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Review

The impact of temperature on the skin barrier and atopic dermatitis

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Key Messages

- Climate change is a real threat to public health in all countries and causes or worsens various diseases including allergic diseases.
- Children born in the colder seasons of fall and winter have a higher risk of developing atopic dermatitis (AD) and the atopic march.
- Cold and low temperatures induce the production of proinflammatory cytokines, deficiency of epidermal barrier proteins, and skin barrier dysfunction in a TRPV1-dependent manner.
- Increased temperature induces the production of proinflammatory cytokines and pruritus and exacerbates AD through TRPV 1, 3, and 4.
- TRPV antagonists alleviate warm temperature and heat-induced skin barrier dysfunction and AD symptoms and signs.

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ABSTRACT

Climate change is a global threat to public health and causes or worsens various diseases including atopic dermatitis (AD), allergic, infectious, cardiovascular diseases, physical injuries, and mental disorders. The incidence of allergy, such as AD, has increased over the past several decades, and environmental factors such as climate change have been implicated as a potential mechanism. A substantial amount of literature has been published on the impact of climate factors, including cold and hot temperatures, on the skin barrier and AD. Studies in several countries have found a greater incidence of AD in children born in the colder seasons of fall and winter. The effect of cold and warm temperatures on itch, skin flares, increased outpatient visits, skin barrier dysfunction, development of AD, and asthma exacerbations have been reported. Understanding mechanisms by which changes in temperature influence allergies is critical to the development of measures for the prevention and treatment of allergic disorders, such as AD and asthma. Low and high temperatures induce the production of proinflammatory cytokines and lipid mediators such as interleukin-1β, thymic stromal lymphopoietin, and prostaglandin E2, and cause itch and flares by activation of TRPVs such as TRPV1, TRPV3, and TRPV4. TRPV antagonists may attenuate temperature-mediated itch, skin barrier dysfunction, and exacerbation of AD.

Introduction

Climate change is a real threat to public health in all countries.[1,2] It contributes to various health conditions including allergic, infectious, cardiovascular diseases, physical injuries related to severe weather events, and mental disorders (Fig 1).[1,3–5] Climate change, together with other natural and human-made health stressors, has been at the forefront of the scientific community interests, including the studies of temperature changes or temperature fluctuations, since weather patterns have shifted largely because of human activities. It has led to not only warmer summers with droughts and fires but also extreme winter weather with increased snow and cold waves.[6] According to the US Environmental Protection Agency, there are certain populations in the US, such as children, black, and indigenous communities, that are particularly vulnerable to the effects of climate change and other environmental hazards.[3,7,8] From a broader perspective, there are public health consequences for the overall transformations in biodiversity, given that these may contribute to increased allergic conditions as our ecosystems are changing.[1,3,6]

The incidence of allergy, such as atopic dermatitis (AD), has increased over the past several decades, and environmental factors such as climate change have been implicated as a potential

