

Skin Barrier Dysfunction and Systemic Sensitization to Allergens Through the Skin

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Abstract: Most allergic, atopic and hypersensitive reactions are associated with Th2-biased immune responses and allergen-specific IgE antibodies. Pathological allergic disorders are on an alarming increase in the industrialized world. Understanding the mechanism of primary sensitization to allergens is important in elucidating the pathogenesis of these diseases and for possibly preventing their development. In this article, we review recent information supporting that epidermal allergen exposure may contribute to systemic allergic diseases and that atopy may be secondary to skin barrier dysfunction in some dermatoses. The skin is an active immunological organ, which functions as a primary defence and biosensor to the external environment. The critical permeability barrier function is mediated by the outmost layer of the epidermis, the stratum corneum. Perturbation of the stratum corneum initiates a chain of event, which activates homeostatic responses in the underlying epidermis. Repeated barrier-disruption, whether environmentally or genetically determined, may however stimulate signaling cascades that lead to inflammation and epidermal hyperplasia. Skin barrier dysfunction may also allow entry of allergens, which can lead to primary systemic sensitization. The altered epidermal microenvironment in barrier-disrupted skin appears to be particularly well suited for the induction of potent Th2-type responses with production of allergen-specific IgE. Epidermal exposure to food antigens can prevent the normal induction of oral tolerance and also lead to airway eosinophilia following inhalation. Exposure to allergens on barrier-disrupted skin may as such serve as a natural sensitization pathway for food allergy and respiratory allergic disease.

Keywords: Skin, barrier dysfunction, langerhans cells, atopic dermatitis, allergy, Th1/Th2 cells, oral tolerance.

INTRODUCTION

The pathogenesis of hypersensitivity, atopic and allergic reactions has been described primarily as a polarised Th2 CD4⁺ response. Most of these conditions are associated with an increased and sustained allergen-specific IgE production, which mediates immediate Type I allergies upon re-exposure to the specific allergen. The incidence and severity of allergic and atopic disorders has steadily increased in the industrialized world over the past 2 to 3 decades [1,2] while their prevalence in developing countries is considerably lower [3]. Why the immune system of individuals in developed countries at an increasing rate is over-responding to environmental and food antigens by making IgE and pathogenic Th2 responses is not known. However, the mechanism of primary sensitization to protein allergens is clearly important in the pathogenesis of these diseases. Interfering with or preventing the development of IgE-mediated responses must be a prime intervention target if the increase of atopic conditions is to be halted.

Both genetic and environmental factors as well as the nature of the sensitizing antigen and the frequency of exposure contribute to the ontogeny of allergic sensitization. Additionally, the route of allergen exposure and the microenvironmental milieu of the specific tissue at the time of exposure may play a pivotal role in determining the

immunological outcome of an allergen encounter. The immune system is most likely to have primary contact with allergens at the interior or exterior body surface, i.e. the gut, the nose, the lung or the skin. Multiple cell types and specific microenvironmental factors at these tissue sites can thus determine the local and systemic response to a particular allergen. The route of antigen exposure has a direct impact on the IgE response and the severity of anaphylactic reactions [4]. The skin is a particularly potent route of induction of Th2 and IgE responses [4,5]. In this review, we will discuss antigen uptake through the skin and the potential development of systemic allergic sensitization by epicutaneous exposure to allergens.

CAUSES OF ALLERGIC DISEASE

Genetic Susceptibility

The ontogeny of allergic and atopic responses is difficult to determine and is most likely a consequence of complex interactions between both genetic and environmental factors. Several genetic polymorphisms have been identified which are likely to contribute to the allergic pathogenesis. Non-specific tendencies to produce high levels of IgE are linked to chromosome 5q31-33 [6]. This region of chromosome 5 codes for multiple Th2 cytokines (e.g. IL-4, IL-5, IL-13 and GM-CSF) [7]. Clinical atopy and the production of allergen-specific IgE has also been linked to 11q12-13 and may be related to polymorphisms of the high-affinity IgE receptor β chain [8,9]. Mutation in the SPINK5 gene on chromosome 5q32, which encodes a serine protease inhibitor, LEKTI,

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expressed by keratinocytes has been shown to cause Netherton syndrome and be critically important in epidermal barrier function [10]. It has been suggested that mutations in SPINK5 cause a distinctive barrier dysfunction with defective cornification [11]. Polymorphisms in SPINK5 show significant association with atopy, allergic disease and atopic dermatitis (AD), suggesting a novel pathway responsible for high serum IgE and atopic disease [10,12].

Environmental Conditions and the Hygiene Hypothesis

Environmental factors undoubtedly also play an important role in the development of atopic disease and IgE production. As the natural gene mutation rate in the population is low, altered environmental and/or lifestyle conditions are ultimately thought to be responsible for the fast increasing prevalence of allergic disease. The theory that has attracted most attention to explain this continuous rise in allergy is 'the hygiene hypothesis', first proposed by Strachan and coworkers [13] and reviewed in [14-17]. This hypothesis proposes that a cleaner environment and frequent use of antibiotics resulting in fewer childhood infections promoting Th1 responses predisposes individuals to later allergic Th2 dominated responses. In particular, prenatal and early childhood are considered to be critical intervals for viral and bacterial infections to prevent allergic Th2 responses and for establishment of the Th1/Th2 balance. A number of epidemiological and clinical studies support this hypothesis [18-21]. However, other studies suggest that viral and/or bacterial infections exacerbate allergic diseases such as bronchial asthma, airway hyperresponsiveness and atopic dermatitis [16]. Additionally, an immunological switch to a Th2 response does not *per se* give rise to an increased frequency of allergy. Pregnancies [22] and chronic helminth infections [23,24] are examples in which a Th2 dominance does not give rise to enhanced incidence of allergy or atopy. The dramatic increase of allergic and atopic diseases in the developed world also shows a striking correlation with Th1-mediated autoimmune diseases [25,26] and diseases of unknown aetiology such as inflammatory bowel disease [27]. An immunological framework where a general imbalance in the development of systemic Th1 and Th2 responses may thus not be sufficient to explain allergic disease. The positive association between common allergic and autoimmune disorders indicate that the potential root cause of the increase in allergic diseases might be the same as that responsible for the escalation in Th1 autoimmune disorders and implies a general increase in immunodysregulatory diseases. It may be that persistent immune challenges in childhood does not specifically dampen Th2 allergic responses but induces the development of a robust regulatory network, which protect against excessive Th2 as well as Th1 diseases [23].

