Molecular mechanisms of mechanotransduction in psoriasis

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Abstract: Psoriasis is an immune disease of the skin that frequently develops upon triggering events of mechanical nature and leads to increased proliferation and damaged differentiation of keratinocytes of the epidermis. Mechanical forces are mediated through mechanotransduction, which is the process that translates physical cues into biochemical signaling networks. Latest updates underline the role of mechanotransduction during the acquisition of aberrant properties by the keratinocytes of the skin, therefore implying a potential contribution that promotes psoriasis pathogenesis. The present review discusses the mechano-induced signaling pathways and individual molecules that become activated in psoriasis and in keratinocytes, along with mechano-based putative treatment strategies. We also suggest emerging mechanosensitive molecules for further investigation with potential diagnostic and therapeutic utility in psoriasis.

Keywords: Mechanotransduction; psoriasis; Yes-associated/TAZ (YAP/TAZ); TRP channels; polycystin

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Introduction

Psoriasis represents a skin disease which is characterized by chronic inflammation with a severe physical and psychological burden (1). In fact, the psychological burden is compared measurably to other chronic diseases that are threatening for the patients' life, such as cancer, depression, myocardial infarction and congestive heart failure (2). While psoriasis has been recognized as a distinct clinical entity from the 19th century, nowadays it still has a major impact on the patients' quality of life (1). It affects approximately 2–4% of the population with various differences depending on age, gender and geographic location (3). Adults present more often with the disease compared to children, whereas countries that are more distant from the equator exhibit higher prevalence compared to the ones closer to it, which benefit from the stronger ultraviolet (UV) radiation (4,5). Prevalence is generally equal in the western countries and it seems that females have a higher incidence when they are <18 years old and adult males have a higher incidence compared to adult females (6,7).

Patients that suffer from psoriasis complain for itch, bleeding and pain (2). There are five distinct clinical types of psoriasis with different histological features that have been described: plaque-type (psoriasis vulgaris) that represents the most common type of the diseases with an incidence of 90%, guttate (droplet) psoriasis, inverse psoriasis, pustular psoriasis that is characterized by blisters, and erythrodermic psoriasis (2). Psoriasis affects the whole skin, however it seems that it has a preference for the extensor surfaces of forearms and shin, peri-anal, peri-umbilical, nails and the scalp (2). Psoriasis is also accompanied by other comorbid

diseases such as psoriatic arthritis, which develops in approximately 20–30% of the patients suffering from psoriasis, metabolic syndrome, cardiovascular diseases, diabetes, cancer and depression (1).

Experimental studies regarding the molecular pathology, molecular genetics and epigenetics of psoriasis have revealed distinct molecular features that govern the onset and the development of the disease (8-10). The engagement of individual molecules has enriched the treatment strategies regarding targeted treatment against psoriasis (11,12). However, many of the aspects of the molecular pathology of keratinocytes and the underpinning mechanisms of the events that trigger psoriasis remain elusive. In this context, a number of studies highlight the impact of mechanical forces and mechanotransduction during triggering events of the disease, therefore inducing mechano-regulated signaling pathways in keratinocytes (13-16). In the present review we discuss the impact of the application of mechanical/physical forces on keratinocytes and molecular mechanisms of mechanotransduction that promote skin pathogenesis and psoriasis, as well as putative therapeutic strategies that can be generated from this specific aspect.

Molecular pathogenesis of psoriasis

Immunopathology

The onset of the illness represents an immune response and it is distinguished in three phases: the sensitization phase, the resting phase, and finally the active phase. At the onset of psoriasis, immature dendritic cells, which are found in tissues, recognize and ingest exogenous antigens, and finally migrate to the secondary lymphoid organs in order to treat and present the antigen to T-cells (17). Following antigen uptake, dendritic cells undergo a maturation process to cope with the inflammatory conditions, largely due to cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), or to deal with microbial products that excite microbial cells through specific receptors (18).

At the active phase, when psoriatic plaques are formed, the first visible events are surface vascular infiltration of lymphocytes and monocytes and the distension of blood vessels in dermal papillae (19). The passage of immune cells through the endothelial wall of the vessels is called dialysis and is probably performed through pores formed between endothelial cells. This process seems to be dependent on the integrins (19). Immune cells can be activated after they migrate to the skin. In dermis and epidermis various groups of antigen presenting cells can stimulate T cells and vice versa. T cells that have migrated to the epidermis may additionally be activated by keratinocytes or also proliferate as a consequence of activation on the skin (20).

