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Pathomechanism of 'skin-originated' allergic diseases

Gyohei Egawa

Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan

ABSTRACT

The skin is outermost barrier of the body and protects us from various kinds of external stimuli. The barrier function of the skin is, however, not wholly perfect but include some 'security holes' where external antigen invades in. Further, external antigens themselves have some specific shunt pathways to breach the skin barrier. Recent studies revealed that percutaneous sensitization is a strong inducer of systemic immune responses and it is now considered that majority of food allergy is sensitized through body surfaces. Thus, to know about the fundamental structure of the skin barrier and its potential weak spots must be important for understanding the pathomechanism of 'skin-originated' allergic diseases. In this review, I overview the fundamental features of the skin barrier, and then, will discuss the pathomechanism how external antigens breach the barrier and induce subsequent systemic allergic reactions.

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1. Introduction

The boundary tissues such as the skin, brachial tracts and intestinal tracts are continuously exposed to external pathogens including bacteria, fungi, viruses, non-self-peptides and various kinds of chemical reagents. These tissues are the first line of defense and lots of immune cells reside in or are recruited upon inflammation to maintain the tissue homeostasis.

Among boundary tissues, the skin covers the body surfaces and has several unique structures to achieve robust barrier function [1]. The impairment of the skin barrier, such as in patients with atopic dermatitis (AD), increases the risk for allergic diseases and sometimes progress to the systemic 'atopic (allergic) March' [2]. Thus, it is important to know about the fundamental structure of the skin barrier for understanding the pathomechanism of 'skin-originated' allergic diseases.

In this review, I provide an overview of the key structures of the skin barrier and then will discuss the pathomechanism how large molecular antigens breach the barrier and cause systemic allergic diseases.

2. Features of the skin barrier

The skin is composed of the epidermis, dermis and subcutaneous adipose tissue and the epidermis is

further divided into four layers: stratum basale, stratum spinosum, stratum granulosum and stratum corneum (Figure 1(A,B)). The barrier function of the skin is largely depends on two structures in superficial area, the stratum corneum and tight junction in the stratum granulosum [1,3]. The stratum corneum is the outermost layer of the epidermis and is a hydrophobic armor for animals to survive outside of water. The tight junction is the secondary barrier structure that is formed beneath the stratum corneum. Of note, in the area which lacks the stratum corneum, the tight junction functions as a primary barrier.

2.1. Stratum corneum

The stratum corneum consists of piles of dead keratinocytes (corneocytes) (Figure 1(B)). In the stratum granulosum, keratinocytes become flattened and denucleated. After the denucleation, they are called corneocytes. Their cell membranes are replaced by highly crosslinked insoluble proteins, which is called cornified envelope. Further, intercellular spaces of corneocytes are filled with lipids and the lipids are anchored on the cornified envelope. These structures are often described as the 'bricks' (corneocytes) and 'mortar' (intercellular lipids), which together provide a highly hydrophobic barrier against the environment (Figure 1(C)).

