Review

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Impact of Temperature on Epidermal Homeostasis and Stem Cell Function

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The epidermis, the outermost layer of the skin, is constantly exposed to temperature fluctuations from both external and internal sources, which can disrupt epidermal barrier function and homeostasis. Keratinocyte stem cells in the basal layer of the epidermis are also influenced by these temperature changes. A recent study has demonstrated that changes in the temperature microenvironment modulate intracellular Ca^{2+} levels in cultured human epidermal keratinocyte stem cells via temperature-sensitive transient receptor potential (TRP) channels, which subsequently influence epidermal stemness through the regulation of mechanistic target of rapamycin 1 (mTORC1) signaling. These findings provide new insights into how temperature fluctuations contribute to the dysregulation of epidermal homeostasis and suggest a previously unrecognized mechanism by which thermal stimuli affect skin biology at the cellular level. This review summarizes the effects of temperature on epidermal homeostasis and highlights the roles of temperature-sensitive TRP channels in epidermal keratinocytes, as well as the thermosensitivity of human keratinocyte stem cells. A comprehensive understanding of how epidermal keratinocytes and their stem cells perceive and respond to temperature fluctuations via temperature-sensitive TRP channels is crucial for elucidating the mechanisms underlying epidermal homeostasis and its disruption in conditions such as atopic dermatitis. Furthermore, these insights may inform strategies to mitigate the impact of temperature fluctuations associated with climate change on skin health.

Key words: skin, epidermis, keratinocytes, epidermal homeostasis, barrier function, keratinocyte stem cells, temperature, TRP channels, thermosensitive TRP channels, mTOR, mTORC1, rapamycin

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1. Introduction

Adult stem cells are defined by their ability to self-renew and to give rise to progeny of differentiated/specialized cells.[1)] In response to extracellular signals, adult stem cells can adopt various fates, including remaining quiescent, undergoing differentiation, apoptosis, or division. Cell division occurs in 2 distinct modes: symmetric division, which produces 2 identical daughter cells, and asymmetric division, which generates 2 distinct daughter cells. The fate of stem cells is regulated by signals from their surrounding microenvironment, known as the stem cell niche.[2–4)] There are a variety of stem cell niche components, including cell-to-cell or cell-to-matrix interactions, soluble factors released from local or systemic sources, neural inputs, and physical and chemical factors of the microenvironment. The physical and chemical microenvironment includes mechanical stress, oxygen tension, pH, and temperature. Among them, temperature is involved in a variety of biological processes, for example, sex determination in crocodiles, lizards, and turtles,[5)] maturation and differentiation of immune cells,[6,7)] and spermatogenesis.[8,9)] However, little is known about how temperature affects adult stem cells in human skin.

The epidermis, the outer layer of the skin, is located at the interface between the body and the external environment and functions as a bidirectional barrier that protects the body from external insults and pathogens while also preventing internal fluid loss. The epidermis is a self-renewing stratified epithelium mainly composed of keratinocytes, and its basal layer contains stem cells and progenitor/transiently amplifying cells that produce terminally differentiated progeny.[10)] These differentiating progeny leave the basal layer, migrate to the skin surface, and form the structural barrier of the skin. Anucleated, terminally differentiated cells (corneocytes) are eventually shed from the skin surface. Whereas keratinocyte stem cells in the interfollicular epidermis primarily maintain epidermal homeostasis, the stem cells in the bulge region of hair follicles also contribute to the regeneration of the interfollicular epidermis following injury.[11–13)]

Owing to its location, the epidermis constantly experiences temperature fluctuations from both external and internal sources. Keratinocyte stem cells in the epidermis are exposed to these fluctuations, which influence stem cell dynamics. In this review, we summarize recent advances in understanding the role of temperature in epidermal homeostasis and stem cell regulation.