Lifestyle Triggers

Exposure to allergens is common throughout the world yet there is a striking variation in the prevalence of atopic and allergic diseases worldwide. Countries like the UK, Australia and the USA have the highest incidence of atopic eczema and asthma while these diseases are up to 60-fold less prevalent in several Eastern European countries and countries in Southeast Asia and Africa [3]. Immigration

from a low-prevalence country to a high-prevalence country increases the frequency of atopic diseases in the immigrating population [28]. The rise in atopic and allergic diseases in the Western world correlates with a rise in general living standards. Together, this strongly suggests that lifestyle factors are important in the development of atopic diseases.

Over the last 3-4 decades there has been a rising emphasis on general cleanliness and personal hygiene. The use of water for personal washing has gone up enormously as has the use of soaps, syndets and detergents. There is a positive epidemiological association between high personal hygiene as measured by the frequency of hand and face washing, bathing and showering and the development of atopic eczema and wheeze in children [29]. This is predicted by the hygiene hypothesis. However, it may not be the relative lack of infections or exposure to pathogens that is promoting an increased frequency of allergy in the Western world, but that the way we are exposed to allergens has changed. Use of water for washing and especially the use of soap and detergents may cause trauma to the skin. Additionally, lifestyle-associated changes in psychological stress appear to induce skin irritability and actual epidermal barrier dysfunction [30,31]. There thus seems to have been a general increase in environmental factors causing trauma to the skin and it may be that exposure to allergens on such distressed skin, which is naturally prone to making Th2 responses, is contributing to an allergic phenotype in susceptible individuals.

SKIN BIOLOGY AND ATOPIC DERMATITIS

Skin Anatomy

The skin functions as a primary defence, a sensory and secretory organ and a critical regulator of body temperature. It consists of several distinct layers with specialized cell types. It is divided into two main compartments: the epidermis and the dermis, which are separated by a thin basement membrane. The epidermis is the outer compartment and consists of a layer of stratified squamous epithelium comprised 95% of keratinocytes. The keratinocytes undergo a tightly regulated differentiation process to serve as a barrier between the skin-associated lymphoid tissue and the external environment. Resistance to microbes, environmental agents, chemicals and ultraviolet radiation is mediated almost entirely by the outmost layer of the epidermis – the stratum corneum [32,33]. Beneath the stratum corneum and interspersed in the keratinocyte layer are specialised antigen presenting cells known as Langerhans cells (LCs), which constitute approximately 2-4% of all epidermal cells [34], and a population of intraepithelial T lymphocytes. The epidermis is separated from the thicker dermis by the complex barrier of the basement membrane where collagen fibrils are tightly packed to form a very dense meshwork [35]. The underlying dermis also consists of a dense collagen meshwork but is less compact than the basement membrane. The dermis and especially the perivascular area contain the highest concentration of immune response-reactive cells of the skin. Dermal dendritic cells (DCs), mast cells, monocytes, macrophages and T cells are present in large numbers close to the vascular endothelial cells [36].

