

# Effects of environmental humidity on epidermal physiology

Mitsuhiro Denda<sup>1</sup>

<sup>1</sup> Meiji Institute for Advanced Study of Mathematical Sciences, Nakano Campus, Meiji University, Nakano-ku, Tokyo, Japan  
Corresponding author: Mitsuhiro Denda ([mitsuhirodenda@yahoo.co.jp](mailto:mitsuhirodenda@yahoo.co.jp))

## Abstract

Previous studies have suggested that changes in season and environmental humidity influence skin health. In particular, hairless human skin is directly affected by environmental conditions. For example, a dry environment influences the water-impermeable barrier function of the epidermis. A drastic decrease in environmental humidity induces barrier dysfunction. A dry environment also induces several inflammatory factors, including those from the peripheral immune system, and affects the skin's endocrine system. However, the mechanisms underlying these effects require further investigation through experimental scientific studies. This paper summarizes current findings and offers a new perspective on the effects of environmental humidity on skin health.

**Key words:** Dry, keratinocyte, stratum corneum, cytokine, calcium, ATP, cortisol

## 1. Introduction

The epidermis is the primary interface between the body and the environment. Life first emerged in aquatic environments, and even in terrestrial organisms, internal tissues originated in an aquatic setting. Therefore, establishing a waterproof barrier is essential to preserve bodily functions. Most amphibians inhabit areas near water. The integumentary system of reptiles consists of scales, birds are covered by feathers, and most mammals have hair. However, humans have minimal hair on their skin. As a result, human skin undergoes significant changes in response to environmental humidity.

According to the literature, evidence suggests that cutaneous pathologies, including the severity of atopic dermatitis, are influenced by seasonal variations [1–3]. A decrease in environmental humidity is particularly relevant for managing skin conditions. Conversely, a recent report described the mechanisms underlying the urban dry island effect [4]. In modern urban environments, residents are exposed to ambient humidity levels below the natural range.

In this concise review, I synthesize the literature on the effects of environmental humidity on skin physiology and explore potential mechanisms underlying these effects. Previous studies have shown that temperature also affects the homeostatic function of epidermal keratinocytes [5–8]. In this paper, I focus on the effects of changes in environmental humidity on the epidermis, rather than temperature. The definition of a dry environment varies among the papers discussed. Generally, an absolute humidity of 50% or less is considered dry, but



Subject editor: Peter Wolf  
Received: 15 September 2025  
Accepted: 18 November 2025  
Published: 10 December 2025

Citation: Denda M (2025) Effects of environmental humidity on epidermal physiology. SKINdeep 1: e172072. <https://doi.org/10.1553/skindeep.2025.172072>

Copyright: © Mitsuhiro Denda.  
This is an open access article distributed under terms of the Creative Commons Attribution License (Attribution 4.0 International – CC BY-NC 4.0).

some reports define a humid environment as around 100% and examine the effects of lower humidity in comparison. This article provides definitions as used in each paper.

## **2. Studies on the effects of seasonal changes on skin diseases**

Several studies have examined the impact of seasonal variations on the prevalence of dermatological conditions. Research indicates that the prevalence of skin diseases is influenced by seasonal factors. A previous review noted that people living in countries near the equator, such as in northern Europe and North America, are exposed to harsh winter weather and may experience dry, itchy skin. The authors suggested that low environmental humidity during winter may be a crucial factor [1].

A study at the Children's Hospital of Nanjing Medical University found a correlation between low humidity (relative humidity [RH] < 50%) and high humidity (RH > 80%) and skin allergies. The authors concluded that changes in humidity might be a risk factor for allergic reactions [2].

A study in Helsinki found a seasonal pattern in the prevalence of atopic dermatitis, with increased cases in January, February, March, and November, and decreased cases in July and August. A significant correlation was identified between temperature and UV index; however, no association was found between precipitation and air humidity [3]. The literature suggests a correlation between changes in environmental humidity and the development of skin pathology, as well as various other factors [1,2].