According to specific studies that have associated the expression of T-cell cytokines, IL-22 and IL-17 cytokines exhibit the highest expression in altered psoriatic epidermis (21). IL-22 has also been found in the blood of patients suffering from psoriasis and its concentration correlates to the severity of the disease (22). IL-22 is produced by activated T-cells and natural killer T (NKT)-cells, but not by other immune cells or tissue cells. The primary source of IL-22 in psoriatic skin is the T-helper 17 (Th17) and Th1 cells (22). Recently, increased IL-17 expression in epidermal psoriatic lesions has also been demonstrated (23). Furthermore, it is also known that in psoriatic skin lesions the number of macrophages is increased and that the amount of NKT-cells is also increased compared to normal skin (24).

Immune cells can be activated following their migration to the skin. In dermis and epidermis various groups of antigen-presenting cells can stimulate T-cells and vice versa. T-cells that have migrated to the epidermis may additionally be activated by keratinocytes or also proliferate as a consequence of their activation in the skin (25). In the epidermis, migrated T-cells can also be activated by keratinocytes. Keratinocytes appear to express molecules of the major histocompatibility complex (MHC) class II and CD54 (cluster of differentiation 54) after exposure to interferon-γ (INF-γ), thus promoting antigen presentation and invitation of T-cells (26). Activated keratinocytes are also able to promote T-cell proliferation from bacterially-derived superantigens (27).

Aberrant function of keratinocytes in psoriasis

Keratinocytes appear to play a role in the activation of NKT-cells through the CD1d molecule. In psoriatic skin, CD1d is overexpressed, and it can also be rapidly induced in healthy skin in cases of trauma that stops the barrier function. In *in vitro* experiments, after exposure to IFN-γ, keratinocytes showed an increased expression of CD1d. By combining $CD1d^+$ keratinocytes with clones of human NKT-cells, they were activated to produce large amounts of INF-γ (28). T-cells, NKT-cells and NK cells produce amounts of IFN-γ, which appear to activate the monocytes/macrophages and dendritic cells that are filtered into the skin. Activation may also include heat-shock proteins

produced by keratinocytes. Cutaneous macrophages in altered dermis may be the major source of TNF-α production (28).

Keratinocytes can also be activated during the onset of psoriatic lesions mainly from mediators produced by Th1 cells (IFN-γ and IL-22) (29). However, many other mediators have been found who may play a role. Activation of keratinocytes leads first to the increasing of their proliferation and to the modification of their maturation. In addition, activated keratinocytes produce numerous and diverse mediators that can cause further migration of the immune system cells, activation of the stromal cells of the dermis and promotion of angiogenesis. Proliferation of the keratinocytes in psoriatic lesions presents an approximately 50-fold increase (30). The cells of the immune system may in part be responsible for their proliferation. It has been found that activated and non-activated T-cells release agents that can increase the proliferation of keratinocytes (31). Of the T-cells mediators that have been studied, there are various, such as IFN-γ and tumor growth factor-β (TGF-β), that appear to inhibit keratinocyte proliferation, while others do not affect or increase their proliferation at high concentrations (32).

The impressive therapeutic effects of TNF-α inhibition in psoriasis make us assume that this cytokine increases keratinocyte proliferation strongly. The macrophages in papillary dermis may be the major source of TNF-α in psoriatic skin (33). Accordingly, macrophages seem to be the main responsible cell type for psoriasis skin lesions. TNF-α promotes the production of TGF-α factor in keratinocytes (34). TGF-α mRNA and the corresponding protein are found with increased expression in psoriatic skin than in seemingly healthy skin (35). TGF-α binds to the epidermal growth factor receptor (EGFR) and stimulates the proliferation of keratinocytes, but also accelerates skin regeneration (36). In addition to TGF-α, there are other factors that are produced by keratinocytes and play a role in their proliferation [e.g., the nerve growth factor (NGF)].