2. Temperature and Epidermal Homeostasis

2.1. Ambient temperature

Excessively high or low temperatures can cause damage to the skin, but it is also known that changes in ambient temperature affect human skin. Several studies have demonstrated that transepidermal water loss (TEWL), a widely used indicator of epidermal barrier function that increases as barrier function declines, is sensitive to ambient temperature changes.[14)] TEWL increases as the ambient temperature rises from 20°C to 30°C[15)] and decreases as the ambient temperature drops from 32°C to 24°C.[16)] However, how normal skin responds to changes in ambient temperature remains poorly understood. Atopic dermatitis (AD) is a chronic inflammatory skin disease whose onset is associated with epidermal barrier dysfunction.[17)] Numerous studies have shown that changes in ambient temperature contribute to both the onset and exacerbation of AD symptoms.[18)] Recent reports have demonstrated that both low and high ambient temperatures are associated with increased AD-related medical visits,[19,20)] with a more pronounced increase observed at lower temperatures.[18,20)] Furthermore, several studies have reported that children born in the fall and winter have a higher risk for developing AD.[21,22)] Given that AD originates from epidermal barrier dysfunction, temperature changes may also affect the barrier function of normal skin. The mechanisms underlying skin barrier dysfunction under high and low ambient temperatures remain unclear. As discussed below, thermosensitive transient receptor potential (thermoTRP) channels, which are expressed in keratinocytes, immune cells, and nerves, are thought to be key players.[18)]

2.2. Body temperature

Compared with ambient temperature, the human body temperature remains relatively constant. In a diverse cohort of 35488 patients (mean age 52.9 years, 64% women, 41% from non-White individuals), based on 243506 temperature measurements, the mean body temperature was 36.6°C (95% confidence interval: 35.7°C–37.3°C; 99% range: 35.3°C–37.7°C).[23)] Body temperature is regulated by the circadian rhythm and follows a stable 24-h cycle, with a fluctuation of approximately 1°C.[24)] Approximately 2 h before sleep onset, human core temperature begins to decrease due to circadian regulation. In mice, the decline in core temperature is influenced by the light–dark cycle and fluctuates by approximately 2°C during the transition from the active phase (lights off) to the sleep phase (lights on).[25)] We also confirmed that subcutaneous temperature continuously oscillates, with variations ranging from 2°C in rats to 3°C in

mice,[26] by monitoring subcutaneous temperature using an implantable wire sensor.[27] The effect of body temperature fluctuations on epidermal homeostasis remains understudied.

2.3. Skin temperature

At ambient temperatures ranging from 10°C to 30°C, the temperature of unprotected human skin stabilizes within a mean steady-state range of 24°C–33°C.[28] Another study has also shown that human skin temperature increases to approximately 36°C when the ambient temperature is 38°C, while it remains approximately 33°C at an ambient temperature of 26°C.[29] A 4-min exposure to an ambient temperature of −110°C in the whole-body cryotherapy chamber reduced skin temperature to approximately 18°C, and its recovery to baseline levels required more than 60 min.[30] Skin temperature is influenced not only by ambient temperature but also by physiological conditions, such as posture-mediated blood redistribution, which can cause temperature changes ranging from 4°C to 6°C.[31] Human skin temperature may rise above 40°C when exposed to direct infrared radiation. These acute heat shocks promote the formation of new blood vessels, attract inflammatory cells, induce oxidative DNA damage, and contribute to the accumulation of elastic materials in both the epidermis and dermis.[32] Thus, human skin temperature varies considerably in response to external factors (Fig. 1A). While rapid changes in skin temperature trigger acute reactions in the skin, it remains unclear how physiological fluctuations in skin temperature influence epidermal homeostasis and the behavior of keratinocyte stem cells.

