bone development, inflammation, skin physiology, and diseases [34]. In skin, AP-1 subunits expressed in keratinocytes are involved in the regulation of the proliferation and differentiation of epidermis. AP-1 target genes include transglutaminase and different members of the cytokeratin gene family such as Keratin1 (K1), K5, K14, K18, and K19 [35]. While Jun is regarded as a positive regulator of keratinocyte proliferation, JunB and JunD are often considered to be the negative regulators of cell proliferation. Fibroblasts overexpressing JunB showed reduced proliferation [36]. AP-1 has been demonstrated to function in wound healing [37], photoaging, melanoma, squamous cell carcinoma (for references, see [33, 34, 38]), psoriasis, as well as skin regeneration [39].

In addition to mediate inflammatory effect, AP-1 is also involved in mechanotransduction. AP-1 and NF-κB were found to be activated by cyclic strain and shear stress in endothelial cells [40, 41], inducing the expression of genes encoding for adhesion molecules, monocyte chemo-attractants, and growth factors. Then, AP-1- and NF-κB-mediated transcriptions were identified to function in bladder muscle cells [42], osteoblasts [43], lung parenchyma [44], and amnion cells [45], in response to mechanical forces. At the initiation of arteriogenesis, stretch-induced AP-1-mediated MCP-1 expression in vascular smooth muscle cells played as a key determinant [46]. With regard to the role of AP-1 in mechanotransduction of skin, previous research showed that by microarray analysis performed on mechanical stretched and normal human skin, significant difference was observed in 77 genes. Among these skin regeneration-related genes, AP-1 was up-regulated in mechanically stretched skin [39], implying that AP-1 may be involved in mechanotransduction of skin.

In brief, the above-mentioned three transcription factors and co-regulators in skin mechanobiology were the most studied, with their roles in skin summarized in Table 1. While β-catenin and YAP have been demonstrated to directly transduce mechanical stimulation in skin, AP-1 has only been found to be significantly up-regulated in mechanical stretched skin. More elaborate research is demanded to reveal the direct mechanosensitive facet of AP-1 in skin, especially epidermis.

**Table 1** Mechanosensitive transcription factors in skin

| Transcription regulators (homo sapiens) | Mechano-pattern | Effect | Skin diseases involved |
|---|---|---|---|
| β-Catenin | Stretch or strain; stiffness of ECM | Promote osteogenic differentiation of MSCs; protect epidermis from mechanical stresses; self-renewal of interfollicular epidermal stem cell | Maintain tight junction proteins of skin barrier [14]; epidermal hyperproliferation [15] |
| YAP | Stretch or strain; stiffness of ECM | Cell proliferation; cell crowd control; activate epidermal stem cell; inhibit epidermal terminal differentiation; skin cancers | Skin tumors [20]; stem/progenitor cell activation; wound healing [28] |
| AP-1 | Stretch or strain; fluid shear stress | Inflammation; initiation of arteriogenesis; adhesion; monocyte chemotaxis; induce expression of epidermal growth factor-like growth factor; activate osteoblast differentiation | Wound healing [37]; skin regeneration [39] |

## Mechanosensitive ion channels of the skin

Mechanical stimuli are known to induce ionic currents in various types of cells. These currents are conducted through different ion channels in the cell membrane [47]. Mechanical sensitivity, much like voltage or ligand sensitivity, is a general characteristic of ion channels. Channels previously considered as "voltage-gated" such as $K^+$ and $Na^+$ channels were also found to be mechanically sensitive [48]. In this mechanosensory transduction system, the opening of stretch-activated channels is the first step, leading to various intracellular events. Although many ion channels are implicated in mechanosensation, few have been shown to be directly stretch activated. Ion channels which are identified to be MS in other cells have also been found to express and function in skin physiology. In the present review, without analysis of structure and function of MS ion channels, we focus on the physiological functions and related cutaneous diseases of four different MS ion channels: CaSR, TRP, Connexins, and Piezo.

