Journal of Research High School

Volume 2023 (1) 137 - 149
ISSN 2688-3651 [online]

Comprehensive Review on Atopic Dermatitis and Therapeutic Potentials

Crystal Shin[1] *

[1]Northwood High School, Irvine, CA USA

Received September 3, 2022; Revised March 7, 2023; Accepted, March 20, 2023

Abstract

Atopic dermatitis (AD) is a type of a skin-related allergy that affects all demographics worldwide, but mostly common amongst the younger population. It is characterized by itchy, red, and swollen skin, and there is currently no cure available. Disease etiology largely arises due to a combination of genetics and environmental influences, coupled with other types of comorbidities such as asthma and hay fever disease. AD largely is associated with a compromised epithelial tissue layer, which leads to decreased water retention and facilitated entry of allergens into the body, which further exacerbates the pathophysiology of the disease. Mechanistically, the progression of AD can be attributed to the overall imbalance of Th1 and Th2 cells, which disturbs the homeostasis between pro-inflammatory and anti-inflammatory polarizations of innate and adaptive immunity. Therefore, most of the current medications that help ameliorate AD's pathogenesis include drugs that inhibit Th2 differentiation and polarization by targeting the activity of IL-13 and IL-4, both of which are implicated in the production of Th2 cells that subsequently induce IgE-mediated allergic reactions. The purpose of this review article is to comprehensively explore the biology of AD, including risk factors, diagnosis, pathophysiology, and the current available treatments.

Keywords: Atopic dermatitis, Allergy, IgE, Inflammation, Hypersensitive immune disorder, Treatment

1. Introduction

Atopic dermatitis (AD) is a chronic form of skin-related inflammation that results in itchy, red, swollen, and cracked skin (U.S. Department of Health and Human Services, 2022). It currently affects approximately 2.4% of the global population, impacting around 15-20% of children and 1-3% of adults worldwide. AD is neither a fatal nor contagious condition, but its Incidence has grown over 3-folds since the 1970s, and the prevalence is expected to rise over the next decade. It affects nearly all demographics, although recent evidence indicates that AD is commonly present in younger individuals under the age of 5 (Woods, 2017).

AD is classified under a broad category of an inflammatory skin condition known as eczema. Eczema can be broadly divided into two types: Atopic dermatitis (which is the focus of this paper) and contact dermatitis (WebMD, 2022). In brief, contact dermatitis, as the name implies, results when a skin comes into contact with an external trigger that causes a rash. Depending on the trigger, contact dermatitis can be grouped into two types: Irritant dermatitis and allergic dermatitis. Irritant dermatitis is much more common, and its triggers include cosmetic products, soaps & detergents, nickel-based jewelry, and industrial chemicals like cement

* Corresponding Author
crystalart0305@gmail.com

Advisor: Min Sub Lee
minsub.lee@ucla.edu

(WebMD, 2022). Allergic dermatitis on the other hand, flares when a skin comes into contact with an allergen that an individual is allergic to. Common allergens include pollen, poison ivy, rubber, latex, fragrances, and in extreme cases, water and sunlight.

Atopic dermatitis on the other hand, is a chronic condition often due to a combination of hereditary, immune, and environmental factors (Tee-Melegrito, 2021). AD can also occur in individuals with a family history of asthma or hay fever disease. The purpose of this review article is to provide a comprehensive background on AD, starting with the risk factors, major causes of the disease, and current diagnosis. It will then discuss the pathophysiology of the disease, including some background in immunology as well as the molecular mechanisms governing disease progression. Finally, the paper will conclude with an insight on some of the currently available therapeutics and treatments for AD.

2. Risk Factors

As with many types of inflammatory pathologies, there is no direct root cause of AD. Instead, it results from a culmination of multiple factors, such as genetics, environmental, and immunological factors. This section breaks down some of the major risk factors that contribute to the development of AD in most individuals.

2.1 Family History of Atopy

Atopy is a type of hypersensitive immune disorder characterized by the production of exaggerated amounts of immunoglobulin E (IgE) to harmless substances in the environment (i.e., non-microbial food or airborne allergens, such as dust mites, pollen, and foods) (Watson, 2021). Upwards of 70% of patients with AD also have a family history of atopy (Woods, 2017). In addition, some studies point out that individuals carrying AD have contracted other atopic diseases prior to acquiring AD, such as food allergies, asthma, and allergic rhinitis, in sequential order (Hahn and Bacharier, 2005). Although these atopic conditions are not necessary precursors for developing AD, it isn't uncommon for an individual to carry some combination of these pathologies (e.g., A patient with AD is also associated with having asthma, food allergy, allergic rhinitis, or a combination of all three).

2.1 Genetic Mutations

Growing evidence increasingly suggests that genetic factors play a role in development of AD, specifically via a loss-of-function mutation in a gene known as *flg*. *Flg* encodes for a protein called filaggrin, whose function is to regulate epidermal homeostasis by bringing together keratin fibers and other structural proteins together to establish a strong epithelial barrier on the skin surface (Sandilands, et al., 2009). Filaggrin deficiency leads to a "leaky" epithelial skin barrier that leads to decreased water retention and facilitated entry of allergens through the epidermis (McLean, 2011). Because of the increased water loss, individuals containing *flg* mutation tend to have dry, scaly skin, and they are much more susceptible to contracting AD due to increased exposures to environmental allergens (McLean, 2011). Defects in *flg* have also been associated with asthma, which further validates the propensity of individuals simultaneously carrying both asthma and AD (Woods, 2017).

While *flg* plays a pivotal role in maintaining the integrity of the epithelial barrier, it is certainly not the only involved protein. In fact, only about 30% of European patients with AD carry a *flg* mutation, suggesting that other epithelial gene variants are yet to be identified (Woods, 2017). Other skin barrier factors include a lack of ceramide production (Yang, et al., 2020). Ceramides are essential lipid molecules that are localized in the plasma membrane of epithelial cells that help regulate the biochemical & biophysical properties of the phospholipid bilayer. A reduction in ceramide concentration in the plasma membrane is associated with a loss of tight junctions that are critical for maintaining the epithelial network (Jennemann, et al., 2007). While no research has specifically investigated the direct relationship between *flg* mutation and a loss of ceramide production, it would be unsurprising to find that *flg*

expression and ceramide biosynthesis could operate in a shared biological pathway.