In normal skin, maturation of keratinocytes from the base layer to the keratinized layer lasts about 28 days. The final stage of the maturation process is the final differentiation, an apoptotic stage resulting in the creation of a mechanically resistant keratinized layer (37). In addition to IL-22, IL-20 appears to have similar effects because it acts through a similar receptor. Interestingly, TNF-α increases keratinocyte susceptibility to IL-20 (38). In general, IL-20 shows increased expression levels in psoriatic skin, and polymorphisms of a nucleotide in the IL-20 gene are associated with psoriasis (39). IL-22 and IL-20 activate core proliferating and differentiating pathways such as the signal transducers and activators of transcription-3 (STAT-3) pathway in keratinocytes (38).

Mechanotransduction in keratinocytes and psoriasis

Among factors that have been implicated for triggering psoriasis, the application of mechanical stress features prominently. A typical example, widely known as Koebner phenomenon, involves the development of psoriatic plaques in apparently healthy skin following trauma and/or mechanical stress (scratches, abrasion, pressure from tight shoes, shaving, etc.) (13,15).

Physical interactions of keratinocytes and modulation of their properties by mechanical forces is regulated by mechanotransduction, this means the process by which cells sense and convert mechanical cues into intracellular biochemical signals in order to evoke a cellular response. Mechanotransduction has been involved in the regulation of proliferation, differentiation, morphology and migration of keratinocytes, ultimately preserving cellular homeostasis (16). The Koebner effect as a phenomenon has been described in many diseases. According to literature, it appears that in an average of 25% of patients with psoriasis, they will develop psoriatic plaques in apparently healthy tissue after injury, but the trauma may not be recognized or be forgotten (40). The localization of psoriatic plaques can be tested experimentally using specific activating agents to cause psoriatic plaques in subjects with skin sensitivity. These triggering factors do not cause psoriasis but are factors or events that determine the localization of psoriatic plaques (41). Factors that have been implicated to trigger the phenomenon are friction, abrasion, pressure from narrow shoes, shaving, finger sucking, and so on (42). The Koebner effect can be induced in a prone person with a variety of experimental techniques, all of which mainly cause epidermal cell injury and skin inflammation (43).

Mechano-induced signaling pathways in psoriasis

Cells interact with the extracellular matrix and their environment and respond to various stimuli. Air, fluid movement and mechanical pressure are some factors that cells are called upon to recognize and react (*Figure 1*). Mechanotransduction regulates the function of cells, as it