3. ThermoTRP Channels and Epidermal Homeostasis

3.1. ThermoTRP channels

TRP channels constitute a superfamily of nonselective cation channels, each composed of 4 subunits that assemble into either homo- or heterotetramers, and play a crucial role in mediating sensory signals, including thermosensation and chemosensation.[33–35] TRP channels are relatively selective for Ca^{2+}; however, their pores permit the nonselective passage of divalent and monovalent cations, including Ca^{2+}, Mg^{2+}, Na^{+}, and K^{+}.[36] The mammalian TRP superfamily comprises 28 members and is divided into 7 subfamilies based on homology: 5 group 1 TRPs (TRPC, TRPV, TRPM, TRPN, and TRPA) and 2 group 2 TRPs (TRPP and TRPML).[37,38] Among these, several TRP channels, including TRPV1, TRPV2, TRPV3, TRPV4, TRPM2, TRPM3, TRPM4, TRPM5, TRPM8, TRPA1, and TRPC5, have been identified as temperature-sensitive and are collectively referred to as thermoTRP channels.[39,40] TRP proteins possess 6 transmembrane domains that form tetrameric, cation-permeable pores. Structural analysis suggests that temperature stimuli induce conformational changes in the protein, leading to pore opening.[41,42] In mammals, the somatosensory system primarily detects changes in ambient temperature, with thermoTRP channels playing a crucial role in thermal transduction at the peripheral terminals of somatosensory neurons.[40] However, several thermoTRP channels are also expressed in epidermal keratinocytes and contribute to epidermal homeostasis[33,43] (Fig. 1B).

3.2. TRPV1

TRPV1 is activated by hot temperatures (>43°C) and capsaicin.[44] Human epidermal keratinocytes express functional TRPV1, and TRPV1-mediated Ca^{2+} influx in cultured human keratinocytes suppresses proliferation and induces apoptosis.[45–48] Activation of TRPV1 by capsaicin and heat (42°C) in the human and mouse skin has been shown to delay barrier recovery after tape stripping.[49] TRPV1 expression was enhanced by ultraviolet (UV) irradiation and aging in human skin,[50] and a study using hairless mice revealed that UV-induced expression of pro-inflammatory cytokines and matrix metalloproteinases was attenuated by a TRPV1-specific inhibitor, 5′-iodoresiniferatoxin.[51] Furthermore, capsaicin-induced activation of TRPV1 in cultured human keratinocytes led to the release of pro-inflammatory cytokines.[47] Recently, it has been demonstrated that TRPV1 mediates the increased expression of pro-inflammatory cytokines and epidermal barrier dysfunction by downregulating epidermal differentiation proteins under low-temperature conditions (25°C and 30°C).[52] These results suggest that TRPV1 activity is involved in the disruption of epidermal homeostasis under both high- and low-temperature conditions.

3.3. TRPV3

TRPV3 is activated by warm temperatures (>30°C–39°C),[53–55] and is predominantly expressed in epidermal keratinocytes rather than in sensory neurons,[53] as well as in the epithelium of hair follicles and outer root sheath keratinocytes.[56] TRPV3 activation decreases proliferation and induces apoptosis in human outer root sheath keratinocytes, leading to suppression of proliferation, induction of apoptosis, and premature hair follicle regression (catagen) in human organ-cultured hair follicles.[56] Studies using TRPV3-null mice have demonstrated impaired epidermal barrier function, curly whiskers, wavy hair, and misaligned hair follicles, which are associated with dysregulation of transforming growth factor-α/epidermal growth factor receptor signaling and of transglutaminase activity.[57] TRPV3 is also involved in the