## **3. Animal and epidermal equivalent models and human studies examined the effects of a dry environment**

### **3.1 Dry conditions and barrier function**

A previous study evaluated the effects of environmental humidity on hairless mouse skin barrier homeostasis. The water-impermeable barrier function, epidermal morphology, and lipid content of the stratum corneum were analyzed after mice were exposed to environments with high (RH > 80%) or low (RH < 10%) humidity for two weeks [9]. In a dry environment, basal trans-epidermal water loss decreased compared to levels in a humid environment. For barrier homeostasis, the synthesis and secretion of lipids by lamellar bodies into the extracellular domain are essential steps. The number of lamellar bodies in stratum granulosum cells, the extent of lamellar body exocytosis, and the number of stratum corneum layers increased in animals kept in a dry environment. In a dry environment, both the dry weight of the stratum corneum and the thickness of the epidermis increased. Recovery of the barrier after acetone treatment or tape stripping was accelerated by prolonged prior exposure to a dry environment, while prior exposure to a humid environment delayed the process [9].

Sun et al. demonstrated that dry conditions (50% humidity vs. 100% humidity) enhance barrier function in a human epidermal equivalent model [10]. Under dry conditions, the number of stratum corneum layers, the density of corneodesmosomes in the SC compactum, transepithelial electrical

resistance, expression of glucosylceramide synthase, and filaggrin mRNA all increased. Additionally, the calcium gradient in the epidermis was more pronounced, and the pH value in the stratum corneum was lower in the model under dry conditions. These characteristics more closely resemble those of human skin [10]. Another study using an epidermal equivalent model indicated that the thickness of the stratum corneum and the number of keratohyalin granules increased in a dry environment with a relative humidity of 30% to 50% [11].

These results suggest that a dry environment may enhance barrier function. This phenomenon may indicate an adaptation of the epidermal barrier to environmental conditions. However, the ability of barrier homeostasis to maintain equilibrium in the face of substantial fluctuations in humidity will be discussed in the following section.

Conversely, a recent paper reported that under dry conditions, barrier function decreased in a reconstructed epidermis model system. This may be due to the quality of the reconstructed system, as well as a drastic decrease in humidity, as discussed later [12].

### **3.2 Effects of drastic decrease of humidity**

As previously demonstrated, a drastic decrease in environmental humidity disrupts the barrier function [13]. Hairless mice were initially kept in a humid environment (relative humidity greater than 80%) for two weeks. They were then transferred to a dry environment (relative humidity less than 10%). Within two days of this transfer, a six- to sevenfold increase in transepidermal water loss was observed. This increase returned to normal within seven days. Electron microscopy showed a significant decrease in lamellar bodies in the outermost stratum granulosum and deposition of lamellar body contents at the stratum granulosum–stratum corneum interface after transfer from a humid to a dry environment.

Skin surface conductance in the stratum corneum of hairless mice, 3–7 days after transfer from a humid to a dry environment, was significantly lower than that of mice transferred from a normal environment (relative humidity 40–70%) to a dry one [14,15]. A significant decrease in the free amino acid content of the stratum corneum was observed 24 hours after mice were transferred from normal to dry conditions. The level then recovered, reaching its original value within three days. However, mice transferred from a humid to a dry environment showed a significant decrease in amino acid content even seven days after transfer. No discernible changes in the relative composition of the predominant free amino acid components were observed during the experiments. The immunoreactivity of filaggrin, the primary precursor of free amino acids in the stratum corneum, declined in the epidermis of mice transferred from humid or normal environments to dry environments [15].

These results suggest that a drastic decrease in environmental humidity may induce barrier dysfunction. A previous study showed a significant difference in relative humidity between indoor and outdoor environments in European cities, likely due to the tightly sealed structures of modern architecture [16]. This phenomenon may contribute to the prevalence of dermatological conditions in Western populations.

### 3.3 Inflammatory responses to dry environment

While the impact of dry conditions on barrier homeostasis is not overt, it is possible that they enhance epidermal proliferation and inflammatory responses. As indicated by Denda [17] and Sato [18], exposure to low humidity (<10%) has been shown to increase DNA synthesis in the epidermis of hairless mice. Additionally, exposure to low humidity for 48 hours has been shown to amplify the DNA synthesis response to barrier disruption, resulting in marked epidermal hyperplasia. Exposure to a dry environment for 48 hours prior to barrier disruption also results in dermal mast cell hypertrophy and degranulation, as well as histologic evidence of inflammation [17].