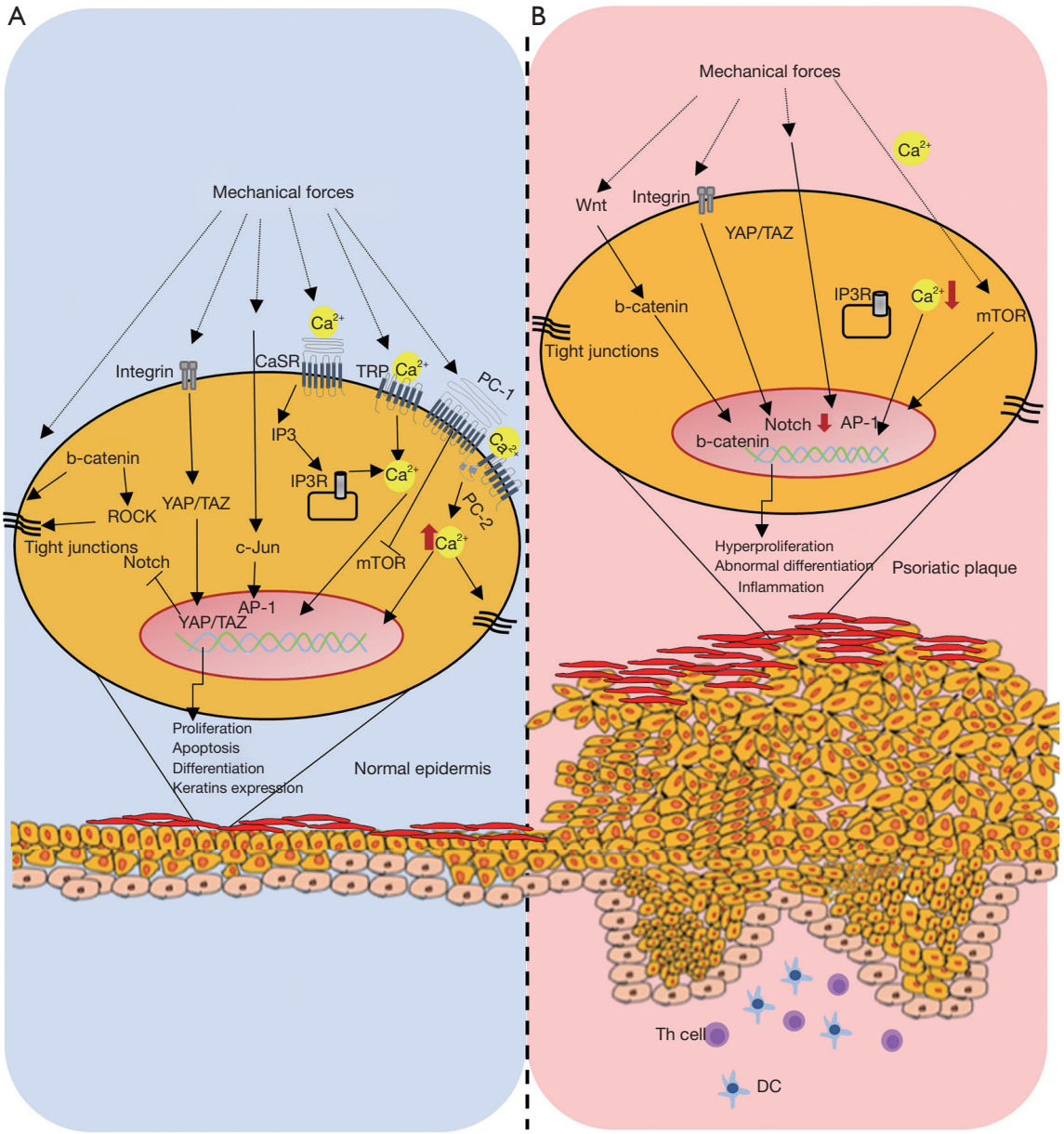

Figure 1 Mechanosignaling in normal keratinocytes and psoriasis. (A) In normal skin, mechanical forces can activate AP-1 (activator protein 1), YAP (Yes-associated protein)/TAZ [transcriptional coactivator with PDZ-binding motif (WWTR1) pathway through integrin-ECM (extracellular matrix) interaction]. They also promote cytoplasmic β-catenin to activate ROCK (Rho-associated protein kinase), therefore supporting the tight junctions (such as E-cadherins), and provoke calcium waves, that are recognized by CaSR (calcium sensing receptor) and TRP (transient receptor potential) channels. This is followed by the proper signaling to promote proliferation of keratinocytes, control of terminal differentiation and expression of keratins. PC1 (polycystin-1) is an important sensor of mechanical forces and operates either by regulating other downstream pathways, such as inactivation of mTOR pathway or in cooperation with the PC2 (polycystin-2) by creating a calcium ion influx channel. (B) In psoriatic plaques, it has been found that mechanical forces activate Wnt pathway and transport of β-catenin into the nucleus, activate Notch pathway and decrease levels of nuclear AP-1. Also, CaSR and TRP channels seem to malfunction or have aberrant expression. As a result, abnormal destruction of tight junctions is observed, abnormal gene regulation and inflammation. In psoriatic plaques, it has been observed decreased expression of PC1, which leads to activation of the mTOR pathway and increase in migration and proliferation of keratinocytes.

is able to control their proliferation, cytoskeleton structure and broader gene expression.

On the epidermis, mechanical stimulation plays a very important role as epidermis is the first tissue that contacts directly with the strongest mechanical forces. Epidermal keratinocytes have developed protective mechanisms to maintain their structure and function after mechanical stimulation. It has been shown that weakness of keratinocyte responsiveness to mechanical stimuli can lead to clamping of adhesive structure (44), resulting in the entry of immune cells into upper layers of the epidermis and their wider aberrant signaling, leading to pathological phenotypes such as psoriasis (45).

Wnt pathway

Catenins are cytoplasmic proteins and can potentially work as transcriptional factors. They also play an important role in the maintenance of normal tissue architecture (46) as cell-to-cell adhesion proteins and by binding to the cytoskeleton and maintain intracellular adhesiveness (47). Beta-catenin (β-catenin) is of central importance in regulating cellular signal transduction through the Wnt pathway and is a crucial mediator of skin development (48). Recent findings suggest that β-catenin regulates self-renewal of interfollicular epidermal stem cells via the Wnt pathway (49). B-catenin seems to mediate mechanotransduction through Rho-associated protein kinase (ROCK) activation that generates collagen production, hyperproliferation of keratinocytes and epidermal stiffness (*Figure 1*) (50). It has been demonstrated *in vivo* that β-catenin protects the epidermis from mechanical stresses by supporting the tight junctions as cell adhesion molecules (51). Several studies which investigated the role of β-catenin in the inhibition of epithelization and wound healing claim that no nuclear β-catenin was detected in normal epidermis (52). Furthermore, it was found that β-catenin was detected only in the cell membrane of the normal epidermis, and not in nucleus (53).