### Calcium channels (calcium-sensing receptor)

The major downstream effect of mechanosensitive ion channel activation in the epidermis is a change in cytoplasmic $Ca^{2+}$ concentration [49]. $Ca^{2+}$ oscillations have been observed in MSCs and are considered as both an indicator and a regulator of the MSC differentiation. Extracellular calcium is essential for initiating keratinocyte differentiation and maintaining epidermal functions [50]. $Ca^{2+}$ concentration oscillation may be caused by mechanical signal [51] as found in human cardiac progenitor cells, keratinocytes, and myofibroblasts [52], indicating that mechanical forces might have the potential to directly regulate the fate of these cell types through modulating calcium signals [53]. It has been reported that changes in the plasma membrane tension can be transmitted to the mechanosensitive L- and N-type $Ca^{2+}$ channel [54, 55]. $Ca^{2+}$ influx can also be mediated by the nonspecific cation channels such as MS transient receptor potential (TRP) channels, connexins, and Piezos (described below), as well as voltage-gated calcium channels [56] and specific calcium-sensing receptors (CaSR) [57, 58].

The CaSR belongs to the family C of GPCRs which exhibit distinct functions in many physiological processes such as inflammation, cellular growth, and differentiation. Although the direct evidence of mechanical sensitivity has not been reported for CaSR yet, a multitude of researches suggested that GPCRs were involved in mechanosensation. $G_{q/11}$-protein-coupled receptors have recently been indicated in the sensing of fluid shear stress in endothelial cells (bradykinin $B_2$ receptor) [59, 60] and mechanical stretch in cardiac myocytes (beta-adrenergic receptor) [61, 62] (For more details about G-protein-mediated stretch reception seen in [63]). In the skin, MS GPCRs are involved in collagen synthesis in cardiac and lung fibroblasts [64], and thought to activate fibroblast contraction during wound healing. Inhibition of CaSR expression in keratinocytes markedly impairs cell differentiation by reducing intracellular $Ca^{2+}$ pools [58] and blocking E-cadherin mediated signaling [65, 66]. Abrogation of CaSR in vivo was shown to perturb the epidermal $Ca^{2+}$ gradient and compromise differentiation and barrier functions [67]. However, CaSR transgenic mice exhibited advanced differentiation and epidermal permeability barrier formation during embryologic development and accelerated hair growth at birth.

### Transient receptor potential (TRP) channels

Members of the TRP family are implicated in a wide variety of mechanical transduction processes in diverse organs and species. These channels can be activated by mechanical, as well as chemical and thermal stimulation. TRP channels play a role in cellular homeostasis and

growth control, regulation of cell fate and survival, immune, and inflammatory mechanisms [68]. The TRP channel family is usually divided into seven subfamilies (TRPC, TRPV, TRPM, TRPN, TRPA, TRPP, and TRPML). These ion channels are non-selectively permeable to cations, including sodium, calcium, and magnesium. Evidences suggest that multiple TRP channels are critically involved in the regulation of cutaneous functions [69]. Among the TRP channels, TRPA1, TRPV1, and TRPV4 are the most studied TRP channels of the skin and their mutations lead to a variety of phenotypic disorders.

TRPA1 can induce marked changes in the expressions of certain adhesion and extracellular matrix proteins in keratinocytes as well as of molecules regulating cell fate and differentiation [70]. The role of TRPA1 in cutaneous inflammation has been further verified in rodent dermatitis models. TRPA1 activation enhanced the migration of dendritic cells to draining lymph nodes, and this effect was antagonized by the TRPA1 antagonist [71]. Activation of TRPV1 on epidermal keratinocytes resulted in the influx of $Ca^{2+}$ into the cells, suppressing cell growth, and inducing apoptosis [68]. Furthermore, TRPV1 stimulation delayed barrier recovery, whereas administration of the TRPV1 antagonist accelerated barrier repair [72]. Stimulation of TRPV1 expressed by outer root sheath keratinocytes of human hair follicles also inhibited hair shaft elongation [73]. Besides, mechanical activation of TRPV1 caused intracutaneous release of a plethora of neuropeptides. The released peptides activated multiple types of skin cells, inducing the release of certain pro-inflammatory cytokines [73, 74]. Similarly, TRPV4, mediating the metabolic response of chondrocytes to mechanical stimuli [75], was also involved in epidermal barrier homeostasis [76, 77]. Most recent research showed that TRPV4 was abrogated both in premalignant lesions and non-melanoma skin cancer in cytokine-dependent manner [78].