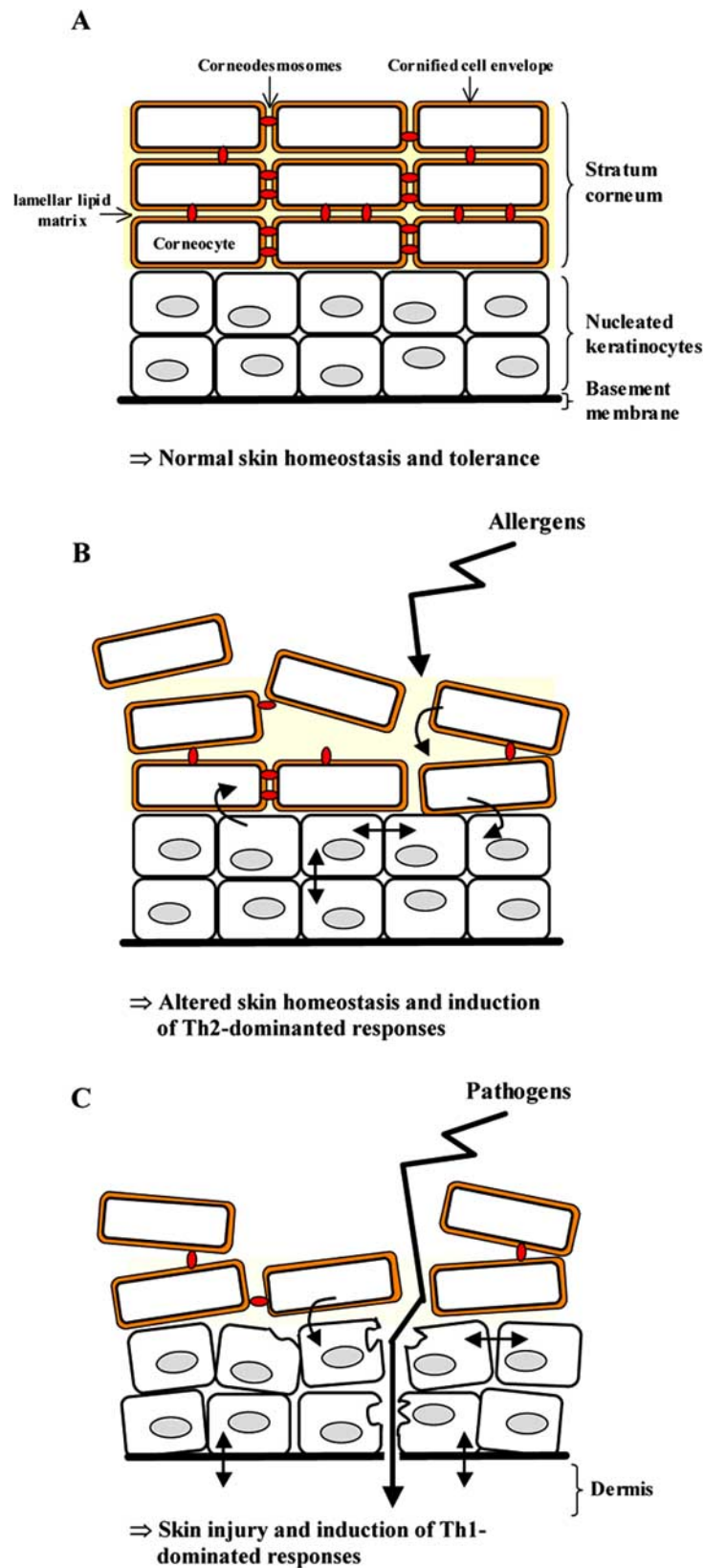


Fig. (1). Epidermal structure and function under normal and perturbed conditions.

Different degrees of epidermal barrier-disruption elicit variable response patterns. (A) "Brick and mortar" representation of normal stratum corneum and the underlying keratinocytes layer. (B) Intracorneal break-up and permeability dysfunction induces a cascade of metabolic events and cytokine secretion in the corneocytes and keratinocytes (small arrows). Exposure to allergens may cause systemic Th2-dominated responses. (C) Deep epidermal injury extending onto the basement membrane and into the dermis. Cytokine and chemokine release in the dermis (small arrows) will induce Th1-dominated responses and attract leucocytes from the circulation to fight invading pathogens.

Keratinocytes play an important role in the immune system of the skin and influence a wide variety of physiological and pathological processes. They are capable of producing and secreting a large array of immune-mediators including IL-1, IL-3, IL-6, IL-7, IL-8, IL-10, IL-12, IL-15, IL-18, IFN- α , β and γ , TNF- α , TGF- α and β , GM-CSF, M-CSF, a steadily increasing number of chemokines as well as various growth factors [36,37]. Most of these biological response modifiers produced by keratinocytes are not constitutively expressed *in vivo*, but can be induced after perturbation of the epidermal homeostasis [36-40]. Upon any epithelial injury, keratinocyte-derived factors act on immune-response cells and stimulate expression of endothelial adhesion molecules necessary for leukocyte migration to and from the circulation. The skin lacks any organised lymphoid tissue within the dermal stroma and induction of immune responses does not normally occur within the skin itself [36]. The migratory capacity of epidermal LCs and dermal DCs thus becomes pivotal in bridging the sites of antigen uptake and clonal T cell activation in draining lymph nodes.

Stratum Corneum and Desquamation

The essential epidermal permeability barrier resides in the stratum corneum, which is the true interface with the external environment and a prerequisite for life. The stratum corneum is a highly specialised two-compartment structure arising from exocytosis of the lipid content of epidermal lamellar bodies and through the terminal differentiation of keratinocytes that culminates in the formation of corneocytes [41,42]. The stratum corneum has been likened to a brick wall in which the compressed corneocytes representing the bricks are embedded in the 'mortar' of the continuous matrix of specialised lipids (Fig. 1A) [32]. The lipid bilayers of the stratum corneum are unique among biological membranes in terms of organization, composition and physical properties. The major lipids in the stratum corneum are ceramides, fatty acids and cholesterol which together form the intercellular cement and maintains the critical barrier to water loss (reviewed in [33]). However, the overall integrity and cohesion of the stratum corneum is primarily dependent on specialized intercellular protein structures called corneodesmosomes (Fig. 1A). These structures are composed of proteins such as desmoglein-1 and desmocollin-1. Another protein, corneodesmosin, appears to coat their external surfaces and initially make the corneodesmosomal structure resistant to proteolysis. This plays a critical role in the cohesiveness of corneocytes in the stratum corneum [43,44].

In the normal epidermis, the continuous generation of corneocytes is balanced by cell shedding on the external surface in a tightly regulated process known as desquamation. The corneodesmosomal structures represent the primary cohesive force in the stratum corneum and these must be degraded to facilitate desquamation and thus maintenance of a constant tissue thickness. Several proteases, especially the serine proteases stratum corneum chymotryptic enzyme (SCCE) and stratum corneum tryptic enzyme (SCTE), are involved in corneodesmosome proteolysis and the ultimate desquamation of corneocytes from the stratum corneum surface [45,46]. Recent studies

suggest that the activity of these proteases are controlled by localized changes in pH and water concentration (reviewed in [32,33]). Normal stratum corneum displays an acidic surface, while both the SCCE and SCTE exhibit neutral to alkaline pH optima [45]. Neutralizing stratum corneum pH induces abnormalities in both stratum corneum integrity, cohesion and permeability barrier homeostasis. The changes in integrity and cohesion are probably due to an increase in serine protease activity induced by stratum corneum neutralization, as these abnormalities in barrier function can be reversed by coapplication of serine protease inhibitors [47]. Enhanced activity of SCCE/SCTE could initiate corneodesmosome degradation in the lower layers of the stratum corneum and pathological desquamation of the skin. In addition, an acute increase in stratum corneum pH reduces the activity of key lipid-processing enzymes resulting in abnormal lipid-processing and the formation of defective lamellar membranes and thus in a disrupted permeability barrier [47]. Similar disruption of the intercellular lamellar bilayers and increased corneodesmosome degradation is induced by prolonged water contact [48,49], while a dry environment enhances epidermal permeability barrier function [50].

