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Article type : Review Article

The role of skin barrier in occupational contact dermatitis

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Title: The role of skin barrier in occupational contact dermatitis

Running title: Skin barrier and contact dermatitis

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/exd.13704

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Key words: review; irritant contact dermatitis; allergic contact dermatitis, occupational skin diseases, stratum corneum, innate immunity

Abstract

Skin diseases represent one of the most common work-related diseases and may have a detrimental effect on social, personal and occupational aspects of life. Contact dermatitis, which comprises predominately irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD) accounts for vast majority of occupational skin diseases, especially in occupations associated with frequent skin contact with irritants and contact allergens. Although ICD and ACD have similar clinical manifestation, their pathophysiology and the role of the skin barrier is different. In ICD, perturbation of the skin barrier is the primary event which sets into motion diverse metabolic processes and triggers activation of innate immunity without involvement of adaptive immune system. In ACD, a type IV hypersensitivity reaction induced by contact allergens, the skin barrier impairment may evoke innate signaling pathways during the sensitization phase required for the activation of T-cell adaptive response. Thus, skin barrier impairment may increase the risk of ICD or ACD not only because of enhanced permeability and ingress of irritants and allergens, but also by generation of innate immune signal needed for the induction of allergic response. Hence, an efficient way to prevent CD is to avoid skin barrier damage in the workplace. This review focuses on the skin barrier, how it is affected by skin irritants and how its impairment contributes to development of ICD and ACD.

Introduction

The skin is an important port of entry for potentially harmful chemicals in occupational settings where they can exert systemic toxic effects once absorbed into the blood circulation. More often, however, the skin itself is the primary victim for toxicity when a worker is exposed to mechanical, physical or chemical agents.

Skin diseases represent one of the most prevalent occupational diseases worldwide. In Europe, they contribute to more than 30% of all recorded occupational diseases [1-3]. The vast majority of occupational skin diseases is due to contact dermatitis (CD), an inflammatory skin disease caused by direct skin contact with a skin irritant or allergen. According to the pathophysiological mechanisms involved, CD can be classified as irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD), with ICD being more prevalent in occupational settings. Moreover, protein contact dermatitis (PCD), common in workers handling food products is a distinct clinical entity where immediate type skin reactions occur [4]. However, in a clinical context, many patients suffer from a mixture of the above.

The highest risk professions for developing CD are hairdressers, health care sector workers, beauticians, workers in food-processing industry, metalworkers and construction workers [1, 3]. Common irritants include soaps, detergents, water, solvents, cutting oils, and food ingredients[5]. In addition to chemical irritants, ICD can develop by physical irritation caused e.g. by skin friction or abrasion which occurs often in construction workers and in cold or dry environment [6-8]. The most common occupational contact allergens are metals such as nickel, cobalt and chromium, fragrances, preservatives such as isothiazolinones and formaldehyde/formaldehyde releasing chemicals, rubber accelerators, acrylates and para-phenylenediamine used in hair dye colors[3, 9].

The spectrum of the clinical presentations of CD is broad, and ICD and ACD often share the same morphological features despite of different pathophysiology. Therefore, differentiation between ICD and ACD is often challenging and is often based on exclusion of ACD and PCD through negative patch testing and skin prick-prick testing, anatomical predilection sites, assessment of domestic and occupation skin exposure to irritants or allergens and disease course pattern.

The diagnostic work-up can be very complex as new allergens are emerging which are not always present in the baseline test series [10, 11]. Furthermore, co-exposure of skin irritants and allergens in the workplace is common.

Recently, several comprehensive review articles have been published on the immunology of contact dermatitis [12-16]. This review will mainly focus on the skin barrier, which has a central role in development of both occupational ICD and ACD.