In psoriatic tissue there has been detected increased nuclear β-catenin in suprabasal lesional epidermis (54). The enhanced distribution of β-catenin in the membrane of normal cells compared to the diminished nuclear localization may be due to its role in the establishment and regulation of adherens junctions by interaction with E-cadherin through alpha (α)-catenin with the actin cytoskeleton. Furthermore, it has also been suggested that β-catenin may be translocated from the nucleus back to the cell membrane, presumably through a soluble, cytosolic intermediate state (55).

Yes-associated protein (YAP)/TAZ coactivators

The YAP family and its transcriptional coactivator with PDZ-binding motif (TAZ) function as skin size, tissue overgrowth and stem cell proliferation mediators (56). YAP/TAZ are mechanotransducers and effectors of the Hippo signalling pathway (57). At the canonical Hippo pathway, YAP/TAZ is regulated by several extracellular stimuli including the G-protein-coupled receptors (GPCRs), Wnt signaling, and mechanical forces. They also interact with a plethora of factors such as α-catenin to regulate cellular activities (58).

YAP is activated and transferred to the nucleus during wound healing of the skin in order to activate the differentiation of stem cells by promoting epidermal proliferation and inhibiting terminal differentiation (*Figure 1*) (59-61). *In vitro* models of keratinocytes suggest that mechanical forces act via integrin adhesions and the actin cytoskeleton to induce the nuclear translocation of YAP/TAZ co-activators in order to upregulate cell proliferation (*Figure 1*) (62). A remaining suprabasal integrin expression alongside with expression of terminal, epidermal differentiation markers has been observed in psoriatic lesions (63). Thus, the hyperproliferation of keratinocytes and the failure to downregulate integrin expression during initiation of terminal differentiation can prevent YAP from its translocation into the nucleus and inhibit terminal proliferation. Furthermore, YAP/TAZ have been found inactivated in cells sensing low mechanical forces, in order to orchestrate the loss of stemness and differentiation. This problem is overlapped by Notch signalling, which is a fundamental negative regulator of epidermal stemness and an inducer of terminal differentiation (64). In epidermal progenitors and inside an environment of high tension, YAP/TAZ interact with Notch activators and inhibit them (65). In conclusion, we can assume that continuous increased mechanical stimuli can induce YAP/TAZ to inhibit Notch signaling and promote abnormal phenotype in psoriatic skin (*Figure 1*).

Activator protein-1 (AP-1)

The transcription factor AP-1 participates in the regulation of crucial cellular processes, including proliferation, apoptosis, differentiation, survival and migration (66).

Extracellular stimuli, such as mechanical forces, can activate AP-1 and mediate gene expression (*Figure 1*) (67). The AP-1 family consists of dimeric proteins, which are members of Jun, Fos, and activating transcription factor (ATF) protein families. The AP-1 complex binds to the promoters of specific genes in specific sequences and transactivates or represses them, therefore it has been recognized as regulator of carcinogenesis and inflammation (51,68).

In skin, AP-1 is expressed in keratinocytes and regulates proliferation and differentiation of the epidermis. AP-1 binds to specific DNA-binding sites and induces transcription of keratins, which are important proteins for terminal keratinocyte differentiation (*Figure 1*) (69). Since mechanotransduction is a modulator of skin gene expression, previous research studies showed that AP-1 was upregulated in mechanically stretched skin (70). In psoriasis, Fos/Jun and Jun/AP-1 proteins are downregulated and this leads to increased cell proliferation and deregulated cytokine expression (71). Since mechanical stimuli can activate AP-1 proteins, impaired cell mechanosensing can induce AP-1 inactivation, followed by aberrant inflammation and proliferation status that characterizes the psoriatic plaques (*Figure 1*).