2.3 Hygiene Hypothesis

Why is it important for kids to play outside while they're young? According to the hygiene hypothesis, childhood exposure to various types of microorganisms is vital for protection against future allergic responses via immune system development (FDA, 2018). The biological basis of the hygiene hypothesis is a disequilibrium between Th1 and Th2 helper T-lymphocytes. Th1 immunity is associated with proinflammatory responses that primarily defends the body against intracellular pathogens (e.g., viruses and parasites) and stimulates autoimmune responses via production of a cytokine, interferon gamma (Berger, 2000). On the other hand, Th2 immunity stimulates the humoral immune response by stimulating B-cell proliferation, differentiation, and antibody production via a cytokine, interleukin-4 (IL-4).

Allergic conditions are caused by inappropriate immunological responses to harmless antigens driven by Th2- mediated immunity. This is because Th2 cells produce IL-4, IL-5, and IL-13, which predominantly stimulates B- cells to produce large quantities of IgE that subsequently activate mast cells (Okada et al., 2010). In alignment with this biological phenomenon, it has been shown that skin lesions of patients carrying AD contains high infiltration of Th2 population of cells relative to other T-helper subtypes, suggesting a link between Th2-dependent stimulation of humoral immunity and IgE-mediated allergic response (Brandt and Sivaprasad, 2011).

Furthermore, the hygiene hypothesis is vital for the development of regulatory T-cells (Tregs). The function of Tregs is to suppress overactive immune response, thereby maintaining immune homeostasis and self-tolerance (Kondelkova, et al., 2010). Individuals with inadequate Tregs response are more susceptible to autoimmune diseases and hypersensitive disorders (e.g., allergies) because of insufficiently repressed Th1 and Th2 cells, respectively (Bufford and Gern, 2005).

Altogether, early childhood exposures to microbes can substantially reduce the likelihood of individuals contracting AD and other forms of allergies. Some studies suggest that children who are exposed to dogs are correlated with lower risk of developing AD, likely because dogs can significantly increase a young child's exposure to environmental pathogens (Pelucchi, et al., 2013). Likewise, children with poor hygiene and those who consume unpasteurized milk tend to have a lower risk of developing AD (Flohr and Mann, 2014). Of course, this does ***not*** imply that all children should abandon practicing personal hygiene and sanitation.

2.4 Nutritional and Dietary Factors

Another fundamental root cause of AD can be attributed by dietary influences, starting as early as fetal development during pregnancy and breastfeeding. This is because diet & nutrition is crucial for the development of a healthy gut microbiome, which can subsequently influence the integrity of the skin barrier. One study has shown that children born to mothers with low vitamin D intake during pregnancy have an increased risk prevalence of AD (Miyake, et al., 2010). Interestingly, it has also shown that children born during fall and winter tend to have greater association with AD compared to children born during spring and summer. This might be attributed to the fact that there is less sunlight exposure during fall and winter, which correlates to lower exposure of vitamin D (Kuzume and Kusu, 2007).

While the relationship between breastfeeding and allergic risk hasn't fully been determined, breastfeeding has been associated with lower incidences of allergic diseases, including AD (Minniti, et al., 2014). This is because breastfeeding supports diversification of microbial colonization as the infant acquires some of their mother's healthy microbes. A healthy gut microbiome is vital for maintaining a well-balanced immune system. Therefore, breastmilk can potentially reduce risk of developing AD via increased diversification of an infant's microbiome compared to intaking baby formulas, although more follow-up studies are needed to validate these early findings (Trikamjee, et al., 2021).

In addition, several studies have shown that early dietary supplementation of long-chain polyunsaturated fatty acids (LCPUFA) in the form of fish oil has shown reduced incidence of allergic diseases. Mechanistically, high amounts of LCPUFA in the plasma membrane of cells reduce the synthesis of prostaglandin E and subsequent inhibition of cytokine and IgE production (Trikamjee, et al., 2021). As stated previously, reduced IgE production is a proxy for reduced allergic diseases, including AD.

2.5 Climate and Environment

Climate and environment can also play a vital role in the development of atopic dermatitis. Winter seasons are characterized with low humidity and low temperatures, and thus, it is common for individuals to have cracked skins due to loss of moisture on the skin surface. Perhaps unsurprisingly, this increases the risk of individuals contracting AD because of the compromised skin barrier functions and increases susceptibility to mechanical stress (Engebretesen, et al., 2016). In addition, there are many environmental toxins and carcinogens that are associated with the acceleration of eczema and atopic dermatitis. These include: Outdoor pollutants (e.g., carbon monoxide, dusts, forest fires, industrial wastes from power plants, etc.), tobacco smoke, and indoor carcinogens (e.g., paint, high exposure to cosmetic products, burning stoves, cleaning products, etc.) (Shi, 2022). All of these products trigger inflammatory reactions on the skin, thus contributing to the loss of skin barrier function and rendering individuals susceptible to increased water loss and subsequent xerosis.

2.6 Final Thoughts

As with many disease models, it's difficult to ascertain whether these risk factors independently spearhead AD development or depend on each other to collectively cause AD. This is largely because of individual differences in genetics, gender, ethnicity, lifestyle, diet, and many more. In some cases, a genetic mutation alone (or a combination of multiple mutations) is sufficient to drive AD development. In other cases, a combination of multiple environmental factors (i.e., climate, diet, pollutants, etc.) may be necessary to exacerbate the pathophysiology of AD but not sufficient to initiate AD development. Therefore, more studies are needed to better evaluate the underlying root causes of AD and the biological basis of its persistence.