## Connexins

Connexins are structurally conserved gap junction (GJ) protein abundantly expressed in bone and skin cells [79], playing a central role in cell-to-cell communication and mechanotransduction. Channel opening and closure are tightly regulated by changes in cytosolic pH, voltage, as well as mechanical stimulation [80]. This process is critical for the maintenance of cellular homeostasis and regulation of proliferation, differentiation, and apoptosis [79, 81]. In vitro studies suggested that gap junctional intercellular communication (GJIC) sensitized bone cells to mechanical signals. Additionally, mechanical signals detected by osteocytes were communicated to osteoblasts via GJIC [80, 82–84]. Connexin43 (Cx43) is the predominant GJ protein in bone. Cx43 expression was enhanced by loading in bones in vivo as well as in cultured osteoblasts and osteocytes, thus preventing osteocyte apoptosis [82, 83]. Under mechanical loading, the c-terminus domain of Cx43 with integrin α5 and β1 led to activation of PI3 K, the kinases FAK/Src, and the ERK pathway, eventually promoting osteocyte survival.

Connexin has also been demonstrated to function in keratinocytes differentiation, wound healing, and skin diseases. Up to 10 different connexins are differentially expressed throughout the terminal differentiation. Cx43 is the main connexin found in basal proliferating cells [85]. Cx43 knockdown resulted in impaired epidermal differentiation and barrier function [86]. During wound healing, Cx43 knockout mice showed shorter wound closure times, making itself a potential therapeutic target to improve wound healing [87]. Cx43 expression at wound margins declined rapidly following injury, returning to normal levels following re-epithelization. The reduction of Cx43 at wound edges is related with the mechanical force which was produced by intrinsic myofibroblats and many extrinsic forces. Another skin disorder associated with connexin is melanoma. The loss of the ability to form heterocellular contacts and exhibit GJIC with keratinocytes was found to be a contributor or suppressor to melanoma growth within the epidermis [88]. While Cx32 knockout mice are more prone to developing chemical- and radiation-induced tumors [89, 90], the role of connexins during the onset and progression of melanoma tumorigenesis is still controversial. Most recently, it was found that Cx43 could act as a tumor suppressor during melanoma tumorigenesis by significantly reducing cellular proliferation and anchorage-independent growth [90].

## Piezos

Piezo1 and Piezo2 were first identified as MS channels in the cell line Neuro2A. Piezo proteins have 2,100–4,700 amino acids which contain approximately 24–39 transmembrane segments showing no homology to other already known voltage sensitive channels [91]. Piezos do not require any additional proteins for their opening, but can directly sense lipid membrane extension [92]. Although currents mediated by Piezo proteins are non-selective cationic currents, Piezo1 protein was classified as a real ion channel that conducts both $K^+$ and $Na^+$. The currents mediated by both Piezo1 and Piezo2 can be pharmacologically inhibited by mechanosensitive channel blockers [93]. Piezo1 expression has been observed in bladder, colon, kidney, lung, and skin which all constantly undergo mechanotransduction. Recent studies found that Piezo1 is present in the mouse and human bladder urothelium and has a functional role in stretch-evoked $Ca^{2+}$ influx and

ATP release in mouse urothelial cell [94] and human neural stem cells [95], indicating the potential MS property of Piezos.

The role of Piezo proteins in skin has not been investigated until most recently. Piezo2 was previously shown to be present at low levels in the skin [91]. However, Woo et al. [96] found that Piezo2 was specifically expressed in Merkel cells (~0.05–0.1 % of total epithelial cells from dorsal skin) in whisker pad, dorsal skin, and foot pad. Using Piezo2 knockout mice, they found that Merkel cells were indeed mechanosensitive, and Piezo2 was required in Merkel cells to produce their mechanical currents. Piezo2 ablation impaired proper mechanosensory encoding in Merkel cell–neurite complexes in the intact skin. The results indicated that Piezo2 was the Merkel-cell mechanotransduction channel and provided the first line of evidence that Piezo channels have a physiological role in mechanosensation in mammals. The function of Piezo proteins in non-Merkel cells of the skin needs further investigation.