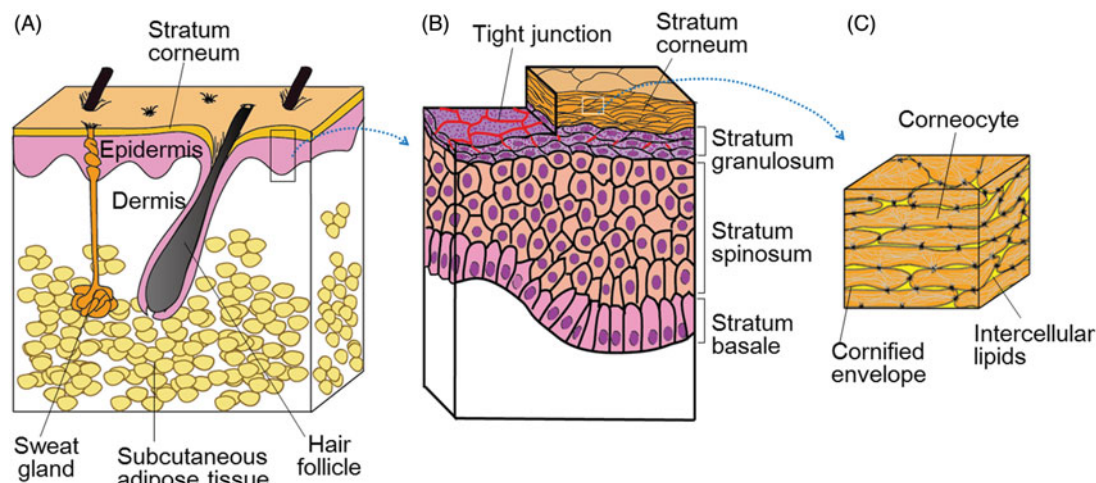


Figure 1. Essential barrier structures of the skin. (A) The skin consists of three layers: the epidermis, the dermis and subcutaneous adipose tissue. (B) The structure of the epidermis. The red line represents tight junctions in the stratum granulosum. (C) The 'bricks and mortars' structure of the stratum corneum.

For the barrier integrity, the whole body should cover with stratum corneum; however, there are many 'holes' in it, for the skin appendages such as hair follicles and sweat ducts. Due to the absence of the stratum corneum, skin appendages are the major route for the transepidermal water loss (inside-to-outside route) and vice versa, for the external antigen invasion (outside-to-inside route). In the skin appendages, the tight junctions are the primary barrier and they limit the molecules that enter into the skin.

2.2. Tight junctions

Tight junctions are composed of transmembrane proteins, such as the claudin and occludin family, and several cytosolic scaffold proteins, including zonulae occludens (ZO)s [4]. The indispensable role of TJs in skin homeostasis was first demonstrated by claudin1-deficient mice that died within 24 h of birth with severe dehydration [5].

In the interfollicular epidermis, tight junctions seal adjacent keratinocytes in the stratum granulosum (Figure 1(B)). In the hair follicles, tight junction barrier is formed in the outermost living layer, thus, the continuous tight junction barrier along interfollicular epidermis and hair follicles is maintained [6]. Tight junction barrier is also maintained in the sweat ducts [7].

2.3. Barrier in skin appendages

Barrier function of skin appendages, which organized by tight junctions, are of great interest because they might be an entry point of external antigens/pathogens. Indeed, percutaneous viral infections such as verruca (percutaneous infection of human papillomavirus [HPV]; Figure 2(A–C)) and Kaposi

varicelliform eruption (percutaneous infection of *human herpes simplex* [HSV]; Figure 2(D)) begin in the skin appendages [8,9]. Further, the initial skin eruptions of irritant contact dermatitis are sometimes start from skin appendages, suggesting that chemical reagents enter into the skin also through the skin appendages, not through the stratum corneum of interfollicular area. Importantly, the claudin1 expression is reduced in patients with AD, and the association of claudin1 polymorphism with AD susceptibility has been reported [10]. These facts suggest that the skin appendages are the 'security holes' of the skin, particularly in AD patients with tight junction deficiency.

On the other hand, skin appendages are the major shunt routes into the skin for drugs which applied topically on the skin [11]. It is well-known that molecules less than molecular weight 1000 can pass through the tight junction barrier in the skin appendages [12,13]. Indeed, the drugs which meet this limitation are available as topically applied drugs. This limitation can also carry over to the oral drugs or inhaled drugs, as the barrier function in mucous membrane, such as in intestine or brachial tracts, are organized by tight junctions. As drugs which molecular weights are greater than 1000 cannot pass through these tight junctions, they must be directly injected into the body (e.g., hypodermic, intramuscular, intravascular injection).