3. Diagnosis

The Hanifin and Rajka criteria are the most notably recognized set of diagnostic criteria used in modern-day medicine to screen patients for AD. It is clinically diagnosed based on symptoms alone, without necessarily performing rigorous testing (Woods, 2017). As of 1980, Hanifin and Rajka standards have categorized AD diagnosis requirements into two sections: Major and Minor. The major features of Hanifin and Rajka in determining the presence of AD include: (1) Pruritis and eczema, both of which are characterized by itchy and dry skin, rashes, scaly patches, and blisters; (2) Typical morphology and distribution; (3) Chronically relapsing dermatitis; and (4) Personal or family history of atopy (asthma, allergic rhinitis, and atopic dermatitis). Currently, there are 23 minor features, such as elevated immunoglobulin E (IgE) levels, food tolerance, tendency towards cutaneous infections, anterior neck folds, and more. These guidelines have proposed to diagnose a patient with AD when they meet at least three of the four major features *and* at least three of the minor features (Akan, et al., 2020).

One ongoing challenge of AD diagnosis is the fact that its symptoms overlap with other related skin diseases. Not only are there several imitators with similar clinical features, but there are many diagnoses that coexist with AD. For example, seborrheic dermatitis is another type of inflammatory skin disease that is very difficult to distinguish from AD, especially in infancy where they can occur concomitantly or separately (Woods, 2017). However, there *are* a few distinguishing features specific to AD. In nearly most cases, AD begins during infantile onset, while other forms of skin

diseases such as contact dermatitis are rarely found in infants. Furthermore, AD does not consist of circumscribed lesions but instead, consist largely of xerosis. This is in contrast with both seborrheic and contact dermatitis, as both skin diseases consist of circumscribed lesions (Siegfried, 2015). Finally, another unique aspect of AD is its distribution in the body at various developmental stages. For infants, AD is largely found in the face and the trunk. In children however, AD is localized near the flexors (e.g., hip, thigh, and torso), while in adults, AD is found mostly in the hands (Siegfried, 2015). Nevertheless, it isn't uncommon for patients to be diagnosed with AD in conjunction to other skin diseases due to large overlaps in symptoms, distributions, and diagnosis.

4. Pathophysiology

At the end of the day, atopic dermatitis is only one specific type of a skin allergy, amongst numerous other pathologies. Most allergic reactions are governed by the secretion of IgE antibodies from mature B-cells, which in turn, activates mast cells to secrete high amounts of histamine and granules that contribute to hyperinflammatory reactions in specific types of organs. This section discusses broad cellular and molecular mechanisms that lead to an allergic reaction and then focus on the specific signaling pathways that become activated during AD. Understanding these processes is crucial because it enables researchers to design appropriate drugs that target and combat disease progression.

4.1 Innate vs. Adaptive Immunity, Antigen Presentation, and IgE Antibody

As described in the above sections, all allergic reactions begin when a non-microbial allergen enters the body and the immune cells *fail* to distinguish an allergen from a real microbe. When a real microbe enters the host tissues, the innate immune cells immediately recognize the foreign microbe as a threat and assemble together to destroy the pathogen. All microbes contain specific elements known as pathogen-associated molecular patterns (PAMPs), and different types of PAMPs are recognized by different innate immune cells via pathogen recognition receptors (PRRs) (Mogensen, 2009). For example, some gram-negative bacterial cells contain a specific toxin within its cell wall known as lipopolysaccharide (LPS). Over evolutionary time, eukaryotic host cells have evolved a receptor known as Toll-Like Receptor (TLR)-4 that specifically recognizes secreted LPS molecules from gram-negative bacteria and subsequently activates inflammatory reactions that enable the host organism to fight against the invading bacteria (Raetz and Whitfield, 2002). In order to maintain long-term memory response against that bacteria, the innate immune system must be able to transmit these signals to the adaptive immune system (consisting of T and B-cells) that generates memory lymphocytes.

Dendritic cells (DCs) are the major type of immune cell that bridges the innate and adaptive immune system. When DCs encounter a foreign pathogen, it usually ingests that microbe via phagocytosis ("cellular eating"), processes that microbe into tiny peptides, and presents those peptides as an antigen in the context of a molecule known as major histocompatibility complex (MHC). Once the DCs present these foreign antigens, circulating naive T-cells (immature T-cells that haven't encountered any antigen) will come into contact with the MHC molecules containing the antigen and subsequently become activated into a mature T-cell (Thery and Amigorena, 2001). These mature T-cells are able to secrete cytokines and other signaling molecules that lead to the proliferation and expansion of an antigen-specific T-cell population that can fight off any remaining pathogens in the body. Once the pathogen is sufficiently cleared, most of these T-cells undergo apoptosis, while some T-cells differentiate into memory T-cells (Harrison, et al., 2019). Memory lymphocytes will re-differentiate into effector T-cells when the same pathogen enters the body, resulting in facilitated pathogen clearance from the host.

The activated T-cells secrete cytokines that also lead to maturation and differentiation of native B-cells into plasma cells, which is the immune system's factory machine that secretes huge amounts of antibodies (Harrison, et al., 2019).

There are 5 main types of antibodies (IgA, IgD, IgE, IgG, and IgM), with each eliciting different effector functions, although the function of IgD isn't well-characterized (Hoffman, et al., 2016). As described in previous sections, IgE is the primary antibody that is responsible for regulating allergic reactions.

4.2 Molecular Mechanisms of Allergic Reactions

An allergic reaction begins when an allergen enters a body and triggers the DCs to uptake the allergen and present it via MHC molecules to circulating naive T-cells, either naive CD8 T-cells or naive CD4 T-cells. Activated CD8 T-cells move on and become engaged in cytotoxic effector functions (e.g., target and kill tumor cells) while activated CD4 T-cells can differentiate into specific subtypes depending on the cytokine exposures: Th1, Th2, Th17, and Tregs (Harrison, et al., 2019). Th2 subtype is most directly engaged in allergic reactions, and thus, it will be the main focus for this section. Th2 cells produce a cytokine called interleukin 4 (IL-4), which directly stimulates B-cells to produce large amounts of IgE antibodies. These IgE antibodies begin to circulate throughout the bloodstream and bind to IgE-receptors that are typically found on the surface of mast cells and basophils (Stone, et al., 2010). It's also important to note that these IgE antibodies are highly specific to the allergen that was originally presented by the DCs into naive T-cells.