Mice exposed to low humidity conditions (<10%) for two days exhibited more pronounced epidermal proliferation 24 hours after topical application of sodium dodecyl sulfate (SDS) compared to mice maintained under high or normal humidity for the same duration. Conversely, mice exposed to a high-humidity environment for two weeks demonstrated increased epidermal proliferation 24 hours after SDS application compared to those in low or normal humidity environments [19].

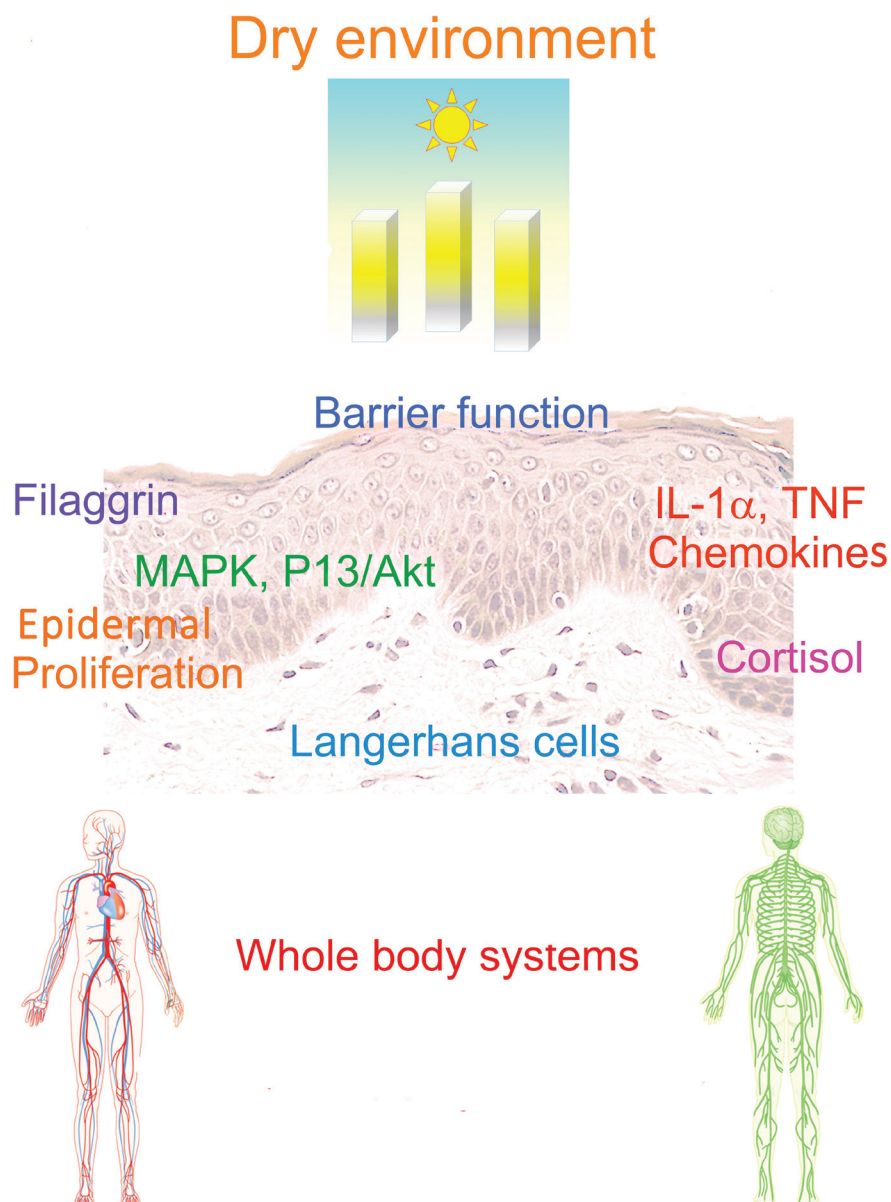
Contact hypersensitivity to 2,4,6-trinitrochlorobenzene was elicited in C57BL/6 mice housed in dry (<10%) or humid (100%) conditions [20]. The reaction was more pronounced in mice housed under low humidity for two days at either the induction or elicitation phase than in those housed under high humidity. After two days of controlled humidity exposure, ear swelling was more evident in mice under low humidity. The number of mouse major histocompatibility complex class II antigen-positive Langerhans cells in the epidermis subjected to dry conditions increased by 16%. The increased population of antigen-positive cells was also found in regional lymph nodes after antibody application during housing under lower humidity [20].