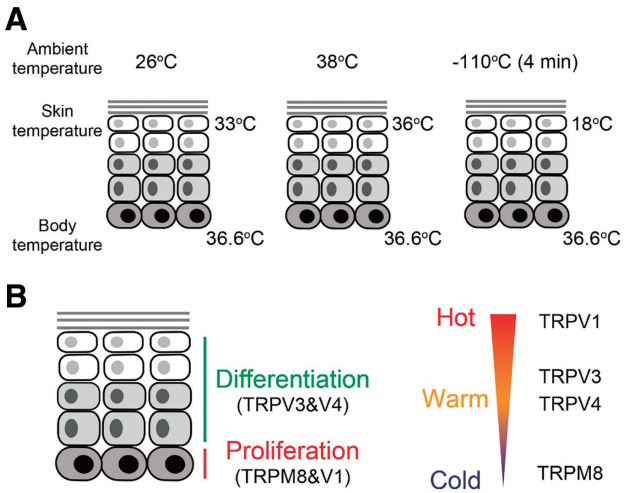

Fig. 1 Temperature-mediated regulation of epidermal homeostasis. (A) The effect of ambient temperature changes on skin temperature. (B) The high-temperature-sensitive receptor TRPV1 and the low-temperature-sensitive receptor TRPM8 play a role in the proliferation of epidermal keratinocytes, while the warm-temperature-sensitive receptors TRPV3 and TRPV4 are involved in keratinocyte differentiation.
TRP, transient receptor potential

differentiation of keratinocytes into corneocytes in the upper stratum granulosum.[58] However, the precise contribution of TRPV3 to cutaneous thermosensation remains unclear.[59,60] Gain-of-function mutations in TRPV3, such as the Gly-573Ser substitution, have been linked to hair abnormalities, AD, spontaneous scratching behavior, and elevated serum cytokine levels, along with mast cell accumulation in the skin.[61,62] TRPV3 mutations have also been identified as the cause of Olmsted syndrome, a rare congenital disorder characterized by palmoplantar and periorificial keratoderma, alopecia in most cases, and severe itching.[63,64] These findings suggest that precise control of TRPV3 activity is required for keratinocyte differentiation, hair growth, barrier formation, and possibly itch sensation.

TRPV3 activity also contributes to wound healing in the skin, cornea, and oral mucosa. Activation of TRPV3 enhances nitric oxide (NO) production, which promotes keratinocyte migration and wound repair in the skin.[65] This NO production is mediated not by NO synthase, but through the proton-driven nitrite-NO pathway, which requires intracellular acidification following TRPV3 activation.[65] In addition, proliferation of corneal and oral keratinocytes, as well as wound healing in these tissues, are accelerated by temperature elevation within the range of 30°C–37°C, effects that are further enhanced by TRPV3 agonist treatment.[66,67]

3.4. TRPV4

In addition to TRPV3, TRPV4 is activated by warm temperatures (>25°C–34°C),[68,69] and is predominantly expressed in epidermal keratinocytes rather than in sensory neurons.[68] TRPV4 activity is involved in the regulation of epidermal barrier function. In mouse keratinocytes, TRPV4 interacts with β-catenin and E-cadherin, which are components of adherens junctions, and also contributes to actin filament dynamics through Rho signaling.[70] TRPV4-deficient mice exhibit increased thickness of the cornified layer and reduced epidermal barrier function, which is thought to result from impaired tight junction formation.[70] Conversely, activation of TRPV4 in human epidermal keratinocytes by physiological skin temperature (33°C) or by TRPV4 agonists (GSK1016790A and 4α-PDD) promotes cell–cell junction formation and enhances barrier function.[71] Furthermore, recovery of the epidermal barrier after tape stripping is accelerated by elevated temperature (33°C) and TRPV4 agonist treatment in both mouse and human skin.[49,71] Studies using keratinocyte-specific TRPV4-deficient mice also have demonstrated that TRPV4 activity contributes to itch sensation in both histaminergic and dry skin itch models.[72,73] The precise contribution of TRPV4 to skin thermosensation needs further study, as is the case for TRPV3.[60,74] These findings suggest that TRPV4 activity is essential for epidermal barrier formation by promoting the maturation of intercellular junctions, as well as for the regulation of itch sensation.