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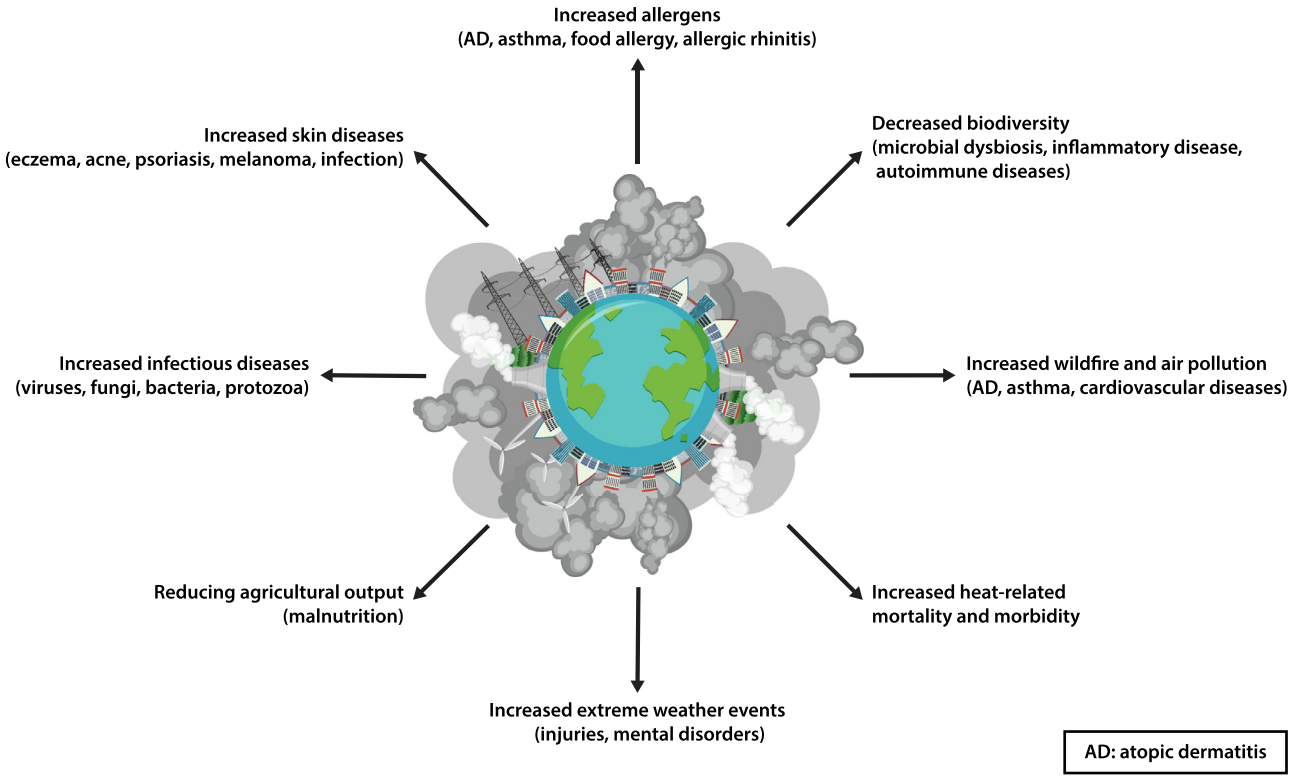

Figure 1. The effects of climate change on human health. AD, atopic dermatitis.

mechanism.[1,3] Eczema is a general term for a group of conditions that cause skin irritation and inflammation. There are many different types of eczema, and atopic dermatitis (AD) is the most common type of eczema. The studies we reference use both AD and eczema as terms to describe skin manifestations. In this review, definitions of eczema and AD are noted accordingly per each study where relevant. We used the term AD according to the definition criteria (Hannifin and Rajka) in this review.[9] AD is a chronic inflammatory skin disease that has become a global health concern affecting individuals of all ages.[10] In the United States, the prevalence of AD in children has increased to 20%, with 7.3% of adults affected.[11,12] A family history of allergic disease and filaggrin mutations are strongly associated with the development and pathogenesis of AD.[13,14] However, the incidence of allergy has increased at a rate that cannot be explained solely by genetics. Changes in the environment must be considered. Climate change has a multitude of effects on the skin, as it modifies skin exposures to ultraviolet (UV) radiation and environmental pollutants, compounding the effects of sun exposure with increased oxidative stress in the skin, premature skin aging, and barrier abnormalities.[1,3,15] UV radiation causes oxidative stress by induction of cyclooxygenase-2 through activation of p38 mitogen–activated protein kinase and phosphoinositide 3 kinase in the skin, leading to photoaging and cancer.[16,17] Moreover, a substantial amount of literature has recently been published on the impact of climate factors, including cold and hot temperatures, low, and high humidity, pollution, and changes in vegetation and allergen production, on the skin barrier, and AD.[18–23] Collectively, these events dramatically impact AD pathogenesis. Temperature is only one factor embodied in climate change, and other factors involved may also affect skin barrier function, skin inflammation, and aggravated skin barrier.[7,23] The association of cold and hot temperatures on skin barrier function, AD prevalence, skin irritability, itch, and AD skin severity have been noted in various studies.[4,7,20,24] Understanding how temperature change influences allergies is critical to the development of measures for the prevention and treatment of allergic disorders.[1,25] Therefore, this review highlights these studies as they relate to AD, along with discussions on potential mechanisms for how temperature contributes to skin barrier dysfunction and allergy development.