An immunohistochemical study demonstrated that IL-1 $\alpha$  levels in the epidermis were elevated in animals housed in a low-humidity (<10%) environment compared to those in a high-humidity (100%) environment [21]. A significant increase in epidermal IL-1 $\alpha$  mRNA and protein levels was observed in animals subjected to low humidity. Furthermore, IL-1 $\alpha$  release from the skin immediately after tape stripping was significantly higher in animals housed in low humidity than in high humidity [21].

The histamine content in the dermis of mice exposed to low environmental humidity (<10%) for three and five days showed a significant increase compared to levels in mice maintained under high environmental humidity (100%) for the same duration [22]. The number of mast cells in the dermis of mice kept in low humidity was significantly higher than in those kept in high humidity. In addition, topical application of petrolatum has been shown to reduce histamine levels in the dermis of mice in a low-humidity environment [22].

A previous study using an epidermal equivalent model demonstrated that a dry environment (10% relative humidity) induced activation of the MAPK, PI3K/Akt, and TNF signaling pathways, as well as increased expression of the chemokine genes CXCL1, CXCL3, CXCL8, CXCL10, CCL20, and CCL28 [23].

A subsequent investigation revealed that the inflammatory response triggered by environmental pollutants was amplified by arid conditions. The presence of tobacco smoke, metal-rich particulate matter (PM 0.3–2.5), and a mixture of volatile organic compounds has been shown to increase the expression of IL-1 $\alpha$ , IL-6,



**Figure 1.** Environmental dry conditions influence epidermal water-impermeable barrier homeostasis and activate biochemical cascades of epidermal proliferation and inflammatory responses. Moreover, cortisol synthesis is accelerated by dry conditions. These changes might affect whole-body immune and nervous systems.

IL-8, and RANTES in an epidermal equivalent model. This effect was enhanced by a dry environment (RH 45% vs. 90%) [24]. These results suggest a potential link between a dry environment and an increased risk of inflammatory skin reactions.

#### 4. Itch

As previously mentioned, seasonal changes and alterations in humidity can induce itchiness, as seen in atopic dermatitis [1]. A previous report indicated that pruritus associated with atopic dermatitis is attributable to an increase in nerve fibers in the epidermis [25]. However, our previous findings showed that the density of nerve fibers in the epidermis of patients with atopic dermatitis was lower than that observed in healthy controls [26]. A study also demonstrated lower nerve

fiber density in patients with both atopic dermatitis and psoriasis [27]. Therefore, the underlying cause of pruritus in atopic dermatitis and psoriasis may be multifactorial. As reported previously, the release of thymic stromal lymphopoietin (TSLP) from keratinocytes has been shown to induce itch [28].

As previously mentioned, stress from environmental humidity changes induces a series of pathological responses in epidermal keratinocytes. Declines in the water-impermeable barrier function have been observed in atopic dermatitis [29]. Furthermore, a recent review suggested that cytokines released from epidermal keratinocytes and dysfunction of barrier homeostasis induce a series of allergic reactions [30]. To develop an effective new strategy for treating itch in atopic dermatitis and psoriasis, it is necessary to focus on the physiology of keratinocytes.

## 5. Epidermal sensory system

A series of studies have suggested that epidermal keratinocytes might possess a sensory system for humidity; however, the mechanism remains to be elucidated. TRPV4, a known sensor of changes in osmotic pressure [31], could serve as the key humidity sensor in the epidermis. Furthermore, TRPV4 activation and expression have been observed to increase in corneal epithelia following exposure to hypotonic solutions, which simulate dry conditions [32]. As previously demonstrated, topical application of a TRPV4 agonist accelerates barrier recovery following disruption [5]. Consequently, TRPV4 emerges as a promising candidate for the role of a humidity sensor.