In summary, direct evidence of ion channels to be MS was only found in Connexin43 and Piezo2 in the skin. Although $Ca^{2+}$ and TRP channels that are also expressed in the skin and play a vital role in skin barrier formation and inflammation have been shown to be activated by various mechanical stimuli in non-cutaneous cells, they have not been demonstrated to mediate a mechanical signal yet (seen in Table 2). Besides, many mechanically activated currents are non-selective cationic currents, such as $Ca^{2+}$ and Connexins, could be conducted through different MS ion channels in the cell membrane. So, the mechanism how these MS ion channels are orchestrated by cutaneous cells under mechanical condition and the identification of the downstream signaling pathways for these currents deserve more further research.

## The association between mechanosensitive microRNAs and skin disorders

MiRNAs are shown to be involved in the mechanical regulation of epidermal biology and functions. The role of MS miRNAs has been widely studied in endothelial cells (ECs) [109, 110]. In vascular endothelial cells, shear stress regulated ECs redox and inflammatory state, cell cycle, cytoskeleton and gap junctions. Furthermore, different shear stress patterns determine distinct endothelial function. While pulsatile shear stress (PS) act as atheroprotective flow, oscillatory shear stress (OS) was identified to be an atheroprone factor, suggesting the specific role of shear stress in endothelial response. Recent studies underline the importance of miRNAs in skin development and epidermal differentiation, wound healing, fibrosis, and skin cancers [111]. For example, miR-203 has been shown to be indispensable in skin mechanobiology. AP-1 subunits c-Jun and JunB were found to drive miR-203 expression in keratinocytes, acting as a switch between keratinocyte proliferation and differentiation. MiR-200 and miR-205 positively regulate E-cadherin and seem to be essential in maintaining epithelial stability (For more

**Table 2** Mechanosensitive ion channels and skin disorders

| Channel family | MS channel isoforms | Skin disorders involved | Effect |
|---|---|---|---|
| $Ca^{2+}$ channels | GPCRs [60–62] | Epidermal differentiation and barrier functions | Advance epidermal differentiation and permeability barrier formation [65–67] |
| TRP channels | TRPA1 [97, 98] | Skin barrier | Accelerate skin permeability barrier recovery [70] |
| | | Skin inflammation | Contact dermatitis [71] |
| | TRPV1 [99] | Skin barrier | Decrease proliferation and induce apoptosis of keratinocytes; inhibit skin barrier recovery [72] |
| | | Skin inflammation | Induce release of pro-inflammatory cytokines [73, 74] |
| | TRPV4 [100] | Skin barrier | Strengthen the tight junction barrier in human epidermal keratinocytes [76, 77] |
| | | Non-melanoma skin cancer | Decreased TRPV4 expression as an early biomarker of skin carcinogenesis [78] |
| Connexins | Connexin43 [82–84, 101, 102] | Wound healing | Enhance wound closure [85, 87, 103, 104] |
| | | Melanoma | Serve as tumor suppressor [88, 90, 105] |
| | | Epidermal homeostasis | Epidermal differentiation and barrier function [81, 86, 106] |
| Piezo | Piezo1 and piezo2 [91, 93] | Merkel cells sensory afferents | Touch-sensitive currents of Merkel cells [96] |
| $Cl^-$ channels | CFTR [107] | Hyperpigmentation | Mediate the procedure of treatment of melasma with estrogen [108] |