Effects of Low Temperature on Skin Barrier and Atopic Dermatitis

The skin is the first organ to respond to climatic insults. The low outdoor temperature has been reported to be associated with an increased prevalence of AD.[20,24,26] In the International Study of Asthma and Allergies in Childhood (ISAAC), an epidemiologic approach was used to understand asthma, rhinitis, and AD, given the increase of these conditions worldwide. Children ages 6 to 7 years and 13 to 14 years old were studied at multiple sites in more than 100 countries.[26] In Western Europe, climate conditions, including daily temperature values, were obtained.[24] ISAAC questionnaire assessed for AD presence by asking whether the child had “an itchy rash which was coming and going for at least 6 months,” whether the child had this rash in the past 12 months, and whether the rash affected “the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, and around the neck, ears, or eyes.” In both age categories, the prevalence of AD symptoms increased with lower mean annual outdoor temperature. In the 10 centers in Spain participating in the ISAAC, the lower outdoor temperature was associated with AD in 6 to 7 year olds.[20] In the United States, a study evaluating children 0 to 17 years old found that the prevalence of AD was lower in those who resided in the states with the highest quartile mean annual temperatures compared with the lowest quartile.[27]. States in the highest quartile mean temperature had a lower prevalence of AD in all seasons except the fall. The prevalence of AD was determined by asking participants whether a health professional diagnosed the child with eczema or a skin allergy.

Several studies highlighted the association of AD risk with the season of birth. Studies in several countries have reported a greater incidence of AD in children born in the colder seasons of fall and

winter.[28–31] A meta-analysis evaluating European and Asian studies in the Northern Hemisphere found that children born in the fall and winter had an increased risk of developing AD compared with the spring and summer.[30] There were 9 studies assessed, in which 6 used questionnaires to assess AD diagnosis whereas 3 were on the basis of physician examinations. Two studies in Denmark, a birth cohort study asking parents whether their child had physician-diagnosed AD, and a registry study using a clinical database, also saw an increased risk of AD in fall and winter births.[31,32] In Korea, a questionnaire-based study using the ISAAC questions in children 6 to 13 years old revealed that the prevalence of AD was higher in the children born in winter than in those born in summer.[33] In Japan, 3 studies—a birth cohort study, a questionnaire-based study in children 7 to 15 years old, and another questionnaire-based study in children 6 to 12 years old using the ISAAC core questions—all found that children born in the fall had the highest AD prevalence.[34–36] In the US, a study using nationwide Medicaid claims data in children 0 to 18 years old revealed higher odds of AD in those born in the fall,[37] and a study using electronic medical record diagnoses in children 0 to 5 years old also saw an increased risk of AD in fall births.[29]

Studies have noted the effects of low temperature on skin irritability, severity, and AD flares. Gerner et al[38] reported that the 3 most typically reported trigger factors for AD among Danish children were cold weather (51.9%), chlorinated water (35.7%), and warm weather (30.2%). Pfab et al[39] stimulated the skin with histamine and then alternatively exposed the skin to cold (25°C) and warm (32°C) temperatures for up to 12 minutes. They noticed that short-term cold temperature (25°C) exposure intensified histamine-induced itch in patients with AD. The mean itch intensity was perceived as more intense in lesional skin compared with nonlesional or healthy control skin. People in Denver, Colorado have more clinical signs of dry skin, scaling, and flakiness.[40] This feature was postulated to be from the damaging effects of the cold in Denver. Furthermore, it has been reported that low temperature enhances skin irritability. Uter et al[41] found that there was a substantial association of existing hand dermatitis with low temperature using logistic regression analysis (odds ratio [OR] = 1.66).

Other researchers have studied the influence of weather and climate on the subjective symptom intensity perception of AD. Kramer et al[42] investigated the influence of temperature on AD symptoms among children under 6 years old and found that children with winter-type AD seemed to be more sensitive to deviations in temperature. Agner et al[43] found that the hydration state of the epidermis was decreased during winter, and the response of skin to irritant application in winter was stronger than in summer in healthy volunteers. Vocks et al[44] reported, by means of univariate analyses and multiple regressions, that itch intensity was found to be correlated with cold temperature. In addition, they noticed that an inverse correlation exists between the air temperature and pruritus intensity (coefficient of correlation: −0.235, $P < .001$). Langan et al[45] also reported that cold weather enhances shampoo-associated skin flares. Chan et al[46] found that symptom score was higher during winter, and the OR of flares was 1.15 ($P = .14$; 95% confidence interval [CI], 0.96-1.39) in cold weeks in patients with AD. These reports suggest that itching and flares in AD are significantly dependent on meteorologic conditions.