We have also demonstrated that exposure of cultured human keratinocytes to air leads to an increase in intracellular calcium concentration and ATP secretion [33]. Evidence has also shown that application of ATP induces IL-6 expression and secretion from cultured human keratinocytes [34]. Another study demonstrated that, following ATP stimulation, IL-1 $\beta$  is released from keratinocytes and may induce inflammation [35]. Current research suggests that ATP plays a crucial role in inflammatory mechanisms induced by environmental factors.

## 6. Skin-brain axis

According to the literature, epidermal keratinocytes have been shown to produce and release various endocrine factors [36,37]. Since the last century, A. Slominski and his colleagues have published a series of papers indicating the presence of endocrinological systems in the epidermis [38–41]. In the context of wound healing, an increase in cortisol synthesis within the epidermis has been observed [42]. These findings prompted further investigation into the impact of a dry environment on cortisol synthesis in epidermal keratinocytes [43]. A skin equivalent model was incubated for 48 hours under two distinct environmental conditions: dry (relative humidity less than 10%) and humid (relative humidity approximately 100%). Subsequently, cortisol secretion and the mRNA levels of the cortisol-synthesizing enzyme steroid 11 $\beta$ -hydroxylase (CYP11B1), as well as IL-1 $\beta$ , were evaluated. Cortisol secretion increased threefold, while CYP11B1 and IL-1 $\beta$  mRNA increased 38-fold and sixfold, respectively, under dry conditions compared to humid conditions. Occlusion with a water-impermeable plastic membrane partially blocked the increases in cortisol secretion and CYP11B1 and IL-1 $\beta$  mRNA expression in the dry condition [43].

In addition, as previously mentioned, environmental dryness has been shown to stimulate the release of various inflammatory cytokines from epidermal keratinocytes [21,23]. Furthermore, oxytocin, a neurohormone that regulates human emotions, is produced by keratinocytes [44]. We previously proposed the hypothesis that these factors may influence the brain and emotional state [45]. Therefore, environmental dryness may not only induce dermatological conditions but also systemic problems, including psychological abnormalities.

## 7. Conclusion

As described above, a decrease in environmental humidity can induce barrier dysfunction and inflammatory responses. Moreover, it might influence whole-body pathology, including psychological problems. Previous reports have indicated that the phenomenon of the “dry island effect” has been documented within metropolitan areas [4]. In addition, a recent proposal [46] has suggested that human skin would undergo significant alterations in water content under spaceflight conditions. *Homo sapiens* are creatures that have demonstrated the ability to persist in the face of environmental changes. This adaptation has enabled humanity to inhabit the entire planet and, in the future, possibly also outer space. However, given the evolutionary history of *Homo sapiens*, which occurred in forest and savanna environments, the species must now adapt to different artificial environments. To prepare for future life, it is imperative to consider epidermal physiology in the context of drastically changing environmental conditions.

## Additional information

### Conflict of interest

The author has declared that no competing interests exist.

### Ethical statements

The author declared that no clinical trials were used in the present study.

The author declared that no experiments on humans or human tissues were performed for the present study.

The author declared that no informed consent was obtained from the humans, donors or donors’ representatives participating in the study.

The author declared that no experiments on animals were performed for the present study.

The author declared that no commercially available immortalised human and animal cell lines were used in the present study.

### Use of AI

InstaText Scholar (Ljubljana, Slovenia) was used for language editing.

### Funding

No funding was reported.

### Author contributions

The author solely contributed to this work.

### Data availability

All of the data that support the findings of this study are available in the main text.