Immune activation

ICD evolves as a result of direct skin contact with chemical or physical agents which activate innate immunity reactions without prior sensitization. The primary event in the development of ICD is skin barrier disruption leading to release of a preformed pool of IL-1 α from the corneocytes[17, 18]. Depending on the intrinsic properties of the irritant and its ability to penetrate across the skin and reach sufficient concentration in the viable epidermis, keratinocyte damage can occur. This will induce production of pro-inflammatory

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stimuli or alarmins which act as a danger signal for the activation of innate immune cells and release of chemokines and cytokines [12]. Kumari et al. [19] showed recently that acute barrier disruption by physical or chemical perturbation may be sufficient to initiate thymic stromal lymphopoietin (TSLP) responses in the skin, and that this process was coordinated by endogenous alarmins including IL-1 α . The innate response is rapid, and in the case of strong irritants like acids, bases and some solvents, occurs shortly after exposure on the exposed skin sites. In the workplace, where relatively mild irritants such as water and soaps are the most common exposures, clinical signs of contact dermatitis occur as a consequence of a cumulative damage of the skin barrier due to frequent and repeated exposure and take weeks to months to develop.

ACD is a T-cell mediated, type IV delayed hypersensitivity reaction triggered by chemical allergens, which is elicited only in an individual who has previously been sensitized to the same allergen [16, 20, 21]. Cutaneous re-exposure to the sensitizing contact allergen results in the recruitment of circulating allergen-specific T-cells into the skin where they induce secretion of pro-inflammatory cytokines leading to an eczematous skin reaction. Most contact allergens are organic chemicals or metal ions with low molecular weight, which favors their percutaneous penetration [16, 21]. Furthermore, they are reactive which enables binding to carrier proteins serving as antigens for the adaptive immune system [16, 21]. Activation of the innate immune system in the sensitization phase is a prerequisite for the activation of *Langerhans* cells and dendritic cells and the adaptive immune response [12, 15, 16, 21]. Important part of the activation of the innate immune system is recognition of endogenous danger signals, known as danger-associated molecular patterns (DAMPs) which promote activation of toll-like receptors (TLR) and the inflammasome resulting in production of proinflammatory cytokines by skin-resident immune cells [12, 16, 21, 22]. Innate immune receptor, TLR can be activated directly or indirectly. For example, nickel induces pro-inflammatory milieu by activating TLR4 directly [23] while organic contact allergens indirectly activate TLR2 and TLR4 via release of hyaluronic acid [24]. Both direct and indirect activation types of contact allergens may induce reactive oxygen species (ROS), which contribute to skin inflammation [12, 15, 16, 21]. Importantly, innate immune stimuli do not necessarily have to be provided by the contact allergen. Examples are the amplification of sensitization to ACD by mixtures of weak contact allergens or combinations of irritants and contact allergens [12, 15, 16, 21].

The normal skin barrier

Permeability barrier function can largely be attributed to the epidermal top layer, stratum corneum (SC). The SC comprises flattened, nucleus-free cells, known as corneocytes enclosed in a resistant protein and lipid rich cell envelopes (cornified envelope, CE) and interconnected by corneodesmosomes [25, 26]. The interior of corneocytes contains keratins aggregated by filaggrin monomers into microfibrils which are cross-linked to the CE. CE acts also as a scaffold for intercellular lipid matrix, the main penetration route for most

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skin irritants and contact allergens. The SC lipids, composed predominantly of ceramides, free fatty acids and cholesterol are synthesized and stored in lamellar granules, and as precursors extruded into the extracellular space between the stratum corneum and stratum granulosum [25, 27, 28]. Next to lipids, lamellar bodies also contain a large number of proteins important for the SC homeostasis such as antimicrobial peptides and the proteolytic enzymes involved in corneodesmosome hydrolysis and lipid synthesis which are excreted in the extracellular lipid matrix [27, 28]. Of note, next to their role in the permeability barrier, SC lipids contribute to the acidification of the SC, desquamation, and cell signaling [27, 28].