Beyond descriptions of increased AD prevalence in the colder months of the year, there are several observations addressing the mechanisms that cause skin barrier dysfunction. Understanding the mechanisms by which low temperature affects the skin barrier is also important because this can direct preventive measures. Transient receptor potential (TRP) channels are expressed in a wide variety of cells including keratinocytes, immune cells, and nerves.[47,48] Activation of TRP channels generally promotes Ca^{2+} influx into cells such as keratinocytes.[47,48] Various TRP channels participate in maintaining skin barrier and homeostasis.[47,48] TRP vanilloid ion channels (TRPVs) have been implicated in temperature sensing by neuronal endings and epithelial cells in the skin.[49–51] It is supposed that the activity of TRPVs is regulated by lipid molecules such as phosphoinositides, glycerophospholipids, and sterols.[52] TRPV1 receptors are expressed on nociceptive afferent nerve fibers and epithelial cells and are activated by polymodal stimuli such as capsaicin, low pH, and temperature.[52] These channels regulate the transmembrane influx of cations into cells.[50] It has been reported that low temperature induces proinflammatory cytokines such as interleukin (IL)-1β, thymic stromal lymphopoietin (TSLP), and tumor necrosis factor (TNF)−alpha and causes epidermal barrier protein deficiency and skin barrier dysfunction consequently. More importantly, this event was found to be TRPV1 dependent (Fig 2).[53]

Effects of Increased Temperature on Skin Barrier and Atopic Dermatitis

Although most studies have reported an increased prevalence of AD in cold temperatures, there have also been studies reporting skin barrier dysfunction and AD after exposure to increased temperature. A study in Korea using insurance claims for more than a 9-year period found that AD was most prevalent in late spring through summer (May-September).[54] Beyond prevalence reports, a prospective study analyzing data from the Pediatric Eczema Elective Registry, a US cohort study of children enrolled over an 8-year period found that higher temperature corresponded with poorly controlled AD.[55] It has been reported that increased temperatures and associated heat stress can increase mortality and morbidity.[1,2] The first descriptions linking heat to inflammation were by Celsus in ancient Rome (30-38 B.C.) postulating heat to be a critical factor causing inflammation by increasing blood flow to local tissue sites.[56,57] To date it has been noted that human-caused factors leading to climate change, such as global warming, and increased pollution, impact allergic diseases including AD.[4,7,25]

Transepidermal water loss (TEWL) is the most widely used objective method for assessing skin integrity, skin barrier function, and severity of skin disease.[58,59] Under conditions of temperature variation, the range of TEWL is far greater in pathologic skin than in normal skin and correlates with temperature changes.[60] It has been reported that TEWL at the forehead is increased during summer.[61,62] In contrast, other researchers have reported that TEWL at the forehead and the cheek is higher during spring and winter compared with summer and fall.[15,63] The results of seasonal TEWL are still controversial. There are several reports that elevated temperature has been associated with increased outpatient visits in patients with AD. Increased temperatures (>25.3°C) and summer are associated with increased flare and AD outpatient visits.[54,64,65] In the South, the hottest US climate zone, summer, is responsible for substantially more AD clinical visits.[64] Another study also found that increased temperatures are associated with increased risk of outpatient visits, particularly of female children less than 14 years of age.[66] In addition, a multivariate logistic regression analysis revealed that higher temperature (OR = 0.90; 95% CI, 0.87-0.93, $P < .001$) and increased sun exposure (OR = 0.93; 95% CI, 0.89-0.98, $P = .009$) were associated with poorly controlled AD in children under 18 years of age with a physician diagnosis of AD.[55]

High temperature and heat are strong triggers of itching in patients with AD.[67,68] Heat and sweating are common aggravating factors of AD.[69] Langan et al[70] reported that hot weather is strongly associated with an increased scratch score in patients with AD. Heat intolerance and excessive sweating, even in Nigeria, Africa, typically exacerbate AD symptoms, such as itching.[71] A case-controlled study reported that there is a significant association between the prevalence of AD and the use of radiators for heating children's bedrooms (OR = 1.50; 95% CI, 1.05-2.16).[67] These results suggest that the temperature of the home environment could be an important factor that contributes to AD flares.