When the individual encounters the same allergen the second and subsequent times, the allergen binds to the IgE antibodies that are coated on the surface of the aforementioned mast cells and basophils. This binding reaction activates the mast cells and basophils to undergo a process known as degranulation, which involves a massive release of histamines and other inflammatory mediators from their stored granules (Stone, et al., 2010).These inflammatory processes lead to vasodilation, rise in body temperature, localized and systemic swelling, and mucous secretion, all of which are common physiological symptoms during acute infection. Depending on the type of allergen, the individual's immune response, and the mode of allergen consumption, allergic symptoms can vary from localized inflammatory reactions to systemic anaphylactic shock (Amin, 2012).

4.3 Pathogenic Insights of Atopic Dermatitis

Systemic secretion of histamines and other inflammatory mediators via mast cells and basophils represents an "umbrella" of all allergic reactions. Many studies have characterized other molecular, cellular, and physiological defects that contribute to the exacerbation of AD-mediated skin inflammation. The previous section has already identified *flg* mutation as a risk factor of AD because the individual has a genetic defect in skin barrier function.

Recent studies have found a novel link between NOD-like receptors (NLRs) and susceptibility to atopic dermatitis. NLRs are intracellular PRRs that sense a wide range of PAMPs such as bacterial cell wall's peptidoglycans and various derivatives of amino acids that are not resident in host organisms (Tsang, et al., 2021; Zhong, et al., 2013). Nlrp12-null genetic models, which are deficient in NLR sensing, have been shown to exhibit attenuated atopic dermatitis-like features, as well as reduced antigen presentation and subsequent T-cell activation (Arthur, et al., 2010). This suggests that the activation and progression of AD could possibly operate through NLR signaling. NLR signaling also leads to the activation of the inflammasome in keratinocytes as well as many residential innate immune cells in the skin, which leads to the production of the cytokines, IL-1β and IL-18 (Jacobs and Damania, 2012). These cytokines in turn can trigger Th2 and IgE-mediated immune responses, which contribute to the activation of mast cells and basophils.

In parallel to these studies, it is also known that patients who have a preliminary exposure to Staphylococcus aureus or herpes simplex virus exhibit increased vulnerability to AD. Products of these pathogens have been shown to downregulate immune responses by downregulating the FcR1 receptor on Langerhan cells upon binding to TLR-2 receptor, resulting in poor TH1 activation but enhanced TH2 response (Schlapbach and Simon,

2014).

Another cytokine that has been shown to trigger pathogenesis of AD is thymic stromal lymphopoietin (TLSP), which is secreted by epithelial cells. The epidermis of the lesions derived from AD patients has been shown to express greater levels of TLSP compared to control patients with nonallergic dermatitis (Soumelis, et al., 2002). Dendritic cells from these lesions show an activated phenotype, in which they migrate away from the epidermis and into the lymph nodes to directly promote Th2 differentiation. This is consistent with the observation that a direct exposure of TLSP enables DCs to activate naive CD4 T-cells and differentiate them into Th2 subtype (Indra, 2013). Furthermore, it is thought that the high levels of cytokine production (e.g., IL-1β, TNFα, IL-4 and IL-13) can synergize to stimulate mass production of TLSP from surrounding epithelium and keratinocytes, suggesting a positive feedback loop of inflammatory circuit within the skin (Indra, 2013). However, these studies are correlation at best because no loss-of-function studies have been performed in the context of TLSP signaling, and thus, more studies are needed to validate this inflammatory circuit between TLSP and DC-dependent Th2 differentiation.

Lastly, Interleukin (IL)-33 has been shown to be overexpressed in keratinocytes derived from patients with AD, suggesting that IL-33 may be involved in triggering AD development (Imai, 2019). IL-33 stimulates a wide range of immune cells, including group 2 innate lymphoid cells (ILC-2) and basophils, both of which produce IL-4, which triggers a Th2 response and subsequent production of IgE antibodies that lead to progression of AD (Imai, 2019). It is also important to note that IL-33 reduces the expression of filaggrin, which as described previously, is integral for maintaining the stability of the epithelial barrier (Imai, 2019). The circuit between IL-33 and filaggrin hasn't fully been explored in AD patients, and thus, it would be an interesting therapeutic target once the cellular and molecular mechanisms are fully deciphered.

5. Current Treatments

This last section will explore different strategies of combating and treating atopic dermatitis. As for many diseases, there is currently no available cure of AD. But with the right treatments, the severity of flares and inflammation can be reduced quite substantially.

5.1 Lifestyle Changes

Getting rid of a disease does not happen overnight. If there were such treatments, everyone on Earth would be disease-free by now. Part of the reason why many patients are unable to recover from certain types of disease is because they lack self-perseverance and consistency. For example, if an individual is diagnosed with obesity, one of the most definite ways of recovering from obesity is to amend diet and exercise every day. Of course, this is grossly oversimplifying the concept because not all obesity conditions can be combated via lifestyle changes. However, many studies have proved over and over that a 30-minute aerobic exercise coupled with a high protein diet for a month is sufficient to shed anywhere between 10-15 pounds in a month (Goldman, 2017).

Likewise, AD can be treated as long as patients maintain consistent routines and adapt to new changes whenever necessary. One daily routine that can help alleviate AD is to bathe in lukewarm and salty water. This can help moisturize skin by restoring the protective barrier of the skin and maintaining proper levels of hydration (Lio, 2013). Saltwater also contains minerals such as potassium, calcium, and magnesium, all of which can bind to water and help with retention of moisture in the skin (NENA skincare, 2022).