Mechanosensitive receptors and ion channels

It has been reported that applied mechanical forces cause calcium waves in keratinocytes (72). Calcium homeostasis plays important roles in various aspects of epidermal physiology. Maintenance of an intracellular calcium concentration in strictly specific levels is strongly associated with the epidermal barrier homeostasis and differentiation (73). Extracellular calcium is a crucial mediator of differentiation and proliferation of keratinocytes. Mechanical stimuli can induce calcium signaling through various receptors and second messengers. Mechanosensitive ion channels are distributed across the plasma membrane of keratinocytes and sense the changes of calcium followed by the proper signalling (74). Signal transducers, such as GPCRs and ion channels, are the main operators of mechanical-stress-induced calcium signaling.

Calcium sensing receptor (CaSR)

CaSR belongs to the GPCR protein family. The expression of the epidermal *CaSR* gene takes place in the suprabasal keratinocyte layers (75). When extracellular calcium gradient is elevated, calcium ions bind to the extracellular domain of CaSR, which allows this protein to monitor and regulate the concentration of calcium in the blood (76). Via G-protein signaling, the inositol triphosphate (IP3) receptor is generated and binds in the endoplasmic reticulum (ER). IP3 binds to its receptor and causes depletion of calcium internal stores. As a result, concentration of calcium increases in the cytoplasm and through second messages affects gene expression (*Figure 1*) (77).

Studies in transgenic knock-out mouse models for the CaSR gene in keratinocytes showed reduced terminal differentiation (78). Regarding the role of the CaSR on the Wnt/β-catenin signaling pathway, which plays an important role in the regulation of keratinocytes, high extracellular calcium leads to the differentiation of keratinocytes via the activation of the CaSR, which depends on Wnt pathway effectors (79). Defective CaSR can probably lead to defective Wnt signaling and acquisition of psoriatic characteristics in the skin (*Figure 1*).

Apart from its role in calcium signaling, CaSR modulates E-cadherin-mediated cell adhesion in keratinocytes (80). As a result, catenins activate and form the E-cadherin/catenin complex followed by PI3K-dependent activation of downstream calcium effectors, PLC-1 (phospholipase C), IP3 (Inositol-3,4,5-trisphosphate), DAG (diacylglycerol) and STIM (stromal interaction molecules) (81). In psoriatic plaques, cell junctions are altered (82). Aberrant CaSR function may destroy tight junctions and the barriers that they construct and allow inflammatory cells to enter the keratinocyte environment.

Transient receptor potential (TRP) channels

TRP channels constitute a protein family of non-selective ion channels, which display great diversity in activation mechanisms and selectivities. They are activated by a variety of different stimuli and function as signal integrators (83). TRP channels are crucial for cell survival and this explains why there are so many homologs of them in different mammalian species. They are categorized according to sequence similarity into seven groups: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPN, TRPA (ankyrin), TRPP (polycystins), TRPML (mucolipin) (84).

The main role of TRP channels in the skin is to respond to mechanical stimuli and induce calcium signaling through activation of fundamental calcium signaling elements. Therefore it regulates cellular homeostasis, vesicles formation, enzymatic activity and gene expression (84). As a result, TRP channels play a critical role in cellular

homeostasis and growth control, but also in the regulation of keratinocyte fate and survival, immune, and inflammatory mechanisms in the epidermis (*Figure 1*) (85).

TRPVs, TRPA1 and TRPCs are the main subgroups that are expressed in epidermal keratinocytes. TRPV1, TRPV3, TRPV4, TRPV6 belong to the subfamily of TRPVs. TRPV1 is activated and promotes calcium-dependent inhibition of cell proliferation and increases apoptosis (86). Activation of TRPV1 can also lead to expression of proinflammatory cytokine genes and protect the epidermis from inflammation (87). TRPV3 is involved with EGFR signalling pathway and TRPV4 is functionally co-expressed with junctional proteins (e.g., β-catenin and E-cadherin), thus forming the proper epidermal barrier (88,89). TRPV4 and TRPV6 orchestrate the terminal differentiation process of keratinocytes by modulating the expression of keratins and involucrin (90). TRPA1 is a member of the TRPA subfamily in the epidermis. TRPA1 can induce the expression of tight junction proteins in mechanically disrupted epidermis and regenerate epidermal barrier (91).