The stratum corneum is, as described, enzymatically very active and functions as a biosensor between the nucleated cell layers and the external environment. Perturbation of the barrier function stimulates release of IL-1 α from preformed pools in the corneocytes [51], which initiates a variety of signaling events activating responses in the underlying epidermis. Levels of TNF- α , IL-1 α , IL-1 β and GM-CSF are quickly elevated several-fold in the epidermis following disruption of the stratum corneum [38-40] and expression of MHCII and costimulatory molecules such as CD54, CD86, CD40 and CD11c are increased on LCs [38]. TNF- α , IL-1 β and IL-18 all play important roles in the induction of LC migration from the epidermis [52-54] and may also promote the maturation of LCs into immunostimulatory DCs. The chain of events that is initiated after an acute perturbation of the barrier ultimately leads to the return of lipids to the stratum corneum and a fast restoration of barrier function. The augmentation of immune reactivity may also be critical for the elimination of microbes or other environmental antigens that gain access to the barrier-disrupted epidermis. However, repeated barrier-disruption may sustain not only the desired epidermal homeostatic response but stimulate signaling cascades that lead to inflammation, epidermal hyperplasia and involvement of the deeper skin layers [55]. It may also result in unwanted immune and/or inflammatory responses to innocuous agents and antigens.

Langerhans Cells

LCs are members of the wider family of DCs but are phenotypically and functionally distinct from the dermal DCs [34]. They reside as a contiguous network above the basal layer of proliferating keratinocytes in the epidermis, where they serve as sentinels of the immune system sampling antigens and responding to changes in the environment. They are the primary antigen-presenting cell (APC) to encounter antigens that get through the stratum corneum and they have potent antigen processing and presenting capabilities. Following antigen uptake they can

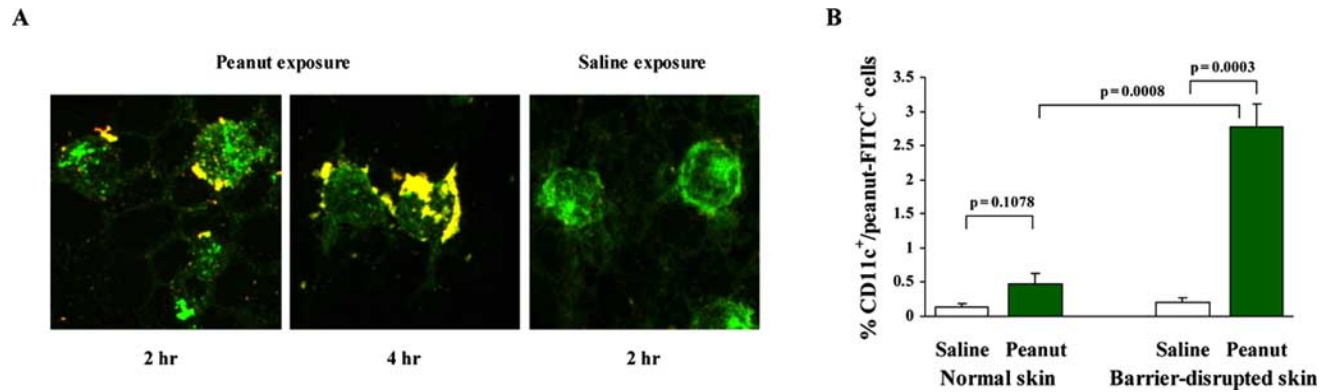


Fig. (2). Langerhans cell migration from the epidermis to draining lymph nodes.

LCs transport antigen from the skin surface to the T cell areas of draining lymph nodes. (A) Confocal microscopy images of fresh epidermal sheets isolated from BALB/c mouse skin after barrier-disruption by adhesive tape-stripping, followed 24 hr later by application of peanut protein. MHCII⁺ LCs (green) have picked up peanut antigens (yellow) 2 and 4 hr after epicutaneous peanut exposure. Note the 'cobblestone' pattern of dimly MHCII⁺ keratinocytes. Original magnification x300. (B) Percentage of CD11c⁺/peanut-FITC⁺ LCs that have reached the draining lymph nodes 18 hr after application of FITC-conjugated peanut protein or saline on barrier-disrupted or normal skin of BALB/c mice as determined by flow cytometry. Results are expressed as mean + 1 SEM of four individual experiments.

relay antigenic information to the adaptive immune system by migrating from the epidermis to the draining lymph nodes, where they present processed antigen to naïve or memory T cells [56,57]. LCs are therefore key regulators in both the quantitative and qualitative development of systemic immune responses to antigenic challenge on the skin surface.

There is evidence to suggest that LCs naturally favour the induction of Th2-type immunity when exposed to protein antigen in the absence of adjuvants [5]. *In vivo*, antigen breaching the stratum corneum and reaching the keratinocytes layer is taken up by LCs which migrate to the draining lymph nodes and induce potent immune responses with a strong Th2-bias (Fig. 1B, Fig. 2 and Fig. 3). In contrast, antigen-delivery into the dermis gives rise to predominantly Th1-type immune responses (Fig. 1C and Fig. 3) [5]. *In vitro*, T cells grown with cultured LCs produce IL-4 and induce IgE production by B cells, consistent with a Th2 bias by this route of antigen presentation [58]. The immunological microenvironment and DCs at other body surface sites also appear to induce predominantly Th2 responses when challenged with protein antigen. Exposure of the lung to aerosolized chicken egg ovalbumin (OVA) without adjuvant results in IgE production and airway hyperresponsiveness in the mouse [59]. Furthermore, resting DCs in the respiratory tract preferentially stimulate Th2 responses and require additional cytokine signals for induction of Th1 immunity [60]. Intranasal exposure to OVA also induces Th2 type responses with IgE production [4,61]. DCs residing at the body surfaces may also have a specialised role by inducing tolerance rather than immunity. Gut lamina propria DCs usually reside in an immature state lacking a full range of costimulatory molecules such as CD80/CD86, CD40 and CD54. These cells may be tolerogenic if they present antigen in absence of inflammation [62,63]. Proliferation but not maturation of DCs *in vivo* with Flt3L enhances the induction of oral tolerance [63] while simultaneous

proliferation and maturation of DC *in vivo* with Flt3L and IL-1 α , indicated by expression of high levels of MHCII and costimulatory molecules, abrogates the induction of oral tolerance and active immunity is achieved [64]. It may be that the immunological microenvironment at the body surface and the LC and DC networks within are naturally prone to promote tolerance and/or to dampen down Th1 responses without affecting Th2 responses when exposed to antigen only at the surface. This may be a mechanism to prevent inflammation at the body surface and to avoid eliciting damaging immune responses towards harmless symbiotic microbes. Inappropriate Th1 immune responses generated at body surfaces may cause injury allowing microbes access to deeper layers. On the other hand, strong Th1-type immunity may be initiated - and needed - if foreign antigen has invaded further into the body as a result of injury or damage to the surface integrity (Fig. 1C and Fig. 3).