3.5. TRPM8

TRPM8 is activated by cool temperatures (<23°C–28°C) and menthol.[75,76] This mildly cold-sensitive thermoTRP channel is also involved in keratinocyte proliferation and epidermal homeostasis. Topical application of TRPM8 agonists, including menthol and WS-12, accelerated barrier recovery after tape stripping and prevented epidermal

hyperplasia induced by barrier disruption under low-humidity conditions in mice. These effects were attenuated by the TRPM8-specific antagonist BTCT.[77] In humans, full-length TRPM8 is not expressed in epidermal keratinocytes, but an epidermis-specific TRPM8 isoform (eTRPM8) has been identified.[78] This eTRPM8 also functions as a Ca^{2+}-permeable ion channel in response to mild cold stimulation (20°C).[78] eTRPM8-deficient mice exhibited decreased basal cell proliferation and reduced epidermal thickness.[78] These results suggest that TRPM8, a mild cold thermoTRP channel, is involved in epidermal homeostasis through the regulation of basal cells in the epidermis.

4. Temperature and Epidermal Stem Cells

4.1. Thermosensitivity of human epidermal keratinocyte stem cells through thermoTRP channels

The temperature of the basal layer of the epidermis in human skin has not been directly measured. However, keratinocyte stem cells within this layer are believed to be influenced by external temperature changes. Recently, we have elucidated the molecular mechanism by which epidermal stem cells respond to temperature changes and alter their behavior (Fig. 2). Initially, to assess the effect of temperature on cultured human keratinocyte stem cells, colony-forming efficiency (CFE) was evaluated at 4 different temperatures: 35°C, 36°C, 37°C, and 38°C.[26] Temperature did not significantly affect the ability of human keratinocytes to adhere and initiate proliferation, since CFE remained similar across all conditions. However, temperature did influence colony size. The mean colony area increased with temperature, and at lower temperatures (35°C and 36°C), keratinocyte proliferation was reduced, resulting in smaller colonies. Notably, cell size was also significantly smaller at lower temperatures. Cell size is closely associated with the differentiation and proliferative potential of human keratinocytes.[79,80] These findings provide strong evidence that even small variations in temperature can impact the long-term growth and maintenance of human keratinocyte stem cells.

Quantitative PCR analysis confirmed the expression of at least 8 different thermosensitive TRP channel genes in human epidermal keratinocytes, including *TRPV1*, *TRPV2*, *TRPV3*, *TRPV4*, *TRPM4*, *TRPM5*, *TRPM8*, and *TRPA1*. The functional activity of these thermoTRP channels, which are Ca^{2+} permeable, was further examined using Ca^{2+} imaging experiments. Intracellular Ca^{2+} levels decreased when the temperature was rapidly increased from 32°C to 37°C, whereas a significant increase was observed when the temperature was rapidly decreased from 37°C to 32°C.[26] The thermal stimulation-induced changes in intracellular [Ca^{2+}] were suppressed by ruthenium red, a broad-spectrum thermoTRP channel antagonist. Furthermore, the strong Ca^{2+} influx observed following a decrease in temperature was replicated using menthol, an agonist of the mildly cold-sensitive thermoTRP channel TRPM8.[26] These findings confirm that cultured human keratinocytes express functional thermoTRP channels and that modulation of their activity leads to changes in intracellular [Ca^{2+}].

4.2. ThermoTRP channel–mTORC1 signaling axis

Calcium plays a crucial role in various intracellular signaling pathways. Therefore, the possibility was examined that a specific signaling pathway is activated or inhibited by temperature in human keratinocyte stem cells. The mechanistic target of rapamycin (mTOR) signaling axis is essential for stem cell function, regulating growth, proliferation, and survival in response to environmental changes.[81,82] mTOR, a conserved serine/threonine kinase, forms 2 distinct complexes: mechanistic target of rapamycin complex 1 (mTORC1), which promotes the synthesis of proteins, lipids, nucleotides, and ATP, and mTORC2, which regulates the actin cytoskeleton and metabolism.[82] Rapamycin inhibits mTORC1 by binding to FKBP12 and interacting with the FBR domain of mTOR.[83] Although rapamycin primarily affects mTORC1, prolonged exposure may also reduce mTORC2 activity.[84,85] Given that mTORC1 signaling integrates environmental cues such as pH, nutrient availability, and oxygen levels, thereby regulating cell growth and proliferation,[82] it was hypothesized that this pathway might be involved in the keratinocyte stem cell response to thermal stimuli. Moreover, the temperature-dependent regulation of cell size and proliferation in human keratinocytes strongly suggests that mTORC1 signaling plays a role in these processes, given its well-established function in cell size regulation.[86,87]