**Table 3** Mechanosensitive microRNAs and associated skin disorders

| MS miRNAs | Targeted genes (under mechanical stimuli) | Effect | MS pattern | Direct effect | Skin disorders involved |
|---|---|---|---|---|---|
| miR-21 [116, 118] | Phosphatase and tensin homolog (PTEN) | Down | Shear stress | Decrease apoptosis and activate the NO pathway | Hypertrophic scar [140]<br>Scleroderma fibrosis [124]<br>Melanoma [133, 134]<br>Psoriasis [141–143]<br>Wound healing [119, 120]<br>Squamous cell carcinoma [144, 145] |
| miR-23b [146] | Retinoblastoma (Rb) | Up | Shear stress | Growth arrest of endothelial cells | Radiation skin injury [147]<br>Melanoma [135, 136]<br>Epidermal differentiation [148] |
| miR-24 [149] | Subtilisin-like proprotein convertase (FURIN) | Up | Mechanical stretch | Induction of TGFβ1 | Epidermal differentiation [150]<br>radiation skin injury [151, 152]<br>melanoma [153] |
| miR-26a [137] | Glycogen synthase kinase-3β (GSK-3β) | Up | Mechanical stretch | Hypertrophy of human airway smooth muscle cells | Melanoma [138, 154]<br>Squamous cell carcinoma [155]<br>Epidermal differentiation [148] |
| miR-34a [156] | Forkhead box j2 (Foxj2) | Up | Shear stress | Promotes endothelial differentiation of endothelial progenitor cells | Non-melanoma skin cancer [157, 158]<br>Merkel cell carcinoma [159]<br>Melanoma [139, 160]<br>Epidermal proliferation [161] |
| miR-17-92a [125] | Cyclin D1 | Down | Shear stress | Cell cycle arrest of endothelial cells | Epidermal Langerhans cells [162]<br>Scleroderma fibrosis [126]<br>Basal cell carcinoma [163]<br>Mycosis fungoides [164] |
| miR-144/451 [165] | AMPKα1 | Down | Mechanical stretch | Promote contractile differentiation of smooth muscle cells | None |
| miR-145 [166–168] | Angiotensin-converting enzyme (ACE) | Down<br>Up | Mechanical stretch<br>Shear stress | Angiotensin-converting enzyme expression | Squamous cell carcinoma [155]<br>Melanoma [169]<br>Basal cell carcinoma [163] |
| miR-146a [127] | IRAK1 and TRAF6 | Up | Oscillatory pressure | Induce inflammation in lung epithelia | Melanoma [135, 170]<br>Chronic inflammation [128, 171]<br>Non-melanoma skin cancers [172] |
| miR-155 [117] | RhoA and myosin light chain kinase (MYLK) | Up | Shear stress | Cytoskeleton organization of endothelial cells | Wound healing [173]<br>Mycosis fungoides [164, 174]<br>Cutaneous lymphoma [175–179] |

details about microRNAs in skin seen in [111–113]). So, in this review, we will focus on the role of reported MS miRNAs in skin disorders, such as wound healing, hypertrophic scar, inflammation or related scleroderma fibrosis, and skin cancers (Table 3).

## MS microRNAs in wound healing, hypertrophic scar, and keloid

Acute wounds undergo a healing process of complex biochemical and cellular events. All the phases are influenced by mechanical forces which are generated by wound contraction and traction forces of ECM and myofibroblasts. It has been well described that the mechanical stretching of fibroblasts can regulate the expression of matrix and inflammatory genes involved in scar formation, suggesting that wound fibrosis can be modulated by fibroblast mechanosensitivity [4]. Keratinocytes are also mechanically responsive: mechanical stretch promotes keratinocyte proliferation and migration in vitro [114]. Thus, clinical application of mechanical forces provides an alternative method for the acceleration of cutaneous wound healing and prevention of hypertrophic scars. Compression treatment is a frequently used therapy for postburn hypertrophic scars. Silicone gel sheeting has been shown effective in reducing tension between the scar and normal skin. Paper or plastic adhesive tape is also used to prevent excessive scarring by decreasing wound tension [115].

MS microRNAs, found in non-cutaneous cells, play essential roles in wound healing or hypertrophic scar. In ECs, shear stress forces increased the expression of miR-21 and miR-155 which influence endothelial biology by decreasing apoptosis [116] and inducing changes in morphology and F-actin organization [117]. In human aortic smooth muscle cells, mechanical stretch modulated miR-21 expression, thus participating in cellular proliferation and apoptosis [118]. Both miR-21and miR-155 are involved in wound healing and the formation of hypertrophic scars, mainly in activated and migrating keratinocytes of the epidermis and mesenchymal cells of the dermis [119, 120]. Antagonizing miR-21 caused significant delay of wound closure with impaired collagen deposition. Interestingly, wounds treated with miR-21 antagomir exhibited significantly impaired wound contraction at an early stage of wound healing, which provided direct evidence of miR-21 to be an MS microRNA during wound healing [119]. MiR-155 was up-regulated in wound tissue when compared with healthy skin. However, lacking expression of miR-155 resulted in an accelerated wound closure. Besides, miR-155 targets two key regulators of the cytoskeleton organization: RhoA and myosin light chain kinase (MYLK) [117], which are key components in mechanotransduction. More research is required to understand the exact function of miR-155 in wound healing. But it is undoubted that biomechanical force and MS miRNAs play a vital role in wound closure and formation of hypertrophic scar.