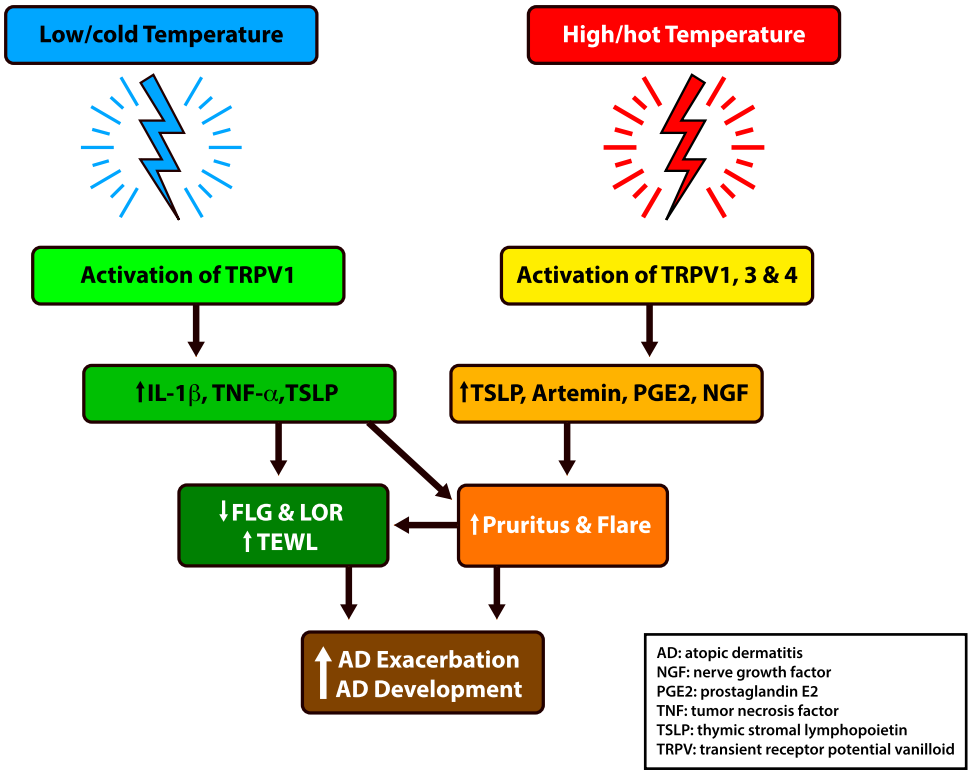

Figure 2. The effects of temperature on skin barrier and atopic dermatitis. AD, atopic dermatitis; FLG, filaggrin; IL, interleukin; LOR, loricrin; NGF, nerve growth factor; PGE2, prostaglandin E2; TEWL, transepidermal water loss; TNF, tumor necrosis factor; TRPV, transient receptor potential vanilloid.

The itching sensation is aggravated by warm or hot temperatures.[67,68] Previously, it has been reported that thermosensitive TRP channels are associated with itching sensation.[48] However, it is not fully understood how hot or warm temperatures induce pruritus in AD skin. Hot temperature and heat activate TRPVs such as TRPV1, TRPV3, and TRPV4 (Fig 2).[72–74]. Yun et al[75] reported that a TRPV1 antagonist (PAC-14028) inhibits capsaicin-induced Ca^{2+} influx in keratinocytes and attenuates capsaicin-induced blood perfusion in the skin. In addition, the study found that PAC-14028 accelerates skin barrier recovery from skin tape-stripping-induced barrier damage in hairless mice.[75] Moreover, PAC-14028 alleviated AD-like symptoms, including serum immunoglobulin E increase, mast cell degranulation, scratching behavior, and clinical severity of dermatitis in hairless mice.[75,76] Recently, Park et al[77] reported that topical application of a TRPV1 antagonist, Asivatrep, improved clinical signs, and symptoms of mild to moderate AD. TRPV3 is highly expressed in AD skin and is activated by heat.[78,79] Researchers have reported that heat stimulation induces the production of keratinocyte-derived pruritogens such as TSLP, nerve growth factor, prostaglandin E2, and artemin from AD keratinocytes, and these events require TRPV3 activation (Fig 2). In addition, it was reported that neutralizing TSLP mitigates heat-induced scratching in a mouse AD model. Therefore, heat-induced TSLP by means of TRPV3 may play an important role in inducing pruritus in AD skin.[79] This report is important because TSLP beyond being one of the key pruritogens, as an alarmin is involved in promoting the atopic march as it promotes skin allergic inflammation and the systemic allergen-induced T helper type 2 response.[80–82] Moreover, recently it has been found that a TRPV3 inhibitor, Trpvicin, inhibits itch in mouse models.[83] Several pharmaceutical companies are now developing TRPV3 antagonists to control pain and pruritus.[84] It was also noted that sunburn and UV overexposure activate the TRPV4 channel, which leads to Ca^{2+} influx into keratinocytes, resulting in skin pain, and epidermal damage.[85] A TRPV4 inhibitor, GSK205, reduced tissue damage, and pain caused by UV exposure.[85] Moreover, Sanders et al[86] reported that local thermal stimulation of the skin substantially increased serotonin-evoked scratching in a mouse model of AD, and the itch was attenuated by a TRPV4 antagonist (GSK205).