This notion was confirmed by a decrease in mTORC1 kinase activity, as indicated by reduced phosphorylation levels of S6 kinase 1 following thermal stimulation (a temperature shift from 37°C to 32°C).[26] Furthermore, activation of the mildly cold-sensitive thermoTRP channel TRPM8 by menthol also suppressed mTORC1 activity, whereas an agonist of heat- and warmth-sensitive thermoTRP channels (TRPV1, TRPV2, and TRPV3) enhanced mTORC1 signaling.[26] Additionally, cluster analysis of gene expression revealed that a 1°C difference in temperature impacted global mRNA expression and that the addition of rapamycin to cells cultured at 37°C had a similar effect to that observed at 32°C.[26] These findings suggest that thermoTRP channels are linked to the mTORC1 signaling pathway through Ca^{2+} influx in human epidermal keratinocytes. The TRPV1-mTORC1 and TRPV4-mTORC1 signaling axes through Ca^{2+} influx have also been shown to be involved in muscle hypertrophy[88] and ovarian cancer progression.[89]

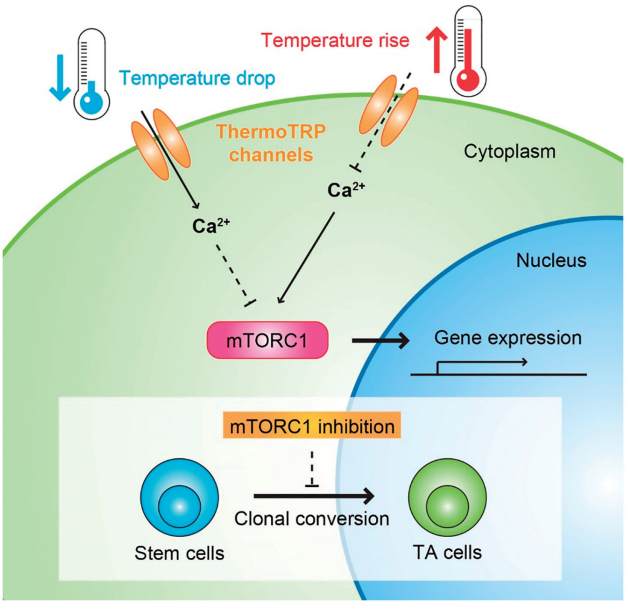

Fig. 2 ThermoTRP channels–mTORC1 signaling axis regulates epidermal stem cells. Temperature-sensitive TRP channels sense the microenvironmental temperature in cultured human epidermal keratinocyte stem cells, leading to an influx of Ca^{2+} into the cells, thereby suppressing mTORC1 signaling. Exposure to low temperatures or treatment with the mTORC1 inhibitor rapamycin promotes the self-renewal of stem cells during continuous culture. In contrast, under high-temperature conditions, such as 38°C, mTORC1 signaling is activated, inducing the differentiation of human epidermal stem cells and ultimately leading to the depletion of stem cells in culture.
mTORC1, mechanistic target of rapamycin complex 1; TRP, transient receptor potential