One of the major functions of the SC is maintenance of water balance in the skin. Dry and scaly SC, characterized by a fragile structure, tendency for cracking and increased permeability is a major hallmark and one of the first symptoms of ICD. Within the SC water exists in different states: tightly bound water, partially bound water and unbound water [29-31]. It has been shown that the amount of bound water largely determines mechanical properties of the skin like stiffness and flexibility. The water binding properties of the SC are predominantly maintained by the presence of hygroscopic components within the corneocytes, keratins and natural moisturizing factors (NMF) [26]. NMF is a complex mixture of low molecular weight, water-soluble compounds which partly originate from enzymatic degradation of filaggrin in the lower layers of the SC. Choe et al., suggested that NMF and intercellular lipids play a basic role in binding the water molecules at least at the uppermost SC layers (0–30% SC depth). In the deeper-located SC layers >30% SC depth, keratin could play a comparable role in binding water molecules [32].

Next to the proteins involved in structural integrity and barrier function, SC harbors large amount of cell-signaling molecules constitutively produced by keratinocytes. In this regard, SC is unique as it acts as a reservoir of preformed biologically active IL-1 α [17, 33]. Upon skin barrier damage, IL-1 α is released from a preformed pool into the intercellular space leading to activation of several distinct signaling pathways and upregulation of the expression of secondary cytokines, adhesion molecules, chemokines, which are potent chemoattractants for leukocytes and may induce T-cell activation independent of exogenous antigen ultimately leading to ICD [19, 33]. Of note, the interaction of the skin barrier and immune response is not unidirectional. Many cytokines can provoke impairment in the skin barrier by altering the expression of structurally important proteins involved in the formation of the cornified envelope, including loricrin and profilaggrin and by inducing lipid synthesis [34, 35]

The effects of skin irritants and allergens on the skin barrier

Virtually all components of the SC can be affected by skin irritants depending on their intrinsic properties, dose, exposure pattern and host-related factors. The most frequent skin irritants in occupational settings are water and detergents, the major risk factors for ICD in health-sector, food-processing industry and hairdressing. Excessive hydration of the skin can lead to the swelling of corneocytes, creation of pockets of water in the intercellular regions, and alterations in the rigid organization of SC lipid bilayers [36, 37].

In respect to ICD, the most studied detergent is sodium lauryl sulphate (SLS), a strong irritant and frequent ingredient in soaps, cosmetic and cleansing products. There is a broad spectrum of mechanisms by which SLS can induce skin barrier damage and irritation response. Several, mainly experimental studies reported that SLS induced corneocyte damage by affecting CE and furthermore keratin, which exposes new water-binding sites and causes hyperhydration of the SC [36, 38]. SLS has also been shown to downregulate expression of structural proteins involucrin and profilaggrin and furthermore of lipid-metabolizing enzymes, transglutaminase and serine proteases kallikreins [39, 40]. Various investigations showed that treatment with detergents including SLS reduces the amount of SC lipids leading to the disorder of the lamellar structure [36, 41]. A recent study showed that even surfactants known to be mild to SC proteins were able to cause lipid order changes as well as removal of fraction of lipids [42]. As an alkaline detergent, SLS increases the pH of the SC affecting activity of serine proteases (especially KLK5 and KLK7), which are known effectors of desquamation and lipid synthesis [43] [44]. Next, SLS dramatically decreased NMF [45-47], and this decrease was correlated with decrease in SC hydration and changes in corneocyte surface topography [46]. Of note, NMF is not only important for skin hydration, but also for the conformation of the keratin fibers within the corneocytes [48], pH of the SC and the SC levels of IL-1 cytokines [35]. The deteriorating effect of detergents is not limited to the SC. A recent study showed that anionic surfactants affect the barrier integrity through disruption of tight junctions [49]. The changes on molecular level observed after exposures to SLS are consistent with reduction of the skin barrier function commonly assessed as transepidermal water loss (TEWL) and decreased hydration [46, 47, 50, 51].