It is important to note that changes in humidity often occur with temperature changes, and both low and high humidity can worsen the skin barrier. It has been reported that low humidity is damaging to the epidermal structure and causes skin inflammation.[18,19] On the other hand, high humidity can cause increased sweating and irritation, leading to skin flares.[20] In the ISAAC study in Spain and Mexico, AD symptoms positively correlated with increased outdoor humidity.[20,21] Whereas in another ISAAC publication, lower indoor humidity was associated with increased AD.[24] Whereas both outdoor and indoor humidity can impact the skin barrier, this review only focuses on temperature effects.

The Effects of Temperature Fluctuation on Asthma and Other Allergic Diseases

Increased temperature because of global warming results in earlier flowering and increased pollen load and pollen season duration.[87,88] Increased production of pollen allergens promotes allergic diseases, including asthma, allergic rhinitis, and allergic conjunctivitis.[89–91] More than 100 epidemiologic studies were analyzed to assess the adverse effects of extreme temperature on asthma attacks.[92–94] They concluded that both extreme heat and cold could substantially increase the risk of asthma exacerbation and allergic diseases. Schinasi et al[95] reported that hot ambient temperature is associated with higher rates of asthma exacerbation in children. Fang et al[96] reported that cumulative relative risks for extremely cold temperature (−6°C) were 2.06 (95% CI, 1.27-3.34) for allergic rhinitis and 4.02 (95% CI, 2.14-7.55) for asthma, whereas the associations between extreme hot temperature (29°C) and respiratory hospital visits were not significant.[96] Other studies have reported that ambient temperature fluctuation is significantly associated with asthma hospitalization and allergic rhinitis exacerbation.[97-100]

Table 1
Profiles of TRPV Antagonists Related to Skin and Atopic Dermatitis

Temperature	TRPV blocker	Agent	Effects	Model	Reference
Cold/low	TRPV1 antagonist	TRPV1 silencing RNA	Prevents low temperature-mediated skin barrier dysfunction	Organotypic skin culture	Kim et al,[53] 2022
Neutral	TRPV1 antagonist	PAC-14028	Alleviates AD-like symptoms	Mouse	Yun et al,[75] 2011; Lee et al,[76] 2018
Neutral	TRPV1 antagonist	Asivatrep	Improves clinical signs and symptoms of AD	Human	Park et al,[77] 2022
High/hot	TRPV3 inhibitor	Trpvicin	Inhibits itch	Mouse	Fan et al,[83] 2023
High/hot	TRPV4 inhibitor	GSK205	Prevents sunburn and UV-related skin pain and epidermal damage	mouse	Moore et al,[85] 2023
High/hot	TRPV4 antagonist	GSK205	Attenuates serotonin-evoked itch	mouse	Sanders et al,[86] 2018

Abbreviations: AD, atopic dermatitis; UV, ultraviolet radiation.

Deng et al[101] reported that both cold and heat exposure increase proinflammatory cytokine release in a mouse model of asthma. Immunologic inflammatory pathways and TRP ion channels are potential mechanisms behind extreme temperatures and asthma exacerbations.[101–103] It was found that exercise during cold air exposure (−15°C) induced signs of airway constriction and increased plasma cytokines such as CCL16 and IL-8.[102] On the other hand, breathing hot air, or elevation of body core temperature because of exercise leads to airways contractions.[93] Du et al[103] reported that repeated exposure to temperature variation exacerbates airway inflammation through the TRP cation channel, subfamily A, member 1 (TRPA1) in a mouse model of asthma. Liu et al[104] reported that cold exposure (8°C-22°C) activates the TRP cation channel, subfamily M, member 8 (TRPM8) and induces expression of cytokines such as IL-1β, IL-4, IL-6, IL-8, IL-10, IL-13, granulocyte-macrophage colony-stimulating factor, and TNF-alpha. TRPV1 is also associated with proinflammatory cytokine expression and is overexpressed in the airways of patients with asthma.[105,106]

Conclusion

Understanding how temperature fluctuation influences allergic diseases is critical to the development of measures for the prevention and treatment of allergic disorders. To date, a number of studies have concluded that both cold and hot temperatures affect skin homeostasis and barrier function and promote the development of AD. Temperature-driven activation of TRPV cation channels is involved in the induction of pruritus, flares, skin barrier dysfunction, development of AD, and asthma attacks. Blocking of TRPV cation channels could potentially prevent and attenuate temperature-mediated itch, barrier dysfunction, exacerbation of AD, and allergic diseases (Table 1).

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