4.3. mTORC1 signaling in keratinocyte stem cells

Lower temperature and mTORC1 inhibition by rapamycin suppress the spontaneous differentiation of cultured human epidermal keratinocytes.[26] Rapamycin also reduces the proliferation of human keratinocyte stem cells,[90] although it remains unclear whether rapamycin treatment affects the stemness of human epidermal keratinocytes. Cultured human keratinocyte stem cells can spontaneously undergo clonal conversion into cells with restricted growth potential.[91–93] Long-term serial cultivation analysis demonstrated that sustained mTORC1 inhibition by rapamycin maintains the stem cell phenotype by suppressing clonal conversion, while prolonged exposure to rapamycin did not affect the ability of keratinocyte stem cells to generate an epidermis.[26] These findings suggest that mTORC1 inhibition delays clonal conversion in keratinocyte stem cells without compromising their ability to maintain epidermal stemness. mTORC1 signaling plays a crucial role in regulating the behavior of various stem cell populations, including hematopoietic stem cells,[94–96] intestinal stem cells,[97] satellite cells,[98–100] and hair follicle stem cells.[101] Given this, the inhibition of mTORC1 signaling through a cooler environment or rapamycin treatment may contribute to the maintenance of human keratinocyte stem cells as well as other adult stem cell populations.

5. Temperature and Aging

5.1. Hypothermia and longevity

Lowering body temperature extends lifespan in animals, including worms,[102–105] flies,[106] fishes,[107,108] and rodents.[109] Conversely, increasing body temperature by exposing rodents to a hot ambient temperature results in a 0.5°C higher body temperature and shortens lifespan.[110] Interestingly, naked mole-rats (NMRs) are known as long-lived animals,[111] and their body temperature is about 32°C.[112] Fibroblasts isolated from NMRs are also maintained at 32°C, whereas mouse-derived fibroblasts are cultured at 37°C.[113] In humans, a correlation between body temperature and lifespan has also been reported.[114–116] An investigation of oral body temperature across the age spectrum in 18630 individuals clearly demonstrated that mean body temperature decreases with age.[115] There are 2 possible explanations for this negative correlation between body temperature and age: a decline in temperature regulatory mechanisms with aging may result in decreased body temperature, or individuals with lower body temperatures might have lived longer. The latter hypothesis

is supported by the observation that men in the lower half of the distribution for body temperature have greater survival rates than those in the upper half of the distribution.[114] Moreover, the mean body temperature in humans has decreased monotonically by 0.03°C per birth decade in the United States since the Industrial Revolution, which provides a framework for considering a correlation between body temperature and lifespan.[116]

5.2. mTORC1 signaling and aging

Inhibition of TOR signaling also extends lifespan in yeast,[117] worms,[118–121] and flies.[122–124] In rodents, rapamycin[125,126] and hypomorphic mTORC1 signaling[127,128] extend longevity. Aging can be defined as a progressive decline in the homeostatic function of organisms and is characterized by the following 12 features: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis.[129] Among these, mTORC1 signaling is involved in disabled macroautophagy, deregulated nutrient sensing, and stem cell exhaustion.[81,82] Although the relationship between temperature and mTORC1 signaling is not fully understood, temperature might regulate cellular processes and stem cell behavior through the thermoTRP channels–mTORC1 signaling axis.

6. Conclusion

Numerous studies,[26] including ours, have demonstrated that changes in ambient temperature can impact epidermal homeostasis, with epidermal stem cells being directly influenced by such temperature variations. Understanding how epidermal keratinocyte stem cells detect and respond to temperature changes through temperature-sensitive TRP channels is crucial not only for preventing diseases such as AD, which result from disruptions in epidermal homeostasis, but also for maintaining healthy skin conditions. These insights may also inform the development of strategies to address challenges posed by temperature fluctuations resulting from climate change, particularly through the application of cosmetic science.

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Conflict of Interest: None.

Abbreviations: AD, atopic dermatitis; CFE, colony-forming efficiency; eTRPM8, epidermis-specific TRPM8; mTOR, mechanistic target of rapamycin; mTORC1, mechanistic target of rapamycin complex 1; NMR, naked mole-rat; NO, nitric oxide; TEWL, transepidermal water loss; TRP, transient receptor potential; UV, ultraviolet

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