Another interesting lifestyle method would be to avoid woolen clothing and instead, wear more silk-based clothing (NENA skincare, 2022). It has been shown that the sericin residue found in silk has a repellent property that prevents the attachment of dust mites, bacteria, and other common allergens (Silk Properties, 2022). Health professionals often advise AD patients to avoid woolen clothing because wool tends to remove moisture from the body, which

can exacerbate the inflammatory reactions on the skin surface (NENA skincare, 2022).

Finally, while this one isn't necessarily a "lifestyle change," it can be a very useful device to help reduce the severity of AD: Humidifier. Winter season can be very dry due to the lack of humidity in the air. A humidifier is an electrical appliance that can help increase humidity in the room, which can significantly prevent skin from drying out and consequently reduce risk of contracting AD (Varothai, et al., 2013). On top of that, consistently applying moisturizers and practicing proper skin hydration routines can also help prevent the progression of AD.

5.2 Medication

Topical treatment of hydrocortisone cream is a widely popular medication used for reducing AD. Hydrocortisone is a corticosteroid that is used as an agonist for glucocorticoid and mineralocorticoid receptors that help suppress inflammatory reactions in the tissues via inhibition of inflammatory mediators, such as phospholipase A2 and NF-kappa-B (National Center for Biotechnology Information, 2022). It was first patented and approved for medical use by 1941, and as of 2019, it was listed as the 147th most commonly prescribed medication in the United States (Kane, 2022).

Tacrolimus (aka Prograf) is a type of ointment that can also be topically treated onto allergic sites (Mayo Foundation for Medical Education and Research, 2022). Mechanistically, it acts as a calcineurin inhibitor in T-cells. When a naive T-cell comes in contact with antigen presenting cells and becomes activated, T-cell receptor stimulates downstream signaling molecules to increase intracellular levels of calcium, which in turn activates calcineurin. Calcineurin is a serine/threonine phosphatase that de-phosphorylates the transcription factor, NF-AT, which in turn, translocated to the nucleus to transcribe pro-inflammatory genes, particularly IL-2 and related cytokines (Macian, 2005). Tacrolimus blocks this T-cell-mediated inflammatory circuit by inhibiting the function of calcineurin (Ganong, 2005). By reducing IL-2 production, T-cells are unable to differentiate into Th2 subtype, which consequently would prevent the activation of B-cells and IgE antibody secretion, thereby suppressing allergic reactions. Ciclosporin is another type of immunosuppressant medication that also acts as a calcineurin inhibitor. However, both tacrolimus and ciclosporin have posed risks of developing skin cancer or lymphoma and thus, not all individuals should be taking these medications.

In 2021, Tralokinumab (aka Adtralza) was approved in the United Kingdom and the United States as a therapeutic for atopic dermatitis (Freitas, et al., 2021). Tralokinumab is a human monoclonal antibody that specifically targets the cytokine, IL-13. Similar to IL-4, IL-13 is a pivotal cytokine involved in the generation of allergic diseases, such as AD via polarization of Th2 lymphocytes. There is increasing evidence that IL-13 is overexpressed in AD patients, and this is correlated with increased trafficking of inflammatory leukocytes and decreased function of epidermal barrier (Bieber, 2020). In parallel to these studies, there is a rationale for potentially targeting the effect of IL-4, the major cytokine that leads to Th2 response (Lernia, 2015). A combinatorial therapy of tralokinumab and IL-4 inhibitor may potentially synergize protection against the development and progression of AD. However, it is also important to consider the side effects because both IL-13 and IL-4 play vital roles in polarization of macrophages toward an M2, anti-inflammatory phenotype that regulate wound healing, tissue repair, and anti-parasitic infection (Liu, et al., 2021). By antagonizing the effects of these cytokines, there would be a systemic imbalance of pro-inflammatory vs. ant-inflammatory signatures, which can lead to many downstream tissue cytotoxicity.

5.3 Alternative Medicine

Traditional Chinese medicine (e.g., acupuncture, tai chi, and herbal products) has always been (and still is) a highly controversial topic in clinical studies and scientific reviews. This is because traditional Chinese medicine, along with many other types of oriental medicine, is not

backed by the scientific method. Recently however, many organizations such as the World Health Organization is beginning to recognize traditional Chinese medicine in its influential global medical compendium (Cyranoski, 2018). Some of these psychological and physical approaches used in oriental medicine can help alleviate pain conditions and improve quality of life (Matos, et al., 2021). In 2013, a study was conducted by Gu et. al to assess the effects of oral ingestion and topical application of Chinese herbal medicine (CHM) for the management and progression of atopic dermatitis. It was a randomized clinical trial consisting of 2306 participants, a mixture of both adults and children with atopic dermatitis. It was collectively shown that the participants in the CHM group (Both oral and topical administration) reported significantly less itching and higher quality of life (QoL) score than the placebo group (Gu, et al., 2013). Overall, CHM was well- tolerated in these clinical trials with no significant adverse side effects, except for a few mentions of reversible transaminitis (Goddard and Lio, 2015).

Another type of alternative medicine that is widely used in clinics is acupuncture and acupressure. Both are forms of traditional Chinese medicine that attempts to restore the body's Qi, which is defined as the vital force of energy that enables proper "flow of energy" (Taking Charge of Your Health & Wellbeing, 2022). Acupuncture requires a licensed, trained professional to insert hair-thin, sterile needles into different points of the body as an attempt to stimulate the body's meridians (i.e., energy pathways) and restore homeostasis (Clayton, 2022). On the other hand, acupressure is a non-invasive traditional Chinese medicine technique that also attempts to restore the body's Qi, but instead of needles, it utilizes gentle pressures to the skin. A study conducted in 2018 by Lee et. al showed that acupressure using a 1.2 mm acupellet at the L11 point significantly reduced the severity of itchiness and pruritus in AD patients compared to the placebo group (Lee, et al., 2012). Additionally, independent trials in animal models suggest that acupuncture and moxibustion (application of heat onto acupuncture points) can reduce AD- mediated pathology by decreasing the expression of phosphorylated STAT6, which as described in the previous section, is the transcriptional factor that becomes activated in response to IL-4 signaling (Pfab et al., 2014). However, more research is needed to understand the specific mechanisms of acupuncture-mediated reduction in AD.