3. Shunt route for large molecular antigens

To understand the pathomechanism of allergic skin inflammations, it is important to pay attention to the size of antigens. Most contact dermatitis is caused by haptens [14]. Haptens are small molecules (less than molecular weight 1000) that acquire antigenicity only when binding to self-proteins in the

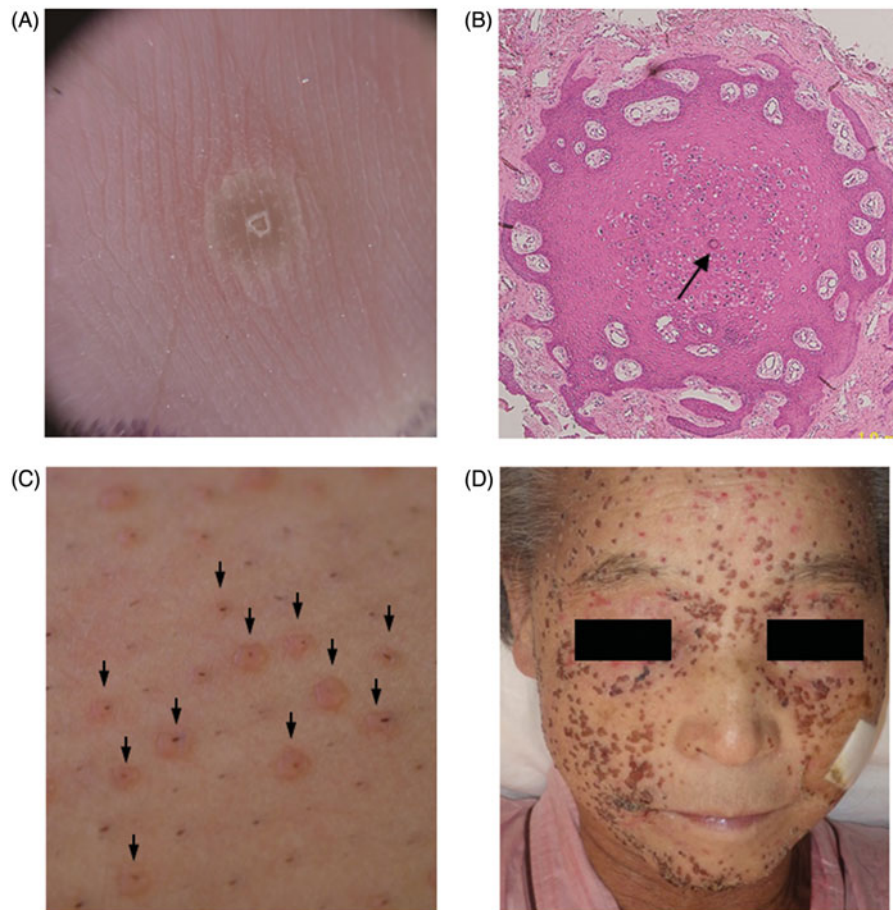


Figure 2. Clinical feature of percutaneous virus infection. (A–B), Clinical photo (A) and histology (B; horizontal slice) of a Myrmecia (HPV1 infection) on the sole. Arrowhead denotes a eccrine duct in the epidermis. (C) Clinical photo of flat wart (HPV3 infection). Arrowheads denote hair follicles. (D) Clinical photo of Kaposi varicelliform eruption. The eruptions formed at skin appendages.

skin. Small molecules that do not bind to self-proteins have no hapten-activity. Haptens, such as fluorescent isothiocyanate (FITC), can easily pass through the tight junction and penetrate to the dermis under physiological conditions (Figure 3(A)). In contrast, large molecular antigens, such as protein and glycans, are too large to penetrate tight junctions and cannot diffuse into the underlying tissues (Figure 3(B)).

Then, how large molecular antigens breach the skin barrier? There are several specific pathways as described below.

3.1. Small traumas

External large molecular antigens need to pass through the stratum corneum and/or tight junction barrier to enter into the skin. If these barriers are disrupted by small traumas, protein-antigens easily reach the internal area (Figure 4(A)). Particularly, small traumas are often formed in hands, soles, lips and oral cavity and genital area where frequently expose to external forces such as frictions. These areas are major entry point of infectious pathogens such as HPV, HSV and *human immunodeficiency viruses* (HIV). As scratch scar is a kind of small traumas, it is possible

to think that severe itching sometimes found in AD patients is a risk factor of barrier disruption and subsequent sensitization by large molecular antigens.