Following an initial induction of Th2-type immunity, production of IL-4 and IL-13 induces class switching to IgE in B cells. IgE can in turn regulate the expression of its own receptors, the high affinity Fc ϵ RI receptor and the low affinity IgE receptor (CD23) on mast cells and basophils [65,66]. IgE-dependent upregulation of Fc ϵ RI and CD23 thus serves as an amplification mechanism in IgE-reactions, and mast cell and basophil mediators can be released at lower concentrations of the specific antigen. In addition, the expression of Fc ϵ RI on DCs is thought to play a major role in the perpetuation and escalation of allergic disease. LCs express Fc ϵ RI in normal resting skin but the expression of both Fc ϵ RI and CD23 is highly increased in allergic disease. In AD, levels of Fc ϵ RI on LCs are significantly higher in both lesional and non-lesional skin compared to healthy skin, and the expression of Fc ϵ RI on LCs correlates with serum levels of IgE [67,68]. Fc ϵ RI on LCs bind specific IgE, which upon ligation with allergen is internalised by receptor-mediated endocytosis. Uptake, processing and presentation of allergen by this route is of a superior

efficiency and specificity to antigen capture *via* non-specific adsorption, fluid phase pinocytosis and macropinocytosis and ultimately leads to a higher density of specific peptides in surface MHC class II molecules [69-72]. In an atopic environment with elevated levels of IgE and increased expression of FcεRI on LCs this receptor will thus serve as an allergen-focusing molecule and exacerbate allergic inflammation by increasing the activation of allergen specific Th2 cells.

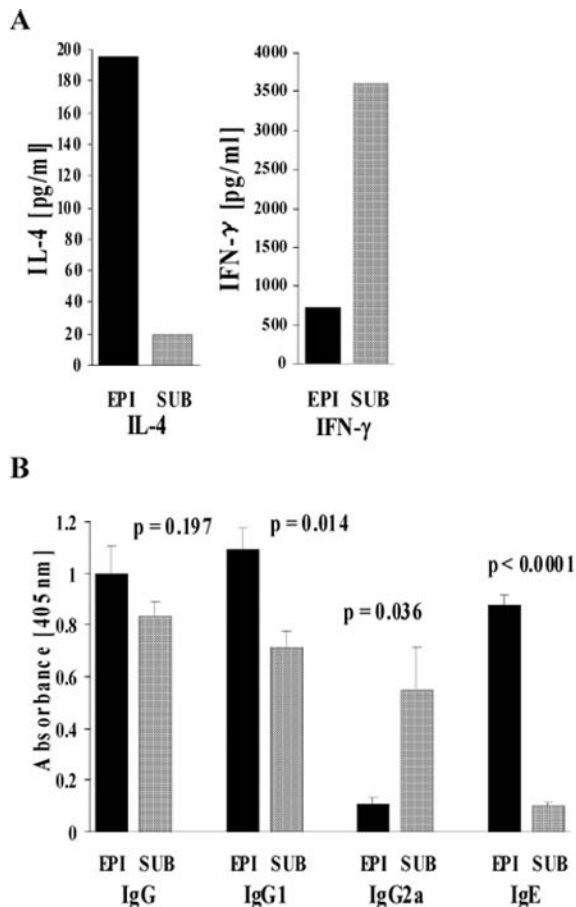


Fig. (3). Exposure to allergens on distressed but not injured skin induces potent Th2-biased immunity.

Epidermal allergen delivery onto barrier-disrupted skin causes a different systemic immune response than dermal allergen delivery. Epicutaneous exposure induces potent Th2-biased immunity with high production of IgE, while dermal exposure induces predominantly Th1 immunity. (A) IL-4 and IFN-γ responses to peanut protein in draining lymph node cells of BALB/c mice 3 weeks after epicutaneous peanut exposure on tape-stripped skin (EPI) or dermal peanut exposure following subcutaneous immunization into the dermis (SUB). (B) Peanut-specific IgG, IgG1, IgG2a and IgE levels in serum 3 weeks after epidermal (EPI) or dermal peanut protein exposure (SUB). Results are expressed as the mean antibody level + 1 SEM (n=6).

Atopic Dermatitis

Atopic dermatitis (AD) is an example of a common inflammatory dermatoses with epidermal pathology. It is a multifactorial, chronic, relapsing inflammatory skin disease characterised by typically distributed eczematous skin lesions with lichenification, pruritic excoriations, severely

dry skin and a susceptibility to cutaneous infection (recently reviewed in [73,74]). The incidence of AD has increased steadily over the past 20-30 years and is now estimated to affect up to 25% of the paediatric population [75]. A unifying pathogenetic concept of AD has not been established, although it is generally viewed as an immunologic disorder [73,74]. Impaired function of the epidermal barrier is characteristic of AD, and is seen even in areas of the skin without lesions [76]. The existence of defects in skin permeability barrier function is well accepted in AD but is commonly thought to be a consequence of the inflammatory phenotype (the 'inside-out' hypothesis) [73,77]. However, the intrinsic defect in keratinocyte biology may be important for the pathogenesis and perhaps even the *primum movens* of the disease (the 'outside-in' hypothesis) [55,78,79]. Lesional skin in AD exhibits a two- to fivefold increase in basal transepidermal water loss compared to clinically uninvolved skin and the extent of the barrier abnormality correlates with the state and severity of the dermatitis [80,81]. An altered lipid composition of the stratum corneum is a basic defect in AD and total skin surface lipids are significantly and consistently lower in AD than in normal skin resulting in higher permeability (reviewed in [78]). In particular, a decreased and abnormal production of ceramides has been reported in the skin of patients with AD, and stratum corneum ceramide content correlates with barrier function in AD [82]. In addition all dermatoses, including AD, are associated with an increased stratum corneum pH. This will stimulate a pH-induced decline in stratum corneum integrity and cohesion which may further exacerbate these conditions, resulting in more severe and/or prolonged clinical manifestations [47].