6. Conclusion

Atopic dermatitis and other hypersensitive immune disorders have been extensively investigated over the course of the last several decades, and they are still gaining much attention today. While this review article explored a relatively minor form of allergy, it is important to understand that allergic reactions can be deadly. For example, food allergy affects about 15 million people in the United States alone, with an average mortality around 150-200 individuals (Radke, et al., 2017). Some individuals contract anaphylactic shock against specific allergens, such as peanut butter, insect bites, or even certain medications. These shocks can be life-threatening if they don't immediately seek medical emergency (Cristol, 2020). Therefore, allergic diseases are not trivial, and more research is needed to identify biological pathways that are targeted for therapeutic purposes, while minimizing side effects.

Of course, there remains many important and unresolved questions about atopic dermatitis. One crucial issue is to properly distinguish atopic dermatitis from other forms of inflammatory conditions in the skin. The symptoms found in AD largely overlap with symptoms found in other skin allergic diseases, such as contact dermatitis, hay fever, and hives. While the Hanifin and Rajka criteria has been developed to clinically diagnose patients of AD, not all individuals have access to a clinical dermatologist. Therefore, many individuals end up consuming generic-brand medications that may alleviate temporary pain but don't fully treat the disease. While lifestyle changes can significantly reduce the development and progression of AD, it can often be burdensome for the individual to adopt these changes.

Altogether, the review paper examines the

characteristics of AD, starting with critical risk factors and diagnosis, followed by its molecular pathophysiology and current knowledge on therapeutic potential. Tackling some of these important unanswered questions regarding the pathophysiology of AD will undoubtedly advance the mechanistic understanding of allergy and hypersensitivity disorders, as well as help uncover novel therapeutic targets to combat the progression of this disease.

Acknowledgment

I gratefully thank and acknowledge my mentor, Min Sub Lee for his guidance, advice, and continuous support throughout the process of my article. This wouldn't have been possible without his exchange of input on technical information, research, and shared knowledge. I would also like to thank Katia Chadaideh, PhD and her lectures on allergies and autoimmune disorders during her summer course, Introduction to Evolutionary Medicine, Harvard Precollege Summer Program.

References

Akan, A., et. al., (2020). Diagnosis of atopic dermatitis in children: comparison of the Hanifin-Rajka and the United Kingdom Working Party criteria. *Allergologia et immunopathologia*, *48*(2), 175–181. https://doi.org/10.1016/j.aller.2019.07.008

Amin K. (2012). The role of mast cells in allergic inflammation. *Respiratory medicine*, *106*(1), 9–14. https://doi.org/10.1016/j.rmed.2011.09.007

Arthur, J. C., et. al., (2010). Cutting edge: NLRP12 controls dendritic and myeloid cell migration to affect contact hypersensitivity. *Journal of immunology (Baltimore, Md. : 1950)*, *185*(8), 4515–4519. https://doi.org/10.4049/jimmunol.1002227

Berger A. (2000). Th1 and Th2 responses: what are they?. *BMJ (Clinical research ed.)*, *321*(7258), 424. https://doi.org/10.1136/bmj.321.7258.424

Bieber T. (2020). Interleukin-13: Targeting an underestimated cytokine in atopic dermatitis. *Allergy*, *75*(1), 54–62. https://doi.org/10.1111/all.13954

Brandt, E. B., & Sivaprasad, U. (2011). Th2 Cytokines and Atopic Dermatitis. *Journal of clinical & cellular immunology*, *2*(3), 110. https://doi.org/10.4172/2155-9899.1000110

Bufford, J. D., & Gern, J. E. (2005). The hygiene hypothesis revisited. *Immunology and allergy clinics of North America*, *25*(2), 247–vi. https://doi.org/10.1016/j.iac.2005.03.005

Carmela Avena-Woods, B. S. P. (n.d.). *Overview of atopic dermatitis*. AJMC. Retrieved September 1, 2022, from https://www.ajmc.com/view/overview-of-atopic-dermatitis-article

Clayton, V. (2022, August 8). *Acupuncture vs. acupressure: What's the difference?* Forbes. Retrieved September 1, 2022, from https://www.forbes.com/health/body/acupuncture-vs-acupressure/

Cristol, H. (2020). *Anaphylactic shock: What you should know*. WebMD. Retrieved September 1, 2022, from https://www.webmd.com/allergies/anaphylactic-shock-facts#:~:text=Anaphylactic%20shock%20is%20a%20rare,911%20for%20emergency%20medical%20help.

Cyranoski D. (2018). Why Chinese medicine is heading for clinics around the world. *Nature*, *561*(7724), 448–450. https://doi.org/10.1038/d41586-018-06782-7

Di Lernia V (January 2015). "Therapeutic strategies in extrinsic atopic dermatitis: focus on inhibition of IL- 4 as a new pharmacological approach". *Expert Opinion on Therapeutic Targets*. **19** (1): 87–96.

Engebretsen, K. A., et. al., (2016). The effect of environmental humidity and temperature on skin barrier function and dermatitis. *Journal of the European Academy of Dermatology and Venereology : JEADV*, *30*(2), 223–249. https://doi.org/10.1111/jdv.13301

FDA. (2018). *Asthma: The hygiene hypothesis*. U.S. Food and Drug Administration. Retrieved September 1, 2022, from https://www.fda.gov/vaccines-blood-biologics/consumers-biologics/asthma-hygiene- hypothesis

Flohr, C., & Mann, J. (2014). New insights into the epidemiology of childhood atopic dermatitis. *Allergy*, *69*(1), 3–16. https://doi.org/10.1111/all.12270

Freitas, E., Guttman-Yassky, E., & Torres, T. (2021). Tralokinumab for the Treatment of Atopic Dermatitis. *American journal of clinical dermatology*, *22*(5), 625–638. https://doi.org/10.1007/s40257-021- 00613-8