3.2. Bites/stings

Bites and stings by insects, animals or plants are other pathway for percutaneous sensitization by large molecular antigens. Like needles, bites and stings avoid the skin barrier structures and large molecular antigens are directly delivered to internal area (Figure 4(B)). Therefore, for example, if tick saliva includes any cross-antigens that are also contained in food, tick bite-induced food allergy can be induced. As is well known, bites/stings sometimes also transmit infectious agents such as in malaria, Lyme disease and Tsutsugamushi disease.

3.3. Protease activity of antigens

Some protein-antigens, such as allergens from house dust mites, fungi and pollens, have protease activity and often act as strong sensitizer (Figure 4(C)) [15,16]. As these proteolytic antigens can break the tight junctions but not lyse the stratum corneum,

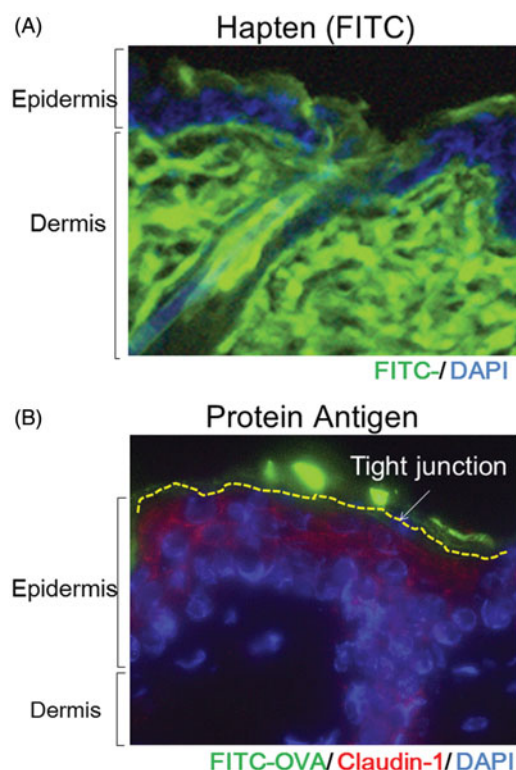


Figure 3. Penetration of haptens and protein antigen into the skin. (A) Fluorescein isothiocyanate (FITC; molecular weight = 389) or B. FITC-conjugated ovalbumin (molecular weight = 66,000) were painted onto the ear skin. Twenty-four hours later, the ears were harvested and nuclei (blue) and Claudin 1 (red) were visualized. FITC (green) distributed into the dermis (A) probably mainly through the hair follicles and cracks in the stratum corneum, while FITC-OVA (green) remained outside of the tight junctions (B).

they invade into the body probably through the sites where lack the stratum corneum such as erosive lesion, mucous membranes including conjunctiva, oral/nasal cavities, respiratory tracts and possibly through the skin appendages. These antigens often become a cause of allergic conjunctivitis, allergic rhinitis and allergic asthma.

3.4. Skin inflammations

The skin inflammations itself is a risk factor of percutaneous sensitization by large molecular antigens. There is two mechanisms how inflammation impairs skin barrier functions; the first mechanism is mediated by activated Langerhans cells [17]. Langerhans cells are antigen-presenting cells which reside in the epidermis. They elongate long dendrites into the space between keratinocytes to capture the antigens. In the steady (non-inflammatory) state, the dendrites of Langerhans cells remain beneath the tight junction; however, during inflammation, activated Langerhans cells elongate their dendrites outward beyond the tight junction and uptake external antigen (Figure 4(D)). This becomes another shunt route into the skin for large molecular antigens.

The second mechanism is mediated by proinflammatory cytokines. Previous studies have shown that interleukin (IL)-4 and IL-13, the two major Th2 cytokines, downregulate the production of Filaggrin (FLG) and other barrier-associated molecules such as keratins, loricrin, involucrin, ZO-1 and ceramide lipids, thus, cause barrier dysfunctions both in the stratum corneum and the tight junctions [18,19]. These facts suggest that to control the skin inflammation in AD patients is of great importance in terms of recovering the skin barriers functions.