A fundamental stratum corneum barrier dysfunction may stimulate a cytokine cascade that can initiate and sustain AD, as well as other inflammatory dermatoses [55]. AD is a biphasic disease where the initial phase is predominated by Th2 cytokines that later switches to a second more chronic Th1-dominated eczematous phase [74]. Barrier-disruption and exposure to antigen induces production of IL-4 and IL-5 in the skin [83,84]. IL-4 alters the homeostasis in the skin, make LCs more efficient in taking up and processing naïve protein [85] and induces the expression of FcεRI on LCs, all of which may play an important role in the initial events of AD. Following continuous perturbation of the skin barrier and the creation of an inflammatory micromilieu, inflammatory dendritic epidermal cells (IDEC) are recruited into the epidermis and these may be involved in the chronic Th1 phase of the disease [68,74]. Because of the continuous activation of epidermal cytokines as a consequence of the underlying barrier dysfunction in AD, only minimal exogenous skin trauma may be needed to amplify cytokine production and activate disease in clinically uninvolved skin and perhaps even induce systemic atopic disease.

SENSITIZATION TO ALLERGENS THROUGH THE SKIN AND MODULATION OF SYSTEMIC TOLERANCE

Epidemiological and Circumstantial Evidence

It is well established that systemic immune responses can affect the skin, as seen in many diseases and for example after clinical food challenges in allergic individuals [86].

However, much less is known about the potential of the skin to influence systemic immunity. Several observations point to the possibility that the skin can affect the course of systemic disease. AD usually predates the development of other atopic diseases such as food allergy, asthma and allergic rhinitis by several years and there is little doubt that these diseases are interlinked in as yet undefined ways. T cells isolated from AD skin lesions proliferate and secrete Th2 cytokines such as IL-4, IL-5 and IL-13 in response to food antigens and dust-mite antigen [77,87]. Food-allergen specific T cells have also been cloned from lesional and non-lesional skin of patients with AD [88]. Likewise, T cells isolated from peripheral blood of infants with AD show increased frequency of allergen-specific T cells producing high levels of IL-4, IL-5 and IL-13, but little IFN- γ [89,90].

Nearly 80% of children with AD develop allergic rhinitis or asthma. Children with AD frequently have more severe asthma than asthmatic children without AD [91], possibly suggesting that allergen sensitization through the skin may predispose to more severe and persistent respiratory disease. Increased severity of AD is additionally directly correlated with the presence of food allergy [92]. In children there is strong exposure of the skin to foodstuffs, even when breastfed, and there often appears to be a striking association of the preferentially affected areas in AD at this age and the cutaneous exposure to food. Most food allergic children also suffer from AD. Of individuals with peanut allergy, 95% suffer from other atopic diseases, and AD is particularly prevalent. Approximately 80% react to their first known oral exposure to peanut, implying some prior occult sensitization [93]. Considering the epidermal permeability dysfunction in AD, primary sensitization through the skin is a likely possibility. AD is often managed with topically applied creams and lotions where peanut oil and vegetable oil containing small amounts of protein is a common ingredient. It has recently been shown that the use of peanut-containing creams is more widespread in children who become allergic to peanut than in control infants [94].

Experimental Evidence

Despite knowledge of the epidermal barrier defects in skin diseases such as AD and the circumstantial links to food allergy and asthma it has been a matter of controversy whether large hydrophilic molecules such as protein antigens and allergens can enter through the hydrophobic skin into systemic circulation. Whether a primary systemic immune response can be elicited through cutaneous exposure to protein antigens has only in recent years been investigated experimentally. The fact that protein allergens that are relevant to atopic disease can elicit eczematous inflammatory reactions in the skin, as in the atopy patch reaction, proves that protein antigens can enter the skin in sufficient amounts and in immunogenic form [95]. Once protein antigen has entered the epidermis it is picked up by the resident LCs and transported to the draining lymph nodes (Fig. 2). In mice, this leads to T cell activation in both lymph nodes and spleen with high levels of secreted IL-4 and only little IFN- γ . Additionally, B cells are stimulated to produce large amounts of antigen-specific IgE and IgG1 but no IgG2a (Fig. 3 EPI) [5,84,96,97]. These experiments prove that epicutaneous antigen exposure can induce primary systemic immune responses and that these are strongly Th2-biased.

The skin and the epidermal micromilieu appear to be particularly suited for the induction of Th2 immunity and epicutaneous exposure to antigen is the most potent route for the induction of IgE [4,5]. This suggests that the skin is a potential potent source of primary allergic sensitization to environmental antigens and allergens.

There is an increase in permeation of antigens through barrier-disrupted skin [38,40] and disruption of the stratum corneum may be pivotal for T cell priming and induction of potent Th2-type immunity [5]. This may however not solely be due to the increased antigenic access to the skin-associated lymphoid tissue, but also due to local responses to barrier-disruption. Among the cytokines produced after acute disruption of the stratum corneum are an array of proinflammatory cytokines as well as GM-CSF and IL-10 [39,40,98]. Normal intact skin is devoid of IL-10, but it is reported to be expressed in the epidermis soon after barrier-disruption [39,98] and may play a role in suppressing Th1 cytokine production. IL-4 and IL-5 are expressed in the skin after barrier-disruption and exposure to antigen [83,84]. Additionally, IL-13, which is highly expressed in AD skin lesions, has been shown to be critically important for Th2 generation in the skin and can substitute the need for IL-4 in mice [97,99]. It is thus conceivable that the cascade of molecular events that occur after perturbation of the epidermal barrier play a role in diminishing Th1-type responses without influencing Th2-type immunity. This could explain the dominant Th2 response that is induced to the hapten picryl chloride following corneum barrier-disruption compared to the normal Th1 contact hypersensitivity response [84].