Another important group of skin irritating compounds in the workplace are alcohols which are commonly used in health sector and food-processing industry as hand sanitizers. The most frequently used alcohols are ethanol, iso- and n-propanol. Although hand sanitizers seem to be less damaging for the skin barrier than soaps [52, 53] it has been demonstrated that they have the ability to induce changes in the SC; for example, n-propanol has pronounced denaturing effects on the SC proteins, pro-filaggrin processing, and desquamatory SC enzymes [54]. Consistently, Soltanipoor et al. [46] showed that n-propanol caused remarkable changes in corneocyte surface topography, and that this effect was strongly associated with decrease in NMF and SC hydration. In the same study of Soltanipoor et al. [46] the changes in corneocyte surface topography were also observed after exposure to SLS and NaOH, but not after acetic acid, likely due to its low irritant potency. Strong reduction of NMF after exposure to detergents and n-propanol may indicate that NMF contribute largely to development of dry skin in wet work occupations associated with frequent hand washing and use of disinfectants.

Impaired skin barrier as a risk factor for contact dermatitis

Obviously, a less efficient skin barrier will lead to a larger absorption of a skin irritant or allergen into the skin, which in turn will increase the likelihood of development of irritant or allergic reactions[55]. Consistently, individuals with a compromised skin barrier, either inherited or acquired, might be at higher risk to acquire ICD or ACD. The importance of a competent skin barrier for susceptibility to acute and chronic ICD is well demonstrated in atopic dermatitis (AD). Reduced skin barrier is one of major hallmarks of AD, even in non-

lesional skin, and cause 2-5 fold increased dermal absorption [56-58]. In addition to reduced skin barrier function, AD subjects have increased surface pH, reduced SC hydration, and slower barrier recovery after induced irritation [51, 59]. Interestingly, ACD which is characterized by the ability to spread to non-exposed skin sites, causes skin barrier impairment even in clinically non-affected skin sites due to compromised ceramide synthesis [60].

Several experimental irritation studies showed that individuals with (a history of) AD had a stronger effect and a lower irritant threshold as compared to the healthy subjects, and that this effect was related to the degree of the skin barrier impairment [51, 61]. Consistently, epidemiological studies showed that AD is a strong risk factor for occupational ICD as almost half of patients with occupational contact dermatitis have a history of AD. Deficiency of filaggrin protein either inherited or due to Th-2 inflammation [35], aberrant composition and organization of the SC lipids [62-64], and impaired desquamation [65] are some of abnormalities in AD associated with the skin barrier function. The presence of AD increases the risk for occupational ICD approximately 2-3 times, while patients with both AD and filaggrin gene (*FLG*) loss-of-function mutations had up to 5-fold increased risk to develop ICD [66-68]. However, the effect of the *FLG* mutations on the risk for occupational ICD was much lower in absence of AD. A Danish study showed that individuals with *FLG* mutations, a history of hand eczema in early childhood and AD steer away from occupations with a high risk of ICD [69]. Interestingly, AD patients with *FLG* loss-of-function showed alterations of the corneocyte surface topography and reduced hydration and NMF, similarly to the effect of skin irritants. Consistently, the resistance of SC to water diffusion of non-lesional skin of AD patients, were similar to those of healthy individuals following SLS irritation, suggesting similar structural abnormalities in AD and ICD [70].