4. Percutaneous sensitization and allergic diseases

As described, large molecular antigens sometimes breach the skin barrier and induce allergic responses. In this section, I will focus these 'skin-originated' allergic diseases (Table 1). We should note that large molecular antigens such as proteins/glycans tend to induce humoral-mediated systemic immune response like urticaria and sometimes lead to anaphylaxis, while haptens induce cell-mediated, local immune responses, for example, eczema.

4.1. Latex-fruits syndrome

Latex is an allergen that contained in the natural rubber [20]. Latex-fruits syndrome often occurs in medical service workers who use rubber gloves. The patients who sensitized with latex may cause allergic reaction when they intake some plant-derived foods such as avocado, banana, chestnut, kiwi, peach, tomato and potato. We should note that protein antigen latex is sensitized percutaneously, probably through the hand eczema which disrupts the skin barrier to be competent to large molecular antigens. This disease is a representative skin-originated systemic allergic disorder that caused by small skin traumas and local inflammations.

4.2. Allergy for cochineal dye

Cochineal is a scale insect and its extract is used as a dye [21]. Cochineal dye is generally used for coloring fabrics, cosmetics and food coloring. Importantly, allergy for cochineal dye has reported only in woman, suggesting that antigen in cosmetics, probably cochineal dye in lipsticks, may the cause the sensitization. The lip often have some small traumas and inflammations, thus, may competent to large molecular antigens. Together with latex-fruits syndrome, this disease is a representative allergy model that caused by small traumas and local inflammations.

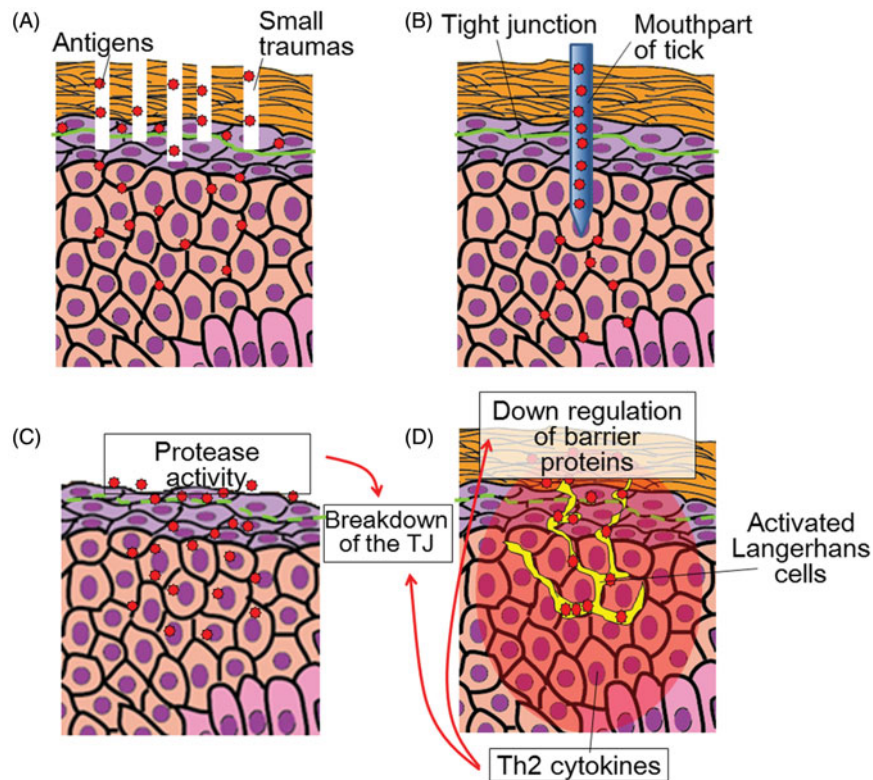


Figure 4. For ways of percutaneous antigen invasion. (A) Antigens can pass through the skin barrier through small traumas. (B) Bites/stings directly deliver antigens into the dermis. (C) Some antigens have protease activity and brake tight junctions. (D) Local skin inflammation activates epidermal Langerhans cells to uptake the external antigens beyond the tight junctions. Th2 cytokines downregulate barrier-associated proteins. TJ: tight junction.