## References

1. Engebretsen KA, Johansen JD, Kezic S, Linneberg A, Thyssen JP. The effect of environmental humidity and temperature on skin barrier function and dermatitis. *J Eur Acad Dermatol Venereol*. 2016;30:223–49. <https://doi.org/10.1111/jdv.13301>
2. Yu S, Bigambo FM, Zhou Z, Mzava SM, Qin H, Gao L, et al. Impact of temperature and relative humidity variability on children's allergic diseases and critical time window identification. *BMC Public Health*. 2024;24:2068. <https://doi.org/10.1186/s12889-024-19573-9>
3. Räisänen E, Remitz A, Salava A. Seasonal Variation of the Burden of Atopic Dermatitis in Finnish Primary Care: A Database Study on Effects of Weather and Air Quality. *Acta Derm Venereol*. 2025;105:adv43041. <https://doi.org/10.2340/act-adv.v105.43041>
4. Huang, X., & Song, J. (2023). Urban moisture and dry islands: spatiotemporal variation patterns and mechanisms of urban air humidity changes across the globe. *Environ Res Lett*. 2023;18:103003. <https://doi.org/10.1088/1748-9326/acf7d7>
5. Denda M, Sokabe T, Fukumi-Tominaga T, Tominaga M. Effects of skin surface temperature on epidermal permeability barrier homeostasis. *J Invest Dermatol*. 2007;127:654–9. <https://doi.org/10.1038/sj.jid.5700590>
6. Denda M, Tsutsumi M, Goto M, Ikeyama K, Denda S. Topical application of TRPA1 agonists and brief cold exposure accelerate skin permeability barrier recovery. *J Invest Dermatol*. 2010;130:1942–5. <https://doi.org/10.1038/jid.2010.32>
7. Tsutsumi M, Denda S, Ikeyama K, Goto M, Denda M. Exposure to low temperature induces elevation of intracellular calcium in cultured human keratinocytes. *J Invest Dermatol*. 2010;130:1945–8. <https://doi.org/10.1038/jid.2010.33>
8. Tsutsumi M, Kumamoto J, Denda M. Intracellular calcium response to high temperature is similar in undifferentiated and differentiated cultured human keratinocytes. *Exp Dermatol*. 2011;20:839–40. <https://doi.org/10.1111/j.1600-0625.2011.01318.x>
9. Denda M, Sato J, Masuda Y, Tsuchiya T, Koyama J, Kuramoto M, et al. Exposure to a dry environment enhances epidermal permeability barrier function. *J Invest Dermatol*. 1998;111:858–63. <https://doi.org/10.1046/j.1523-1747.1998.00333.x>
10. Sun R, Celli A, Crumrine D, Hupe M, Adame LC, Pennypacker SD, et al. Lowered humidity produces human epidermal equivalents with enhanced barrier properties. *Tissue Eng Part C Methods*. 2015;21:15–22. <https://doi.org/10.1089/ten.tec.2014.0065>
11. Cau L, Pendaries V, Lhuillier E, Thompson PR, Serre G, Takahara H, et al. Lowering relative humidity level increases epidermal protein deimination and drives human filaggrin breakdown. *J Dermatol Sci*. 2017;86:106–13. <https://doi.org/10.1016/j.jdermsci.2017.02.280>
12. Izutsu-Matsumoto Y, Okano Y, Masaki H, Tokudome Y, Iwabuchi T. Effect of low humidity on the barrier functions of keratinocytes in a reconstructed human epidermal model. *Int J Cosmet Sci*. 2025;47:523–34. <https://doi.org/10.1111/ics.13048>
13. Sato J, Denda M, Chang S, Elias PM, Feingold KR. Abrupt decreases in environmental humidity induce abnormalities in permeability barrier homeostasis. *J Invest Dermatol*. 2002;119:900–4. <https://doi.org/10.1046/j.1523-1747.2002.00589.x>
14. Sato J, Katagiri C, Nomura J, Denda M. Drastic decrease in environmental humidity decreases water-holding capacity and free amino acid content of the stra-