## MS microRNAs in scleroderma fibrosis and chronic inflammatory diseases

Scleroderma is a complex systemic autoimmune disease characterized by extensive chronic fibrosis, primarily of the skin. Overproduction of pathological ECM components by fibroblasts plays a major role in the pathogenesis of scleroderma. Importantly, functional alterations of scleroderma are accompanied by changes in the mechanical properties and morphology of fibroblasts. The architecture of the fibrosis-associated ECM is fundamentally different from that of the normal tissue stroma. Previous data showed that ongoing myofibroblast activation and TGF-β signaling can be driven by altered mechanical tension in a feed-forward loop [121]. Compared to normal dermal fibroblasts, significant differences in cellular stiffness have been detected in dermal fibroblasts derived from sclerodermal lesions using atomic force microscopy [122]. Another explanation for the overproduction of ECM in scleroderma is the activation of fibroblasts by cytokines and growth factors, endothelin1 and thrombin [123], as well as chronic inflammation. Matrix-generated biomechanical tension via integrin signaling seems to be involved in this process. These findings suggest an association between scleroderma, chronic inflammation, and mechanotransduction.

Besides TGF-β signaling and inflammatory cytokines, miRs have recently been identified to play a role in the pathogenesis of inflammatory cutaneous diseases such as scleroderma, psoriasis, and diabetic wound healing. While TGF-β leads to an increased expression of miR-21 and decreased expression of fibrosis-inhibitor gene Smad7, overexpression of miR-21 in fibroblasts decreases the expression of Smad7, suggesting that miR-21 may act as a potential therapeutic target of scleroderma [124]. MiR-19a is another MS microRNA that is involved in the pathogenesis of scleroderma. Using microRNA chip array, miR-19a expression in ECs was found to be regulated by laminar shear stress [125]. MiR-19a level was also shown to be significantly higher in the serum and dermal fibroblasts of scleroderma patients [126]. Similarly, miR-146a is rapidly up-regulated by oscillatory pressure in airway epithelial cells, playing an important role in mechanically induced inflammation in lung epithelia [127]. IRAK1 and TRAF6, two important mediators of inflammatory responses, were then identified as targets of miR-146a. In cutaneous diseases, miR-146a is known to be up-regulated both in lesions and peripheral blood mononuclear cells (PBMCs) of psoriatic patients, correlated with IRAK1 expression [128]. Thus, mechanical cues may contribute to the persistent inflammation of psoriasis mediated by miR-

146a. Chronic inflammation is also thought to play a central role in the pathogenesis of diabetic wound. Notably, miR-146a expression is markedly down-regulated in diabetic mouse wounds [128].

### MS microRNAs in melanoma and non-melanoma skin cancers

Cutaneous melanoma is a highly malignant tumor type due to its tendency to metastases. Recent work has identified BRAF and NRAS mutations in melanoma, which lead to constitutive activation of MAPK and phosphoinositide 3-kinase (PI3K) pathway [129]. Both MAPK and PI3 K pathways were found to mediate biomechanical signal, implying the potential role of BRAF and NRAS in mechanotransduction of melanoma. It has been shown that many stromal components are able to activate varieties of cellular processes in melanoma [130]. Cutaneous melanoma cells have varied morphological characteristics, and the stroma can show myxoid or desmoplastic changes. Members of the matrix metalloproteinase (MMP) family are expressed by melanoma cells [131], which indicates that frequent ECM remodeling and collagen deposition happened during melanoma progression. The ECM stiffness can regulate melanoma cells and tissue behavior by initiating biomechanical signaling cascades in cells through interactions with a number of specialized transmembrane ECM receptors. Furthermore, tumor growth cannot be sustained unless the tumor cells attract and stimulate fibroblasts, which are the main source of extracellular matrix. Recruited fibroblasts are converted into myofibroblasts, differentiated to fibrocytes that secrete fibrillated extracellular matrix components, which further stiffen the ECM [132]. Importantly, biophysical force generated by contraction of myofibroblasts and stiff ECM in the microenvironment has a significant role in melanoma growth and metastases.