Table 1. ‘Skin-originated’ allergic disorders.

Disorder	Allergens	Site of allergen entry	Mechanism of allergen entry
Contact dermatitis	Haptens	Anywhere on the skin	Free entry
Latex-fruits syndrome	Latex	Hands	Small traumas/Local inflammations
Cochineal dye allergy	Cochineal extract	Lip	Small traumas/Local inflammations
Pollen-food syndrome	Profilin, PR-10	Eyes/Respiratory tracts	Protease activity
Meat allergy	α -gal	Skin	Tick bites
Natto allergy	γ PGA	Skin	Jellyfish stings

4.3. Pollen-food syndrome

Pollen-food syndrome, also known as oral allergy syndrome, is caused by cross-reacting allergens found in both pollen and raw fruits, vegetables or some tree nuts [22,23]. Patients experience swelling and itching at lips and/or oral cavity. The major antigen is profilin and PR-10. Profilin is contained in the pollens of ragweed and rice, as well as avocado, banana, watermelon, cucumber and pineapple. PR-10 is contained in the pollens of white birch, as well as peach, apples, pears, cherries and soybeans. This disease is a representative allergy model that caused by proteolytic antigens.

4.4. Allergy for meats

Meat allergy is initiated by tick bites [24]. The common allergen between tick saliva and meats is galactose- α -1,3-galactose (α -gal). α -gal is included in beef, pork and lamb. Importantly, α -gal also exist in

cetuximab, an monoclonal antibody against epidermal growth factor receptor (EGFR) [25]. Cetuximab is used for the treatment of colon cancers and cancer of head and neck lesion. Thus, we need check the presence of meat allergy when we start cetuximab in clinic. This disease is a representative allergic model that caused by bites/stings.

4.5. Allergy for ‘natto’

Japanese traditional food ‘Natto’ is fermented soybeans. During the fermentation, poly- γ -glutamic acid (γ PGA) is produced. The patients who have allergy to Natto are sensitized with γ PGA. Interestingly, sensitization to γ PGA occurs in the sea. γ PGA is included in jellyfish stings, thus, most Natto allergy patients are Japanese surfers [26]. Together with beef allergy, this disease is a representative allergic model that caused by bites/stings.

5. Conclusion: toward the management of skin barrier function

As percutaneous antigen uptake strongly induces allergic responses, maintaining the skin barrier function is important to prevent the development of allergic diseases. Recently, two groups investigated whether protecting the skin barrier during the neonatal period prevents the development of AD [27,28]. In these studies, neonates who have family history of AD were recruited and were treated with moisturizer at an early stage of life. They reported that the strict moisturizer treatment suppressed the development of food allergy, as well as decreased the incidence of AD. These results suggest that reinforcing the skin barrier function in the neonatal period is a promising strategy to avoid the development of allergic diseases, particularly in barrier-deficient individuals.

Another strategy to reinforce the skin barrier function should be to enhance the production FLG in the skin. FLG is a key molecule for the barrier function of the stratum corneum and mutation in FLG gene is the strong predisposing factor for AD development [29]. Candidate drugs include agonists of peroxisome proliferator-activated receptors (PPARs) [30], a serine-rich diet [31], apigenin [32], JTC801 [33], JTE-052 [34] and urea [35]. All of these drugs have been demonstrated to induce keratinocyte differentiation and increase FLG expression levels. Recently, anti-IL-4 receptor- α antibody dupilumab was started to use in clinic for the treatment of severe AD patients [36]. Dupilumab blocks the Th2 cytokine signals, thus, is expected to strengthen the skin barrier functions.

Intensive research to identify promising candidates to enhance the skin barrier function is ongoing and in the near future, it is expected to lead to better management of AD and prevention of subsequent development of allergic diseases.

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Disclosure statement

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