Goddard, A. L., & Lio, P. A. (2015). Alternative, Complementary, and Forgotten Remedies for Atopic Dermatitis. *Evidence-based complementary and alternative medicine : eCAM*, *2015*, 676897. https://doi.org/10.1155/2015/676897

Goldman, R. (2017, October 12). *How much weight can you lose in a month?* Healthline. Retrieved September 1, 2022, from https://www.healthline.com/health/food-nutrition/weight-loss-in-a-month

Gu, S., Yang, A. W., Xue, C. C., et. al., (2013). Chinese herbal medicine for atopic eczema. *The Cochrane database of systematic reviews*, (9), CD008642. https://doi.org/10.1002/14651858.CD008642.pub2

Hahn, E. L., & Bacharier, L. B. (2005). The atopic march: the pattern of allergic disease development in childhood. *Immunology and allergy clinics of North America*, *25*(2), 231–v. https://doi.org/10.1016/j.iac.2005.02.004

Harrison, D. L., Fang, Y., & Huang, J. (2019). T-Cell Mechanobiology: Force Sensation, Potentiation, and Translation. *Frontiers in physics*, *7*, 45. https://doi.org/10.3389/fphy.2019.00045

Hoffman, W., Lakkis, F. G., & Chalasani, G. (2016). B Cells, Antibodies, and More. *Clinical journal of the American Society of Nephrology : CJASN*, *11*(1), 137–154. https://doi.org/10.2215/CJN.09430915

Imai Y. (2019). Interleukin-33 in atopic dermatitis. *Journal of dermatological science*, *96*(1), 2–7. https://doi.org/10.1016/j.jdermsci.2019.08.006

Indra A. K. (2013). Epidermal TSLP: a trigger factor for pathogenesis of atopic dermatitis. *Expert review of proteomics*, *10*(4), 309–311. https://doi.org/10.1586/14789450.2013.814881

Jacobs, S. R., & Damania, B. (2012). NLRs, inflammasomes, and viral infection. *Journal of leukocyte biology*, *92*(3), 469–477. https://doi.org/10.1189/jlb.0312132

Jennemann, R., et. al., (2007). Integrity and barrier function of the epidermis critically depend on glucosylceramide synthesis. *The Journal of biological chemistry*, *282*(5), 3083–3094.

Kane SP. Hydrocortisone, ClinCalc DrugStats Database, Version 2022.08. ClinCalc: https://clincalc.com/DrugStats/Drugs/Hydrocortisone Updated August 24, 2022. Accessed September 1, 2022.

Kane SP. The Top 300 of 2020, ClinCalc DrugStats Database, Version 2022.08. ClinCalc: https://clincalc.com/DrugStats/Top300Drugs.aspx. Updated August 24, 2022. Accessed September 1, 2022.

Kondělková, K., et. al., (2010). Regulatory T cells (TREG) and their roles in immune system with respect to immunopathological disorders. *Acta medica (Hradec Kralove)*, *53*(2), 73–77. https://doi.org/10.14712/18059694.2016.63

Kuzume, K., & Kusu, M. (2007). Before-birth climatologic data may play a role in the development of allergies in infants. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*, *18*(4), 281–287. https://doi.org/10.1111/j.1399-3038.2006.00526.x

Lee, K. C., Keyes, A., Hensley, J. R., et. al., (2012). Effectiveness of acupressure on pruritus and lichenification associated with atopic dermatitis: a pilot trial. *Acupuncture in medicine : journal of the British Medical Acupuncture Society*, *30*(1), 8–11. https://doi.org/10.1136/acupmed-2011-010088

Lio P. A. (2013). Non-pharmacologic therapies for atopic dermatitis. *Current allergy and asthma reports*, *13*(5), 528–538. https://doi.org/10.1007/s11882-013-0371-y

Liu, J., *et al.* New insights into M1/M2 macrophages: key modulators in cancer progression. *Cancer Cell Int* 21, 389 (2021). https://doi.org/10.1186/s12935-021-02089-2

Macian F. (2005). NFAT proteins: key regulators of T-cell development and function. *Nature reviews. Immunology*, *5*(6), 472–484. https://doi.org/10.1038/nri1632

Matos, L. C., Machado, J. P., Monteiro, F. J., & Greten, H. J. (2021). Understanding Traditional Chinese Medicine Therapeutics: An Overview of the Basics and Clinical Applications. *Healthcare (Basel, Switzerland)*, *9*(3), 257. https://doi.org/10.3390/healthcare9030257

Mayo Foundation for Medical Education and Research. (2022, August 1). *Tacrolimus (oral route) side effects*. Mayo Clinic. Retrieved September 1, 2022, from https://www.mayoclinic.org/drugs-supplements/tacrolimus-oral-route/side-effects/drg-20068314?p=1#:~:text=Tacrolimus%20is%20used%20together%20with,medicines%20known%20as%20immunosuppressive%20agents

McLean W. H. (2011). The allergy gene: how a mutation in a skin protein revealed a link between eczema and asthma. *F1000 medicine reports*, *3*, 2. https://doi.org/10.3410/M3-2

Meyer-Hoffert, U., & Schröder, J. M. (2011). Epidermal proteases in the pathogenesis of rosacea. *The journal of investigative dermatology. Symposium proceedings*, *15*(1), 16–23. https://doi.org/10.1038/jidsymp.2011.2

Minniti, F., et. al., (2014). Breast-milk characteristics protecting against allergy. *Endocrine, metabolic & immune disorders drug targets*, *14*(1), 9–15. https://doi.org/10.2174/1871530314666140121145045

Miyake, Y., Sasaki, S., Tanaka, K., & Hirota, Y. (2010). Dairy food, calcium and vitamin D intake in pregnancy, and wheeze and eczema in infants. *The European respiratory journal*, *35*(6), 1228–1234. https://doi.org/10.1183/09031936.00100609

Mogensen T. H. (2009). Pathogen recognition and inflammatory signaling in innate immune defenses. *Clinical microbiology reviews*, *22*(2), 240–273. https://doi.org/10.1128/CMR.00046-08

Nall, R. (2020, August 13). *Contact dermatitis: Causes, symptoms, and treatment*. Healthline. Retrieved September 1, 2022, from https://www.healthline.com/health/contact-dermatitis

National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 5754, Hydrocortisone. Retrieved September 2, 2022 from https://pubchem.ncbi.nlm.nih.gov/compound/Hydrocortisone.