A large number of MS miRNAs were demonstrated to act in melanoma. MiR-21 was shown to be MS in ECs and aortic smooth muscle cells, and significantly increased in primary melanoma tissues as compared to benign nevi. Upregulation of miR-21 in melanocytes resulted in increased proliferation and decreased apoptosis [133]. MiR-21 has also been found in plasma and its expression was associated with tumor burden in cutaneous melanoma and squamous cell carcinoma patients [134]. MS miR-23b on the other hand mediated flow-regulation of Rb phosphorylation in EC growth. MiR-23b was found to be decreased in melanomas, as assessed by an in-depth analysis of the miRs transcriptome [135, 136]. MiR-26a is an MS gene to mechanical stretch and plays an important role in the regulation of human airway smooth muscle hypertrophy [137]. MiR-26a was identified to be specifically down-regulated in human melanoma cells [138] and squamous cell carcinoma. Another example, miR-34a can modulate differentiation of endothelial progenitor cells in response to shear stress. In melanoma, miR-34a was found to be tumor suppressive by targeting ULBP2, a natural killer cell immunoreceptor NKG2D ligand and it is widely expressed in tumor cells [139]. Furthermore, miR-34a was also found in non-melanoma skin cancers (Table 3). Taken together, these findings imply a strong association between mechanotransduction and skin cancers. These MS miRs modulators (antagonist or agonist) may serve as promising novel therapies for subsets of melanoma.

## What is known and unknown about the regulatory network induced by mechanical force?

Interestingly, some MS miRNAs are found to target MS transcription factors (Table 4). miRNAs regulate gene expression by binding to the 3′ untranslated region of the

**Table 4** Mechanosensitive transcription regulators related to microRNAs

| Transcription factors (homo sapiens) | MiRNAs validated[a] | MS miRNAs | Effect |
|---|---|---|---|
| YAP1 | mir-141, 181a, 374a, 375, 519a, 630 | mir-141 | Target the E-cadherin transcriptional repressors ZEB1 and ZEB2, inducing invasion and metastasis of skin tumor cells [180, 181] |
| β-Catenin | mir-1, 30, 122, 125a, 145, 148a, 150, 155, 183, 192, 193a, 200a, 214, 224, 517a, 520c; let-7b | mir-145 | Target the junctional adhesion molecule A, the actin-bundling protein fascin and c-Myc [182, 183], involved in melanoma and non-melanoma skin tumors |
| AP-1 | mir-1, 9, 15, 16, 21, 24, 25, 26a, 30, 34a, 99, 100, 125a, 126, 141, 143, 144, 145,146a, 150, 155, 194, 195, 200a, 214, 203, 206, 223; let-7b | mir-21, 24, 26a, 34a, 141, 144, 145, 146a | mir-21 targets a number of tumor suppressors; mir-24 can directly repress cytoskeletal modulators in keratinocytes [150]; mir-26a can repress gene expression of SODD (silencer of death domains) in melanocytes [138]; mir-34a: repressed by p63 to maintain keratinocyte cycle progression [161] |

[a] Results from miRWalk. (http://www.umm.uni-heidelberg.de/apps/zmf/mirwalk/micrornapredictedtarget.html)