TRPC1, TRPC4, TRPC5, TRPC6 and TRPC7 are key representatives of TRP channels in epidermal keratinocytes (92). TRPC1, TRPC4, TRPC6 mediate calcium influx and induce terminal differentiation of keratinocytes (93). TRPC4 can, also, stimulate via DAG and enhance calcium entry to the cytoplasm (94). Impaired function of TRCs induces keratinocyte proliferation and increases terminal differentiation. Accumulating evidence suggests that TRPC channels show suppressed expression levels in psoriatic plaques (*Figure 1*) (95).

Polycystins as putative mechano-induced molecules in keratinocytes

Polycystins constitute a subfamily of proteins that have emerged as chief mechanosensors in epithelial cells and. The main representatives of this family are polycystin-1 (PC1) and polycystin-2 (PC2). PC1 is a transmembrane protein with a large, pliable, mechanosensitive N-extracellular end, and a C-terminus that produces transcriptionally active cleavages. PC2 constitutes a non-selective cation channel permeable for Ca^{2+} ions, which belongs to the family of TRP (TRPP) channels (96). Studies generated from our research group revealed that polycystins participate as transcriptional regulators of the expression of osteoblastic genes upon mechanical stimulation, but also during pathogenic mechanisms of different clinical entities such as colorectal cancer and atheromatosis (97-100). It was conceivable to hypothesize that since polycystins regulate mechanotransduction and calcium homeostasis, which in turn have been incriminated in psoriasis pathogenesis, polycystins could get involved in molecular mechanisms responsible for the development of the disease.

Our preliminary data show that keratinocytes demonstrate basic levels of endogenous expression of PC1 and PC2 and that PC1 seems to be downregulated in psoriatic lesions. Advancing further in elucidating a potential molecular mechanism through which PC1 downregulation could be a part of the development of psoriatic plaques, the mammalian target of rapamycin (mTOR) pathway emerges as a powerful link that could mediate PC1 impact on psoriasis pathogenesis. The PI3K/Akt/mTOR pathway has been associated with immunopathogenic mechanisms, hyperplasia of the epidermis and angiogenesis (101). mTOR and its downstream substrates have been found activated in psoriatic lesions and mTOR inhibition attenuates cell proliferation in keratinocytes (102,103). Given our emerging findings showing PC1 downregulation in psoriatic lesions, a potential mechanism that associates PC1 downregulation with mTOR activation in psoriatic lesions and keratinocytes *in vitro* seems appealing in order to be explored (*Figure 1*).

Putative treatment strategies against psoriasis

Current treatments include conventional therapies with adverse effects and a short-term remission of symptoms, but also targeted therapy with monoclonal antibodies and a receptor fusion protein against TNF-α, inhibitors against IL-12/IL-23p40, IL-17, IL-22, IL-23, IL-36, IL-1, type I IFN-γ and small molecules against Janus kinase (JAK) and phosphodiesterase-4 (PDE-4), which show promising results (2,11). Given this fact, targeted therapy seems to be the answer and an area where research is employed to cover unmet needs regarding psoriasis treatment. In this context, mechanobiology and the exploitation of mechanical forces emerge as a novel field that it could be very useful in order to reveal new predictive biomarkers that will assess individual response to treatment and help tailor individual treatment protocols, but also novel molecular targets in order to develop new agents.

Mechanosensing is being thoroughly investigated in carcinogenesis as a field that regulates interactions between cancer cells, extracellular matrix and stromal cells (104). Aberrant tumor mechanosensing has been

strongly associated with resistance to applied treatments (104,105). Such mechanisms are mediated through activation of YAP/TAZ coactivators, which were described previously to be also activated in mechano-induced events in keratinocytes (104,105). Therefore, such mechanisms could be investigated in psoriasis as potential mediators of treatment resistance, but also as novel therapeutic targets. Investigation of mechanotransduction and its impact on the development of the psoriatic plaques may also give rise to novel molecules that may serve as predictive biomarkers or new pharmaceutical targets. In this context, polycystins have been already associated with cancer progression and it would be interesting to decipher their role in keratinocyte aberrant proliferation and psoriasis.

Conclusions

The development of psoriasis upon triggering events such as the Koebner phenomenon implies a decisive impact of mechanical cues on the onset of the disease. However, distorted function of mechanosensitive molecules potentially creates a vicious circle during the development of the disease. The field of mechanobiology and mechanotransduction offers novel routes in order to decipher the molecular mechanisms that accompany the formation of psoriatic lesions, but also reveal signalling networks with diagnostic and therapeutic potential.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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