The resident LCs in the skin may be primarily affected by the production of immunoregulatory cytokines following barrier-disruption. IL-4 has been shown to make LCs more efficient in taking up and processing naïve protein [85] and GM-CSF either alone or in combination with IL-4 augments the rate of pinocytosis by precursor DCs [100]. Disruption of the stratum corneum also changes the morphology and immunological phenotype of epidermal LCs and significantly enhances the migration of LCs following antigen exposure (Fig. 2B). This ultimately causes a marked increase in the systemic response following antigen exposure on barrier-disrupted skin [5]. However, other studies have shown a similar Th2-predominant response with production of IgE following epicutaneous exposure without prior intentional disruption of the stratum corneum [96,97,101]. These studies use a patch method where the skin is shaved and exposed to antigen for prolonged periods under occlusion. It is reasonable to assume however that both shaving and changes in hydration as a consequence of prolonged occlusion cause some stratum corneum disruption and alterations in skin immune function.

Experimental evidence has unequivocally demonstrated that primary sensitization to protein allergens can occur through the skin. The resulting Th2 immune response with strong production of specific IgE antibodies, suggests that epicutaneous allergen exposure may play a role in promoting systemic allergic disease. Indeed, some intriguing data indicate that sensitization through the skin can affect both mucosal responses in the gut-associated lymphoid tissue (GALT) and airway reactivity in the lung. Epicutaneous

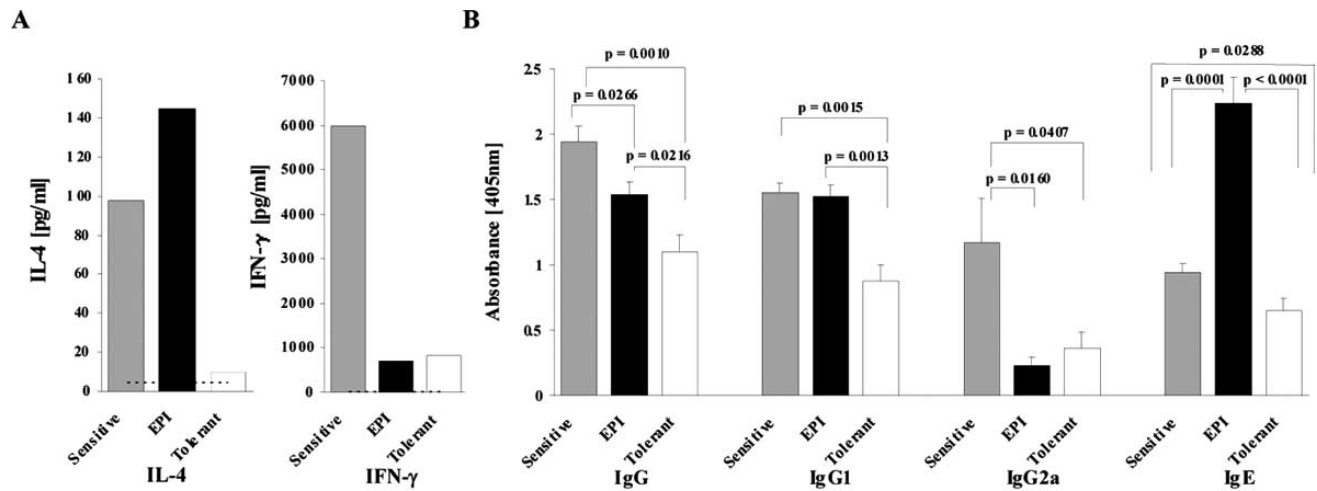


Fig. (4). Exposure to peanut protein on barrier-disrupted skin prevents induction of oral tolerance.

Feeding of antigens normally induces a state of antigen-specific systemic hyporesponsiveness (oral tolerance) upon secondary challenge. Epicutaneous antigen exposure can influence responses in the GALT and prevent the induction of oral tolerance. (A) IL-4 and IFN- γ responses to peanut protein in para-aortic lymph nodes of peanut-sensitive control mice (Sensitive), peanut-tolerant control mice (Tolerant) and in mice epicutaneously exposed to peanut prior to oral tolerance induction (EPI). (B) Levels of peanut-specific IgG, IgG1, IgG2a and IgE in serum. Results are expressed as the mean $\pm$ 1 SEM ($n=8$). Note that suppression of peanut-specific IL-4 and IgE responses is not only prevented by prior epicutaneous peanut exposure (EPI) but these responses are significantly enhanced upon oral challenge. [Sensitive: Fed saline, immunized subcutaneously with peanut protein in adjuvant and recall immunized; Tolerant: Exposed to saline on tape-stripped skin, fed a tolerogenic dose of peanut protein, immunized subcutaneously with peanut protein in adjuvant and recall immunized; EPI: Exposed to peanut protein on tape-stripped skin, fed a tolerogenic dose of peanut protein, immunized subcutaneously with peanut protein in adjuvant and recall immunized].

exposure to peanut protein on barrier-disrupted skin prevents the normal induction of oral tolerance (Fig. 4) [102]. It not only prevents the induction of oral tolerance, but affects mucosal responses to further enhance Th2 responses and IgE production upon gastrointestinal exposure. Mice epicutaneously sensitized to peanut additionally develop clinical signs of systemic anaphylaxis following gastrointestinal challenge [102]. In patients with peanut allergy the primary route of sensitization is often not clear. These observations however suggest that epicutaneous exposure might play a role in the primary pathogenesis of peanut allergy. Furthermore, epicutaneous exposure to OVA can induce airway eosinophilia in mice following a single inhalation of OVA [101]. It can also induce airway hyperresponsiveness to methacholine, suggesting that epicutaneous allergen exposure may enhance the development of allergic asthma [101]. Together these experiments indicate that allergen exposure through barrier-disrupted skin could serve as a natural sensitization pathway for food allergy and respiratory allergic disease.