The role of AD and *FLG* mutations in ACD is less obvious, and the literature data are conflicting [71-73]. Theoretically, reduced skin barrier in AD and presence of *FLG* mutations would increase the levels of allergens penetrating across the SC and hence the risk of ACD. Consistently Kubo et al. [74] showed that trivalent chromium, a potent contact allergen penetrated filaggrin-deficient murine stratum corneum more easily than normal mouse skin. Specifically for nickel, it has been hypothesized that reduced levels of filaggrin would lead to larger amounts of nickel that penetrate the skin due to its ability to bind to histidine, an abundant amino acid and a degradation product of filaggrin [75]. While, Ross-Hansen [76] found no difference in the elicitation dose-response relationship between *FLG* mutation and non-mutation carriers in already nickel allergic individuals, the risk of nickel ACD is higher in *FLG* mutation carriers from large Danish and German general population cohorts [75, 77]. A recent systematic review and meta-analysis [72] reported no association of AD with contact sensitization to common allergens in patient studies, but a positive relationship in general population studies. The discrepancies in the various experimental, clinical and epidemiological studies have recently been discussed and argued that multiple allergen and host factors may affect the association between AD and contact sensitization including Th-2 cytokine milieu in AD which might lower the risk of contact sensitization, difference in exposure pattern to allergens between AD patients and healthy individuals and a higher

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prevalence of false-positive patch test reactions in AD, particularly in the case of metal allergens [71]. Interestingly, Kohli et al. [78] found that AD predisposes to sensitization only to less potent allergens arguing that potent sensitizers are often strong irritants that damage the skin barrier and trigger innate immune response needed for the induction of allergic response. Consistently, Koppes et al.[45] reported that a strong contact allergen methyl / chloromethylisothiazolinone known of its corrosive and irritant properties, causes remarkable alterations of the corneocyte surface topography and reduction of NMF, similarly to SLS. This effect was, however not seen for nickel, a less irritant contact allergen.

Several studies have shown that skin irritation achieved with SLS decreases the threshold dose for allergic response in patients previously sensitized to nickel or cobalt [79-82]. Moreover, pre-treatment with SLS seems not to be additive but synergistic [79]. Most contact allergens have irritant properties and consequently an intrinsic potential to activate innate immune response, whereas the strength of the irritant effect determines the strength of the allergic potential [21, 83]. Along these lines, exposure to a mixture of contact allergens also increases the risk of ACD, the so-called 'cocktail effect' [84].

Undoubtedly, skin irritation potentiates contact sensitivity, however it is difficult to dissect the role of skin barrier impairment from concomitant irritation and keratinocyte damage. Several studies showed that impaired permeability barrier itself in the absence of cell death e.g. by mechanical stress increases epidermal cytokine production and release [85]. Various immune cells present in the skin act as sensors and are activated or induced to migrate when barrier defects occur which potentially can lead to immune response [22]. Consistently, in a mouse model complete filaggrin deficiency associated with altered barrier integrity showed enhanced sensitization, despite of the absence of cutaneous inflammation [86, 87]. Together, this suggests that skin barrier itself is a likely contributor to the development of contact sensitization. Clinical studies have also shown the same temporal relationship, i.e. ICD often precedes ACD [88].

To this end, skin barrier can modify the risk for ICD and ACD in different ways. As irritation, sensitization and elicitation responses are all dose-dependent, an impaired barrier will increase the chance for ICD and ACD. In addition, skin barrier damage can act as a danger signal promoting activation of innate immunity crucial for development of sensitization. Therefore, in addition to use of protective wear and reduction of occupational irritancy and allergen exposure, increasing awareness on the importance of a competent skin barrier in the workplace and strategies aimed at avoidance of skin barrier damage are essential in prevention of occupational skin diseases[89, 90]. A recent Cochrane review reported that moisturizers used alone or in combination with barrier creams may have a clinically important protective effect for the primary prevention of occupational contact dermatitis [91]. In line with the conclusions of that review, use of moisturizers has been recommended by the European Society of Contact Dermatitis in their recent guidelines for the prevention and therapy of occupational hand dermatitis [92]. Though, skin protection and use of moisturizers in the workplace is low[93], emphasizing the need for a systematic knowledge

dissemination on risk factors and prevention bridging the gap between research and practice[94].

Conflicts of interest/disclosures:

Authors declared no conflict of interest

Author Contribution

IJ, JPT, and SK drafted the paper together, revised it critically and approved the submitted version.

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