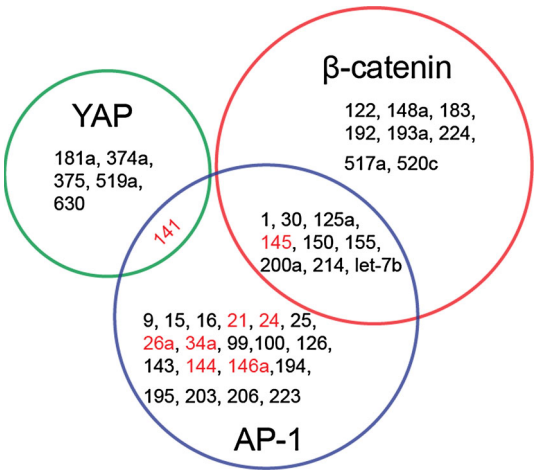


**Fig. 2** Mechanosensitive transcription regulators and microRNAs. Validated gene-microRNA interactions are gathered from the miRWalk database. MicroRNAs which target MS transcription factors β-catenin, YAP and AP-1 are shown by Venn Diagram respectively. These microRNAs, which have been confirmed to be activated directly or responsively by mechanical stimuli, are shown in red

target mRNAs. Specific binding of MS miRNAs to MS transcription factors (YAP1, β-catenin and AP-1) is validated and gathered, according to an open-access miRNAs database miRWalk (http://www.umm.uni-heidelberg.de/apps/zmf/mirwalk/micrornapredictedtarget.html). For example, YAP1 can be regulated by mir-141, 181a, 374a, 375, 519a, and 630, during which mir-141 (belong to mir-200 family) is abundantly expressed in skin. Mir-141 targets the E-cadherin transcriptional repressors ZEB1 and ZEB2, inducing invasion and metastasis of skin tumor cells [180, 181]. Furthermore, both YAP1 and AP-1 are regulated by mir-141. β-catenin and AP-1 can be targeted by many miRNAs, during which mir-21, 24, 26a, 34a, 141, 144, 145, and 146a are identified to be MS (Fig. 2). Mir-145 targets junctional adhesion molecule A and the actin-bundling protein fascin, modulating cancer cell motility [182]. Mir-145 is also expressed through the phosphoinositide-3 kinase (PI-3K)/Akt and p53 pathways, and then targets the expression of c-Myc [183]. Most listed MS miRNAs were found to regulate AP-1, but direct evidence that these miRNAs are activated and target AP-1 expression under mechanical stimulation is still missing.

However, it is still largely unknown about the regulatory network of miRNAs under mechanical stimuli conditions. For example, pulsatile flow down-regulates miR-17 which targets SOD2, GPx2, and TrxR2. In contrast, oscillatory flow down-regulates SOD1 by miR-872 [109], indicating that different mechanical patterns were sensed and mediated by different membrane proteins and downstream signaling pathways. Although diverse mechanotransduction pathways under specific patterns of mechanical stimuli have been identified, the underlying complex mechanisms require more further investigation to understand how slight difference in mechanical patterns may cause tremendous divergence of cell responses. Mechanical stimuli-induced miRNAs could responsively regulate MS cell sensors such as e-cadherin, cytoskeleton constituent RhoA, and MS transcription factors such as YAP1, β-catenin, and AP-1 (Table 4). Moreover, it remains largely unknown how mechanical force regulates the network of miRNAs. Therefore, it is still unknown if these mechanical-induced feedback regulations are positive or negative.

## Conclusion and future directions

Taken together, the exploitation of cutaneous mechanobiology will help researchers and clinicians to gain a more comprehensive understanding of wound healing, hypertrophic scar formation, skin regeneration, and skin tissue engineering. However, different magnitude of mechanical force also seems to exert distinct biological effects by targeting different genes. MS transcription factors and microRNAs interweave in a complex regulatory network of cellular-responses. On the other hand, the reciprocal cell-ECM remodeling mechanisms of this circuit and the model of skin stem cells (interfollicle or hair follicle) activation under mechanical stimuli remain unknown. Identification of the mechanical property divergence of ECM under pathological or physiological conditions or stem cells niche, the association of ECM mechanical modulus with different Rho GTPases, and the convergence of mechano-sensors with canonical biochemical receptors may be the possible steps to overcome these challenges. Advances in nanotechnology, molecular imaging, and gene manipulation will further accelerate the investigation of the mechanically activated regulatory network within the cells. Finally, in-depth research of these questions is urgently needed not only in cutaneous biology, skin, and hair follicle morphogenesis, but also in the progression and initiation of skin diseases like cancers.

**Conflict of interest** The authors state no conflict of interest.

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