NENA Skincare. (2020, February 13). *Mineral water benefits for skin and health*. NENA Skincare. Retrieved September 1, 2022, from https://us.nenaskincare.com/blogs/wellness/mineral-water-benefits-for- skin-and-health

Okada, H., Kuhn, C., Feillet, H., & Bach, J. F. (2010). The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. *Clinical and experimental immunology*, *160*(1), 1–9. https://doi.org/10.1111/j.1365-2249.2010.04139.x

Pelucchi, C., et al., (2013). Pet exposure and risk of atopic dermatitis at the pediatric age: a meta-analysis of birth cohort studies. *The Journal of allergy and clinical immunology*, *132*(3), 616–622.e7. https://doi.org/10.1016/j.jaci.2013.04.009

Pfab, F., et. al., (2014). Acupuncture for allergic disease therapy--the current state of evidence. *Expert review of clinical immunology*, *10*(7), 831–841. https://doi.org/10.1586/1744666X.2014.924855

Radke, T. J., et. al., (2017). Restaurant Food Allergy Practices - Six Selected Sites, United States, 2014. *MMWR. Morbidity and mortality weekly report*, *66*(15), 404–407. https://doi.org/10.15585/mmwr.mm6615a2

Raetz, C. R., & Whitfield, C. (2002). Lipopolysaccharide endotoxins. *Annual review of biochemistry*, *71*, 635–700. https://doi.org/10.1146/annurev.biochem.71.110601.135414

Sandilands, A., Sutherland, C., Irvine, A. D., & McLean, W. H. (2009). Filaggrin in the frontline: role in skin barrier function and disease. *Journal of cell science*, *122*(Pt 9), 1285–1294. https://doi.org/10.1242/jcs.033969

Schlapbach, C., & Simon, D. (2014). Update on skin allergy. *Allergy*, *69*(12), 1571–1581. https://doi.org/10.1111/all.12529

Shi, V. (n.d.). *Common air pollutants that trigger*

eczema | learnskin. Retrieved September 2, 2022, from https://www.learnskin.com/articles/how-does-air-pollution-affect-eczema

Siegfried EC, Hebert AA. Diagnosis of Atopic Dermatitis: Mimics, Overlaps, and Complications. J Clin Med. 2015 May 6;4(5):884-917. doi: 10.3390/jcm4050884. PMID: 26239454; PMCID: PMC4470205.
Silk properties. marimichel.nl. (2022). Retrieved September 1, 2022, from https://marimichel.nl/pages/silk- properties

Soumelis, V., et. al., (2002). Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nature immunology*, *3*(7), 673–680. https://doi.org/10.1038/ni805

Stone, K. D., Prussin, C., & Metcalfe, D. D. (2010). IgE, mast cells, basophils, and eosinophils. *The Journal of allergy and clinical immunology*, *125*(2 Suppl 2), S73–S80. https://doi.org/10.1016/j.jaci.2009.11.017

Tee-Melegrito, R. A. (2021). *What is the difference between atopic and contact dermatitis?* Medical News Today. Retrieved September 1, 2022, from https://www.medicalnewstoday.com/articles/atopic-dermatitis- vs-contact-dermatitis#differences

Théry, C., & Amigorena, S. (2001). The cell biology of antigen presentation in dendritic cells. *Current opinion in immunology*, *13*(1), 45–51. https://doi.org/10.1016/s0952-7915(00)00180-1

Trikamjee, T., et. al., (2021). Nutritional Factors in the Prevention of Atopic Dermatitis in Children. *Frontiers in pediatrics*, *8*, 577413. https://doi.org/10.3389/fped.2020.577413

Tsang, M. S., Hou, T., Chan, B. C., & Wong, C. K. (2021). Immunological Roles of NLR in Allergic Diseases and Its Underlying Mechanisms. *International journal of molecular sciences*, *22*(4), 1507. https://doi.org/10.3390/ijms22041507

U.S. Department of Health and Human Services. (2022, June 22). *Atopic dermatitis*. National Institute of Arthritis and Musculoskeletal and Skin Diseases. Retrieved September 1, 2022, from https://www.niams.nih.gov/health-topics/atopic-dermatitis

Varothai, S., Nitayavardhana, S., & Kulthanan, K. (2013). Moisturizers for patients with atopic dermatitis. *Asian Pacific journal of allergy and immunology*, *31*(2), 91–98.

Watson, S. (2021). *What is atopy?* WebMD. Retrieved September 1, 2022, from https://www.webmd.com/skin-problems-and-treatments/eczema/what-is-atopy

WebMD. (2022). *Eczema: Types, symptoms, causes, diagnosis, and treatment*. WebMD. Retrieved September 1, 2022, from https://www.webmd.com/skin-problems-and-treatments/eczema/atopicdermatitis- eczema

What is Qi? (and other concepts). Taking Charge of Your Health & Wellbeing. (2022). Retrieved September 1, 2022, from https://www.takingcharge.csh.umn.edu/explore-healing-practices/traditional-chinese-medicine/what-qi-and-other-concepts

William F. Ganong (8 March 2005). *Review of medical physiology* (22nd ed.). Lange medical books. p. 530. ISBN 978-0-07-144040-0.

Yang, G., et. al., (2020). Skin Barrier Abnormalities and Immune Dysfunction in Atopic Dermatitis. *International journal of molecular sciences*, *21*(8), 2867. https://doi.org/10.3390/ijms21082867

Zhong, Y., Kinio, A., & Saleh, M. (2013). Functions of NOD-Like Receptors in Human Diseases. *Frontiers in immunology*, *4*, 333. https://doi.org/10.3389/fimmu.2013.00333