Susceptibility to Epicutaneous Sensitization

Epicutaneous sensitization and the possibility of systemic disease manifestations may be particularly relevant for patients already suffering from AD and other desquamating skin conditions. However, excessive washing and the frequent use of soaps and syndets may cause disruption of the stratum corneum in children. In adults, washing, shaving, waxing and the frequent use of various exfoliants and cosmetics may cause a similar barrier-disruption. The mechanisms of this barrier-disruption may be *via* mechanical abrasion of the skin surface (washing with

rough materials, shaving, use of exfoliants) and *via* metabolic events induced by raised skin surface pH and directly deleterious effects on stratum corneum lipid structure (excessive use of water and soap). It is tempting to speculate that such repeated mild disruption of the skin surface may be enough to cause sensitization in genetically susceptible individuals. Recent reports suggest that continuous activation of resident APCs can lead to a breakdown of tolerance to self and possibly to environmental antigens. Continuous activation of LCs in the skin by overexpressing CD40-ligand in the epidermis results in chronic skin inflammation and in systemic autoimmunity [103]. In the rat insulin promotor-glycoprotein double transgenic mouse model, T cell interactions with peptide only induce autoimmunity when APCs are continuously activated with anti-CD40 and not when peptide is presented in a resting or naïve environment [104]. It is possible that a similar continual activation of the IgE-bearing LCs in AD through scratching and abrasion of the pruritic skin excoriations may break the homeostatic balance and tolerance in the skin, and sensitization to innocuous environmental and food antigens could occur as a result. Likewise, continued activation of resident LCs in normal skin through repeated mild corneum barrier-disruption may promote the induction of Th2 and IgE responses and allergic sensitization.

PREVENTION OF SENSITIZATION

As systemic sensitization to environmental allergens is probably most likely to occur through barrier-disrupted skin, maintaining or restoring a healthy skin barrier may prevent sensitization. Most existing treatment strategies for skin

diseases with barrier dysfunction, such as AD, targets the immunogenic abnormalities. The use of corticosteroids, tacrolimus, cyclosporin and other immunosuppressive agents is common place in the management of AD [73]. However, the atopy and inflammatory component of AD may be secondary to the skin barrier abnormalities as suggested by the 'outside-in' hypothesis [55,78,79]. Recent studies show that repair of the skin barrier by application of specially formulated emollients to AD skin is beneficial not only for the uninvolved dry skin but also for the inflammatory component in children with severe AD [105]. Use of emollients is already mainstay therapy in the symptomatic treatment of AD, however care must be taken as current water-in-oil emollients and improperly formulated moisturizers can aggravate permeability barrier abnormalities and delay recovery of barrier function [106-108]. In contrast, the use of a physiological mixture of the 3 key stratum corneum lipids comprising ceramide, cholesterol and free fatty acids can accelerate barrier repair and lead to normalization of barrier function in a variety of external, acute or sustained perturbations of the skin barrier [106,109,110]. Results from a phase I trial suggests that substitution of the standard non-physiological lipid-based emollients and moisturizers with a ceramide-dominant formulation in children with recalcitrant AD significantly reduces Severity Scoring of Atopic Dermatitis (SCORAD) values, normalises transepidermal water loss, increases skin hydration and improves stratum corneum integrity [105]. Lipids that are physiological to the stratum corneum appear to have a different mechanism of action to standard emollients, which typically form an occlusive semi-permeable layer on the skin surface [107]. Physiological lipid mixtures of free fatty acids, cholesterol and ceramides penetrates through the disrupted stratum corneum, reaches the nucleated epidermal cell layers where they are taken up by keratinocytes. The keratinocytes finally releases the lipids into nascent lamellar bilayers in the stratum corneum interstices [106].

In addition to the presence of sufficient extracellular lipids to form a competent lamellar bilayer system, optimal barrier function is dependent on a controlled balance between protease and protease-inhibitor activity. Uncontrolled activity of epidermal serine proteases such as SCCE and SCTE results in pathological desquamation of the skin as seen most dramatically in Netherton disease [10,12]. Polymorphisms in the SPINK5 gene underlying Netherton disease show significant association with atopy and AD, indicating a role also for protease inhibitors in the development of common atopic illnesses [12]. Patients with Netherton disease as well as patients with more common inflammatory dermatoses may benefit from topical application of serine protease inhibitors in combination with key physiological lipids. Skin barrier dysfunction and abnormalities in stratum corneum integrity can in animal models be reversed by application of protease inhibitors [47]. However, this possibility remains to be tested in humans.

CONCLUSION

This review has examined the potential causes and effects of skin barrier dysfunction and the possible links to

systemic allergic disease. Perturbations to the efficiency of the epidermal permeability barrier, whether a consequence of environmental factors or inherent genetics, can have profound effects on both skin quality and systemic immunity. Antigens relevant to allergic disease can readily enter through barrier-disrupted skin and cause primary systemic Th2 responses with particularly elevated levels of IgE. Importantly, epicutaneous antigen exposure can affect responses to antigen challenge in distant sites such as the GALT and the lung mucosae. This can prevent the induction of normal oral tolerance to food proteins and cause airway hyperreactivity. Such potent sensitization to allergens through the skin has so far been demonstrated unequivocally in mice but is likely also to occur in humans.

It is beyond doubt that the skin is an active immunological organ and its potential role in the pathogenesis of various allergic diseases should be further investigated. Already, cutaneous allergen exposure must be considered when therapeutic regimens for atopic diseases are developed. Indeed, also the possible systemic sensitizing potential of allergic patch testing need to be monitored. Regulation or restoration of healthy cutaneous barrier function may be a prime target for immunotherapeutic intervention to correct the cytokine imbalance seen in AD and other dermatoses. This may circumvent some allergic and classical DTH responses. Together, the data reviewed here indicate that alterations in normal skin health through changes in skin care and obsession with cleanliness could provide part of the explanation for the increase in allergic responses to environmental antigens in the Western world.

ABBREVIATIONS

AD	= Atopic dermatitis
LC	= Langerhans cell
DC	= Dendritic cell
SCCE	= Stratum corneum chymotryptic enzyme
SCTE	= Stratum corneum tryptic enzyme
APC	= Antigen-presenting cell
OVA	= Chicken egg ovalbumin
GALT	= Gut-associated lymphoid tissue

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