- tum corneum. *Arch Dermatol Res.* 2001;293:477–80. <https://doi.org/10.1007/s004030100262>
15. Katagiri C, Sato J, Nomura J, Denda M. Changes in environmental humidity affect the water-holding property of the stratum corneum and its free amino acid content, and the expression of filaggrin in the epidermis of hairless mice. *J Dermatol Sci.* 2003;31:29–35. [https://doi.org/10.1016/S0923-1811\(02\)00137-8](https://doi.org/10.1016/S0923-1811(02)00137-8)
  16. Nguyen JL, Dockery DW. Daily indoor-to-outdoor temperature and humidity relationships: a sample across seasons and diverse climatic regions. *Int J Biometeorol.* 2016;60:221–9. <https://doi.org/10.1007/s00484-015-1019-5>
  17. Denda M, Sato J, Tsuchiya T, Elias PM, Feingold KR. Low humidity stimulates epidermal DNA synthesis and amplifies the hyperproliferative response to barrier disruption: implication for seasonal exacerbations of inflammatory dermatoses. *J Invest Dermatol.* 1998;111:873–8. <https://doi.org/10.1046/j.1523-1747.1998.00364.x>
  18. Sato J, Denda M, Ashida Y, Koyama J. Loss of water from the stratum corneum induces epidermal DNA synthesis in hairless mice. *Arch Dermatol Res.* 1998;290:634–7. <https://doi.org/10.1007/s004030050364>
  19. Denda M. Epidermal proliferative response induced by sodium dodecyl sulphate varies with environmental humidity. *Br J Dermatol.* 2001;145:252–7. <https://doi.org/10.1046/j.1365-2133.2001.04342.x>
  20. Hosoi J, Hariya T, Denda M, Tsuchiya T. Regulation of the cutaneous allergic reaction by humidity. *Contact Dermatitis.* 2000;42:81–4. <https://doi.org/10.1034/j.1600-0536.2000.042002081.x>
  21. Ashida Y, Ogo M, Denda M. Epidermal interleukin-1 alpha generation is amplified at low humidity: implications for the pathogenesis of inflammatory dermatoses. *Br J Dermatol.* 2001;144:238–43. <https://doi.org/10.1046/j.1365-2133.2001.04007.x>
  22. Ashida Y, Denda M. Dry environment increases mast cell number and histamine content in dermis in hairless mice. *Br J Dermatol.* 2003;149:240–7. <https://doi.org/10.1046/j.1365-2133.2003.05408.x>
  23. Shinohara K, Hara-Chikuma M. Low humidity altered the gene expression profile of keratinocytes in a three-dimensional skin model. *Mol Biol Rep.* 2022;49:7465–74. <https://doi.org/10.1007/s11033-022-07549-0>
  24. Seurat E, Verdin A, Cazier F, Courcot D, Fitoussi R, Vié K, et al. Influence of the environmental relative humidity on the inflammatory response of skin model after exposure to various environmental pollutants. *Environ Res.* 2021;196:110350. <https://doi.org/10.1016/j.envres.2020.110350>
  25. Tominaga M, Tenggara S, Kamo A, Ogawa H, Takamori K. Psoralen-ultraviolet A therapy alters epidermal Sema3A and NGF levels and modulates epidermal innervation in atopic dermatitis. *J Dermatol Sci.* 2009;55:40–6. <https://doi.org/10.1016/j.jdermsci.2009.03.007>
  26. Tsutsumi M, Kitahata H, Fukuda M, Kumamoto J, Goto M, Denda S, et al. Numerical and comparative three-dimensional structural analysis of peripheral nerve fibres in epidermis of patients with atopic dermatitis. *Br J Dermatol.* 2016;174:191–4. <https://doi.org/10.1111/bjd.13974>
  27. Tan Y, Ng WJ, Lee SZX, Lee BTK, Nattkemper LA, Yosipovitch G, et al. 3-Dimensional Optical Clearing and Imaging of Pruritic Atopic Dermatitis and Psoriasis Skin Reveals Downregulation of Epidermal Innervation. *J Invest Dermatol.* 2019;139:1201–4. <https://doi.org/10.1016/j.jid.2018.11.006>

28. Wilson SR, Thé L, Batia LM, Beattie K, Katibah GE, McClain SP, et al. The epithelial cell-derived atopic dermatitis cytokine TSLP activates neurons to induce itch. *Cell*. 2013;155:285–95. <https://doi.org/10.1016/j.cell.2013.08.057>
29. Berardesca E, Fideli D, Borroni G, Rabbiosi G, Maibach H. In vivo hydration and water-retention capacity of stratum corneum in clinically uninvolved skin in atopic and psoriatic patients. *Acta Derm Venereol*. 1990;70:400–4. <https://doi.org/10.2340/0001555570400404>
30. Ogulur I, Mitamura Y, Yazici D, Pat Y, Ardicli S, Li M, et al. Type 2 immunity in allergic diseases. *Cell Mol Immunol*. 2025;22:211–42. <https://doi.org/10.1038/s41423-025-01261-2>
31. Galindo-Villegas, J., Montalban-Arques, A., Liarte, S., de Oliveira, S., Pardo-Pastor, C., Rubio-Moscardo, F., et al. TRPV4-mediated detection of hyposmotic stress by skin keratinocytes activates developmental immunity. *J Immunol*. 2016;196:738–749. <https://doi.org/10.4049/jimmunol.1501729>
32. Lapajne, L., Lakk, M., Yarishkin, O., Gubeljak, L., Hawlina, M., and Krizaj, D. Polymodal sensory transduction in mouse corneal epithelial cells. *Invest Ophthalmol Vis Sci*. 2020;61:2. <https://doi.org/10.1167/iovs.61.4.2>
33. Denda M, Denda S. Air-exposed keratinocytes exhibited intracellular calcium oscillation. *Skin Res Technol*. 2007;13:195–201. <https://doi.org/10.1111/j.1600-0846.2007.00210.x>
34. Inoue K, Hosoi J, Denda M. Extracellular ATP has stimulatory effects on the expression and release of IL-6 via purinergic receptors in normal human epidermal keratinocytes. *J Invest Dermatol*. 2007;127:362–71. <https://doi.org/10.1038/sj.jid.5700526>
35. Burnstock, G., Knight, G. E. The potential of P2X7 receptors as a therapeutic target, including inflammation and tumour progression. *Purinergic Signal*. 2018;14:1–18. <https://doi.org/10.1007/s11302-017-9593-0>
36. Denda M, Nakanishi S. Do epidermal keratinocytes have sensory and information processing systems? *Exp Dermatol*. 2022;31:459–474. <https://doi.org/10.1111/exd.14494>
37. Denda M, Elias PM. Review of sensory systems deployed by epidermal keratinocytes. *Front Cell Dev Biol*. 2025;13:1598326. <https://doi.org/10.3389/fcell.2025.1598326>
38. Slominski AT, Zmijewski MA, Zbytek B, Tobin DJ, Theoharides TC, Rivier J. Key role of CRF in the skin stress response system. *Endocr Rev*. 2013;34:827–84. <https://doi.org/10.1210/er.2012-1092>
39. Slominski RM, Raman C, Elmets C, Jetten AM, Slominski AT, Tuckey RC. The significance of CYP11A1 expression in skin physiology and pathology. *Mol Cell Endocrinol*. 2021;530:111238. <https://doi.org/10.1016/j.mce.2021.111238>
40. Slominski AT, Li W, Kim TK, Semak I, Wang J, Zjawiony JK, Tuckey RC. Novel activities of CYP11A1 and their potential physiological significance. *J Steroid Biochem Mol Biol*. 2015;151:25–37. <https://doi.org/10.1016/j.jsbmb.2014.11.010>
41. Slominski, R. M., Raman, C., Jetten, A. M., and Slominski, A. T. Neuroimmuno-endocrinology of the skin: how environment regulates body homeostasis. *Nat Rev Endocrinol*. 2025;21:495–509. <https://doi.org/10.1038/s41574-025-01107-x>
42. Vukelic S, Stojadinovic O, Pastar I, Rabach M, Krzyzanowska A, Lebrun E, et al. Cortisol synthesis in epidermis is induced by IL-1 and tissue injury. *J Biol Chem*. 2011;286:10265–75. <https://doi.org/10.1074/jbc.M110.188268>

43. Takei K, Denda S, Kumamoto J, Denda M. Low environmental humidity induces synthesis and release of cortisol in an epidermal organotypic culture system. *Exp Dermatol*. 2013;22:662–4. <https://doi.org/10.1111/exd.12224>
44. Denda S, Takei K, Kumamoto J, Goto M, Tsutsumi M, Denda M. Oxytocin is expressed in epidermal keratinocytes and released upon stimulation with adenosine 5'-[γ-thio]triphosphate in vitro. *Exp Dermatol*. 2012;21:535–7. <https://doi.org/10.1111/j.1600-0625.2012.01507.x>
45. Denda M, Takei K, Denda S. How does epidermal pathology interact with mental state? *Med Hypotheses*. 2013;80:194–6. <https://doi.org/10.1016/j.mehy.2012.11.027>
46. Denda M. Epidermal Homeostasis in Space from the Stand Point of Keratinocyte Physiology. *Skin Pharmacol Physiol*. 2025;15:1–11. <https://doi.org/10.1159/000547984>